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 July 13, 2020]

Since completion of this report, additional potentially relevant papers have come to attention, to be reviewed for inclusion in any possible future update of this literature synthesis:

Sun, K., Wang, W., Gao, L., Wang, Y., Luo, K., Ren, L., Zhan, Z., Chen, X., Zhao, S., Huang, Y., Sun, Q., Liu, Z., Litvinova, M., Vespignani, A., Ajelli, M., Viboud, C., & Yu, H. (2021). Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. Science, 371(6526). https://doi.org/10.1126/science.abe2424

Context

- Significant asymptomatic transmission of SARS-CoV-2 would reduce the effectiveness of public health control measures that are related to symptom onset (isolation, face masks and enhanced hygiene for symptomatic persons, and parameters of contact tracing).
- There is a lack of clarity and common usage of the terms asymptomatic, presymptomatic, and paucisymptomatic states in the COVID-19 literature.
- Concerns regarding asymptomatic transmission are driven by select early reports suggesting high proportions of people with positive RT-PCR in various outbreak settings were asymptomatic at the time of testing, and subsequent epidemiologic modelling suggesting that these cases may be responsible for potentially significant transmission. However, these studies generally did not exclude paucisymptomatic and presymptomatic states, and prolonged RTPCR positivity was not well understood earlier in the pandemic. New data are synthesized here.
- Even a small rate of asymptomatic or presymptomatic transmission could impact communities as public health measures are relaxed, if core control measures are neglected (including physical distancing, hygiene, appropriate use of face masks as recommended by current public health guidelines).
- There is new data emerging around diagnostic test utility, sensitivity and specificity, and the role of community based serologic testing to ascertain seroprevalence within communities and better delineate the fraction of undetected infections, and the possibility of asymptomatic and presymptomatic transmission as a community risk.
- Between the updated literature search date and the release of this update repeated searches were carried out to include high profile publications in this topic area, including the recent WHO Transmission Scientific Brief, released July 9, 2020. The author of the report reviewed this document in detail and there are no significant discrepancies or new information between this rapid review and the WHO updated scientific brief although it adds information on short range aerosols and the theoretic risk of fomite transmission, which are outside the scope of this document.

Key Messages from the Evidence Summary

1. Evidence thus far has not adequately defined or assessed “asymptomatic” individuals who test positive for SARS-CoV-2 by RT-PCR, making much of the current data unreliable. A single positive RT-PCR without current symptoms could be classified as 1) Presymptomatic, 2) Asymptomatic (or paucisymptomatic), or 3) Positive after infection (regardless of symptoms) or rarely, a false positive result (which cannot transmit infection.) Transmission might occur from only the first two types of individuals (pre and asymptomatic infected persons).

- Interpretation of existing data (including that used in modeling studies) is clouded by a lack of clarity in 1) definition of “asymptomatic” (whether defined by Influenza Like Illness screening (absence of cough and fever) or a more comprehensive symptom list was used) and 2) lack of reporting of symptoms for 4 weeks prior to, and 2 weeks after the test.
- There is evolving data on viral kinetics in asymptomatic, pre-symptomatic, and paucisymptomatic SARS-CoV-2 infection. One series documented higher viral loads (by 60 fold) and a longer time to RT-PCR clearance in patients with severe illness, and a median of 24d to become RT-PCR negative (with 32.1% still positive at 1 month post onset). Importantly, other studies have shown that SARS-CoV-2 RT-PCR can remain positive for 4 weeks in patients with milder outpatient managed COVID-19 as well.
- Therefore a RT-PCR positive result in a currently asymptomatic person is of unclear significance and RT-PCR positive status cannot be used to infer potentially infectious status.

2. Studies suggest that levels of SARS-CoV-2 can be high by RT-PCR and detected by virus cultivation early in infection, prior to symptom onset, with replication in upper respiratory (nasal lining) and respiratory cells. This is distinct from SARS-CoV and would support the potential importance of presymptomatic transmission. Two publications demonstrate a lack of viable virus detected after day 8 of symptoms, with another suggesting a possible longer duration of shedding of viable virus in severe illness.

In addition, the RT-PCR CT (threshold cycle) value may eventually become useful as a proxy for cultivatable virus - one source suggested <24 is associated with cultivatable virus. However development of validated methodologies to use SARS-CoV-2 CT as a quantification assay would be required.

3. To define the role of asymptomatic transmission, processes to rule out post infectious and presymptomatic RT-PCR positive states are required, as the proportion of people with truly asymptomatic infection cannot be accurately inferred from studies that report “asymptomatic” status at the time of testing. Prevalence studies carried out after epidemics in high risk closed populations are potentially more likely to include post infection RT-PCR positives, and overestimate the proportion of people who may transmit infection.

To establish asymptomatic SARS-CoV-2 infection:

- Post symptomatic PCR positivity should be ruled out by documentation of a negative 4 week symptom history and potentially with concurrent serologic testing, where available, for the presence of SARS-CoV-2 antibodies. Current evidence suggests that a positive PCR with positive antibody test would suggest past infection and low likelihood of current transmission potential.
- Presymptomatic PCR positivity should be ruled out by documenting absence of compatible symptoms over a 14 day period from test collection.
- If an asymptomatic person who is RT-PCR positive is seronegative, documentation of seroconversion at 3-4 weeks after the initial test should be considered.

4. The best individual studies of the true asymptomatic proportion in high risk populations suggest a range of 15 to 20%, in studies of individuals who were close contacts isolated in centralized quarantine facilities. Similarly, a well conducted RT-PCR and serology based study of US service members aboard an aircraft carrier reported an asymptomatic proportion of 18.9%, raising the possibility that younger

people may be more likely to be paucisymptomatic or asymptomatic. Finally, a pre-print metaanalysis of these epidemiologic data suggested the asymptomatic proportion is 15% (12-18%). Uncertainty in these studies is related to the possibility of prior infectious contacts in the community during exponential growth rate epidemics in some of these reports, coupled with a lack of detailed symptom history prior to the positive test, which would tend to overestimate the asymptomatic positive proportion through inclusion of post symptomatic positive cases. Importantly, a population of close contacts to documented cases are at higher risk of infection (symptomatic or asymptomatic) compared to the general population so observing that a proportion of 15% positives in high risk populations are asymptomatic does not suggest that 15% of asymptomatic people in the community are infected.

5 The efficiency of observed transmission of infection from asymptomatic RT-PCR positive people appears to be low (two studies reported no transmission from asymptomatic cases, one quarantine center series reported an incidence of secondary infection of 0.3%, which was 20 fold lower than transmission to contacts from severe cases, and another reported transmission to 2.2% of traced contacts of asymptomatic people. A preprint systematic review (including many of the papers reviewed here) estimated that secondary attack rates were 2.5X higher from symptomatic versus those who were symptom free at diagnosis.

6. Presymptomatic transmission merits separate consideration from asymptomatic transmission, because of more robust documentary data and because of practical contact tracing implications. Presymptomatic spread has been well documented in individual case reports and reported case series, usually involving close/household contacts. Newer data suggests that presymptomatic transmission may in some circumstances be considerable, although it is unclear whether these events are related to characteristics of the index case, the setting of transmission, or both. Case series have shown relatively high secondary attack rates with exposure just prior to symptom (for example, presymptomatic cases transmitted to 0.7% of contacts compared to while presymptomatic versus symptomatic cases transmitting to 1.1% of contacts). In another household study where index cases isolated themselves and masked within the household upon symptom development, however, there were no household transmissions versus a 17% attack rate in other households. Contact tracing studies overall suggest that most transmission risk occurs before day 6 of symptoms, with no nosocomial transmissions among 852 hospital contacts after day 6 of symptoms, although the contribution of presymptomatic spread was not clarified in that study.

7. Modeling data has suggested the possibility that presymptomatic or asymptomatic transmission could contribute to significant community transmission, but models have generally been based on data with the discussed shortcomings. Existing models are based on assumptions generated from studies in high risk populations that that did not rule out postsymptomatic and presymptomatic RT-PCR positives in the reported proportions of asymptomatic cases, as previously discussed. As such, these models establish an upper range of potential community transmission from asymptomatic and presymptomatic cases.

8. The role of paucisymptomatic individuals in COVID-19 transmission is very unclear, as on detailed review this group may have been called either “asymptomatic” or “mildly symptomatic” in previous studies. There is some suggestion that less severe disease is associated with a shorter duration of shedding of infectious virus.

Recommendations

1. The office of the Chief Medical Officer of Health, Alberta Health should develop and use standardized definitions for Asymptomatic, Presymptomatic, and Paucisymptomatic COVID-19 cases to support data collection and case classification, to clarify the assessment of transmission dynamics in Alberta.
2. All COVID-19 RT-PCR positive patients should be administered a brief global symptom history for current or recent symptoms suggestive of COVID-19 and if no current symptoms are documented, a specific symptom history over the previous 6 weeks should be recorded as a

searchable data field. Patients with prior symptoms would be able to be assigned “possible post-symptomatic” status.

3. A pilot of periodic administration of this current/previous 6 weeks symptom history questionnaire should be resourced to allow data collection on a sample of all patients presenting for testing at assessment centres to document the baseline prevalence of these symptoms in the Albertan population and the association with COVID-19 testing results.
4. If an asymptomatic person is documented to be RT-PCR positive, they should be monitored during self isolation and reclassified as “presymptomatic RT-PCR positive” if symptoms develop.
5. When serologic testing is available, the Serology working group of the provincial laboratory and Public Health should consider a pilot of serologic testing in asymptomatic RT-PCR positive patients to evaluate what proportion of test positive asymptomatic people are seropositive, suggesting past infection and likely noninfectious status. If seronegative, the serology should be repeated 3-4 weeks after the RT-PCR test to document if seroconversion has occurred.
6. The office of the Chief Medical Officer of Health, Alberta Health should consider further public education in two main areas:
   a) Identification of symptoms and prompt self isolation: Topics may include the importance of recognition of mild possible COVID-19 symptoms, the need to self isolate/get tested, and reinforce employer responsibilities to support employees with adequate sick leave policies.
   b) Highlight need for contact tracing: Topics may include the need for individuals to be able to list their contacts if subsequently identified as potentially infectious, to reduce further spread of infection. Therefore, if a contact tracing app is not used, people should be encouraged to keep a running diary of their daily contacts/types of contacts with others in the event that contact tracing is required.
7. Based on evidence identified in this review, it is suggested that adequate resources and infrastructure adaptation are currently required to prioritize specimens for COVID-19 RT-PCR testing in the following order: symptomatic (highest priority), asymptomatic people who are close contacts of known cases (high priority due to high pre-test probability), and then asymptomatic people without high risk contacts. Testing of asymptomatic people who are not identified case contacts should not delay testing, reporting and contact tracing efforts for people who are symptomatic or close contacts to known COVID-19 cases.
8. To clarify the utility of widespread testing of people who are asymptomatic, a pilot of strategic testing of asymptomatic people (with symptom documentation as above) should be considered to better describe population infections dynamics, with consideration for
   a. RT-PCR testing programs for those potentially at higher risk of exposure to infection (essential workers, those with higher numbers of community contacts, teachers, staff and children upon return to school), and those of higher risk of severe disease if acquiring infection (older persons, comorbidities).
   b. Population based prevalence studies using representative sampling, and both RT-PCR and serologic testing.

Committee Discussion

Third Revision:

This revision saw reasonable committee agreement that presymptomatic spread has evolved to have a more supported role in community transmission and that existing data on the proportion of transmission for completely asymptomatic persons is unclear. Committee members supported a recommendation to better delineate this in an Albertan context, primarily though documenting an expanded symptom history at the time of swabs and ensuring a 6 week retrospective history review is documented in those who are positive. The recommendation was originally 4-6 weeks but 6 weeks was felt to be better operationally. Use of serology in conjunction with RT-PCR in people who are truly asymptomatic and not post symptomatic was seen as potentially promising but committee survey suggested that this should not be recommended directly given the nascent state of serologic testing so the recommendation was changed

to request that the COVID-19 Serology provlab group to work with Public Health to consider a pilot of this approach.

Second revision:
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.

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. This brief should be re-visited frequently to ensure all evidence is accounted for.

Summary of Evidence
The literature searches were conducted by KRS within the Knowledge Management Department of Alberta Health Services. Critical appraisal was conducted using an adapted Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). A key limitation of this review is that 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.

Research Gaps
There is not yet a reliable estimate of the burden of truly asymptomatic infection and its consequent transmission potential. Existing studies have failed to report methods, sampling frames, case definitions, extent of contact tracing, followup periods, and clear separation of asymptomatic, presymptomatic and mildly symptomatic/paucisymptomatic cases. Future studies should seek to fill this gap. In addition, modelling studies using newer estimates of the proportion of, and transmissibility from asymptomatic SARS-CoV-2 infected people are needed.

Population serosurveys should also include symptom documentation over the course of the potential exposure period recognizing increasing risk of recall bias.

Methodologies for laboratories to quantitatively report SARS-CoV-2 RT-PCR results from respiratory specimens should be developed. It is recognized that cycle threshold (Ct) values may assist clinicians and PH personnel in assessing cases in the overall clinical context of cases but that validation and controls for this reporting are not developed.

Detailed Evidence Review: What is the evidence supporting the possibility of asymptomatic transmission of SARS-CoV-2?

Data informing an assessment of symptomatic transmission has been collated from studies in 4 main categories: 1) virologic studies, 2) epidemiologic observations (outbreak investigations and transmission chain analysis), 3) modelling studies, and 4) high quality population serologic surveys which include symptom questionnaires.

1. SARS-CoV-2 viral testing kinetics

1.1 Viral load data and culture data, in humans

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 et al., 2020; Pan et al., 2020; Zou et al., 2020). Two reports described successful culture of virus from presymptomatic (Arons et al) and asymptomatic (Hoehl et al) people, although in both of these reports, it was unclear that postsymptomatic RT-PCR positivity was excluded. There is emerging data suggesting that infectiousness may be inferred from cycle threshold (Ct) levels, where a higher number suggests that more cycles were required to detect the SARS-CoV-2 RNA, and thus a lower value would suggest a higher viral load. In a study in a long term care home, 13 of 23 individuals who tested initially positive by RT-PCR were asymptomatic at the time of testing (Kimball et al., 2020). In a detailed laboratory publication from this care home with prevalence surveys, high amounts of viral RNA based on RT-PCR was detected in people who were identified as asymptomatic, presymptomatic or symptomatic at the time of testing, with no significant differences between the three groups. Prevalence testing was performed 23 days after the first identified case with 48/76 residents were positive, of which 27 (56%) were asymptomatic. Twenty four (89%) subsequently developed symptoms (median onset at 4 days). Seventeen (71%) of these presymptomatic patients had viable virus recovered. The mean Ct value was 24.2 for presymptomatic and 27.3 for asymptomatic patients (Arons et al 2020). In this study the highest cycle threshold of RT-PCR in samples where virus was culture positive was 34, with 2 over 30, and the culture were positive over a range from 6 days before onset of fever, cough, or shortness of breath through to 9 days after symptom onset. A significant flaw is that the earliest non ILI symptoms were not recorded, and the accuracy of symptom assessment in this patient population may be limited.

A recent retrospective cross sectional study attempted Vero cell culture from RT-PCR positive samples, with 26/89 (29%) demonstrating growth. In this paper there was no viral growth from specimens with a Ct of >24, or symptom onset to test time of >8 days (Bullard et al, 2020). Similarly, an earlier paper suggested that no replicating virus (assessed by subgenomic RNA) was detectable after day 8 in a detailed virological assessment was carried on nine patients 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 (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 (Pan et al., 2020a). 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., 2020a). In another study of18 patients, those with early symptoms had high viral RT-PCR values, as did 1 asymptomatic patient, which was distinguished from SARS-CoV infection which had higher loads (also based on RT-PCR not cultivation) later in illness (Zou et al., 2020; World Health Organization, 2020b). Interestingly, a letter to the editor by Xu et al. (2020), suggests that the salivary glands may be important in asymptomatic infections due to the high expression of ACE2 receptors in the salivary gland. They discuss other literature where SARS-CoV viral RNA was detected in the saliva prior to identification of lung lesions, and COVID-19 saliva positivity by RT-PCR can be over 90% and virus can be cultivated, suggesting this should be further investigated (Xu et al., 2020).

A variety of additional publications have confirmed prolonged PCR positivity, with a paper by Xiao et al. (2020) describing 56 hospitalized patients, in which severe illness was associated with higher viral loads (by 60 fold) and a longer time to RT-PCR clearance in patients. Viral RNA shedding was prolonged with a median of 24d to become SARSCoV-2 RT-PCR negative (and 32.1% still positive at 1 month post onset). A preprint study of 1343 probable and confirmed outpatient COVID19 cases in New York were assessed with serologic and nasopharyngeal RT-PCR testing. 249/584 participants with antibody and PCR testing

were RTPCT positive at 20 days (11-42 days) from symptom onset and 12 days (5-28d) from symptom resolution. In this cohort, 19% of survey participants with previous self reported symptoms were PCR positive at testing (Wajnberg et al).

The severity of disease may affect the duration of infectious virus shedding, and antibody testing may be useful to guide infection control measures as assessment of likely infectivity. A preprint study from van Kampen et al, of critically ill patients suggests that a higher viral load (>7 log/ml) in respiratory tract specimens was associated with isolation of infectious SARS-CoV-2, and the presence of neutralizing antibody was associated with absence of infectious virus. In these patients infectious virus could be isolated for up to 20 days (median 8 days, <5% probability after 15,2d of symptoms), which is longer than the 8 day duration of viable virus shedding in less ill patients described by Wolfel et al.

1.2 Viral load data and culture data, in animal studies

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, peaking at day 4 after infection compared to young (peaking at day 2) (Rockx et al). There was shedding for up to 10 days by RT-PCR, and no infectious virus was detected after day 4. Viral replication was suggested by RTPCT positivity in respiratory tract tissues including ciliated nasal mucosal tissue, with urinary, cardiac, endocrine and CNS tissues negative, and an ileal specimen positive. 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).

1.3 Summary- virologic data

In summary, there is a reasonable body of literature that supports early viral presence in saliva and in upper aerodigestive tract specimens in early infection, including in asymptomatic and presymptomatic states. The factors affecting transmission and likelihood of transmission in these states of “unapparent positivity” remain less clear, however. Detection of viable virus drops rapidly over the first 8 days of infection, but may be prolonged with a suggestion this may be more common in the elderly (based on macaque study, and a LTC study in which virus was cultivated after 9 days or symptoms in one patient). Prolonged RT-PCR positivity is well documented (not uncommonly for 3-6 weeks from onset) so a positive laboratory result without a detailed symptom history is of limited value in assessing whether and “asymptomatic infection” is associated with possible transmission.

2.0 Epidemiologic Data from human COVID-19 clusters and cohorts

Reported rates of positive RT-PCR screening in patients without symptoms at the time of testing range considerably. Some of this variability could be related to differences in how “asymptomatic” status was assessed: some groups included a variety of generalized mild symptoms as “asymptomatic.” In a report of 16749 hospitalized COVID-19 patients in the UK, 7% of hospitalized patients would not meet an ILI case definition and 4% had enteric symptoms only (Docherty et al, 2020). In addition, many reports potentially fail to exclude paucisymptomatic or symptomatic infection in the previous 6 weeks. See Appendix A for a complete table of “asymptomatic” RT-PCR positive series/studies. A summary of representative studies is extracted below, favoring studies where contacts of cases or cases were monitored with serial testing, with reasonable exclusion of presymptomatic or postsymptomatic status (Bi, Cheng, and Tian et al). These report a range of the proportion of truly asymptomatic cases of 5-20%. Some reports of “asymptomatic” transmission clearly outline probably presymptomatic transmission, including a 2 family cluster of 7 patients with presymptomatic and postsymptomatic contact over a 5 day period (Li. Ji et al, 2020). Most reports have come from China, where undetected community transmission could not be ruled out, describe household, family, and meal sharing contact (Bai et al, 2020, Hu et al, 2020)

2.1 Quarantine Centre Studies

Two papers explicitly mention asymptomatic over presymptomatic transmission, one familial cluster which suggested an asymptomatic person infected 1 household contact, and one contact tracing/centralized quarantine series (preprint, Luo) which noted transmission from asymptomatic cases to 0.3% of contacts.

This latter study yields other interesting transmission data: 2950 contacts of 347 cases were placed in 14 days of quarantine with RT-PCR monitoring every 2 days. There were 129 secondary cases within the contacts. Of the contacts, 0.2% developed asymptomatic infection, and 2.4% developed symptomatic infection over the 14 day quarantine period. In this paper, older contacts had increased risk of infection with a gradient across age (1.8% in <18y through 4.2% in 60+ years). Seventy percent of the contacts were in a household setting with 10.2% acquiring COVID-19, with healthcare contact risk of 1.0% and public transport risk at 0.1%. Clinical severity of source case data was reported for 2610 contacts, of which 305 had an asymptomatic source case (based on incomplete data), and one secondary case was attributed to this group (1/305=0.3%) There was a gradient of risk from there was 0.3% risk to contacts of asymptomatic COVID-19 cases through 6.2% of contacts acquiring disease from index patients with severe symptoms (Luo et al., 2020).

In a Taiwanese report of 100 patients, 2761 contacts were traced, tested, monitored for 14 days, and tested again if symptoms developed. Twenty two secondary cases were found, all with exposure within 5 days of the index cases symptom onset, with an attack rate of 0.7% (2 secondary cases of 277 contacts) for exclusively presymptomatic contacts and 1.1% (12/1083) in those exposed at or after the day of symptom onset. Where exposure started in the presymptomatic period (not restricted to exclusively presymptomatic contact), the attack rate was 4/100 (4%) for household, 1/10 (10%) for nonhousehold family, 2/236 (0.8%) for health care contacts, and 0/389 for other contacts. However, contacts prior to symptom onset were not completely ascertained and a suggestion to extend to 4 days prior to onset was made. There was no transmission to 852 contacts exposed after day 6. None of the 9 asymptomatic case patients transmitted a secondary case (to 91 contacts). The attack rate from those with mild illness was 0.4%, severe 1.4%, and ARDS/Sepsis 1.5%. Detailed review reveals that four asymptomatic secondary cases were identified, all of which were household or nonhousehold family contacts, out of 227 household and nonhousehold family contacts followed, suggesting that 1.76% of all identified household-family contacts developed asymptomatic infection, versus 4.8% (11/227) with symptomatic infection. Overall household and nonhousehold family contact secondary attack rates were 4.6% and 5.3% respectively (Cheng et al, 2020).

In a report of 392 household contacts of 105 index cases who were exposed in Wuhan, family contacts were quarantined and monitored daily, and 14.1% of contacts found to be RT-PCR positive were asymptomatic. A proportion (13.3%) of index patients had quarantined themselves at home after symptom onset with masking, sleeping and eating separately within the house. Importantly, the attack rate from those who self isolated at home with onset of symptoms was 0% versus a 16.9% attack rate in households in which the index case did not isolate within the home, so no presymptomatic transmission occurred in this cohort, and transmission was prevented by home self isolation. The secondary attack rate was highest to spouses at 27.8%, and transmission to children was 4% versus 17.1% to adult household contacts adults overall. (Li et al, CID).

In a report of 262 confirmed cases in Beijing, 13 (5.0%) were asymptomatic close contacts, and an asymptomatic case was defined as “a confirmed case with normal body temperature or minor discomfort”, with cases comprised of all positive COVID-19 cases, who were referred to centralized hospitals for therapy or monitoring. The vast majority of cases in this series were (92%) were identified in contact tracing, and 67.2% were cluster cases (Tian et al, 2020).

A research letter from Wuhan by Yang et al described close contact screening and quarantine (December 25 to February 24,2019) followed all COVID-19 RTPCT patients who were admitted to hospital after contact tracing 26 clusters of infection. In this series, 42.3% of patients 33/79) were asymptomatic at testing, However, a symptom checklist and “asymptomatic” definition was not provided and pre test symptom history was not described, and CT scans were abnormal in a proportion of “asymptomatic” cases. The “asymptomatic” cases were more likely to be younger (27 versus 56 year old), female (67 versus 31%), and had shorter duration of viral shedding (8 versus 19 days). Clinical variables were less severe including improvement of CT scan abnormalities (9 versus 15 days), CD4 count (720 versus 474), and abnormal liver biochemistry (3% versus 20 percent.)

A prospective study by Chau et al, at a quarantine centre in Hi Chi Min City, Vietnam enrolled and followed PCR positive cases. Between March 10 and April 4, 49 of about 14000 people were positive, of which 30 were enrolled. Thirteen (43%) had no symptoms (the history duration and data collection instrument were not defined). A cluster of 11 participants was described with a suggestion of possible asymptomatic transmission, although insufficient detail is provided to assess this. Despite initially similar RTPCT Ct values, the there was a suggestion of faster viral clearance from the respiratory tract in asymptomatic persons,

2.2 Other Studies of Close Contacts

A recent US publication has been suggested to support asymptomatic transmission, describing positivity rates in household contacts of the first 229 cases in New York State during an exponential phase epidemic. The household infection prevalence was much higher than in other series at 38%, with an age gradient from 23% among those <5 years to 68% among those over 65, on a background of a percent positivity of all tests in NYS in March of 33%. There were 498 household members tested, of which 148 had symptom data recorded. Of these, 82.6% reported “any” symptoms, suggesting that 27.4% were asymptomatic at testing. Transmission chains were not assessed. Antecedent symptoms or subsequent symptoms were not assessed. As such, this report has the same weakness of others where previous infection was not excluded (Rosenberg et al, 2020). Similarly, a study on an “asymptomatic” hospitalized case suggested that there was no transmission to 455 contacts, however, post symptomatic RT-PCR positivity was not ruled out: the individual had been short of breath (due to proposed CHF from congenital heart disease) for a month prior to admission, was admitted for the same then screened after being in hospital for 4 weeks (screened by RT-PCR for an in hospital transfer). Multiple patients, patients’ family members and hospital staff were tested an observed in quarantine (Gao et al, 2020).

Chaw et al describe a superspreading event in Brunei, at a religious gathering in Malaysia on February 28-March 1st. Of 75 attendees, 19 tested positive, with 52 secondary cases identified. Attack rates were 14.8% at a subsequent religious gathering (March 5th), and 10.6% in households. The household AR from symptomatic cases was 14.4%, versus 5.4% from asymptomatic or presymptomatic cases, with very low transmission in social or workplace settings. Symptom assessment was only performed at the time the swab was collected and during the followup period.

A report from Huang et al described transmission of COVID-19 from a presymptomatic youth starting 3 days before symptom onset, with 7/22 contacts developing infection (food sharing, indoor restaurant, karaoke) developing infection, highlighting significant presymptomatic spread among young people in social environments.

2.3 Prevalence Studies and Outbreak investigations

A comprehensive analysis of 382 service members (of 1417 total exposed) involved in an outbreak aboard an aircraft carrier was reported by Payne et al, with symptom questionnaires, serologic assessment and 267 (70%) also providing NP swabs. The investigation took place April 20-24 (the outbreak was in March,) 60% were antibody positive, and symptoms were assessed as Category A (Cough, shortness of breath) or Category B (2 or more fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s) (Council of State and Territorial Epidemiologists, 2020) Twenty three of 154 (15%) of those with negative serology had a previous PCR positive result, and 82 of 131 (63%) of seronegatives without previous positive PCR were tested by PCR and 4 (5%) were RT-PCR positive. Overall, 238 of participants had documented previous or current SARS-CoV-2 infection, of which 18.5% were asymptomatic. Taste and smell alterations were strongly associated with infection (OR 10.2). Self reported distancing, avoidance of common areas, and face covering use were potentially protective. Level of antibody was not reported in asymptomatic versus symptomatic confirmed positive cases. Specimens were collected that were RT-PCR positive to 48 days after symptom onset.

The perils of interpretation of RT-PCR positive results and absence of current symptoms at the time of testing are illustrated in correspondence in the Lancet, which described screening of asymptomatic HCW

in a hospital in London, with collection of nasal swabs, health questionnaires and blood samples over 16 weeks. The first 400 tests yielded 44 SARS-CoV-2 positive HCW (11%) of which 12 (27%) reported no symptoms of COVID-19 during the week before or after their positive test(s). During the study, 7 HCW tested positive on two consecutive weeks and 1 tested positive on three consecutive weeks by RT PCR (Treibel et al., 2020), and the rates mirrored the epidemic curve in the community. However, this is a short correspondence and many details of methodology are not available for review. To exclude prolonged shedding in this cohort, symptom assessment for 4 weeks prior to testing and observation for symptom for two weeks post testing would have been optimal. No serologic assessments, or attempts to cultivate virus were performed.

A call centre outbreak investigation in South Korea described by Park et al investigated all workers, inhabitants and visitors to a commercial/residential building between February 21-March 8 2020, with testing March 9-12 (17 days from start of exposure risk period). There is no documentation that history of previous symptoms was sought, and asymptomatic cases were followed for 14 days from testing. Testing was performed for 1143 of the 1145 persons under investigation, was 8.5% documented positive, 94/97 of these were in the 11th floor call centre. The attack rate in the call centre was 43.5%. Of the case patients, 89/97 (91.7%) were symptomatic, and 4 developed symptoms, and a further 4 remained asymptomatic (4.1%) The case patients had 225 household contacts with a household attack rate of 6.2%, with no transmission from presymptomatic or asymptomatic cases.

A followup study on a subset of the highly described Diamond Princess cruise ship cohort has been published by Sakurai et al, in which 712 of 3711 passengers and crew were documented RT-PCR positive, and 410 (58%) asymptomatic at testing, Ninety six of the asymptomatic positive cases and 36 cabinmates were quarantined and observed in hospital, with 11/96 (11.5%) developing symptoms at a median of 4 days from testing positive, with 8/32 (25%) of cabinmates also testing positive after an initial negative test but remaining asymptomatic. This study described becoming RT-PCR negative as “resolving infection”, which is arguably inaccurate, and this occurred 15 days after the initial positive test in 90%. The likelihood of developing symptoms, and of remaining PCR positive for longer periods increased with age. Previous symptoms, symptom assessment, and serology results are not reported.

A final study described screening of all passengers and crew on an isolated Antarctic cruise: a passenger developed fever on day 6, and on day 20 of the cruise 128/217 (58.9%) of people tested were positive, of which 81 (64%) were asymptomatic at testing. There was no description of how symptom history was assessed or of followup post testing for symptom development (Ing,et al 2020). There was no description of symptom assessment, followup, and no serology was done.

The role of pediatric SARSCoV-2 in transmission remains unclear, and given the apparent lower rates of infection in chidren there is interest in assessing the possibility of asymptomatic children as transmission sources.In a preprint evaluating reported household transmission clusters, 9.5% of the clusters had a pediatric index case. To reduce the possibility that an asymptomatic index case child was overlooked, cases in which a symptomatic adult was identified as the index case in a household with an asymptomatic positive child was also identified were reviewed, with the results that up to 21% of the household MAY have had an asymptomatic child as the index case. In comparison, H5N1 influenza transmission cluster analysis revealed children as index case in over half (Zhu et al, 2020).

Presymptomatic transmission merits separate consideration from asymptomatic transmission, because of more robust data and because of different practical contact tracing implications. Presymptomatic spread has been well documented in individual case reports and reported case series, usually involving close/household contacts. Newer data suggests that presymptomatic transmission may in some circumstances be considerable, although it is unclear whether these events are related to characteristics of the index case, the setting of transmission, or both. Multiple case series have shown high secondary attack rates with exposure just prior to symptoms. In one study, the attack rate among exclusively presymptomatic close contacts was 0.7% (versus 1.1% overall). However, in another study of contacts and household transmission, there were no household transmissions when the index patient self isolated

(masked, resided separately) within the home versus 17% attack rate in other households contacts, weighing against significant presymptomatic transmission. Contact tracing studies further suggest that most transmission risk occurs before day 6 of symptoms, with no nosocomial transmissions among 852 hospital contacts after day 6 of symptoms.

Thus, although it seems a proportion of people may remain asymptomatic but PCR positive, transmission from presymptomatic cases is currently more clearly supported by these data. The relative contribution of presymptomatic spread to community transmission was detailed in am epidemiologic report from Singapore, in which all 243 cases of COVID-19 between Jan 23 and Mar 16, 2020 were investigated. Seven clusters of cases with probable presymptomatic transmission were identified, and the overall proportion of transmission from these cases comprised 6.3% of overall documented transmission. Diagnostic testing was correlated with clinical signs and thoracic CT scans. Individuals were thought to be infected from contact presymptomatic cases, not unidentified asymptomatic cases, as strong surveillance was in place and minimal community transmission was occurring. Two of these clusters involved people who gathered together to sing. (Wei, 2020).

2.4 Reviews and Meta Analyses

Finally, three preprint systematic reviews and meta-analyses addressing this topic have been identified, as well as a narrative review. The first, a rapid living systematic review and meta-analysis on asymptomatic transmission (Buitrago-Garcia et al) gave the overall estimate of the proportion of people who become infected with SARS-CoV-2 that remain asymptomatic throughout infection as 15% (95% CI 10 to 22%) This review did not evaluate the possibility that some of the studies included did not rule out postsymptomatic shedding. A systematic overestimation of the proportion with asymptomatic infections due to the inclusion of asymptomatic cases in contact investigations was also noted.

The second systematic review and metaanalysis preprint specifically included only studies where the sample frame included the at risk population and there was adequate followup to identify presymptomatic cases, as is assessed as higher quality. It should be noted that this review excluded 25 studies which were included in the above metaanalysis, which were felt to be at high risk of bias, and missed 6 of the articles included in this report. Review of 998 articles identified 9 studies for inclusion, with 21035 people tested, of which 559 (2.7%) were positive and 83 (14.8% of those positive) were asymptomatic. The proportion of asymptomatic cases ranged from 4-41%, and metaanalysis gave the proportion as 15% (12-18% overall.) Transmission from asymptomatic cases was suggested in 4 studies, at a lower rate than symptomatic cases (Byambasuren et al, 2020). Two studies documented zero transmission from asymptomatic cases, and the other two risk estimates were .06 and .79.

A recent narrative review, by Oran and Topol is a significant outlier in interpreting the extant literature. The authors suggested that 40-45% of SARS-CoV-2 infections are asymptomatic and that asymptomatic people can transmit to others for >14 days. Studies felt to be at high risk of bias were included, with prevalence sampling, and studies without definition of asymptomatic, or symptom assessment pre and post test. Serosurveys and PCR testing were both included in aggregate estimates. This is therefore not felt to be a useful synthesis. A recent open latter to Oran and Topol, and the Annals of Internal Medicine highlighted the lack of clear definition of asymptomatic infection and the selective inclusion of cross sectional studies, with the suggestion that this overestimate of asymptomatic infection could misinform policy response (Cevik et al).

Table 1. Select Studies –COVID-19 Cases - Asymptomatic at Testing (See appendix for complete list)

Setting	Author	Total Positive cases	Number (%) with no symptoms at testing	% who remained asymptomatic	Comments
Long Term Care	Arons	48	27 (56%)	6.3%	Symptom Screening for

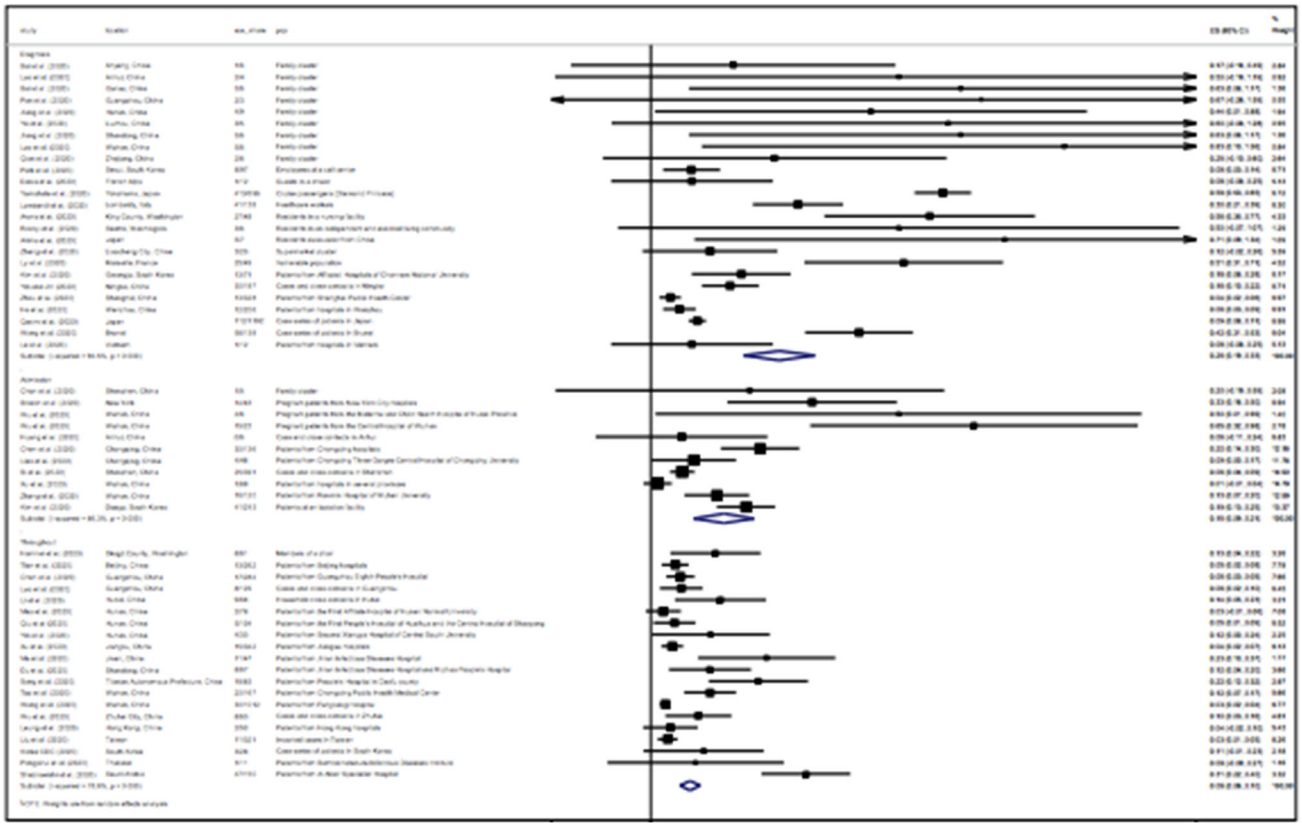
					-14d to +14d of test, outbreak started 23 days prior – poss post Sx
Monitored Contact Quarantine	Bi	98 (of 1286 contacts)	17 (20%)	Unknown	Well defined symptom list, did not clinically report if developed Sx
Monitored Contact Quarantine	Cheng	22 (of 2761 contacts)	4 (18%)	NR but monitored 14 day quarantine	Contact with presymptomatic case attack rate 0.7% (versus 1.1% contact in in first 5 days). Contacts to severe/critical cases higher risk.
Pediatric cases (Chinese CDC)	Dong	731 PCR confirmed cases	94 (12.8%)	NR	Did not exclude presymptomatic or postsymptomatic
Contact tracing (conference)	Hijnen	10 (of 12 contacts)	2 (175)	NR	Presymptomatic transmission 2-3 days after index case exposure
Airline flight	Hoehl	114 airline passengers with RT-PCR results	2 (1.8%)	1 (50%)	Mild rash/sore throat
Contact Tracing (Fitness class)	Jang	112 contacts pf 8 positive instructors (12 facilities)	30 (26.8%)	NR	Did not exclude presymptomatic or postsymptomatic
Long Term Care	Kimball	23 residents	13 (56.5%)	13%	Did not exclude presymptomatic or postsymptomatic,tested 16d after introduction
Prevalence survey, community based	Lavezzo	I. 73 cases (of 2812) 14 days later, II.29 cases (8 new) of 2343	30 (41%) 13(29%) (unclear if new or old)	NR	Did not exclude presymptomatic or postsymptomatic
Monitored Contact Quarantine	Li	64 (of 392 household contacts)	9 (14.1%)	9 (14.1%)	Close monitoring for 14 d from exposure, no transmission in index case self isolation households
Monitored Contacts, Quarantine	Luo	129 cases (in 4950 contacts)	8 (2.5%)	8 (2.5%)	Incidence of secondary infection 6.2% from critical, 3.3% from mild, and 0.33% from asymptomatic cases.
Cruise Ship	Mizumoto	634	113 (17.9%)	NR	Did not exclude presymptomatic or postsymptomatic., testing 10-17 days after outbreak start
Evacuees from Wuhan	Nishuira	13	4 (31%)	No	Testing long after Wuhan departure. Did not exclude presymptomatic or postsymptomatic
Centralized assessment - all cases	Tian	262	12 (5%)		Asymptomatic – included confirmed case with

Hospitalized, Beijing					normal temperature or minor discomfort

Finally a very recent preprint systematic review and metaanalysis by Koh et al. included analysis of transmission and secondary attack rates, serial intervals, and asymptomatic data. They and estimated that 25.8% of CIVD-19 cases were asymptomatic at diagnosis, and given the observation from multiple settings that 2/3 develop symptoms on monitoring suggested the “true asymptomatic” proportion to be 5.4%. From observational studies, the RR of transmission was 2.55 from symptomatic index cases, suggesting that testing strategies should prioritize symptomatic persons when resources are constrained. However, given the difficulty in rapid detection of asymptomatic infections, it was noted that some degree of physical distancing is likely required to account for this.

However, it is noted the evidence base included many of the studies reviewed here, that failed to account for post symptomatic shedding in epidemic situations, where the RTPCR prevalence testing was carried out late in the epidemic, where positive RTPCR would be less likely to indicate transmissible infection. The forest plot of asymptomatic cases from this paper is below, provided with the caution about the lack of standardized case definitions for asymptomatic infections and also acknowledging the possibility of publication bias related to media attention to this particular topic. The findings of this paper suggested that setting specific transmission risk should guide control measures with quarantine more appropriate for congregate living community settings such as workplaces and dormitories, and contact tracing utilized to identify hotspots and vulnerable populations.

Figure 1. Koh et al, Forest plot of the proportion of asymptomatic cases. ES is the estimated asymptomatic proportion, with 95% confidence intervals (CI). I-squared is the squared percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.



2.5 Summary

Higher quality epidemiologic studies from centralized quarantine facilities, in which close contacts (a high risk population) have been monitored and serially tested, AND methods suggest better exclusion of presymptomatic and post symptomatic cases suggest that 2.5 to 20% of RT-PCR positive contacts remain asymptomatic. A good quality preprint metaanalysis of these epidemiologic data suggested the asymptomatic proportion is 15% (12-18%), and another estimated that 25% could be positive-asympotmatic but that the true asymptomatic proportion was likely 8.6% (excluding presymptomatic). Uncertainty in this proportion is related the possibility of prior infectious contacts in the community during exponential growth rate epidemics in some reports, and in addition, a population of close contacts to documented cases may tend to overestimate compared to the general population. Data from an aircraft carrier outbreak and multiple household transmission studies suggests that asymptomatic and paucisymptomatic infection status may be more common in younger people and children. In these studies **the efficiency of observed transmission of infection of asymptomatic** infection appears to be low (two studies reported no transmission from asymptomatic cases, one quarantine center series reported an incidence of secondary infection of 0.3%, 20 fold lower than transmission to contacts from severe cases, another reported 2.2% transmission from asymptomatic cases, and the RR of transmission as 2.5 in symptomatic compared with asymptomatic in another.)

So, although existing data have significant shortcomings it appears that transmission from presymptomatic, pauci-symptomatic or asymptomatic people, particularly in close contact settings may occur, with more data supporting that transmission from presymptomatic cases may be more substantial. Close contact settings such as household exposures or possibly long term care facilities appear to be higher risk, and limited data suggest that transmission risk from asymptomatic persons is much less efficient (0.03% of contacts of asymptomatic COVID-19 cases compared with 6.2% in contacts of severe cases in one study). Physical distancing, masking and hand hygiene would be expected to mitigate some of this risk. Standardizing definitions, and protocolizing assessment of “asymptomatic” cases to differentiate these from paucisymptomatic, and presymptomatic is important to both clarify the evidence around transmission potential and because the latter conditions may still allow testing and rapid contact tracing to have a beneficial effect. This will require public education around paying attention to and documenting timing of even mild symptoms, seeking testing, mindfulness and documentation of exposures and contacts to assist possible contact tracing, and seeking history of symptoms from -4 weeks to +2 weeks after testing.

3.0 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 4 days (95% CI 3.53 – 4.39) which is significantly shorter than SARS-COV1 (8.4 days) or MERS-COV (14.6 days) (Bi et al. 2020; Zhao et al., preprint; Nishiura, Linton & Akmetzhanov, 2020), suggesting presymptomatic transmission. However, estimates of the serial interval vary. In a description of 468 confirmed cases in China, presymptomatic transmission was suggested in up to 13% of transmission chain cases (serial intervals were negative, with the infectee developing symptoms before the infector) (Du et al., 2020). In another preprint article that described viral shedding and modeled 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. These studies of primary and secondary cases may be limited by recall bias, as secondary cases are more likely to remember recent exposures.

In a study modeling infectiousness from 77 predominantly household based transmission pairs, He et all observed infectiousness peaked at or before symptom onset and that 44% of cases were infected during

the index cases presymptomatic stage (in predominantly household clusters). The relative proportion of post symptom transmission was reduced by isolation (He et al.2020).

In a preprint of a statistical transmission model applied to contact tracing data from Guangzhou, 249 cases forming 195 unrelated clusters were examined, with cluster sizes from 1-274 (median 6). Most transmissions occurred among household members. Modeling the spatial and temporal epidemiology suggested the daily transmission probability during the incubation period was similar to that in the illness period (Jing et al).

There are a number of new studies looking at serial intervals in different countries, with different testing strategies. A preprint of a modelling study by Tindale et al. from Simon Fraser University, based on outbreak information from Singapore and Zianjin, China estimated the mean serial interval at 4.56 (2.69, 6.42) days in Singapore and 4.22 days (3.43, 5.01) in Tianjin using a mixture model approach, with the mean serial interval 2-4 days shorter than the incubation, suggesting that presymptomatic transmission was occurring. Limitations include variability in exposure time, presumed infectors and incubations period as well as the lack of uncertainty in the model around symptom onset (Tindale 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 however the relative proportion of asymptomatic infection was not discussed (Flaxman et al., 2020). In contrast, 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 3.0.

Ferreti et al (2020) describe a compartmental mathematical model based on linked case data from Hubei, assuming a fraction of 46% asymptomatic SARS-CoV-2 infections and reduced infectiousness from asymptomatic cases) that pre-symptomatic patients account for 47% (95% credibility interval 11 to 58%) of the total transmission, and asymptomatic transmission comprised 6% (0 to 57%) of the total. This and other models attempting to estimate the proportion of infections caused by undetected infections (asymptomatic, presymptomatic and paucisymptomatic) vary widely, suggesting that 50-80% of cases could be related to undetected infection (Ferreti et al, Li et al).

A preprint from Koh et al indicated the mean SI of single-location studies is estimated to be 4.87 days (95% CI: 3.98, 5.77), and there was significant heterogeneity observed in multiple location studies.

Overall, current model assumptions are based on data on the prevalence of asymptomatic infection that did not account for the possibility of prolonged postinfection shedding, and thus would be expected to overestimate transmission from asymptomatic positive persons. The chain of transmission data (see Table 2) has been consistent in suggesting shorter range serial interval data (with considerable variability, from 1.9-7.5 days) and does support spread early in infection and the possibility of presymptomatic spread being significant.

Modelling data therefore should be seen as potentially illustrating the upper limits of impact of transmission from asymptomatic persons, and newer studies using updated assumptions would be valuable.

Table 2. Summary of Serial Interval Studies

Author	**Country**	**Data type**	**n (total cases)**	**Mean or Median Incubation Period (days)**	**Mean Serial Interval (days)**	Comment
Aguilar, J.B. et al Preprint	13 countries (10 in Europe and Australia, Canada, Japan)	Case numbers				Re 15.4 (5.5-25.4)
Backer, J.A. et al Rapid Communication	Imported cases from Wuhan, China; Jan 21-Feb 8	Government sources	88 case	Mean: 6.4 (95% CrI: 5.6-7.7) (sd)		
Bi, Q. et al Research Article	Shenzhen, Guangdong Province, China	Contact tracing	391 cases and 1206 close contacts	4.8 (95% CI: 4.2-5.4)	6.3 (95% CI 5.2 – 7.6)	Reproduction number 0.4 (0.3-0.5)
Cheng, H. et al Preprint	Taiwan, Republic of China	Contact tracing	32 cases and 12 paired transmission cases, from 1043 contacts; then updated with 48 pairs	4.9 (95% Credible Interval 2.7-8.4)	5.4 days (95% CrI 4.1–7.2 days) with 48 pairs	
Du, Z. et al. Research Letter	Imported cases outside of Wuhan, China; Jan 21-Feb 8	Government sources	468		Mean: 3.96 (95% CrI: 3.53-4.39); sd 4.75 (95% CrI: 4.46-5.07); 12.6% of serial intervals were neg	59 reports of negative serial interval (suggest presymptomatic transmission)
Feretti. L. et al Research Article	NR	40 infector/infectee data pairs			R0 estimated at 2.0 in early stages with 46% presymptomatic, 38% symptomatic; 10% asymptomatic and 6% environmental transmission.	
He, X. et al Brief Communication	Guangzhou, Guangdong Province, China	Hospital admissions	94 cases and a separate 77 transmission pairs	Not calculated, assumed at 5.2 from other studies	Mean 5.8 (95% CI: 4.8-6.8); median 5.2 (95% CI: 4.1-6.4)	Infectiousness from -2.3 days and peak at -0.6 days from symptoms
Lavezzo, E. et al Preprint	Vo, Italy	Government Sources			Mean: 6.9 d (95% CrI: 2.6-13.4) before lockdown and 10.1 d (95% CrI:	Risk of household transmission OR: 84.5 (95% CI 16.8-425.4) in adults; SEIR model

					1.7 - 25.9) after lockdown.	estimates asymptomatic infection 41-42%, transmissibility of virus decrease 89-99% with lockdown
Liao, J. et al Preprint	Chongqing, Sichuan Province, China	Pediatric hospital cases and their contacts	3.3%). On the second survey, which was conducted at the end of the lockdown, we found a	Mean: symptomatic cases 6.6 days (95% CI 4.4 - 9.6)	Median: for symptomatic cases was 1.9 days (95% CI 0.4 - 6.2)	
Li, R. et al, 2020a Research Article	Early transmission in Wuhan, China; before Jan 20, 2020	Observations of infections, mobiity data, metapopulation network	prevalence of 1.2% (95% CI 0.8-1.8%).	Mean: Early transmission in wuhan 5.2 + 2.1 (sd)	Mean: Early transmission in Wuhan 7.5 +/- 3.4 (sd)	Precontrol measures: undocumented infections were the source of 82% of infections, post control these dropped to 79%.
Mizumoto, K. et al Rapid Communication	Cruise ship, Diamond Princess	Time series data from quarantine period	634 cases/3711 passengers, 2 week quarantine; 328 asymptomatic		Estimated asymptomatic proportion of positive cases was 17.9% (95% CrI: 15.5-20.2). Most asymptomatic transmission occurred before quarantine	
Nishiura et al, 2020b Letter to the Editor	Cruise ship, Diamond Princess	Japanese evacuees from Wuhan	64/565 symptotatic; using RT-PCR 4/565 asymptomatic and 9/565 were symptomatic			
Nishiura et al, 2020a Research Article	NR	Publically available data	28 data pairs		Median: 4.0 d (95% CrI: 3.1, 4.9); mean 4.7 d (95% CrI: 3.7, 6.0) and sd 2.9 d (95% CrI: 1.9, 4.9)	
Tindale, L.C. et al Preprint	Singapore and Zianjin, China	Government sources	S: 93 cases; T: 155 caes	Mean - Singapore: 7.1 (6.13-8.25); Zianjin: 9 (7.92-10.2)	Mean - Singapore: 4.56 (2.69-6.42); Zianjin: 4.22 (3.43-5.01)	Early in outbreak transmission estimated 2-3 days before symptoms

Wong, J. et al Accepted Manuscript	Brunei	Government sources all cases and 53 pairs for Sii calculations	16/138 (12%) asymptomatic; 42/138 (30%) presymptomatic	Median calculated: 4.5	21/53 pairs had calculated SI < 3 d; 6/53 and 0 or negative SI values	High proportion presymptomatic cases
Yin, G. ad Jin, H. Preprint	Ningbo, Zhejiang Province, China	Government sources	157 Symptomatic cases -2001 close contacts, 30 asymptomatic cases -145 close contacts			Transmission rates between symptomatic (0.064,0.049) and asymptomatic (0.041,0.041) cases and contacts not statistically different
Zhang, J et al Preprint	Beijing, Hebei Province, China	Familial cluster	2 scenarios - early transmission in Wuhan, imported cases outside Wuhan			Presymptomatic transmission 3.8 d prior to Sx – based on Backer, Du and Li

4.0 The evolving role of population based serologic surveys

A number of serologic studies are in progress and some have been published to considerable controversy regarding methodology as biased sampling and poor serologic point of care tests have been problematic. However, the interim report of the Spanish Ene-Covid19 study (April 27 - May 11, 2020) is highlighted here as it is robust design: a representative national sample of 60,983 recruited patients with a participation rate of 62.3% (Instituto de Salud Carlos III, 2020). The overall seroprevalence was 5.0% (no differenced by sex) and prevalence increased by age (by decade) : from 1.1% in infants, 2.2-3.8% in children aged 1-19, 3.8-5.9% in those age 20-64, and 5.1-6.9% in those over 65. The seropositivity rate was lower in those deemed essential workers (5.3 versus 5.4%). Seropositivity was documented in 6.4% of those residing in communities of >100,000 population versus 3.8-4.3% in smaller communities. Geographic variation was considerable with antibody prevalence ranging from 1.1% to 14.2% across areas. Of those with self reported PCR positivity, 87% had SARS-CoV-2 IgG antibodies, and in people without a confirmed diagnosis the prevalence increased with number of symptoms (4.6% if 1-2 symptoms through 14.7% if > 5 symptoms, and strikingly, 43.3% in those with anosmia).

Of those who did not report ANY symptoms prior to serologic testing, 2.5% were antibody positive. This was a fingerstick test, and so far 16953 of participants have been also assessed using a central high throughput laboratory assay, with 97.3% concordance thus far by informal report (Yasinski, 2020).

With respect to the context of this serosurvey - according to Our World in Data, there were 227770 confirmed cases in Spain as of May 11, with 26744 deaths and 11.74% case fatality rate (CFR). There is likely a large number of uncaptured cases based on the high CFR and testing rate of 0.87 tests per 1000 people, and ongoing 3.1% percent positivity in RT-PCR testing. Using a population of 46 million, 0.5% pf the population has had lab confirmed infection, which is10 fold lower than the serologic prevalence detected thus far, based on IgG testing by a lateral flow assay.

Potential issues with such studies involve recall bias, collection of symptom survey data, and, importantly, test characteristics – if the test is 98% specific and the real prevalence is 5%, one would expect a false positive rate of 2.0%, making it difficult to interpret the asymptomatic positive rate in this study. In addition, it remains possible that truly asymptomatic infection may not result in as high antibody titres,

leading to potential underestimation of asymptomatic infection by serosurveys. Nevertheless, the estimate of 2.5% asymptomatic infection detected by a seroprevalence survey (with recall bias expected) is not unexpected. Close contact/high risk populations in quarantine and shipboard outbreak studies would have a higher risk and suggest 15-20% rates of asymptomatic infection in these groups.

Discussion

In summary, evolving data continues to support transmission early in infection including potentially before symptom developments, and better definition of asymptomatic, paucisymptomatic, and presymptomatic states will inform better data.

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, with RT-PCR positivity documented for up to 6 weeks postinfection. The relative incidence of asymptomatic and presymptomatic SARS-CoV-2 infection, public health interventions to prevent asymptomatic transmission, and whether asymptomatic infection confers immunity remain important knowledge gapes (Furukawa et al, 2020). This review suggest that existing data on patients who were asymptomatic at the time of positive testing may be muddied by a lack of consistent definitions of “asymptomatic” (what symptom screening was used, and the time period discussed) as well inconsistent followup to determine if the individuals were presymptomatic.

A 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. Epidemiologic modelling based on mean interval estimates suggests concern for potentially significant transmission from asymptomatic or presymptomatic persons. However, the assumptions made are based on the potentially misleading extant data around asymptomatic cases, and in addition the accuracy of epidemiologic symptom onset data (determination of any symptoms versus symptoms that limited activity, for example) are weaknesses in these analysis, as potentially reflected in the serial intervals differing by significantly 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).

Given the importance of real world data to clarify the transmission dynamics and allow optimally focused control efforts, this revision has focused on optimizing local data collection to inform policies and practices during the remainder of the pandemic period. It is therefore recommended that standardized definitions of presymptomatic, asymptomatic, and paucisymptomatic RT-PCR positive cases be developed to help clarify local transmission patterns as well as to allow more comparable assessment of public health data sets. In addition, public education around paying attention to seemingly unimportant symptoms to allow early testing and rapid contact tracing is highlighted, as existing data highlights a more robust role for presymptomatic spread than asymptomatic spread. Rapid contact tracing, testing and quarantine will be crucial to limit secondary cases as public health restrictions are reduced. Depending on the degree to which truly asymptomatic spread occurs and presymptomatic spread cannot be mitigated a degree of public health measures such as physical distancing, hand hygiene, appropriate masking and environmental hygiene will be required for the foreseeable future to limit community spread of infection.

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.

Date question received by advisory group: started by previous group (before 24 March 2020)

Date report submitted to committee: April 8, 2020

Date of reassessment: April 13, 2020.

(If applicable) Date of most recent re-assessment: June 13, 2020 – July 12, 2020

The Scientific Advisory Group (SAG) supports decision making based on best available evidence, reflecting both the precautionary principle and an ethical framework (Bean et al., 2020).

Authorship & Committee Members

This report was written initially by Lynora Saxinger (co-chair), building on an initial report drafted by Ranjani Somyani, and the first review was conducted by Sylvia Checkley (and team), with primary reviewer Melissa Potestio. The third rewrite was performed by Lynora Saxinger, Sylvia Checkley, and the full Scientific Advisory Group, who were involved in discussion and revision of the document: Braden Manns (co-chair), John Conly, Alexander Doroshenko, Nelson Lee, Elizabeth MacKay, Andrew McRae, James Talbot, Shelley Duggan, Jeremy Slobodan, Brandie Walker, and Nathan Zelyas. External reviewers of the initial review included Joseph Kim, Uma Chandran, and Michael Parkins. The third rewrite was additionally reviewed by Robyn Harrison, Joseph Kim, and Uma Chandran.

COVID-19 Scientific Advisory Group Rapid Response Report

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

The literature search was conducted by Lauren Seal from Knowledge Resource Services, Knowledge Management, Alberta Health Services.

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)
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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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