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Modeling transmission of SARS-CoV-2 Omicron in China

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Abstract

Having adopted a dynamic zero-COVID strategy to respond to SARS-CoV-2 variants with higher transmissibility since August 2021, China is now considering whether and for how long this policy can remain in place. The debate has thus shifted towards the identification of mitigation strategies for minimizing disruption to the healthcare system in the case of a nationwide epidemic. To this aim, we developed an age-structured stochastic compartmental susceptible-latent-infectious-removed-susceptible (SLIRS) model of SARS-CoV-2 transmission calibrated on the initial growth phase for the 2022 Omicron outbreak in Shanghai, to project COVID-19 burden (i.e., number of cases, patients requiring hospitalization and intensive care, and deaths) under hypothetical mitigation scenarios. The model also considers age-specific vaccine coverage data, vaccine efficacy against different clinical endpoints, waning of immunity, different antiviral therapies, and non-pharmaceutical interventions. We find that the level of immunity induced by the March 2022 vaccination campaign would be insufficient to prevent an Omicron wave that would result in exceeding critical care capacity with a projected intensive care unit peak demand of 15.6-times the existing capacity and causing approximately 1.55 million deaths. However, we also estimate that protecting vulnerable individuals by ensuring accessibility to vaccines and antiviral therapies, and maintaining implementation of non-pharmaceutical interventions could be sufficient to prevent overwhelming the healthcare system, suggesting that these factors should be points of emphasis in future mitigation policies.

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Introduction

First discovered in Southern Africa in November 2021[1], the Omicron variant of SARS-CoV-2 has swiftly spread across the world and replaced the Delta variant to become the dominant strain globally[2]. Omicron has demonstrated an increased transmissibility relative to Delta[1,3-5] and immune escape capability[6,7]. Together with the progressive waning of the protection against the infection associated with previous infections and/or vaccination[8-12], these characteristics have led to major Omicron epidemics in most countries[13]. Despite signs of a possibly lower clinical severity than Delta[14-18], the sheer volume of Omicron infections has strained healthcare systems worldwide, including in the US[19,20] and the UK[21]. For instance, in the UK, the Omicron wave has led to higher infection rates than during the second wave in the winter of 2021, with substantial hospitalizations and deaths (over 1,000 deaths reported per week between January 14 and February 4, 2022)[21].

After controlling the initial epidemic wave in Hubei in early 2020, China has deployed multilayer non-pharmaceutical intervention (NPI) protocols to contain sporadic COVID-19 outbreaks, largely introduced from international travelers. Maintaining a low infection rate in the general population throughout the pandemic has provided China time to mass immunize the population against SARS-CoV-2. As of April 18, 2022, 91.4% of the population aged ≥3 years has received the full primary schedule of the COVID-19 vaccination (either inactivated vaccines administered on a two-dose schedule, or recombinant subunit vaccines administered on a three-dose schedule, or recombinant adenovirus type-5-vectored vaccines administered as a single dose); 53.7% of them have received a booster shot[22]. However, the vaccine-induced population immunity may be insufficient to prevent COVID-19 outbreaks. From March 1 to April 22, 2022, more than 500,000 local Omicron infections have been reported in almost all provinces across China, with the majority (about 93%) occurring in Shanghai[22]. To contain the highly infectious and immune evasive Omicron variant, additional NPI measures will be required to maintain the dynamic zero-COVID policy. This policy, adopted by China to respond to SARS-CoV-2 variants with higher transmissibility since August 2021, consists of a comprehensive set of measures to identify SARS-CoV-2 infections and stop any transmission chain, thus repeatedly zeroing local transmission[23]. Whether and for how long a zero-

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COVID policy can remain in place is questionable and, as recommended by the WHO[24], every country should be prepared to chart its own path to transit from a pandemic to an endemic phase while accounting for local epidemiology, vaccination levels, population immunity, and the strength of health systems. In this regard, as of May 2022, two approved antiviral treatments (BRII-196/BRII-198 combination and nirmatrelvir tablet/ritonavir tablet combination package) have been used in China, providing a new tool against COVID-19[25,26].

Here, we explore the feasibility of a COVID-19 mitigation strategy to safeguard China's shift from pandemic containment to mitigation, while minimizing the disease burden and social cost. Specifically, we leverage a mathematical model (Extended Data Figure 1) to simulate a hypothetical Omicron wave in China based on the data from the 2022 Omicron outbreak in Shanghai (Extended Data Figure 2), project the demand for hospital beds and intensive care units (ICUs), and explore mitigation strategies combining vaccinations, antiviral therapies, and NPIs to reduce COVID-19 burden while preventing the healthcare system being overwhelmed.

Results

Baseline scenario

The baseline scenario considers a homologous booster vaccination in the absence of NPIs and antiviral therapies. Specifically, the following conditions are simulated: 1) the introduction of 20 Omicron-infected individuals into the Chinese population on March 1, 2022; 2) the reproduction number (R) at the beginning of the simulation is set at 3.9; when considering the partial protection of the population induced by vaccination, the reproduction number decreases to 3.4, in agreement with what we estimated for the early phase (from March 1 to 8, 2022) of the epidemic in Shanghai (Extended Data Figure 2), before strict control measures were implemented (see Methods); 3) booster doses of inactivated vaccines are rolled out at a speed of 5 million doses per day from March 1, 2022; before that date the daily vaccination rates were informed by the cumulative number of doses administered in China; 4) 90% of individuals who have completed the primary vaccination schedule by at least 6 months receive a booster shot; 5) vaccine efficacy (VE) is set according to the values reported in Supplementary Table 1, considering a low immune escape scenario with

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same VEs against hospitalization and deaths between homologous booster and heterologous booster vaccination as observed in Hong Kong[27]; and 6) antiviral therapies are not distributed.

Our simulated baseline scenario suggests that, in the absence of NPIs, the introduction of the Omicron variant in China in March 2022 could have the potential to generate a tsunami of COVID-19 cases. Over a 6-month simulation period, such an epidemic is projected to cause 112.2 million symptomatic cases (79.58 per 1,000 individuals), 5.1 million hospital admissions (3.60 per 1,000 individuals), 2.7 million ICU admissions (1.89 per 1,000 individuals), and 1.6 million deaths (1.10 per 1,000 individuals), with a major wave occurring between May and July 2022 (Figures 1–2).

According to our model simulations, 41.3% of non-ICU hospitalizations and 28.2% of ICU admissions would occur among vaccinated individuals. Most non-ICU hospitalizations are estimated to occur in the adult population (26.6% among individuals aged 18–59 years and 59.1% among individuals aged ⩾60 years), while over 90% of ICU admissions would occur among individuals aged ⩾60 years (Figure 1). The majority of deaths (76.7%) are estimated to occur among non-vaccinated individuals, despite representing only 12.1% of the population (Figure 1). Unvaccinated individuals aged ≥60 years are projected to account for 74.7% of the total number of deaths due to the gap in vaccination coverage in this portion of the population, approximately 52 million people aged ≥60 years are not fully vaccinated as of March 18, 2022[28].

In addition to presenting analyses for a national average, we analyze three highly diverse areas of China: Shanghai, Shandong, and Shanxi. For each of these areas we consider a specific vaccination coverage, age structure of the population, contact patterns of the population (Supplementary Figure 1), and number of available hospital beds and ICUs (Supplementary Table 2). The results show a considerable heterogeneity across the different areas. For example, the number of deaths per 1,000 inhabitants in the baseline scenario is projected to be 1.79 in Shanghai (where, as of April 15, 2022, 62% of individuals aged ≥60 years were fully vaccinated and 38% have received a booster dose[29]) compared with 0.84 in Shandong (the province with

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the highest vaccination coverage in individuals aged ≥60 years; as of March 21, 2022, 89.16% of them were fully vaccinated and 72.45% have received a booster dose[30]) (Figure 2).

To evaluate the impact of an uncontrolled Omicron epidemic on the national healthcare system, we considered that all COVID-19 hospitalizations require hospital beds for respiratory illness, and critically ill cases require ICU beds, and computed the corresponding demands. At the national scale, it is estimated that 1.57 million hospital beds for respiratory illness would be required at the epidemic peak, which is fewer than the number of existing hospital beds for respiratory illness (3.1 million) in China[31]. However, the peak demand of ICU beds (1.00 million) corresponds to 15.6 times the number of existing ICU beds in China (i.e., 64,000)[31]. The period of ICU bed shortage is estimated to last for approximately 44 days (Figure 3). In the regional analyses, substantial shortages of ICU beds were also predicted to occur in Shanghai, Shandong, and Shanxi province (Extended Data Figure 3).

When considering a more conservative scenario on the immune escape of the Omicron variant (referred as to high immune escape scenario), with i) lower VEs against all clinical endpoints as compared to low immune escape scenario, and ii) lower VEs against hospitalization and deaths for homologous booster as compared to heterologous booster vaccination (as observed in Brazil[32], Supplementary Table 1), the projected number of hospitalizations, ICU admissions, and deaths at the national level would increase by 77.3%, 62.1% and 50.2%, respectively (Extended Data Figure 4).

Impact of individual mitigation strategies

We separately investigated the impact of three categories of strategies to mitigate COVID-19 burden: i) vaccination, including heterologous booster doses and promoting vaccination coverage among unvaccinated individuals aged ≥60 years, ii) antiviral therapies, and iii) NPIs. Regarding booster vaccination, if we consider the administration of a heterologous booster based on a subunit vaccine (subunit vaccines scenario) in the low immune escape scenario, little difference would be observed in terms of COVID-19 burden (Figure 4); on the other hand, in the high immune escape scenario, a larger decrease of COVID-19 burden (8.4% in the number of deaths and

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17.7% in the number of hospital admissions) could be achieved by administrating a heterologous booster based on a subunit vaccine (Extended Data Figure 5). Filling the gap in the vaccination coverage among the elderly (i.e., vaccinating all eligible individuals aged 60 years or more), including both primary and booster vaccination as in the baseline scenario (vaccinating elderly scenario) would lead to a 33.8%, 54.1%, and 60.8% decrease in hospital admissions, ICU admissions, and deaths, respectively (Figure 4).

In the absence of NPIs, assuming that 50% of symptomatic cases could be treated with the approved Chinese COVID-19 BRII-196/BRII-198 combination therapy, which has been reported to be 80% effective in preventing hospitalization and death[33], a 36.5%, 39.9%, and 40.0% decrease in hospital admissions, ICU admissions, and deaths is estimated (50% uptake and 80% efficacy scenario). In the best-case scenario in which all symptomatic cases are treated with the highly efficacious oral COVID-19 drug nirmatrelvir tablet/ritonavir tablet combination (which is 89% effective in preventing hospitalization and death[34] and has already been used in China[26]), the number of hospital admissions, ICU admissions, and deaths could be substantially reduced by 81.2%, 88.8%, and 88.9% (100% uptake and 89% efficacy scenario) (Figure 4).

We then modeled the impact of introducing different levels of NPIs (in the presence of vaccination, but absence of antiviral therapies). First, we tested the implementation of a national-level school closure strategy (school closure scenario); although the number of infections decrease by 3.5%, COVID-19 burden does not, due to a shift in the age-distribution of infections towards older ages. Additionally closing all workplaces (school and workplace closure scenario) would lead to a decrease of 23.8%, 13.1% and 22.4% for the number of hospitalizations, ICU admissions and deaths, respectively. Second, we considered a scenario where NPIs equally reduce the risk of infection across all age groups, and we simulated different intensity of NPIs leading to $R_t \leqslant 3$ (similar to values observed in England[35] and India[36] during the Omicron wave in winter 2021–2022). In this scenario, only the adoption of NPIs capable of reducing R_t to values no larger than 2 would lead to a substantial decrease in health outcomes (namely, a decrease of 40.1%, 33.4%, and 48.6% of the number of

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hospitalizations, ICU admissions, and deaths, respectively) (Figure 4).

In summary, none of the analyzed scenarios is estimated to have the potential to reduce the number of COVID-19 deaths to a level closer to the annual influenza-related deaths in China (88,000)[37] (Figure 4). In all scenarios, the peak demand for ICUs is projected to be 1.7–14.8 times the maximum capacity, with a total of 19–48 days of bed shortages (Figure 3b). We emphasize that closing all school and workplace as well as implementing stringent NPIs to reduce R_t to 2 would result in highly delayed epidemics that extend beyond our projection window (6 months); as such, their final impact is not evaluated in this analysis (Figure 3b).

Impact of combined mitigation strategies

None of the investigated individual mitigation strategies alone is capable to reduce the death toll to the level of an influenza season or to prevent exceeding critical care capacity (Figures 3–4). Here, we assessed the effects of synergetic strategies leveraging heterologous booster vaccination, increasing vaccination coverage among the unvaccinated individuals aged 60 years or more, distributions of antiviral therapies, and adoption of NPIs at the same time (Figure 5).

None of the simulated interventions is projected to exceed the national capacity of hospital bed capacity for respiratory illness. Instead, a synergetic effort of combining different strategies would be needed to prevent exceeding ICU capacity and limiting the number of deaths to a value comparable to that of seasonal influenza. According to our analysis, key aspects of this synergetic effort are the increase of vaccine uptake in the elderly and the widespread use of antiviral therapies (Figure 5). If these two conditions are not met, relying on NPIs capable of reducing R to 2 or lower is needed to prevent overwhelming the healthcare system.

Discussion

Using a stochastic dynamic model of SARS-CoV-2 transmission, our study projects the COVID-19 burden caused by the importation of Omicron infections in mainland China, should the dynamic zero-COVID policy be lifted. In the context of the vaccination strategy adopted until March 2022, we estimated that the introduction of

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the Omicron variant would cause substantial surges in hospitalizations, ICU admissions, and deaths, and would overwhelm the healthcare system with an estimated burden of 15.6 times the available ICU capacity.

Should an Omicron variant epidemic be allowed to spread uncontrolled in mainland China, we project 1.10 deaths per 1,000 inhabitants over a 6-month period. By comparison, 187,372 deaths have been reported in the USA[38] (i.e., 0.57 deaths per 1,000 inhabitants) over the period from December 15, 2021 to April 15, 2022, roughly corresponding to the Omicron wave. We estimate that around 77% of the death toll in China would occur in unvaccinated individuals, with most deaths occurring among unvaccinated individuals aged 60 years or more (52 million people). A similar trend has been observed in the Omicron-driven fifth COVID-19 wave in Hong Kong Special Administrative Region (SAR) of China, which began in early 2022[39]. Our findings highlight the key role of increasing vaccine uptake rate among the elderly to limit COVID-19 burden and to prevent overwhelming the healthcare system. A second key factor to reach these goals is represented by the widespread and timely distribution of a highly efficacious antiviral therapy. When both vaccine uptake in the elderly is substantially increased (97%) and 50% or more of symptomatic infections are treated with antiviral therapies, the peak occupancy of ICUs may not exceed the national capacity and the death toll may be comparable to that of seasonal influenza. In the absence of these two conditions, the most optimistic strategy to prevent overwhelming the healthcare system appears to be the reliance of strict NPIs.

China is a highly diverse country with urban megalopolises on the eastern seaboard and rural areas in the northwest. Such diversity is also reflected by heterogeneous vaccination coverage, demographic structure of the population, mixing patterns, and capacity of the healthcare system. When accounting for these heterogeneities, our simulations show considerable differences in the projected COVID-19 burden for different areas of China. According to our projections, the population of Shanghai would experience a higher COVID-19 burden than other areas such as Shandong and Shanxi. This increased burden would be led by a much larger incidence of severe infections in the population aged 60 years or older, which is associated with a lower vaccination coverage in this segment of the population. This result confirms the importance of filling the vaccination gap among the elderly and the need to tailor

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interventions on the specific immunological landscape of the population.

Our study has several limitations. First, we assumed that the mortality rate remains constant over the projection period; however, studies have suggested that the mortality rate may increase during periods of high strain on hospital services[40,41]. Second, although we conducted a comprehensive literature search, the epidemiological characteristics of Omicron, clinical severity, VEs of primary and booster vaccination and its persistence against different clinical endpoints, as well as the effectiveness of antiviral therapies are not fully understood. For this reason, we have conducted extensive sensitivity analyses to explore the impact of the uncertainty of model parameters. Third, data on antiviral therapy availability by region is unknown and thus not included in our analysis. Possible regional differences in stockpiles of antiviral therapies could widen the already large differences in COVID-19 burden that we have estimated among the study locations.

In conclusion, should the Omicron outbreak continue unabated, despite a primary vaccination coverage of ≥90% and homologous booster vaccination coverage of ⩾40% as of March 2022, we project that the Chinese healthcare system will be overwhelmed with a considerable shortage of ICUs. The contemporary increasing of vaccine uptake in the elderly and widespread distribution of antiviral therapies or the implementation of strict NPIs would be needed to prevent overwhelming the healthcare system and reduce the death toll of an epidemic wave to a level comparable with that of an influenza season. Protecting vulnerable individuals by ensuring access to vaccination and antiviral therapies, as well as maintaining implementation of NPIs (e.g., mask-wearing, enhanced testing, social distancing, and reducing mass gatherings), should be emphasized together with tailoring region-specific interventions. In the long term, improving ventilation, strengthening critical care capacity, and the development of new highly efficacious vaccines with long-term immune persistence would be key priorities.

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Author contributions

H.Y. conceived, designed, and supervised the study. J.C. designed the model. X.D. and H.L. developed the model. J.C., X.D., J.Y., X.C., Q.W., J.Z., W.Z., Z.Z., Z.C., W.L., Y.L., and X.Z. collected the data. K.S. and M.A. contributed to the methodology. X.D. and J.C. analyzed the model output. J.C., X.D., J.Y., K.S., M.A., and H.Y. interpreted the results. Z.C., X.D., C.P., J.C., and R.S. prepared the figures. J.C., J.Y., X.D., Z.C., and H.L. wrote the first draft of the manuscript. M.A. and K.S. critically revised the content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Competing interests

H.Y. received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company, and SINOVAC Biotech Ltd. Except for research funding from SINOVAC Biotech Ltd, which is related to the data analysis of clinical trials of immunogenicity and safety of CoronaVac, the others are not related to COVID-19. M.A. has received research funding from Seqirus; the funding is not related to COVID-19. All the other authors have no competing interests.

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Figure legends

Fig. 1 | Projected SARS-CoV-2 Omicron burden in China for baseline scenario from March, 2022 to September, 2022. a, daily hospital (non-ICU) admissions per 10,000 individuals. **b**, epidemiological status of hospitalized (non-ICU) patients. **c**, age distribution of hospitalized (non-ICU) patients. **d**, distribution of hospitalized (non-ICU) patients per 10,000 by age group and epidemiological status. **e**, daily ICU admissions per 10,000 individuals. **f**, epidemiological status of ICU patients. **g**, age distribution of ICU patients. **h**, distribution of ICU patients per 10,000 by age group and epidemiological status. **i**, daily deaths per 10,000 individuals. **j**, epidemiological status of deaths. **k**, age distribution of deaths. **l**, distribution of deaths per 10,000 by age group and epidemiological status. In panels **b**, **f**, and **j**, susceptible refers to individuals who do not receive COVID-19 vaccines; primary refers to those individuals who have received at least one dose of COVID-19 vaccines, considering a primary vaccination which entails a two-dose schedule; booster refers to those individuals who have received a third dose; recovery refers to individuals who have recovered from SARS-CoV-2 Omicron infection. Data are presented as median with 2.5% and 97.5% quantiles of n=200 simulations.

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Fig. 2 | Age-specific and overall incidence rates of different clinical outcomes across four settings (China, Shanghai, Shanxi and Shandong) under the baseline scenario from March, 2022 to September, 2022. a, cumulative hospital admissions per 1,000 individuals. **b**, cumulative ICU admissions per 1,000 individuals. **c**, cumulative deaths per 1,000 individuals. China represents the "national average". Number denotes median, and error bars denote 2.5% and 97.5% quantiles of n=200 simulations.

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Fig. 3 | Projected demand and shortage of hospital beds and ICUs when adopting individual mitigation strategies in China under optimistic VE scenario from March, 2022 to September, 2022. a, daily demand of hospital (non-ICU) beds. **b**, daily demand of ICU beds. In panel **b**, the green dashed line indicates the number of ICU beds available in China, and the inset plot shows days of shortage of ICU beds as a function of the number of insufficient ICU beds compared with the capacity of ICU beds. The curves in the inset are smoothed by B-spline with 8 degrees of freedom. The scenarios included in legend are as follows: Subunit vaccines refer to using a third dose of subunit vaccines as booster after two doses of inactivated vaccines as priming. Vaccinating elderly refers to vaccinating approximately 52 million people ≥60 years who have not been vaccinated yet as of March 18, 2022. 50% uptake and 80% efficacy corresponds to a scenario where 50% of symptomatic cases receive an antiviral therapy with an efficacy of 80% in preventing hospitalization and death. 100% uptake and 89% efficacy corresponds to a scenario where all symptomatic cases receive an antiviral therapy with an efficacy of 89% in preventing hospitalization and death. School and workplace closure corresponds to a scenario where, on the top of baseline strategy, all schools and workplaces remain closed for the duration of the epidemic. R_t: 3.0 and 2.0 correspond to scenarios assuming different levels of non-pharmaceutical interventions leading to reduced values of the reproduction number. Note that no strict non-pharmaceutical intervention is implemented in the baseline scenario. Data are presented as median with 2.5% and 97.5% quantiles of n=200 simulations.

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Fig. 4 | Projected impact of adopting individual mitigation strategies on COVID-19 burden in China under optimistic VE scenario from March, 2022 to September, 2022. a, cumulative number of hospital (non-ICU) admissions. The scenarios indicated on y-axis are as follows: Subunit vaccines refer to using a third dose of subunit vaccines as booster after two doses of inactivated vaccines as priming. Vaccinating elderly refers to vaccinating approximately 52 million people ≥60 years have not been vaccinated yet as of March 18, 2022. 50% uptake and 80% efficacy corresponds to a scenario where 50% of symptomatic cases receive an antiviral therapy with an efficacy of 80% in preventing hospitalization and death. 100% uptake and 89% efficacy corresponds to a scenario where all symptomatic cases receive an antiviral therapy with an efficacy of 89% in preventing hospitalization and death. School closure corresponds to a scenario where, on the top of baseline strategy, all schools remain closed for the duration of the epidemic. Similarly, School and workplace closure corresponds to a scenario, where on the top of baseline strategy, all schools and workplaces remain closed for the duration of the epidemic. R_t: 3.0, 2.5, and 2.0 correspond to scenarios assuming different levels of non-pharmaceutical interventions (NPIs) leading to reduced values of the reproduction number. Note that no strict NPI is implemented in the baseline scenario. Data are presented as median with 2.5% and 97.5% quantiles of n=200 simulations.

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Fig. 5 | Projected healthcare demand and number of deaths for combined mitigation strategies under optimistic VE scenario in China from March, 2022 to September, 2022. a, peak hospital (non-ICU) bed occupancy, with red numbers indicating peak hospital beds demand is lower than the beds capacity for respiratory illness in China. **b**, peak ICU beds occupancy, with red numbers indicating peak ICU beds demand is below the existing ICU capacity in China. **c**, cumulative death tolls, with red numbers indicating the number of death is below the number of annual influenza-related death toll in China (i.e., 88,000 deaths[37]). The circular-Manhattan plot from the innermost concentric circle to the outermost concentric circle indicates the combinations of adopting different intervention measures: homologous (inactivated) or heterologous (subunit) booster regimen; whether or not vaccinating the approximately 52 million people ≥60 years who have not been vaccinated yet as of March 18, 2022; receiving antiviral therapies with an efficacy of 80% or 89% in preventing hospitalization and death; 50% or 100% symptomatic cases receiving an antiviral therapy ; R_t representing varying intensity of non-pharmaceutical interventions. R_t = 3.9 corresponds to the scenario in the absence of strict non-pharmaceutical interventions. Data are presented as median of n=200 simulations.

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Methods

This modeling study relies on publicly available aggregated data only. As such, institutional review and informed consent are waived by the Institutional Review Board of the School of Public Health, Fudan University (Shanghai, China).

Model SARS-CoV-2 transmission and vaccination

We developed an age-structured stochastic compartmental susceptible-latent-infectious-removed-susceptible (SLIRS) model (Extended Data Figure 1) to simulate the transmission of the SARS-CoV-2 Omicron variant in China. The model considers 14 age groups (0–2, 3–11, 12–17, 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years) and age-mixing patterns for China prior to the COVID-19 pandemic[42]. The model accounts for primary and booster vaccination, disease progression, antiviral therapies, and waning immunity. All compartments and parameters are defined in Supplementary Tables 3–4. Transitions between compartments are simulated through a stochastic chain binomial process[43]. For instance, susceptible individuals move to the latent compartment at the rate $\Delta_a(t) \sim Binomial\left(S_a(t), 1 - e^{-\lambda_a(t)}\right)$, where $\lambda_a(t)$ is the force of infection for age group a at time t.

Baseline simulations were seeded with 20 imported infections on March 1, 2022 and run forward for 6 months. We consider 5 and 10 seeds as sensitivity analyses (Supplementary Figure 2). Upon infection with SARS-CoV-2, susceptible individuals (S) enter an exposed (latent) compartment (L) before becoming infectious. We consider children and adolescents were less susceptible to infection compared with adults[44,45]. A sensitivity analysis considering homogeneous susceptibility across age groups is presented in Supplementary Figure 3. Exposed individuals stay in their compartment for an average of $1/\gamma_E$=1.2 days before moving to either asymptomatic (I_A) or symptomatic (I_S) compartments according to the age-specific probability of being asymptomatic ($1 - p_a^s$). No difference in infectiousness between asymptomatic and symptomatic individuals was considered in the main analyses[46]; whereas, asymptomatic individuals were considered to be 65% less infectious than symptomatic ones in a sensitivity analysis[47] (Supplementary Figure 4). An age-dependent proportion (p_a^h) of symptomatic cases require hospitalization (H), while the

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rest of symptomatic cases and all asymptomatic infections recover naturally (R) (Extended Data Figure 1a). We assume asymptomatic infections and non-hospitalized symptomatic cases to stay in their compartments for an average of $1/\gamma_I$=5.6 days, thus resulting in mean intrinsic generation time of 6.8 days, as previously estimated for Omicron[48] (Supplementary Table 5).

For patients requiring hospitalization (H), the average time from symptom onset to hospital admission was $1/\gamma_{SH}$=2.2 days[49]. We assume that hospitalized patients do not transmit the virus. We divided the hospital settings (H) into two parts: the general ward (Hosp) and ICU ward (ICU), as illustrated in Extended Data Figure 1b. Once admitted to the hospital, a patient either remain in the general ward until discharge or is transferred into an ICU according to an age-dependent ICU admission risk. We assume that patients admitted to an ICU entered the ICU on the same day they were admitted in the hospital. Patients in the general ward (or ICU) could either stay in the general ward (or ICU) until they are discharged or die, based on the corresponding mortality risk. We assume that all deaths occur among hospitalized patients.

To capture the potential impact of newly available antiviral therapies, we divided symptomatic cases (I_S) into two categories: those who timely received an antiviral therapy after symptom onset, and those who did not (see Extended Data Figure 1c).

All compartments and transition flows are duplicated into parallel branches that represent primary (V) and booster (B) vaccinations (Extended Data Figure 1d). We assume that only susceptible individuals in compartment S are eligible for primary vaccination. To describe the recommended two-dose primary vaccination (common to the two inactivated vaccines currently widely used in China: Sinovac/CoronaVac and Sinopharm/BBIBP-CorV), compartment V was further stratified into two vaccination strata (V_1 and V_2), differentiating individuals who received one or two doses, respectively. Only uninfected individuals who have completed their primary vaccinations will receive a booster shot (B) 6 months after the completion of the primary vaccination schedule ($1/\omega_p$). Each dose produces a vaccine protection (V_1^e, V_2^e, B^e) after an average of 14 days ($1/\omega_1$, $1/\omega_3$, and $1/\omega_4$).

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We model VE against infection using a "leaky" vaccine in which all vaccinated individuals are exposed to a lower risk of infection, which is 1-VE times that of non-vaccinated individuals[50]. Like vaccination-induced protection, infection-induced immunity wanes over time (Extended Data Figure 1d). After an average of 180 days ($1/\omega_P$) since the second dose, primary-vaccinated individuals move to a new compartment ("waning vaccine effectiveness", V_2W); individuals in this compartment are ready for receiving their booster shots. Likewise, 180 days ($1/\omega_B$) after the booster shot, boosted individuals move to a new compartment ("waning vaccine effectiveness", BW). Waning of infection-induced immunity acts in a different manner from that of the vaccine. Individuals who have recovered from SARS-CoV-2 infection (R) are protected against reinfection with the same variant for an exponentially distributed duration with mean $1/\omega_R$ days, after which they move back to the susceptible compartment. The transition rates for vaccine- ad infection-induced immunity processes are defined in Supplementary Table 6.[51] The VEs against different clinical endpoints in the different stages of vaccine protection are reported in Supplementary Table 1. Details are reported in the Vaccine effectiveness section.

Model of COVID-19 burden

Age-specific risks

To measure the burden (i.e., hospitalisations, ICU admissions, and deaths) and the strain of the healthcare system, we rely on the age-specific infection fatality risk (IFR) and infection hospitalization risk (IHR) among unvaccinated individuals from the Omicron wave in Hong Kong SAR, China[39]. The Hong Kong Center for Health Protection publishes reported case fatality ratios (CFR) by age group and vaccination status[52], and compares the age profiles of reported cases against resident population[53]. Since the age profile of cumulative reported cases is very similar to the resident population by the end of 2021 in Hong Kong SAR, we assume the undetected infections have the same age profile as the reported cases. We thus estimate the age-specific IFR by dividing the age-specific CFR among unvaccinated individuals by the overall infection-reporting ratio. A report on the fifth wave of COVID-19 in Hong Kong SAR[54] estimates that around 4.5 million residents of Hong Kong had been

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infected by April 21, 2022, as of which day 1.18 million cumulative case were reported. We further calculate age-specific IHR from the Hong Kong Omicron wave[39] by dividing the estimated IFR by the age-specific fatality risk among hospitalized patients (HFR) who were not fully vaccinated (personal communication, Prof. Benjamin J. Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong) (Supplementary Table 7).

For the age-specific ICU admission risk of hospitalized patients, we adjusted the ICU admission risk associated with the ancestral lineage reported in China[55], by the ratio of the overall ICU admission risk among unvaccinated hospitalized patients infected with the Omicron variant (19.0%[56]) and those infected with the ancestral lineage (6.4%[55]). The estimated age-specific risks of disease progression are presented in Supplementary Tables 7–8.[57]

Duration of hospital and ICU stay

We set the length of stay (LoS) in hospital to 6 days; 8 days are considered for non-ICU hospitalizations with fatal outcomes based on observations in the Hong Kong Omicron wave[39] (personal communication, Prof. Benjamin J. Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong). We assumed the ICU LoS to be 8 days, consistent with references[58,59].

Healthcare resources

As of 2020, a total of 9.1 million hospital beds were available in China. Among them, 3.14 million were reserved for respiratory illness (including hospital beds in departments of internal medicine, pediatrics, infectious disease, and ICUs), 64,000 of which are ICUs[31].

Model validation against the Omicron outbreak in Shanghai

We calibrated the transmissibility and proportion of symptomatic cases to the field data of the Omicron BA.2 variant outbreak in Shanghai, China. We used a Bayesian approach[60] to estimate the net reproduction number R_t for the initial phase (from March 1 to 8, 2022) of the epidemic in Shanghai, before strict control measures were implemented. The method is based on the analysis of the epidemic curve of symptomatic cases and on the knowledge of the generation time, which is assumed to

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be Gamma distributed with mean 6.8 days (shape=2.39, scale=2.95) as estimated for the Omicron variant in a previous study[48]. The resulting estimate of the average reproduction number R_t is 3.4. We then follow the approach in Marziano et al.[61] based on the Next Generation Matrix (NGM) to calculate the model transmission rate from the estimated reproduction number while accounting for the vaccine-induced partial protection of the population. When removing the effect of vaccination, we estimated the reproduction number R of the Omicron BA.2 variant to be 3.9 at the beginning of the 2022 outbreak in Shanghai. Such estimate is conditional on the situation on the ground at the beginning of March 2022 where, although no strict NPIs were implemented, but a mask mandate was still in place and the behavior of the population may have been different from pre-pandemic standards.

City-wide screenings are being conducted frequently throughout the course of the Shanghai outbreak allowing the identification of most infected individuals, regardless of the presence/absence of symptoms. Therefore, to estimate the association between symptoms and infection, we simulated our compartmental model for the population of Shanghai (which also consider city-specific vaccination rates) assuming R_t is 3.4. We then modulated the age-specific probability of developing symptoms[62] by a scaling factor that is chosen to fit both the curves of symptomatic and asymptomatic infections in Shanghai between March 1 and April 8, 2022 (Extended Data Figure 2). We further adjusted the calibrated age-specific probability of developing symptoms by the ratio of the proportion of confirmed cases among total infections observed in Shanghai during the initial phase (from March 1 to 8, 2022) (3.50%) to that from March 1 to April 28, 2022 (9.24%)[63].

Finally, as a sensitivity analysis, we also calibrated the model using a shorter generation time, in line with estimates for the Delta variant in the UK (4.7 days[64]) (Supplementary Figure 5).

Mitigation with vaccination

A mass vaccination campaign has been launched in China since December 2020[65]. On October 3, 2021, a homologous booster vaccination campaign (relying on the same vaccine as the initial inactivated vaccine shots) has been initiated among individuals aged ≥18 years who completed primary vaccination at least 6 months earlier[66,67]. As

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of April 12, 2022, >90% of populations aged ≥3 years have completed primary vaccination and >50% of the populations has received a booster dose[68]. Compared to other age groups (86.4%, 100%, and 92.3% fully vaccinated individuals for the age groups 3–11, 12–17, and 18–59 years, respectively), individuals aged ≥60 years have the lowest vaccination coverage (about 80%)[69], corresponding to approximately 52 million unvaccinated individuals[28].

From March 1, 2022 onwards, homologous booster rollout was set at 5 million doses per day in the baseline analysis. Sensitivity analyses on heterologous booster vaccination using subunit, mRNA, and vector vaccines were conducted (Supplementary Figure 6). The only difference between heterologous and homologous booster considered in the model is vaccine efficacy (values reported in Supplementary Table 1). Vaccine coverage over time and by age group for the baseline scenario is presented in Supplementary Figure 7.

Vaccine effectiveness

We considered different VEs against different clinical endpoints (namely, infection, symptomatic illness, hospitalization, death) and onward transmission. As shown in Supplementary Table 1, VEs against these clinical outcomes at the following five time points are considered: 14 days after receiving the first dose, 14 days after receiving the second dose, 14 days after the booster dose, 6 months after the second dose of primary 2-dose vaccination (2W), and 6 months after the booster dose (BW). To account for the decay of VEs, either 6 months after the second dose of primary vaccination or after the booster dose, vaccinated individuals move to the "waned effectiveness" compartments 2W and BW, respectively.

VEs against symptomatic disease, hospitalization, and death after receiving two doses of inactivated vaccines, a homologous booster using inactivated vaccines, and a heterologous booster using mRNA vaccines were estimated during the Omicron waves in Hong Kong or Brazil[27,32]. For other VEs without field estimates, we used a verified statistical model[70] to predict vaccine protection based on the levels of neutralizing antibody titers (NATs) against Omicron between different booster

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759 regimens and time points summarized in Supplementary Table 9[71-74]. The Omicron
760 variant shows very high immune escape potential. Peiris et al.[75] found a 6.4-fold and
761 9.7-fold decrease in the level of NATs against Omicron 6 months after administering
762 two doses and one month after administering a booster dose of inactivated vaccines,
763 respectively, compared with those against the ancestral lineage (low immune escape
764 scenario). We further conducted a sensitivity analysis for a high immune escape
765 scenario, which considers a 19.1-fold decrease in the NAT against Omicron both after
766 administering two doses and a booster dose of inactivated vaccines, compared with
767 that against the ancestral lineage[76]. For VEs against symptomatic illness,
768 hospitalization, and death, we use conditional VEs, which are calculated according to
769 the formulas presented in Supplementary Table 10.
770
771 **Mitigation through antiviral therapies**
772 A homegrown monoclonal neutralizing antibody therapy (BRII-196/BRII-198
773 combination) and an imported antiviral therapy (nirmatrelvir tablet/ritonavir tablet
774 combination) have been approved for emergency use in China[25,26]. In the baseline
775 scenario, we do not consider antiviral therapies. To quantify the mitigating effect of
776 antiviral therapies, we simulated two alternative scenarios: i) 50% of symptomatic
777 cases will receive an antiviral therapy with an efficacy of 80% in preventing
778 hospitalizations and deaths (in agreement with the estimate for the Chinese
779 manufactured BRII-196/BRII-198 combination)[33], and ii) 100% of symptomatic cases
780 will receive an antiviral therapy with an efficacy of 89% in preventing
781 hospitalizations and deaths (in agreement with the estimate for the imported
782 nirmatrelvir tablet/ritonavir tablet combination[34,77]). Only symptomatic cases aged
783 ≥12 years are eligible to receive COVID-19 antiviral therapies[25] (Supplementary
784 Table 6). The rationale for the 50% treatment uptake scenario is that not all
785 symptomatic cases may be promptly identified, thus leading either to receive the
786 treatment well after symptom onset (and thus the effectiveness of the antiviral therapy
787 is reduced) or to entirely missing potential eligible individuals. The 100% treatment
788 uptake scenario represents an ideal scenario where all eligible symptomatic infections
789 receive the treatment at the peak of its efficacy.

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Mitigation through NPIs

We tested the impact of NPIs in two ways: 1) implementing a national school closure or a national school and workplace closure by removing contacts that occurred in schools or workplaces from the baseline mixing patterns (Supplementary Figure 1); 2) reducing effective contacts equally across age groups, which is modeled as a reduction in the reproduction number; specifically, we considered R_t = 2.0, 2.5, 3.0, and 3.9 that represent varying intensities of NPIs (Supplementary Table 5).

Geographical heterogeneity across the Chinese population

To account for within-China heterogeneity, we run the baseline analysis for three other highly diverse contexts: i) an urbanized setting with a relatively low vaccine coverage (Shanghai), ii) a rural setting with a relatively low vaccine coverage (Shanxi, a central province in China), and iii) a high vaccination setting (Shandong, an eastern coastal province). In our analysis, these settings differ in terms of primary and booster vaccination coverages, age structure of the population, contact patterns of the population[42], number of available hospital beds and ICUs[31] (Supplementary Table 2 and Supplementary Figure 1). The overall and age-specific incidence rates of different clinical endpoints over a 6-month simulated period across the three settings are compared to the "national average".

Statistical analysis

For each scenario, 200 stochastic simulations were performed. The outcomes of these simulations determined the distribution of the number of symptomatic infections, hospital admissions, ICU admissions, and deaths by age. We defined 95% credible intervals as quantiles 0.025 and 0.975 of the estimated distributions.

Data availability

The data used in the study are provided in Supplementary Information and are available with the code on GitHub at `https://github.com/DXW-sola1015/Model_Omicron_China`.

Code availability

The codes used in this study are available on GitHub at `https://github.com/DXW-`

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sola1015/Model_Omicron_China.

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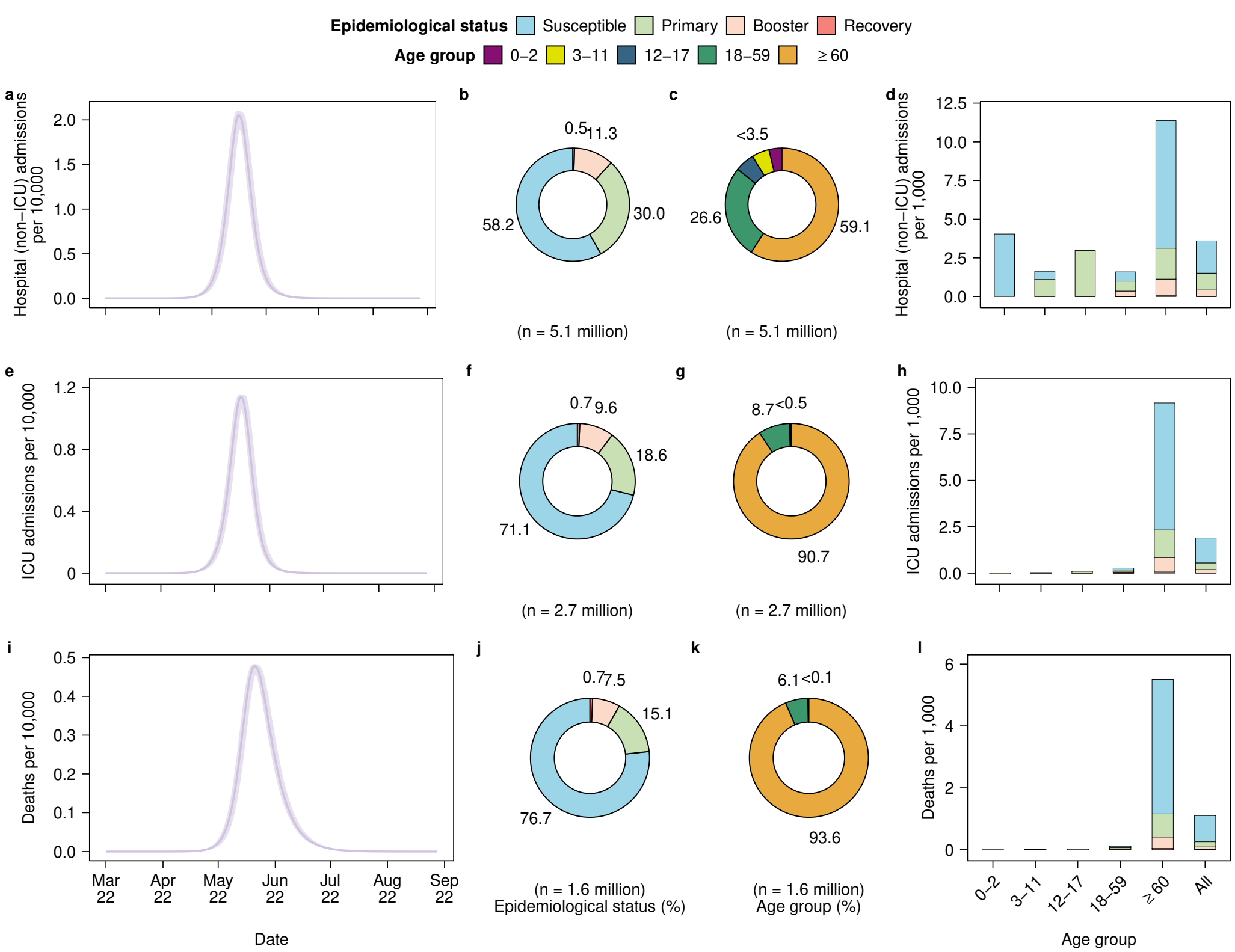
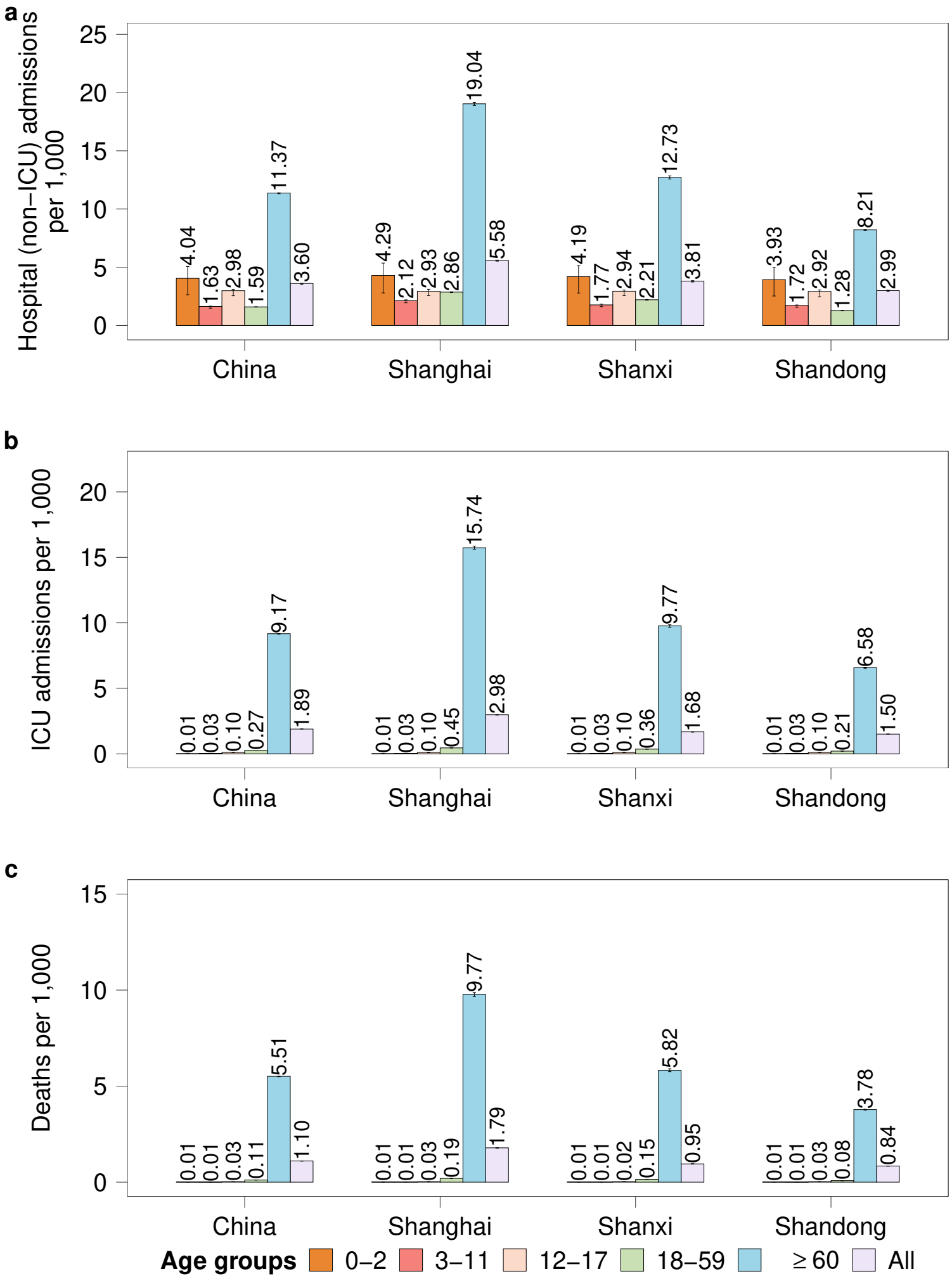
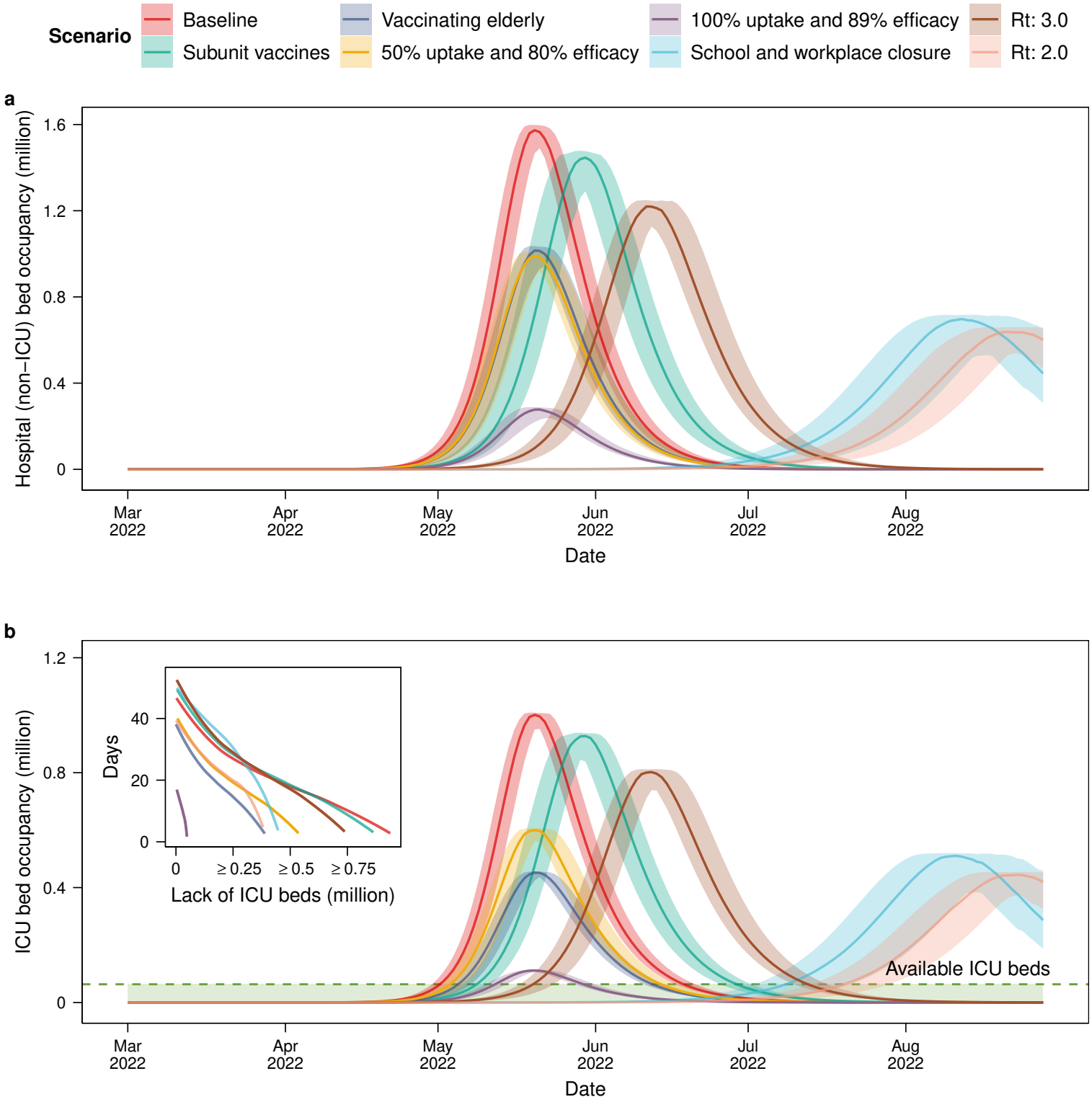
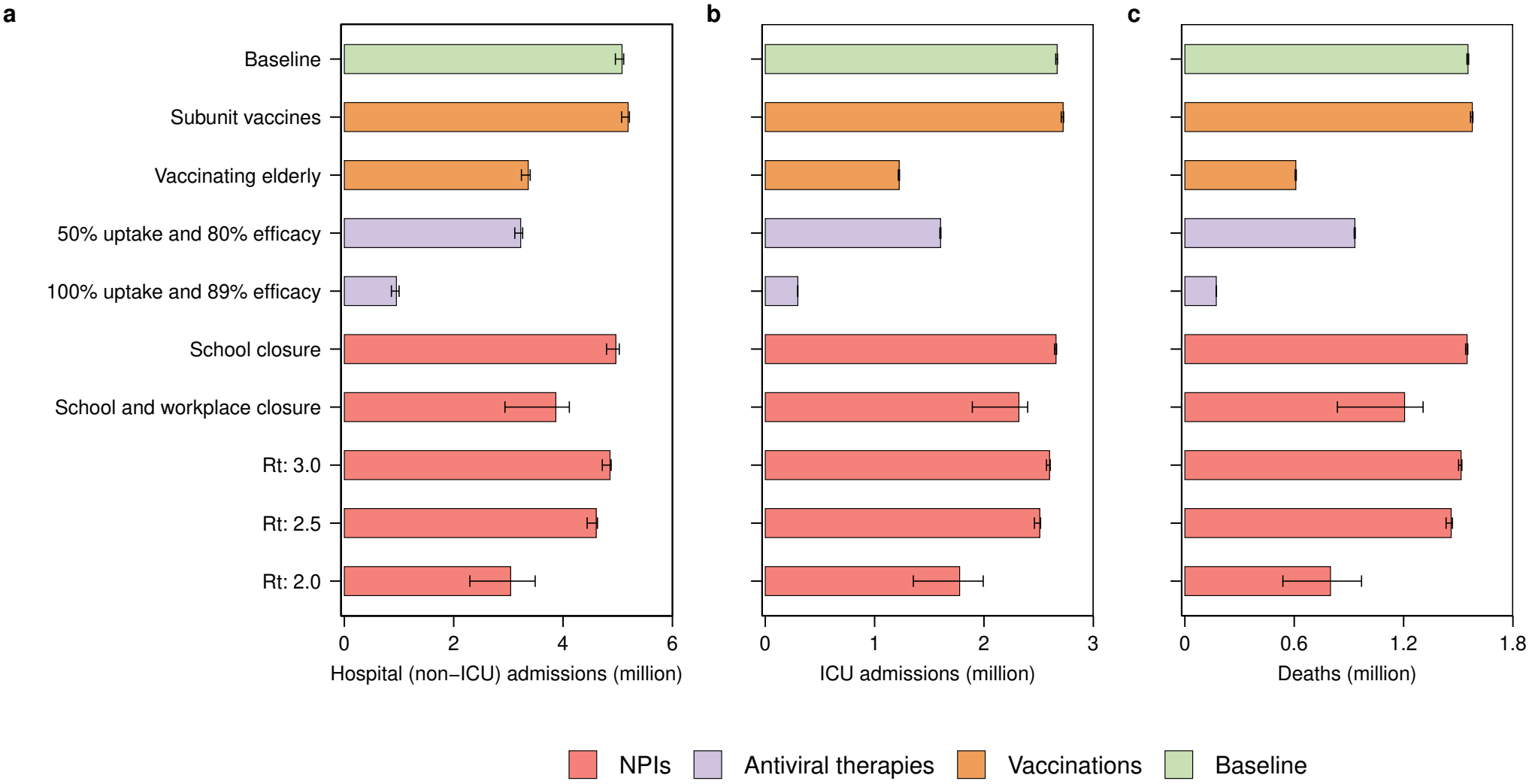
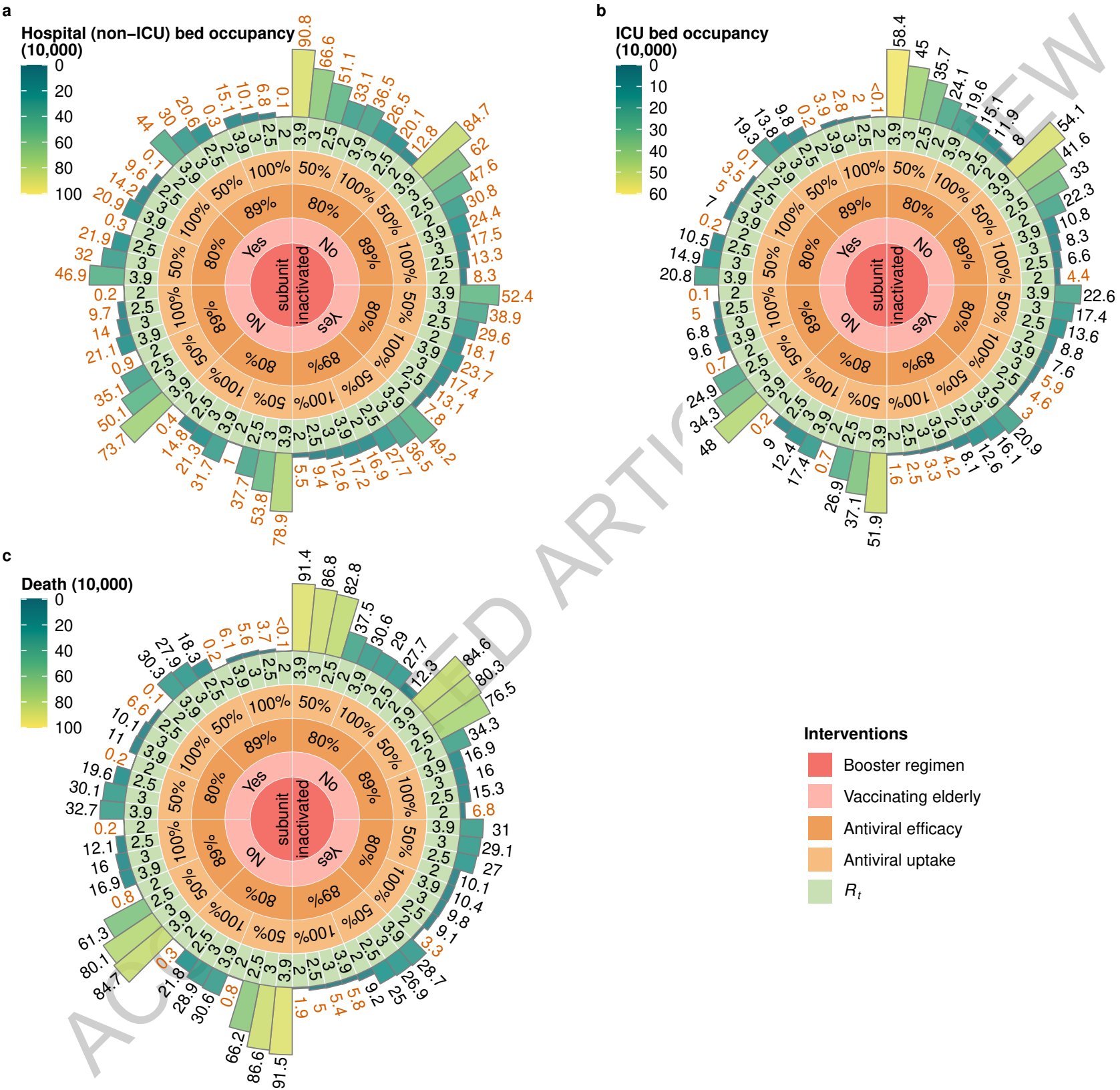

Epidemiological status
Susceptible
Primary
Booster
Recovery
Age group
0–2
3–11
12–17
18–59
≥ 60
a
Hospital (non–ICU) admissions per 10,000
2.0
1.5
1.0
0.5
0.0
b
0.5
11.3
30.0
58.2
(n = 5.1 million)
c
<3.5
26.6
59.1
(n = 5.1 million)
d
Hospital (non–ICU) admissions per 1,000
12.5
10.0
7.5
5.0
2.5
0.0
e
ICU admissions per 10,000
1.2
0.8
0.4
0
f
0.7
9.6
18.6
71.1
(n = 2.7 million)
g
8.7
<0.5
90.7
(n = 2.7 million)
h
ICU admissions per 1,000
10.0
7.5
5.0
2.5
0.0
i
Deaths per 10,000
0.5
0.4
0.3
0.2
0.1
0.0
Mar 22
Apr 22
May 22
Jun 22
Jul 22
Aug 22
Sep 22
Date
j
0.7
7.5
15.1
76.7
(n = 1.6 million)
Epidemiological status (%)
k
6.1
<0.1
93.6
(n = 1.6 million)
Age group (%)
l
Deaths per 1,000
6
4
2
0
0–2
3–11
12–17
18–59
≥ 60
All
Age group

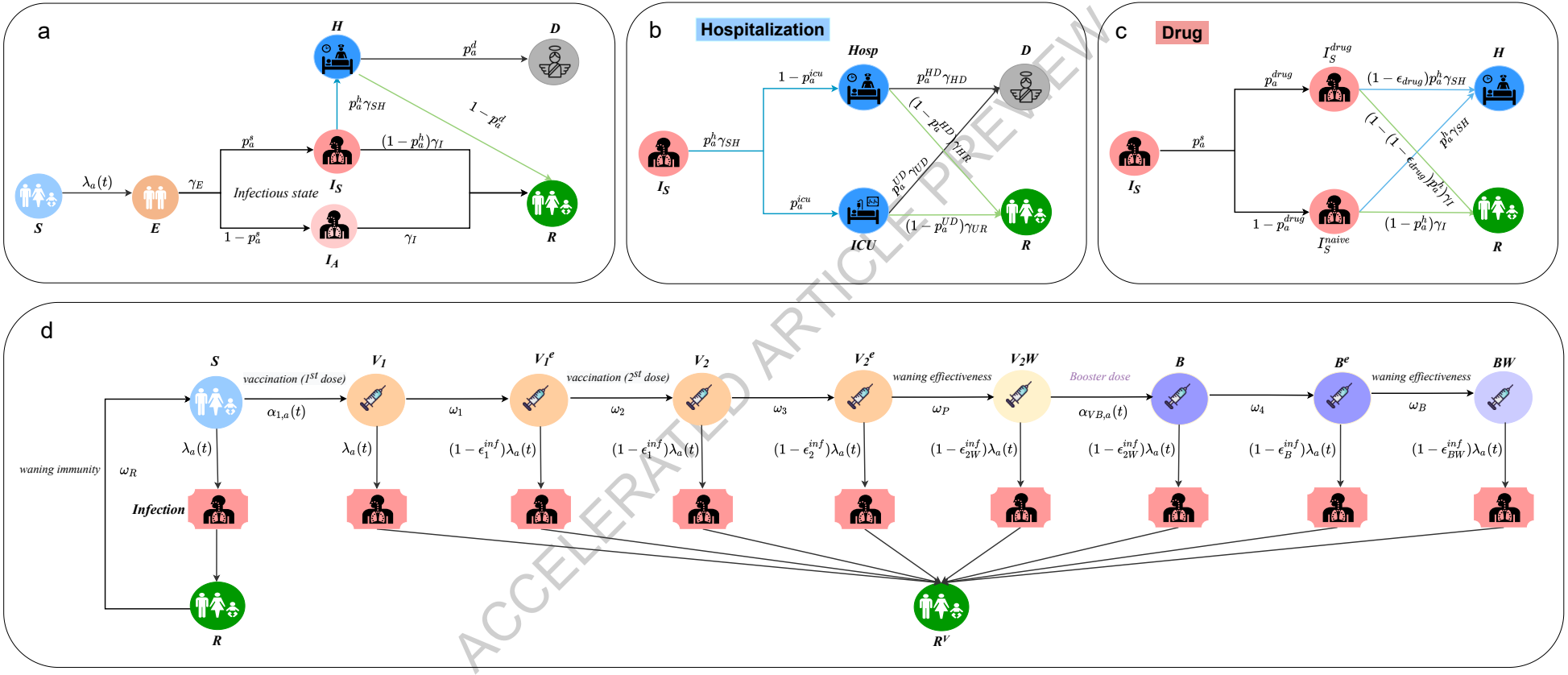

a
Hospital (non–ICU) admissions per 1,000
25
20
15
10
5
0
4.04
1.63
2.98
1.59
11.37
3.60
4.29
2.12
2.93
2.86
19.04
5.58
4.19
1.77
2.94
2.21
12.73
3.81
3.93
1.72
2.92
1.28
8.21
2.99
China
Shanghai
Shanxi
Shandong
b
ICU admissions per 1,000
20
15
10
5
0
0.01
0.03
0.10
0.27
9.17
1.89
0.01
0.03
0.10
0.45
15.74
2.98
0.01
0.03
0.10
0.36
9.77
1.68
0.01
0.03
0.10
0.21
6.58
1.50
China
Shanghai
Shanxi
Shandong
c
Deaths per 1,000
15
10
5
0
0.01
0.01
0.03
0.11
5.51
1.10
0.01
0.01
0.03
0.19
9.77
1.79
0.01
0.01
0.02
0.15
5.82
0.95
0.01
0.01
0.03
0.08
3.78
0.84
China
Shanghai
Shanxi
Shandong
Age groups
0–2
3–11
12–17
18–59
≥ 60
All


Scenario
Baseline
Subunit vaccines
Vaccinating elderly
50% uptake and 80% efficacy
100% uptake and 89% efficacy
School and workplace closure
Rt: 3.0
Rt: 2.0
a
Hospital (non−ICU) bed occupancy (million)
1.6
1.2
0.8
0.4
0
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Date
b
ICU bed occupancy (million)
1.2
0.8
0.4
0
Days
40
20
0
0
≥ 0.25
≥ 0.5
≥ 0.75
Lack of ICU beds (million)
Available ICU beds
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Date

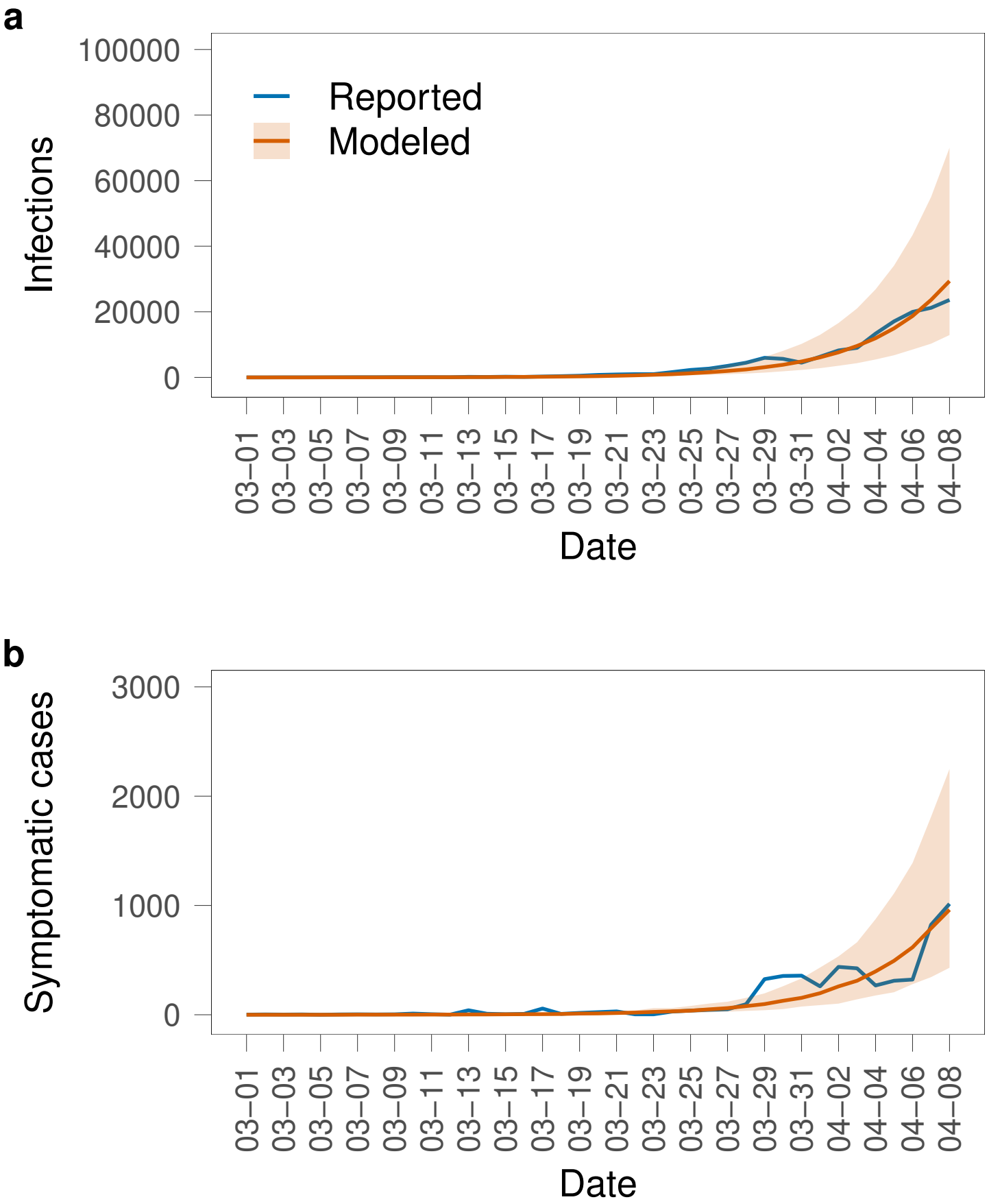

a
b
c
Baseline
Subunit vaccines
Vaccinating elderly
50% uptake and 80% efficacy
100% uptake and 89% efficacy
School closure
School and workplace closure
Rt: 3.0
Rt: 2.5
Rt: 2.0
0
2
4
6
Hospital (non−ICU) admissions (million)
0
1
2
3
ICU admissions (million)
0
0.6
1.2
1.8
Deaths (million)
NPIs
Antiviral therapies
Vaccinations
Baseline

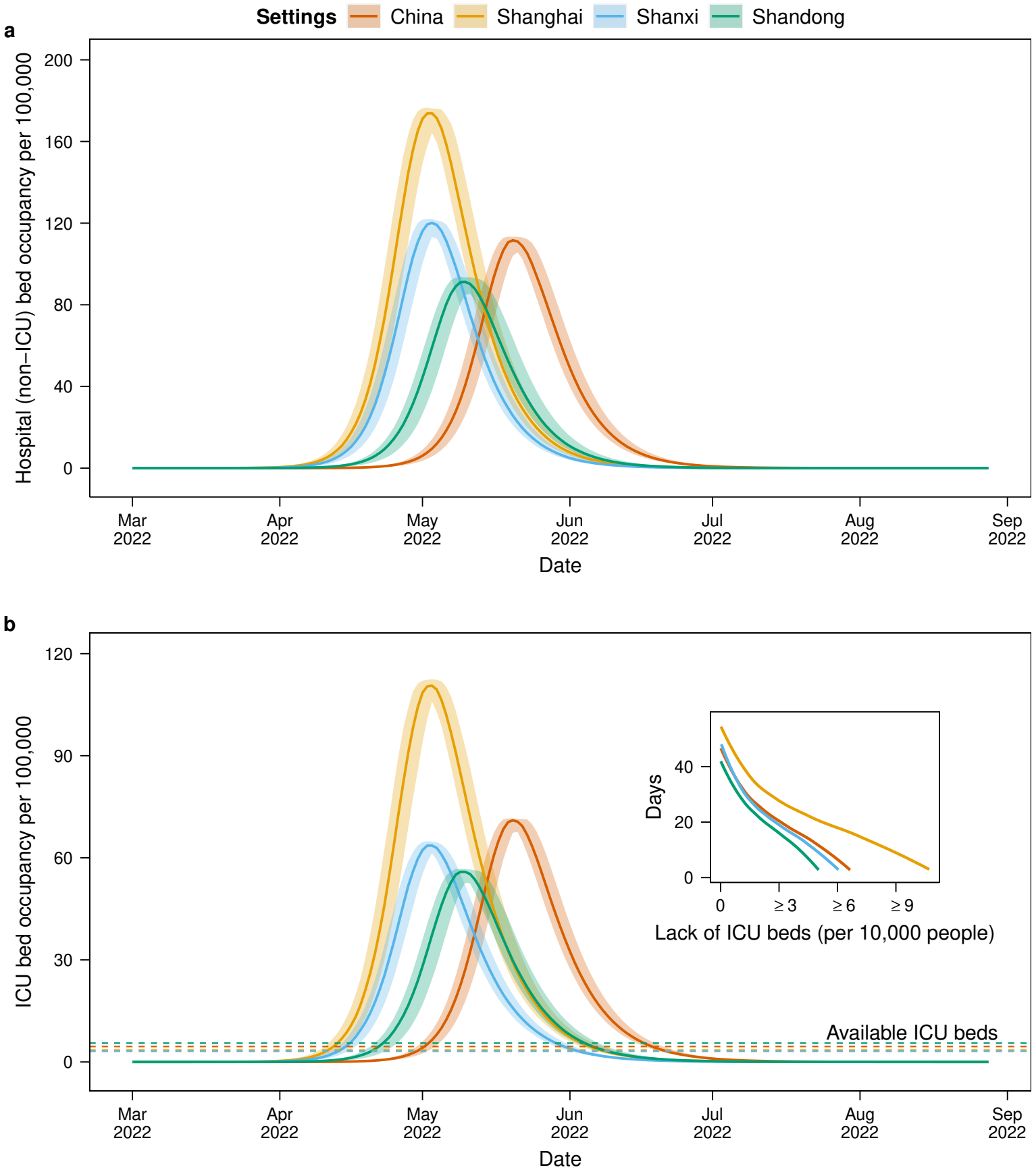


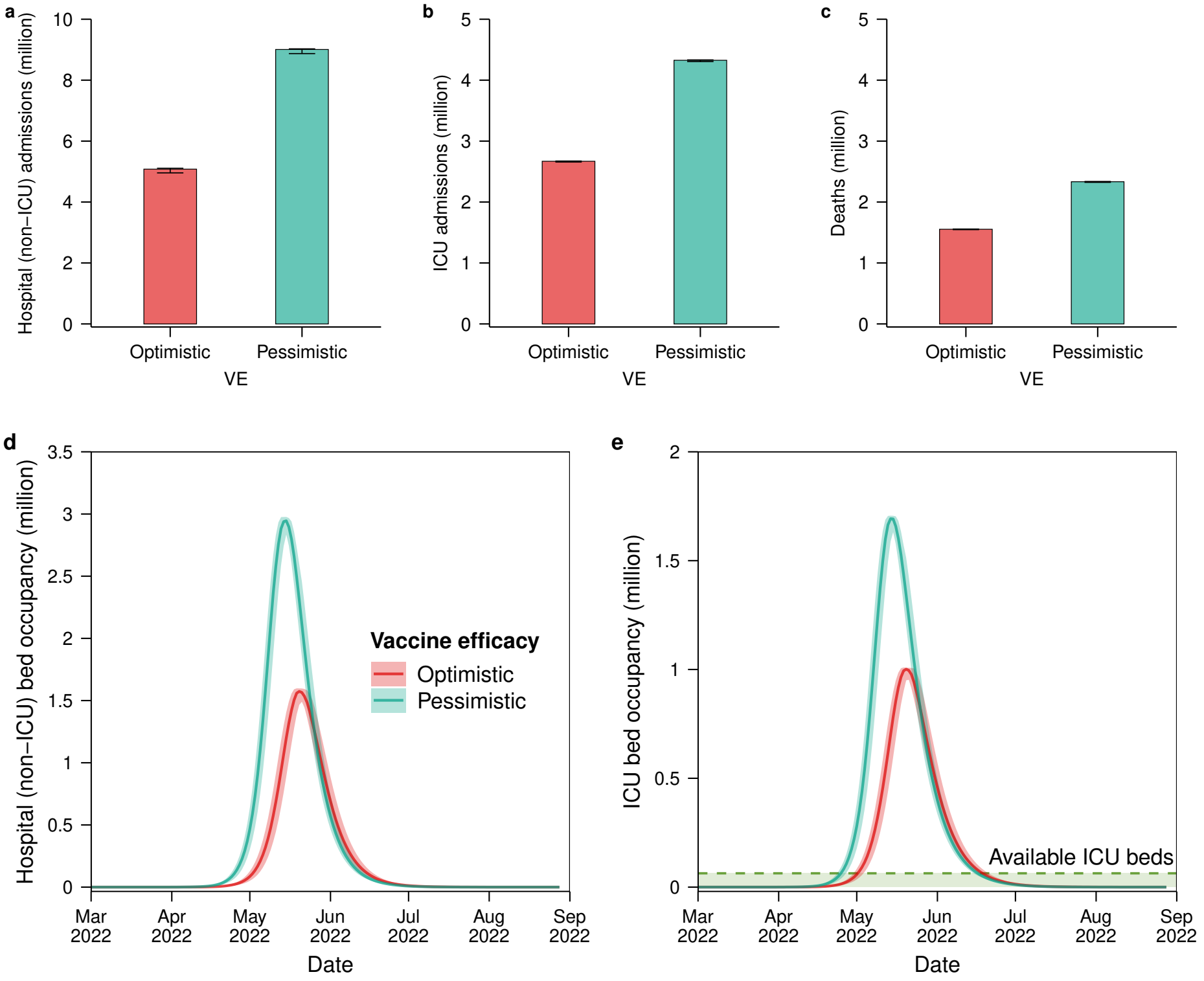
ACCEPTED ARTICLE

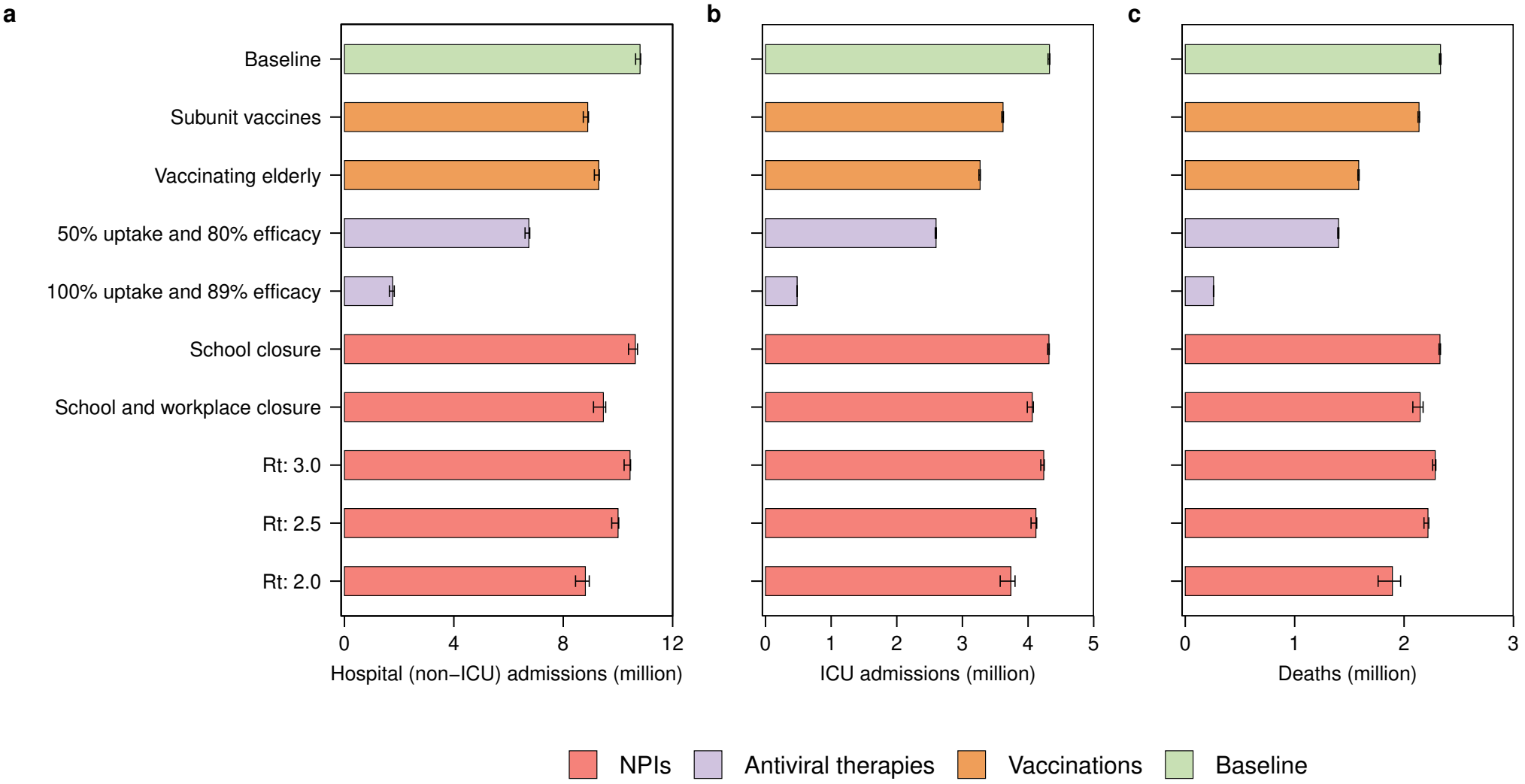


ACCELERATED ARTICLE PREVIEW


a
Infections
100000
80000
60000
40000
20000
0
Reported
Modeled
03–01
03–03
03–05
03–07
03–09
03–11
03–13
03–15
03–17
03–19
03–21
03–23
03–25
03–27
03–29
03–31
04–02
04–04
04–06
04–08
Date
b
Symptomatic cases
3000
2000
1000
0
03–01
03–03
03–05
03–07
03–09
03–11
03–13
03–15
03–17
03–19
03–21
03–23
03–25
03–27
03–29
03–31
04–02
04–04
04–06
04–08
Date


a
Settings
China
Shanghai
Shanxi
Shandong
Hospital (non–ICU) bed occupancy per 100,000
200
160
120
80
40
0
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Sep 2022
Date
b
ICU bed occupancy per 100,000
120
90
60
30
0
Days
40
20
0
0
≥ 3
≥ 6
≥ 9
Lack of ICU beds (per 10,000 people)
Available ICU beds
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Sep 2022
Date


a
Hospital (non–ICU) admissions (million)
10
8
6
4
2
0
Optimistic
Pessimistic
VE
b
ICU admissions (million)
5
4
3
2
1
0
Optimistic
Pessimistic
VE
c
Deaths (million)
5
4
3
2
1
0
Optimistic
Pessimistic
VE
d
Hospital (non–ICU) bed occupancy (million)
3.5
3
2.5
2
1.5
1
0.5
0
Vaccine efficacy
Optimistic
Pessimistic
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Sep 2022
Date
e
ICU bed occupancy (million)
2
1.5
1
0.5
0
Available ICU beds
Mar 2022
Apr 2022
May 2022
Jun 2022
Jul 2022
Aug 2022
Sep 2022
Date


a
b
c
Baseline
Subunit vaccines
Vaccinating elderly
50% uptake and 80% efficacy
100% uptake and 89% efficacy
School closure
School and workplace closure
Rt: 3.0
Rt: 2.5
Rt: 2.0
0
4
8
12
Hospital (non−ICU) admissions (million)
0
1
2
3
4
5
ICU admissions (million)
0
1
2
3
Deaths (million)
NPIs
Antiviral therapies
Vaccinations
Baseline

nature research

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Last updated by author(s): May 2, 2022

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
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☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	R version 4.1.0 were used to perform collation and analyses.
Data analysis	C (gcc version 10.2.0-1 and Cygwin version 3.2.0-1), gsl version 2.3-2 and R version 4.1.0 were used to build the simulation model. R version 4.1.0 was used to present the results. All codes are available on GitHub at https://github.com/DXW-sola1015/Model_Omicron_China.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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- A description of any restrictions on data availability

All the data used in the study are provided in Supplementary Information and are available with the code on GitHub at https://github.com/DXW-sola1015/Model_Omicron_China.

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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

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Sample size	This is a modeling study. The number of simulations (n=200) was empirically determined to guarantee stability of the results.
Data exclusions	N/A. This is a modeling study
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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging