Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions

Sheik Taslim Ali1, Lin Wang2,3, Eric H. Y. Lau1, Xiao-Ke Xu1, Zhanwei Du5, Ye Wu6,7, Gabriel M. Leung1, Benjamin J. Cowling1†

Studies of novel coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have reported varying estimates of epidemiological parameters, including serial interval distributions—i.e., the time between illness onset in successive cases in a transmission chain—and reproduction numbers. By compiling a line-list database of transmission pairs in mainland China, we show that mean serial intervals of COVID-19 shortened substantially from 7.8 to 2.6 days within a month (9 January to 13 February 2020). This change was driven by enhanced nonpharmaceutical interventions, particularly case isolation. We also show that using real-time estimation of serial intervals allowing for variation over time provides more accurate estimates of reproduction numbers than using conventionally fixed serial interval distributions. These findings could improve our ability to assess transmission dynamics, forecast future incidence, and estimate the impact of control measures.

In December 2019, a novel coronavirus disease [coronavirus disease 2019 (COVID-19)], caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China. It has since spread to more than 212 countries, causing more than 10 million confirmed cases and 500,000 deaths worldwide as of 30 June 2020 (1). Recent studies have suggested that several demographic and social factors can influence the transmission of COVID-19, including age and gender-related differences in infection risk (2–4), reduced risk of infection as a result of intensive nonpharmaceutical interventions (NPIs) (e.g., isolation and social distancing) (5–7), and abrupt changes in social mixing patterns because of lockdowns and confinement (8–10). Serial interval, defined as the duration between the symptom-onset time of the infector and that of the infectee, is an essential metric for estimating many other key epidemiological parameters (e.g., reproduction number, generation time, and attack rate), which are used in turn to predict disease trends and health care demands (11). In early studies, before the availability of specific data on COVID-19, the serial interval distribution of COVID-19 was assumed to be similar to those of severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), with a mean >8 days (12, 13). Once specific data became available on COVID-19 transmission pairs, several studies examined the serial interval distribution of COVID-19 in different locations, with estimates of the mean serial interval varying from 3.1 to 7.5 days (6, 14–21). All of these studies have assumed that the timing of transmission events can be described by a single, stable distribution of serial intervals at different stages of an epidemic.

In fact, the serial interval depends on the incubation period, the profile of infectiousness after infection, and the variation in contact structure of the population (as explained in fig. S1) (22). The incubation period describes the biological process of disease progression and tends to follow a more similar distribution from one location to another, with minor variations resulting from social or cultural differences in how symptoms are perceived or reported. However, the profile of infectiousness over time can vary because of human behavior. Changes in contact patterns and the use of public health measures can reshape the timing of infection events by limiting successful contacts overall (e.g., social distancing) or after illness onset (e.g., case isolation). Interventions such as the isolation of confirmed and suspected cases, suspension of intra- and intercity travel, and different forms of social distancing were widely implemented in different Chinese cities. This provides an opportunity to study the temporal changes in the serial interval distribution and its association with NPIs. Here, we show that variation in the serial interval can occur and has important implications for the assessment of transmission dynamics and the impact of control measures.

We compiled a database of 1407 COVID-19 transmission pairs, in which symptom-onset dates and social relationships were available for both the infectee and infector of 677 transmission pairs [see table S1 for entire database (23) and supplementary materials for details]. Household and nonhousehold transmissions were identified on the basis of the information on social relationships (e.g., familial members of the same household, non-household relatives, colleagues, classmates, friends, and other face-to-face contacts). The data were reconstructed from the publicly available reports of 9120 confirmed COVID-19 cases reported by 27 provincial and 264 urban health commissions in China outside Hubei province. Data from Hubei province were excluded because there was less reliable information on chains of transmission during the widespread community circulation of COVID-19; outside Hubei province, it was more straightforward to link connected cases and derive serial intervals. We focused on 677 transmission pairs with infectors having developed symptoms from 9 January through 13 February 2020. This 36-day period spans a series of key interventions related to the evolving epidemiology and transmission dynamics of COVID-19 in mainland China (24–26).

We first calculated the number of transmission pairs in our database by the onset dates of infectors (fig. S3). Because many infectors (339) developed symptoms during 23 to 29 January 2020, we defined this 1-week period as the peak week, the previous 14-day period (9 to 22 January 2020) as the prepeak period, and the following 15-day period (30 January to 13 February 2020) as the postpeak period. We computed the serial interval as the number of days between the symptom-onset date of the infector and that of the infectee for each transmission pair. Empirical serial interval distributions for transmission pairs, counting from symptom onsets of the infectors during each period, indicate that the serial intervals shortened over time (Fig. 1A).

We estimated the serial interval distribution during each nonoverlapping period by fitting a normal distribution to the corresponding serial intervals data (supplementary materials). Analysis of all 677 transmission pairs revealed that the serial interval distribution had a mean of 5.1 [95% credibility interval (CrI): 4.7, 5.5] days and a standard deviation (SD) of 5.3 (95% CrI: 5.0, 5.6) days (table S2) overall, which is consistent with other recent
Fig. 1. Serial intervals of SARS-CoV-2 substantially shortened over time in mainland China. (A) Empirical serial interval distributions. From top to bottom, transmission pairs were analyzed by selecting infectors who developed symptoms during 9 to 22 January 2020 (prepeak); 23 to 29 January 2020 (peak week); 30 January to 13 February 2020 (postpeak); and 9 January to 13 February 2020 (whole period), respectively. In each panel, vertical dashed lines in red and blue colors indicate the median and interquartile range (IQR), respectively. (B) Estimated serial interval distributions by fitting a normal distribution using MCMC. From top to bottom, each group of bars corresponds to the transmission pairs with infectors who developed symptoms during the prepeak (162 pairs), peak week (339 pairs), postpeak (176 pairs), and whole 36-day period (677 pairs), respectively. Colored dots and bars correspond to the transmission pairs within households (blue), outside households (yellow), with isolation delays shorter than the median isolation delay of each period (green), and with isolation delays longer than the median isolation delay of each period (orange), respectively. Dark gray bars correspond to transmission pairs with no stratification. Dots and bars indicate the estimated median and IQR, respectively.

In practice, the time-varying serial interval may affect the estimation of epidemic parameters, including the transmissibility. The real-time transmissibility of an infectious disease is often characterized by the instantaneous reproduction number \( R_t \), which is defined as the expected number of secondary infections caused by an infector on day \( t \). The pathogen spreads when \( R_t > 1 \) and is under control when \( R_t < 1 \). To examine the effect of serial intervals on \( R_t \), we first obtained the daily number of cases on the basis of the onset dates of infectors and infectees among the 1407 transmission pairs (Fig. 2, B to D). By applying the statistical method developed by Cori et al. (28), we estimated \( R_t \) for each day between 20 January and 13 February 2020. We noticed substantial differences in estimates of \( R_t \) between using a single stable serial interval distribution and time-varying effective serial interval distributions. The magnitude of this difference is more prominent during the prepeak and postpeak periods than it is during the peak week when \( R_t \approx 1 \) (Fig. 2, B to D).

We observed that the serial interval for COVID-19 in mainland China was shortened by more than a factor of 3 in the 36 days between 9 January and 13 February 2020. This reduction was driven by intensive NPIs, particularly the reduction of the isolation delay period. Isolation of an infectee on day \( t \) is expected to reduce the mean serial interval by 0.7 days. The instantaneous transmission number \( R_t \) is then multiplied by the serial interval to obtain the serial interval distribution. Therefore, the serial interval distribution is an important factor in determining the transmissibility of an infectious disease. The real-time transmissibility of an infectious disease is often characterized by the instantaneous reproduction number \( R_t \), which is defined as the expected number of secondary infections caused by an infector on day \( t \). The pathogen spreads when \( R_t > 1 \) and is under control when \( R_t < 1 \). To examine the effect of serial intervals on \( R_t \), we first obtained the daily number of cases on the basis of the onset dates of infectors and infectees among the 1407 transmission pairs (Fig. 2, B to D). By applying the statistical method developed by Cori et al. (28), we estimated \( R_t \) for each day between 20 January and 13 February 2020. We noticed substantial differences in estimates of \( R_t \) between using a single stable serial interval distribution and time-varying effective serial interval distributions. The magnitude of this difference is more prominent during the prepeak and postpeak periods than it is during the peak week when \( R_t \approx 1 \) (Fig. 2, B to D).

We observed that the serial interval for COVID-19 in mainland China was shortened by more than a factor of 3 in the 36 days between 9 January and 13 February 2020. This reduction was driven by intensive NPIs, particularly the reduction of the isolation delay period. Isolation of an infectee on day \( t \) is expected to reduce the mean serial interval by 0.7 days. Thus, the serial interval was shortened by >3 days if infectors were rapidly isolated (Figs. 1B and 2A and tables S2 and S3). This is consistent with advocating isolation of cases that reduc-
and quarantining contacts within 1 day from symptom onset, which has been estimated to reduce COVID-19 transmission by 60% (8). We have not identified any substantial effects of gender or age of infectors on serial interval, but the NPIs were found to be significant for the transmission in communities rather than in households (table S5). Other studies (15, 20) have estimated that the infectiousness of COVID-19 is greater at symptom onset. Although a short serial interval indicates that a substantial proportion of transmission events have occurred by the time symptoms are apparent (14), because of prolonged viral shedding (14, 29, 30) case isolation is still likely to reduce further transmission. Changes in the serial interval can therefore indicate effective implementation of specific transmission-reduction measures.

There are some limitations to our work. First, it is possible that there was recall bias on the onset of first symptoms in the line-list data; however, given the centralized pandemic response in mainland China, we expected that recall bias would not affect our main conclusions (figs. S12 and S13). Second, other factors may have influenced the reduction of effective serial intervals, as we can only explain up to 72% of the variance in observed serial intervals. Finally, our current transmission pair data do not contain variables about the potential exposure window of each case, which do not allow further inferences on the transmission potential.

Our results indicate that caution is needed when attempting to generalize estimates of the serial interval distribution to other places or to other periods of time in the same place, especially when estimating instantaneous reproductive numbers (Fig. 2). The real-time metric of effective serial intervals indicates that transmission models also need to account for the temporal variation in serial intervals as an epidemic proceeds. Effective serial intervals may provide better measurements of instantaneous transmissibility ($R_t$)—because they include the effects of possible drivers of transmission—and could be helpful.
to policy-makers because they offer real-time information on the impact of public health measures.

REFERENCES AND NOTES

1. World Health Organization (WHO), "Coronavirus disease 2019 (COVID-19). Situation report – 162" (WHO, 2020); www.who.int/docs/default-source/coronaviruse/situation-reports/20200629-covid-19-sitrep-161.pdf?sfvrsn=74fe6e4_2.
2. M. U. G. Kraemer et al., Science 368, 493–497 (2020).
3. C. Wenham, J. Smith, R. Morgan, Gender and COVID-19: Working Group. Lancet 395, 846–848 (2020).
4. J. M. Jin et al., Front. Public Health 8, 152 (2020).
5. J. Hellewell et al., Lancet Glob. Health 8, e488–e496 (2020).
6. L. Ferretti et al., Science 368, eaab6936 (2020).
7. R. Armitage, L. B. Nellums, Lancet Public Health 5, e256 (2020).
8. R. M. Anderson, H. Heesterbeek, D. Klinkenberg, Lancet Glob. Health 395, 382–395 (2020).
9. R. M. Anderson, H. Heesterbeek, D. Klinkenberg, Lancet 395, 1382–1393 (2020).
10. K. Prem et al., Lancet Infect. Dis. 20, 793–802 (2020).
11. M. A. Vink, M. C. Bootsma, J. Wallinga, Lancet Infect. Dis. 20, 411–412 (2020).
12. J. T. Wu, K. Leung, G. M. Leung, Lancet 395, 1322–1323 (2020).
13. M. Chinazzi et al., Science 368, 365 (2020).
14. H. Nishiura, N. M. Linton, A. R. Akhmetzhanov, et al., Science 368, 365–369 (2020).
15. H. Y. Cheng, JAMA Intern. Med. 180, 865–875 (2014).
16. J. T. Wu, K. Leung, G. M. Leung, Lancet 395, 899–907 (2020).
17. M. Chinazzi et al., Science 368, 365–369 (2020).
18. H. Nishiura, N. M. Linton, A. R. Akhmetzhanov, Int. J. Infect. Dis. 93, 284–296 (2020).
19. H. Y. Cheng et al., JAMA Intern. Med. 10.1001/jamainternmed.2020.2020 (2020).
20. Z. Du et al., Emerg. Infect. Dis. 26, 1341–1343 (2020).
21. Q. Li et al., Nat. Engl. J. Med. 382, 1199–1207 (2020).
22. J. M. Griffin et al., medRxiv 2020.08.20.20095075 [Preprint].
23. L. W. acknowledges the computational and storage services provided by the IT department at the Institut Pasteur. Author contributions: W., S.T.A., E.H.Y.L., and B.J.C. conceived the study, designed the statistical and modeling methods, conducted analyses, interpreted results, and wrote and revised the manuscript. X.-K.X., Z.Y., and Y.W. collected and compiled data, interpreted results, and revised the manuscript. G.M.L. supervised the study, interpreted results, and revised the manuscript. Competing interests: B.J.C. reports honoraria from Sanofi Pasteur and Roche. The authors report no other potential conflicts of interest.

ACKNOWLEDGMENTS
We thank all the health workers and volunteers who collected data throughout the COVID-19 outbreak. We thank H. Salje, S. Cauchemez, L. A. Meyers, J. Paireau, Q. Bi, B. Yang, X. Liu, and L. Hu for discussions. Funding: We acknowledge financial support from the Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region, China (grant no. COVID200128); the Investissement d’Avenir program (Investissements d’avenir-Excellence Integrative Biology of Emerging Infectious Diseases program (grant no. ANR-10-LABX-62-IBED)); the European Research Council (grant no. 804744); the European Union’s Horizon 2020 research and innovation program under grant agreement no. 101003589 (RECOVER); the National Institutes of Health (no. U01 GM07719); the Open Fund of Key Laboratory of Urban Land Resources Monitoring and Simulation, Ministry of Land and Resources, China (no. KF-2019-04-034); the National Natural Science Foundation of China (nos. 61773091, 11875005, 61976205, and 11975025); and a University of Cambridge COVID-19 Rapid Response Grant. S.T.A. acknowledges

SUPPLEMENTARY MATERIALS
science.sciencemag.org/content/369/6507/1106/suppl/DC1
Materials and Methods
Figs. S1 to S14
Tables S1 to S5
References (S1–49)
MDAR Reproducibility Checklist
View/request a protocol for this paper from Bio-protocol.
20 May 2020; accepted 13 July 2020
Published online 21 July 2020
10.1126/science.abc9004
Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions
Sheikh Taslim Ali, Lin Wang, Eric H. Y. Lau, Xiao-Ke Xu, Zhanwei Du, Ye Wu, Gabriel M. Leung and Benjamin J. Cowling

Science 369 (6507), 1106-1109.  
DOI: 10.1126/science.abc9004 originally published online July 21, 2020

From cough to splutter
In epidemiology, serial intervals are measured from when one infected person starts to show symptoms to when the next person infected becomes symptomatic. For any specific infection, the serial interval is assumed to be a fixed characteristic. Using valuable transmission pair data for coronavirus disease (COVID-19) in mainland China, Ali et al. noticed that the average serial interval changed as nonpharmaceutical interventions were introduced. In mid-January 2020, serial intervals were on average 7.8 days, whereas in early February 2020, they decreased to an average of 2.2 days. The more quickly infected persons were identified and isolated, the shorter the serial interval became and the fewer the opportunities for virus transmission. The change in serial interval may not only measure the effectiveness of infection control interventions but may also indicate rising population immunity.

Science, this issue p. 1106