COVID-19 Scientific Advisory Group Rapid Response Report

Key Research Question: What is the evidence supporting the possibility of asymptomatic transmission of SARS-CoV-2? [Updated April 13, 2020]

Context

- Asymptomatic transmission (including pre-symptomatic transmission) of SARS-CoV-2 could reduce the effectiveness of control measures that are related to symptom onset (isolation, face masks and enhanced hygiene for symptomatic persons, and parameters of contact tracing), particularly if routine practices, including the use of diligent hand hygiene and environmental disinfection after patient encounters are not adhered to.
- Concerns regarding asymptomatic transmission are driven by observations in various populations that suggested 18% – 50.5% of people with positive RT-PCR in various settings were asymptomatic at testing, and epidemiologic modelling suggesting that asymptomatic or presymptomatic cases may be responsible for potentially significant transmission, with a wide range of estimates from 0% to 44%. However, this is discrepant from epidemiologic descriptions from the initial epidemic in China and elsewhere which do not suggest that asymptomatic transmission is a major driver for the COVID19 epidemic.
- The Public Health Agency of Canada (PHAC) has indicated that wearing a non-medical (cloth) mask in the community has not been proven to protect the person wearing it, however, it can be an additional measure to protect others around you, and might be useful in situations where physical distancing is not possible (e.g., grocery stores and public transit). (Tasker, 2020; Public Health Agency of Canada, 2020)

Key Messages from the Evidence Summary

- It is biologically plausible that SARS-CoV-2 can be transmitted when patients are asymptomatic, pre-symptomatic, or mildly symptomatic (potentially from 2.5 days prior to onset of symptoms), based on the finding that RT-PCR levels are high early in infection. Asymptomatic transmission has been documented in individual case reports and reported case series, usually involving close/household contacts.
- Importantly, the efficiency of transmission of infection during asymptomatic through pauci-symptomatic infection is unclear, with some conflict between epidemiologic data modelling and other reports. The extent to which RT-PCR positivity in the absence of symptoms reflects cultivatable, and (in the absence of symptoms that strongly promote droplet generation) transmissible virus remains unclear.
- Transmission events and their dynamics are complex, but most evidence from other respiratory viruses suggest that transmission events predominantly occur with the peak of symptoms (highest fever, levels of coughing, sneezing and rhinorrhea).
- There is minimal data on cultivatable viral loads with SARS-CoV-2 in asymptomatic, pre-symptomatic, and pauci-symptomatic infection, and on the proportion of transmission which may be attributed to these categories, which currently precludes definitive recommendations.
- Further evidence is required to elucidate the transmission dynamics of SARS-CoV-2 in multiple populations in the community, long-term care and the acute care hospital. The diligent use of

routine infection prevention and control practices would be expected to reduce risk of asymptomatic transmission, which may be more likely to be related to contact and possible droplet spread in situations of prolonged close contact/food sharing.

- A large proportion of pre-symptomatic transmission would limit the effectiveness of control measures that are initiated by symptom onset, including additional precautions (droplet /contact) guided by point-of-care risk assessment, self-isolation, and contact tracing. The proportion of transmission events from asymptomatic or pre-symptomatic people via droplet and/or contact would be needed to inform an evidence based decision, and the evidence must be monitored.

Recommendations for Discussion

The Scientific Advisory Group was unable to provide consensus recommendations, due to shortcomings in existing data, but acknowledges there are expected publications and additional guidance forthcoming that will be incorporated into an updated review once available. The Scientific Advisory Group supported consideration of ethical frameworks and the precautionary principle in decision making in the context of an evolving risk assessment.

Committee Discussion

The SAG did not reach a consensus recommendation based on available evidence after discussion of this update. The new data considered was seen as supportive that asymptomatic and presymptomatic persons may test positive for SARS-CoV2 and that there are case reports of transmission without overt symptoms. The degree to which this may drive transmission in various settings (outside of close or household contact as has been reported) was debated. There were considerably varied opinions on the likelihood of asymptomatic transmission as a major contributor to transmission. That said, some committee members felt that the lack of concrete evidence to show cultivatable virus, and/or transmission in community or healthcare setting (versus close household settings) from presymptomatic cases is currently a critical evidence gap. Committee members felt that further data on asymptomatic cases may become available shortly, which would support a potential evidence based consensus recommendation. Seven committee members were in agreement with the key messages while two committee members felt that the current epidemiological situation supported that asymptomatic or presymptomatic transmission is occurring to a significant degree, which would have implications for risk assessment, and control measures.

Why the evolution of evidence in this area matters

Implications for Personal Protective Equipment (PPE) Recommendations: The possibility of significant asymptomatic spread via a droplet route of SARS-CoV-2 may affect recommendations for universal mask use in COVID-19 exposed healthcare workers (HCW) (to reduce the risk of nosocomial spread) and recommendations for HCW protection in direct patient care of patients who do not have a positive screen for COVID-19 symptoms in higher risk areas. However, defining the nature and duration of contact that would be considered “higher risk” in a health care setting with asymptomatic COVID-19 positive would depend on the relative contribution of droplet spread in the absence of symptoms that are usually felt to generate droplets (cough, sneeze) versus direct contact and fomite spread from people with no/few symptoms (example, touching nares then touching a fomite). In the latter case, and in all cases hand hygiene and environmental cleaning of high touch areas remains a mainstay of protection.
It is acknowledged that in some areas PPE shortages are a practical issue, and there is a possibility of worsening the degree of overall HCW risk over the course of the epidemic if PPE supplies are not targeted appropriately. The Scientific Advisory Group (SAG) supports the use of both the precautionary

principle and ethical framework to aid in application of decisions made on the basis of the best possible evidence (Bean et al., 2020).

Implications for Public Health Control Strategies: Physical distancing strategies, which are not predicated on symptom development, remain a cornerstone control measure. Contact tracing has been expanded to include presymptomatic phase contacts in the hospital setting. Enhanced community surveillance of representative groups (by implementation of approved viral testing and validated serologic tests once available) in the community will need to be prioritized to guide application of public health measures and inform an understanding of local epidemiology. If pre-symptomatic or asymptomatic droplet spread is found to contribute significantly to transmission, a review of optimal mask practices in community settings would be warranted and would have major implications for contact tracing.

The evidence for this topic is changing very rapidly. It is necessary to monitor the literature for new estimates of spread from asymptomatic persons, information around rapid potential screening of asymptomatic persons, efficacy of face shields, masks, and cloth masks, alone and in combination. Further evidence on what interventions can mitigate risk of both asymptomatic and presymptomatic spread is also needed. This brief should be re-visited frequently to ensure all evidence is accounted for.

Summary of Evidence

Literature for this review was collected from a pragmatic search of the new COVID-19 literature. Key limitations of this review are related to limited inclusion of evidence from SARS and MERS and the speed with which evidence is available. In addition, some of the evidence is preprint, which has not been subject to peer review, published as correspondence not subject to peer review, or are observational studies, with lower rigor than formal epidemiological studies

Current understanding of transmission of COVID-19

The World Health Organization (WHO) issued a scientific brief March 29, 2020 that stated the following. “According to current evidence, COVID-19 virus is transmitted between people through respiratory droplets and contact routes. Droplet transmission occurs when a person is in close contact (within 1 m) with someone who has respiratory symptoms (e.g. coughing or sneezing) and is therefore at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infective respiratory droplets (which are generally considered to be > 5-10 μm in diameter). Droplet transmission may also occur through fomites in the immediate environment around the infected person. Therefore, transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g. stethoscope or thermometer)” (World Health Organization, 2020c). The WHO also indicates that airborne transmission may occur with procedures where aerosols are created, for example, endotracheal intubation, turning the patient to the prone position and cardiopulmonary resuscitation (World Health Organization, 2020c).

What is the evidence supporting the possibility of asymptomatic transmission or SARS-CoV-2?

Viral load data (humans and animal models): Small studies have demonstrated very high viral loads (by RT-PCR) in patients identified as presymptomatic, asymptomatic, or mildly symptomatic, making this a plausible concern (Kimball, 2020; Zou, 2020). These studies do not verify that patients are not actually post-symptomatic as they don’t assess virus viability. A virological assessment was carried out of nine patients after they present with early symptoms (Wolfel et al, 2020). Patients demonstrated high virus shedding by RT-PCR, peaking at day 4, and live virus was isolated during this time frame. They also used

sub-genomic RNA to demonstrate active viral replication in the upper respiratory tract. Seroconversion occurred by day 7 in 50% of patients and by day 14 in all patients. Shedding of viral RNA based on RT-PCR with high quantitative burden continued into the second week even though no virus was isolated after day 8 (Wolfel et al, 2020), indicating that RT-PCR positivity does not confirm live virus shedding. Congruent findings from 82 people in Beijing were reported in a correspondence that reported the viral load peak at five to six days after symptom onset, with the viral load very high early in the course of disease (Pan et al, 2020). There were two people in this group with known exposure to an infected individual who were RT-PCR positive one day before symptom onset (Pan et al, 2020).

In a study in a long term care home, 13 of 23 individuals who tested positive by RT-PCR, were asymptomatic at the time of testing (Kimball et al., 2020). In this study, high amounts of viral RNA based on RT-PCR not viable viral load testing were detected in people who were identified as asymptomatic, presymptomatic or symptomatic at the time of testing, with no significant differences between the three groups (Kimball et al, 2020). Although these RT-PCR Ct values were not correlated to cultivable virus, this data suggests there may be viral shedding during the presymptomatic period, but the amount of viable virus and the likelihood of transmission of infectious virus from a non coughing patient remains unclear.

In experimental SARS-CoV-2 infection of four macaques, early and prolonged virus excretion (through RT-PCR and virus isolation from the nose and throat in the absence of clinical disease was seen. Higher nasal shedding of SARS-CoV-2 virus RNA was identified in older animals compared to young (Rockx et al., preprint). The early viral shedding in this study is suggested similar to what is seen with influenza virus kinetics in both humans and macaques. This similarity to influenza is also suggested by other authors (Pan et al, 2020; Zou et al, 2020). Rhesus macaques have been primarily used as a non-human primate model for human disease as they have a similar physiology to humans and adapt well to captivity (Gardner & Luciw, 2008; Cai et al 2014). Multiple sequence alignment of the ACE2 protein sequence between humans and macaques revealed 100% alignment of the ACE2 interface (Chan et al, 2020). These animal model findings were supported by a human study of 18 patients, where those with early symptoms had high viral RT-PCR values, as did 1 asymptomatic patient as distinguished from SARS-CoV, which had higher loads (also based on RT-PCR not cultivation) later in illness (Zou et al., 2020; World Health Organization, 2020b). In summary, early viral presence in asymptomatic and presymptomatic states is suggested by these studies but there is no correlation yet to our knowledge with cultivatable virus. However, it is important to remember, the main mode of transmission of the SARS-CoV-2 is felt to be by droplet spread or direct contact with infected persons or surfaces. This observation is supported by the observation that in a Wuhan hospital where HCWs used full PPE, working in a high risk department, longer hours at work and suboptimal hand hygiene were all factors associated with COVID-19 infection in health care workers (Ran et al, 2020).

Data from human COVID-19 clusters: Reported rates of infection detected by PCR based screening in patients without symptoms at testing range from 15.8% in children with infection (Lu et al, 2020), to estimates of 17.9% (95% CI 15.5% - 20.2%) in a cruise ship cluster in which up to 50.5% of the cases were asymptomatic at the time of diagnosis (Mizumoto et al., 2020) and estimates of 33.3% (95% CI 8.3% - 58.3%) in a study of Japanese evacuees from Wuhan (Nishiura et al., 2020). It is unknown how many individuals in these cohorts developed symptoms after testing.

Therefore patients reporting no significant symptoms may have objective indicators of infection, and may also be “presymptomatic.” However, in the absence of a rapid turnaround screening test, this group is still

of concern for possible transmission. Another rapid release published in MMWR indicates that in a residential long-term care facility experiencing rapid transmission of COVID-19 infection, 13/23 (56.5%) of COVID19 positive residents were asymptomatic at the time of the test (Kimball et al, 2020) with 10 going on to develop symptoms within 7 days. Other cases and series of asymptomatic transmission have been reported in familial and non-familial settings, with one case study suggesting transmission may occur 1-2 days prior to development of symptoms (Chan et al, 2020; Bai et al., 2020; He et al., preprint; Lu et al, 2020b; Feng et al, Preprint). An additional publication reviewing undocumented cases in China (with a presumption that a proportion of these were asymptomatic) suggested undocumented cases may account for 79% of documented cases (Li et al., 2020a). The news report suggesting that four fifths of COVID-19 cases in China are asymptomatic was considered, but not included as evidence at this time (Day, 2020).

Stronger evidence of asymptomatic transmission is found in a study from China, where 24 asymptomatic individuals were identified as close contacts of SARS-CoV-2 positive individuals with epidemiologic investigation identified transmission from one of these asymptomatic individuals to close household contacts (Hu et al, 2020).

It is unclear whether infectivity via droplet spread of virus from asymptomatic persons in the absence of strongly droplet generating events such as coughing or sneezing is a driver of transmission, but droplet generation by talking or singing is a theoretic concern, particularly when physical distancing is not observed. In a study in Singapore, all 243 cases of COVID-19 between Jan 23 and Mar 16, 2020 were investigated, and seven clusters of cases with probable presymptomatic transmission were identified, with the overall proportion of transmission from these cases comprising 6.3% of overall transmission. Diagnostic testing was correlated with clinical signs and thoracic CT scans. Individuals were thought to be presymptomatic cases, not unidentified asymptomatic cases, as strong surveillance was in place and minimal community transmission was occurring. Two of these clusters involving asymptomatic people who gathered together to sing (Wei, 2020). This article also mentions a choir outbreak in the USA reported in the lay media (Wei, 2020). In summary, the above two studies suggest transmission from presymptomatic or asymptomatic people in close contact settings may occur, and that some settings may facilitate exposure and asymptomatic or presymptomatic transmission. Physical distancing would be expected to mitigate some of this risk.

Epidemiologic modelling: If the mean interval estimate (the time between symptoms developing in the infector and infectee) is shorter than the mean incubation period, presymptomatic transmission is suggested, and would support that transmission can occur early after infection and possibly before symptoms. Modelling the serial interval estimate (efficiency of propagation) suggests that the serial interval estimate for SARS-COV2 is 3.96 days (95% CI 3.53 – 4.39) which is significantly shorter than SARS-COV1 (8.4 days) or MERS-COV (14.6 days) (Zhao et al., preprint; Nishiura, Linton & Akmetzhanov, 2020), suggesting earlier transmission. However, estimates of the serial interval vary. In a description of 468 confirmed cases in China, 12.6% of the serial intervals were negative (the infectee developed symptoms before the infector) suggestive of pre-symptomatic transmission (Du et al., 2020). In another preprint article that described viral shedding and modelled transmission chain data, the mean interval estimate was longer at 5.8 days, with infectiousness estimated to start at -2.5 days before symptom onset, and peak at -0.6 days before symptom onset with decline over 7 days. The proportion of transmission before symptom onset was estimated at 44%, noting that the relative proportion of post symptom transmission was reduced by isolation (He et al 2020). A March 30, 2020 report from the Imperial College COVID-19 Response Team also estimated that the percentage of total population infected is orders of magnitude higher than case counts, related to mild and asymptomatic infections as

well as limited testing capacity, with the model suggesting attack rates ranging from 0.7% of the population in Germany through to 15% in Spain. The relative proportion of asymptomatic infection was not discussed (Flaxman et al., 2020). A preprint by Zhou investigates dynamics and spread of the outbreak using a modified Susceptible-Exposed-Infected-Resistant (SEIR) model with empirical data from the people evacuated from Wuhan from Jan 29 to Feb 2, 2020. The model provided little support for asymptomatic transmission although findings are subject to assumptions used, and the subgroup studied has low case confirmation and perhaps different social behavioural and environmental factors. (Zhou et al, Preprint). Reassuringly, in this paper, the reproductive number (R0) was found to be 2.12 which is consistent with the majority of the findings globally of an R0 range between 2.0 to 2.5.

Discussion

There are consistent laboratory data supporting early high levels of RT-PCR detectable SARS-CoV-2 before or at the time of symptom development, and in some persistently asymptomatic or subclinical cases. The pattern of earlier virus shedding with SARS-CoV-2 appears to be similar to that seen with Influenza virus than SARS-CoV1 or MERS-CoV viruses, and may suggest a prodromal phase similar to influenza is likely. Asymptomatic or presymptomatic transmission is believed widely to occur with influenza, and is important to inform mitigation strategies (Thai et al 2014). The key practical question is whether asymptomatic or presymptomatic RT-PCR positive individuals account for significant spread of infection, compared to spread from individuals with “droplet generating” symptoms such as coughing and sneezing. It may be more plausible that asymptomatic spread would be most likely to occur via contact (nasal secretion contamination of hands and fomites) in closer quarters and with shared meals, and potentially by droplet generation while talking or singing. A higher likelihood of asymptomatic transmission from close and prolonged exposure is supported by observations in family cluster case reports, and this may be less relevant within healthcare settings outside of higher risk procedures and health care settings. Epidemiologic modelling based on mean interval estimates suggests concern for potentially significant transmission from asymptomatic or presymptomatic persons. However, the assumptions made and the accuracy of epidemiologic symptom onset data (determination of any symptoms versus symptoms that limited activity, for example) are potential weaknesses in these analysis, as potentially reflected in the serial intervals differing by > 1.5 days in different reports. Further, the nature of the contacts in the transmission chains used in modelling studies is not well described (specifically if there was prolonged household contact or food sharing). It is noted that for containment control strategies the definition of contacts covered 2-3 days prior to symptom onset of the index case in these reports (in Hong Kong since 22 February and in mainland China since 21 February 2020.) These epidemiologic models seem to contradict the finding that close household contacts made up the majority of identified clusters in the initial epidemic, with droplet and fomite transmission suggested as the major driver of the initial SARS-CoV-2 epidemic in China (World Health Organization, 2020a). In addition, an epidemiologic model using SEIR methodology and empirical data did not find evidence of asymptomatic transmission (Zhou et al). It will be crucial to follow evolving evidence to resolve these discrepancies and support appropriate precautions and control measures if a significant role of asymptomatic spread is more strongly supported. .

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Date of first assessment: April 13, 2020

(If applicable) Date of re-assessment: N/A

Authorship & Committee Members

This report was written by Lynora Saxinger (co-chair), building on an initial report drafted by Ranjani Somyani, and the update review was conducted by Sylvia Checkley (and team),with primary reviewer Melissa Potestio.The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Jing Hu, Nelson Lee, Andrew McRae, Jeremy Slobodan, Brandie Walker, and Nathan Zelyas. External reviewers included Joseph Kim, Uma Chandran, and Michael Parsons.

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Appendix

List of Abbreviations

CDC: Centers for Disease Control and Prevention, US Department of Health and Human Services

CoV: Coronavirus

COVID-19: Coronavirus Disease 2019

CT: Computed Tomography Scan

MERS: Middle East Respiratory Syndrome

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

PHAC: Public Health Agency of Canada

PPE: Personal protective equipment

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

SAG: Scientific Advisory Group

SARS: Severe Acute Respiratory Syndrome

SARS-CoV-2: Severe Acute Respiratory Syndrome – Coronavirus – 2

WHO: World Health Organization

Literature Search Details

Medline/PubMed

1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (19061)
2 exp Asymptomatic Diseases/ (6863)
3 asymptomatic*.mp. (151914)
4 (no adj1 symptom*).mp. (11029)
5 "not showing symptom*".mp. (6)
6 "not displaying symptom*".mp. (1)
7 subclinical.mp. (40536)
8 2 or 3 or 4 or 5 or 6 or 7 (198567)
9 exp Disease Transmission, Infectious/ (67240)
10 transmission.mp. (507091)
11 transmit*.mp. (175260)
12 infectivity.mp. (25885)
13 infectiousness.mp. (1367)
14 9 or 10 or 11 or 12 or 13 (670831)
15 1 and 8 and 14 (121)

16 limit 15 to last 2 years (40)

CINAHL

S1	(MH "Coronavirus+")	
S2	(MH "Coronavirus Infections+")	
S3	coronaviru*	
S4	"corona virus"	
S5	ncov*	
S6	n-cov*	
S7	COVID-19 OR COVID19 OR COVID-2019 OR COVID2019	
S8	SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019	
S9	"severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*"	
S10	"2019 ncov" OR 2019ncov OR Hcov*	
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	
S12	asymptomatic OR subclinical OR no n2 symptom* OR "not showing symptoms" OR "not displaying symptoms"	45,757
S13	(MH "Disease Transmission+")	15,176
S14	transmission OR transmit* OR infectivity OR infectiousness	92,851
S15	S13 OR S14	93,800
S16	S11 AND S12 AND S15	31

TRIP Pro/Google Scholar/Google/ LitCovid/CEBM/WHO/Stanford Medicine/NEJM/CochraneLibrary/CDC

(asymptomatic OR paucisymptomatic OR "no symptoms" OR "not showing symptoms" OR "not displaying symptoms" subclinical) AND (transmission OR transmit OR transmitting OR infectivity OR infectiousness) AND ("covid-19" OR coronavirus OR COVID19 OR “corona virus” OR ncov OR “n-cov” OR “covid-2019” OR covid2019 OR “SARS-COV-2” OR “sarscov-2” OR sarscov2 OR sarscov19 OR “sars-cov-19” or “sarscov-19” OR sarscov2019 OR “sars-cov-2019” OR “severe acute respiratory syndrome”) from:2018

(asymptomatic OR paucisymptomatic OR "no symptoms" OR "not showing symptoms" OR "not displaying symptoms" OR subclinical) AND (transmission OR transmit OR transmitting OR infectivity OR infectiousness) AND ("covid-19" OR coronavirus OR “corona virus”)

(asymptomatic OR paucisymptomatic OR "no symptoms" OR "not showing symptoms" OR "not displaying symptoms" OR subclinical) AND (transmission OR transmit OR transmitting OR infectivity OR infectiousness)

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