

## RESEARCH ARTICLE

# Estimating the effects of asymptomatic and imported patients on COVID-19 epidemic using mathematical modeling

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**Abstract**

The epidemic of Coronavirus Disease 2019 has been a serious threat to public health worldwide. Data from 23 January to 31 March at Jiangsu and Anhui provinces in China were collected. We developed an adjusted model with two novel features: the asymptomatic population and threshold behavior in recovery. Unbiased parameter estimation identified faithful model fitting. Our model predicted that the epidemic for asymptomatic patients (ASP) was similar in both provinces. The latent periods and outbreak sizes are extremely sensitive to strongly controlled interventions such as isolation and quarantine for both asymptomatic and imported cases. We predicted that ASP serve as a more severe factor with faster outbreaks and larger outbreak sizes compared with imported patients. Therefore, we argued that the currently strict interventions should be continuously implemented, and unraveling the asymptomatic pool is critically important before preventive strategy such as vaccines.

**KEYWORDS**

computer modeling, coronavirus, epidemiology

## 1 | INTRODUCTION

The early pneumonia cases were identified in December 2019 with unclear origin.<sup>1</sup> The novel coronavirus has been named by the World Health Organization as Coronavirus Disease 2019 (COVID-19), which shares similarity to severe acute respiratory syndrome coronavirus.<sup>2</sup> Especially, older people and individuals with coexisting diseases are particularly susceptible to COVID-19 and are more commonly seen in patients with severe diseases.<sup>1</sup> Now, the COVID-19 has spread to many countries over the past 2 months and become a serious threat to public health worldwide.

To impede the outbreak of COVID-19, series of precautionary measures nationwide have been taken such as activation of emergency response system, quarantine, isolating suspicious cases, community surveillance, and epidemiological investigations.<sup>3</sup> As a result, the transmission of COVID-19 in China has been effectively blocked. However, the occurrence of asymptomatic patients (ASP) has posed a novel challenge regarding the epidemic of COVID-19.<sup>1,4</sup> ASP are not quarantined but also have considerable infectivity.<sup>5</sup> The viral loads in

ASP were quantitatively similar to those identified in patients with symptoms.<sup>5</sup> Meanwhile, the ASP have not been diagnosed as the laboratory-confirmed cases.<sup>6</sup> Therefore, imported cases and ASP have become novel challenges in China.

Modeling-based work may provide critical insight into the impact of interventions and epidemic of COVID-19.<sup>7</sup> Recently, many models have been developed to estimation the epidemic trend and evaluate the effect of controlled interventions.<sup>8-14</sup> However, the epidemic data have been updated and the number of laboratory-confirmed cases fall to zero on March 20 at several provinces in China. Therefore, novel data-driven model should be reconstructed to better characterize the epidemic features of COVID-19.

In current work, we developed a refined model with two novel features. We considered the effect of maximum capacity in health-care facility on the recovery rate of infected cases. Meanwhile, we also incorporated the ASP into our model. These two features significantly improved the model fitting. Under strongly controlled measures, ASP or imported cases would not lead to a concomitant outbreak. However, if the average effective contact rate within

population was increased, our model could predict a second outbreak with only a few asymptomatic or imported patients. Meanwhile, the ASP will accelerate the epidemic outbreak of COVID-19 with reduced latent period and larger outbreak size compared with imported patients. Our model may provide guidance for formulating controlled measures and re-evaluation of the diagnostic criteria for COVID-19.

## 2 | MATERIALS AND METHODS

### 2.1 | Data collection

Jiangsu and Anhui are two provinces adjacent to Wuhan (Hubei province) in China. We collected the number of confirmed and cured patients from 23 January to 31 March on the official website for Commission of Health of Jiangsu and Anhui provinces.<sup>15,16</sup> The total susceptible population was set to be the total population in Jiangsu and Anhui provinces, respectively. The data were collected from National Bureau of Statistics (<http://www.stats.gov.cn/>). We obtained that the initial susceptible population at Jiangsu and Anhui provinces (2019) was 80.7 and 63.659 million, respectively.

### 2.2 | Model construction

Owing to the epidemiological features of COVID-19 and declaration of public health emergency in Jiangsu and Anhui provinces immediately following the closure of Wuhan on 23 January 2020, interventions such as isolation, precaution, and quarantine have been implemented. Therefore, the migration of population was cutdown and we did not consider Wuhan returnees since 23 January as previously described.<sup>17,18</sup> The effect of Wuhan returnees after 23 January was discussed in Supporting Information Discussion 1.1. To simplify model construction, we divided the total population in Jiangsu and Anhui provinces into five variables, termed as susceptible population with no resistance to disease (*S*), closely observed population (*C*, including the individuals under public health intervention or people with potentially close contacts), infected patients (*I*), recovered (*R*, cured/dead), and ASP (*A*). The total infected population (*I*) was of interest for monitoring the epidemic of COVID-19. The complete model was formulated as follows:

$$\begin{aligned} dS/dt &= \lambda C - \beta_1 SC - \beta_2 SA + \varepsilon A - \beta_3 SI \\ dC/dt &= \beta_1 SC + \beta_2 SA - \nu_1 C - \nu_2 C - \lambda C + \beta_3 SI \\ dl/dt &= \nu_2 C + \nu_3 A - \mu \frac{K^n}{K^n + C^n + I^n} I \\ dR/dt &= \mu \frac{K^n}{K^n + C^n + I^n} I \\ dA/dt &= \nu_1 C - \varepsilon A - \nu_3 A \end{aligned} \quad (1)$$

$\lambda$  is a theoretical reversal rate discharged from quarantine or close observation period. A usual period for COVID-19 is around 14 days corresponding to  $\lambda = 1/14$ . However, *C* all includes "potential close contacts" without quarantine, the actual  $\lambda$  should be larger than 1/14

and reestimated in model.  $\beta_i$  ( $i = 1, 2, 3$ ) describes the average effective contact rate between the susceptible population (*S*) and closely observed population (*C*), ASP (*A*), and infected patients (*I*), respectively.  $\varepsilon$  is the assumed self-recovery rate for ASP.<sup>19-21</sup>  $\nu_1$  and  $\nu_2$  denote the transition from close contacts to asymptomatic and infected/diagnosed patients, respectively.  $\nu_3$  is the transition rate from ASP to diagnosed cases.<sup>19-21</sup>  $\mu$  describes the average recovery rate for infected patients. Since the health-care facility/workers in the hospital has maximum capacity, a reasonable assumption argues that higher number of inpatients or quarantined cases will lower the recovery rate. As the number of infected cases decreased, the clinical care and treatments may be improved. These concerns may lead to threshold behavior in recovery rate. We used a Hill function to depict the dependence of  $\mu$  on asymptomatic to diagnosed patients, in which *K* denotes the threshold and *n* is the cooperativity.

The initial values of susceptible population "*S*" were set to be the total population in Jiangsu and Anhui provinces as described above. The initial value for "*I*" and "*R*" Commission of Health in Jiangsu and Anhui provinces ( $R = 0$ ).<sup>15,16</sup> The initial values of close contacts and ASP were estimated.

The simplified version of the model without the effect of ASP and health-care capacity related recovery rate is described by following equations

$$\begin{aligned} dS/dt &= \lambda C - \beta_1 SC - \beta_3 SI \\ dC/dt &= \beta_1 SC - \nu_2 C - \lambda C + \beta_3 SI \\ dl/dt &= \nu_2 C - \mu I \\ dR/dt &= \mu I \end{aligned} \quad (2)$$

A more complex "mutant" model without the effect of ASP was described by following equations:

$$\begin{aligned} dS/dt &= \lambda C - \beta_1 SC - \beta_3 SI \\ dC/dt &= \beta_1 SC - \nu_2 C - \lambda C + \beta_3 SI \\ dl/dt &= \nu_2 C - \mu \frac{K^n}{K^n + C^n + I^n} I \\ dR/dt &= \mu \frac{K^n}{K^n + C^n + I^n} I \end{aligned} \quad (3)$$

### 2.3 | Parameter estimation

The parameter estimation was performed using the *PottersWheel*.<sup>22</sup> The trust region method was adopted. During simulation, initial values of *S*, *I*, and *R* were fixed. Other parameters and initial conditions were allowed to vary with lognormal distributions. A fit sequence with at least 400 stochastic runs was implemented to exclude the potential local minima in parametric space. The basic  $\chi^2$  criteria was used for model identification ( $\chi^2/N < 1$ , where *N* denotes the number of data points).<sup>22</sup>

### 2.4 | Sensitivity coefficient

Local sensitivity analysis provides dynamic responses to an infinitesimal disturbance in kinetic parameters and initial conditions.

A dynamic system can be defined by  $x' = f(x, \theta)$ , where  $x$  and  $\theta$  donate state and parameter vector, respectively. Relative sensitivity  $S$  is defined as

$$S = \frac{\partial I_{\max} / I_{\max}}{\partial \theta / \theta} = \frac{\partial \ln(I_{\max})}{\partial \ln(\theta)}$$

Note that this sensitivity coefficient is only locally valid in parameter space.

## 2.5 | Model simulation

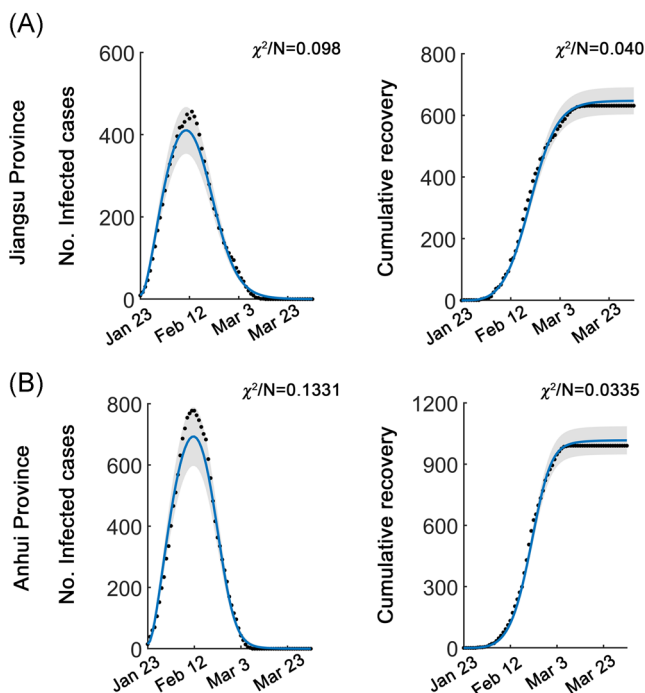
The ordinary differential equations were integrated using ode23s solver in MATLAB (R2018b).

## 3 | RESULTS

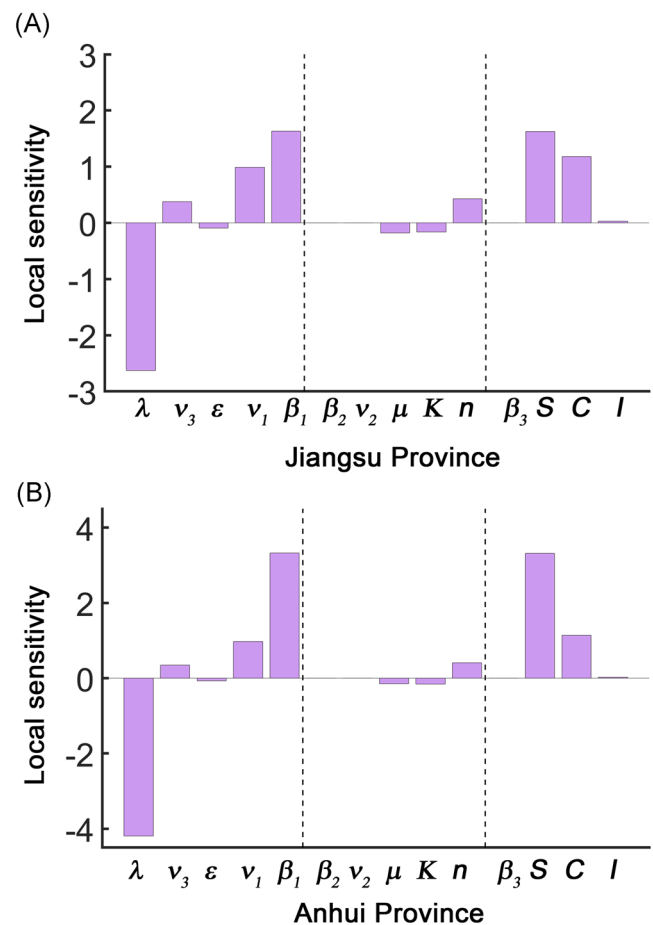
### 3.1 | Series of model constructions identify critical factors in model fitting

We first formulated a simplified model similar to the SEIR model<sup>23</sup> which captured the major interactions among susceptible population, close contacts, infected patients and recovered cases (model 2). With reasonable guess for parameter values, we performed model fitting to reported data from Jiangsu Province.<sup>15</sup> A total of 400 stochastic runs were performed. However, the best fit from 400 runs did not

satisfy the basic criteria for a convincible model ( $\chi^2/N > 1$  for both infected and recovered population, Figure S1A). A speculation argued that the actual recovery was slower than model predictions at early time points (Figure S1A, right). Notably, the temporal recovery exhibited a moderate cooperativity with a Hill coefficient 4.857 (95% confidence interval: [4.7, 5.014]) implying that the recovery rate  $\mu$  might be dynamically adjusted. Since the number of health-care facility/workers in hospital might affect the maximally admitted inpatients and medical treatment, we modified the recovery rate  $\mu$  by multiplying a scaling factor (model 3). We assumed that higher infected/quarantined cases may lower the recovery rate. The cooperativity was also subject to model fitting. Results suggested that the  $\chi^2$  penalty from model fitting was significantly decreased (Figure S1B). However, the model could not faithfully match the infected numbers ( $\chi^2/N > 1$ ; Figure S1B, left). Since the occurrence of ASP had raised extensive concerns about a possible outbreak and community spread of COVID-19,<sup>19-21</sup> we then incorporated the effect of asymptomatic cases (model 1, the complete model). We found the fitting was markedly improved and several fits to epidemic data from Jiangsu Province had even reached a  $\chi^2/N < 0.1$  (Figure 1A;



**FIGURE 1** Improved model fitting in complete model. A, Model fitting for data from Jiangsu province. B, Kinetic fitting for data from Anhui province.  $\chi^2$  penalty was provided on top right. The shaded area characterized a 95% confidence interval



**FIGURE 2** Local sensitivity analysis. A, The local sensitivity coefficient for Jiangsu model. Kinetic parameters and nonzero initial conditions were subject to sensitivity analysis. B, Sensitivity analysis for Anhui Model. The maximal number of infected patients was used as the metric

parameters were shown in Table S1). We further fit our model to data from Anhui province (kinetic parameters,  $C$  and  $A$  were reestimated, Table S1) and the results showed that the revised model formulation could also faithfully match the data (Figure 1B). These results suggested that the effect of ASP and threshold behaviors in health-care capacity contributed significantly to model fitting.

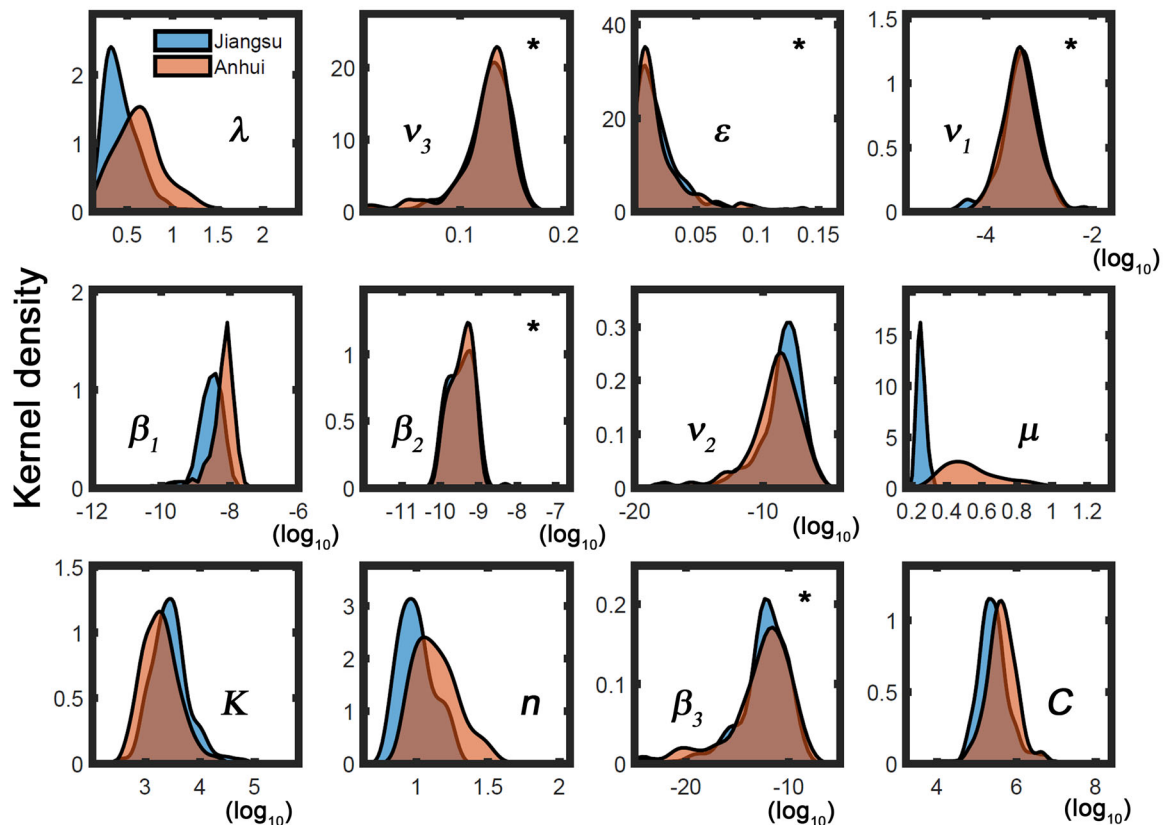
### 3.2 | Sensitivity analysis for Jiangsu and Anhui model

We next performed local sensitivity analysis to identify critical parameters for COVID-19 epidemic. We used maximal infected patients as the metric to evaluate the local sensitivity. We found that only a small fraction of parameters exhibited strong or moderate sensitivities. The sensitivity patterns were qualitatively similar between Jiangsu and Anhui model (Figure 2A,B). The discharge rate  $\lambda$  showed strong negative regulation for maximally infected patients in both models (Figure 2A,B). The transition from close contacts to ASP ( $\nu_1$ ) and contacts between susceptible population and close contacts ( $\beta_1$ ) profoundly increased the maximal infection. Not surprisingly, the size of susceptible population (" $S$ ") and close contacts (" $C$ ") positively

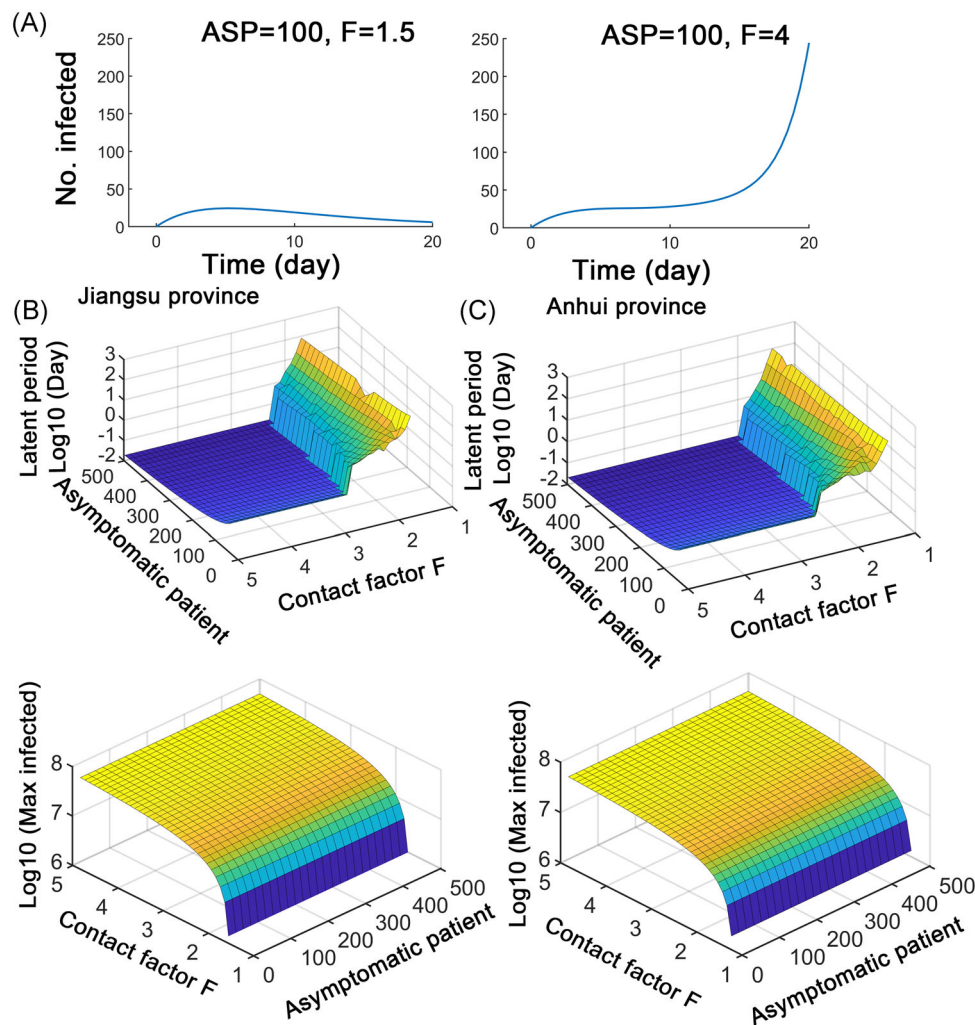
contributed to viral outbreak. These results characterized the locally sensitive parameters which potentially affected viral outbreaks.

### 3.3 | Sequential fitting identifies different epidemic features in Jiangsu and Anhui provinces

To avoid fitting bias toward local minimum in parametric space, we then performed model fitting from stochastic parameter sets. Totally, 400 runs were performed and the top 50% (200 sets, with a maximal total  $\chi^2/N = 0.0904$ ) were selected for analysis. We found that parameters related to ASP were not significantly different between Jiangsu and Anhui provinces suggesting that asymptomatic cases had similar epidemic ( $\nu_3$ ,  $\nu_1$ ,  $\varepsilon$ , and  $\beta_2$ , Figure 3). The discharge rate  $\lambda$  in Anhui province was faster (Figure 4). Meanwhile, patient recovery rate  $\mu$  was also significantly larger than that in Jiangsu province (Figure 3), which is consistent with the epidemic data that all infected patients were cured before March 9 (upto 6 days ahead compared with Jiangsu province). During stochastic fitting, we found that the initial number of ASP approached zero ( $\sim 0.0024$  in Jiangsu province and  $\sim 0.1268$  in Anhui province). Therefore, we set initial ASP to zero. The parameter " $n$ " in Jiangsu and Anhui model was only slightly larger than one implying minimal cooperativity. However, the



**FIGURE 3** Fit sequence analysis. All parameters and close contacts (" $C$ ") were subject to stochastic parameter fitting procedure. 400 stochastic runs were performed and the best 200 sets were selected for analysis. The distribution of each fitted parameters was shown. Blue area: Jiangsu province; orange area: Anhui province. Note that several parameters were shown in log<sub>10</sub> scale. The asterisks indicated that the estimated parameters in Jiangsu and Anhui province were not statistically different



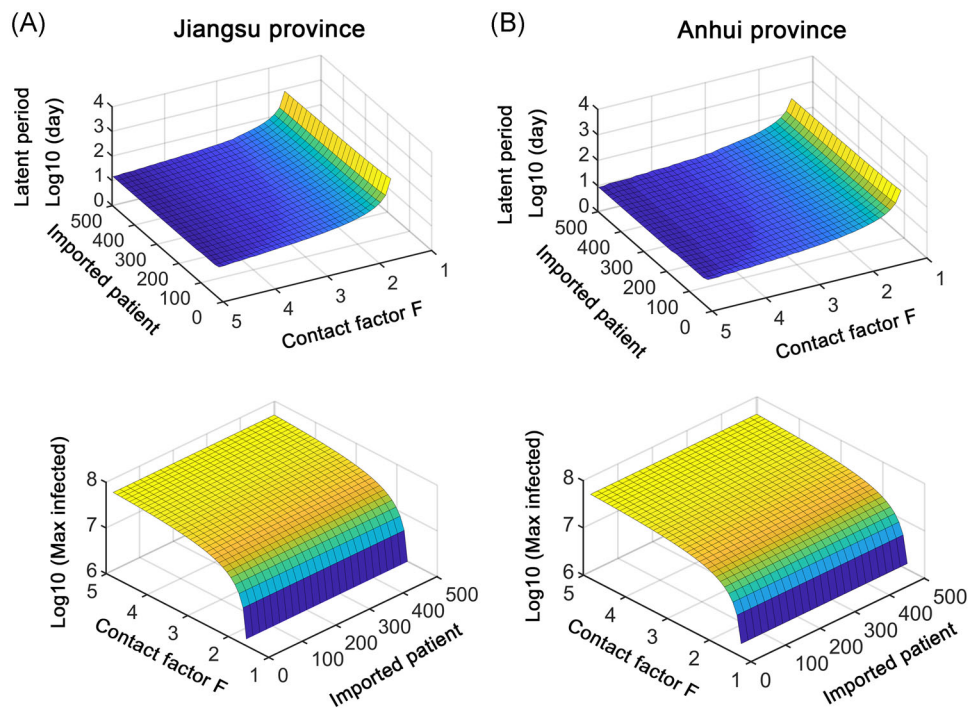
**FIGURE 4** The effect of asymptomatic patients (ASP) on infected maximum. A, The temporal changes of infected cases.  $F$ : contact factor  $F$ . Left:  $ASP = 100$  and  $F = 1.5$ ; right:  $ASP = 100$  and  $F = 4$ . B, The latent period (top) and maximally infected patients (bottom) for COVID-19 outbreak with varying numbers of ASP and contact factor  $F$  in Jiangsu model. The area without surface plots indicated no potential outbreak. Data were in  $\log_{10}$  scale at z-axis. C, Similar as in (B) in Anhui model

threshold level for health-care capacity ( $K$ ) in Jiangsu province was significantly larger than that in Anhui province ( $P = 2.6982 \times 10^{-7}$ , Figure 3) implying better health-care resources in Jiangsu province. The initial number of close contacts ( $C$ ) and their interaction with susceptible population ( $\beta_1$ ) were enhanced in Jiangsu province possibly owing to the larger population in Jiangsu province (Figure 3). Collectively, the stochastic parameter fitting could unravel both the differences and similarity of COVID-19 epidemic in Jiangsu and Anhui provinces.

### 3.4 | Evaluation the impact of asymptomatic patients on potential viral outbreaks

The ASP (covert cases or patients with no symptoms) have become a new epidemiological puzzle and may potentially trigger a secondary outbreak.<sup>19-21</sup> Under strong controlled interventions such as quarantine

and community surveillance, the mutual contact among susceptible population, close contacts, infected patients, and asymptomatic cases was almost completely blocked (ie, extremely low  $\beta_i$ ,  $i = 1, 2, 3$ ). However, if the strong intervention becomes mild, the mutual contacts among all population will be increased (ie, larger  $\beta_i$ ). The increased fold in all  $\beta_i$  values was simulated by multiplying  $\beta_i$  with a contact factor  $F$  ( $\beta_i' = F \cdot \beta_i$ ,  $i = 1, 2, 3$ ). Therefore,  $F = 1$  indicated strongly controlled interventions, whereas higher  $F (>1)$  values indicated mild or no interventions. We also varying the number of ASP and then recorded the maximal infected population if there was a COVID-19 outbreak. The latent period was defined as the time when the total infected cases became monotonically increased and finally reached a high peak (at least two orders of magnitude larger than the initial patient numbers). An exemplified case was shown (Figure 4A). When  $ASP = 100$  and controlled intervention was slightly reduced (ie, mutual contact was increased,  $F = 1.5$ ), the infected cases were rapidly tolerated (Figure 4A, left). However, if  $F$  was increased to 4, there would be an outbreak (Figure 4A, right). Extensive



**FIGURE 5** The effect of imported patients outside China on the epidemic features. A, The temporal changes of infected cases. The latent period (top) and maximally infected patients (bottom) for COVID-19 outbreak with varying numbers of imported patients and contact factor  $F$  in Jiangsu model. The area without surface areas indicated no outbreak. Data were in  $\log_{10}$  scale at z-axis. B, Predictions made using Anhui model

simulations showed there was no outbreak if  $F \leq 1.6$  irrespective of the initial asymptomatic populations (Figure 4B). However, if  $F > 1.6$ , even a small size of asymptomatic population ( $ASP = 20$ ) would lead to outbreak although the latent period seemed longer (Figure 4B, top). For  $F \geq 2.8$ , the latent period was less than 10 days (Figure 4B, top). The latent period and outbreak size were sensitive to contact factor  $F$  increase (mutual contact among populations) while remained relatively insensitive to initial number of ASP (Figure 4B). Similar behaviors could be observed in Anhui model although the threshold for  $F$  was reduced to 1.3 (Figure 4C). These results suggested that strongly controlled intervention to reduce mutual contact is highly effective to block viral outbreak.

### 3.5 | Effect of imported patients to COVID-19 outbreak

There are more and more imported patients in China since the coronavirus outbreak surges worldwide. We then investigated the effect of imported cases to viral epidemic. We varied the initial population of imported patients and contact factor  $F$  to explore whether an outbreak would be initiated. We found that mutual contact (contact factor  $F$ ) among different populations (susceptible, close contact, infected and asymptomatic) was also the major determinant for viral outbreak in both Jiangsu and Anhui models (Figure 5A,B). The latent period and the outbreak size were both sensitive to changes in contact factor  $F$  in both Jiangsu and Anhui models (Figure 5A,B). We further considered dynamic importation. A daily importation occurs with different

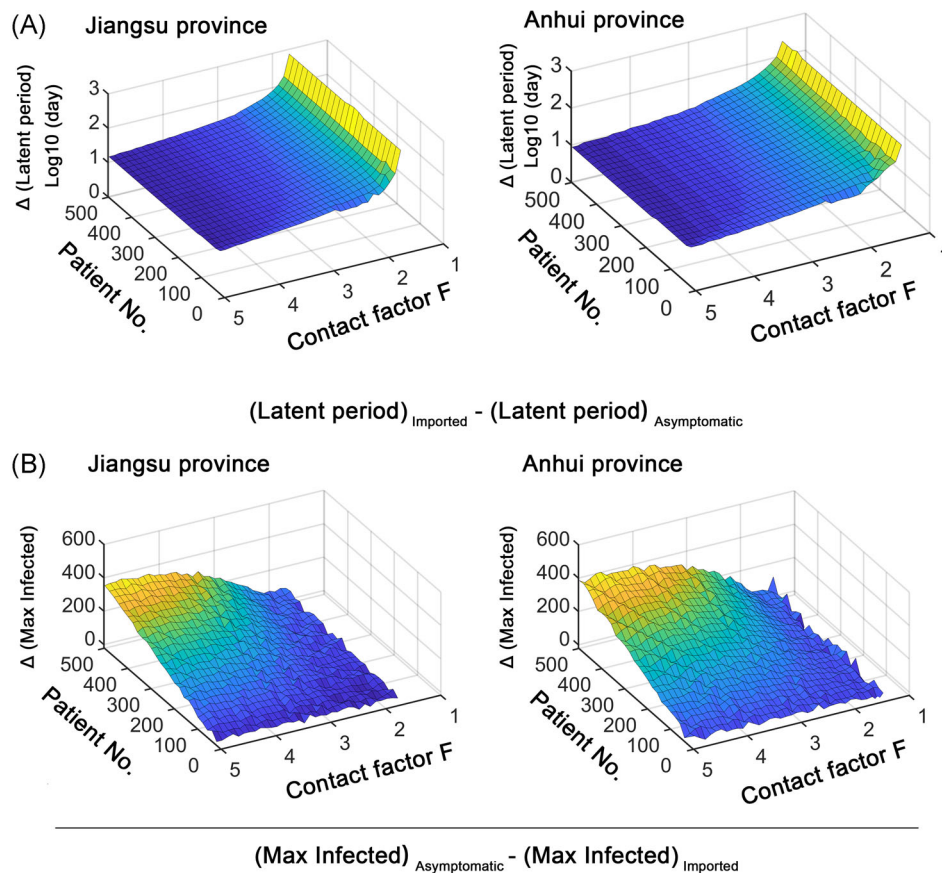
numbers of imported patients. Results suggested that the mutual contact markedly affected the outbreak size (see Supporting Information Discussion 1.2). Taken together, lowering mutual contact remains a sensitive strategy to impede coronavirus spreading.

### 3.6 | Comparison between imported and asymptomatic cases on coronavirus outbreak

The latent periods and outbreak sizes were compared for identical contact factor  $F$  and initial imported/asymptomatic populations. Results suggested that the latent period for imported cases was uniformly longer than that of asymptomatic cases (Figure 6A). Accordingly, the outbreak size for asymptomatic cases were larger than that of imported cases (Figure 6B). Collectively, the simulation suggested that ASP can more rapidly trigger a coronavirus outbreak with larger outbreak sizes.

## 4 | DISCUSSION

In current work, we used modeling-based approaches to investigate the impact of asymptomatic and imported cases on the potentially new outbreaks. We developed a model with two novel features: asymptomatic cases and threshold behavior in recovery. Our model can faithfully fit the epidemic data from Jiangsu and Anhui provinces in China. The model predictions indicated that asymptomatic cases are a more serious threat compared with importation into China.



**FIGURE 6** Comparison of the effects between asymptomatic and imported cases. A, The difference in latent period [ $\Delta$  (latent period)] between imported and asymptomatic cases. Results in Jiangu model (left) and Anhui model (right) were shown, respectively. B, The difference in infected maximum [ $\Delta$  (max infected)] between asymptomatic and imported cases. Results in Jiangu model (left) and Anhui model (right) were shown

The asymptomatic or covert patients can trigger outbreaks more rapidly and terminate with larger outbreak sizes if the strongly controlled measures become mild.

Based on the daily reports from Jiangu and Anhui Commission of Health, we constructed a refined model after the closure of Wuhan, the start of outbreak in China. We evaluated the epidemic features based on unbiased parameter estimation. Results suggested that both Jiangu and Anhui provinces have implemented highly effective interventions (low  $\beta_1$ , values upto  $10^{-12}$ ). Specifically, there is stronger control in Jiangu province with significantly lower  $\beta_1$ , possibly leading to fewer total infections in Jiangu province. Furthermore, based on the temporal data, the proportion of asymptomatic cases in dynamic and we estimated a median proportion approximately 44.46% (interquartile range: [37.31%-53.72%]) which is consistent with a recent report.<sup>19</sup>

From the sensitivity analysis, we found that regulating  $\beta_2$  or  $\beta_3$  alone plays neglectable role to block coronavirus outbreak. There is no feasible way to alter total population  $S$  and discharge rate  $\lambda$  either. The seemingly only way to impede viral transmission is simultaneously lowering mutual contacts ( $\beta_i$ ). We found that the latent periods and outbreak sizes are remarkably sensitive to the contact

factor  $F$  (note that the surface plot was removed if there was no predicted outbreak). Under strong interventions ( $F$  approaches 1), our model predictions suggested that even a total of 500 imported or ASP will not lead to coronavirus outbreak (Figures 5 and 6). However, if the strict interventions were attenuated ( $F > 1.6$  in Jiangu and  $> 1.3$  in Anhui), there will be a predicted outbreak. A recent estimation of mutual contact suggested that under uncontrolled situations, the average contact rate (ie, mutual contact) is increased by approximately 3.0799 ( $10/3.2469$ ) fold<sup>17</sup> corresponding to a contact factor  $F = 3.0799$  in our model. If  $F = 3$ , our model predictions demonstrated that the latent period (ie, decision time to trigger an outbreak) is less than 1 day and a potentially final outbreak size approximately  $10^7$ . Therefore, strongly controlled interventions are still required provided the undetectable populations of asymptomatic cases. Notably, since the middle of March, China has taken strong measures to control imported personnels in airports and railway stations (eg, quarantine and COVID-19 test), the imported cases will be immediately isolated with no contact with susceptible populations. However, ASP are not easily found and remain a major threat.

Our model predictions emphasized that the ASP seem to be a more devastating factor compared with imported patients. Identical

numbers of asymptomatic cases give rise to faster outbreaks and larger outbreak sizes. Even minimal ASP may result in significant viral transmissions (or local outbreaks). We suggested that COVID-19 tests should be used for individuals in dense populations (eg, students, teachers, or health-care workers). The extensive tests may help to identify the hidden ASP to impede potential outbreaks. Since April 1, China has begun to include detected asymptomatic cases in daily report.<sup>24</sup> Therefore, strong interventions should be taken especially for ASP owing to the unpredictable and covert features.

Liu et al<sup>25</sup> recently showed a model with “asymptomatic patients.” However, the “asymptomatic patients” all become diagnosed ones with symptoms and are more likely to be “pre-symptomatic.”<sup>26</sup> This is in contrast with the recent definition for ASP.<sup>19–21</sup>

Our model also has limitations. We did not incorporate death into our model similar to some recent models.<sup>8,18,27</sup> For Jiangsu province, there is no mortality. In Anhui province, the mortality is extremely low (6/990, ~0.6%). The model can provide faithful fitting under these situations. Therefore, our model might be helpful for understanding the epidemic features in most provinces from China. However, high mortality rates occur in Wuhan, China and several countries in Europe. A variable describing dead cases should be integrated with reestimated parameters. The peak predictions in Jiangsu and Anhui model are lower than official epidemic data. Note that the coronavirus outbreak coincides with the Traditional Chinese New Year. The capacity for testing is, therefore, lowered at the start of epidemic. A time-varying diagnosed rate could be incorporated to reach better model fitting.

## 5 | CONCLUSION

Despite the limitations above, the current study faithfully fits the epidemic data. Our model has predicted that the asymptomatic cases are factors with higher risk compared with imported cases and emphasized the critical role of strict interventions. The demographic stochasticity is worthy of further investigations using stochastic models.

## ACKNOWLEDGMENT

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

TZS and DW supervised the study, designed the study, performed the computational simulations, analyzed the data, and wrote the manuscript.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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