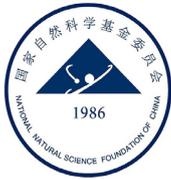


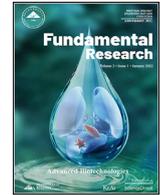


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Article

The impacts of gradually terminating nonpharmaceutical interventions for SARS-CoV-2: A mathematical modelling analysis

Bin Wu^{a,*}, Yuetian Yu^b, Xinglin Feng^c^a Medical Decision and Economic Group, Department of Pharmacy, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong University, Shanghai, China^b Department of Critical Care Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200001, China^c Department of Health Policy and Management, School of Public Health, Peking University, Beijing, China

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ABSTRACT

With the expansion of vaccination programs, the policy of terminating nonpharmaceutical interventions for preventing the SARS-CoV-2 pandemic should become more flexible. The current study investigated the clinical and economic outcomes of intervention policies combining nonpharmaceutical interventions and vaccination programs for dealing with the SARS-CoV-2 pandemic. An agent-based transmission model was adopted that describes how a SARS-CoV-2 virus spreads in the populations of China. The model inputs were derived from the literature and expert opinion. The following intervention policies were simulated: no intervention, strict nonpharmaceutical interventions, and nonpharmaceutical interventions for workplace, community, school and home gradually terminated by combining vaccination programs for specified age groups (vaccination age in years: 20–60, 20–70, 20–80, ≥ 20 , ≥ 10 and whole population). Cumulative infections and deaths in one calendar year, costs and quality-adjusted life years (QALYs) were measured. When the vaccination program was taken up in at least the ≥ 20 years age group in all populations, nonpharmaceutical interventions for workplace and community settings could be gradually terminated because the cumulative number of infections was < 100 per 100,000 persons. Further ending nonpharmaceutical interventions in school and home settings could not meet the target even when the vaccination program had been taken up in all populations. When cumulative deaths were used as the endpoint, nonpharmaceutical interventions in workplace, community and school settings could be gradually terminated. Vaccine efficacy and coverage have substantial impacts. Terminating nonpharmaceutical interventions in workplace settings could produce the lowest cost when vaccination programs are taken up at least in the ≥ 10 years age group; this method dominates most intervention strategies due to its lower costs and higher QALYs. According to our findings, nonpharmaceutical interventions might be gradually terminated in Chinese settings.

1. Introduction

As a Public Health Emergency of International Concern defined by the World Health Organization, the SARS-CoV-2 pandemic has challenged all aspects of life and wellbeing around the world [1,2]. The traditional public health containment strategy, also referred to as non-pharmaceutical interventions (NPIs), has prevailed as a means to prevent and control the pandemic. Measures include border closures and entry bans, closing facilities and communities, testing and contact tracing, and quarantine policies [1,2]. Aside from being a threat to public health, which resulted in approximately one million excess deaths in 2020 in 29 high-income countries [3], the SARS-CoV-2 pandemic has also negatively impacted society. It was reported that approximately 90% of annual gross domestic product loss could be attributed to the cumulative financial costs associated with lost output and health im-

pairment [4]. Adopting a strict containment strategy, China has been a success around the globe. However, worries have emerged about the perverse impact of societal containment policies on the health system and the country's economic development and social wellbeing [5].

Historically, mass vaccination to achieve herd immunity was proven to be effective in controlling many communicable diseases [6]. Successful vaccines are urgently needed to combat the COVID pandemic because they are a potential substitute that does not require strict containment and extensive testing. Data from the National Health Commission showed that more than 3.30 billion SARS-CoV-2 vaccine doses have been administered in the Chinese mainland. However, challenges such as vaccine hesitation and rapid SARS-CoV-2 mutations may delay the achievement of herd immunity through mass vaccination [7–9]. Despite this, questions have arisen regarding whether the benefits of a massive vaccination campaign are worth the costs. Considering that the coronavirus outbreak is likely to cost the global economy at least \$10

* Corresponding author.

E-mail address: scilwsjtu-wb@yahoo.com (B. Wu).<https://doi.org/10.1016/j.fmre.2022.05.007>2667-3258/© 2022 The Authors. Publishing Services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

trillion [10], a SARS-CoV-2 vaccine will probably be deemed a good buy, not least because of the savings in costs associated with current pandemic measures. However, to the best of our knowledge, there is a lack of evidence comparing the cost-effectiveness of balancing various containment strategies and population immunisation status.

In this paper, we adopted Covasim, a well-defined agent-based model of SARS-CoV-2, to examine the impact of massive vaccination on health and economic outcomes in China. We set up five scenarios that considered varied containment policies targeting different public places, that is, workplaces, communities, and schools, to model the effect of various immunisation strategies targeting people of different ages. We benchmarked the health outcomes of COVID against those of seasonal influenza and compared cost-effectiveness across the five predefined policy scenarios, stratified by various strategies targeting people of different ages, and tested the sensitivity by setting various examples of vaccination coverage and efficacy. Depending on the vaccinations, we provided evidence of the conditions of when and how societal containment policies could be relaxed or stopped.

2. Materials and methods

The institutional review board confirmed that there was no patient involvement directed by the investigators.

2.1. The dynamic transmission model

The Covasim model, developed by Kerr et al. [11] from the Bill & Melinda Gates Foundation, is a well-established agent-based model that simulates the transmission dynamics of SARS-CoV-2 at the individual level, with key model inputs derived from the published literature. By providing full open-source codes, the methods have been adapted for use in the contexts of many countries in predicting the clinical impact of COVID-19 [12,13].

We adapted Covasim using Marshall and Galea's approach [14]. Each agent (person) in the model is characterised by three sets of stochastic variables. The first set, the traits matrix, documents each agent's demographic characteristics, including age, uniquely identified household, school, work contacts and community; his or her (we do not specify sex) daily viral load, disease status (susceptible, exposed, asymptomatic, recovered or dead), and disease severity (presymptomatic, mild, severe, critical); his or her daily intervention status, including diagnostic status (untested, tested and waiting for results, tested and received results) and quarantine status; and economic aspects (see 2.3 for details). The second set, the interaction matrix, documents for each agent whether he or she has a relation (and possible contact) with other agents in the model for each of the four location types: household, community, school, and household. For each type of interaction, we set varied frequencies of contact and intensity weight within a day based on previously reported Chinese data [15]. The third set, the environment matrix, documents the age-specific (16 age groups) probabilities of being symptomatic should a person be infected and, on a sequential daily basis, whether the agent is fully immunised. The details and sources of age-specific probabilities can be found in a published report [11].

The agent's vaccination status was depicted in the traits matrix. The vaccine was assumed to be an imperfect "all or nothing" vaccine, such that with a certain probability, it would provide either perfect protection from infection or none at all (primary vaccine failure) [16]. In the current analysis, we set the vaccine efficacy (the probability that the vaccine would provide protection from infection) at 75.5% after a two-dose vaccine according to the latest clinical trial of inactivated SARS-CoV-2 vaccines [17]. We conservatively assumed that full immunity would be achieved only when two-dose vaccines were fully administered. Based on one recent analysis, the protective effect of vaccines could last for at least a year [18,19].

The simulation analysis was conducted for each agent on a daily basis. Transmission occurred when a susceptible individual came in con-

tact with an infectious individual through one of his or her contact networks, including the household, community, school, and workplace, with his or her contact exogenously defined in the interaction matrix and the varied probability of infection drawn from the environment matrix. The "transmissibility", that is, the per-day probability of transmission per contact with an infected person, was calibrated against the real daily case information released by the Chinese government. Key model inputs are summarised in Table 1.

2.2. Model calibration

The model was calibrated to real data on the incidence of diagnosed SARS-CoV-2 infections, irrespective of clinical presentation (symptomatic or asymptomatic), and mortality in mainland China except Hubei Province. In the calibration, the default settings of the Covasim model were used to generate a cohort of 100,000 agents who interacted over all four types of networks. We performed an automated search for the optimal values of the number of initially infected people and the per-contact transmission probabilities (β) during January and June 2020 by minimising the sum of squared differences between the model's estimates of confirmed cases and deaths and the real government reported data during Jan 15 and June 30, 2020 [20]. We excluded Hubei Province to tease out the effects of insufficient screening testing in the initial stage and the lockdown.

2.3. Model inputs in estimating economic outcomes

Total costs involved both direct health care costs and costs associated with productivity loss due to COVID and NPIs. Health care costs included those associated with testing, managing symptomatic illness, hospitalisation and ICU admission. From the published literature, we obtained the cost of hospitalisation in general and ICU wards due to symptomatic SARS-CoV-2 in China [21]. Due to the lack of robust evidence, the treatment cost for mild cases was excluded from the current analysis. Regarding nonpharmaceutical interventions, the daily cost of quarantine was approximately 75.00 RMB with a duration of 14 days [21]. Based on the clinical practice guidelines for managing SARS-CoV-2, unquarantined individuals with symptoms and quarantined individuals regardless of symptoms would receive the nucleic acid test for SARS-CoV-2. We assumed that the probability of these individuals receiving the test was 95%, which was a conservative estimate based on expert opinion. The costs related to vaccination and administration were ¥108.00 per person. We used the human capital approach to estimate productivity losses due to quarantine and isolation. The national average daily wage was 271.9 RMB, and the average number of working days lost was approximately 23.26 days [21].

To estimate quality-adjusted life years (QALY), the quality of life weights for patients suffering from SARS-CoV-2 were collected from a published report [22], which reported the disutility scores in SARS-CoV-2 patients with symptoms, hospitalisation in the general ward, and ICU admission with and without ventilation. The disutility score of quality of life due to isolation and quarantine was 0.05 [23,24]. The wide implementation of NPIs can also hinder people's quality of life, and we conservatively estimated that the disutility of social distancing was 0.01 [23,24].

2.4. Policy scenarios

Table 2 summarises the 6 policy scenarios. Policy 0 is a control scenario with neither a containment policy nor any vaccination coverage. Policy 1 is the current policy, which proposes nonpharmaceutical interventions in all places, including families, communities, schools and workplace settings. Despite social distancing and hygiene, the policy requires all possible contacts of a suspected case in any of the four settings to receive tracing, screening, and isolation interventions, and those close contacts of confirmed cases are quarantined under medical observation

Table 1
Model inputs.

Variable	Value	Source
Parameters for the dynamic transmission modelling		
Population Parameters		
Age distribution,%		China statistical yearbook
<10 y	11.14%	
10–20 y	11.89%	
20–59 y	62.64%	
60–75 y	10.78%	
≥75 y	3.55%	
Percent female,%	53	
Pre-existing population immunity	0% (0 to 10%)	
Parameters for infection transition		
Infected individuals at start of pandemic, n	10	Assumed
Transmission rate per day	0.0184 (0.0157 to 0.0204)	Calibrated
Incubation time, days	Lognormal(4.6,4.8)	[11]
Timing from infectious to symptomatic	Lognormal(1,1)	[11]
Duration of asymptomatic and mild symptomatic illness, days	Lognormal(8,2)	[11]
Duration of severe and critical symptomatic illness, days	Lognormal(14,2.4)	[11]
Duration of critical symptoms to death, days	Normal(5.1, 1.7)	[11]
Age-specific relative susceptibility	0–9y: 0.34; 10–19y: 0.67; 20–29y: 1.00; 30–39y:1.00; 40–49y: 1.00; 50–59y: 1.00; 60–69y: 1.00; 70–79y: 1.24; 80+y: 1.47	[11]
Age-specific probability to symptomatic illness	0–9y: 50%; 10–19y: 55%; 20–29y: 60%; 30–39y:65%; 40–49y:70%; 50–59y: 75%; 60–69y:80%; 70–79y: 85%; 80+y:90%	[11]
Age-specific probability to severe illness	0–9y: 0.004%; 10–19y: 0.04%; 20–29y: 1.1%; 30–39y:3.4%; 40–49y: 4.3%; 50–59y: 8.2%; 60–69y: 11.8%; 70–79y: 16.6%; 80+y: 18.4%	[11]
Age-specific probability to critical illness	0–9y: 0.040%; 10–19y: 0.011%; 20–29y: 0.05%; 30–39y:0.12%; 40–49y: 0.21%; 50–59y: 0.80%; 60–69y: 2.75%; 70–79y: 6.00%; 80+y:0.33%	[11]
Age-specific probability of mortality	0–9y: 0.002%; 10–19y: 0.006%; 20–29y: 0.03%; 30–39y:0.08%; 40–49y:0.15%; 50–59y: 0.6%; 60–69y:2.2%; 70–79y: 5.1%; 80+y:9.3%	[11]
Parameters for vaccination efficacy		
Effectiveness of 1-dose vaccine,%	0.0%	[28]
Effectiveness of 2-dose vaccine,%	75.5%	[17]
Interval between 2 doses, d	14	[28]
Time to immunity, d	21	[28]
Vaccine coverage,%	90%	[16]
Parameters for the specific NPIs		
Probability of tracing contacts	Household: 100%; School: 99%; Workplace: 99%; Community: 95%	Expert opinion*
Probability of isolation and quarantine	99%	Expert opinion*
Time taken to trace, d	1	Expert opinion*
Probability of laboratory SARS-CoV-2 diagnostic test		
Isolated and quarantined people regardless of symptoms	100%	Expert opinion*
Symptomatic people with no isolation and quarantine	99%	Expert opinion*
Asymptomatic people with no isolation and quarantine	Policy 1: 0.36%; Policy 2–6: 0%	Estimated [‡]
Parameters for economic analysis		
Reduction in quality of life due to the disease		
Symptomatic disease	0.3	[22]
Severe disease	0.5	[22]
Critical disease	0.6	[22]
Isolation and quarantine	0.05	[23,24]
Social distancing	0.01	Assumed [§]
Costs, CNY ¥		
Vaccine per two dose	80.0	Local charge [§]
Administration per person	28.0	Local charge [§]
Laboratory SARS-CoV-2 diagnostic test (per test)	80.0	Local charge [§]
Symptomatic disease per event	6489	[21]
Severe disease per event	61,352	[21]
Critical disease per event	176,744	[21]
Quarantine room (per day)	250.0	[21]
Productivity loss (per day)	271.9	[21]

* Due to the SARS-CoV-2 “dynamic zeroing” strategy in China, nearly perfect non-pharmaceutical interventions were scaled up sufficiently to avoid a second SARS-CoV-2 wave, which is a conserved estimator based on the expert opinion.

‡ It was estimated by multiplying the production capacity of nucleic acid test per day in China (<https://www.chinairm.com/scfx/20210122/160447602.shtml>) and (1- the proportion of export quantity [<https://m.jiemian.com/article/5565343.html>]).

§ The wide implementation of non-pharmaceutical interventions can also hinder people’s quality of life, and we conservatively estimated that the disutility of social distancing was 0.01 [23,24].

§ These cost data were collected from our hospital.

Table 2
Policies modelled.

Policy Number	Policy Description
0	No any intervention, such as NPIs and no vaccination programs
1	Non-pharmaceutical interventions for home, school, workplace and community, such as test–trace–isolate intervention, mandatory quarantine and testing for close contacts of COVID-19 patients and travellers returning from overseas, close the facility where COVID-19 patients have been confirmed and policies that facilitated masque wearing, physical distancing, and hand hygiene
2	Seeking a minimal vaccination age groups (Vaccination age years: 20–60, 20–70, 20–80, ≥ 20 , ≥ 10 and All population) under the context of dismissing the nonpharmaceutical intervention for workplace setting
3	Seeking a minimal vaccination age groups (Vaccination age years: 20–60, 20–70, 20–80, ≥ 20 , ≥ 10 and All population) under the context of dismissing the nonpharmaceutical intervention for workplace and community settings
4	Seeking a minimal vaccination age groups (Vaccination age years: 20–60, 20–70, 20–80, ≥ 20 , ≥ 10 and All population) under the context of dismissing the nonpharmaceutical intervention for workplace, community and school settings
5	Seeking a minimal vaccination age groups (Vaccination age years: 20–60, 20–70, 20–80, ≥ 20 , ≥ 10 and All population) under the context of dismissing the nonpharmaceutical intervention for all four settings

and receive nucleic acid testing for SARS-CoV-2 regardless of symptoms. We conservatively assumed that 95% of contacts were traced because the government data reported 99%. Policies 2–5 gradually withdraw the containment policy, that is, nonpharmaceutical interventions, from workplaces, communities, schools, and homes. For example, in policy 2, contacts in workplaces are not traced and screened; in policy 3, contacts in either workplaces or schools are traced, screened, and isolated.

In policy scenarios 2–5, we set the vaccine coverage as 90% for every-one eligible for vaccination, which was assumed to be similar to vaccination against pandemic influenza [13]. We stratified the analysis for each scenario by setting various target age groups for vaccinations, where we assume there might be situations in which mass vaccination with or without age targeting may achieve desired health outcomes (defined as no higher than 100 infections or 10 deaths per 100,000 population on an annual basis, which is the consensus of clinical experts for seasonal influenza [25–27]).

2.5. Analysis

Due to the stochastic nature of the Covasim model, each policy was simulated under 100 different random number seeds, and the results were represented with the median estimates along with ranges corresponding to the upper (97.5%) and lower (2.5%) bounds produced by these seeds [12]. We set the acceptable impact of cumulative numbers of infections and deaths no higher than 100 and 10 per 100,000 persons,

respectively, on an annual basis, under which the disease burden was comparable with seasonal influenza in China [25–27]. To this end, we sought minimal age groups for vaccination for each policy scenario. In addition, we calculated the incremental cost-effectiveness ratio (ICER) using quality-adjusted life years (QALY) to define effectiveness, where we set the acceptable cost-effective thresholds to be 36,223 RMB/QALY (0.5 times the per capita gross domestic product of China in 2020) [28].

2.6. Sensitivity analysis

We provided two types of sensitivity analyses by setting varied vaccination coverage and efficacy levels. Specifically, we compared the health outcomes across six vaccine coverage levels (ranging from 50 to 95%) and three vaccine efficacy levels (ranging from 50%–95%).

3. Results

3.1. Calibration output and model validation

Fig. 1 According to the Chinese government, there were 14,239 infections (symptomatic or asymptomatic) and 119 deaths attributed to COVID during Jan 15 and June 30, 2020, in mainland China (excluding Hubei Province). Using the daily incidence data, the calibration process found that the per-contact transmission probability varied before and after the lockdown policies. It was observed that the number of daily infec-

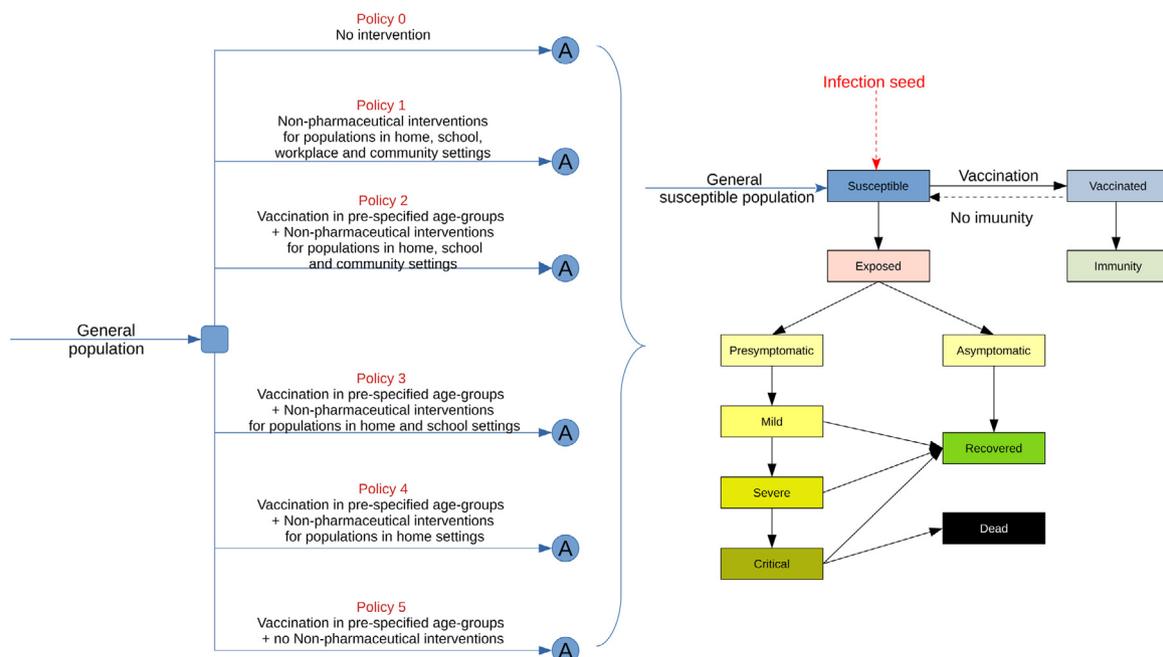


Fig. 1. Modelling policies and model structure.

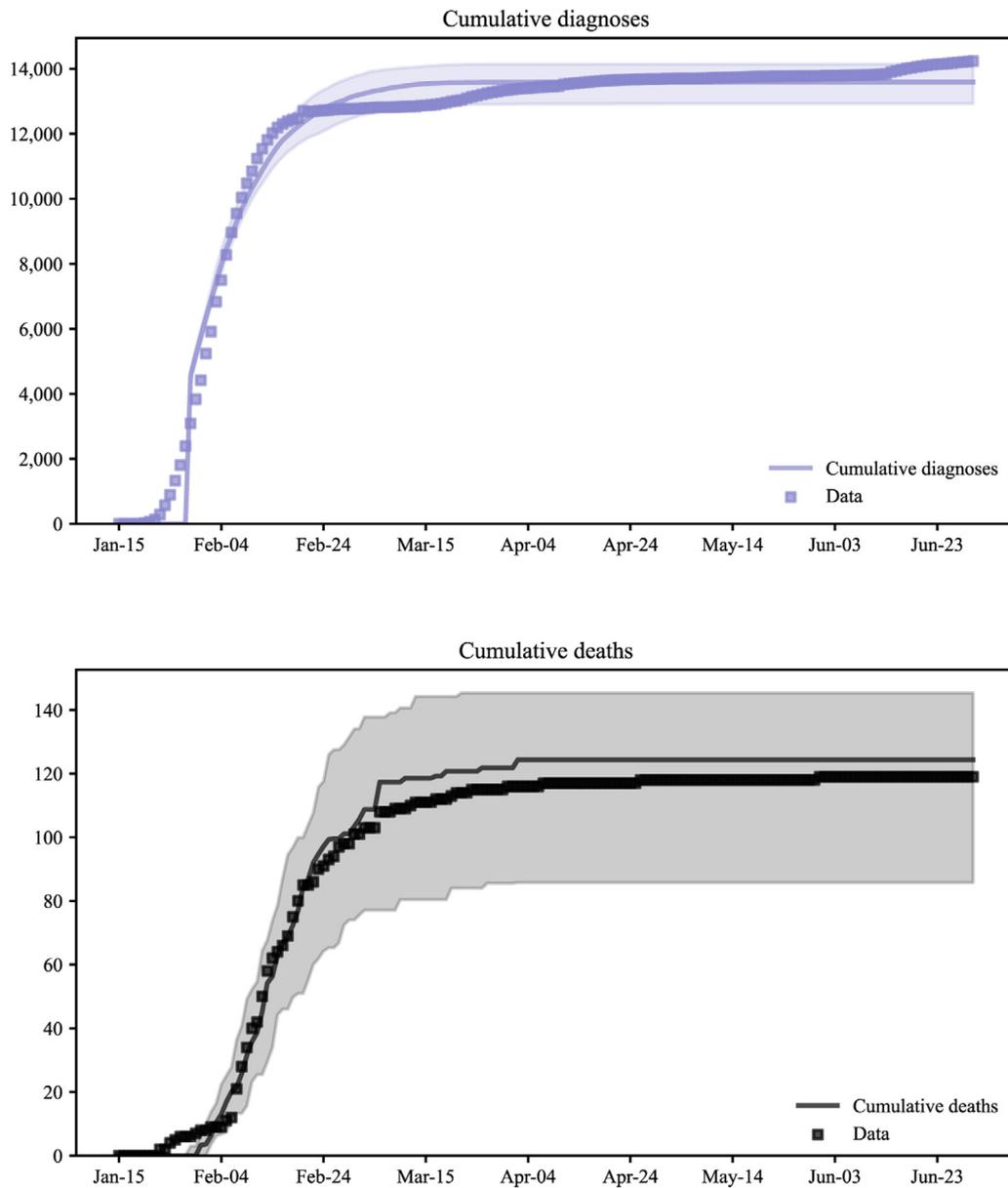


Fig. 2. Model calibration and baseline projection for the initial epidemic wave in mainland China. The data from Hubei Province were excluded because the initial number of cases was underestimated. Squares represent the observed data; solid lines and shaded areas represent model projections (median and 95% CI). Data were available for cumulative diagnoses and deaths, whereas the model also projects cumulative diagnoses and deaths.

tions and deaths increased exponentially before strict NPIs were implemented. By reducing the probability of per-contact transmission, strict NPIs substantially reduced the numbers of daily infections and deaths after March. As shown in Fig. 2, the fit of the baseline model was acceptable because it could accurately project the detailed time trends of both cumulative infections and deaths. The projection included the initial increase in cases observed and the subsequent platform after the NPIs were implemented [29]. One recent systematic review suggested that at least one-third of SARS-CoV-2 infections were asymptomatic [30]. This finding was consistent with the model outputs, which estimated that the proportion of asymptomatic people was 32.8% (95% CI: 31.0% to 36.6%).

3.2. Herd immunity

To achieve herd immunity, the proportion of the population with immunity should be 74.3% (95% CI: 66.9% to 78.2%) when cumulative infections are used as the target endpoint (Fig. 3a). When the vaccine

efficacy was lower than 68%, herd immunity in terms of cumulative infections could not be attained even when vaccination coverage reached 100% (Fig. 3c). When cumulative deaths were used as the target endpoint for herd immunity, the proportion of the population with immunity was 62.2% (95% CI: 50.9% to 67.8%) (Fig. 3b). When the vaccine efficacy was lower than 53%, herd immunity in terms of cumulative deaths could not be attained even when vaccination coverage reached 100% (Fig. 3d).

3.3. Health outcomes by policy scenario

Under the context without any intervention measures, we estimate that the no intervention strategy (Policy 0) would lead to cumulative infections and deaths amongst 48% and 0.28% of the population, respectively (Fig. 4). The nonpharmaceutical intervention strategy (Policy 1) would reduce cumulative infections to 32 and deaths to 0 per 100,000 population. In the scenario of dismissing NPIs from workplace settings (Policy 2), the number of cumulative infections might be lower

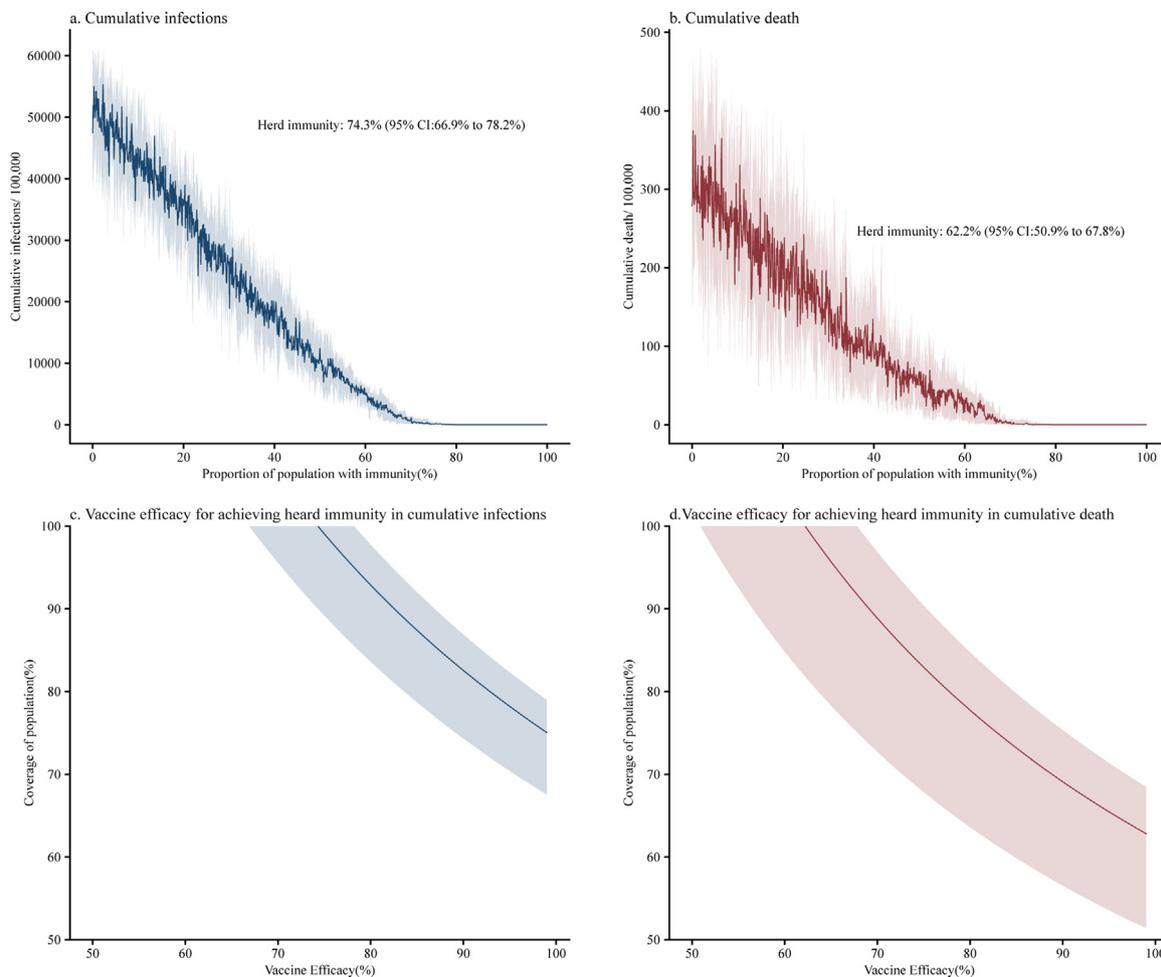


Fig. 3. Modelling the impacts of the proportion of the population with herd immunity, vaccine efficacy and vaccination coverage on achieving herd immunity. (a and b) To achieve herd immunity against both cumulative infections and deaths, the proportion of the population with herd immunity should be increased. (c and d) The relationship between vaccination coverage and vaccine efficacy for achieving herd immunity against both cumulative infections and deaths. Solid lines and shaded areas show the median and 95% CI values.

than 100 per 100,000 population when the vaccination program is taken up at least in individuals aged ≥ 20 years. In this scenario, the cumulative death rate might be lower than 10 per 100,000 population when the vaccination programme is taken up in people aged 20 to 60 years. The addition of terminating NPIs from the community setting to Policy 2 requires higher vaccination uptake (Policy 3). In this scenario, the cumulative infection rate might be lower than 100 per 100,000 population when the vaccination program covers the entire population, and the cumulative death rate might be lower than 10 per 100,000 population when the vaccination program covers at least those aged 20 to 70 years. The addition of terminating NPIs from the school setting to Policy 3 leads the number of cumulative infections to be higher than 100 per 100,000 population, even when the vaccination program covers all populations (Policy 4). However, the cumulative death rate remains lower than 10 per 100,000 population when the vaccination program is taken up at least in people aged 20 to 70 years in this scenario. In the scenario of terminating NPIs from all four settings (Policy 5), both the cumulative infections and deaths exceed the target value even when the vaccination program is taken up in all populations.

To consider sensitivity to vaccine efficacy and coverage, we analysed the cumulative infections and deaths due to SARS-CoV-2 predicted by the model in policies 2–5. In these four scenarios, when the vaccine efficacy declined to 50%, both the cumulative infections and deaths exceeded the target values even when the vaccination program was taken up in all populations (Fig. 5). When the vaccine efficacy increased to

95%, the number of cumulative infections fell within the target value in the following strategy: policy 2 with vaccination uptake at least in people aged ≥ 20 years, policy 3 with vaccination uptake at least in people aged ≥ 10 years, and policies 4 and 5 with vaccination uptake in all populations (Fig. 5). When cumulative deaths were used as the endpoint, the following strategy achieved the target value: policy 2 with vaccination uptake at least in people aged 20 to 60 years of age, policies 3 and 4 with vaccination uptake at least in people aged 20 to 70 years, and policy 5 with vaccination uptake at least in people aged 20 to 80 years.

When the vaccine coverage was reduced to be lower than 80%, the cumulative infections in policy 2 exceeded the target value even when the vaccination program was taken up in all populations (Fig. 6). In policy 3, when the vaccination program was taken up in all populations, the vaccine coverage could not be lower than 90% or the cumulative infections would exceed the target value. Even when vaccine coverage increased to 95%, the number of cumulative infections in policies 4 and 5 exceeded the target value even when the vaccination program was taken up in all populations. When cumulative deaths were used as the endpoint and vaccine coverage was reduced to $\geq 60\%$, the vaccination program had to at least be taken up in people aged 20 to 80 years in policy 2. In the scenario of policy 3, the vaccination program had to be taken up at least in individuals aged 20 to 70 years when cumulative deaths were used as the endpoint and vaccine coverage was reduced to $\geq 70\%$. When vaccine coverage was reduced to lower than 90%, the

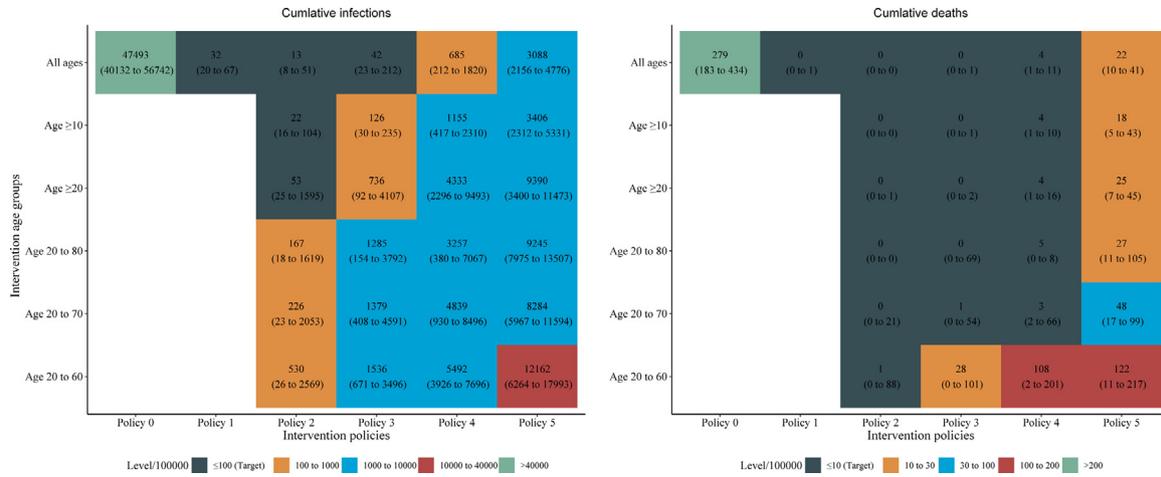


Fig. 4. Strategies for cumulative infections and deaths according to various NPIs and vaccination implementation for different age groups. Each parameter combination on the plane is colour-coded according to the strategies that yielded cumulative infections and deaths with medians and their 95% CIs.

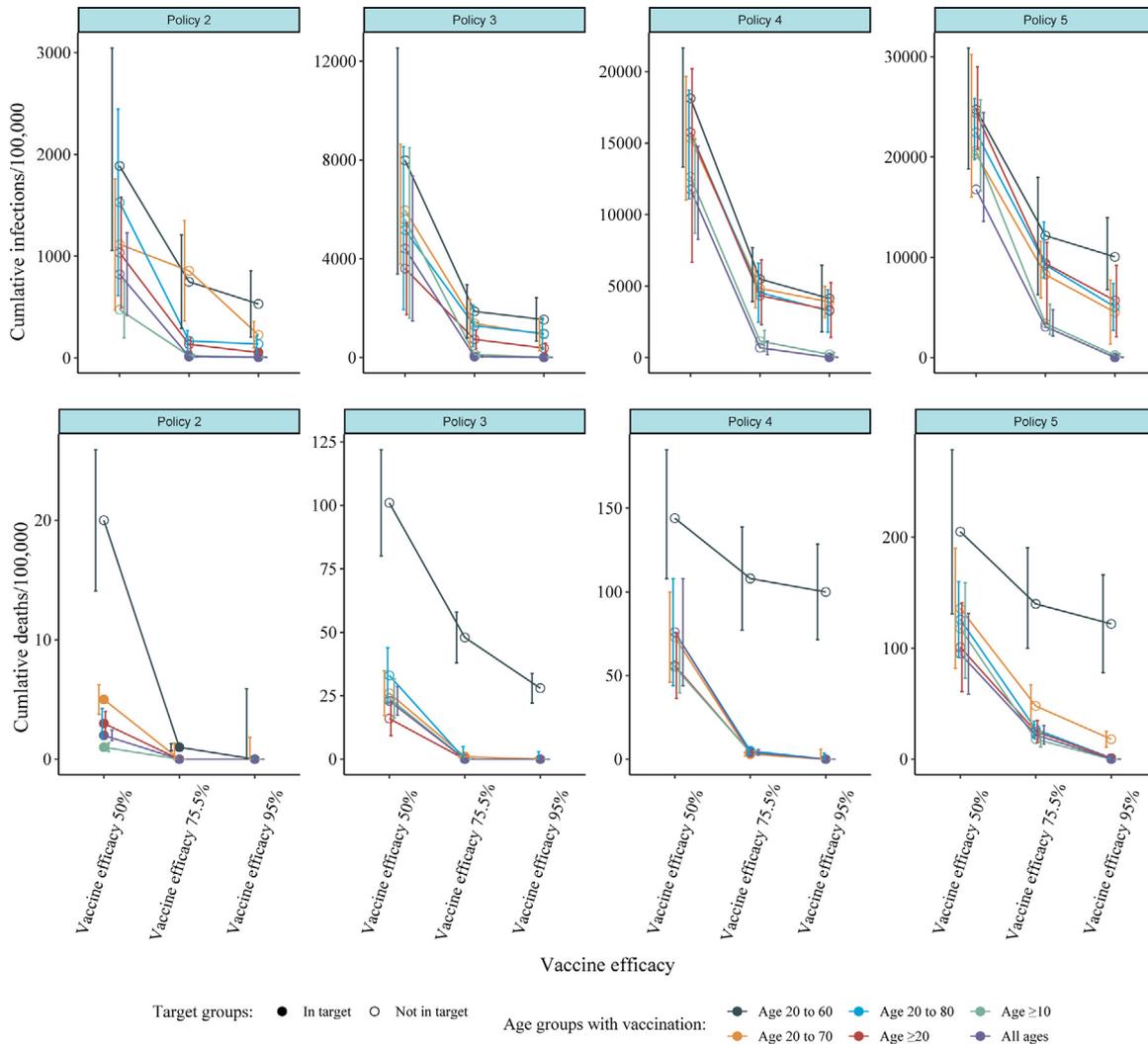


Fig. 5. Impacts of vaccine efficacy on cumulative infections and deaths. The hollow circle indicates that the median value is not in the prespecified target, and the solid circle indicates that the median value is in the prespecified target. The error bar indicates the 95% CI, whose values in the six age groups indicated statistical significance.

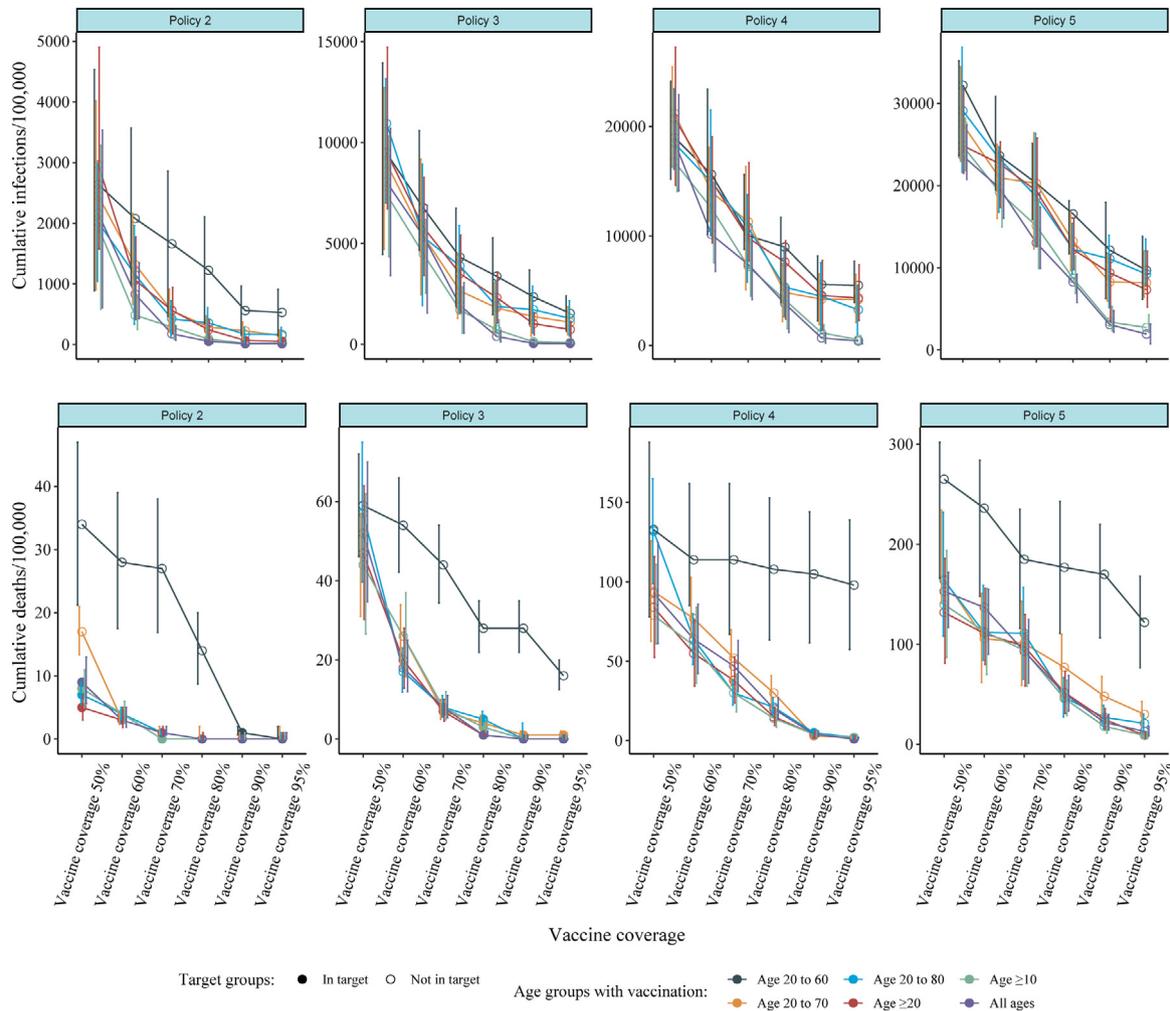


Fig. 6. Impacts of vaccine coverage on cumulative infections and deaths. The hollow circle indicates that the median value is not in the prespecified target, and the solid circle indicates that the median value is in the prespecified target. The error bar indicates the 95% CI, whose values in the six age groups indicated statistical significance.

cumulative deaths in policies 4 and 5 exceeded the target value even when the vaccination program was taken up in all populations.

3.4. Economic impact by policy scenario

Different interventions led to substantially different costs per QALY. Table 3 and Fig. 7 show the economic results and highlight the efficient strategies. The no intervention strategy (Policy 0) incurred the highest cost (4924 RMB per person) and QALY loss (0.1159 per person), which was dominated by other intervention policies. In the scenario of terminating NPIs in workplace settings (Policy 2), the ICERs of vaccine uptake at least in individuals aged 20–70 years were lower than the cost-effective threshold (36,223 RMB/QALY) compared with policy 1. In Policies 3 and 4, the ICERs of the intervention options were lower than the threshold only when the vaccination program was implemented at least in people aged ≥ 10 years and all ages, respectively. In Policy 5, there were no ICERs of the intervention options lower than the threshold. Vaccine uptake in people aged ≥ 10 years in policy 2 was the reference strategy in terms of efficiency amongst all 26 intervention options. This strategy lost 0.0094 QALYs per person and incurred a cost of 105.4 RMB per person, and the vaccine cost was approximately 81.2%. The following strategies described vaccine uptake at all ages in policies 3 and 4, in terms of the efficient frontier. The incremental costs per QALY were 4892 RMB (policy 2 of vaccination of all people aged ≥ 10 years versus policy 3 of vaccination of people of all ages) and 133,786 RMB

(policy 3 of vaccination of people of all ages versus policy 4 of vaccination of people of all ages). Other strategies that were not evaluated regarding the efficient frontier, such as the no intervention strategy (Policy 0) and the nonpharmaceutical intervention strategy for all settings and all ages (Policy 1), dominated or nearly dominated.

4. Discussion

This analysis explored the health outcomes and cost-effectiveness of gradually terminating NPIs with the expansion of the SARS-CoV-2 vaccination program in the population. To fulfil the prespecified target of cumulative infections (lower than 100 infections/100,000 persons), our model findings suggested that NPIs might be gradually terminated for workplace and community settings if the vaccination program has been taken up in individuals aged ≥ 20 years and the entire population. NPIs should be kept in school and home settings even when the vaccination program is taken up in all age populations. However, when cumulative deaths are adopted as the target (lower than 10 deaths/100,000 persons), NPIs might be laxly terminated compared with the prespecified target of cumulative infections. If vaccination programs have been implemented at least in individuals aged 20–60 and 20–70 years, NPIs might be gradually terminated in workplace, community and school settings. However, NPIs should still be kept in the home setting even in the scenario that cumulative deaths were the target. The findings were consistent with others [31,32], which also suggested that continued physi-

Table 3
Cost-Effectiveness of COVID-19 invention policies in the Chinese setting.

Intervention policies	Cost (RMB) per person				Lost QALYs per person	ICER (RMB/QALY, VS. Policy 1)
	Disease cost	Nonpharmaceutical intervention cost	Vaccination cost	Total cost		
Policy 0	4924	0.00	0.00	4924	0.1159	Dominated
Policy 1	2.88	131.7	0.00	134.6	0.0126	Not applicable
Policy 2						
Vaccination age: 20–60	31.07	250.0	67.75	348.8	0.0105	102,542
Vaccination age: 20–70	8.78	132.4	72.60	213.8	0.0097	27,815
Vaccination age: 20–80	3.18	30.16	73.50	106.8	0.0095	Dominant
Vaccination age: ≥20	7.58	98.61	74.40	180.6	0.0096	15,719
Vaccination age: ≥10	1.86	17.65	85.66	105.2	0.0094	Dominant
Vaccination age: All population	1.55	10.05	97.19	108.8	0.0094	Dominant
Policy 3						
Vaccination age: 20–60	298.0	332.4	67.75	698.1	0.0105	270,155
Vaccination age: 20–70	58.46	392.1	72.60	523.2	0.0086	97,605
Vaccination age: 20–80	52.24	383.7	73.50	509.4	0.0085	90,993
Vaccination age: ≥20	29.83	251.2	74.40	355.4	0.0074	42,836
Vaccination age: ≥10	8.65	59.97	85.66	154.3	0.0065	3244
Vaccination age: All population	3.98	19.09	97.19	120.3	0.0063	Dominant
Policy 4						
Vaccination age: 20–60	1074	576.0	67.75	1718	0.0199	Dominated
Vaccination age: 20–70	212.0	452.8	72.60	737.4	0.0113	463,062
Vaccination age: 20–80	159.0	345.1	73.50	577.6	0.0086	111,906
Vaccination age: ≥20	199.6	570.0	74.40	844.0	0.0106	355,779
Vaccination age: ≥10	93.70	227.7	85.66	407.1	0.0057	39,433
Vaccination age: All population	73.02	160.6	97.19	330.8	0.0048	25,139
Policy 5						
Vaccination age: 20–60	1410	11.23	67.75	1489	0.0266	Dominated
Vaccination age: 20–70	762.8	8.01	72.60	843.4	0.0178	Dominated
Vaccination age: 20–80	637.5	8.89	73.50	719.9	0.0185	Dominated
Vaccination age: ≥20	581.4	8.12	74.40	663.9	0.0169	Dominated
Vaccination age: ≥10	355.6	3.74	85.66	445.1	0.0084	74,065
Vaccination age: All population	350.0	3.26	97.19	450.5	0.0075	62,542

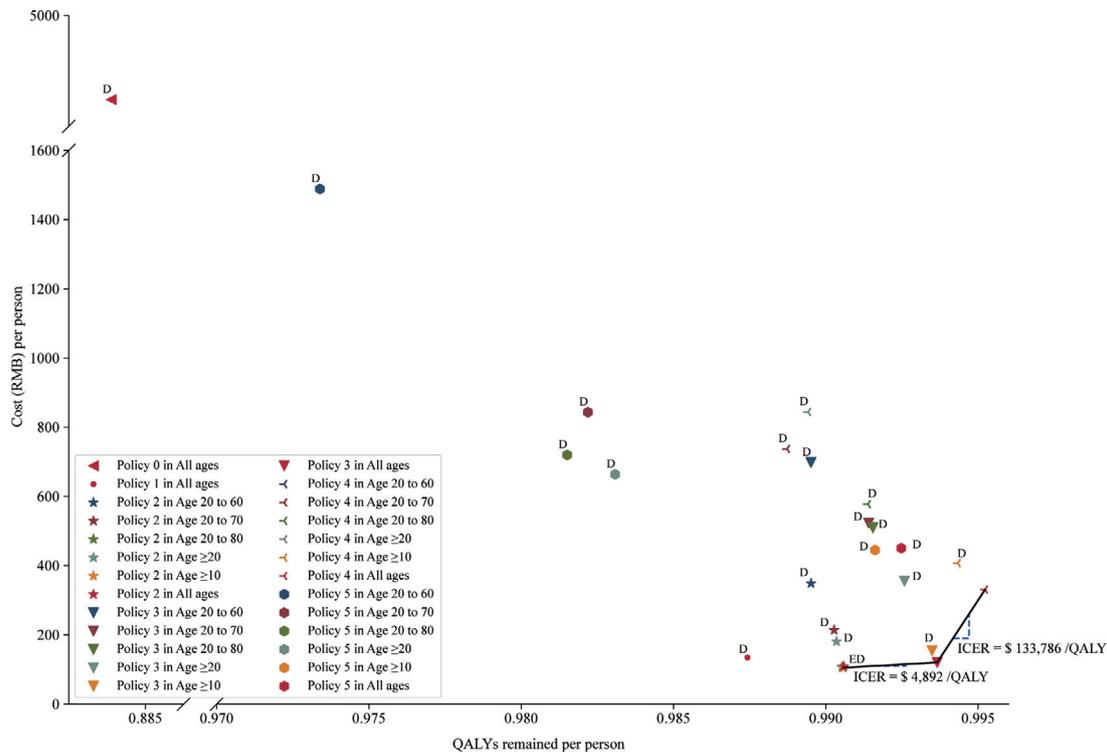


Fig. 7. The efficient frontier (cost per QALY per person) for SARS-CoV-2 intervention strategies. Policy 2 for people aged ≥10, policy 3 for all ages and policy 4 for all ages comprised the efficiency frontier, where policy 2 for people aged ≥10 had the lowest cost and policy 4 for all ages had the highest number of QALYs. Other less prevalent interventions were not on the efficiency frontier. The capital letter D indicates that this strategy was dominant, and ED indicates that this strategy was nearly dominant.

cal distancing might be needed until high population-wide coverage is achieved with vaccines.

Recently emerged SARS-CoV-2 variants may pose a threat to immunity [33]. Therefore, our model checked the impacts of vaccine coverage reduction on the policy. If the vaccine efficacy was reduced to 50%, our model found that the number of cumulative infections could exceed the prespecified target in all policies even when vaccine uptake occurred amongst the entire population. In the case of reduced immunity, NPIs should be deployed in all four settings again. These results suggested that SARS-CoV-2 surveillance is crucial to obtain reliable evidence about whether new variants are more contagious, virulent, or resistant to the available COVID-19 vaccines well before they spread throughout the world [34]. One recent study supports efforts to maximise vaccine uptake with two doses because the vaccine effectiveness was notably lower for the Delta variant than for the Alpha variant after the receipt of the first dose, and only modest differences were noted after the receipt of two vaccine doses [35]. Because the Delta variant has become prevalent, two or more vaccine doses might be a preferential option for preventing outbreaks caused by the Delta variant. With the improvement in vaccine efficacy, the policy of terminating NPIs might become more flexible. For example, NPIs could be removed from all four settings if the vaccine efficacy improved from baseline efficacy (75.5%) to 95% and vaccine uptake occurred in all populations. This finding indicated that the national vaccination program should purchase vaccines with as much efficacy as possible.

Another factor that was considered in this analysis was vaccination coverage and vaccine uptake in various age groups. To achieve herd immunity against cumulative infections and deaths, the estimated proportions of the population with immunity should be at least approximately 74.3% and 62.2%, respectively. According to the baseline efficacy (75.5%) of vaccines that are widely used in the Chinese vaccination program, vaccination coverage should not be lower than 90% and 70% in the whole population to achieve herd immunity against cumulative infections and deaths, respectively. However, several recent studies have reported that only approximately 70% of the population was reportedly willing to accept COVID-19 vaccination [36–38], which was far lower than the vaccination coverage target. Within the framework of the sensitivity analysis, our model results also indicated that the current lower vaccination coverage in the whole population could still not support the termination of NPIs from all four settings if the prespecified target of cumulative infections was used as the endpoint. However, if the vaccination coverage in adults was higher than 90% and vaccine efficacy remained stable, terminating NPIs in workplace and community settings might be a policy option.

The value of intervention policies in restoring society could be in the billions and possibly trillions of dollars. Within the framework of the economic analysis, our model results indicated that intervention policies, including NPIs and vaccination programs, were prevalent compared with no interventions due to their lower cost and better health outcomes. This finding suggested that investments in vaccines and NPIs is worthwhile to avoid complications and costs related to SARS-CoV-2 infections. When the vaccination program has been sufficiently implemented, the cost associated with quarantine and massively scaled clinical testing could be saved by terminating NPIs in some settings. Our study indicated that terminating NPIs in workplace settings could produce the lowest cost when vaccination programs have been taken up at least amongst people aged ≥ 10 years, which was also seen in most intervention strategies due to its lower costs and better health outcomes, including policy 1 (NPIs). With the addition of terminating NPIs in community and school settings, the loss of QALYs caused by isolation and quarantine could be prevented compared with a strategy of only terminating NPIs in workplace settings. When the vaccination program was taken up in the whole population, the ICER of policy 3 against the cheapest intervention (policy 2 with vaccine uptake at least in people aged ≥ 10 years) was lower than the willingness-to-pay threshold, and it was shown to be a cost-effective option. However, policy 4 was not cost-

effective because its ICER compared with policy 3 was higher than the threshold. These findings indicated that terminating NPIs in workplace and community settings could achieve a balance between health and economic outcomes caused by infections and NPIs.

To date, few evaluations have investigated the health and economic outcomes of different intervention policies for gradually terminating NPIs with the expanding vaccine uptake in the population. The current study was meant to fill this gap. However, our results should be viewed in the context of several weaknesses. First, due to the absence of specific contact patterns, we did not consider the impact of allocating vaccines in priority groups that maintained essential core societal functions during the COVID-19 pandemic [39], such as essential health services and food delivery. Second, we did not indirectly include lost revenue from reopening society, such as tourism and transportation, because we could not find reliable data on the accuracy of economic output related to various distancing measures. Third, masque wearing might accrue a daily cost and have some negative impacts on daily life. However, we did not consider this impact in the current analysis because the public's masque-wearing behaviours varied and included a lack of hand hygiene before and during masque wearing, not choosing an appropriate type of face masque and reusing disposable face masks [40]. Finally, there is uncertainty about many aspects of SARS-CoV-2. We used the best currently available data and limited our analysis to one year.

In conclusion, to achieve the target of herd immunity, where COVID only affects society to the extent of a normal flu, we examined the outcome both in terms of the annual number of infections and fatalities. Our findings highlight that NPIs might be terminated in workplace and community settings in China only if the number of infections is considered. If fatalities are considered, NPIs might be terminated in workplace, community and school settings. Due to the uncertainties and unknown characteristics of the vaccine for the variants, intervention policies, including NPIs and vaccination programs, should be more flexible depending on the evidence from SARS-CoV-2 surveillance.

Author contributors

BW conceived the study and is the guarantor. BW, YY and XF designed the study methods, analysed the data and interpreted all data and analyses. All authors were involved in the revision of this manuscript. All authors read and approved the final manuscript and are accountable for all aspects of the work, including the accuracy and integrity. BW is the guarantor.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest in this work.

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Bin Wu, Ph.D., is a senior researcher and a deputy director pharmacist at Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University. Dr. Wu's major research topics involve health economics and outcomes, drug utilization, health outcomes and medical decision making in clinical oncology, diabetes, infections, cardiovascular disease, women's health and rheumatology.