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Is presymptomatic spread a major contributor to COVID-19 transmission?

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Recent reports have shown COVID-19 transmission prior to disease onset, raising concerns that people who appear healthy may be major contributors to the COVID-19 pandemic. Few studies have directly determined the proportion of transmission events that occur before symptom onset, but a recent modeling study by He et al.[1] inferred that 44% of secondary cases were infected during presymptomatic stages of disease. Here, we raise questions regarding the approach and interpretation of the He et al. transmission model.

Using polymerase chain reaction with reverse transcription (RT-PCR) data from throat swabs obtained 0–28 days after symptom onset, He et al.[1] showed that SARS-CoV-2 viral load was highest on the day of symptom onset (day 0) and declined thereafter (He et al.[1], fig. 2). Data were fitted with a smoothing spline average trend line that was highest on the day of symptom onset and, based on this trend, the authors proposed that virus titers would peak at or prior to symptom onset. However, visual inspection of individual viral load tracings appears to refute this interpretation. Although a request for viral shedding data was denied by the Guangzhou Eighth People's Hospital, we believe that there could be potential issues with the interpretation of the data. First, it is unclear from the methods if a mixed-effects model was used to take into account the longitudinal nature of the data. If a mixed-effects model was not used, it is concerning that there was only a limited amount of data at day 0, because this may have resulted in leverage points that overly influenced the increasing angle of the average viral load trend line near the date of symptom onset. Importantly, we suspect that a large portion of individual viral load kinetic lines do not follow the general trend line and should be considered in the evaluation of the data. For example, one male subject (blue line, fig. 2, lower left[1]) began with a low but detectable viral load cycle threshold (CT) = 39 at day 1 and day 2 (CT = 39) before peaking at day 3 (CT = 28), which then remained elevated with viral loads of CT = 34, 34 and 35 at days 4, 5 and 9 post symptom onset, respectively. Several lines appear to have this pattern, but it is difficult to determine from the figure whether the estimated average trend fits the data well, as many profile lines were indiscernible. If individual peaks in viral load are found to mostly occur after symptom onset or after the first available viral load time point, then this may indicate that the current generalized additive model and derived average trend line do not fit the data well and that individual peak infectiousness may be more similar to previous studies that found throat swab virus titers peaking after symptom onset[2].

In the He et al. model, the serial interval was experimentally determined to be 5.8 days, based on 77 infector–infectee transmission pairs using secondary sources including news articles[1] (Fig. 1, top panels). The study did not include observed incubation period data and therefore used a previously published incubation period of 5.2 days based on observations from only 10 subjects[3] (Fig. 1, middle left). A study by Bi et al. measured a mean incubation period of 5.95 days based on 183 subjects[4] (Fig. 1, middle right). To examine the effect of assumed incubation period on inferred infectiousness, we ran the original R code published by the authors, changing only the assumed incubation period (lognormal distribution), with parameters 1.57 and 0.65 (mean and standard deviation of the incubation period's natural logarithm) based on Bi et al.[4] instead of a lognormal distribution with parameters 1.434065 and 0.6612 as based originally on ref. [3]. With this modest difference in assumed incubation period, the probability density function of inferred infectiousness changes from a peak at −0.7 days prior to symptom onset (Fig. 1, bottom left) to become a monotonically decreasing function (Fig. 1, bottom right). In other words, the model predicts that infectiousness is low at the time of symptom onset but continuously increases to infinity with increasing time before symptom onset, which is not a plausible infectiousness profile. The model also predicts that infectiousness starts at 1.56 days before symptom onset but peaks at 2.32 days before symptom onset, but, because this is not biologically possible, one would have to assume that 1.56 days is both the start and peak of infectiousness, which is also a biologically implausible scenario. Together, this indicates that inferred infectiousness is sensitive to the assumed incubation period.

Although the levels of infectious virus needed to achieve COVID-19 transmissibility are unknown, the best way to determine transmission potential is from carefully conducted epidemiological studies that determine the proportion of presymptomatic versus post-symptomatic spread. A review of several COVID-19 case studies[5] found multiple instances of transmission before symptom onset. However, it is difficult to determine the proportion of pre- and post-symptom onset transmission from individual case studies, because there is little to no information on the number of asymptomatic/presymptomatic COVID-19 cases that had close contacts but did not result in a transmission event. Modeling studies can provide value in the interpretation of epidemiological data, but, as noted previously[5], COVID-19 models are highly dependent on the assumptions built into them and sometimes can be misinterpreted. For example, one model estimated that the transmission rate of undocumented infections per person was 55% of the transmission rate of documented infections[6] and undocumented infections were the source of 79% of the documented cases. Although often referred to as evidence supporting an important role

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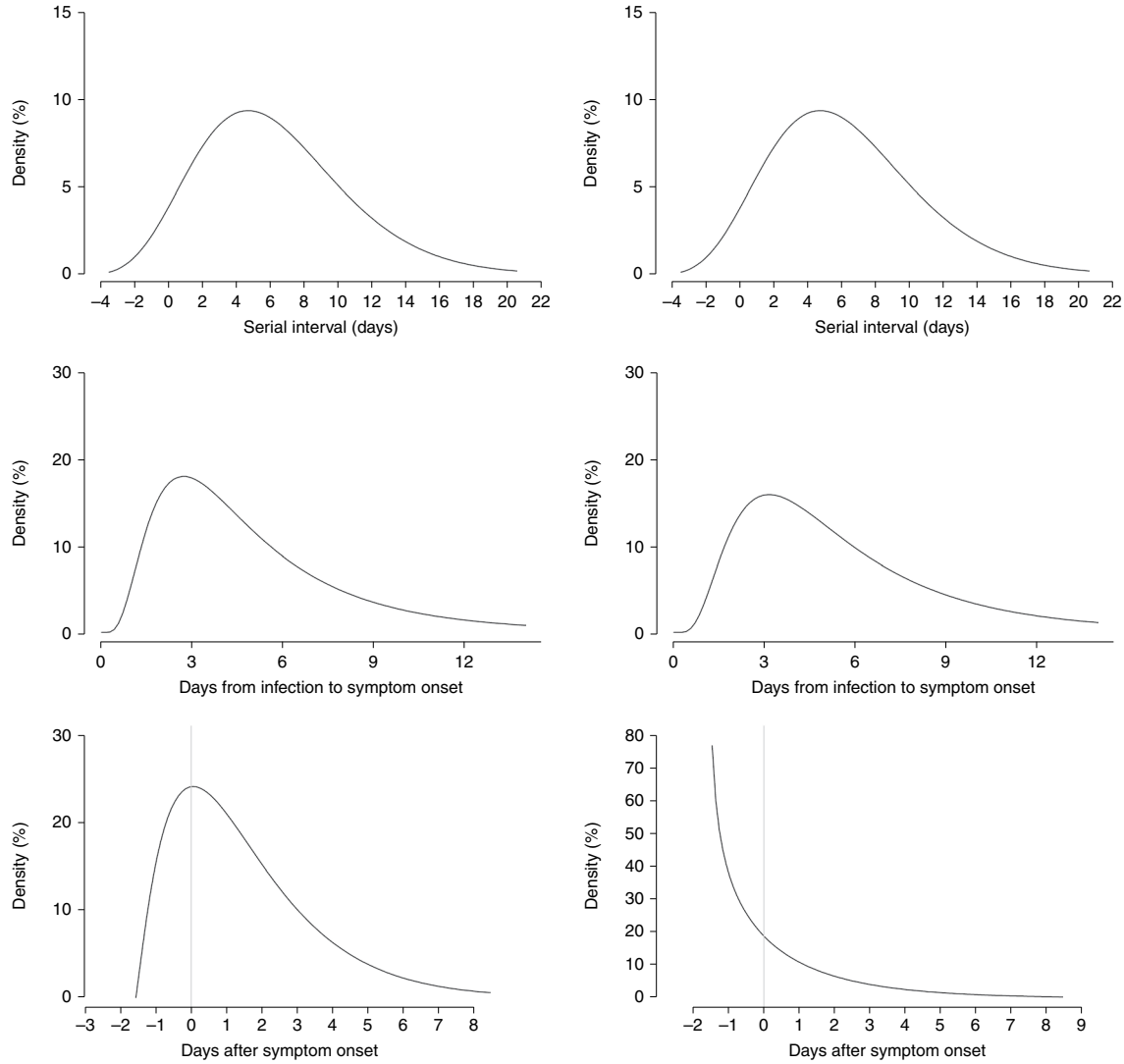

Fig. 1 | The inferred infectiousness profile by He et al.[1] is sensitive to incubation-period assumptions. Estimated serial interval distribution (top), assumed incubation period (middle) and inferred infectiousness profile of COVID-19 (bottom). Left: figures drawn from the original model provided by He et al.[1] using a published incubation period based on 10 subjects by Li et al. (ref. [3]). Right: figures drawn from the same model using the serial interval distribution provided by He et al.[1] but using a published incubation period based on 183 subjects by Bi et al. (ref. [4]). Note the contrast in infectiousness profiles (bottom left versus bottom right) obtained when using different published incubation periods within the same model.

for asymptomatic/presymptomatic transmission, the term undocumented infection included '… mild, limited or lack of symptoms…'. Because cases '… many of which were likely not severely symptomatic…' reflected a range of potential spreaders, this modeling study should not be confused with transmission solely by asymptomatic/presymptomatic COVID-19 cases. Despite the utility of modeling studies, the most informative data often come from direct observations. For example, one study found that 31% (5/16) of transmissions occurred prior to symptom onset[7]. By contrast, another COVID-19 study ($n=19$ asymptomatic cases and 5 presymptomatic cases) found that only 4.2% (1/24) of cases resulted in secondary transmission[8]. Although it is unclear how long these individuals had been infected while in close contact with others prior to diagnosis, this low rate of asymptomatic/presymptomatic transmission may be due in part to hospitalized isolation during the outbreak. Interestingly, other secondary transmission studies have shown that, although symptomatic cases transmitted COVID-19 to 16.2% (34/210) of household contacts, asymptomatic or presymptomatic spread to household contacts was not observed (0/15)[9]. Comparing these small studies is useful because it confirms that asymptomatic and presymptomatic spread is possible, but also places the results into the context of how commonly these types of transmission might occur. Interestingly, studies on SARS, a related coronavirus with a similar reproductive number (R_0) to COVID-19[10], provide analogous results. Symptomatic SARS cases spread the disease to 15.1% (101/669) of close contacts, whereas 0% (0/363) of close contacts to SARS cases during the presymptomatic incubation period became infected[11]. In terms of larger COVID-19 studies that calculated the proportion of presymptomatic versus post-symptomatic spread, a study examining 468 COVID-19 cases in China found that 12.6% of transmission occurred prior to symptom onset[12]. Likewise, contact tracing studies of 157 locally acquired cases in Singapore identified 10 cases of presymptomatic COVID-19 transmission, but this only accounted for 6.4% of transmission events[13]. Although many factors are involved with transmission efficiency, it appears that asymptomatic/presymptomatic transmission measured by direct contact tracing studies[7–9,12,13] is lower than that predicted by COVID-19 transmission models[1,6]. As more clinical data emerge,

our understanding of presymptomatic and post-symptomatic transmission will improve and this will be critical for future public health initiatives aimed at controlling the COVID-19 pandemic.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-1046-6.

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Data availability

Modeling was performed using the original R code published by He et al. (ref. [1]) using the assumed incubation period (lognormal distribution with parameters 1.57 and 0.65 (mean and standard deviation of the incubation period's natural logarithm) published by Bi et al.[4] or the lognormal distribution with parameters 1.434065 and 0.6612 published by Li et al. (ref. [3]).

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Author contributions

Both authors contributed to the concept and study design. M.K.S. organized the manuscript and L.G. prepared the figure and performed the statistical analysis. Both authors wrote the manuscript and both had full access to the data included in the study. M.K.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

The authors declare no competing interests.

Additional information

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