

# BMJ Open 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.<sup>1</sup> In China,

## Strengths and limitations of this study

- We generated estimates of presymptomatic transmission for different countries.
- As this is a secondary analysis of published estimates, we did not analyse data at individual transmission-pair level.
- As control measures such as rapid isolation of symptomatic people may increase the proportion of presymptomatic transmission, we generated estimates based on single locations and did not pool them.

14% and 5% of cases were classified as severe and critical, respectively.<sup>2</sup> There are also major indirect impacts of COVID-19 and its control measures on other aspects of health-care<sup>3-5</sup> and on the economy.<sup>6 7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

Reports of presymptomatic transmission<sup>10–19</sup> emerged as detailed contact tracing was conducted during early outbreaks of COVID-19. Further, both viral genome<sup>18 20–26</sup> and live virus<sup>21</sup> 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,<sup>27–32</sup> and even cases of symptoms manifesting in the infectee prior to the infector.<sup>24 30 33–37</sup>

Several studies have quantified the proportion<sup>27–30 38</sup> and timing<sup>27 30 38</sup> 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 time<sup>39</sup> and rapid systematic review and meta-analysis of incubation period<sup>40</sup> with a secondary analysis of published data to estimate the proportion and timing of presymptomatic transmission of COVID-19.

## METHODS

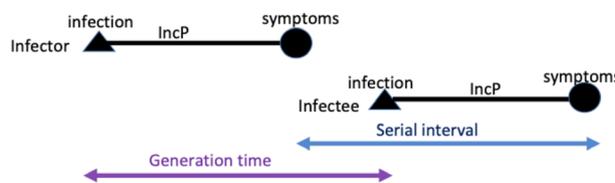
### Principles of methodology

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,<sup>41 42</sup> although serial interval will have more variation.<sup>28</sup> 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.

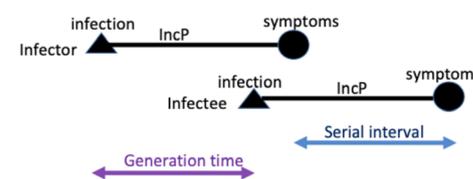
### Incubation period data

We used the incubation period estimate from our separately published rapid systematic review and meta-analysis<sup>40</sup>. 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)

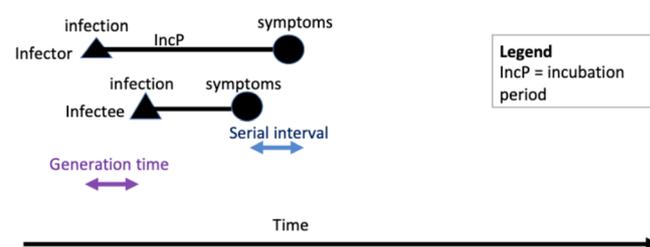
#### A: Symptomatic transmission: Incubation period $\leq$ [Serial interval or Generation time]



#### B: Pre-symptomatic transmission: Incubation period $>$ [Serial interval or Generation time] and Serial interval $>$ 0



#### C: Pre-symptomatic transmission: Incubation period $>$ [Serial interval or Generation time] and Serial interval $<$ 0



**Figure 1** Schematic illustration of incubation period, generation time and serial interval at transmission pair level. Scenario A: if transmission occurs after symptom onset, mean generation time/serial interval is longer than mean incubation period. Scenario B: if presymptomatic transmission occurs, mean generation time/serial interval is shorter than mean incubation period. Scenario C: a negative serial interval is possible if symptoms manifest in the infectee before the infector. Relevant to all scenarios, if incubation period is assumed to be independent and identically distributed, mean serial interval will approximate mean generation time.

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 period<sup>40</sup> 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.<sup>39</sup> In contrast to incubation period, interventions such as case isolation are reported to affect serial interval.<sup>39 43 44</sup> 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.

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

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 (infecter).
Generation time or generation interval	The duration in days between time of infection of a secondary case (infectee) and that of its primary case (infecter).
Transmission pair	An infected person (infecter) 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 infecter to an infectee in days relative to the onset of symptoms in the infecter.
Proportion of presymptomatic transmission	The proportion of all transmission events that occur before the onset of symptoms in the infecter.

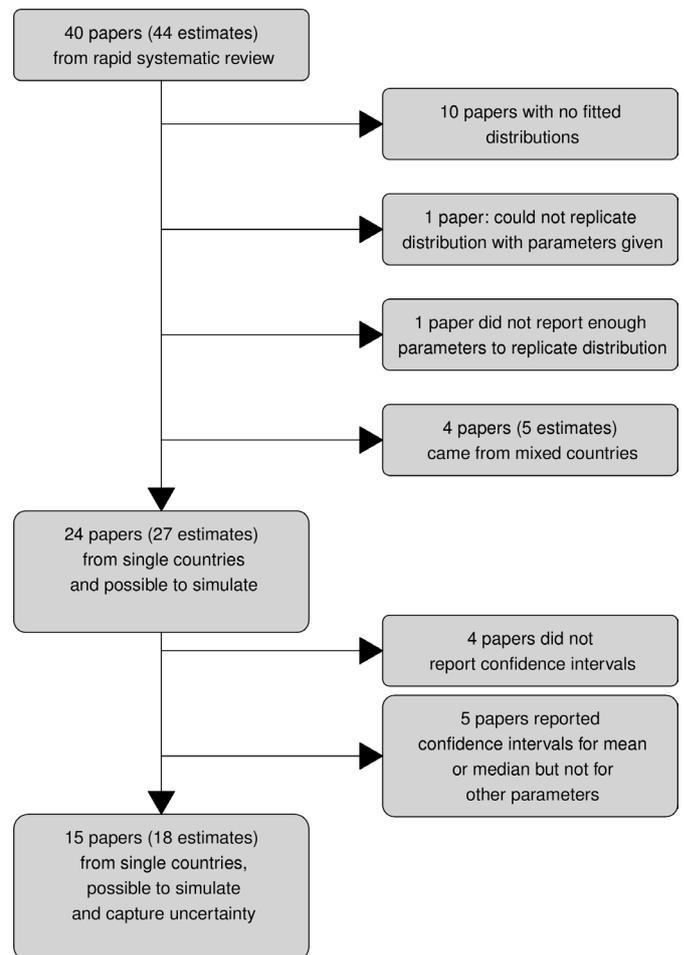
From the 40 published papers included in the rapid review,<sup>39</sup> we selected serial interval and generation time estimates based on data from single countries, for which statistical distributions were fitted, and which we could replicate (n=27 estimates from 24 papers). From this subset, we identified 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,<sup>39</sup> 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.



**Figure 2** A summary of how serial interval and generation time estimates were selected for analyses.

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.<sup>40</sup> 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.



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.<sup>45</sup> The extracted data and code that we used to generate our simulation is available through GitHub ([https://github.com/miriamcasey/covid-19\\_presymptomatic\\_project](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.

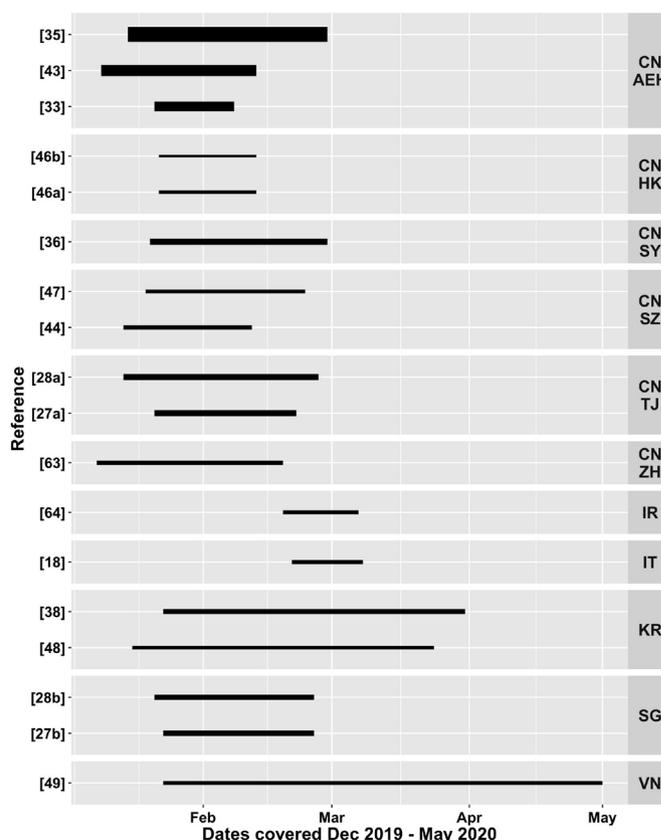
## RESULTS

### Description of serial interval/ generation time data

Building on the description of the serial interval and generation time estimates by Griffin *et al*,<sup>39</sup> 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<sup>46</sup> to 1407<sup>35</sup> 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 ( $n=1407$ ,<sup>35</sup> 677<sup>43</sup> and 468<sup>33</sup> transmission pairs), and were associated with the same group of authors, who confirmed some overlap between the datasets underlying each paper. Xu *et al*<sup>35</sup> and Ali *et al*<sup>43</sup> 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,<sup>46</sup> 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<sup>44</sup> had some overlap in date range but differed in sample size (48 transmission pairs,<sup>44</sup> 27 transmission pairs<sup>47</sup>). Ganyani *et al*<sup>28</sup> and Tindale *et al*<sup>27</sup> used the same datasets from Tianjin and Singapore. Son *et al*<sup>48</sup> reported a serial interval estimate based on data from Busan in the

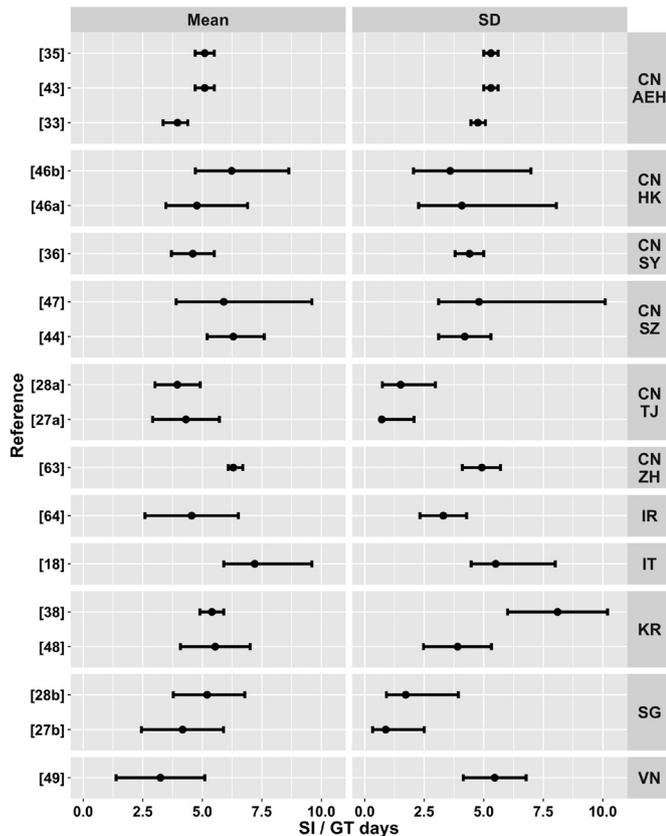


**Figure 3** A summary of country or region and date ranges for the 18 serial interval and generation time estimates from 15 papers that were included in simulations to infer presymptomatic transmission. Line thickness is scaled to reflect sample size (ie, Kwok *et al*<sup>46</sup> have the smallest and Xu *et al*<sup>35</sup> the largest sample size). CN AEH, China: all regions excluding Hubei; CN HK, China: Hong Kong; CN SY, China: Shiyen (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.

Republic of Korea, whereas Chun *et al*<sup>38</sup> used data from the whole country. Shiyen (Hubei province) and Zhuhai in China were associated with one estimate each, as were the remaining countries (figures 3 and 4).

Only Ganyani *et al*<sup>28</sup> 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<sup>18</sup> <sup>27</sup> <sup>28</sup> <sup>35</sup> <sup>38</sup> <sup>47</sup> 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*<sup>44</sup> 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*<sup>43</sup> quantified the contraction of serial interval over time, driven primarily by case isolation, and advocated for real-time estimation of serial intervals.

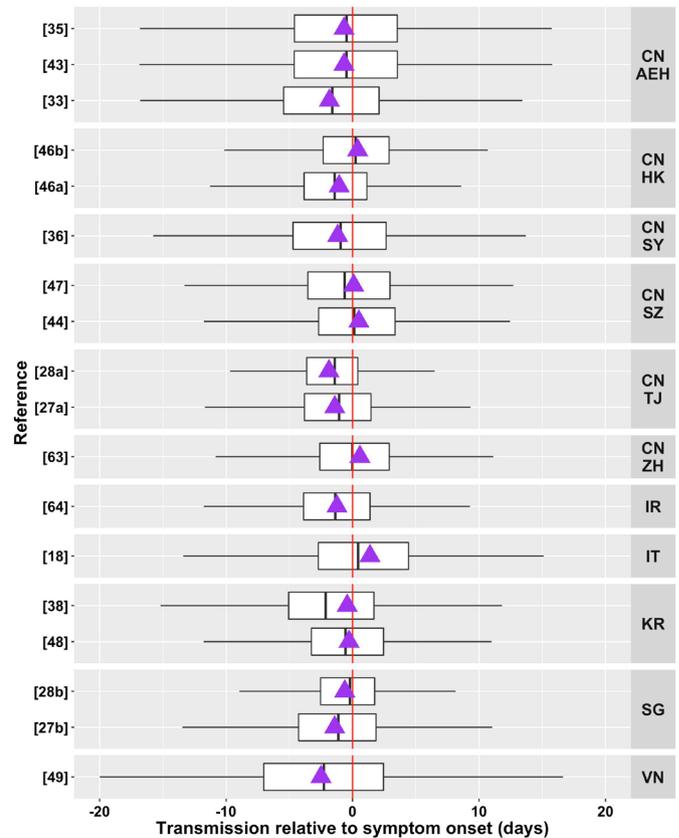


**Figure 4** A summary of the parameters from the serial interval and generation time estimates that were used in the simulation, by country or region and reference. Points indicate means and bars indicate 95% CIs. CN AEH, China: all regions excluding Hubei; CN HK, China: Hong Kong; CN SY, China: Shyan (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.

### 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<sup>49</sup> to  $1.4$  (95% CI  $1.0$  to  $1.8$ ) days after symptom onset in Italy.<sup>18</sup> The proportion of presymptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI 42.9% to 49.0%) in Italy<sup>18</sup> to 69.1% (95% CI 66.2 to 71.9) in Tianjin.<sup>28</sup> 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



**Figure 5** A boxplot summarising simulation results showing transmission time in days relative to infector symptom onset. Purple triangles represent the mean of the simulation samples. CN AEH, China: all regions excluding Hubei; CN HK, China: Hong Kong; CN SY, China: Shyan (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.

generation time estimates from 24 papers, including the nine studies for which we could not incorporate uncertainty. The extra nine studies came from Brazil,<sup>34</sup> Brunei Darussalam,<sup>24</sup> China (all regions excluding Hubei),<sup>32 50</sup> Tianjin,<sup>51</sup> Wuhan,<sup>52 53</sup> Iran<sup>54</sup> and the Republic of Korea.<sup>22</sup> 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*,<sup>28</sup> Tindale *et al*<sup>27</sup> 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

**Table 2** A summary of simulation results

Reference	Mean	SD	Median	PST
<b>China—all excluding Hubei</b>				
Xu <i>et al</i> <sup>35</sup>	-0.7 (-1.1 to -0.3)	6.2 (5.9 to 6.5)	-0.5 (-1 to -0.1)	53.5 (50.4 to 56.6)
Ali <i>et al</i> <sup>43</sup>	-0.7 (-1.1 to -0.3)	6.2 (5.9 to 6.5)	-0.5 (-1 to 0)	53.2 (50.1 to 56.3)
Du <i>et al</i> <sup>33</sup>	-1.8 (-2.1 to -1.4)	5.8 (5.5 to 6)	-1.6 (-2 to -1.1)	61.2 (58.2 to 64.3)
<b>China—Hong Kong</b>				
Kwok <i>et al</i> <sup>46</sup>	-1 (-1.4 to -0.7)	5.3 (4.3 to 6.3)	-1.3 (-1.6 to -1.1)	64.5 (61.5 to 67.4)
Kwok <i>et al</i> <sup>46</sup>	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)
<b>China—Shiyan (Hubei)</b>				
Yang <i>et al</i> <sup>36</sup>	-1.2 (-1.5 to -0.8)	5.7 (5.4 to 6)	-1 (-1.4 to -0.5)	57.1 (54.1 to 60.2)
<b>China—Shenzhen</b>				
Wang <i>et al</i> <sup>47</sup>	0.1 (-0.2 to 0.5)	6.2 (5.4 to 6.9)	-0.5 (-0.9 to -0.1)	54.2 (51.1 to 57.2)
Bi <i>et al</i> <sup>44</sup>	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)
<b>China—Tianjin</b>				
Ganyani <i>et al</i> <sup>28</sup>	-1.8 (-2 to -1.6)	3.5 (3.3 to 3.8)	-1.4 (-1.6 to -1.1)	69.1 (66.2 to 71.9)
Tindale <i>et al</i> <sup>27</sup>	-1.4 (-1.7 to -1.1)	4.2 (3.9 to 4.5)	-1.1 (-1.4 to -0.8)	61.1 (58.1 to 64.2)
<b>China—Zhuhai</b>				
Wu <i>et al</i> <sup>63</sup>	0.5 (0.2 to 0.9)	5.8 (5.1 to 6.4)	0 (-0.3 to 0.3)	50.2 (47.1 to 53.3)
<b>Iran—Qom</b>				
Aghaali <i>et al</i> <sup>64</sup>	-1.2 (-1.5 to -0.9)	4.7 (4.4 to 5)	-1.4 (-1.7 to -1.1)	63.5 (60.5 to 66.5)
<b>Italy—Vo (village in Northern Italy)</b>				
Lavezzo <i>et al</i> <sup>18</sup>	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)
<b>Republic of Korea—all</b>				
Chun <i>et al</i> <sup>38</sup>	-0.4 (-1 to 0.1)	8.8 (6.6 to 10.8)	-2 (-2.4 to -1.6)	64.2 (61.2 to 67.2)
<b>Republic of Korea—Busan</b>				
Son <i>et al</i> <sup>48</sup>	-0.3 (-0.6 to 0.1)	5.1 (4.7 to 5.4)	-0.6 (-0.9 to -0.2)	55.4 (52.3 to 58.4)
<b>Singapore</b>				
Ganyani <i>et al</i> <sup>28</sup>	-0.6 (-0.8 to -0.4)	3.7 (3.5 to 4)	-0.2 (-0.4 to 0)	52.5 (49.4 to 55.6)
Tindale <i>et al</i> <sup>27</sup>	-1.4 (-1.7 to -1.1)	4.8 (4.5 to 5)	-1.1 (-1.5 to -0.8)	60.0 (57.0 to 63.1)
<b>Vietnam</b>				
Pham <i>et al</i> <sup>49</sup>	-2.6 (-3.0 to -2.1)	7.2 (6.9 to 7.6)	-2.4 (-3 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: Shyan (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.

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 infector 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).<sup>43 44</sup> 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. Consistently with this study, virological studies that show that viral load in upper respiratory samples peaks around symptom onset and rapidly declines towards undetectable levels about 2 weeks after symptom onset.<sup>30 55–58</sup> Similarly,

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.<sup>44</sup> 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<sup>18 20 21 23–25 59 60</sup> and live virus<sup>21</sup> detection in upper respiratory samples prior to symptom onset. Bae *et al*<sup>22</sup> reported viral genome detection up to 13 days prior to symptom onset and Arons *et al*<sup>21</sup> 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*<sup>21</sup> 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<sup>10–19</sup> (online supplemental table 4) further corroborate evidence from this study that transmission can occur well in advance of symptom onset.

In the majority of studies included in our simulation, there was commentary on the possibility of presymptomatic transmission, given reported serial intervals that were similar to, or shorter than, estimates for the incubation period of COVID-19 (online supplemental table 1). Another quantitative study investigating presymptomatic transmission<sup>30</sup> used 77 transmission pairs 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*<sup>29</sup> 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*<sup>28</sup> and Tindale *et al*<sup>27</sup> 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*,<sup>28</sup> and the serial intervals of Tindale *et al*<sup>27</sup> also 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*<sup>38</sup> 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<sup>28</sup> in our analyses. 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,<sup>41 42</sup> although serial interval will have more variation.<sup>28</sup> 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*<sup>46</sup> 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*<sup>41 61</sup>) for inferring transmission pairs from clusters of cases could also impact serial interval or generation time estimates. Griffin *et al*<sup>39</sup> and Du *et al*<sup>33</sup> 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*<sup>27</sup> reported an intermediate signal for covariation 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*<sup>62</sup> 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



reports and other quantitative studies. This means that extremely rapid and effective contact tracing, as well as isolation of contacts of cases before potential symptoms manifest, may be required to control disease spread.

## 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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**Contributors** MC-B conceptualised the study, extracted parameter definitions from the literature, performed the analyses and drafted the manuscript. JG led the rapid review upon which the generation time and serial interval simulations are based. CM led the meta-analysis upon which the incubation period simulations are based upon. AC, KH, KOB and KW performed literature searches upon which the incubation period, generation time, serial interval and presymptomatic transmission information reported here are based upon. SM conceptualised, initiated and managed the overall project. MC-B, JG, CM, AByrne, JM, DME, AC, KH, ABarber, FB, EAL, KOB, PW, KW and SJM supplemented the literature review, discussed the study design, reviewed and edited the manuscript.

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