



Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study

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ABSTRACT OBJECTIVE

To estimate population health outcomes with delayed second dose versus standard schedule of SARS-CoV-2 mRNA vaccination.

DESIGN

Simulation agent based modeling study.

SETTING

Simulated population based on real world US county.

PARTICIPANTS

The simulation included 100 000 agents, with a representative distribution of demographics and occupations. Networks of contacts were established to simulate potentially infectious interactions through occupation, household, and random interactions.

INTERVENTIONS

Simulation of standard covid-19 vaccination versus delayed second dose vaccination prioritizing the first dose. The simulation runs were replicated 10 times. Sensitivity analyses included first dose vaccine efficacy of 50%, 60%, 70%, 80%, and 90% after day 12 post-vaccination; vaccination rate of 0.1%, 0.3%, and 1% of population per day; assuming the vaccine prevents only symptoms but not asymptomatic spread (that is, non-sterilizing vaccine); and an alternative

vaccination strategy that implements delayed second dose for people under 65 years of age, but not until all those above this age have been vaccinated.

MAIN OUTCOME MEASURES

Cumulative covid-19 mortality, cumulative SARS-CoV-2 infections, and cumulative hospital admissions due to covid-19 over 180 days.

RESULTS

Over all simulation replications, the median cumulative mortality per 100 000 for standard dosing versus delayed second dose was 226 v 179, 233 v 207, and 235 v 236 for 90%, 80%, and 70% first dose efficacy, respectively. The delayed second dose strategy was optimal for vaccine efficacies at or above 80% and vaccination rates at or below 0.3% of the population per day, under both sterilizing and non-sterilizing vaccine assumptions, resulting in absolute cumulative mortality reductions between 26 and 47 per 100 000. The delayed second dose strategy for people under 65 performed consistently well under all vaccination rates tested.

CONCLUSIONS

A delayed second dose vaccination strategy, at least for people aged under 65, could result in reduced cumulative mortality under certain conditions.

Introduction

The global public health response to the covid-19 pandemic has resulted in the massive investment of resources into the production of an effective vaccine.¹ This unparalleled approach has led to the development of multiple effective vaccines in record time. The first two vaccines to be approved in the US, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) both use an mRNA encoding the SARS-CoV-2 spike protein. These mRNA vaccines are both two dose regimens, with the second dose administered 21 or 28 days after the initial dose.^{2,3} Viral vector vaccines have also been developed: ChAdOx1 (Oxford-AstraZeneca) received approval for use in most of Europe and the UK,⁴ and Ad.26.COV2.S (Johnson & Johnson) was approved in the US.⁵

Despite relatively high vaccination rates in the US and UK, even developed countries such as Germany, Spain, and France have vaccinated less than 10% of their population, and most countries worldwide have vaccinated less than 1% of their populations, with vaccination rates in these countries often well below 0.5% of the population per day.^{6,7} Even in the

WHAT IS ALREADY KNOWN ON THIS TOPIC

BNT162b2 (Pfizer) and mRNA-1273 (Moderna) covid-19 vaccines in a standard two dose regimen are highly effective at preventing symptomatic infections and mortality over 180 days

Despite the development of effective vaccines, the disease burden of covid-19 remains high, as immunity worldwide remains low, partly owing to low vaccination rates globally

The longer taken to effectively vaccinate the global population, the greater the likely risk of vaccine resistant strains developing

WHAT THIS STUDY ADDS

In certain conditions, a beneficial trade-off can be made of lower vaccine efficacy (single dose) but higher population vaccination coverage and therefore population-wide covid-19 immunity

Delaying the second dose could result in up to 20% lower mortality for vaccination rates of 0.1% to 0.3% of the population per day and a one dose vaccine efficacy of 80% or higher.

Delaying the second dose but prioritizing it for people aged ≥65 can result in lower mortality rates compared with the standard two dose strategy, even at vaccination rates up to 1% of the population per day

US, the vaccination rate has just reached 1% of the population per day. The result has been a continued high burden of SARS-CoV-2 infection worldwide and increasing pressure to increase vaccination rates in most countries. The emergence of new variant strains such as B.1.1.7 in the UK, B.135 in South Africa, and P.1 in Brazil has only increased the pressure to achieve global immunity as quickly as possible.⁸⁻¹² As the BNT162b2 and mRNA-1273 vaccines, and other two dose vaccines, represent one of the largest supplies of covid-19 vaccines globally, optimizing distribution and administration has become a focus as demand has outstripped supply in most countries.¹³

Multiple public health authorities have proposed prioritizing single dose vaccination for as many people as possible, even if this means delaying a second dose beyond the studied 21 or 28 day time frame.¹⁴⁻¹⁶ The justification for this relies on the assumption that meaningful protection against covid-19 can be achieved after a single dose of vaccine, a point that is the subject of intense debate. People taking a conservative interpretation of available data argue that a delayed second dose regimen was not explicitly studied in clinical trials, and nor was the possibility of asymptomatic infectious spread, so public health agencies should use only the regimens explicitly studied to be certain of the results they will achieve. Others more willing to extrapolate from clinical trial results on the basis of previous immunologic research argue that meaningful protection against covid-19 is probably achieved after one dose of vaccine.

Recent calculations using clinical trial data have estimated the efficacy of the first dose for the Pfizer and Moderna vaccines to be 92.6% and 92.1%, respectively,² and the Centers for Disease Control and Prevention (CDC) estimates a single dose vaccine efficacy of 80%.¹⁷ Of note, this is higher than the efficacy of Johnson & Johnson's one dose regimen, which is estimated at 66%.⁵ This has led some authors to suggest a delayed second dose strategy for BNT162b2 and mRNA-1273 vaccines, given their high first dose efficacy and in hopes of both increasing vaccination rate and reducing cumulative mortality.¹⁴⁻¹⁸ However, the risk of infection depends on complex network dynamics, and the case fatality rate can be up to two orders of magnitude higher for different demographic groups.¹⁹ Estimating the impact of different vaccination strategies requires the use of methods that can take these non-linear effects into consideration.

Therefore, we used agent based modeling to measure the relative impact of delayed second dose vaccine policies on infections, hospital admissions, and mortality compared with the current on-schedule two dose regimen. To account for uncertainty, we used sensitivity analysis and examined multiple different scenarios such as whether the vaccine offers sterilizing, versus only symptomatic, immunity. We also examined a novel dosing strategy in which a delayed second dose regimen is used for people younger than 65 years old, but not before fully vaccinating older people.

Methods

We extended an open source agent based model from the literature to model the impact of the delayed second dose versus standard dosing vaccination strategies on SARS-CoV-2 infections and covid-19 related hospital admissions and deaths in a population with 100 000 agents over a time period of six months.²⁰ The results were aggregated over 10 runs of the simulation. The original open source model was limited to modeling spread of covid-19.²⁰ Our extension improved the processing speed by using matrix computation and added the possibility of implementing different vaccination policies. We used Python 3.7; the full list of packages can be found in the supplementary material (appendix 1).

In the model, agents interact with each other in three types of networks: an occupation network, a family network, and a random encounter network. Each encounter between an infectious and a susceptible agent has a probability of transmission of infection. Once infected, agents have a certain probability of having asymptomatic infection; if they have symptoms, they have a pre-symptomatic period, followed by a probability distribution of symptom severity and a subsequent probability distribution of death. Our assumptions about disease progression, transmission characteristics, and family, occupation, and random network interactions are the same as in the original agent based modeling and are available in our supplementary materials (appendix 1).²⁰

In addition, we explicitly modeled the confirmation of infections with polymerase chain reaction testing and quarantining of known infected agents with imperfect compliance over time. We report results on relevant outcomes (deaths, cumulative infections, and fraction immune) averaged over 10 replications of our agent based modeling simulation. To simulate a natural pattern of infection at the point vaccinations begin, we started our simulation with 10 agents infected and ran the simulation for 20 days before starting vaccinations, which corresponds to a cumulative infection rate of 1%, similar to the one in the US, UK, and most of Europe when vaccinations were started. We then ran the simulation for a total of 180 days, using discrete time by day. In all our vaccination strategies, we started administering vaccines on the basis of age, starting with people over 75, then those over 65, and so on. For further information on the agent based modeling and the exact vaccine prioritization under each strategy considered, please see the supplementary materials (appendix 1).

Vaccine and infection characteristics

We did four analyses to derive insights about four different variations in model parameters. In all our analyses, vaccines were administered in an age prioritized fashion, with the oldest individuals receiving their vaccines first, regardless of the vaccine regimen examined. For comparisons of our vaccine regimens and their prioritization, as well as estimates of time to fully vaccinate each age group, see the

supplementary materials (appendix 3). Sections 1-3 assume that covid-19 vaccines prevent both symptoms of infection and transmission of virus (sterilizing vaccine), whereas section 4 examines the possibility that vaccines prevent only symptoms and not asymptomatic infection and spread (non-sterilizing vaccine). All simulations assume an efficacy of two vaccine doses of 95%. A simulation using a 90% estimate for the vaccine efficacy after two doses can be found in the supplementary material (appendix 2).

Our first analysis sought to understand potential risks or benefits of delayed second dose versus standard dosing strategies under varying estimates of single dose efficacy. In this analysis, we examined outcomes of deaths, hospital admissions, and infections. To model single dose efficacy, we assumed no protection against covid-19 infection for the first 12 days after the initial dose and thereafter a protection of 90%, 80%, 70%, 60%, or 50% that persists for the remainder of our 180 day simulation. We selected these estimates on the basis of examination of the BNT162b2 trial results, which showed that between days 1 and 11 the number of cases was similar between the vaccinated and unvaccinated groups. Between days 12 and 21, four infections occurred in the treatment arm and 30 in the control arm. This suggests a vaccine efficacy from a single dose of 87%. The CDC estimated a single dose efficacy of either BNT162b2 or mRNA-1273 to be 80%.¹⁷ Assuming that cases in the vaccine and control groups follow two different Poisson random distributions, on the basis of the trial data the 95% confidence interval for the rate ratio between them (which corresponds to the vaccine effectiveness) is 66% to 96%. We set the vaccination rate to doses per day of 0.3% of the population.

Our second analysis examined the effect of varying vaccination rates on total deaths by using the same two dosing regimens as our first analysis and a fixed single dose efficacy estimate of 80%, which we considered relatively conservative given our point estimate of 87%. For this analysis, we used vaccination rates of 0.1%, 0.3%, and 1% doses administered per person per day. We used a broad range of vaccination rates because the vaccination rate in the US is in the range of 0.5-1% per day as of April 2021 but is much less than 0.5% per day for most other countries in the world.^{6,7}

Our third analysis examined the utility of an additional age-split vaccination strategy, across the vaccination rates used in our second analysis, for preventing death. This additional vaccination strategy proposed using a delayed second dose strategy in people under 65 years old, but not before fully vaccinating those 65 and above. We proposed this strategy on the basis that older people have the highest mortality risk, so providing them with maximal vaccine protection is likely to avert the most deaths.

We also did a sensitivity analysis to consider the possibility that the vaccine prevents only symptomatic disease and not asymptomatic infection and spread. In this analysis, we replicated the method of our first

analysis, using different single dose efficacy rates and a fixed administration rate of 0.3% of the population per day, but we annulled the assumption that the vaccine prevents asymptomatic spread.

We display our results by using time series line plots over our 180 day modeling period, with a central line corresponding to the median value of our 10 runs for a given day and a shaded band corresponding to the 25-75% centile of values for a given day across all runs.

Patient and public involvement

In the context of the institutional review board and ethics review of our paper, we used only publicly available data, and there was no patient involvement that was directed by the investigators.

Results

We present our results in four sections. Section 1 examines the effect of different estimates of single dose efficacy on outcomes. Section 2 describes the effects of different rates of vaccination. Section 3 examines the effect of a hypothetical vaccine regimen in which second doses are delayed only for those under age 65. Section 4 replicates the analysis of section 1 with the modification that the vaccine prevents only symptoms and not asymptomatic spread.

Section 1: effect of standard versus delayed second dose regimens using various efficacy estimates, with intermediate vaccination rate

Figure 1 shows the results for cumulative mortality comparing the standard vaccination strategy and a delayed second dose vaccination strategy with four different values of first dose efficacy: 60%, 70%, 80%, and 90%, all with an intermediate vaccination rate of 0.3% (see appendix 4 in supplementary materials for additional first dose efficacy of 50%). Total mortality per 100 000 for standard versus delayed second dose was 226 versus 179, 233 versus 207, and 235 versus 236 for 90%, 80%, and 70% first dose efficacy, respectively. These results suggest that higher first dose efficacy estimates favor delaying the second dose and that for a first dose efficacy of 70% or below, no meaningful difference is apparent between the standard and delayed second dose strategy.

Figure 2 shows the total number of infections and the number of hospital admissions for the same efficacy estimates and vaccination regimens. The cumulative number of infections per 100 000 for standard versus delayed second dose was 69 577 versus 64 220, 69 350 versus 64 859, and 69 670 versus 65 891 for 90%, 80%, and 70% first dose efficacy, respectively. Thus, the number of cumulative infections was similar between the two strategies in these three scenarios studied.

Section 2: effect of standard versus delayed second dose regimens using various vaccination rates, with single dose vaccine efficacy held constant at 80%

Figure 3 shows the cumulative mortality in three different vaccination rate scenarios in which 0.1%,

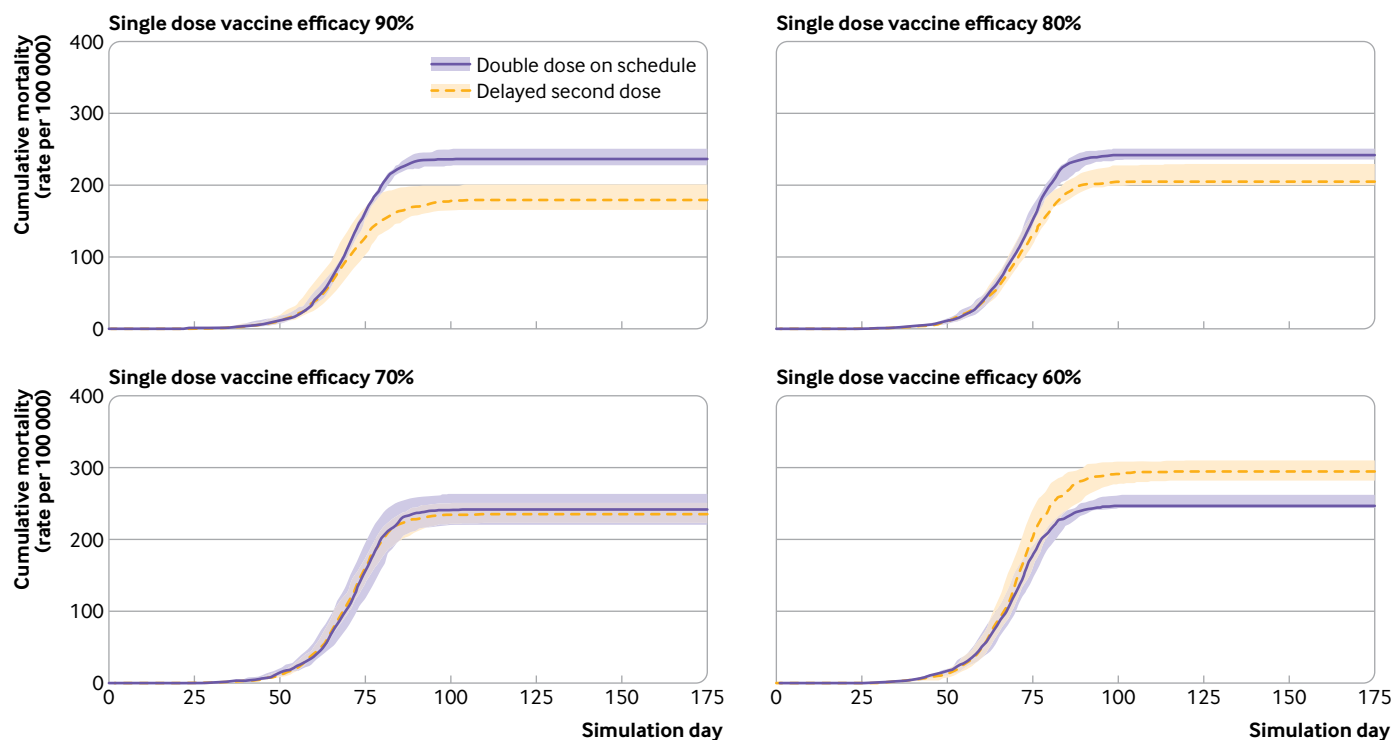


Fig 1 | Comparison of cumulative mortality for delayed second dose versus standard vaccination strategy under four different first dose effectiveness assumptions. Results are shown for a vaccination rate of 0.3% of the population per day. The total cumulative mortality on day 180 is lower for the delayed second dose scenario under the assumption that the first dose effectiveness is $\geq 80\%$

0.3%, or 1% of the population is vaccinated per day. These results suggest that at a single dose vaccine efficacy estimate of 80%, population mortality is lower when the second vaccine dose is delayed, except in scenarios of high vaccination rates (greater than 1%), higher than current rates in most countries.

The number of total deaths was lower for higher vaccination rates, with the optimal strategy switching at a value between 0.3% and 1%. Total estimated mortality per 100 000 for delayed versus standard second dose was 402 versus 442, 204 versus 241, and 85 versus 50 for vaccination rates of 0.1%, 0.3%, and 1%, respectively. This suggests that the delayed second dose strategy is optimal for vaccination rates at or below 0.3% population per day if the vaccine efficacy from one dose is 80% or greater.

Section 3: effects of additional age-split dosing strategy at different vaccination rates, with single dose vaccine efficacy held constant at 80%

Figure 4 explores the effect on cumulative mortality of an additional vaccination strategy that prioritizes second doses for people older than 65 years, across three different vaccination rates. The total number of deaths was lower for higher vaccination rates, as expected. This strategy, which we call “delay second dose except for 65+,” had lower cumulative mortality than the standard strategy for low and medium vaccination rates (0.1% and 0.3%) and a lower mortality than the delayed second dose strategy for high vaccination rates (1%).

The cumulative mortality rate for delayed versus standard versus delayed except for 65+ strategies was 402 versus 442 versus 394, 204 versus 241 versus 222, and 86 versus 50 versus 55. This suggests that the delayed second dose except for 65+ strategy is optimal or close to optimal assuming a conservative first dose efficacy of 80% and for vaccination rates at or below 1% population per day.

Section 4: effect of standard versus delayed second dose regimens using various efficacy estimates, with intermediate vaccination rate, assuming non-sterilizing vaccine

Figure 5 presents similar results to figure 1, but this time under the assumption that the vaccine prevents only symptoms and not spread of infection. Under this assumption, with a vaccination rate of 0.3% population per day, the estimated cumulative mortality for delayed versus standard second dose were 179 versus 226, 207 versus 233, and 235 versus 236 for a first dose effectiveness of 90%, 80%, and 70%, respectively. The delayed second dose strategy seems optimal or close to optimal for a one dose vaccine efficacy of at least 70%.

Discussion

Our study compared two covid-19 vaccination strategies that delayed the second dose versus the on-schedule two dose strategy that is being used for the BNT162b2 and mRNA-1273 vaccines. The results suggest that under specific conditions a decrease in cumulative mortality, infections, and hospital

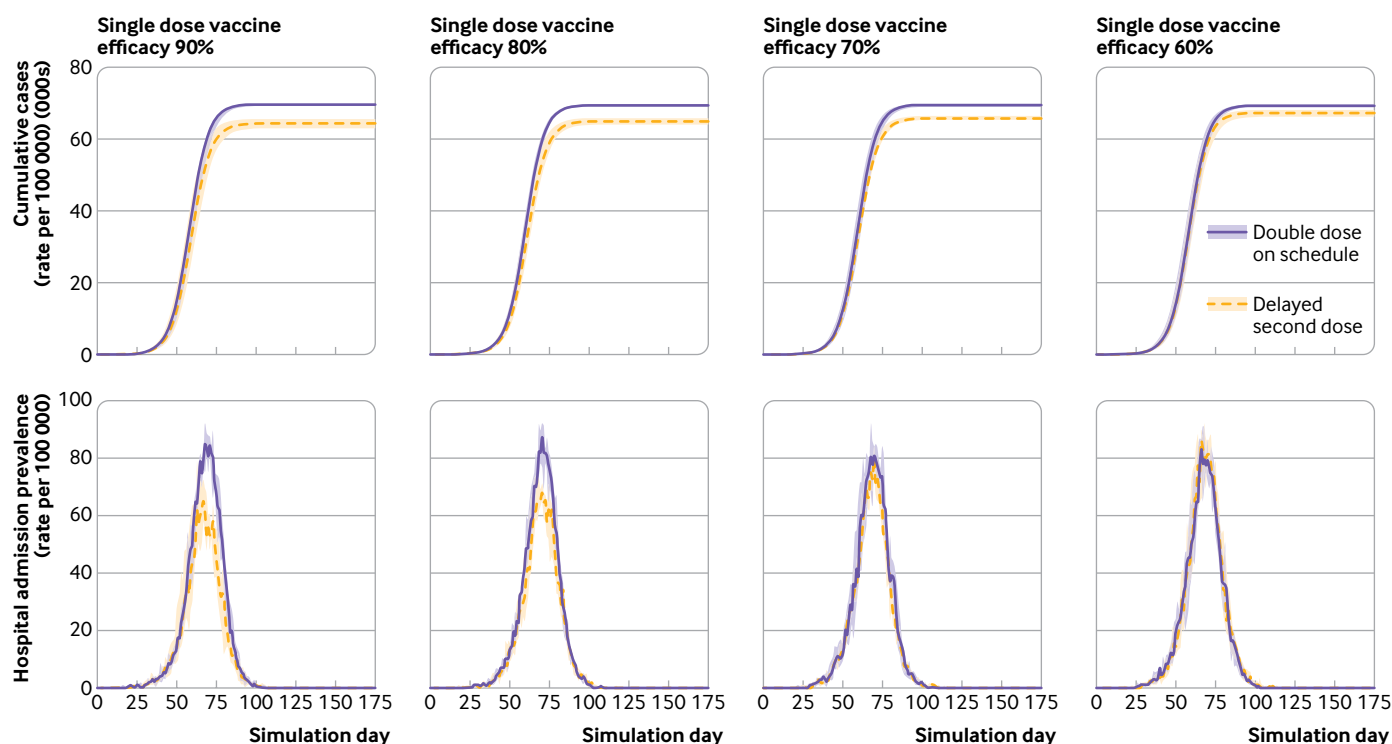


Fig 2 | Comparison of cumulative number of infections and hospital admissions for delayed second dose versus standard vaccination strategy under four different first dose effectiveness assumptions. Results are shown for a vaccination rate of 0.3% of the population per day. The cumulative number of infections on day 180 is lower for the delayed second dose approach. The peak hospital census becomes similar for both approaches as the efficacy of the first dose of vaccine is reduced

admissions can be achieved when the second dose of vaccine is delayed. This was most significant when the second dose was delayed in people below 65 years of age, with second doses still prioritized for those over 65. The conditions in which these benefits were observed included the first dose vaccine efficacy being above 70% and vaccination rates remaining below 1% of the population per day. These two conditions seem reasonable on the basis of the CDC's estimate of first dose vaccine efficacy being 80% and only a couple countries such as the US reaching a vaccination rate close to 1%.^{7 17 21 22} The timeframe of 180 days used in our study was thought to be important to policy makers who face the immediate challenge of increasing their population immunity by increasing vaccination rates but also balancing these decisions with the lack of data on sustained vaccine effectiveness beyond this period.

Our findings suggest that vaccination rate is an important factor in choosing a strategy. A delayed second dose strategy either in people below 65 years old or the entire population did not show a cumulative mortality benefit compared with an on-schedule two dose regimen when the vaccination rate was 1% of the population or above. At very low vaccination rates, the differences in delay strategy were not observed but favored delays in people aged 65 years and younger when rates were 0.3% to 1% of the population per day. Our findings also suggest that changes in cumulative mortality are larger than the corresponding decrease in the number of infections. For example, the relative

reduction in the cumulative number of infections for a vaccination rate of 0.3% and a first dose efficacy of 80% is around 6%, whereas the reduction for mortality is 11%.

These results may be broadly informative for covid-19 vaccine strategy. Other than a select few countries such as the US and UK, vaccination rates remain well below 1% of the population per day. The strategy in most locations continues to be a strict two dose schedule for either the BNT162b2 or mRNA-1273 vaccine. The vaccination rates used in our study ranged from 0.1% to 1%, which represents a large range of observed rates and is therefore likely to be useful for policy makers in various countries globally. With the continued large death toll from covid-19 and reports of mutant strains, each country is facing increasing urgency to vaccinate its population rapidly.²³ The multiple vaccines in phase III trials offer promise for increasing availability and therefore vaccination rates, but BNT162b2 and mRNA-1273 still account for a large portion of the world's covid-19 vaccine supply.^{13 24} The strategy of delaying the second dose has been an active discussion given its ability to rapidly increase covid-19 immunity in the population by increasing single dose vaccination rates, but empiric research to understand its implications was lacking.

Strengths and limitations of study

The primary strength of our study is the use of agent based modeling to forecast the effects of different

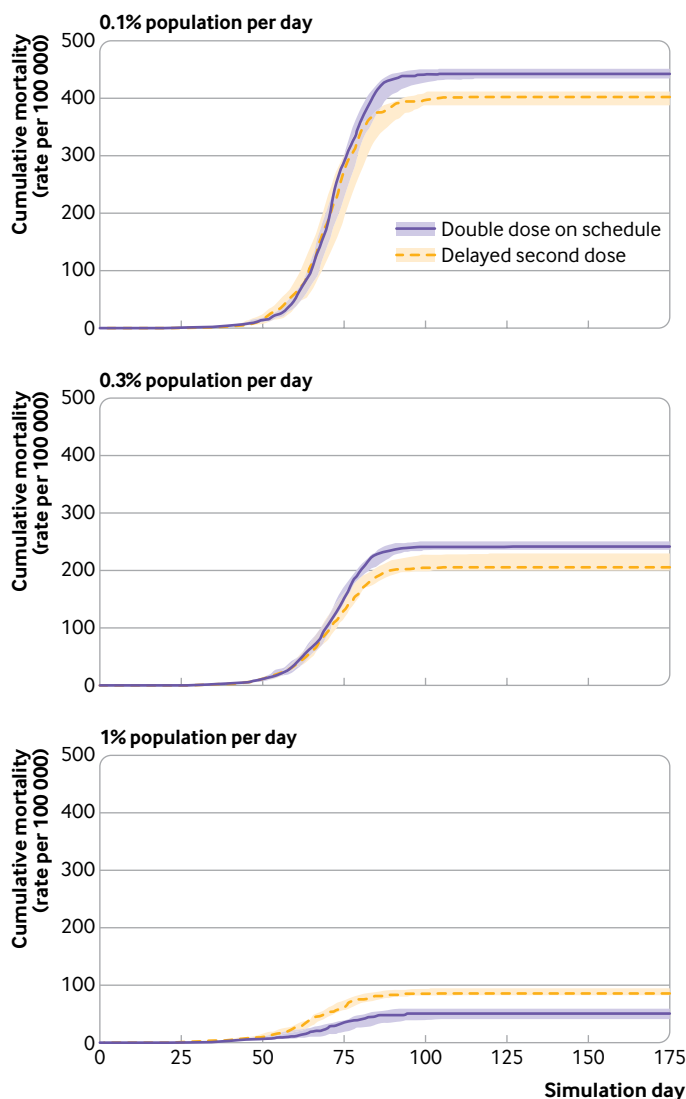


Fig 3 | Comparison of cumulative mortality for delayed second dose versus standard vaccination strategy under three different vaccination rate assumptions. The comparative effectiveness of double dose on schedule and delayed second dose strategies is dependent on vaccination rate. For a vaccination rate of 1% of the population per day, the standard strategy seems to be superior. For a vaccination rates of 0.3% or lower, the delayed second dose strategy results in a lower cumulative mortality

vaccine strategies across a timeframe that is useful to decision makers, while capturing the complexity of human interactions, which are critical in covid-19 transmission. Additionally, our results are strengthened by the use of 100 000 agents with age based demographics reflective of a sample population in the US, simulated over various human interaction networks reflecting real world behavior, and for a duration of 180 days.

Our model estimates that, without any intervention, the infection spreads to saturation within 180 days. This may be a pessimistic estimate if infection containment measures are put in place, as they already are in most countries. However, the key parameter is the relation between rate of vaccination and spread of infection, and this would likely not

affect the relative effectiveness of different vaccination strategies.

As a simulation study, our study has several limitations based on the assumptions used in the model. Firstly, we used a range of estimates for single dose vaccine efficacy based on the CDC's estimates and our own analysis, but the true efficacy may fall outside of those ranges. Secondly, we did not include immune decay in our model. Strong data support clinical effectiveness and lack of immune decay for the standard two dose regimen in a six month time period,^{17 25} but evidence on clinical effectiveness and immune decay for a single dose of either the BNT162b2 or mRNA-1273 vaccine in this same time interval is more limited. This is an important consideration, especially with the rise of variants and concern about possible increased susceptibility in people who have received only a single dose. Thirdly, several assumptions about the infectious spread (for example, the rate of contact between individuals in work, family, and random environments or the likelihood of infection during a random contact) were incorporated into the model, which seemed to match observations at the time the model was run, but these assumptions may not hold in all environments or if circumstances change. For example, receiving a vaccination dose may change individuals' behavior, affecting their risk of infection. Details about the parameters used can be found in the supplementary material. Finally, our study did not measure the effect of mutant strains of SARS-CoV-2 and various infectivity rates, or differences in behavior geographically, or the impact of other preventive measures such as digital exposure notification or availability and turnaround times of testing that vary between states and between countries.²⁶ We do not believe that these limitations would meaningfully change the relative differences measured between strategies in six months.

In the BNT162b2 and mRNA-1273 vaccine trials, the single dose vaccine efficacy was initially reported to be 52% and 80%, respectively. This was estimated in the small subset of participants who did not receive the second dose during the trial.^{2 3 27} As these were not defined study sub-groups, the advantages of randomization in preventing bias cannot be assumed to hold true, and unknown bias in these individuals is likely. This limitation cannot be overcome using simulation modeling. However, we believe that reasonable estimates can be made using the data available. The 52% vaccine efficacy in the Pfizer study was attributed to inclusion of the first 12 days after vaccination in the estimate. Including the first 12 days underestimates the true vaccine efficacy because sufficient time to develop immunity had not occurred. This is well established in vaccine and immunity literature and holds true regardless of vaccine type. In our study, we re-estimated the BNT162b2 vaccine efficacy to be approximately 87%, and this fits with the reported estimate for mRNA-1273. The CDC now estimates a single dose of either BNT162b2 or mRNA-1273 to be 80% effective.^{17 28} However, we remained conservative and did a sensitivity analysis for a range

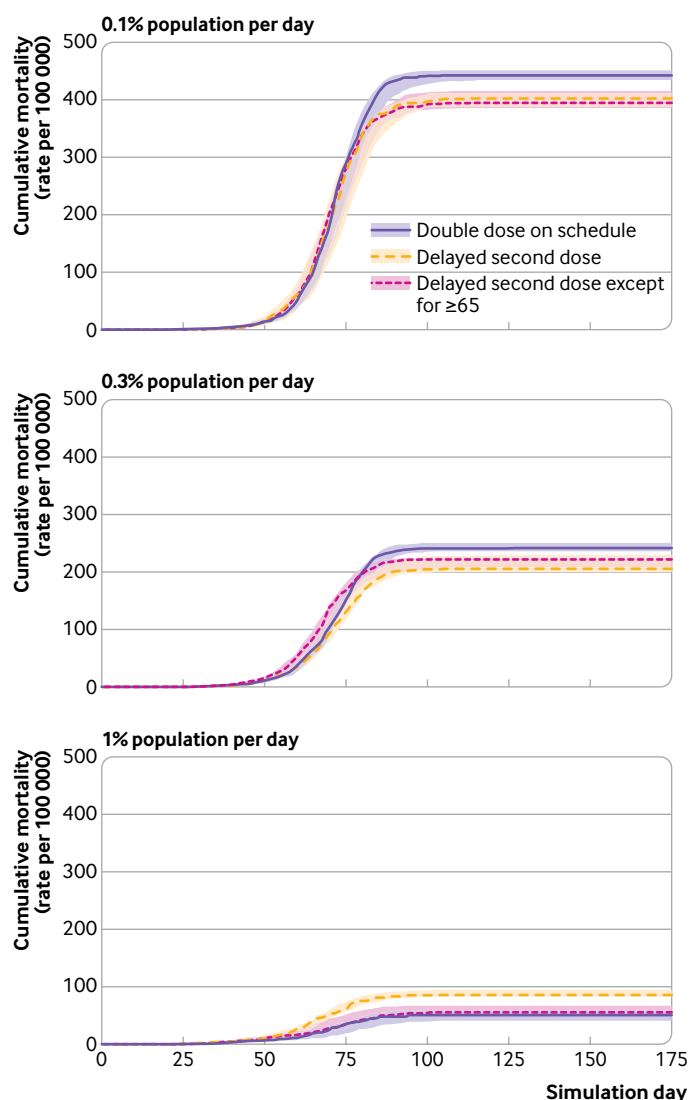


Fig 4 | Comparison of cumulative mortality for three different vaccination strategies (delayed second dose versus standard vaccination versus delayed second dose except for 65+) under three different vaccination rate assumptions. The “delayed second dose except for 65+” (pink line) strategy seems optimal or close to optimal under all three assumptions, making it a safe choice in the face of an uncertain future vaccination rate

of first dose vaccine efficacies from 50% to 90% to reduce this limitation in our study design.

To account for immune decay, we analyzed existing and growing literature on the BNT162b2 and mRNA-1273 vaccines. Both have been shown to be clinically effective without any significant evidence of immune decay in six months for a standard two dose strategy.^{28 29} From clinical trial data in which participants received only a single dose, we observed clinical effectiveness through three months but still lack strong data between three and six months.³ Comparing clinical trial data on immunogenicity between different vaccines is challenging given their varying methods and assays used. However, in phase I/II trials, increased immunogenicity was seen for the double dose versus single dose for both BNT162b2 and mRNA-1273 vaccines.^{30 31} The clinical significance of these differences remains unknown. However, the

immunogenicity of BNT162b2 and mRNA-1273 for a single dose was comparable to that of the plasma of people with previous covid-19 infection.^{30 31} The reported re-infection rates of SARS-CoV-2 remain low within six months, and a lack of immune decay in this timeframe is also apparent.^{29 32} In our study, we assumed no clinically relevant immune decay within 180 days for either the single or double dose of BNT162b2 and mRNA-1273 vaccines. Although uncertainty about immune decay exists, especially in a single dose, the current data would suggest limited decay in six months, the timeframe used in our study. Therefore, we believe this is a reasonable assumption, but it is one that decision makers should consider as more data become available.

To understand the impact of whether the vaccine is sterilizing (prevents transmission and serious symptoms) or non-sterilizing (prevents only serious symptoms, including death) on the outcomes between the vaccine strategy groups, we modeled both scenarios. In either case, the differences between vaccine strategy groups did not meaningfully change. Although lack of data about the sterilizing properties of either the BNT162b2 or mRNA-1273 vaccine is a limitation, our analysis of both scenarios was a strength of our study design.

Comparison with other studies

To date, our study is the first to analyze the impact of delaying a second dose for the BNT162b2 and mRNA-1273 vaccines under conditions we believe are necessary for decision makers considering second dose delay strategies. Moreover, our study is the first to look at applying the second dose delay in people younger than 65 years old, but only before vaccinating older people. A pre-print study has also analyzed this question by using an agent based model, but the design used fixed delay periods and a shorter time horizon and did not include sensitivity analysis on various first dose vaccine efficacies or effectiveness of a non-sterilizing vaccine. However, it suggested that if first dose vaccine efficacy is 80%, a delayed second dose strategy is optimal.³³ Another recent study randomized participants to a delayed dose of 12 weeks or longer of the AstraZeneca vaccine.⁴ This vaccine is adenovirus based and has a lower overall effectiveness compared with the Pfizer and Moderna mRNA vaccines, so comparisons should be made cautiously. The results showed the single dose efficacy of AstraZeneca's vaccine to be 76% after 21 days and showed negligible immune decay over three months. Interestingly, this study also found that delaying the second dose boosted the efficacy of the second dose compared with the typical two dose schedule of 22 days apart.⁴

Implications of findings

The covid-19 pandemic continues to take thousands of lives daily worldwide. The promise of vaccines mitigating the pandemic has been overshadowed by disappointment in many countries about the vaccine

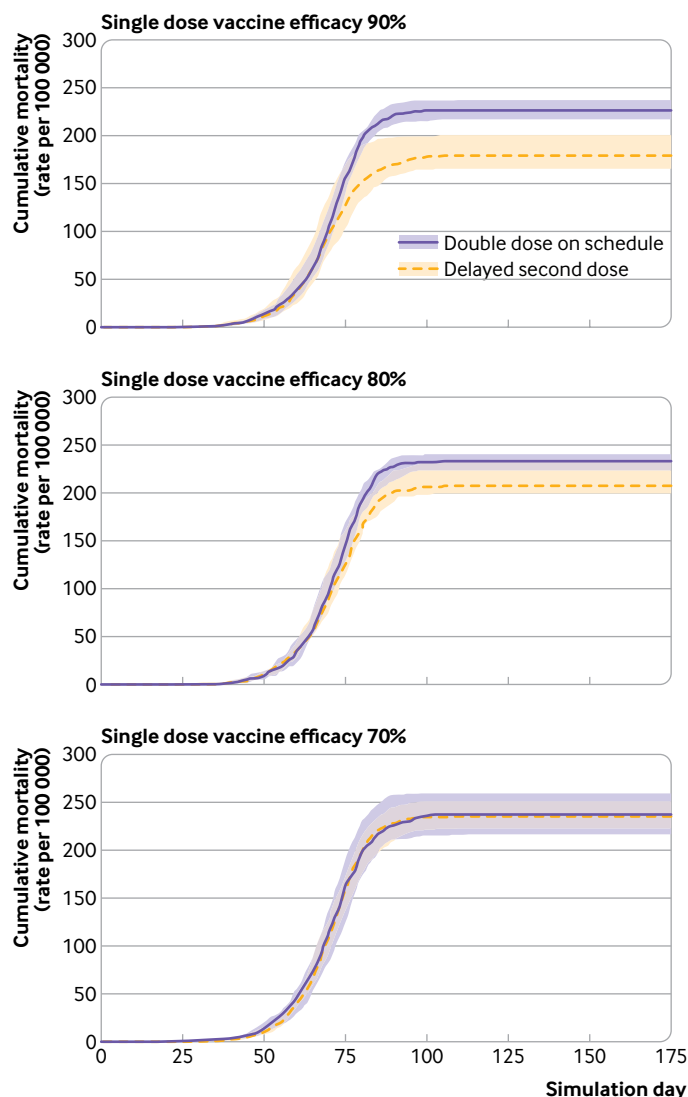


Fig 5 | Cumulative mortality for delayed second dose versus standard dosing under a non-sterilizing vaccine assumption. The results are similar to those under a sterilizing vaccine assumption: the delayed second dose strategy seems optimal for a first dose efficacy of $\geq 80\%$

roll-out. The inequality of vaccine supply has left most countries largely unvaccinated and searching for ways to increase their vaccination rate. Additionally, the supply and logistics of delivering a regimented two dose schedule of the BNT162b2 and mRNA-1273 vaccines have proven challenging. Delaying the second dose of either of these vaccines has been an appealing strategy because it would significantly increase vaccine availability and reduce the logistics of a strict two dose schedule. Hesitation about delaying a second dose is understandable given the limitations of any study design that is not a randomized trial. However, our agent based model can provide estimates of relative differences between these strategies that can be helpful in making policy decisions. The risks associated with delaying a second dose could also be mitigated by selectively doing so in people younger than 65, who have an approximately 10 times lower risk of mortality

than those aged 75 or above and likely a more robust immune response to single dose vaccination.^{19 34 35}

Importantly, our results suggest that this may also be the optimal strategy to prevent deaths under certain conditions. This could provide reassurance to people who are hesitant about a delay strategy. Decision makers will need to consider their local vaccination rates and weigh the benefits of increasing these rates by delaying a second dose versus the risks associated with the remaining uncertainty in this strategy. These decisions should continue to be re-evaluated as new data become available.

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Contributors: TCK, EG, RR, and SRB conceptualized the study. TCK, SRB, and EG designed the study. AC and AS did the analyses, with mentorship from SRB, EG, TCK, JS, and BK. SRB, EG, TCK, and WK interpreted the results. AJR, TCK, SRB, and EG drafted the manuscript, and KP, YD, JOH, WW, and MO revised it critically. All authors reviewed and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. TCK is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Mayo Clinic Institutional Review Board concluded that the study did not need formal review on the basis of its design.

Data sharing: The code and data for the agent based model are publicly available at <https://github.com/ayushchopra96/deepabm-covid>.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The authors of the study plan to share the results with communities through presentations and discussions with public health leaders, some of whom have been aware of the research but were not directly involved in it.

Provenance and peer review: Not commissioned; externally peer reviewed.

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