Study on the virulence evolution of SARS-CoV-2 and the trend of the epidemics of COVID-19

Mengyue Wang\textsuperscript{1,2} | Jiabiao Yi\textsuperscript{1,2} | Wen Jiang\textsuperscript{1,2} \\
\textsuperscript{1}Department of Mechanics, Huazhong University of Science and Technology, Wuhan, China \textsuperscript{2}Hubei Key Laboratory for Engineering Structural Analysis and Safety Assessment, Huazhong University of Science and Technology, Wuhan, China

Correspondence
Wen Jiang, Department of Mechanics, Huazhong University of Science and Technology, Wuhan 430074, China.
Email: wjiang@hust.edu.cn

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This is the first attempt to investigate the effects of the factors related to non-pharmaceutical interventions (NPIs) and the physical condition of the public on virulence evolution of SARS-CoV-2 and the trend of the epidemics of COVID-19 under an adaptive dynamics framework. Qualitative agreement of the prediction on the epidemics of COVID-19 with the actual situations convinced the rationality of the present model. The study showed that enhancing both NPIs (including public vigilance, quarantine measures, and hospitalization) and the physical condition of the public (including susceptibility and recovery speed) contributed to decreasing the prevalence of COVID-19 but only increasing public vigilance and decreasing the susceptibility of the public could also reduce the virulence of SARS-CoV-2. Therefore, controlling the contact rate and infection rate was the key to control not only the epidemic scale of COVID-19 but also the extent of its harm. On the other hand, the best way to control the epidemics was to increase the public vigilance and physical condition because both of them could reduce the prevalence and case fatality rate (CFR) of COVID-19. In addition, the enhancement of quarantine measures and hospitalization could bring the (slight) increase in the CFR of COVID-19.

KEYWORDS
adaptive dynamics, compartment model, COVID-19, non-pharmaceutical intervention, physical condition, virulence evolution

MSC CLASSIFICATION
92D15; 92D30

1 | INTRODUCTION

The COVID-19 which was caused by SARS-CoV-2 and began in Wuhan, China at the end of 2019 has rapidly spread all over the world in several months. On March 11, 2020, it was declared as a pandemic by the World Health Organization (WHO).\textsuperscript{1} The unpredictable pandemic of COVID-19 and the rapid growth of confirmed cases and deaths put human beings at big risk.

Due to the unpredictable progress of COVID-19 on a global scale, multiple researchers attempted to simulate the spread of the disease and predict its trend by distinct methods, including generalized logistic growth models,\textsuperscript{2} binomial distribution models,\textsuperscript{3} Bayesian ridge regression,\textsuperscript{4} neural network models,\textsuperscript{5} cellular automata models,\textsuperscript{6} and widely used compartment models.\textsuperscript{7-10} Most statistical models used to estimate the spread of disease adopted binomial, Poisson, Gaussian, or exponential distributions, which are intrinsically different, but led to similar results. Compared with the
statistical model, the deterministic model is more straightforward to investigate the spread of diseases and to understand how restrictive measures could control the epidemics. SEIR models are widely adopted to predict the outbreak of COVID-19, where the exposed component as the source of infection accounts for a large proportion of the spread of COVID-19 and cannot be neglected. Model parameters are usually obtained by fitting the infection data by Bayesian method and Markov chain Monte Carlo method. The influences of age structure, population mobility, non-pharmaceutical interventions (NPIs), and other factors are also included in these models to study the control of COVID-19. Most of these studies on the trend of the epidemics of COVID-19 under relevant measures mainly focus on the time-varying basic reproduction number and time-varying confirmed cases. However, the mathematical model for studying the virulence evolution of SARS-CoV-2 is rare, but both of them indicate that the virulence of SARS-CoV-2 is undergoing adaptive evolution.

The goal of this paper is to offer a framework to investigate the virulence evolution of SARS-CoV-2 and the trend of the epidemics of COVID-19 under different interventions. The factors related to NPIs, such as public vigilance to the epidemics, quarantine, and hospitalization, were all involved. In addition, the impact of age structure on the epidemics of COVID-19 was replaced by different physical condition of the public to facilitate analyses. Since accurate prediction is scarcely possible, some qualitative predictions on the virulence of the virus and the epidemics of the disease were presented to give a new insight into the evolution of SARS-CoV-2 under different interventions. It should be noted that in this article, SARS-CoV-2 will be used to refer specifically to the virus, while COVID-19 will be used when we speak of the disease.

2 | METHODS

2.1 | Transmission dynamic model of COVID-19

Based on the epidemiological characteristics of COVID-19, we built an SEIR model that can explicitly involve the role of NPIs to simulate the transmission dynamics of COVID-19. The total population $N$ was divided into several components: the susceptible ($S_f$, $S_q$), the exposed (i.e., the asymptomatic incubation patients $E_f$, $E_q$), the infected (i.e., the symptomatic patients $I_f$, $I_q$), and the recovered ($R$). All the components except the recovered consisted of two parts to distinguish the free (with subscript $f$) and quarantined (with subscript $q$) individuals under quarantine measures and hospitalization, where only free individuals could be infected. The interaction between different components, including infection, quarantine, hospitalization, and other factors, was depicted by a transmission diagram (Figure 1). In this transmission diagram, the NPIs were reflected by the control of the scope of social activities (i.e., the contact rate $c$), the
tracking and quarantine of close contacts (i.e., quarantine rate \( q \)), and the treatment of free asymptomatic incubation patients after onset (i.e., hospitalization rate \( h \)).

\[
\begin{align*}
\frac{dS_f}{dt} &= b + \theta S_q - \beta E c \frac{S_f}{N} E_f - (q - q\beta_t + \beta_t) c \frac{S_f}{N} I_f - dS_f \\
\frac{dS_q}{dt} &= q(1 - \beta_t) c \frac{S_f}{N} I_f - (\theta + d) S_q \\
\frac{dE_f}{dt} &= \beta E c \frac{S_f}{N} E_f + (1 - q) \beta_t c \frac{S_f}{N} I_f - (\mu + d) E_f \\
\frac{dE_q}{dt} &= q\beta_t c \frac{S_f}{N} I_f - (\mu + d) E_q \\
\frac{dI_f}{dt} &= (1 - h) \mu E_f - \left( \gamma_{I_f} + d + \alpha \right) I_f \\
\frac{dI_q}{dt} &= h \mu E_f + \mu E_q - \left( \gamma_{I_q} + d + \alpha \right) I_q \\
\frac{dR}{dt} &= \gamma_{I_q} I_q + \gamma_{I_f} I_f - dR
\end{align*}
\]

(1)

To reflect the actual situation but to construct the spread of COVID-19 as simply as possible, we made the following assumptions: (1) the asymptomatic patients are parts of the exposed components, and both are regarded as the asymptomatic incubation patients; (2) both the asymptomatic incubation patients and the symptomatic patients are infectious, and the infection rate of the symptomatic (\( \beta_t \)) is higher than that of the asymptomatic (\( \beta_E \)); (3) once quarantined, neither the asymptomatic incubation patients nor the symptomatic patients are no longer infectious; (4) the recovered patients will no longer be susceptible; (5) the recovery rate of the quarantined infected (\( \gamma_{I_q} \)) is higher than that of the free infected (\( \gamma_{I_f} \)); and (6) the birth and natural death of population (\( b \) and \( d \)) are considered because the evolution of SARS-CoV-2 is a long-term process, and the symptomatic patients suffer additional death rate due to infection (\( \alpha \)). Assumptions (1) and (4) we made were to simplify the mathematical model and analyses. It would not change the variation tendency of the results, which will be discussed in detail in the next section. Assumption (2) was presented because the infection rate of asymptomatic infections per person was 55% the transmission rate of symptomatic

| Symbol | Description |
|--------|-------------|
| \( S_f (S_q) \) | Number of free (quarantined) susceptible individuals |
| \( E_f (E_q) \) | Number of free (quarantined) asymptomatic incubation patients |
| \( I_f (I_q) \) | Number of free (quarantined) symptomatic patients |
| \( R \) | Number of recovered patients |
| \( b \) | Population birth rate |
| \( d \) | Per capita natural death rate |
| \( c \) | Contact rate |
| \( \beta_E (\beta_t) \) | Infection rate of asymptomatic (symptomatic) patients |
| \( \theta \) | Release rate of quarantined susceptible |
| \( \mu \) | Transition rate of asymptomatic to symptomatic patients |
| \( \alpha \) | Additional death rate due to infection |
| \( q \) | Quarantine rate |
| \( h \) | Hospitalization rate |
| \( \gamma_{I_f} (\gamma_{I_q}) \) | Recovery rate of free (quarantined) symptomatic patients |
infections on the basis of case report, and the proportion of infection among the symptomatic and the asymptomatic is 8.8% and 3.4%, respectively, in a screening among health care workers. Moreover, considering the facts that isolation is effective for COVID-19 control, the isolated patients are administered with a variety of treatments to attenuate virus infection, and the death case of COVID-19 cannot be neglected, we made Assumptions (3), (5), and (6).

Based on these assumptions, we can represent the transmission diagram in Figure 1 by the following group of differential equations (Equation 1). And the explanation for each variable in Equation 1 is listed in Table 1.

The endemic equilibrium of Equation 1 is \( W_+ = (S_f, S_p, E_f, E_p, I_f, I_p, R) \) (see Appendix A for more details), and whether the endemic equilibrium \( W_+ \) exists is determined by the basic reproduction number \( R_0 \) of the transmission dynamics of COVID-19, which is the spectral radius of the next-generation matrix as defined in the theory of van den Driessche and Watmough. can be derived from Equation 1 and expressed as follows (see Appendix A for more details):

\[
R_0 = \frac{\beta c}{\mu + d} + \frac{\beta_c \mu (1-q)(1-h)}{(\mu + d)(\gamma_I + d + \alpha)}
\]  

If \( R_0 > 1 \), the endemic equilibrium \( W_+ \) exists. Otherwise, there is only a disease-free equilibrium \( W_0 = (b/d, 0, 0, 0, 0, 0, 0) \).

2.2 Evolutionary dynamic model of SARS-CoV-2

Evolution is a process repeated as the mutation occurs constantly. It is closely related to the mutation of traits owned by pathogen which can finally act on the population through infection. Actually, the processes such as within-host replication of pathogen, shifting transmission routes, and interactions with immune system are interrelated. Increasing pathogen replication will increase the transmissibility but also increase the risk of host death given that pathogen replication will consume host resource and have adverse effects on it. Meanwhile, the increase of host death will decrease the likelihood of the host clearing the infection via immunological responses. Mathematically, such correlations are represented through saturation functions, that is, making transmission rate increase and recovery rate decrease with the increase of pathogen-induced death rate, respectively. Generally, virulence \( \alpha \) (additional death rate due to infection) is regarded as the evolutionary trait of pathogen, and the “virulence-transmission trade-off” hypothesis is commonly adopted to build the relation between pathogen and population in evolutionary dynamics. Based on this widely accepted criterion and given that the severity of COVID-19 makes people more vigilant, we constructed the relations between the transmission-related parameters (i.e., contact, infection, and recovery rates) and virulence (see Equation 3, where all coefficients are non-negative). The biological implications of the coefficients in Equation 3 and the determination of their values or value ranges are detailed in Section 2.3.

\[
c = c_0 e^{-c_0 \alpha}; \quad \beta_I = \frac{\alpha}{c_p \alpha + \kappa_p}; \quad \beta_E = \frac{\alpha}{c_{pe} \alpha + \kappa_{pe}}; \\
\gamma_{Iq} = \frac{1}{c_{Iq} \alpha + \kappa_{Iq}}; \quad \gamma_{Iq} = \frac{1}{c_{Iq} \alpha + \kappa_{Iq}};
\]  

Thus, the evolution of SARS-CoV-2 can be depicted by the mutation of the virus in virulence. Suppose that when the population infected by the resident SARS-CoV-2 with virulence \( \alpha_r \) is at the endemic equilibrium \( W_+ \) of Equation 1, a mutant SARS-CoV-2 with virulence \( \alpha_m \), whose virulence is slight different from \( \alpha_r \), will appear in the resident system and compete with the resident. In the adaptive dynamics framework, the competition among these two different types of SARS-CoV-2 can be regarded as an invasion of the mutant to the resident system, and the virus with higher fitness will succeed. This framework provides a standard procedure to calculate the invasion fitness which can be obtained from the dynamics of population infected by the invading mutant in the environment determined by the resident infected population. The invasion dynamics of mutant SARS-CoV-2 can therefore be described as follows.
\[ \frac{dE_f^{(m)}}{dt} = \beta_f^{(m)} c^{(m)} \frac{\hat{S}_f E_f}{N} + (1-q)\beta_t^{(m)} c^{(m)} \frac{\hat{S}_t I_f^{(m)}}{N} - (\mu + d)E_f^{(m)} \]
\[ \frac{dE_q^{(m)}}{dt} = q\beta_t^{(m)} c^{(m)} \frac{\hat{S}_t I_f^{(m)}}{N} - (\mu + d)E_q^{(m)} \]
\[ \frac{dI_f^{(m)}}{dt} = (1-h)\mu E_f^{(m)} - \left( \gamma_f^{(m)} + d + \alpha_m \right) I_f^{(m)} \]
\[ \frac{dI_q^{(m)}}{dt} = h\mu E_f^{(m)} + \mu E_q^{(m)} - \left( \gamma_q^{(m)} + d + \alpha_m \right) I_q^{(m)} \]

(4)

The superscript \((m)\) is related to the mutant SARS-CoV-2. And transmission-related parameters, that is, \(c^{(m)}, \beta_f^{(m)}, \beta_t^{(m)}, \gamma_f^{(m)}, \) and \(\gamma_q^{(m)}\) in Equation 4 are all functions of the virulence of the mutant SARS-CoV-2, \(\alpha_m\), and satisfy those relations described by Equation 3. \(\hat{S}_f, N\) are the number of free susceptible individuals and the total population at the endemic equilibrium, respectively.

Given that mutations occur continuously, the invasion dynamics (Equation 4) is only a small step in the long-term evolution and used to derive invasion fitness to measure whether the mutant can invade the current resident system that has reached its endemic equilibrium. Therefore, unlike the endemic equilibrium obtained directly from transmission dynamics (Equation 1), whether the evolution reaches an equilibrium requires further discussion on invasion fitness. The invasion fitness, that is, the invasion reproduction number \(R_m\) of the invasion system, can be defined as the number of individuals infected by a mutant during its infection period in an environment determined by the resident virus, which can also be derived by the next-generation matrix method on the basis of Equation 4 (see Appendix B for more details).

\[ R_m(\alpha_r, \alpha_m) = \frac{\hat{S}_f}{N} \left( D_E^{(m)} + D_I^{(m)} \right) \]

(5)

where

\[ D_E^{(m)} = \frac{\beta_f^{(m)} c^{(m)}}{\mu + d}; \quad D_I^{(m)} = \frac{\beta_t^{(m)} c^{(m)} \mu (1-q) (1-h)}{(\mu + d) (\gamma_f^{(m)} + d + \alpha_m)} \]

(6)

and \(R_m = 1\) always holds when \(\alpha_m = \alpha_r\).

From Equation 5, whether the mutant can beat the resident or be expelled depends both on the resident and mutant (i.e., the ratio of free susceptible in the environment determined by the resident \((\hat{S}_f/N)\) and the asymptomatic \((D_E^{(m)})\) and symptomatic \((D_I^{(m)})\) infection intensity of the mutant). If \(R_m > 1\), the mutant SARS-CoV-2 with virulence \(\alpha_m\) can invade the resident system and replace the resident SARS-CoV-2 with virulence \(\alpha_r\). Otherwise, it cannot invade the system. Thus, the evolutionary direction of the mutant near the resident with specific virulence \(\alpha_r\) is determined by the selection gradient at this point: \(\partial R_m / \partial \alpha_m |_{\alpha_m = \alpha_r}\) (i.e., the first-order partial derivative of \(R_m\) with respect to \(\alpha_m\) at \(\alpha_m = \alpha_r\)). If \(\partial R_m / \partial \alpha_m |_{\alpha_m = \alpha_r} > 0\), the mutant with high virulence \((\alpha_m > \alpha_r)\) can invade. If \(\partial R_m / \partial \alpha_m |_{\alpha_m = \alpha_r} < 0\), the mutant with low virulence \((\alpha_m < \alpha_r)\) can invade. The \(\alpha^*\) satisfying Equation 7, defined as the evolutionary singularity, is a possible new value of virulence of SARS-CoV-2 after continuous mutation until the evolution reaches an equilibrium.

\[ \frac{\partial R_m}{\partial \alpha_m} |_{\alpha_m = \alpha^*} = \frac{\hat{S}_f}{N} \left( D_E^{(m)} + D_I^{(m)} \right) = 0 \]

(7)

This implies that the direction of virulence evolution is to maximize the invasion reproduction number. For simplicity, the first derivative with respect to \(\alpha_m\) (or \(\alpha_r\)) and second derivative with respect to \(\alpha_m\) in this article are represented by \(\alpha^*\) and \(\alpha^{-}\) respectively.

According to Geritz et al.\(^{30}\) the evolutionary singularity can be classified as follows:

1. When the singularity can be achieved and cannot be invaded by any mutants, that is, \(A + B < 0\) and \(A < 0\), it is a continuous stable strategy (CSS);
2. When the singularity can be achieved and can be invaded by mutants, that is, \(A + B < 0\) and \(A > 0\), it is a branch point;

3. When the singularity cannot be achieved, that is, \(A + B > 0\), it is a repeller,

where

\[
A = \left. \frac{\partial^2 R_m}{\partial \alpha r^2} \right|_{\alpha m = \alpha r = \alpha^*} = \frac{\hat{S}_f}{N} \left( D_E^{(m)''} + D_I^{(m)''} \right);
\]

\[
B = \left. \frac{\partial^2 R_m}{\partial \alpha r \partial \alpha m} \right|_{\alpha m = \alpha r = \alpha^*} = \left( \frac{\hat{S}_f}{N} \right) \left( D_E^{(m)'} + D_I^{(m)'} \right);
\]

\(B = 0\) always holds in the present framework, so the type of evolutionary singularity of the virulence evolution of SARS-CoV-2 is totally determined by \(A\): If \(A < 0\), it is a CSS; otherwise, it is a repeller. It is impossible for the evolutionary singularity to be a branch point, which implies that the evolutionary bifurcation cannot occur with assumptions in the present model.

Combining Sections 2.1 and 2.2, one can find that the basic reproduction number \(R_0\) and invasion reproduction number \(R_m\) are both obtained by the next generation matrix method and have the similar forms, but they are essentially different. \(R_0\), derived from Equation 1, is an important indicator for judging the existence of COVID-19 in a virus-free environment in epidemiological dynamics. However, it is not a necessary and sufficient indicator in evolutionary dynamics where \(R_m\) obtained from Equation 4 together with its second derivative contributes to judge whether the new mutant virus can invade the current system and can exist for a long time. Evolution results from the competition between different types of viruses (i.e., the resident virus and the mutant it produces), but there is no competition among viruses in a virus-free environment, which emphasizes that a precise distinction between epidemiological basic reproduction number and invasion fitness is a prerequisite for any discussion of the adaptive evolution of virus.\(^{31}\)

### 2.3 Range of numerical values of related parameters and coefficients

The epidemiological parameters like contact rate, quarantine observation days, incubation period, infection rate, and infection period used in the present model were collected from relevant studies (Table 2). Among them, transmission-related parameters are closely related to the severity of the disease and can be represented by saturation functions of the virulence of the virus (Equation 3). Since there is not enough experimental support for the selection of coefficients in trade-offs shown in Equation 3, we determined part of those coefficients by data fitting with Wuhan’s early infection. Based on these determined coefficients (Table 3) and the value range of transmission-related parameters (Table 2), we could then obtain the range of other coefficients (Table 3).

| Parameter | Value (per day) and source | Value used in the present model (per day) |
|-----------|---------------------------|------------------------------------------|
| \(b\)     | \(3.85\) \(\times\) 10\(^{-5}\) | 3.85                                     |
| \(d\)     | \(3.5 \times 10^{-5}\) | 3.5 \(\times\) 10\(^{-5}\)               |
| \(c\)     | (2, 18) \(^{40-43}\)    | (1, 30)                                  |
| \(\theta\) | 1/14 \(^{40,44}\)       | 0.07                                     |
| \(\mu\)   | (1/5, 1/7) \(^{17,40,41,45}\) | 0.14                                     |
| \(q\)     | \(*\)                    | (0, 1)                                   |
| \(h\)     | \(*\)                    | (0, 1)                                   |
| \(\beta\) | (0.004, 0.13) \(^{8,40,41,46,47}\) | (0.003, 0.2)                             |
| \(\gamma\) | (1/40, 1/3.6) \(^{40,45,46,49}\) | (0.01, 0.4)                              |

Note: * is the estimated value.
In Table 2, the data of Wuhan was selected as an example to obtain the birth rate. The population of Wuhan is 11.081 million, and per capita mortality is $3 \times 10^{-5}$, which were selected as $N_0 = 1.1 \times 10^7$, $d = 3.5 \times 10^{-5}$ in the model. And the population birth rate $b$ herein was obtained by $b = N_0 d = 385$ per day. The release rate of quarantined susceptible was equal to the inverse of the quarantine observation days. And the same treatment was used for the transition rate of asymptomatic to symptomatic patients and recovery rate. Besides, the quarantine rate and hospitalization rate were considered to vary between (0, 1).

In Section 2.2, the commonly adopted “virulence-transmission” trade-off (Equation 3) was used to construct the relations between the micro level and the macro level. The coefficient $c_0$ in $c$ is the number of contacts without infection, and $c_\kappa$ measures how quickly the contact rate changes with virulence, which is related to the degree of public vigilance. We chose $c_0 = 30$, which could cover the maximum contact rate in Table 2. The coefficient $c_\kappa (c_\beta)$ in $\beta_\ell (\beta_\beta)$ measures the regulation of infection rate by the physical condition of the public, and $1/\kappa_\beta (1/\kappa_\beta)$ represents the rate of change of infection rate in the early stage of infection, which are related to the virus only so there is no difference between $\kappa_\beta$ and $\kappa_\beta$ (i.e., $\kappa_\beta = \kappa_\beta = \kappa_\beta$). $1/\kappa_\gamma (1/\kappa_\gamma)$ in $\gamma_\tau (\gamma_\tau)$ corresponds to the recovery rate of individuals without infection, which has no difference between the quarantined and free infected so $\kappa_\gamma = \kappa_\gamma = \kappa_\gamma$, and the coefficient $c_\gamma (c_\gamma)$ can be regarded as the regulation of recovery rate by medicine. We summarized the research on Wuhan’s infection$^{33–39}$ to determine the coefficients associated with $\beta_\ell$ and $\gamma_\tau$ by data fitting and obtained that $c_\beta = 13.68$, $\kappa_\beta = 0.218$, $\kappa_\gamma = 1.36$, $c_\gamma = 1049$.

### 3 RESULTS AND DISCUSSIONS

Now we are going to study the effects of NPIs and the physical condition of the public on the virulence evolution of SARS-CoV-2 and the epidemics of COVID-19. The NPIs mentioned above can be represented by contact rate-related parameter $c_\kappa$, quarantine rate $q$, and hospitalization rate $h$ in the present framework. And the differences in infection rates and recovery rates due to the physical condition of the public are reflected by $c_\kappa$, $c_\beta$, and $\kappa_\gamma$, respectively. $c_0$, $\kappa_\beta$, and $c_\gamma$ are regarded as invariants in the following analyses since they are independent of NPIs and the physical condition of the public. Here, we adopted $c_0 = 30$, $\kappa_\beta = 0.218$, and $c_\gamma = 1049$ according to Wuhan’s infection. According to the analyses in Section 2.3 and Equation 3, we can obtain the range of numerical values of other parameters associated with $c$, $\beta_\ell$, and $\gamma_\tau$.

$$c_\kappa \in [0.56, 3.39]; \ c_\beta \in [4.97, 294.32]; \ \kappa_\gamma \in [0.33, 2.19]$$

(9)

The virulence $\alpha$ was thought to vary from $1 \times 10^{-4}$ to 1. And the range of $c_\kappa$, $c_\beta$, and $\kappa_\gamma$ in Equation 9 was further expanded to $[0.1, 3.5]$, $[1, 350]$, and $[0.1, 18]$, respectively, to study the effects of different factors on the virulence evolution of SARS-CoV-2 on a large scale. With this parameter setting in Table 3, one can only obtain one evolutionary singularity, which is always a CSS, for the virulence evolution of SARS-CoV-2.

In this section, both the virulence and the case fatality rate (CFR) associated with the death of COVID-19 were investigated in our study. The former emphasizes the probability of a patient dying of the infection of COVID-19 per unit time. And the latter represents the ratio of the death due to infection to the total number of the infected during the period of infection, which is more intuitive to reflect the overall impact of the disease just like the prevalence of the disease. The CFR or the prevalence obtained in the present adaptive dynamics framework when the infection reaches equilibrium is used to predict the final evolutionary scenario regardless of the intermediate process. Here, we assumed

| Coefficients | Default value and source | Coefficients | Value range |
|--------------|--------------------------|--------------|-------------|
| $c_0$        | 30                       | $c_\kappa$   | $[0.1, 3.5]$ |
| $\kappa_\beta$ | 0.218$^{33–39}$        | $c_\beta$    | $[1, 350]$  |
| $c_\gamma$  | 1049$^{33–39}$         | $\kappa_\gamma$ | $[0.1, 18]$ |
that the infection lasts long enough to reach equilibrium. Under this assumption, the CFR can be expressed as a function of state variables at the endemic equilibrium:

\[
\text{CFR} = \frac{\alpha^* (I_f + I_q)}{\mu (E_f + E_q)} = \frac{\alpha^* (I_f + I_q)}{(\gamma_f + d + \alpha^*) I_f + (\gamma_q + d + \alpha^*) I_q}
\]  

(10)

Similarly, the prevalence of the disease can also be expressed as a function of state variables at the endemic equilibrium:

\[
\text{prevalence} = 1 - \frac{S_f + S_q}{N}
\]  

(11)

### 3.1 The effects of NPIs on virulence evolution of SARS-CoV-2 and epidemics of COVID-19

The effects of the factors related to NPIs on the virulence evolution of SARS-CoV-2 are investigated in Figure 2. The contact rate-related parameter \(c_c\) reflects the degree of public vigilance to the epidemics. A larger \(c_c\) represents more likely for people to wear masks or keep social distance. If the public socialize as usual, there is no restriction on the spread of COVID-19, and the selection for high virulence supporting high transmissibility would make COVID-19 spread among people to the greatest extent. While, if the public is vigilant to the epidemics, it was more likely to select low virulence to ensure COVID-19 progresses slowly with mild symptoms to increase its sphere of transmission before people are aware of being infected (Figure 2A). Both quarantine rate \(q\) and hospitalization rate \(h\) directly control the number of free patients during the spread of COVID-19 and thus have the similar impact on the virulence evolution of SARS-CoV-2. Strengthening quarantine measures and increasing hospitalization rate weaken the role of symptomatic patients and enhance the relative role of asymptomatic incubation patients (see Equation 6). Therefore, increased virulence of SARS-CoV-2 was more favorable to improve its transmissibility in asymptomatic incubation patients (Figure 2B,C). Furthermore, the impact of simultaneous changes in contact rate and hospitalization rate on the virulence evolution of SARS-CoV-2 is investigated in Figure 2D. Within the range of available values, similar variation tendencies of the virulence of SARS-CoV-2 could still be captured. And compared with the situation of high public vigilance, the virulence was more sensitive to hospitalization rate when public vigilance is low given that SARS-CoV-2 does not need further adaptation to unrestricted transmission at this time (the change range of virulence at evolutionary equilibrium induced by hospitalization rate was [0.0198, 0.0275] when \(c_c = 3.5\) but was [0.0219, 0.0914] when \(c_c = 0.3\)).

There are two main transmission routes of COVID-19 all over the world: the cluster of cases and the community transmission (Table 4). The prevalence and CFR of COVID-19 in these continents can be roughly obtained by dividing the confirmed cases by the population size of each continent and dividing the deaths by the confirmed cases (Table 4), respectively. The differences in transmission routes in three continents seem to account for the different epidemic situations of COVID-19 in these areas. The contact rate-related parameter \(c_c\) in the present model can be used to reflect the differences in transmission routes: (1) A small \(c_c\) represents community transmission (i.e., America); (2) a large \(c_c\) represents cluster of cases (i.e., Asia); and (3) the value between the above two values represents the coexistence of two transmission routes (i.e., Europe). The effect of the contact rate-related parameter \(c_c\) on the epidemic situation is investigated in Figure 3A. The change of the prevalence with \(c_c\) was consistent with the actual situation of the three continents. However, the trend of the CFR was inconsistent with that in Table 4, where the CFR is larger than the other two cases when both of the two transmission routes coexist. This may result from the high level of aging of the population in Europe, which will be illustrated in Section 3.2 later. In addition, it should be noted that we collected the epidemic data of these regions from WHO as of September 30, 2020, when the infection had just spread all over the world for months and the prevention and control measures of various countries were relatively simplistic and the infection dynamics of COVID-19 can be supposed to be relatively stable.

Besides the transmission routes, the prevention and control measures involving quarantine measures (\(q\)) and hospitalization (\(h\)) also vary in countries. The epidemic situations of some countries in Asia (India, the Republic of Korea, and China) are shown in Table 5. And the impact of quarantine measures on the epidemic situation of COVID-19 is demonstrated in Figure 3B. The prevalence decreased, and the CFR slightly increased with the increase of quarantine
The variation trends of them with quarantine measures were consistent with the epidemic situations in India, the Republic of Korea, and China, which have the same transmission route, but the intensity of prevention and control measures increases gradually. The impact of hospitalization rate $h$ on the epidemic situation of COVID-19 was similar to that of quarantine rate $q$ (Figure 3C) due to the similar effects of them on transmission of COVID-19.

Results shown in Figures 2 and 3 reveal that the enhancement of NPIs, such as wearing masks or keeping social distance, strengthening quarantine measures, and increasing hospitalization rate, would reduce the prevalence of COVID-19.
However, the effects of these measures on the virulence of SARS-CoV-2 and the CFR of COVID-19 were inconsistent. It should be noted that the CFR of the disease is positively correlated with the virulence of the virus. Decreasing contact rate via wearing masks or keeping social distance was beneficial to the evolution of SARS-CoV-2 to low virulence and therefore reduced the CFR of COVID-19. From the present analyses, decreasing contact rate of the disease could fundamentally curb the spread of COVID-19, reduce the risk of death due to infection, and achieve the regulation of the virulence of SARS-CoV-2. Therefore, one can conclude that controlling the contact rate was the key to control not only the epidemic scale of COVID-19 but also the extent of its harm. Strengthening quarantine measures and increasing hospitalization rate would bring an increase in the virulence of SARS-CoV-2 and a slight increase in the CFR of COVID-19. Considering that the slight increase in the CFR of COVID-19 can be made up by improving medical conditions, we would also recommend these two measures since they could reduce the epidemic scale of COVID-19 effectively.

![Figure 3](wileyonlinelibrary.com)

**Figure 3** The effects of the factors related to NPIs on the prevalence (the line in black) and CFR (dotted line in red) of COVID-19: (A) contact rate-related parameter $c_\kappa$; (B) quarantine rate $q$; and (C) hospitalization rate $h$. Parameters in (A) are the same as those in Figure 2A; (B) $c = 30e^{-2a}$, $h = 0.9, \beta_I = \alpha/(40\alpha + 0.218), \beta_E = \alpha/(200\alpha + 0.218), \gamma_{Ie} = 1/(5245\alpha + 10), \gamma_{Iq} = 1/(1049\alpha + 10)$; (C) $q = 0.9$, and others are the same as those in (B) [Colour figure can be viewed at wileyonlinelibrary.com]

**Table 5** Epidemic situations in India, the Republic of Korea, and China as of September 30, 2020

| Country            | Confirmed cases | Deaths | Population size | Prevalence | CFR   |
|--------------------|-----------------|--------|----------------|------------|-------|
| India              | 6,225,763       | 97,497 | 1,378,100,000  | 0.452%     | 1.57% |
| Republic of Korea  | 23,812          | 413    | 51,781,000     | 0.0460%    | 1.73% |
| China              | 91,041          | 4,746  | 1,400,050,000  | 0.00650%   | 5.21% |
3.2 The effects of the physical condition of the public on virulence evolution of SARS-CoV-2 and epidemics of COVID-19

Next, the effect of the physical condition of the public on the virulence evolution of SARS-CoV-2 was studied. The coefficients associated with infection and recovery rates have been determined in Section 2.3 and the beginning part of Section 3 except $c_{\beta I}$ and $c_{\gamma q}$, which are different from $c_{\beta}$ and $c_{\gamma}$ to reflect the difference between $\beta_E$ and $\beta_I$ and $\gamma_I q$ and $\gamma_I$, respectively. Such difference can be represented by the relative infection rate $c_{\beta E} / c_{\beta}$ and relative recovery rate $c_{\gamma q} / c_{\gamma}$ regulated by the physical condition of the public and medicine, respectively.

In Figure 4A, the effect of $c_{\beta I}$ and $\kappa y$ on virulence evolution of SARS-CoV-2 is investigated with $c_{\beta E} / c_{\beta} = 5$ and $c_{\gamma q} / c_{\gamma} = 5$. The related parameters of infection and recovery rates, $c_{\beta I}$ and $\kappa y$, reflect the susceptibility of the public and the recovery speed of the patients, respectively. In short, the public with good physical condition holds low susceptibility (large $c_{\beta}$) and fast recovery speed (small $\kappa y$). Low susceptibility makes the public unlikely to be infected, which would lead to low virulence of SARS-CoV-2 that causes mild symptoms of COVID-19 to increase its sphere of transmission before people are aware of being infected. However, fast recovery speed shortens the infection period of the symptomatic patients and thus weakens its role in infection making high virulent SARS-CoV-2 be selected to improve its transmissibility in asymptomatic incubation patients. Within the range of available values, the variation trends of the

![Graph showing the effects of factors related to the physical condition of the public on the virulence evolution of SARS-CoV-2.](wileyonlinelibrary.com)
virulence of SARS-CoV-2 with susceptibility and recovery speed imply that the good physical condition could bring opposite effects on the virulence evolution of SARS-CoV-2.

The effects of susceptibility and recovery speed on virulence evolution of SARS-CoV-2 with different relative infection rate $c_{\beta_E}$ and relative recovery rate $c_{\gamma_{I_{FI}}}$ are discussed in Figure 4B,C, respectively. It can be revealed that the relative infection and recovery rates would not qualitatively influence the virulence evolution of SARS-CoV-2 induced by susceptibility and recovery speed.

As mentioned in Section 3.1, the aging of the population may affect the epidemic situation of COVID-19. Table 6 shows the different epidemic situations of some countries in Europe (Norway, Germany, and Italy), with similar degrees of NPIs but ascending levels of aging of the population. The differences in epidemic situations due to the aging of the population can be indicated by the impact of recovery rate on the prevalence and CFR of COVID-19, that is, a high level of aging of the population holds a low recovery rate (large $\kappa_r$). As shown in Figure 5A, both the prevalence and CFR of COVID-19 increased with the decrease of recovery rate. It was consistent with the situations in Norway, Germany, and Italy. The impact of susceptibility measured by $c_{\beta_E}$ on the epidemic situation is investigated in Figure 5B, where low susceptibility of the public led to the reduction of the prevalence as well as the CFR.

From Figures 4 and 5, one can conclude that enhancing the physical condition of the public by decreasing the susceptibility and increasing the recovery speed could both help to contain the spread of COVID-19, thereby reducing its epidemic scale. Decreasing the susceptibility would promote the evolution of SARS-CoV-2 to low virulence, thus decreasing the CFR of COVID-19. On the other hand, increasing the recovery speed could lead to high virulence of SARS-CoV-2 but low CFR of COVID-19, because the high recovery capacity of the patients contributes to reducing the harm to them. Danchin and Turinici also concluded that the recovery component plays an important role in controlling the epidemic burden of COVID-19 (i.e., the number of deaths).

Here, we first built a transmission dynamic model of COVID-19 that divides the total population into four components (i.e., the susceptible, exposed, symptomatic, and recovered), and all of them consist of free and quarantined parts except the recovered. Such treatment is generally used when measuring the short-term effect of NPIs on the epidemics of COVID-19. Based on the transmission dynamics, we then constructed an invasion dynamic model to further

| Table 6 | Epidemic situations in Norway, Germany, and Italy as of September 30, 2020 |
|---------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|         | Confirmed cases$^{52}$ | Deaths$^{52}$ | Population size$^{53}$ | Prevalence | CFR         |
| Norway  | 13,788                     | 274                        | 5,367,600                  | 0.257%   | 1.99%       |
| Germany | 289,219                    | 9,488                      | 83,149,000                 | 0.348%   | 3.28%       |
| Italy   | 313,011                    | 35,875                     | 60,015,000                 | 0.522%   | 11.5%       |

**Figure 5** The effects of the factors related to the physical condition of the public on the prevalence (solid line in black) and CFR (dotted line in red) of COVID-19: (A) recovery rate-related parameter $\kappa_r$; (B) infection rate-related parameter $c_{\beta_E}$. Parameters in (A) $\beta_I = \alpha/(250\alpha + 0.218), \beta_E = \alpha/(1250\alpha + 0.218)$, and other parameters are the same as those in Figure 4A; (B) $\gamma_{I_{FI}} = 1/(5245\alpha + 10), \gamma_{I_{Iq}} = 1/(1049\alpha + 10)$, and other parameters are the same as those in Figure 4A [Colour figure can be viewed at wileyonlinelibrary.com]
study virulence evolution of SARS-CoV-2. The present research on virulence evolution of SARS-CoV-2 is still limited,\textsuperscript{19,20} but both of them indicate that the virulence is undergoing adaptive evolution. In a stage-structured model, virulence will select for decreased virulence under the effective control of social distance.\textsuperscript{19} And in the model where transmissibility results from the interaction between respiratory tract compartments, vaccination will lead to the increase of virulence but reduction of the scale of infection.\textsuperscript{20} The evolutionary outcomes induced by the two factors are similar to that of decreasing contact rate and increasing recovery rate in this paper, respectively, which indicates that our results have a certain credibility, even if a different method is used.

From the present analyses, one can figure out that the trends of the prevalence and CFR shown herein were qualitatively consistent with the actual epidemic situations. This qualitative agreement reveals that adopting the present adaptive dynamics framework to predict the epidemics of COVID-19 was reasonable. And the best situation for epidemic prevention and control for reducing both the prevalence and CFR could be achieved by decreasing the contact rate and enhancing the physical condition of the public.

3.3 Discussion on the simplification in the model

Two important assumptions were made to simplify the present mathematical model and analyses. One is that the asymptomatic patients were not explicitly involved but was considered as a part of the exposed components acting as the asymptomatic incubation patients together with incubation patients, both of which are infectious. To confirm the rationality of this assumption, the asymptomatic patients were explicitly involved in the model (see Appendix C for more details). In this case, the invasion reproduction number $R_m^A$, which is a decisive indicator of evolutionary results, can be rewritten from Equation C3 in Appendix C as follows:

\[
R_m^A = \frac{\hat{S}_f}{N} \left( D_{EA}^{(m)} + D_{IA}^{(m)} \right) (12)
\]

where

\[
D_{EA}^{(m)} = \frac{\beta_{E}^{(m)} c_{E}^{(m)} [1 + (1 - \phi) \mu / (d + \gamma_A)]}{\mu + d},
\]

\[
D_{IA}^{(m)} = \frac{\phi \beta_{I}^{(m)} c_{I}^{(m)} \mu (1 - q)(1 - h)}{(\mu + d) \left( \gamma_I^{(m)} + d + \alpha_m \right)} (13)
\]

where $\phi$, the percentage of symptomatic patients in the exposed components, and $\gamma_A$, the recovery rate of the asymptomatic patients, are constants. Comparing Equations 12 and 13 with the invasion reproduction number $R_m^L$ in the previous analyses (Equation 5 and 6), one can find that the differences are constant multipliers only, which would not change the variation tendency of the evolutionary scenario of SARS-CoV-2.

The other assumption is that the recovered patients were no longer susceptible once recovered. The situation considering the loss of immunity of the recovered was also discussed (see Appendix D for more details). In this case, the invasion reproduction number $R_m^L$ was the same as that in the previous analyses, that is,

\[
R_m^L = R_m^A = \frac{\hat{S}_f}{N} \left( D_{E}^{(m)} + D_{I}^{(m)} \right) (14)
\]

In fact, the loss of immunity affected the transmission dynamics of COVID-19 only but did not affect the evolutionary dynamics of SARS-CoV-2 (see Equation D1 in Appendix D); therefore, it would not change the final evolutionary scenario.

4 CONCLUSIONS AND OUTLOOKS

The effects of the factors related to NPIs and the physical condition of the public on the virulence evolution of SARS-CoV-2 and the epidemics of COVID-19 were investigated on the basis of adaptive dynamics framework. The qualitative agreement of the prediction on the epidemics with the actual epidemic situations of COVID-19 in some countries and regions convinced the rationality of the present model.

From the analyses based on the above framework, we figure out the severity of infection to individuals, the overall harm of COVID-19, and its epidemic scale all decreased with the increase of public vigilance to the epidemics. The
enhancement of other two factors related to NPIs, such as strengthening quarantine measures and increasing hospitalization rate, increased the probability of dying of infection and slightly increased the overall harm of COVID-19 but decreased the number of the infected greatly. Therefore, these two measures were also recommended and that slight increase in the overall harm of COVID-19 can be made up by improving medical conditions. On the other hand, the public could also significantly regulate the virulence of SARS-CoV-2 and the epidemic situation of COVID-19 by enhancing their physical condition such as decreasing the susceptibility and increasing the recovery speed. Decreasing the susceptibility would bring the same trend of the epidemics of COVID-19 and evolutionary scenario of SARS-CoV-2 as increasing the public vigilance. The effect of increasing the recovery speed was similar to that of strengthening quarantine measures and increasing hospitalization rate, except that the high recovery rate supported more severity of infection to individuals but less overall harm of the diseases. In summary, the best intervention to reduce both the epidemic scale of COVID-19 and its overall harm to patients was increasing the public vigilance to the epidemics and enhancing the physical condition of the public.

This is the first attempt to predict the virulence evolution of SARS-CoV-2 under different interventions, where the connection between the micro and macro level was constructed through “virulence-transmission” trade-off hypothesis. The implications of all the coefficients involved in the trade-offs have been explained from a biological point of view. Fitting data in the early stage of infection under given trade-offs can determine the range of coefficients involved in the study and make the study in line with the actual situation and convincing. Moreover, if the infection dynamics of SARS-CoV-2 within the individuals can be further involved in the present framework instead of “virulence-transmission” trade-off hypothesis, a more accurate prediction on the real-time changes of the virus virulence and the evolutionary scenarios caused by the mutations under such embedded model will be offered. Meanwhile, the micro-level study on the heterogeneity in host immunity to SARS-CoV-2 as well as the possible multiple infections and limited cross-immunity of the virus might bring the evolutionary diversity of SARS-CoV-2.

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CONFLICT OF INTEREST
We declare we have no conflict of interest.

AUTHOR CONTRIBUTIONS
Mengyue Wang: Formal analysis; investigation; methodology; software. Jiabiao Yi: Investigation; methodology; software. Wen Jiang: Conceptualization; funding acquisition; methodology; supervision.

ORCID
Wen Jiang © https://orcid.org/0000-0001-6393-2575

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APPENDIX A: THE ENDEMIC EQUILIBRIUM $W_+$ AND THE BASIC REPRODUCTION NUMBER OF SARS-CoV-2

The endemic equilibrium $W_+ = (\hat{S}_f, \hat{S}_q, \hat{E}_f, \hat{E}_q, \hat{I}_f, \hat{I}_q, \hat{R})$ of Equation 1 can be obtained as follows:

\[
\begin{align*}
\hat{E}_q & = \frac{b[C_1 \psi_1(\mu + d)/C_0] + C_1 \psi_2}{d(M_1 - M_2)}; \\
\hat{I}_q &= \frac{\mu(\hat{E}_q + \hat{I}_q)}{\gamma_q + \alpha}; \\
\hat{I}_f &= \frac{\hat{E}_f}{\psi_1 q}; \\
\hat{R} &= \frac{\gamma_q \hat{I}_q + \gamma_f \hat{I}_f}{d}; \\
\hat{S}_q &= \psi_2 \frac{d(\mu + d)}{\beta_f} \hat{E}_q; \\
\hat{S}_f &= \frac{b}{d} \left(1 + \frac{M_2}{M_1 - M_2}\right)
\end{align*}
\]  

(A1)
where

\[
M_1 = \psi_1 \left( \frac{\mu + d}{\beta_1 c} \right) \left[ \psi_5 (\psi_3 h + 1) + \frac{\psi_5}{\psi_4 q} \left( 1 + \frac{\gamma_1}{d} \right) + 1 + \psi_5 \frac{d(\mu + d)}{\beta_1} \right]
\]

\[
M_2 = m_{21} m_{22} = \left[ \psi_5 - \psi_1 \left( \frac{\mu + d}{\beta_1 c} \right) \right] \left\{ \frac{\mu + d}{\beta_1} \left[ \frac{-qd(1 - \beta_1) - (\theta + d)\beta_1}{\theta} - \psi_1 \beta_E \right] \right\}
\]

(A2)

the expressions of \( \psi_1, \psi_2, \psi_3, \psi_4, \) and \( \psi_5 \) are

\[
\psi_1 = \frac{\gamma_1}{\mu q(1 - h)}; \quad \psi_2 = 1 - \frac{\beta_1}{d(\theta + d)}; \quad \psi_3 = \frac{q - q\beta_1 + \beta_1}{qd};
\]

\[
\psi_4 = \frac{\mu (\gamma_4 + d)}{d(\gamma_4 + d + \alpha)}; \quad \psi_5 = \psi_1 \frac{\beta_E}{\beta_1} + \frac{1 - q}{q};
\]

(A3)

According to van den Driessche and Watmough, the basic reproduction number \( R_0 \) is the spectral radius of the next-generation matrix. The next-generation matrix in the early stage of infection, \( F(V)^{-1} \), can be obtained by rewriting the third to sixth equation of Equation 1 as:

\[
\begin{pmatrix}
\frac{dE_f}{dt} \\
\frac{dE_q}{dt} \\
\frac{dI_f}{dt} \\
\frac{dI_q}{dt}
\end{pmatrix} = \begin{pmatrix}
\beta_E c S_f N E_f + (1 - q)\beta_1 c S_f N I_f \\
q\beta_1 c S_f N I_f \\
0 \\
0
\end{pmatrix} - \begin{pmatrix}
\mu + d)E_f \\
(\mu + d)E_q \\
(\gamma_1 + d + \alpha)I_f - (1 - h)\mu E_f \\
(\gamma_1 + d + \alpha)I_q - h\mu E_f - \mu E_q
\end{pmatrix}
\]

\[
= f(x) - v(x)
\]

(A4)

where \( x = (x_1, x_2, x_3, x_4) = (E_f, E_q, I_f, I_q) \). We compute

\[
F = \frac{\partial f(x)}{\partial x_k} \bigg|_{k=1, \ldots, 4} = \begin{pmatrix}
\beta_E c & 0 & (1 - q)\beta_1 c & 0 \\
0 & 0 & q\beta_1 c & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\]

(A5)

and

\[
(V)^{-1} = \left( \frac{\partial v(x)}{\partial x_k} \bigg|_{k=1, \ldots, 4} \right)^{-1}
\]

\[
= \begin{pmatrix}
\frac{1}{\mu + d} & 0 & 0 & 0 \\
0 & \frac{1}{\mu + d} & 0 & 0 \\
\frac{(1 - h)\mu}{(\mu + d)(\gamma_1 + d + \alpha)} & 0 & \frac{1}{\gamma_1 + d + \alpha} & 0 \\
\frac{h\mu}{(\mu + d)(\gamma_1 + d + \alpha)} & \frac{\mu}{(\mu + d)(\gamma_1 + d + \alpha)} & 0 & \frac{1}{\gamma_1 + d + \alpha}
\end{pmatrix}
\]

(A6)
The next-generation matrix is

\[
F(V)^{-1} = \frac{S_f}{N} \begin{bmatrix}
\frac{\beta_E c}{\mu + d} + \frac{\beta_I c \mu (1-q)(1-h)}{(\mu + d)(\gamma_I + d + \alpha)} & 0 & \frac{\beta_I c (1-q)}{\gamma_I + d + \alpha} \\
\frac{\beta_I c q(1-h)}{(\mu + d)(\gamma_I + d + \alpha)} & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}.
\]  (A7)

And in the early stage of infection, \( S_f = N = b/d \); therefore, the characteristic polynomial of \( F(V)^{-1} \) can be written as follows:

\[
J(\lambda) = (-\lambda)^3 \left( \frac{\beta_E c}{\mu + d} + \frac{\beta_I c \mu (1-q)(1-h)}{(\mu + d)(\gamma_I + d + \alpha)} - \lambda \right).
\]  (A8)

Thus, the basic reproduction number \( R_0 \) is

\[
R_0 = \frac{\beta_E c}{\mu + d} + \frac{\beta_I c \mu (1-q)(1-h)}{(\mu + d)(\gamma_I + d + \alpha)}
\]  (A9)

**APPENDIX B: THE INVASION REPRODUCTION NUMBER OF SARS-CoV-2**

Similar to the derivation of the basic reproduction number, the invasion reproduction number \( R^m \) can also be derived from the next-generation matrix of the invasion system \( F^m(V^m)^{-1} \), which can be obtained from Equation 4.

\[
F^m(V^m)^{-1} = \frac{S_f}{N} \begin{bmatrix}
\frac{\beta_E^{(m)} c^{(m)}}{\mu + d} + \frac{\beta_I^{(m)} c^{(m)} \mu (1-q)(1-h)}{(\mu + d)(\gamma_I^{(m)} + d + \alpha_m)} & 0 & \frac{\beta_I^{(m)} c^{(m)} (1-q)}{\gamma_I^{(m)} + d + \alpha_m} \\
\frac{\beta_I^{(m)} c^{(m)} q(1-h)}{(\mu + d)(\gamma_I^{(m)} + d + \alpha_m)} & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}.
\]  (B1)

Then the characteristic polynomial of the next-generation matrix \( J^m(\lambda) \) can be derived:

\[
J^m(\lambda) = (-\lambda)^3 \left( \frac{S_f}{N} \left( \frac{\beta_E^{(m)} c^{(m)}}{\mu + d} + \frac{\beta_I^{(m)} c^{(m)} \mu (1-q)(1-h)}{(\mu + d)(\gamma_I^{(m)} + d + \alpha_m)} - \lambda \right) \right)
\]  (B2)

And the invasion reproduction number \( R^m \) is

\[
R^m = \frac{S_f}{N} \left( D^{(m)}_E + D^{(m)}_I \right); \quad D^{(m)}_E = \frac{\beta_E^{(m)} c^{(m)}}{\mu + d}; \quad D^{(m)}_I = \frac{\beta_I^{(m)} c^{(m)} \mu (1-q)(1-h)}{(\mu + d)(\gamma_I^{(m)} + d + \alpha_m)}
\]  (B3)
APPENDIX C: TRANSMISSION AND EVOLUTIONARY DYNAMICS WHEN CONSIDERING THE ASYMPTOMATIC PATIENTS

The transmission diagram of COVID-19 explicitly considering asymptomatic patients and the loss of immunity of the recovered was depicted in Figure C1.

The orange parts in Figure C1 represent the case of considering the asymptomatic patients, where the exposed components can turn into symptomatic and asymptomatic patients after the incubation period. Similar to the symptomatic patients, the asymptomatic patients also consist of both the free (Af) and quarantined (Aq) individuals, which have the same infection rate as the incubation patients. \( \varphi \) represents the percentage of symptomatic patients in exposed components, and \( \gamma_A \) is the recovery rate of the asymptomatic patients, both of which are constants and irrelevant to virulence. Now the transmission dynamics of COVID-19 can be described by Equation C1, where the differential equations of the components which are the same as in Equation 1 are omitted for brevity.

\[
\begin{align*}
    \frac{dS_f}{dt} &= b + \theta S_q - \beta_e\frac{S_f}{N}(E_f + A_f) - (q - q\beta_i + \beta_i)c\frac{S_f}{N}I_f - dS_f \\
    \frac{dE_f}{dt} &= \beta_e\frac{S_f}{N}(E_f + A_f) + (1-q)\beta_i\frac{S_f}{N}I_f - (\mu + d)E_f \\
    \frac{dI_f}{dt} &= \varphi(1-h)\mu E_f - \left(\gamma_{I_f} + d + \alpha\right)I_f \\
    \frac{dI_q}{dt} &= \varphi \mu E_f + \varphi \mu E_q - \left(\gamma_{I_q} + d + \alpha\right)I_q \\
    \frac{dA_f}{dt} &= (1-\varphi)\mu E_f - (d + \gamma_A)A_f \\
    \frac{dA_q}{dt} &= (1-\varphi)\mu E_q - (d + \gamma_A)A_q \\
    \frac{dR}{dt} &= \gamma_{I_q}I_q + \gamma_{I_f}I_f + \gamma_A A_f + \gamma_A A_q - dR
\end{align*}
\]

\[\text{(C1)}\]

**Figure C1** Transmission diagram of COVID-19 when considering the asymptomatic patients (orange parts) and the loss of immunity (magenta parts) [Colour figure can be viewed at wileyonlinelibrary.com]
Then the invasion dynamics of mutant SARS-CoV-2 can be depicted by

\[
\begin{align*}
\frac{dE^{(m)}}{dt} &= \beta^{(m)} E^{(m)} I^{(m)} + (1 - q)\beta^{(m)} I^{(m)} - (\mu + d)E^{(m)} \\
\frac{dE^{(m)}}{dt} &= q\beta^{(m)} E^{(m)} I^{(m)} - (\mu + d)E^{(m)} \\
\frac{dI^{(m)}}{dt} &= \phi(1 - h)\mu E^{(m)} - \left(\gamma^{(m)} + d + \alpha_m\right)I^{(m)} \\
\frac{dI^{(m)}}{dt} &= \phi h \mu E^{(m)} + \phi \mu I^{(m)} - \left(\gamma^{(m)} + d + \alpha_m\right)I^{(m)} \\
\frac{dA^{(m)}}{dt} &= (1 - \varphi)\mu E^{(m)} - (d + \gamma_A)A^{(m)} \\
\frac{dA^{(m)}}{dt} &= (1 - \varphi)\mu E^{(m)} - (d + \gamma_A)A^{(m)}
\end{align*}
\]

From Equation C2 and the method shown in Appendix B, the invasion reproduction number, \(R^m_A\), can be obtained:

\[
R^m_A = \frac{\hat{S}_f}{N} \left( \frac{\beta^{(m)} E^{(m)} + \phi \beta^{(m)} I^{(m)} \mu (1 - q)(1 - h)}{(\mu + d)(\gamma^{(m)} + d + \alpha_m)} + \frac{\beta^{(m)} I^{(m)} (1 - \varphi)\mu}{(d + \gamma_A)(\mu + d)} \right)
\]

**APPENDIX D: TRANSMISSION AND EVOLUTIONARY DYNAMICS WHEN CONSIDERING THE LOSS OF IMMUNITY**

The consideration of the loss of immunity is represented by magenta parts in Figure C1, where the recovered can become susceptible again with probability \(\rho\). Now the transmission dynamics of the free susceptible and recovered are changed to Equation D1, while those of other components are the same as in Equation 1.

\[
\begin{align*}
\frac{dS_f}{dt} &= b + \theta S_q - \beta E c \frac{S_f}{N} E_f - (q - q\beta I_f + \beta f) c \frac{S_f}{N} I_f - dS_f + \rho R \\
\frac{dR}{dt} &= \gamma I_q + \gamma f I_f - (d + \rho)R
\end{align*}
\]

Therefore, the evolutionary dynamics of SARS-CoV-2 was the same as that in Section 2.2.