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Counterfactual analysis of the 2023 Omicron XBB wave in China

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ABSTRACT

Background: China has experienced a COVID-19 wave caused by Omicron XBB variant starting in April 2023. Our aim is to conduct a retrospective analysis exploring the dynamics of the outbreak under counterfactual scenarios that combine the use of vaccines, antiviral drugs, and nonpharmaceutical interventions.

Methods: We developed a mathematical model of XBB transmission in China, which has been calibrated using SARS-CoV-2 positive rates per week. Intrinsic age-specific infection-hospitalization risk, infection-ICU risk, and infection-fatality risk were used to estimate disease burdens, characterized as number of hospital admissions, ICU admissions, and deaths.

Results: We estimated that in absence of behavioral change, the XBB outbreak in spring 2023 would have resulted in 0.86 billion infections (~61% of the total population). Our counterfactual analysis shows that the synergetic effect of vaccination (70% vaccination coverage), antiviral treatment (20% receiving antiviral treatment), and moderate non-pharmaceutical interventions (20% isolation and L1 PHSMs) could reduce the number of deaths to levels close to seasonal influenza (1.17 vs. 0.65 per 10,000 individuals and 5.85 vs. 3.85 per 10,000 individuals aged 60+, respectively). The maximum peak prevalence of hospital and ICU admissions are estimated to be lower than the corresponding capacities (8.6 vs. 10.4 per 10,000 individuals and 1.2 vs. 2.1 per 10,000 individuals, respectively).

Conclusion: Our findings suggest that the capacity of the Chinese healthcare system was adequate to face the Omicron XBB wave in spring 2023 but, at the same time, supports the importance of administering highly effective vaccine with long-lasting immune response, and the use of antiviral treatments.

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1. Background

China experienced a nationwide wave of COVID-19 dominated by the SARS-CoV-2 Omicron BA.5/BF.7 variants from December 2022 to January 2023, following the relaxation of stringent COVID-19 restrictions, known as the "zero-COVID" policy (Chinese Center for Disease Control and Prevention; Xinhua). During this two-month period, an estimated 80–90% of the Chinese population was infected (Gang Lu et al., 2022; Leung et al., 2023). This is a marked contrast to other parts of the world, where immunity was built through repeated vaccination and multiple waves of infection over more than two years (Our World in Data). As of April 27, 2023, 3.49 billion COVID-19 vaccine doses had been administered in mainland China, with 74% of adults (population over 18) having received their first booster dose. Among the older adults (population over 60), 73% had received their first booster dose (Chinese Center for Disease Control and Prevention). However, recent studies show that the protection against Omicron infection wanes within months since last vaccine administration or infection (Bobrovitz et al., 2023; Cerqueira-Silva et al., 2022; Chen et al., 2023; Menegale et al., 2023). For instance, Singapore experienced a 2-month XBB wave in September 2022 following a BA.5 wave in May 2022 (Ministry of Health in Singapore; Our World in Data; Tan et al., 2023). Similarly, in April 2023, China has experienced a COVID-19 wave caused by Omicron XBB variant.

Since the BA.5/BF.7 wave in late 2022-early 2023, China strengthened its healthcare capacity (The State Council of the People's Republic of China) and antiviral drugs such as Molnupiravir and Paxlovid as well as more than 10 domestically-made products (e.g., RAY1216, XIANNUOXIN, and VV116) have either been granted official or conditional market approval, or have been authorized to treat symptomatic patients (National Medical Products Administration of China). In this study, we developed a mathematical model of XBB variant transmission in China to conduct a retrospective analysis of the XBB outbreak in China in April 2023. Specifically, our aim is to explore a set of counterfactual scenarios that combine the use of vaccines, antiviral drugs, and nonpharmaceutical interventions (NPIs).

2. Methods

2.1. Transmission model

We developed an age-structured stochastic model to simulate the transmission of XBB, taking into account China's population (Office of the Leading Group of the State Council for the Seventh National Population Census) and heterogeneous contact patterns (Mistry et al., 2021) (Supplementary Tables 1–2 and Supplementary Fig. 1). In the model, the population is divided into four epidemiological categories: susceptible, latent, infectious, and temporarily protected (removed) individuals, stratified by 9 age groups (0–2, 3–17, 18–29, 30–39, 40–49, 50–59, 60–69, 70–79 and 80+). Susceptible individuals comprise two distinct categories: fully susceptible individuals, and four subgroups of partially susceptible individuals. Transitions among these partially susceptible subgroups are attributed to the vaccination and immunity-waning processes. Upon infection, susceptible individuals enter a latent compartment and become infectious after a latent period ($1/\gamma_E = 1.20$ days). Infectious individuals can potentially infect susceptible individuals within their infectious period ($1/\gamma_R = 5.64$ days), after which they naturally recover. The resulting distribution of the generation time (T_g) follows a gamma distribution of average 6.84 days, in agreement with the literature (Manica et al., 2022). We modeled transitions between compartments using a stochastic chain binomial process (Davis et al., 2021). The model has one free parameter, the per-contact transmission risk β, which shapes XBB transmissibility. Details on the transmission model are reported in the Supplementary Method.

2.2. Model calibration

To enhance our understanding of the COVID-19 wave in April 2023 and ensure reliable simulation results, we collected weekly SARS-CoV-2 Omicron XBB positive rates (Chinese Center for Disease Control and Prevention). The data was used to calibrate the per-contact transmission risk β and the number of XBB infected individuals at the beginning of the wave. These positive rates reflect the percentage of COVID-19 positive samples among all influenza-like illness (ILI) samples and serve as an indicator representing the COVID-19 activity. Notably, China experienced a national Omicron BA.5/BF.7 wave in the winter of 2022, marked by low COVID-19 activity from February to April 2023, followed by an XBB outbreak in the April 2023 (Supplementary Table 3). In this study, we calibrated the model using the positive rate during the major period of the XBB wave, specifically from April 3 to June 5, 2023, predating any shifts in human behavior associated with the upcoming national higher education entrance examination (Started on June 7) and summer holiday (from July–September).

First, we fitted the exponential growth stage of the daily COVID-19 positive rate to calculate the growth rate r. The daily positive rate was derived through cubic spline interpolation of the weekly positive rate. To ensure a robust estimate of the growth rate, our analysis employed a rolling window of 21 days, with the starting date varying from Apri1 10 to April 23, 2023. By combining the growth rate with empirical distribution of generation time (Wallinga et al., 2007), we calculated the initial net reproduction number R_e. The transmission rate was then determined based on its relation with reproduction number and population immunity status (Diekmann et al., 2010). The estimated mean values for the growth rate, reproduction number and transmission rate were 0.098/day (95% CI: 0.082–0.107), 1.73 (95% CI: 1.60–1.80) and 0.054 (95% CI: 0.050–0.057), respectively (Supplementary Table 4 and Supplementary Fig. 2). Second, we assumed that COVID-19 activity is proportional to infectious individuals and set the seeding date to April 3, 2023. We then run the transmission model to estimate the fraction

of initially infected individuals by optimizing R-squared between the simulation results and the observed positive rate. The resulting fraction was 0.35% and R-squared was 0.995.

2.3. Hybrid immunity

China experienced a COVID-19 wave dominated by Omicron BA.5/BF.7 variants in the winter of 2022. Around 80–90% of the population was infected within 2 months (Gang Lu et al., 2022; Leung et al., 2023). Therefore, a homogeneous hybrid immunity of 85% generated by inactivated vaccine and BA.5/BF.7 infection was considered. The remaining 15% of the population was assumed to be fully susceptible to infection. Immunity was assumed to wane over time, starting from February 2023, with different waning rates depending on the clinical endpoints. We used an average duration of protection against infection of 6 months following an exponential waning rate (Bobrovitz et al., 2023). Hybrid immunity provided more significant and long-lasting protection against hospitalization and severe disease (Bobrovitz et al., 2023; Cerqueira-Silva et al., 2022). As such, we assumed protection against hospitalization and severe disease to be 95% after 12 months since the last infection/vaccination administration. Supplementary Table 5 summarizes the protection of hybrid immunity against different clinical endpoints.

2.4. Disease burden

Intrinsic age-specific infection-hospitalization risk (IHR), infection-ICU risk (IUR), and infection-fatality risk (IFR) were used to estimate the disease burdens (i.e., number of hospital admissions, ICU admissions, and deaths) given the number of infections projected by the transmission model. The overall IHR and IFR of BA.5 variant were estimated to be around 4.1% and 0.5% in China (Leung et al., 2022). A similar intrinsic clinical severity of BA.1 variant (i.e., IHR = 3.5%, IFR = 0.6%) was reported by Perez-Guzman et al. (Perez-Guzman et al., 2023). According to the World Health Organization, XBB variant does not show signs of change or increase in clinical severity (World Health Organization). Therefore, we used the rates estimated for BA.5 variant (Supplementary Table 6) for modeling the burden of XBB variant. We considered the time periods between infection and hospital admission and from infection to death to follow two gamma distributions of mean 6.7 and 22.3 days, respectively (Jansen et al., 2021; Li et al., 2020; Verity et al., 2020). The length of hospital stays (regardless of whether the patient required an ICU admission) were set at 8 days (Rees et al., 2020).

2.5. Health system capacity

In 2022, the total number of hospital beds in China reached 9,750,000, equating to 69.16 beds per 10,000 individuals (National Bureau of Statistics of China). In Hong Kong, 15% of the hospital beds were dedicated to COVID-19 patients (Leung et al., 2022). In China, 20% of the hospital beds dedicated to COVID-19 were designated as intensive care units (ICUs) (National Health Commission of the People's Republic of China). In sum, the number of hospital beds and ICUs designated for COVID-19 patients were 10.4 and 2.1 per 10,000, respectively.

2.6. Excess respiratory mortality rate

Between the 2010–11 and 2014-15 seasons, the mean excess respiratory mortality rate per season per 10,000 person in China was 0.15 for individuals younger than 60 years, 3.85 for individuals aged 60 years or older, and 0.65 for the overall population (Li et al., 2019).

2.7. Counterfactual analysis

2.7.1. Vaccination

Vaccination was temporarily suspended attributed to a slight increase in vaccine coverage (Chinese Center for Disease Control and Prevention). We assumed that the booster immunization campaign would continue, with 50% of adults who had hybrid immunity receiving a heterologous bivalent booster shot 3 months after recovering from a previous infection (National Health Commission of the People's Republic of China; Rzymski et al., 2021). We set the daily booster vaccination rate at 0.5%, which is equivalent to 30% of the maximum daily vaccination rate during the rapid rollout of mass vaccination in 2021 (National Health Commission of the People's Republic of China). We assumed that the bivalent booster dose would provide a slightly higher level of protection against clinical endpoints than hybrid immunity (Supplementary Table 5). Furthermore, we examined alternative scenarios where 30% and 70% of eligible adults would receive a bivalent vaccine as a booster shot 3 months after the last vaccination/recovering from a previous infection.

2.7.2. Antiviral drugs

We assumed that 10% of adult patients would receive antiviral treatment using Nirmatrelvir/Ritonavir. This is in line with what was observed in Hong Kong since mid-March 2022, where nearly 60% of the eligible symptomatic patients received

antiviral treatment (Leung et al., 2022). We examined two additional scenarios to evaluate the effect of antiviral drugs: (1) no patients would receive antiviral treatment, and (2) 20% of adult patients would receive antiviral treatment. For individuals who received combined Nirmatrelvir/Ritonavir antiviral treatment, their risks of hospitalization and death were reduced by 24% and 66%, respectively (Wong et al., 2022).

2.7.3. Nonpharmaceutical interventions

We modeled two types of NPIs: 10% home isolation and L1 PHSMs (level 1 public health and social measures). Home isolation entailed isolating infectious individuals at their place of residence, lowering their transmissibility by an estimated 70% (Leung et al., 2022). L1 PHSMs included measures such as voluntary universal face masking and improved hand hygiene, and was found to decrease the reproduction number by 15% (Leung et al., 2022). The home isolation probability factored in the test sensitivity, the probability of being tested if infected, and the probability of complying with the home isolation policy. Specifically, we also examined following scenarios: (1) no isolation, and (2) 20% of all infected individuals being isolated at home after a positive rapid antigen test result, and (3) no L1 PHSMs being implemented.

2.8. Statistical analysis

For each scenario, 100 stochastic model realizations were performed. We estimated mean and 95% confidence intervals as the 2.5th and 97.5th percentiles of the distribution of the analyzed quantity derived from the 100 stochastic model realizations.

3. Result

Our model captures the dynamics of the Omicron XBB wave in China between the start of the outbreak in April 2023 until early June 2023 (Fig. 1). Then, the model trajectory starts to diverge from the data possibly as a consequence of behavioral changes that took place in light of the National Higher Education Entrance Exam (Gaokao) and the start of the summer vacation. We estimate the reproduction number to have peaked at 1.80 (95% CI: 1.73–1.87) between April 15 and May 6, 2023 (Supplementary Table 4). In the absence of behavioral change, our model estimates a cumulative infection attack rate of 61%, with 85% of all infections taking place among individuals aged 0–59 years (Fig. 2).

We then investigated a set of counterfactual scenarios that vary the intensity of each intervention separately (Fig. 3 and Supplementary Table 7). We defined a reference scenario where booster vaccination coverage, antiviral treatment, and isolation were all set at 0%, with no implementation of L1 PHSMs. In comparison to this reference scenario, increasing vaccination coverage to 50% would have had the highest impact, leading to a 22–28% reduction in the projected number of hospital admissions, ICU admissions, and deaths. This is followed by the implementation of L1 PHSMs (14–19% reduction) and 10% isolation (6–8% reduction). Increasing the probability of receiving antiviral treatment to 10% would have resulted in the smallest reduction (2–7%). The estimated overall incidence of deaths and among individuals aged 60+ years are 3.88–5.40 per 10,000 and 19.13–26.44 per 10,000, respectively. These figures are 5–8 folds higher than to the corresponding annual

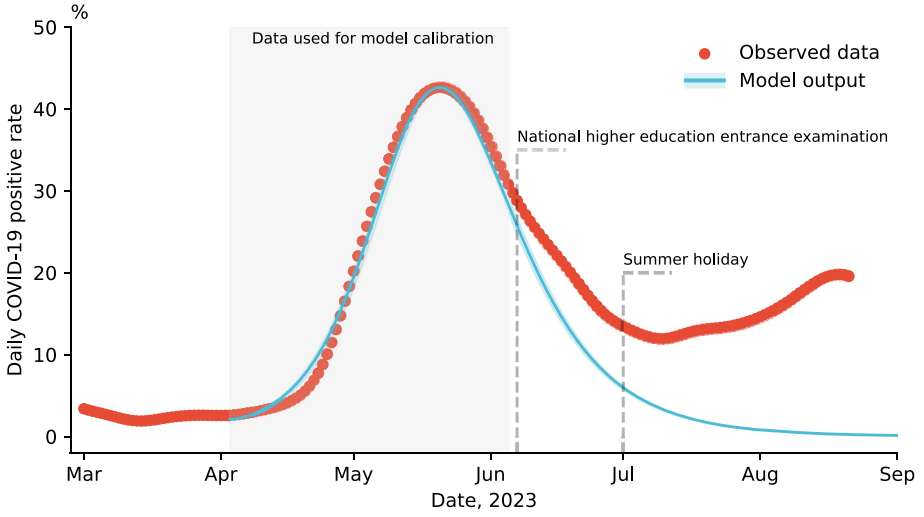

Fig. 1. Comparisons between the observed COVID-19 positive rate in China and model output. Blue line and shaded areas: mean and 95% CIs of 100 stochastic simulations. The grey shaded area represents the period used for model calibration (from April 3 to June 5). The two vertical lines represent the national higher education entrance examination (June 7) and the start of the summer holiday (July 1).

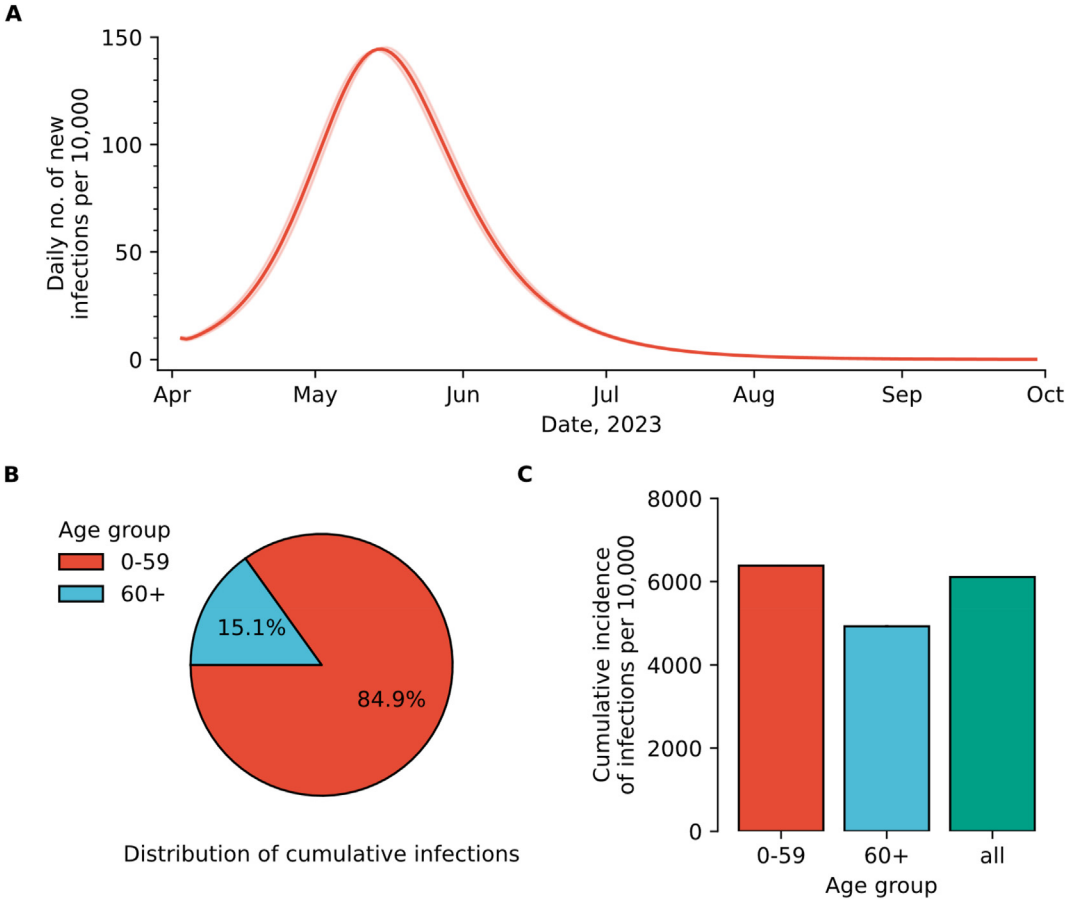

Fig. 2. Estimated infection rates during the Omicron XBB wave in April 2023 in China. A Daily number of new infections per 10,000 individuals. Line and shaded area: mean and 95% CIs of 100 stochastic model realizations. **B** Distribution of cumulative infections by age group. The percentages are presented as mean of 100 stochastic model realizations. **C** Cumulative incidence of infections per 10,000 individuals in that age group. The data are presented as mean and 95% CIs of 100 stochastic model realizations.

influenza-related excess deaths (0.65 per 10,000 and 3.85 per 10,000). Supplementary Table 7 and Supplementary Fig. 3 summarize the results for infections.

Next, we evaluated the synergetic effect of multiple interventions (Fig. 4). A combination of high coverage of booster doses (70% coverage) with antiviral treatment (20% receive antiviral treatment) would have reduced the number of deaths to 3.20 per 10,000 individuals and 15.81 per 10,000 individuals aged 60+. These figures are 4 folds higher than the corresponding annual influenza-related excess deaths (Fig. 4A–B). The additional use of moderate level of NPIs (20% home isolation and L1 PHSMs) would have lowered the number of deaths to a level close to seasonal influenza (1.17 per 10,000 and 5.85 per 10,000), albeit still slightly higher (Fig. 4A–B). The projected peak prevalence of hospital admissions and ICU admissions would have been 8.55 and 1.24 per 10,000 individuals, respectively (Fig. 4C-D). These figures are lower than the hospital bed capacity (10.4 per 10,000) and ICU bed capacity (2.1 per 10,000) designated to COVID-19 in China during the XBB wave. Supplementary Fig. 4 summarizes the results for infections.

4. Discussion

In this study, we developed a stochastic compartmental model of SARS-CoV-2 transmission in the Chinese population. Our model was calibrated to reproduce the Omicron XBB wave that started in April 2023 and then used to explore a set of counterfactual scenarios on the implementation of different mitigation strategies. During this outbreak, we estimated the reproduction number to have reached a peak value of 1.8 (95% CI: 1.73–1.87), which is remarkably lower than the pooled estimate of 4.74 reported in the literature for the Omicron BA.5/BF.7 wave (Bai et al., 2023). We estimated that, in the absence of behavioral change, the XBB outbreak would have resulted in 0.86 billion infections (~61% of the total population), lower than the 80–90% infection attack rate estimated during the Omicron BA.5/BF.7 wave (Gang Lu et al., 2022; Leung et al., 2023).

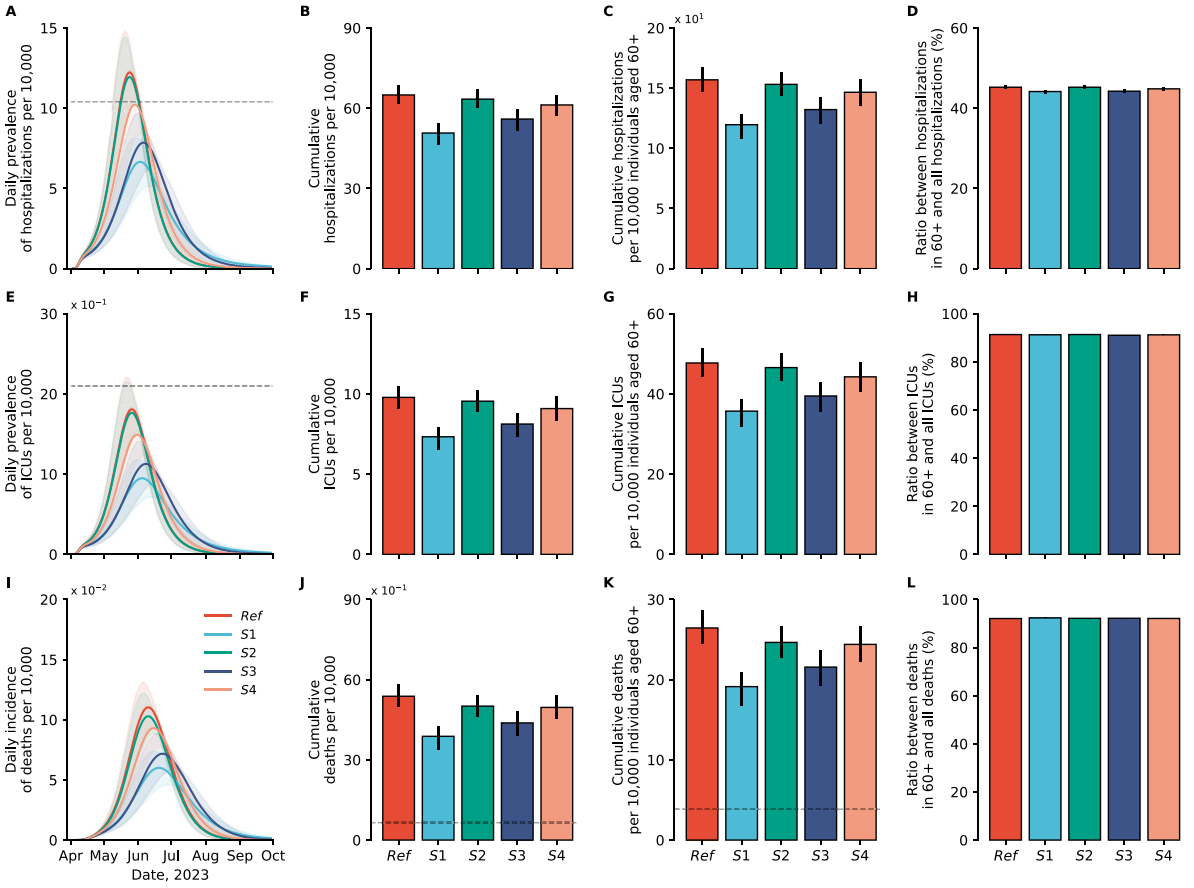

Fig. 3. Projected impact on COVID-19 burden: varying the intensity of each intervention separately. A Daily prevalence of hospitalizations per 10,000 individuals. **B** Cumulative hospitalizations per 10,000 individuals. **C** Cumulative hospitalization in 60+ individuals per 10,000 individuals aged 60+. **D** Ratio between hospitalizations in 60+ individuals and all hospitalizations. **E-H** same as **A-D**, but for ICUs. **I** Daily incidence of deaths per 10,000 individuals. **J-L** same as **B-D**, but for deaths. *Ref* represents the reference scenario in which booster vaccination coverage, antiviral treatment, and isolation were all set at 0%, with no implementation of L1 PHSMs. *S1–S4* represent counterfactual scenarios when changing a single parameter at the time as compared to the reference scenario (*S1* = 50% booster vaccination coverage, *S2* = 10% antiviral drugs, *S3* = L1 PHSMs, *S4* = 10% isolation). The horizontal lines in figure A and E are the maximum hospital bed capacity and ICU bed capacity. The horizontal lines in figure J and K represent the corresponding influenza-related excess mortality. Data are presented as mean and 95% CIs of 100 stochastic model realizations.

The synergetic effect of vaccination (70% vaccination coverage) and antiviral treatment (20% receive antiviral treatment) could have reduced the number of deaths to level comparable to that of seasonal influenza (3.20 per 10,000 residents and 15.81 per 10,000 individuals aged 60+). The additional use of moderate NPIs (20% home isolation and L1 PHSMs) could have further reduced the number of deaths to a level close to seasonal influenza (1.17 per 10,000 and 5.85 per 10,000). The maximum peak prevalence of hospital admissions and ICU admissions were projected to be lower than the corresponding capacities (8.6 and 1.2 per 10,000), highlighting that the strengthening of the Chinese healthcare system that took place during the COVID-19 pandemic was sufficient to manage the disease burden of an XBB wave.

To accurately interpret our findings, it is important to consider that our study does not consider provincial heterogeneities within China. Due to variations in factors such as demographic characteristics, contact patterns, vaccination rates, and natural immunity across different regions of China, it would be difficult to draw definitive conclusions that apply to every single area. For example, we estimated that for Shanghai the incidence of hospitalizations, ICUs, and deaths is smaller than the corresponding incidences for the overall Chinese population (Supplementary Figs. 5–6). Another study limitation is that the clinical severity of XBB variant is still not fully understood, and we assumed it to be similar to that of BA.5 variant. Finally, we cannot conclude that the discrepancy between the model estimates and the SARS-CoV-2 positivity rate observed since June 6, 2023, is the result of behavioral changes that we did not consider in the model or other factors have played a role. Further analyses are needed to investigate this pattern.

In conclusion, our study shows that the strengthening of the Chinese healthcare system that took place throughout the COVID-19 pandemic played a key role in managing the burden of an XBB wave. Moreover, our results support the key role of

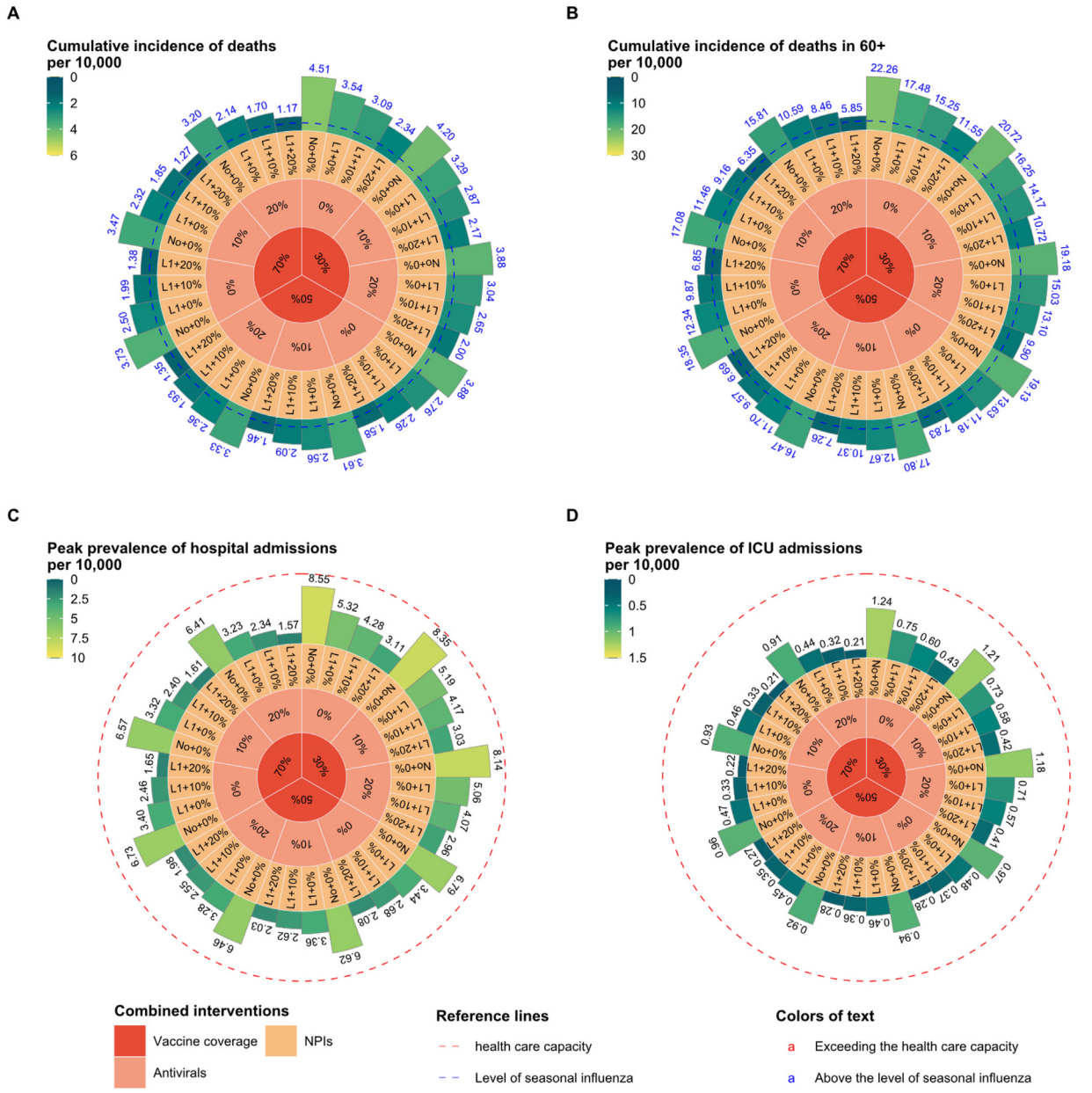

Fig. 4. Projected healthcare demand and the number of deaths when adopting combined interventions. A Cumulative incidence of deaths per 10,000 individuals. **B** Same as A, but for individuals aged 60+. **C** Peak prevalence of hospitalized patients per 10,000 individuals. **D** Same as C, but for ICUs. No+0%: no NPIs. L1+0%: L1 PHSMs. L1+10%: L1 PHSMs and 10% probability of home isolation. L1+20%: L1 PHSMs and 20% probability of home isolation. Data are presented as mean of 100 stochastic model realizations.

vaccines and antiviral treatments in reducing COVID-19 burden. Hence, the development and use of highly effective vaccines with long-term immune persistence and antiviral treatments remain key public health priorities to further reduce disease burden and the pressure on the healthcare system.

Competing interests

H.Y. has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, and Shanghai Roche Pharmaceutical Company. M.A. has received research funding from Seqirus. None of those funding is related to this research. All other authors report no competing interests.

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Availability of data and materials

The code and data used to conduct these analyses are found at: https://github.com/HengcongLiu/China-XBB.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Hengcong Liu: Conceptualization, Formal analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Xiangyanyu Xu:** Data curation, Project administration, Visualization. **Xiaowei Deng:** Formal analysis, Methodology. **Zexin Hu:** Data curation. **Ruijia Sun:** Data curation. **Junyi Zou:** Data curation. **Jiayi Dong:** Data curation. **Qianhui Wu:** Data curation. **Xinhua Chen:** Data curation. **Lan Yi:** Data curation. **Jun Cai:** Formal analysis. **Juanjuan Zhang:** Formal analysis. **Marco Ajelli:** Supervision. **Hongjie Yu:** Funding acquisition, Supervision.

Declaration of competing interest

H.Y. has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, and Shanghai Roche Pharmaceutical Company. M.A. has received research funding from Seqirus. None of those funding is related to this research. All other authors report no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2023.12.006.

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