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Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data

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Abstract

Objective: To estimate the proportion of pre-symptomatic transmission of SARS-CoV-2 infection that can occur and 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 systematic review of serial interval and generation time, which are published separately.

Participants: Studies were selected for analysis if they had transparent methods and data sources and they provided enough information to simulate full distributions of serial interval or generation time. Twenty-three estimates of serial interval and five of generation time from 17 publications were included.

Methods: Simulations were generated of incubation period and of serial interval or generation time. From these, transmission times relative to symptom onset were calculated and the proportion of pre-symptomatic transmission was estimated.

Outcome measures: Transmission time of SARS-CoV-2 relative to symptom onset and proportion of pre-symptomatic transmission.

Results: Transmission time ranged from a mean of 2.91 (95% CI: 3.18-2.64) days before symptom onset to 1.20 (0.86-1.55) days after symptom onset. Unweighted pooling of estimates of transmission time based on serial interval resulted in a mean of 0.60 days before symptom onset (3.01 days before to 1.81 days after). Proportion of pre-symptomatic transmission ranged from 42.8% (39.8%-45.9%) to 80.6% (78.1%-83.0%). The proportion of pre-symptomatic transmission from pooled estimates was 56.4% (34.9%-78.0%).

Conclusions: Whilst contact rates between symptomatic infectious and susceptible people are likely to influence the proportion of pre-symptomatic transmission, there is substantial potential for pre-symptomatic transmission of SARS-CoV-2 in a range of different contexts. Our work suggests that transmission is most likely in the day before symptom onset whereas estimates suggesting most pre-symptomatic transmission highlighted mean transmission times almost three days before symptom onset. This highlights the need for rapid case detection, contact tracing and quarantine.

Strengths and weaknesses of this study

- We estimate the extent and variation of pre-symptomatic transmission of SARS-CoV-2 infection across a range of contexts. This provides important information for development and targeting of control policies and for the parameterisation of transmission models.
- This is a secondary analysis using simulations based on published data, some of which is in pre-print form and not yet peer-reviewed. There is overlap in the contact tracing data that informed some of our source publications. We partially address this by summarising data at source location level as well as at study level.
- Populations where symptomatic people are rapidly isolated are likely have relatively more pre-symptomatic transmission. This should be borne in mind whilst interpreting our results, but does not affect our finding that there is substantial potential for pre-symptomatic transmission of SARS-CoV-2 infection.
- A strength of our approach is that it builds an understanding of pre-symptomatic transmission from a range of estimates in the literature, facilitates discussion for the drivers of variation between them, and highlights the consistent message that consideration of pre-symptomatic transmission is critical for COVID-19 control policy.

Introduction

There is currently a pandemic of coronavirus disease **(**COVID-19), a recently emerged and rapidly spreading infectious disease that is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are large direct impacts of COVID-19 amongst known cases. As of 2nd of June 2020, the World Health Organization has reported 6, 194, 533 confirmed cases and 376, 320 deaths due to COVID-19 [1]. In China, 14% and 5% of cases were classified as severe and critical, respectively [2], and a report from Italy showed that 18% of cases required intensive care [3]. There are also major indirect impacts of COVID-19 and its control measures on other aspects of health care [4–6] and on the economy [7,8].

As there is currently no COVID-19 vaccine ready for widespread use, primary control measures entail reducing transmission from infectious individuals. These include case isolation, contact tracing and quarantine, physical distancing and hygiene measures [9]. Infectious people are predominantly identified by reported symptoms of COVID-19.

In absence of active surveillance, infectious people without symptoms may not be quarantined, and therefore may have more contacts with susceptible people resulting in increased COVID-19 transmission. Therefore, quantifying the transmission potential of COVID-19 before or in the absence of symptoms will inform disease control measures and predictions of epidemic progression.

Characteristics of pre-symptomatic and asymptomatic transmission are potentially different, and separate approaches may be required to understand them. We aimed to capitalise upon the considerable information about pre-symptomatic transmission that can be inferred from contact tracing studies. Therefore, we focus here on transmission from people before they develop symptoms rather than that from people who never develop symptoms. This addresses the urgent need for more data on extent of pre-symptomatic transmission which has been highlighted by those developing models to inform policies [10].

The pre-symptomatic transmission potential of COVID-19 has been highlighted by case reports [11–20]. The potential for pre-symptomatic transmission was also suggested by detection of viral genome in upper respiratory samples prior to symptoms [21–23].

Live virus has been isolated very soon after symptom onset [24]. These findings are supported by quantitative studies based on contact tracing, reporting serial intervals or generation times similar in duration or shorter than incubation periods in some situations [25–28], and even evidence of symptoms manifesting in the infectee prior to the infector in some cases [28–31]. Several studies have quantified the proportion [25,27–29,32] and timing [25,28,29,32] of pre-symptomatic transmission, using a variety of datasets and methodologies.

Here, using secondary analysis of data collated in meta-analysis [33] and a rapid systematic review [34] that are published separately, we apply a standardised methodology to estimate the proportion and timing of pre-symptomatic transmission of COVID-19 in a range of different contexts.

Methods

Principles of methodology

If 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 incubation period, the time between infection and symptom onset in the infector, transmission will have occurred after symptom onset (Scenario A in Figure 1). If generation time is shorter than incubation period, pre-symptomatic transmission will have occurred (Scenarios B and C in Figure 1). If an infector and infectee incubation periods 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 [35,36], although serial interval will have more variation [26]. Table 1 contains definitions relevant to our analysis.

Meta-analysis and rapid systematic review

Data about incubation period, serial interval and generation time were sourced through on our separately published metanalysis of incubation period [33] and rapid systematic review of serial interval and generation time [34]. As described fully elsewhere [33,34], literature searches covered publication dates between the 1st of December 2019 and 8th of April 2020 for incubation period, extending to the 27th of April 2020 for generation time / serial interval. A dedicated team searched for publications on the electronic databases PubMed [37], Google

Scholar [38], MedRxiv [39] and BioRxiv [40] with the following keywords: "Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "serial interval" OR "latent period" OR "incubation period" OR "generation time" OR "infectiousness" OR "pre-symptomatic" OR "asymptomatic"). The dynamic curated PubMed database "LitCovid" [41,42] was also monitored. In addition, publicly available reports from the World Health Organization [1,9,43], European Centre for Disease Prevention and Control [44] and Centres for Disease Control and Prevention Morbidity and Mortality Weekly Reports [45] were monitored, as well as curated summaries on relevant topics from the American Association for the Advancement of Science [46] and the Nature Journal [47]. Both our meta-analysis [33] and rapid systematic review [34] completed checklists to show fulfilment of Preferred Reporting Items for Systematic reviews and Meta-Analyses - extension for Scoping Reviews (PRISMA-ScR) [48].

Based on the estimates reported by our meta-analysis [33] and rapid systematic review [34], we simulated data for incubation period, serial interval and generation time. We subtracted incubation period from serial interval or generation time to infer transmission time relative to onset of symptoms and to estimate the proportion of pre-symptomatic transmission.

Data extraction

All analyses were conducted in the R statistical environment [49]. For each publication included in our analyses, parameters describing the distributions of generation time or serial interval, and the location and dates of collection of the contact tracing data from which they were generated were collated.

If not reported directly, gamma shape and rate parameters were calculated from mean and standard deviation, either directly or using the "epitrix" [50] package as follows.

$$Gamma\ shape = \frac{Mean^2}{SD^2}$$

$$Gamma\ rate = \frac{Mean}{SD^2}$$

If lognormal distribution parameters (Meanlog and SDlog) were not directly reported, they were estimated from the reported mean and standard deviation (SD) as follows:

$$SDlog = \sqrt{\ln\left(\frac{Variance}{Mean^2}\right) + 1}$$

$$Meanlog = \ln(Mean) - \frac{logSD^2}{2}$$

Weibull parameters were estimated from the reported mean and standard deviation using the " "mixdist" [51] R package.

The incubation period that we used from the meta-analysis [33] had a lognormal distribution (Mean = 5.8 (95% CI (5.01, 6.69 days). It, Median = 5.1 (4.5, 5.8) days, , SD = 3 (,2.68-3.34), Meanlog = 1.63, (1.51, 1.75) and SDlog = 0.5 (0.45, 0.55) respectively.).

As serial interval has more variation than generation time [26], we considered them separately for plotting and summary purposes. For the two studies [26,27] that estimated generation time, we also generated serial interval simulations to allow a more direct comparison with the other estimates based on serial interval. One of these, [26], related serial interval to generation time with the following approach: Serial interval of an infectee can be expressed as generation time of the infectee plus the difference between the incubation periods of the infectee and the infector (Figure 1). That is, the incubation period used for the generation time estimation was simulated twice to generate two samples ("inc 1" and "inc2"). The extra variation in serial interval compared to generation time was then simulated by:

$$serial\ interval = generation\ time + inc1 - inc2$$

We repeated this estimation to simulate the serial interval for study [26] and cross-checked the simulation against the summary statistics were reported in that publication. We then estimated a serial interval from the generation time of study [27], using the same methodology and the same incubation period as was used to infer generation time in study [27].

One further study [52] did not directly supply enough information to simulate a distribution, but supplied their code and data from which they estimated the serial interval. For this study,

we fitted distributions to their data by maximum likelihood estimation with the "fitdistrplus" package [53] and chose one based on AIC values and visual cross-checking by plotting.

Simulation A

Simulation A was conducted to take into account the uncertainty around the reported parameter estimates for incubation period, generation time and serial interval. Where we could extract enough information from the publications, we sampled from distributions capturing the 95% confidence intervals around the mean and standard deviation for each reported distribution (n=1000). We converted these samples to the relevant parameters for the distribution (e.g. shape and rate for a gamma distribution) and 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% confidence intervals from bootstrapping were calculated.

As there are known drivers of variation of generation time and serial interval [34], and therefore of transmission time relative to symptom onset estimated based upon them, estimates were plotted and summarised individually to show this variation. Estimates were also grouped, plotted and summarised at the level of source location for the contact tracing data that they were inferred from. Simple unweighted pooled estimates of transmission time relative to symptom onset based on serial interval and generation time were presented for interpretation in the context of the variation between the individual results.

Simulation B

Simulation B incorporated data from every study that reported enough information to simulate a full distribution for serial interval or generation time but did not take uncertainty around the parameter estimates into account (as this was not reported in all of the studies). We simulated data (n = 100,000 samples) for incubation period and generation time or serial interval from each study. The distributions were plotted, summarised and cross-checked against the summary statistics and plots reported in the papers. The incubation period sample was subtracted from the generation time or serial interval sample to give a resultant distribution indicating

transmission time relative to onset of symptoms. This was plotted and summarised and the proportion of samples of transmission times relative to symptom onset that were negative (indicating transmission before symptoms was reported) was calculated. This simulation was repeated 20,000 times to explore the uncertainty from within the simulation. As with Simulation A, summaries at estimate, source location and pooled level were reported. Unlike Simulation A, confidence intervals were based only on the variation from within the simulation.

4. Results

Included studies

Of the 19 studies reporting serial interval or generation time included in our rapid systematic review [34], 17 were included in this study. We excluded the study [54] as it defined the start of the exposure window for the infectee as the time of symptom onset in the infector, excluding the possibility of transmission before symptom onset. We excluded one further study, [20], pending clarification from the authors, as we could not replicate the distribution described for serial interval. Table 2 lists the estimates considered for inclusion. Figure 2 describes the data available for 28 estimates for serial interval or generation time from the 17 publications that were included in this study.

Simulation A results

Studies that reported 95% confidence intervals for both the mean and standard deviation of the generation time or serial interval could be incorporated into Simulation A (Table 2). These included four generation time estimates and nine serial interval estimates from eight different studies. Four of these estimates came from mixed locations, two each came from Hong Kong, Mainland China excluding Hubei, Singapore and Tianjin, and one came from Shenzhen. The uncertainty captured by the simulation was slightly less than that reported in the source publications for serial interval and generation time. (Supplementary Table 1).

Table 3 summarises transmission time relative to symptom onset for each of the 13 estimates included in Simulation A. These ranged from a mean of 2.91 (95% CI: 3.18, 2.64) days before symptom onset to 1.20 (95% CI: 0.86, 1.55) days after symptom onset. Simple unweighted

pooling of estimates of transmission time relative to symptom onset based on serial interval estimates resulted in a mean of 0.60 days before symptom onset (95% CI: 3.01 days before, 1.81 days after). Pooling based on generation time estimates gave a mean of 1.83 (95% CI: 3.48, 0.17) days before symptom onset.

Proportion of pre-symptomatic transmission calculated from the 13 individual estimates ranged from 42.8% (95% CI:39.8%, 45.9%) to 80.6% (78.1%, 83.0%) (Table 3).

From unweighted pooling of serial interval and generation time estimates respectively, the proportion of pre-symptomatic transmission was estimated to be 56.4% (95% CI: 34.9%, 78.0%) and 68.3% (95% CI: 47.9%, 88.6%) (Table 3).

Simple unweighted pooling at source location level resulted in mean transmission time relative to symptoms ranging from 2.38 (95% CI: 3.45, 1.30) days before symptom onset in Tianjin to a mean of 0.51 (95% CI: 0.18, 0.84) days after symptom onset in Shenzhen. Proportion of pre-symptomatic transmission ranged from 48.6% (95% CI: 45.5%, 51.7%) in Shenzhen to 74.9% (95% CI: 63.5%, 86.3%) in Tianjin (Table 4).

Further details of standard deviation, 2.5th, 25th, 50th, 75th and 97.5th quantiles of the distributions described above, and their 95% confidence intervals are shown in Tables 3 and 4.

Simulation B results

A total of 28 estimates from 17 studies were included for Simulation B. Transmission time relative to symptom onset estimates were based on five estimates of generation times and 23 estimates of serial interval. Several studies generated more than one estimate. This was due to separate estimates for different locations [25,26], different models used to infer generation time [26], sub-setting of data depending on confidence in transmission pair identification and exposure windows [52,55], and estimation of both generation times and serial intervals from the same papers [26,27]. Of the two models used in [26] , one only allowed positive serial intervals to be inferred for missing data whereas a second model allowed negative serial intervals for missing data.

Table 5 shows the counts of estimates and studies that came from specific locations or mixed sources under nine different data source categories (Mixed sources, Tianjin, Singapore, Mainland China excluding Hubei, Hong Kong, northern Italy, pooled data from Hong Kong and Shenzhen, and Wuhan).

Results for Simulation B, incorporating a relatively broader range of studies, were similar to those for Simulation A. Figure 3 and Table 6 show the variation in transmission time relative to symptom onset amongst the 28 estimates ranging from a mean (median) of 2.92 (2.91) days before symptom onset to 1.72 (1.69) days after symptom onset. Proportion of pre-symptomatic transmission associated with the 28 different estimates ranged from 33.5% to 80.7%.

Table 6 also shows the summary statistics for a simple unweighted pooling of the estimates based on serial interval and the five estimates based on generation time. The mean (median) time of transmission for the pooled samples based on serial interval was 0.66 (0.62) days before symptoms and pre-symptomatic transmission was estimated to be 56.0%. The pooling of five generation time based estimates for transmission time relative to symptom onset gave a mean (median) estimate of 1.60 (1.31) days before symptom onset and 65.5% pre-symptomatic transmission.

Figure 4 and Table 7 show the variation in transmission relative to symptom onset amongst estimates based on the nine different source categories ranging from a mean (median) of 2.05 (1.90) days before symptom onset for Hong Kong to 1.72 (1.68) days after symptom onset for Wuhan. Proportion of pre-symptomatic transmission amongst the different data source categories ranged from 33.5% in Wuhan to 72.7% in Hong Kong.

For simulation B, the uncertainty captured by 20,000 repeat simulations was small (Table 6), as would be expected for large samples in simulations from defined distributions.

5. Discussion

Our results show that transmission time ranged from mean of 2.92 days before symptom onset to 1.72 days after symptom onset. Simple unweighted pooling of the 23 estimates based on serial intervals resulted in a mean time of transmission of 0.66 days before symptoms. From

this, it can be inferred that transmission of SARS-CoV-2 is most likely in the day before symptom onset. The estimates suggesting most pre-symptomatic transmission highlighted a mean transmission times almost 3 days before symptom onset. This is consistent with other estimates in the literature, ranging from 2.65 days before symptoms to 2.3 days after symptoms [25–29,32]. A study focussed on inferring infectiousness profile from 77 transmission pairs, reported that infectiousness started from 2.3 days before symptom onset and peaked at 0.7 days before symptom onset [28]. Our study, analysing all estimates from a variety of locations has produced a similar estimate (mean from pooled estimate of 0.67 days before symptom onset).

We estimated that the proportion of pre-symptomatic transmission ranged from 33.5% to 80.7% depending on the study analysed. Pooled serial interval based estimates suggested 56.0% pre-symptomatic transmission. Our source level analyses describe a trend in pre-symptomatic transmission ranging from the greatest proportion in Hong Kong (72.7%) to the smallest proportion in Wuhan (33.5%). The range in the proportion of pre-symptomatic transmission that we report is consistent with other studies [25,26,28,29,32] where reports of pre-symptomatic transmission range from 37% to >80%.

The wide variation in estimates of the proportion of pre-symptomatic transmission and transmission time relative to symptom onset is expected, as the observed transmission events depend on contact rates between infectious and susceptible people as well as the natural course of infectiousness. The variation in observed transmission events is manifested by variations in serial interval and generation time, and therefore in transmission relative to symptom onset. Griffin et al. [34] discuss drivers of this variation and the limitations in different approaches to estimating generation time and serial interval from transmission pairs. If people are quarantined once their symptoms become apparent, a greater proportion transmission will be pre-symptomatic. Whilst data relating to the early stages of the COVID-19 outbreak in Wuhan amount to only six pairs, we see a trend towards lower proportions of pre-symptomatic transmission in this context, as well as in the early stages of the outbreaks in Italy, possibly corresponding to relatively more transmission from symptomatic people in the early stages of disease incursion. Three other studies also highlight this contrast in the proportion of pre-symptomatic transmission in a different context. Zhao et al. [52] show that serial interval became shorter in Hong Kong and Shenzhen as time elapsed from initial cases, and suggest that this is due to increasing effectiveness of quarantining people with symptoms over time. Zhang [32] contrasts a mean transmission time of 2.3 days after symptoms in the early stages

of the Wuhan outbreak (with relatively fewer quarantine measures) to a mean transmission time of 2.4 days before symptom onset amongst imported cases outside Wuhan. A study in Shenzhen [64] highlighted the valuable information that can be inferred from knowledge of when transmission occurred and when the infector was isolated. Serial interval was much shorter when the infectors were isolated within two days of symptom onset compared to those isolated 3-5 days after symptom onset. However, lack of isolation beyond five days made little difference, suggesting that there may be relatively more potential for transmission before compared to after five days of symptom onset. A further analysis [56] highlights the difference in pre-symptomatic transmission in Shenzhen between a subset with accelerated case isolation (46% pre-symptomatic transmission) one without (23%).

Despite this understandable variation in estimates from different contexts, our work consistently suggests the potential for pre-symptomatic transmission. A person presenting with COVID-19 symptoms has potentially been infectious to others for several days. Therefore, in absence of severe social distancing measures, extremely effective and rapid contact tracing and quarantine will be required to control the spread of COVID-19.

This potential of the COVID-19 spread to be too fast to be controlled by conventional contact tracing been highlighted with Ferretti et al.'s model [27]. This model suggests that pre-symptomatic transmission alone can account for a basic reproductive number of 0.9 (47% of the overall reproductive basic number), almost enough to sustain an epidemic on its own. However, this estimate may be influenced by the low level of asymptomatic infectiousness (10% relative to a symptomatic case) assumed by that model. This uncertainty highlights the need for transmission from asymptomatically infected people to be more fully understood, and to be considered as having potentially distinct characteristics compared to the pre-symptomatic transmission that we report on in this paper.

We used a straightforward approach of simulating large numbers of samples from both the incubation period distribution from our meta-analysis [33] and the distributions of 28 serial interval or generation time estimates from our rapid systematic review [34], and subtracting the incubation period samples from the serial interval or generation time samples to give a resultant distribution of transmission time relative to symptom onset. This methodology is similar to that applied by Tindale et al. and Ganyani et al. [25,26] to data from Singapore and Tianjin. An alternative method, using maximum likelihood estimation, was used by He et al.

[28] and Zhang [32], and a Bayesian approach to estimate the probability of pre-symptomatic transmission was used by Ferretti et al. [27]. Ma et al. [29] estimated transmission time directly from manual interrogation of the data. Despite the variety of methodologies used to estimate transmission time, results of our analysis gave similar ranges to the six other studies that investigated pre-symptomatic transmission in different contexts [25–29,32].

Case reports [11–20] and virological studies [21–23] support the occurrence of pre-symptomatic transmission suggested by the quantitative approaches reported here and elsewhere [25–29,32]. Whilst samples testing positive by polymerase chain reaction (PCR) do not always fully correlate with infectiousness [24,57,58], relatively lower cycle threshold (CT) values suggest higher virus loads. Two studies [21,23] that reported pre-symptomatic PCR CT values included some relatively low values. A report of pre-symptomatic PCR positive samples in ten nursing home residents reported a mean time of 3 days from sampling to onset of symptoms. In addition, the isolation of live virus from upper respiratory samples very soon after patient presentation with symptoms has been reported [24].

Limitations and strengths

Table 4 shows the potential overlap in contact tracing data that the studies we analysed are based on. Therefore, a limitation of our study is that all our data sources cannot be considered completely independent. We partially address this by grouping estimates by the source location of the contact-tracing data upon which they were based. Another challenge was to fully capture the uncertainty in estimates with a simulation study. Where enough information was available from the source publications, we incorporated measures of uncertainty into Simulation A, and reported a comparison of the uncertainty suggested in our simulation to that in the original estimates. A strength of our approach is that it builds a picture of pre-symptomatic transmission from a range of estimates in the literature, facilitates discussion for the drivers of variation between them, and highlights the consistent message that consideration of pre-symptomatic transmission is critical for COVID-19 control policy. The important insights into COVID-19 transmission gleaned from the studies that contributed to our analyses, that used publicly available transmission pair data, highlights the immense value of allowing public access to anonymised transmission pair data.

Conclusion

Although contact rates between symptomatic infectious and susceptible people are likely to influence the proportion of pre-symptomatic transmission, our study highlights substantial potential for pre-symptomatic transmission of COVID-19 in a range of different contexts. Our work suggests that transmission of SARS-CoV-2 is most likely in the day before symptom onset, whereas estimates suggesting most pre-symptomatic transmission highlighted a mean transmission times almost 3 days before symptom onset. These findings highlight the urgent need for extremely rapid and effective case detection, contact tracing and quarantine measures if strict social distancing measures are to be eased.

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Competing interests

All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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

Author contributions

MC conceptualized the study, extracted parameter definitions from the literature, performed the analyses and drafted the manuscript. JG led the rapid systematic 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, KW and KOB performed systematic literature searches upon which the incubation period, generation time, serial interval and pre-symptomatic transmission information reported here are based upon. SM conceptualized, initiated and managed the overall project. All authors supplemented the

literature review and assessed the literature. All authors contributed to the manuscript and reviewed it.

Data sharing statement

The data and code used for the analyses described in this paper are available in the Github repository: https://github.com/miriamcasey/covid-19_presymptomatic_project

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Table 1: Definitions referred to in this review.

Asymptomatic	An infected person who never develops symptoms of the disease
Pre-symptomatic	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 [59].
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 [59].
Serial interval	The duration in days between symptom onset of a secondary case and that of its primary case.
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 who they transmit the pathogen to (infectee).
Latent period	The period from the point of infection to the beginning of the state of infectiousness [60]. This period corresponds to the "exposed" (E) compartment of a susceptible-exposed-infectious-recovered/removed (SEIR) 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 pre-symptomatic transmission	The proportion of all transmission events that occur before the onset of symptoms in the infector.

Table 2: A summary of all generation time and serial interval estimates included in our rapid systematic review [34] considered for inclusion in this study, those included in both Simulations A and B, those included in Simulation A only, and those excluded. SI = Serial interval. GT = Generation time. Ref = reference.

Included in Simulation A and B				
Ref	**Sub-set/Location**	**N**	**Distribution**	**SI or GT**
[64]	Shenzhen	48 pairs	Gamma	SI
[26a]	Singapore Model 1	91 cases (54 with known contacts)	Gamma	GT
[26c]	Singapore Model 2 (allowing inference of negative values for unknown SI's)	91 cases (54 with known contacts)	Gamma	GT
[26e]	Tianjin Model 1	135 cases (114 with known contacts)	Gamma	GT
[26g]	Tianjin Model 2	135 cases (114 with known contacts)	Gamma	GT
[60]	Mixed	43 pairs	Gamma	SI
[63a]	Hong Kong: 12 more certain pairs	12 case pairs	Gamma	SI
[63b]	Hong Kong: 21 (all available pairs)	21 transmission chains	Gamma	SI
[55b]	Mixed: 28 pairs (all available pairs)	28 pairs	Lognormal	SI
[55a]	Mixed: 18 more certain pairs	18 pairs	Weibull	SI
[30]	MCNH	468 pairs	Normal	SI
[31]	MCNH	339 pairs	Normal	SI
[29]	Mixed	689 pairs	Normal	SI
Included in Simulation B only: Confidence intervals for specific distribution parameters could not be incorporated into Simulation A using asymptotic approach				
	Sub-set/Location	**N**	**Distribution**	**SI or GT**
[3]	Northern Italy	90 pairs	Gamma	SI
[27a]	Mixed: GT from paper	40 pairs	Weibull	GT
[52]	Hong Kong and Shenzhen	48 pairs	Gamma	SI
Included in Simulation B only: The serial interval was simulated from the generation time and incubation period from the same paper. A distribution for serial interval was not defined. For simulation B we repeated this simulation to generate the serial interval.				
	Sub-set / Location	**N**	**Distribution**	**SI or GT**
[26b]	Singapore Model 1 SI	91 cases (54 with known contacts)	Not reported	SI
[26d]	Singapore Model 2 SI	91 cases (54 with known contacts)	Not reported	SI
[26f]	Tianjin Model 1 SI	135 cases (114 with known contacts)	Not reported	SI
[26h]	Tianjin Model 2 SI	135 cases (114 with known contacts)	Not reported	SI
[27a]	Mixed: SI estimated from GT	40 pairs	Not reported	SI
Included in Simulation B only: Confidence intervals for standard deviation not reported				
	Sub-set/ Location	**N**	**Distribution**	**SI or GT**
[19]	Northern Italy	166 cases, 120 pairs	Gamma	SI
[65]	Wuhan	6 pairs	Gamma	SI
[62]	MCNH	35 pairs	Gamma	SI
[25a]	Singapore	93 pairs	Normal	SI
[25b]	Tianjin	125 pairs	Normal	SI
[28]	Mixed	77 pairs	Shifted Gamma 7.6% negative SIs	SI
Included in Simulation B only: Confidence intervals for mean and standard deviation not reported				
	Sub-set / Location	**N**	**Distribution**	**SI or GT**
[61]	Tianjin	112 cases	Gamma	SI
Excluded				
	Sub-set / Location	**N**	**Distribution**	**SI or GT**
[54]	Taiwan	12 pairs	Gamma	SI
[20]	Chongqing, China	12 pairs	Gamma	SI

Table 3: Summary statistics for transmission time relative to symptom onset and proportion pre-symptomatic transmission estimated from Simulation A. The studies are ordered first by whether they are based on generation time (GT) or serial interval (SI), and then by median transmission time relative to symptoms. A negative number means days before symptom onset. MCNH = Mainland China excluding Hubei province. Mixed = SI or GT was calculated from pooled data from multiple countries. HKSZ = pooled data from Hong Kong and Shenzhen. SD = Standard deviation. Ref = reference number corresponding to Table 2 and main text. Confidence intervals in Simulation A are based on incorporating measures of uncertainty from the source publications into the simulation.

Ref	Location	SI or GT	Percentage pre-symptomatic transmission 95% CI)	Mean (95% CI)	SD (95% CI)	2.5th percentile (95% CI)	25th percentile (95% CI)	Median (95% CI)	75th percentile (95% CI)	97.5th percentile (95% CI)
[26a]	Singapore	GT	52.1 (49.0, 55.2)	-0.57 (-0.80, -0.34)	3.71 (3.44, 3.98)	-9.03 (-10.17, -7.89)	-2.48 (-2.80, -2.16)	-0.16 (-0.40, 0.08)	1.79 (1.55, 2.02)	5.55 (4.96, 6.15)
[26e]	Tianjin	GT	69.3 (66.4, 72.1)	-1.84 (-2.06, -1.63)	3.54 (3.27, 3.81)	-10.13 (-11.27, -8.99)	-3.60 (-3.91, -3.28)	-1.38 (-1.61, -1.15)	0.43 (0.22, 0.64)	3.76 (3.25, 4.27)
[26c]	Singapore	GT	71.1 (68.3, 73.9)	-1.98 (-2.25, -1.71)	4.35 (3.99, 4.71)	-10.87 (-12.00, -9.73)	-4.31 (-4.63, -3.98)	-1.91 (-2.17, -1.64)	0.41 (0.11, 0.71)	6.44 (5.28, 7.61)
[26g]	Tianjin	GT	80.6 (78.1, 83.0)	-2.91 (-3.18, -2.64)	4.39 (4.01, 4.77)	-11.70 (-12.82,-10.58)	-5.19 (-5.50, -4.87)	-2.91 (-3.15, -2.66)	-0.71 (-1.01, -0.40)	6.03 (4.70, 7.35)
[29]	Mixed	SI	42.8 (39.8, 45.9)	0.90 (0.52, 1.28)	6.11 (5.81, 6.40)	-11.59 (-12.81,-10.37)	-3.01 (-3.54, -2.48)	1.08 (0.62, 1.53)	5.03 (4.54, 5.52)	12.31 (11.38, 13.23)
[60]	Mixed	SI	43.4 (40.4, 46.5)	1.20 (0.86, 1.55)	5.54 (5.19, 5.88)	-8.86 (-9.96, -7.76)	-2.20 (-2.56, -1.83)	0.56 (0.00, 1.12)	4.24 (3.76, 4.72)	13.38 (11.92, 14.84)
[64]	Shenzhen	SI	48.6 (45.5, 51.7)	0.51 (0.18, 0.84)	5.28 (4.95, 5.62)	-9.31 (-10.46, -8.17)	-2.67 (-3.02, -2.32)	0.05 (-0.39, 0.50)	3.41 (2.95, 3.86)	11.97 (10.59, 13.35)
[31]	MCNH	SI	51.9 (48.8, 55.0)	-0.47 (-0.86, -0.08)	6.28 (5.97, 6.58)	-13.24 (-14.50,-11.98)	-4.51 (-5.04, -3.97)	-0.30 (-0.77, 0.18)	3.77 (3.26, 4.28)	11.29 (10.34, 12.24)
[55a]	Mixed	SI	56.2 (53.1, 59.3)	-0.78 (-1.06, -0.50)	4.46 (3.45, 5.46)	-10.10 (-11.22, -8.97)	-3.44 (-3.80, -3.08)	-0.86 (-1.09, -0.33)	2.18 (1.82, 2.53)	7.26 (6.63, 7.90)
[55b]	Mixed	SI	58.8 (55.7, 61.9)	-0.81 (-1.11, -0.50)	4.81 (4.29, 5.33)	-10.23 (-11.37, -9.08)	-3.59 (-3.94, -3.24)	-0.92 (-1.24, -0.61)	1.96 (1.58, 2.35)	8.68 (7.58, 9.78)
[30]	MCNH	SI	61.7 (58.6, 64.7)	-1.84 (-2.19, -1.48)	5.75 (5.47, 6.04)	-13.69 (-14.89,-12.48)	-5.47 (-5.96, -4.99)	-1.64 (-2.07, -1.21)	2.05 (1.59, 2.51)	8.81 (7.97, 9.64)
[63b]	Hong Kong	SI	65.1 (62.1, 68.1)	-1.42 (-1.70, -1.13)	4.54 (4.20, 4.89)	-10.51 (-11.64, -9.37)	-3.93 (-4.26, -3.60)	-1.43 (-1.72, -1.15)	1.10 (0.77, 1.43)	7.67 (6.46, 8.88)
[63a]	Hong Kong	SI	79.3 (76.8, 81.8)	-2.69 (-2.93, -2.45)	3.83 (3.46, 4.20)	-11.16 (-12.32, -9.99)	-4.62 (-4.94, -4.31)	-2.36 (-2.60, -2.13)	-0.40 (-0.64, -0.16)	3.85 (3.08, 4.62)
Unweighted pooling		GT	68.3 (47.9,88.6)	-1.83 (-3.48, -0.17)	4.00 (3.19, 4.80)	-10.43 (-12.66, -8.20)	-3.89 (-5.86, -1.92)	-1.59 (-2.54, 0.37)	0.48 (-1.27, 2.23)	5.45 (3.22, 7.67)
		SI	56.4 (34.9,78.0)	-0.60 (-3.01, 1.81)	5.18 (3.58, 6.77)	-10.96 (-14.22, -7.70)	-3.72 (-5.67, -1.76)	-0.59 (-2.72, 1.54)	2.59 (-0.55, 5.74)	9.47 (3.76, 15.18)

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Table 4: Summary statistics for transmission time relative to symptom onset and proportion pre-symptomatic transmission estimated from Simulation A. MCNH = Mainland China excluding Hubei province. N Italy = Northern Italy. Mixed = data came from multiple countries. SD = Standard deviation. Confidence intervals in Simulation A are based on incorporating measures of uncertainty from the source publications into the simulation.

Location	Percentage pre-symptomatic transmission	Mean (95% CI)	SD (95% CI)	2.5th percentile (95% CI)	25th percentile (95% CI)	Median (95% CI)	75th percentile (95% CI)	97.5th percentile (95% CI)
Shenzhen	48.6 (45.5, 51.7)	0.51 (0.18, 0.84)	5.28 (4.95, 5.62)	-9.31 (-10.46, -8.17)	-2.67 (-3.02, -2.32)	0.15 (-0.19, 0.5)	3.41 (2.95, 3.86)	11.97 (10.59, 13.35)
Mixed	50.3 (35.8, 64.9)	0.13 (-1.72, 1.98)	5.23 (3.84, 6.62)	-10.19 (-12.41, -7.98)	-3.06 (-4.19, -1.92)	0.06 (-1.68, 1.8)	3.35 (0.74, 5.97)	10.41 (5.36, 15.46)
MCNH	56.8 (46.8, 66.8)	-1.15(-2.55, 0.24)	6.01 (5.42, 6.61)	-13.46 (-14.77,-12.15)	-4.99 (-6.07, -3.91)	-0.97 (-2.36, 0.41)	2.91 (1.16, 4.67)	10.05 (7.45, 12.64)
Singapore	61.6 (42.7, 80.5)	-1.2 (-2.68, 0.13)	4.03 (3.33, 4.73)	-9.95 (-12.08, -7.82)	-3.39 (-5.21, -1.57)	-1.04 (-2.77, 0.7)	1.10 (-0.27, 2.47)	6.00 (4.72, 7.27)
Hong Kong	72.2 (58.0, 86.3)	-2.05(-3.33,-0.78)	4.19 (3.40, 4.97)	-10.83 (-12.15, -9.52)	-4.28 (-5.03, -3.52)	-1.90 (-2.84, -0.9)	0.35 (-1.15, 1.85)	5.76 (1.88, 9.64)
Tianjin	74.9 (63.5, 86.3)	-2.38(-3.45,-1.30)	3.97 (3.07, 4.86)	-10.91 (-12.83, -9.00)	-4.39 (-5.98, -2.80)	-2.14 (-3.66, -0.6)	-0.14 (-1.29, 1.01)	4.89 (2.46, 7.33)

Table 5: A summary of the counts (N) of studies and estimates used in Simulation B coming from specific locations, or mixed sources.

Location / data source	Count of estimates	Count of studies	References
Mixed	7	5	[27–29,55,61]
Tianjin	6	3	[25,26,62]
Singapore	5	2	[25,26]
Mainland China excluding Hubei	3	3	[30,31,63]
Hong Kong	2	1	[64]
Northern Italy	2	2	[3,19]
Hong Kong and Shenzhen	1	1	[52]
Shenzhen	1	1	[65]
Wuhan	1	1	[66]
Total	**28**	**19**	

Table 6: Summary statistics based on Simulation B for transmission time relative to symptom onset and proportion pre-symptomatic transmission (PPS) for each of 5 estimates based on generation time (GT) and 23 estimates based on serial interval (SI). The studies are ordered first by whether they are based on generation time or serial interval, and then by median transmission time relative to symptoms, to correspond to Figure 3. A negative number means days before symptom onset. MCNH = Mainland China excluding Hubei province. Mixed = SI or GT was calculated from pooled data from multiple countries. HKSZ = pooled data from Hong Kong and Shenzhen. SD = Standard deviation. Figure 2 ref = Reference number corresponding to Table 2, Figure 3 and main text. Confidence intervals are based on the variation between 20,000 repeat simulations.

Reference	Location (description)	N for study	Based on	% pre-symptomatic transmission	Mean	Standard deviation	2.5th percentile	25th percentile	Median	75th percentile	97.5th percentile
[26a]	Singapore	91 (54) cases	GT	52.14 (51.83, 52.46)	-0.59 (-0.61, -0.57)	3.53 (3.50, 3.55)	-8.87 (-8.99, -8.76)	-2.38 (-2.41, -2.35)	-0.16 (-0.18, -0.13)	1.71 (1.69, 1.73)	5.13 (5.09, 5.18)
[27a]	Mixed	40 pairs	GT	54.14 (53.83, 54.45)	-0.74 (-0.76, -0.71)	3.64 (3.61, 3.66)	-9.19 (-9.30, -9.07)	-2.66 (-2.69, -2.63)	-0.33 (-0.35, -0.30)	1.70 (1.68, 1.73)	5.16 (5.12, 5.20)
[26e]	Tianjin	135 (114) cases	GT	69.42 (69.14, 69.71)	-1.83 (-1.85, -1.81)	3.43 (3.41, 3.46)	-10.01 (-10.12, -9.89)	-3.53 (-3.56, -3.50)	-1.35 (-1.38, -1.33)	0.42 (0.39, 0.44)	3.58 (3.53, 3.62)
[26c]	Singapore Model 2	93 (54) cases	GT	70.89 (70.61, 71.18)	-1.93 (-1.95, -1.90)	4.06 (4.04, 4.09)	-10.63 (-10.74, -10.52)	-4.13 (-4.16, -4.09)	-1.81 (-1.83, -1.78)	0.43 (0.40, 0.46)	5.99 (5.91, 6.08)
[26g]	Tianjin Model 2	137 (114) cases	GT	80.70 (80.45, 80.94)	-2.92 (-2.95, -2.90)	4.18 (4.15, 4.21)	-11.61 (-11.72,-11.50)	-5.13 (-5.16, -5.10)	-2.88 (-2.90, -2.85)	-0.73 (-0.76, -0.70)	5.74 (5.63, 5.84)
[65]	Wuhan	6 pairs	SI	33.47 (33.18, 33.76)	1.72 (1.69, 1.75)	4.59 (4.56, 4.62)	-7.63 (-7.74, -7.52)	-1.00 (-1.04, -0.97)	1.69 (1.66, 1.73)	4.50 (4.46, 4.54)	10.89 (10.80, 10.98)
[19]	N Italy	120 pairs	SI	36.20 (35.90, 36.49)	1.15 (1.13, 1.18)	4.20 (4.17, 4.22)	-7.81 (-7.92, -7.70)	-1.23 (-1.26, -1.20)	1.29 (1.26, 1.32)	3.76 (3.73, 3.79)	9.11 (9.03, 9.19)
[29]	Mixed	689 pairs	SI	42.69 (42.39, 43.00)	0.92 (0.88, 0.95)	6.04 (6.02, 6.07)	-11.48 (-11.60,-11.35)	-2.96 (-3.02, -2.91)	1.09 (1.05, 1.14)	5.01 (4.96, 5.06)	12.27 (12.18, 12.36)
[60]	Mixed	43 pairs	SI	43.22 (42.91, 43.53)	1.22 (1.18, 1.25)	5.45 (5.42, 5.49)	-8.80 (-8.91, -8.69)	-2.14 (-2.18, -2.11)	0.77 (0.73, 0.81)	4.23 (4.18, 4.28)	13.29 (13.15, 13.43)
[3]	N Italy	90 pairs	SI	47.77 (47.46, 48.09)	0.90 (0.86, 0.93)	5.78 (5.74, 5.81)	-9.30 (-9.41, -9.19)	-2.66 (-2.70, -2.63)	0.26 (0.22, 0.30)	3.93 (3.88, 3.98)	14.12 (13.96, 14.28)
[64]	Shenzhen	48 pairs	SI	48.68 (48.37, 49.00)	0.52 (0.48, 0.55)	5.21 (5.18, 5.24)	-9.24 (-9.35, -9.13)	-2.63 (-2.66, -2.59)	0.14 (0.11, 0.18)	3.39 (3.34, 3.43)	11.95 (11.82, 12.08)
[28]	MCNH	339 pairs	SI	51.54 (51.23, 51.85)	-0.02 (-0.06, 0.01)	5.44 (5.41, 5.47)	-10.49 (-10.60, 10.38)	-3.49 (-3.53, -3.45)	-0.19 (-0.23, -0.16)	3.34 (3.29, 3.38)	11.18 (11.07, 11.29)
[31]	Mixed	77 pairs	SI	52.15 (51.84, 52.46)	-0.49 (-0.53, -0.46)	6.15 (6.12, 6.18)	-13.07 (-13.20,-12.95)	-4.45 (-4.50, -4.40)	-0.32 (-0.37, -0.28)	3.67 (3.62, 3.72)	11.08 (10.98, 11.17)

Reference	Location (description)	N for study	Based on	% pre-symptomatic transmission	Mean	Standard deviation	2.5th percentile	25th percentile	Median	75th percentile	97.5th percentile
[26b]	Singapore	92 (54) cases	SI	53.02 (52.71, 53.33)	-0.59 (-0.62, -0.56)	5.30 (5.28, 5.33)	-11.78 (-11.90,-11.66)	-3.80 (-3.85, -3.76)	-0.37 (-0.41, -0.33)	2.87 (2.83, 2.91)	9.35 (9.26, 9.44)
[27b]	Mixed	40 pairs	SI	54.30 (53.99, 54.61)	-0.74 (-0.77, -0.71)	4.67 (4.65, 4.70)	-10.82 (-10.94,-10.71)	-3.50 (-3.54, -3.46)	-0.46 (-0.49, -0.43)	2.36 (2.32, 2.39)	7.70 (7.63, 7.77)
[62]	MCNH	35 pairs	SI	56.19 (55.88, 56.50)	-0.67 (-0.70, -0.65)	4.09 (4.06, 4.11)	-9.46 (-9.57, -9.35)	-2.93 (-2.96, -2.90)	-0.53 (-0.56, -0.50)	1.81 (1.78, 1.84)	7.11 (7.04, 7.19)
[25a]	Singapore	93 pairs	SI	59.57 (59.26, 59.87)	-1.22 (-1.24, -1.20)	3.23 (3.20, 3.25)	-9.20 (-9.31, -9.09)	-2.74 (-2.77, -2.71)	-0.62 (-0.64, -0.60)	0.98 (0.96, 1.00)	3.25 (3.22, 3.27)
[55a]	Mixed (n=18)	18 pairs	SI	58.22 (57.91, 58.53)	-0.98 (-1.01, -0.96)	3.85 (3.82, 3.87)	-9.62 (-9.74, -9.51)	-3.09 (-3.12, -3.05)	-0.69 (-0.72, -0.66)	1.53 (1.50, 1.56)	5.70 (5.64, 5.75)
[61]	Tianjin	112 cases	SI	59.96 (59.66, 60.27)	-0.98 (-1.01, -0.96)	4.10 (4.07, 4.12)	-9.77 (-9.88, -9.66)	-3.24 (-3.27, -3.21)	-0.85 (-0.88, -0.83)	1.48 (1.45, 1.51)	6.90 (6.81, 6.98)
[25b]	Tianjin	125 pairs	SI	64.88 (64.59, 65.18)	-1.56 (-1.58, -1.54)	3.11 (3.08, 3.13)	-9.41 (-9.52, -9.29)	-2.96 (-2.99, -2.93)	-0.90 (-0.92, -0.88)	0.59 (0.57, 0.60)	2.42 (2.41, 2.44)
[52]	HKSZ	48 pairs	SI	59.34 (59.04, 59.65)	-0.61 (-0.64, -0.58)	5.05 (5.02, 5.09)	-10.12 (-10.23, -10.01)	-3.56 (-3.59, -3.53)	-0.98 (-1.01, -0.94)	2.07 (2.02, 2.11)	10.60 (10.46, 10.74)
[55b]	Mixed (n=28)	28 pairs	SI	62.63 (62.33, 62.93)	-1.08 (-1.11, -1.06)	4.23 (4.20, 4.26)	-9.84 (-9.95, -9.73)	-3.34 (-3.37, -3.31)	-1.03 (-1.05, -1.00)	1.19 (1.16, 1.22)	7.50 (7.39, 7.61)
[63b]	Hong Kong (n=21)	21 pairs	SI	65.24 (64.94, 65.53)	-1.38 (-1.41, -1.36)	4.30 (4.27, 4.33)	-10.30 (-10.41,-10.19)	-3.78 (-3.81, -3.74)	-1.38 (-1.40, -1.35)	1.08 (1.04, 1.11)	7.32 (7.22, 7.41)
[30]	MCNH	468 pairs	SI	63.17 (62.87, 63.47)	-1.83 (-1.86, -1.80)	5.24 (5.21, 5.27)	-12.93 (-13.05,-12.81)	-4.99 (-5.03, -4.94)	-1.60 (-1.63, -1.56)	1.59 (1.55, 1.63)	7.96 (7.87, 8.05)
[26f]	Tianjin	136 (114) cases	SI	61.74 (61.45, 62.04)	-1.82 (-1.86, -1.79)	5.66 (5.63, 5.69)	-13.53 (-13.65,-13.41)	-5.42 (-5.47, -5.37)	-1.63 (-1.67, -1.59)	2.01 (1.97, 2.06)	8.72 (8.63, 8.80)
[26d]	Singapore Model 2	94 (54) cases	SI	63.91 (63.61, 64.20)	-1.93 (-1.96, -1.89)	5.67 (5.64, 5.70)	-13.51 (-13.63,-13.39)	-5.43 (-5.48, -5.39)	-1.85 (-1.89, -1.81)	1.68 (1.64, 1.72)	9.18 (9.07, 9.28)
[63a]	Hong Kong (n=12)	12 pairs	SI	79.90 (79.65, 80.15)	-2.68 (-2.71, -2.66)	3.57 (3.54, 3.59)	-10.97 (-11.08,-10.85)	-4.49 (-4.52, -4.46)	-2.29 (-2.31, -2.27)	-0.44 (-0.47, -0.42)	3.37 (3.31, 3.42)
[26h]	Tianjin Model 2	138 (114) cases	SI	71.10 (70.82, 71.38)	-2.92 (-2.96, -2.89)	5.76 (5.72, 5.79)	-14.51 (-14.63,-14.39)	-6.47 (-6.51, -6.42)	-2.91 (-2.95, -2.87)	0.64 (0.59, 0.68)	8.61 (8.49, 8.73)
Simple pooled estimate of GT based transmission time relative to symptom onset				65.46 (65.27, 65.65)	-1.60 (-1.62, -1.58)	3.88 (3.85, 3.90)	-10.25 (-10.34,-10.15)	-3.71 (-3.73, -3.68)	-1.31 (-1.33, -1.29)	0.88 (0.87, 0.90)	5.12 (5.09, 5.14)
Simple pooled estimate of SI based transmission time relative to symptom onset				56.04 (55.89, 56.19)	-0.66 (-0.68, -0.64)	5.05 (5.03, 5.06)	-11.10 (-11.17,-11.03)	-3.51 (-3.54, -3.49)	-0.62 (-0.64, -0.60)	2.21 (2.20, 2.23)	9.60 (9.58, 9.63)

Table 7: Summary statistics from Simulation B for transmission time relative to symptom onset and proportion pre-symptomatic transmission (PPS) for simulated samples, based on 23 estimates of serial interval, pooled according to the source location of the original data upon which estimates were based. MCNH = Mainland China excluding Hubei province. N Italy = Northern Italy. Mixed = data came from multiple countries. The studies are ordered by median transmission time relative to symptoms, to correspond to Figure 4. SD = Standard deviation.

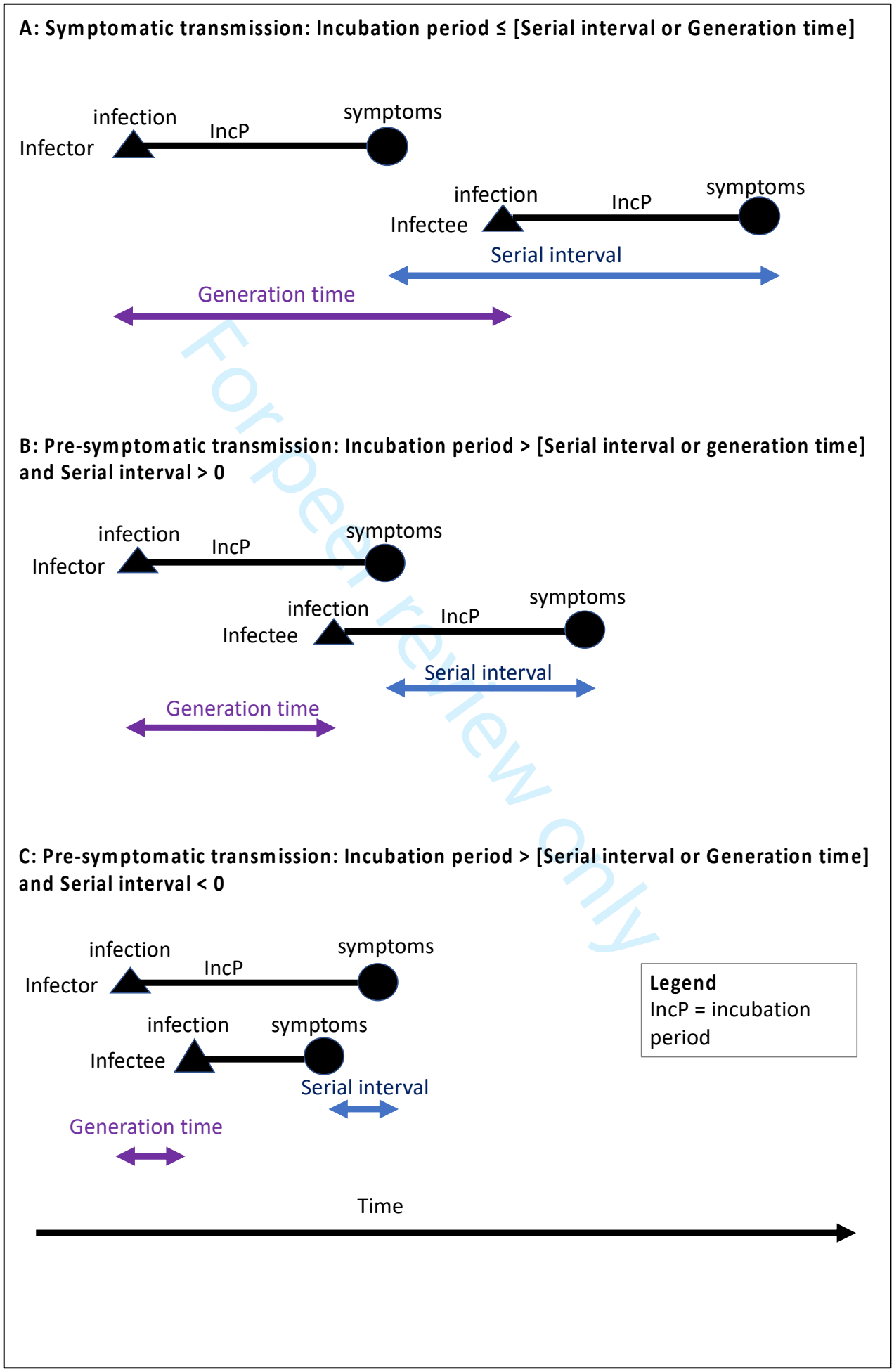
Location	Count of estimates	Proportion pre-symptomatic transmission	Mean	SD	2.5th percentile	25th percentile	Median	75th percentile	97.5th percentile
Wuhan	1	33.5%	1.72	4.62	-7.63	-1.02	1.68	4.38	10.96
N Italy	2	42.1%	1.01	5.05	-8.66	-2.00	0.83	3.8	11.76
Shenzhen	1	48.9%	0.50	5.22	-9.26	-2.65	0.12	3.5	11.90
Mixed	6	52.2%	-0.13	5.09	-10.29	-3.13	-0.23	2.8	10.49
MCNH	3	56.8%	-1.01	5.41	-12.48	-4.19	-0.80	2.4	9.35
Singapore	3	58.8%	-1.25	4.89	-11.95	-3.97	-0.87	1.5	8.27
HKSZ	1	59.3%	-0.62	5.06	-10.16	-3.59	-0.96	2.3	10.64
Tianjin	4	64.9%	-1.84	4.72	-12.31	-4.40	-1.40	0.9	7.09
Hong Kong	2	72.7%	-2.05	4.00	-10.67	-4.19	-1.90	0.4	5.81

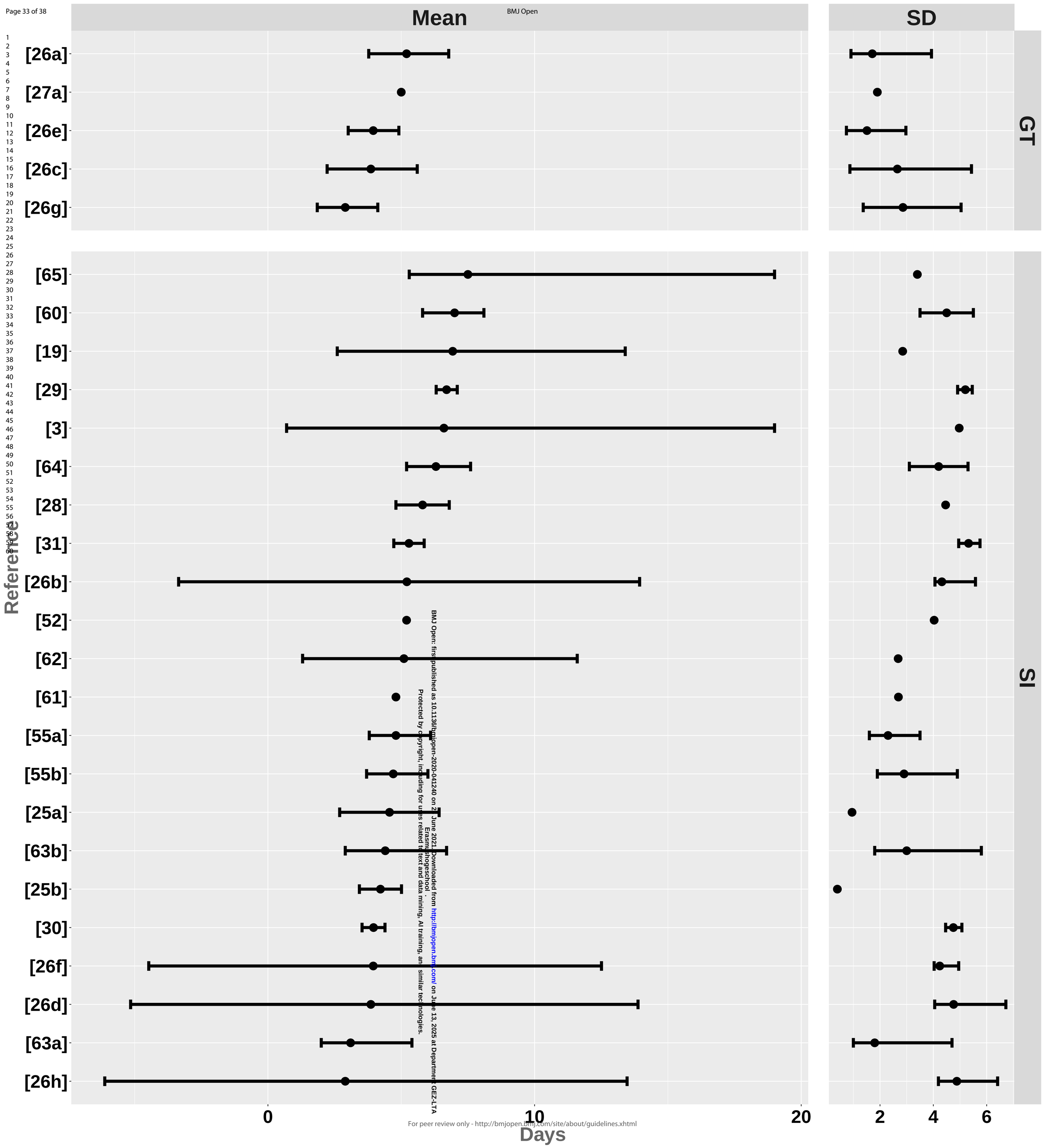
Figure 1: Schematic illustration of incubation period, generation time and serial interval at infector-infectee pair level. Scenario A: if serial interval/generation time is longer than incubation period, transmission occurs after symptom onset. Scenario B: if serial interval/generation time is shorter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

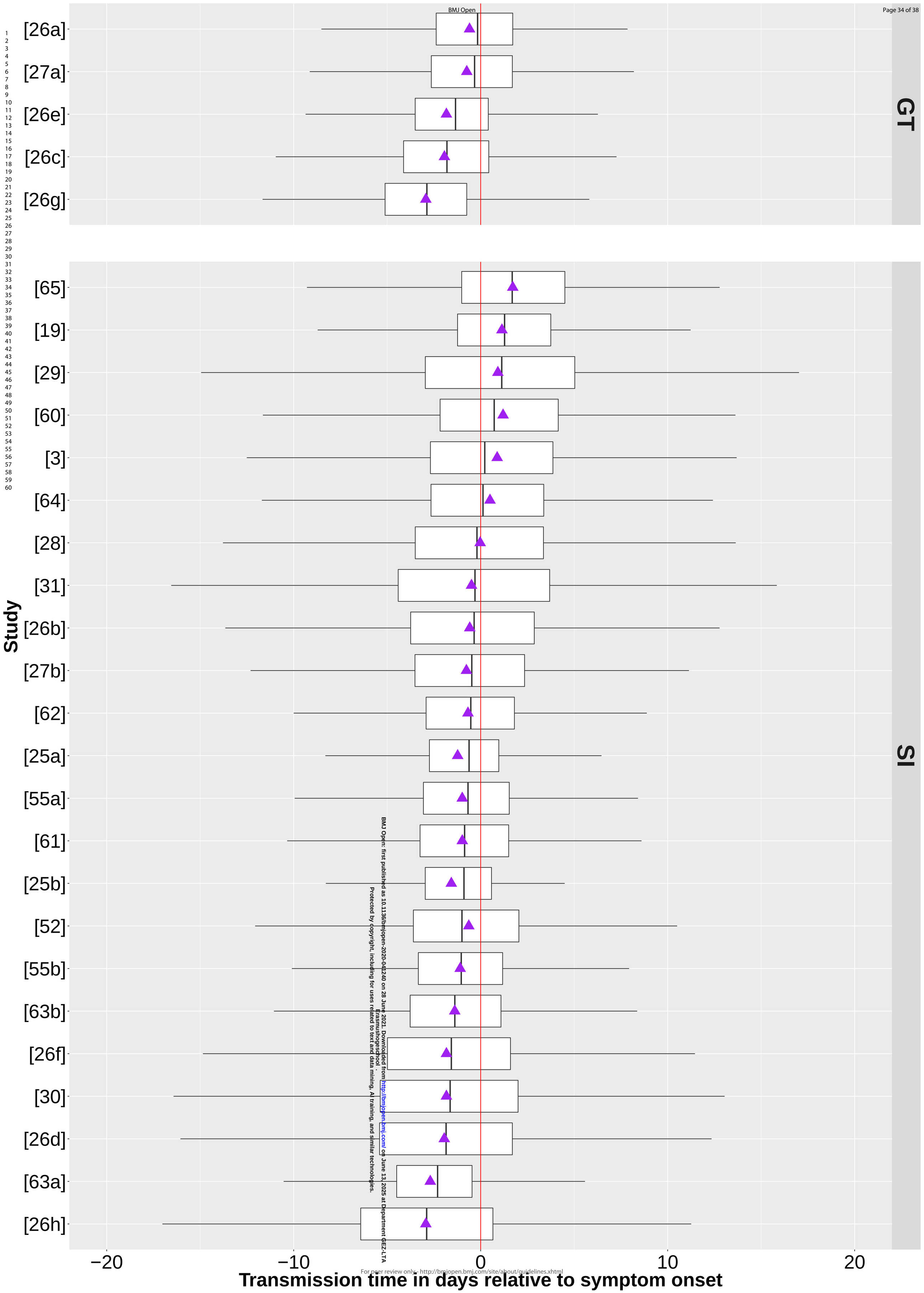
Figure 2: Generation time (GT, upper panels) and serial interval (SI, lower panels) estimates from the publications included in this study. Mean (left panels) and Standard Deviation (SD, right panels) are shown. Circles represent mean estimates and bars represent 95% confidence intervals.

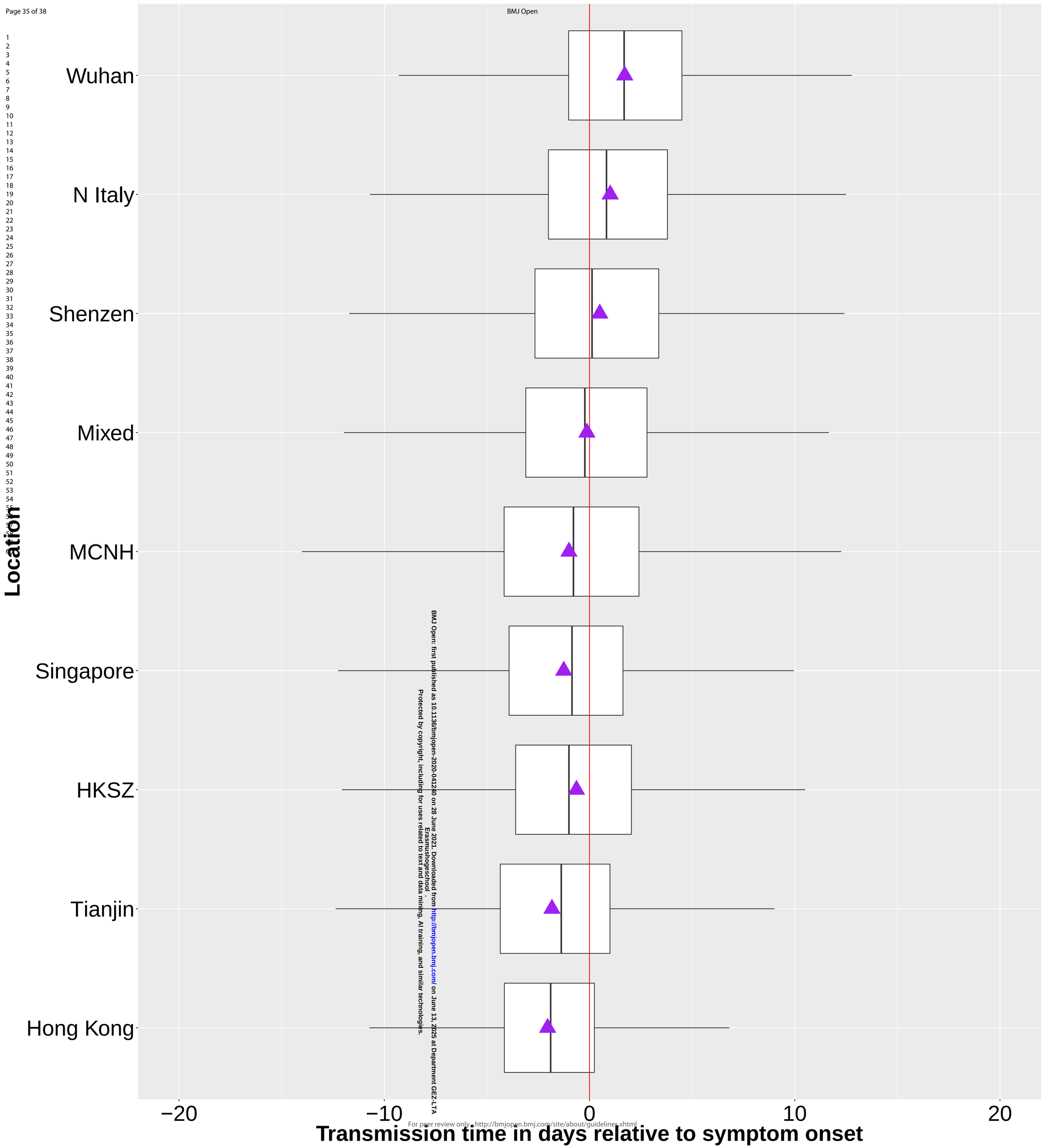
Figure 3: A boxplot showing time of transmission relative to onset of symptoms inferred from simulations of incubation period and generation time (GT) (n = 5 estimates) or serial interval (SI) (n = 23 estimates). The purple triangles represent the mean of the simulated samples. The vertical red line represents onset of symptoms. The numbers on the left axis are the reference numbers for each estimate (described in Table 2).

Figure 4: A boxplot showing time of transmission relative to onset of symptoms inferred from simulations from incubation period and serial interval (n = 23 estimates). The purple triangles represent the mean of the simulated samples. The vertical red line represents onset of symptoms. The simulated samples were pooled according to the source location of the original data upon which estimates were based. MCNH = Mainland China excluding Hubei province. N Italy = Northern Italy. HKSZ = pooled data from Hong Kong and Shenzhen. Mixed = data came from multiple countries.









Supplementary table 1: Comparison of the simulation A output for serial interval or generation time and the estimates reported in the papers.

					Mean of Mean (95% CI)		Mean of SD (95% CI)	
Reference	**Location**	**N**	**Distribution**	**SI or GT**	**Simulation**	**Data**	**Simulation**	**Data**
[26a]	Singapore	91 cases (54 with known contacts)	Gamma	GT	5.23 (5.10, 5.35)	5.20 (3.78, 6.78)	2.00 (1.83, 2.16)	1.71 (0.91, 3.93)
[26c]	Singapore	91 cases (54 with known contacts)	Gamma	GT	3.82 (3.63, 4.00)	3.86 (2.22, 5.60)	3.02 (2.63, 3.40)	2.65 (0.87, 5.43)
[26e]	Tianjin	135 cases (114 with known contacts)	Gamma	GT	3.95 (3.85, 4.06)	3.95 (3.01, 4.91)	1.68 (1.54, 1.81)	1.51 (0.74, 2.97)
[26g]	Tianjin	135 cases (114 with known contacts)	Gamma	GT	2.88 (2.69, 3.08)	2.90 (1.85, 4.12)	3.09 (2.67, 3.52)	2.86 (1.37, 5.04)
[64]	Shenzhen	48 pairs	Gamma	SI	6.30 (6.04, 6.57)	6.30 (5.20, 7.60)	4.26 (3.95, 4.57)	4.20 (3.10, 5.30)
[30]	MCNH	468 pairs	Normal	SI	3.95 (3.65, 4.26)	3.96 (3.53, 4.39)	4.83 (4.62, 5.04)	4.75 (4.46, 5.07)
[31]	MCNH	339 pairs	Normal	SI	5.33 (4.99, 5.66)	5.29 (4.72, 5.86)	5.45 (5.21, 5.68)	5.32 (4.95, 5.75)
[29]	Mixed	689 pairs	Normal	SI	6.69 (6.37, 7.02)	6.70 (6.31, 7.10)	5.25 (5.02, 5.48)	5.20 (4.91, 5.46)
[55a]	Mixed	18 pairs	Weibull	SI	5.01 (4.81, 5.22)	4.80 (3.80, 6.10)	2.17 (1.82, 4.53)	2.30 (1.60, 3.50)
[55b]	Mixed	28 pairs	Lognormal	SI	4.99 (4.76, 5.22)	4.70 (3.70, 6.00)	3.66 (3.11, 4.22)	2.90 (1.90, 4.90)
[60]	Mixed	43 pairs	Gamma	SI	6.99 (6.71, 7.28)	7.00 (5.80, 8.10)	4.58 (4.26, 4.89)	4.50 (3.50, 5.50)
[63a]	Hong Kong	12 pairs	Gamma	SI	3.11 (2.97, 3.24)	3.10 (2.00, 5.40)	2.22 (1.80, 2.64)	1.80 (1.00, 4.70)
[63b]	Hong Kong	21 pairs	Gamma	SI	4.38 (4.18, 4.59)	4.40 (2.90, 6.70)	3.29 (2.95, 3.64)	3.00 (1.80, 5.80)

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Identified as a secondary analysis
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5-6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5-6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	5-6
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5-6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	5-6
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6-9
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Page 9, Tables 2-6, Supplementary Table 1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Reference to associated manuscripts that do this and Table 2
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Tables 2-6, Supplementary Table 1
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Figures 3 and 4, Tables 2-6
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	11-15
Limitations	20	Discuss the limitations of the scoping review process.	14
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	11-15
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	15

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable

to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

BMJ Open

Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data

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Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data

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Abstract

Objective: To estimate the proportion of pre-symptomatic 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.

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 pre-symptomatic transmission, were estimated.

Outcome measures: Transmission time of SARS-CoV-2 relative to symptom onset and proportion of pre-symptomatic 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, -2.1) days before infector symptom onset in to 1.4 (95% CI: 1.0, 1.8) days after symptom onset. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0) to 69.1% (95% CI: 66.2%, 71.9%).

Conclusions: There is substantial potential for pre-symptomatic 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 will vary according to context. Rapid isolation of symptomatic cases creates a relatively greater proportion of pre-symptomatic transmission.

Strengths and weaknesses of this study

- We estimate the extent and variation of pre-symptomatic transmission of SARS-CoV-2 infection across a range of contexts. This provides important information for development and targeting of control policies and for the parameterisation of transmission models.
- Transmission patterns we report reflect the combination of biological infectiousness and transmission opportunities which will vary according to context. Interventions such as rapid isolation of symptomatic people result in a greater proportion of transmission occurring earlier in the infectious period (that is, shorter serial intervals and relatively more pre-symptomatic transmission) This should be borne in mind whilst interpreting our results but does not affect our finding that there is substantial potential for pre-symptomatic transmission of SARS-CoV-2 infection.
- A strength of our approach is that it builds an understanding of pre-symptomatic transmission from a range of estimates in the literature, facilitates discussion for the drivers of variation between them, and highlights that consideration of pre-symptomatic transmission is critical for COVID-19 control policy.

Introduction

There is currently a pandemic of coronavirus disease (COVID-19), a recently emerged and rapidly spreading infectious disease that is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are large direct impacts of COVID-19 amongst known cases. As of 25th September 2020, the World Health Organization has reported 32,110,656 confirmed cases and 980,031 deaths due to COVID-19 [1]. In China, 14% and 5% of cases were classified as severe and critical, respectively [2]. There are also major indirect impacts of COVID-19 and its control measures on other aspects of health care [3–5] and on the economy [6,7].

As there is currently no COVID-19 vaccine for widespread use, primary control measures entail reducing transmission from infectious individuals. These include case isolation, contact tracing and quarantine, physical distancing and hygiene measures [8]. Infectious people are identified when they report symptoms, and are tested for COVID-19. 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 COVID-19 transmission. Therefore, quantifying the transmission potential of COVID-19 before or in the absence of symptoms will inform disease control measures and predictions of epidemic progression.

Characteristics of pre-symptomatic and asymptomatic transmission are potentially different, and separate approaches may be required to understand them. In this paper, we capitalise upon the considerable information about pre-symptomatic transmission that can be inferred from contact tracing studies. Therefore, we focus here 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 pre-symptomatic transmission which has been highlighted by those developing models to inform policies [9].

Reports of pre-symptomatic transmission [10–19] emerged as detailed contact tracing was conducted during early outbreaks of COVID-19. Further, both viral genome [18,20–26] and live virus [21] 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 proportion [27–30,38] and timing [27,30,38] of pre-symptomatic transmission, using a variety of datasets and methodologies. Here, we compare pre-symptomatic 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 [39] and rapid systematic review and meta-analysis of incubation period [40] with a secondary analysis of published data to estimate the proportion and timing of pre-symptomatic transmission of COVID-19.

Methods

Principles of methodology

If 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 incubation period, the time between infection and symptom onset in the infector, transmission will have occurred after symptom onset (Scenario A in Figure 1). If generation time is shorter than incubation period, pre-symptomatic transmission will have occurred (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 [28]. Our method entailed subtracting simulated values for incubation period from serial interval to estimate the timing and proportion of pre-symptomatic 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 [40]; 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 to investigate pre-symptomatic 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 [39], 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= 26 estimates from 23 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 =15 estimates from 13 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 [39], we presented the serial interval

and generation time data to highlight 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 distribution to generate a distribution of transmission time relative to symptom onset.

We replicated the reported serial interval/generation time distributions and the incubation period distribution from our metanalysis [43]. To achieve this, we sampled distribution parameters from their respective 95% confidence intervals 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% confidence intervals from bootstrapping were calculated.

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

In Supplementary Figures 1-3 and Supplementary Table 1, we also present the result of simulations from the larger dataset of 26 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, if only central estimates of serial interval/generation time parameters were available, we also used only central parameter estimates of the incubation period (meanlog 1.63, sdlog 0.5).

All analyses were conducted in the R Statistical Environment [45]. 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. [39], 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 standard deviation of each estimate. Of the 18 estimates from 15 papers for which we could incorporate uncertainty into our simulations, eleven came from China, two each came from the Republic of Korea and form Singapore, and one each from the Islamic Republic of Iran, Italy and Vietnam. Sample sizes ranged from 17 [46] to 1407 [35] transmission pairs.

Of the eleven estimates from China, three 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 [35], 677 [43] and 468 [33] transmission pairs), and were associated with the same group of authors, who confirmed some overlap between the datasets underlying each paper. Xu et al. [35] and Ali et al. [43] 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 [46], but are based on samples of certain (n=17) and mixed certain and probable (n=26) infector-infectee pairs. There is a difference of over a day in these two data subsets although they came from the same from the same region and date range. The two estimates from Shenzhen [44,47] had some overlap in date range but differed in sample size (48 case pairs [44], 27 case pairs [47]). Ganyani et al. [28] and Tindale et al. [27] used the same datasets from Tianjin and Singapore. Son et al. [48] reported a serial interval estimate based on data from Busan in the Republic of Korea, whereas Chun et al [38] used data from the whole country. Shiyan (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. [28] inferred generation time. The remainder of the estimates were based on serial intervals. Ten of the estimates were based on direct observation of infector-infectee pairs. Eight serial interval estimates from six papers [18,27,28,35,38,47] were based on inferences about infector-infectee 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. [44] quantified this as mean serial interval of 3.6 days if a case was isolated within less than three 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 six days after symptom onset. Ali et al. [43] 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 pre-symptomatic transmission. Mean transmission time relative to symptom onset ranged from -2.6 (95% CI: -3.0, -2.1) days before infector symptom onset in Vietnam [49] to 1.4 (95% CI: 1.0, 1.8) days after symptom onset in Italy [18]. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0%) in Italy [18] to 69.1% (95% CI: 66.2, 71.9) in Tianjin [28]. It was only possible to estimate the proportion of negative serial intervals from the five estimates that were fitted with distributions that allowed negative serial intervals (normal distributions rather than gamma, lognormal or Weibull). Simulations based on Chinese data ranged from 16.7% (95% CI: 14.4, 19.0) to 20.4% (95% CI: 17.9, 22.9) whereas the simulation using the data from Vietnam resulted in 30.9% (95% CI: 28.0, 33.8) negative serial intervals.

Supplementary figures 1-3 and Supplementary 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 [34], Brunei Darussalam [24], China (all regions excluding Hubei) [32,50], Tianjin [51], Wuhan [52,53], Iran [54] and the Republic of Korea [22]. Supplementary Table 1 also shows any estimates or comments relating to pre-symptomatic transmission that we found in the serial interval or generation time papers. Supplementary table 2 compares the pre-symptomatic transmission time estimates of Ganyani et al. [28], Tindale et al. [27] and this study which all refer to the same datasets from Singapore and Tianjin. Supplementary tables 3 and 4 summarise virological studies and case reports of pre-symptomatic 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 showed the potential for substantial pre-symptomatic transmission.

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 pre-symptomatic transmission) [43,44]. Well characterised infector-infectee data is 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.

Our findings in support of transmission potential prior to symptom onset are consistent with multiple reports of both SARS-CoV-2 genome [18,20,21,23–25,55,56] and live virus [21] detection in upper respiratory samples prior to symptom onset. Bae et al. [22] reported viral genome detection up to 13 days prior to symptom onset and Arons et al. [22] isolated live

virus from upper respiratory samples from nursing home residents six days prior to symptom onset. Of 48 residents testing positive for viral genome in upper respiratory tract samples, Arons et al. [21] reported that 24 of these residents tested positive a median of 4 (IQR 3-5) days in advance of symptom onset. (Please see Supplementary table 3 for a more detailed summary of the virological studies that we refer to).

Viral load in upper respiratory tract samples appears to peak around symptom onset and rapidly declines towards undetectable levels about two weeks after symptom onset [30,57–59]. This early peak and rapid drop off in viral load in the upper respiratory tract fits with the conclusion of Bi et al. that isolation less than three days following symptom onset has a large effect in shortening serial interval whereas isolation at six days or later after symptom onset has no effect [44].

Case series with detailed descriptions of contact patterns and symptom onset [10–19] (Supplementary table 4) further strengthen evidence 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 pre-symptomatic transmission, given reported serial intervals that were similar to, or shorter than, estimates for the incubation period of COVID-19 (Supplementary table 1). Another quantitative study investigating pre-symptomatic transmission [30] used 77 transmission pairs from a mixture of countries to infer that infectiousness peaked at symptom onset (95% CI: –0.9, –0.9 days). The authors estimated that 44% (95% confidence interval, 30–57%) of transmission was pre-symptomatic. A further study [29], also using data from a mixture of countries (40 transmission pairs), inferred that 37% (95% CI: 27.5, 45) of transmission was pre-symptomatic 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. [28] and Tindale et al. [27] used the same dataset to infer transmission pairs and estimate pre-symptomatic transmission. Their estimates were 48% (95% CrI: 32, 67) and 74% for Singapore, and 62% (50,76) 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 pre-symptomatic transmission based on the generation times of

Ganyani et al [28], and the serial intervals of Tindale et al. [27] also differ from the authors' estimates due to using a different estimate for incubation period and a slightly different approach to transmission time calculation. Similarly, we estimate more pre-symptomatic transmission (64.2%) based on the serial interval of Chun et al. [38] than what is estimated in the paper (37%) as the incubation period used for our estimation of pre-symptomatic transmission (median 5.1 days) is much longer that that used in Chun et al. 's calculations (median 2.87 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 a only a single estimate of generation time [28] 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 [41,42], although serial interval will have more variation [28]. The extra variation associated with serial interval should be borne in mind whilst 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. [46] 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 (for example [41,60]) for inferring transmission pairs from clusters of cases could also impact serial interval or generation time estimates. Griffin et al. [39] and Du et al. [33] 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.

Despite the challenges associated with a highly variable international dataset, this study gives a clear signal that substantial pre-symptomatic 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 pre-symptomatic transmission of COVID-19 in a range of different contexts. The proportion of pre-symptomatic 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.

Tables

Table 1: Definitions referred to in this review.

Asymptomatic	An infected person who never develops symptoms of the disease
Pre-symptomatic	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 [61].
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 [61].
Serial interval	The duration in days between symptom onset of a secondary case and that of its primary case.
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 who they transmit the pathogen to (infectee).
Latent period	The period from the point of infection to the beginning of the state of infectiousness [62]. This period corresponds to the “exposed” (E) compartment of a susceptible-exposed-infectious-recovered/removed (SEIR) 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 pre-symptomatic transmission	The proportion of all transmission events that occur before the onset of symptoms in the infector.

Table 2: A summary of simulation results. The table shows showing the mean, standard deviation and median of transmission time relative to symptom onset in days as well as the proportion of pre-symptomatic transmission and the proportion of negative serial intervals. 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 brackets represent the 95% confidence intervals form 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.

Reference	Mean	SD	Median	PST
China - All excluding Hubei				
Xu et al. [35]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, -0.1)	53.5 (50.4, 56.6)
Ali et al. [43]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, 0)	53.2 (50.1, 56.3)
Du et al. [33]	-1.8 (-2.1, -1.4)	5.8 (5.5, 6)	-1.6 (-2, -1.1)	61.2 (58.2, 64.3)
China - Hong Kong				
Kwok et al. [46]	-1 (-1.4, -0.7)	5.3 (4.3, 6.3)	-1.3 (-1.6, -1.1)	64.5 (61.5, 67.4)
Kwok et al. [46]	0.5 (0.2, 0.8)	5 (4.4, 5.7)	0.4 (0.1, 0.7)	46.3 (43.2, 49.4)
China - Shiyan (Hubei)				
Yang et al. [36]	-1.2 (-1.5, -0.8)	5.7 (5.4, 6)	-1 (-1.4, -0.5)	57.1 (54.1, 60.2)
China - Shenzhen				
Wang et al. [47]	0.1 (-0.2, 0.5)	6.2 (5.4, 6.9)	-0.5 (-0.9, -0.1)	54.2 (51.1, 57.2)
Bi et al. [44]	0.5 (0.2, 0.8)	5.3 (5, 5.6)	0.1 (-0.2, 0.5)	48.6 (45.5, 51.8)
China - Tianjin				
Ganyani et al. [28]a	-1.8 (-2, -1.6)	3.5 (3.3, 3.8)	-1.4 (-1.6, -1.1)	69.1 (66.2, 71.9)
Tindale et al. [27]a	-1.4 (-1.7, -1.1)	4.2 (3.9, 4.5)	-1.1 (-1.4, -0.8)	61.1 (58.1, 64.2)
China - Zhuhai				
Wu et al. [63]	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0 (-0.3, 0.3)	50.2 (47.1, 53.3)
Iran - Qom				
Aghaali et al.[64]	-1.2 (-1.5, -	4.7 (4.4, 5)	-1.4 (-1.7, -	63.5 (60.5,

Reference	Mean	SD	Median	PST
	0.9)		1.1)	66.5)
Italy - Vo (Village in Northern Italy)				
Lavezzo et al. [18]	1.4 (1.0, 1.8)	6.4 (6.0, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49.0)
Republic of Korea - Busan				
Son et al. [48]	-0.3 (-0.6, 0.1)	5.1 (4.7, 5.4)	-0.6 (-0.9, -0.2)	55.4 (52.3, 58.4)
Republic of Korea - All				
Chun et al [38]	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)
Singapore				
Ganyani et al. [28]b	-0.6 (-0.8, -0.4)	3.7 (3.5, 4)	-0.2 (-0.4, 0)	52.5 (49.4, 55.6)
Tindale et al. [27]b	-1.4 (-1.7, -1.1)	4.8 (4.5, 5)	-1.1 (-1.5, -0.8)	60 (57, 63.1)
Vietnam				
Pham et al. [49]	-2.6 (-3.0, -2.1)	7.2 (6.9, 7.6)	-2.4 (-3, -1.9)	63.4 (60.5, 66.4)

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Competing interests

All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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

Author contributions

MC conceptualized 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. ÁC, KH, KOB and KW performed literature searches upon which the incubation period, generation time, serial interval and pre-symptomatic transmission information reported here are based upon. SM conceptualized, initiated and managed the overall project. MC, JG, CM, AB, JM, DM, ÁC, KH, AB, FB, EL, KOB, PW, KW and SM supplemented the literature review, discussed the study design, reviewed and edited the manuscript.

Data sharing statement

The data and code used for the analyses described in this paper are available in the Github repository: https://github.com/miriamcasey/covid-19_presymptomatic_project

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Figure legends

Figure 1: Schematic illustration of incubation period, generation time and serial interval at infector-infectee pair level. Scenario A: if serial interval/generation time is longer than incubation period, transmission occurs after symptom onset. Scenario B: if serial interval/generation time is shorter than incubation period, transmission occurs prior to symptom onset. 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.

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

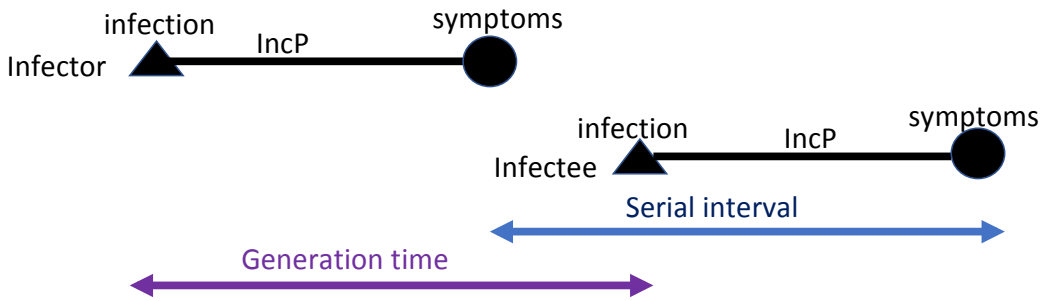
Figure 3: A summary of country or region and date ranges for the 18 serial interval estimates from 15 papers that were included in simulations to infer pre-symptomatic transmission. Line thickness is scaled to reflect sample size (i.e. reference [47a] has the smallest and [48], the largest sample size). 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.

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. 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. Points indicate means and bars indicate 95% confidence intervals.

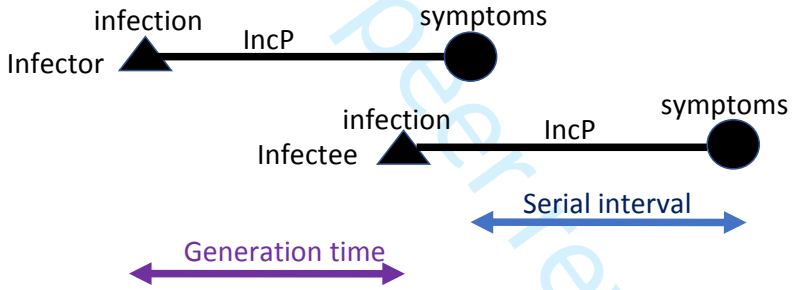
Figure 5: A boxplot summarising simulation results showing transmission time in days relative to infector symptom onset. Purple triangles reflect the mean of the simulation samples. CN AEH = China: All regions excluding Hubei, CN HK =China: Hong Kong, CN SY = China: Shiyan (Hubei), CN SZ = China: Shenzhen, CN TJ = China Tianjin, CN ZH =

China: Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam.

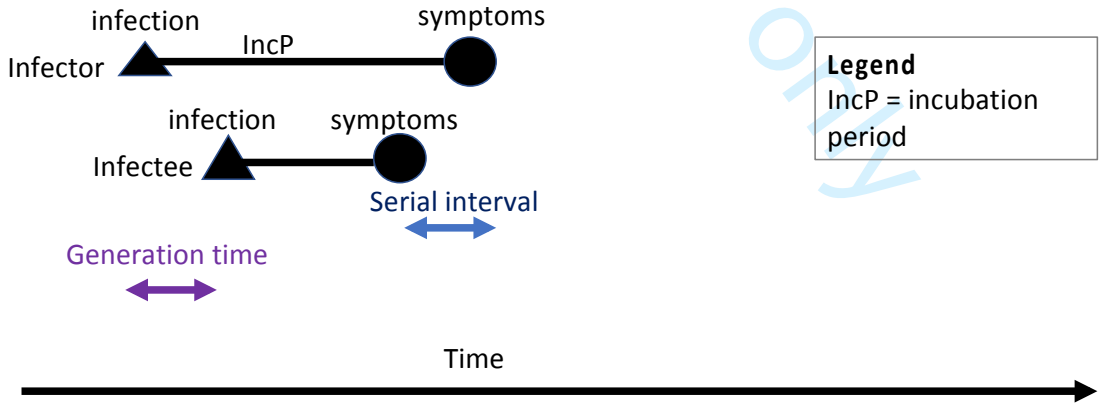
A: Symptomatic transmission: Incubation period ≤ [Serial interval or Generation time]

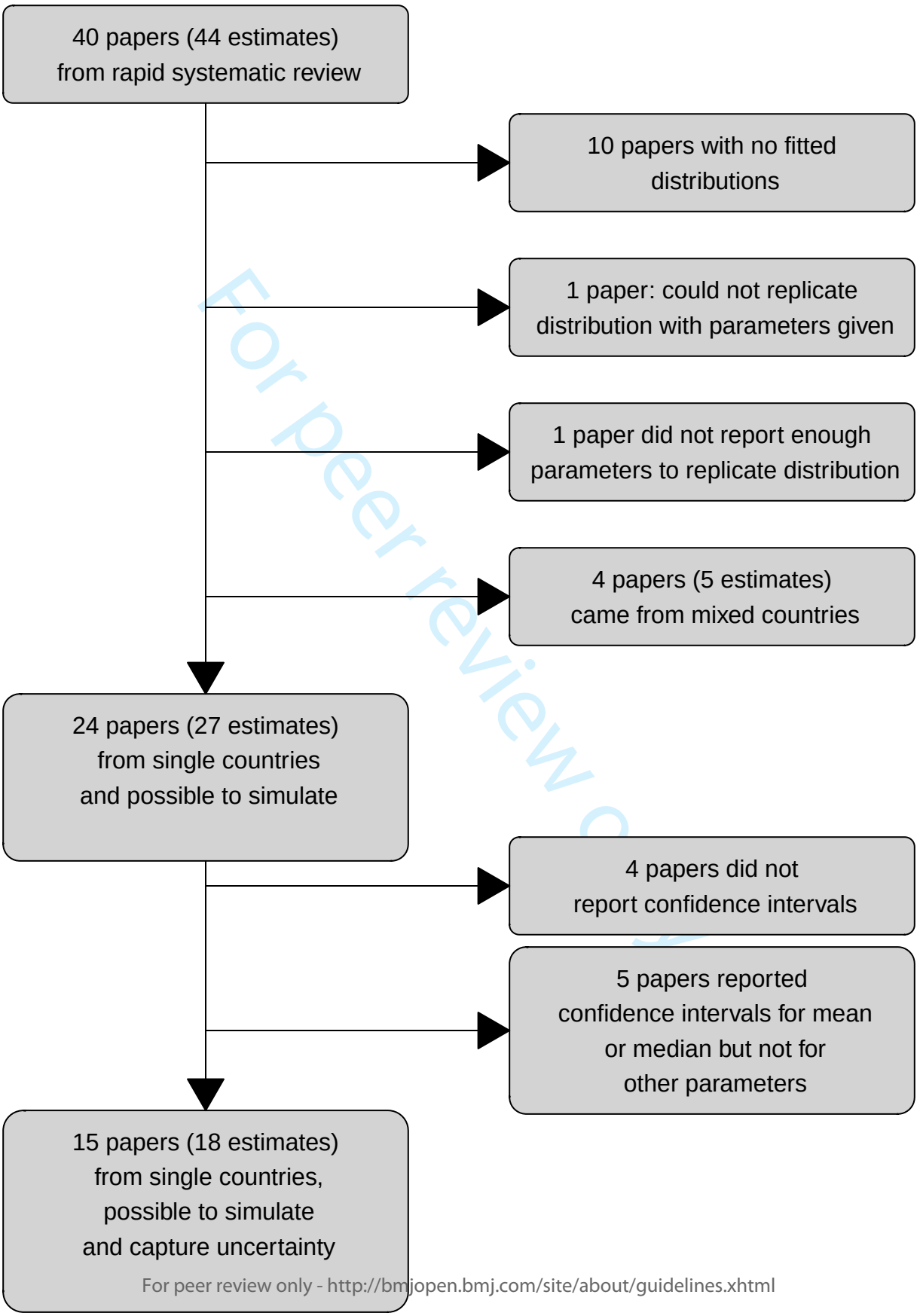


B: Pre-symptomatic transmission: Incubation period > [Serial interval or Generation time] and Serial interval > 0



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





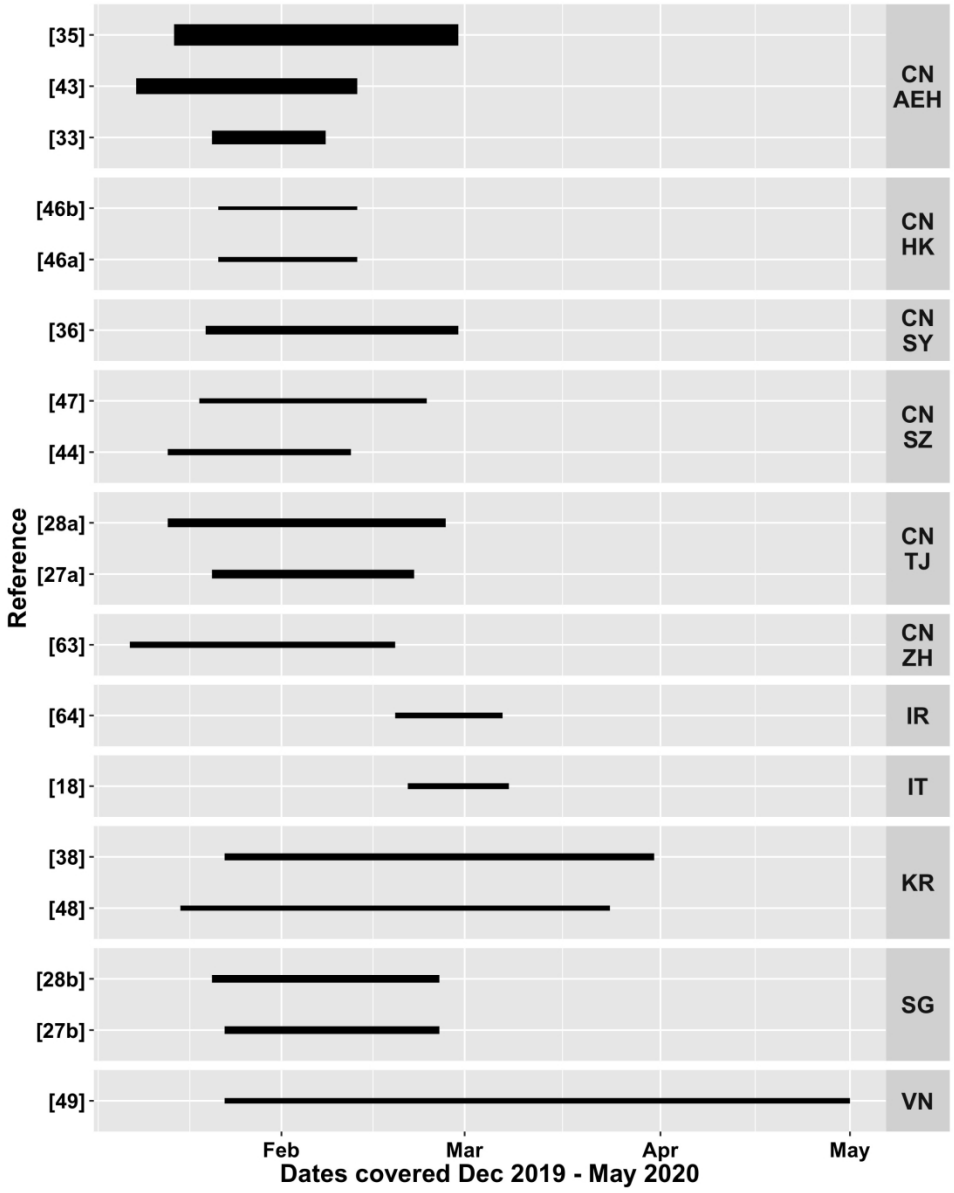


Figure 3: A summary of country or region and date ranges for the 18 serial interval estimates from 15 papers that were included in simulations to infer pre-symptomatic transmission. Line thickness is scaled to reflect sample size (i.e. reference [47a] has the smallest and [48], the largest sample size). 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.

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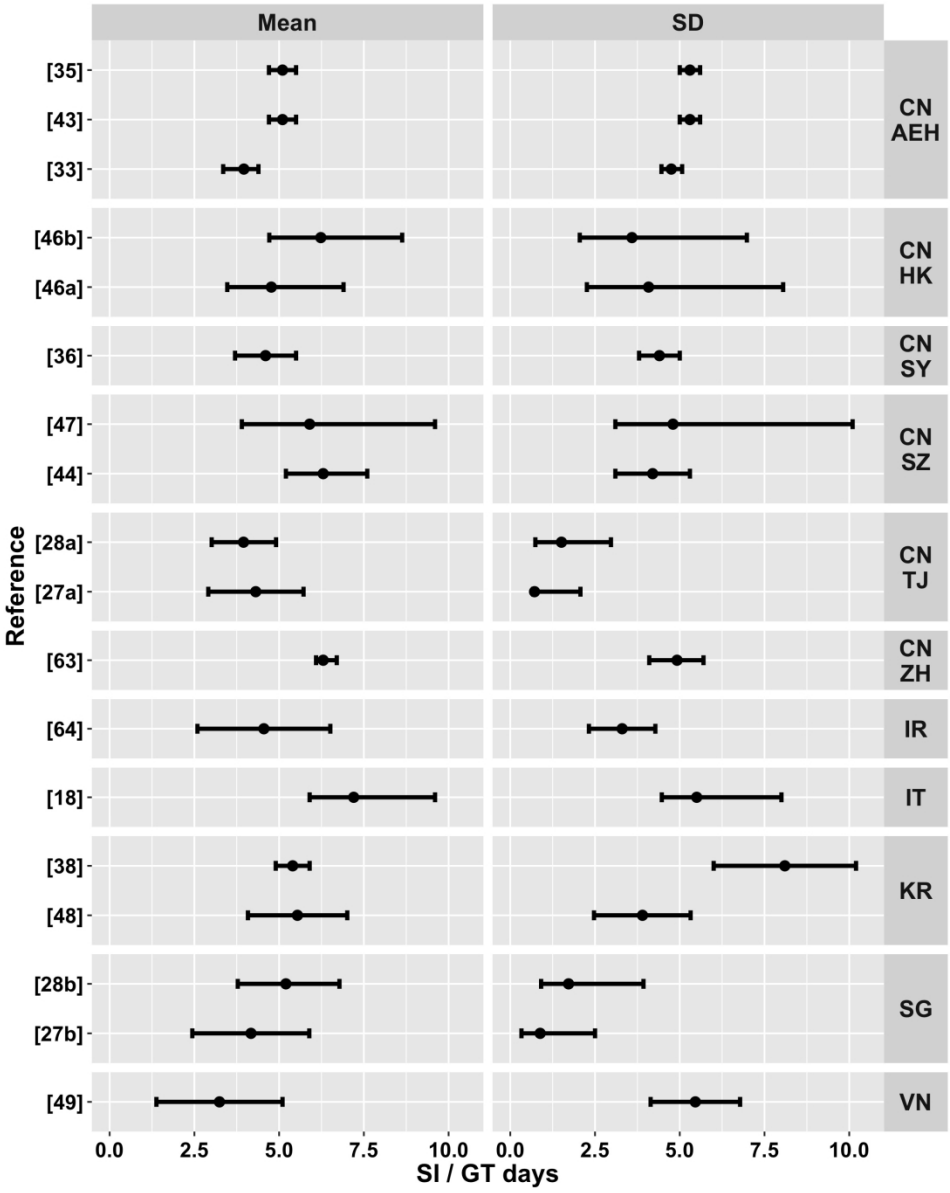

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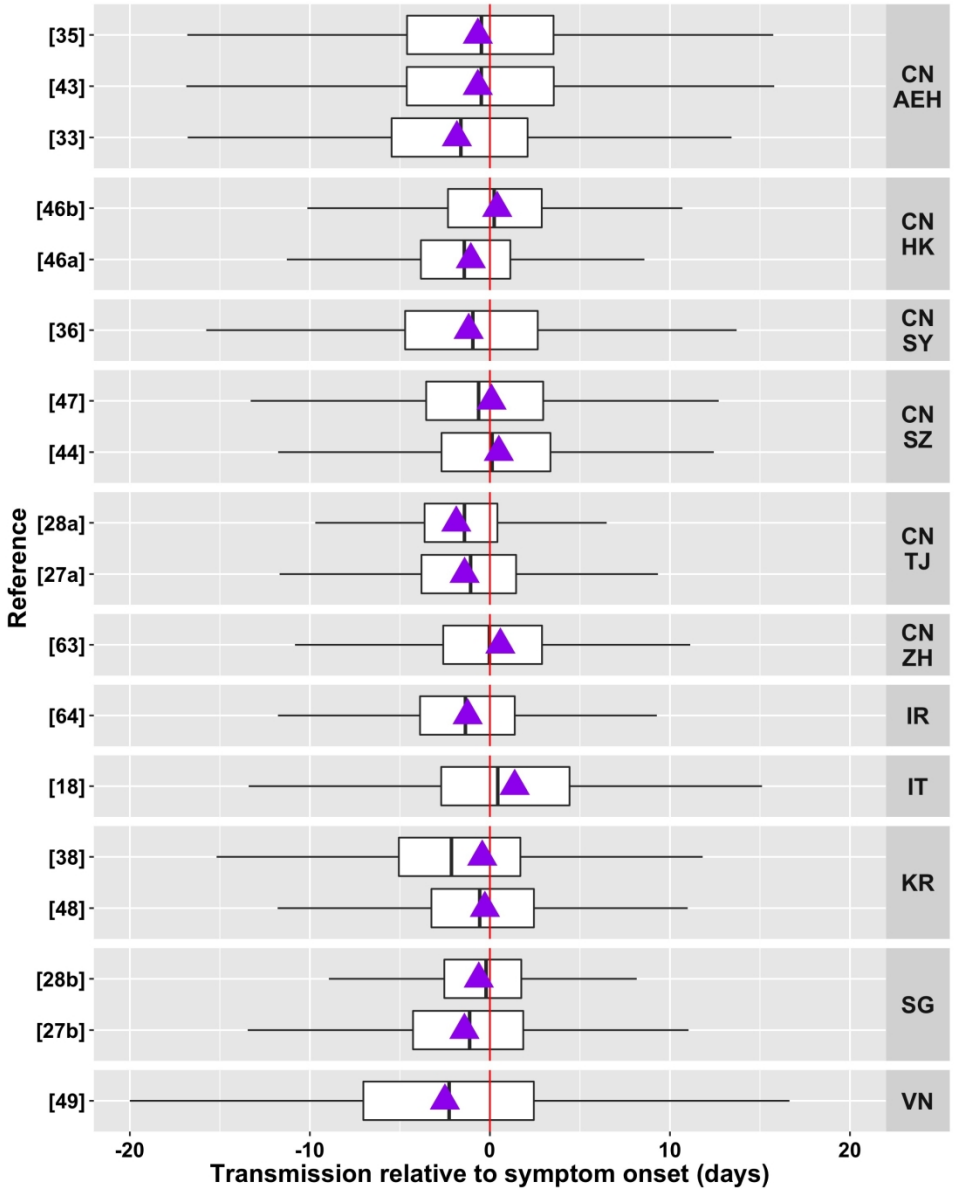

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Supplementary tables

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 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, -0.1)	53.5 (50.4, 56.6)	1407		
Zhang et al. [50]	24/12/19 - 17/02/20	-0.8	4.1	-0.6	57.2	35		Comment: serial interval about same as incubation period, suggesting possible transmission before symptoms.
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)
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		
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. [46]	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
Kwok et al. [46]	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
China - Shiyan (Hubei)								

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)	-1.0 (-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 isolation = shorter SI (mean: 3.6 days.) Delayed isolation = longer SI (mean: 8.1 days)
China - Tianjin								
Ganyani et al. [28]a	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%)	
Tindale et al. [27]a	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		
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]	08/01/20 - 19/02/20	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0.0 (-0.3, 0.3)	50.2 (47.1, 53.3)	48		most secondary cases were likely infected around the time of symptom onset of the primary cases
Iran - West								
Najafi et al. [54]	22/02/20 - 09/04/20	-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]	19/02/20 - 07/03/20	-1.2 (-1.5, -0.9)	4.7 (4.4, 5)	-1.4 (-1.7, -1.1)	63.5 (60.5, 66.5)	37		
Italy - Vo (Village in northern Italy)								
Lavezzo et al. [18]	21/02/20 - 08/03/20	1.4 (1, 1.8)	6.4 (6, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49)	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]	23/01/2020-31/03/2020	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)	69	37% (16-52%)	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. [27]b	23/01/20 - 26/02/20	-1.4 (-1.7, -1.1)	4.8 (4.5, 5)	-1.1 (-1.5, -0.8)	60.0 (57.0, 63.1)	91 cases	74%	Mean transmission time of 1.99 days before symptom onset
Ganyani et al. [28]b	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%)	

Reference	Date range	Mean	SD	Median	PST	N	PSTp	Comment
Vietnam								
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% CrI: 32, 67)	52.52% (49.43, 55.6)	74%	60.0% (57, 63.1)
Tianjin	62% (50-76%)	69.06% (66.2, 71.94)	81%	61.1% (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. The median time to symptom onset reported by Arons et al. [22] was 4 days (IQR 3-5 days)
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. [55]	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.

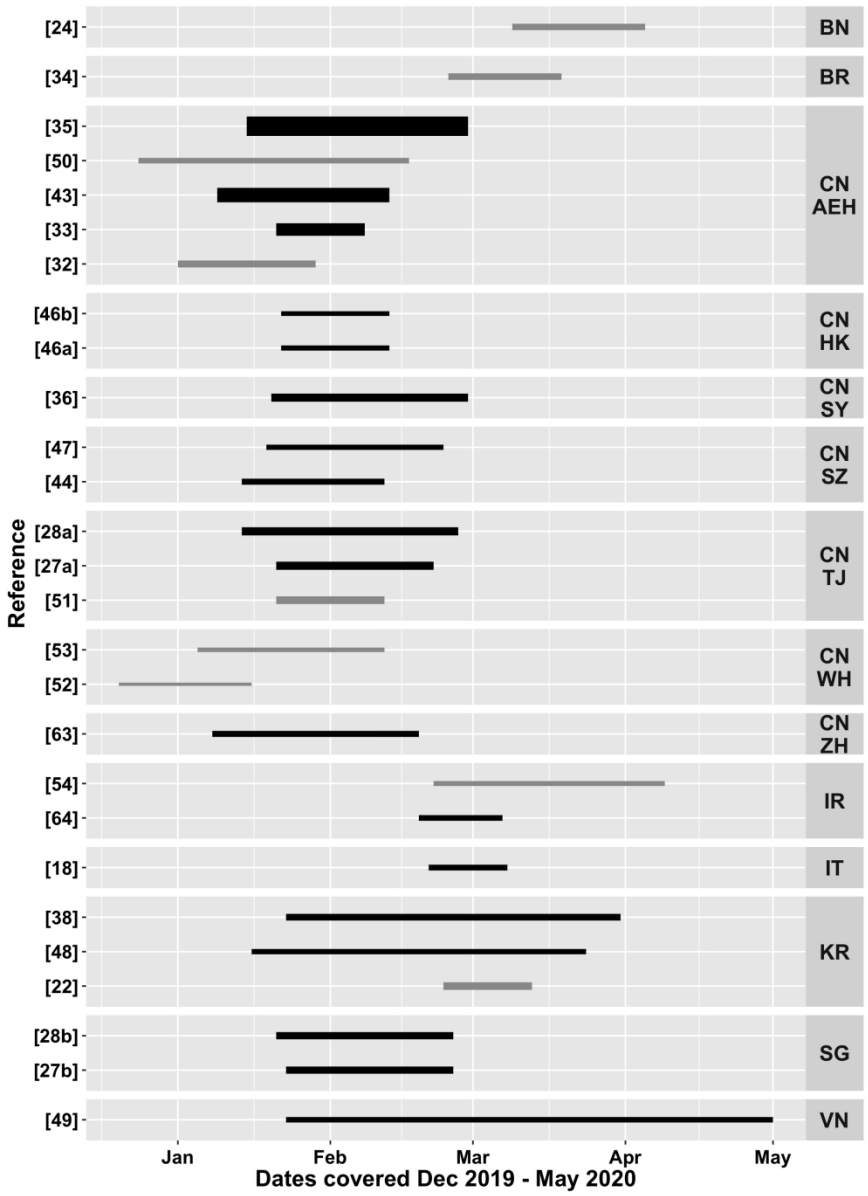
Study	Date and location	Description	Duration before symptom onset was exposure window for infectee? (minimum)
Huang et al. [10]	Nanjing China 21st-28th Jan 2020	Index case infected 6 others before symptoms. Two secondary cases potentially infected three others before symptom onset.	4-7 days 5 or 7 days 5 days 5days 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. [56]	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

Study	Date and location	Description	Duration before symptom onset was exposure window for infectee? (minimum)
Zhang et al. [17]	Ningxia, China 22nd Jan – 1st Feb	2 cases attributed to pre-symptomatic transmission.	10 days (n=2)
Lavezzo et al. [18]	Vo, northern Italy	Evidence of pre-symptomatic transmission to 1-4 people.	3-4 days
Liao et al. [19]	Chongquing, 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

Supplementary figure 1: A summary of source locations and date ranges covered 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). 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: 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.

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: 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.

Supplementary figure 3: A boxplot summarising simulation results showing transmission time in days relative to infector symptom onset. Purple triangles reflect 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: 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.



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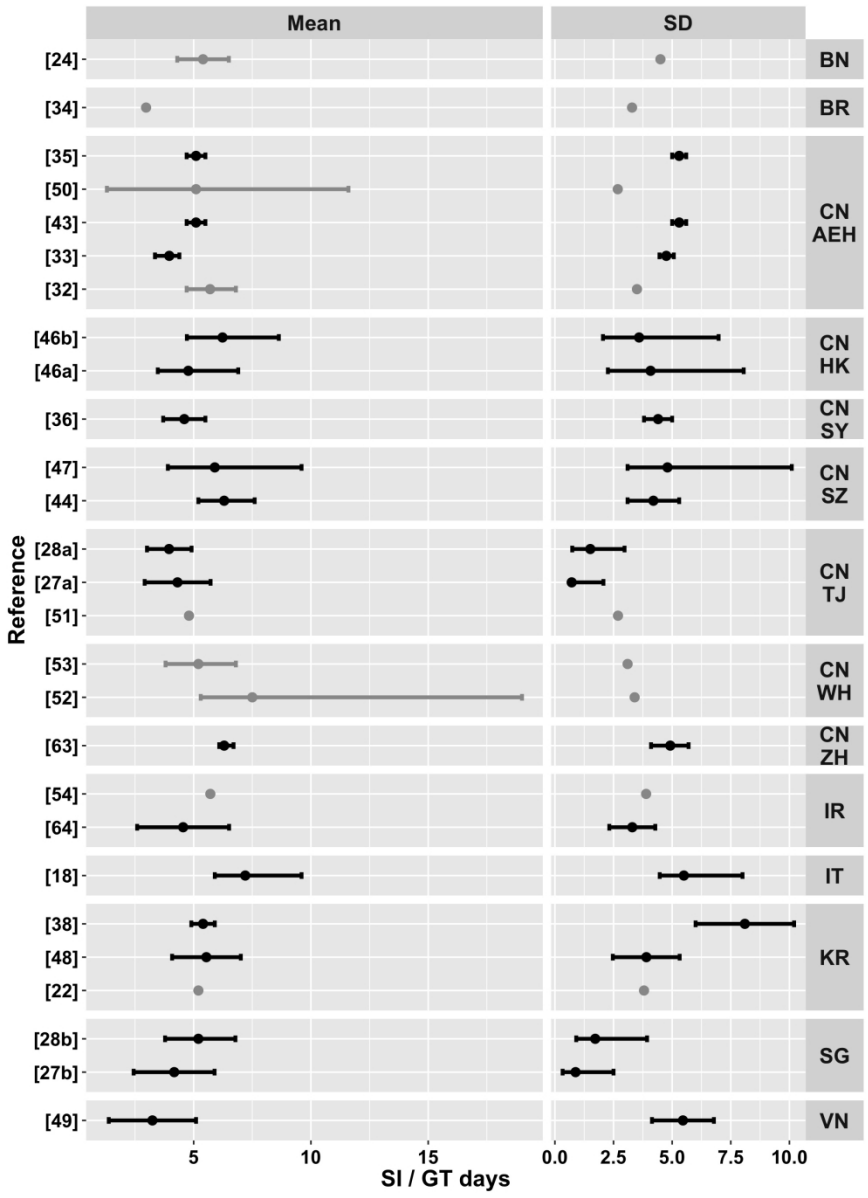

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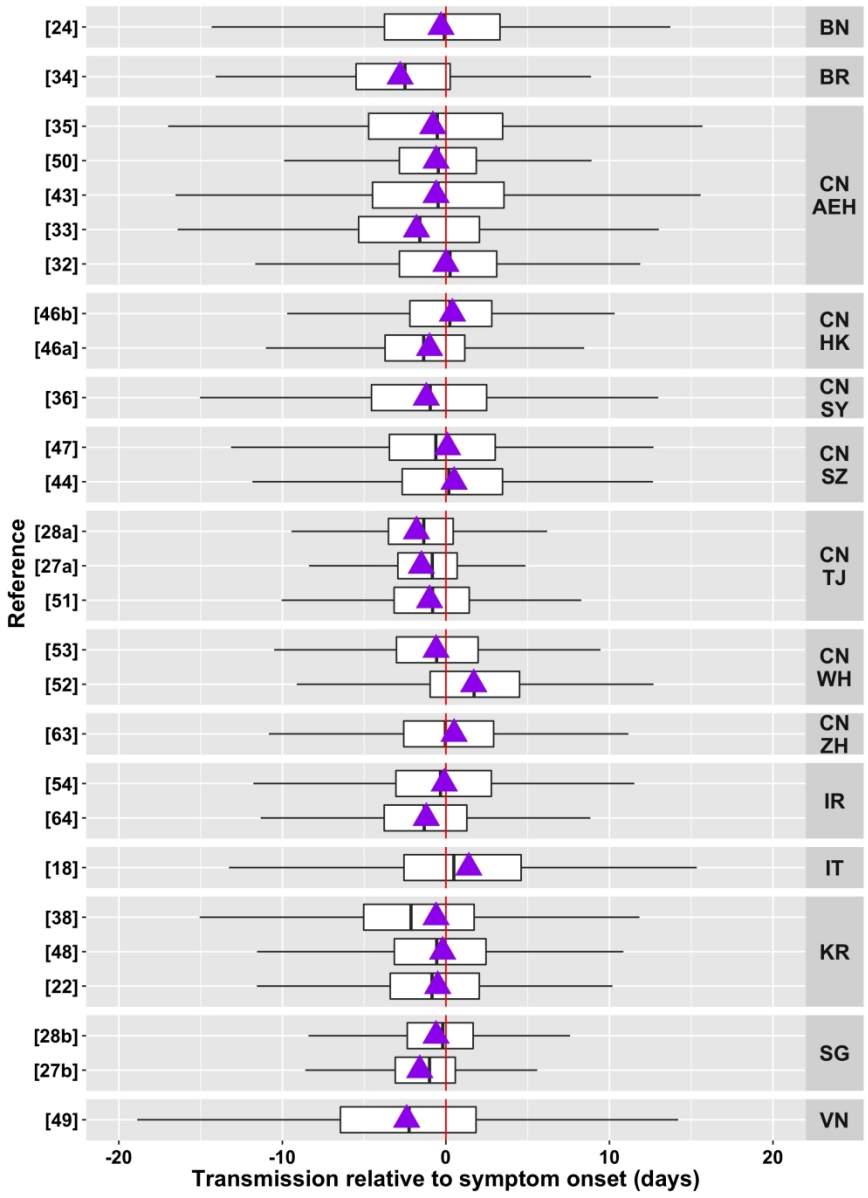

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Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data

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Key words: "COVID-19"; 'SARS-CoV-2", "Pre-symptomatic"; "Transmission"

Abstract

Objective: To estimate the proportion of pre-symptomatic 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.

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 pre-symptomatic transmission, were estimated.

Outcome measures: Transmission time of SARS-CoV-2 relative to symptom onset and proportion of pre-symptomatic 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, -2.1) days before infector symptom onset in to 1.4 (95% CI: 1.0, 1.8) days after symptom onset. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0) to 69.1% (95% CI: 66.2%, 71.9%).

Conclusions: There is substantial potential for pre-symptomatic 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.

Strengths and weaknesses of this study

- We estimate the extent and variation of pre-symptomatic transmission of SARS-CoV-2 infection across a range of contexts and highlight its importance for COVID-19 control policy.
- This is a secondary analysis of published estimates of incubation period, generation time and serial interval.
- Transmission patterns we report reflect the combination of biological infectiousness and transmission opportunities which vary according to context.

Introduction

There is currently a pandemic of coronavirus disease (COVID-19), a recently emerged and rapidly spreading infectious disease that is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are large direct impacts of COVID-19 amongst known cases. As of 19th of April 2021, the World Health Organization has reported 140, 886,773 confirmed cases and 3,012,251 deaths due to COVID-19 [1]. In China, 14% and 5% of cases were classified as severe and critical, respectively [2]. There are also major indirect impacts of COVID-19 and its control measures on other aspects of health care [3–5] and on the economy [6,7].

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 [8]. 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 pre-symptomatic and asymptomatic transmission are potentially different, and separate approaches may be required to understand them. In this paper, we capitalise upon the considerable information about pre-symptomatic transmission that can be inferred from contact tracing studies. Therefore, we focus here 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 pre-symptomatic transmission which has been highlighted by those developing models to inform policies [9].

Reports of pre-symptomatic transmission [10–19] emerged as detailed contact tracing was conducted during early outbreaks of COVID-19. Further, both viral genome [18,20–26] and live virus [21] 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 proportion [27–30,38] and timing [27,30,38] of pre-symptomatic transmission, using a variety of datasets and methodologies. Here, we compare pre-symptomatic 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 [39] and rapid systematic review and meta-analysis of incubation period [40] with a secondary analysis of published data to estimate the proportion and timing of pre-symptomatic 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 pre-symptomatic 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 [28]. Our method entailed subtracting simulated values for incubation period from serial interval to estimate the timing and proportion of pre-symptomatic 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 [40]; that is, a lognormal distribution with meanlog and sdlog parameters of 1.63 (95% CI 1.51, 1.75) and 0.50 (95% CI 0.46, 0.55), respectively. The corresponding mean and median were 5.8 (95% CI 5.0, 6.7) days and 5.1 (95% CI 4.5, 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 [40] to investigate pre-symptomatic 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 [39], 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 [39], we presented the serial interval

and generation time data to highlight 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 metanalysis [43]. To achieve this, we sampled distribution parameters from their respective 95% confidence intervals 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% confidence intervals 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 pre-symptomatic transmission at the level of each underlying serial interval or generation time estimate, grouped by country or region.

In Supplementary Figures 1-3 and Supplementary 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, if only central estimates of serial interval/generation time parameters were available, we also used only central parameter estimates of the incubation period (meanlog 1.63, sdlog 0.5).

All analyses were conducted in the R Statistical Environment [45]. 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. [39], 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 standard deviation of each estimate. Of the 18 estimates from 15 papers for which we could incorporate uncertainty into our simulations, eleven came from China, two each came from the Republic of Korea and form Singapore, and one each from the Islamic Republic of Iran, Italy and Vietnam. Sample sizes ranged from 17 [46] to 1407 [35] transmission pairs.

Of the eleven estimates from China, three 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 [35], 677 [43] and 468 [33] transmission pairs), and were associated with the same group of authors, who confirmed some overlap between the datasets underlying each paper. Xu et al. [35] and Ali et al. [43] 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 [46], 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 from the same region and date range. The two estimates from Shenzhen [44,47] had some overlap in date range but differed in sample size (48 transmission pairs [44], 27 transmission pairs [47]). Ganyani et al. [28] and Tindale et al. [27] used the same datasets from Tianjin and Singapore. Son et al. [48] reported a serial interval estimate based on data from Busan in the Republic of Korea, whereas Chun et al [38] used data from the whole country. Shiyan (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. [28] 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 [18,27,28,35,38,47] 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. [44] quantified this as mean serial interval of 3.6 days if a case was isolated within less than three 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 six days after symptom onset. Ali et al. [43] 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 pre-symptomatic transmission. Mean transmission time relative to symptom onset ranged from -2.6 (95% CI: -3.0, -2.1) days before infector

symptom onset in Vietnam [49] to 1.4 (95% CI: 1.0, 1.8) days after symptom onset in Italy [18]. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0%) in Italy [18] to 69.1% (95% CI: 66.2, 71.9) in Tianjin [28]. 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 (normal distributions rather than gamma, lognormal or Weibull). Simulations based on Chinese data ranged from 16.7% (95% CI: 14.4, 19.0) to 20.4% (95% CI: 17.9, 22.9) whereas the simulation using the data from Vietnam resulted in 30.9% (95% CI: 28.0, 33.8) negative serial intervals.

Supplementary figures 1-3 and Supplementary 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 [34], Brunei Darussalam [24], China (all regions excluding Hubei) [32,50], Tianjin [51], Wuhan [52,53], Iran [54] and the Republic of Korea [22]. Supplementary Table 1 also shows any estimates or comments relating to pre-symptomatic transmission that we found in the serial interval or generation time papers. Supplementary table 2 compares the pre-symptomatic transmission time estimates of Ganyani et al. [28], Tindale et al. [27] and this study which all refer to the same datasets from Singapore and Tianjin. Supplementary tables 3 and 4 summarise virological studies and case reports of pre-symptomatic 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 pre-symptomatic 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 pre-symptomatic transmission) [43,44]. Well characterised infector-infectee data is 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 two weeks after symptom onset [30,55–58]. Similarly, findings of detailed contact tracing in Shenzhen showed that isolation less than three days following symptom onset has a large effect in shortening serial interval whereas isolation at six days or later after symptom onset has no effect [44]. 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 [18,20,21,23–25,59,60] and live virus [21] detection in upper respiratory samples prior to symptom onset. Bae et al. [22] reported viral genome detection up to 13 days prior to symptom onset and Arons et al. [21] isolated live virus from upper respiratory samples from nursing home residents six days prior to symptom onset. Of 48 residents testing positive for viral genome in upper respiratory tract samples, Arons et al. [21] reported that 24 of these residents tested positive a median of 4 (IQR 3-5) days in advance of symptom onset. Supplementary table 3 provides a more detailed summary of the virological studies that we refer to. Case series with detailed descriptions of contact patterns and symptom onset [10–19] (Supplementary 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 pre-symptomatic transmission, given reported serial intervals that were similar to, or shorter than, estimates for the incubation period of COVID-19 (Supplementary table 1). Another quantitative study investigating pre-symptomatic transmission [30] used 77 transmission pairs from a mixture of countries to infer that infectiousness peaked at symptom onset (95% CI: –0.9, 0.9 days). The authors estimated that 44% (95% CI: 30, 57%) of transmission was pre-symptomatic. Ferretti et al. [29], also using data from a mixture of countries (40 transmission pairs), inferred that 37% (95% CI: 27.5, 45) of transmission was

pre-symptomatic 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. [28] and Tindale et al. [27] used the same dataset to infer transmission pairs and estimate pre-symptomatic transmission. Their estimates were 48% (95% CrI: 32, 67) and 74% for Singapore, and 62% (95% CrI: 50,76) 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 pre-symptomatic transmission based on the generation times of Ganyani et al [28], and the serial intervals of Tindale et al. [27] also differ from the authors' estimates (Supplementary table 2) due to using a different estimate for incubation period and a slightly different approach to transmission time calculation.

We estimate more pre-symptomatic transmission (64.2%) based on the serial interval of Chun et al. [38] than what is estimated in their paper (37%), as the incubation period used for our estimation of pre-symptomatic transmission (median 5.1 days) is much longer that that used in Chun et al. 's calculations (median 2.87 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 [28] 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 [41,42], although serial interval will have more variation [28]. The extra variation associated with serial interval should be borne in mind whilst 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. [46] 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 (for example [41,61]) for inferring transmission pairs from clusters of cases could also impact serial interval or generation time estimates. Griffin et al. [39] and Du et al. [33] 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 pre-symptomatic 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. [27] reported an intermediate signal for covariation between incubation period and serial interval. However, Tindale et al. showed that the degree of positive correlation did not greatly impact estimates of pre-symptomatic transmission. Liu et al. [62] simulated the effect of full correlation and anti-correlation between serial interval and incubation period on pre-symptomatic transmission estimates. However, the direction and magnitude of effects varied depending on which published estimates the simulations were based upon. 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 pre-symptomatic 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 pre-symptomatic transmission of COVID-19 in a range of different contexts. The proportion of pre-symptomatic 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.

Tables

Table 1: Definitions referred to in this review.

Asymptomatic	An infected person who never develops symptoms of the disease
Pre-symptomatic	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 and that of its primary case.
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 who 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 (SEIR) 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 pre-symptomatic transmission	The proportion of all transmission events that occur before the onset of symptoms in the infector.

Table 2: A summary of simulation results. The table shows showing the mean, standard deviation (SD) and median of transmission time relative to symptom onset in days as well as the proportion of pre-symptomatic 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 brackets represent the 95% confidence intervals form 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.

Reference	Mean	SD	Median	PST
China - All excluding Hubei				
Xu et al. [35]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, -0.1)	53.5 (50.4, 56.6)
Ali et al. [43]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, 0)	53.2 (50.1, 56.3)
Du et al. [33]	-1.8 (-2.1, -1.4)	5.8 (5.5, 6)	-1.6 (-2, -1.1)	61.2 (58.2, 64.3)
China - Hong Kong				
Kwok et al. [46a]	-1 (-1.4, -0.7)	5.3 (4.3, 6.3)	-1.3 (-1.6, -1.1)	64.5 (61.5, 67.4)
Kwok et al. [46b]	0.5 (0.2, 0.8)	5 (4.4, 5.7)	0.4 (0.1, 0.7)	46.3 (43.2, 49.4)
China - Shiyan (Hubei)				
Yang et al. [36]	-1.2 (-1.5, -0.8)	5.7 (5.4, 6)	-1 (-1.4, -0.5)	57.1 (54.1, 60.2)
China - Shenzhen				
Wang et al. [47]	0.1 (-0.2, 0.5)	6.2 (5.4, 6.9)	-0.5 (-0.9, -0.1)	54.2 (51.1, 57.2)
Bi et al. [44]	0.5 (0.2, 0.8)	5.3 (5, 5.6)	0.1 (-0.2, 0.5)	48.6 (45.5, 51.8)
China - Tianjin				
Ganyani et al. [28a]	-1.8 (-2, -1.6)	3.5 (3.3, 3.8)	-1.4 (-1.6, -1.1)	69.1 (66.2, 71.9)
Tindale et al. [27a]	-1.4 (-1.7, -1.1)	4.2 (3.9, 4.5)	-1.1 (-1.4, -0.8)	61.1 (58.1, 64.2)
China - Zhuhai				
Wu et al. [63]	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0 (-0.3, 0.3)	50.2 (47.1, 53.3)
Iran - Qom				
Aghaali et al.[64]	-1.2 (-1.5, -0.9)	4.7 (4.4, 5)	-1.4 (-1.7, -1.1)	63.5 (60.5,

Reference	Mean	SD	Median	PST
				66.5)
Italy - Vo (Village in Northern Italy)				
Lavezzo et al. [18]	1.4 (1.0, 1.8)	6.4 (6.0, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49.0)
Republic of Korea - All				
Chun et al [38]	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)
Republic of Korea - Busan				
Son et al. [48]	-0.3 (-0.6, 0.1)	5.1 (4.7, 5.4)	-0.6 (-0.9, -0.2)	55.4 (52.3, 58.4)
Singapore				
Ganyani et al. [28b]	-0.6 (-0.8, -0.4)	3.7 (3.5, 4)	-0.2 (-0.4, 0)	52.5 (49.4, 55.6)
Tindale et al. [27b]	-1.4 (-1.7, -1.1)	4.8 (4.5, 5)	-1.1 (-1.5, -0.8)	60 (57, 63.1)
Vietnam				
Pham et al. [49]	-2.6 (-3.0, -2.1)	7.2 (6.9, 7.6)	-2.4 (-3, -1.9)	63.4 (60.5, 66.4)

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Competing interests

All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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

Author contributions

MC conceptualized 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. ÁC, KH, KOB and KW performed literature searches upon which the incubation period, generation time, serial interval and pre-symptomatic transmission information reported here are based upon. SM conceptualized, initiated and managed the overall project. MC, JG, CM, AB, JM, DM, ÁC, KH, AB, FB, EL,

KOB, PW, KW and SM supplemented the literature review, discussed the study design, reviewed and edited the manuscript.

Data sharing statement

The data and code used for the analyses described in this paper are available in the Github repository: https://github.com/miriamcasey/covid-19_presymptomatic_project

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Figure legends

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 pre-symptomatic 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.

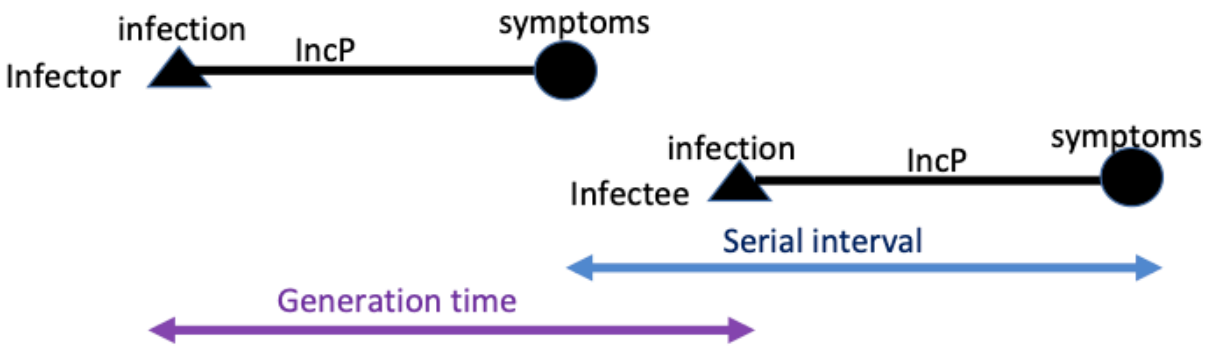
Figure 2: A summary of how serial interval and generation time estimates were selected for analyses.

Figure 3: A summary of country or region and date ranges for the 18 serial interval estimates from 15 papers that were included in simulations to infer pre-symptomatic transmission. Line thickness is scaled to reflect sample size (i.e. reference [46a] has the smallest and [35], the largest sample size). 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.

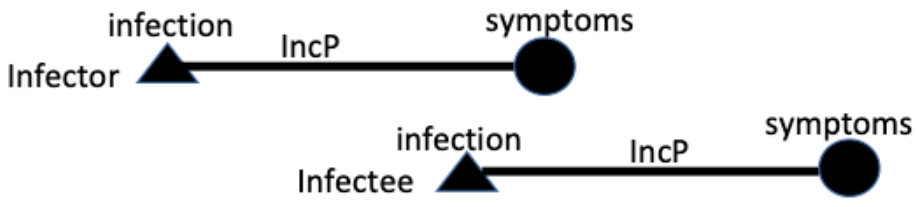
Figure 4: A summary of the parameters from the serial interval and generation time estimates that were used in the simulation, by country or region and reference. CN AEH = China: All regions excluding Hubei, CN HK =China: Hong Kong, CN SY = China: Shyan (Hubei), CN SZ = China: Shenzhen, CN TJ = China Tianjin, CN ZH = China: Zhuhai, IR = Iran, IT= Italy, KR = The Republic of Korea, SG = Singapore, VN = Vietnam. Points indicate means and bars indicate 95% confidence intervals.

Figure 5: A boxplot summarising simulation results showing transmission time in days relative to infector symptom onset. Purple triangles show the mean of the 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.

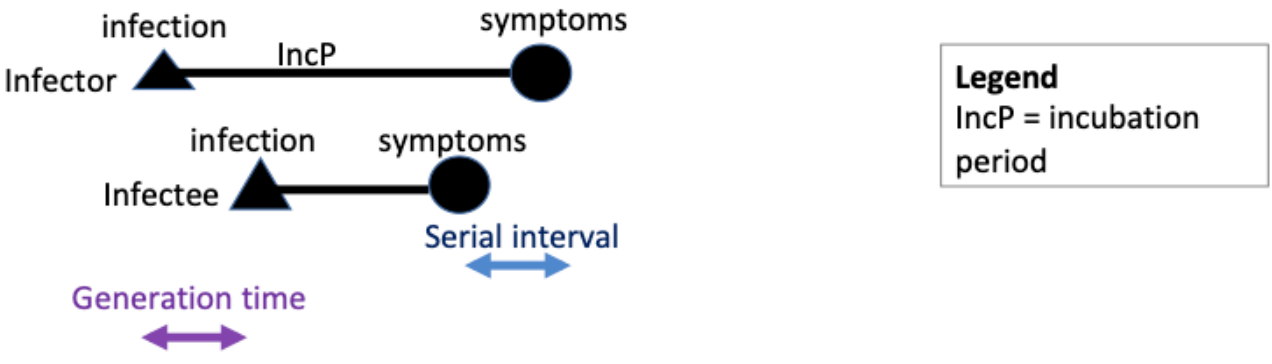
A: Symptomatic transmission: Incubation period ≤ [Serial interval or Generation time]

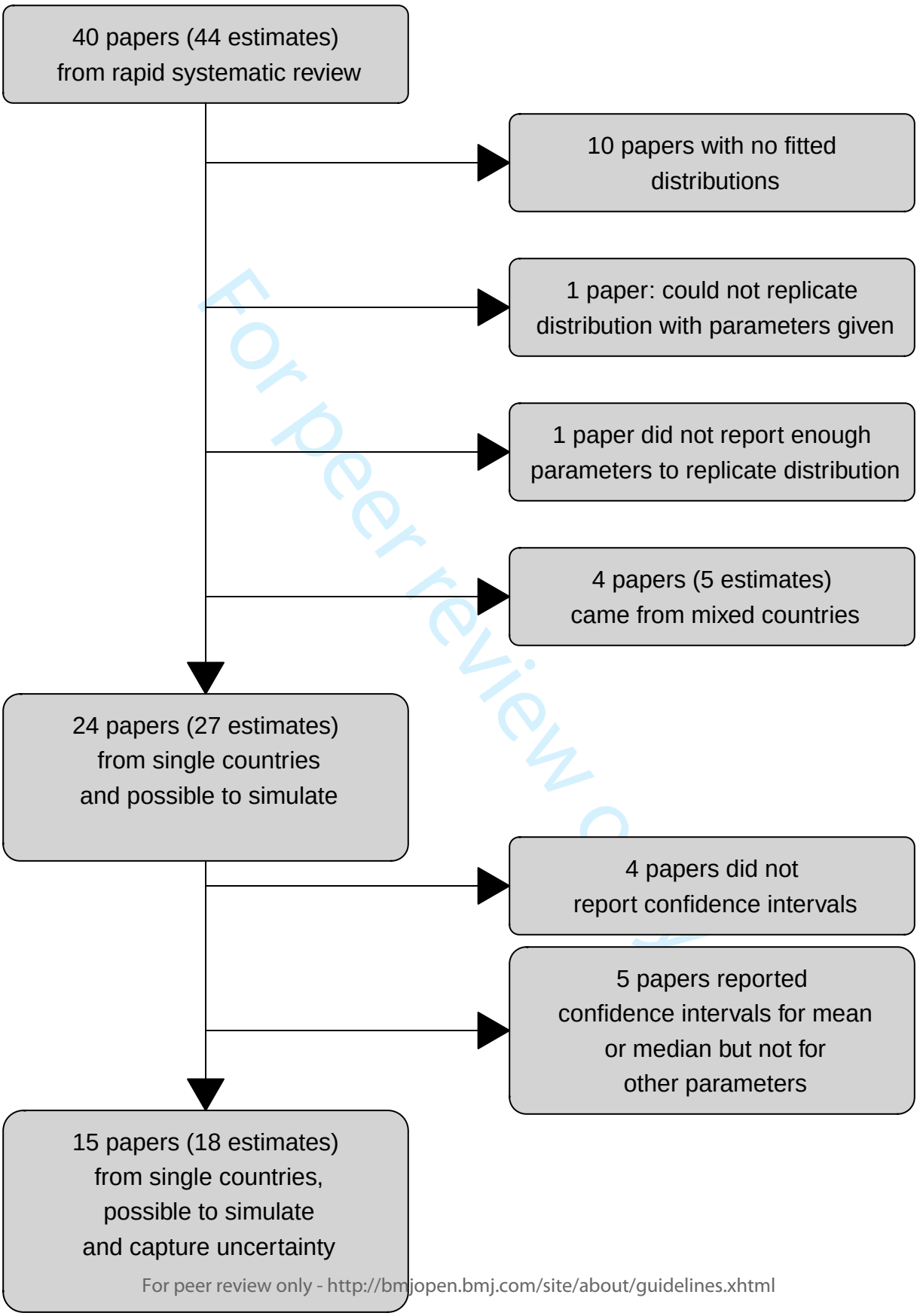


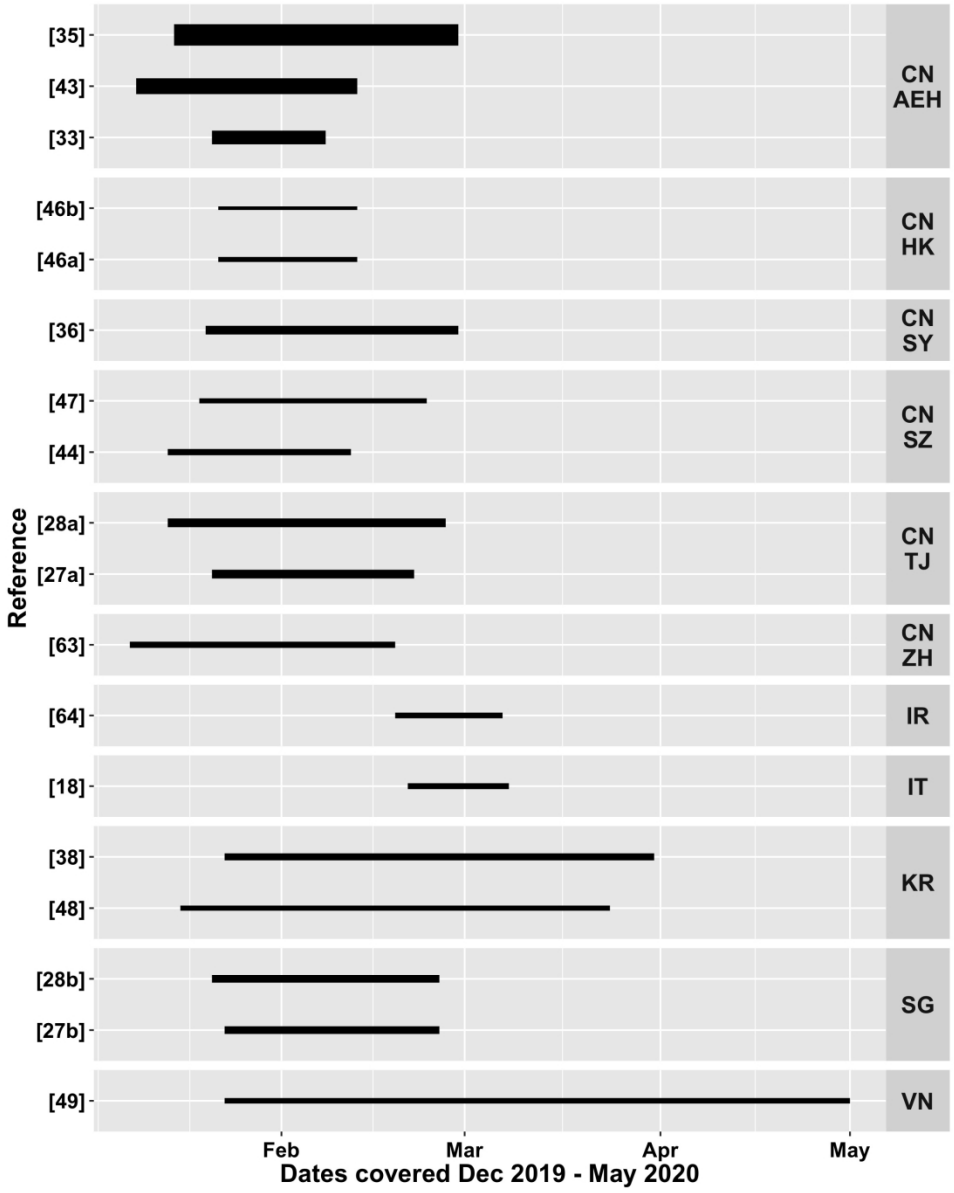
B: Pre-symptomatic transmission: Incubation period > [Serial interval or Generation time] and Serial interval > 0



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







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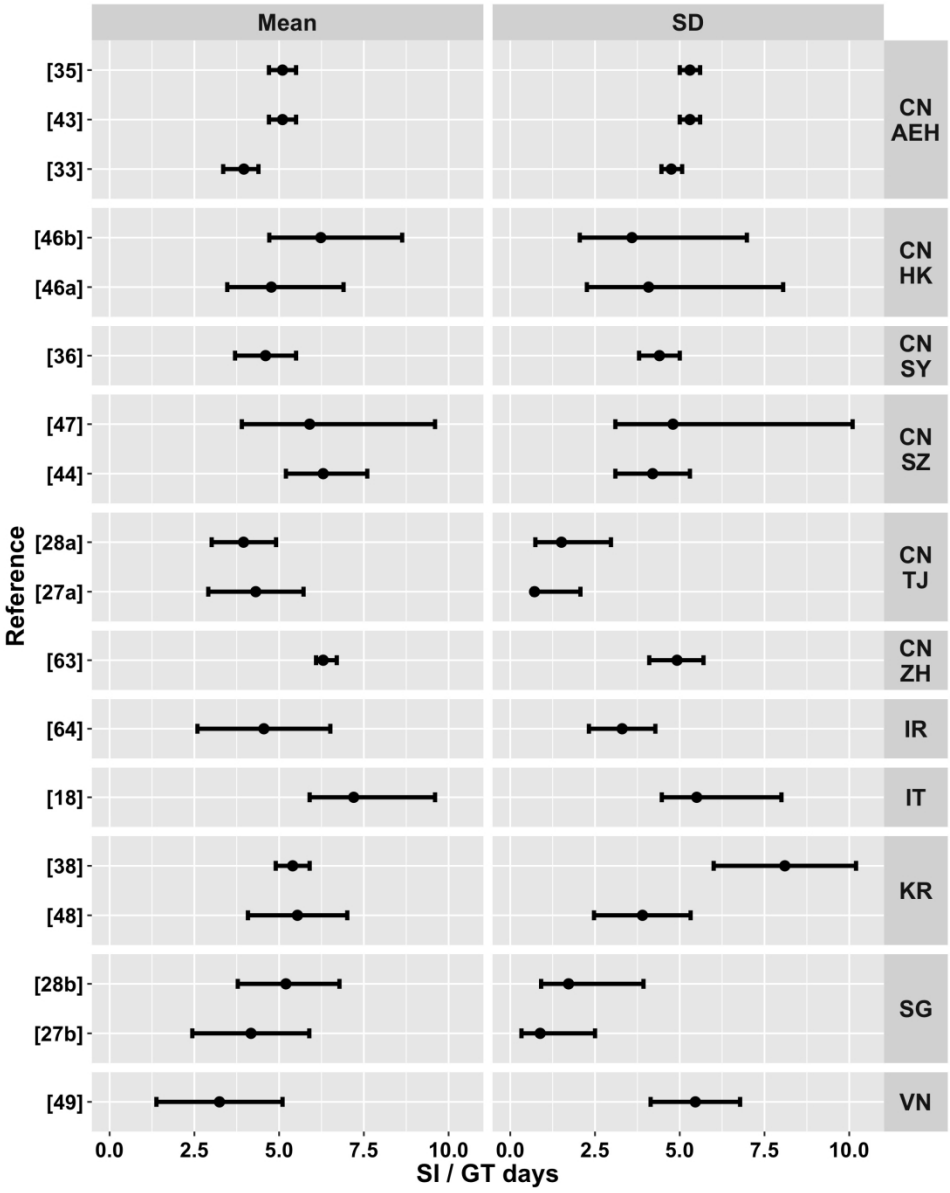

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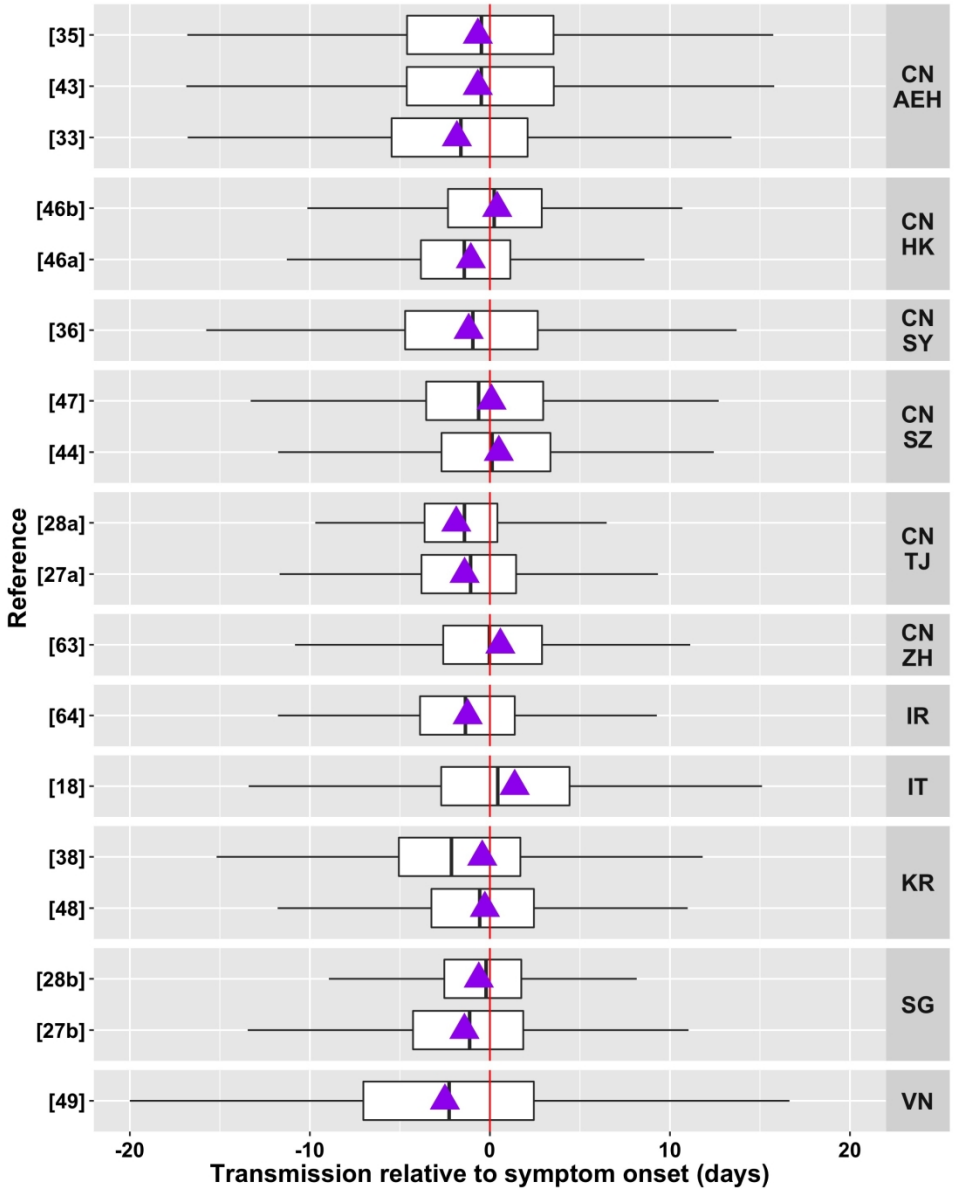

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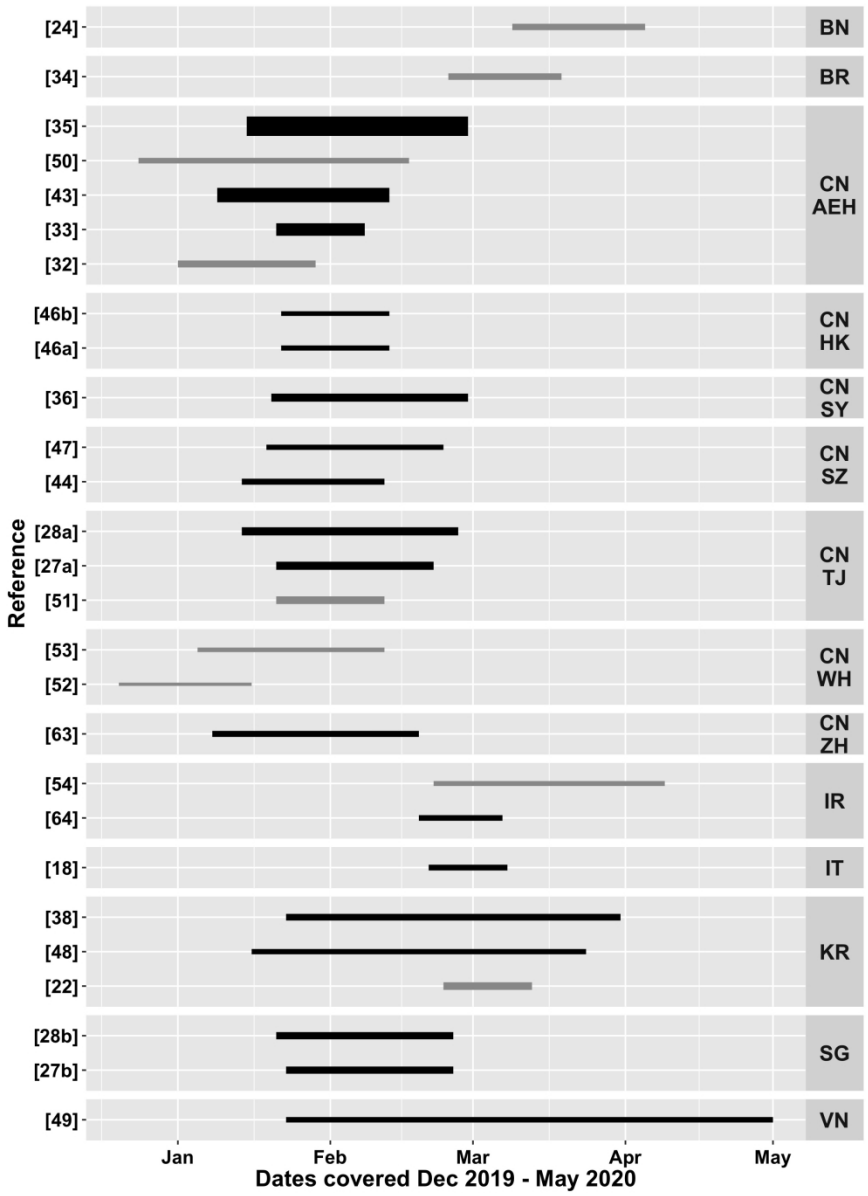

Supplementary figure 1: A summary of source locations and date ranges covered for the 27 serial interval estimates from 24 papers that were included in simulations to infer pre-symptomatic transmission. This plot refers both to the estimates from the main text for which we could capture uncertainty (black colour) and other estimates for which we could simulate distributions but not capture uncertainty (grey colour). 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: 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.

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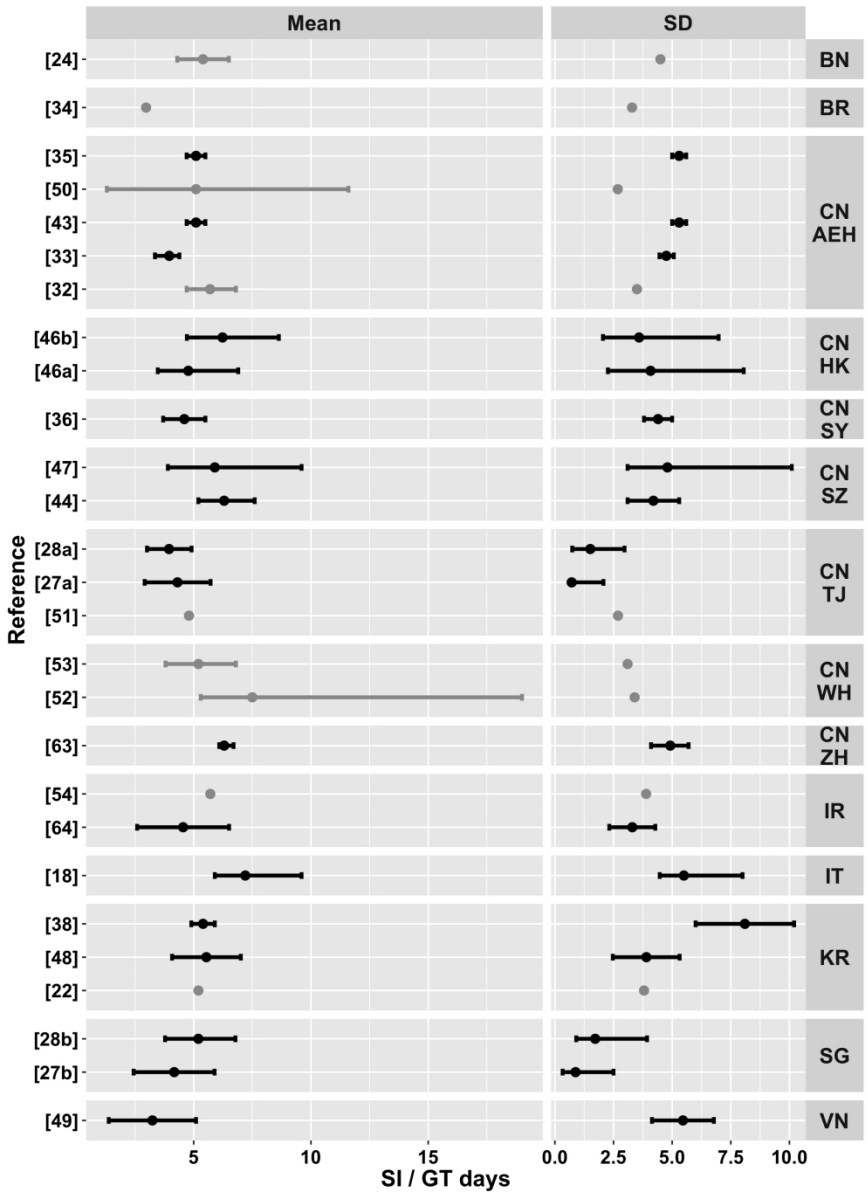

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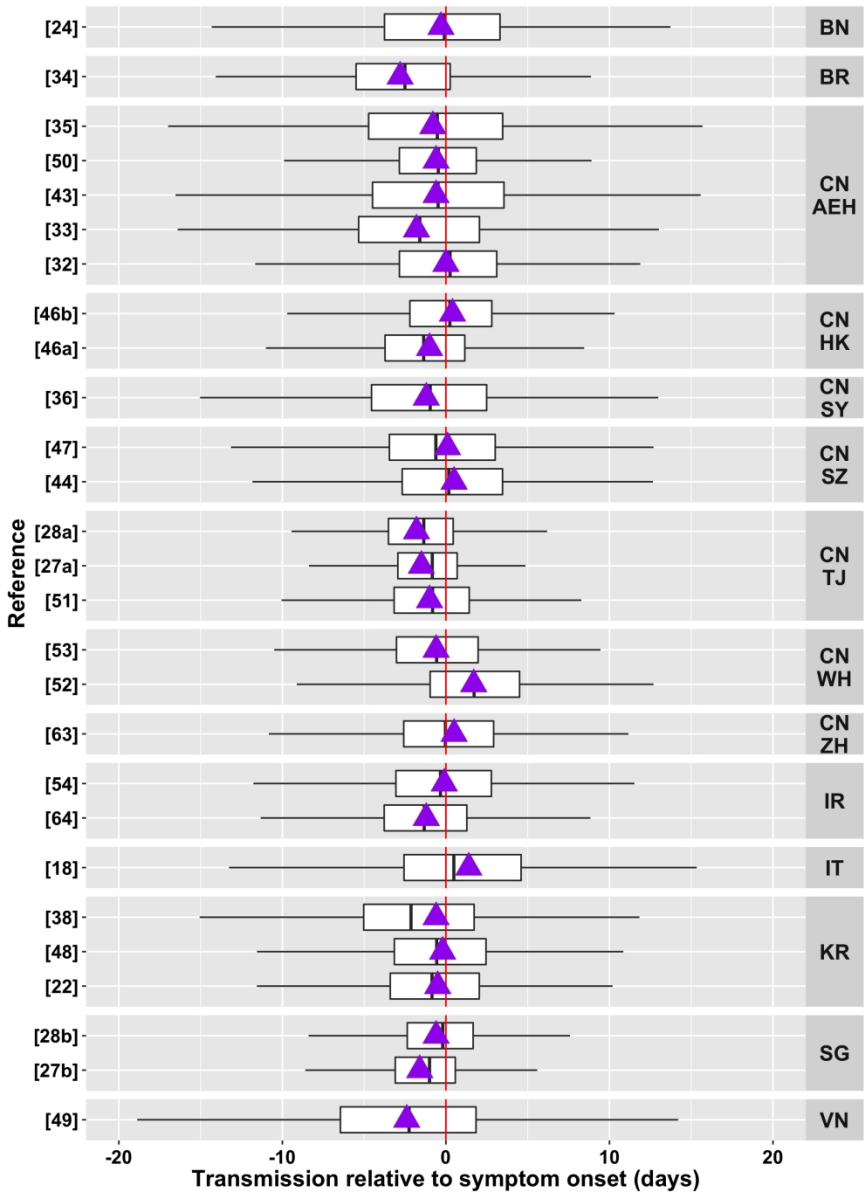

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Supplementary tables

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 it 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		
Zhang et al. [50]	24/12/19 - 17/02/20	-0.8	4.1	-0.6	57.2	35		Comment: serial interval about same as incubation period, suggesting possible transmission before symptoms.
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)
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		
Ren et al. [32]	01/01/20 - 29/01/20	-0.2	4.7	0.1	48.5	80	10%	
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)								

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 isolation = 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%)	
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		
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]	08/01/20 - 19/02/20	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0 (-0.3, 0.3)	50.2 (47.1, 53.3)	48		most secondary cases were likely infected around the time of symptom onset of the primary cases
Iran - West								
Najafi et al. [54]	22/02/20 - 09/04/20	-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]	19/02/20 - 07/03/20	-1.2 (-1.5, -0.9)	4.7 (4.4, 5)	-1.4 (-1.7, -1.1)	63.5 (60.5, 66.5)	37		
Italy - Vo (Village in northern Italy)								
Lavezzo et al. [18]	21/02/20 - 08/03/20	1.4 (1, 1.8)	6.4 (6, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49)	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]	23/01/2020-31/03/2020	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)	69	37% (26, 52%)	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% 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% CrI: 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.%1 (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. The median time to symptom onset reported by Arons et al. [21] was 4 days (IQR 3-5 days)
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	Duration before symptom onset was exposure window for infectee? (minimum)
Huang et al. [10]	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 5days 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)
Lavezzo et al. [18]	Vo, northern Italy	Evidence of pre-symptomatic transmission to 1-4 people.	3-4 days
Liao et al. [19]	Chongquing, 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

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Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data

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Abstract

Objective: To estimate the proportion of pre-symptomatic 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 pre-symptomatic transmission, were estimated.

Outcome measures: Transmission time of SARS-CoV-2 relative to symptom onset and proportion of pre-symptomatic 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, -2.1) days before infector symptom onset in to 1.4 (95% CI: 1.0, 1.8) days after symptom onset. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0) to 69.1% (95% CI: 66.2%, 71.9%).

Conclusions: There is substantial potential for pre-symptomatic 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.

Strengths and weaknesses of this study

- We generated estimates of pre-symptomatic 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 pre-symptomatic transmission, we generated estimates based on single locations and did not pool them.

Introduction

There is currently a pandemic of coronavirus disease (COVID-19), a recently emerged and rapidly spreading infectious disease that is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are large direct impacts of COVID-19 amongst known cases. As of 19th of April 2021, the World Health Organization has reported 140, 886,773 confirmed cases and 3,012,251 deaths due to COVID-19 [1]. In China, 14% and 5% of cases were classified as severe and critical, respectively [2]. There are also major indirect impacts of COVID-19 and its control measures on other aspects of health care [3–5] and on the economy [6,7].

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 [8]. 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 pre-symptomatic and asymptomatic transmission are potentially different, and separate approaches may be required to understand them. In this paper, we capitalise upon the considerable information about pre-symptomatic transmission that can be inferred from contact tracing studies. Therefore, we focus here 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 pre-symptomatic transmission which has been highlighted by those developing models to inform policies [9].

Reports of pre-symptomatic transmission [10–19] emerged as detailed contact tracing was conducted during early outbreaks of COVID-19. Further, both viral genome [18,20–26] and live virus [21] 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 proportion [27–30,38] and timing [27,30,38] of pre-symptomatic transmission, using a variety of datasets and methodologies. Here, we compare pre-symptomatic 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 [39] and rapid systematic review and meta-analysis of incubation period [40] with a secondary analysis of published data to estimate the proportion and timing of pre-symptomatic 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 pre-symptomatic 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 [28]. Our method entailed subtracting simulated values for incubation period from serial interval to estimate the timing and proportion of pre-symptomatic 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 [40]; that is, a lognormal distribution with meanlog and sdlog parameters of 1.63 (95% CI 1.51, 1.75) and 0.50 (95% CI 0.46, 0.55), respectively. The corresponding mean and median were 5.8 (95% CI 5.0, 6.7) days and 5.1 (95% CI 4.5, 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 [40] to investigate pre-symptomatic 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 [39], 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 [39], we presented the serial interval

and generation time data to highlight 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 metanalysis [40]. To achieve this, we sampled distribution parameters from their respective 95% confidence intervals 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% confidence intervals 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 pre-symptomatic transmission at the level of each underlying serial interval or generation time estimate, grouped by country or region.

In Supplementary Figures 1-3 and Supplementary 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 only central parameter estimates of the incubation period (meanlog 1.63, sdlog 0.5).

All analyses were conducted in the R Statistical Environment [45]. 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. [39], 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 standard deviation of each estimate. Of the 18 estimates from 15 papers for which we could incorporate uncertainty into our simulations, eleven came from China, two each came from the Republic of Korea and form Singapore, and one each from the Islamic Republic of Iran, Italy and Vietnam. Sample sizes ranged from 17 [46] to 1407 [35] transmission pairs.

Of the eleven estimates from China, three 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 [35], 677 [43] and 468 [33] transmission pairs), and were associated with the same group of authors, who confirmed some overlap between the datasets underlying each paper. Xu et al. [35] and Ali et al. [43] 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 [46], 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 from the same region and date range. The two estimates from Shenzhen [44,47] had some overlap in date range but differed in sample size (48 transmission pairs [44], 27 transmission pairs [47]). Ganyani et al. [28] and Tindale et al. [27] used the same datasets from Tianjin and Singapore. Son et al. [48] reported a serial interval estimate based on data from Busan in the Republic of Korea, whereas Chun et al [38] used data from the whole country. Shiyan (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. [28] 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 [18,27,28,35,38,47] 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. [44] quantified this as mean serial interval of 3.6 days if a case was isolated within less than three 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 six days after symptom onset. Ali et al. [43] 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 pre-symptomatic transmission. Mean transmission time relative to symptom onset ranged from -2.6 (95% CI: -3.0, -2.1) days before infector

symptom onset in Vietnam [49] to 1.4 (95% CI: 1.0, 1.8) days after symptom onset in Italy [18]. The proportion of pre-symptomatic transmission was substantial in all contexts, ranging from 45.9% (95% CI: 42.9%, 49.0%) in Italy [18] to 69.1% (95% CI: 66.2, 71.9) in Tianjin [28]. 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, 19.0) to 20.4% (95% CI: 17.9, 22.9) whereas the simulation using the data from Vietnam resulted in 30.9% (95% CI: 28.0, 33.8) negative serial intervals.

Supplementary figures 1-3 and Supplementary 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 [34], Brunei Darussalam [24], China (all regions excluding Hubei) [32,50], Tianjin [51], Wuhan [52,53], Iran [54] and the Republic of Korea [22]. Supplementary Table 1 also shows any estimates or comments relating to pre-symptomatic transmission that we found in the serial interval or generation time papers. Supplementary table 2 compares the pre-symptomatic transmission time estimates of Ganyani et al. [28], Tindale et al. [27] and this study which all refer to the same datasets from Singapore and Tianjin. Supplementary tables 3 and 4 summarise virological studies and case reports of pre-symptomatic 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 pre-symptomatic 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 pre-symptomatic transmission) [43,44]. Well characterised infector-infectee data is 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 two weeks after symptom onset [30,55–58]. Similarly, findings of detailed contact tracing in Shenzhen showed that isolation less than three days following symptom onset has a large effect in shortening serial interval whereas isolation at six days or later after symptom onset has no effect [44]. 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 [18,20,21,23–25,59,60] and live virus [21] detection in upper respiratory samples prior to symptom onset. Bae et al. [22] reported viral genome detection up to 13 days prior to symptom onset and Arons et al. [21] isolated live virus from upper respiratory samples from nursing home residents six days prior to symptom onset. Of 48 residents testing positive for viral genome in upper respiratory tract samples, Arons et al. [21] reported that 24 of these residents tested positive a median of 4 (IQR 3-5) days in advance of symptom onset. Supplementary table 3 provides a more detailed summary of the virological studies that we refer to. Case series with detailed descriptions of contact patterns and symptom onset [10–19] (Supplementary 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 pre-symptomatic transmission, given reported serial intervals that were similar to, or shorter than, estimates for the incubation period of COVID-19 (Supplementary table 1). Another quantitative study investigating pre-symptomatic transmission [30] used 77 transmission pairs from a mixture of countries to infer that infectiousness peaked at symptom onset (95% CI: –0.9, 0.9 days). The authors estimated that 44% (95% CI: 30, 57%) of transmission was pre-symptomatic. Ferretti et al. [29], also using data from a mixture of countries (40 transmission pairs), inferred that 37% (95% CI: 27.5, 45) of transmission was

pre-symptomatic 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. [28] and Tindale et al. [27] used the same dataset to infer transmission pairs and estimate pre-symptomatic transmission. Their estimates were 48% (95% CrI: 32, 67) and 74% for Singapore, and 62% (95% CrI: 50,76) 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 pre-symptomatic transmission based on the generation times of Ganyani et al [28], and the serial intervals of Tindale et al. [27] also differ from the authors' estimates (Supplementary table 2) due to using a different estimate for incubation period and a slightly different approach to transmission time calculation.

We estimate more pre-symptomatic transmission (64.2%) based on the serial interval of Chun et al. [38] than what is estimated in their paper (37%), as the incubation period used for our estimation of pre-symptomatic transmission (median 5.1 days) is much longer that 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 [28] 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 [41,42], although serial interval will have more variation [28]. The extra variation associated with serial interval should be borne in mind whilst 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. [46] 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 (for example [41,61]) for inferring transmission pairs from clusters of cases could also impact serial interval or generation time estimates. Griffin et al. [39] and Du et al. [33] 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 pre-symptomatic 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. [27] reported an intermediate signal for covariation between incubation period and serial interval. However, Tindale et al. showed that the degree of positive correlation did not greatly impact estimates of pre-symptomatic transmission. Liu et al. [62] simulated the effect of full correlation and anti-correlation between serial interval and incubation period on pre-symptomatic transmission estimates. However, the direction and magnitude of effects varied depending on which published estimates the simulations were based upon. 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 pre-symptomatic 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 pre-symptomatic transmission of COVID-19 in a range of different contexts. The proportion of pre-symptomatic 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.

Tables

Table 1: Definitions referred to in this review.

Asymptomatic	An infected person who never develops symptoms of the disease
Pre-symptomatic	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 and that of its primary case.
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 who 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 (SEIR) 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 pre-symptomatic transmission	The proportion of all transmission events that occur before the onset of symptoms in the infector.

Table 2: A summary of simulation results. The table shows showing the mean, standard deviation (SD) and median of transmission time relative to symptom onset in days as well as the proportion of pre-symptomatic 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 brackets represent the 95% confidence intervals form 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.

Reference	Mean	SD	Median	PST
China - All excluding Hubei				
Xu et al. [35]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, -0.1)	53.5 (50.4, 56.6)
Ali et al. [43]	-0.7 (-1.1, -0.3)	6.2 (5.9, 6.5)	-0.5 (-1, 0)	53.2 (50.1, 56.3)
Du et al. [33]	-1.8 (-2.1, -1.4)	5.8 (5.5, 6)	-1.6 (-2, -1.1)	61.2 (58.2, 64.3)
China - Hong Kong				
Kwok et al. [46a]	-1 (-1.4, -0.7)	5.3 (4.3, 6.3)	-1.3 (-1.6, -1.1)	64.5 (61.5, 67.4)
Kwok et al. [46b]	0.5 (0.2, 0.8)	5 (4.4, 5.7)	0.4 (0.1, 0.7)	46.3 (43.2, 49.4)
China - Shiyan (Hubei)				
Yang et al. [36]	-1.2 (-1.5, -0.8)	5.7 (5.4, 6)	-1 (-1.4, -0.5)	57.1 (54.1, 60.2)
China - Shenzhen				
Wang et al. [47]	0.1 (-0.2, 0.5)	6.2 (5.4, 6.9)	-0.5 (-0.9, -0.1)	54.2 (51.1, 57.2)
Bi et al. [44]	0.5 (0.2, 0.8)	5.3 (5, 5.6)	0.1 (-0.2, 0.5)	48.6 (45.5, 51.8)
China - Tianjin				
Ganyani et al. [28a]	-1.8 (-2, -1.6)	3.5 (3.3, 3.8)	-1.4 (-1.6, -1.1)	69.1 (66.2, 71.9)
Tindale et al. [27a]	-1.4 (-1.7, -1.1)	4.2 (3.9, 4.5)	-1.1 (-1.4, -0.8)	61.1 (58.1, 64.2)
China - Zhuhai				
Wu et al. [63]	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0 (-0.3, 0.3)	50.2 (47.1, 53.3)
Iran - Qom				
Aghaali et al.[64]	-1.2 (-1.5, -0.9)	4.7 (4.4, 5)	-1.4 (-1.7, -1.1)	63.5 (60.5,

Reference	Mean	SD	Median	PST
				66.5)
Italy - Vo (Village in Northern Italy)				
Lavezzo et al. [18]	1.4 (1.0, 1.8)	6.4 (6.0, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49.0)
Republic of Korea - All				
Chun et al [38]	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)
Republic of Korea - Busan				
Son et al. [48]	-0.3 (-0.6, 0.1)	5.1 (4.7, 5.4)	-0.6 (-0.9, -0.2)	55.4 (52.3, 58.4)
Singapore				
Ganyani et al. [28b]	-0.6 (-0.8, -0.4)	3.7 (3.5, 4)	-0.2 (-0.4, 0)	52.5 (49.4, 55.6)
Tindale et al. [27b]	-1.4 (-1.7, -1.1)	4.8 (4.5, 5)	-1.1 (-1.5, -0.8)	60 (57, 63.1)
Vietnam				
Pham et al. [49]	-2.6 (-3.0, -2.1)	7.2 (6.9, 7.6)	-2.4 (-3, -1.9)	63.4 (60.5, 66.4)

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Competing interests

All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

Not applicable as our study did not involve human participants. Our study is a secondary analysis using estimates already published and widely publicly available.

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

Author contributions

MC conceptualized 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. ÁC, KH, KOB and KW performed literature searches upon which the incubation period, generation time, serial interval and pre-symptomatic transmission information reported here are based upon. SM conceptualized, initiated and managed the overall project. MC, JG, CM, AB, JM, DM, ÁC, KH, AB, FB, EL, KOB, PW, KW and SM supplemented the literature review, discussed the study design, reviewed and edited the manuscript.

Data sharing statement

The data and code used for the analyses described in this paper are available in the Github repository: https://github.com/miriamcasey/covid-19_presymptomatic_project

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Figure legends

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 pre-symptomatic 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.

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

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 pre-symptomatic transmission. Line thickness is scaled to reflect sample size (i.e. reference [46a] has the smallest and [35], the largest sample size). 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.

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. 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. Points indicate means and bars indicate 95% confidence intervals.

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: 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.

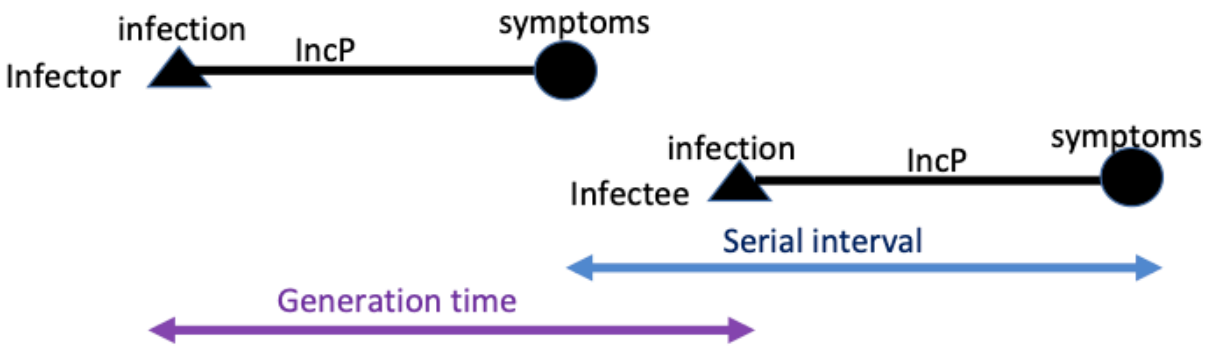
Supplementary figure legends

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: 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.

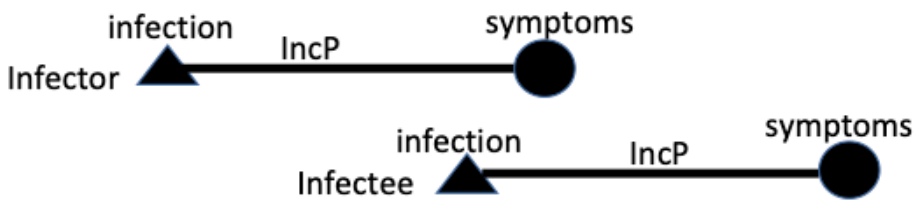
Supplementary figure 2: A summary of the parameters from the serial interval and generation time estimates for the 27 serial interval estimates from 24 papers that were included in simulations to infer pre-symptomatic transmission. This plot refers both to the estimates from the main text for which we 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: 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.

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: 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.

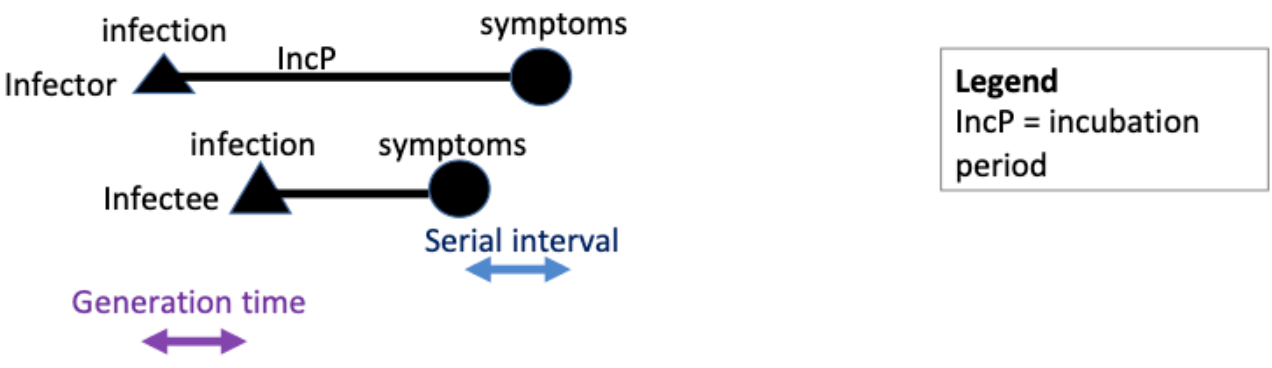
A: Symptomatic transmission: Incubation period ≤ [Serial interval or Generation time]

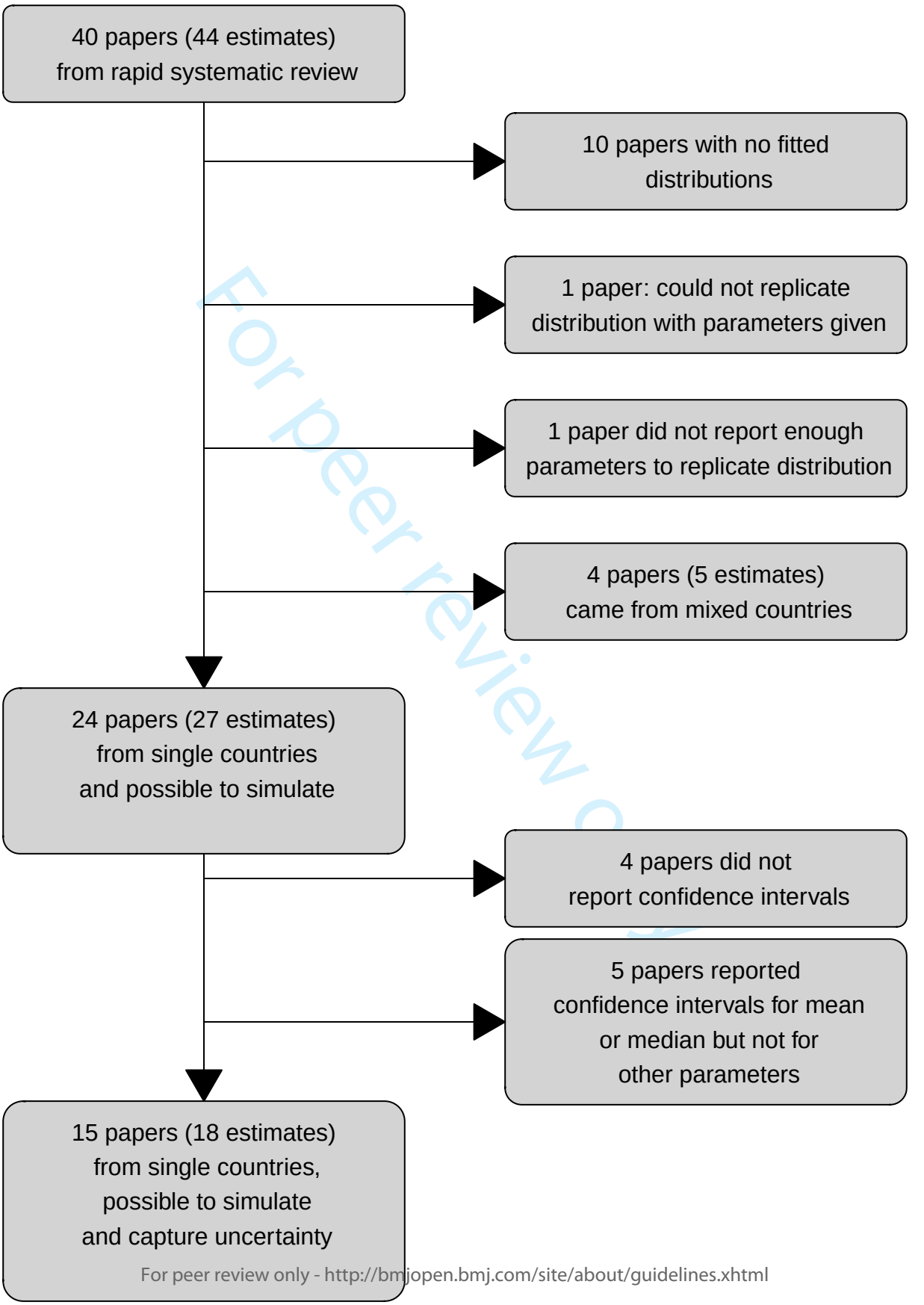


B: Pre-symptomatic transmission: Incubation period > [Serial interval or Generation time] and Serial interval > 0



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





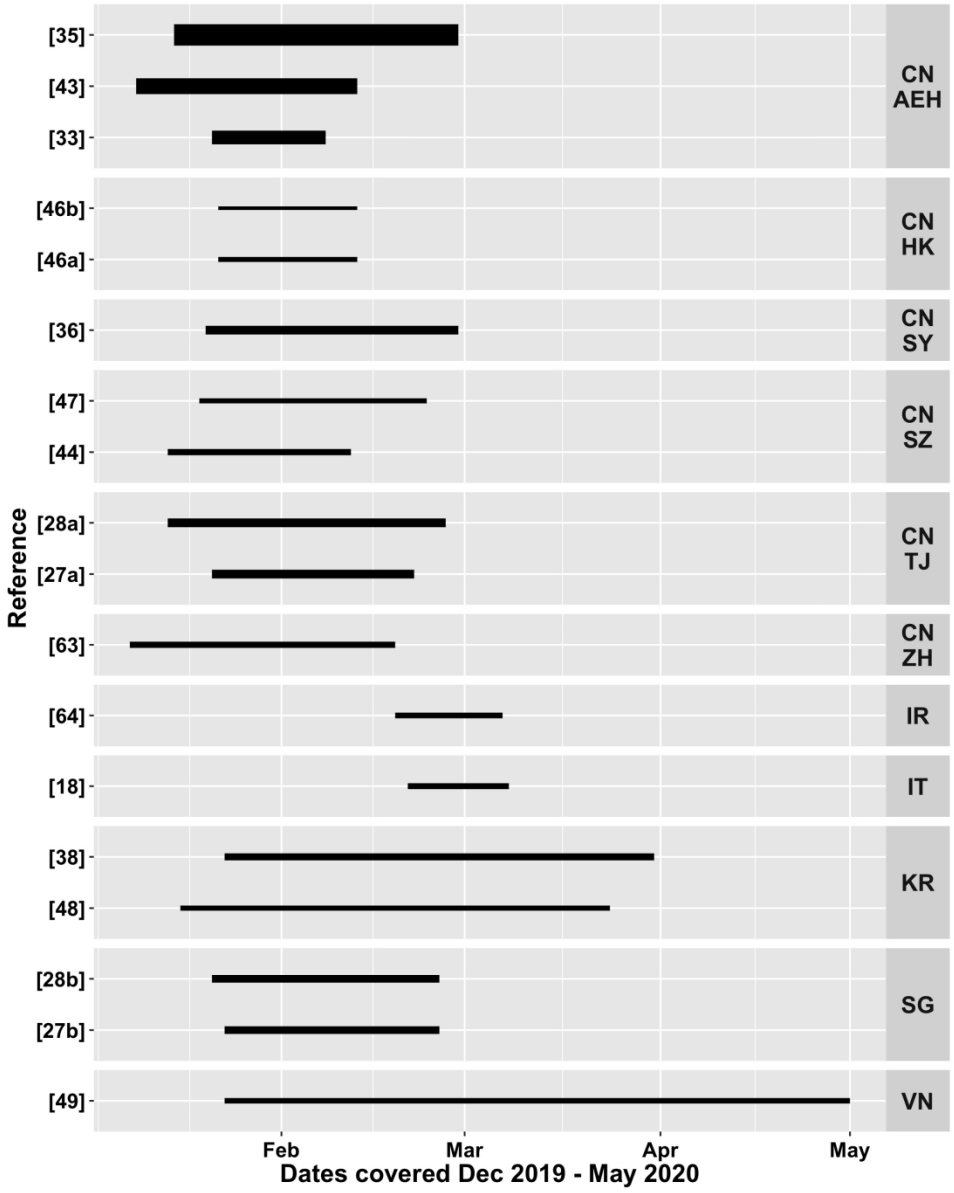


Figure 3: A summary of country or region and date ranges for the 18 serial interval estimates from 15 papers that were included in simulations to infer pre-symptomatic transmission. Line thickness is scaled to reflect sample size (i.e. reference [46a] has the smallest and [35], the largest sample size). 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.

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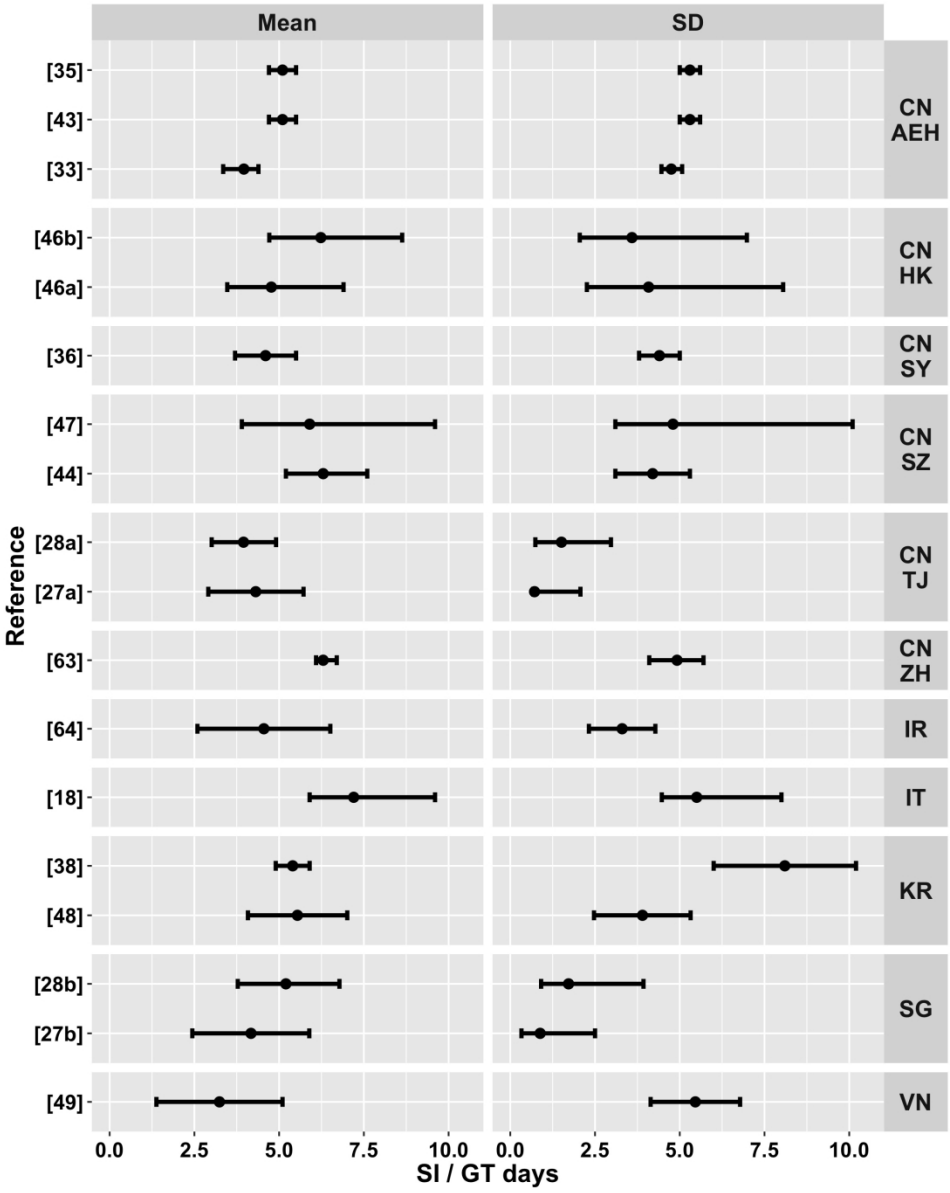

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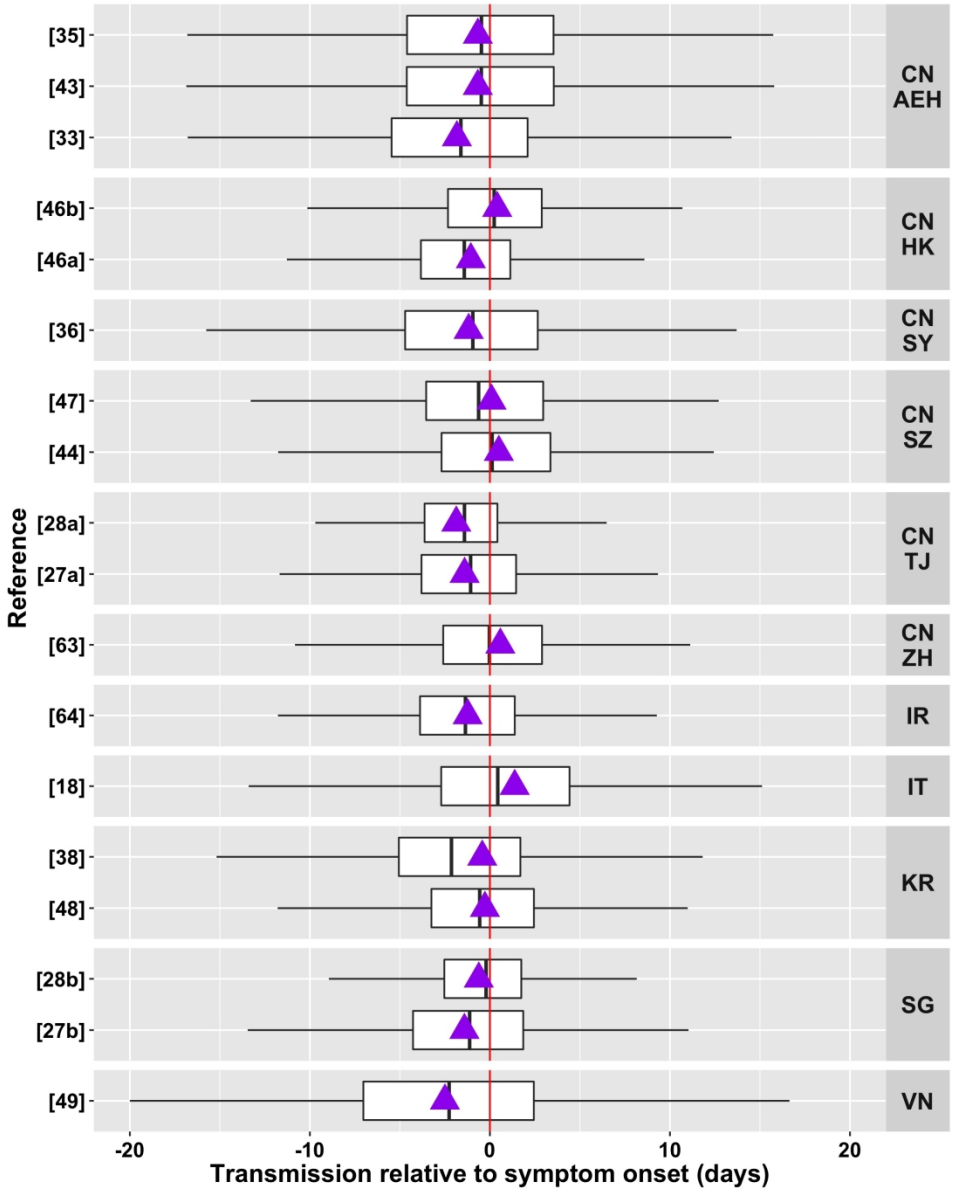

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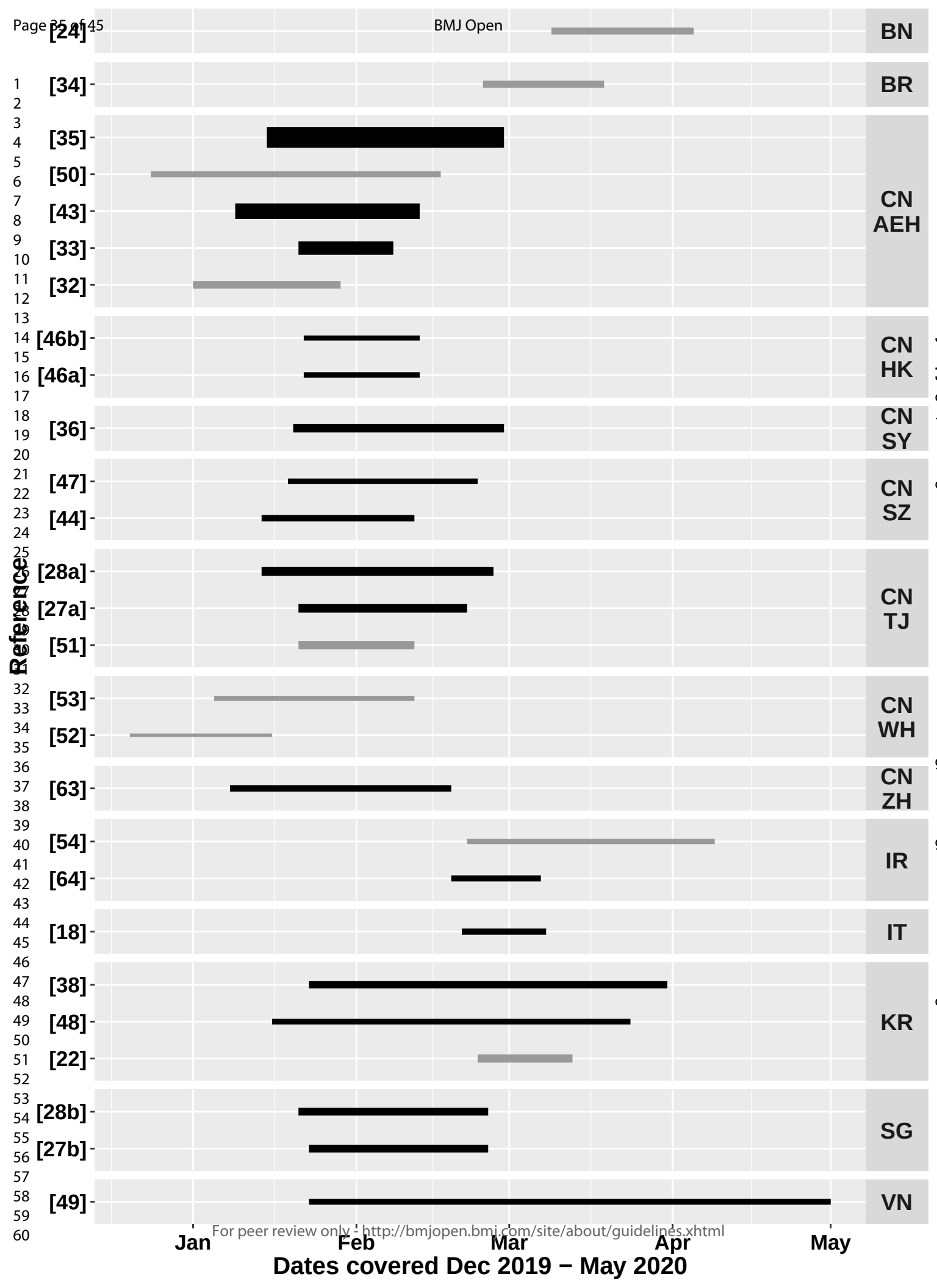

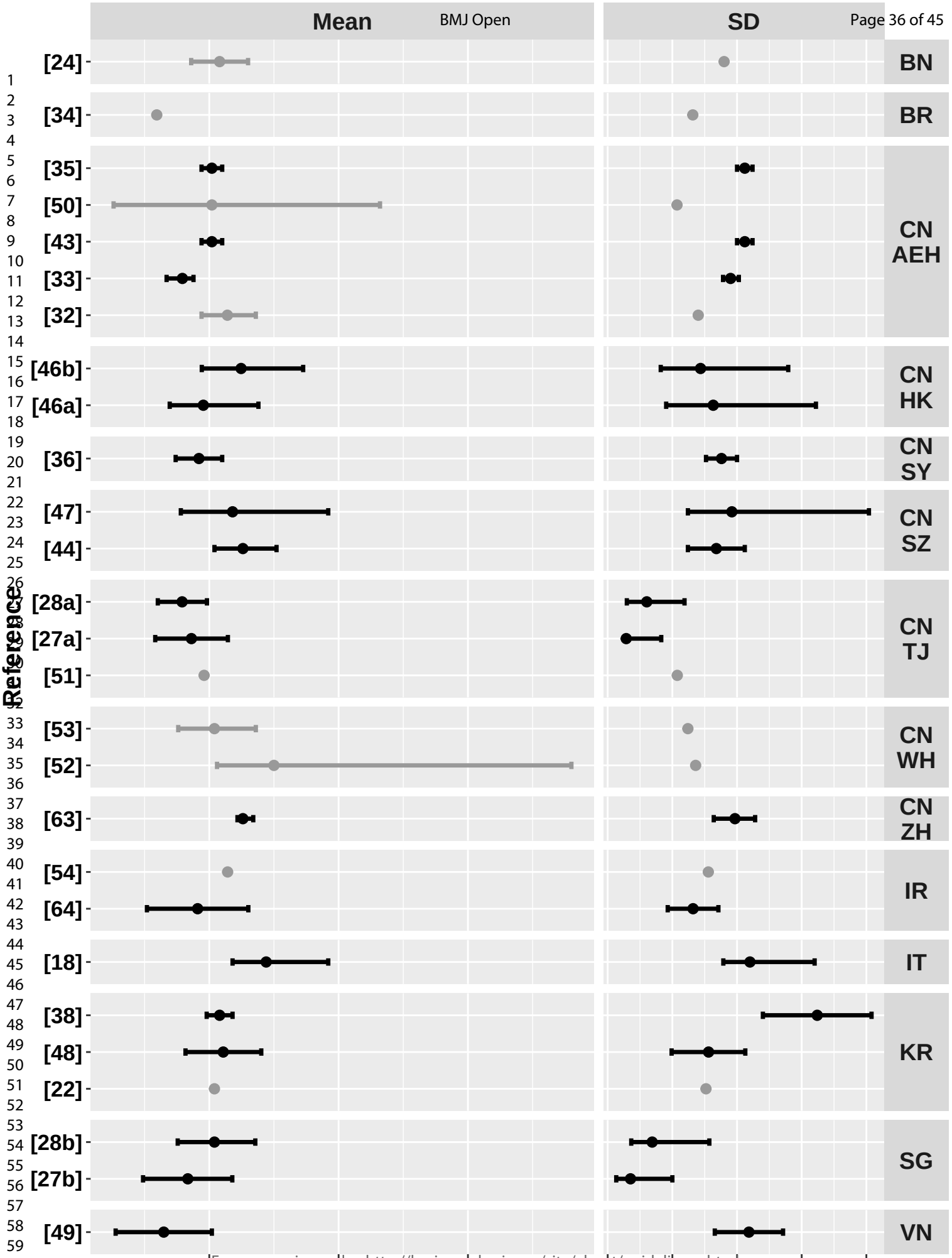

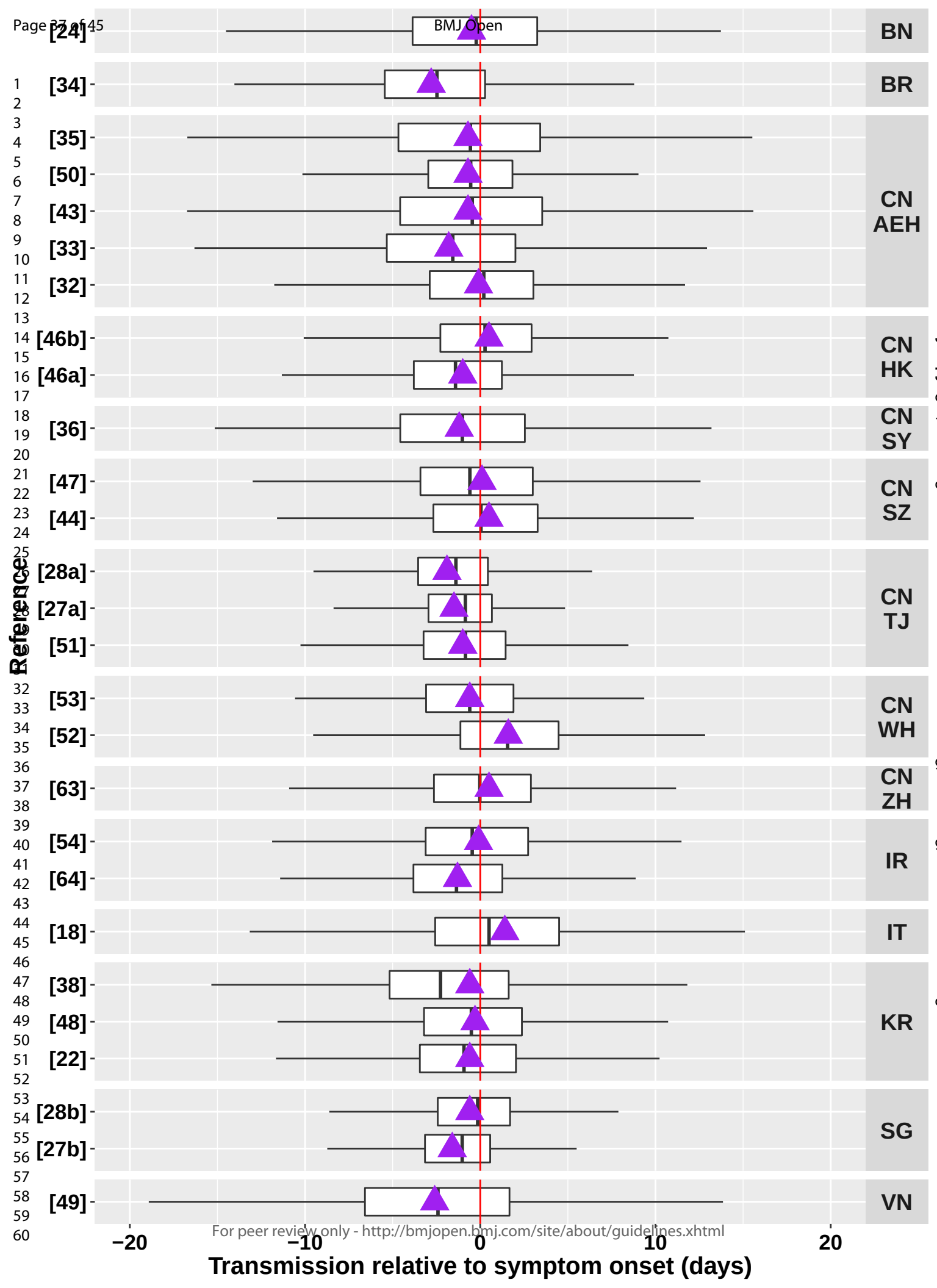

Supplementary tables

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 it 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		
Zhang et al. [50]	24/12/19 - 17/02/20	-0.8	4.1	-0.6	57.2	35		Comment: serial interval about same as incubation period, suggesting possible transmission before symptoms.
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)
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		
Ren et al. [32]	01/01/20 - 29/01/20	-0.2	4.7	0.1	48.5	80	10%	
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)								

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 isolation = 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%)	
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		
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]	08/01/20 - 19/02/20	0.5 (0.2, 0.9)	5.8 (5.1, 6.4)	0 (-0.3, 0.3)	50.2 (47.1, 53.3)	48		most secondary cases were likely infected around the time of symptom onset of the primary cases
Iran - West								
Najafi et al. [54]	22/02/20 - 09/04/20	-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]	19/02/20 - 07/03/20	-1.2 (-1.5, -0.9)	4.7 (4.4, 5)	-1.4 (-1.7, -1.1)	63.5 (60.5, 66.5)	37		
Italy - Vo (Village in northern Italy)								
Lavezzo et al. [18]	21/02/20 - 08/03/20	1.4 (1, 1.8)	6.4 (6, 6.9)	0.5 (0.1, 0.9)	45.9 (42.9, 49)	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]	23/01/2020-31/03/2020	-0.4 (-1, 0.1)	8.8 (6.6, 10.8)	-2 (-2.4, -1.6)	64.2 (61.2, 67.2)	69	37% (26, 52%)	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% 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% CrI: 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.%1 (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. [10]	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 5days 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
Lavezzo et al. [18]	Vo, northern Italy	Evidence of pre-symptomatic transmission to 1-4 people.	3-4 days
Liao et al. [19]	Chongquing, 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