Serial interval of novel coronavirus (2019-nCoV) infections

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

Author affiliations: Hokkaido University, Sapporo, Japan (H. Nishiura, N.M. Linton, A.R. Akhmetzhanov)

Running Head: Serial interval of 2019-nCoV

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

Abstract: We estimated the serial interval of novel coronavirus (2019-nCoV) infections from 26 infector-infectee pairs. Accounting for right truncation, the median serial interval was estimated at 2.6 days and is shorter than estimates of the median incubation period, suggesting that a substantial proportion of secondary transmission occurs before illness onset.

To the Editor: The epidemic of novel coronavirus (2019-nCoV) infections that began in China has rapidly grown and cases have been reported worldwide. To understand the turnover of case generations and transmissibility of the disease an empirical estimate of the serial interval—the time from illness onset in a primary case to illness onset in the secondary case—is needed (*1*). However, estimates of the serial interval can only be obtained by linking dates of onset for infector-infectee pairs, and these dates are not always exactly determined. Nonetheless, if pairs are found through contact tracing, even inexact dates can be utilized to infer the serial interval (*2*). A published epidemiological study used contact tracing data from cases reported in Hubei Province early in the epidemic (mostly in December 2019) to estimate the mean serial interval at 7.5 days (*3*), which is consistent with the 8.4-day mean serial interval reported for severe acute respiratory syndrome (SARS) from Singaporean household contact data (*4*). However, there were only six infector-infectee pairs in this dataset and sampling bias may have been introduced to the variance and mean. Here we compiled a dataset including 20 additional known infector-infectee pairs to estimate the serial interval using a larger dataset.

By scanning publicly available case reports we were able to aggregate 26 infector-infectee pairs of confirmed cases with known or coarsely reported dates of onset (see Supplementary Table). For three infectees with no known reported date of illness onset, we set the lower possible date of onset at the last date of exposure of the infector. For an additional case where the infector exposure date was also unknown, we set the lower possible date of onset to December 1, 2019. Its upper date of illness onset was set to date of diagnosis. For all other cases we set the lower possible date of onset as the reported date of onset, and the upper date of onset as the reported date of onset plus one day. We employed a doubly interval censored likelihood to obtain the maximum likelihood estimate of the serial interval (*2*):

$$L\left(\Theta_g;\boldsymbol{D}\right)=\prod_i\int_{E_{L.i}}^{E_{R.i}}\int_{S_{L.i}}^{S_{R.i}}g(e)f(s-e)\mathrm{d}s\mathrm{d}e, \tag{1}$$

where *i* represents the identity of each pair, $E(R,L)$ is the interval for symptom onset of the infector and $S(R,L)$ is the interval for symptom onset of the infectee. Here $g(.)$ is the probability density function (p.d.f.) of exposure following a uniform distribution, and $f(.)$ is the p.d.f. of the serial interval, assumed to be governed by three different distributions, i.e., lognormal, gamma and Weibull distribution. Since the epidemic continues to increase, an alternative p.d.f. that accounts for right truncation was also considered, i.e.,

$$f'(s,e)=\frac{f(s)}{\int_0^{T-e}\frac{r\exp(-ru)}{1-\exp\,(-ru)}f(T-e-u)\mathrm{d}u}, \tag{2}$$

where r is the exponential growth rate estimated at 0.14 (*5*) and T is the latest time of observation. For both likelihood with and without truncation, Widely Applicable Information Criterion (WAIC) was compared and the model with minimum WAIC value was selected as the best fit model.

For both with and without truncation due to sampling in the early stage of the epidemic, the lognormal distribution model was selected as the best fit model (WAIC=49.8 and 130.3, respectively). Without truncation, the median serial interval was estimated at 3.1 days (95% credible interval (CrI): 2.1, 4.2). The mean and standard deviation (SD) of serial interval were estimated at 4.2 days (95% CrI: 2.9, 5.7) and 3.9 days (95% CrI: 1.9, 6.4), respectively. Accounting for the right truncation, the median, mean and SD of the serial interval were estimated at 2.6 days (95% credible interval (CrI): 1.8, 3.5), 3.4 days (95% CrI: 2.5, 4.4) and 2.9 days (95% CrI: 1.7, 4.4), respectively. Figure 1A shows the best-fit distributions overlaid with the published distribution of SARS (*4*). The difference between these distributions suggests that using serial intervals from SARS data will result in overestimation of the basic reproduction number of 2019-nCoV.

Our mean estimate of 2.6 days indicates that 2019-nCoV 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 will likely soon exceed what available healthcare workers are able to handle.

More importantly, the estimated median serial interval is shorter than the preliminary estimate of the median incubation period (5.0 days) (*3,6*). Figure 1B illustrates when the serial interval takes shorter value than the incubation period, indicating that pre-symptomatic transmission must have taken place and could be more frequent than the symptomatic transmission. This must be regarded as bad news. A substantial proportion of secondary transmission occurring before illness onset means that there are many transmissions not preventable by case isolation of symptomatic cases. By the time contacts are traced they may have already become infectious and generated secondary cases (*7*). Rapid cycles of transmission and substantial pre-symptomatic transmissions make containment via contact tracing alone very challenging.

Funding acknowledgement: 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].

References

1. Fine PE. The interval between successive cases of an infectious disease. Am J Epidemiol 2003;158:1039-1047.

2. Reich NG, Lessler J, Cummings DA, Brookmeyer R. Estimating incubation period distributions with coarse data. Stat Med 2009;28:2769-2784.

3. 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

4. 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.

5. Jung S-M, 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

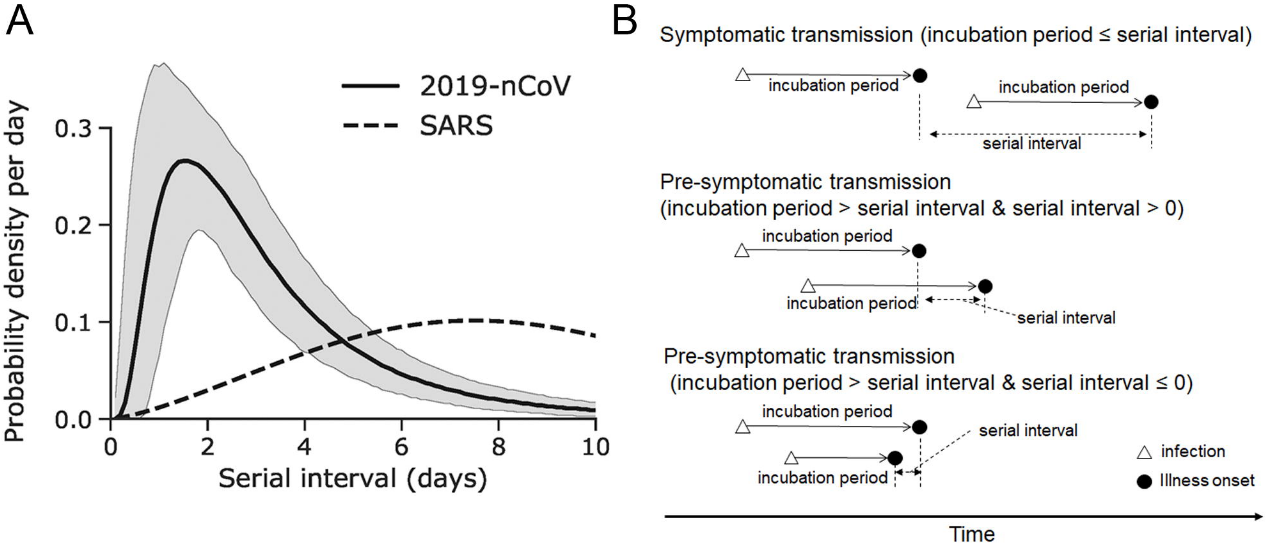
6. Linton NM, Kobayashi T, Yang Y, Hayashi K, Andrei, AR, Jung S-M, Yuan B, Kinoshita R, Nishiura H. (2020). Epidemiological characteristics of novel coronavirus infection: A statistical analysis of publicly available case data. medRxiv. http://dx.doi.org/10.1101/2020.01.26.20018754

7. 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.

Address for correspondence: Hiroshi Nishiura, Graduate School of Medicine, Hokkaido University, Kita 15 Jo Nishi 7 Chome, Kita-ku, Sapporo-shi, Hokkaido 060-8638, Japan, Tel: +81-11-706-5066; Fax: +81-11-706-7819; Email: nishiurah@med.hokudai.ac.jp

Figure. Serial interval of novel coronavirus (2019-nCoV) infections and its relationship with the incubation period.

A. Serial interval distribution of novel coronavirus (2019-nCoV) infections. The solid line shows the estimated serial interval distribution of 2019-nCoV infections using the best-fit lognormal distribution. 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. B. The relationship between incubation period and serial interval. If the transmission takes place during symptomatic period, serial interval is longer than the incubation period. However, the relationship can be reversed if pre-symptomatic transmission takes place, and sometimes, the order of illness onset as a function of time is reversed between primary case and its secondary case.


A
2019-nCoV
SARS
Probability density per day
0.0
0.1
0.2
0.3
0
2
4
6
8
10
Serial interval (days)
B
Symptomatic transmission (incubation period ≤ serial interval)
incubation period
incubation period
serial interval
Pre-symptomatic transmission
(incubation period > serial interval & serial interval > 0)
incubation period
incubation period
serial interval
Pre-symptomatic transmission
(incubation period > serial interval & serial interval ≤ 0)
incubation period
serial interval
incubation period
△ infection
● Illness onset
Time