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Article

Estimating the time interval between transmission generations and the presymptomatic period by contact tracing surveillance data from 31 provinces in the mainland of China

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ABSTRACT

The global pandemic of 2019 coronavirus disease (COVID-19) is a great assault to public health. Presymptomatic transmission cannot be controlled with measures designed for symptomatic persons, such as isolation. This study aimed to estimate the interval of the transmission generation (TG) and the presymptomatic period of COVID-19, and compare the fitting effects of TG and serial interval (SI) based on the SEIHR model incorporating the surveillance data of 3453 cases in 31 provinces. These data were allocated into three distributions and the value of AIC presented that the Weibull distribution fitted well. The mean of TG was 5.2 days (95% CI: 4.6–5.8). The mean of the presymptomatic period was 2.4 days (95% CI: 1.5–3.2). The dynamic model using TG as the generation time performed well. Eight provinces exhibited a basic reproduction number from 2.16 to 3.14. Measures should be taken to control presymptomatic transmission in the COVID-19 pandemic.

1. Introduction

Diverse mechanisms drive the transmission of infectious disease, and decide the enactment of control measures. Mathematical models can be introduced to simulate these mechanisms, with core parameters like reproduction number (R_0), serial interval (SI) and transmission generation (TG) [1]. The reproductive number is a parameter derived from generation interval distribution and exponential growth rate [2]. Serial interval, the interval between the time points of symptom onset in an infector and his/her infectees, can be calculated using the public surveillance data. SI is often used as an alternative parameter to generation time (generation time (GT), the interval between the time points

of latent period initiation in one infector and his/her infectees) because the clinical symptoms are observable. However, due to discrepancy in their distributions, the two parameters are not always identical. The time interval between two transmission generations (TGs) is defined as the period between the onset in the primary case (infector) and that in the secondary infected case (infector). Infectiousness may appear before the onset of symptoms, so the TG may lag behind clinical symptoms, suggesting the existence of presymptomatic transmission [3]. These definitions are shown in Fig. 1.

TG and SI are the same only as infectiousness synchronizes with symptoms. However, the infectiousness often shows up before the onset of symptoms. If the second generation has a short latent period, its

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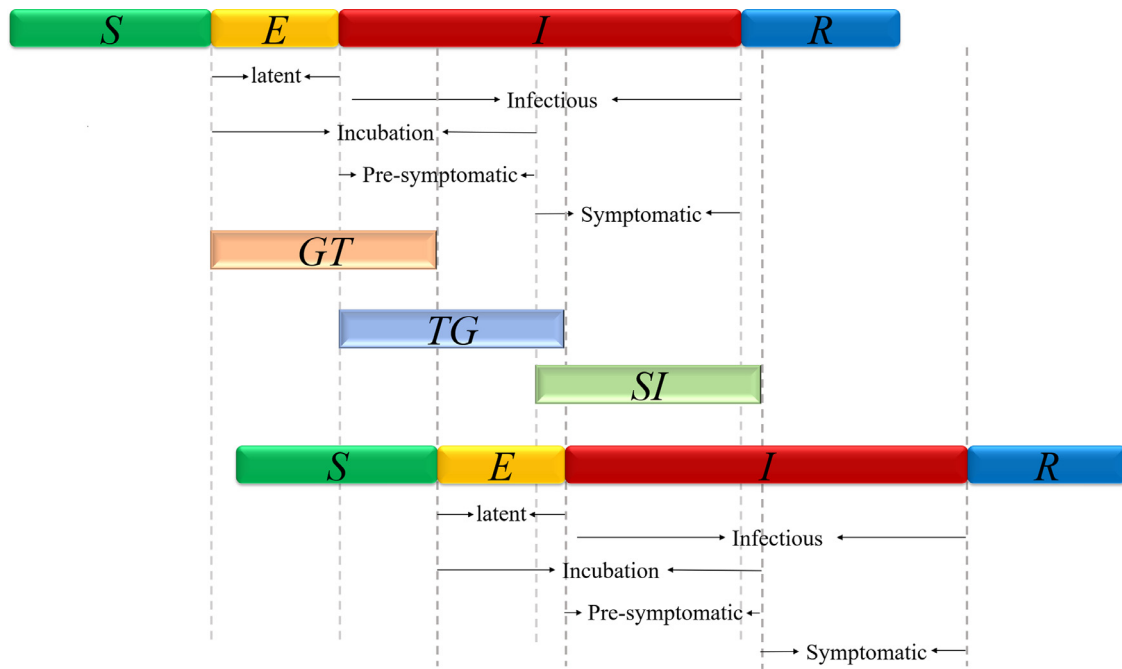


Fig. 1. Illustrative timelines and various stages during the course of infection and transmission of an infectious disease. A classical illustration of concepts when SI is positive.

symptoms set on earlier than those in the first generation, giving SI a negative value. In this condition, SI cannot predict GT, but TG is always non-negative and can be used to estimate TG directly.

The COVID-19 pandemic has spread into more than 200 countries with over 100 million confirmed cases. Studies have shown different SI in infector-infectee pairs [4–15]. Negative SI was found as 24.5% of cases by Bao et al. [7] and 7.6% by Yang et al. [9]. The discrepancy between TG and SI is also caused by asymptomatic transmission common in the COVID-19 pandemic [10]. Furthermore, the reproduction number may be more accurately predicted by TG, rather than SI [11].

Based on the SI data from 31 provinces in the mainland of China, the SEIHR Model was used to test fitting effect of SI and TG and calculate the reproduction numbers in eight provinces.

2. Material and methods

2.1. Data

Independently, three researchers collected a total of 3453 infectors from the official websites of 31 provinces between January 1, 2020 and April 15, 2020 (Fig. 2A and B). After the supervision, the cases were included after agreement was reached after discussion.

2.2. TG distributions

The incubation period spans the latent and presymptomatic periods. The presymptomatic period was defined as $p(p \geq 0)$. p_1 and p_2 represented the presymptomatic periods of the infector and the infectee, respectively, both as independent and identically distributed random variables determined by a probability density function $\omega(\cdot)$ with mean μ_p and standard deviation σ_p . The TG was denoted by g that followed a probability density function $\pi(\cdot)$ with mean μ_g and standard deviation σ_g . SI was denoted by random variable s determined by a probability density function $f(\cdot)$ with mean μ_s and standard deviation σ_s , then $s = g + p_2 - p_1$. Therefore, $f(\cdot)$ was expressed by the convolution formula

in (1):

$$f(x) = \int_{-\infty}^{+\infty} \pi(x - y) \left[\int_{-\infty}^{+\infty} \omega(z) \omega(y + z) dz \right] dy. \tag{1}$$

According to the method proposed in [3], the log likelihood of TG was estimated with the following Eq. (2)

$$l(\Theta | s_1, s_2, \dots, s_n) = \sum_{i=1}^n \ln f(s_i | \Theta), \tag{2}$$

2.3. Reproduction numbers

A SEIHR model was set up for estimating the curve of cumulative COVID-19 incidence as follows [16]:

$$\begin{cases} \frac{dS}{dt} = (\beta c(t) + c(t)q(t)(1 - \beta))SI/N - ms + \lambda S_q + b(1 - f)B, \\ \frac{dE}{dt} = \beta c(t)(1 - q(t))SI - \sigma E + P_E(t), \\ \frac{dI}{dt} = \sigma E - (\delta(t) + \alpha + \gamma_I)I + P_I(t), \\ \frac{dB}{dt} = \beta c(t)q(t)SI/N + ms - bB + P_B(t), \\ \frac{dS_q}{dt} = (1 - \beta)c(t)q(t)SI/N - \lambda S_q, \\ \frac{dH}{dt} = \delta(t)I + bfB - (\alpha + \gamma_H)H + P_H(t), \\ \frac{dK}{dt} = \gamma_I I + \gamma_H H. \end{cases} \tag{3}$$

This transmission model fitted the COVID-19 trend under different control measures in China, such as isolation, and case tracking. In this model, the population naturally infected was divided into susceptible (S), latent (E), infected (I), suspected (B), hospitalized (H) and recovered (R). Under control measures, the population with close contact was divided into isolated susceptible (S_q) and latent (E_q). Through case tracking, it was supposed that a certain proportion (q) of contacted individuals were isolated. Those infected in this proportion were set into E_q compartment, otherwise into S_q compartment. In the proportion $(1 - q)$ of contacted individuals missed in case tracking, those infected were set into E_q compartment, otherwise into S_q compartment. In each contact, the transmission rate was β and the number of contacts was c . In those isolated, the infected (uninfected) individuals were switched into E_q (S_q) compartment with a rate of Bcq ((or $(1 - \beta)cq$). In those not isolated, the infected individuals were switched into E compartment with

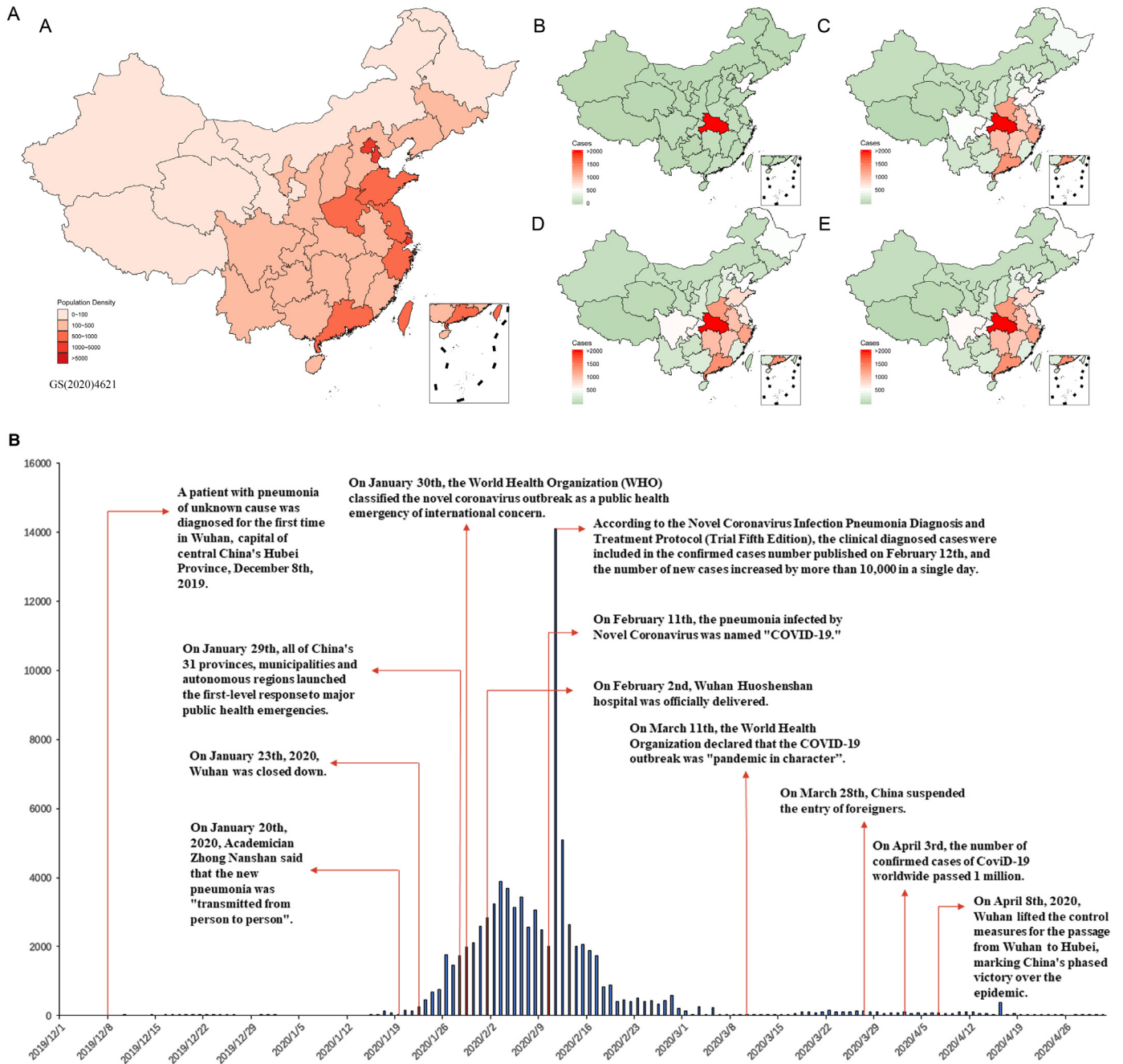


Fig. 2A. A: The population density distribution map of China in 2019. B-E: the density of novel coronavirus pneumonia patients in China on January 25, 2020 (B), February 15, 2020 (C), March 5, 2020 (D), and March 25, 2020 (E). **Fig. 2B:** New COVID-19 cases confirmed weekly and control measures taken at critical time points.

a rate of $Bc(1-q)$. The diagnosis for the infected was established with a rate of δ_{I0} , and these cases were moved to R compartment with a rate of γ_H . The outpatient cases with fever who were regarded as suspected cases were set into B compartment. $P_E(t)$, $P_I(t)$, $P_B(t)$ and $P_H(t)$ represented the numbers of cases allocated into latent, infected, suspected and confirmed, respectively. These data were illustrated with Poisson's distributions. The dynamics model flowchart is shown in Fig. 3, and other parameters in this model are shown in Table 1.

In the early stage of the COVID-19 pandemic (before January 23, 2020), the control measures were not strict enough. Therefore, the three parameters closely associated with control measures were set as constants, including number of contacts ($c(t)$), rate of isolation ($q(t)$), and diagnostic rate ($\delta(t)$). Therefore, the dynamic model was an autonomous

system, with the propagation threshold of R_0 . To reflect the beefed-up measures, each of the three parameters could make a monotone decreasing or increasing function with time. With threshold time set before January 23, 2020, the functions of three parameters were as follows: the function of $c(t)$:

$$c(t) = (c_0 - c_b)e^{-r_1(t-t_c)} + c_b \quad (4)$$

the function of $q(t)$:

$$q(t) = (q_0 - q_m)e^{-r_2(t-t_c)} + q_m \quad (5)$$

the function of $1/\delta(t)$:

$$\frac{1}{\delta(t)} = \left(\frac{1}{\delta_{I0}} - \frac{1}{\delta_{Ij}} \right) e^{-r_3(t-t_c)} + \frac{1}{\delta_{Ij}} \quad (6)$$

Table 1
Parameters and definitions in the SEIHR model.

Parameters	Definition	Parameters	Definition
c_0	Number of early exposures to disease outbreaks	b	Detection rate of suspected population
c_b	The minimum number of exposures after implementation of the control strategy	f	Detection rate of suspected cases
r_1	The exponential decline rate of the number of exposures	σ	Conversion rate from latent to infective
r_2	<u>Index increase rate of Track the isolation rate</u>	λ	Remove isolation rate
r_3	The exponential growth rate of diagnosis	δ_{I0}	Initial rate of diagnosis from infected persons to diagnosis
q_0	Trace isolation rate for early exposures	δ_{If}	Maximum rate of diagnosis from infection to diagnosis
q_m	Maximum tracking isolation rate after control measures are implemented	γ_I	Recovery rate of infected people
β	Probability of propagation per contact	γ_H	Recovery rate of in hospital cases
m	Isolation rate of suspected population entering through fever clinic	α	Mortality rate related to disease

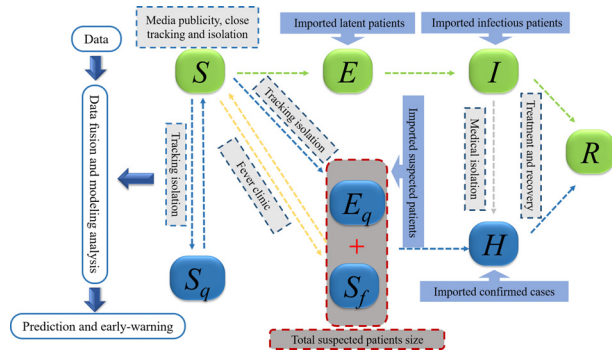


Fig. 3. The schematic of the SEIHR model constructed based on the model of COVID-19 propagation mechanism, prevention and control strategy, which includes integrated multi-source data, model building, prediction, risk analysis and decision-making.

The R_t calculated with the SEIHR model:

$$R(t) = \frac{\beta c(t)(1 - q(t))}{\delta(t) + \alpha + \gamma_I} \tag{7}$$

We calculated the basic reproduction number by formula (7).

3. Results and discussions

A total of 3452 infectors were collected from the first burst of the pandemic between January 1, 2020 and April 15, 2020. Tianjin had a maximum of 255 cases, followed by Beijing (248 cases) and Jilin (238 cases). The 3452 confirmed infectees included 1436 males, with a mean age of 36.8, median of 39, inter-quartile range (IQR) between 30 and 58, and all ages ranged from 3 to 85 years. Among the 3452 infectors, 185 showed a negative serial interval.

First, we used three distributions to fit the average incubation period of the COVID-19 patients from eight provinces (Table 2). Next, we allocated the data into three distributions and found that the Weibull

Table 2
The summary of mean and 95% CI estimates (unit: day) of incubation period COVID-19.

Province/city	Mean incubation period and 95%CI (day)		
	Gamma distribution	Lognormal distribution	Weibull distribution
Beijing	6.15 (2.50, 9.46)	6.46 (2.62, 10.76)	5.97 (2.00, 9.02)
Guizhou	7.53 (2.63, 13.00)	7.55 (2.81, 13.18)	7.61 (2.43, 13.01)
Hunan	6.40 (2.22, 10.86)	6.42 (2.46, 11.03)	6.42 (1.85, 10.62)
Jilin	8.68 (3.18, 17.23)	8.74 (3.29, 20.73)	8.59 (2.75, 13.83)
Jiangsu	8.20 (0.90, 22.61)	8.36 (1.33, 23.34)	8.22 (0.88, 21.47)
Shanghai	6.15 (1.64, 12.06)	6.12 (1.83, 12.34)	6.23 (1.43, 11.75)
Sichuan	5.96 (2.31, 12.23)	5.93 (2.28, 16.06)	5.86 (1.92, 10.07)
Tianjin	7.77 (3.06, 13.34)	7.71 (3.09, 13.30)	7.75(2.56, 12.94)

Table 3
The summary of mean and 95% CI (unit: day) of TG and presymptomatic period COVID-19.

Distribution	Parameter	Mean (95% CI)	AIC
Gamma	TG	5.2 (4.4–5.8)	2863.3
	presymptomatic period	2.3 (1.0–4.5)	
Weibull	TG	5.2 (4.6–5.8)	2862.2
	presymptomatic period	2.4 (1.5–3.2)	
Lognormal	TG	5.3 (4.5–5.8)	2867.6
	presymptomatic period	3.0 (2.0,7.1)	

Table 4
The intrinsic growth rate (unit: per day) and reproduction numbers for eight Chinese provinces in the mainland of China.

Province/city	Intrinsic growth rate (95% CI)	Reproduction number (95% CI)
Tianjin	0.20 (0.19–0.21)	2.52 (2.40–2.64)
Beijing	0.14 (0.13–0.15)	2.16 (2.02–2.38)
Jilin	0.22 (0.20–0.25)	2.55 (2.44–2.68)
Guizhou	0.24 (0.23–0.25)	2.94 (2.68–3.29)
Jiangsu	0.19 (0.17–0.21)	2.23 (2.01–2.48)
Sichuan	0.23 (0.20–0.26)	2.37 (2.29–2.46)
Hunan	0.27 (0.25–0.29)	3.14 (2.92–3.39)
Shanghai	0.17 (0.16–0.18)	2.20 (2.09–2.32)
China	0.18 (0.17–0.19)	2.38 (2.26–2.53)

distribution model fitted TG best: the smaller the AIC, the better the fitting. As shown in Fig. 4A and B, the log-likelihood profiles of TG fitted the Weibull model well, so did the presymptomatic period (Table 3). The mean of TG (μ_g) was 5.2 days (95% CI: 4.7–5.8), which is consistent with much previous research [17–19]. The value of SI was estimated as 4.0 (95% CI: 2.1–5.8) by infectors data [6].

To obtain the basic reproduction number of COVID-19, the intrinsic growth rates need to be estimated firstly. We found that the SEIHR model fitted the observed pandemic curve well, as shown in Fig. 3. Under the condition of TG following Weibull distribution, we took TG and SI as the generation time into the model to compare their accuracy with the actual observed cases. The result showed that TG performed a bit better than SI (Fig. 5). Rare studies have been conducted to compare the fitness of TG or SI in the transmission model. Zhao et al. suggested that TG was inestimable and inaccessible directly but meaningful for explaining the transmission pattern. In the present study, therefore, a likelihood framework was established with observed data to estimate TG and presymptomatic period. R_0 was a parameter used for describing the average transmission intensity. During the early stage of COVID-19 appearance in China, R_0 was high and instable before the implementation of control measures. By taking these measures, especially the release of a tertiary-controlling system, the virus transmission has been effectively contained (Fig. 2B). In the present study, the intrinsic growth rates and reproduction numbers for eight provinces were obtained. As listed in Table 4, the basic reproduction number was cal-

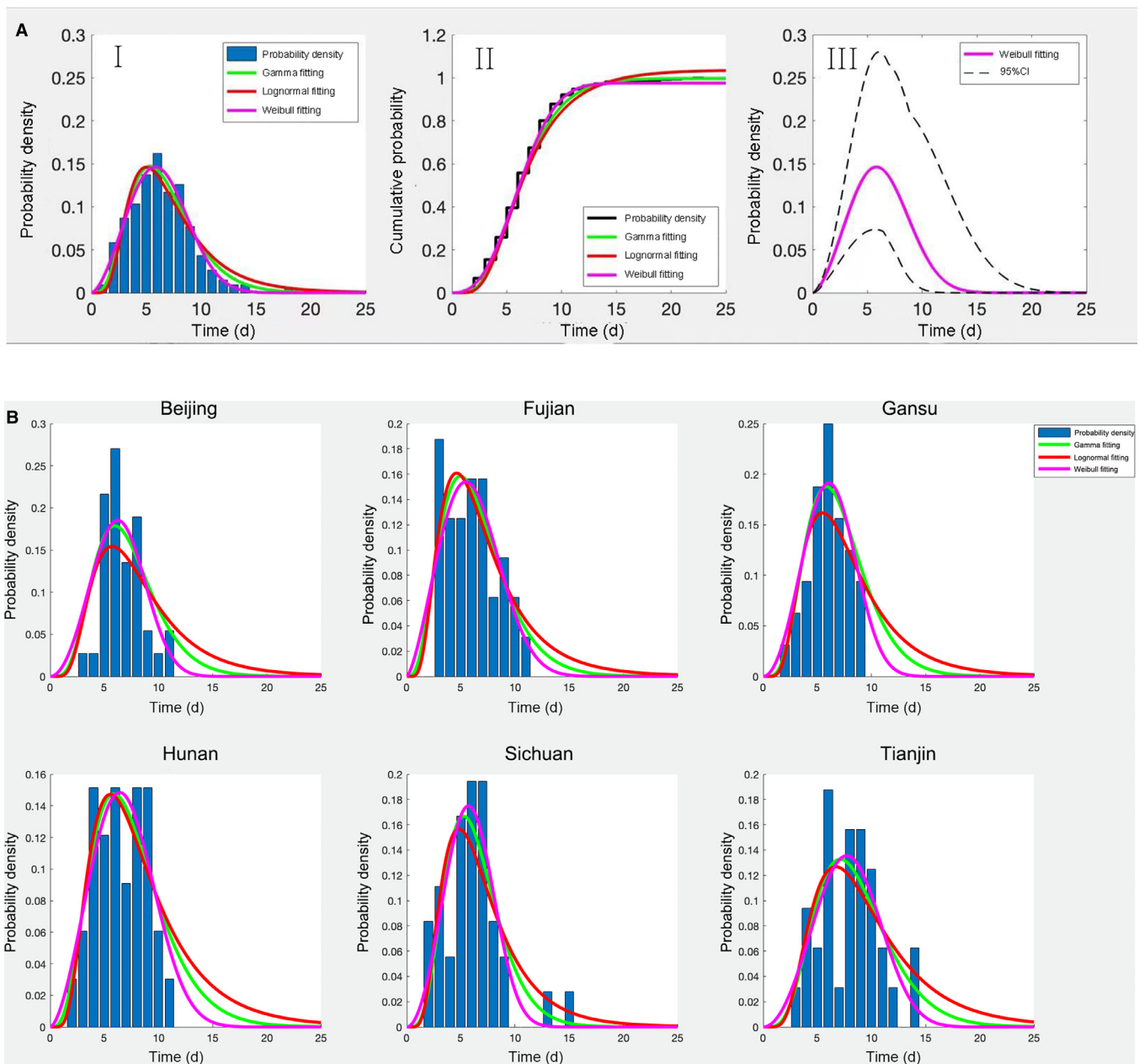


Fig. 4. **A. Part I** shows the frequency distribution of transmission generation of 3452 cases of COVID-19 in China and the fitting figure of three distribution models. **Part II** compares the cumulative distribution curves of case data using gamma, lognormal and Weibull distribution models. **Part III** shows the Weibull distribution of COVID-19 transmission generation after 1000 MCMC simulations (mean and 95%CI). **B.** Fitting chart of transmission generation of six provinces and cities (Beijing, Fujian, Gansu, Hunan, Sichuan, Tianjin) based on most of the samples.

culated as 2.38, consistent with previous estimates [16, 20-23]. For instance, Li et al. [20] estimated R_0 of COVID-19 to be 2.2 (95% CI: 1.4–3.9). Zhao et al. estimated R_0 at 2.24–3.58 in the early outbreak of COVID-19 [21]. Similarly, Ferretti et al. estimated the infectivity period and calculated the R_0 as 2.0 in the early stage using the exponential growth rate [22]. Pan et al. predicted the R_t in Wuhan (Hubei Province, China) rising from January 10 to 24 (peak 3.82) and falling thereafter below 1 on February 6 in 2020 [23]. Given the basic reproduction number of COVID-19 [21, 24], we think that timely and effective isolation of all symptomatic cases is necessary to curb the COVID-19 spread.

This study has two limitations. First, the SI observation collected from the public domains might be biased with more severe cases, which was also pointed out by Du et al. [25]. Together with the recalling bias-

ness, this might lead to an underestimation of the mean GT compared to that in a COVID-19 outbreak without control measures. However, the online data source screening was conducted till April 15, 2020, when both mild and severe COVID-19 cases were publicly reported, and thus we consider the first limitation is minor. Second, if the isolation data of each infector were available, the likelihood function of SI could be extended to a right-truncated version [26]. In practice, the individual infectiousness is not necessarily identical, but we presume this difference is unlikely large.

4. Conclusions

The mean of TG is estimated to be 5.2 days (95% CI: 4.6–5.8). The presymptomatic period is estimated by a Weibull distribution with an

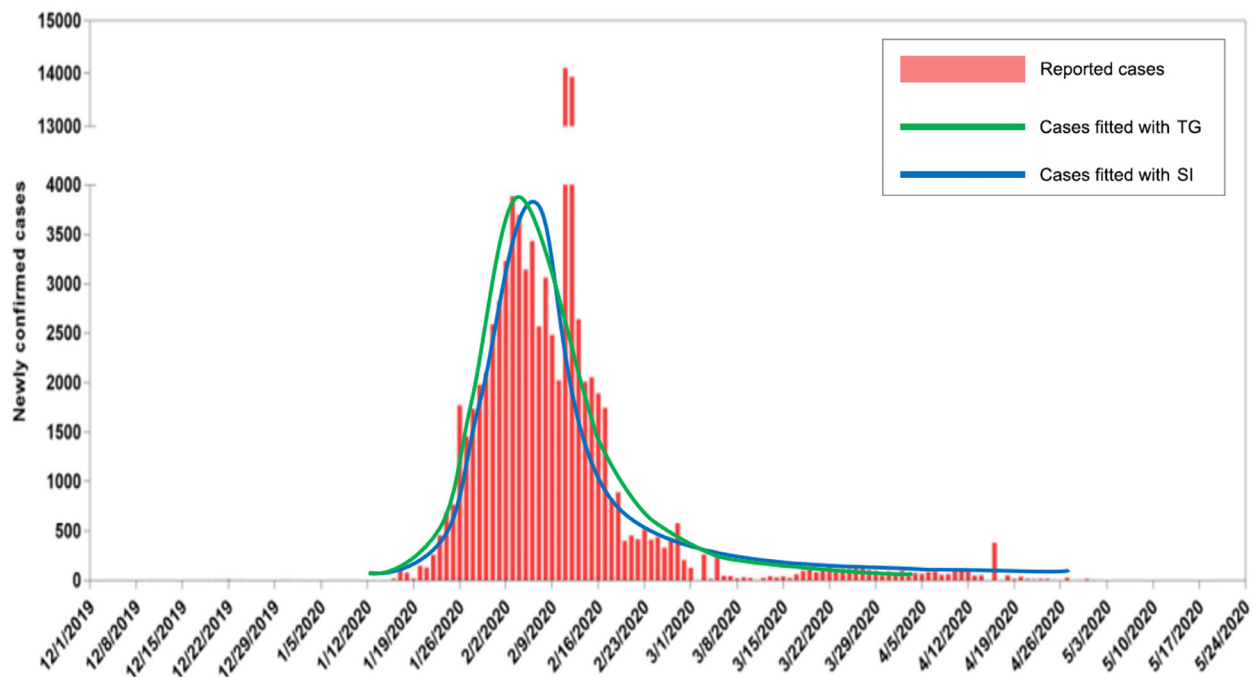


Fig. 5. Modeling with Parameter TG or SI. The fitting effect of TG is more accurate than that of SI.

average time of 2.4 days (95% CI: 1.5–3.2). The basic reproduction numbers of COVID-19 in eight provinces are between 2.16 and 3.14. The parameter TG fits the observed epidemic curves slightly better than SI. More reliable parameters should be explored to increase the predictive ability of the model.

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Compliance with ethics guidelines

All authors declare that they have no conflict of interest or financial conflicts to disclose.

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