Serial intervals and case isolation delays for COVID-19: a systematic review and meta-analysis

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Summary: This study examines reasons for variability in serial intervals, and identifies associations of shorter serial intervals with shorter delays to case isolation and other control measures.

Abstract

Background

Estimates of the serial interval distribution contribute to our understanding of the transmission dynamics of coronavirus disease 2019 (COVID-19). Here, we aimed to summarize the existing evidence on serial interval distributions and delays in case isolation for COVID-19.

Methods

We conducted a systematic review of the published literature and preprints in PubMed on two epidemiological parameters namely serial intervals and delay intervals relating to isolation of cases for COVID-19 until 22 October, 2020 following predefined eligibility criteria. We assessed the variation in these parameter estimates by correlation and regression analysis.

Results

Of 103 unique studies identified on serial intervals of COVID-19, 56 were included providing 129 estimates and of 451 unique studies on isolation delays, 18 studies were included providing 74 estimates. Serial interval estimates varied from 1.0 to 9.9 days, while case isolation delays varied from 1.0 to 12.5 days which were associated with spatial, methodological and temporal factors. In mainland China, the pooled mean serial interval was 6.2 (range, 5.1-7.8) days before the epidemic peak and reduced to 4.9 (range, 1.9-6.5) days after the epidemic peak. Similarly, the pooled mean isolation delay related intervals were 6.0 (range, 2.9-12.5) days and 2.4 (range, 2.0-2.7) days before and after the epidemic peak, respectively. There was a positive association between serial interval and case isolation delay.

Conclusions

Temporal factors, such as different control measures and case isolation in particular led to shorter serial interval estimates over time. Correcting transmissibility estimates for these time-varying distributions could aid mitigation efforts.

Key words

COVID-19, Serial intervals, isolation delays, systematic review and meta-analysis, regression analysis.

Introduction

The novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to more than 70 million confirmed cases and 1.6 million deaths worldwide by 15 December 2020.[1] Several key epidemiological parameters have been important in allowing us to characterize patterns in COVID-19 transmission, including the incubation period, infectious period, generation time, serial interval, growth rate and reproduction number etc.[2-4] The generation time is defined as the time between successive infections in a transmission chain of an infectious disease. The estimates of the generation time distribution allow us to infer the reproductive number from epidemic growth rates.[5] However, it is not usually possible to determine exact infection times, and hence there are relatively few estimates available for the generation time distribution for COVID-19.[6-8] The serial interval is defined as the time between the successive illness onsets in a transmission chain, and the serial interval distribution is often used as an approximation for the generation time distribution for further inference on transmissibility.[4,9-12] Several other epidemiological distributions including time from onset to isolations, onset to hospitalizations or quarantine have also been estimated to inform the real-time status of the effects of public health measures on suppressing the spread of COVID-19.[12-14]

Estimating epidemiological parameters have provided useful information for public health responses and communication. We defined the isolation delay related interval as the time between onset to isolation or hospitalization (if isolation date is not available) for each COVID-19 confirmed case. However, there have been variations in the estimates of serial interval distributions and isolation delay related intervals for COVID-19.[4,12,15-17] Recent studies have established the impact of public health measures on shortening the serial interval,[12,18] but other factors could also play a role. For example, case isolation could truncate the infectious period of an infector and restrict further transmission in the chain, hence reducing serial intervals.[12] Here, we carried out a systematic review and meta-analysis for these epidemiological distributions. The objectives were to examine the reported serial intervals and the isolation delay related intervals for COVID-19 cases, and to identify key factors associated with variation in the estimates of these epidemiological parameters.

Methods

We followed the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols guidelines.[19] Two co-authors (AY and SS) performed the article search and data extraction independently with a standardized form. Conflicts over inclusion of the studies and retrieving the estimates of these variables were resolved by another co-author (STA). We focused on the estimates of interval related parameters including serial intervals and isolation delay related intervals for COVID-19.

Search strategy and selection criteria

All searches were carried out on 23 October 2020, on PubMed for articles published from 1 January 2020 to 22 October 2020. We included all relevant articles that were published in peer-reviewed journals or available as pre-prints in English or Chinese, as well as some articles recommended by experts. Search terms for COVID-19 serial interval included #1: "serial interval" OR "generation interval" OR "generation time" OR "serial distribution", #2: "COVID-19" OR "coronavirus" OR "2019 nCoV" OR "SARS CoV 2" OR "SARS-CoV-2" OR "SARS-CoV" OR "SARS CoV" OR "2019 CoV" OR "Pneumonia", #3: #1 AND #2. After reading the abstract and full text, we included studies in which the serial interval estimates were reported along with their uncertainty, clear timing of the data (data window) from which the estimates were derived. Systematic reviews and meta-analyses were excluded from our analyses, but we included relevant studies referenced in those reviews. Data from the Chinese literature was extracted by a Chinese-speaking co-author (SS). For studies that compared multiple serial interval estimates using different statistical methods, all estimates were included if the lower and upper bounds of uncertainty were provided (see Tables S1 and S2).

Only a few studies from our search for serial intervals had also reported the estimates for isolation delay related intervals. We conducted a similar literature search on the isolation delay related intervals, using search terms: #1: "interval" OR "delay" OR "latency", #2: "Isolation" OR "hospital admission" OR "containment" OR "quarantine", #3: "COVID-19" OR "coronavirus" OR "2019 nCoV" OR "SARS CoV 2" OR "SARS-CoV-2" OR "SARS-CoV" OR "SARS CoV" OR "2019 CoV" OR "Pneumonia", #4: #1 AND #2 AND #3. After reading the abstract and full text, we included articles that clearly mentioned the time interval between symptom onset to isolation or hospital admission for COVID-19 patients (see tables S1 and S2).

Data extraction and analysis

The information retrieved from the identified studies was broadly classified into the following outcome and factor variables. We considered the *outcome variables* as serial interval estimates and isolation delay related interval estimates, along with their respective uncertainty measures, which were often reported as 95% confidence intervals (CI), 95% credible intervals (CrI), standard deviation (sd), inter-quartile range (IQR) or range. We standardized the uncertainty measure for comparison purposes (see appendix, section 3). Differences in the estimates of interval measures reported by these studies could be the result of several factors, including methodological factors, calendar time or timing during the epidemic, and geographical differences.

To account the impact of methodological factors, we retrieved the information of the estimates and defined the following variables. *Estimation types*: the central tendency measure of the reported estimates were of mean or median; *distribution types*: whether the estimates were derived empirically or by fitting probabilistic distributions (e.g. normal, Gumbel, Weibull, Gamma, lognormal, etc.); *truncation*: whether the data was truncated to address incomplete observation of the outcome

variables; *settings*: whether the estimates were evaluated based on the transmission pairs in household or community settings; *data types*: whether the time intervals were based on illness onset, case reports, confirmation or hospitalizations; and *sample sizes*: the number of transmission pairs/cases used to estimate the *outcome variables*. To evaluate temporal factors, we retrieved information on the timing of the data window used in the respective studies and defined the variables *start date*, *end date* and *mid date* of the data window. We then constructed a *duration* variable, which was the data length (in days) for analysis. To evaluate the effect of spatial factors, we retrieved information on the *location* including the country and provinces (specific regions) for which the outcome variables were estimated (appendix, section 3). More details on these variables are presented in table S3 and S4, available online at https://osf.io/c37zh/.

We generated boxplots for the *outcome variables* over each factor variable to visualise the potential associations. We further used correlation tests to evaluate the association between the *outcome variables* and possible factor variables. We carried out these analyses on the full dataset for all locations and also for individual locations (e.g. mainland China) whenever possible. Considering the fact that the start time of the pandemic were different across locations, and most studies were based on data from mainland China, further analysis was restricted to mainland China only. To evaluate the temporal variations in the estimates, we first considered the timing for respective estimates as mid dates of data window used in the study, and then defined the pre-peak period, peak period and post-peak period as the timing before 20 January 2020, during 20-31 January, 2020 and after 31 January, 2020 respectively.

Since some studies reported several estimates on outcome and factors variables, predefined rules were used to select a representative estimate for better comparison (appendix, section 4). We used two sample t-tests to compare the difference of outcome variables estimated before and after epidemic peak. Finally, we used a regression model to identify and quantify the association between serial intervals and isolation delay related intervals from different studies. Considering that these estimates were not always simultaneously reported by the same studies, we pooled these estimates by week over the mid date of the data windows and used the linear regression models for serial interval on isolation delay related intervals in the analysis. All the analyses were done in R version 4.0.3.

Results

For serial interval estimations, we identified 91 studies from our search on PubMed and had 27 recommended studies from reviews. We identified 56 studies which reported raw data COVID-19 transmission pairs, providing 129 serial interval estimates.[2-4,12,16,20-70] The detailed selection process is illustrated in figure 1A. Of these 56 studies, 58 estimates used data from mainland China only[2,4,12,16,22-31,33-37,39,52,58,59,61,63,65,69,70], 14 estimates used data from other countries along with China[3,32,39-41]. Some studies reported estimates from other locations, including 13 from Hong

Kong[45,51]; 12 from South Korea[44,47,49,50,53,54]; 6 from India[66]; 4 each from Singapore[22,26,71], Taiwan[39,60], Italy[43,46], and Argentina[67]; 2 each from Brunei[20,68], Iran[42,48], and Brazil[21]; 1 each from Philippines[57], Germany[38], Vietnam[64] and the Diamond Princess Cruise Ship[56] (table S5).

For the estimates on isolation delay related intervals, we identified 441 studies, among which 18 unique studies with 74 estimates reported on COVID-19[2,4,17,29,37,45,52,58,72-82] (in particular, 8 studies with onset-to-isolation intervals[2,37,44,45,73,77,78,80] and 11 studies with onset-to-hospitalization intervals[2,4,17,29,52,74-76,79,81,82]). We extracted 23 estimates of onset-to-isolation intervals and 51 of onset-to-hospitalization intervals. The detailed selection process is illustrated in figure 1B. Of 74 isolation delay related estimates, 53 estimates were from mainland China data only[2,4,17,29,37,52,75,77,79,81,82], and 21 were on data from other regions, including 16 from Hong Kong[45,73,74,80], 2 each from South Korea[44] and Singapore[78] and 1 from the United Kingdom[76] (table S5).

From 56 studies, 129 estimates of serial intervals reported for COVID-19 were much diverse, ranging from 1.0 to 9.9 with varied uncertainty (figure 2). 88 (68%) of the estimates were reported as mean values, while 41 (32%) as median values (table S5). Further, different uncertainty measures were reported, with 78 (60%) using 95% CI, 32 (25%) using 95% CrI, 15 (12%) using IQR and 4 (3%) using range. 24 (19%) of all estimates used Normal distribution (includes negative and positive value of serial intervals) for fitting the data, 74 (57%) used the distribution with positive support only i.e. Gamma (47, 63%), lognormal (13, 18%), Weibull (11, 15%), loglogistic (1, 1%), statistical simulation (2, 3%) and 31 (24%) estimates used empirical distribution directly. Of all 129 estimates, only 12 (9%) estimates used truncated data and only 11 (9%) estimates were obtained from household transmission setting while all others were obtained from community transmission settings.

From a total of 18 studies, 74 estimates of isolation delay related intervals for COVID-19 were reported, ranging from 1.0 to 12.5 days with varied uncertainty (figure 3). The types of estimation and related uncertainty were also varied. 52 (70%) estimates were reported as mean values, while 22 (30%) as median values (table S5) with 50 (68%) estimates using 95% CI, 6 (8%) using 95% CrI, 13 (18%) using IQR and 5 (6%) using range. 41 (55%) estimates used fitting of the distributions i.e. Gamma (12, 29%), lognormal (17, 41), Weibull (12, 29%), and 33 (45%) estimates are derived using empirical distribution directly. Of all 74 estimates, 11 (15%) estimates used truncated data and 63 (85%) used non-truncated data. All (74) estimates were performed on non-household transmission setting.

We assessed the association between outcome variables and the possible factors. Noticeable variations in the estimated outcome variables were found across the levels of some factors (figures S1-6) including types of estimates (table S6). In mainland China, we found clear differences among serial interval and isolation delay related interval estimates when evaluated before, during and after epidemic peak, in fact monotonically decreasing over time (figures S3 and S6). While comparing

mean estimates during pre- and post-epidemic peak found to be significant for serial interval (p-value = 0.014) and isolation delay related interval (p-value = 0.001). The serial interval estimates had a pooled mean of 6.2 (range, 5.1-7.8) days during pre-peak period and reduced to 4.9 (range, 1.9-6.5) days during post-peak period (figure S3). Similarly, the mean estimated isolation delay related intervals were 6.0 (range, 2.9-12.5) days and 2.4 (range, 2.0-2.7) days during before and after epidemic peak respectively (figure S6). Uncertainty in serial interval estimates were lower with larger sample sizes, but no clear pattern was observed with the duration (length of the data window). We found a negative and significant association between serial interval estimates and the start date (Pearson's correlation coefficient (r) = -0.35, p-value = 0.033), mid date (r = -0.33, p-value = 0.041) and sample size (Spearman's rank correlation coefficient (ρ) = -0.42, p-value = 0.011) of the data windows for COVID-19 in mainland China (table S7). Similar associations (r = -0.47, p-value = 0.037 for start date and r = -0.64, p-value = 0.002 for mid date) were found for the isolation delay related interval estimates with these factors (table S8).

We found a trend of shortened serial interval estimates over time in mainland China, especially during the later phase of the epidemic (Figure 4). The estimated isolation delay related intervals also shortened over time (figure 5). As a sensitivity analysis, a similar trend was observed when analysed by the start dates of the data window (figures S7-8). Therefore, we identified a positive association between the estimates of serial intervals and isolation delay related intervals in different studies using data from mainland China. For every one day reduction in the estimated isolation delay related intervals, the estimated serial intervals reduced by 0.43 (95% CI: (0.32, 0.53)) days (figure 6 and S9).

Discussion

The serial interval depends on the infectiousness profile of the infector and the properties of contacts (e.g., contact patterns, structure of contacts) in a transmission chain.[12,83,84] Public health measures can modify these properties of effective contacts, and hence re-shape the serial interval distribution. For instance, isolation delays can be shortened by enhancing contact tracing and testing capacities, which restrict the opportunity for transmission.[12,18] On the other hand, time to isolation infectors may change over time with relaxing or tightening of control measures.

The serial interval estimates for COVID-19 were diverse across different countries (figure 2 and table S5). Non-pharmaceutical control measures implemented in these locations also differed in terms of types, timing and effectiveness according to the respective health policies in the jurisdiction.[85] Furthermore, diversity in population structure, culture and beliefs, and human behaviour might have shaped the contact pattern and hence the transmission dynamics in these locations. Meanwhile within the same location, diversity in isolation delays can depend on the health policies of respective countries, which change from time to time as a response to the epidemic situation.[86]

The variation in serial interval estimates from a single location (mainland China) alone was considerable, with a wide range of estimates (1.0 – 7.8 days) (figure 2 and figures S1-2). Furthermore, even within the same studies, different estimation methods and assumptions may result in different serial interval estimates.[41,45,70] Choice of the *estimation types* (table S6) and probability distribution models (*distribution types*) for estimating serial intervals is crucial and should be based on the realistic assumptions. For example, fitting distributions with positive support (Gamma, Weibull etc.) directly to datasets that include negative serial intervals may distort the estimated distribution. The household and non-household *settings* might have different characteristics on contact pattern, mode of transmission and NPI effectiveness, which might be a potential factor of the variation in serial interval estimates.[31,34] Similarly, the differences in the estimates for the isolation delay related intervals might have been driven by these methodological factors and their related assumptions (figure 4 and figures S4-5). On the other hand, the *uncertainty* of these estimates were much more diverse, as presented by different types of uncertainty measures (figures 2 and 3), even statistically misrepresented for some studies.[20,24,26,28,33,36,45,55,60,66]

Along with the above spatial and methodological factors, our results suggested that the temporal factors as the timing of data window used for estimating the serial interval and isolation delays might lead to this disagreements of these reported estimates (tables S7-8).The reported estimates on serial interval and isolation delay related intervals for China data were found to be shortened as the data window progressed along with the epidemic timing (figures 4-5 and figures S7-8). On the other hand, the infectiousness profile and contact patterns during the timing of these respective data widows might have been changed or modified by the NPIs, particularly the shortened isolation delays over time. The positive association between the estimates of serial interval and isolation delays supports the earlier findings of one day early isolation could shorten the serial interval by 0.7 days.[12] This indicates the serial interval shortened over time due to the potential impact of NPIs, and hence it may not be realistic to assume the serial interval distribution remains constant across an epidemic. This implies that methodological improvements are needed to correct for this phenomenon when estimating other important epidemic parameters including reproduction numbers.

The main strength of our review is not only to document the evidence on the estimates of the outcome variables but also to disentangle the reasons of the disagreement of these estimates. However, our review study has several limitations. First, we could identify temporal factors of the variation in serial interval estimates as the isolation delays by analysing the estimates in the studies on the data from mainland China only. Availability of such estimates at temporal scale in other locations could have strengthened our findings, and more than a year after the start of the pandemic it is perhaps surprising that so few estimates of the serial interval distribution were reported from outside of China. Secondly, the estimates of the outcome variables were typically based on self-reported illness onset dates which could be subject to recall bias. Finally, in our review, except for the isolation delay, we could not identify or quantify the impact of any other NPIs on the serial intervals for COVID-19.

In conclusion, varying estimates of the serial interval distribution have been reported for COVID-19, which might be associated with study settings and locations where the data were collected and effectiveness of control measures. Temporal factors were found to be an important driver for diversity in estimates of serial intervals and isolation delays, and serial intervals were significantly modulated by isolation delay and potentially other control measures. Changes in serial interval distribution through an epidemic will affect the estimation of key transmission parameters for COVID-19 and affect assessments of the impact of mitigation efforts.

NOTES

Contributors

STA, LW and BJC conceived the study. STA and BJC designed the study. AY and SS undertook the literature review and extracted the data with help from STA. AY and STA coded the statistical analysis, figures, and appendix with support from SS. STA, EHYL, LW, PW and BJC interpreted the data. STA and BJC wrote the first draft of the manuscript. All authors reviewed and revised subsequent drafts and approved the final version.

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Potential conflict of interests

BJC consults for Sanofi, Roche, AstraZeneca, Moderna and GSK. All other authors report no other potential conflicts of interest.

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Figure legends

Figure 1: PRISMA flow diagram indicating the search process to obtain studies reporting (A) serial intervals and (B) isolation delay related intervals for COVID-19. We used PubMed for our primary search, as well as the papers mentioned in existing reviews (Park et al [87], Koh et al [88], and Griffin et al [89]), and additional recommended studies by experts.

Figure 2: All 129 COVID-19 serial interval estimates reported in 56 studies are presented by country. Points represent the estimates reports as mean, triangles as median, and the horizontal segments indicate confidence interval (in red), credibility interval (in green), inter-quartile range (in blue) or range (in purple). We termed China+ for those estimates, which considered the data from other locations along with mainland China.

Figure 3: All 74 isolation delay related intervals estimates for COVID-19, reported in 18 unique studies are presented by country. Points represent the estimates reports as mean, triangles as median, and the horizontal segments indicate confidence interval (in red), credibility interval (in green), inter-quartile range (in blue) or range (in purple).

Figure 4: The temporal variation in reported estimates on serial intervals for COVID-19 in mainland China. The plot showing the reported serial interval estimates (in red circles) over time by mid dates of the data windows used for estimation the serial intervals. Where the horizontal bars indicate the data window (indicating start dates and end dates) of the individual experiments, with the colour gradient representing the sample sizes (transmission pairs), constructed for each data window (with shades, in light blue: log-value of smaller pair size, dark blue: log-value of larger pair size, grey: pair size was not available). The epidemic curve with the onsets of confirmed cases (in gray line) and epidemic curve with the onset of infectors and infectee in the transmission pairs (in teal columns as available from 7 January 2020 to 28 February 2020) for mainland China alone, shown for reference of the epidemic timing [12,70].

Figure 5: The temporal variation in reported estimates on isolation delay related intervals for COVID-19 in mainland China. The plot showing the reported isolation delay related interval estimates (in red circles) over time by mid dates of the data windows used for estimation the isolation delay related intervals. Where the horizontal bars indicate the data window (indicating start dates and end dates) of the individual experiments, with the colour gradient representing the sample sizes (number of cases), constructed for each data window (with shades, in light blue: log-value of smaller sample size, dark blue: log-value of larger sample size, grey: sample size was not available). The epidemic curve with the onsets of confirmed cases (in gray line) and epidemic curve with the onset of infectors and infectee in the transmission pairs (in teal columns as available from 7 January 2020 to 28 February 2020) for mainland China alone, shown for reference of the epidemic timing [12,70].

Figure 6: The association between serial interval and case isolation. The regression model prediction of estimated serial intervals (weekly pooled estimates by taking average) by the estimates of isolation delay related intervals (weekly pooled estimates by taking average) in the mainland China. The black dots are scattered plot of weekly pooled serial interval and isolation delay related estimates. Blue line is the fitted serial intervals predicted by case isolation delay related intervals with 95% CI (in dashed red lines). Gray shaded region indicates the standard error for the liner prediction.

Figure 1

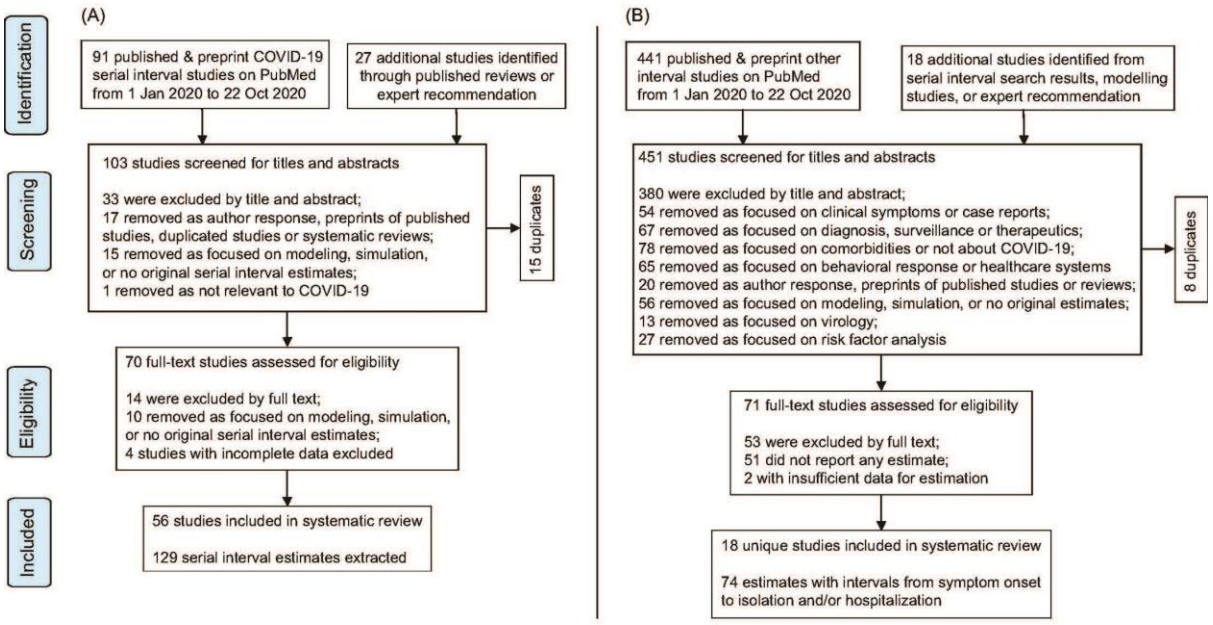

Figure 2

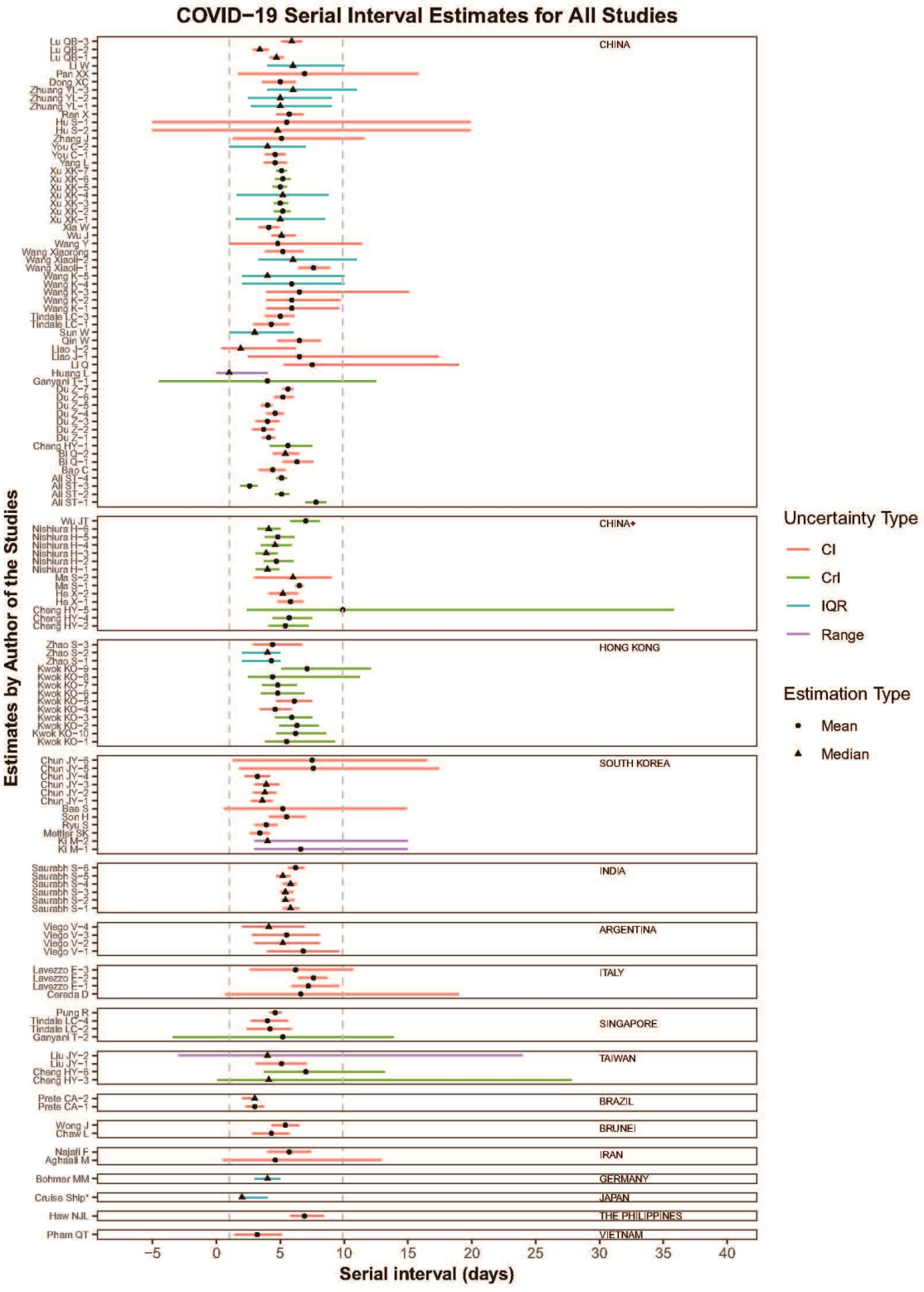
COVID−19 Serial Interval Estimates for All Studies
Estimates by Author of the Studies
Serial interval (days)
−5
0
5
10
15
20
25
30
35
40
CHINA
CHINA+
HONG KONG
SOUTH KOREA
INDIA
ARGENTINA
ITALY
SINGAPORE
TAIWAN
BRAZIL
BRUNEI
IRAN
GERMANY
JAPAN
THE PHILIPPINES
VIETNAM
Uncertainty Type
CI
CrI
IQR
Range
Estimation Type
Mean
Median

Figure 3

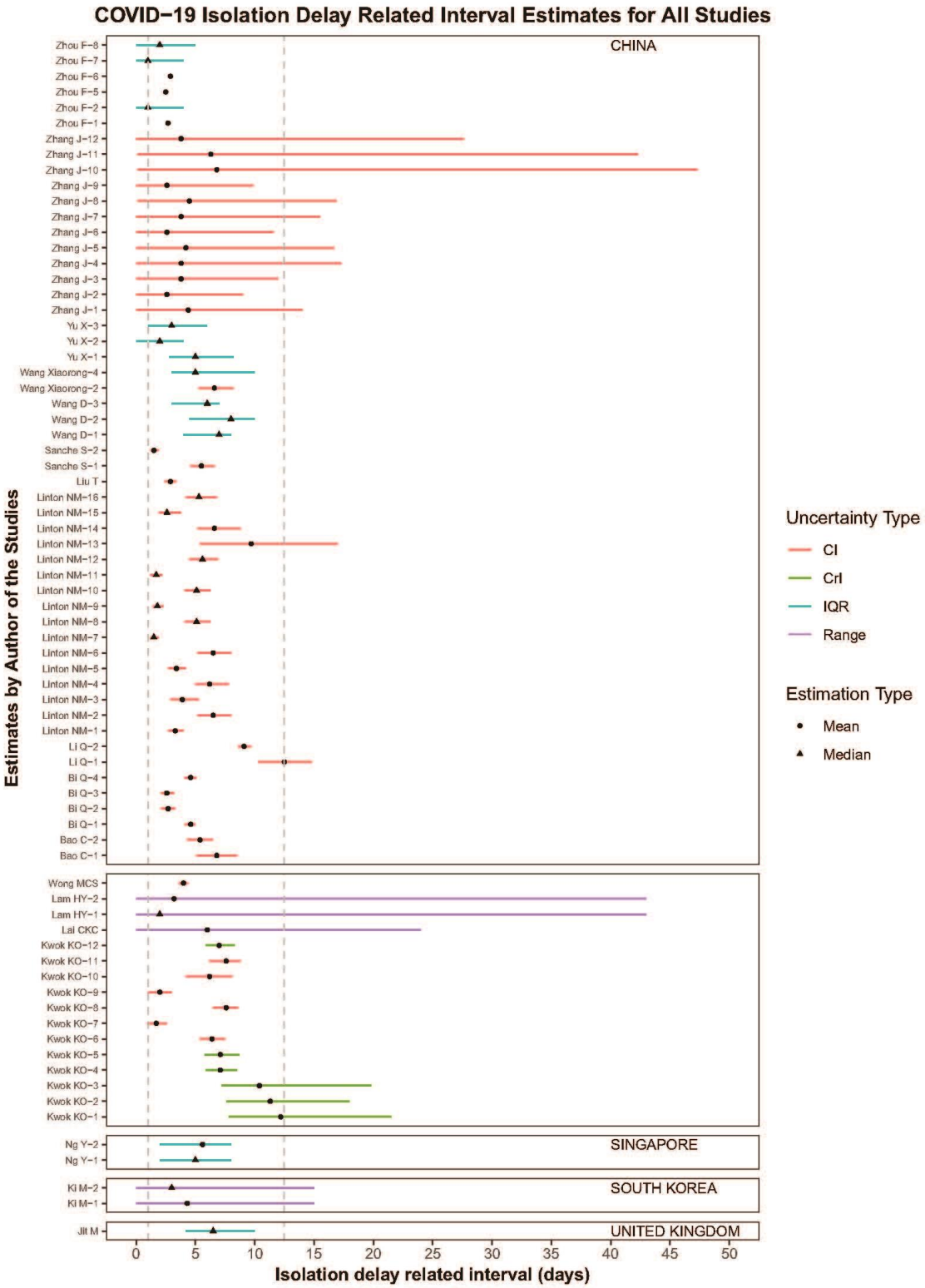
COVID−19 Isolation Delay Related Interval Estimates for All Studies
Estimates by Author of the Studies
CHINA
Zhou F−8
Zhou F−7
Zhou F−6
Zhou F−5
Zhou F−2
Zhou F−1
Zhang J−12
Zhang J−11
Zhang J−10
Zhang J−9
Zhang J−8
Zhang J−7
Zhang J−6
Zhang J−5
Zhang J−4
Zhang J−3
Zhang J−2
Zhang J−1
Yu X−3
Yu X−2
Yu X−1
Wang Xiaorong−4
Wang Xiaorong−2
Wang D−3
Wang D−2
Wang D−1
Sanche S−2
Sanche S−1
Liu T
Linton NM−16
Linton NM−15
Linton NM−14
Linton NM−13
Linton NM−12
Linton NM−11
Linton NM−10
Linton NM−9
Linton NM−8
Linton NM−7
Linton NM−6
Linton NM−5
Linton NM−4
Linton NM−3
Linton NM−2
Linton NM−1
Li Q−2
Li Q−1
Bi Q−4
Bi Q−3
Bi Q−2
Bi Q−1
Bao C−2
Bao C−1
Wong MCS
Lam HY−2
Lam HY−1
Lai CKC
Kwok KO−12
Kwok KO−11
Kwok KO−10
Kwok KO−9
Kwok KO−8
Kwok KO−7
Kwok KO−6
Kwok KO−5
Kwok KO−4
Kwok KO−3
Kwok KO−2
Kwok KO−1
SINGAPORE
Ng Y−2
Ng Y−1
SOUTH KOREA
Ki M−2
Ki M−1
UNITED KINGDOM
Jit M
0
5
10
15
20
25
30
35
40
45
50
Isolation delay related interval (days)
Uncertainty Type
CI
CrI
IQR
Range
Estimation Type
Mean
Median

Figure 4

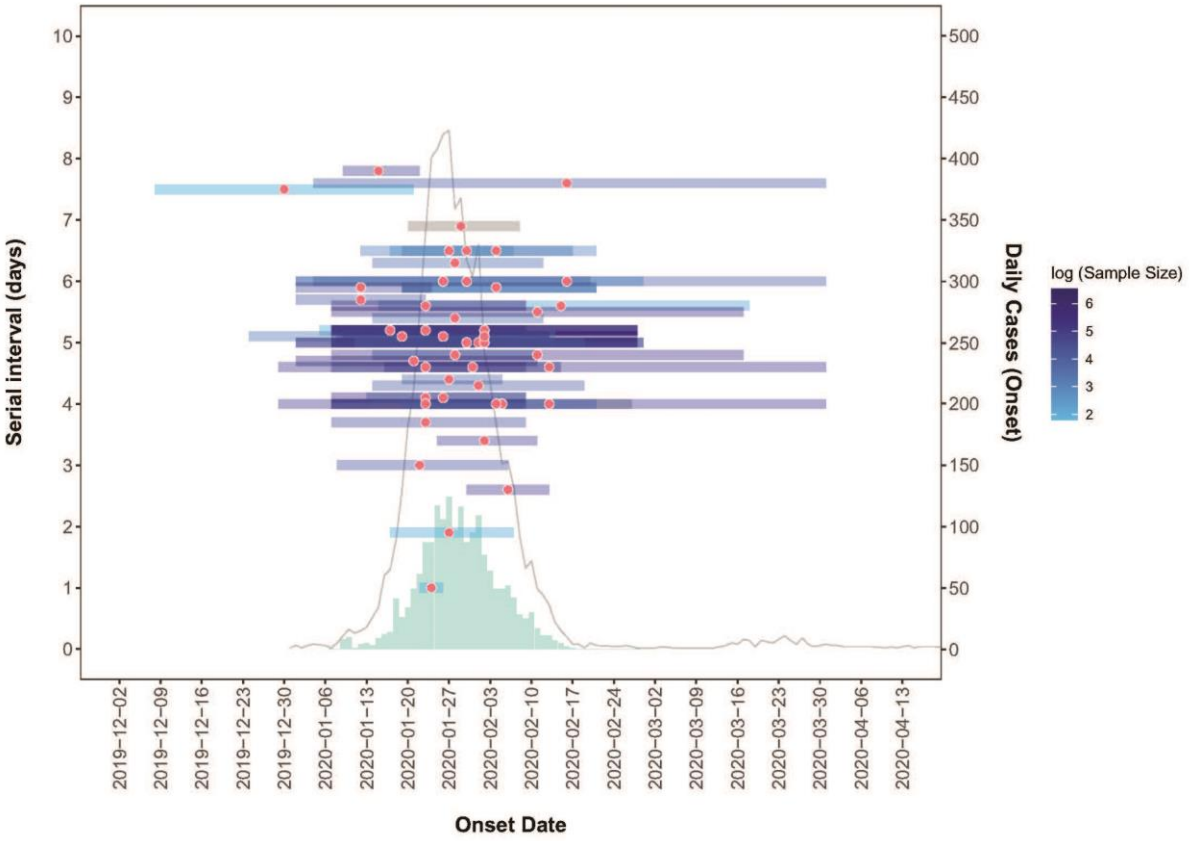

Figure 5

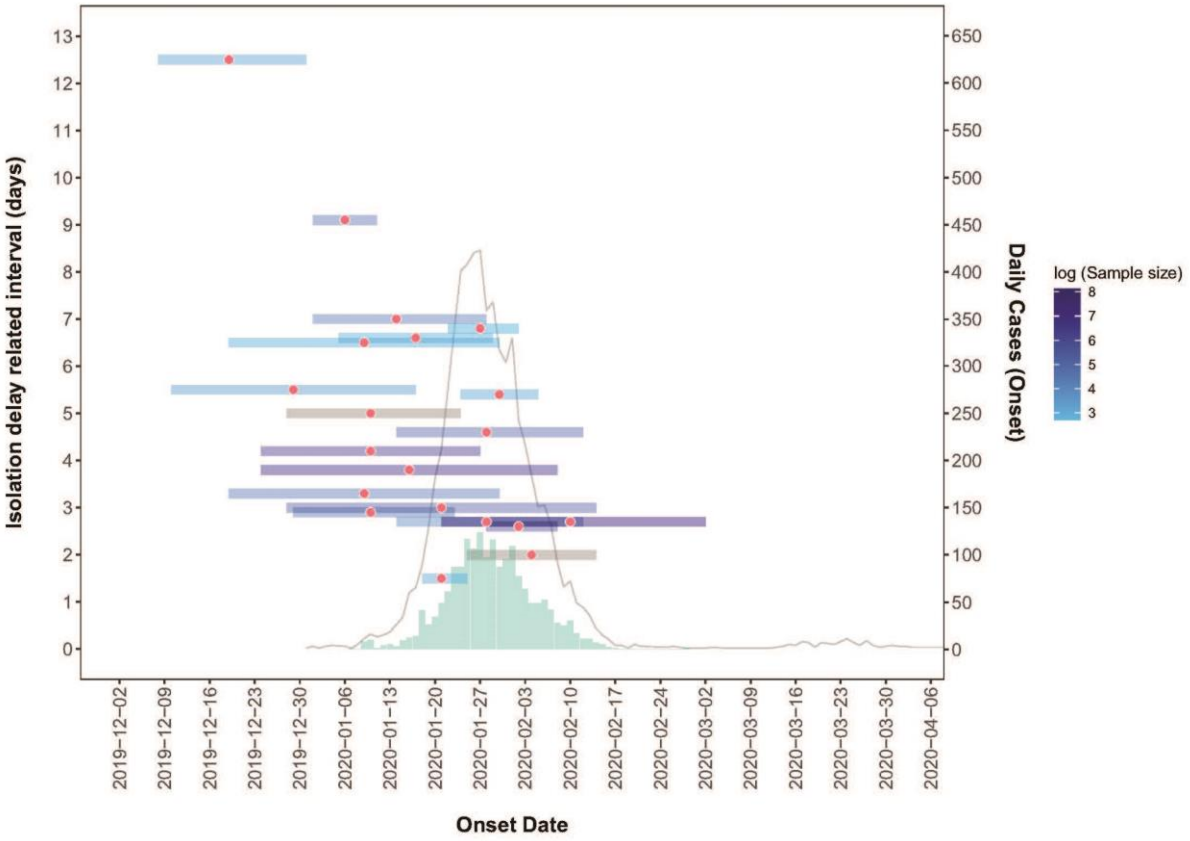

Figure 6