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

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Abstract

Background : The emerging virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a large outbreak of novel coronavirus disease (COVID-19) in Wuhan, China since December 2019. As of February 15, there were 56 COVID-19 cases confirmed in Hong Kong since the first case with symptom onset on January 23, 2020.

Methods : Based on the publicly available surveillance data, we identified 21 transmission events, which occurred in Hong Kong, and had primary cases known, as of February 15, 2020. An interval censored likelihood framework is adopted to fit three different distributions, Gamma, Weibull and lognormal, that govern the SI of COVID-19. We selection the distribution according to the Akaike information criterion corrected for small sample size (AICc).

Findings : We found the Lognormal distribution performed lightly better than the other two distributions in terms of the AICc. Assuming a Lognormal distributed model, we estimated the mean of SI at 3.9 days (95%CI: 2.7–7.3) and SD of SI at 3.1 days (95%CI: 1.7–10.1) by using the information of all 21 transmission events in Hong Kong.

Conclusion : The SI of COVID-19 may be shorter than the preliminary estimates in previous works. Given the likelihood that SI could be shorter than the incubation period, pre-symptomatic transmission may occur, and extra efforts on timely contact tracing and quarantine are crucially needed in combating the COVID-19 outbreak.

Introduction

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as the ‘2019-nCoV’), which has emerged in Wuhan, China at the end of 2019 (1-5). The COVID-19 cases were soon exported to other Chinese cities and overseas (6), and the travel-related risk of disease spreading was suggested by previous studies (4, 7-9). The risks of rapid spreading were evaluated based on the early surveillance data and also compared to other previous respiratory infectious diseases (5, 10-14). Since the first confirmed imported case in Hong Kong on January 23 (15), the local government has implemented a series of control and prevention measures for COVID-19, including enhanced border screening and traffic restrictions (16, 17).

The COVID-19 pandemic has affected most of the regions around the world, including those places with less developed healthcare systems. Hong Kong was the hit-hardest region in the severe acute respiratory syndrome (SARS) outbreaks in 2003 (18, 19), and thus it is expected to be more prepared in mitigation of emerging infectious disease outbreaks. The lesson in Hong Kong shall be an example for other regions, in particularly those less developed places with poor settings. As of February 15, there were 56 COVID-19 cases confirmed in Hong Kong (16), and local transmission was also recognized by the contact tracing investigation. Given the risk of human-to-human transmission, the serial interval (SI), which refers to the time interval from illness onset in a primary case (i.e., infector) to that in a secondary case (i.e., infectee)

(20-23), was of interested to iterative rate of transmission generations of COVID-19. SI could be used to assist strategic decision-making of public health policies and construct analytical frameworks for studying the transmission dynamics of SARS-CoV-2.

In this study, we examined the publicly available materials released by the Centre for Health Protection (CHP) of Hong Kong. Adopting the case-ascertained design (24), we identified the transmission chain from index cases to secondary cases. We estimated the SI of COVID-19 based on 21 identified transmission chains from the surveillance data and contact tracing data in Hong Kong.

Data And Methods

As of February 15, there were 56 confirmed COVID-19 cases in Hong Kong (16), which followed the case definition in official diagnostic protocol released by the World Health Organization (WHO) (25). To identify the pairs of infector (i.e., index case) and infectee (i.e., secondary case), we scanned all news press released by the CHP of Hong Kong between January 16 and February 15, 2020 (17). The exact symptoms onset dates of all individual patients were released by CHP (16), which were publicly available, and used to match each transmission chain. For those infectees associated with multiple infectors, we record the range of onset dates of all associated infectors, i.e., lower and upper bounds. With all publicly available information from CHP, we constructed the transmission events by subjectively screening the exposure link between consecutive COVID-19 infections. We identified 21 transmission events, including 12 infectees matched with only one infector, that were used for SI estimation. Note that all the 21 transmission events occurred in Hong Kong, and most of the cases were Hong Kong residents.

Following previous study (20), we adopted a distribution function with mean μ and standard deviation (SD) σ, denoted by $g(\bullet|\mu,\sigma)$, to govern the distribution of SI. We defined $g(\bullet|\mu,\sigma)$ as three different distributions, and they are Gamma, Weibull and lognormal distribution. The interval censored likelihood (26), denoted by L, of SI estimates is defined in Eqn (1).

[Please see the supplementary files section to view the equation.] (1)

The $h(\bullet)$ was the probability density function (PDF) of exposure following a uniform distribution with a range from T^{low} to T^{up}. The terms T_i^{low} and T_i^{up} denoted the lower and upper bounds, respectively, for the range of onset dates of multiple infectors linked to the i-th infectee. Specially, for the infectees with only one infector, $T^{low} = T^{up}$, and thus $h(\bullet) = 1$. The τ_i was the observed onset date of the i-th infectee. Hence, the likelihood function in Eqn (1) can be interpreted as the probability of the SI being observed with uncertain onset dates of infectors but fixed onset date of infectee (20, 26). We calculated the maximum likelihood estimates of μ and σ. Their 95% confidence interval (95%CI) were calculated by using the profile likelihood estimation framework with cutoff threshold determined by a Chi-square quantile (27). We selection the distribution of $g(\bullet|\mu,\sigma)$ according to the Akaike information criterion corrected for small sample size, denoted by AICc. We employed both Pearson's correlation and coefficient of determination, i.e., R-squared, to measure the goodness-of-fit of the models.

In the dataset, the latest onset date of all infectors was on January 31 while the study was conducted on February 15. This gives the minimum investigation period (from the onset of an infector to the study date) at (15 – 0 + 1 =) 16 days, which is approximately twice of the SI of SARS (28), we therefore conclude that the risk of right-truncated selection bias is low thus ignored for simplicity.

Results And Discussion

The observed SIs of all 21 samples have a mean at 4.3 days, median at 4 days, interquartile range (IQR) between 2 and 5, and range from 1 to 13 days. For the 12 'infector- infectee' pairs, the observed SIs have a mean at 3 days, median at 2 days, IQR between 2 and 4, and range from 1 to 8 days. Fig 1 shows the likelihood profiles of varying SI with respect to μ and σ of SI. In Table 1, we found the three distributions have almost equivalent fitting performance in terms of the AICc. The Lognormal distribution has the lowest AICc, and thus it is presented as the main results for the SI estimation. By using all 21 samples, we estimated the mean of SI at 3.9 days (95%CI: 2.7–7.3) and SD of SI at 3.1 days (95%CI: 1.7–10.1). Between the observed and the fitted distributions, the Pearson's correlation is 0.98, and the R-squared is 0.97. These estimates largely matched the results in the existing literatures (29-31). Limiting to only consider the 12 'infector-infectee' pairs, we found the Lognormal distribution also outperformed, and we estimated the mean of SI at 2.9 days (95%CI: 2.0–6.7) and SD of SI at 1.8 days (95%CI: 1.0–10.5). In this case, the Pearson's correlation is 0.96, and the R-squared is 0.92. The fitted Lognormal distributions were shown in Fig 2.

Comparing to the SI of SARS with mean at 8.4 days and SD at 3.4 days (28), the estimated 3.9-day SI for COVID-19 indicated rapid cycles of generation replacement in the transmission chain. Hence, highly efficient public health control measures, including contact tracing, isolation and screening, were strongly recommended to mitigate the epidemic size. The timely supply and delivery of healthcare resources, e.g., facemasks, alcohol sterilizer and manpower and equipment for treatment, were of required in response to the rapid growing incidences of COVID-19. In the places with less developed healthcare systems and limited medical resources, such rapid growing of the epidemic may cause huge burden to public health system. Therefore, preparedness and pre-cautious for the risk of COVID-19 are crucial to minimize impacts.

As also pointed out by recent works (29-31), the mean of SI at 3.9 days is notably smaller than the mean incubation period, roughly 5 days, estimated by many previous studies (32-35). The pre-symptomatic transmission may occur when the SI is shorter than the incubation period. If isolation can be conducted immediately after the symptom onset, the pre-symptomatic transmission is likely to contribute to the most of SARS-CoV-2 infections. This situation has been recognized by a recent epidemiological investigation evidently (36), and implemented in the mechanistic modelling studies of COVID-19 epidemic (4, 37), where the pre-symptomatic cases were contagious. As such, merely isolating the symptomatic cases will lead to a considerable proportion of secondary cases, and thus contact tracing and immediately quarantine were crucial to reduce the risk of infection. In addition, we would like to point out that minor negative SI observations were reported in recent studies (30, 38-41). The negativity in the SI

may occur when the incubation period is short with a large variance. However, negative value was not observed in our dataset, which may be due to the small sample size. We further remark that this is unlikely to bias estimation of mean SI, but may lead to a slight underestimation of the SD of SI. The purpose of estimating SI is to approximate the generation interval (time lag of infections of successive cases) which is strictly positive. Caution should be taken when dealing with negative SI.

A recently epidemiological study used 5 'infector-infectee' pairs from contact tracing data in Wuhan, China during the early outbreak to estimate the mean SI at 7.5 days (95%CI: 5.3–19.0) (33), which appeared larger than our SI estimate at 3.9 days. Although the 95%CIs of SI estimate in this study, consistent with previous studies (29-31), and those in Li *et al* (33) were not significantly separated, the difference in the SI estimates might exist. If this difference was not due to sampling chance, one of the possible explanations could be enhanced public awareness and swift control measures including the contact tracing and isolation implemented in Hong Kong. Since Hong Kong was the hit-hardest in the SARS outbreaks in 2003 (18, 19), the local public health control was one of the most effective in the world. In the initial phase of the outbreak in Wuhan, the transmission occurred without sufficient awareness and effective intervention, thus the SI estimate in Li *et al* (33) may be regarded as the intrinsic (wild) SI of COVID-19. Whereas the SI estimate in Hong Kong may be regarded as the effective SI, in more practical situation when timely action (quarantining cases and their close contacts) in place (42), such that one case could be isolated before having chance to further infect others. If timely action was not in place, infections of longer serial interval may occur. Thus, shorter SI observations might be an outcome of effectiveness in control in a location. The practice in Hong Kong is an example for other regions, including less developed countries.

The SI estimate can benefit from larger sample size, and the estimates in our study was based on 21 identified transmission events including 12 'infector-infectee' pairs. Although the sample size was smaller than 28 transmission events in Nishiura *et al* (29), 71 in You *et al* (30) and 468 in Du *et al* (31), the advantage of this analysis included the 21 transmission events are all identified in Hong Kong. Hence, the surveillance data were under consistent reporting and recording standards, which further reduced the heterogenicity in the observations. Our analysis can be improved if larger records on the local transmission events. Furthermore, a comparison between different localities is important, which sheds light on the effects of different external factors on SI.

Accurate and consistent records on dates of illness onset were essential to the estimation of the SI. All samples used in this analysis were identified in Hong Kong and collected consistently from the CHP (16, 17). Hence, the reporting criteria were most likely to be the same for all COVID-2019 cases, which potentially made our findings more robust.

The clusters of cases can occur by person-to-person transmission within the cluster, e.g.,

- scenario (**I**): person A infected B, C and D, or
- scenario (**II**): A to B to C to D, or

- scenario (**III**): a mixture of (**I**) and (**II**), e.g., A to B, B to C and D, or

or they can occur through a common exposure to an unrecognized source of infection, e.g.,

- scenario (**IV**): unknown person X infected A, B, C and D; or
- scenario (**V**): a mixture of (**IV**) and (**I**) or (**II**), e.g., X to A and B, B to C and D; or

The lack of information in the publicly available dataset made it difficult to disentangle such complicated situations. The scenarios (**I**) and (**II**) can be covered by the pair of 'infector-infectee' such that we could identify the link between two unique consecutive infections. Under the scenario (**III**), we cannot clearly identify the pairwise match between the infector and infectee, which means there were multiple candidate of infector for one infectee. As such, we employed the PDF $h(\bullet)$ in Eqn (1) to account for the possible time of exposure ranging from T^{low} to T^{up}. There is no information available on the SI for scenarios (**IV**) as well as (**V**) due to the onset date of person X is unknown, and thus our analysis was limited in the scenarios (**I**)-(**III**). We note that extra-cautious should be needed to interpret the clusters of cases because of this potential limitation. Although we used interval censoring likelihood to deal with the multiple-infector matching issue, more detailed information of the exposure history and clue on 'who acquires infection from whom' (WAIFW) would improve our estimates.

Longer SI might be difficult to occur in reality due to the isolation of confirmed infections, or to identify and link together due to the less accurate information associated with memory error occurred in the backward contact tracing exercise. The issue associated with isolation could possibly bias the SI estimates and lead to an underestimated result. Due to lack of information in the public dataset, our estimation framework could be benefit from detailed records on the date of isolation of individual cases. It is possible that at the initial stage the SI is longer than later when strict isolation takes place. Nevertheless, a comparison of estimated SI for SARS and COVID-19 in Hong Kong is still meaningful. We found that the SI of COVID-19 estimated appears shorter than that of SARS. It would be hard to imagine that isolation is responsible for the difference. It is unlikely that the isolation is more rapid in cases of COVID-19 than cases in SARS in Hong Kong, as well as other limitations (would have happened for both). Thus, the difference we observed for COVID-19 and SARS is likely intrinsic. In conclusion, given the rapid spreading of the COVID-19, effective contact tracing and quarantine/isolation were even more crucial for successful control.

Conclusion

Together with the basic reproductive number, the serial interval is one of the most important epidemiological parameters, which is also difficult to estimate and caught less attention than the former. Here we found that the SI of COVID-19 may be shorter than the preliminary estimates in previous works. Since SI could be shorter than the incubation period among some cases, pre-symptomatic transmission may occur, and extra efforts on timely contact tracing and quarantine are crucially needed in combating the COVID-19 outbreak.

Declarations

Ethics approval and consent to participate

The follow-up data of individual patients were collected via public domain (16, 17), and thus neither ethical approval nor individual consent was not applicable.

Availability of materials

All data used in this work were publicly available via (16, 17), and the exacted dataset was attached as a supplementary files of this study.

Consent for publication

Not applicable.

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Disclaimer

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Conflict of interests

DH received funding from an Alibaba (China) - Hong Kong Polytechnic University Collaborative Research project. Other authors declared no competing interests.

Authors' contributions

SZ conceived the study and carried out the analysis. SZ and DH drafted the first manuscript. All authors discussed the results, critically read and revised the manuscript, and gave final approval for publication.

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Table

Table 1.

Summary of the estimates of the serial interval (SI) mean and standard deviation (SD) from three different distributions.

Dataset	Distribution	Serial interval (day)		AICc
		mean	SD	
all transmission events (n = 21)	Gamma	4.0 (2.9, 5.9)	2.3 (1.7, 4.5)	96.1
	Weibull	4.0 (2.9, 5.6)	2.3 (1.8, 4.4)	96.6
	Lognormal	3.9 (2.7, 7.3)	3.1 (1.7, 10.1)	95.8
infector-infectee' pairs (n = 12)	Gamma	3.1 (2.0, 5.4)	1.8 (1.0, 4.6)	50.1
	Weibull	3.0 (2.0, 5.4)	1.8 (1.3, 5.1)	51.2
	Lognormal	2.9 (2.0, 6.7)	1.8 (1.0, 10.5)	49.1

Figures

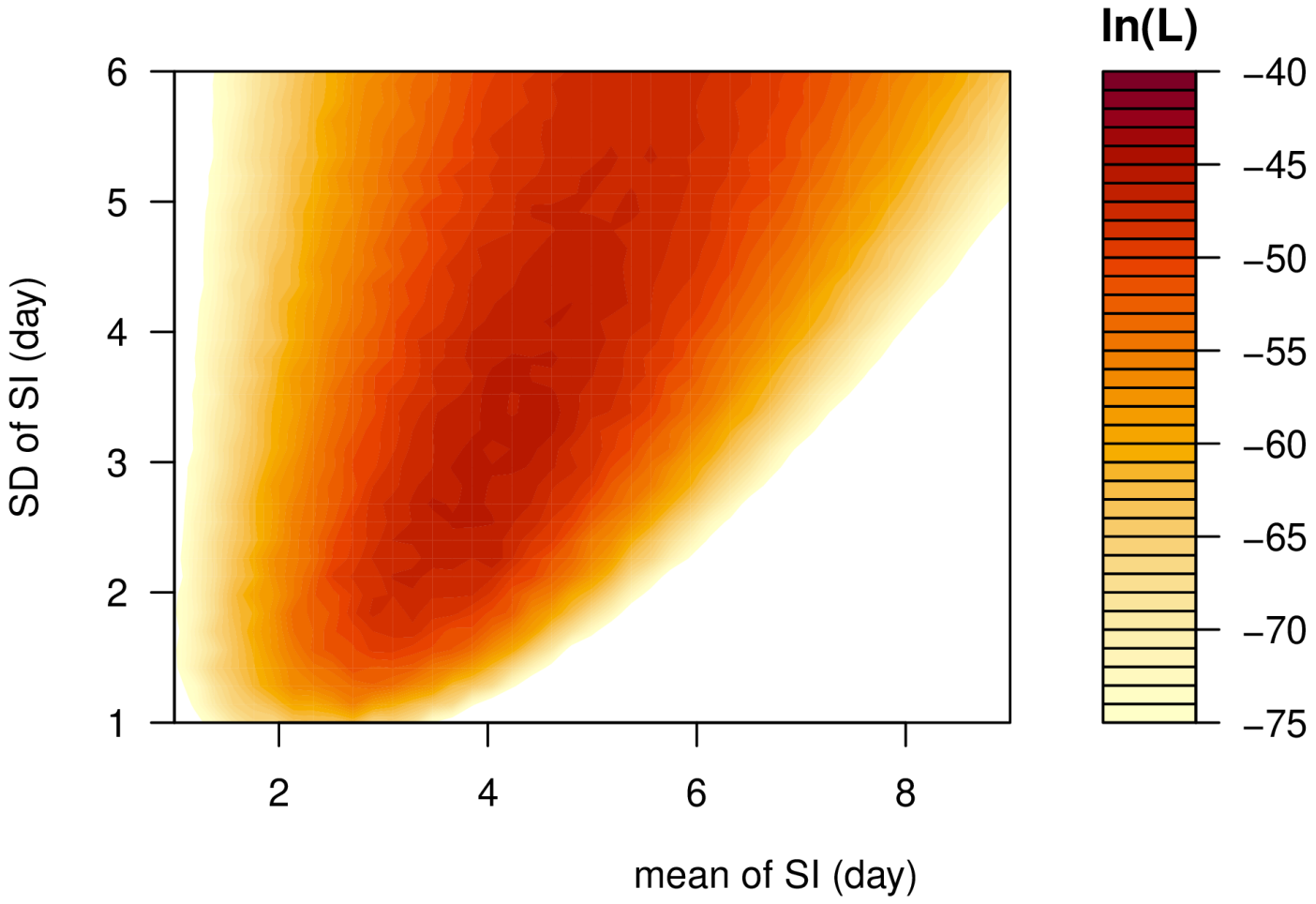

Figure 1

The likelihood profile of the varying serial interval (SI) of COVID-19 by using all samples. The color scheme is shown on the right-hand side, and a darker color indicates a larger log-likelihood, i.e., ln(L), value.

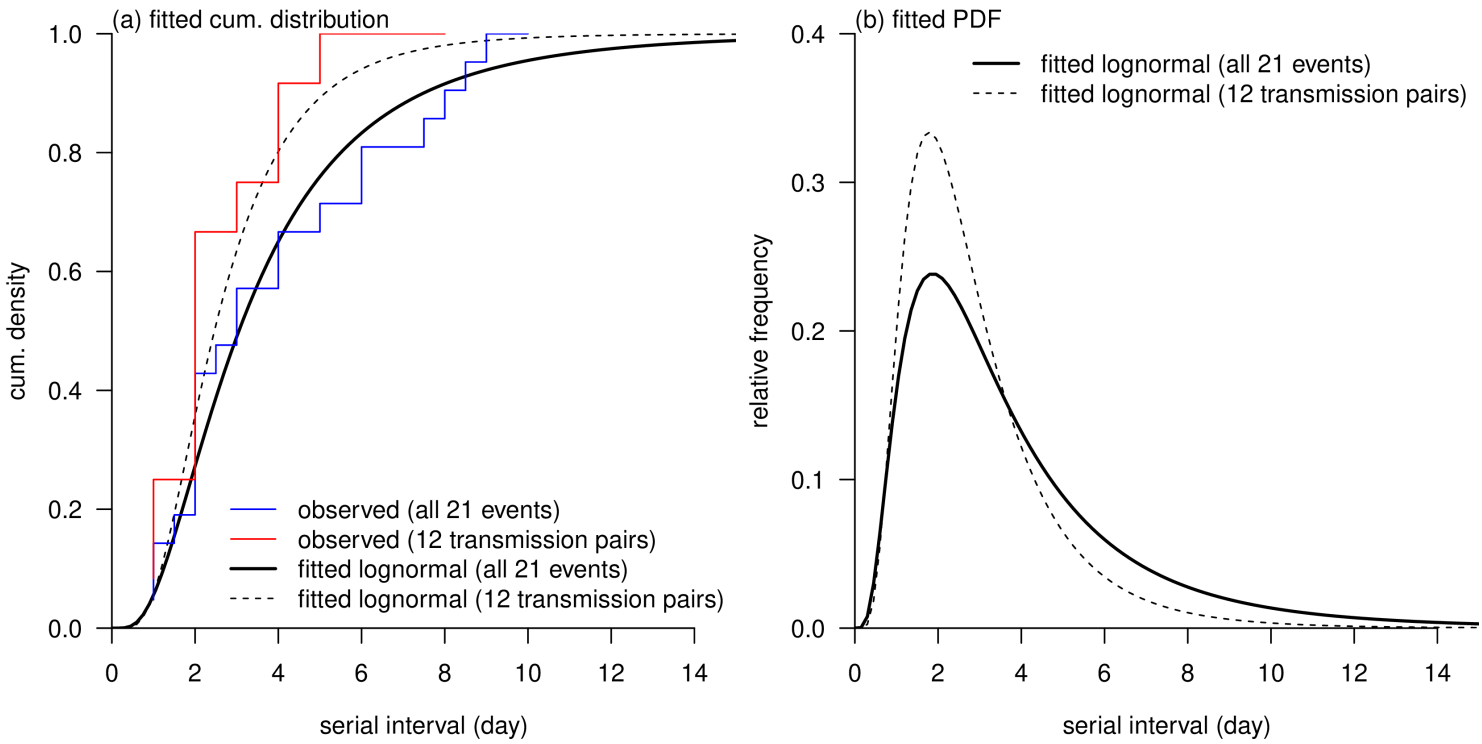

Figure 2

The distribution of serial interval (SI). In panel (a), the red curve is the observed cumulative distribution of SI from 12 transmission pairs, and the blue curve is the observed cumulative distribution of SI from all 21 transmission events. In both panels, the black bold curve is the fitted lognormal distribution using all 21 transmission events, and the dashed thin curve is the fitted lognormal distribution using 12 transmission pairs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- dataset.xlsx
- Equation.docx