Methods and Applications

The Impact of Medical Resources and Oral Antiviral Drugs on SARS-CoV-2 Mortality — Hong Kong SAR, China, 2022

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ABSTRACT

Introduction: The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrates increased transmissibility compared to earlier strains, contributing to a significant number of fatalities in Hong Kong Special Administrative Region (HKSAR), China. Adequate medical resources and medications are essential in mitigating these deaths. This study evaluates the effects of supplementary resources from the Chinese mainland during the fifth wave of the pandemic in HKSAR.

Methods: Vector autoregression (VAR) was employed to analyze data from the Oxford coronavirus disease 2019 (COVID-19) Government Response Tracker to assess the effectiveness of control measures during five waves of the pandemic in HKSAR. Additionally, a transmission dynamics model was created to investigate the influence of supplementary medical resources from the Chinese mainland and oral medications on mortality.

Results: In the initial four waves, workplace closures, restrictions on public events, international travel bans, and shielding the elderly significantly influenced pandemic management. Contrarily, during the fifth wave, these measures showed no notable effects. When comparing a situation without extra medical resources or COVID-19 oral medication, there was a 17.7% decrease in COVID-19 fatalities with mainland medical resources and an additional 10.2% reduction with oral medications. Together, they contributed to a 26.6% decline in fatalities.

Discussion: With the rapid spread of the virus, regional reallocation of medical resources may reduce mortality even when the local healthcare system is overstretched.

The initiation of the pandemic's fifth wave has been attributed to the emergence of the Omicron variant, with the initial outbreak traced back to the Seaview Silhouette Hotel, a quarantine facility where cross-infection occurred in early January 2022 (*1*). The concurrence of this outbreak with the Chinese New Year celebrations, a period characterized by increased social interactions, significantly exacerbated the spread of the virus. The escalation in case numbers began to place an immense burden on the healthcare infrastructure from February 9 onward, ultimately leading to an overwhelming of public hospitals and isolation centers (*2*).

In the past, the Hong Kong Special Administrative Region (HKSAR) has faced four outbreaks and has generally adopted China's epidemic prevention policies effectively (*3*). However, during the fifth wave of the pandemic, the prevalent strain was Omicron subtype BA.2, known for its high infectivity but low pathogenicity. Coupled with a significant number of asymptomatic cases, the dense population in HKSAR, China, and inadequate medical tracing methods, this scenario resulted in challenges in implementing effective control measures and contributed to the rapid spread of the pandemic.

To support the HKSAR and decrease mortality rates, the Central Government of China mobilized resources on February 16, 2022. These resources included testing facilities, medical staff, construction of isolation centers, medical equipment, and provision of coronavirus disease 2019 (COVID-19) medications (*4*). Furthermore, the HKSAR government made a crucial decision by introducing effective oral medications for COVID-19 treatment, specifically Nirmatrelvir/ritonavir (Paxlovid, Pfizer). This drug significantly reduced hospitalizations and mortality by 89% among high-risk COVID-19 patients and has been authorized for commercialization following successful clinical trials (*5*).

The study aims to evaluate the impact of timely medical resource allocation and oral medication usage on decreasing mortality during the fifth wave of the

HKSAR pandemic. The findings will serve as a scientific reference for managing future pandemics caused by other SARS-CoV-2 strains or viruses.

METHODS

Data Sources

Data were extracted from the Oxford COVID-19 Government Response Tracker (OxCGRT) (*6*) to analyze the evolution of government responses during the pandemic. Information on twelve indicators was collected from October 1, 2020, to July 7, 2022, from the OxCGRT database (https://github.com/OxCGRT/covid-policy-tracker). COVID-19 confirmed cases, deaths, and serial interval data were obtained from the official HKSAR Department of Health database (*7*).

Correlation and Causality Analysis

We examined 12 specific indicators concerning interventions implemented to reduce COVID-19 spread in HKSAR. Details on the definition, source, and unit of measurement for each indicator can be found in Supplementary Table S1 (available at https://weekly.chinacdc.cn/). Among these indicators, eight pertain to closures and containment measures (school closure, workplace closure, cancelation of public events, restrictions on gatherings, public transport closure, stay-at-home orders, restrictions on internal movement, and international travel controls), while four are associated with health measures (testing policy, contact tracing, vaccination policy, and protection of older adults).

To evaluate the impact of different control measures on the growth of the pandemic in HKSAR, we utilized the R vars package (Bernhard Pfaff, Germany) within the R statistical software (version.3.6.1; R Foundation for Statistical Computing, Vienna, Austria) (*8*). Initially, we employed vector autoregression (VAR) modeling to examine the interrelationships of various variables over time. To strengthen the causality assessment, we incorporated the Granger Causality test into the VAR model to determine if changes in predictors lead to alterations in infection growth. A Wald test was conducted to calculate the *P* value.

Construction of the Dynamics Model

To facilitate the transmission of SARS-CoV-2 Omicron variants in the HKSAR, we established a pandemic model known as the Susceptible-Exposed-Infected-Active-Quarantined-Recovered-Hospitalized-Death (SEIAQRHD) model (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). The model parameters predominantly encompass viral properties and variables associated with severity rates and mortality. Our calculations and analyses were conducted using R statistical software and Python (version 3.8; Python Software Foundation, Beaverton, OR, US).

Simulation Scenarios

In order to assess whether the distribution of domestic medical resources to HKSAR was associated with a reduction in fatalities during the pandemic, this study created simulations of the fatality curves with and without the allocation of these resources. The medical resource allocation to HKSAR commenced on February 16, 2022. It was hypothesized that there would be a seven-day lag in the initiation of an effective response and in the turnaround time for nucleic acid test results. Therefore, daily mortality rates were calculated for the periods before and after February 22 to evaluate the impact of resource distribution. The fifth wave of the outbreak in HKSAR, which began to result in fatalities on February 7, served as a baseline. For the control scenario, actual data from February 7 to February 22, a period with no medical resource allocation, was used. For the intervention analysis, actual data from February 23 to March 26, following the commencement of resource distribution, was collated.

The study simulated the trend in fatalities without domestic medical resource allocation by referencing the Omicron mortality rate in Japan from January 16 to March 26, 2022, as control measures in HKSAR mirrored those in Japan during this time (Supplementary Figure S2, available at https://weekly.chinacdc.cn/) (*9*). Exponential regression was applied to estimate the mortality rate trend in HKSAR from February 7 to February 22 using fatalities data, given the exponential distribution of the overall trend (Equation 1). Subsequently, the modified SEIAQRHD model was used to project fatalities from the fifth wave of the pandemic without domestic medical resource allocation. For scenarios involving domestic medical resource allocation, logarithmic regression demonstrated superiority over other methods, as shown in Supplementary Table S3 (available at https://weekly.chinacdc.cn/). Therefore, the mortality rate trend in HKSAR was forecasted using fatalities data from February 23 to March 26, 2019, through logarithmic regression (Equation 2), followed by predicting the number of deaths using the SEIAQRHD model.

$$\lambda = k \times e^{x} + b \quad (1)$$

$$\lambda' = k' \times \ln(x') + b' \quad (2)$$

COVID-19 oral medications (nirmatrelvir/ritonavir, molnupiravir) were introduced in the HKSAR on March 15, 2022 to potentially reduce pandemic fatalities. This study evaluated the effectiveness of these medications in a transmission dynamics model at that time to determine their impact on reducing mortality rates.

RESULTS

The Fifth COVID-19 Pandemic in HKSAR

In early January 2022, the Omicron variant was first identified in the HKSAR and quickly spread. Subsequently, on January 7, the HKSAR government reinforced social distancing measures, leading to the cancellation of traditional events like the New Year's Eve Flower Market and Chinese New Year celebrations. The HKSAR recorded 1,161 new confirmed COVID-19 cases on February 9, marking the highest daily tally in the past two years (Figure 1).

One week later, the Chinese central government provided a substantial quantity of medical resources to HKSAR, which included hospital beds, medical personnel, and materials for epidemic prevention. A module hospital in Tsingyi and a temporary nucleic acid testing laboratory were established (Table 1). Subsequently, the "Vaccine Pass" policy was officially enacted, allowing individuals with at least one vaccine dose or those exempted to access public areas such as shopping centers and hotels. Additionally, the HKSAR government introduced new medicines to combat coronavirus infections (Figure 2). However, on March 12, HKSAR reported 32,430 new confirmed cases, the highest daily count in this pandemic wave. Following April 16, the fifth wave of the COVID-19 pandemic in HKSAR began to gradually decrease, leading to a significant reduction in the number of fatalities.

Evaluation of the HKSAR Government's Efficacy in Combating Various Waves of the Pandemic

Twelve specific indicators (C1–C8, H2, H3, H7, and H8) were analyzed to assess their trends in HKSAR during different pandemic waves. Results depicted in Table 2 and Figure 3 show that during the first to fourth waves, only C2, C3, C7, and C8 had a significant correlation with incident cases. However, the Granger causality test revealed that interventions were not significantly related to incident cases during the fifth wave before medical aid (Table 2). These findings suggest that the previous measures were insufficient in controlling the surge in cases caused by the Omicron variant.

Effectiveness of Medical Resources and Oral Antiviral Drugs on Preventing Deaths

In the model without timely domestic medical

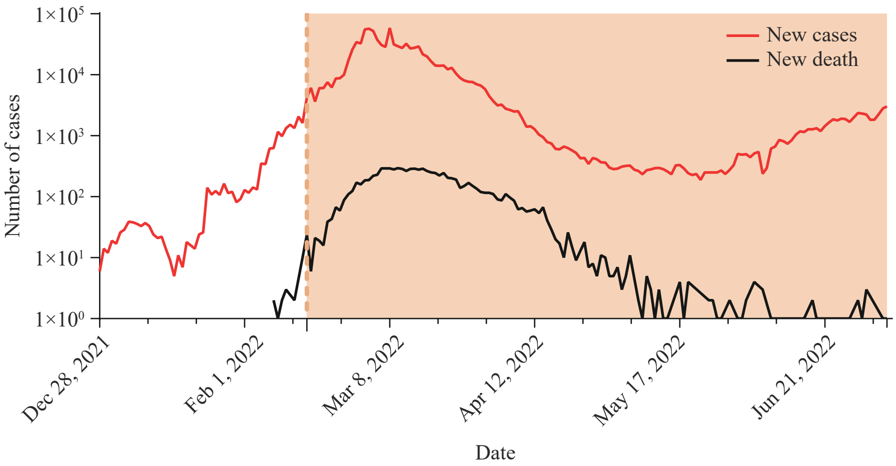


FIGURE 1. The fifth wave of the pandemic in HKSAR.

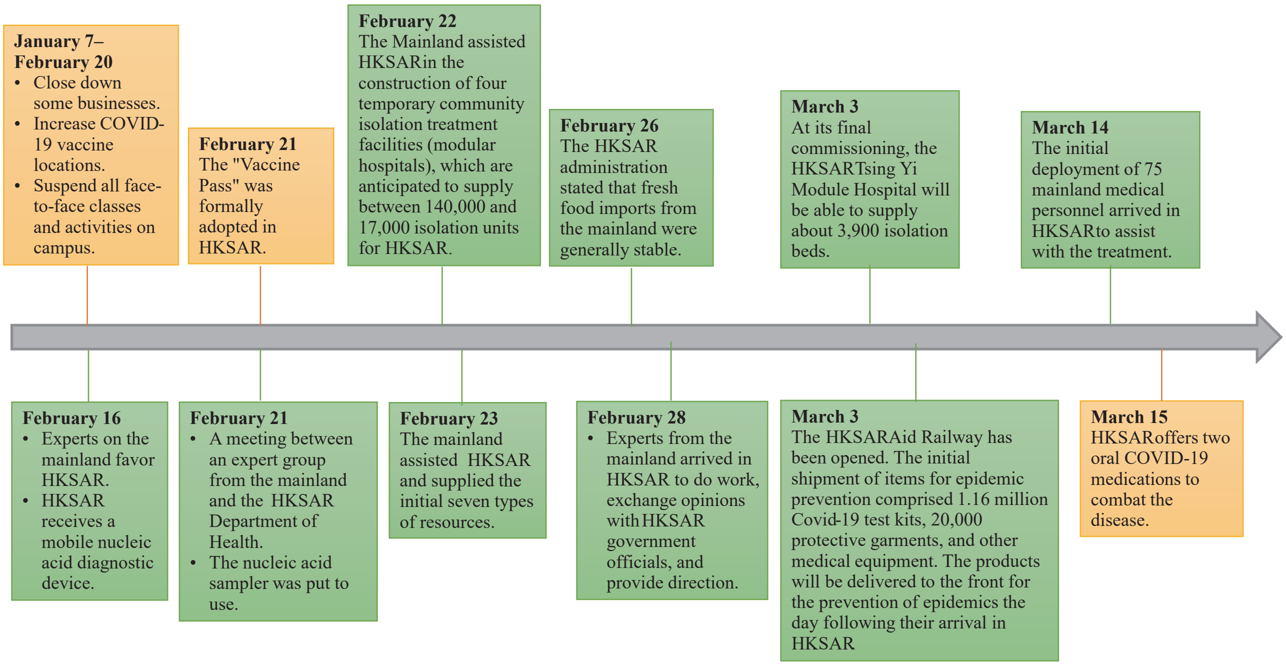
Note: The orange areas indicate the distribution period in the Chinese mainland since February 16, 2022.

Abbreviation: HKSAR=Hong Kong Special Administrative Region.

TABLE 1. Distribution of medical resources to HKSAR during the fifth wave of the pandemic.

Medical resource	Before distributing to HKSAR	After distributing to HKSAR
Medical bed Common beds, isolation beds (or negative pressure)	A total of 29,000 medical beds in HKSAR	About 20,000 isolation beds be added after the aid to HKSAR
Nucleic acid detection capability	The largest nucleic acid production in HKSAR is 100,000 per day	Nucleic acid production reached 300,000 per day after mainland China's aid to HKSAR
Number of doctors	By the end of 2020, there were 15,298 doctors and 61,295 nurses in HKSAR	The number of doctors from the Chinese mainland who assisted HKSAR: First batch; 4 experts, 8 nucleic acid testers The second batch: 114 medical personnel The third batch: 300 medical personnel and 5 experts Fourth batch: 132 medical personnel Fifth batch: 6 experts
Medical consumables	–	100 million rapid antigen test kits, more than 120 million N95, KN95, 1.10656 million new coronavirus detection kits, 157 million surgical masks, 19 million pairs of surgical gloves, 3.62 million protective suits, 6.45 million thermometers, 194 million sheets of alcohol paper, etc.
Drug	–	195,000 boxes of Jinhua Qinggan Granules, more than 6 million boxes of Lianhua Qingwen Capsules, and 24,000 boxes of Huoxiang Zhengqi Tablets
Other	–	730,000 clip-on pulse oximeters, 2 mobile nucleic acid testing vehicles and 1 material transportation support vehicle

Note: "–" means no medical resources.
Abbreviation: HKSAR=Hong Kong Special Administrative Region.



January 7–February 20
- Close down some businesses.
- Increase COVID-19 vaccine locations.
- Suspend all face-to-face classes and activities on campus.

February 21
The "Vaccine Pass" was formally adopted in HKSAR.

February 22
The Mainland assisted HKSARin the construction of four temporary community isolation treatment facilities (modular hospitals), which are anticipated to supply between 140,000 and 17,000 isolation units for HKSAR.

February 26
The HKSAR administration stated that fresh food imports from the mainland were generally stable.

March 3
At its final commissioning, the HKSARTsing Yi Module Hospital will be able to supply about 3,900 isolation beds.

March 14
The initial deployment of 75 mainland medical personnel arrived in HKSARto assist with the treatment.

February 16
- Experts on the mainland favor HKSAR.
- HKSAR receives a mobile nucleic acid diagnostic device.

February 21
- A meeting between an expert group from the mainland and the HKSAR Department of Health.
- The nucleic acid sampler was put to use.

February 23
The mainland assisted HKSAR and supplied the initial seven types of resources.

February 28
- Experts from the mainland arrived in HKSAR to do work, exchange opinions with HKSAR government officials, and provide direction.

March 3
The HKSARAid Railway has been opened. The initial shipment of items for epidemic prevention comprised 1.16 million Covid-19 test kits, 20,000 protective garments, and other medical equipment. The products will be delivered to the front for the prevention of epidemics the day following their arrival in HKSAR

March 15
HKSARoffers two oral COVID-19 medications to combat the disease.

FIGURE 2. Timeline of HKSAR government interventions during the fifth wave of the COVID-19 pandemic in 2022.
Note: The yellow boxs indicate the anti-epidemic measures taken by the HKSAR government, while the green boxs represent the allocation of medical resources from the Chinese central government.
Abbreviation: HKSAR=Hong Kong Special Administrative Region; COVID-19=coronavirus disease 2019.

resource allocation, the fatality rate increased through day 10, stabilizing at 1.07% by day 50 (Figure 4A). Conversely, with prompt deployment of domestic resources, the model projected a continual decrease in the death rate to 0.73% by day 30 (Figure 4B). The study compared actual and predicted fatality rates under scenarios with or without domestic medical resource deployment through a modified transmission dynamics model. Without timely domestic resource allocation, the maximum cumulative fatalities were estimated at 12,057 [95% confidence interval (*CI*): 11,454, 12,660] (Table 3, Figure 5). Most infected individuals were aged over 80, comprising 8,563 cases (95% *CI*: 8,135, 8,992). Following the deployment of domestic medical resources, the projected maximum cumulative fatalities reduced to 9,917 (95% *CI*: 9,421,

TABLE 2. Results of the Granger causality test and Akaike information criterion (AIC) days for various waves of the pandemic in HKSAR.

Factor	Definition	First-Forth wave (January 1, 2020–April 30, 2021)		The fifth wave (December 1, 2021–Febuary 15, 2022)†	
		Granger	AIC days	Granger	AIC day
C1	School closing	0.43	1	0.92	1
C2	Workplace closing	0.88	1	N/A	1
C3	Cancel public events	0.75	1	0.26	1
C4	Restrictions on gatherings	0.98	1	0.95	1
C5	Close public transport	0.27	1	N/A	1
C6	Stay at home requirements	0.32	1	N/A	1
C7	Movement restrictions	0.66	1	N/A	1
C8	International travel	0.0045*	1	N/A	1
H2	Testing policy	0.011*	1	N/A	1
H3	Contact tracing	0.16	1	N/A	1
H7	Vaccination policy	0.015*	1	N/A	1
H8	Protection of older adults	0.0002*	1	N/A	1

Note: N/A means that according to the VAR model, the indicator shows no significant correlation with incident cases.

Abbreviation: HKSAR=Hong Kong Special Administrative Region; VAR=vector autoregression.

* The *P* value from a Wald test was less than 0.05, suggesting that an increase in the predictor is linked with a reduction in infections.

† To assess the specific influence of HKSAR governmental actions on the fifth wave of the pandemic, data was analyzed from December 1, 2021 (one month prior to the outbreak) to February 15, 2022 (the day preceding medical intervention).

10,413), indicating a 17.7% decrease, with 7,044 deaths in the over-80 age group (95% *CI*: 6,692, 7,396). Furthermore, with the inclusion of molnupiravir on February 22 and nirmatrelvir/ritonavir on March 15 in the model, the total deaths decreased to 8,851, showing a continuous 10.7% decline. Overall, the combined effect of domestic medical resources and COVID-19 oral medications led to a 26.6% reduction in the number of deaths.

DISCUSSION

The Omicron variant is highly transmissible, with an estimated basic reproduction number (R0) of up to 8.2. Despite its high transmissibility, studies have shown that the Omicron variant predominantly causes mild upper respiratory tract infections with low pathogenicity, leading to mostly mild symptoms (*10*). By April 2022, the Omicron variant had spread to 166 countries and regions (*11*), contributing to a more severe fifth wave of the pandemic compared to previous waves. Previous interventions such as international travel restrictions, nucleic acid testing, contact tracing, vaccination strategies, and protection measures for older adults were effective during the initial four waves of the pandemic in the HKSAR. However, these measures became less effective during the fifth wave. Our study suggests that the timely allocation of domestic resources could significantly reduce deaths by 2,140, and the introduction of oral COVID-19 medications further decreased deaths by 1,066. The prompt deployment of resources from mainland China potentially reduced deaths among infected patients by 17.7%. Moreover, our model, which includes parameters for oral COVID-19 medications, aligns closely with actual trends. The utilization of oral drugs continued to reduce deaths among infected patients by 10.2%, particularly effective for severely ill patients. Stockpiling oral medications for SARS-CoV-2 infection, both in China and globally, is crucial for future management strategies.

By the end of 2022 and since 2023, globally prevalent strains include BQ.1, BQ.1.1, XBB, XBB.1, and XBB.1.5, alongside EG.5. Currently, EG.5, a variant derived from XBB.1.9.2, exhibits a spike protein amino acid profile shared with XBB.1.5. Notably, there is an additional F456L amino acid substitution in the spike protein of EG.5 compared to its precursor XBB.1.9.2 subvariant and XBB.1.5 (*12*).

The likelihood of secondary infections is expected to increase due to the enhanced transmissibility and immune evasion capabilities of emerging mutant strains, necessitating a reliance on targeted therapeutics. The primary treatment modalities for COVID-19 include therapeutic repurposing,

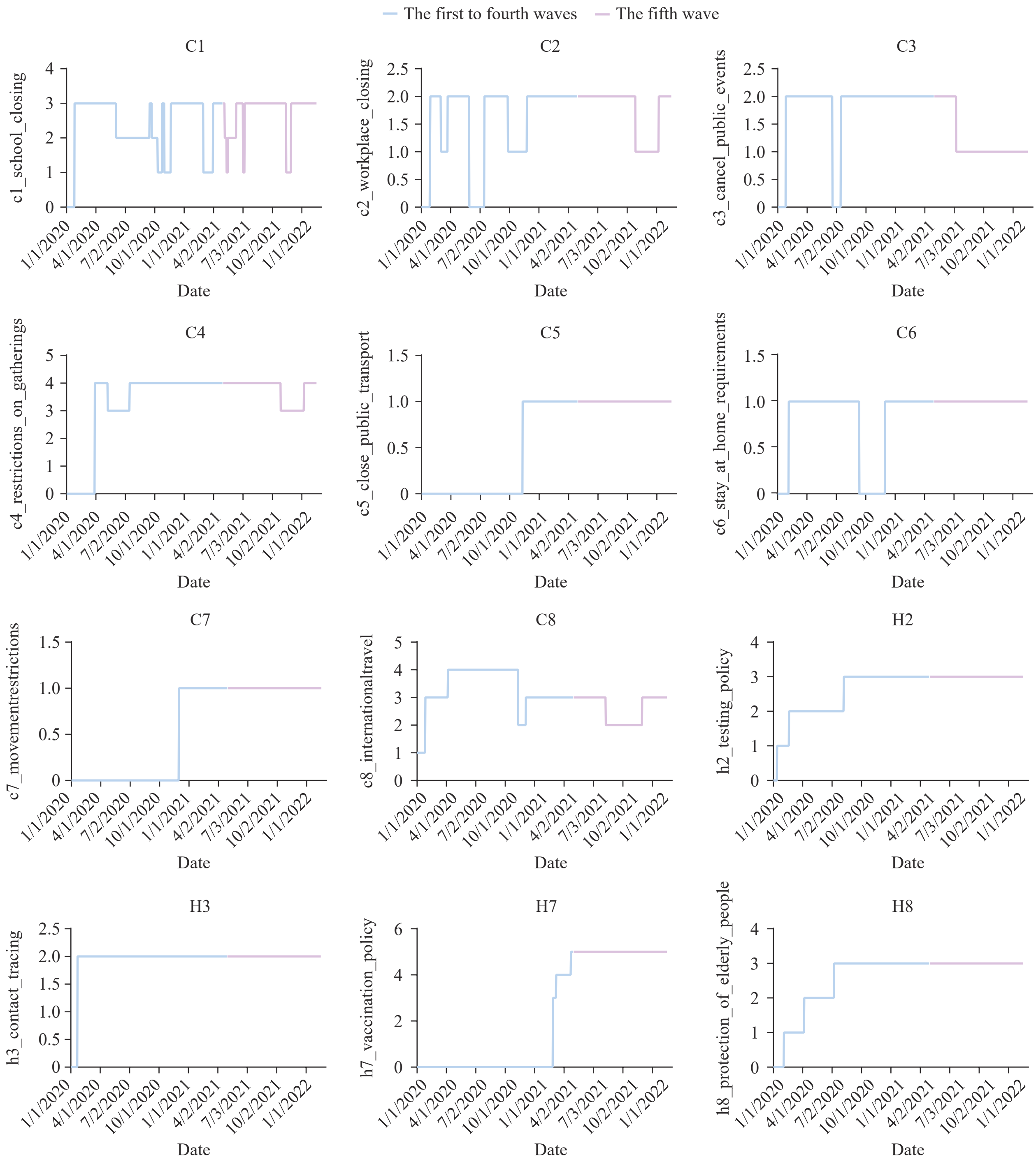


FIGURE 3. Scores of indicators related to measures in the OxCGRT.

Note: The measures include School closure (C1), Workplace closure (C2), Cancellation of public events (C3), Restrictions on gatherings (C4), Closure of public transport (C5), Stay-at-home requirements (C6), Restrictions on internal movement (C7), International travel controls (C8), Testing policy (H2), Contact tracing (H3), Vaccination policy (H7), and Protection of older adults (H8). The blue line represents the period from the beginning of the COVID-19 pandemic (January 1, 2020) until before the onset of the fifth wave (December 30, 2022), while the purple line depicts the fifth wave of the COVID-19 pandemic.

Abbreviation: OxCGRT=Oxford COVID-19 Government Response Tracker; COVID-19=coronavirus disease 2019.

monoclonal antibody therapy, convalescent plasma therapy, and drug development based on specific viral targets (*13*). Drug repurposing is a rapid and efficient approach, utilizing approved drugs for alternative

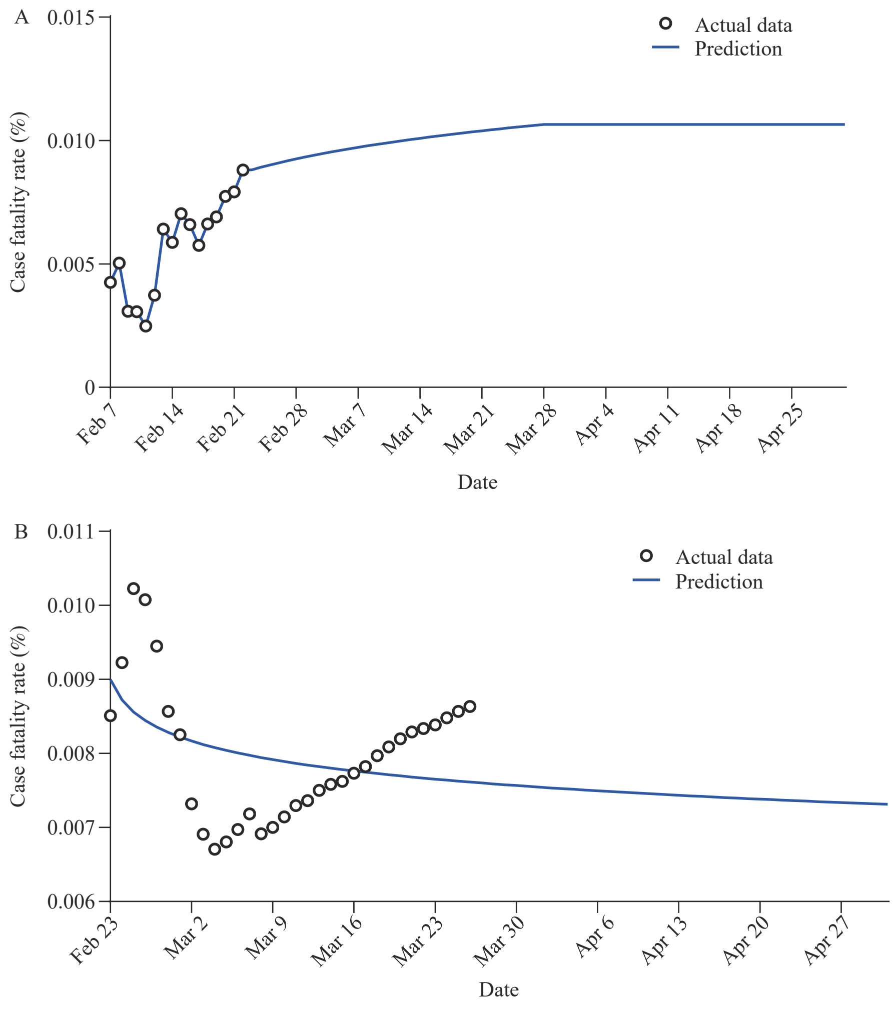


FIGURE 4. Mortality simulations without or with medical resource provision. (A) without medical resource provision; (B) with medical resource provision in 2022.

TABLE 3. Number of fatalities simulated by the model among different age groups.

Measures	Age groups	Number of fatality cases
Actual data	All age groups	9,094
Without medical resource distribution from Chinese mainland	All age groups	12,057 (95% *CI*: 11,454, 12,660)
	<60 years	476 (95% *CI*: 452, 500)
	60–79 years	3,018 (95% *CI*: 2,867, 3,168)
	>80 years	8,563 (95% *CI*: 8,135, 8,992)
With medical resource distribution from Chinese mainland	All age groups	9,917 (95% *CI*: 9,421, 10,413)
	<60 years	391 (95% *CI*: 371, 411)
	60–79 years	2,482 (95% *CI*: 2,358, 2,606)
	>80 years	7,044 (95% *CI*: 6,692, 7,396)
With medical resource distribution from Chinese mainland and oral drug	All age groups	8,851 (95% *CI*: 8,408, 9,293)
	<60 years	350 (95% *CI*: 332, 366)
	60–79 years	2,215 (95% *CI*: 2,104, 2,326)
	>80 years	6,286 (95% *CI*: 5,972, 6,601)

Abbreviation: *CI*=confidence interval.

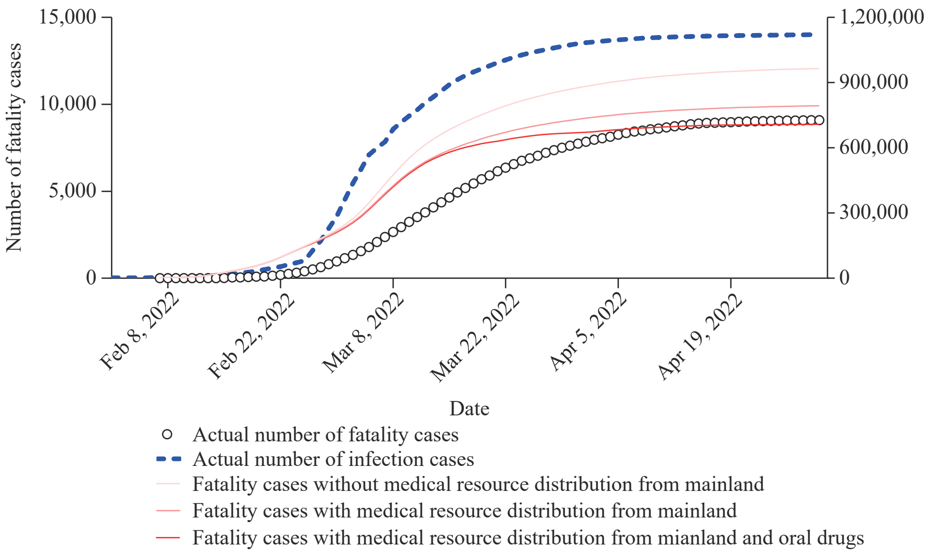


FIGURE 5. Number of fatality cases under various scenarios.
Note: The actual fatality case data points were fitted onto the curve (circles).

indications, such as remdesivir, lopinavir/ritonavir, and hydroxychloroquine, including RAY 1216, to manage COVID-19 (*14*–*15*). Nonetheless, resistance to antiviral medications may develop due to mutations in viral proteins targeted by these drugs, suggesting that a combination of antiviral agents with different mechanisms of action might provide a viable treatment strategy for certain drug-resistant strains.

However, this study was subject to some limitations. It is challenging to differentiate the impact of the strengthening measures implemented by the government of HKSAR on the anticipated fatalities from mainland China’s resource allocation. Therefore, this study aims to objectively assess the outcomes of mainland China’s support for HKSAR and the policies implemented by HKSAR through a comprehensive observation of both factors.

The prompt allocation of medical resources in HKSAR and the use of appropriate medications could effectively reduce the mortality rate linked to Omicron infection.

Conflicts of interest: No conflicts of interest.

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REFERENCES

1. Hong Kong Special Administrative Region. Statistics on 5th wave of COVID-19. 2022. https://www.coronavirus.gov.hk/chi/5th-wave-statistics.html. [2022-3-19]. (In Chinese).
2. Xie RP, Edwards KM, Adam DC, Leung KSM, Tsang TK, Gurung S,

et al. Resurgence of Omicron BA.2 in SARS-CoV-2 infection-naive Hong Kong. Nat Commun. 2023;14(1):2422. https://doi.org/10.1038/s41467-023-38201-5.

3. Wikipedia. COVID-19 pandemic in Hong Kong. 2020. https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Hong_Kong.
4. www.chinanews.com. Central government gives full support to help Hong Kong get out of the "epidemic" as soon as possible. 2022. https://www.chinanews.com.cn/ga/2022/04-21/9735577.shtml. [2022-4-21]. (In Chinese).
5. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ 2021;375:n2713. https://doi.org/10.1136/bmj.n2713.
6. Blavatnik School of Government. COVID-19 government response tracker. 2020. https://www.bsg.ox.ac.uk/research/covid-19-government-response-tracker. [2022-8-1].
7. The Government of the Hong Kong Special Administrative Region. https://www.coronavirus.gov.hk/chi/index.html. [2022-8-1]. (In Chinese).
8. Gianino MM, Nurchis MC, Politano G, Rousset S, Damiani G. Evaluation of the strategies to control COVID-19 pandemic in four European countries. Front Public Health 2021;9:700811. https://doi.org/10.3389/fpubh.2021.700811.
9. Ministry of Health, Labour and Welfare. Visualizing the data: information on COVID-19 infections. https://covid19.mhlw.go.jp/en/. [2022-5-1].
10. Liu Y, Rocklöv J. The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. J Travel Med 2022;29(3):taac037. https://doi.org/10.1093/jtm/taac037.
11. Thakur V, Ratho RK. OMICRON (B. 1.1.529): a new SARS-CoV-2 variant of concern mounting worldwide fear. J Med Virol 2022;94(5):1821 – 4. https://doi.org/10.1002/jmv.27541.
12. World Health Organization. EG.5 initial risk evaluation, 9 August 2023. 2023. https://www.who.int/docs/default-source/coronaviruse/09082023eg.5_ire_final.pdf?sfvrsn=2aa2daee_1. [2023-8-9].
13. Kim S. COVID-19 drug development. J Microbiol Biotechnol 2022;32(1):1 – 5. https://doi.org/10.4014/jmb.2110.10029.
14. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Dis 2004;3(8):673 – 83. https://doi.org/10.1038/nrd1468.
15. Wang B, Li HJ, Cai MM, Lin ZX, Ou XF, Wu SH, et al. Antiviral efficacy of RAY1216 monotherapy and combination therapy with ritonavir in patients with COVID-19: a phase 2, single Centre, Randomised, double-blind, placebo-controlled trial. eClinicalMedicine 2023;63:102189. https://doi.org/10.1016/j.eclinm.2023.102189.

SUPPLEMENTARY MATERIAL

The SEIAQRHD Model

The population is segmented into various groups as delineated in Supplementary Figure S1 of this model: susceptible (S), exposed (E), infected (I), active infection without confirmation (I), confirmed and quarantined (Q), recovered (R), hospitalized (H), and deceased (D). Transmission occurs when a susceptible individual (S) gets exposed (E) following contact with an unidentified infected patient (I), which is dictated by the infection rate (β). Subsequently, the exposed individual (E) may progress to becoming an infected patient (I) capable of transmitting the infection after an incubation period (α).

We stratified the infection (I) category into two subgroups to capture the influence of nucleic acid and antigen testing methodologies. The first subgroup encompasses patients identified and quarantined within the testing sensitivity (δ), denoted as the post-testing quarantine group (Q). The second subgroup consists of individuals with active infections falling outside the sensitivity range ($1-\delta$), who continue to contribute to community transmission (A).

Considering the specific context of the Hong Kong Special Administrative Region (HKSAR), we adjusted our model to include the diagnostic delay, which is the interval between test administration and result notification. We stratified active infections (A) and individuals in quarantine (Q) according to age and vaccination status, establishing

SUPPLEMENTARY TABLE S1. Indicators, definitions, and coding details.

Indicators	Definition	Coding details
C1	School closing	0 - No measures; 1 - recommend closing; 2 - Require closing (only some levels or categories, e.g., just high school or just public schools); 3 - Require closing all levels; No data - blank.
C2	Workplace closing	0 - No measures; 1 - recommend closing (or work from home); 2 - require closing (or work from home) for some sectors or categories of workers; 3 - require closing (or work from home) all-but-essential workplaces (e.g., grocery stores, doctors); No data - blank.
C3	Cancel public events	0 - No measures; 1 - Recommend canceling; 2 - Require canceling; No data - blank.
C4	Restrictions on gatherings	0 - No restrictions; 1 - Restrictions on very large gatherings (the limit is above 1,000 people); 2 - Restrictions on gatherings between 101–1,000 people; 3 - Restrictions on gatherings between 11–100 people; 4 - Restrictions on gatherings of 10 people or less; No data - blank.
C5	Close public transport	0 - No measures; 1 - Recommend closing (or significantly reduce volume/route/means of transport available); 2 - Require closing (or prohibit most citizens from using it).
C6	Stay at home requirements	0 - No measures; 1 - recommend not leaving house; 2 - require not leaving the house with exceptions for daily exercise, grocery shopping, and 'essential' trips; 3 - Require not leaving the house with minimal exceptions (e.g. allowed to leave only once a week, or only one person can leave at a time, etc.); No data - blank.
C7	Restrictions on internal movement	0 - No measures; 1 - Recommend not to travel between regions/cities; 2 - internal movement restrictions in place.
C8	International travel controls	0 - No measures; 1 - Screening; 2 - Quarantine arrivals from high-risk regions; 3 - Ban on arrivals from some regions; 4 - Ban on all regions or total border Closure; No data - blank.
H2	Testing policy	0 - No testing policy; 1 - Only those whom both (a) have symptoms AND (b) meet specific criteria (e.g., key workers, admitted to hospital, came into contact with a known case, returned from overseas); 2 - testing of anyone showing COVID-19 symptoms; 3 - open public testing (e.g., "drive through" testing available to asymptomatic people); No data; N.B. we are looking for policies about testing for having an infection (PCR tests) - not for policies about testing for immunity (antibody tests).
H3	Contact tracing	0 - No contact tracing; 1 - Limited contact tracing - not done for all cases; 2 - Comprehensive contact tracing - done for all identified cases.
H7	Vaccination Policy	0 - No availability; 1 - Availability for ONE of following: key workers/clinically vulnerable groups/old adult groups; 2 - Availability for TWO of following: key workers/ clinically vulnerable groups/old adult groups; 3 - Availability for ALL of following: key workers/ clinically vulnerable groups/old adult groups; 4 - Availability for all three plus partial additional availability (select broad groups/ages); 5 - Universal availability.
H8	Protection of old adults	0 - no measures; 1 - Recommended isolation, hygiene, and visitor restriction measures in LTCFs and/or old adults to stay at home; 2 - Narrow restrictions for isolation, hygiene in LTCFs, some limitations on external visitors and/or restrictions protecting old adults at home; 3 - Extensive restrictions for isolation and hygiene in LTCFs, all non-essential external visitors prohibited, and/or all old adults required to stay at home and not leave the home with minimal exceptions, and receive no external visitors; No data-blank.

Abbreviation: PCR=polymerase chain reaction; COVID-19=coronavirus disease 2019.

Model Parameters: The model parameters primarily involve viral attributes, as well as factors associated with severity rates and mortality, such as vaccination coverage, protection rates across different age groups, and medication effectiveness. Detailed information can be found in Supplementary Table S2.

four distinct cohorts: vaccinated younger individuals among the infected ($A_Y V$), vaccinated older adults among the infected ($A_O V$), unvaccinated younger individuals among the infected (A_Y'), and unvaccinated older individuals without vaccine protection among the infected (A_O'). Further, we recognized the disparity in vaccination coverage between older adults aged 60–79 years and those over 80 years in HKSAR, a significant finding reported by reference (*1*). Hence, we subdivided the population into three age brackets: ω_1 represents those aged 0–59 years, ω_2 denotes individuals aged 60–79 years, and ω_3 encompasses residents over 80 years of age. In addition, we noted the vaccination rates for HKSAR residents aged 60–79 (V_{O1}) and for those over 80 (V_{O2}). The effectiveness of vaccines in preventing severe disease — resulting in variable rates of severe cases among each demographic group (θ_1, θ_2, θ_3, θ_4) — leads to some patients progressing to critical illness (H). Individuals with infection (encompassing both active infections and quarantine cases) and critical illness eventually progress to recovery (R) at rates γ and γ', respectively. Meanwhile, a proportion of those with severe illness succumb to the disease (classified as D), at a fatality rate of λ .

Equation 3 for this model is as follows:

$$\begin{cases} \dfrac{dS(t)}{dt} = -\dfrac{\beta \times S(t) \times \left(A_\gamma V(t) + A_o V(t) + A_Y'(t) + A_o'(t)\right)}{N} \\ \dfrac{dE(t)}{dt} = \dfrac{\beta \times S(t) \times \left(A_\gamma V(t) + A_o V(t) + A_\gamma'(t) + A_o'(t)\right)}{N} - \alpha \times E(t) \\ \dfrac{dI(t)}{dt} = \alpha \times E(t) - I(t) \\ \dfrac{dA_\gamma V(t)}{dt} = (1-\delta) \times \omega_1 \times V_Y \times \alpha \times E(t) - \gamma^{\times} A_\gamma V(t) - \theta_1 \times A_\gamma V(t) \\ \dfrac{dA_o V(t)}{dt} = (1-\delta) \times (\omega_2 \times V_{O1} + \omega_3 \times V_{o2}) \times \alpha \times E(t) - \gamma \times A_o V(t) - \theta_2 \times A_o V(t) \\ \dfrac{dA_\gamma'(t)}{dt} = (1-\delta) \times \omega_1 \times \left(1 - V_\gamma\right) \times \alpha \times E(t) - \gamma^{\times} A_\gamma'(t) - \theta_3 \times A_\gamma'(t) \\ \dfrac{dA_o'(t)}{dt} = (1-\delta) \times (\omega_2 \times (1 - V_{o1}) + \omega_3 \times (1 - V_{O2})) \times \alpha \times E(t) - \gamma^{\times} A_o'(t) - \theta_4 \times A_o'(t) \\ \dfrac{dQ_\gamma V(t)}{dt} = \delta \times \omega_1 \times V_\gamma \times \alpha \times E(t) - \gamma \times Q_\gamma V(t) - \theta_1 \times Q_\gamma V(t) \\ \dfrac{dQ_o V(t)}{dt} = \delta \times \left(\omega_2 \times V_{o1} + \omega_3 \times V_{O_2}\right) \times \alpha \times E(t) - \gamma^{\times} Q_o V(t) - \theta_2 \times Q_o V(t) \\ \dfrac{dQ_\gamma'(t)}{dt} = \delta \times \omega_1 \times \left(1 - V_\gamma\right) \times \alpha \times E(t) - \gamma^{\times} Q_\gamma'(t) - \theta_3 \times Q_\gamma'(t) \\ \dfrac{dQ_o'(t)}{dt} = \delta \times \left(\omega_2 \times (1 - V_{O1}) + \omega_3 \times \left(1 - V_{o_2}\right)\right) \times \alpha \times E(t) - \gamma^{\times} Q_o'(t) - \theta_4 \times Q_o'(t) \\ \dfrac{dH(t)}{dt} = \theta_1 \times A_\gamma V(t) + \theta_2 \times A_o V(t) + \theta_3 \times A_\gamma'(t) + \theta_4 \times A_o'(t) + \theta_1 \times Q_r V(t) + \theta_2 \times Q_o V(t) + \theta_3 \times \\ \qquad Q_\gamma'(t) + \theta_4 \times Q_o'(t) - \gamma' \times H(t) - d \times H(t) \\ \dfrac{dR(t)}{dt} = \gamma \times \left(A_y V(t) + A_o V(t) + A_\gamma'(t) + A_o'(t) + Q_\gamma V(t) + Q_o V(t) + Q_\gamma'(t) + Q_o'(t)\right) + \gamma' \times H(t) \\ \dfrac{dD(t)}{dt} = d \times H(t) \\ S = N - E_0 - I_0 - H_0 - R_0 - D_0 \\ \beta = R_t^{\times} \gamma \\ \delta = \dfrac{T}{N} \end{cases} \tag{3}$$

S(t): Susceptible population in HKSAR

E(t): Exposed population in HKSAR

I(t): Infected population in HKSAR

$A_Y V(t)$: Young people protected by vaccine among the active infection

$A_O V(t)$: Older adults protected by vaccine among the active infection

$A_Y'(t)$: Young people without vaccination among the active infection

$A_O'(t)$: Older adults without vaccination among the active infection

$Q_Y V(t)$: Young people protected by vaccine and quarantine

$Q_O V(t)$: Older adults protected by vaccine and quarantine

SUPPLEMENTARY TABLE S2. Parameters of the SEIAQRHD model.

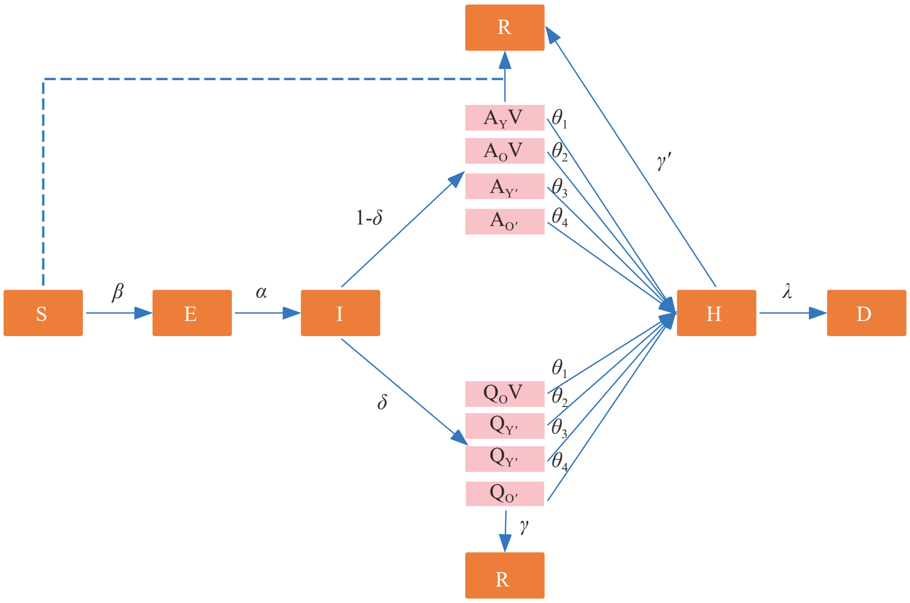
Parameter	Label	Value	Reference
Incubation period	α	(BA.1) 3.2 days (SD2.2 days)	(2)
Population of HKSAR	S	7,394,700	(3)
Vaccination rates for the old adult	V_O	59.85% (60–79 years old) 20.51% (over 80 years old)	(3)
Vaccination rate for young people	V_Y	64.8%	(3)
The proportion of youth to old adults	ω_1, ω_2, ω_3	Youth (ω1, 0–59 years): 53,60,600, 72.5%; Old adult (ω2, 60–79 years): 1,632,300, 22.1%; Old adult (ω3, ≥80 years): 401,800, 5.4%;	(3)
The percentage of vaccinated young infected people who develop serious illness	θ_1	0%	(4)
The percentage of vaccinated old adults infected people who develop serious illness	θ_2	0.2%–0.8%	(4)
The percentage of young unvaccinated infected people who develop severe illness	θ_3	0.5%	(4)
The percentage of old adults unvaccinated infected people who develop severe illness	θ_4	6.6%–8.1%	(4)
Recovery rate for severe patients	γ'	2–3 months	(5)
Recovery rate in patients with mild symptoms	γ	2 weeks	(5)
Daily maximum amount of nucleic acid testing	δ	300,000	(6)
COVID-19 Oral medicine: Effectiveness of Pfizer's PAXLOVID	ε_1	89%	(7)
COVID-19 Oral medicine: Effectiveness of Molnupiravir	ε_2	30%	(8)

SUPPLEMENTARY TABLE S3. RMSE comparison in data fitting by different methods.

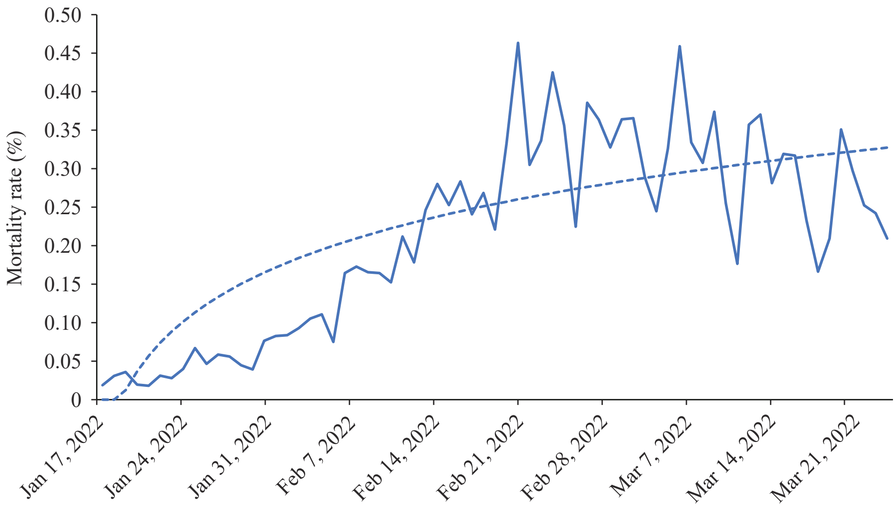
Methods	RMSE
linear regression	0.000890
exponential regression	0.000892
logarithmic regression	0.000832

Note: Various methods were employed to analyze the trend in mortality rates of HKSAR using data from February 23 to March 26, 2019.
Abbreviation: RMSE=Root-Mean-Square Error; HKSAR=Hong Kong Special Administrative Region.

$Q_Y'(t)$: Young people without vaccination but quarantined
$Q_O'(t)$: Older adults without vaccination but quarantined
$H(t)$: Severe patients
$R(t)$: Recovered
$D(t)$: Death
γ': Recovery rate in severe patients
γ : Recovery rate in patients with mild symptoms
λ: Death rate in severe patients
α : The probability of conversion from exposed to infected
β: The probability of conversion from susceptible to exposed
δ: Daily proportion of individuals tested for nucleic acid
t_d: Delay in reporting results from nucleic acid tests
ω_1: The proportion of young people (0–59 years) in HKSAR
ω_2: The proportion of older adults (60–79 years) in HKSAR
ω_3: The proportion of older adults (≥80 years) in HKSAR
V_Y: The proportion of young people (0–59 years) vaccinated
V_{O1}: The proportion of older adults (60–79 years) vaccinated
V_{O2}: The proportion of older adults (≥80 years) vaccinated
θ_1: The percentage of vaccinated young infected people who develop serious illness
θ_2: The percentage of vaccinated older infected adults who develop serious illness
θ_3: The percentage of young unvaccinated infected people who develop severe illness



SUPPLEMENTARY FIGURE S1. The SEIAQRHD model.
Abbreviation: SEIAQRHD=susceptible-exposed-infected-active-quarantined-recovered-hospitalized-death.



SUPPLEMENTARY FIGURE S2. The Omicron mortality rate in Japan from January 16 to March 26, 2022.
Note: An exponential function was utilized to align with the mortality trend (dotted curve).

θ_4: The percentage of older unvaccinated infected adults who develop severe illness

We calculated the propagation coefficient and effective regeneration number (Rt) according to the method outlined by Wallinga et al., which involves a specific equation (Equation 4 and 5) based on the intergenerational interval.

$$p_{ij} = w\left(t_i - t_j\right) / \sum_{i \neq k} w\left(t_i - t_k\right) \tag{4}$$

$$R_j = \sum_{i} p_{ij} \tag{5}$$

P_{ij} represents the relative likelihood of a case I being infected by case j based on the interval distribution of symptom onset differences. By utilizing Equation 5, we calculate the current effective reproduction number (Rt) along with a 95% confidence interval for Rt. Subsequently, after determining the distribution of Rt, we update the SEIAQRHD model to predict future exposed and infected individuals, and the distribution and peak values of recovered/deceased cases using Equation 3.

S(t): Susceptible population in HKSAR; E(t): Exposed population in HKSAR; I(t): Infected population in HKSAR; $A_YV(t)$: Young people protected by vaccine among those with active infection; $A_OV(t)$: Older adults protected by vaccine among those with active infection; $A_{Y'}$ (t): Young people without vaccination among the active infection; $A_{O'}(t)$: Older adults without vaccination among the active infection; Q_YV (t): Young people protected by vaccine and quarantine; $Q_OV(t)$: Older adults protected by vaccine and quarantine; $Q_{Y'}(t)$: Young unvaccinated people who have been quarantined; $Q_{O'}(t)$: Older unvaccinated adults who have been quarantined; H(t): Severely ill patients; R(t): Recovered; D(t): Death; γ': Recovery rate in severe patients; γ: Recovery rate in patients with mild symptoms; λ: Death rate in severe patients; α: The probability of conversion from exposed to infected; β: The probability of conversion from susceptible to exposed; δ: Daily proportion of individuals tested for nucleic acid; θ_1: The percentage of vaccinated young infected people who develop serious illness; θ_2: The percentage of vaccinated older infected adults who develop serious illness; θ_3: The percentage of young unvaccinated infected people who develop severe illness; θ_4: The percentage of older unvaccinated infected adults who develop severe illness.

REFERENCES

1. The Government of the Hong Kong Special Administrative Region. Hong Kong vaccination dashboard. 2022. https://www.covidvaccine.gov.hk/zh-HK/dashboard. [2022-8-12]. (In Chinese).
2. Backer JA, Eggink D, Andeweg SP, Veldhuijzen IK, van Maarseveen N, Vermaas K, et al. Shorter serial intervals in SARS-CoV-2 cases with Omicron BA.1 variant compared with Delta variant, the Netherlands, 13 to 26 December 2021. Euro Surveill 2022;27(6):2200042. http://dx.doi.org/10.2807/1560-7917.ES.2022.27.6.2200042.
3. The Government of the Hong Kong Special Administrative Region. https://www.coronavirus.gov.hk/chi/index.html. [2022-8-1]. (In Chinese).
4. Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities - surveillance results from southern Sweden, July 2021 to January 2022. Euro Surveill 2022;27(9):2200121. https://doi.org/10.2807/1560-7917.ES.2022.27.9.2200121.
5. Kenneth McIntosh M. COVID-19: clinical features. https://www.uptodate.com/contents/zh-Hans/covid-19-clinical-features. [2022-9-1]. (In Chinese).
6. News.gov.hk. Make every effort to enhance Hong Kong's anti-epidemic capabilities. 2022. https://sc.news.gov.hk/TuniS/www.news.gov.hk/chi/2022/02/20220216/20220216_141619_780.html. [2022-2-16]. (In Chinese).
7. Business Wire. Pfizer receives U.S. FDA emergency use authorization for novel COVID-19 oral antiviral treatment. 2021. https://www.businesswire.com/news/home/20211221005795/en/Pfizer-Receives-U.S.-FDA-Emergency-Use-Authorization-for-Novel-COVID-19-Oral-Antiviral-Treatment. [2021-12-21].
8. Johnson MG, Puenpatom A, Moncada PA, Burgess L, Duke ER, Ohmagari N, et al. Effect of molnupiravir on biomarkers, respiratory interventions, and medical services in COVID-19: a randomized, placebo-controlled trial. Ann Intern Med 2022;175(8):1126 – 34. https://doi.org/10.7326/M22-0729.