SARS-CoV-2 and COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus. There are six other coronaviruses that are known to infect humans. Four coronaviruses, HCoV-NL63, HCoV-HKU1, HCoV-229E, and HCoV-OC43 circulate worldwide and together are the second most common cause of the common cold.[1, 2] Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) infected 8096 people in 2003 resulting in 774 deaths.[3] After 2003 there has not been any further human to human transmission. Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in humans in 2012.[4] MERS-CoV continues to cause sporadic infection and outbreaks in the Arabian peninsula, as well as occasional other cases and outbreaks in other parts of the world linked to travelers to the Arabian peninsula.[5]

Bats were the source of SARS-CoV-1,[6] and are known to be a natural reservoir for related coronaviruses,[7, 8] SARS-CoV-2 was likely circulating in bats for decades.[9] In late 2019, SARS-CoV-2 was first detected in humans and is established as the cause of the disease now designated coronavirus disease 2019 (COVID-19). Approximately 10-20% of persons with SARS-CoV-2 infection are asymptomatic.[10, 11] In those who are symptomatic, there is a wide range of illness from those with mild symptoms such as runny nose to those with severe disease affecting particularly the respiratory tract with high mortality.[12] Most people with SARS-CoV-2 infection are asymptomatic or have mild-moderate symptoms not requiring hospitalization. In one study of a relatively healthy population, those with COVID-19 requiring hospital care was < 2%, and the mortality rate was < 0.1%.[11]

SARS-CoV-2 transmission and mortality

The timing of peak SARS-CoV-2 transmission is primarily affected by seasonal patterns (i). The scale of SARS-CoV-2 transmission in a susceptible population is primarily determined by population density (ii). The mortality of COVID-19 is primarily determined by the age structure of the population (iii). Each of these important factors for SARS-CoV-2 transmission and mortality is non-modifiable.

(i) The timing of peak SARS-CoV-2 transmission is primarily affected by seasonal patterns

The four human coronaviruses (OC43, 229E, NL63, HKU1) are known to have a seasonal pattern of increased transmission.[1] The peak of the transmission wave in the United States is in the coldest months of the year, usually January. SARS-CoV-2 transmission appears to have a similar seasonal pattern of transmission to the other seasonal human coronaviruses.[13] There are numerous studies that show climate (season) is one of the most important factors for SARS-CoV-2 transmission.[14-26] In general, colder temperatures and less humidity are associated with increased SARS-CoV-2 transmission.

(ii) The scale of SARS-CoV-2 transmission is primarily determined by population density

The transmission of SARS-CoV-2 is strongly associated with population density, particularly population-weighted density.[15-18, 24, 27-31] In the United States, incidence and mortality are ten times higher in the most densely populated areas compared to the least densely populated areas.[32,33] The association between population density and SARS-CoV-2 transmission has been identified in Europe,[34] Italy,[35] India,[36,37] Argentina,[38] Turkey,[39] Algeria,[40] Brazil,[22] Japan,[25] and China.[41]

This is also evident in Canada. Provinces with the highest population density (e.g. Ontario) tend to have the highest number of cases. Within provinces (e.g. Ontario), regions with the highest population density tend to have the highest number of cases (e.g. Toronto).

(iii) The mortality of COVID-19 is primarily determined by the age structure of the population

Age is the most important risk factor for COVID-19 mortality. Compared to persons under age 40, persons over the age of 80 have a greater than 300 times chance of dying from COVID-19.[42] The infection fatality ratio (IFR) in persons over 80 is approximately 1000 times the IFR in those under 20.[43] In Canada, 68% of deaths are in persons over 80, 87.5% of deaths are in persons over 70, and > 95% of deaths are in persons over 60.[13]

The risk of death due to COVID-19 in persons under 60 is very small.[44] In Canada, there have been 1,010 COVID-19 related deaths in persons < 60 years old as of April 16, 2021.[13] In Canada in 2018 there were 1,191 motor vehicle fatalities in persons under 55.[45] So, the risk of death due to COVID-19 in persons < 60 is less than the risk of death due to a motor vehicle fatality.

Asymptomatic transmission

A *British Medical Journal* editorial concisely summarizes the risk of asymptomatic transmission: "The transmission rates to contacts within a specific group (secondary attack rate) may be 3-25 times lower for people who are asymptomatic than for those with symptoms."[46] This is consistent with the conclusions from several peer-reviewed systematic reviews and meta-analyses.[47-50]

To further exemplify the risk of asymptomatic transmission, it is useful to look specifically at a few large or comprehensive studies. A very large study in Wuhan China of 9,899,828 city residents found 300 asymptomatic cases but there were no positive tests amongst 1,174 close contacts of asymptomatic cases.[51] Similarly, a very thorough study of 100 cases from Taiwan, found that "none of the 9 asymptomatic case patients transmitted a secondary case."[52]

Household transmission is one of the most important modes of transmission. In a meta-analysis of household transmission, which included 54 studies and 77 758 participants,[53] transmission from asymptomatic cases was 0.7% compared to 18% transmission from symptomatic cases. In other words, symptomatic transmission was roughly 25 times higher than asymptomatic transmission.

Asymptomatic transmission does occur but the rates of transmission from asymptomatic persons is substantially less than from symptomatic persons and does not warrant being considered a significant contributor to the overall transmission burden.

Evidence for lockdown measures, such as physical/social distancing, to control SARS-CoV-2 transmission

Almost all of the research done prior to 2020 examining the effectiveness of interventions such as avoiding crowding to control respiratory tract infections was done with influenza. Prior to 2020, social distancing was a term that included quarantine, school closures, work closures as well as avoiding crowding.[54]

As noted in a recent systemic review, “clear biological and epidemiologic rationale supports the potential effectiveness of social distancing measures”[55] in the control of viral respiratory tract infections. However, the actual evidence for avoiding crowding by the general public for the control of viral respiratory tract infections is negligible.

A 2019 WHO review[54] of non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza found only three studies[56-58] relevant to “avoiding crowding”. In all three studies the quality of evidence was rated as very low. Two of those studies were retrospective analysis of the 1918 pandemic[56-57], both published in 2007. The limitations of studies done almost a century after an event should be self-evident, and hence the quality of that evidence is rated as very low. Importantly, in reference to “avoiding crowding” the WHO document notes:[54]

> *Ethical considerations*
> In urban locations it can be difficult to avoid crowding without considerable social costs.
> Modification, postponement or cancellation of mass gatherings may have cultural or religious considerations, in addition to public health aspects.
>
> *Knowledge gaps*
> There are still major gaps in our understanding of person-to-person transmission dynamics. Reducing mass gatherings is likely to reduce transmission in the community, but the potential effects are difficult to predict with accuracy. Large-scale RCTs [randomized controlled trials] are unlikely to be feasible.

A 2020 Cochrane systematic review[59] “found only one RCT [randomized controlled trial] of quarantine, and <u>no trials of</u> screening at entry ports or <u>physical distancing</u> [emphasis added].” Since there is a complete absence of high-quality evidence regarding physical distancing, the authors state: “Physical distancing represents another major research gap which needs to be addressed expediently, especially within the context of the COVID-19 pandemic setting as well as in future epidemic settings.”[59]

In summary, there is an absence of high-quality evidence, such as randomized-controlled trials, that prove the effectiveness of lockdown measures to avoid crowding in particular groups or contexts.

Evidence for masks to prevent the spread of SARS-CoV-2

In short, and as stated by the World Health Organization (WHO), "there is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2".[60]

The best evidence for any medical intervention comes from large randomized controlled trials or meta-analysis of randomized trials. There are no randomized controlled trials or meta-analysis of randomized controlled trials that support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2.

There is only one published randomized controlled trial on the effectiveness of masking of healthy people in the community to prevent infection with SARS-CoV-2. That study found there was no significant difference in SARS-CoV-2 infection rates between those who wore masks and those who did not wear masks.[61]

Three recent meta-analyses show no benefit of masking healthy people in the community to prevent infection with respiratory viruses. Cochrane systematic reviews are widely recognized in the medical community as authoritative. A 2020 Cochrane meta-analysis of masks versus no masks in preventing viral respiratory illness found no difference in preventing influenza-like illness or laboratory confirmed illness.[62] Similarly, another meta-analysis published in 2020 showed that masks make no difference in preventing pandemic influenza in nonhealthcare settings.[63] Another meta-analysis by the WHO in 2019 also failed to show a substantial protective effect of face masks.[64]

When the analysis is limited to the strongest types of evidence (randomized trials and meta-analyses of randomized trials), there is no evidence that healthy persons wearing masks in non-healthcare settings prevents the spread of SARS-CoV-2.

In the absence of evidence from randomized controlled trials and meta-analyses, the WHO's report on masking from December 1, 2020[60] references a number of other types of studies that report to show that healthy persons wearing masks in non-healthcare settings prevents the spread of SARS-CoV-2. However, these studies have significant limitations that need to be considered.

The majority of the studies referenced by the WHO are ecological studies,[65-86] also called correlational studies. The ecological studies referenced by WHO compare mask use and COVID-19 rates between geographic region, such as country, state, or city. The descriptive analysis of these rates does not provide an evidentiary base for concluding causation. Ecological studies have "many methodologic problems that severely limit causal inference, including ecologic and cross-level bias, problems of confounder control, within-group misclassification, lack of adequate data, temporal ambiguity, collinearity, and migration across groups."[87] The WHO report also acknowledges those studies "have important limitations to consider".[60, 88-90]

Cohort studies,[91] case control,[92-94] and case series[95-97] are all referenced in the WHO document, but these study types are considered much weaker than randomized controlled trials or meta-analysis. Due to the limitation of the study designs, particularly bias and confounding, the true effect of masking is uncertain. Many of these studies also have limited generalizability. For example, a study looking at secondary transmission of SARS-CoV-2 in households[91] has limited generalizability to universal masking in the wider general public. The findings from case series of persons who traveled on the same flight[95, 96] cannot be generalized to universal masking.

Finally, a comment should be made on the study[98] by Chu et al. as that study is referenced by the WHO and has been widely cited in the media. As noted in the 2020 Cochrane review referenced above, the Chu et al. study "has been criticised for several reasons: use of an outdated 'Risk of bias' tool; inaccuracy of distance measures; and not adequately addressing multiple sources of bias, including recall and classification bias and in particular confounding. Confounding is very likely, as preventive behaviours such as mask use, social distancing, and hand hygiene are correlated behaviours, and hence any effect estimates are likely to be overly optimistic."[62]

In summary, there is "inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2".[60] Studies that support the effectiveness of masking are of poorer methodological quality and hence provide weaker evidence. Randomized controlled trial and meta-analysis, which provide stronger scientific evidence, do not support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2.

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April 22, 2021