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Multi-Faceted Analysis of COVID-19 Epidemic in Korea Considering Omicron Variant: Mathematical Modeling-Based Study

Youngsuk Ko [ID],[1] **Victoria May Mendoza** [ID],[1,2] **Renier Mendoza** [ID],[1,2] **Yubin Seo** [ID],[3] **Jacob Lee** [ID],[3] **Jonggul Lee** [ID],[4] **Donghyok Kwon** [ID],[4] and **Eunok Jung** [ID] [1]

[1]Department of Mathematics, Konkuk University, Seoul, Korea
[2]Institute of Mathematics, University of the Philippines Diliman, Quezon City, Philippines
[3]Division of Infectious Disease, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea
[4]Division of Public Health Emergency Response Research, Korea Disease Control and Prevention Agency, Cheongju, Korea

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Address for Correspondence:
Eunok Jung, PhD
Department of Mathematics, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea.
Email: junge@konkuk.ac.kr

ORCID iDs
Youngsuk Ko [ID]
https://orcid.org/0000-0001-9063-176X
Victoria May Mendoza [ID]
https://orcid.org/0000-0003-0953-9822
Renier Mendoza [ID]
https://orcid.org/0000-0003-3507-0327
Yubin Seo [ID]
https://orcid.org/0000-0001-5183-1996
Jacob Lee [ID]
https://orcid.org/0000-0002-7041-065X
Jonggul Lee [ID]
https://orcid.org/0000-0002-5771-3015
Donghyok Kwon [ID]
https://orcid.org/0000-0003-4756-6477
Eunok Jung [ID]
https://orcid.org/0000-0002-7411-3134

ABSTRACT

Background: The most recent variant of concern, omicron (B.1.1.529), has caused numerous cases worldwide including the Republic of Korea due to its fast transmission and reduced vaccine effectiveness.

Methods: A mathematical model considering age-structure, vaccine, antiviral drugs, and influx of the omicron variant was developed. We estimated transmission rates among age groups using maximum likelihood estimation for the age-structured model. The impact of non-pharmaceutical interventions (NPIs; in community and border), quantified by a parameter μ in the force of infection, and vaccination were examined through a multi-faceted analysis. A theory-based endemic equilibrium study was performed to find the manageable number of cases according to omicron- and healthcare-related factors.

Results: By fitting the model to the available data, the estimated values of μ ranged from 0.31 to 0.73, representing the intensity of NPIs such as social distancing level. If μ < 0.55 and 300,000 booster shots were administered daily from February 3, 2022, the number of severe cases was forecasted to exceed the severe bed capacity. Moreover, the number of daily cases is reduced as the timing of screening measures is delayed. If screening measure was intensified as early as November 24, 2021 and the number of overseas entrant cases was contained to 1 case per 10 days, simulations showed that the daily incidence by February 3, 2022 could have been reduced by 87%. Furthermore, we found that the incidence number in mid-December 2021 exceeded the theory-driven manageable number of daily cases.

Conclusion: NPIs, vaccination, and antiviral drugs influence the spread of omicron and number of severe cases in the Republic of Korea. Intensive and early screening measures during the emergence of a new variant is key in controlling the epidemic size. Using the endemic equilibrium of the model, a formula for the manageable daily cases depending on the severity rate and average length of hospital stay was derived so that the number of severe cases does not surpass the severe bed capacity.

Keywords: COVID-19; Mathematical Modeling; Omicron Variant, Nonpharmaceutical Interventions; Endemic; Vaccination

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Author Contributions

Conceptualization: Ko Y. Data curation: Ko Y, Lee J,[2] Kwon D. Formal analysis: Ko Y, Mendoza R, Mendoza VM, Seo YB, Lee J,[1] Lee J,[2] Kwon D, Jung E. Funding acquisition: Jung E. Investigation: Ko Y, Mendoza R, Mendoza VM, Jung E. Methodology: Ko Y. Software: Ko Y. Validation: Ko Y, Mendoza R, Mendoza VM, Seo YB. Visualization: Ko Y. Writing - original draft: Ko Y, Mendoza R, Mendoza VM, Jung E. Writing - review & editing: Ko Y, Mendoza R, Mendoza VM, Seo YB, Lee J,[1] Lee J,[2] Kwon D, Jung E.

Lee J,[1] Jacob Lee; Lee J,[2] Jonggul Lee.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19), which originated in China at the end of 2019, has become a global public health issue and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[1,2] In mid-November 2021, a new variant, called omicron, was detected in Gauteng province, South Africa.[3] On November 26, 2021, omicron variant was designated by the Technical Advisory Group on SARS-CoV-2 Virus Evolution of WHO as a variant of concern (VOC).[4] In sample serums from vaccinated individuals, the neutralization of omicron variant was much less compared to the previous variants.[5] Moreover, the vaccine effectiveness of primary dose was shown to be reduced against symptomatic omicron infections.[6,7] Vaccine-breakthrough omicron infections are higher when compared to delta.[8] On the other hand, reduced hospitalization rates and fewer severe cases are observed.[9,10] Vaccination remains a key intervention strategy as it offers protection against hospitalization.[6,11-13] Furthermore, booster shots can provide a substantial increase in protection against symptomatic infection.[6,7,14,15] The development of safe and effective oral antiviral drugs can significantly impact control measures for COVID-19.[16] In particular, Pfizer's Paxlovid has been shown to be 89% effective in reducing the risk of hospitalization.[17]

In Korea, omicron variant cases have been detected since November 2021 and later, omicron variant has become the dominant strain, reaching over 50% in mid-January 2022 and more than 90% among confirmed cases since February 2022.[18] Omicron infections were shown to have caused significant local community transmission in Korea.[19] After the omicron variant became dominant, the number of cases increased significantly. Average daily confirmed cases in December 2021 (delta-dominant) and March 2022 (omicron-dominant) were approximately 6,000 and 300,000, respectively. Since February 10, 2022 and February 21, 2022, the antiviral drug Paxlovid has been given to infected individuals over 60 years and over 40 years, respectively.[20,21]

Mathematical modelling has been extensively used throughout the different phases of the pandemic. During the early stage of COVID-19, mathematical models were used to forecast the number of cases in various countries.[22-25] Non-pharmaceutical interventions (NPIs) such as massive testing, contact tracing, social distancing, mobility restrictions, school closure, mask mandate, etc., have been incorporated in models to come up with effective policies in curbing the rise of infections.[26-30] Strategies for vaccine rollout were also proposed using mathematical models.[31-34] Because variants may have different epidemiological characteristics, they have been incorporated into models to capture their dynamics and propose strategies to mitigate their spread.[35,36]

In our proposed mathematical model, we considered the delta and omicron variants. We incorporated age structure, foreign entrant cases, vaccination, and antiviral drugs in the model. The aim of this study is to quantify and analyze the impacts of NPIs, such as social distancing and screening measures at the border, in controlling the spread of the disease. Furthermore, we forecasted the number of daily incidence and severe infections caused by the omicron variant in the Republic of Korea in 2022. By analyzing the endemic equilibrium of the model, we determined the number of manageable daily cases so that the number of severe cases will not surpass the severe bed capacity in Korea.

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METHODS

Data

Both public and non-public data that were used in this study were from the Korea Disease Control and Prevention Agency (KDCA). Publicly available daily number of confirmed cases and vaccine administration were aggregated from daily presses and were used in the mathematical model simulation.[37] Two types of information, symptom onset date and diagnosis date, were aggregated from the non-publicly available, individual based data and were used in the maximum likelihood estimation (MLE) process.

Mathematical modeling of COVID-19 considering delta and omicron variants

In this study, a deterministic mathematical model that includes age, vaccines, antiviral drugs, and influx of the omicron variant was developed. We consider eight age groups and two strains of COVID-19 virus, delta (δ) and omicron (o). These variants have different basic reproductive numbers, transmission rates, and severe rates. **Fig. 1** illustrates the flow diagram of the mathematical model. Note that X indicates vaccine- or waning-related status of the host and i refers to age group. There are seven vaccine- or waning-related compartments (X); u (unvaccinated), w (unvaccinated, previously infected, but natural immunity has waned), $v1$ (two weeks before finishing primary doses), $v2$ (two weeks after finishing primary doses), wv (waned after primary doses), b (boostered), wb (waned after booster).

An unvaccinated host (u_i) moves to the $v1^i$ compartment after administration of the first dose and has partial vaccine effectiveness. Two weeks after receiving the second dose, the
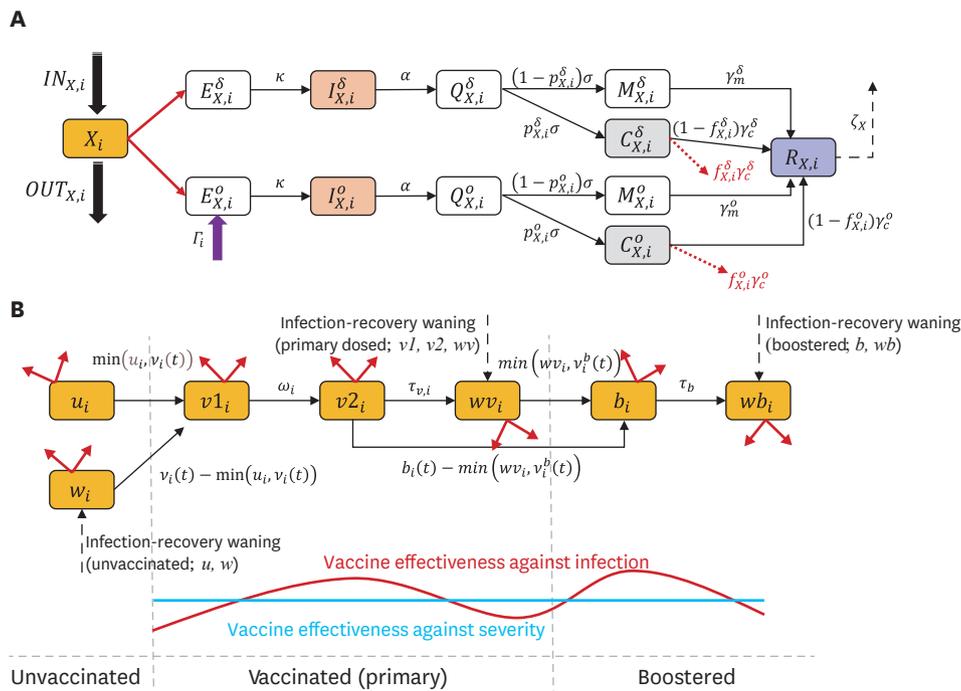
Fig. 1. Flow diagrams of the mathematical model of coronavirus disease 2019 in Korea. (**A**) Epidemiological flow diagram, where X_i represents a vaccine- or waning-related status of a host in compartment X and age group i. Note that X can be u, w, $v1$, $v2$, wv, b, or wb and each follows this epidemiological flow. (**B**) Flow diagram describing vaccination, including booster, and waning of immunity after vaccination or infection, which constitute the IN flow to and OUT flow from each X_i in (**A**). The time-dependent parameters $v_i(t)$ and $vib(t)$ are the number of primary and booster doses administered per day and are obtained from data. The blue line in the bottom graph shows that the values used for vaccine effectiveness against severe infection are the same across all vaccinated individuals but the vaccine effectiveness against infection (red curve) peaks after completing the primary dose and after getting a booster shot.

host has full vaccine effectiveness ($v2_i$). Later, vaccine-induced immunity wanes and so the host moves to the wv_i compartment. The host goes to b_i compartment after receiving a booster shot and later to wb_i, considering the waning of booster shots. In this study, we assume that the immunity against symptomatic infection wanes but the immunity against severe infection does not. This assumption is supported by studies, where a population-wide decline in effectiveness against infection was observed but effectiveness against hospitalization remained high and with no significant change over time.[38,39] For both variants, an exposed host $E_{X,i}$ becomes infectious ($I_{X,i}$) and spreads the disease until case confirmation, and so the host moves to the $Q_{X,i}$ compartment. After confirmation, the isolated host either develops mild symptoms $M_{X,i}$, including asymptomatic case, or severe/critical symptoms $C_{X,i}$. An isolated host with mild symptoms recovers ($R_{X,i}$), while those with severe symptoms may either recover or die. We assume that recovered individuals, whether vaccinated or not, develop natural immunity which wanes over time. Since recovered individuals retain protection against severe infection, they move to a different compartment w_i for unvaccinated, wv_i for primary-dosed, or wb_i for boostered, after the natural immunity has waned.[39] It was demonstrated that in unvaccinated participants, the infection-acquired immunity waned after about 1 year but remained consistently high in previously vaccinated-participants, even for individuals who were infected 18 months prior.[40] Hence, we use a different natural immunity waning rate for those who were unvaccinated (ζ) and vaccinated (ζ_v), with $\zeta_v < \zeta$. The parameter Γ_i represents the number of overseas entrant cases from age group i who are not screened and entered the local community. Its value is calculated using data on average daily number of overseas entrant cases across all ages from November 24 to December 31, 2021. The detailed description of the mathematical model, including the governing equations, can be found in the **Supplementary Data 1**.

Parameter estimation

Transmission rates among age groups were estimated using MLE. For MLE, we considered two events for a host at one unit time: not being infected and being infected. Individual based data provided by the KDCA were used for the MLE procedure to capture every infection event (also uninfected events) of age groups. Detailed formulation is described in the **Supplementary Data 1**.

To quantify the impact of NPIs, a time-dependent parameter μ is introduced to indicate the reduction in transmission caused by NPIs. For example, ignoring other factors, if the basic reproductive number is 2 and μ is 0.7, then the effective reproductive number becomes $(1 - 0.7) \times 2 = 0.6$. We estimated the value of μ every week using least squares curve fitting method, by minimizing the difference between the cumulative incidence calculated using the model ($\int \sum_X \sum_i \alpha (I_{X,i}\delta + I_{X,i}o))dt$) and the available data. The model simulation time was done from August 1, 2021 to February 2, 2022, because the testing policy has been changed since February 3, 2022.[41] Furthermore, we proceeded with parameter bootstrapping to examine the reliability of the estimation and data. Detailed description of the bootstrapping method and results are in the **Supplementary Data 1**. During the parameter estimation period, antiviral drugs were provided for certain age groups.[20,21] To apply impact of antiviral drugs, we simply set that severity rate of age over 60 and 40 has reduced since January 14 and February 21, 2022, by 80%, respectively. Note that the 80% severity reduction is between the lowest and highest values that were considered in a recent study.[42] For example, delta variant's severity rate for the unvaccinated individuals aged 60 to 69 reduces from 7.49% to 1.50% since January 14, 2022.

In this research, we performed a multifaceted approach to examine critical factors which affected the COVID-19 epidemic. First, we did a forecast considering different NPIs-related factors and vaccine hesitancy. Second, we examined the time-dependent sensitivity of screening measures to the disease spread since the omicron variant has arrived in Korea. Finally, we derived a manageable daily incidence number from the endemic equilibrium state of the mathematical model.

Forecast of omicron variant epidemic in 2022

For the forecast, we extended the simulation time until the end of 2022 and varied the factors related to NPIs and booster shots. We set the range for the NPIs-related reduction factor (μ) from 0.4 to 0.65 in 0.05 increments (six scenarios), and the maximum number of daily booster shots as 300,000 or 100,000, to observe the influence of vaccine hesitancy. Furthermore, to consider the implementation of the antiviral drugs, we set that groups of age over 60 (age over 40) have reduced severity after February 10, 2022 (February 21, 2022).

Examination of the time-dependent impact of screening measure

We examined the impact of screening measures by varying the value of Γ_i by factors of 0.1 to 10, and the date of entry of omicron to the local community from November 24 to December 1, December 8, and December 22. The rest of the parameters are fixed to their values on **Supplementary Tables 1** and **2**.

Endemic equilibrium study

As the number of cases rapidly increases, endemicity of COVID-19 becomes an issue. We performed an endemic equilibrium analysis to investigate how COVID-19 cases can be maintained on a manageable level. Ignoring age structure (i), vaccination-related history (X), and strains, and considering endemic equilibrium (assuming that there is natural death and birth in susceptible groups, therefore endemic equilibrium can exist), ordinary differential equations of confirmed (Q) and severe patients (C) are:

$$\frac{dQ}{dt} = \alpha I - \sigma Q = 0, \qquad \therefore \alpha I = \sigma Q,$$

$$\frac{dC}{dt} = p^*\sigma Q - \gamma^* C = 0, \qquad p^*\sigma Q = \gamma^* C, \qquad \therefore \sigma Q = \frac{1}{p^*}\gamma^* C,$$

where p^* and γ^* are average severe rate and recovery rate, respectively. Combining the two results above, we get:

$$\alpha I = \frac{1}{p^*}\gamma^* C$$

Because the number of severe patients should be below the severe bed capacity, C_{max}, the following inequality is formulated:

$$\alpha I = \frac{1}{p^*}\gamma^* C < \frac{1}{p^*}\gamma^* C_{max}$$

Considering that αI is the daily incidence and $1/\gamma^*$ is the average length of hospital stay, then the threshold value of the inequality, referred to as the manageable daily incidence, is given as follows:

$$Manageable\ Daily\ Incidence\ =\ \frac{1}{p^*} \times \frac{1}{t_H} \times C_{max} \qquad \text{Equation 1}$$

The manageable daily incidence is a function of three input parameters, average length of hospital stay (t_H), average severe rate (p^*), and severe patient capacity (C_{max}).

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Konkuk University (7001355-202101-E-130). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

Estimation of transmission rates among age groups

Fig. 2 shows the transmission rate matrix, M_1, represented as a heatmap. The maximum value is 6.14, which is the value among age group 8. Estimated reproductive number from M_1 is 6.16, which is affected by NPIs but not by vaccine because reduced probability of being infected was considered in the MLE process. To exclude the effect of NPIs, the adjusted matrix M_2 was introduced using the basic reproductive number of the variant and the estimated effective reproductive number from the transmission rate matrix, M_1 (**Supplementary Data 1**). The adjusted matrix M_2 was applied into the mathematical model.

Qualification of NPIs in Korea

Fig. 3 shows that the daily and cumulative incidences from the model simulation fit the data well (**Fig. 3A and B**, respectively). Also, the number of administered severe patients captures the trend well (**Fig. 3C**), even if the parameters related to severe patients were not fitted but aggregated from references.
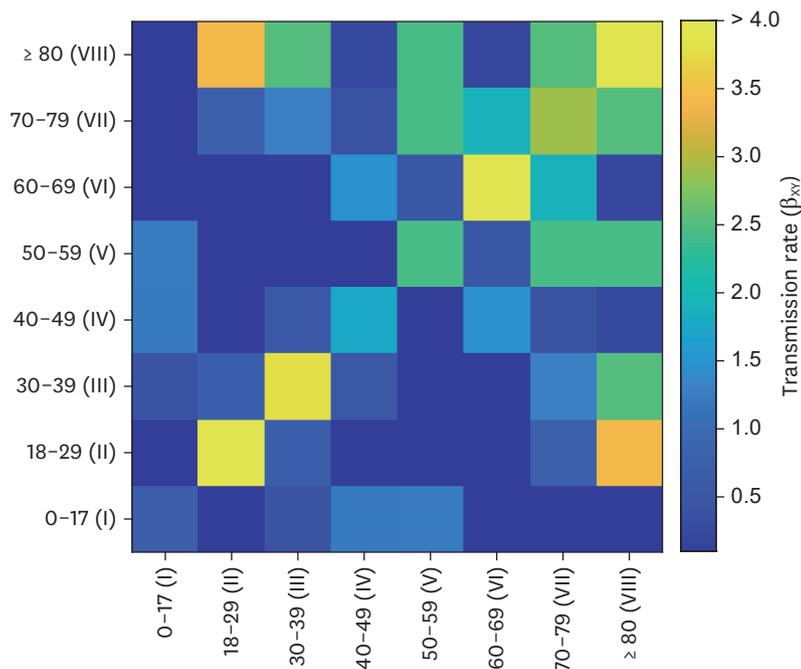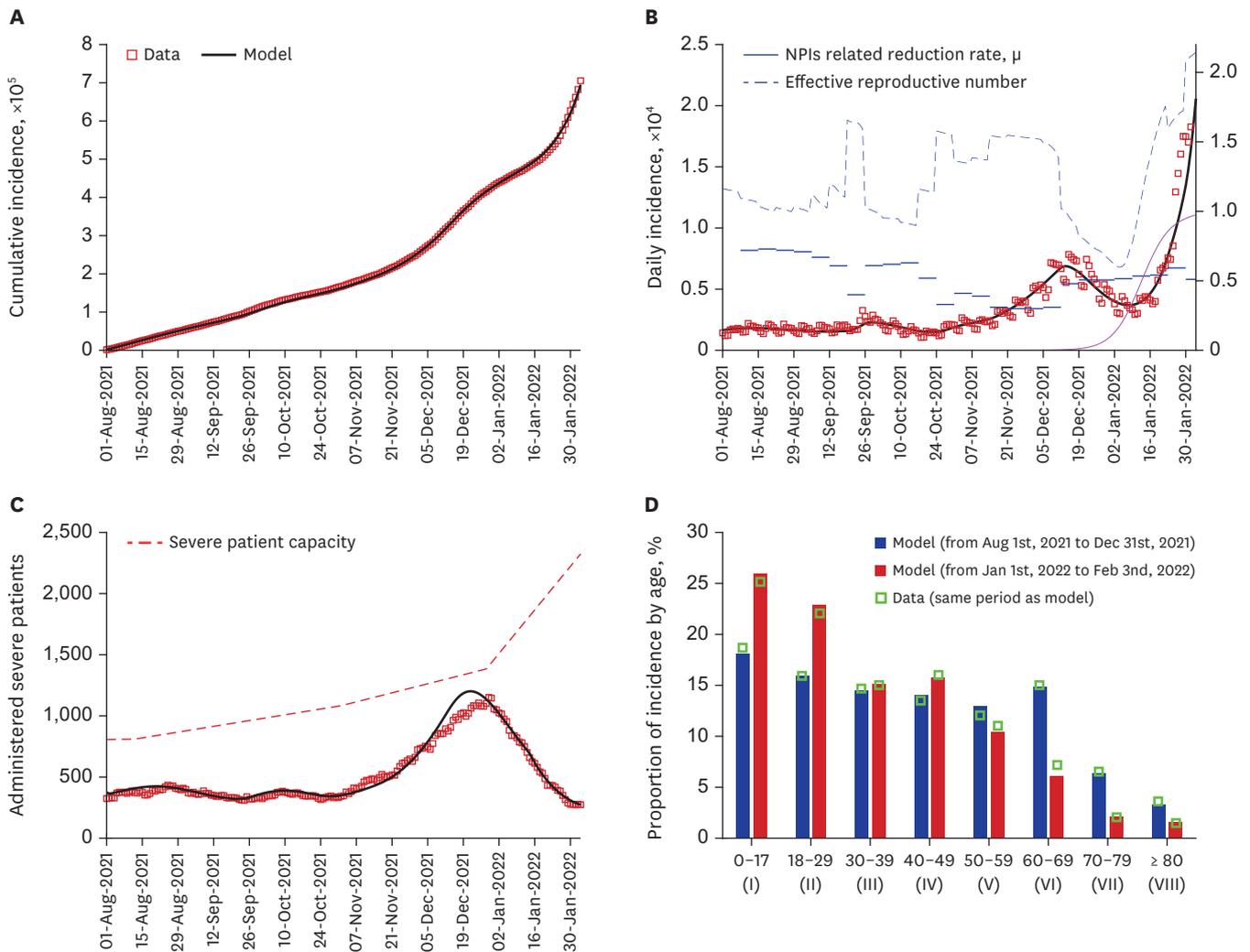

Fig. 2. The transmission rate matrix among age groups using maximum likelihood estimation.

Fig. 3. Estimation results of the qualification of NPIs. (**A**) Daily incidence, NPIs-related reduction factor, and reproductive number. Dark solid curve is the model simulation and red boxes are data. Pale blue solid lines indicate NPIs-related reduction factor and dashed curve is the effective reproductive number. The magenta curve is the proportion of omicron variant among new cases. (**B**) Cumulative incidence. (**C**) Administered severe patients. Red dashed curve indicates the severe patient capacity of Korea. (**D**) Proportion of incidence by age on two different periods. The blue bar is from August 1 to December 31, 2021, and the red bar is from January 1 to February 3, 2022. The green boxes indicate data.
NPI = non-pharmaceutical intervention.

During social distancing level 4 (August to October 2021), the range of estimated μ was from 0.61 to 0.73, except near the national holiday season (Chuseok, September 20 to September 22, 2021) when μ dropped to 0.4. Since November, as the gradual recovery policy began, μ decreased and ranged from 0.31 to 0.41, and later becomes 0.52 as suspended gradual recovery was announced because the number of severe patients reached more than 1,100. The obtained μ estimates and the corresponding values of the effective reproductive number R_t are illustrated as horizontal lines and dashed curves, respectively, in **Fig. 3A**. Note that all the estimated values of μ were within the 95% confidence intervals of the parameter bootstrapping results and the details are displayed in **Supplementary Fig. 1** and listed in the **Supplementary Table 3**. The proportion of omicron among new cases (magenta curve) increased from 7% to 71% from December 16, 2021 to January 16, 2022 and reached 97% by the end of the simulation period.

Age groups 1 and 2 (age under 30) showed the maximum and second maximum incidence among age groups in both phases, August 1 to December 31, 2021 and January 1 to February 3, 2022, respectively. Age group 6 (60 to 69) had the third highest incidence number in 2021 but third lowest in 2022. Age groups 8 and 7 (age over 70) had the minimum and second minimum incidence during the simulation period.

### Forecast results of omicron epidemic in 2022

Forecast from February 3 to the end of 2022 considering various NPIs-related reduction factor (μ) and maximum number of daily booster shot administration, showing the range of confirmed cases and administered severe patients, are displayed in **Fig. 4**. If the maximum number of booster per day is 300,000 (100,000), the peak size of incidence and administered severe patients will range from 320,300 (420,900) to 1,409,200 (1,518,900) and 1,210 (1,530) to 5,120 (5,410) according to the value of μ which varies from 0.4 to 0.65, respectively. A secondary wave towards the end of 2022 is observed in each scenario, and the size of the secondary peak (incidence: less than 300,000, severe patient: less than 1,000) is smaller than the first peak. We display the data (red boxes) until March 13, 2022, before testing policy was changed to include positive rapid antigen test done in an accredited facility as a confirmed case.[43]

Time dependent impact of screening measure

Fig. 5 shows the log-scaled simulation results using filled curves with different colors. Red, green, blue, and cyan areas indicate the ranges of daily incidence for the various numbers of overseas entrant cases ($0.1\Gamma_i$ to $10\Gamma_i$), initiated on November 24, December 1, December 8, and December 22, respectively. As the date is delayed, the ranges of incidence become narrow. The black curve indicates the incidence when Γ_i is set to its baseline value and initiated on November 24. The ratio of the maximum (minimum) to the baseline incidence value when Γ_i is initiated on November 24, December 1, December 8, and December 22 are 8.64 (0.13), 2.61 (0.84), 1.36 (0.96), and 1.04 (0.99), respectively. In particular, if the impact of screening (Γ_i) is varied since November 24, 2021, the range of values of the number of daily cases by February 3, 2022, is (2,730–190,420). On the contrary, if the screening is varied since December 22, 2021, the range of daily cases is (21,800–22,780).

Endemic equilibrium study

Using Equation 1, if the severe rate, length of hospital stay, and severe patient capacity are 5%, 28 days, and 500, respectively, which might be similar to the early stage of COVID-19 in Korea, then the manageable number of incidence is approximately 360. **Fig. 6** illustrates the manageable daily incidence if the severe patient capacity is fixed to 2,800 (**Fig. 6A**) or when the average length of hospital stay is set to 7 days (**Fig. 6B**). **Fig. 6C** shows the actual incidence data and theory-driven manageable incidence using aggregated data of each day, interpolated data of hospital stay, severe rate, and severe patient capacity.[44,45] Blue square indicates that the manageable daily incidence of Korea in mid-February 2022 is around 600,000 assuming that severe patient capacity is 2,800, average severe rate is 0.16%, and average length of hospital stay is 7 days. Moreover, it is visible that actual daily incidence exceeded the theory-driven manageable incidence in December 2021, when the government declared the suspended gradual recovery.
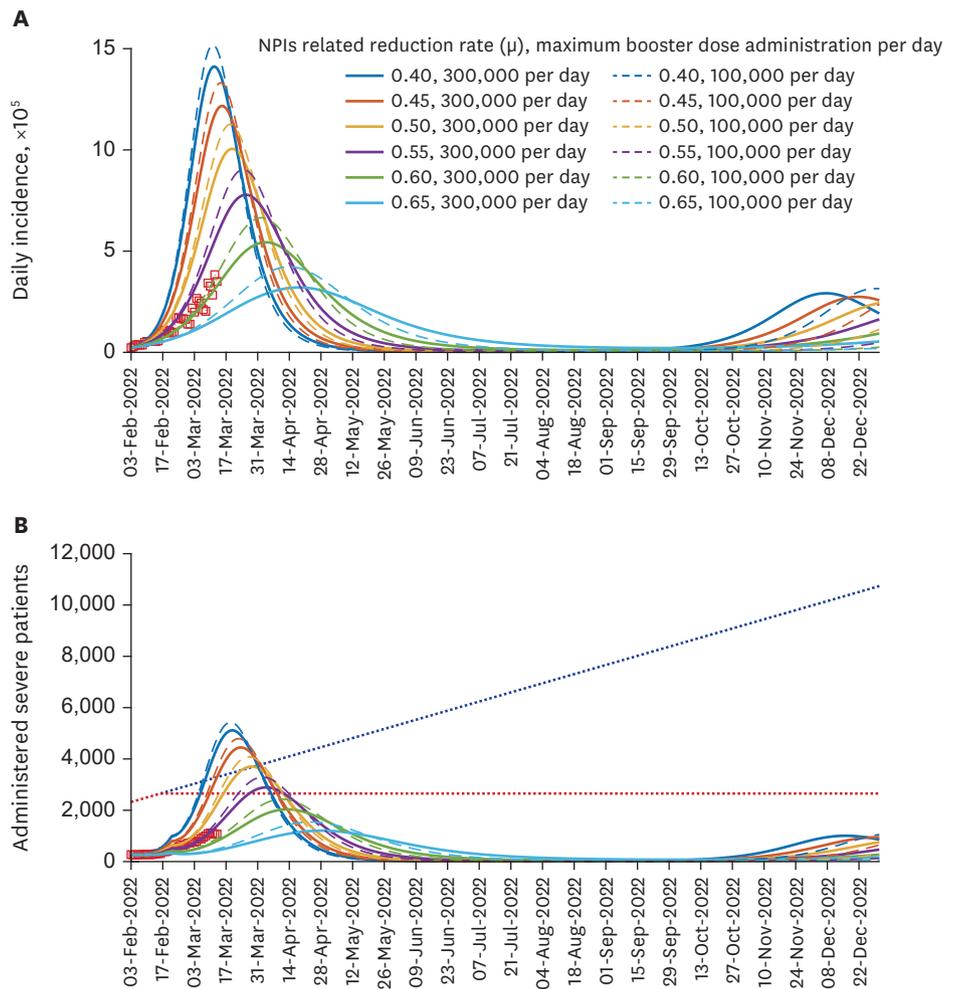
Fig. 4. Forecast results considering different intensity of NPIs and vaccine hesitancy. (**A**) Daily incidence. (**B**) Administered severe patient. Colors of model simulation curves indicate the value of NPIs related factor (μ). The solid and dashed curves correspond to maximum daily booster shot administration set to 300,000 and 100,000, respectively. Blue dotted line in (**B**) is the expected severe patient capacity assuming that the increasing trend continues (25.42 per day, based on historical data), while the red dotted line indicates a constant trend. Red boxes are the data points.
NPI = non-pharmaceutical intervention.

DISCUSSION

Age-structured models are useful to analyze the heterogeneity of transmission patterns according to different age groups and suggest age-specific policies, such as vaccine prioritization or protocols related to school closures. To solve an age-structured model, transmission rate matrix (or contact matrix) is required. However, obtaining a contact matrix through survey during epidemic would be challenging. In this work, we construct the transmission matrix using MLE. The maximum value of the estimated transmission rate for age over 60 and under 60 were 6.22 and 4.06, respectively. Considering that approximately 300,000 of seniors are using elderly facilities, the transmission matrix shows the importance of disease control in elderly facilities during an epidemic.[46]

We quantified the impact of NPIs by using μ, whose value was varied to indicate the different levels of social distancing policies. The range of the value of μ is a useful guide for the
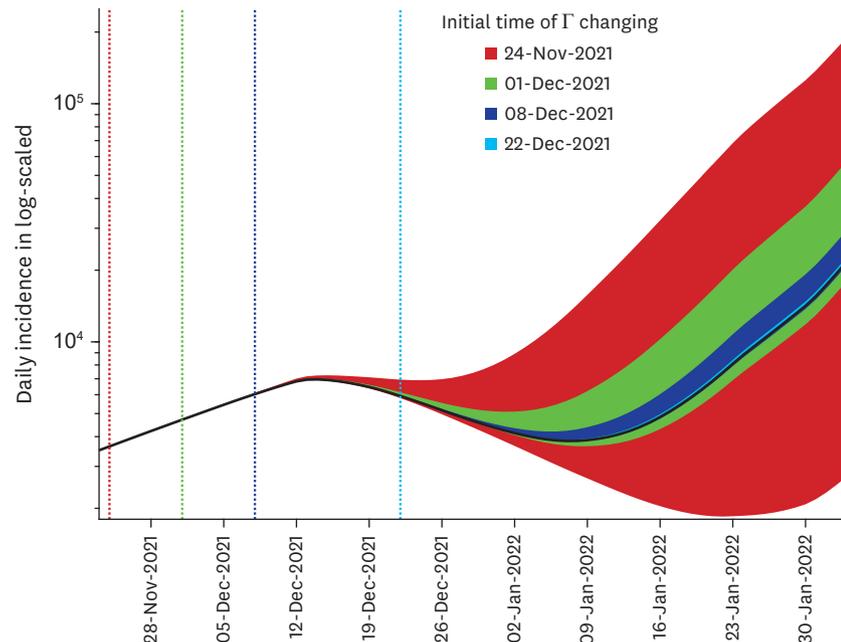
Fig. 5. Examination of screening measure. Colored area indicates the range of daily incidence in log-scaled simulation as the number and date of daily overseas entrant case is varied.

healthcare authorities in deciding the intensity of the intervention. Using a parameter bootstrapping approach, we showed that the estimated impact of NPIs was within the confidence interval. Furthermore, sensitivity analysis of the μ_i's and the other parameters (latent period, infectious period, vaccine effectiveness, waning rates, impact of omicron variant, impact of antiviral drugs) was performed. Results of the sensitivity analysis (displayed in **Supplementary Fig. 2**) emphasized that the factors with most impact to the epidemic are the NPIs (μ) and the infectious period ($1/\alpha$). The arrival time (T_o) of the omicron variant has an increasing correlation on the number of cases as time goes by. Antiviral drugs do not affect the number of cumulative confirmed cases but over time, the effect on cumulative severe cases becomes more apparent. We could also observe the risk of spreading during the holiday season, with an estimated lower μ value, which is a considerable factor for the policymakers. Strict social distancing, associated with high μ value, remains a good control measure to minimize the size of epidemic. However, there is serious economic burden if a strict policy is continued. Therefore, our model can be used as a guide in determining a more relaxed policy considering changes in the number of severe bed capacity.

In **Fig. 4**, we observe the impact of booster shots on the number of administered severe patients under different values of NPIs-related reduction factor μ. In particular, it is possible for the initial peak of the green curve ($\mu = 0.6$) to reach the assumed value of severe patient capacity. If the maximum number of booster shots per day is small (dashed), indirectly expressing vaccine hesitancy, then the green curve reached the red-dotted line, which is a pessimistic assumption that the number of severe beds has not increased. On the other hand, the number of administered severe patients is manageable if the number of booster shots is large (solid). This result highlights the importance of booster shots in reducing the number of mild and severe infections. Finally, we observe that incidence data (red boxes) follow the green dashed curve while the administered severe patients follow the green solid curve. In the official national data, critically ill patients are defined as individuals who have $SpO_2 < 94\%$
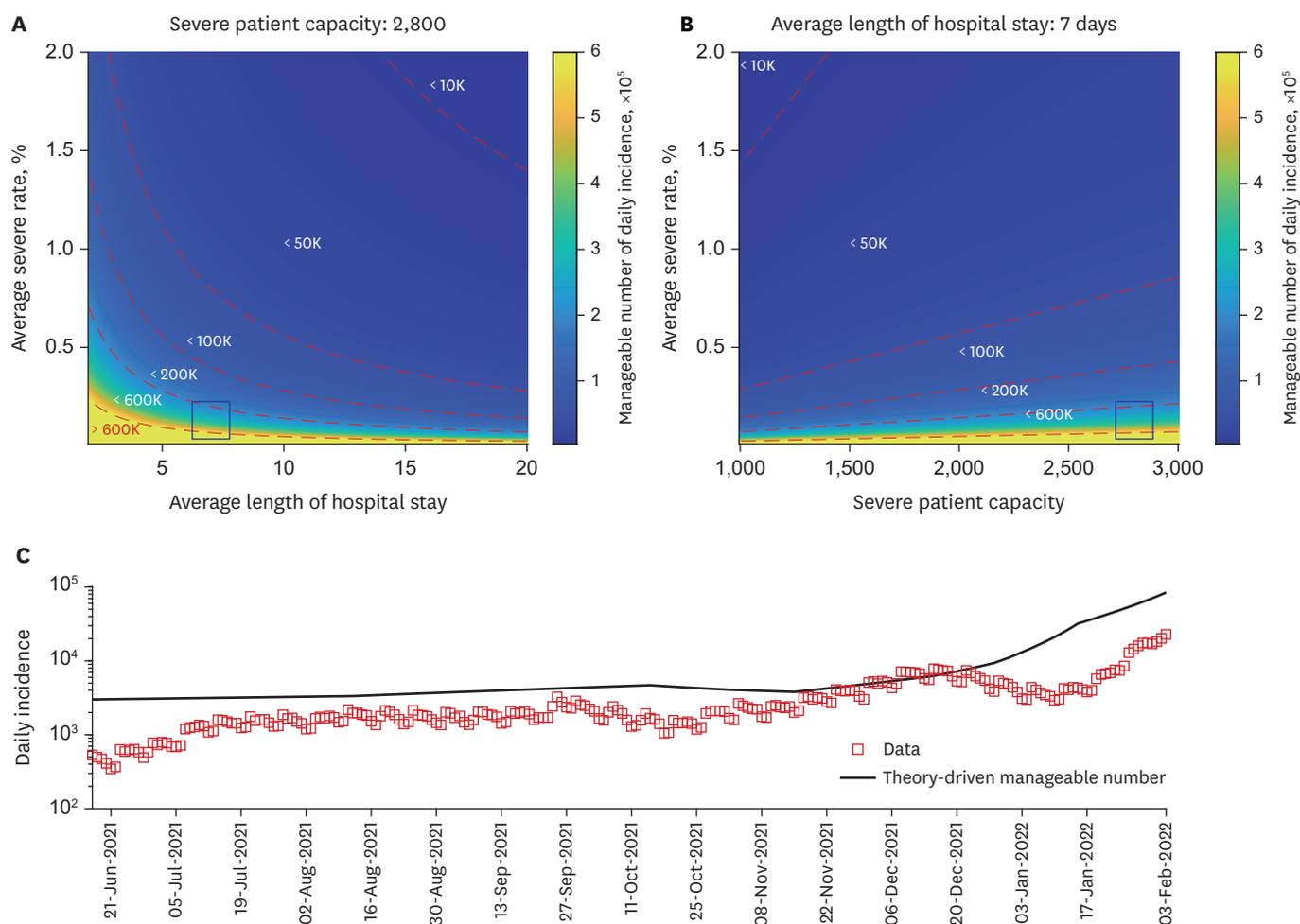
Fig. 6. Theory-driven manageable number of daily incidence considering endemic equilibrium. (**A**) Color-scaled result considering varying length of hospital stay and severe rate, with fixed severe patient capacity to 2,800. Blue square indicates the severe rate of Korea in mid-February 2022. (**B**) Color-scaled result considering varying severe patient capacity and severe rate, with fixed length of hospital stay as 7 days. (**C**) Real daily incidence data and theory-driven manageable number of daily incidence using real data.

on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. Therefore, a patient who is infected with SARS-CoV-2 and needs intensive care unit care for a disease other than a respiratory system problem is not defined as a critically ill patient. For this reason, data on bed use may be underestimated.

Screening measures are the primary NPIs in blocking the arrival of a new strain in the local community. However, we found that the impact of screening measures is reduced as the incoming strain becomes more dominant in the local community. Since strict screening policies incur serious socio-economic costs, strengthening screening measures might have less effect on the current situation (March 2022). Nevertheless, strengthening screening measures would be important if there is an emerging VOC outside of the country because our results suggest that strong screening measures can delay the new peak if they are applied early.

The derived formula (Equation 1) calculates the manageable number of daily incidence cases using the data on severe rate, the average duration of hospital stay, and severe patient capacity. Factors such as emergence of relatively mild variants, vaccines, and enhanced medical support

have decreased the severe rate of COVID-19 infections. Furthermore, the average duration of hospital stay reduced significantly, from 28 days to 7 days, since February 2020 to March 2022.[45,46] The endemic equilibrium study can be useful in crafting policies that ensure the number of incidence and severe cases are within safe levels. For example, our theory-driven model indicates that the declaration of suspended gradual recovery on mid-December 2021 might have been inevitable to control the surge in daily incidence. Data on the severe patient capacity also showed a steep rise during this period (dashed curve in **Fig. 3C**).

Our mathematical-modeling-based approach is not only valid on the delta or omicron variants of COVID-19 but can be adopted for other emerging infectious disease in the future, or new variant of COVID-19. Because NPIs are incorporated using the parameter μ, our model would be useful as a guide in policymaking. Analysis considering various important factors, such as waning effects of vaccine and natural recovery, or variants, may give insights for the disease control.

A limitation of the study is that breakthrough infection during MLE process was not considered due to the lack of available data. On March 14, 2022, confirmation of cases was expanded to include positive rapid antigen tests, which has a lower accuracy compared to polymerase chain reaction test. This may lead to under-reporting, which is also not considered in this study. In this study, we assumed that the waning of immunity decays exponentially after vaccination (or natural recovery). Waning rates were estimated using vaccine effectiveness of primary and third doses, and a single value for the waning rate of booster shot for all age groups is applied. Furthermore, we did not include the administration of a second booster shot in the model and assumed that the protection against severe infections does not wane. Because of these model uncertainties, we added an appendix in the supplementary file to analyze the sensitivity of the relevant parameters with respect to the cumulative confirmed and severe cases. The model was formulated to reflect the COVID-19 policy of the Korean government. If a policy is changed, for example, when the self-isolation policy for confirmed individuals is lifted, our model may need to be modified. In our simulations, antiviral drugs were incorporated during the last 20 days of the parameter estimation. A more comprehensive analysis of administering antiviral drugs to all age groups, the effect of varying effectiveness on future scenarios, and cost-effectiveness analysis are interesting research topics but will demand a separate study. These and the above-mentioned limitations can be pursued in future works.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

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Supplementary Table 1
Model parameters, non-age dependent

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Supplementary Table 2

Model parameters, age-and-strain dependent. Note that subscript and superscript indicate strain and age group, respectively

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Supplementary Table 3

Bootstrapping results showing the mean values, standard deviations, and 95% CIs of the re-estimates of μ

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Supplementary Fig. 1

Distribution of the bootstrapping results. Titles of the panels indicate the central date of each estimation period. Red triangles are the estimated values.

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Supplementary Fig. 2

PRCC values of the parameters for model outputs (A) cumulative confirmed cases and (B) cumulative severe cases.

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Supplementary References

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REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed* 2020;91(1):157-60.
   PUBMED | **CROSSREF**
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;55(3):105924.
   PUBMED | **CROSSREF**
3. Thakur V, Kanta Ratho R. Omicron (B. 1.1. 529): a new SARS-CoV-2 variant of concern mounting worldwide fear. *J Med Virol* 2022;94(5):1821-4.
   PUBMED | **CROSSREF**
4. Rahimi F, Talebi Bezmin Abadi A. Omicron: a highly transmissible SARS-CoV-2 variant. *Gene Rep* 2022;27:101549.
   PUBMED | **CROSSREF**
5. Rössler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron variant neutralization in serum from vaccinated and convalescent persons. *N Engl J Med* 2022;386(7):698-700.
   PUBMED | **CROSSREF**
6. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. COVID-19 vaccine effectiveness against the Omicron (B. 1.1. 529) variant. *N Engl J Med* 2022;386(16):1532-46.
   PUBMED | **CROSSREF**
7. Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Schommers P, Lehmann C, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. *Nat Med* 2022;28(3):477-80.
   PUBMED | **CROSSREF**

8. Zhou R, To KK, Peng Q, Chan JM, Huang H, Yang D, et al. Vaccine-breakthrough infection by the SARS-CoV-2 Omicron variant elicits broadly cross-reactive immune responses. *Clin Transl Med* 2022;12(1):e720.
   PUBMED | **CROSSREF**

9. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. *JAMA* 2022;327(6):583-4.
   PUBMED | **CROSSREF**

10. Christensen PA, Olsen RJ, Long SW, Snehal R, Davis JJ, Ojeda Saavedra M, et al. Signals of significantly increased vaccine breakthrough, decreased hospitalization rates, and less severe disease in patients with coronavirus disease 2019 caused by the Omicron variant of severe acute respiratory syndrome coronavirus 2 in Houston, Texas. *Am J Pathol* 2022;192(4):642-52.
    PUBMED | **CROSSREF**

11. Shin DH, Oh HS, Jang H, Lee S, Choi BS, Kim D. Analyses of confirmed COVID-19 cases among Korean military personnel after mass vaccination. *J Korean Med Sci* 2022;37(3):e23.
    PUBMED | **CROSSREF**

12. Choe PG, Kim Y, Chang E, Kang CK, Kim NJ, Cho NH, et al. Kinetics of neutralizing antibody responses against SARS-CoV-2 Delta Variant in patients infected at the beginning of the pandemic. *J Korean Med Sci* 2022;37(8):e67.
    PUBMED | **CROSSREF**

13. Yi S, Kim JM, Choe YJ, Hong S, Choi S, Ahn SB, et al. SARS-CoV-2 Delta variant breakthrough infection and onward secondary transmission in household. *J Korean Med Sci* 2022;37(1):e12.
    PUBMED | **CROSSREF**

14. Um J, Choi YY, Kim G, Kim MK, Lee KS, Sung HK, et al. Booster BNT162b2 COVID-19 vaccination increases neutralizing antibody titers against the SARS-CoV-2 Omicron variant in both young and elderly adults. *J Korean Med Sci* 2022;37(9):e70.
    PUBMED | **CROSSREF**

15. Kwon SR, Kim N, Park H, Minn D, Park S, Roh EY, et al. Strong SARS-CoV-2 antibody response after booster dose of BNT162b2 mRNA vaccines in uninfected healthcare workers. *J Korean Med Sci* 2022;37(19):e135.
    PUBMED | **CROSSREF**

16. Mohapatra RK, Tiwari R, Sarangi AK, Islam MR, Chakraborty C, Dhama K. Omicron (B.1.1.529) variant of SARS-CoV-2: concerns, challenges, and recent updates. *J Med Virol* 2022;94(6):2336-42.
    PUBMED | **CROSSREF**

17. Mahase E. COVID-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. *BMJ* 2021;375:n2713.
    PUBMED | **CROSSREF**

18. Korea Disease Control and Prevention Agency. *Regular Briefing (February 14, 2022)*. Cheongju: Korea Disease Control and Prevention Agency; 2022.

19. Lee JJ, Choe YJ, Jeong H, Kim M, Kim S, Yoo H, et al. Importation and transmission of SARS-CoV-2 B.1.1.529 (Omicron) variant of concern in Korea, November 2021. *J Korean Med Sci* 2021;36(50):e346.
    PUBMED | **CROSSREF**

20. Ministry of Health and Welfare (KR). Press release: introduction of 210,000 oral treatment for COVID-19, available from January 14 at the earliest. https://www.korea.kr/news/pressReleaseView.do?newsId=156491164. Updated 2022. Accessed June 17, 2022.

21. Korea Disease Control and Prevention Agency. Policy briefing: administering treatment for COVID-19 expands to patients with underlying diseases age over 40s. https://www.korea.kr/news/policyNewsView.do?newsId=148899171. Updated 2022. Accessed June 17, 2022.

22. Roosa K, Lee Y, Luo R, Kirpich A, Rothenberg R, Hyman JM, et al. Real-time forecasts of the COVID-19 epidemic in China from February 5th to February 24th, 2020. *Infect Dis Model* 2020;5:256-63.
    PUBMED | **CROSSREF**

23. Kim S, Seo YB, Jung E. Prediction of COVID-19 transmission dynamics using a mathematical model considering behavior changes in Korea. *Epidemiol Health* 2020;42:e2020026.
    PUBMED | **CROSSREF**

24. Tuite AR, Fisman DN, Greer AL. Mathematical modelling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada. *CMAJ* 2020;192(19):E497-505.
    PUBMED | **CROSSREF**

25. Sarkar K, Khajanchi S, Nieto JJ. Modeling and forecasting the COVID-19 pandemic in India. *Chaos Solitons Fractals* 2020;139:110049.
    PUBMED | **CROSSREF**

26. Kucharski AJ, Klepac P, Conlan AJ, Kissler SM, Tang ML, Fry H, et al. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. *Lancet Infect Dis* 2020;20(10):1151-60.
    PUBMED | CROSSREF

27. Kretzschmar ME, Rozhnova G, Bootsma MC, van Boven M, van de Wijgert JH, Bonten MJ. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Health* 2020;5(8):e452-9.
    PUBMED | CROSSREF

28. Kim S, Ko Y, Kim YJ, Jung E. The impact of social distancing and public behavior changes on COVID-19 transmission dynamics in the Republic of Korea. *PLoS One* 2020;15(9):e0238684.
    PUBMED | CROSSREF

29. Kim S, Kim YJ, Peck KR, Jung E. School opening delay effect on transmission dynamics of coronavirus disease 2019 in Korea: based on mathematical modeling and simulation study. *J Korean Med Sci* 2020;35(13):e143.
    PUBMED | CROSSREF

30. Eikenberry SE, Mancuso M, Iboi E, Phan T, Eikenberry K, Kuang Y, et al. To mask or not to mask: modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. *Infect Dis Model* 2020;5:293-308.
    PUBMED | CROSSREF

31. Bubar KM, Reinholt K, Kissler SM, Lipsitch M, Cobey S, Grad YH, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science* 2021;371(6532):916-21.
    PUBMED | CROSSREF

32. Ko Y, Lee J, Kim Y, Kwon D, Jung E. COVID-19 vaccine priority strategy using a heterogenous transmission model based on maximum likelihood estimation in the Republic of Korea. *Int J Environ Res Public Health* 2021;18(12):6469.
    PUBMED | CROSSREF

33. Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. *Lancet Infect Dis* 2021;21(6):793-802.
    PUBMED | CROSSREF

34. Min KD, Tak S. Dynamics of the COVID-19 epidemic in the post-vaccination period in Korea: a rapid assessment. *Epidemiol Health* 2021;43:e2021040.
    PUBMED | CROSSREF

35. Murayama H, Kayano T, Nishiura H. Estimating COVID-19 cases infected with the variant alpha (VOC 202012/01): an analysis of screening data in Tokyo, January-March 2021. *Theor Biol Med Model* 2021;18(1):13.
    PUBMED | CROSSREF

36. Sonabend R, Whittles LK, Imai N, Perez-Guzman PN, Knock ES, Rawson T, et al. Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. *Lancet* 2021;398(10313):1825-35.
    PUBMED | CROSSREF

37. Korea Disease Control and Prevention Agency. Current COVID-19 status in local. http://ncov.mohw.go.kr/bdBoardList_Real.do?brdId=1&brdGubun=11&ncvContSeq=&contSeq=&board_id=&gubun=. Updated 2022. Accessed June 17, 2022.

38. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. COVID-19 vaccine effectiveness in New York state. *N Engl J Med* 2022;386(2):116-27.
    PUBMED | CROSSREF

39. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27(7):1205-11.
    PUBMED | CROSSREF

40. Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A, et al. Protection against SARS-CoV-2 after COVID-19 vaccination and previous infection. *N Engl J Med* 2022;386(13):1207-20.
    PUBMED | CROSSREF

41. Korea Disease Control and Prevention Agency. *Regular Briefing (February 3, 2022)*. Cheongju: Korea Disease Control and Prevention Agency; 2022.

42. Jo Y, Kim SB, Radnaabaatar M, Huh K, Yoo JH, Peck KR, et al. Model-based cost-effectiveness analysis of oral antivirals against SARS-CoV-2 in Korea. *Epidemiol Health* 2022; e2022034.
    PUBMED | CROSSREF

43. Korea Disease Control and Prevention Agency. *Regular Briefing (March 14, 2022)*. Cheongju: Korea Disease Control and Prevention Agency; 2022.

44. Korea Disease Control and Prevention Agency. Public Health Weekly Report, PHWR (Vol.14, No.37, 2021). https://www.kdca.go.kr/board/board.es?mid=a30501000000&bid=0031&list_no=716914&act=view#. Updated 2021. Accessed June 17, 2022.

45. Seoul Metropolitan Government. *The Daily News Review of COVID-19 (March 4, 2022)*. Seoul: Seoul Metropolitan Government; 2022.

46. Ministry of Health and Welfare (KR). Current status of welfare facilities for the elderly. https://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_117N_B00003. Updated 2020. Accessed June 17, 2022.