Model-informed COVID-19 vaccine prioritization strategies by age and serostatus

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Limited initial supply of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine raises the question of how to prioritize available doses. We used a mathematical model to compare five age-stratified prioritization strategies. A highly effective transmission-blocking vaccine prioritized to adults ages 20 to 49 years minimized cumulative incidence, but mortality and years of life lost were minimized in most scenarios when the vaccine was prioritized to adults greater than 60 years old. Use of individual-level serological tests to redirect doses to seronegative individuals improved the marginal impact of each dose while potentially reducing existing inequities in COVID-19 impact. Although maximum impact prioritization strategies were broadly consistent across countries, transmission rates, vaccine rollout speeds, and estimates of naturally acquired immunity, this framework can be used to compare impacts of prioritization strategies across contexts.

Evaluation of vaccine prioritization strategies

We evaluated the impact of vaccine prioritization strategies using an age-stratified SEIR model (susceptible, exposed, infectious, recovered) because age has been shown to be an important correlate of susceptibility (12–14), seroprevalence (12, 15), severity (16–18), and mortality (19, 20). This model includes an age-dependent contact matrix, susceptibility to infection, and infection fatality rate (IFR), allowing us to estimate cumulative incidence of SARS-CoV-2 infections, mortality due to infection, and years of life lost (YLL) by means of forward simulations of 1 year of disease dynamics. Cumulative incidence, mortality, and YLL were then used as outcomes by which to compare vaccine prioritization strategies. These comparisons may be explored by using accompanying open-source and interactive calculation tools that accompany this study (21).

We first examined the impact of five vaccine prioritization strategies for a hypothetical infection- and transmission-blocking vaccine of varying efficacy. The strategies prioritized vaccines to (i) children and teenagers, (ii) adults between ages 20 and 49 years, (iii) adults 20 years or older, (iv) adults 60 years or older, and (v) all individuals (Fig. 1A). In all strategies, once the prioritized population was vaccinated, vaccines were allocated irrespective of age—that is, in proportion to their numbers in the population. To incorporate vaccine hesitancy, at most 70% of any age group was eligible to be vaccinated (22).

We measured reductions in cumulative incidence, mortality, and YLL achieved by each strategy, varying the vaccine supply between 1 and 50% of the total population, under two scenarios. In scenario 1, vaccines were administered to 0.2% of the population per day until supply was exhausted, with basic reproduction number \( R_0 = 1.15 \), representing highly effective transmission-blocking vaccines, showing that even those with lower efficacy for direct protection may be more valuable if they also provide better indirect protection by blocking transmission (8). Prioritization of transmission-blocking vaccines can also be dynamically updated on the basis of the current state of the epidemic, shifting prioritization to avoid decreasing marginal returns (9). These efforts to prioritize and optimize doses complement other work showing that under different vaccine efficacy and durability of immunity, the economic and health benefits of COVID-19 vaccines will be large in the short and medium terms (10). The problem of vaccine prioritization also parallels the more general problem of optimal resource allocation to reduce transmission, such as with masks (11).

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mitigated spread during vaccine rollout. In scenario 2, vaccines were administered to 0.2% of the population per day until supply was exhausted, but with $R_0 = 1.5$, representing substantial viral growth during vaccine rollout (example model outputs are provided in Fig. 1). Results for additional scenarios in which vaccines were administered before transmission began are described in the supplementary materials, supplementary text, corresponding to countries without ongoing community spread such as South Korea and New Zealand. We considered two ways in which vaccine efficacy ($\text{ve}$) could be below 100%: an all-or-nothing vaccine, in which the vaccine provides perfect protection to a fraction $\text{ve}$ of individuals who receive it, or as a leaky vaccine, in which all vaccinated individuals have reduced probability $\text{ve}$ of infection after vaccination (supplementary materials, materials and methods).

Of the five strategies, direct vaccination of adults older than 60 years of age (60+) always reduced mortality and YLL more than the alternative strategies when transmission was high [$R_0 = 1.5$, scenario 2, 90% efficacy (Fig. 1); 30 to 100% efficacy (fig. S5)]. For lower transmission ($R_0 = 1.15$, scenario 1), vaccination of adults aged 20 to 49 years reduced mortality and YLL more than the alternative strategies, but differences between prioritization of adults aged 20 to 49 years, 20+ years, and 60+ years were small for vaccine supplies above 25% (Fig. 1 and fig. S5). Prioritizing adults aged 20 to 49 years minimized cumulative incidence in both scenarios for all vaccine efficacies (Fig. 1 and fig. S5). Prioritizing adults aged 20 to 49 years also minimized cumulative incidence in both scenarios under alternative rollout speeds (0.05 to 1% vaccinated per day) (fig. S6). When rollout speeds were at least 0.3% per day and vaccine supply covered at least 25% of the population, the mortality-minimizing strategy shifted from prioritization of ages 20 to 49 years to adults aged 20+ or 60+ years for scenario 1; when rollout speeds were at least 0.75% per day and covered at least 24% of the population, the mortality-minimizing strategy shifted from prioritization of adults aged 60+ years to adults aged 20+ or 20 to 49 years for scenario 2 (fig. S6).

Findings for mortality and YLL were only slightly changed by modeling vaccine efficacy as all or nothing (fig. S5) or leaky (fig. S7).

**Impact of transmission rates, age demographics, and contact structure**

To evaluate the impact of transmission rates on the strategy that most reduced mortality, we varied the basic reproductive number $R_0$ from 1.1 to 2.0 when considering a hypothetical infection- and transmission-blocking vaccine with 90% vaccine efficacy. We found that prioritizing adults aged 60+ years remained the best way to reduce mortality and YLL for $R_0 \geq 1.3$, but prioritizing adults aged 20 to 49 years was superior for $R_0 \leq 1.2$ (Fig. 2, A and B, and fig. S8). Prioritizing adults aged 20 to 49 years minimized infections for all values of $R_0$ investigated (fig. S8).

To determine whether our findings were robust across countries, we analyzed the ranking of prioritization strategies for populations with the age distributions and modeled contact structures of the United States, Belgium, Brazil, China, India, Poland, South Africa, and Spain. Across these countries, direct vaccination of adults aged 60+ years minimized mortality for all levels of vaccine supply when transmission was high ($R_0 = 1.5$, scenario 2) (Fig. 2E) but in only some cases when transmission was lower ($R_0 = 1.15$, rollout 0.2% per day, scenario 1) (Fig. 2D). Decreasing rollout speed from 0.2% to 0.1% per day caused prioritization of adults aged 60+ years to be favored in additional scenarios (Fig. 2C). Across countries, vaccination of adults aged 20 to 49 years nearly always minimized infections, and vaccination of adults aged 60+ years nearly always minimized YLL for scenario 2, but no clear ranking of strategies emerged consistently to minimize YLL in scenario 1 (fig. S9).

**Vaccines with imperfect transmission-blocking effects**

We also considered whether the rankings of prioritization strategies to minimize mortality would change if a vaccine were to block COVID-19 symptoms and mortality with 90% efficacy but with variable impact on SARS-CoV-2 infection and transmission. We found that direct vaccination of adults aged 60+ years would still be the best strategy when transmission was high, but in countries with lower transmission rates, the strategy that minimized infections would switch to prioritizing adults aged 20 to 49 years.
for varying values of \((A)\) and \((B)\) the basic reproductive number \(R_0\), and across nine countries, for vaccine supplies between 1 and 50% of the total population, for an all-or-nothing and transmission-blocking vaccine, 90% vaccine efficacy. \((A)\) and \((B)\) Contact patterns and demographics of nine countries, for vaccine supplies between 1 and 50% of transmission was blocked in scenario 2 (supplementary text and fig. S10).

**Fig. 2. Mortality-minimizing vaccine prioritization strategies across reproductive numbers \(R_0\) and countries.** (A to E) Heatmaps show the prioritization strategies that result in maximum reduction of mortality for varying values of \((A)\) and \((B)\) the basic reproductive number \(R_0\) and \((C), (D), \) and \((E)\) across nine countries, for vaccine supplies between 1 and 50% of the total population, for an all-or-nothing and transmission-blocking vaccine, 90% vaccine efficacy. \((A)\) and \((B)\) Contact patterns and demographics of the United States (38, S3). \((C), (D), \) and \((E)\) Contact patterns and demographics of POL, Poland; ZAF, South Africa; CHN, China; BRA, Brazil; ZWE, Zimbabwe; ESP, Spain; IND, India; USA, United States of America; and BEL, Belgium, with \(R_0\) and rollout speeds as indicated.

minimized mortality for all vaccine supplies and transmission-blocking effects under scenario 2 and for all vaccine supplies when up to 50% of transmission was blocked in scenario 1 (supplementary text and fig. S10).

**Variation in vaccine efficacy by age**

COVID-19 vaccines may not be equally effective across age groups in preventing infection or disease, a phenomenon known to affect influenza vaccines (23–26). To understand the impact of age-dependent COVID-19 vaccine efficacy, we incorporated a hypothetical linear decrease from a baseline efficacy of 90% for those younger than 60 years to 50% in those 80 years and older (Fig. 3). As expected, this diminished the benefits of any prioritization strategy that included older adults. For example, strategies that prioritize adults aged 20 to 49 years were unaffected by decreased efficacy among adults aged 60+ years, whereas strategies prioritizing adults aged 60+ years were markedly diminished (Fig. 3). Despite these effects, prioritization of adults aged 60+ years remained superior to the alternative strategies to minimize mortality in scenario 2.

To test whether more substantial age-dependent vaccine effects would change which strategy minimized mortality in scenario 2, we varied the onset age of age-dependent decreases in efficacy, the extent to which it decreased, and the baseline efficacy from which it decreased. We found that as long as the age at which efficacy began to decrease was 70 years or older and vaccine efficacy among adults aged 80+ years was at least 25%, prioritizing adults aged 60+ years remained superior in the majority of parameter combinations. This finding was robust to whether the vaccine was modeled as leaky versus all or nothing, but we observed considerable variation from country to country (fig. S11).

**Incorporation of population seroprevalence and individual serological testing**

Because of early indications that naturally acquired antibodies correlate with protection from reinfection (27), seroprevalence will affect vaccine prioritization in two ways. First, depending on the magnitude and age distribution of seroprevalence at the time of vaccine distribution, the ranking of strategies could change. Second, distributing vaccines to seropositive individuals would reduce the marginal benefit of vaccination per dose.

To investigate the impact of vaccinating midepidemic while using serology to target the vaccine to seronegative individuals, we included age-stratified seroprevalence estimates in our model by moving the data-specified proportion of seropositive individuals from susceptible to recovered status. We then simulated two approaches to vaccine distribution. In the first, vaccines were distributed according to the five prioritization strategies introduced above, regardless of any individual’s serostatus. In the second, vaccines were distributed with a serological test, so that individuals with a positive serological test would not be vaccinated, allowing their dose to be given to someone else in their age group.

We included age-stratified seroprevalence estimates from New York City [August 2020; overall seroprevalence 26.9% (29)] and demographics and age-contact structure from the United States in evaluations of the previous five prioritization strategies. For this analysis, we focused on scenario 2 (0.2% rollout per day, \(R_0 = 1.5\) inclusive of seropositives) and found that the ranking of strategies to minimize incidence, mortality, and YLL remained unchanged: Prioritizing adults aged 60+ years most reduced mortality, and prioritizing adults aged 20 to 49 years most reduced incidence, regardless of whether vaccination was limited to seronegative individuals (Fig. 4).

These rankings were unchanged when we used lower or higher age-stratified seroprevalence estimates to test the consistency of results [Connecticut, July 2020, overall seroprevalence 3.1% (29) and synthetic, overall seroprevalence 39.5% (figs. S12 and S13)]. Despite lowered sensitivity to detect past exposure due to seroreversion (30, 31), preferentially vaccinating seronegative individuals yielded large additional reductions in cumulative incidence and mortality in locations with higher seroprevalence (Fig. 4 and fig. S13) and modest reductions in locations with low seroprevalence (fig. S12). These results remained unchanged when statistical uncertainty, because of sample size and imperfect test sensitivity and specificity, was incorporated into the model (32).

**Discussion**

This study demonstrated the use of an age-stratified modeling approach to evaluate and compare vaccine prioritization strategies for SARS-CoV-2. After accounting for country-specific age structure, age-contact structure, infection fatality rates, and seroprevalence, as well as the age-varying efficacy of a hypothetical vaccine, we found that across countries, those aged 60 years and older should be prioritized to minimize deaths, assuming a return to high contact rates and prepandemic behavior during or after vaccine rollout. This recommendation is robust because of the dramatic differences in IFR by age. Our model identified three general regimes in which prioritizing adults aged 20 to 49 years would provide greater mortality benefits than would prioritizing older adults. One such regime was in the presence of substantial transmission-mitigating interventions \((R_0 = 1.15)\) and a vaccine with 80% or higher transmission-blocking effects. A second regime was characterized by substantial transmission-mitigating interventions \((R_0 = 1.15)\) and either rollout speeds of at most 0.2%
Conclusions. The ranking of infection-minimizing prioritization strategies is a function of vaccine properties, vaccine efficacy distributions, and the epidemiological characteristics of a disease. As we demonstrated for COVID-19, there can be dramatic differences in the value of prioritization approaches depending on vaccine efficacy, the rate of vaccination, and the characteristics of the population. Our framework can be adapted to consider goals such as minimizing hospitalizations, intensive care unit occupancy, or economic costs. We demonstrated that there is value in pairing individual-level serological tests with vaccination, even when accounting for the uncertainties in seroprevalence estimates and seroreversion. The marginal gain in effective vaccine supply, relative to no serological testing, must be weighed against the challenges of serological testing before vaccination. Serostatus itself is an imperfect indicator of protection, and the relationship of prior infection, serostatus, and protection may change over time. Delays in serological test results would impair vaccine distribution, but partial seronegative-targeting effects might be worth the cost in the context of a vaccine with weak transmission-blocking properties.
be realized if those with past polymerase chain reaction (PCR)-confirmed infections voluntarily deprioritized their own vaccinations.

The best-performing strategies depend on assumptions about the extent of a population’s interactions. We used prepandemic contact matrices (38), reflecting the goal of a return to prepandemic routines once a vaccine is available, but more recent estimates of age-stratified contact rates could be valuable in modeling midpandemic scenarios (39, 40). Whether prepandemic or midpandemic contact estimates are representative of contact patterns during vaccine rollout remains unknown and may vary on the basis of numerous social, political, and other factors. The scenarios modeled here did not incorporate explicit nonpharmaceutical interventions, which might persist if vaccination coverage is incomplete, but are implicitly represented in scenario 1 ($R_0 = 1.15$).

Our study relies on estimates of other epidemiological parameters. In local contexts, these include age-structured seroprevalence and IFR, which vary by population (19, 20, 41). Globally, key parameters include the degree to which antibodies protect against reinfection or severity of disease and relative infectiousness by age. From vaccine trials, we also need evidence of efficacy in groups vulnerable to severe outcomes, including the elderly. Additionally, it will be critical to measure whether a vaccine that protects against symptomatic disease also blocks infection and transmission of SARS-CoV-2 (42).

The role of children during this pandemic has been unclear. Under our assumptions about susceptibility by age, children are not the major drivers of transmission in communities, which is consistent with emerging evidence (12). Thus, our results differ from the optimal distribution for influenza vaccines, which prioritize school-age children and adults aged 30 to 39 years (5). However, the relative susceptibility and infectiousness of SARS-CoV-2 by age remain uncertain. Although it is unlikely that susceptibility to infection conditional on exposure is constant across age groups (12), we ran our model to test the sensitivity of this parameter. Under the scenario of constant susceptibility by age, vaccinating those under 20 years of age has a greater impact on reducing cumulative cases than vaccinating those aged 20 to 49 years (figs. SI4 and 15).

Our study is subject to a number of limitations. First, our evaluation strategy focuses on a single country at a time, rather than on between-population allocation (43). Second, we only consider variation in disease severity by age. However, other factors correlate with disease outcomes, such as treatment and health care access and comorbidities, which may correlate with factors such as rural versus urban location, socioeconomic status, sex (44, 45), and race and ethnicity (46), which are not accounted for in this study. Inclusion of these factors in a model would be possible, but only with statistically sound measurements of their stratified infection risk, contact rates, and disease outcomes. Even in the case of age stratification, contact surveys have typically not surveyed those 80 years and older, yet it is this population that suffers dramatically more severe COVID-19 disease and higher infection fatality rates. We extrapolated contact matrices to those older than 80, but direct measurements would be superior. Last, our study focused on guiding strategy rather than providing more detailed forecasting or estimates (10). As such, we have not made detailed parameter fits to time series of cases or deaths but rather have used epidemiologic models to identify robust strategies across a range of transmission scenarios.

Our study also considers variation in disease risk only by age, through age-structured contact matrices and age-specific susceptibility, whereas many discussions around COVID-19 vaccine distribution have thus far focused on prioritizing health care or essential workers (47, 48). Contact rates, and thus infection potential, vary greatly not only by occupation and age but also by living arrangement (such as congregate settings or dormitories), neighborhood and mobility (49–52), and whether the population has a coordinated and fundamentally effective policy to control the virus. With a better understanding of population structure during the pandemic, and risk factors of COVID-19, these limitations could be addressed. Meanwhile, the robust findings in favor of prioritizing those age groups with the highest IFR to minimize mortality could potentially be extended to prioritize those with comorbidities that predispose them to a high IFR because the strategy of prioritizing the older age groups depends on direct rather than indirect protection.

Vaccine prioritization is not solely a question of science but a question of ethics as well. Hallmarks of the COVID-19 pandemic, as with other global diseases, are inequalities and disparities. Although these modeling efforts focus on age and minimizing incidence and death within a simply structured population, other considerations are crucial, from equity in allocation between countries to disparities in access to health care, including vaccination, that vary by neighborhood. Thus, the model’s simplistic representation of vulnerability (age) should be augmented by better information on the correlates of infection risk and severity. Fair vaccine prioritization should avoid further harming disadvantaged populations. We suggest that after distribution, pairing serological testing with vaccination in the hardest-hit populations is one possible equitable way to extend the benefits of vaccination in settings where vaccination might otherwise not be deemed cost effective.
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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S15
Tables S1 and S2
References (55–57)
MDAR Reproducibility Checklist

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Vaccine prioritization

There is likely to be high demand for the limited supplies of vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), so how should vaccine distribution be prioritized? Bubar et al. modeled across countries how uncertainty about a vaccine’s characteristics affects prioritization strategies for reducing deaths and transmission (see the Perspective by Fitzpatrick and Galvani). In the model, vaccine efficacy and its ability to reduce disease and/or block transmission was accounted for in relation to age-related variations in susceptibility, fatality rates, and immune decline. In almost all circumstances, reducing fatalities required distributing the vaccine to those who are most at risk of death, usually persons over 60 years of age and those with comorbidities. If a vaccine is leaky or poorly efficacious in older adults, then priority could be given to younger age groups. To increase the available doses, further priority should be given to seronegative individuals.

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