Inferring epidemic containment probability from non-pharmaceutical interventions using a Gillespie-based epidemic model

Running title: Inferring epidemic containment probability from stochastic epidemic modelling

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Summary

The Gillespie algorithm, which is a stochastic numerical simulation of continuous-time Markovian processes, has been proposed for simulating epidemic dynamics. In the present study, using the Gillespie-based epidemic model, we focused on each single trajectory by the stochastic simulation to infer the probability of controlling an epidemic by non-pharmaceutical interventions (NPIs). The single trajectory analysis by the stochastic simulation suggested that a few infected people sometimes dissipated spontaneously without spreading of infection. The outbreak probability was affected by basic reproductive number but not by infectious duration and susceptible population size. A comparative analysis suggested that the mean trajectory by the stochastic simulation has equivalent dynamics to a conventional deterministic model in terms of epidemic forecasting. The probability of outbreak containment by NPIs was inferred by trajectories derived from 1000 Monte Carlo simulation trials using model parameters assuming COVID-19 epidemic. The model-based analysis indicated that complete containment of the disease could be achieved by short-duration NPIs if performed early after the import of infected individuals. Under the correctness of the model assumptions, analysis of each trajectory by Gillespie-based stochastic model would provide a unique and valuable output such as the probabilities of outbreak containment by NPIs.

Keywords: Gillespie algorithm, epidemic model, stochastic simulation, COVID-19, non-pharmaceutical interventions

1 | Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first identified in Wuhan, China, in December 2019 (Li et al., 2020a). Since then, it has rapidly spread globally, partly owing to pre-symptomatic or asymptomatic transmission (Ferretti et al., 2020; Cheng et al., 2020; He et al., 2020). Non-pharmaceutical interventions (NPIs), such as school closures, social distancing, and lockdown measures, have been applied to contain the pandemic. NPIs will be continuously needed to control COVID-19 propagation until the development of a vaccine or therapeutic agent as recurrent outbreaks are projected after the initial pandemic wave (Kissler et al., 2020). However, it is essential to select effective and appropriate NPIs because some measures can result in significant adverse damage to society and the economy.

The effectiveness of NPIs has been largely evaluated using epidemic mathematical models (Prem et al., 2020; Wu, Leung, and Leung, 2020; Ferguson et al., 2020; Kraemer et al., 2020; Tian et al., 2020). Various deterministic models involving the solution of ordinary differential equations have realized epidemic forecasting producing different types of output data (Anderson, 1991). Stochastic models are also important for predicting disease outbreaks because epidemic patterns are variable and highly associated with human mobility, which could be assumed to consist of stochastic random events (Grassly and Fraser, 2008). In studies on COVID-19, the probability of occurrence of a large outbreak based on the number of imported cases (Kucharski et al., 2020) and the probability of an outbreak being controlled by the isolation of cases and contacts (Hellewell et al., 2020) have been inferred using different stochastic models: a geometric random walk process and a branching process model. However, information

on the probability of COVID-19 containment by NPIs is still limited, and evaluating the controlling probability using different stochastic model is important for complementary or alternative evaluation of the effectiveness of NPIs.

The Gillespie algorithm, which is a stochastic numerical simulation of continuous-time Markovian processes, has been widely used in chemical reaction simulations (Gillespie, 1977; Gillespie, 2007). The algorithm has proven useful for the simulation of epidemic process in a population (Cota and Ferreira, 2017; Masuda and Rocha 2018). Accumulation of stochastically simulated trajectories using the Gillespie-based epidemic model leads to numerical solutions equivalent to those of the deterministic model. Nevertheless, there are few instances for the practical application of the Gillespie-based epidemic model for inferring actual epidemic information (e.g., the case of COVID-19) (Choi, Lee, and Kim, 2017). In the present study, we exploited a single trajectory of the Gillespie-based epidemic simulation to infer the probability of controlling an epidemic by NPIs. Here, we first characterized the dynamics of the Gillespie-based epidemic model and compared them to those of an equivalent deterministic model using ordinary differential equations. Then, the probability of the containment of COVID-19 using NPIs was evaluated using the Gillespie-based epidemic model for specific model parameters relevant to the COVID-19 epidemic.

2 | Methods

2.1 | Model construction2.1.1 | Stochastic epidemic model based on the Gillespie algorithm

The basic algorithm used in this study is shown in Figure 1A. For the stochastic epidemic model, we classified an epidemic population of fixed density in seven classes: susceptible (*S*), exposed (*E*), infectious-asymptomatic (*Ia*), infectious-mild (*Im*), infectious-severe (*Is*), recovered (*R*), and deceased (*D*) (Figures 1B and 1C). The corresponding quarantined populations were denoted by *QIa*, *QIm*, and *QIs*; these classes presumably dissipated the infectiousness through isolation (Figures 1B and 1C). In the model, 1 out of 15 events (shown in Figure 1D) was randomly selected, and class transition was performed at a time point (¿τ) according to the rule shown in Figure 1A. The probability of event selection depends on uniform random number generated at each time point (Figure 1A) and parameters relevant to the events (Figure 1D). For our epidemic analysis, we assumed $\Delta t = 1$, corresponding to one day. The parameters in Figure 1D were calculated using the base and simulation parameters shown in Table 1 and Table 2, respectively. In the present model, population density is fixed, and population mobility, birth, and natural death are ignored.

2.1.2 | Deterministic epidemic model

For comparative analysis with our stochastic model, the ordinary differential equations of the deployed deterministic model, named *SEIamsQamsRD*, were constructed as shown in Eqs. (1)–(10):

$$\frac{dS(t)}{dt} = -\beta S(t)\{Ia(t) + \Im(t) + Is(t)\} \quad (1)$$

$$\frac{dE(t)}{dt} = \beta S(t)\{Ia(t) + \Im(t) + Is(t)\} - (onset_{Ia} + onset_{\Im} + onset_{Is})E(t) \quad (2)$$

$$\frac{dIa(t)}{dt} = onset_{Ia} E(t) - (quarantine¿¿ Ia + recover_{Ia}) Ia(t) ¿ (3)$$

$$\frac{dIm(t)}{dt} = onset_{\Im} E(t) - (quarantine¿¿ \Im + recover_{\Im}) \Im(t) ¿ (4)$$

$$\frac{dIs(t)}{dt} = onset_{Is} E(t) - (quarantine¿¿ Is + recover_{Is} + dead_{Is}) Is(t) ¿ (5)$$

$$\frac{dQIa(t)}{dt} = quarantine_{Ia} Ia(t) - recover_{QIa} QIa(t) \quad (6)$$

$$\frac{dQIm(t)}{dt} = quarantine_{\Im} \Im(t) - recover_{QIm} QIm(t) \quad (7)$$

$$\frac{dQIs(t)}{dt} = quarantine_{Is} Is(t) - (recover¿¿ QIs + dead_{QIs}) QIs(t) ¿ (8)$$

$$\frac{dR(t)}{dt} = recover_{Ia} Ia(t) + recover_{\Im} \Im(t) + recover_{Is} Is(t) + recover_{QIa} QIa(t) + recover_{QIm} QIm(t) + recover_{QIs} QIs(t) \quad (9)$$

$$\frac{dD(t)}{dt} = dead_{Is} Is(t) + dead_{QIs} QIs(t) \quad (10)$$

The system of differential equations is equivalent to susceptible-exposed-infectious-recovered (SEIR) compartment model which is often used in several COVID-19 research (Tian et al. 2020, Wu, Leung, and Leung, 2020, Barbarossa et al. 2020). On the other hand, the model classes and parameters expressed by Eqs. (1)–(10) are identical to those of the stochastic model illustrated in Figure 1.

2.2 | Characterization of the Gillespie-based epidemic model

A simulation program for the stochastic epidemic model based on the Gillespie algorithm was constructed using Visual Basic Applications in Microsoft Excel. For the deterministic model, simulations based on the *SEIamsQamsRD* model shown in Eqs. (1)–(10) were performed on R version 3.6.1 using the same parameter settings as in the stochastic model. The dynamics of the stochastic and deterministic models were compared for different parameters, as described in Sections 2.2.1–2.2.5. For the stochastic model, 300 Monte Carlo simulation trials were performed to obtain a result for each parameter setting. An outbreak was defined as the appearance of over 100 infected individuals (*Ia*, *Im*, and/or *Is*), and the probability of an outbreak was calculated by the 300 simulations. In addition, the mean number of infectious individuals when the outbreak was recorded was used as a representative trajectory of the stochastic model in the particular parameter setting. The simulated results of the deterministic model were output in CSV files, and both stochastic and deterministic data were visualized in Microsoft Excel. Statistical analysis for the outbreak probability based on two-way analysis of variance (two-way ANOVA) was performed on R version 3.6.1 using package dplyr.

2.2.1 | Initial number of infected people

The onset ratio of *Im* (O_{rm}) and infectious duration of *Im* (I_{dm}) were fixed to 1 and 14 days, respectively, indicating that the infected population enters the *Im* (infectious-mild) stage with an infectious duration of 14 days. Each simulation of 800 days was performed assuming that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 100 infected individuals (*E*) invaded a susceptible population of 10,000. All simulations were performed for four different values of R_0 (1.5, 2.0, 2.5 and 3.0).

2.2.2 | Infectious duration

The model dynamics for infectious durations of 7, 14, and 21 days were compared, and O_{rm} was fixed to 1. Each simulation of 800 days was performed assuming that 1 infected person invaded a susceptible population of 10,000. All simulations were performed for four different values of the basic reproductive number R_0 (1.5, 2.0, 2.5, and 3.0).

2.2.3 | Size of susceptible population

O_{rm} and I_{dm} were fixed to 1 and 14 days, respectively. Each simulation of 800 days was performed assuming that 1 infected person invaded a susceptible population of 1,000, 10,000 or 100,000. All simulations were performed for four different values of R_0 (1.5, 2.0, 2.5, and 3.0).

2.2.4 | Ratios of *Ia*, *Im*, and *Is*

To validate the ratios of *Ia*, *Im*, and *Is*, the onset rates of *Ia* (O_{ra}), *Im* (O_{rm}), and *Is* (O_{rs}) were set to 0.1–0.7, 0.1–0.7, and 0.2, respectively, so that they summed to 1. The infectious durations of *Ia* (I_{da}), *Im* (I_{dm}), and *Is* (I_{ds}) were fixed to 7, 14, and 21 days, respectively. Each simulation of 800 days was performed assuming that 10 infected individuals invaded a susceptible population of 10,000. All simulations were performed with $R_0 = 2.5$.

2.2.5 | Quarantine setting

Quarantine setting was investigated when O_{rm} was fixed to 1 and I_{dm} was set to 7, 14, or 21 days. Q_{dm} was fixed to 5 days, meaning that *Im* populations were quarantined and isolated at 5 days after infectiousness onset. The rate of quarantine of

Im (Q_{rm}) was set to 0, 0.5, and 1.0 for comparison. Each simulation of 800 days was performed assuming that 100 infected individuals invaded a susceptible population of 10,000. All simulations were performed with $R_0 = 2.5$.

2.3 | Parameter assumption for COVID-19

All parameters used to simulate the COVID-19 epidemic were estimated as follows. We adopted $R_0 = 2.5$ (Ferretti et al., 2020; Prem et al., 2020; Wu, Leung, and Leung, 2020; Kucharski et al., 2020; Wu et al., 2020) and a mean incubation period of 5–6 days (Wu et al., 2020; Backer, Klinkenberg, and Wallinga, 2020). However, the periods of transmission from a pre-symptomatic person (Cheng et al., 2020; Tong et al., 2020; Rothe et al., 2020) and viral shedding before symptom onset (Zou et al., 2020; Pan et al., 2020) should also be considered. The infectiousness onset was estimated to be 2–3 days before symptom onset (He et al., 2020). Therefore, a latency period of 4 days was used instead of the incubation period. The ratios of the asymptomatic (O_{ra}), mildly symptomatic (O_{rm}), and severely symptomatic populations (O_{rs}) were assumed to be 0.3, 0.6, and 0.1, respectively, based on previous studies (Nishiura et al., 2020; Mizumoto et al., 2020; Gao et al., 2020). With respect to the infectious duration, it is reported that the virus could be transmitted within 5 days of symptom onset (Cheng et al., 2020), and the infectiousness declines quickly within 7 days (He et al., 2020). In viral-shedding data, the viral genome is detected by real-time PCR for approximately 20 days in the saliva or sputum of patients, whereas the viral load peak appears in the first week after symptom onset (He et al., 2020; Zou et al., 2020; Pan et al., 2020; To et al.,

2020; Wolfel et al., 2020; Zhou et al., 2020). No virus is isolated from sputum samples after 8 days from symptom onset, which could be a significant biological indicator of virus transmission (Wolfel et al., 2020). Additionally, transmission from asymptomatic carriers is confirmed (Bai et al., 2020), and prolonged duration of virus detection is reported more often in severely symptomatic patients than in mildly symptomatic patients (Zheng et al., 2020). Considering the abovementioned epidemiological information of COVID-19, the infectious durations for *Ia*, *Im*, and *Is* were assumed to be 5, 10, and 15 days, respectively. In the stochastic model, the size of the fatal population could be output if the fatality rate (F_r) of *Is* was fixed. Although the fatality information was not considered for the evaluation in this study, *Fr* was fixed to 0.1, i.e., 10% of severe cases (1% of all infected individuals) were fatal in our simulations (Wu et al., 2020a; Verity et al., 2020).

2.4 | Evaluation of NPIs

The effectiveness of NPIs was evaluated by utilizing the stochastic model using parameters relevant to the COVID-19 epidemic. Four scenarios were compared for different NPI durations (30, 60, 90, 120, 150, and 180 days). Scenario 1 only considered an 80% reduction of β, assuming city lockdown. Scenarios 2, 3, and 4 assumed populations *Im* and *Is* were quarantined 7, 5, and 3 days after infectiousness onset, respectively, in addition to the city lockdown. Simulations were performed assuming that 10 imported cases invaded a susceptible population of 100,000. The NPIs were established 10, 20, 30, 40, 50, and 60 days post invasion (dpi) of the infected individuals. Each simulation of 730 days involved the mean patient number and

probability of outbreak containment calculated by performing 1,000 Monte Carlo simulation trials. The mean patient numbers were simply the sums of *Ia*, *Im*, and *Is*, and the detection ratio of the infected population and delay in case reporting were not taken into account. The probability of outbreak containment was calculated by the numbers of single trajectories when the number of infected individuals was 0 and there was no recurrence of the epidemic after NPI relaxation within 1,000 simulations.

3 | Results and Discussion

3.1 | Characterization of the Gillespie-based epidemic model

3.1.1 | Dynamics of single trajectory by stochastic simulation

We evaluated the dynamics of the Gillespie-based stochastic model using several fixed parameters and simultaneously compared them with those obtained from an equivalent deterministic model using the same parameters. First, the dynamics of the Gillespie-based epidemic simulation were determined by focusing on a single trajectory in a fixed condition. The results indicate that the output single trajectories by the stochastic simulation were varied in each simulation trial, whereas the trajectory between the mean of 300 trials and the deterministic model was quite similar (Figure. 2A). Interestingly, the infected people are sometimes spontaneously dissipated without causing an outbreak, even in the same parameter setting (Figure. 2B). Because the Gillespie-based epidemic model assumes Poisson processes, which are assigned to

presumed individuals, the dissipated result of infected people is considered to be a statistically exact event (Masuda and Rocha, 2018). Namely, each single trajectory by the stochastic simulation is a possible prediction from the parameter setting; hence, the probability of the outbreak for each parameter setting was calculated based on the single trajectory analysis via 300 Monte Carlo simulation trials. The probability of an outbreak is less than 50% for a single infected individual (E), and R_0 is less than 2.0 (Table 3), which seems to be a plausible disease spread scenario considering random human mobility and contact processes. Therefore, an outbreak caused by the introduction of a few infected individuals could be prevented if the effective reproductive number (R_e) is reduced by adopting appropriate NPIs.

3.1.2 | Parameters affecting probability of outbreak

We next analyzed the model dynamics for different values of R_0, the infectious duration, and initial size of susceptible population (S_0). The results indicated that R_0 affected the total number of infected individuals, i.e., when R_0 was 1.5, 2.0, 2.5, and 3.0, the cumulative percentage of the population infected was approximately 60%, 80%, 90%, and 95%, respectively. The speed of the disease outbreak increased with increasing R_0 (Figures 3 and 4), and the infectious duration was inversely related to the speed of the disease outbreak (Figure 3). Although S_0 did not affect the cumulative percentage of the population infected, the epidemic duration was prolonged when S_0 was larger because the disease took longer to spread (Figure 4). The results indicate that an epidemic in a small town could cease quickly, whereas pandemics at larger scales could be prolonged for years. With respect to the probability of outbreak, two-way ANOVA analyses indicated that the infectious duration and S_0 did not affect the

probability of outbreak. Contrarily, R_0 and the initial value of E significantly affected the probability of outbreak when E was less than 5 ($P < 0.01$), suggesting that R_0 or R_e and the number of infected persons could be key factors for disease containment using NPIs. The trajectory by the deterministic model, which had the same composition as our stochastic model, was almost identical to the mean trajectory by the stochastic simulation regardless of R_0, the infectious duration, and S_0 (Figure 3 and Figure 4).

3.1.3 | Dynamics of constructed epidemic model

Finally, we examined the ratios of the infectious populations and model dynamics under different quarantine parameters which were incorporated into the epidemic model (Figure 1). Each infectious population was divided into subclasses *Ia*, *Im*, and *Is* according to specified parameters (Figure 5A). Further, infectious individuals were quarantined on specified days when the quarantine rate was 100% or 0% (Figure 5B). However, more infectious individuals than the specified rate were quarantined when the infectious duration was much longer than the specified quarantine day under 50% quarantine rate (Figure 5B). This phenomenon occurred because quarantine measures were applied to the present infectious population instead of the cumulative infectious population. The obtained results were confirmed by the deterministic model (Figure 5B), indicating that the Gillespie-based stochastic model accurately inferred the effectiveness of quarantine measures for a specified infectious population, duration, and rate. Both stochastic and deterministic model constructed in this study adhere to systems of SEIR compartment model, but extended to account for asymptomatic, mild, and severe cases. The expansion enables simulating feasible quarantine measure, e.g., the asymptomatic population can be excluded for quarantine simulation as they are hardly

to be quarantined unless active surveillance.

3.2 | Inference of NPIs effects for COVID-19

3.2.1 | Model parameters for COVID-19 and NPIs

The results of the previous section indicate that R_0 constitutes a critical factor for epidemic progression, including the probability of disease outbreak determined from the Gillespie-based epidemic simulation. In this study, R_0 was set to 2.5 for the simulation baseline of the COVID-19 epidemic, as previous studies give an estimate of 2-3 (Ferretti et al., 2020; Prem et al., 2020; Wu, Leung, and Leung, 2020; Kucharski et al., 2020; Wu et al., 2020). Based on the COVID-19 studies, the infectious durations for *Ia*, *Im*, and *Is* were assumed to be 5, 10, and 15 days, respectively (Figure 6). When O_{ra}, O_{rm}, and O_{rs} were fixed to 0.3, 0.6, and 0.1, respectively, the mean infectious duration was calculated to be 9 days, which is a plausible value considering the epidemic data of infectiousness (He et al., 2020) and virus isolation period (Wolfel et al., 2020). With respect to NPIs, an 80% reduction of β, which is equivalent to the reduction of human mobility and contact, was applied for all scenarios assuming city lockdown. As symptoms are considered to appear 2.4 days after infectiousness onset in this study, the quarantining of *Im* and *Is* was enforced 4.6, 2.6, and 0.6 days after symptom onset in Scenarios 2, 3, and 4, respectively (Figure 6). Quarantining was not imposed on population *Ia* in the simulation because it is impossible to estimate the size of *QIa*

quantitatively unless PCR testing targeting all population or active surveillance is performed.

3.2.2 | Evaluation of NPIs

We compared four NPI scenarios for the COVID-19 epidemic assuming 10 infected individuals were invaded in a population of 100,000. In 1,000 Monte Carlo simulation trials, the trajectories, which were either completely contained or recurred after NPI relaxation, were observed; hence, the probability of outbreak containment could be calculated by analysis of each trajectory. The results indicated that the epidemic could be completely contained through short-duration NPIs if they were enforced immediately after the introduction of infected individuals (Figure 7A). For example, in Scenario 1, when NPI was enforced at 10 dpi of the infected individuals, an outbreak exceeding 80% was inferred to be contained by the NPI for 90 days. Contrarily, an NPI of 180 days was required to achieve a similar level for the probability of outbreak containment if NPI was enforced at 60 dpi. In fact, New Zealand imposed a lockdown measure in March 2020 when the number of COVID-19 cases was still ~200 and successfully contained the disease within two months.

Our simulation results also indicate that implementing a lockdown combined with quarantining the symptomatic populations is essential to control COVID-19 effectively (Figure 7). Nearly half a year was required to contain the outbreak completely when an 80% reduction of β was achieved via lockdown (Figure 7A, Scenario 1). In contrast, over 80% of the outbreak was controlled by applying a combination of NPIs for 2 months, which consisted of a lockdown and quarantining the

symptomatic populations immediately after symptom onset (Figure 7A, Scenario 4). A comparison of Scenarios 2, 3, and 4 indicates that the effectiveness of the quarantine measure is higher when the period between symptom and quarantine onset is short. Similar results have been reported previously using another stochastic epidemic model: a branching process model (Hellewell et al., 2020). Those simulation results indicated that early isolation of symptomatic individuals as much as possible should be imposed, even when asymptomatic or pre-symptomatic populations cannot be not quarantined. Currently, PCR-based testing is the primary measure for early isolation of infected individuals (To et al., 2020) but notifying the contacts of positive cases using a digital contact tracing tool could also lead to early self-isolation (Ferretti et al., 2020).

After NPI relaxation, a second wave is unavoidable if the infected population is not completely dissipated by the NPIs (Figure 7C). This implies that further NPIs will be enforced to control the outbreak. The probability of outbreak containment suggests that prolonged NPIs causing significant damage to human society are required once the magnitude of epidemic is large. Thus, elimination of infected individuals by imposing early NPIs seems to be a reasonable measure for mitigating the damage in human society. The newly introduction of infected individuals can be preventable by adopting quarantine measures at border control. Currently, countries applying early lockdown and strict border control seem to control the COVID-19 epidemic (https://covid19.who.int/table). The probability of outbreak containment by the Gillespie-based epidemic simulation could be a useful indicator to infer the elimination of infected individual in the population when the duration and magnitude of NPIs will be determined.

To the best of our knowledge, this is the first report on the effectiveness of NPIs for the COVID-19 epidemic inferred using Gillespie-based epidemic modelling. Although the Gillespie algorithm has been discussed in epidemic simulations (Cota and Ferreira, 2017; Masuda and Rocha 2018), there exist limited simulations of actual disease epidemics. The proposed epidemic model provides unique outputs, such as the probability of outbreak containment, which are useful for making inferences about the effectiveness of NPIs. However, our simulation results for the COVID-19 epidemic may be weakened because they are highly associated with the asymptomatic population (Hellewell et al., 2020; Fraser et al., 2004), whose actual magnitude remains unclear (Ferretti et al., 2020; Nishiura et al., 2020; Mizumoto et al., 2020; Gao et al., 2020). Thus, more data for the asymptomatic population are required to infer feasible measures for the containment of the COVID-19 pandemic.

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Conflict of interest

We declare no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability statements

The data that support the findings of this study are available on request from the corresponding author.

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Tables

TABLE 1 Base parameters for the epidemic model.

Base Parameter	Explanation	Value for COVID-19	Reference
R_0	Basic reproductive number	2.5	Ferretti et al., 2020 Prem et al., 2020 Wu, Leung, and Leung, 2020 Kucharski et al., 2020 Hellewell et al., 2020
L_d	Days of latent period	4 days	He et al., 2020 Wu et al., 2020 Backer, Klinkenberg, and Wallinga, 2020
O_{ra}[†]	Onset rate of asymptomatic case	0.3	Nishiura et al., 2020 Mizumoto et al., 2020 Gao et al., 2020
O_{rm}[†]	Onset rate of mild case	0.6	Nishiura et al., 2020 Mizumoto et al., 2020 Gao et al., 2020
O_{rs}[†]	Onset rate of severe case	0.1	Nishiura et al., 2020 Mizumoto et al., 2020 Gao et al., 2020
Q_{da}	Days between onset and quarantine of asymptomatic case	NA[‡]	-
Q_{dm}	Days between onset and quarantine of mild case	NA	-
Q_{ds}	Days between onset and quarantine of severe case	NA	-
Q_{ra}	Quarantine rate of asymptomatic case	NA	-
Q_{rm}	Quarantine rate of mild case	NA	-
Q_{ds}	Quarantine rate of severe case	NA	-

I_{da}	Infectious days of asymptomatic case	5	Wolfel et al., 2020 Bai et al., 2020 Zheng et al., 2020
I_{dm}	Infectious days of mild case	10	Wolfel et al., 2020 Bai et al., 2020 Zheng et al., 2020
I_{ds}	Infectious days of severe case	15	Wolfel et al., 2020 Bai et al., 2020 Zheng et al., 2020
F_r	Fatality rate of severe case	0.1	Wu et al., 2020 Verity et al., 2020

†$O_{ra}+O_{rm}+O_{rs}=1$

‡NA (not applicable); depends on the case.

TABLE 2 Simulation parameters for the epidemic model.

Simulation Parameter	Explanation	Calculation
β	Transmission rate	$R_0/\{S_0^{\dagger}(O_{ra}I_{da}+O_{rm}I_{dm}+O_{rs}I_{ds})\}$
$onset_{Ia}$	Rate of onset from E to Ia	O_{ra}/L_d
$onset_{\mathfrak{I}}$	Rate of onset from E to $\mathfrak{I}$	O_{rm}/L_d
$onset_{Is}$	Rate of onset from E to Is	O_{rs}/L_d
$quarantine_{Ia}$	Rate of quarantine from Ia to QIa	Q_{ra}/Q_{da}
$quarantine_{\mathfrak{I}}$	Rate of quarantine from $\mathfrak{I}$ to QIm	Q_{rm}/Q_{dm}
$quarantine_{Is}$	Rate of quarantine from Is to QIs	Q_{rs}/Q_{ds}
$recover_{Ia}$	Rate of recovery from Ia to R	$(1-Q_{ra})/I_{da}$
$recover_{\mathfrak{I}}$	Rate of recovery from $\mathfrak{I}$ to R	$(1-Q_{rm})/I_{dm}$
$recover_{Is}$	Rate of recovery from Is to R	$(1-Q_{rs})(1-F_r)/I_{ds}$
$recover_{QIa}$‡	Rate of recovery from QIa to R	$1/(I_{da}-Q_{da})$
$recover_{QIm}$§	Rate of recovery from QIm to R	$1/(I_{dm}-Q_{dm})$
$recover_{QIs}$¶	Rate of recovery from QIs to R	$(1-F_r)/(I_{ds}-Q_{ds})$
$deceased_{Is}$	Fatality rate from Is to D	$F_r(1-Q_{rs})/I_{ds}$
$deceased_{QIs}$	Fatality rate from QIs to D	$F_r/(I_{ds}-Q_{ds})$

†S_0: Initial size of susceptible population

‡If $I_{da} \leq Q_{da}$, then $recover_{QIa}$ is 0.

§If $I_{dm} \leq Q_{dm}$, then $recover_{QIm}$ is 0.

¶If $I_{ds} \leq Q_{ds}$, then $recover_{QIs}$ is 0.

TABLE 3 Probability of outbreak (%) for different *E* and R_0.

R_0	E										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**100**
1.5	37.0	58.3	70.7	80.7	86.0	92.3	95.3	95.7	96.7	98.7	100.0
2.0	47.7	70.7	88.7	94.0	96.7	100.0	98.3	99.7	99.7	100.0	100.0
2.5	61.3	82.3	93.3	98.0	98.7	99.0	100.0	100.0	100.0	100.0	100.0
3.0	65.0	90.7	96.3	99.3	99.7	100.0	100.0	100.0	100.0	100.0	100.0

Figure legends

FIGURE 1 Stochastic epidemic model based on the Gillespie algorithm developed in this study. (A) Schematic diagram of the Gillespie algorithm used in this study. Variable k corresponds to the event numbers shown in Figure 1D. $Event(t,k)$ indicates the parameter shown in Figure 1D when the event number is k at the time point t. $Event_0(t,k)$ indicates the sum of all parameters shown in Figure 1D at the time point t. In the simulation model, $t=1$ was assumed to be 1 day, and the simulation program was constructed so that a specified number of days could be simulated. (B) Classes in the epidemic population used in this study. (C) Schematic image of class transition in the stochastic model. Branches and event numbers corresponding to the class transition are indicated. (D) Parameters relevant to events and class transitions are indicated. The calculation method for each parameter is shown in Table 1 and Table 2. In this model, quarantined individuals (*QIa*, *QIm*, and *QIs*) were isolated completely and did not contribute to the production of new infected individuals.

FIGURE 2 Dynamics of the Gillespie-based epidemic simulation. R_0, O_{rm}, and I_{dm} were set to 2.5, 1, and 14 days, respectively. Each simulation of 800 days was performed assuming that 1 infected individual invaded a susceptible population of 10,000 people. (A) Grey dashed lines represent the randomly selected 16 trajectories by the stochastic simulation. Black dashed lines indicate the single trajectories of maximum and minimum progression of the cumulative infected people in 150 days. The red solid line and blue dotted line indicate the mean trajectory of the stochastic simulation and single trajectory calculated by the deterministic model, respectively. (B) Black dotted lines

indicate the single trajectories when the infected individuals were spontaneously dissipated, indicating there was no outbreak in the stochastic simulation.

FIGURE 3 Comparison of infectious duration and R_0. (A) The pink, blue, and gray areas indicate the newly introduced numbers of infected people (*Im*) when infectious duration was set to 7, 14, and 21 days, respectively. The line and dot charts in red, blue, and black indicate the cumulative numbers of infected people (*Im*) when infectious duration was set to 7, 14, and 21 days, respectively. The lines and dots indicate the simulation results of the stochastic and deterministic models, respectively. (B) The red, blue, and grey charts indicate probability of outbreak in 300 stochastic simulations when the infectious duration was set to 7, 14, and 21 days, respectively.

FIGURE 4 Comparison of susceptible population size and R_0. (A) The pink, blue, and gray areas indicate the newly introduced numbers of infected people (*Im*) when the size of the susceptible population was set to 1,000, 10,000, and 100,000 people, respectively. The line and dot charts in red, blue, and black indicate the cumulative ratios of infected people (*Im*) when the size of the susceptible population was set to 1,000, 10,000, and 100,000 people, respectively. The lines and dots indicate the simulation results of the stochastic and deterministic models, respectively. (B) The red, blue, and grey charts indicate probability of outbreak in 300 stochastic simulations when the size of the susceptible population was set to 1,000, 10,000, and 100,000 people, respectively.

FIGURE 5 Dynamics of the constructed epidemic model assuming symptom division and quarantine setting. (A) Comparison of ratio of onset. The stacked area charts simulated by the stochastic model when onset rate of asymptomatic cases (O_{ra}), mild cases (O_{rm}), and severe cases (O_{rs}) were set to 0.1–0.7, 0.1–0.7, and 0.2, respectively, so

that their sum would equal 1. The sky blue, gray, and pink areas indicate the cumulative numbers of asymptomatic cases (*Ia*), mild cases (*Im*), and severe cases (*Is*), respectively. The stacked line charts in blue, black, and red indicate the cumulative numbers of *Ia*, *Im*, and *Is*, respectively, which were simulated by the deterministic model using the same parameters as the stochastic model. (B) Comparison of quarantine setting. The multiple line and dot charts indicate the cumulative numbers of infected people (*Im*) and quarantined people (*QIm*), respectively, simulated by the stochastic model (left) and deterministic model (right). The red, blue, and black charts indicate the simulation results when the quarantine rate (Q_{rm}) was set to 0, 0.5, and 1.0, respectively. I_{dm} indicates the infectious duration of the infected people (*Im*).

FIGURE 6 Schematic image of the estimated progression of COVID-19 and quarantine measures for epidemic simulation. Grey-filled cells indicate the latency period (4 days). Orange, pink, and red cells indicate the infectious durations of populations *Ia*, *Im*, and *Is*, respectively. The incubation period was assumed to be 6.4 days (Backer et al. 2020). The period between symptoms onset and case report was set to 7, 5, and 3 days for Scenarios 2, 3, and 4, respectively.

FIGURE 7 Inference of NPI effect based on the Gillespie-based epidemic simulation. The following four scenarios of NPIs were compared: Scenario 1 assumed an 80% reduction of β (city lockdown); Scenarios 2, 3, and 4 involved the implementation of a quarantine measure such that all *Im* and *Is* were quarantined and isolated at 7, 5, or 3 days after the start of infectiousness, respectively, in addition to the condition of Scenario 1. (A) Probability of outbreak containment in 1,000 simulations of each scenario. The line charts in blue, green, light green, yellow, orange, and red indicate the

probabilities when NPIs were started from 10, 20, 30, 40, 50, and 60 dpi, respectively. (B) Total patient numbers (=sum of *Ia*, *Im*, and *Is*) in the first 100 days of the simulations when NPIs were performed for 180 days. The results are the mean values of 1,000 simulations. The line charts in blue, green, light green, yellow, orange, and red indicate the total numbers of patients when NPIs were started at 10, 20, 30, 40, 50, and 60 dpi, respectively. The black dashed lines indicate the simulation results obtained when no NPI were performed (No-NPI). (C) Total patient numbers in 500 days when NPIs were started at 60 dpi and outbreak recurred after releasing of the NPIs. The results are the mean values only when more than 100 re-outbreaks were confirmed in 1,000 simulations. The line charts in red, pink, orange, light green, green, and blue indicate the total numbers of patients when NPIs were performed for 30, 60, 90, 120, 150, and 180 days, respectively. The black dashed lines indicate the simulation results obtained when no NPIs were performed (No-NPI).