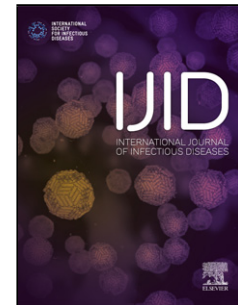


Journal Pre-proof

Serial interval of novel coronavirus (COVID-19) infections

Hiroshi Nishiura, Natalie M. Linton, Andrei R. Akhmetzhanov



PII: S1201-9712(20)30119-3

DOI: <https://doi.org/10.1016/j.ijid.2020.02.060>

Reference: IJID 4006

To appear in: *International Journal of Infectious Diseases*

Received Date: 14 February 2020

Revised Date: 25 February 2020

Accepted Date: 27 February 2020

Please cite this article as: Nishiura H, Linton NM, Akhmetzhanov AR, Serial interval of novel coronavirus (COVID-19) infections, *International Journal of Infectious Diseases* (2020), doi: <https://doi.org/10.1016/j.ijid.2020.02.060>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier.

Title: Serial interval of novel coronavirus (COVID-19) infections**Running title:** Serial interval of COVID-19**Authors:**Hiroshi Nishiura^{1,2}, Natalie M. Linton¹, Andrei R. Akhmetzhanov¹**Affiliations:**

¹Graduate School of Medicine, Hokkaido University, Kia 15 Jo Nishi 7 Chome, Kitaku, Sapporo, 060-8638, Japan; ²CREST, Japan Science and Technology Agency, Honcho 4-1-8, Kawaguchi, Saitama, 332-0012 Japan;

Correspondence to: H. Nishiura, Graduate School of Medicine, Hokkaido University, Kia 15 Jo Nishi 7 Chome, Kitaku, Sapporo, 060-8638, Japan Tel: +81 11 706 5066 Fax: +81 11 706 7819, E-mail: nishiurah@med.hokudai.ac.jp

Article type:

Original article

Highlights

- The serial interval of novel coronavirus (COVID-19) infections was estimated from a total of 28 infector-infectee pairs.

- The median serial interval is shorter than the median incubation period, suggesting a substantial proportion of pre-symptomatic transmission.
- A short serial interval makes it difficult to trace contacts due to the rapid turnover of case generations.

Abstract

Objective: To estimate the serial interval of novel coronavirus (COVID-19) from information on 28 infector-infectee pairs.

Methods: We collected dates of illness onset for primary cases (infectors) and secondary cases (infectees) from published research articles and case investigation reports. We subjectively ranked the credibility of the data and performed analyses on both the full dataset ($n=28$) and a subset of pairs with highest certainty in reporting ($n=18$). In addition, we adjust for right truncation of the data as the epidemic is still in its growth phase.

Results: Accounting for right truncation and analyzing all pairs, we estimated the median serial interval at 4.0 days (95% credible interval [CrI]: 3.1, 4.9). Limiting our data to only the most certain pairs, the median serial interval was estimated at 4.6 days (95% CrI: 3.5, 5.9).

Conclusions: The serial interval of COVID-19 is close to or shorter than its median incubation period. This suggests that a substantial proportion of secondary transmission may occur prior to illness onset. The COVID-19 serial interval is also shorter than the serial interval of severe acute respiratory syndrome (SARS), indicating that calculations made using the SARS serial interval may introduce bias.

Keywords: coronavirus; outbreak; illness onset; generation time; statistical model; epidemiology; viruses

Introduction

The epidemic of novel coronavirus (COVID-19) infections that began in China in late 2019 has rapidly grown and cases have been reported worldwide. An empirical estimate of the serial interval—the time from illness onset in a primary case (infector) to illness onset in a secondary case (infectee)—is needed to understand the turnover of case generations and transmissibility of the disease [1]. Estimates of the serial interval can only be obtained by linking dates of onset for infector-infectee pairs, and these links are not easily established. A recently published epidemiological study used contact tracing data from cases reported in Hubei Province early in the epidemic to estimate the mean serial interval at 7.5 days [2], which is consistent with the 8.4-day mean serial interval reported for severe acute respiratory syndrome (SARS) from Singaporean household contact data [3]. However, there were only six infector-infectee pairs in this dataset, and sampling bias may have been introduced to the variance and mean. To further assess the serial interval of COVID-19 infections we compiled a dataset of 28 publicly shared infector-infectee pairs and calculated the serial interval from these data.

Materials and Methods

We scanned publicly available information published in research articles and quoted from official reports of outbreak investigations to obtain our dataset.

The date of illness onset was defined as the date on which a symptom relevant to COVID-19 infection appeared and was determined by the reporting governmental body. We subjectively ranked the credibility of the ascertained pairs into “certain” and “probable,” where the former was used for pairs and dates of illness onset were clearly defined in an academic article and the latter was applied to pairs and dates of illness onset that were clearly defined but quoted from outbreak investigation reports. Pairs of cases that cannot be scientifically linked were classified as “uncertain” and removed from our analysis, and the verification of illness onset date was ensured following an erratum report of presymptomatic transmissions in Germany [4]. Estimates were obtained for certain and probable pairs combined ($n=28$) as well as for the certain pairs alone ($n=18$).

The interval censored data were handled in units of days. We employed a Bayesian approach with doubly interval censored likelihood to obtain estimates of the serial interval [5]:

$$L(\theta_g; \mathbf{D}) = \prod_i \int_{E_{L,i}}^{E_{R,i}} \int_{S_{L,i}}^{S_{R,i}} g(e)f(s-e)dsde, \quad (1)$$

where i represents the identity of each pair, $(E_{R,i}, E_{L,i})$ is the interval for symptom onset of the infector and $(S_{R,i}, S_{L,i})$ is the interval for symptom onset of the infectee. Intervals are allowed for illness onset event so that the serial interval can be inferred even when we do not have exact dates of illness onset for infector-infectee pairs. Here, $g(\cdot)$ is the probability density function (p.d.f.) of exposure following a uniform distribution, because there is no indication of time-dependence in the frequency of illness onset among primary cases. $f(\cdot)$ is the p.d.f. of the serial interval, assumed to be governed by three different

distributions—lognormal, gamma, and Weibull. We sampled the posterior distributions using CmdStan version 2.22.1 [6] (<http://github.com/aakhmetz/nCoVSerialInteval2020>).

As the epidemic will continue to grow beyond our data collection cutoff point of 12 February 2020, it is possible that the naïve likelihood (1) underestimates the serial interval as sampling during the early stage of the epidemic preferentially excludes infector-infectee pairs with longer serial intervals. We adjusted for this selection bias—called right truncation—in our model. The alternative p.d.f. that accounts for right truncation during the exponential growth phase of the epidemic is written as:

$$f'(s - e, e) = \frac{f(s - e)}{\int_0^{T-e} \frac{r \exp(-ru)}{1 - \exp(-ru)} F(T - e - u) du} \quad (2)$$

where r is the exponential growth rate estimated at 0.14 [7] and T is the latest time of observation (12 February 2020). We account for the exponential growth rate of cases, because recently infected individuals are more likely to be sampled during the exponential growth phase of an epidemic. The widely applicable information criterion (WAIC) was used to compare between distributions and the model with the minimal WAIC value was selected as the best-fit model for each set of estimates with and without right truncation.

Results

We were able to obtain data on 28 infector-infectee pairs (see Supplementary Table). Of these, 12 pairs were family clusters. Accounting for right truncation and analyzing all pairs, the model using the lognormal distribution was selected as the best-fit model (WAIC=224.0), while no

significant differences from other models were identified. The median serial interval was estimated at 4.0 days (95% credible interval [CrI]: 3.1, 4.9) while the mean and standard deviation (SD) of the serial interval were estimated at 4.7 days (95% CrI: 3.7, 6.0) and 2.9 days (95% CrI: 1.9, 4.9), respectively. Without truncation, the model using the lognormal distribution was also the best-fit model (WAIC=128.0) with the median serial interval was estimated at 3.9 days (95% CrI: 3.1, 4.8).

Limiting our dataset to only certain observations, the median serial interval of the best-fit Weibull distribution model was estimated at 4.6 days (95% CI: 3.5, 5.9) with a mean and SD of 4.8 days (95% CrI: 3.8, 6.1) and 2.3 days (95% CrI: 1.6, 3.5), respectively. Without truncation, the best-fit model used the lognormal distribution and estimated the median serial interval at 4.1 days (95% CrI: 3.2, 5.0). Figure 1 shows the best-fit distributions overlaid with a published distribution of the SARS serial interval [3].

Discussion

Our estimate of the median serial interval as 4.0 days indicates that COVID-19 infection leads to rapid cycles of transmission from one generation of cases to the next. The shorter serial interval compared to SARS implies that contact tracing methods must compete against the rapid replacement of case generations, and the number of contacts may soon exceed what available healthcare and public health workers are able to handle. The difference between these distributions suggests that using serial intervals estimates from SARS data will result in overestimation of the COVID-19 basic reproduction number.

More importantly, the estimated median serial interval is shorter than the preliminary estimates of the mean incubation period (approximately 5 days) [2,8]. As illustrated in Figure 2, when the serial interval is shorter than the incubation period, pre-symptomatic transmission is likely to have taken place and may even occur more frequently than symptomatic transmission. A substantial proportion of secondary transmission occurring before illness onset indicates that many transmissions cannot be prevented solely through isolation of symptomatic cases, as by the time contacts are traced they may have already become infectious themselves and generated secondary cases [9]. It is possible that serial intervals were shortened due to case isolation, especially outside of China, but even the subset of data in China alone can indicate that the mean is shorter than 7.5 days.

Correct ascertainment of dates of illness onset is critical to the calculation of the serial interval. Considering the overall mild nature of the infection [10] it is possible that different reporting jurisdictions have different criteria for determining what qualifies as illness onset for COVID-2019 cases, which is a potential bias we are unable to account for. However, the present study addresses the issue of data quality of the reported pairs in two ways. First, our data include the updated information from a recent report of pre-symptomatic transmission in Germany [4] where it was later found that the primary case was already symptomatic while in contact with persons who later became infected (Supplementary Material in [4]). Second, classification of the credibility of the data and comparing analyses including and excluding less certain (but nonetheless highly probable) pairs allowed us to determine that our results using

all pairs (and therefore a greater sample size) did not differ significantly from the results using only the most credible data.

In conclusion, we have estimated the median serial interval of COVID-19 at 4.0 days, which is close to or shorter than the disease's median incubation period indicating that rapid cycles of transmission and substantial pre-symptomatic transmissions are occurring. Thus, containment via case isolation alone is likely to be very challenging.

Funding source

H.N. received funding support from Japan Agency for Medical Research and Development [grant number: JP18fk0108050] the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (KAKENHI in Japanese abbreviation) grant nos. 17H04701, 17H05808, 18H04895 and 19H01074, and the Japan Science and Technology Agency (JST) Core Research for Evolutional Science and Technology (CREST) program [grant number: JPMJCR1413]. NML received a graduate study scholarship from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval

This study was based on publicly available data and did not require ethical approval.

Conflict of interest

The authors declare no conflicts of interest.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Fine PE. The interval between successive cases of an infectious disease. *Am J Epidemiol* 2003;158:1039-1047.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020; in press. doi:10.1056/NEJMoa2001316
3. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, Gopalakrishna G, Chew SK, Tan CC, Samore MH, Fisman D, Murray M. Transmission dynamics and control of severe acute respiratory syndrome. *Science*. 2003;300(5627):1966-70.
4. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirgmaier K, Zange S, Wölfel R. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Eng J Med*. 2020; in press. doi:10.1056/NEJMc2001468.
5. Reich NG, Lessler J, Cummings DA, Brookmeyer R. Estimating incubation period distributions with coarse data. *Stat Med* 2009;28:2769-2784.
6. Stan Development Team. Stan Modeling Language Users Guide and Reference Manual. 2014, URL<http://mc-stan.org/manual.html>.

7. Jung S, Akhmetzhanov AR, Hayashi K, Linton NM, Yang Y, Yuan B, Kobayashi T, Kinoshita R, Nishiura H. Real time estimation of the risk of death from novel coronavirus (2019-nCoV) infection: Inference using exported cases. medRxiv, [http://dx.doi.org/ 10.1101/2020.01.29.20019547v1](http://dx.doi.org/10.1101/2020.01.29.20019547v1)
8. Linton NM, Kobayashi T, Yang Y, Hayashi K, Andrei, AR, Jung S, Yuan B, Kinoshita R, Nishiura H. (2020). Epidemiological characteristics of novel coronavirus infection: A statistical analysis of publicly available case data. medRxiv. <http://dx.doi.org/10.1101/2020.01.26.20018754>
9. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(16):6146–6151.
10. Nishiura H, Kobayashi T, Yang Y, Hayashi K, Miyama T, Kinoshita R, Linton NM, Jung S, Yuan B, Suzuki A, Akhmetzhanov AR. The rate of underascertainment of novel coronavirus (2019-nCoV) infection: Estimation using Japanese passengers data on evacuation flights. *J Clin Med*. 2020; in press. doi:10.3390/jcm9020419.

Figure Legends

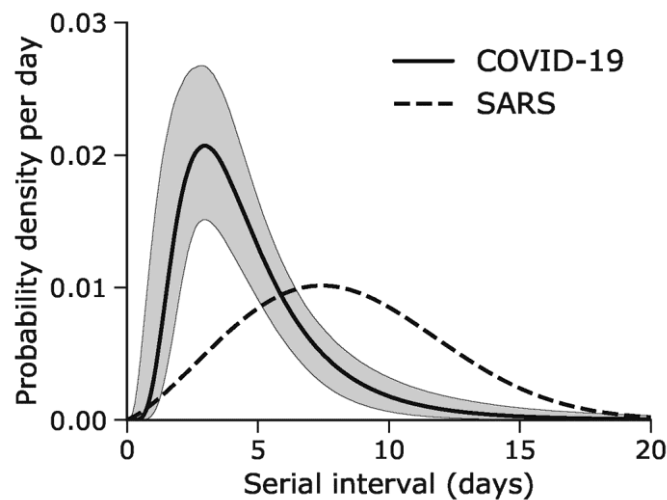


Figure 1. Serial interval of novel coronavirus (COVID-19) infections.

The solid line shows the estimated serial interval distribution of COVID-19 infections using the best-fit lognormal distribution with right truncation. A distribution based on a published estimate of the serial interval for severe acute respiratory syndrome [3] is overlaid as a dashed line for comparison.

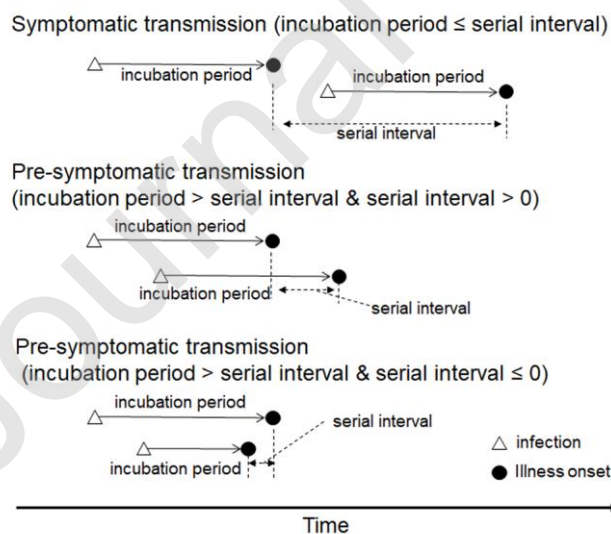


Figure 2. The relationship between the incubation period and serial interval.

If the transmission takes place during the symptomatic period of the primary case, the serial interval is longer than the incubation period. However, this relationship can be reversed when pre-symptomatic transmission takes place. Furthermore, it is possible that the secondary case may even experience illness onset prior to onset in their infector.