**Presymptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data**

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**ABSTRACT**

**Objective** To estimate the proportion of presymptomatic transmission of SARS-CoV-2 infection that can occur, and the timing of transmission relative to symptom onset.

**Setting/design** Secondary analysis of international published data.

**Data sources** Meta-analysis of COVID-19 incubation period and a rapid review of serial interval and generation time, which are published separately.

**Participants** Data from China, the Islamic Republic of Iran, Italy, Republic of Korea, Singapore and Vietnam from December 2019 to May 2020.

**Methods** Simulations were generated of incubation period and of serial interval or generation time. From these, transmission times relative to symptom onset, and the proportion of presymptomatic transmission, were estimated.

**Outcome measures** Transmission time of SARS-CoV-2 relative to symptom onset and proportion of presymptomatic transmission.

**Results** Based on 18 serial interval/generation time estimates from 15 papers, mean transmission time relative to symptom onset ranged from –2.6 (95% CI –3.0 to –2.1) days before infector symptom onset to 1.4 (95% CI 1.0 to 1.8) days after symptom onset. The proportion of presymptomatic transmission ranged from 45.9% (95% CI 42.9% to 49.0%) to 69.1% (95% CI 66.2% to 71.9%).

**Conclusions** There is substantial potential for presymptomatic transmission of SARS-CoV-2 across a range of different contexts. This highlights the need for rapid case detection, contact tracing and quarantine. The transmission patterns that we report reflect the combination of biological infectiousness and transmission opportunities which vary according to context.

**INTRODUCTION**

There is currently a pandemic of COVID-19, a recently emerged and rapidly spreading infectious disease that is caused by the novel coronavirus, SARS-CoV-2. There are large direct impacts of COVID-19 among known cases. As of 19 April 2021, the WHO has reported 140,886,773 confirmed cases and 3,012,251 deaths due to COVID-19. In China, 14% and 5% of cases were classified as severe and critical, respectively.

There are also major indirect impacts of COVID-19 and its control measures on other aspects of healthcare and the economy.

In addition to vaccination, primary control measures entail reducing transmission from infectious individuals. These include case isolation, contact tracing and quarantine, physical distancing, hygiene and ventilation measures. Infectious people are identified when they report symptoms, and are tested for SARS-CoV-2. Infectious people without symptoms may be identified when an active surveillance programme is in place.

In the absence of active surveillance, infectious people without symptoms may not be quarantined, and therefore may have more contacts with susceptible people resulting in increased SARS-CoV-2 transmission. Therefore, quantifying the transmission potential before or in the absence of symptoms will inform disease control measures and predictions of epidemic progression.

Characteristics of presymptomatic and asymptomatic transmission are potentially different, and separate approaches may be required to understand them. In this paper, we capitalise on the considerable information
about presymptomatic transmission that can be inferred from contact tracing studies. Therefore, we focus on transmission from people before they develop symptoms rather than from people who never develop symptoms. This addresses the urgent need for more data on the extent of presymptomatic transmission which has been highlighted by those developing models to inform policies.3

Reports of presymptomatic transmission10–19 emerged as detailed contact tracing was conducted during early outbreaks of COVID-19. Further, both viral genome18 and live virus21 have been detected in upper respiratory samples prior to symptom onset. These findings are supported by quantitative studies based on contact tracing, with reports of serial intervals or generation times similar in duration or shorter than incubation periods in some situations,27–32 and even cases of symptoms manifesting in the infectee prior to the infector.24 30 33–37

Several studies have quantified the proportion27–30 38 and timing27 30 38 of presymptomatic transmission, using a variety of datasets and methodologies. Here, we compare presymptomatic transmission across a range of different contexts using a consistent methodology. We build on our rapid review of SARS-CoV-2 serial interval and generation time39 and rapid systematic review and meta-analysis of incubation period40 with a secondary analysis of published data to estimate the proportion and timing of presymptomatic transmission of COVID-19.

METHODS

Principles of methodology

If transmission occurs after symptom onset, mean generation time, the duration in days between time of infection of a secondary case (infectee) and that of its primary case (infector), is longer than mean incubation period, the time between infection and symptom onset in the infector (scenario A in figure 1). If presymptomatic transmission occurs, mean generation time is shorter than mean incubation period (scenarios B and C in figure 1). If the incubation period of an infector and of an infectee are taken to be independent and identically distributed, serial interval, the time between infector and infectee symptom onset, can be taken as an approximation of generation time,41 42 although serial interval will have more variation.43 44 Our method entailed subtracting simulated values for incubation period from serial interval to estimate the timing and proportion of presymptomatic transmission in a range of different settings. Table 1 contains definitions relevant to our analysis.

Incubation period data

We used the incubation period estimate from our separately published rapid systematic review and meta-analysis40. That is, a lognormal distribution with meanlog and sdlog parameters of 1.63 (95% CI 1.51 to 1.75) and 0.50 (95% CI 0.46 to 0.55), respectively. The corresponding mean and median were 5.8 (95% CI 5.0 to 6.7) days and 5.1 (95% CI 4.5 to 5.8) days, respectively. As there is currently no evidence of country-specific drivers in variation of incubation period, we deemed it reasonable to use the estimate from this meta-analysis of incubation period40 to investigate presymptomatic transmission across a range of settings.

Serial interval and generation time data

We used serial interval estimates from our separately published rapid review of serial interval and generation time.39 In contrast to incubation period, interventions such as case isolation are reported to affect serial interval.39 43 44 Therefore, we analysed each serial interval or generation time estimate separately and excluded estimates based on data from a mixture of countries.

Figure 2 summarises how we selected serial interval or generation time estimates for inclusion in our analysis.
From the 40 published papers included in the rapid review, we selected serial interval and generation time estimates based on data from single countries, for which statistical distributions were fitted, and which we could replicate (n=27 estimates from 24 papers). From this subset, we identified estimates for which enough information was provided, to allow us to simulate the uncertainty associated with their distributions (n=18 estimates from 15 papers).

**Description of serial interval/generation time data**

Building on initial data screening and assessment for quality and central estimates presented in our rapid review of serial interval and generation time, we highlighted country or region of origin, date-range for gathering of the data underlying the estimates, and sample-size.

**Simulation**

We subtracted samples from a simulated incubation period distribution from samples from simulated serial interval/generation time distributions to generate distributions of transmission time relative to symptom onset.

To calculate transmission time relative to symptom onset, we first replicated the reported serial interval/generation time distributions and the incubation period distribution from our meta-analysis. To achieve this, we sampled distribution parameters from their respective 95% CIs for each reported distribution (n=1000). We then simulated distributions using these parameters (n=1000). The incubation period sample was subtracted from each generation time or serial interval sample to give a resultant distribution indicating transmission time relative to onset of symptoms. The resultant 1 000 000 samples were resampled with replacement (n=1000 samples from each of 10 000 repeats) and 95% CIs from bootstrapping were calculated.

As we were conducting a secondary analysis based on published data, we did not incorporate potential correlations between serial interval and incubation period at transmission pair level. That is, we assumed that incubation period and generation time/serial interval were independent.

We presented the resultant simulated transmission time relative to symptom onset, and the proportion of presymptomatic transmission at the level of each underlying serial interval or generation time estimate, grouped by country or region.

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**Table 1** Definitions referred to in this review

| Term | Description |
|------|-------------|
| Asymptomatic | An infected person who never develops symptoms of the disease. |
| Presymptomatic | An infected person before they develop symptoms of the disease. |
| Duration of infectiousness | The time interval in days during which an infectious agent may be transferred directly or indirectly from an infected person to another person. |
| Incubation period | The time interval in days between invasion by an infectious agent and appearance of the first signs or symptoms of the disease in question. |
| Serial interval | The duration in days between symptom onset of a secondary case (infectee) and that of its primary case (infector). |
| Generation time or generation interval | The duration in days between time of infection of a secondary case (infectee) and that of its primary case (infector). |
| Transmission pair | An infected person (infector) and a person whom they transmit the pathogen to (infectee). |
| Latent period | The period from the point of infection to the beginning of the state of infectiousness. This period corresponds to the ‘exposed’ (E) compartment of a susceptible-exposed-infectious-recovered/removed model. |
| Transmission time relative to symptom onset | The time of transmission of an infectious agent from an infector to an infectee in days relative to the onset of symptoms in the infector. |
| Proportion of presymptomatic transmission | The proportion of all transmission events that occur before the onset of symptoms in the infector. |

**Figure 2** A summary of how serial interval and generation time estimates were selected for analyses.
In online supplemental figures 1–3 and table 1, we also present the result of simulations from the larger dataset of 27 estimates (defined in figure 2). These supplementary results include estimates based on serial intervals/generation times for which we could simulate distributions but not take the associated uncertainty into account. For this simulation, as only central estimates of serial interval/generation time parameters were used, we also used central parameter estimates of the incubation period (meanlog 1.63, sdlog 0.5).

All analyses were conducted in the R Statistical Environment. The extracted data and code that we used to generate our simulation is available through GitHub (https://github.com/miriamcasey/covid-19_presymptomatic_project).

**Patient and public involvement statement**

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

**RESULTS**

**Description of serial interval/generation time data**

Building on the description of the serial interval and generation time estimates by Griffin et al. figure 3 summarises the country or region, collection date-range and sample size of the data underlying the serial interval and generation time that went into our simulation. Figure 4 summarises the mean and SD of each estimate. Of the 18 estimates from 15 papers for which we could incorporate uncertainty into our simulations, 11 came from China, 2 each came from the Republic of Korea and from Singapore and 1 each from the Islamic Republic of Iran, Italy and Vietnam. Sample sizes ranged from 17 to 1407 transmission pairs.

Of the 11 estimates from China, 3 were based on datasets covering all of China excluding Hubei province. These three estimates were associated with the largest datasets in the study (n=1407, 67743 and 46833 transmission pairs), and were associated with the same group of authors, who confirmed some overlap between the datasets underlying each paper. Xu et al. and Ali et al. both reported mean serial interval estimates of 5.1 days. It is also possible that there is some overlap between these general Chinese datasets and the smaller datasets associated with individual regions in China.

Both estimates from Hong Kong came from the same paper and dataset, but were based on samples of certain (n=17) and mixed certain and probable (n=26) transmission pairs. There is a difference of over a day in these two data subsets although they came from the same region and date range. The two estimates from Shenzhen had some overlap in date range but differed in sample size (48 transmission pairs, 27 transmission pairs). Ganyani et al. and Tindale et al. used the same datasets from Tianjin and Singapore. Son et al. reported a serial interval estimate based on data from Busan in the Republic of Korea, whereas Chun et al. used data from the whole country. Shiyian (Hubei province) and Zhumai in China were associated with one estimate each, as were the remaining countries (figures 3 and 4).

Only Ganyani et al. inferred generation time. The remainder of the estimates were based on serial intervals. Ten of the estimates were based on direct observation of transmission pairs. Eight serial interval estimates from six papers were based on inferences about transmission pairs from clusters of cases.

Many of the papers highlighted that serial interval was likely to be shorter if symptomatic cases were rapidly isolated. Bi et al. quantified this as mean serial interval of 3.6 days if a case was isolated within less than 3 days of developing symptoms, increasing to 8.1 days if the infected individual was isolated on the third day after symptom onset or later, but with no further increase if isolation was delayed beyond 6 days after symptom onset. Ali et al. quantified the contraction of serial interval over time, driven primarily by case isolation, and advocated for real-time estimation of serial intervals.
Simulation results

Figure 5 summarises the distributions of transmission time relative to symptom onset that were generated by the simulation. Table 2 provides summary statistics from the simulation output including the proportion of presymptomatic transmission. Mean transmission time relative to symptom onset ranged from −2.6 (95% CI −3.0 to −2.1) days before infector symptom onset in Vietnam to 1.4 (95% CI 1.0 to 1.8) days after symptom onset in Italy. The proportion of presymptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI 42.9 to 49.0%) in Italy to 69.1% (95% CI 66.2 to 71.9) in Tianjin. It was only possible to estimate the proportion of negative serial intervals, reflecting symptom onset in the infectee prior to the infector, from the five estimates that were fitted with distributions that allowed negative serial intervals. Simulations based on Chinese data ranged from 16.7% (95% CI 14.4 to 19.0) to 20.4% (95% CI 17.9 to 22.9), whereas the simulation using the data from Vietnam resulted in 30.9% (95% CI 28.0 to 33.8) negative serial intervals.

Online supplemental figures 1–3 and table 1 show the results from simulations based on all 27 serial interval or generation time estimates from 24 papers, including the nine studies for which we could not incorporate uncertainty. The extra nine studies came from Brazil, Brunei Darussalam, China (all regions excluding Hubei), Tianjin, Wuhan, Iran and the Republic of Korea. Online supplemental table 1 also shows any estimates or comments relating to presymptomatic transmission that we found in the serial interval or generation time papers. Online supplemental table 2 compares the presymptomatic transmission time estimates of Ganyani et al., Tindale et al. and this study which all refer to the same datasets from Singapore and Tianjin. Online supplemental tables 3 and 4 summarise virological studies and case reports of presymptomatic transmission which we refer to in our discussion.

DISCUSSION

Our simulation study highlights the value of contact tracing data as a source of information about transmission dynamics of recently emerged diseases such as COVID-19. Using estimates of serial interval, generation time and incubation period from the published literature, our
simulations highlight substantial potential for presymptomatic transmission of SARS-CoV-2.

Our estimation of mean transmission times ranged from 2.6 days before to 1.37 days after symptom onset. Virus transmission from an infected to an infectee requires both shedding of infectious virus from the infector and contact with a susceptible person under conditions that allow the virus to be transferred. Interventions such as rapid isolation of symptomatic people result in a greater proportion of transmission occurring earlier in the infectious period (shorter serial intervals and relatively more presymptomatic transmission).\(^{43,44}\) Well characterised infector–infectee data are required for serial interval estimation. It is possible that some of the cases associated with these data may be isolated more promptly than cases that were not detected by the public health authorities. Our transmission time estimates are therefore more likely to overlap with the earlier part of the infectious period.

Table 2  A summary of simulation results

| Reference | Mean | SD (SD range) | Median | PST (PST range) |
|-----------|------|---------------|--------|-----------------|
| China—all excluding Hubei | Xu et al\(^{35}\) | $-0.7 (-1.1 \text{ to } -0.3)$ | 6.2 (5.9 to 6.5) | $-0.5 (-1 \text{ to } -0.1)$ | 53.5 (50.4 to 56.6) |
| | Ali et al\(^{43}\) | $-0.7 (-1.1 \text{ to } -0.3)$ | 6.2 (5.9 to 6.5) | $-0.5 (-1 \text{ to } 0)$ | 53.2 (50.1 to 56.3) |
| | Du et al\(^{43}\) | $-1.8 (-2.1 \text{ to } -1.4)$ | 5.8 (5.5 to 6) | $-1.6 (-2 \text{ to } -1.1)$ | 61.2 (58.2 to 64.3) |
| China—Hong Kong | Kwok et al\(^{36}\) | $-1 (-1.4 \text{ to } -0.7)$ | 5.3 (4.3 to 6.3) | $-1.3 (-1.6 \text{ to } -1.1)$ | 64.5 (61.5 to 67.4) |
| | Kwok et al\(^{36}\) | 0.5 (0.2 to 0.8) | 5 (4.4 to 5.7) | 0.4 (0.1 to 0.7) | 46.3 (43.2 to 49.4) |
| China—Shiyan (Hubei) | Yang et al\(^{36}\) | $-1.2 (-1.5 \text{ to } -0.8)$ | 5.7 (5.4 to 6) | $-1 (-1.4 \text{ to } -0.5)$ | 57.1 (54.1 to 60.2) |
| China—Shenzhen | Wang et al\(^{47}\) | 0.1 (0.2 to 0.5) | 6.2 (5.4 to 6.9) | $-0.5 (-0.9 \text{ to } -0.1)$ | 54.2 (51.1 to 57.2) |
| | Bi et al\(^{44}\) | 0.5 (0.2 to 0.8) | 5.3 (5 to 5.6) | 0.1 (0.2 to 0.5) | 48.6 (45.5 to 51.8) |
| China—Tianjin | Ganyani et al\(^{48}\) | $-1.8 (-2 \text{ to } -1.6)$ | 3.5 (3.3 to 3.8) | $-1.4 (-1.6 \text{ to } -1.1)$ | 69.1 (66.2 to 71.9) |
| | Tindale et al\(^{27}\) | $-1.4 (-1.7 \text{ to } -1.1)$ | 4.2 (3.9 to 4.5) | $-1.1 (-1.4 \text{ to } -0.8)$ | 61.1 (58.1 to 64.2) |
| China—Zhu hai | Wu et al\(^{43}\) | 0.5 (0.2 to 0.9) | 5.8 (5.1 to 6.4) | $0 (-0.3 \text{ to } 0.3)$ | 50.2 (47.1 to 53.3) |
| Iran—Qom | Aghaali et al\(^{44}\) | $-1.2 (-1.5 \text{ to } -0.9)$ | 4.7 (4.4 to 5) | $-1.4 (-1.7 \text{ to } -1.1)$ | 63.5 (60.5 to 66.5) |
| Italy—Vo (village in Northern Italy) | Lavezzo et al\(^{28}\) | 1.4 (1.0 to 1.8) | 6.4 (6.0 to 6.9) | 0.5 (0.1 to 0.9) | 45.9 (42.9 to 49.0) |
| Republic of Korea— all | Chun et al\(^{38}\) | $-0.4 (-1 \text{ to } 0.1)$ | 8.8 (6.6 to 10.8) | $-2 (-2.4 \text{ to } -1.6)$ | 64.2 (61.2 to 67.2) |
| Republic of Korea— Busan | Son et al\(^{48}\) | $-0.3 (-0.6 \text{ to } 0.1)$ | 5.1 (4.7 to 5.4) | $-0.6 (-0.9 \text{ to } -0.2)$ | 55.4 (52.3 to 58.4) |
| Singapore | Ganyani et al\(^{48}\) | $-0.6 (-0.8 \text{ to } -0.4)$ | 3.7 (3.5 to 4) | $-0.2 (-0.4 \text{ to } 0)$ | 52.5 (49.4 to 55.6) |
| | Tindale et al\(^{27}\) | $-1.4 (-1.7 \text{ to } -1.1)$ | 4.8 (4.5 to 5) | $-1.1 (-1.5 \text{ to } -0.8)$ | 60.0 (57.0 to 63.1) |
| Vietnam | Pham et al\(^{49}\) | $-2.6 (-3.0 \text{ to } -2.1)$ | 7.2 (6.9 to 7.6) | $-2.4 (-3 \text{ to } -1.9)$ | 63.4 (60.5 to 66.4) |

The table shows the mean, standard deviation (SD) and median of transmission time relative to symptom onset in days as well as the proportion of presymptomatic transmission (PST).

For transmission time relative to symptom onset, negative values mean transmission before symptom onset and positive values mean transmission after symptom onset. The figures in parentheses represent the 95% confidence intervals from bootstrapping of simulation samples.

CN AEH, China: all regions excluding Hubei; CN HK, China: Hong Kong; CN SY, China: Shiyan (Hubei); CN SZ, China: Shenzhen; CN TJ, China Tianjin; CN ZH, China: Zhuhai; IR, Iran; IT, Italy; KR, The Republic of Korea; SG, Singapore; VN, Vietnam.
findings of detailed contact tracing in Shenzhen showed that isolation less than 3 days following symptom onset had a large effect in shortening serial interval whereas isolation at 6 days or later after symptom onset had no effect. This suggests reduced biological infectiousness beyond the first week of symptoms.

Our findings in support of transmission potential prior to symptom onset are consistent with multiple reports of both SARS-CoV-2 genome and live virus detection in upper respiratory samples prior to symptom onset. Bae et al reported viral genome detection up to 13 days prior to symptom onset and Arons et al isolated live virus from upper respiratory samples from nursing home residents 6 days prior to symptom onset. Of 48 residents testing positive for viral genome in upper respiratory tract samples, Arons et al reported that 24 of these residents tested positive a median of 4 (IQR 3–5) days in advance of symptom onset. Online supplemental table 3 provides a more detailed summary of the virological studies which we refer to. Case series with detailed descriptions of contact patterns and symptom onset inferred that 37% (95% CI 27.5 to 45) of transmission from a mixture of countries to infer that infectiousness peaked at symptom onset (95% CI −0.9 to 0.9 days). The authors estimated that 44% (95% CI 30% to 57%) of transmission was presymptomatic. Ferretti et al also using data from a mixture of countries (40 transmission pairs), inferred that 37% (95% CI 27.5 to 45) of transmission was presymptomatic and that this accounted for almost enough transmission (0.9 of the effective reproduction number) to maintain an epidemic of its own.

Ganyani et al and Tindale et al used the same dataset to infer transmission pairs and estimate presymptomatic transmission. Their estimates were 48% (95% Credible interval (CrI) 32 to 67) and 74% for Singapore, and 62% (95% CrI 50 to 76) and 81% for Tianjin, respectively. This difference was likely to be due to different methods used to infer transmission pairs, different incubation periods and slightly different methods of estimating transmission time relative to symptom onset. Our estimates of presymptomatic transmission based on the generation times of Ganyani et al and the serial intervals of Tindale et al differ from the authors’ estimates (online supplemental table 2) due to using a different estimate for incubation period and a slightly different approach to transmission time calculation.

We estimate more presymptomatic transmission (64.2%) based on the serial interval of Chun et al than what is estimated in their paper (37%), as the incubation period used for our estimation of presymptomatic transmission (median 5.1 days) is much longer than that used in Chun et al’s calculations (median 2.9 days). This variation in estimates highlights the impact of inference method and also of incubation period on results. One of our motivations in this study was to facilitate comparisons between different countries or regions by removing some of the methodological variation due to different incubation period estimates and approaches to calculating transmission time.

The principle behind our analyses is that subtraction of incubation period from generation time allows us to estimate transmission time relative to symptom onset (figure 1). Generation time is difficult to observe directly and few papers estimate it. We included only a single estimate of generation time in our analyses. If the incubation period of an infectee can be taken to be independent and identically distributed, serial interval, the time between infector and infectee symptom onset, can be taken as an approximation of generation time, although serial interval will have more variation. The extra variation associated with serial interval should be borne in mind while interpreting our results.

There were further sources of variation that are challenging to address. Our description of the data sources underlying our simulation show large variation in sample size. With a relatively small sample size of 26, Kwok et al reported variation of more than a day in serial interval when certain and less certain subsets of transmission pairs were used, even though they were based on the same location and date range. The various methods (eg, Vink et al and te Beest et al) for inferring transmission pairs from clusters of cases could also impact serial interval or generation time estimates. Griffin et al and Du et al highlight further variation associated with serial interval and generation time estimation, such as recall bias, resources for contact tracing and stage of epidemic, that could not be addressed with this current study.

We used published estimates rather than individual symptom onset data to inform our measures of presymptomatic transmission. Therefore, we could not investigate potential correlation between generation time/serial interval and incubation period. Using contact tracing data from Singapore and Tianjin, Tindale et al reported an intermediate signal for covariance between incubation period and serial interval. However, these authors showed that the degree of positive correlation did not greatly impact estimates of presymptomatic transmission. Liu et al simulated the effect of full correlation and anti-correlation between serial interval and incubation period on presymptomatic transmission estimates. However, the direction and magnitude of effects varied depending on which published estimates the simulations were based on. This highlights the need for ongoing investigations into SARS-CoV-2 transmission biology.

Despite the challenges associated with a highly variable international dataset, this study gives a clear signal that substantial presymptomatic transmission is occurring. This is consistent with evidence of virological studies, case
CONCLUSION

Our study highlights substantial potential for presymptomatic transmission of COVID-19 in a range of different contexts. The proportion of presymptomatic transmission will vary by context, as this parameter is influenced by the contact rates between symptomatic infectious and susceptible people. These findings highlight the urgent need for extremely rapid and effective case detection, contact tracing and quarantine measures if the spread of SARS-CoV-2 is to be effectively controlled.

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Supplementary figures legends

Supplementary figure 1: A summary of source locations and date ranges covered for the 27 serial interval and generation time estimates from 24 papers that were included in simulations to infer pre-symptomatic transmission. This plot refers both to the estimates from the main text for which we could capture uncertainty (black colour) and other estimates for which we could simulate distributions but not capture uncertainty (grey colour). Line widths are scaled to reflect sample size. BN = Brunei Darussalam, BR = Brazil, CN AEH = China: All regions excluding Hubei, CN HK = China: Hong Kong, CN SY = China: Shiyian (Hubei), CN SZ = China: Shenzhen, CN: TJ = China Tianjin, CN: WH = China Wuhan, CN: ZH = China: Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam.

Supplementary figure 2: A summary of the parameters from the serial interval and generation time estimates for the 27 serial interval estimates from 24 papers that were included in simulations to infer pre-symptomatic transmission. This plot refers both to the estimates from the main text for which we could capture uncertainty (black colour) and other estimates for which we could simulate distributions but not capture uncertainty (grey colour). Points indicate means and bars indicate 95% confidence intervals. BN = Brunei Darussalam, BR = Brazil, CN AEH = China: All regions excluding Hubei, CN HK = China: Hong Kong, CN SY = China: Shiyian (Hubei), CN SZ = China: Shenzhen, CN: TJ = China Tianjin, CN: WH = China Wuhan, CN: ZH = China: Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam.

Supplementary figure 3: A boxplot summarising simulation results showing transmission time in days relative to infector symptom onset. Purple triangles represent the mean of the simulation samples. Unlike for the simulation results presented in the main text, the uncertainty associated with serial interval, generation time and incubation period estimates was not incorporated in these simulations. BN = Brunei Darussalam, BR = Brazil, CN AEH = China: All regions excluding Hubei, CN HK = China: Hong Kong, CN SY = China: Shiyian (Hubei), CN SZ = China: Shenzhen, CN: TJ = China Tianjin, CN: WH = China Wuhan, CN:
ZH = China, ZH = Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam.
**Supplementary tables**

**Supplementary table 1**: Simulation results showing transmission time relative to symptom onset based on 27 estimates of serial interval and generation time from 24 papers. If it was possible to incorporate uncertainty into the simulation, we report it with 95% confidence intervals. We also include any estimates and a summary other information relating to pre-symptomatic transmission if this was reported in the papers. Mean, Standard deviation (SD) and Median refer to the transmission times relative to symptom onset estimated from our simulation. PST is the proportion of pre-symptomatic transmission from our simulation. PSTp is the proportion of pre-symptomatic transmission reported in the papers. BN = Brunei Darussalam, BR = Brazil, CN AEH = China: All regions excluding Hubei, CN HK = China: Hong Kong, CN SY = China: Shiyan (Hubei), CN SZ = China: Shenzhen, CN: TJ = China Tianjin, CN: WH = China Wuhan, CN: ZH = China: Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam. Dates are in day/month/year format. "N" refers to transmission pairs unless stated otherwise.

| Reference                  | Date range        | Mean | SD  | Median | PST  | N  | PSTp | Comment                                                                 |
|----------------------------|-------------------|------|-----|--------|------|----|------|-------------------------------------------------------------------------|
| Brunei - Zuhai             |                   |      |     |        |      |    |      |                                                                         |
| Wong et al. [24]           | 09/03/20 - 05/04/20 | -0.5 | 5.5 | -0.3   | 52.3 | 59 |      | 41/135 PCR positive cases were pre-symptomatic (30.4%). Mean SI stayed constant throughout 4 weeks of epidemic. |
| Brazil - All regions       |                   |      |     |        |      |    |      |                                                                         |
| Prete et al. [34]          | 25/02/20 - 19/03/20 | -2.9 | 4.5 | -2.6   | 73.9 | 65 |      |                                                                         |
| China - All excluding Hubei|                   |      |     |        |      |    |      |                                                                         |
| Reference      | Date range         | Mean       | SD         | Median    | PST       | N    | PSTp | Comment                                                                 |
|---------------|--------------------|------------|------------|-----------|-----------|------|------|--------------------------------------------------------------------------|
| Xu et al. [35] | 15/01/20 - 29/02/20| -0.7 (-1.1, -0.3) | 6.2 (5.9, 6.5) | -0.5 (-1, 0.1) | 53.5 (50.4, 56.6) | 1407 |      | Comment: serial interval about same as incubation period, suggesting possible transmission before symptoms. |
| Zhang et al. [50] | 24/12/19 - 17/02/20 | -0.8 | 4.1 | -0.6 | 57.2 | 35 |      | Early isolation = shorter SI (mean: 3.3 (2.7, 3.8) days. Delayed isolation = longer SI (mean: 6.8 (6.2, 7.3) days.) |
| Ali et al. [43] | 09/01/20 - 13/02/20 | -0.7 (-1.1, -0.3) | 6.2 (5.9, 6.5) | -0.5 (-1, 0) | 53.2 (50.1, 56.3) | 677 |      | Early isolation = shorter SI (mean: 3.3 (2.7, 3.8) days. Delayed isolation = longer SI (mean: 6.8 (6.2, 7.3) days.) |
| Du et al. [33]  | 21/01/20 - 08/02/20 | -1.8 (-2.1, -1.4) | 5.8 (5.5, 6) | -1.6 (-2, -1.1) | 61.2 (58.2, 64.3) | 468 |      | Early isolation = shorter SI (mean: 3.3 (2.7, 3.8) days. Delayed isolation = longer SI (mean: 6.8 (6.2, 7.3) days.) |
| Ren et al. [32] | 01/01/20 - 29/01/20 | -0.2 | 4.7 | 0.1 | 48.5 | 80 | 40% | China - Hong Kong
| Kwok et al. [46a] | 22/01/20 - 13/02/20 | -1 (-1.4, -0.7) | 5.3 (4.3, 6.3) | -1.3 (-1.6, -1.1) | 64.5 (61.5, 67.4) | 26 |      | Comment: Pre-symptomatic transmission occurred |
| Kwok et al. [46b] | 22/01/20 - 13/02/20 | 0.5 (0.2, 0.8) | 5 (4.4, 5.7) | 0.4 (0.1, 0.7) | 46.3 (43.2, 49.4) | 17 |      | Comment: Pre-symptomatic transmission occurred |
| China - Shiyan (Hubei) | |

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| Reference | Date range       | Mean     | SD        | Median     | PST | N   | PSTp | Comment                                                                 |
|-----------|------------------|----------|-----------|------------|-----|-----|------|--------------------------------------------------------------------------|
| Yang et al. [36] | 20/01/20 - 29/02/20 | -1.2 (-1.5, -0.8) | 5.7 (5.4, 6) | -1 (-1.4, -0.5) | 57.1 (54.1, 60.2) | 131 |      | Comment: Median SI is shorter than median incubation period suggesting that a considerable proportion of transmissions occur before symptom onset |
| China - Shenzhen |               |          |           |            |     |     |      |                                                                          |
| Wang et al. [47] | 19/01/20 - 24/02/20 | 0.1 (-0.2, 0.5) | 6.2 (5.4, 6.9) | -0.5 (-0.9, -0.1) | 54.2 (51.1, 57.2) | 27  |      | Comment: Pre-symptomatic transmission is important                       |
| Bi et al. [44] | 14/01/20 - 12/02/20 | 0.5 (0.2, 0.8) | 5.3 (5, 5.6) | 0.1 (-0.2, 0.5) | 48.6 (45.5, 51.8) | 48  |      | Early pre-symptomatic transmission = shorter SI (mean: 3.6 days) Delayed isolation = longer SI (mean: 8.1 days) |
| China - Tianjin |               |          |           |            |     |     |      |                                                                          |
| Ganyani et al. [28a] | 14/01/20 - 27/02/20 | -1.8 (-2, -1.6) | 3.5 (3.3, 3.8) | -1.4 (-1.6, -1.1) | 69.1 (66.2, 71.9) | 135 cases | 62% (95%CI: 50-76%) | Mean transmission time of 3.68 days before symptom onset |
| Tindale et al. [27a] | 21/01/20 - 22/02/20 | -1.4 (-1.7, -1.1) | 4.2 (3.9, 4.5) | -1.1 (-1.4, -0.8) | 61.1 (58.1, 64.2) | 135 cases | 81% | Mean transmission time of 3.68 days before symptom onset |
| Wang & Teunis [51] | 21/01/20 - 12/02/20 | -1.1 | 4.2 | -0.9 | 60.2 | 112 cases |      | Comment: Transmission in absence of symptoms can occur                   |
| China - Wuhan |               |          |           |            |     |     |      |                                                                          |
| Wang et al. [53] | 05/01/20 - 12/02/20 | -0.6 | 4.4 | -0.6 | 56.7 | 15 |      | Comment: Transmission in absence of symptoms can occur                   |
| Reference       | Date range         | Mean  | SD    | Median | PST   | N   | PSTp   | Comment                                                      |
|-----------------|--------------------|-------|-------|--------|-------|-----|--------|---------------------------------------------------------------|
| Li et al. [52]  | 20/12/19 - 16/01/20| 1.6   | 4.6   | 1.7    | 34.1  | 6   |        |                                                               |
| China - Zhuhai  | Wu et al. [63]     | 0.5   | 0.9   | 0      | 34.1  | 48  |        | most secondary cases were likely infected around the time of symptom onset of the primary cases |
| Iran - West     | Najafi et al. [54] | -0.2  | 5     | -0.4   | 53.4  | 21  |        | Comment: SI is shorter than incubation period for COVID-19 - possible pre-symptomatic transmission |
| Iran - Qom      | Aghaali et al. [64]| -1.2  | 4.7   | -1.4   | 63.5  | 37  |        |                                                               |
| Italy - Vo (Village in northern Italy) | Lavezzo et al. [18] | 1.4   | 6.4   | 0.5    | 45.9  | 41  |        | 13.7% of PCR positive cases pre-symptomatic in first survey and 3.4% in second survey (after lockdown of Vo) |
| Republic of Korea - Busan |                   |       |       |        |       |     |        |                                                               |
| Reference          | Date range          | Mean   | SD      | Median     | PST     | N      | PSTp | Comment                                                                                                                                 |
|--------------------|---------------------|--------|---------|------------|---------|--------|------|---------------------------------------------------------------------------------------------------------------------------------------|
| Son et al. [48]    | 16/01/20 - 24/03/20 | -0.3 (-0.6, 0.1) | 5.1 (4.7, 5.4) | -0.6 (-0.9, -0.2) | 55.4 (52.3, 58.4) | 28     |      |                                                                                                                                 |
| Republic of Korea - All regions |                      |        |         |            |         |        |      |                                                                                                                                         |
| Bae et al. [22]    | 24/02/20 - 13/03/20 | -0.7   | 4.9     | -0.9       | 58.8    | 108    |      | 30 (out of 108) pre-symptomatic PCR positive cases. Earliest PCR positive was 13 days before symptom onset. Four pre-symptomatic cases transmitted to others.        |
| Chun et al. [38]   | 23/01/2020-31/03/20 | -0.4 (-1, 0.1) | 8.8 (6.6, 10.8) | -2 (-2.4, -1.6) | 64.2 (61.2, 67.2) | 69     |      | Peak transmission 0.72 days before symptom onset, Median transmission time 1.31 days after symptom onset. Median incubation period of 2.87 days (95% CI, 2.33–3.50 days) used for estimation. |
| Singapore          |                      |        |         |            |         |        |      |                                                                                                                                         |
| Tindale et al. [27b] | 23/01/20 - 26/02/20 | -1.4 (-1.7, -1.1) | 4.8 (4.5, 5) | -1.1 (-1.5, -0.8) | 60 (57, 63.1) | 91 cases | 74%  | Mean transmission time of 1.99 days before symptom onset                                                                                   |
| Ganyani et al. [28b] | 21/01/20 - 26/02/20 | -0.6 (-0.8, -0.4) | 3.7 (3.5, 4) | -0.2 (-0.4, 0) | 52.5 (49.4, 55.6) | 91 cases | 48% (32, 67%) |                                                                                                                                         |
| Vietnam            |                      |        |         |            |         |        |      |                                                                                                                                         |
| Reference          | Date range               | Mean        | SD          | Median      | PST         | N   | PSTp       | Comment                                                                 |
|--------------------|--------------------------|-------------|-------------|-------------|-------------|-----|------------|--------------------------------------------------------------------------|
| Pham et al. [49]   | 23/01/20 - 01/05/20      | -2.6 (-3, -2.1) | 7.2 (6.9, 7.6) | -2.4 (-3, -1.9) | 63.4 (60.5, 66.4) | 33  |            |                            |
| Not included (mixture of countries) |                        |             |             |             |             |     |            |                            |
| He et al.[30]      |                          |             |             |             |             |     |            | 44% (30, 57%) Inferred infectiousness peaked at symptom onset, started from 12.3 days before symptom onset, only 1% of transmission would occur before 5 days |
| Ferretti et al [29]|                          |             |             |             |             |     |            | 37% (27.5%, 45%) Total contribution to R0 from pre-symptomatic is 0.9 (0.2 - 1.1), almost enough to sustain an epidemic on its own |
| Nishiura et al.[31]|                          |             |             |             |             |     |            | The median serial interval is shorter than the median incubation period, suggesting a substantial proportion of pre-symptomatic transmission |
**Supplementary table 2:** Comparison between the estimates of Gaynani et al [28], Tindale et al. [27] and this paper relating to the same data from Singapore and Tianjin.

|        | Ganyani et al. [28] | Tindale et al. [27] |
|--------|---------------------|---------------------|
|        | Original paper      | This paper          | Original paper | This paper |
| Singapore | 48% (95% CI: 32, 67) | 52.52% (49.43, 55.6) | 74%           | 60% (57, 63.1) |
| Tianjin   | 62% (50-76%)        | 69.06% (66.2, 71.94) | 81%           | 61.6% (58.1, 64.2) |
**Supplementary table 3:** A summary of virological reports referred to in the discussion.

| Study                          | Date and location               | Description                                                                                                                                                                                                 |
|-------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kimball et al. [26] and Arons et al. [21] | Washington, USA Feb and March 2020 | 76 nursing home residents PCR tested after detection in index case, 23 positive, 10 pre-symptomatic (and 3 asymptomatic). Of 10 pre-symptomatic positives, 2 had cycle threshold (CT) values <18, 4 had CT values 21-29 and 3 had CT values >33. The mean interval from testing to symptom onset was 3 days.  
Arons et al. [21] reported 24 pre-symptomatic residents with a median CT value of 23.1. Viable virus was recovered from 17 pre-symptomatic residents. The median time to symptom onset reported was 4 days (IQR 3-5 days). Live virus was cultured from samples taken from two patients six days in advance of symptom onset. |
| Hu et al. [20]                | Nanjing, China, Jan and Feb 2020 | 24 people without symptoms tested positive for SARS-CoV-2 using PCR. Of these seven younger people remained asymptomatic but the others went on to develop symptoms.                                           |
| Kam et al. [59]               | Singapore February 2020         | A six month old infant tested positive by PCR on a nasopharyngeal swab one day before he showed a fever.                                                                                                     |
| Hoehl et al. [25]             | Germany, February 2020          | 114 passengers without symptoms on a flight from Wuhan were tested by RT-PCR throat swab. 2 were confirmed positive, 1 asymptomatic and 1 who developed mild symptoms 1 day after                                                                 |
| Pan et al. [23]               | Beijing, China (published February 2020) | Two individuals who were under active surveillance tested positive with PCR one day before symptom onset.                                                                                             |
| Wong et al [24]              | Brunei Darussalam March and April 2020 | 41/135 PCR positive cases were pre-symptomatic (30.4%).                                                                                                                                                  |
| Bae et al [22]               | Republic of Korea Feb and March 2020 | 30 (out of 108) pre-symptomatic PCR positive cases. Earliest PCR positive was 13 days before symptom onset. 4 pre-symptomatic cases transmitted to others.                                                  |
**Supplementary table 4:** A summary of the case reports of pre-symptomatic transmission referred to in the discussion.

| Study          | Date and location   | Description                                                                 | Infector symptom onset minus infectee exposure window |
|----------------|---------------------|-----------------------------------------------------------------------------|-------------------------------------------------------|
| Huang et al.   | Nanjing China 21st-28th Jan 2020 | Index case infected 6 others before symptoms. Two secondary cases potentially infected three others before symptom onset. | 4-7 days 5 or 7 days 5 days 5 days 4 days 3 days |
| Wei et al. [11]| Singapore, Jan 19-March 12th | 10 cases (6.4%) within 7 clusters (n=157 cases) attributed to pre-symptomatic transmission. | 3 or 5 days (n=3) 1 day (n=1) 1-7 days (n=1) 1-5 days (n=1) 1-2 days (n=1) 2 days (n=2) 1 day(n=1) |
| Tong et al. [12]| Zoushan China 4th January – 1st February 2020 | 2 cases attributed to pre-symptomatic transmission. | 2-3 days 2-3 days |
| Qian et al. [13]| Zhejiang, China 19th Jan – 11th Feb | At least 2 cases attributed to pre-symptomatic transmission. | 1-4 days |
| Liu et al. [60]| Taiwan, 20-25th Jan | Index and secondary case developed symptoms on the same day indicating pre-symptomatic transmission. | 1-5 days |
| Yu et al. [15]| Shanghai China, 7-25th Jan | Index and secondary case developed symptoms on the same day indicating pre-symptomatic transmission. | 1-5 days |
| Rothe et al [16]| Germany, 19th – 29th Jan | 4 cases attributed to pre-symptomatic transmission. | 1-2 days 1 day 3-4 days 1-4 days |
| Zhang et al. [17]| Ningxia, China 22nd Jan – 1st Feb | 2 cases attributed to pre-symptomatic transmission. | 10 days (n=2) |
| Study         | Date and location   | Description                                                                 | Infector symptom onset minus infectee exposure window |
|--------------|---------------------|-----------------------------------------------------------------------------|--------------------------------------------------------|
| Lavezzi et al. [18] | Vo, northern Italy | Evidence of pre-symptomatic transmission to 1-4 people.                      | 3-4 days                                               |
| Liao et al. [19]   | Chongqing, China    | Infector believed to have developed symptoms at least 39 days after exposure. Two infectees who lived with infector developed symptoms 29 days before infector. | 29-38 days                                            |