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SHORT COMMUNICATION

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Estimation of the serial interval of monkeypox during the early outbreak in 2022

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Abstract

With increased transmissibility and novel transmission mode, monkeypox poses new threats to public health globally in the background of the ongoing COVID-19 pandemic. Estimates of the serial interval, a key epidemiological parameter of infectious disease transmission, could provide insights into the virus transmission risks. As of October 2022, little was known about the serial interval of monkeypox due to the lack of contact tracing data. In this study, public-available contact tracing data of global monkeypox cases were collected and 21 infector-infectee transmission pairs were identified. We proposed a statistical method applied to real-world observations to estimate the serial interval of the monkeypox. We estimated a mean serial interval of 5.6 days with the right truncation and sampling bias adjusted and calculated the reproduction number of 1.33 for the early monkeypox outbreaks at a global scale. Our findings provided a preliminary understanding of the transmission potentials of the current situation of monkeypox outbreaks. We highlighted the need for continuous surveillance of monkeypox for transmission risk assessment.

KEYWORDS

contact tracing, monkeypox, reproduction number, serial interval, statistical modeling

1 | INTRODUCTION

Since early 2022, monkeypox, a zoonosis caused by an orthopox virus, has been quickly spreading globally.[1] The virus has achieved increased transmissibility and a new transmission mode, and invaded new territories beyond its endemic regions. The World Health Organization declared monkeypox a global public health emergency on July 23, 2022.[2] From January 1 to September 4, 2022, over 52 000 laboratory-confirmed monkeypox cases were reported in 102 countries,[3] posing an additional threat to public health systems during the COVID-19 pandemic.

With the expansion of the monkeypox outbreaks, assessing the epidemiological characteristics of the monkeypox virus is crucial for understanding the disease transmission potential and planning control strategies. A recent study estimated the distribution of the incubation period (i.e., the duration between the exposure and clinical symptom onset) for the recent monkeypox outbreaks,[4] and suggested a 21-day quarantine period for the close contacts of the infected

Zihao Guo and Shi Zhao contributed equally to this study, and thus they were joint-first authors.

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cases. The knowledge of another key epidemiological feature—serial interval (SI), which is defined as the time interval between the clinical symptom onset date of the secondary case (infectee) and the primary case (infector) was limited for the monkeypox virus. The SI could not only reflect the speed of the transmission[5] but could also provide a reliable estimation of the reproduction number (R) if measured correctly.[5] R is defined as the average number of cases generated by an index case, and is called the basic reproduction number in the context of a completely susceptible population. An outbreak would go extinct if R is below one but would constantly spread if R is above one. Mathematical models[6–9] have been important tools to study the stability, extinction, and continuity of infectious disease dynamics to inform control policies. A recent stochastic modeling study characterized the condition of eradication and continuity for the current monkeypox outbreaks.[9]

The estimation of SI relied on contact tracing data. However, for the current monkeypox outbreaks where the diseases mainly spread through sexual contact, contact tracing data can be limited as people tend not to share full details of their sex lives,[10] such that information like symptom onset date may not be available. To our knowledge, there are no statistical models that contributed to estimating the SI when the symptom onset dates of the infector and infectee were unknown.

In this study, we proposed a statistical model to estimate the SI of monkeypox during the early phase of the global outbreaks, applying to a limited set of contact tracing data where the symptom onset dates were unknown for the infector and infectee. Given the estimated SI distribution, we also estimated the R of the early monkeypox outbreaks.

2 | METHOD

2.1 | Data

A set of line-list data collected from different countries between January and August 2022 was obtained from reference.[11] For each case, we extracted information on the symptom onset date, case confirmation date, contact tracing history, epidemiological link with other cases, and source governmental reports. Infector-infectee transmission pairs were identified based on the reported epidemiological links on contacts, which were further examined by confirming with original source reports. For all identified transmission pairs, the case confirmation date was available but not the symptom onset date.

2.2 | Statistical analysis

Here, we proposed a statistical model for estimating the SI distribution when symptom onset dates were unknown for transmission pairs. In summary, we estimated the model parameters of SI distribution using a likelihood constructed based on the observation of confirmation interval, that is, the time interval from infector confirmation to infectee confirmation. We denoted random variable H for the confirmation interval, random variable W for the reporting delay, that is, the time interval between the symptom onset date and case confirmation date, and random variable S for the SI. The reporting delay and SI were assumed to follow gamma distributions, denoted by $g(.)$ and $f(.)$, respectively. The SI can be calculated as $S = H + W_{\text{Infector}} - W_{\text{Infectee}}$, as shown in the diagram in Figure 1.

We further denoted X as the time difference between the reporting delay of the infector and his/her infectee, and thus the confirmation interval can be written as $H = S + X$. Therefore, the probability ($L(h)$) of observing a confirmation interval of h can be calculated by convoluting the SI distribution and reporting delay distribution, given by:

$$L(h) = \int_{-\infty}^{\infty} f(h - x)\left[\int_{-\infty}^{\infty} g(x + w)g(w)dw\right]dx$$

Similar modeling strategies were adopted previously for estimating the generation interval distribution (which is defined as the time interval between the exposure time of infector and infectee and is difficult to observe directly), where the probability of observing the SI was calculated by convoluting the generation interval distribution and incubation period distribution.[12,13] This method required an independence assumption of the reporting delay/incubation period for the infector and infectee.

As the symptom onset date was not available for the symptom onset date, the distribution of reporting delay was estimated from

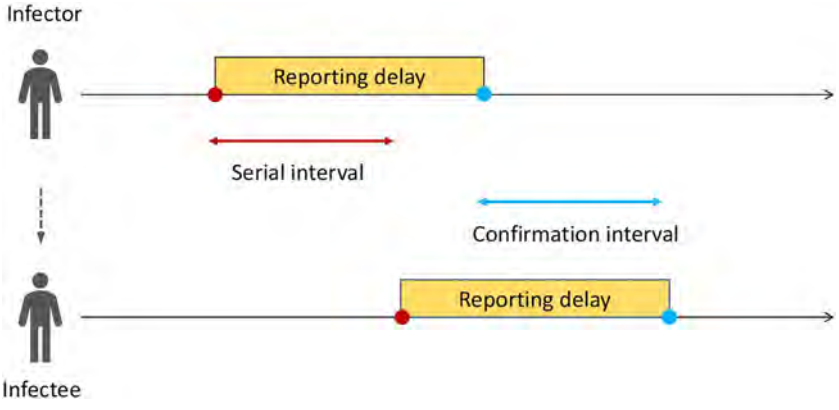

FIGURE 1 Schematic diagram of the timeline for the transmission between infector and infectee. The red solid circle represented the symptom onset date, and the blue solid circle represented the case confirmation date.

other cases with known confirmation and symptom onset date, and we assumed the reporting delay of identified infector and infectee were independent samples from this estimated distribution.

During the early phase of an outbreak, shorter SI is more likely to be identified due to the exponential growth of the number of cases.[5] Followed by previous work,[5] we corrected such sampling bias in $f(.)$ by adjusting the exponential growth with a rate r of 0.05 per capita per day (estimated from the data, see Supporting Information materials). Then, we have the corrected distribution function denoted as $f'(s)$, given by[5]:

$$f'(s) = \frac{f(s)e^{-rs}}{\int_{-\infty}^{\infty} f(s)e^{-rs}\mathrm{d}s}$$

Here, e represented the exponential function. $f'(s)$ is also called forward SI distribution. In addition, we also considered the right truncation of the time interval,[14,15] that is, the SI generated by each infector is truncated due to timely case ascertainment and then followed by case isolation. Thus, the truncation-adjusted distribution function was given by:

$$f_{\text{adjust}}(s) = \frac{f'(s)}{F'(T)}$$

Here, the $F'(.)$ is the cumulative density function of $f'(.)$. The T is the reporting delay of the infector (i.e., the time interval from illness onset to being confirmed positive). For each transmission pair, we sampled T from the estimated reporting delay distribution. We assumed all cases were isolated once they were confirmed by the local government. Thus, the likelihood function becomes:

$$L(h) = \int_{-\infty}^{\infty} f_{\text{adjust}}(h - x)\left[\int_{-\infty}^{\infty} g(x + w)g(w)\mathrm{d}w\right]\mathrm{d}x$$

2.3 | Parameter estimations

To estimate the model parameters of SI and reporting delay distribution simultaneously, we confirmed the likelihood functions $L(h)$ for the observations of confirmation interval and $g(w)$ for the observations of reporting delay.

The parameters were estimated by using the Metropolis −Hastings algorithm, which is a Markov chain Monte Carlo (MCMC) method, with noninformative prior distributions. The marginal posterior distribution was obtained from 100 000 iterations, among which the first 40 000 samples were discarded for burn-in. The convergence of each MCMC chain was checked by using the trace plot and Gelman−Rubin-Brooks convergence diagnostic. The median and the 95% credible interval (CrI) of posterior samples for the mean and standard deviation (SD) of SI and reporting delay distributions, as well as other metrics, were calculated. Given the estimated forward SI distribution with right truncation adjusted and r, we estimated the R followed by previous work[16] (Supporting Information materials).

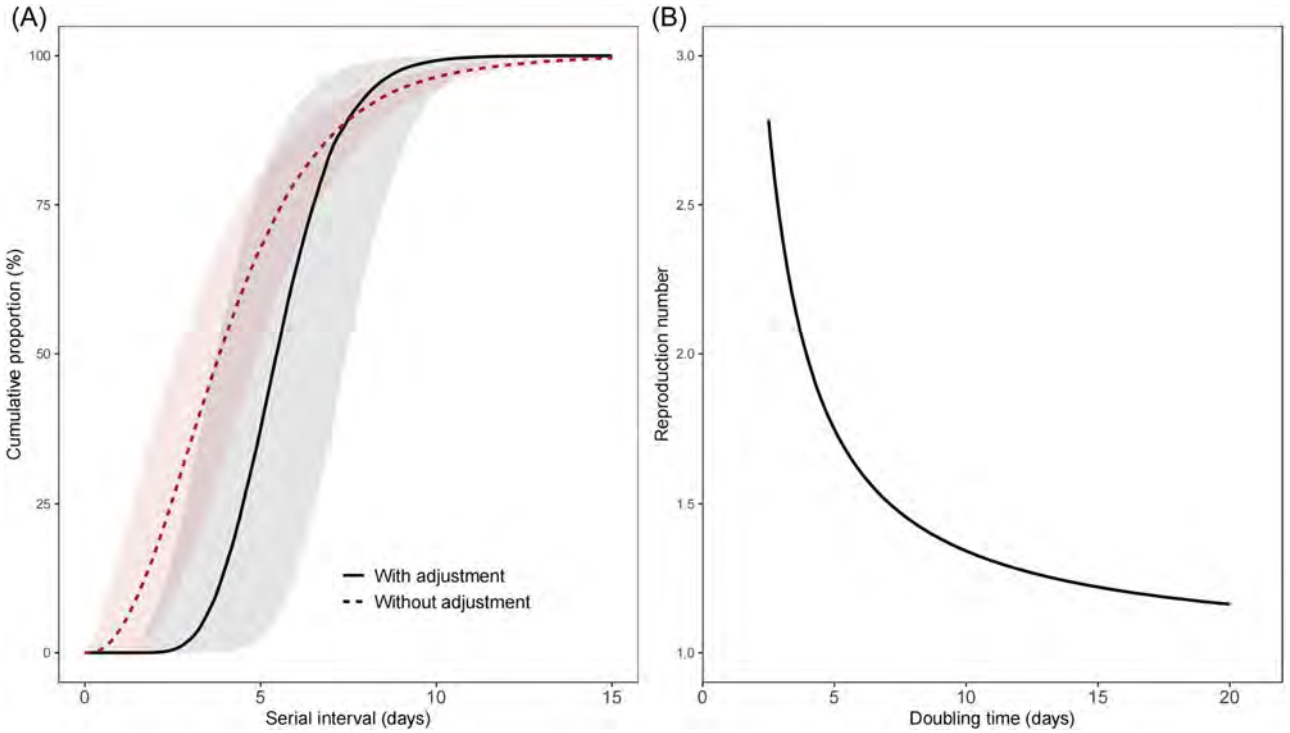

FIGURE 2 The estimated cumulative distribution of the monkeypox serial interval (SI, in A), and the relation between the doubling time and reproduction number (in B). In (A), the effective SI (without truncation adjustment) was in black, and SI with truncation and exponential growth adjustment was in red. The solid lines represented the median of the cumulative distribution of posterior MCMC samples with the 50% high-density range indicated in shade regions. In (B), the estimates of effective SI were used to calculate the relation between doubling time and reproduction number. MCMC, Markov chain Monte Carlo; SI, serial interval.

3 | RESULTS

A total of 21 transmission pairs were identified, and the estimated effective SI mean is 4.3 days (95% CrI: 1.9–7.0), with an SD estimated at 2.6 days (95% CrI: 1.1–3.2). After adjusting for right truncation and sampling bias, the forward SI mean was estimated at 5.6 days (95% CrI: 1.7–10.4) with an SD of 1.5 days (95% CrI: 0.4–2.4). Figure 2A showed the cumulative distribution of estimated SI. We estimated the forward SI median at 5.5 days (95% CrI: 1.4–10.4) and the 95% percentile at 8.3 days (95% CrI: 3.7–13.4). Given the estimated adjusted SI distribution and an estimated doubling time of 13.9 days, we calculated the *R* at 1.33. Figure 2B showed the relationship between *R* and doubling time. The mean reporting delay and confirmation interval were estimated at 8.0 days (95% CrI: 7.0–9.3) and 4.5 days (95% CrI: 2.9–7.6). Figure 3 showed the estimated and observed cumulative distribution for reporting delay and confirmation interval.

4 | DISCUSSION

In this study, we proposed a statistical method applied to limited contact tracing data to estimate the SI of the monkeypox. Our mean SI estimates appeared shorter than those reported by the UK governments with 6.4 days (95% CrI: 4.8–8.9) or 9.8 days (95% CrI: 5.9–21.4) for non-truncated or truncated versions,[17] respectively. Nevertheless, we observe that the 95% CrIs were largely consistent in both studies for both versions of SI estimates, and the discrepancy could be due to the small sample size of identified transmission pairs during the early phase of the outbreak.

The observational process of the time-to-event interval of infectious disease transmission could be subjected to sampling bias when using the contact tracing data, where the tracing process of close contacts was usually performed backward in time (i.e., retrospectively).[18] As more recent infectors would be sampled when the incidence increases, the backward SI is shorter in the initial phase of an outbreak.[5,13,18] Modeling study[5] indicated that the *R* estimates were underestimated in the early studies where the backward SI was used. An adjustment on the likelihood function by taking account of the exponential growth rate would correct such bias and the resultant forward SI distribution approaches the intrinsic generation interval during the early phase of the outbreaks.[18] Nonetheless, variations on the intrinsic SI are expected due to control measures like contact tracing and case isolation, which potentially shorten the SI.[18,19] It is therefore important to also adjust such effects in the likelihood function to provide a more reliable estimation of *R*. The calculated *R* based on our estimated forward SI appeared to be in line with a recent pooled estimate at 1.39.[20] Reliable *R* estimates could aid

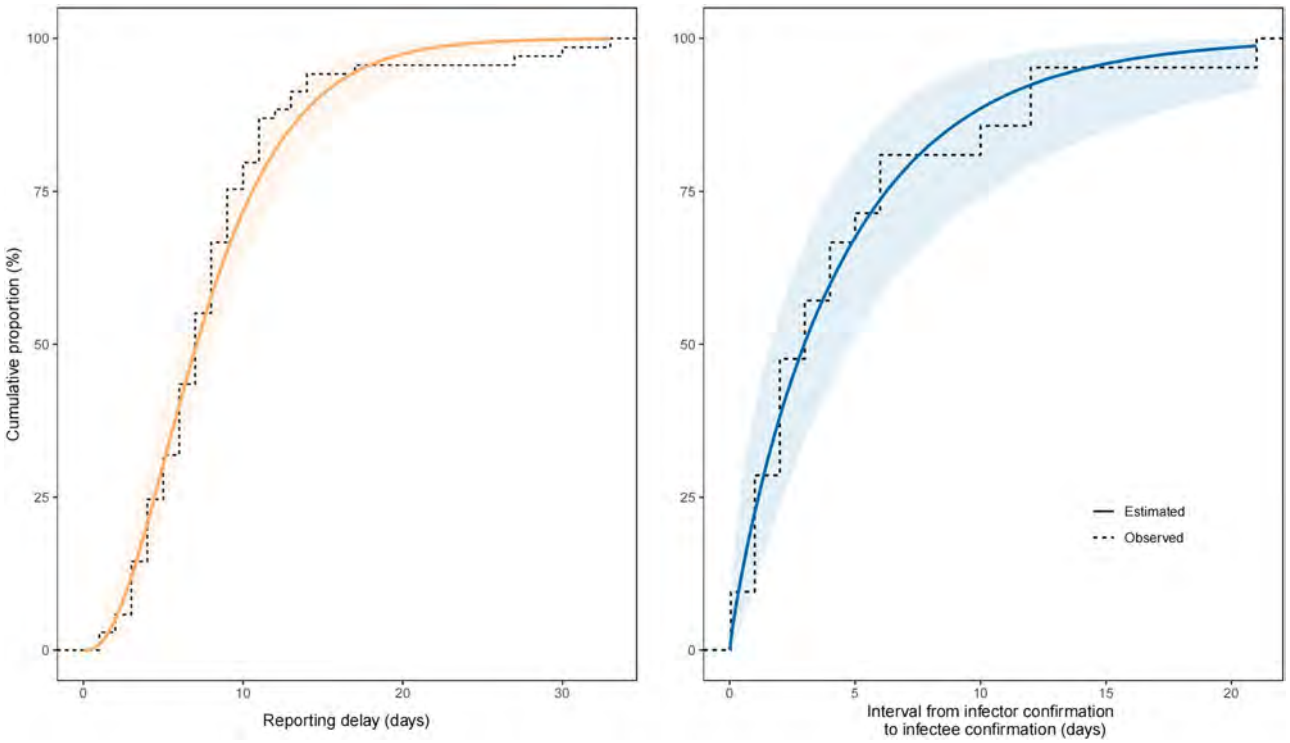

FIGURE 3 The observed and estimated cumulative distributions for the reporting delay (in the left panel), and confirmation interval (i.e., the interval from infector confirmation to infectee confirmation, in the right panel). The solid lines represented the median of cumulative distributions of posterior MCMC samples, and the 95% credible intervals were indicated in shade regions. MCMC, Markov chain Monte Carlo.

the assessment of disease transmissibility, and the effectiveness of control measures. As the estimated *R* exceeded the critical threshold of one, the monkeypox outbreak is likely to continue in the short future with an increasing number of cases. Thus, monitoring the transmission dynamics and epidemiological characteristics of monkeypox in both the MSM community and the general population is important to inform control policy for mitigating the epidemic risk.

Our study had some limitations. First, the estimation of the SI relies on the epidemiological contact tracing data, which was subjected to the recall bias that would affect the accuracy of identified transmission pairs. Since public-available data set were used, our estimates may be biased toward the cases that were likely to be detected and reported by the government. Second, considering the public health capacity and disease surveillance systems varied across countries and regions, it is possible that there is a significant difference in the criteria and procedure for case confirmation for different locations, which violated our independent assumption on the reporting delay for cases. Third, due to a small sample size of transmission pairs, there is significant uncertainty surrounding the mean estimates of the SI and we were not able to elucidate the heterogeneity in SI across the geographical regions and demographic characteristics (e.g., age). Additionally, as the monkeypox vaccine is widely available worldwide, the estimated *R* should be interpreted by taking into account the effect of vaccination. Finally, as the transmission route for the recent monkeypox outbreaks has not been well-established, our findings could not be generalizable to the general population and may only serve as preliminary estimates of SI for the current monkeypox epidemics.

AUTHOR CONTRIBUTIONS

Shi Zhao designed the study. Zihao Guo and Shi Zhao collected the data. Shi Zhao built the model, and Zihao Guo carried out the analysis. Zihao Guo write the original draft. Shi Zhao, Shengzhi Sun, Daihai He, and Ka Chun Chong gave critical revisions of the manuscript with important intellectual contents. Ka Chun Chong and Eng Kiong Yeoh supervised this study. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

All data used in this study were publicly available, and the computer codes used for statistical analysis may be available based on request to the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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