IMMUNE NETWORK

Original Article

Check for updates

*Correspondence to
Eui-Cheol Shin
Graduate School of Medical Science and Engineering, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Korea.
Email: ecshin@kaist.ac.kr

Jae Kyoung Kim
Department of Mathematical Sciences, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Korea.
Email: jaekkim@kaist.ac.kr

†Hyukpyo Hong and Ji Yun Noh contributed equally to this work.

ORCID iDs
Hyukpyo Hong
https://orcid.org/0000-0001-7419-8345
Ji Yun Noh
https://orcid.org/0000-0001-8541-5704
Hyojung Lee
https://orcid.org/0000-0001-9880-3044

Modeling Incorporating the Severity-Reducing Long-term Immunity: Higher Viral Transmission Paradoxically Reduces Severe COVID-19 During Endemic Transition

Hyukpyo Hong [1,2,†], **Ji Yun Noh** [3,4,†], **Hyojung Lee** [5], **Sunhwa Choi** [6], **Boseung Choi** [2,7], **Jae Kyoung Kim** [1,2,*], **Eui-Cheol Shin** [3,8,*]

[1]Department of Mathematical Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea
[2]Biomedical Mathematics Group, Institute for Basic Science (IBS), Daejeon 34126, Korea
[3]Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea
[4]Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul 02841, Korea
[5]Department of Statistics, Kyungpook National University, Daegu 41566, Korea
[6]Division of Fundamental Research on Public Agenda, National Institute for Mathematical Sciences, Daejeon 34047, Korea
[7]Division of Big Data Science, Korea University, Sejong 30019, Korea
[8]The Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon 34126, Korea

ABSTRACT

Natural infection with severe acute respiratory syndrome-coronavirus-2 or vaccination induces virus-specific immunity protecting hosts from infection and severe disease. While the infection-preventing immunity gradually declines, the severity-reducing immunity is relatively well preserved. Here, based on the different longevity of these distinct immunities, we develop a mathematical model to estimate courses of endemic transition of coronavirus disease 2019 (COVID-19). Our analysis demonstrates that high viral transmission unexpectedly reduces the rates of progression to severe COVID-19 during the course of endemic transition despite increased numbers of infection cases. Our study also shows that high viral transmission amongst populations with high vaccination coverages paradoxically accelerates the endemic transition of COVID-19 with reduced numbers of severe cases. These results provide critical insights for driving public health policies in the era of 'living with COVID-19.'

Keywords: COVID-19; SARS-CoV-2; Immunity; Severity; Endemic transition

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is ongoing, resulting in devastating impact on public health, economy, and society. To halt the current pandemic, COVID-19 vaccines have been rapidly developed at an unprecedented pace. These vaccines provide protective immunity against severe acute respiratory syndrome-coronavirus-2 (SARS-

Sunhwa Choi (iD)
https://orcid.org/0000-0002-6608-6981
Boseung Choi (iD)
https://orcid.org/0000-0001-7512-118X
Jae Kyoung Kim (iD)
https://orcid.org/0000-0001-7842-2172
Eui-Cheol Shin (iD)
https://orcid.org/0000-0002-6308-9503

Conflict of Interest

Abbreviations

COVID-19, coronavirus disease 2019; nAb, neutralizing Ab; NPIs, nonpharmaceutical interventions; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

Author Contributions

Data Availability Statement

CoV-2) to prevent infection and limit disease severity, which can also be achieved by natural infection. However, neutralizing Ab (nAb) titers decline after SARS-CoV-2 infection or vaccination in a pattern of initial rapid decay followed by a slower decrease [1,2], with the half-life of SARS-CoV-2-specific antibodies estimated to be 6–8 months [1,3]. In addition, SARS-CoV-2 variants exhibit reduced the neutralizing activities of nAb. For example, sera from COVID-19 convalescent patients and vaccine recipients showed reduced neutralizing activities against the Delta (B.1.617.2) and the Omicron (B.1.1.529) variants [4,5], which became a predominant SARS-CoV-2 strains worldwide. Consequentially, waning humoral immunity to SARS-CoV-2 and the spread of nAb-escaping viral strains (e.g., the Omicron variant) reduce vaccine effectiveness against infection and pose an increasing risk of breakthrough infection over time [6,7]. However, vaccine effectiveness against severe disease is relatively preserved, indicating that different immune components with different half-lives are responsible for preventing infection versus severe disease.

Natural infection or vaccination elicits not only nAbs but also virus-specific $CD4^+$ and $CD8^+$ memory T cells. nAbs can prevent infection and disease progression by interfering with viral entry to host cells. When hosts are infected, T cells produce effector cytokines and directly eliminate virus-infected cells, leading to rapid control of viral infection and reduction of disease severity. Compared with nAbs, SARS-CoV-2-specific memory T cells are maintained for a relatively long time [8]. Intriguingly, the persistence of memory T-cell responses to SARS-CoV-1 for 17 years has been demonstrated [9]. The long half-life of memory T cells explains the relatively preserved vaccine effectiveness against severe COVID-19 [10]. SARS-CoV-2-specific T cells can reduce disease severity in patients and animals with SARS-CoV-2 infection. Mice immunized with vaccines expressing T-cell epitopes exhibited reduced lung pathology and better survival when challenged with SARS-CoV-2, even in the absence of nAbs [11,12]. In addition, higher levels of $CD8^+$ T-cell immunity are associated with improved patient survival among patients with COVID-19 who have humoral immunodeficiency caused by anti-CD20 therapy [13]. These data indicate that T cells contribute to severity-reducing immunity against SARS-CoV-2, particularly when nAb activity is suboptimal and insufficient.

SARS-CoV-2 is likely to ultimately become endemic and continue circulating among the human population as a common cold virus [14,15]. Indeed, several countries are already considering implementing 'living with COVID-19' policies. However, the path to an endemic phase in terms of its duration and public health impact is likely to be highly variable, depending on multiple parameters such as vaccination rates, levels of immunity, transmission rates, and emergence of new variants. Most importantly, being able to control the burden of severe COVID-19 disease, which has the potential to overwhelm health care systems, will be crucial during this transition to an endemic phase.

To enable effective adaptation of public health policies to reduce the overall damage to the community, the future course of the pandemic has been simulated with mathematical models early after the emergence of COVID-19 [16-22]. In addition, models incorporating immunity and vaccination were developed [19-21]. In particular, a model demonstrated that infection-induced immunity in children may facilitate endemic transition of COVID-19 [22]. However, previous studies did not incorporate the different kinetics of severity-reducing and infection-preventing immunities. Here, we estimate courses of endemic transition of COVID-19 and dynamical changes in progression rates for severe COVID-19 during the transition period, using a mathematical model based on the concept that severity-preventing immunity decay more slowly than infection-preventing immunity. Our results demonstrate that increasing

viral spread, for example by relaxing NPIs or emergence of new variants, paradoxically reduces progression rates to severe COVID-19 and stabilizes the development of severe cases during the endemic transition.

MATERIALS AND METHODS

Model parameters

We have used a plausible range for model parameters from the published literature (**Supplementary Table 1**) rather than a single parameter set to get robust model prediction against parameter perturbation.

Reproduction numbers and steady state formulae derivation

We derived formula for the basic reproduction number R_0, the average number of secondary infections by an infected individual when the whole populations are susceptible (see **Supplementary Data 1** for details). A reproduction number incorporating vaccination was also derived similarly. Furthermore, we derived the steady-state values of the variables in the model for a given set of parameters (see **Supplementary Data 1** for details). It allowed us to obtain the late-phase status without performing numerical simulation of the model.

RESULTS

We developed a simple mathematical model based on the different kinetics of the two distinct immunities to predict the courses of endemic transition of COVID-19, from the early phase to the steady state (**Fig. 1A**), including dynamical changes in rates of progression to severe COVID-19 (**Fig. 1B and C**). Specifically, we extended the Susceptible-Infected-Recovered-Susceptible model, where individuals are separated into five populations: infected individuals with severe disease (I_S); infected individuals with mild to moderate disease (I_M); individuals susceptible to infection and without immunity (S_H), thus a high probability of progression to severe COVID-19 (h_S); susceptible individuals with only severity-reducing immunity (S_L), thus a low probability of severe COVID-19 progression (l_S); and recovered or vaccinated individuals (R) with both infection-preventing and severity-reducing immunities (**Fig. 1B**; see **Supplementary Data 1** for details). Upon SARS-CoV-2 infection with a transmission rate β, S_H and S_L can progress to severe (I_S) or mild (I_M) COVID-19. Because the probabilities of progression to severe disease are h_S and l_S for S_H and S_L, respectively (**Fig. 1C**), we refer to $1-\frac{l_S}{h_S}$ as the efficacy of severity-reducing immunity. A recovery rate is γ, and a vaccination rate per day is ν. Infection-preventing and severity-reducing immunities wane from R to S_L and then to S_H at rates $\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$, respectively, with $\omega_{R \to S_L} > \omega_{S_L \to S_H}$ (15).

We first calculated the numbers of daily infections and severe disease at the steady state, i.e., the late phase during endemic transition, according to the level of transmissibility, $R_0 = \frac{\beta}{\gamma}$ (see **Supplementary Data 1** for details). When the efficacy of severity-reducing immunity is 95% (l_S = 0.05h_S), considering vaccine efficacy in preventing severe COVID-19 (23), higher R_0 increases daily infection cases as expected (**Fig. 2A**, the third panel from the left). However, higher R_0 decreases the rates of severe disease (i.e., proportion of severe cases among all cases) across a wide range of daily vaccination rates (**Fig. 2B**, the third panel from the left). Consequently, the relation between the number of daily severe cases and R_0 is not monotonic (**Fig. 2C**, the third panel from the left). Specifically, when R_0 is low ($R_0 < 1.6$), caused for example by strict
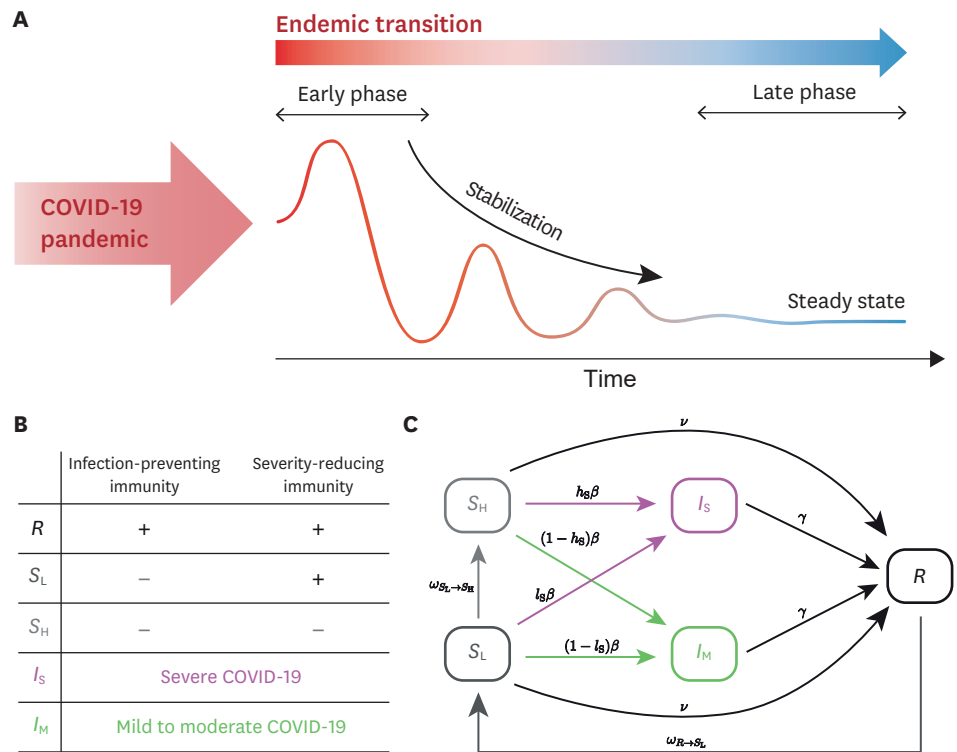
Figure 1. A compartmental model for COVID-19 transmission dynamics incorporating different levels of immunity and disease severity. (A) Schematic illustration for the time-course of endemic transition of the COVID-19 pandemic. (B) The population is divided into five groups: recovered after being infected or vaccinated (R); susceptible with a low probability (S_L) or a high probability (S_H) of experiencing severe disease when they are infected; infected with severe disease (I_S), and infected with mild to moderate disease (I_M). R carry both infection-preventing and severity-reducing immunities, and S_L possesses only severity-reducing immunity. (C) While S_H and S_L can be infected with the same rate β, S_L has a lower rate (l_S) of progressing to severe disease (I_S) compared to S_H (h_S) (i.e., $h_S > l_S$) due to the presence of severity-reducing immunity. I_M and I_S are converted to R at a rate γ. The infection-preventing and severity-reducing immunities wane at a rate of $\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$, respectively. S_H and S_L can also obtain immunity by vaccination at a rate of ν.

nonpharmaceutical interventions (NPIs) such as social distancing, the number of daily severe cases decreases with decreasing R_0. However, when R_0 is greater than 1.6, we unexpectedly found that the number of daily severe cases decreases now with increasing R_0. This result is observed when the efficacy of severity-reducing immunity is ≥ 90%, but disappears when it is 80%.

When R_0 is increased for example by relaxing NPIs or emergence of new variants, the S_L population (i.e., susceptible individuals with severity-reducing immunity) has a high chance of infection but is less likely to have severe disease due to their low rates (l_S) for severe disease progression. S_L experiencing re-infection or breakthrough infection is converted to R by re-gaining infection-preventing immunity. In summary, high R_0 reduces the proportion of S_H (non-immune population) and maintains individuals within a cycle of $S_L \leftrightarrow R$, leading to a paradoxical decrease in the number of severe cases (I_S) at the late phase of endemic transition (**Fig. 2D**). However, this effect was not observed when a vaccination rate per day is extremely high (**Fig. 2**, sky blue lines). Similar patterns are demonstrated when we calculate the results in **Fig. 2** based on the reproduction number incorporating vaccination (R_v; **Supplementary Fig. 1**) and even when we change values for major parameters γ, h_S, l_S, and $\omega_{S_L \to S_H}$ (**Supplementary Figs. 2-5**), which have not yet been exactly determined for COVID-19, within a reasonable range (**Supplementary Tables 1** and **2**).
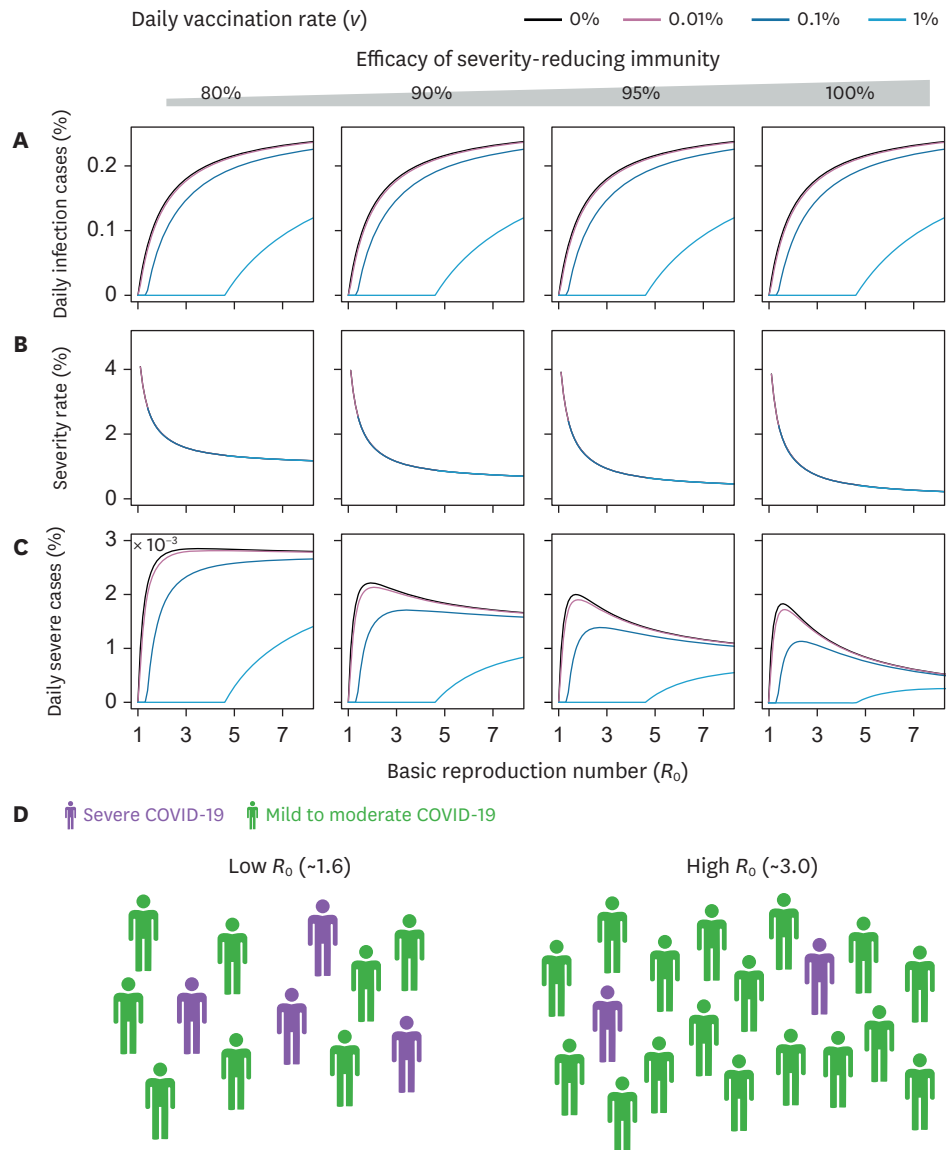
Figure 2. A higher transmission rate can reduce cases of severe disease during the late phase of endemic transition. Steady-state values of the mathematical model over the basic reproduction number ($R_0 = \frac{\beta}{\gamma}$), the average number of secondary infections by an infected individual when the whole populations are susceptible, with different daily vaccination rates (v) and efficacy of the severity-reducing immunity ($1 - \frac{I_S}{R_S}$). The daily vaccination rates were chosen based on the data of COVID-19 vaccination programs in each country (24). (A) As transmissibility (R_0) increases, the percentage of daily infections ($\gamma I_S + \gamma I_M$) in the whole populations increases. (B) The percentage of daily infections classified as severe decreases as R_0 increases because infection prevents waning of severity-reducing immunity ($S_L \rightarrow S_H$). (C) Under strong NPIs ($R_0 < \sim 1.6$), the percentage of severe cases in the whole population increases as R_0 increases. On the other hand, under weak NPIs ($R_0 > \sim 1.6$), the percentage of severe cases in the whole population decreases as R_0 increases. (D) In summary, higher R_0 increase the daily cases (green + purple) but decreases the severity rate and severe cases (purple). See **Supplementary Table 2** for the parameter values.

Although the daily severe cases at the late phase during endemic transition can be reduced by increasing R_0, the number of severe cases will transiently surge during the early phase of endemic transition, which may exceed critical care capacity. Therefore, we investigated transition dynamics during the time-course to an endemic phase under various conditions. When 10% of the population possess infection-preventing immunity, higher R_0 robustly increases the number of daily infection cases during the time-course (**Fig. 3A**). Although
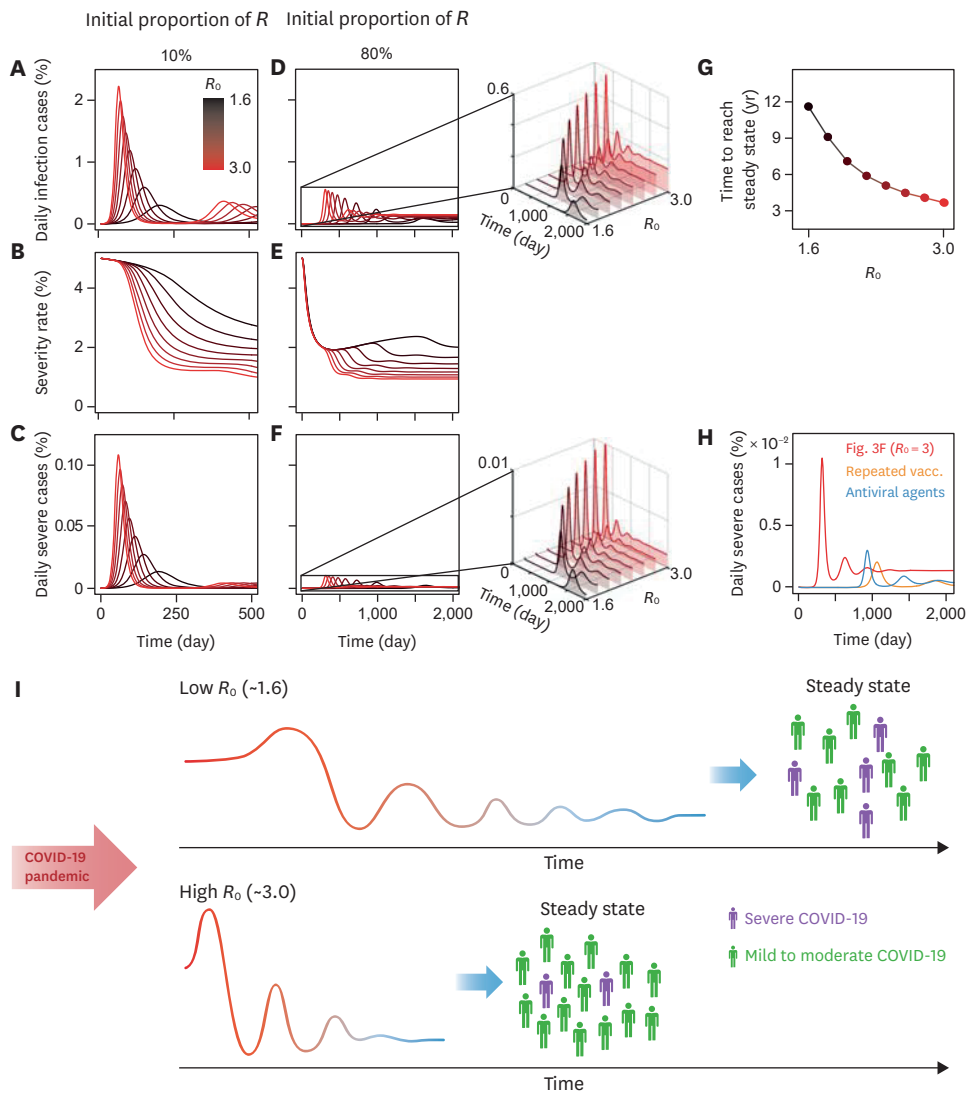
Figure 3. A higher transmission rate can accelerate the transition from the epidemic to the endemic phase without a substantial increase in severe cases. (A) The predicted dynamics of the proportion of daily infection cases in the whole population with varying R_0 from 1.6 to 3.0 for initial infection-preventing immunity of 10% in the population (initial proportion of R), acquired by natural infection or vaccination. During the early phase of the endemic transition, higher R_0 increases the daily infection cases. (B, C) Although the percentage of severe cases among all infections becomes lower as R_0 increases (B), the surge of percentage of severe cases across the whole population dramatically increases (C). (D-F) Predicted transition dynamics are shown for higher initial infection-preventing immunity of 80% (initial proportion of R). The surge of severe cases is greatly reduced compared with when the initial immunity is 10% (F), because both infection cases (D) and rate of severe cases (E) decrease. Furthermore, higher R_0 accelerates the stabilization of the number of daily cases (D) and severe cases (F). (G) Time to reach the stage when the number of severe cases fluctuates between 70% and 130% of the steady-state value. (H) The percentage of severe cases when two interventions are implemented. The red line is recalled from (F) when R_0=3.0, the orange line is dynamics from reduced waning rates ($\omega_{R \to S_L}$ and $\omega_{S_L \to S_u}$), and the blue line is dynamics from increased recovery rate (γ) and decreased probability of experiencing severe disease (h_S and l_S). See **Supplementary Table 2** for the parameter values. (I) A graphical summary of the results. Compared with the low R_0, the high R_0 leads to an earlier endemic transition and a reduced severity rate and the number of severe cases.

higher R_0 reduces rates for severe disease progression (**Fig. 3B**), the number of daily severe cases transiently, but sharply increases early during the time-course due to the robust increase in the number of infection cases (**Fig. 3C**).

The spike of severe cases is dramatically attenuated when a high proportion of the population (e.g., 80%) possess infection-preventing immunity, by natural infection or vaccination (**Fig. 3D-F**). Moreover, with higher R_0, the curves of severe cases are stabilized more quickly

to the steady state without fluctuation (**Fig. 3F**). Times to reach the steady state are estimated to be 12 and 4 years with R_0=1.6 and 3.0, respectively (**Fig. 3G**). When the proportion of the population with infection-preventing immunity is 30% or 50%, similar patterns are observed while peaks of infection and severe cases occur earlier and are higher compared to 80% immunity (**Supplementary Fig. 6**). This demonstrates that permissive viral spread under high vaccination coverages accelerates the endemic transition with subsequent controllable COVID-19 disease burden. However, sharp peaks of severe cases in the early phase could still threaten overwhelming healthcare systems.

To circumvent this, we evaluated the effects of repeated vaccinations (i.e., boosters) and antiviral agents on the curves of severe cases. Repeated vaccinations, which increase the longevity of both infection-preventing and severity-reducing immunities (i.e., decrease in $\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$) (25,26), reduced the peak of severe cases (**Fig. 3H**, orange line). Indeed, an additional third dose of the mRNA vaccine showed a 92% effectiveness in preventing severe COVID-19 disease compared with two-dose vaccination (27). Novel antiviral agents, which will increase the recovery rate γ and decrease progression to severe disease, h_S and l_S, also reduced the peak of severe cases (**Fig. 3H**, blue line). In fact, molnupiravir, a newly developed antiviral agent, has been shown to reduce the risk of hospitalization or death by 30% in patients with mild-to-moderate COVID-19 (28).

DISCUSSION

As the COVID-19 pandemic is ongoing, predicting the future course of the pandemic is needed to enable effective adaptation of public health policies to reduce the overall damage to the community. The concept of an endemic transition of SARS-CoV-2 has been proposed (14,15,22), however the possible impact of severe COVID-19 cases during this transition has not been estimated. This is crucial for driving appropriate public health policies and ensuring that healthcare systems can subsequently withstand the disease burden.

For this, we developed a simple model focusing on two heterogeneous features: immunity and clinical severity. This allowed us to forecast courses of endemic transition of COVID-19 based on the concept that severity-preventing immunity decays more slowly than infection-preventing immunity. In particular, increasing viral spread, for example by relaxing NPIs, under high vaccination coverages paradoxically reduces progression rates to severe COVID-19 and stabilizes the development of severe cases during the transition to an endemic phase, with reduced numbers of severe cases.

Emergence of new SARS-CoV-2 variants can also change the course of the endemic transition and the number of severe cases. Natural selection of mutant viruses occurs under the pressure of increasing viral fitness or escaping from immunity. New variants with higher fitness that more efficiently enter host cells or replicate can change the course of endemic transition by increasing R_0. In the case of immune-evading variants, both $\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$ can be increased in theory. Given that nAbs prevent infection by interfering with viral entry and are easily evaded by variants, the emergence of variants can reduce infection-preventing immunity and increase $\omega_{R \to S_L}$. However, variants rarely escape SARS-CoV-2-specific memory T cell responses that can prevent severe disease because T-cell epitopes are scattered across the viral proteome, suggesting that the emergence of variants minimally changes severity-reducing immunity or $\omega_{S_L \to S_H}$.

Recently, the Omicron variant (B.1.1.529), a new variant of concern harbouring the high number of mutations in the spike protein, has emerged (29). The Omicron variant was estimated to have higher reproduction number than the Delta variant (30). It was also experimentally demonstrated that Omicron spike-pseudovirus exhibits greater efficiency of target cell entry than other SARS-CoV-2 pseudoviruses (31). Moreover, the Omicron variant has been shown to reduce the neutralizing activities of nAbs elicited by COVID-19 vaccination or infection with other SARS-CoV-2 strains (5,31). However, the Omicron variant is known to result in less severe infection than other SARS-CoV-2 strains. Low pathogenicity of the Omicron variant is explained by preferential infection of the upper airway rather than the lungs (32). Such distinct characteristics of the Omicron variant can be flexibly incorporated into our model. Importantly, spread of the Omicron variant with high transmissibility is likely to facilitate the endemic transition of COVID-19 according to our model prediction.

The limitation of our study is that some population heterogeneities such as age, underlying diseases, and cross-reactive immunity elicited by other coronaviruses were not incorporated in the model (20). Models containing population heterogeneities will allow more precise quantitative prediction. Although the present simple model does not explicitly describe the different characteristics of individuals, the model could implicitly describe them by changing the values of parameters, which represents the averaged effect of the heterogeneities. For instance, if a large portion of population has underlying disease or there are more elderly people in community, it can be incorporated to the model by increasing the rate of progression to severe disease (i.e., h_S and l_S).

In conclusion, we demonstrate that increasing viral spread, for example by relaxing NPIs or emergence of new variants, under high vaccination coverages paradoxically reduces progression rates to severe COVID-19 and stabilizes the development of severe cases during the endemic transition, with reduced numbers of severe cases (**Fig. 3I**). While our prediction needs to be interpreted appropriately depending on each country, it provides important insights for establishing or adjusting public health policies in the era of 'living with COVID-19'.

ACKNOWLEDGEMENTS

SUPPLEMENTARY MATERIALS

Supplementary Data 1
Supplementary methods.

Click here to view

Supplementary Table 1

Parameters of COVID-19 transmission model

Click here to view

Supplementary Table 2

The parameter values and initial conditions used in Figures

Click here to view

Supplementary Figure 1

Parallel figure of **Fig. 2** generated with varying the reproduction number incorporating vaccination (R_v). (A) The percentage of daily infections, (B) severity rates, and (C) the percentage of daily severe cases at the steady state depending on the reproduction number incorporating vaccination, $R_v = \frac{\omega_{R \to S_L}}{\omega_{R \to S_L} + \nu} R_0$. Although R_v is used instead of R_0, the major patterns such as an initial increase followed by a decrease of daily severe cases are preserved compared with **Fig. 2**. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary Figure 2

Parallel figure of **Fig. 2** generated by changing the recovery rate (γ) and immunity waning rates ($\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$). (A) The percentage of daily infections, (B) severity rate, and (C) the percentage of daily severe cases at the steady state over the basic reproduction numbers (R_0) with increased recovery rate (γ) and reduced waning rates ($\omega_{R \to S_L}$ and $\omega_{S_L \to S_H}$). The major patterns, such as an initial increase followed by a decrease of the daily severe cases, are preserved compared with **Fig. 2**. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary Figure 3

Parallel figure of **Fig. 2** generated by increasing the progression rates to severe cases, h_S and l_S, by five times. (A) The percentage of daily infections, (B) severity rate, and (C) the percentage of daily severe cases at the steady state over the basic reproduction numbers (R_0). The major patterns, such as an initial increase followed by a decrease of the daily severe cases, are preserved compared with **Fig. 2**. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary Figure 4

Parallel figure of **Fig. 2** generated by increasing the progression rates to severe cases, h_S and l_S, by 10 times. (A) The percentage of daily infections, (B) severity rate, and (C) the percentage of daily severe cases at the steady state over the basic reproduction numbers (R_0). The major patterns, such as an initial increase followed by a decrease of the daily severe cases, are preserved compared with **Fig. 2**. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary Figure 5

Parallel figure of **Fig. 2** generated by increasing the waning rate of severity-reducing immunity, $\omega_{S_L \to S_H}$, by three times. (A) The percentage of daily infections, (B) severity rate, and (C) the percentage of daily severe cases at the steady state over the basic reproduction numbers (R_0). The major patterns, such as an initial increase followed by a decrease of the daily severe cases, are preserved compared with **Fig. 2**. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary Figure 6

The predicted dynamics of the proportion of daily cases among the whole population, the rate of severe disease among all infections, and the proportion of daily severe cases among the whole population, varying R_0 from 1.6 to 3.0. See **Supplementary Table 2** for the parameter values.

Click here to view

Supplementary References

Click here to view

REFERENCES

1. Cohen KW, Linderman SL, Moodie Z, Czartoski J, Lai L, Mantus G, Norwood C, Nyhoff LE, Edara VV, Floyd K, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. *Cell Rep Med* 2021;2:100354.
   PUBMED | CROSSREF

2. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, Doolman R, Asraf K, Mendelson E, Ziv A, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med* 2021;385:e84.
   PUBMED | CROSSREF

3. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, Ledgerwood JE, Mascola JR, Graham BS, Lin BC, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for covid-19. *N Engl J Med* 2021;384:2259-2261.
   PUBMED | CROSSREF

4. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, Nutalai R, Zhou D, Mentzer AJ, Zhao Y, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell* 2021;184:4220-4236.e13.
   PUBMED | CROSSREF

5. Liu L, Iketani S, Guo Y, Chan JF, Wang M, Liu L, Luo Y, Chu H, Huang Y, Nair MS, et al. Striking antibody evasion manifested by the omicron variant of SARS-CoV-2. *Nature* 2021;602:676-681
   PUBMED | CROSSREF

6. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, Al Khatib HA, Coyle P, Ayoub HH, Al Kanaani Z, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med* 2021;385:e83.
   PUBMED | CROSSREF

7. Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, Chodick G, Gazit S, Patalon T. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. *Nat Commun* 2021;12:6379.
   PUBMED | CROSSREF

8. Jung JH, Rha MS, Sa M, Choi HK, Jeon JH, Seok H, Park DW, Park SH, Jeong HW, Choi WS, et al. SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells. *Nat Commun* 2021;12:4043.
   PUBMED | CROSSREF

9. Le Bert N, Tan AT, Kunasegaran K, Tham CY, Hafezi M, Chia A, Chng MH, Lin M, Tan N, Linster M, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* 2020;584:457-462.
   PUBMED | CROSSREF

10. Noh JY, Jeong HW, Kim JH, Shin EC. T cell-oriented strategies for controlling the COVID-19 pandemic. *Nat Rev Immunol* 2021;21:687-688.
    PUBMED | CROSSREF

11. Matchett WE, Joag V, Stolley JM, Shepherd FK, Quarnstrom CF, Mickelson CK, Wijeyesinghe S, Soerens AG, Becker S, Thiede JM, et al. Cutting edge: Nucleocapsid vaccine elicits spike-independent sars-cov-2 protective immunity. *J Immunol* 2021;207:376-379.
    PUBMED | CROSSREF

12. Zhuang Z, Lai X, Sun J, Chen Z, Zhang Z, Dai J, Liu D, Li Y, Li F, Wang Y, et al. Mapping and role of t cell response in sars-cov-2-infected mice. *J Exp Med* 2021;218:e20202187.
    PUBMED | CROSSREF

13. Bange EM, Han NA, Wileyto P, Kim JY, Gouma S, Robinson J, Greenplate AR, Hwee MA, Porterfield F, Owoyemi O, et al. CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer. *Nat Med* 2021;27:1280-1289.
    PUBMED | CROSSREF

14. Veldhoen M, Simas JP. Endemic SARS-CoV-2 will maintain post-pandemic immunity. *Nat Rev Immunol* 2021;21:131-132.
    PUBMED | CROSSREF

15. Antia R, Halloran ME. Transition to endemicity: understanding COVID-19. *Immunity* 2021;54:2172-2176.
    PUBMED | CROSSREF

16. Lovell-Read FA, Funk S, Obolski U, Donnelly CA, Thompson RN. Interventions targeting non-symptomatic cases can be important to prevent local outbreaks: SARS-CoV-2 as a case study. *J R Soc Interface* 2021;18:20201014.
    PUBMED | CROSSREF

17. Sahai SY, Gurukar S, KhudaBukhsh WR, Parthasarathy S, Rempała GA. A machine learning model for nowcasting epidemic incidence. *Math Biosci* 2022;343: 108677.
    PUBMED | CROSSREF

18. Kucharski AJ, Russell TW, Diamond C, Liu Y, Edmunds J, Funk S, Eggo RM, Sun F, Jit M, Munday JD, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *Lancet Infect Dis* 2020;20:553-558.
    PUBMED | CROSSREF

19. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science* 2020;368:860-868.
    PUBMED | CROSSREF

20. Saad-Roy CM, Morris SE, Metcalf CJ, Mina MJ, Baker RE, Farrar J, Holmes EC, Pybus OG, Graham AL, Levin SA, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. *Science* 2021;372:363-370.
    PUBMED | CROSSREF

21. Saad-Roy CM, Wagner CE, Baker RE, Morris SE, Farrar J, Graham AL, Levin SA, Mina MJ, Metcalf CJ, Grenfell BT. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. *Science* 2020;370:811-818.
    PUBMED | CROSSREF

22. Lavine JS, Bjornstad ON, Antia R. Immunological characteristics govern the transition of COVID-19 to endemicity. *Science* 2021;371:741-745.
    PUBMED | CROSSREF

23. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Polack FP, Zerbini C, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 2021;385:1761-1773.
    PUBMED | CROSSREF

24. Our World in Data. Coronavirus pandemic (COVID-19) [Internet]. Available at https://ourworldindata.org/coronavirus [accessed on 24 April 2022].

25. Falsey AR, Frenck RW Jr, Walsh EE, Kitchin N, Absalon J, Gurtman A, Lockhart S, Bailey R, Swanson KA, Xu X, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. *N Engl J Med* 2021;385:1627-1629.
    PUBMED | CROSSREF

26. Bertrand D, Hamzaoui M, Lemée V, Lamulle J, Laurent C, Etienne I, Lemoine M, Lebourg L, Hanoy M, Le Roy F, et al. Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients. *Kidney Int* 2021;100:1337-1340.
    PUBMED | CROSSREF

27. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, Reis BY, Balicer RD. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;398:2093-2100.
PUBMED | CROSSREF

28. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martin-Quiros A, Caraco Y, Williams-Diaz A, Brown ML, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386:509-520.
PUBMED | CROSSREF

29. Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G. Omicron and delta variant of SARS-CoV-2: a comparative computational study of spike protein. *J Med Virol* 2022;94:1641-1649.
PUBMED | CROSSREF

30. Nishiura H, Ito K, Anzai A, Kobayashi T, Piantham C, Rodríguez-Morales AJ. Relative reproduction number of SARS-CoV-2 omicron (b.1.1.529) compared with delta variant in South Africa. *J Clin Med* 2021;11:11.
PUBMED | CROSSREF

31. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, Berrios C, Ofoman O, Chang CC, Hauser BM, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell* 2022;185:457-466.e4.
PUBMED | CROSSREF

32. Kozlov M. Omicron's feeble attack on the lungs could make it less dangerous. *Nature* 2022;601:177.
PUBMED | CROSSREF