Clinical Infectious Diseases

MAJOR ARTICLE

Serial Intervals and Case Isolation Delays for Coronavirus Disease 2019: A Systematic Review and Meta-Analysis

Sheikh Taslim Ali,[1,2] Amy Yeung,[1] Songwei Shan,[1,2] Lin Wang,[3] Huizhi Gao,[1] Zhanwei Du,[1,2] Xiao-Ke Xu,[4] Peng Wu,[1,2] Eric H. Y. Lau,[1,2] and Benjamin J. Cowling[1,2]

[1]World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong Special Administrative Region, China; [2]Laboratory of Data Discovery for Health, Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China; [3]Department of Genetics, University of Cambridge, Cambridge, United Kingdom; and [4]College of Information and Communication Engineering, Dalian Minzu University, Dalian, China

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 2 epidemiological parameters, namely, serial intervals and delay intervals relating to isolation of cases for COVID-19 from 1 January 2020 to 22 October 2020 following predefined eligibility criteria. We assessed the variation in these parameter estimates using correlation and regression analysis.

Results. Of 103 unique studies on serial intervals of COVID-19, 56 were included, providing 129 estimates. Of 451 unique studies on isolation delays, 18 were included, providing 74 estimates. Serial interval estimates from 56 included studies varied from 1.0 to 9.9 days, while case isolation delays from 18 included studies 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 days (range, 5.1–7.8) before the epidemic peak and reduced to 4.9 days (range, 1.9–6.5) after the epidemic peak. Similarly, the pooled mean isolation delay related intervals were 6.0 days (range, 2.9–12.5) and 2.4 days (range, 2.0–2.7) 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.

Keywords. COVID-19; serial intervals; isolation delays; systematic review and meta-analysis; regression analysis.

The novel coronavirus disease 2019 (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 [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. 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 and 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].

Estimations of 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 are not available) for each confirmed COVID-19 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

Received 21 January 2021; editorial decision 20 May 2021; published online 25 May 2021.
Correspondence: B. J. Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong (bcowling@hku.hk).

Clinical Infectious Diseases® 2022;74(4):685–94
© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/ciab491

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

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 guidelines [19]. Two co-authors (A. Y. and S. S.) performed the article search and data extraction independently using a standardized form. Conflicts over inclusion of the studies and retrieving the estimates of these variables were resolved by another co-author (S. T. A.). 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 preprints 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"; and (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 were extracted by a Chinese-speaking co-author (S. S.). 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 Supplementary Tables 1 and 2).

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"; and (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 Supplementary Tables 1 and 2).

Data Extraction and Analyses

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 (CIs), 95% credible intervals (CrIs), standard deviation (SD), interquartile range (IQR), or range. We standardized the uncertainty measure for comparison purposes (see Supplementary Materials, 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 for 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 (eg, normal, Gumbel, Weibull, Gamma, lognormal); truncation, whether the data were 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 (Supplementary Materials, section 3). More details on these variables are presented in Supplementary Tables 3 and 4 [20].

We generated boxplots for the outcome variables over each factor variable to visualize 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 (eg, mainland China) whenever possible. Considering the facts that the start times of the pandemic were different across locations and that 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 the 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

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

representative estimate for better comparison (Supplementary Materials, section 4). We used 2-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 that reported raw data COVID-19 transmission pairs, providing 129 serial interval estimates [2–4, 8, 12, 16, 21–71], which also accounted the studies from 3 reviews [72–74]. The detailed selection process is illustrated in Figure 1A. Of these 56 studies, 58 estimates used data from mainland China only [2, 4, 8, 12, 16, 22–30, 32–36, 38, 51, 57, 58, 60, 62, 64, 68, 69], and 14 estimates used data from other countries along with data from China [3, 31, 38–40]. Some studies reported estimates from other locations, including 13 from Hong Kong [44, 50]; 12 from South Korea [43, 46, 48, 49, 52, 53]; 6 from India [65]; 4 each from Singapore [8, 25, 70], Taiwan [38, 59], Italy [42, 45], and Argentina [66]; 2 each from Brunei [67, 71], Iran [41, 47], and Brazil [21]; and 1 each from Philippines [56], Germany [37], Vietnam [63], and the Diamond Princess Cruise Ship [55] (Supplementary Table 5).

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, 28, 36, 44, 51, 57, 75–85] (in particular, 8 studies with onset-to-isolation intervals [2, 36, 43, 44, 76, 80, 81, 83] and 11 studies with onset-to-hospitalization intervals [2, 4, 17, 28, 51, 77–79, 82, 84, 85]). 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, 28, 36, 51, 78, 80, 82, 84, 85], and 21 were from other regions, including 16 from Hong Kong [44, 76, 77, 83], 2 each from South Korea [43] and Singapore [81], and 1 from the United Kingdom [79] (Supplementary Table 5).

From 56 studies, 129 estimates of serial intervals reported for COVID-19 varied considerably, ranging from 1.0 to 9.9 (Figure 2); 88 (68%) of the estimates were reported as mean values, while 41 (32%) were reported as median values (Supplementary Table 5). 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. Twenty-four (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, that is, Gamma (47, 63%), lognormal (13, 18%), Weibull (11, 15%), loglogistic (1,

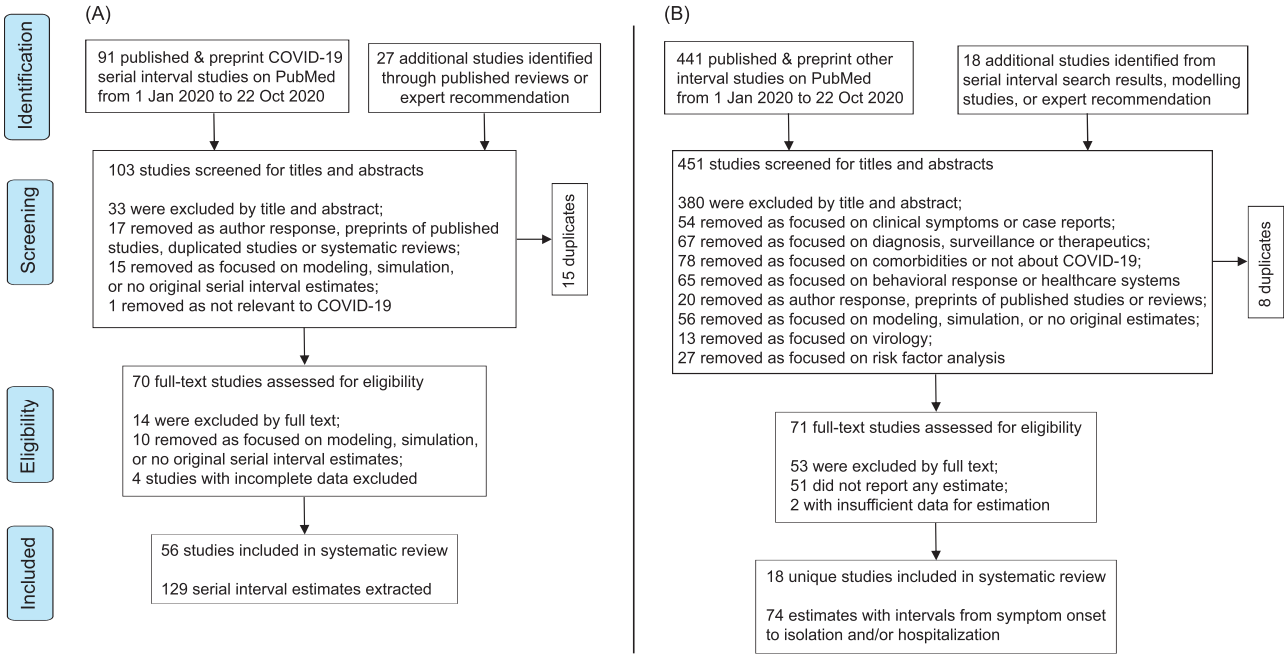

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram indicating the search process used to obtain studies that reported *(A)* serial intervals and *(B)* isolation delay related intervals for COVID-19. We used PubMed for our primary search, as well as the papers mentioned in existing reviews (Park et al [72], Koh et al [73], and Griffin et al [74]) and additional studies recommended by experts. Abbreviation: COVID-19, coronavirus disease 2019.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

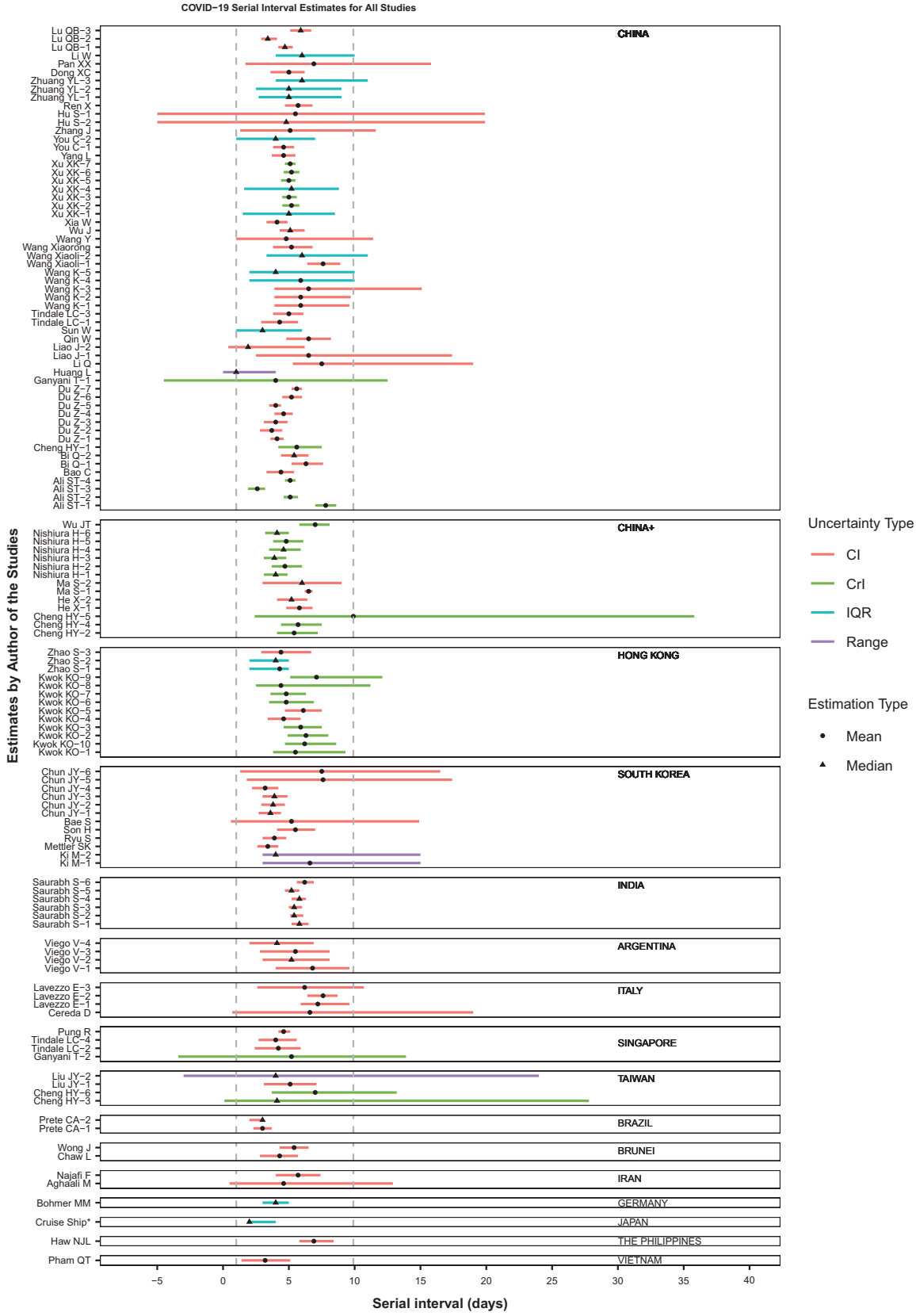

Figure 2. All 129 coronavirus disease 2019 (COVID-19) serial interval estimates reported in 56 studies are presented by country. Points represent the estimates reported as mean and triangles as median. The horizontal segments indicate CI (in red), CrI (in green), IQR (in blue), and range (in purple). We termed China+ for those estimates that considered the data from other locations along with mainland China. Abbreviations: CI, confidence interval; CrI, credibility interval; IQR, interquartile range.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

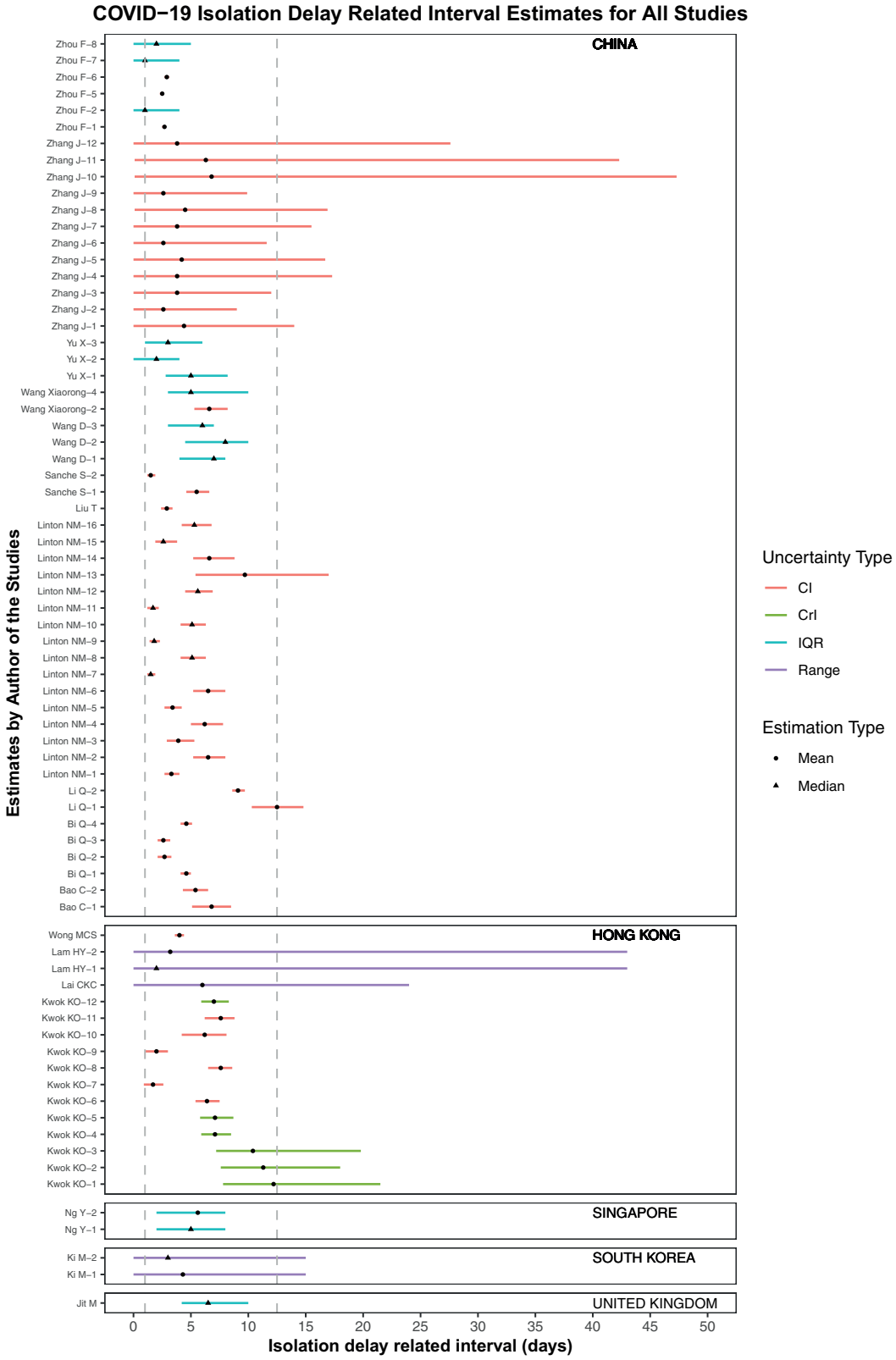

Figure 3. All 74 isolation delay related interval estimates for coronavirus disease 2019 (COVID-19) reported in 18 unique studies are presented by country. Points represent the estimates reported as mean and triangles as median. The horizontal segments indicate CI (in red), CrI (in green), IQR (in blue), and range (in purple). Abbreviations: CI, confidence interval; CrI, credibility interval; IQR, interquartile range.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

1%), and statistical simulation (2, 3%); 31 (24%) estimates used empirical distribution directly. Of all 129 estimates, only 12 (9%) used truncated data and only 11 (9%) were obtained from household transmission setting, while all others were obtained from community transmission settings.

From 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. There were 52 (70%) estimates that were reported as mean values, while 22 (30%) were reported as median values (Supplementary Table 5) with 50 (68%) estimates using 95% CI, 6 (8%) using 95% CrI, 13 (18%) using IQR, and 5 (6%) using range. Forty-one (55%) estimates used fitting of the distributions, that is, Gamma (12, 29%), lognormal (17, 41), and Weibull (12, 29%), and 33 (45%) estimates were derived using empirical distribution directly. Of all 74 estimates, 11 (15%) used truncated data and 63 (85%) used nontruncated data. All (74) estimates were performed on nonhousehold transmission settings.

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 (Supplementary Figures 1–6) including types of estimates (Supplementary Table 6). 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 (Supplementary Figures 3 and 6). The mean estimates during pre- and post-epidemic peak were significantly different for serial interval (P value = .014) and isolation delay related interval (P value = .001). The serial interval estimates had a pooled mean of 6.2 days (range, 5.1–7.8) during the pre-peak period and reduced to 4.9 days (range, 1.9–6.5) during the post-peak period (Supplementary Figure 3). Similarly, the mean estimated isolation delay related intervals were 6.0 days (range, 2.9–12.5) and 2.4 days (range, 2.0–2.7) before and after epidemic peak, respectively (Supplementary Figure 6). 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 correlation coefficient (r) = −0.35, P = .033), mid date (r = −0.33, P = .041), and sample size (Spearman rank correlation coefficient (ρ) = −0.42, P = .011) of the data windows for COVID-19 in mainland China (Supplementary Table 7). Similar associations (r = −0.47, P = .037 for start date and r = −0.64, P = .002 for mid date) were found for the isolation delay related interval estimates with these factors (Supplementary Table 8).

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

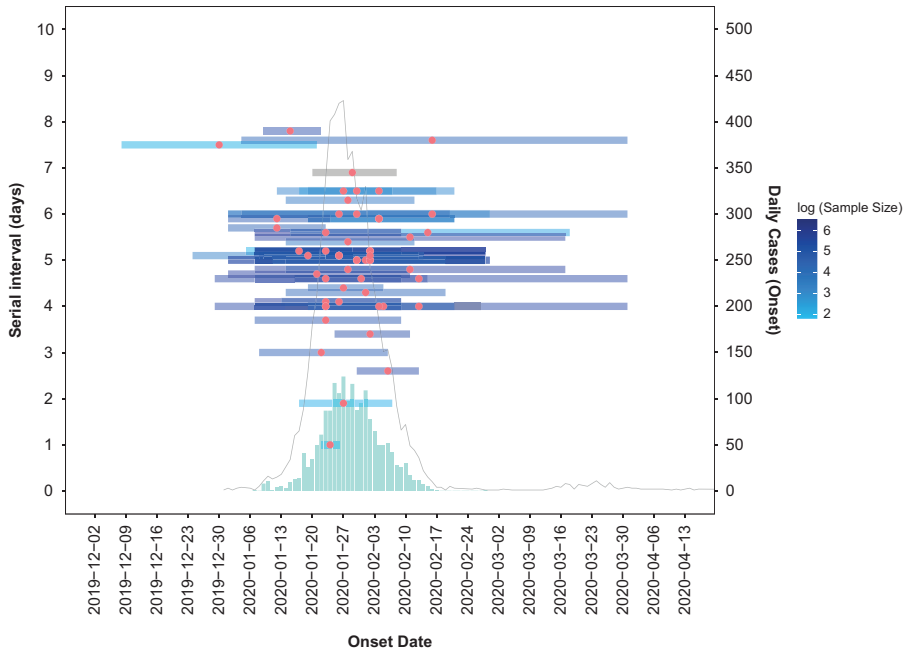

Figure 4. The temporal variation in reported estimates of serial intervals for coronavirus disease 2019 in mainland China. The plot showing the reported serial interval estimates (in red circles) over time by mid dates of the data windows used for estimation of the serial intervals. The horizontal bars indicate the data window (indicating start dates and end dates) of the individual experiments, with the color 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, gray; pair size was not available). The epidemic curve with the onset of confirmed cases (gray line) and epidemic curve with the onset of infectors and infectee in the transmission pairs (teal columns as available from 7 January 2020 to 28 February 2020) for mainland China alone, shown for reference of the epidemic timing [12, 69].

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

intervals also shortened over time (Figure 5). As a sensitivity analysis, a similar trend was observed when analyzed by the start dates of the data window (Supplementary Figures 7 and 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 1-day reduction in the estimated isolation delay related intervals, the estimated serial intervals reduced by 0.43 days (95% CI, .32–.53; Figure 6, Supplementary Figure 9).

DISCUSSION

The serial interval depends on the infectiousness profile of the infector and the properties of contacts (eg, contact patterns, structure of contacts) in a transmission chain [12, 86, 87]. Public health measures can modify these properties of effective contacts and hence reshape 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 of infectors may change over time with relaxing or tightening of control measures.

The serial interval estimates for COVID-19 varied across different countries (Figure 2, Supplementary Table 5). Nonpharmaceutical control measures implemented in these locations also differed in terms of types, timing, and effectiveness according to the respective health policies in the jurisdiction [88]. Furthermore, diversity in population structure, culture and beliefs, and human behavior 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 [89].

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, Supplementary Figures 1 and 2). Furthermore, even within the same studies, different estimation methods and assumptions may result in different serial interval estimates [40, 44, 69]. The choice of the estimation types (Supplementary Table 6) and probability distribution models (distribution types) for estimating serial intervals is crucial and should be based on realistic assumptions. For example, fitting distributions with positive support (eg, Gamma, Weibull) directly to datasets that include negative serial intervals may distort the estimated distribution. The household and nonhousehold settings might have different characteristics on contact pattern, mode of transmission, and non-pharmaceutical interventions (NPIs) effectiveness, which might be a potential factor of the variation in serial interval estimates [30, 33]. Similarly, the differences in the estimates for the isolation delay related intervals might

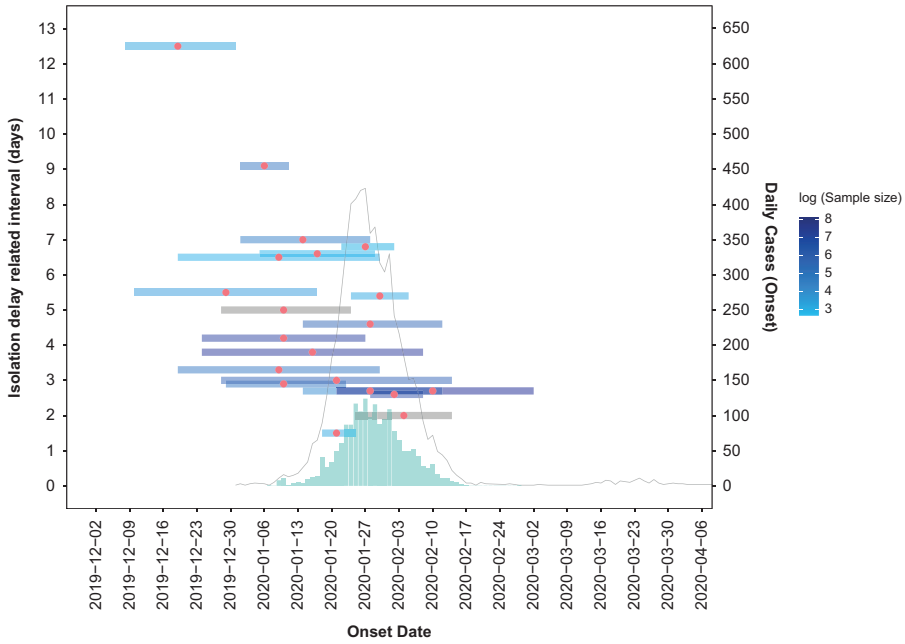

Figure 5. The temporal variation in reported estimates of isolation delay related intervals for coronavirus disease 2019 in mainland China. The plot showing the reported isolation delay related interval estimates (in red circles) over time by mid dates of the data windows used for estimation of the isolation delay related intervals. The horizontal bars indicate the data window (indicating start dates and end dates) of the individual experiments, with the color 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, gray; sample size was not available). The epidemic curve with the onset of confirmed cases (gray line) and epidemic curve with the onset of infectors and infectee in the transmission pairs (teal columns as available from 7 January 2020 to 28 February 2020) for mainland China alone, shown for reference of the epidemic timing [12, 69].

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

have been driven by these methodological factors and their related assumptions (Figure 4, Supplementary Figures 4 and 5). On the other hand, the uncertainty of these estimates was much more diverse, as presented by different types of uncertainty measures (Figures 2 and 3), even statistically misrepresented for some studies [23, 25, 27, 32, 35, 44, 54, 59, 65, 71].

Along with the above spatial and methodological factors, our results suggest that the temporal factors as the timing of data window used for estimating the serial interval and isolation delays might lead to the disagreements of these reported estimates (Supplementary Tables 7 and 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 and 5, Supplementary Figures 7 and 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 finding that early isolation of 1 day 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 that we document the evidence on the estimates of the outcome variables but also disentangle the reasons for 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 analyzing the estimates in the studies on the data from mainland China only. Availability of such estimates at the temporal scale in other locations could have strengthened our findings. More than 1 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. Second, the estimates of the outcome variables were

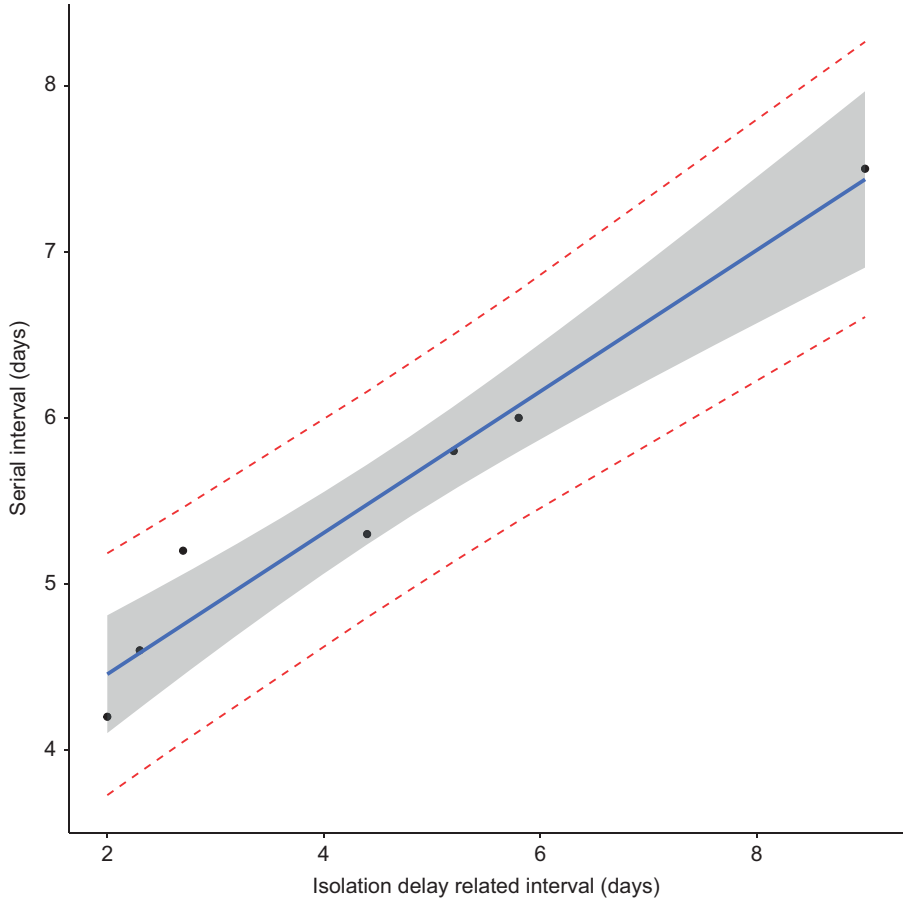

Figure 6. The association between serial interval and case isolation. The regression model prediction of estimated serial intervals (weekly pooled estimates by taking average) by the estimates of isolation delay related intervals (weekly pooled estimates by taking average) in mainland China. The black dots are a 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% confidence interval (dashed red lines). Gray shaded region indicates the standard error for the linear prediction.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

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 with the 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. S. T. A., L. W., and B. J. C. conceived the study. S. T. A. and B. J. C. designed the study. A. Y. and S. S. performed the literature review and extracted the data, and S. T. A. provided assistance. A. Y. and S. T. A. coded the statistical analysis, figures, and appendix, and S. S. provided support. S. T. A., E. H. Y. L., L. W., P. W., and B. J. C. interpreted the data. S. T. A. and B. J. C. wrote the first draft of the manuscript. All authors reviewed and revised subsequent drafts and approved the final version.

Acknowledgments. The authors thank Julie Au for technical assistance.

Disclaimer. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Financial support. This work was supported by the Theme-based Research Scheme (project T11-712/19-N) of the Research Grants Council of the Hong Kong SAR Government.

Potential conflicts of interest. B. J. C. consults for Sanofi, Roche, AstraZeneca, Moderna, and GSK. All remaining authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Weekly epidemiological update–15 December 2020. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update. Accessed 15 December 2020.
2. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis **2020**; 20:911–9.
3. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med **2020**; 26:672–5.
4. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med **2020**; 382:1199–207.
5. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci **2007**; 274:599–604.
6. Knight J, Mishra S. Estimating effective reproduction number using generation time versus serial interval, with application to covid-19 in the Greater Toronto Area, Canada. Infect Dis Model **2020**; 5:889–96.
7. Deng Y, You C, Liu Y, Qin J, Zhou XH. Estimation of incubation period and generation time based on observed length-biased epidemic cohort with censoring for COVID-19 outbreak in China. Biometrics **2020**.
8. Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Euro Surveill **2020**; 25:2020.03.05.20031815.
9. Cowling BJ, Ali ST, Ng TWY, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. Lancet Public Health **2020**; 5:e279–88.
10. Leung K, Wu JT, Liu D, Leung GM. First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment. Lancet **2020**; 395:1382–93.
11. Pan A, Liu L, Wang C, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA **2020**; 323:1915–23.
12. Ali ST, Wang L, Lau EHY, et al. Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. Science **2020**; 369:1106–9.
13. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health **2020**; 8: e488–96.
14. Lai S, Ruktanonchai NW, Zhou L, et al. Effect of non-pharmaceutical interventions to contain COVID-19 in China. Nature **2020**; 585:410–3.
15. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH; Taiwan COVID-19 Outbreak Investigation Team. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med **2020**; 180:1156–63.
16. Liao J, Fan S, Chen J, et al. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. Innovation **2020**; 1:100001.
17. Linton NM, Kobayashi T, Yang Y, et al. Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly available case data. J Clin Med **2020**; 9:538.
18. Sun K, Wang W, Gao L, et al. Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. Science **2021**; 371.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ **2009**; 339:b2535.
20. Supplementary data (Tables S3 and S4) for "Serial intervals and case isolation delays for Coronavirus Disease 2019: a systematic review and meta-analysis". **2020**. Available at: https://osf.io/c37zh/.
21. Prete CA, Buss L, Dighe A, et al. Serial interval distribution of SARS-CoV-2 infection in Brazil. J Travel Med **2021**; 28:taaa115.
22. Huang L, Zhang X, Zhang X, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: a prospective contact-tracing study. J Infect **2020**; 80:e1–e13.
23. Qin W, Sun J, Xu P, et al. The descriptive epidemiology of coronavirus disease 2019 during the epidemic period in Lu'an, China: achieving limited community transmission using proactive response strategies. Epidemiol Infect **2020**; 148:e132.
24. Sun WW, Ling F, Pan JR, et al. [Epidemiological characteristics of COVID-19 family clustering in Zhejiang Province]. Zhonghua Yu Fang Yi Xue Za Zhi **2020**; 54:625–9.
25. Tindale LC, Stockdale JE, Coombe M, et al. Evidence for transmission of COVID-19 prior to symptom onset. Elife **2020**; 9:e57149.
26. Wang K, Zhao S, Liao Y, et al. Estimating the serial interval of the novel coronavirus disease (COVID-19) based on the public surveillance data in Shenzhen, China, from 19 January to 22 February 2020. Transbound Emerg Dis **2020**; 67(6):2818–22.
27. Wang X, Pan Y, Zhang D, et al. Basic epidemiological parameter values from data of real-world in mega-cities: the characteristics of COVID-19 in Beijing, China. BMC Infect Dis **2020**; 20:526.
28. Wang X, Zhou Q, He Y, et al. Nosocomial outbreak of COVID-19 pneumonia in Wuhan, China. Eur Respir J **2020**; 55:2000544.
29. Wang Y, Teunis P. Strongly heterogeneous transmission of COVID-19 in mainland China: local and regional variation. Front Med (Lausanne) **2020**; 7:329.
30. Wu J, Huang Y, Tu C, et al. Household transmission of SARS-CoV-2, Zhuhai, China, 2020. Clin Infect Dis **2020**; 71:2099–108.
31. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med **2020**; 26:506–10.
32. Xia W, Liao J, Li C, et al. Transmission of corona virus disease 2019 during the incubation period may lead to a quarantine loophole. medRxiv **2020**: 2020.03.06.20031955.
33. Xu XK, Liu XF, Wu Y, et al. Reconstruction of transmission pairs for novel coronavirus disease 2019 (COVID-19) in mainland China: estimation of superspreading events, serial interval, and hazard of infection. Clin Infect Dis **2020**; 71:3163–7.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022

34. Yang L, Dai J, Zhao J, Wang Y, Deng P, Wang J. Estimation of incubation period and serial interval of COVID-19: analysis of 178 cases and 131 transmission chains in Hubei province, China. Epidemiol Infect **2020**; 148:e117.
35. You C, Deng Y, Hu W, et al. Estimation of the time-varying reproduction number of COVID-19 outbreak in China. Int J Hyg Environ Health **2020**; 228:113555.
36. Bao C, Pan E, Ai J, et al. COVID-19 outbreak following a single patient exposure at an entertainment site: an epidemiological study. Transbound Emerg Dis **2021**; 68:773–81.
37. Böhmer MM, Buchholz U, Corman VM, et al. Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series. Lancet Infect Dis **2020**; 20:920–8.
38. Cheng HY, Jian SW, Liu DP, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med **2020**; 180:1156–63.
39. Ma S, Zhang J, Zeng M, et al. Epidemiological parameters of coronavirus disease 2019: a pooled analysis of publicly reported individual data of 1155 cases from seven countries. medRxiv **2020**: 2020.03.21.20040329.
40. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. Int J Infect Dis **2020**; 93:284–6.
41. Aghaali M, Kolifarhood G, Nikbakht R, Saadati HM, Hashemi Nazari SS. Estimation of the serial interval and basic reproduction number of COVID-19 in Qom, Iran, and three other countries: a data-driven analysis in the early phase of the outbreak. Transbound Emerg Dis **2020**; 67:2860–8.
42. Cereda D, Tirani M, Rovida F, et al. The early phase of the COVID-19 outbreak in Lombardy, Italy. arXiv **2020**.
43. Ki M; Task Force for 2019-nCoV. Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Korea. Epidemiol Health **2020**; 42:e2020007.
44. Kwok KO, Wong VWY, Wei WI, Wong SYS, Tang JW. Epidemiological characteristics of the first 53 laboratory-confirmed cases of COVID-19 epidemic in Hong Kong, 13 February 2020. Euro Surveill **2020**; 25:2000155.
45. Lavezzo E, Franchin E, Ciavarella C, et al; Imperial College COVID-19 Response Team. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature **2020**; 584:425–9.
46. Mettler SK, Kim J, Maathuis MH. Diagnostic serial interval as a novel indicator for contact tracing effectiveness exemplified with the SARS-CoV-2/COVID-19 outbreak in South Korea. Int J Infect Dis **2020**; 99:346–51.
47. Najafi F, Izadi N, Hashemi-Nazari SS, Khosravi-Shadmani F, Nikbakht R, Shakiba E. Serial interval and time-varying reproduction number estimation for COVID-19 in western Iran. New Microbes New Infect **2020**; 36:100715.
48. Ryu S, Ali ST, Jang C, Kim B, Cowling BJ. Effect of nonpharmaceutical interventions on transmission of severe acute respiratory syndrome coronavirus 2, South Korea, 2020. Emerg Infect Dis **2020**; 26:2406–10.
49. Son H, Lee H, Lee M, et al. Epidemiological characteristics of and containment measures for COVID-19 in Busan, Korea. Epidemiol Health **2020**; 42:e2020035.
50. Zhao S, Gao D, Zhuang Z, et al. Estimating the serial interval of the novel coronavirus disease (COVID-19): a statistical analysis using the public data in Hong Kong from January 16 to February 15, 2020. Front Phys **2020**; 8.
51. Zhang J, Litvinova M, Wang W, et al. Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. Lancet Infect Dis **2020**; 20:793–802.
52. Bae S, Kim H, Jung TY, et al. Epidemiological characteristics of COVID-19 outbreak at fitness centers in Cheonan, Korea. J Korean Med Sci **2020**; 35:e288.
53. Chun JY, Baek G, Kim Y. Transmission onset distribution of COVID-19. Int J Infect Dis **2020**; 99:403–7.
54. Dong XC, Li JM, Bai JY, et al. [Epidemiological characteristics of confirmed COVID-19 cases in Tianjin]. Zhonghua Liu Xing Bing Xue Za Zhi **2020**; 41:638–41.
55. Expert Taskforce for the C-CSO. Epidemiology of COVID-19 outbreak on cruise ship quarantined at Yokohama, Japan, February 2020. Emerg Infect Dis **2020**; 26:2591–7.
56. Haw NJL, Uy J, Sy KTL, Abrigo MRM. Epidemiological profile and transmission dynamics of COVID-19 in the Philippines. Epidemiol Infect **2020**; 148:e204.
57. Hu S, Wang W, Wang Y, et al. Infectivity, susceptibility, and risk factors associated with SARS-CoV-2 transmission under intensive contact tracing in Hunan, China. Nat Commun **2021**; 12:1533.
58. Li W, Zhang B, Lu J, et al. Characteristics of household transmission of COVID-19. Clin Infect Dis **2020**; 71:1943–6.
59. Liu JY, Chen TJ, Hwang SJ. Analysis of community-acquired COVID-19 cases in Taiwan. J Chin Med Assoc **2020**; 83:1087–92.
60. Lu QB, Zhang Y, Liu MJ, et al. Epidemiological parameters of COVID-19 and its implication for infectivity among patients in China, 1 January to 11 February 2020. Euro Surveill **2020**; 25:2000250.
61. Ma S, Zhang J, Zeng M, et al. Epidemiological parameters of COVID-19: case series study. J Med Internet Res **2020**; 22:e19994.
62. Pan XX, Chen Y, Wang AH, et al. [Study on transmission dynamic of 15 clusters of coronavirus disease 2019 cases in Ningbo]. Zhonghua Liu Xing Bing Xue Za Zhi **2020**; 41:E066.
63. Pham QT, Rabaa MA, Duong HL, et al. The first 100 days of SARS-CoV-2 control in Vietnam. Clin Infect Dis **2020**; 71:2679–87.
64. Ren X, Li Y, Yang X, et al. Evidence for pre-symptomatic transmission of coronavirus disease 2019 (COVID-19) in China. Influenza Other Respir Viruses **2021**; 15:19–26.
65. Saurabh S, Verma MK, Gautam V, et al. Transmission dynamics of the COVID-19 epidemic at the district level in India: prospective observational study. JMIR Public Health Surveill **2020**; 6:e22678.
66. Viego V, Geri M, Castiglia J, Jouglard E. Incubation period and serial interval of Covid-19 in a chain of infections in Bahia Blanca (Argentina). Cien Saude Colet **2020**; 25:3503–10.
67. Wong J, Chaw L, Koh WC, et al. Epidemiological investigation of the first 135 COVID-19 cases in Brunei: implications for surveillance, control, and travel restrictions. Am J Trop Med Hyg **2020**; 103:1608–13.
68. Zhuang YL, Zhang YT, Li M, et al. [Analysis on the cluster epidemic of coronavirus disease 2019 in Guangdong Province]. Zhonghua Yu Fang Yi Xue Za Zhi **2020**; 54:720–5.
69. Du Z, Xu X, Wu Y, Wang L, Cowling BJ, Meyers LA. Serial interval of COVID-19 among publicly reported confirmed cases. Emerg Infect Dis **2020**; 26:1341–3.
70. Pung R, Cook AR, Chiew CJ, et al. Effectiveness of containment measures against COVID-19 in Singapore: implications for other national containment efforts. Epidemiology **2021**; 32:79–86.
71. Chaw L, Koh WC, Jamaludin SA, Naing L, Alikhan MF, Wong J. Analysis of SARS-CoV-2 Transmission in Different Settings, Brunei. Emerg Infect Dis **2020**; 26(11):2598–606.
72. Park M, Cook AR, Lim JT, Sun Y, Dickens BL. A systematic review of COVID-19 epidemiology based on current evidence. J Clin Med **2020**; 9.
73. Koh WC, Naing L, Rosledzana MA, et al. What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate, serial interval, and asymptomatic infection. medRxiv **2020**: 2020.05.21.20108746.
74. Griffin J, Casey M, Collins Á, et al. Rapid review of available evidence on the serial interval and generation time of COVID-19. BMJ Open **2020**; 10:e040263.
75. Kim HJ, Hwang HS, Choi YH, et al. The delay in confirming COVID-19 cases linked to a religious group in Korea. J Prev Med Public Health **2020**; 53:164–7.
76. Lai CKC, Ng RWY, Wong MCS, et al. Epidemiological characteristics of the first 100 cases of coronavirus disease 2019 (COVID-19) in Hong Kong Special Administrative Region, China, a city with a stringent containment policy. Int J Epidemiol **2020**; 49:1096–105.
77. Lam HY, Lam TS, Wong CH, et al. The epidemiology of COVID-19 cases and the successful containment strategy in Hong Kong—January to May 2020. Int J Infect Dis **2020**; 98:51–8.
78. Yu X, Sun X, Cui P, et al. Epidemiological and clinical characteristics of 333 confirmed cases with coronavirus disease 2019 in Shanghai, China. Transbound Emerg Dis **2020**; 67:1697–707.
79. Jit M, Jombart T, Nightingale ES, et al. Estimating number of cases and spread of coronavirus disease (COVID-19) using critical care admissions, United Kingdom, February to March 2020. Euro Surveill **2020**; 25:2000632.
80. Liu T, Hu J, Xiao J, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). bioRxiv **2020**: 2020.01.25.919787.
81. Ng Y, Li Z, Chua YX, et al. Evaluation of the effectiveness of surveillance and containment measures for the first 100 patients with COVID-19 in Singapore—January 2-February 29, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:307–11.
82. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis **2020**; 26:1470–7.
83. Wong MCS, Ng RWY, Chong KC, et al. Stringent containment measures without complete city lockdown to achieve low incidence and mortality across two waves of COVID-19 in Hong Kong. BMJ Glob Health **2020**; 5:e003573.
84. Zhou F, You C, Zhang X, et al. Epidemiological characteristics and factors associated with critical time intervals of COVID-19 in eighteen provinces, China: a retrospective study. Int J Infect Dis **2021**; 102:123–31.
85. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA **2020**; 323:1061–9.
86. Zhang J, Litvinova M, Liang Y, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. Science **2020**; 368:1481–6.
87. Park SW, Champredon D, Dushoff J. Inferring generation-interval distributions from contact-tracing data. J R Soc Interface **2020**; 17:20190719.
88. Li Y, Campbell H, Kulkarni D, et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: a modelling study across 131 countries. Lancet Infect Dis **2021**; 21:193–202.
89. Haug N, Geyrhofer L, Londei A, et al. Ranking the effectiveness of worldwide COVID-19 government interventions. Nat Hum Behav **2020**; 4:1303–12.

Downloaded from https://academic.oup.com/cid/article/74/4/685/6284329 by University of Hong Kong user on 16 June 2022