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Dynamic optimization of COVID-19 vaccine prioritization in the context of limited supply

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Summary

Strategic prioritization of COVID-19 vaccines is urgently needed, especially in light of the limited supply that is expected to last for most, if not the entire, 2021. Dynamically adapting the allocation strategy to the evolving epidemiological situation could thus be critical during this initial phase of vaccine rollout. We developed a data-driven mechanistic model of SARS-CoV-2 transmission to explore optimal vaccine prioritization strategies in China that aim at reducing COVID-19 burden measured through different metrics. We found that reactively adapting the vaccination program to the epidemiological situation (i.e., allocate vaccine to a target group before reaching full coverage of other groups with initial higher priority) can be highly beneficial as such strategies are capable to simultaneously achieve different objectives (e.g., minimizing the number of deaths and of infections). The highest priority categories are broadly consistent under different hypotheses about vaccine efficacy, differential vaccine efficacy in preventing infection vs. disease, vaccine hesitancy, and SARS-CoV-2 transmissibility. Our findings also suggest that boosting the daily capacities up to 2.5 million courses (0.17% rollout speed) or higher could greatly reduce COVID-19 burden should a new wave start to unfold in China with reproduction number equal to 1.5 or lower. Finally, we estimate that a high vaccine supply in the early phase of the vaccination campaign is key to achieve large gains of strategic prioritizations.

Words: 2210

Introduction

Vaccination is promising to end the COVID-19 pandemic while allowing restoring social activities^{1,2}. However, the anticipated global vaccine capacity in 2021 would not be enough to vaccinate every human being on the planet^{3,4}. The situation may be worse if we account for possible failures of vaccine candidates, financing shortfalls, logistical challenges⁵, or difficulties in expanding manufacturing capacity⁶. Moreover, because of unavoidable inequalities among countries, more than half of the world's population would probably remain unvaccinated until 2023³.

For 2021, China targets to reach a daily supply of about 2.78 million courses for a two-dose vaccine ([Supplementary Table 1](#)), corresponding to 0.19% rollout speed. Therefore, a considerable fraction of the Chinese population will not be covered until 2022. The long-term shortfall in daily supply calls a strategic prioritization. Although optimal prioritization strategies are estimated to provide a larger reduction of COVID-19 burden compared to a random mass vaccination^{7,8}, they remain elusive and intrinsically connected to the target of the program (e.g., averting deaths vs. reducing the strain on the healthcare system) designed offline.

In this context of limited vaccine supply, it is of paramount importance for governments to set up effective vaccination campaigns as COVID-19 cases can grow at a far higher pace than immunity accumulates in the population. Therefore, defining vaccination strategies able to adapt to the evolving epidemiological situation on the ground may be highly beneficial^{8,9}. Here we propose a data-driven allocation model coupled with SARS-CoV-2 transmission to optimize the prioritized allocation of vaccines to averting the largest possible number infections, symptomatic cases, hospitalizations, ICU admissions, and deaths.

Results

For each risk metric (infections, cases, hospital admissions, ICU admissions, and deaths), we minimize the total incidences over 400 days. We consider 2.0 million courses supplied per day (0.14% rollout speed), as estimated from manufacturing data in China. Daily allocation decisions are coupled with the transmission dynamics of an epidemic spreading under the hypothesis the non-pharmacological interventions (NPIs) are capable to keep SARS-CoV-2 reproduction number R at 1.5.

When the vaccination program aims to minimize the number of SARS-CoV-2 infections, we estimate that the optimal strategy prioritizes individuals aged 15-39 year until 46.6% coverage is reached; then, vaccines are administered to individuals aged 40-64 years until 26.9% coverage is reached (Fig. 1 and Supplementary Fig. 1). Different age-prioritizations are identified if the goal is to reduce SARS-CoV-2 severe outcomes. For example, to minimize the number of deaths, individuals aged 65 years and older are identified as the first priority until 58.6% coverage is reached, followed by aged 40-64 until 18.5% coverage and then aged 65+ until an almost full coverage is achieved (Fig. 1 and Supplementary Fig. 1). To minimize the number of ICU admissions, first priority is given to individuals aged 65+ years and nearly all of them need to be vaccinated before moving to other age groups (Fig. 1 and Supplementary Fig. 1).

Optimal prioritization strategies, although performing best to achieve their specific goals, are capable of dramatically reducing COVID-19 burden, preventing 618-628 million infections (87.8-89.3% reduction), 167-169 million symptomatic cases (88.5-89.4% reduction), 55.3-55.8 million hospital admissions (88.6-89.5% reduction), 3.62-3.81 million ICU admissions (88.2-92.7% reduction), and 5.83-6.15 million deaths (87.4-92.3% reduction) (Fig. 2a-e). We compare the five optimal prioritization strategies with a uniform strategy (random mass vaccination)

where vaccines are allocated proportionally to the size of the unvaccinated susceptible population in each age group. We estimate that the optimal prioritization strategies perform dramatically better than the uniform strategy with respect to any risk metric (more than 87% reduction vs. less than 70%; [Fig. 2f](#)).

We conduct a univariate analysis to explore the impact of key parameters on the definition of the priority groups and coverages as well as the benefits of the optimal prioritization strategies. We estimate that, for each optimal strategy, the two age categories with the highest priority are broadly consistent under different hypotheses on vaccine supply, vaccine efficacy, differential vaccine efficacy in preventing infection and disease, vaccine hesitancy, and SARS-CoV-2 transmissibility. Not only the identified priority orders are identical ([See Fig.1, Extended Data Figs. 3, 6 and 9](#)), but also the associated coverages show only little variations in most cases ([Extended Data Fig.7](#)). However, if vaccination programs target at minimizing symptomatic cases or hospitalizations, the identified priority orders may change when we consider alternative small R ([Supplementary Fig. 5b and c](#)).

Considering $R=1.5$, we estimate that the advantage of optimal prioritization strategies over a uniform mass vaccination increases with vaccine supply 2.0 million courses per day (0.14% rollout speed) is reached and decreases as the supply further increases. When the supply is sufficiently large (3.5 million courses; 0.24% rollout speed), also a uniform mass vaccination would be sufficient to avert nearly all deaths as compared with an epidemic controlled with NPIs only ($R=1.5$). The advantage of the optimal strategies with respect to a uniform vaccination remain unaltered for variations in all other parameters regulating the vaccination, namely vaccine efficacy, differential vaccine efficacy in preventing infection vs. disease, and vaccine hesitancy ([Fig. 3 and Extended Data Fig. 8](#)).

Considering alternative values of R (and thus different levels of NPIs) greatly affects the effectiveness of these strategies, and thus the relative advantages of optimal strategies to the mass vaccination. The benefits are negligible when $R = 1.25$, as all strategies can reduce the epidemic burden by almost 100%. For R larger than 1.5, the benefits may depend on the program targets, e.g., only those aiming at minimizing deaths and ICUs performing markedly better than the random mass vaccination in averting deaths or ICUs ([Fig. 3e](#) and [Extended Data Fig. 8d](#)).

We also test an alternative vaccine model, replacing the baseline all-or-nothing mechanism (i.e., vaccines provide full protection for a fraction of vaccinated individuals with fractions given by the vaccine efficacy), with the “leaky model”, where all vaccinated individuals are exposed to a lower risk of infection corresponding to the vaccine efficacy (see [Methods](#)). The leaky model identifies optimal prioritization strategies highly similar to those for the all-or-nothing model ([Extended Data Fig. 9](#)). However, the estimated effectiveness of the vaccination strategies is remarkably lower, especially for low levels of vaccine supply ([Supplementary Figs. 2 and 3](#)).

Finally, we investigate the vaccine supply needed for a prioritized vaccination campaign to keep the total number of deaths under 10,000. We estimate that, for $R=1.5$ and all-or-nothing vaccine, the minimal daily supply corresponds to 3.5 million courses (0.24% of the population).

Discussion

Our results show that COVID-19 vaccination strategies able to adapt to the evolving epidemiological situation can greatly reduce COVID-19 burden. The optimal vaccination strategies with specific program targets (e.g., minimize the number of deaths) are shown to be driven by the targeted risks of population segments as epidemic unfolds. Benefits of optimal strategies as comparison to random mass vaccination is substantial when the supply is modestly

low, or the transmission is modestly high. Nonetheless, the random mass vaccination may potentially represent an alternative to targeted vaccination strategies should the supply be sufficiently high ([Extended Data Fig. 2a](#)), the transmissibility R controlled be at a very low level ([Extended Data Fig. 2c](#)), or the vaccine be administered to individuals aged 15-64 years only ([Extended Data Fig. 5c](#)) – i.e., the age groups for which the administrated vaccine in the early phase has proved to be safe and efficacious.

Given the uncertainty still surrounding many of the key parameters regulating the vaccination process, we tested several scenarios on vaccine supply, vaccine efficacy, differential vaccine efficacy in preventing infection vs. disease ([Extended Data Fig. 4](#)), and vaccine hesitancy of the population ([Extended Data Fig. 5](#)) as well as two alternative vaccine mechanisms (“all-or-nothing” vs. “leaky” vaccine; [Extended Data Fig. 9](#)). We found that all those factors have little effect in determining the optimal prioritization strategies. Although this increases the confidence in our findings, it is important to stress that the identified optimal strategies could be sensible to variation in SARS-CoV-2 transmissibility for certain program targets (e.g., minimizing hospitalizations). This highlights the need to potentially adapt vaccination choices to the implemented NPIs.

Our findings suggest that boosting the daily capacities into 2.5 million courses (0.17% rollout speed) or higher could greatly reduce COVID-19 burden would a new wave start to unfold in China. Moreover, we estimate that a high vaccine supply in the early phase of the vaccination campaign is key to achieve large gains of strategic prioritizations. All strategies result in a much larger disease burden when vaccine rollouts gradually increase over time (although the same total amount of courses is administered; [Supplementary Fig. 4](#)).

It is key to remark that our baseline results are obtained by assuming $R=1.5$, with NPIs implemented throughout the entire vaccine rollouts. As a consequence, our results neither provide estimates of the herd immunity threshold for COVID-19 nor can be used to estimate the overshoot of the epidemic after the herd immunity threshold is reached.

Our study adds to the literature in several ways. First, although investigating dynamic vaccine allocation is not novel, to the best of our knowledge, this is the first investigation at the population level and in a data-driven context accounting for estimates of vaccine supply. Dynamic vaccine allocation allows the campaign to track the eligible population and adapt the targeted vaccination populations to the evolving epidemiological situation, and thus protect individuals who are at the highest risks at each time. Second, previous studies have shown that optimal prioritization strategies for single objectives (e.g., minimize the number of death) may sacrifice secondary objectives (e.g., minimize the number of infections)¹⁰. Instead, our results show that, thanks to the data-driven dynamic allocations, the sacrifices are lower than previously estimated. Indeed, the dynamic optimal allocations can quickly react to changes in age-specific risks (e.g., of infection, hospitalization) over time. This finding supports the relevance of both direct and indirect protection of the population¹¹ to define prioritized vaccination strategies. Our findings are of particularly relevance for China at this early phase of vaccine rollout when vaccination is restricted to people mainly aged 18-59, due to the lack of vaccine safety and efficacy thus far.

To properly interpret our findings, it is important to consider the limitations of the performed analysis. First, the analysis is based on a deterministic model and does not consider the stochasticity of the real-world infection transmission process, although the former can be considered as a good approximation of the latter when the number of infections is large. In the

early phase of the epidemic, the stochastic variability may affect the timing of the epidemic peak, resulting in inaccuracy in the estimated effectiveness of vaccination programs. Also, we consider average values of model parameters (e.g., the contact matrix, age-specific estimates of the susceptibility to infection). Despite we recognize lack of estimates of the uncertainty around our point projections, we have conducted extensive sensitivity analysis showing to what extent model parameters affect the obtained results. Second, we leveraged contact data collected before the COVID-19 pandemic to model SARS-CoV-2 transmission through 2021 and accounted for the impact of NPIs on contact numbers through a reduction on R , but the future contact pattern by age remains elusive. Moreover, we used the contact pattern data collected in Shanghai and extrapolated it into the entire China. Although this surely represents a limitation, several independent studies showed little variation in age-mixing patterns across China^{12–14}. Third, for model tractability, we optimize allocation of only the first dose of the two-dose vaccines and simply require that the second dose to be administrated following the schedule, although this may not be optimal from the mathematical point of view.

In sum, our analysis identified optimal COVID-19 vaccination prioritizations as the epidemic unfolds. Our model-based evaluation highlights the benefit of these strategies in simultaneously minimizing different objectives (e.g., number of deaths and infections). Finally, the modeling framework presented here general enough to be adopted by other countries to identify optimal vaccine prioritization strategies conditional on the country-specific socio-demographic features, evolving epidemiological situation and vaccine supply.

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Fig. 1 | Estimated vaccine coverages over time for different prioritization strategies (0.14% rollout speed, $R = 1.5$). **a-e**, Five optimal prioritization strategies minimizing the total incidence of infections, symptomatic cases, hospitalizations, ICU admissions, and deaths, respectively. **f**, Uniform vaccination strategy. Shaded area refers to vaccine administration to the general populations. Lines refers to the vaccinated proportions including essential workers. Keys and labels apply to all panels.

Fig. 2 | Risk incidences for different prioritization strategies and the scenario with no vaccination (0.14% rollout speed, $R = 1.5$). **a**, Number of averted infections under the scenario with no vaccination, uniform vaccination strategy, and the five optimal prioritization strategies we identified. **b-e**, As panel **a**, but for the number of symptomatic cases, hospitalizations, ICUs, and deaths, respectively. **f**, Averted proportion of infections, symptomatic cases, hospitalizations, ICUs, and deaths for the six vaccination strategies as compared to the scenario with no vaccination. Keys apply to all panels.

Fig. 3 | Effectiveness of alternative vaccination strategies under alternative assumptions. **a**, Averted proportion of deaths for different strategies (uniform vaccination and the five optimal strategies) as compared to no vaccination for different values of the daily vaccine supply. **b**, As **a**, but for different values of the vaccine efficacy. **c**, As **a**, but assuming that the vaccine may have a lower efficacy in preventing the infection (namely 60% and 70%) than in preventing the disease (which is kept fixed at 80%). **d**, As **a**, but considering possible vaccine hesitancy. In particular, we consider three alternative scenarios: i) “Whole population”, i.e., all individuals are willing to accept the vaccine; ii) “Chinese survey”, i.e., on average 83% of the population is willing to accept the vaccine as estimated in a survey conducted on the Chinese population¹⁵ (age-specific estimates reported in [Extended Data Table 2](#)); iii) “Global survey”, i.e., on average 61% of the population is willing to accept the vaccine as estimated in a survey at the global level¹⁶. **e**, As **a**, but for different values of the reproduction number. Keys and labels apply to all panels. Results for other risk metrics are similar and displayed in [Extended Data Fig.8](#).

Methods

Model

We model SARS-CoV-2 transmission dynamics using an age-structured compartmental model with 17 age groups {0-4,5-9,10-14,15-19,20-24,25-29,30-34,35-39,40-44,45-49,50-54,55-59,60-64,65-69,70-74,75-79,80+; total number of age groups denoted with J }. For each age group, the population is divided into five compartments: unvaccinated susceptible individuals (S), vaccinated individuals (V), unprotected individuals who received the vaccine (U), infectious individuals (I), and immune individuals (either recovered from the infection or protected by the vaccine) (R) ([Extended Data Fig. 1](#)). Note that the infectious compartment (I) includes both asymptomatic and symptomatic infections as no statistical difference in transmissibility was found between them ¹⁷ and we are not explicitly simulating interventions that act differently on those two groups.

The transmission depends on contacts between susceptible and infectious individuals and the risk of infection given a contact (β). Contacts are modeled through the use of a contact matrix C_{ij} representing the mean number of contacts that an individual in age group i has with individuals in age group j . Contact patterns are estimated by relying on 2017/2018 survey data for Shanghai ¹⁸. We use bootstrap (sample with replacement where the sampling weights are given by the distributions of age groups in China) to estimate mixing patterns at the country level ¹⁸. We estimate the contact patterns using the package ‘socialmixr’ in R version 4.0.3 ¹⁹. The resulting contact matrix is shown in [Supplementary Fig. 6](#). The number of individuals in each age group is taken from Chinese statistical year book 2019 ²⁰ and denoted with N_i .

We also consider age-specific susceptibility to infection s_i as estimated in reference ¹⁷. For simplicity, we denote the contact matrix multiplied by the susceptibility to infection by age as $C^s_{i,j} = s_i C_{i,j}$. The mean generation time is set at 5.5 days ¹⁷ (and the rate of transition, which is the inverse of the generation time, is denoted with γ).

We consider $1/w$ days from the administration of the first vaccine dose to maxim protection ²¹ (and denote the transition rate with w); e_i represents the vaccine efficacy for age group i . Further, we denote by $v_i(t)$ the allocation decision variables for age group i on the day t . We consider “all-or-nothing” mechanism, where vaccines are assumed to provide fully immunity for e_i proportions of vaccinated individuals.

The model is represented by the following system of differential equations:

$$\begin{aligned}
\frac{dS_i(t)}{dt} &= -v_i(t) - (S_i(t) - v_i(t)) \cdot \beta \sum_{j=1}^J C^s_{i,j} \frac{I_j(t)}{N_j} \\
\frac{dV_i(t)}{dt} &= v_i(t) - w(V_i(t) + v_i(t)) - (1-w)(V_i(t) + v_i(t)) \cdot \beta \sum_{j=1}^J C^s_{i,j} \frac{I_j(t)}{N_j} \\
\frac{dU_i(t)}{dt} &= (1-e_i) \cdot w(V_i(t) + v_i(t)) - U_i(t) \cdot \beta \sum_{j=1}^J C^s_{i,j} \frac{I_j(t)}{N_j} \\
\frac{dI_i(t)}{dt} &= (S_i(t) + U_i(t) + (1-w)V_i(t) - wv_i(t)) \cdot \beta \sum_{j=1}^J C^s_{i,j} \frac{I_j(t)}{N_j} - \gamma I_i(t) \\
\frac{dR_i(t)}{dt} &= \gamma I_i(t) + e_i \cdot w(V_i(t) + v_i(t)).
\end{aligned} \tag{1}$$

We consider five types of epidemiological interest: infections, symptomatic cases, hospitalizations, ICUs, and deaths, that we refer to as “risk” metric. We then use the model to minimize the total risk incidence, namely the sum of daily new risk incidences over T days, for each of the five risk metrics. Mathematically, this can be written as

$$\min \sum_{t=0}^{T-1} \sum_{i=1}^J r_i^{type} \cdot (I_i(t+1) - (1-\gamma)I_i(t)), \quad (2)$$

where r_i^{type} , $type \in \{symp, hosp, ICU, death, infec\}$, represents that, among infections, the risks of symptomatic infections, requiring hospitalizations, ICU admissions and deaths in age group i , with r_i^{infec} simply set to 1 for all age groups.

Baseline scenario

We assume that the vaccine efficacy to prevent the infection is the same as the vaccine efficacy in preventing the disease. The efficacy of the vaccine currently administrated in China was estimated to be 80% for the age group 15-59 years²²; for the other age groups we used a 25% reduction^{23,24} (i.e., $0.75 \times 80\%$). We assume that the first dose is given upon allocation and does not confer protection^{21,23}. Vaccinated people may get protection after the second dose take effect, 14 days after its administration plus 21 days after the first dose (i.e., $w = 1/(14+21) \text{ day}^{-1}$)²¹. We also assume the vaccines has a long-term immunity (i.e., longer than the full study period T , $T = 400$, days).

The transmission rate β is calculated using the next-generation matrices approach²⁵,

$$\beta = \frac{R \cdot \gamma}{\max\{\text{eigen values } (C_{ij}^s)\}} \quad (3)$$

As baseline value, we assume the reproduction number R to be 1.5, to account for the effect of NPIs. Other values are explored as sensitivity analysis.

The age-specific probabilities of developing symptoms, hospitalization, requiring ICU admission, and death are taken from the literature^{26,27,28} and reported in [Extended Data Table 2](#).

All the parameters in the study are calibrated based on state-of-the-art knowledge of COVID-19 epidemiology and vaccination in China. [Extended Data Table 1](#) summarizes the parameters.

Sine only sporadic local transmission reported in China ²⁹, we consider the vaccination starts at the same time of an extensive epidemic outbreak with locally transmitted SARS-CoV-2 infections. The simulations are arbitrarily initialized with one infectious individual in each age group. Since Wuhan was the only location in China that has experienced prolonged local SARS-CoV-2 transmission, we assume a fully susceptible population at the beginning of the simulation.

Vaccination parameters

We estimate the daily vaccine supply at 2.0 million courses (0.14% rollout speed) by scaling down the daily breakdowns from the targeted production capacity in 2021, accounting for possible financing shortfalls, logistical challenges, and difficulties in expanding production capacity ([Supplementary Table 1](#)).

Each age group is stratified into two categories: essential workers (tier 1) and other individuals (tier 2). Essential workers include healthcare workers (either front-line or not) and workers in the following sectors: law enforcement and security, nursing home and social welfare institutes, community, energy, food and transportation ³⁰. Vaccination is administered to essential workers first ^{30,31}. Then, we investigate optimal vaccine allocation strategies to the general population.

Optimization methods

We explore a two-step optimization strategy to solve model (2). First, we solve the problem using the myopic strategy where we minimize daily outcomes iteratively for 400 days. Second, we use the dynamics from the myopic strategy to construct an approximation counterpart and solve it over the full period. Although the myopic strategy does not attempt to minimize the total

outcomes over the full period, they greatly reduce the total outcomes, performing close to the optimal solutions in similar problems ^{32,33}.

Due to the tier constraint in vaccine allocation, we break down the vaccine allocation for each age group $v_i(t)$ into two variables, as

$$v_i(t) = \sum_{k=1}^2 v_{i,k}(t), \quad (4)$$

for each $i = 1, \dots, J$.

The optimization method is divided into the two following steps.

Step 1: Myopic optimal strategy. At the beginning of each day, we optimize vaccine allocation to minimize the risk incidences on that day:

$$\min \sum_{i=1}^J r_i^{type} \cdot (I_i(t+1) - (1-\gamma)I_i(t)), \quad (5a)$$

$$\text{s.t.} \sum_{k=1}^2 \sum_{i=1}^J v_{i,k}(t) \leq c, \quad (5b)$$

$$0 \leq \sum_{k=1}^2 v_{i,k}(t) \leq S_i(t), \quad i=1, \dots, J, \quad (5c)$$

$$W_{i,k}(t) = W_{i,k}(t-1) + v_{i,k}(t-1), \quad i=1, \dots, J, \quad k=1, 2, \quad (5d)$$

$$W_{i,k}(t) \leq N_{i,k} \cdot d_{i,k}, \quad i=1, \dots, J, \quad k=1, 2, \quad (5e)$$

$$\sum_{i=1}^J v_{i,2}(t) \leq b_i(t) \cdot M, \quad (5f)$$

$$\sum_{i=1}^J v_{i,1}(t) \leq (1-b_i(t)) \cdot (M + W_{i,1}(t) - N_{j,1}a_{j,1}), \quad (5g)$$

$$v_{i,1}(t) \geq c \cdot \left(\frac{N_{j,1}}{\sum_{j=1}^J N_{j,1}} - b_i(t) \right), \quad i=1, \dots, J, \quad (5h)$$

$$b_i \in \{0, 1\}, \quad S_i(t), I_i(t), V_i(t), U_i(t) \geq 0, \quad i=1, \dots, J,$$

where r_i^{type} , $type \in \{infec, symp, hosp, death, ICU\}$.

Constraint (5a) minimizes the total risk incidence across age groups on that day. Vaccine allocations across tiers and age groups cannot exceed the daily supplied vaccines (constraint 5b) or the unvaccinated susceptible populations (constraint 5c). Constraint (5d) tracks the cumulative number of allocated vaccines for each age group within each tier, denoted by $W_{i,k}(t)$, and constraint (5e) limits the cumulative number of allocated vaccines, where $d_{i,k}$ represents the maximum coverage for age group i within tier k and $N_{i,k}$ the population size for age group i within tier k . Constraints (5f) and (5g) guarantee that people in the first tier are allocated prior to people in the second tier. M is a large number, with $M = c + N_{j,1}$ in the implementation. Constraint (5h) ensures that vaccines are uniformly allocated among age groups in the first tier.

Model (5) is a linear optimization problem with box constraints. Geometrically, the optimal solutions rest at the corners of the polyhedron comprised by the box constraints. Note that

objective (5a) is equivalent to $\sum_{i=1}^J r_i^{type} (S_i(t) + (1-w)V_i(t) + U_i(t) - w \sum_{k=1}^2 v_{i,k}(t)) \cdot \beta \sum_{j=1}^J C_{i,j}^s \frac{I_j(t)}{N_j}$. The myopic optimization thus determines the prioritization based on the modeled risk metrics. Namely, the myopic policy gives the highest priority to the age group that has the largest risk at the time t . If the number of unvaccinated susceptible population is smaller than the daily supply c , it then diverts to the age group that has the second largest risk. If there are vaccines left after satisfying the first two groups, it further diverts to the third group that has the third largest risk, and so forth. Moreover, because the myopic optimal strategy performs well and close to the optimal solution in similar problems^{32,33}, the final optimal solutions is expected to share similar properties to it.

The model was coded in Gurobi R interface with R version 4.0.3¹⁹ and solved using Gurobi 9.10³⁴. We simplify the implementation of the model by replacing the last three constraints on vaccine allocation to groups in tier 1 with a pre-allocation. Specifically, we first allocate uniformly to the age groups in tier 1, and then use the remaining vaccine supply, if there is any, to optimize the allocation to the age groups in tier 2.

Using aggregated $v_i(t)$, $i = 1, \dots, J$, from the myopic solutions, we update all the states to get the states status on day $t + 1$. We solve the equations using lsoda ODE solver from the package ‘deSolve’³⁵ in R version 4.0.3¹⁹. This iteration of optimization-updating procedure was repeated from day 0 to day T , generating the myopic solutions for the full period.

Step 2: Approximated optimization. Using the myopic solutions from the Step 1, we explore the approximation strategy and minimize the total outcomes of the targeted risk metric. The full model is:

$$\min \sum_{t=0}^{T-1} \sum_{i=1}^J r_i^{type} \cdot (I_i(t+1) - (1-\gamma)I_i(t)) \quad (6a)$$

$$\text{s.t.} \sum_{k=1}^2 \sum_{i=1}^J v_{i,k}(t) \leq c, \quad t=0, \dots, T, \quad (6b)$$

$$0 \leq \sum_{k=1}^2 v_{i,k}(t) \leq S_i(t), \quad i=1, \dots, J, \quad t=0, \dots, T, \quad (6c)$$

$$W_{i,k}(t+1) = W_{i,k}(t) + v_{i,k}(t), \quad i=1, \dots, J, \quad k=1, 2, \quad t=0, \dots, T, \quad (6d)$$

$$W_{i,k}(t) \leq N_{i,k} \cdot d_{i,k}, \quad i=1, \dots, J, \quad k=1, 2, \quad t=0, \dots, T, \quad (6e)$$

$$\sum_{i=1}^J v_{i,2}(t) \leq b_i(t) \cdot M, \quad t=0, \dots, T, \quad (6f)$$

$$\sum_{i=1}^J v_{i,2}(t) \leq (1-b_i(t)) \cdot (M + W_{i,1}(t) - N_{j,1} a_{j,1}), \quad t=0, \dots, T, \quad (6g)$$

$$v_{i,1}(t) \geq c \cdot \left(\frac{N_{j,1}}{\sum_{j=1}^J N_{j,1}} - b_i(t) \right), \quad i=1, \dots, J, \quad t=0, \dots, T, \quad (6h)$$

$$\left| \sum_{j=1}^J C_{i,j}^r \frac{I_j(t)}{N_j} - \sum_{j=1}^J C_{i,j}^r \frac{I_j^{Myopic}(t)}{N_j} \right| \leq \epsilon, \quad t=0, \dots, T, \quad (6i)$$

$$\begin{aligned} & \text{Equations (1) with } I_j(t) \text{ replaced by } I_j^{Myopic}(t), \quad t=0, \dots, T, \\ & b_i \in \{0, 1\}, \quad S_i(t), I_i(t), V_i(t), U_i(t) \geq 0, \quad i=1, \dots, J, \quad t=0, \dots, T. \end{aligned}$$

Constraint (6i) bounds the error of approximation. ϵ is a small number to control the approximation errors.

To choose the candidate myopic optimal solutions (denoted with $I_j^{Myopic}(t)$) for constructing the approximation counterpart in the second step, we use the "try and error" method to test varying $d_{i,k}$. We found that the myopic strategy with $d_{i,k}$ set around 80% performs well. In particular, we found that the myopic solution minimizing the incidence of infections perform relatively well on the other four risk metrics as well. We therefore use the myopic solutions from the scenario to construct the approximation counterparts where we set $d_{i,k} = 1$, $i = 1, \dots, J$, $k = 1, 2$, in (6e). The model was coded in Gurobi Python interface with Python 3.9.0³⁶, and solved using Gurobi 9.10

Sensitivity analyses

We designed a variety of sensitivity analyses to evaluate the robustness of optimal prioritization strategies and to estimate their benefits.

Vaccine supply

We explore different levels of vaccine supply $c = 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ million courses per day. Moreover, as vaccine production capacity may increase over time, we consider a scenario where the vaccine supply linearly increases from 1.5 million courses on the first day to 2.5 million courses at day 400.

Reproduction number

We explore different levels of $R = 1.25, 1.5, 1.75, 2.0$.

Vaccine efficacy

While more evidence about vaccine efficacy is collected, we test alternative levels of vaccine efficacy: $e_i = 0.6, 0.7, 0.9$, for $i = 4, \dots, 12$ and $e_i = 0.6 \times 0.75, 0.7 \times 0.75$ or 0.9×0.75 for $i \leq 3$ or $i \geq 14$.

Vaccine hesitancy

People may be hesitant to accept a COVID-19 vaccine for a variety of reasons³⁷. To model vaccine hesitancy, we let $d_{i,k}$ in (6e) to be equivalent to the vaccine acceptance, $a_{i,k}$. We estimate $a_{i,k}$ by using the data from a large-scale telephone survey conducted on June 2020¹⁸. The potential acceptance of a COVID-19 vaccine within the first tier was estimated to be 96%. The estimated potential acceptance in the second tier is relatively stable by age, ranging from 78% to 89% (see [Extended Data Table 2](#)). Further, we conduct an analysis assuming 61% as vaccine acceptance for all age groups, as estimated in reference¹⁶ where a global-scale survey was conducted.

Differential vaccine efficacy in preventing infection vs. disease

In baseline, we have assumed the vaccine efficacy is the same in preventing both the infection and the disease. Here we conduct an alternative analysis with 60% efficacy for preventing the infection, but three efficacy levels in preventing the disease, namely: 60%, 80% and 90%.

Specifically, we set $e_i = 0.6$, $e_i^{Symp} = 0.6, 0.8$ or 0.9 , for $i = 4, \dots, 12$, and $e_i = 0.6 \times 0.75$, $e_i^{Symp} = 0.6 \times 0.75, 0.8 \times 0.75$ or 0.9×0.75 for $i \leq 3$ or $i \geq 14$. This feature is incorporated into the model by defining new risk of disease after vaccination, $r_i^{Vac_symp}$, by adjusting the risk of developing symptoms as follows:

$$r_i^{Vac_Symp} = \frac{r_i^{Symp} \cdot (1 - e_i^{Symp})}{r_i^{Symp} \cdot (1 - e_i^{Symp}) + (1 - r_i^{Symp}) \cdot (1 - e_i^{Asymp})},$$

where e_i^{Asymp} is calculated by rearranging the following equation:

$$e_i = (1 - r_i^{Symp}) \times e_i^{Asymp} + r_i^{Symp} \times e_i^{Symp}.$$

Following the same arguments used in the baseline scenario (see [Methods](#)), we update the risk of requiring hospitalization, ICU admission, and death as well ($r_i^{Vac_hosp}$, $r_i^{Vac_ICU}$, $r_i^{Vac_death}$).

Excluding individuals aged under 15 years and over 65 years in vaccine rollout

Because optimal prioritization strategy aiming to minimize infections does not allocate to people under 15 and over 65, we test the scenario where these age groups are excluded in vaccinations.

Leaky mechanism

We also consider a variant of model (1) where, for each age group i , instead of assuming a fully protective vaccine for e_i proportion of vaccinated individuals, we consider that vaccination induces an e_i reduction of the risk of infection (“leaky” vaccine) for all vaccinated individuals.

This alternative model is represented by the following system of equations:

$$\begin{aligned}
\frac{dS_i(t)}{dt} &= -v_i(t) - (S_i(t) - v_i(t)) \cdot \beta \sum_{j=1}^J C_{i,j}^s \frac{I_j(t)}{N_j} \\
\frac{dV_i(t)}{dt} &= v_i(t) - w(V_i(t) + v_i(t)) - (1-w)(V_i(t) + v_i(t)) \cdot \beta \sum_{j=1}^J C_{i,j}^s \frac{I_j(t)}{N_j} \\
\frac{dU_i(t)}{dt} &= w(V_i(t) + v_i(t)) - U_i(t) \cdot (1-e_i) \cdot \beta \sum_{j=1}^J C_{i,j}^s \frac{I_j(t)}{N_j} \\
\frac{dI_i(t)}{dt} &= (S_i(t) + U_i(t) \cdot (1-e_i) + (1-w)V_i(t) - wv_i(t)) \cdot \beta \sum_{j=1}^J C_{i,j}^s \frac{I_j(t)}{N_j} - \gamma I_i(t) \\
\frac{dR_i(t)}{dt} &= \gamma I_i(t).
\end{aligned} \tag{7}$$

The full analysis conducted for the baseline scenario (all-or-nothing vaccine, $R = 1.5$) is repeated for the leaky vaccine model. To further investigate the discrepancies between the two models, we explore different levels of vaccine supply $c = 1.5, 2.0, 2.5, 3.0, 3.5$ million courses per day for leaky model. Compared to the all-or-nothing model, the averted incidences under the leaky model are sustainably smaller with small supply, but close with large supplies for optimal prioritization strategies (3.5 million; [Supplementary Fig. 2](#)). Uniform strategy needs even larger supplies to achieve close performances under the two models, e.g., 2.5 million under $R = 1.25$ ([Supplementary Fig. 3](#)).

Data and code availability

The data analyzed in this study are presented in the online methods and supplementary information. Codes will be made available on GitHub upon manuscript acceptance.

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Author contributions

H.Y. designed the study. M.A., X.-H.Z., and H.Y. supervised the work. S.H. developed the model. S.H. and J.C. conducted the research. J.C., J.Z., Q.W., W.Z., and H.S. collected data. S.H., J.C., J.Y., M.A., X.-H.Z., and H.Y. interpreted the findings. S.H., J.C., and M.A. wrote the manuscript. J.Y., X.-H.Z., and H.Y. commented on and revised the manuscript. All authors approved the final manuscript as submitted.

Competing interests

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Figures

Figure 1

Estimated vaccine coverages over time for different prioritization strategies (0.14% rollout speed, $R = 1.5$). a-e, Five optimal prioritization strategies minimizing the total incidence of infections, symptomatic cases, hospitalizations, ICU admissions, and deaths, respectively. f, Uniform vaccination strategy. Shaded area refers to vaccine administration to the general populations. Lines refers to the vaccinated proportions including essential workers. Keys and labels apply to all panels.

Figure 2

Risk incidences for different prioritization strategies and the scenario with no vaccination (0.14% rollout speed, $R = 1.5$). a, Number of averted infections under the scenario with no vaccination, uniform vaccination strategy, and the five optimal prioritization strategies we identified. b-e, As panel a, but for the number of symptomatic cases, hospitalizations, ICUs, and deaths, respectively. f, Averted proportion of infections, symptomatic cases, hospitalizations, ICUs, and deaths for the six vaccination strategies as compared to the scenario with no vaccination. Keys apply to all panels.

Figure 3

Effectiveness of alternative vaccination strategies under alternative assumptions. a, Averted proportion of deaths for different strategies (uniform vaccination and the five optimal strategies) as compared to no vaccination for different values of the daily vaccine supply. b, As a, but for different values of the vaccine efficacy. c, As a, but assuming that the vaccine may have a lower efficacy in preventing the infection (namely 60% and 70%) than in preventing the disease (which is kept fixed at 80%). d, As a, but considering possible vaccine hesitancy. In particular, we consider three alternative scenarios: i) “Whole population”, i.e., all individuals are willing to accept the vaccine; ii) “Chinese survey”, i.e., on average 83% of the population is willing to accept the vaccine as estimated in a survey conducted on the Chinese population 15 (age-specific estimates reported in Extended Data Table 2); iii) “Global survey”, i.e., on average 61% of the population is willing to accept the vaccine as estimated in a survey at the global level 16. e, As a, but for different values of the reproduction number. Keys and labels apply to all panels. Results for other risk metrics are similar and displayed in Extended Data Fig.8.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryv21.docx](#)