Modelling the adjustment of COVID-19 response and exit from dynamic zero-COVID in China

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Abstract

Background

Since the initial Wuhan outbreak, China has been containing COVID-19 outbreaks through its "dynamic zero-COVID" policy. Striking a balance between sustainability and cost-benefit, China has recently begun to adjust its COVID-19 response strategies, e.g. by announcing the "20 measures" on 11 November and further the "10 measures" on 7 December 2022. Strategies for safely exiting from dynamic zero-COVID (i.e. without catastrophically overburdening health systems and/or incurring unacceptably excessive morbidity and mortality) are urgently needed.

Methods

We use simulations to assess the respective and combined effectiveness of fourth-dose heterologous boosting, large-scale antiviral treatment and public health and social measures (PHSMs) that might allow China to further adjust COVID-19 response and exit from zero-COVID safely after 7 December 2022. We also assess whether local health systems can cope with the surge of COVID-19 cases posed by reopening, given that *chunyun,* a 40-day period with extremely high mobility across China associated with Spring Festival, will begin on 7 January 2023.

Findings

Reopening against Omicron transmission should be supported by the following interventions: 1) fourth-dose heterologous boosting 30-60 days before reopening by vaccinating 4-8% of the population per week with ≥85% uptake across all ages; 2) timely antiviral treatment with ≥60% coverage; 3) moderate PHSMs to reduce transmissibility by 47-69%. With fourth-dose vaccination coverage of 85% and antiviral coverage of 60%, the cumulative mortality burden would be reduced by 26-35% to 448-503 per million, compared with reopening without any of these interventions. Simultaneously reopening all provinces under current PHSMs would still lead to hospitalisation demand that are 1.5-2.5 times of surge hospital capacity (2.2 per 10,000 population per day).

Interpretation

Although the surge of disease burden posed by reopening in December 2022 – January 2023 would likely overload many local health systems across the country, the combined effect of vaccination, antiviral treatment and PHSMs could substantially reduce COVID-19 morbidity and mortality as China transits from dynamic-zero to normality. Planning for such a nationwide, coordinated reopening should be an urgent priority as part of the global exit from the acute phase of the COVID-19 pandemic.

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Research in context

Evidence before this study

We searched PubMed and preprint archives for articles published up to 7 December 2021, that contained information about exit strategies of zero-COVID or reopening in China after the emergence of Omicron using the terms “China”, “Omicron”, “B.1.1.529”, “COVID-19”, “SARS-CoV-2”, “vaccin*”, “vaccine”, “antiviral”, “control measures”, “non-pharmaceutical intervention”, “public health and social measure”, “zero-COVID”, “exit strategy” and “reopen*”. We only found one study by Wang et al (doi: 10.1101/2022.05.07.22274792) but they assessed the feasibility of sustaining SARS-CoV-2 containment with zero-COVID strategy in China. To our knowledge, there is no discussion of exit strategies of the zero-COVID strategy or assessment of feasibility of reopening in China.

Added value of this study

Reopening against Omicron transmission should be supported by the following interventions: 1) fourth-dose heterologous boosting 30-60 days before reopening by vaccinating 4-8% of the population per week with ≥85% uptake across all ages; 2) timely antiviral treatment with ≥60% coverage; 3) moderate PHSMs to reduce transmissibility by 47-69%. With fourth-dose vaccination coverage of 85% and antiviral coverage of 60%, the cumulative mortality burden would be reduced by 26-35% to 448-503 per million, compared with reopening without any of these interventions. Simultaneously reopening all provinces under current PHSMs would still lead to hospitalisation demand that are 1.5-2.5 times of surge hospital capacity (2.2 per 10,000 population per day).

Implications of all the available evidence

Although the surge of disease burden posed by reopening in December 2022 – January 2023 would likely overload many local health systems across the country, the combined effect of vaccination, antiviral treatment and PHSMs could substantially reduce COVID-19 morbidity and mortality as China transits from dynamic-zero to normality. Planning for such a nationwide, coordinated reopening should be an urgent priority as part of the global exit from the acute phase of the COVID-19 pandemic.

Introduction

Since March 2020, China has been containing successive sporadic clusters of COVID-19 infection through its "dynamic zero-COVID" policy – by mass lockdowns, universal compulsory testing of entire districts or even whole cities, stringent quarantine and isolation enforced down to the neighbourhood level, universal digital contact tracing and importation controls [1,2]. Although this zero-COVID strategy had remained effective in 2020-2021, the emergence and spread of Omicron since early 2022 has triggered prolonged lockdowns and major disruptions in megacities such as Beijing and Shanghai, with ramifications far beyond its own shores nationally and globally in terms of the economy, trade, and commerce. Striking a balance between sustainability and cost-benefit of dynamic-zero, China has recently begun to adjust its COVID-19 response strategies, notably by announcing the "20 measures" on 11 November and further the "10 measures" on 7 December 2022 [3,4].

Elsewhere in other parts of the world, the majority of countries are transiting to a "living with the virus" strategy, having built up considerable population immunity through multiple infection waves of ancestral strain and variants of concern (VOCs) and with the majority population having received two or three (sometimes even four) doses of vaccines. Given the interdependency of infectious disease dynamics at the meta-population level, when and how China can safely exit from its dynamic zero-COVID policy (in terms of significant morbidity and mortality as well as exceedance of the surge capacity of local health systems) has important implications to health security and economic stability globally.

As of 6 December 2022, mainland China has tallied just over 349,938 confirmed COVID-19 cases and 5,235 COVID-related deaths. Before the mass vaccination programme, the seroprevalence was <5% in Wuhan and <1% outside Wuhan in Hubei, even though they were the epicentres of the first wave in 2020 [5]. As such, existing population immunity nationwide is primarily conferred by passive immunisation with the domestically produced inactivated virus vaccines. As of 28 November 2022, the vaccine uptake of two- and three-dose vaccination are 91% and 57%, respectively. Although three-dose homologous vaccinations are highly effective in reducing the risk of Omicron hospitalisation and death, they have limited lasting impact in boosting immunity against Omicron (or future VOCs) transmission. Recent data suggests that for individuals who have received two doses of inactivated vaccines, a third dose of a heterologous vaccine increases neutralising antibodies to levels that correlate with substantial reduction in susceptibility to Omicron infection [6]. Thus, our basic premise is that high uptake of three-dose inactivated vaccines followed by heterologous boosters (i.e., fourth dose) would provide significant protection against Omicron transmission for 2-3 months to create a time window for safer reopening.

Timely antiviral treatment of symptomatic Omicron patients has now been proven to be effective in substantially reducing their risk of hospitalisation and death [7]. Nirmatrelvir/Ritonavir has already been approved for treating COVID in mainland China whilst five domestic companies are manufacturing Nirmatrelvir/Ritonavir for exports [8]. In addition, several domestic candidate oral drugs, including SIM0417 (a 3CL protease inhibitor similar to Nirmatrelvir), are undergoing Phase 2/3 trials. In this study, we assume that large-scale antiviral treatments are widely available by the time of reopening.

Here, we investigate to what extent optimal deployment of vaccines, antivirals and public health and social measures (PHSMs) could allow China to further adjust COVID-19 response and exit from zero-COVID safely after 7 December 2022. We also assess whether the local health systems can cope with the surge of disease burden posed by reopening, given that *chunyun,* a 40-day period with extremely high mobility across China associated with Spring Festival, will begin on 7 January 2023.

Methods

Vaccine effectiveness (VE) of 4th-dose heterologous boosting

As of 28 November 2022, the two- and three-dose vaccine uptake in mainland China was 91% and 57%. Since more than 95% of vaccines administered are inactivated virus vaccines, we assume that all vaccinees would receive inactivated virus vaccines for their first three doses. Following the widely used method developed by Khoury et al for predicting vaccine effectiveness from neutralisation antibody titres, we estimate that several domestically-made vaccines have substantial VE in reducing Omicron transmission (for a limited duration) if given as 4th-dose heterologous booster (see **Table S1** and **Appendix** for details) [9]. We assume that VEs conferred by 4th-dose boosting in reducing hospitalisations and deaths are equivalent to that from three doses of inactivated virus vaccines against the Omicron wave in Hong Kong (**Table S2**) [10].

We use a "leaky" vaccine action model to estimate vaccine-induced population immunity in reducing susceptibility to infection, infectiousness, hospitalisation, and death as a function of 4th-dose uptake over time (**Figure 1**). We assume that 4th-dose heterologous boosting would be delivered via two hypothetical vaccines A and B, and VEs and production capacities are similar to that of V-01 and NVSI-06-08 (i.e., 80% Vaccine A and 20% Vaccine B), respectively.

Effectiveness and availability of oral antivirals

Two oral antiviral medications, namely Molnupiravir and Nirmatrelvir/Ritonavir, have been used in Hong Kong since mid-March 2022 to treat COVID patients with a coverage of around 60% among eligible patients (i.e., patients aged 60 or above and high-risk patients under 60 years old). Given the current trajectory of COVID-19 antiviral availability and development in mainland China, we assume that Nirmatrelvir/Ritonavir would be used with 60% coverage when mainland China reopens, and that their effectiveness in reducing hospitalisations and deaths are similar to that observed in Hong Kong (**Table S3** and **Appendix**) [11].

Effectiveness of PHSMs

Hong Kong has experienced six waves of community wide COVID transmission (with the fifth and sixth wave being Omicron) whereas Shanghai has had one driven by Omicron BA.2 that had led to 2 months of city-wide lockdown. We categorise PHSMs implemented during these waves into four levels and estimate their effectiveness from the associated changes in reproductive number (**Figure S1** and **Table S4**). In Hong Kong, PHSMs at Levels 1-3 reduced R_t by 15%, 47% and 55%, respectively. Level 4 PHSMs reduced R_t by 69% in Hong Kong and 72% in Shanghai.

We map mainland China's combinations of PHSMs and their intensity to the abovementioned PHSM levels after the announcement of adjustment of COVID-19 response on 7 December 2022. We assume that the current PHSMs are as effective as Level 2, which would reduce R_t by 47%. A dynamic adjustment of PHSMs is anticipated during reopening, but we assume that PHSMs more stringent than Level 4 would not be considered because it would lengthen the time needed for populations to attain their herd immunity thresholds.

Modelling the spread and disease burden of Omicron

We assume that R_0 of the SARS-CoV-2 variant that spread during reopening would be similar to that of the most recent prevailing strain worldwide, Omicron BA.5 (i.e., around 8.3) and 1,000 cases would be seeded into the reopened populations on the first ten days of reopening. With the vaccination coverage as of November 2022 as the starting point, we assess the respective and combined impact of vaccination, antivirals and PHSMs in five scenarios, and the effects of prioritising different age groups in four sub-scenarios **(Table 1)**. We adopt a previously used age-structured susceptible-exposed-infectious-removed (SEIR) meta-population model of SARS-CoV-2 transmission dynamics parameterized with local-specific age demographics and contact patterns [12,13]. Population movements before, during and after *chunyun* among more than 300 prefecture-level cities are modelled based on previously constructed mobility networks adjusted with the relative changes in provincial transportation volumes between 2020 and 2021 [14].

Health system capacity

Among all Chinese cities, Hong Kong has one of the most well-resourced healthcare systems for managing the disease burden posed by COVID-19. As a best-case scenario, we use 100% and 200% of the maximum number of hospital beds designated for COVID-19 patients in Hong Kong in May 2022 (which correspond to its baseline/regular and surged capacity, respectively) as the benchmarks for health system capacity constraints across mainland China during reopening (**Table S3**). Assuming an average hospitalisation duration of 8 days [15,16], these constraints correspond to a daily incidence of 1.1 and 2.2 hospitalisations per 10,000 population, which also correspond to 21-42% of hospital beds in secondary/tertiary hospitals and 15-25% of all the existing hospital beds across all Chinese provinces (**Figure S2, Table S5** and **Table S6**).

Reopening strategies

In view of the COVID-19 response adjustments announced on 11 November and 7 December, we assume that the full reopening would start in December 2022. Using simulations, we compare two reopening strategies:

Strategy 1: Simultaneously reopen all provinces on 1 December 2022 for simplicity of execution and to minimise the duration of the associated socio-economic disruption, including cities with major outbreaks recently (e.g., Beijing, Chongqing and Guangzhou)

Strategy 2: Start mass vaccination of the 3rd dose homologous booster for the elderly and 4th dose heterologous booster for other ages on 1 December 2022, and simultaneously reopen all provinces on 1 January 2023

Specifically, we simulate Strategies 1 and 2 in the following regions (**Figure S3**): (i) the greater Yangtze River Delta (YRD, including cities and counties in Shanghai, Jiangsu, Zhejiang, and Anhui) and greater Pearl River Delta (PRD, including cities and counties in Guangdong) as exemplars of Chinese megalopolises; (ii) Henan and Guangxi as exemplars of regions with a substantial proportion of rural populations.

Results

VEs and population immunity conferred by 4th-dose heterologous boosting

We estimate that VE at 14 days after 4th-dose heterologous boosting in reducing Omicron susceptibility (VE_S), infectiousness (VE_I), hospitalisations (VE_H) and deaths (VE_D) are: (i) 58%, 47%, 96% and 98% for Vaccine A; and (ii) 88%, 70%, 96% and 98% for Vaccine B, respectively (**Table 2**). However, VE_S and VE_I wane quickly such that both vaccines would have minimal effect in reducing Omicron transmission 60-90 days after 4th-dose boosting (**Figure 1**). The population immunity against Omicron transmission during reopening is sensitive to the start time of 4th-dose boosting and the associated rollout rate (with respect to the time of reopening). Assuming that 4th-dose uptake would reach 85% at a weekly rate of 8%, 6% and 4% of the population, population immunity against infection and infectiousness would reach 20-30% and 15-25% within 70, 90, and 120 days, respectively. Slower rollout of the 4th dose would fail to generate significant population immunity against Omicron transmission (**Figure 1**). Immunity from 4th-dose boosting would be sustained at peak levels for about 60 days and then drop substantially afterwards. Taken together, if population immunity is one of the prerequisites for safer reopening, 4th-dose heterologous boosting should start and finish within 1-2 months before the commencement of reopening by vaccinating 4-8% of the population per week.

Impact of combining vaccination, antiviral treatment and PHSMs

We first consider status quo without 4th-dose vaccination, antivirals and PHSMs (**Scenario 1** in **Table 1**) and epidemics are simultaneously seeded in all provinces. In this case, reopening at the status quo would result in a cumulative mortality burden of 684 per million (**Figure 2**).

We next consider vaccinations, antiviral treatments and PHSMs individually (**Figure S4**). Assuming that the basic reproductive number R_0 of Omicron BA.5 is 8.3 (7.8-8.9) and a fast rollout of the 4th dose would provide 25% and 20% population immunity against infection and infectiousness (**Figure 1**), R_t of Omicron BA.5 under Leve1 1-4 PHSMs would be around 4.2, 2.6, 2.2 and 1.5, respectively. If vaccination, antiviral treatments and PHSMs are only implemented in isolation, the disease burden posed by reopening would substantially exceed the health system capacity in all provinces.

Therefore, we consider vaccination, antiviral treatments and PHSMs in different combinations **(Table 1)**. **Scenario 2** shows that with vaccination and antivirals but not PHSMs, hospitalisations and deaths would again exceed by a large margin the capacity of local health systems for 2-3 weeks in all provinces (**Figure 2**). Specifically, the daily number of hospitalisations would peak at 4.8 (3.8-6.2) per 10,000 population which is more than twice the surge capacity constraint (i.e., 2.2 per 10,000), although the cumulative number of deaths would be reduced by 26% to 503 per million compared with Scenario 1.

Similarly, **Scenario 3** shows that, although adding PHSMs could further reduce the spread and overall mortality (to 448 per million), peak hospitalisation burden would still overload the health systems for weeks albeit with smaller excess margins. **Scenarios 4 and 5** show that in addition to PHSMs, faster rollout of 4th-dose boosting would slightly reduce the overall mortality to 426 and 416 per million, but they would be unable to completely avert overloading of the local health systems beyond the surge capacity constraint.

Increasing booster uptake to 95% among 18-59 and 3-59 years old would further reduce the overall mortality to 305 and 249 per million, respectively (**Figure 3**). However, prioritising boosting among younger age groups that contribute more to transmission would only modestly reduce the peak incidence of infection and hospitalisation with minimal additional indirect protection of the elderly population. Peak hospitalisation incidence would still exceed the baseline capacity constraint (i.e., 1.1 per 10,000) even when 4th-dose uptake reaches 95% among 3-59 years old and >85% in other age groups.

Populations with 4th-dose uptake below 85% would require more stringent PHSMs to reduce R_t by >65% (entailing closure of most indoor premises and different sectors of business, amongst others) in order to prevent peak daily incidence of hospitalisation from exceeding 2.2 per 10,000 (**Table S5**). Populations with older age structures also require more stringent or prolonged PHSMs for safe reopening, because those aged 60 or above have much higher risks of hospitalisation and death if infected. In what follows, we only simulate **Scenario 4** unless specified otherwise.

Simultaneous reopening of all provinces without 4^th^ dose heterologous booster (Strategy 1)

Under **Strategy 1**, simultaneous reopening of all provinces without 4^{th} dose vaccination would result in almost synchronised epidemics in both YRD and PRD, especially under their higher connectivity with all provinces, cities and counties during the *chunyun* period (**Figure 4**).

The epidemic lasts longer and peaks slightly earlier in the cities where epidemics are first seeded. In other cities within YRD and PRD, daily incidence of hospitalisation peaks at nearly the same time, and the surge in hospital admissions would exceed the capacity of health systems in all cities. At peak, the daily number of hospitalisations could reach 6-7 per 10,000 population which is about 3-4 times the surge capacity threshold of health system capacity (2.2 hospitalisations per 10,000). The mean daily incidence of deaths is 2.3-3.5 per 100,000 at peak, and the mean cumulative incidence of deaths is 568-770 per million in all populations. For example, the peak daily number of deaths is 573-872 and the cumulative number of deaths is 14,138-19,166 in Shanghai (24.89 million population).

The epidemics in Henan and Guangxi would be similar to that in YRD and PRD except for a longer time lag between the first epidemic wave in cities where epidemics are seeded and the subsequent epidemics in other cities (which are synchronised) due to relatively weaker population mobility between them (**Figure 4**).

Simultaneous reopening of all provinces with 4^{th} dose heterologous booster (Strategy 2)

Under **Strategy 2**, simultaneous reopening of all provinces with 4^{th} dose vaccination would similarly result in almost synchronised epidemics in both YRD and PRD, but mass vaccination with 4^{th} dose heterologous boosting would reduce the peak incidence of hospitalisations and deaths (**Figure 5**). At peak, the daily number of hospitalisations is reduced to 4-6 per 10,000 population which is about 1.5-2.5 times the surge capacity threshold of health system capacity (2.2 hospitalisations per 10,000). The mean daily incidence of deaths is also reduced to 1.7-2.4 per 100,000 at peak, and the mean cumulative incidence of deaths is 434-615 per million in all populations. For example, the peak daily number of deaths is 424-598 and the cumulative number of deaths is 10,803-14,885 in Shanghai.

More stringent PHSMs are required during reopening

Given that the surge of COVID-19 hospitalisations would overload health systems of all provinces in Strategies 1-2, we estimate that more stringent PHSMs are required during reopening (**Figure 6**). Without 4^{th} dose heterologous boosting, implementing PHSMs at Level 4 could only reduce the peak hospitalisation to 4.3 per 100,000. Therefore, more stringent PHSMs to reduce R_t by 80-88% (similar to lockdown) are required to keep peak hospitalisation below the surge capacity threshold of health system. There is a trade-off between higher vaccination coverage and less stringent PHSMs: if 4^{th} dose heterologous vaccination coverage could reach >75% or above nationally, PHSMs at Level 3 would be able to keep peak hospitalisation below the surge capacity threshold of health system.

Discussion

Our results suggest that local health systems across all provinces would be unable to cope with the surge of COVID-19 cases posed by reopening in December 2022 – January 2023 in the context of the adjusted COVID-19 responses announced on 7 December [4]. However, safer exit from dynamic zero-

COVID could be achieved by adopting a multi-pronged approach comprising vaccination, antiviral treatment, PHSMs and sequential reopening. As of 28 November 2022, the nationwide three-dose vaccine uptake was 57% and 69% among population aged <60 and ≥60. As such, it is crucial to substantially boost population immunity to minimise morbidity and mortality during the reopening.

A high uptake of heterologous boosting with an efficacious fourth dose is the cornerstone for reopening more safely. As of 7 December 2022, among all domestic vaccines under emergency use or development, recombinant protein subunit vaccines (e.g., V-01, SCB-2019 and SCTV-01C) and inhaled adenovirus-vectored vaccines (e.g., Ad5-nCoV-IH) have shown good potential for inducing immunity against Omicron infections (**Table S1**). Boosting population immunity (especially among the elderly population and high-risk groups) are current top priorities for setting the stage for safe reopening. Increasing vaccine uptake in all age groups, including children aged under 3, should be also considered. Given the fast waning of VEs, mass vaccination programme of the fourth dose should start within 30-60 days before reopening and complete within 60 days (**Figure 1**).

China is a highly heterogenous country with megalopolises and developed urban areas in the East and Southeast, but the majority of rural areas are in the North, Northwest, and Southwest. Economically prosperous regions have relatively more abundant healthcare resources and are therefore more resilient in coping with the surge of cases and hospitalisations during reopening (**Table S5**). When these regions reopen, PHSMs should ideally be kept at Level 2-3 to minimise the associated socio-economic disruption whenever possible, but PHSMs at Level 4 should be considered when surge of hospitalisations is expected to overload the health system. Antivirals should be prescribed in a timely manner in symptomatic cases at high coverage, and treatment and management of COVID-19 patients should be risk stratified. For example, a primary-care supported home recovery programme could be introduced for low-risk patients (i.e., those who are asymptomatic or mildly symptomatic), whereas high-risk patients should be provided with necessary medical care (especially with timely antivirals) and closely monitored with the help of telemedicine. In this regard, antivirals should be made more widely accessible at a much lower cost.

In contrast, a large proportion of China's elderly population live in rural areas where treatment and care are most needed during the reopening transition. Therefore, ramping up temporal hospital capacity in rural areas should be emphasised in the interim. Ideally, vaccination coverage of the 3rd and 4th dose should exceed 90%, and logistics infrastructure should be set up for efficient and timely on-demand antiviral distribution at the household level. When these rural areas reopen, more stringent PHSMs of Level 4 could be considered near the epidemic peaks to further minimise the surge demand of hospital care. However, in the context of reopening, the functional aim of PHSMs is to strike an optimal balance between: (i) keeping the peak hospital load just below the surge capacity constraint **(Figure 6)**; and (ii) allowing epidemics to infect around 1-1/R_0 (the herd immunity threshold) proportion of the population within 6 months in order for natural infections to generate enough long-lasting hybrid immunity against substantial resurgence afterwards. As such, PHSMs should not be overly stringent and city-wide lockdown (i.e., PHSMs above Level 4) should be avoided, because cases will resurge as soon as those PHSMs are lifted otherwise.

Although safe reopening might reduce the surge of COVID-19 severe cases to more manageable levels, reopening mainland China at an initial R_t close to 3 would still result in a large number of infections that could potentially accelerate mutation, selection and evolution of SARS-CoV-2 viruses [17,18]. Genomic surveillance for SARS-CoV-2 variants must be strengthened, particularly in megalopolises that are highly connected domestically and internationally. Multidisciplinary studies of the transmissibility, severity, immune/vaccine escape of variants and antiviral resistance should be coordinated nationwide to track the evolution of the pandemic [19].

In conclusion, although the surge of disease burden posed by reopening in December 2022 – January 2023 would likely overload most local health systems nationwide, a reopening strategy that combines vaccination, antiviral treatment and PHSMs could allow China to exit zero-COVID more safely. This would require a nationally coordinated effort for reopening, including planning, execution, and surveillance.

Contributors

All authors designed the study, developed the model, analysed data, interpreted the results, and wrote the manuscript.

Declaration of interests

The authors declare no competing interests.

Data sharing statement

We collated all data from publicly available data sources. All data included in the analyses are available in the main text or the supplementary materials.

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Table 1. Scenarios of combining pharmaceutical and non-pharmaceutical interventions

Scenario	Combination of vaccinations, antivirals and PHSMs
1	• Status-quo with two-dose and three-dose vaccine uptake as of November 2022 • No 4^{th}-dose vaccinations • No antivirals • No PHSMs
2	• Mass vaccination of 4^{th} dose begins 30 days before the reopening and 4% of the population would receive the 4^{th} dose per week. The maximum vaccine uptake of the 4^{th} dose would reach 85% and 80% and 20% of individuals would receive Vaccine A and Vaccine B as the 4^{th} dose. • Antiviral coverage is 60%. • No PHSMs
3	• Mass vaccination of 4^{th} dose begins 30 days before the reopening and 4% of the population would receive the 4^{th} dose per week. The maximum vaccine uptake of the 4^{th} dose would reach 85% and 80% and 20% of individuals would receive Vaccine A and Vaccine B as the 4^{th} dose. • Antiviral coverage is 60%. • PHSMs at Level 2 which reduce R_t by 47% are implemented 14 days after the seeding of epidemics, and PHSMs at Level 2 are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days.
4	• Mass vaccination of 4^{th} dose begins 30 days before the reopening and 6% of the population would receive the 4^{th} dose per week. The maximum vaccine uptake of the 4^{th} dose would reach 85% and 80% and 20% of individuals would receive Vaccine A and Vaccine B as the 4^{th} dose. • Antiviral coverage is 60%. • PHSMs at Level 2 which reduce R_t by 47% are implemented 14 days after the seeding of epidemics, and PHSMs at Level 2 are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days.
5	• Mass vaccination of 4^{th} dose begins 30 days before the reopening and 6% of the population would receive the 4^{th} dose per week. The maximum vaccine uptake of the 4^{th} dose would reach 85%. Individuals would receive any of the five vaccines, including V-01, NVSI-06-08, Ad5-nCoV-IM, Ad5-nCoV-IH and BNT162b2, with equal probability as the 4^{th} dose. • Antiviral coverage is 60%. • PHSMs at Level 2 which reduce R_t by 47% are implemented 14 days after the seeding of epidemics, and PHSMs at Level 2 are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days.

Scenario	Vaccination coverage of the 4^{th} dose and prioritisation of age groups in the vaccination programme under Scenario 4
4.1	• The maximum vaccine uptake of the 4^{th} dose would reach 85% in all age groups aged 3 or above. • Roll-out of 4^{th} dose vaccination follows the age-specific vaccine uptake of the 3^{rd} dose as of November 2022.
4.2	• The maximum vaccine uptake of the 4^{th} dose would reach 85% in all age groups aged 3 or above. • Prioritise 4^{th}-dose vaccination of older adults and seniors aged 60 or above.
4.3	• The maximum vaccine uptake of the 4^{th} dose would reach 95% among 18-59 year olds and 85% in other age groups. • Prioritise 4^{th}-dose vaccination of adults aged 18 to 59
4.4	• The maximum vaccine uptake of the 4^{th} dose would reach 95% among 3-59 year olds and 85% in other age groups. • Prioritise 4^{th}-dose vaccination of adults aged 3 to 59

Table 2. Assumption about neutralising antibody titres (IC50) and vaccine effectiveness (VE) against Omicron BA.2 after the fourth dose in mainland China (with BBIBP-CorV as the first three doses)

IC50 titres	**Time after the 4th dose**				
Vaccine	**0 days**	**14 days**	**60 days**	**90 days**	**180 days**
Vaccine A	5 (5, 5)	148 (101, 215)	68 (48, 100)	35 (24, 53)	5 (3, 6)
Vaccine B	5 (5, 5)	368 (296, 457)	169 (135, 208)	86 (69, 108)	10 (8, 12)
VE in reducing susceptibility	**Time after the last dose**				
Vaccine	**0 days**	**14 days**	**60 days**	**90 days**	**180 days**
Vaccine A	0	0.58	0	0	0
Vaccine B	0	0.88	0.52	0	0
VE in reducing infectiousness	**Time after the last dose**				
Vaccine	**0 days**	**14 days**	**60 days**	**90 days**	**180 days**
Vaccine A	0	0.47	0	0	0
Vaccine B	0	0.70	0.42	0	0
VE in reducing hospitalisation	**Time after the last dose**				
Vaccine	**0 days**	**14 days**	**60 days**	**90 days**	**180 days**
Vaccine A	0.80	0.96	0.96	0.95	0.95
Vaccine B	0.80	0.96	0.96	0.95	0.95
VE in reducing death	**Time after the last dose**				
Vaccine	**0 days**	**14 days**	**60 days**	**90 days**	**180 days**
Vaccine A	0.90	0.98	0.98	0.96	0.96
Vaccine B	0.90	0.98	0.98	0.96	0.96

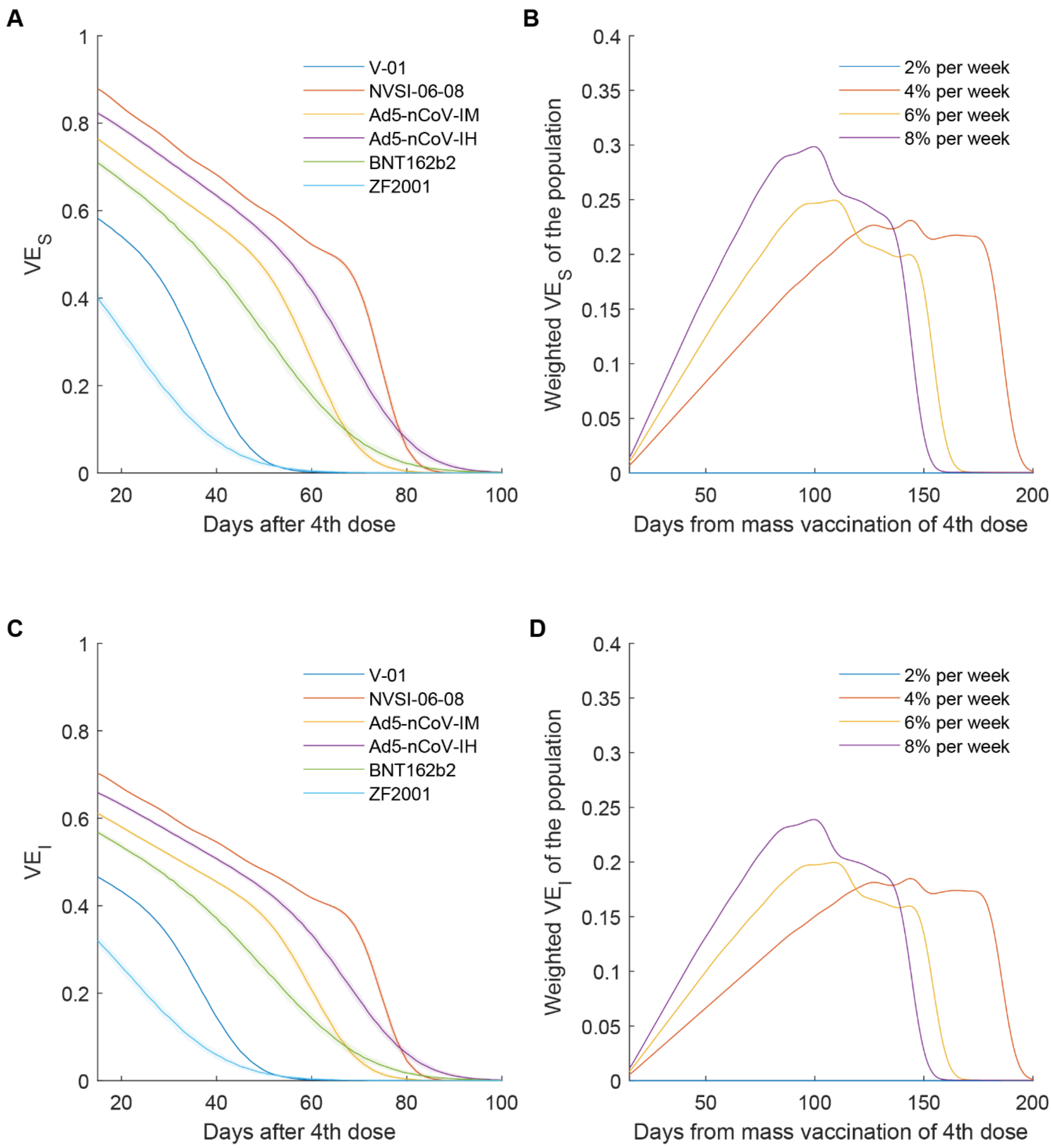
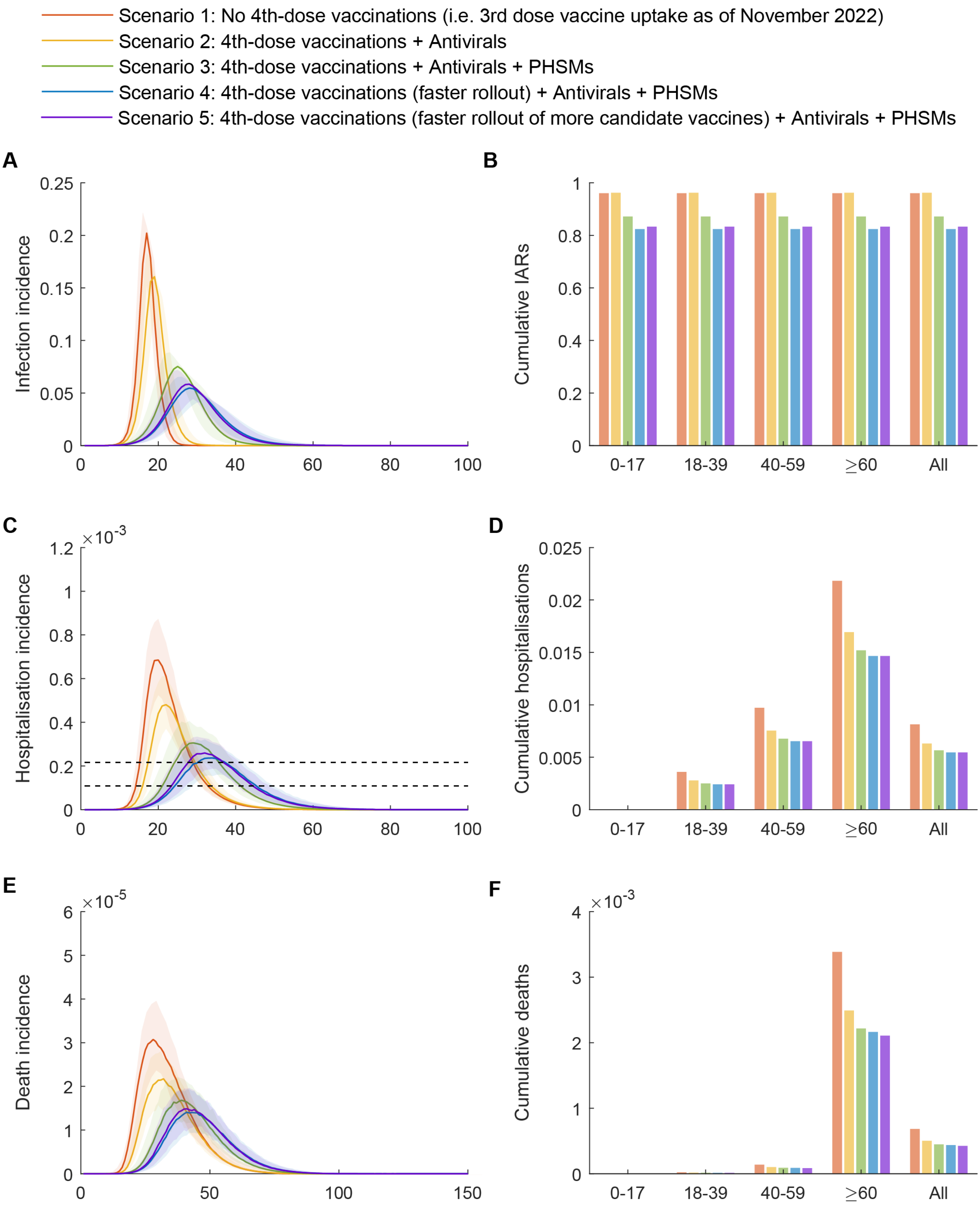
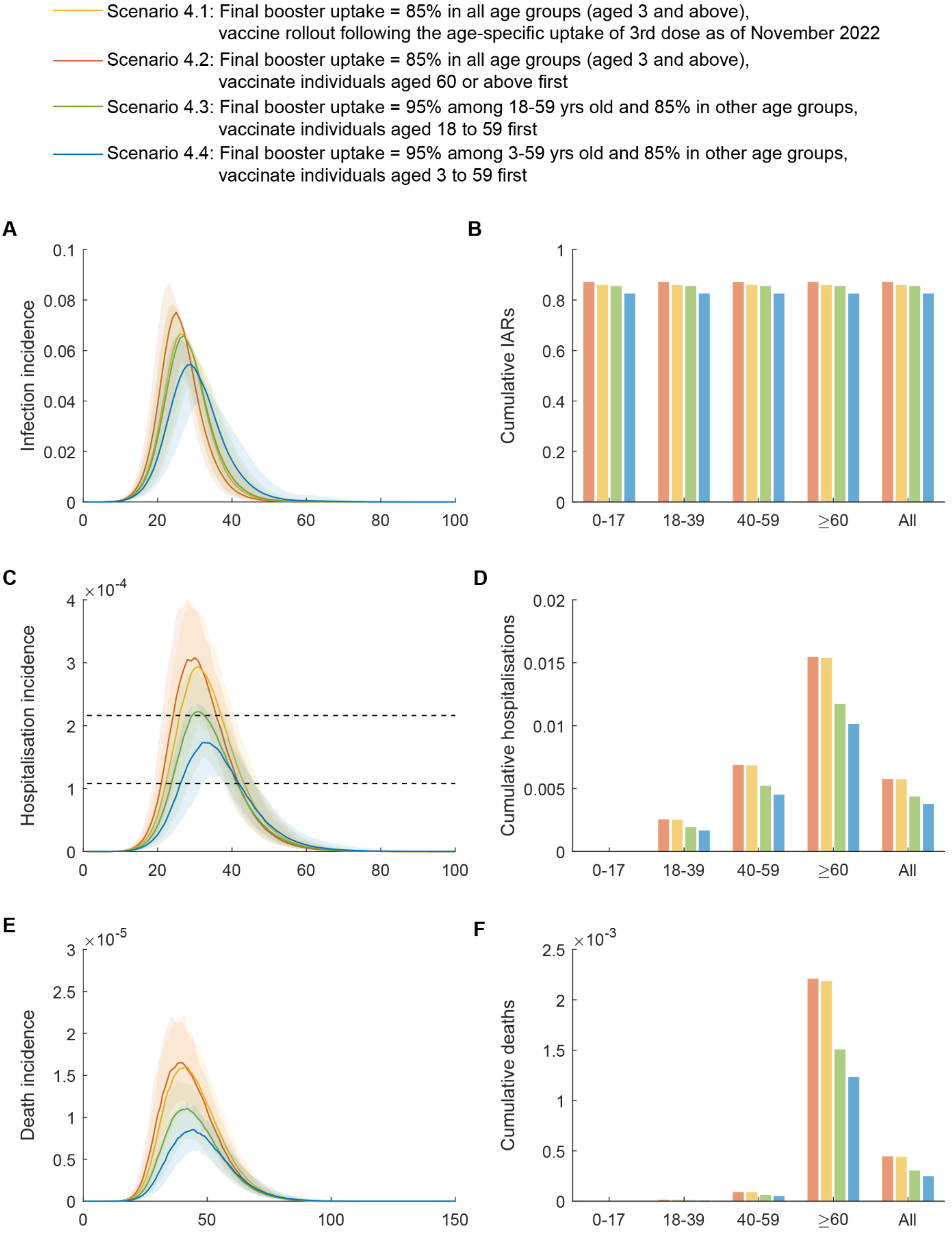


Figure 1. Vaccine effectiveness of heterologous boosting with the 4th dose against Omicron BA.2 in reducing susceptibility (VE_S) and infectiousness (VE_I). (A-B) VE_S and VE_I by days after the 4th dose which is assumed to be equivalent to that conferred by a heterologous booster following 2 doses of inactivated virus vaccines (which was estimated from neutralising Ab titres 14-28 days after the 3rd dose; **Table S1**). We assume that the Ab titres decay exponentially after the 3rd and 4th dose at the same rate (**Appendix**). (C-D) Population immunity against infection and infectiousness by days since the start of mass heterologous boosting at a maximum rate of vaccinating 2, 4, 6 and 8% of the population per week. Based on the national vaccination coverage data as of 28 November 2022, we assume the maximum vaccine uptake of the 3rd and 4th dose was 85%. We assume that 80% and 20% of vaccinees would be allocated with Vaccine A (with VEs similar to V-01) and Vaccine B (with VEs similar to NVSI-06-08), respectively. Assuming leaky vaccine action, we estimate population immunity as the product of vaccine uptake and VE. For example, if VE_S = 30% and vaccine uptake is 68%, then population immunity against infection is 21%.



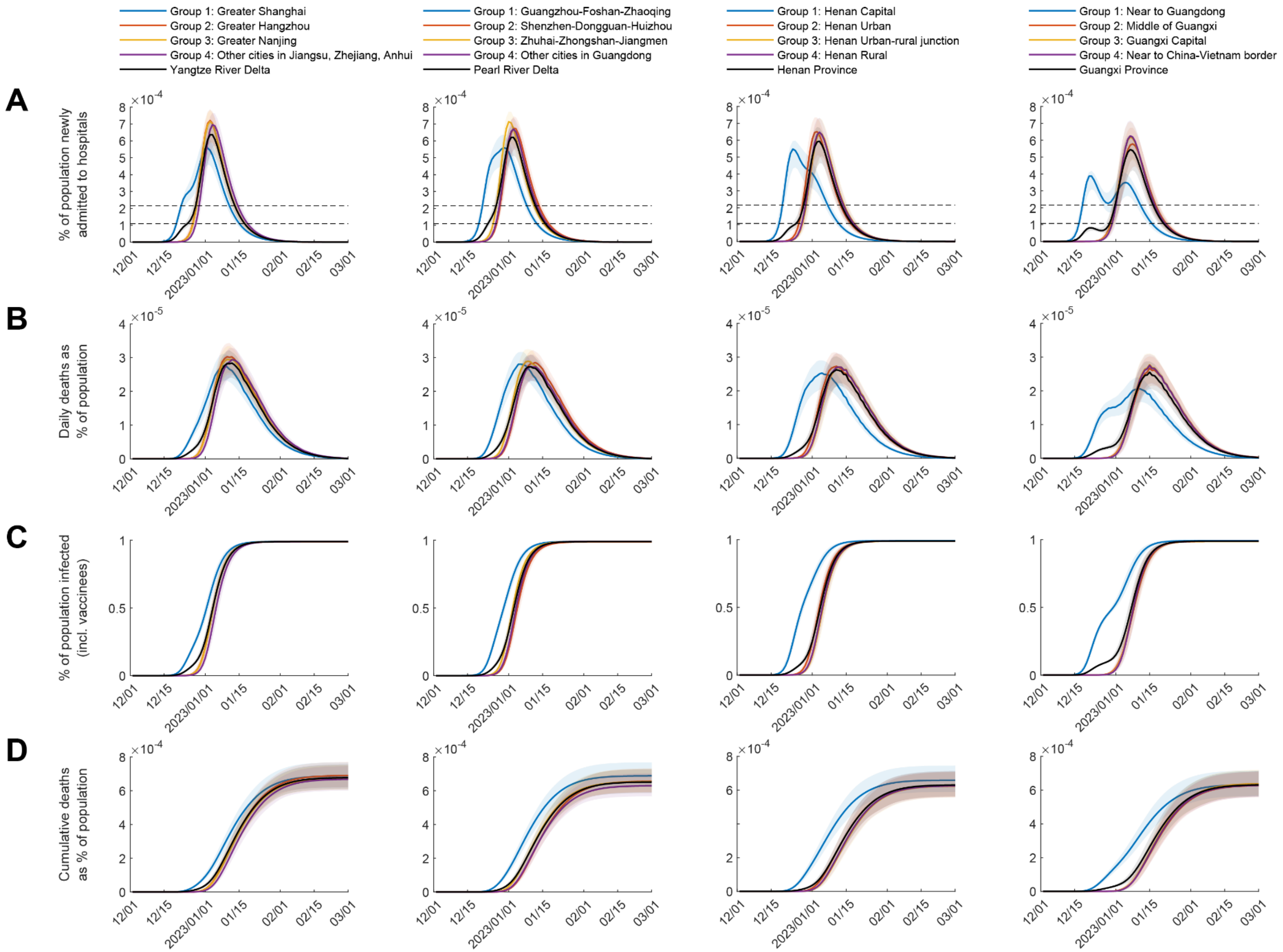
376

377 **Figure 2. The impacts of 4th dose heterologous boosting, antiviral treatments and PHSMs if they**
378 **are combined during reopening.** Please see Table 1 for descriptions of the five scenarios. **(A)**
379 **Infection incidence as proportion of the population. (B) Cumulative infection attack rates by**
380 **age. (C-D) Daily and cumulative number of cases requiring who require hospitalisation. (E-F)**
381 **Daily and cumulative incidence of death.** Solid lines indicate the 50th percentile of the estimates
382 and shades indicate the ranges between 2.5th and 97.5th percentiles. The two horizontal dashed lines
383 indicate the two health system capacity constraints based on the experience of Hong Kong during its
384 Omicron wave (see Methods).



385

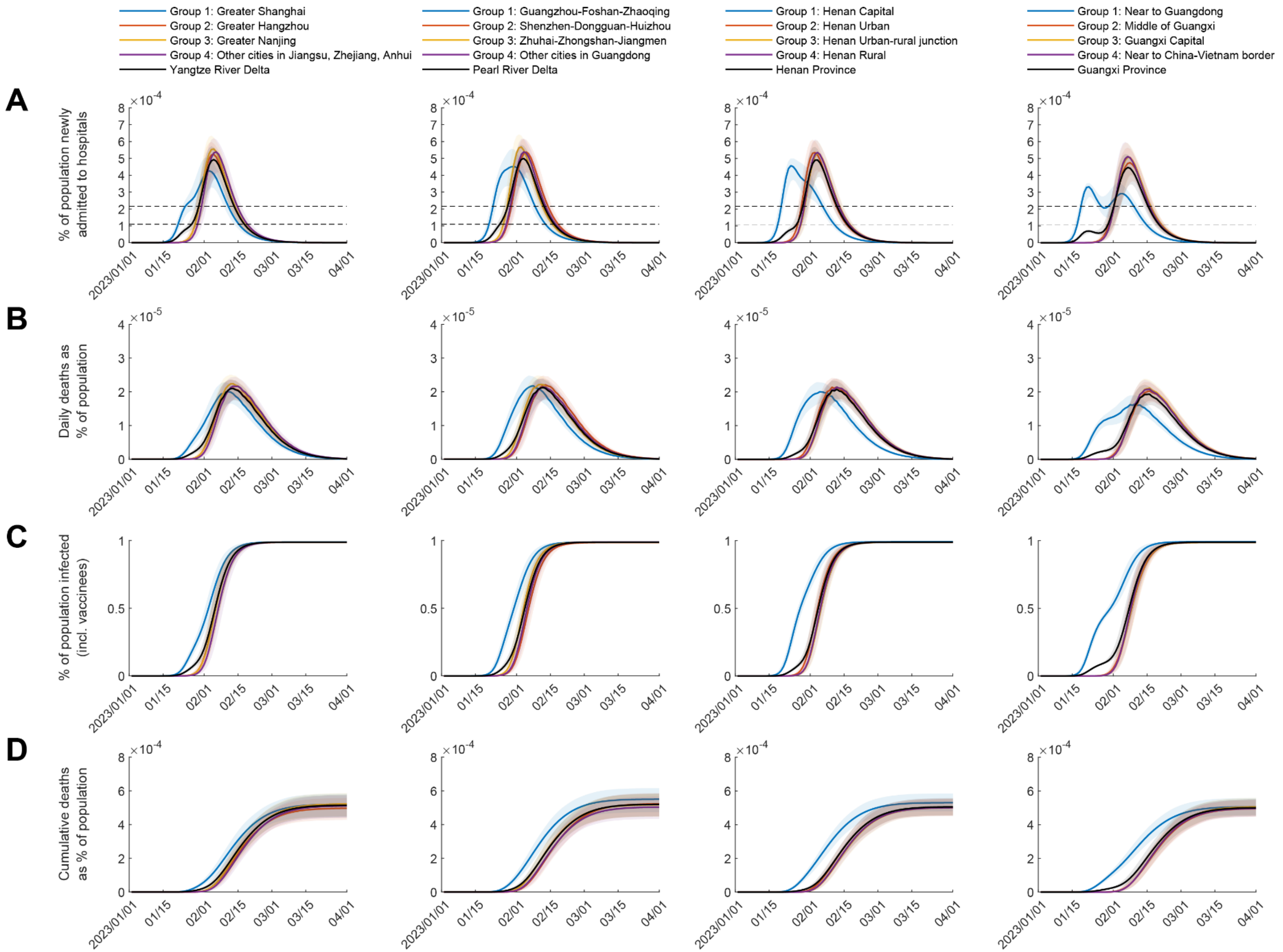
386 **Figure 3. The impact of prioritising different age groups for 4th dose heterologous boosting.** We
387 consider four prioritisation schemes for boosting (Table 1). Other parameters are the same as Scenario
388 4 in **Figure 2.**



Group 1: Greater Shanghai
Group 2: Greater Hangzhou
Group 3: Greater Nanjing
Group 4: Other cities in Jiangsu, Zhejiang, Anhui
Yangtze River Delta
Group 1: Guangzhou-Foshan-Zhaoqing
Group 2: Shenzhen-Dongguan-Huizhou
Group 3: Zhuhai-Zhongshan-Jiangmen
Group 4: Other cities in Guangdong
Pearl River Delta
Group 1: Henan Capital
Group 2: Henan Urban
Group 3: Henan Urban-rural junction
Group 4: Henan Rural
Henan Province
Group 1: Near to Guangdong
Group 2: Middle of Guangxi
Group 3: Guangxi Capital
Group 4: Near to China-Vietnam border
Guangxi Province
A
% of population newly admitted to hospitals
B
Daily deaths as % of population
C
% of population infected (incl. vaccinees)
D
Cumulative deaths as % of population
12/01
12/15
2023/01/01
01/15
02/01
02/15
03/01

389

Figure 4. Simultaneous reopening of Yangtze River Delta Region, Pearl River Delta Region, Henan, and Guangxi without 4th dose vaccination. We assume that mass vaccination of the 4th dose would not be implemented. Antiviral coverage is 60%. PHSMs at Level 2 are implemented 14 days after the seeding of epidemics, and PHSMs at Level 2 are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days. In four regions, we assume COVID-19 outbreaks are seeded by importations in Group 1 (Shanghai, Guangzhou, Zhengzhou, and Guilin) on 1 December 2022. Solid lines show the 50th percentile of the estimations and shades show the ranges between 10th and 90th percentiles. Other parameters are the same as Scenario 4 in **Figure 2**.



Group 1: Greater Shanghai
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Group 4: Near to China-Vietnam border
Guangxi Province
A
% of population newly admitted to hospitals
B
Daily deaths as % of population
C
% of population infected (incl. vaccinees)
D
Cumulative deaths as % of population
2023/01/01
01/15
02/01
02/15
03/01
03/15
04/01

Figure 5. Simultaneous reopening of Yangtze River Delta Region, Pearl River Delta Region, Henan, and Guangxi with 4th dose vaccination. We assume that mass vaccination of the 4th dose starts 30 days before the reopening to vaccinate 6% of the population per week, and uptake of the 4th dose would reach 85%. Antiviral coverage is 60%. PHSMs at Level 2 are implemented 14 days after the seeding of epidemics, and PHSMs at Level 2 are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days. In four regions, we assume COVID-19 outbreaks are seeded by importations in Group 1 (Shanghai, Guangzhou, Zhengzhou, and Guilin) on 1 January 2022. Solid lines show the 50th percentile of the estimations and shades show the ranges between 10th and 90th percentiles. Other parameters are the same as Scenario 4 in **Figure 2**.

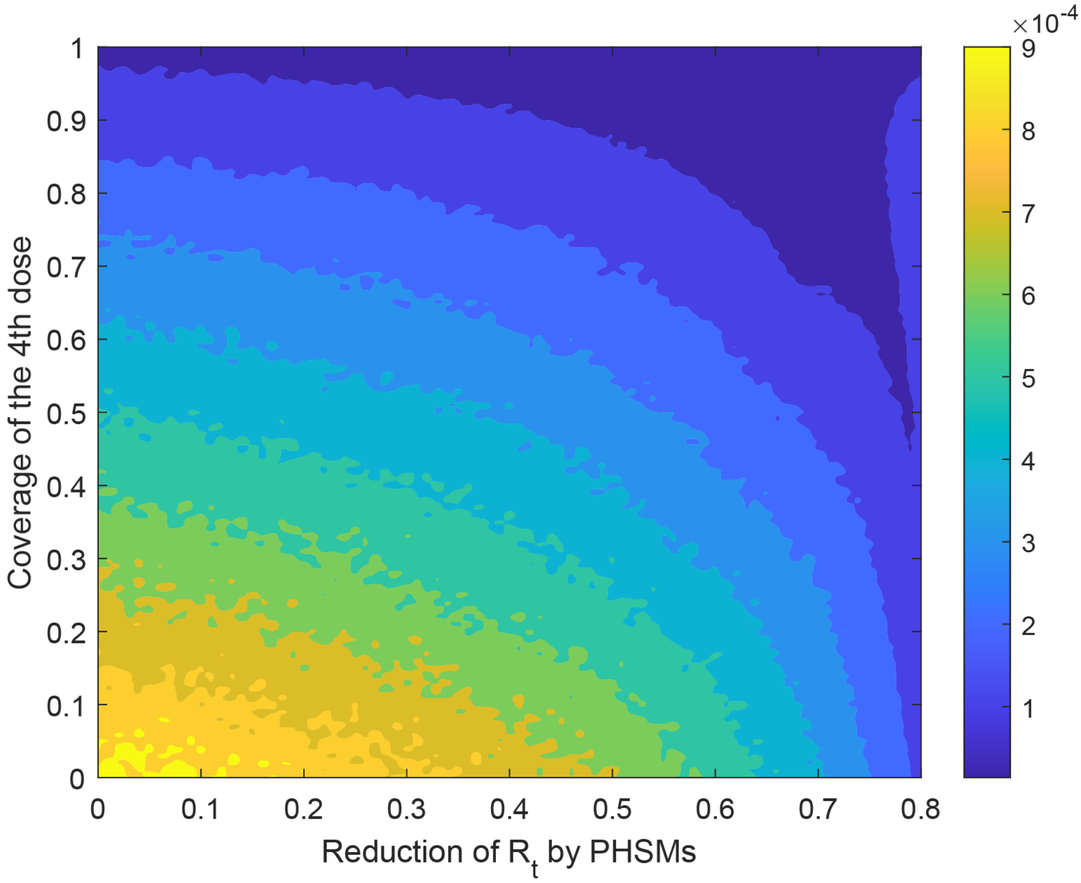

Figure 6. Peak daily incidence of hospitalisation as a function of PHSM intensity and 4th dose uptake. We assume that reopening would begin 30 days after the start of 4th-dose boosting and 6% of the population would receive the 4th dose per week. PHSMs would be implemented 14 days after the seeding of epidemics and maintained for 60 days (i.e., until day 74 after reopening has begun). PHSMs would then be gradually over the next 30 days. Other parameters are the same as Scenario 4 in **Figure 2.**

Appendix

Estimating vaccine effectiveness of heterologous boosting in reducing Omicron susceptibility and infectiousness

As of 28 November 2022, the two- and three-dose vaccine uptake in mainland China was 91% and 57%, respectively. The corresponding uptake among those aged 60 or above was 86% and 69%, respectively (http://www.nhc.gov.cn/).

Since more than 95% of vaccines administered in mainland China currently are inactivated virus vaccines, we assume that all vaccinees would receive inactivated virus vaccines (namely, BBIBP-CorV or CoronaVac) for the first three doses. The IC50 neutralising antibody (Ab) titres against Omicron after the first three doses were obtained from the Brazilian study RHH-001 [6] and the Phase-3 trial of V-01 vaccine [20].

We assume that 4th-dose heterologous boosting would be delivered via two hypothetical vaccines A and B whose VEs and production capacities are similar to that of V-01 and NVSI-06-08 (**Table 2, Table S1 and Table S2**):

1) V-01 is a recombinant SARS-CoV-2 fusion protein vaccine (i.e. RBD dimer-IFN-Pan Fc fusion protein) developed by Livzon. In the Phase-3 trial of 10,218 participants in Pakistan and Malaysia with a follow-up period of 60-90 days, the vaccine efficacy of V-01 as the third dose was 64% (23-83) and 39% (3-62) against Omicron infection among 4,935 participants who had received BBIBP-CorV or CoronaVac vaccines in their primary course [20].

2) NVSI-06-08 is a recombinant COVID-19 vaccine based on the antigen of a mutation-integrated trimetric RBD developed by Sinopharm. In the Phase-2 trial, the neutralising Ab titres against Omicron was increased to 368 (95% CI: 296-457) among participants who had received BBIBP-CorV as their primary course and NVSI-06-08 as the third dose [21].

We apply the Khoury method to predict the vaccine effectiveness (VE) in reducing Omicron susceptibility and infectiousness as described in Leung et al [9]. The prediction is based on the neutralising Ab data from Brazil and Hong Kong [6,22,23] and the VE data from Phase-3 trial of V-01, RHH-01 study from Brazil, and UKHSA reports from the UK [6,20,24]. Using the same method, we model the waning of VE based on the following assumptions regarding the waning of Ab titres: (i) The waning rate of Ab titres after the third dose is the same for inactivated virus vaccines and BNT162b2; (ii) the waning rate after the third and fourth dose are the same. We estimate the waning rate of Ab titres for BNT162b2 by mapping the neutralising titres after three doses of BNT162b2 vaccines from Cheng et al [22] to the 3-dose VEs estimates from UKHSA by Andrews et al [24].

It is believed that the immune response after receiving the third or fourth dose of vaccine, especially cellular immunity (e.g., via T cells), may provide greater and more long-lasting protection against severe disease than mild or asymptomatic infection [25-29]. As such, we assume that the VE against severe disease, hospitalisations and death after 4th-dose heterologous boosting would be similar to the corresponding VEs among recipients of three doses of CoronaVac vaccines in Hong Kong [10], regardless of VE waning over time and the emergence of VOCs (**Table 2**).

Estimating the vaccine-induced population immunity

We model the rollout of vaccination programme under the following assumptions:

1) The target vaccine uptake of the 2nd, 3rd and 4th dose is 90%, 85% and 85% for all age groups, respectively, based on the age-specific 2-dose and 3-dose vaccine uptake in mainland China as of 28 November 2022.
2) For the 4th dose, we assume that 80% of vaccinees would be allocated with Vaccine A, and the remaining 20% of vaccinees would be allocated with Vaccine B. According to the press release of V-01 vaccine manufacturer Livzon on 12 April 2022, their Guangdong branches have been approved to produce the V-01 vaccine. The annual production capacity could reach 1.5 billion doses of packaged V-01 vaccines (https://www.livzon.com.cn/ and http://www.news.cn/english/2021-08/30/c_1310155999.htm). According to the press release of NVSI-06-08 vaccine manufacturer Sinopharm on 3 April 2022, their factories in Beijing and Gansu have been producing NVSI-06-08 vaccines. Between October and December 2021, Sinopharm had produced 80 million doses of NVSI-06-08 vaccines and delivered 20 million doses outside mainland China (http://www.sinopharm.com/s/1223-4131-40132.html). Currently, the annual production capacities of the two vaccines are 1.5 billion and 0.32 billion doses and we assume a similar ratio in the vaccine allocation of the 4th dose.
3) The roll-out of the 4th dose will be considered after the 3rd-dose uptake has reached 80%.
4) The time interval between the 1st and 2nd dose is 28 days.
5) The time interval between the 2nd and 3rd dose is at least 90 days.
6) The time interval between the 3rd and 4th dose is at least 180 days.
7) The maximum weekly vaccination rate is 8% of the population. During the rapid rollout of mass vaccination in 2021, the maximum number of vaccine doses given to the Chinese population reached 24 million per day in May 2021, which was equivalent to a weekly rate of 12% of the population (http://www.nhc.gov.cn/).

Estimating the effects of PHSMs from the past waves of COVID-19 in Hong Kong and Shanghai

Since the emergence of the COVID-19 pandemic, various PHSMs have been used to suppress and mitigate the spread of SARS-CoV-2 in Hong Kong. We analyse data on locally laboratory-confirmed cases of the first four waves of COVID-19 outbreaks and estimated the daily effective reproductive number (R_t) to estimate the changes in transmissibility over time (**Figure S1**). During each wave, PHSMs were progressively tightened with the increase of reported cases. Without loss of generality, we group the PHSMs into four levels in each wave using the time when civil servants were required to work from home (WFH) as a cut-off:

1) **Level 1:** Voluntarily universal face masking and improved hand hygiene
2) **Level 2: Level 1** PHSMs + PHSMs announced or implemented before civil servants WFH, which usually included tightened social distancing measures in restaurants and indoor leisure facilities, and closure of kindergartens and primary schools of Grade 1-3 or Grade 1-4.
3) **Level 3: Level 2** PHSMs + PHSMs announced or implemented together with civil servants WFH, which often included closure of most indoor leisure facilities, closure of all schools, no dine-in in restaurants after 9 pm.
4) **Level 4: Level 3** PHSMs + PHSMs announced or implemented after civil servants WFH, which included more stringent control measures of restaurants, such as no dine-in after 6 pm or all day.

We assume that the basic reproductive number was 2.0 for the first wave (the original virus strain), 2.2 for the second wave (70% of original virus and 30% of D614G mutant virus which was estimated to be 30% more transmissible than the original virus), 2.6 for third and fourth wave (D614G mutant virus), in the absence of any PHSMs and COVID-19 vaccination. Then we estimate the effectiveness of PHSMs at Level 1-4 by overlaying these PHSMs with R_t in the first four waves (**Figure S1 and Table S4**).

In the fifth wave of Omicron BA.2 in Hong Kong, we estimate the effectiveness of Level 4 PHSMs in parameter inference in the epidemic model [16]. Similarly, we estimate the effectiveness of PHSMs in Shanghai before the lockdowns of Pudong (the east of Huangpu River) on 27 March 2022 and Puxi (the west of Huangpu River) on 1 April 2022.

Reopening in regions with substantial proportion of rural populations

We define urban, urban-rural junction and rural area as administrative regions with <64%, 64-71% and >71% of sub-administrative regions coded as "rural", based on the coding of National Bureau of Statistics (http://www.stats.gov.cn/tjsj/tjbz/tjyqhdmhcxhfdm/2020/index.html). The urbanisation rate of China is 60% in 2019, and at the national level, the 20th, 40th, 60th and 80th percentile of the proportion of sub-administrative regions coded as "rural" are 55%, 64%, 71% and 77%, respectively.

In Henan, we assume that the reopening starts simultaneously with the epidemics seeded in the provincial capital region (Zhengzhou and Xuchang) and spread to urban area, urban-rural junction, and rural area, respectively (**Table S7**). In Guangxi, we assume that the reopening starts with the epidemics seeded in the area adjacent to PRD/Guangdong and spread geographically in a diffusion manner to the middle of Guangxi, provincial capital, and area next to China-Vietnam border (**Figure S3**).

Impact of vaccination, antiviral treatment and PHSMs if they are singly implemented during reopening

We assess the impact of vaccination, antiviral treatments and PHSMs if they are singly implemented during reopening as follows: (i) 4th-dose boosting would be rolled out at a weekly rate of 6% of population; (ii) antiviral treatments would be deployed at 60% coverage; and (iii) Level 4 PHSMs (which reduce R_t by 69-72%; see **Table S4**) are implemented between day 15 and 74 of reopening and then gradually relaxed to normalcy by Day 104. The final cumulative infection attack rate would be >95%, >95% and 79% in the three scenarios, respectively. The number of cases who require hospitalisation would far exceed the local health system capacity for weeks to months with cumulative incidence of 91, 266, 323 per 10,000 and cumulative deaths of 8.1, 23.5 and 33.9 per 10,000, respectively (**Figure S4**). Among those aged 60 or above, the cumulative number of hospitalisations is 242, 714 and 868 per 10,000 and the cumulative number of deaths is 40, 116 and 168 per 10,000. That is, this age group accounts for more than 50% of hospitalisations and 92% of deaths associated with COVID-19.

Table S1. Neutralising antibody titres (IC50 or PRNT50 or PNAb50) of COVID-19 vaccines against Omicron by time and dose

Vaccine (combination)	Time since the last dose			Source
	0 days	14/28 days	180 days	
CoronaVac × 2	--	11 (9, 15)	11 (9, 15)	Costa Clemens et al [6]
CoronaVac × 2 + BNT162b2	10 (10, 10)	223 (108, 458)	--	
CoronaVac × 2 + Ad26.COV2-S	10 (10, 10)	138 (72, 264)	--	
CoronaVac × 2 + ChAdOx1	10 (10, 10)	102 (57, 182)	--	
CoronaVac × 3	11 (9, 15)	17 (11, 26)	--	
BBIBP-CorV × 2	--	6 (5, 8)	--	Ai et al [30]
BBIBP-CorV × 2 + ZF2001*	19 (11, 32)	109 (54, 221)	--	
BBIBP-CorV × 3	5 (5, 5)	48 (26, 84)	--	
CoronaVac × 2 + Ad5-nCoV-IM	--	261 (178, 382)	--	Li et al [31] Zhang et al [32]
CoronaVac × 2 + Ad5-nCoV-IH	--	320 (191, 538)	--	
CoronaVac × 2 + ZF2001*	--	86 (59, 127)	--	
CoronaVac × 3	--	54 (42, 71)	--	
BBIBP-CorV × 2 + NVSI-06-08*		368 (296, 457)	--	Kaabi et al [21]
BBIBP-CorV × 3	--	45 (36, 56)	--	
BBIBP-CorV × 2 + V-01*†	--	149 (102, 207)	--	Wang et al [20]
CoronaVac × 2 + V-01*†	--	59 (54, 65)	--	

* Protein subunit vaccines

† Estimated from vaccine efficacy data (see Table S2)

Table S2. Vaccine efficacy or effectiveness in preventing Omicron infection, hospitalisation, fatal disease, and death

Vaccine (combination)	Vaccine efficacy or effectiveness				Source
	Infection	Hospitalisation	Fatal disease	Death	
CoronaVac × 2, 20-59 yrs	--	25% (15-34)	92% (89-94)	93% (90-96)	McMenamin et al [10]
BNT162b2 × 2, 20-59 yrs	--	35% (27-43)	96% (95-97)	97% (95-98)	
CoronaVac × 3, 20-59 yrs	--	51% (40-60)	99% (98-100)	99% (98-100)	
BNT162b2 × 3, 20-59 yrs	--	74% (67-80)	99% (98-100)	99% (98-100)	
CoronaVac × 2, ≥ 60 yrs	--	--	Age 60-69: 79% (72-85) Age 70-79: 74% (67-80) Age ≥ 80: 58% (45-68)	Age 60-69: 84% (78-89) Age 70-79: 77% (69-83) Age ≥ 80: 63% (50-73)	
BNT162b2 × 2, ≥ 60 yrs	--	--	Age 60-69: 91% (87-94) Age 70-79: 90% (85-93) Age ≥ 80: 87% (45-92)	Age 60-69: 93% (89-95) Age 70-79: 92% (88-95) Age ≥ 80: 90% (85-94)	
CoronaVac × 3, ≥ 60 yrs	--	32% (8-51)	Age 60-69: 97% (95-99) Age 70-79: 95% (92-97) Age ≥ 80: 97% (95-99)	Age 60-69: 99% (97-100) Age 70-79: 97% (94-99) Age ≥ 80: 98% (96-99)	
BNT162b2 × 3, ≥ 60 yrs	--	70% (53-82)	Age 60-69: 99% (97-100) Age 70-79: 99% (97-100) Age ≥ 80: 97% (94-99)	Age 60-69: 99% (97-100) Age 70-79: 99% (97-100) Age ≥ 80: 98% (94-99)	
BBIBP-CorV × 2 + V-01* (<60 days after the 3rd dose)	64% (23-83)	--	--	--	Wang et al [20]
CoronaVac × 2 + V-01* (<60 days after the 3rd dose)	39% (3-62)	--	--	--	

* Recombinant protein subunit vaccines

540 **Table S3. Model parameters**

Parameter	Description, assumption, and source	Value
R_0	Basic reproductive number of Omicron BA.2 in the absence of vaccination [16,33]	BA.2: 7.1 (6.9-7.3) BA.4/BA.5: 8.3 (7.8-8.9) We estimate R_0 of BA.2 from the epidemiological data of the fifth wave in Hong Kong, and estimate R_0 of BA.4/BA.5 from the growth rates of England published by UKHSA as follows (https://www.gov.uk/guidance/the-r-value-and-growth-rate). We assume that 86% of the England population had immunity against infection of BA.1, BA.2 or BA.2.12.1 by 1 May (i.e., $R_t = 1$ and 1-1/7.1 = 86%). In the week of 24 Jun, BA.4/BA.5 became the dominant variant and the daily growth rate was 2-5%, which corresponds to the relative increase in R_t of 9.5-25.1%. The R_0 of BA.4/BA.5 is estimated to be 8.3 (7.8-8.9) accordingly.
T_{GT}	Mean generation time [34]	4.6 days
f_{GT}	Probability density function of generation time [34]	Gamma (2.20, 2.09)
VE_S	Vaccine effectiveness in reducing susceptibility	Table 1; Estimated by bootstrapping the neutralising antibody titres from Table S1
VE_I	Vaccine effectiveness in reducing infectiousness	Table 1; Assumed to be $0.8 \times VE_S$
VE_H	Vaccine effectiveness in reducing hospitalisation [10]	Table 1
VE_D	Vaccine effectiveness in reducing death [10]	Table 1
ε_S	Antiviral effectiveness in reducing susceptibility	0
ε_I	Antiviral effectiveness in reducing infectivity	0
ε_H	Antiviral effectiveness in reducing hospitalisations [11]	Nirmatrelvir/Ritonavir: 0.24 (0.14-0.33)
ε_D	Antiviral effectiveness in reducing deaths [11]	Nirmatrelvir/Ritonavir: 0.66 (0.48-0.78)
σ_{AR}	Coverage of antivirals among eligible patients [16]	60%, estimated from preliminary data from Hong Kong

$p_{a,death}$	Age-specific infection-fatality and infection-hospitalisation risk among unvaccinated individuals of a VOC similar to the Omicron variant [35,36] with no COVID-specific antivirals; assuming the hazard ratio of Delta variant was 1.45 times of that of Alpha variant and the hazard ratio of Omicron variant was 0.3 times of Delta variant [16,37,38]; assuming Beta distributed with the coefficient of variation of 0.05.	Age 0-9: 0.0005% Age 10-19: 0.0005% Age 20-29: 0.0005% Age 30-39: 0.023% Age 40-49: 0.023% Age 50-59: 0.126% Age 60-69: 0.126% Age 70-79: 2.00% Age ≥ 80: 8.70%
$p_{a,hospitalisation}$		Age 0-9: 0.011% Age 10-19: 0.027% Age 20-29: 0.72% Age 30-39: 2.34% Age 40-49: 2.94% Age 50-59: 5.52% Age 60-69: 7.98% Age 70-79: 11.28% Age ≥ 80: 12.48%
$f_{incubation}$	Probability density function of incubation period [39,40]	Lognormal distribution Mean: 3.5 days SD: 2.6 days
$f_{hospitalisation}$	Probability density function of the time between infection and hospitalisation [41]	Gamma distribution Mean: 6.7 days SD: 3.0 days
f_{death}	Probability density function of the time between infection and death; estimated from $f_{incubation}$ and the probability density function of the time between onset and death (Mean 18.8 days and SD 8.46 days) from Verity et al [41]; estimated from preliminary data from Hong Kong [16]	Gamma distribution Mean: 22.3 days SD: 9.5 days
$\tau_{hospitalisation}$	The maximum daily incidence of hospitalisations that the health system could manage; assuming to be 100% and 200% of hospital beds designated for COVID patients in May 2022 in Hong Kong which correspond to its regular and surged capacity, respectively	1.1 and 2.2 per 10,000 population In late March 2022 when the daily incidence of hospitalisations peaked, the maximum number of hospital beds designated for COVID patients was 13,654 which corresponds to a maximum daily incidence of 2.28 hospitalisations per 10,000 population. http://www.takungpao.com.hk/news/232109/2022/0325/701676.html https://www.news.gov.hk/eng/2022/03/20220331/20220331_195929_222.html
m_{death}	Increase in IFRs when health systems are overloaded	We assume that IFRs track the number of patients who require

		hospital care: IFRs would increase by 10%, 20%, 30%, 40% and 50% when demand outstrips supply of available hospital beds by a ratio of 1-2, 2-3, 3-4, 4-5 and >5 to 1. Our assumptions are based on data below: (i) the estimated IFRs in Wuhan were about 50% higher than estimated IFRs in other provinces outside Hubei in 2020 [42,43]; (ii) the incident rate ratios for hospital-based resources on COVID-19 deaths in the US between March and July 2020: geographical areas with fewer ICU beds (IRR = 0.194), nurses (IRR = 0.927) and general hospital beds (IRR = 0.800) per COVID-19 case were statistically associated with increased deaths in April 2020 [44]; (iii) in-hospital mortality between March and August 2020 in the US: the adjusted mortality dropped from 25.6% in March 2020 to 7.6% in August 2020, and the standardized mortality ratio dropped from 1.26 in March to 0.38 in August 2020 [45].

Table S4. Effectiveness of PHSMs during the previous waves of COVID in Hong Kong and Shanghai

Second wave in Hong Kong (Ancestral strain Wuhan-Hu-1 and D614G, 29 February to 15 April 2020)					
PHSM	**Date**	**R_t before**	**R_t after**	**Reduction in R_t**	**Level**
School closure (entire 2nd wave)	2/29	2.27 (1.70-2.93)	1.28 (1.04-1.53)	44% (33-54)	2
Tightened travel control	2/29-3/20				
Civil servants work-from-home	3/21	1.28 (1.04-1.53)	0.55 (0.38-0.70)	76% (69-83)	3
Tightened measures in restaurants and indoor amenities	3/27	0.55 (0.38-0.70)	0.20 (0.09-0.38)	91%* (83-96)	4
Closure of outdoor amenities	3/27				
Closure of indoor amenities	4/1				
Third wave in Hong Kong (Ancestral strain D614G, 30 June to 20 September 2020)					
PHSM	**Date**	**R_t before**	**R_t after**	**Reduction in R_t**	**Level**
Tightened measures in amenities	7/9	2.60 (2.27-3.52)	1.83 (1.54-2.23)	30% (14-41)	2
Closure of kindergartens and P1-3	7/10				
Gathering in groups of 4 only	7/13	1.83 (1.54-2.23)	1.55 (1.37-1.75)	52% (46-55)	3
Closure of all indoor amenities	7/13				
No dine-in after 6 pm	7/13				
Closure of all schools	7/14				
Civil servants work-from-home	7/20	1.55 (1.37-1.75)	1.26 (1.16-1.40)		
Gathering in groups of 2 only	7/29	1.26 (1.16-1.40)	0.57 (0.49-0.69)	78% (73-81)	4
No dine-in all day (lasted 2 days)	7/29				
Fourth wave in Hong Kong (Ancestral strain D614G, 30 October 2020 to 31 January 2021)					
PHSM	**Date**	**R_t before**	**R_t after**	**Reduction in R_t**	**Level**
School closure (P1-P3, kindergarten)	11/20	2.26 (1.99-2.79)	1.76 (1.50-2.04)	47% (40-53)	2
Closure of singing and dancing venues incl. pubs and clubs	11/20				
Closure of most indoor amenities	11/24	1.76 (1.50-2.04)	1.20 (1.06-1.36)		
Closure of all schools	11/29	1.20 (1.06-1.36)	1.05 (0.97-1.16)	55% (51-59)	3
Civil servants work-from-home	11/30	1.05 (0.97-1.16)	1.01 (0.93-1.11)		
No dine-in after 9 pm	11/30				
No dine-in after 6 pm	12/2	1.01 (0.93-1.11)	0.69 (0.61-0.78)	69% (65-73)	4
Fifth wave in Hong Kong (Omicron BA.2, 1 January 2022 – Now)					
PHSM	**Date**	**R_t before**	**R_t after**	**Reduction in R_t**	**Level**
School closure	1/5	7.1 (6.9-7.3)	1.9 (1.8-2.0)	73% (71-75)	4
Closure of singing and dancing venues	1/5				
Closure of most indoor amenities	1/5				
Closure of all schools	1/5				
Civil servants work-from-home	1/5				
No dine-in after 6 pm	1/5				
Banning gathering across families	1/5				
Omicron BA.2 in Shanghai (1 March 2022 – Now)					
PHSM	**Date**	**R_t before**	**R_t after**	**Reduction in R_t**	**Level**
PHSMs with similar intensity of Level 4 in Hong Kong	3/8	7.1 (6.9-7.3)	2.4 (2.2-2.8)	72% (67-75)	4
Lockdown of communities with case reports (before city-wide lockdowns)	3/11-3/26		2.0 (1.77-2.32)		

* Overestimated because the outbreak died out

Table S5. Number of hospital beds per 10,000 in the 31 provinces in mainland China in 2020*

Province	Number of hospital beds	Number of hospital beds per 10,000 population	Maximum number of hospital beds designated to COVID-19 patients per 10,000†	Maximum daily incidence of hospitalisations that the health system could manage per 10,000†
Beijing	127033	58.0	8.7	1.1
Tianjin	68275	49.2	7.4	0.9
Hebei	441962	59.2	8.9	1.1
Shanxi	223650	64.1	9.6	1.2
Inner Mongolia	162072	67.4	10.1	1.3
Liaoning	314488	73.9	11.1	1.4
Jilin	173123	72.2	10.8	1.4
Heilongjiang	253345	79.9	12.0	1.5
Shanghai	152191	61.2	9.2	1.2
Jiangsu	535006	63.1	9.5	1.2
Zhejiang	361317	55.9	8.4	1.1
Anhui	407813	66.8	10.0	1.3
Fujian	216753	52.1	7.8	1.0
Jiangxi	285847	63.3	9.5	1.2
Shandong	646863	63.6	9.5	1.2
Henan	667156	67.1	10.1	1.3
Hubei	411351	71.6	10.7	1.3
Hunan	519902	78.2	11.7	1.5
Guangdong	564773	44.7	6.7	0.8
Guangxi	295562	58.9	8.8	1.1
Hainan	58474	57.8	8.7	1.1
Chongqing	235520	73.4	11.0	1.4
Sichuan	649756	77.6	11.6	1.5
Guizhou	276379	71.6	10.7	1.3
Yunnan	325212	68.9	10.3	1.3
Tibet	18586	50.8	7.6	1.0
Shaanxi	272424	68.9	10.3	1.3
Gansu	171866	68.7	10.3	1.3
Qinghai	41285	69.6	10.4	1.3
Ningxia	41261	57.2	8.6	1.1
Xinjiang	181455	70.1	10.5	1.3

* Data from https://data.cnki.net/Trade/Home/Index/Z020

† Assumed to be 15% of total number of hospital beds and the average length of stay is 8 days

Table S6. Number of secondary and tertiary hospitals in the 31 provinces in mainland China in 2020*

Province	Number of secondary hospitals	Number of tertiary hospitals	Number of secondary hospitals per 1,000,000	Number of tertiary hospitals per 1,000,000
Beijing	158	106	7.2	4.8
Tianjin	76	43	5.5	3.1
Hebei	601	99	8.1	1.3
Shanxi	381	61	10.9	1.7
Inner Mongolia	314	87	13.1	3.6
Liaoning	338	156	7.9	3.7
Jilin	280	53	11.6	2.2
Heilongjiang	364	102	11.4	3.2
Shanghai	104	44	4.2	1.8
Jiangsu	470	192	5.5	2.3
Zhejiang	220	137	3.4	2.1
Anhui	513	98	8.4	1.6
Fujian	272	87	6.5	2.1
Jiangxi	256	88	5.7	1.9
Shandong	714	197	7.0	1.9
Henan	605	115	6.1	1.2
Hubei	361	143	6.3	2.5
Hunan	519	107	7.8	1.6
Guangdong	560	231	4.4	1.8
Guangxi	311	85	6.2	1.7
Hainan	58	36	5.8	3.6
Chongqing	263	61	8.2	1.9
Sichuan	741	269	8.9	3.2
Guizhou	364	65	9.4	1.7
Yunnan	470	106	10.0	2.2
Tibet	53	14	14.5	3.8
Shaanxi	420	73	10.6	1.8
Gansu	210	47	8.4	1.9
Qinghai	88	24	14.9	4.1
Ningxia	87	15	12.1	2.1
Xinjiang	233	55	9.0	2.1

* Data from https://data.cnki.net/Trade/Home/Index/Z020

Table S7. Proportion of sub-administrative regions coded as "rural" in cities and counties in Henan, Guangxi, and Guangdong (PRD).

City/county	Code of city/county	Number of sub-administrative regions	Number of urban sub-administrative regions	Number of rural sub-administrative regions	Proportion of rural sub-administrative regions
Henan					
Zhengzhou*	4101	3206	1739	1467	46%
Kaifeng	4102	2573	916	1657	64%
Luoyang	4103	3228	984	2244	70%
Pingdingshan	4104	2828	759	2069	73%
Anyang	4105	3300	933	2367	72%
Hebi	4106	1030	413	617	60%
Xinxiang	4107	3820	1219	2601	68%
Jiaozuo	4108	2021	807	1214	60%
Puyang	4109	3201	895	2306	72%
Xuchang	4110	2492	816	1676	67%
Luohe	4111	1331	423	908	68%
Sanmenxia	4112	1379	324	1055	77%
Nanyang	4113	4960	1270	3690	74%
Shangqiu	4114	4834	1269	3565	74%
Xinyang	4115	3463	775	2688	78%
Zhoukou	4116	5099	1452	3647	72%
Zhumadian	4117	2906	550	2356	81%
Guangxi					
Nanning*	4501	1845	614	1231	67%
Liuzhou	4502	1237	461	776	63%
Guilin	4503	1924	444	1480	77%
Wuzhou	4504	1015	318	697	69%
Beihai	4505	436	122	314	72%
Fangchenggang	4506	349	84	265	76%
Qinzhou	4507	1042	213	829	80%
Guigang	4508	1179	349	830	70%
Yulin	4509	1510	434	1076	71%
Baise	4510	1897	265	1632	86%
Hezhou	4511	761	225	536	70%
Hechi	4512	1661	231	1430	86%
Laibin	4513	822	186	636	77%
Chongzuo	4514	932	147	785	84%
Guangdong					
Guangzhou*	4401	2827	2136	691	24%
Shaoguan	4402	1476	459	1017	69%
Shenzhen	4403	784	784	0	0%
Zhuhai	4404	339	254	85	25%
Shantou	4405	1089	666	423	39%
Foshan	4406	815	736	79	10%
Jiangmen	4407	1334	522	812	61%
Zhanjiang	4408	1986	565	1421	72%
Maoming	4409	1916	747	1169	61%
Zhaoqing	4412	1553	415	1138	73%
Huizhou	4413	1345	487	858	64%
Meizhou	4414	2267	696	1571	69%

Shanwei	4415	907	349	558	62%
Heyuan	4416	1443	336	1107	77%
Yangjiang	4417	871	289	582	67%
Qingyuan	4418	1230	331	899	73%
Dongguan	4419	608	572	36	7%
Zhongshan	4420	279	235	44	16%
Chaozhou	4451	1035	421	614	59%
Jieyang	4452	1651	647	1004	61%
Yunfu	4453	980	339	641	65%

* Provincial capital

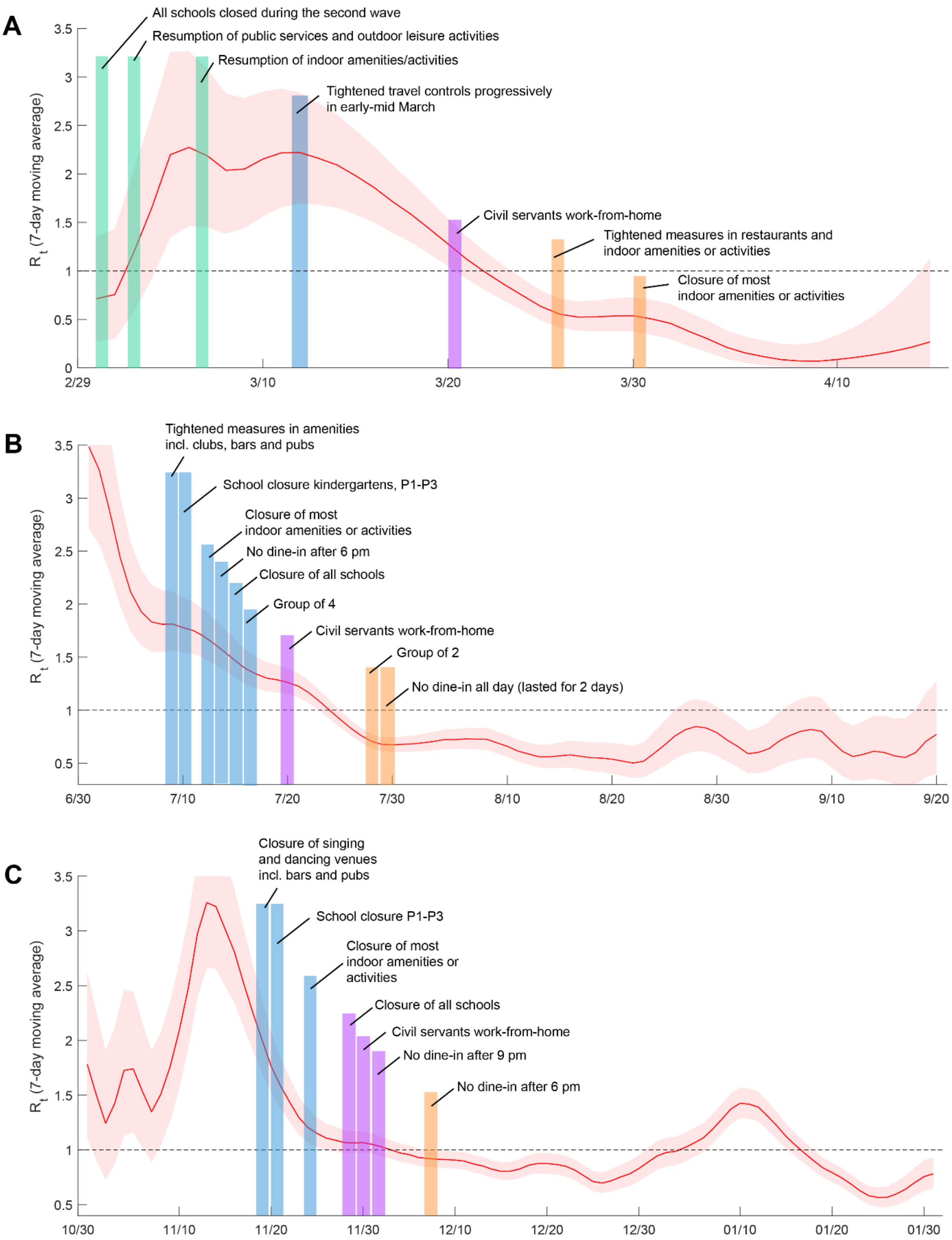

Figure S1. Correlation between R_t and public health and social measures (PHSMs) implemented in the second, third and fourth wave in Hong Kong. R_t were estimated from deconvoluted time series of daily number of cases in the EpiEstim model [43].

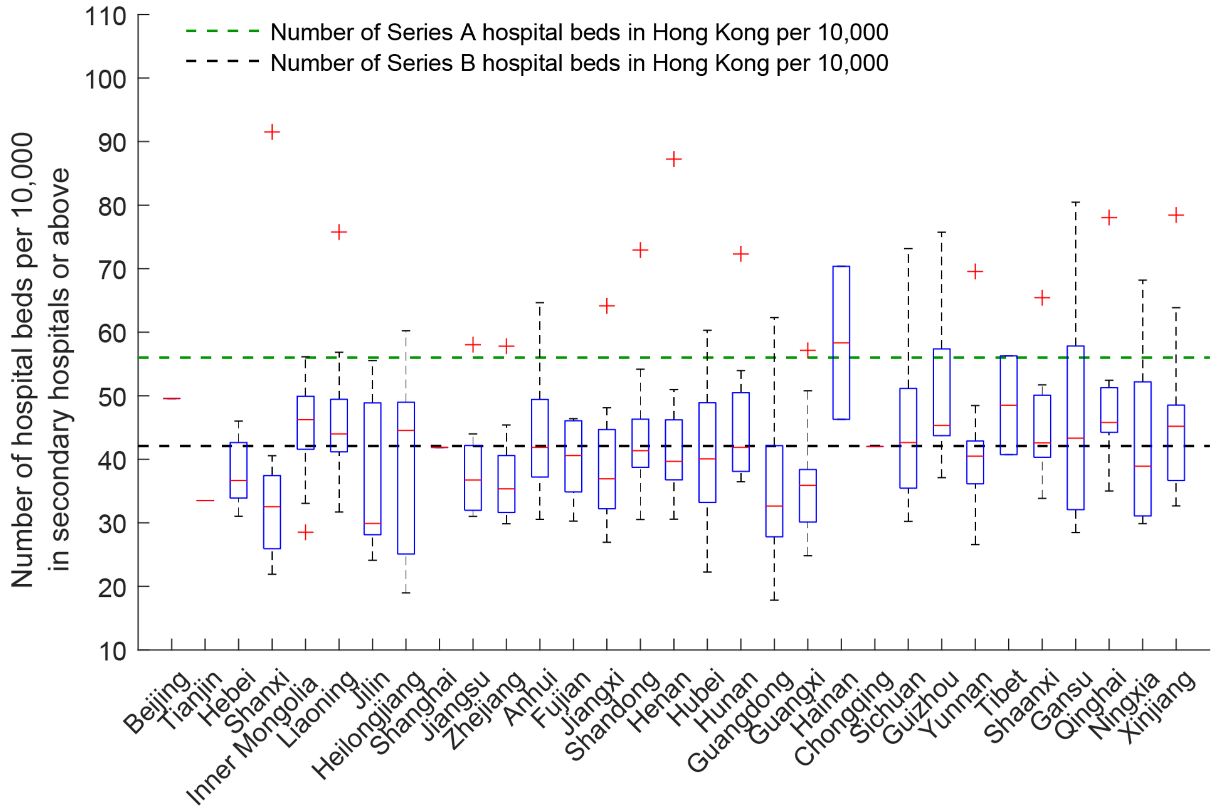

Figure S2. Number of hospital beds per 10,000 in secondary hospitals or above in more than 300 cities in mainland China. Cities are grouped by provinces where they are located. Hospitals in mainland China are classified into three levels including primary, secondary, and tertiary hospitals: 1) A primary hospital is typically a township hospital that contains less than 100 beds, and primary hospitals provide preventive care, minimal health care and rehabilitation services; 2) A secondary hospital is one that tend to be affiliated with a medium size city, county or district and contain more than 100 beds but less than 500 and secondary hospitals are responsible for providing comprehensive health services; 3) A tertiary hospital is a comprehensive, referral, general hospitals at the city, provincial or national level with a bed capacity exceeding 500 and tertiary hospitals serve as medical hubs providing care to multiple regions. The national average number of hospital beds in secondary hospitals or above is 42 per 10,000. The two dashed lines show the number of hospital beds of Service A (56 per 10,000) and Service B (42 per 10,000) in 2020 in Hong Kong (https://www.fhb.gov.hk/statistics/en/health_statistics.htm). Series A included all hospital beds in Hospital Authority hospitals, private hospitals, nursing homes and correctional institutions. Series B included only hospital beds in Hospital Authority hospitals and private hospitals excluding accident and emergency observation beds, day beds and nursery beds, which followed the definition of OECD Health Data.

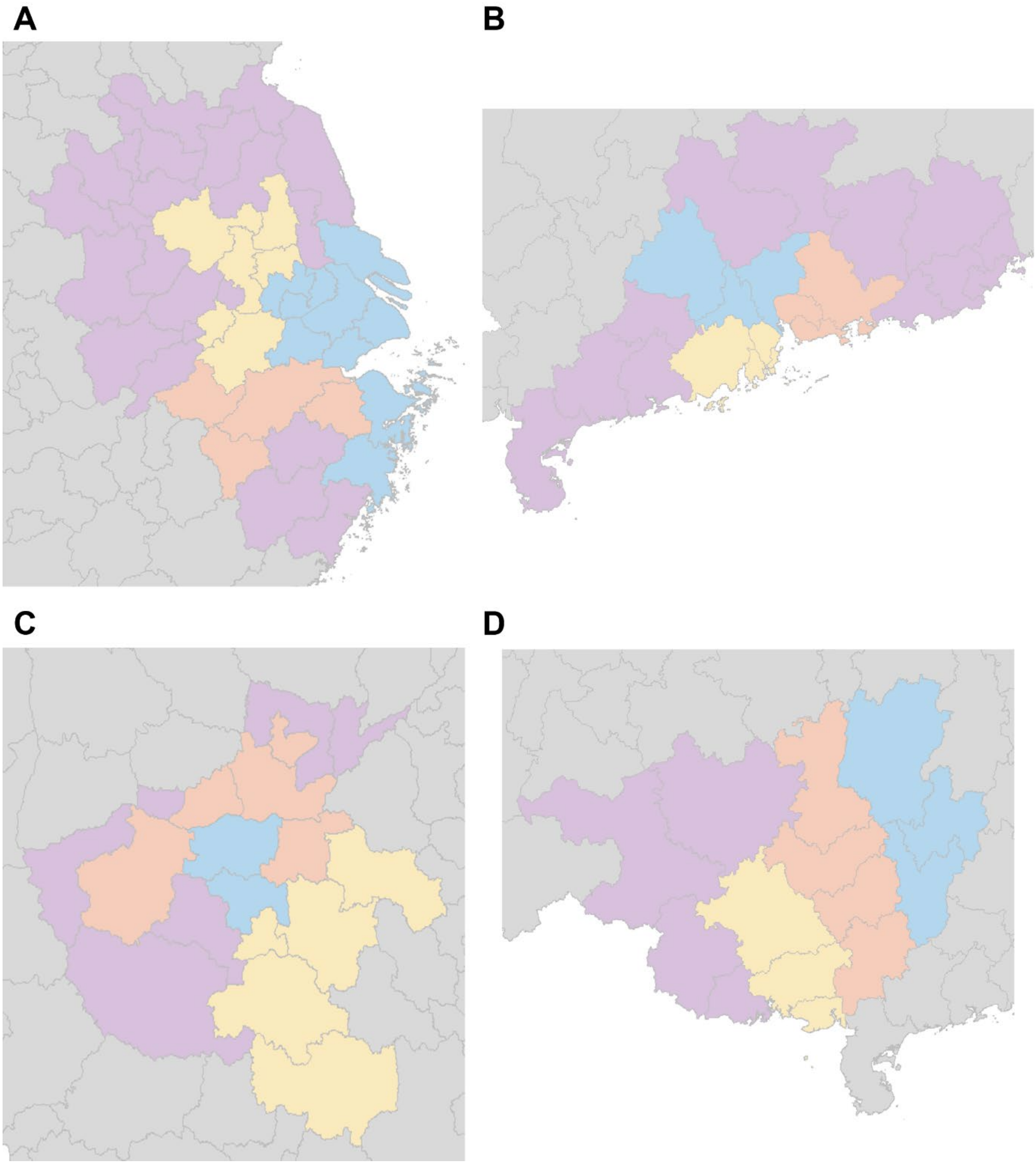

Figure S3. Simultaneous reopening of Yangtze River Delta Region, Pearl River Delta Region, Henan, and Guangxi. (A) Yangtze River Delta: Yangtze River Delta is assumed to be reopened simultaneously in Greater Shanghai (blue), Greater Hangzhou (orange), Greater Nanjing (yellow) and all cities in Anhui, Jiangsu, and Zhejiang (purple). **(B) Pearl River Delta:** Pearl River Delta is assumed to be reopened simultaneously in Guangzhou-Foshan-Zhaoqing (blue), Shenzhen-Dongguan-Huizhou (orange), Zhuhai-Zhongshan-Jiangmen (yellow) and all cities in Guangdong (purple). **(C) Henan:** Henan is assumed to be reopened simultaneously in provincial capital area (blue), urban area (orange), urban-rural junction (yellow) and rural area (purple). **(D) Guangxi:** Guangxi is assumed to be reopened simultaneously in the areas adjacent to the most developed parts of Guangdong (blue), the central areas of Guangxi (orange), the provincial capital area (yellow), and the areas next to China-Vietnam border (purple).

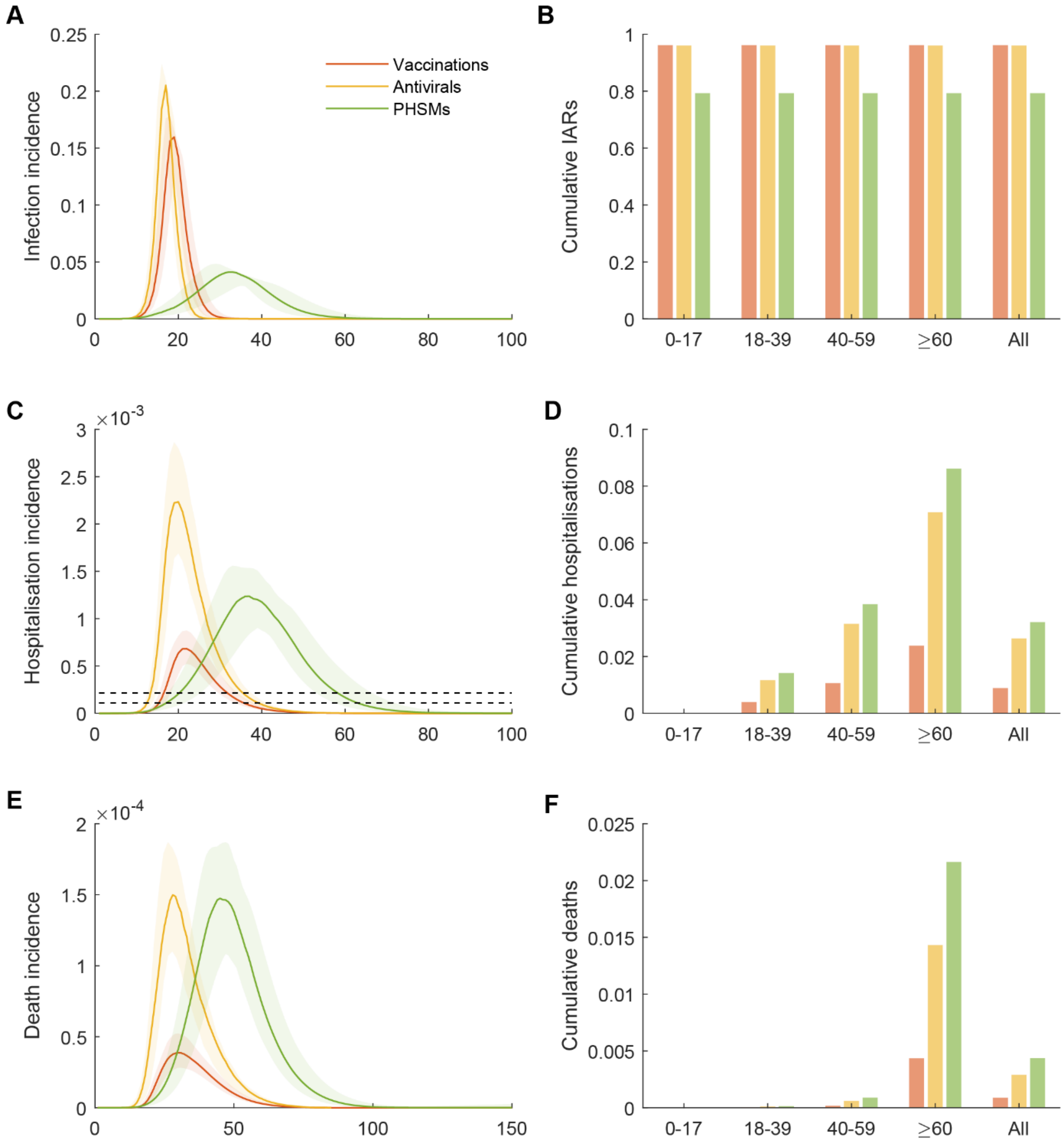

Figure S4. The impacts of 4th dose heterologous boosting, antiviral treatments and PHSMs if they are singly implemented during reopening under Strategy 1. We assume that the three interventions would be implemented follows: 1) Increasing the vaccine uptake of the 3rd and 4th dose to 85% across all age groups aged 3 or above and the mass vaccination of the 4th dose starts 30 days before the reopening; 2) Increasing the antiviral coverage to 60%; 3) PHSMs at Level 4 which reduce R_t by 69-72% are implemented 14 days after the seeding of epidemics, and PHSMs are maintained between 15 and 74 days after the seeding of epidemics, and gradually relaxed between 75 and 104 days. **(A) Infection incidence as proportion of the population. (B) Cumulative infection attack rates by age. (C-D) Daily and cumulative number of cases requiring who require hospitalisation. (E-F) Daily and cumulative incidence of death.** Figure legend and other parameters are the same as Figure 2.

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