Are asymptomatic people with COVID-19 infectious?

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Aim

The aim of this report is to assess current evidence for asymptomatic transmission of SARS-CoV-2.

Background

The ability of reactive measures to control an outbreak is related to the proportion of infections that transmit whilst asymptomatic or pre-symptomatic (during the incubation period) combined with the Ro, in addition to population compliance rates(Figure 1).

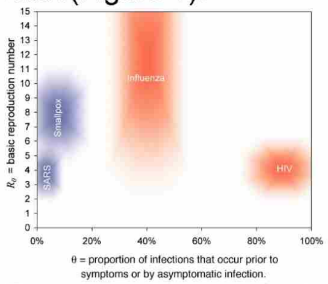

Figure 1. Possible ranges for the key parameters R_0 *and θ for four viral infections of public concern are shown as shaded regions. (taken from Fraser et al.[1]).*

For respiratory viral infections (such as influenza), whilst it is clear that a proportion of infections are asymptomatic/paucisymptomatic[2–4] and that viable virus can be detected in the upper respiratory tract before onset of symptoms, obtaining direct evidence of the contribution to overall transmission is challenging.
There are several ways to approach an assessment of asymptomatic/pre-symptomatic transmission:

1. Direct epidemiological approaches

These are dependent on spatio-temporal analysis of contact betweenf individuals combined with clinical observations and assessment of symptom onset. Caveats of this approach include uncertainties around infector-infectee pairs, especially in situations where community transmission is occurring. This is particularly challenging when trying to estimate the role of asymptomatic transmission, as by definition these infectors may not have been identified. Combining genomic analysis of viral strains within transmission chains may provide the most meaningful evidence when combined with epidemiological data. Recall bias, when subjects are asked to recall their illness retrospectively, can also contribute uncertainty.

2. Indirect epidemiological approaches

Studies that estimate the serial interval and compare this to the incubation period have been used to infer the extent of pre-symptomatic transmission[5]. Such studies

may be based on imputations from real world epidemiological data, or be compiled from fully parameterised models, or may take a Bayesian approach.
Other approaches involve fitting a model to data (particularly the age-patterns of cases) to infer the role of asymptomatic transmission. This was successfully applied for H1N1 in 2009[6] but attempts for COVID-19 have not revealed any reliable information.

3. Virological approaches

Whilst identification of virus in a respiratory sample is necessary for transmission, it may not be sufficient. Isolation of infectious virus by culture is generally accepted to be more predictive of infectivity than PCR. However, there is some uncertainty around this assumption. For example, studies on influenza in humans[7] and animals[8–10] suggest that infectious viral load in the respiratory tract may not necessarily predict the kinetics of infectious virus release into the air and its transmissibility. It remains uncertain to what extent the quantity of virus isolated from a clinical sample is predictive of transmissibility. Combining genomic analysis of viral strains within transmission chains may provide the most meaningful evidence when combined with epidemiological data.

Evidence of asymptomatic infection with SARS-CoV-2

Completely asymptomatic infections have been reported for SARS-CoV-2 and the asymptomatic fraction has been estimated at ~1-3%[11–14]. There appears to be a significantly higher proportion of cases that are pauci-symptomatic or have a mild-to-moderate illness, with estimates ranging between 40-80% of infections.
Persons who are reported as asymptomatic at the time of testing may subsequently go on to develop symptoms (i.e. they are in the incubation period). Therefore, data that offers a snapshot view of asymptomatic infections should be interpreted with this in mind. For example, early on in the SARS-CoV-2 pandemic, reports from the Diamond Princess cruise ship identified that ~50% of confirmed SARS-CoV-2 cases were asymptomatic[15,16]. Given the lack of clinical follow up, this figure is capturing both pre-symptomatic and asymptomatic infections and cannot be used to understand the true asymptomatic fraction.
In a care home outbreak in the USA where 13 of 23 (57%) confirmed cases were asymptomatic at the time of testing, 77% (n=10) subsequently developed symptoms.

Kinetics and quantity of virus shedding in pre-symptomatic or asymptomatic infection

Question: How much SARS-CoV-2 is shed during the incubation period?

Answer: The median incubation period for SARS-CoV-2 is estimated to be 5.1 days (95% CI, 4.5 to 5.8 days)[17]. From published studies (Appendix 1) and preliminary UK data (Appendix (A-D)), the highest detected viral load appears to occur early after symptom onset. Viral load remains high for ~7 days post symptom onset, with a trend to decline over time. Viral RNA remains detectable until ~ day 12-14 (though may persist for longer in some individuals, including in faeces (Appendix 2-E)). The ability to isolate live virus is dependent on Ct value (Appendix 2 -F+G). In one small

study from Germany, live virus was successfully isolated until day 8 post symptom onset[18].

It is a reasonable assumption based on this, that virus is likely to be detectable during the late incubation period. However, virological studies on pre-symptomatic patients with COVID-19 are lacking. In a US care home outbreak, Ct values from n=10 persons in pre-symptomatic illness were in a similar range as for symptomatic cases (Ct range 15-38 versus 18-30). Two case reports describing data from n=3 patients identified SARS-CoV-2 on the day before symptom onset. Viral load was high (>10^7 RNA copies/mL) from 2 cases and no Ct value given for the third[19].

Question: How much virus is shed from asymptomatic persons?

Answer: Whether comparatively lower viral loads exist in asymptomatic compared to symptomatic persons can provide supporting evidence for the propensity for asymptomatic transmission. However, whether and how significant amounts of virus are released into the air from asymptomatic individuals is not known.
To date, only a few case reports exist that have assessed Ct values or infectious virus isolation from asymptomatic cases. Zou *et al.*[20] report on one asymptomatic case with positive nasal swab (CT value 22-28) and throat swab (CT value 30-32) on days 7, 10 and 11 after contact. Viral loads detected in the asymptomatic patient were similar to that in 17 symptomatic patients. In a German study, both viral RNA (Ct value 24.39 and 30.25) and infectious virus were detected in throat swabs from two persons repatriated from Hubei province, who were reported to be asymptomatic/pauci-symptomatic[21]. In a US care home outbreak, Ct values reported from n=3 asymptomatic cases were similar to that from cases with typical symptoms (Ct range 22-31 versus 18-30).
Of 4 UK cases repatriated from the Diamond Princess, 2 patients had detectable SARS-CoV-2 RNA upon return to the UK, both of whom were asymptomatic/pauci-symptomatic. Peak Ct value was 26.8 (from nasal swab of case 1) and 31.3 (from combined nose and throat swab of case 2), which is similar to that detected in symptomatic individuals. One individual who was identified to be infected with SARS-CoV-2 in Japan remained completely asymptomatic and PCR negative following return to the UK.

Evidence for asymptomatic transmission of SARS-CoV-2

Whilst virological reports of asymptomatic infection and pre-symptomatic shedding are informative, they do not provide direct evidence for transmission. Evidence for asymptomatic/pre-symptomatic transmission to date is derived from case reports and modelling studies

Case reports:

1. In a widely cited paper, Rothe *et al*. reported on the first case of asymptomatic transmission in Germany from a Chinese business partner to a German colleague[22]. However, data subsequently provided by the authors in a supplementary appendix described that the index case had mild symptoms and took an anti-pyretic, disclosed in a telephone interview carried out after the initial rapid publication, which may have lessened any subsequent

symptoms. The report therefore represents transmission from a pauci-symptomatic rather than asymptomatic case. Two secondary German cases in the same company reported only contact with the first German case though the short time since exposure of German case 1 to the original index case from China suggests the possibility of unidentified exposure of the secondary cases to the index case.

2. Five studies from China[19,23–26] report on small family clusters of SARS-CoV-2 where transmission potentially occurred in the incubation period. In such reports it is proposed that transmission occurred from the supposed index case, identified based on travel history e.g. to Hubei province. These studies make the assumption that there was no significant risk of exposure to infection in the community in other areas of China at the time, which may not hold true. Recall bias of symptoms[23] and inconsistent PCR results[25] add further uncertainty to reports.

3. Yu *et al*[27] describe a single pre-symptomatic transmission event. An elderly housebound male became infected and his only contacts were 3 family members who were all reported to be pre-symptomatic prior to his becoming unwell and testing positive for SARS-CoV-2. It is unclear which of 3 family member contacts infected the housebound male.

Epidemiological studies:

1. Two recent papers[28,29] that report on a large proportion of "undocumented" infections in China early in the epidemic have been cited widely in the media as evidence for asymptomatic transmission. These "undocumented infections" would include any case that failed to be tested, the reasons for which are not known. Therefore, this may include persons with mild-to-moderate symptoms who do not seek medical care, those with a lack of access to testing, as well as true asymptomatic infections. The reports therefore do not provide evidence of a major contribution of asymptomatic transmission.

2. Modelling papers[30,31] have estimated the median serial interval to be shorter than the median incubation period and inferred this as evidence of significant pre-symptomatic transmission. Nishiura *et al.* estimated a median serial interval of 4.0 days (95% CrI 3.1-4.9) based on 28 infector-infectee pairs from a combination of published literature and media reports. Tindale *et al.* used publicly available data (press releases) to estimate a mean serial interval of 4.56 (2.69-6.42) using data from Singapore and 4.22 (3.43-5.01) using data from Tianjin. This was compared with mean incubation periods of 7.1 (6.13-8.25) in Singapore and 9 (7.92-10.2) in Tianjin. The quality of the data used is uncertain. An earlier estimate of the serial interval from Li *et a.l* based on 6 infector-infectee pairs was reported as 7.5 +/- 3.4 days (95 CI 5.3 to 19).

3. In addition Yi *et al*. (http://html.rhhz.net/zhlxbx/028.htm) suggest that in Ningbo City, the risk of onward transmission from symptomatic (126/2001) vs.

asymptomatic (6/146) cases is not statistically different. Furthermore 107/126 infections from symptomatic cases are also symptomatic; whereas only 3/6 infections from asymptomatic cases are symptomatic. These data could point to a possible dose-response relationship, although this pattern has not been reported elsewhere.

Conclusions

The presentation of a large proportion of COVID-19 cases is of mild illness. A small proportion of asymptomatic infections with SARS-CoV-2 have also been reported. Direct evidence for the ability of virus to transmit during the incubation period is lacking. However, emerging data of the kinetics of virus shedding from symptomatic cases demonstrates a peak and substantial viral load around the time of symptom onset, leading to the reasonable assumption virus may be shed during the late incubation period.

Overall, available evidence to date suggests the possibility that some asymptomatic/presymptomatic transmission is occurring. However, whether this is occurring on a significant scale and how it contributes to the overall transmission dynamics of the pandemic, remains uncertain.

Detailed epidemiological and virological studies from cases and contacts, that combine viral genomic analysis and serological data would provide the best evidence that transmission can occur from asymptomatic individuals or during the incubation period.

This is an interim report and will be updated as further evidence becomes available.

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Appendix 1 – Examples of sequential virological data from published studies

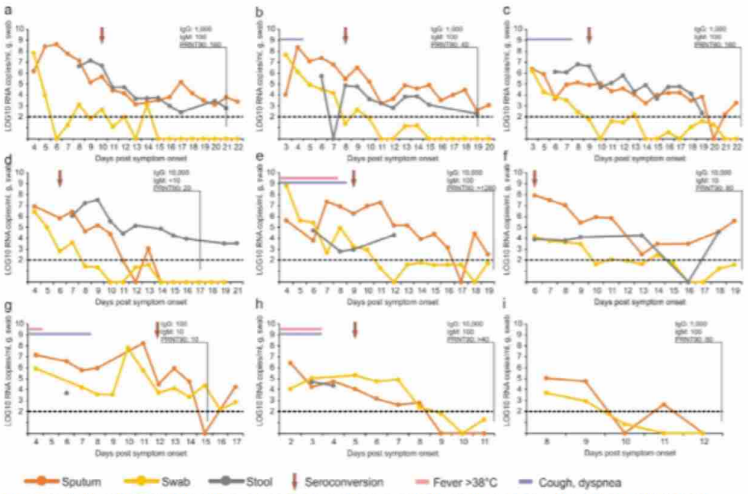


Figure 2. Viral load kinetics, seroconversion and clinical observations in individual cases. Panels A to I correspond to cases #1, #2, #3, #4, #7, #8, #10, #14, and #16 in Böhmer et al.(accompanying manuscript). Dotted lines, limit of quantification

Taken from Wolfel et al. Nature 2020 https://doi.org/10.1038/s41586-020-2196-x

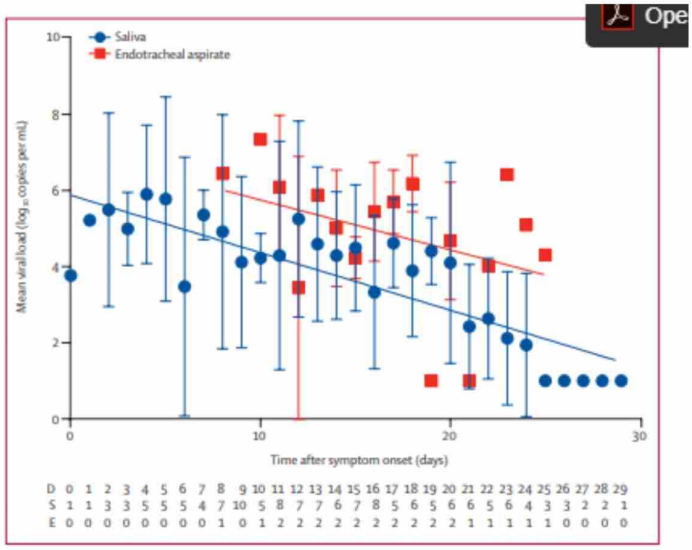
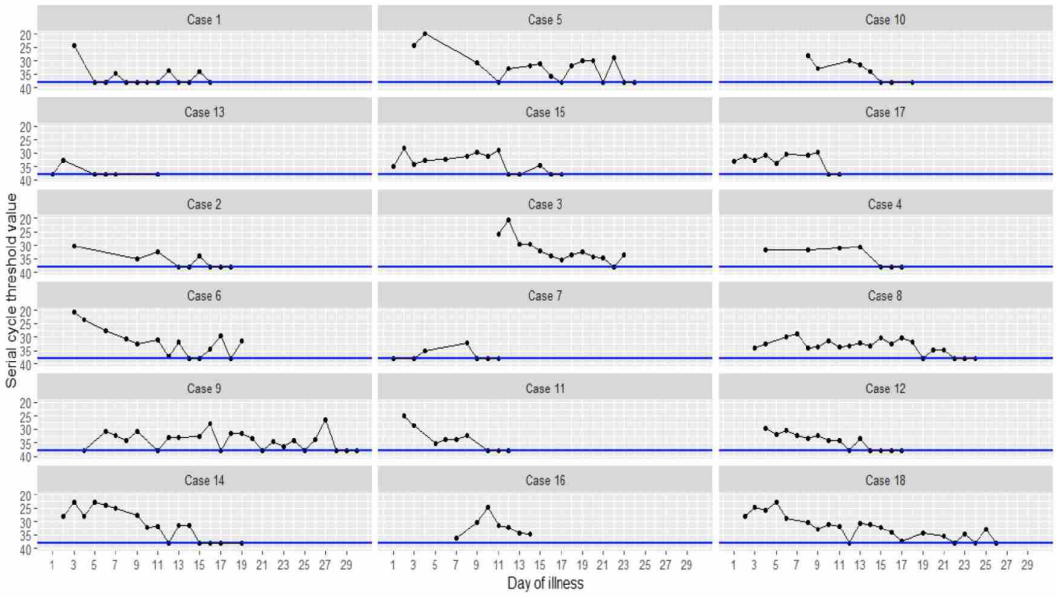


Figure 2: Temporal profile of serial viral load from all patients (n=23)
Most viral load data are from posterior oropharyngeal saliva samples, except for three patients who were intubated, in whom viral load data from endotracheal aspirates are shown separately. Datapoints denote the mean; error bars indicate SD; slope represents best fit line. The number of patients who provided a sample on each day is shown in the table below the plot. D=days after symptom onset. S=saliva. E=endotracheal aspirate.

Take from To et al. Lancet ID 2020 https://doi.org/10.1016/ S1473-3099(20)30196-1

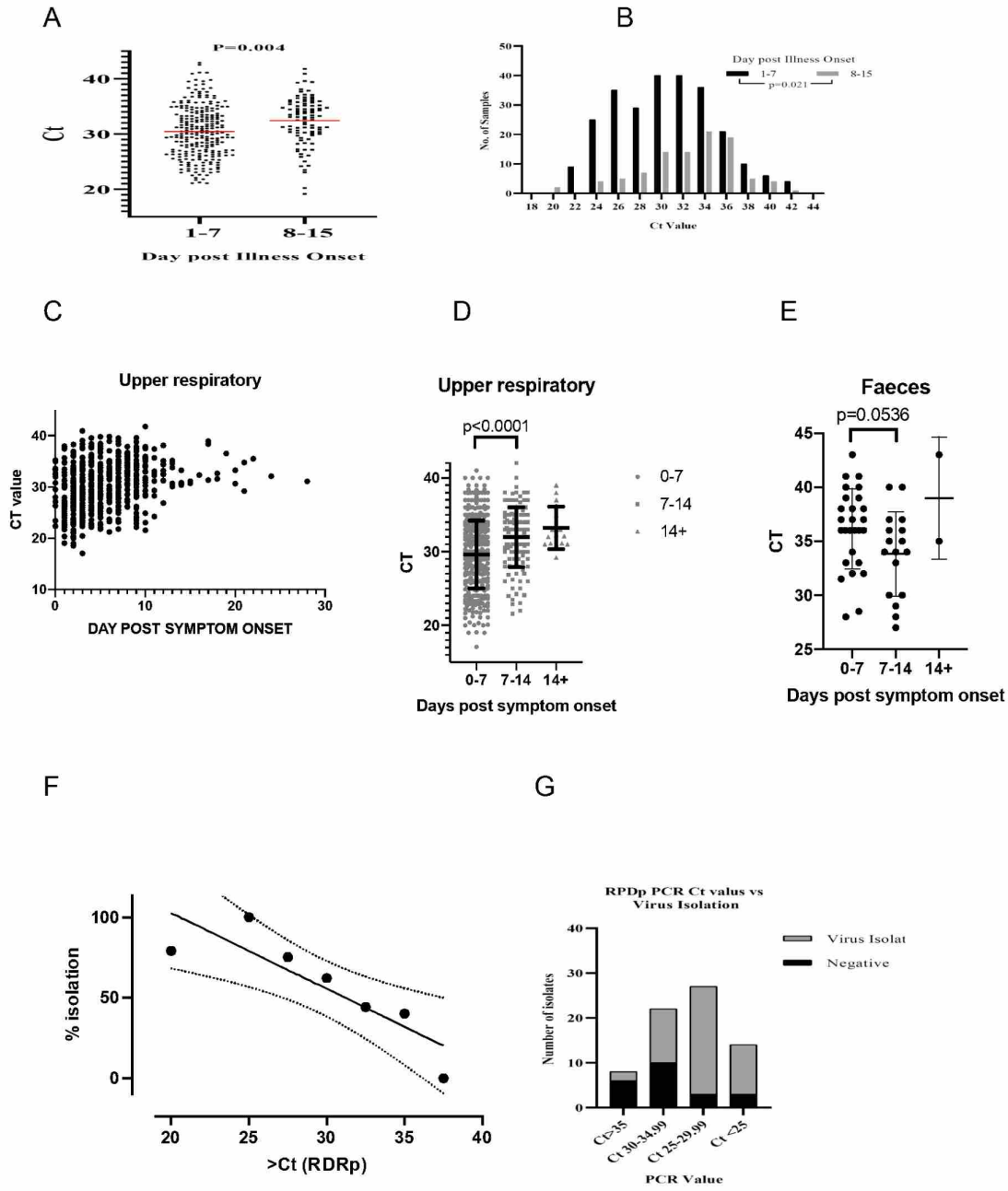


Six patients (Case 1, 5, 10, 13, 15 and 17) required supplemental oxygen, while the other 12 patients did not require supplemental oxygen. Cases 1, 5, 10, 15 and 15 also received lopinavir-ritonavir. Negative PCR results (target not detected) are graphed as a Ct value of 38 for ease of viewing and interpretation (blue horizontal blue line). Cycle Threshold Value corresponds with the number of copies of the virus in a biological sample, in an inversely proportional and exponential manner.

Taken from Young BE et al. JAMA. 2020 Mar 3. doi: 10.1001/jama.2020.3204.

Appendix 1 – Preliminary virological shedding data from UK cases

All UK data shown is at a preliminary stage of analysis and may be subject to change.



Preliminary virological shedding data from UK cases. (A) Virus detection over time from n=352 respiratory samples from n=74 UK HCID cases (B) Observed virus detection over time from n=352 respiratory samples from n=74 UK HCID cases. (C) Upper respiratory tract samples from n=569 samples from n=262 UK cases (D) Upper respiratory tract samples from n=569 samples from n=262 UK cases grouped over time (E) Faecal samples from n=46 samples from n=21 UK cases; (F and G) Virus isolation from n=73 respiratory samples.