Testing fractional doses of COVID-19 vaccines

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Abstract

Due to the enormous economic, health, and social costs of the COVID-19 pandemic, there are high expected social returns to investing in parallel in multiple approaches to accelerating vaccination. We argue there are high expected social returns to investigating the scope for lowering the dosage of some COVID-19 vaccines. While existing evidence is not dispositive, available clinical data on the immunogenicity of lower doses combined with evidence of a high correlation between neutralizing antibody response and vaccine efficacy suggests that half- or even quarter-doses of some vaccines could generate high levels of protection, particularly against severe disease and death, while potentially expanding supply by 450 million to 1.55 billion doses per month, based on supply projections for 2021. An epidemiological model suggests that even if fractional doses are less effective than standard doses, vaccinating more people faster could substantially reduce total infections and deaths. The costs of further testing alternative doses are much lower than the expected public health and economic benefits. However, commercial incentives to generate evidence on fractional dosing are weak, suggesting that testing may not occur without public investment. Governments could support either experimental or observational evaluations of fractional dosing, for either primary or booster shots. Discussions with researchers and government officials in multiple countries where vaccines are scarce suggest strong interest in these approaches.

Main Text

Introduction

Early in the COVID-19 pandemic, the IMF estimated that it would cost the world $12 trillion in short-run GDP losses alone over a two-year period (1). Subsequent estimates including health costs and long-run impacts are much larger (2). Based on these estimates, accelerating mass vaccination by even a month would be worth at least $500 billion (3).

The high value of accelerating vaccination suggests that decisions early in the pandemic to invest in multiple vaccine candidates and in installing manufacturing capacity for vaccines in parallel with research and development, rather than in sequence, had high expected social value, despite risks that individual investments might fail or prove redundant. For example, a rough estimate suggests that the United States' Operation Warp Speed (OWS) would have paid for itself if it advanced vaccination in the U.S. by less than a day.[1] Because the social value of accelerating vaccine availability so greatly exceeds the commercial value to vaccine manufacturers, vaccine capacity investments on the scale of OWS would likely not have occurred without public financing.

While OWS generated sufficient vaccines for the U.S., many countries still do not expect to vaccinate large shares of their population until 2023 (5). Similar to at the beginning of the pandemic, pursuing multiple options in parallel that have even a modest chance of accelerating mass vaccination would both have high expected return on investment and would promote equity. This could include improving vaccine delivery systems, investing in expanding supply, and exploring options for using existing supply more efficiently, as insurance against a range of plausible scenarios, including against downside risk from new variants that require booster shots, or shocks to the supply chain.

Using fractional doses of vaccines is one such option, which has been employed successfully for multiple diseases, including in 2016-2018 when several countries used 1/5-doses of yellow fever vaccine to combat epidemics based on advice from the WHO (6). For COVID-19 vaccines, immunogenicity data coupled with a model-based analysis suggest that half- or even quarter-doses of some vaccines could be almost as efficacious as currently-used doses of the same vaccines, and more efficacious than other

[1] Between March and September of 2020, the COVID-19 pandemic cost the United States an estimated $16 trillion in long-term losses, approximately $75 billion per day (2). OWS spent $18 billion (4).

vaccines currently in use. They may also have lower side effects. Even if fractional doses are less effective than standard doses, our epidemiological analysis suggests that increasing the speed of vaccination would reduce total infections and deaths under a wide range of conditions. Given the large potential benefits, investing in generating evidence on the efficacy of fractional doses and validating processes for delivery at scale has a high expected return. Alternative dosing regimens may be beneficial for both primary vaccination and boosters.

The emergence of variants of concern (VOCs) has shown that outbreaks can occur even in settings where the majority of the population has been vaccinated with highly effective vaccines. However, even the less effective vaccines are still very effective at preventing hospitalizations and deaths, even for VOCs. Moreover, when vaccination rates are low (as is the case currently in many low- and middle-income countries), the direct benefits of vaccination far outweigh the indirect epidemiological impacts. This suggests that where vaccine supply is constrained or VOCs dominate, outbreaks would occur regardless of dose size, but fractional dosing could protect more of the population from severe disease and death.

In some countries, vaccination may no longer be constrained by supply, but rather by demand or distribution capacity. However, in many countries, vaccine availability has been low despite surveys suggesting high vaccine acceptance (7). There is also ongoing risk of shortages due to potential need for boosters or seasonal vaccination, the emergence of new variants, and possible manufacturing or supply chain disruptions. Demand is also likely to increase when cases surge or new variants emerge, as observed, for example, in the US during the Delta wave (8).

In this paper, we first argue that the tight relationship between neutralizing antibody response and vaccine efficacy, combined with existing evidence on immune response for lower doses, suggests there is a realistic possibility that high levels of protection could be generated by much lower doses, potentially dramatically accelerating vaccination. We then use an epidemiological model to assess the trade-off between efficacy for those receiving vaccines and overall public health impact, and discuss the potential risks of switching to fractional doses. We outline possible designs for gathering more evidence and argue that there is a gap between the social value and commercial incentives for such research, suggesting that it may not occur without public financing.

Potential efficacy of lower doses

Efficacy of fractional doses of COVID-19 vaccines has not been tested (except for ChAdOx1 nCoV-19, produced by AstraZeneca, where a low dose-full dose regimen appears to have worked well).[2] However, phase 1-2 clinical trials of various vaccines measured immune response in the form of neutralizing antibody (NAb) titers for different doses (e.g. for mRNA-1273, produced by Moderna, four doses were tested). We summarize evidence from trials in Supplementary Material 1 (SM1) and Table S1. More recently, NAb titers for standard doses were found to be remarkably predictive of efficacy against symptomatic infection in phase 2-3 clinical trials (9).[3] We used that modeled relationship together with data on NAb titers in fractional doses from dose-ranging studies (Table S2) to derive their predicted efficacy against symptomatic infection (Figure 1).

Despite the exploratory nature of this approach and the small sample sizes involved, the results strongly suggest that fractional doses of some vaccines produce immune responses that are similar to those produced by larger doses and greater than those produced by standard doses of many other,

[2] Throughout the article we say *efficacy* in relation to either the effect of vaccines measured in clinical trials or if hypothesized based on a model. We say *effectiveness* to highlight the cases when the effect has been observed in real-world studies.

[3] In addition to population-level analyses such as the one we use in our model, emerging individual-level data (analyzing clinical trial data for mRNA-1273) also suggest strong association between neutralizing antibodies (at second dose) and risk of disease (10).

currently-approved vaccines. For example, at fourteen days after the second dose, 50μg and 25μg doses of the mRNA-1273 vaccine produced NAb titres not significantly different from the currently used 100μg doses: the model-predicted efficacy of the first two and the measured efficacy of the standard dose are all within the 90-95% range for symptomatic disease. For BNT162b2, produced by Pfizer, 10μg and 20μg doses have model-predicted efficacy of 70-85%, versus roughly 95% for 30μg, the standard dose. Later in the paper we will discuss evidence generated by more recent trials, as well as ongoing studies of fractional doses.

Many of the phase 2-3 trials did not measure efficacy against VOCs, against which the levels of protection from symptomatic disease may be lower. For example, for BNT162b2 and ChAdOx1, real-world data suggest that effectiveness of the standard dose decreased to 88% and 67%, respectively, against the Delta variant (11). We summarize effectiveness data in Table S4. These decreases are also predicted by drops in NAb titres against variants. We summarize NAb data and compare it to effectiveness in SM1.2.

However, all vaccines with available data are highly effective against severe outcomes, even in the presence of VOCs. For example, in the UK, BNT162b2 and ChAdOx1 were found to be 96% and 92% effective against hospitalization, respectively (12); data from Chile suggests that even CoronaVac (the least effective of the vaccines in Figure 1) is 86-88% effective against hospitalization and death (13). Cell-mediated immunity, rather than neutralizing antibody titres, may be the basis of high levels of durable protection from severe disease (14, 15, 16, 17). Although no clinical data exists, it is therefore reasonable to expect that the decrease in protection against severe disease and death from fractional doses is much smaller than for symptomatic infection.

At this stage of the pandemic, large portions of the unvaccinated population have already been exposed to COVID-19 and acquired some immunity through infection (e.g., 18, 19). Due to age prioritization and demographic patterns in low- and middle-income countries, the current global population of unvaccinated individuals is also younger on average than the world population, and perhaps younger than the populations in which vaccines were originally tested. Recent evidence suggests that previously infected individuals may only need one vaccine dose to be highly protected against reinfection (20). Similarly, because immune responses in younger people are stronger (Table S2), the optimal dose for children and young adults may be lower than for older adults.

Some clinical data also suggest that fractional doses produce fewer side effects (21). If efficacy is comparable to that of standard doses, and side effects are lower, fractional doses might even be superior to current doses in terms of individual benefits.

Simulating public-health benefits of fractional dosing

The traditional research and development process for vaccines is designed to maximize health benefits for the individual taking the vaccine, trading off efficacy and side effects. However, when there is a shortage of vaccines, switching to a lower vaccine dose and vaccinating more people can increase overall public health benefits, even if vaccine efficacy for the individuals taking vaccines is significantly reduced, since the alternative is to leave more people completely unprotected for longer.

We use an epidemiological model to investigate under what conditions fractional dosing would be optimal at the population level. We simulate vaccination across a range of epidemic scenarios in a modified susceptible-exposed-infected-recovered (SEIR) model with a single epidemic peak (to focus on the immediate impact of vaccination), which accounts for the age-varying effect of vaccination on infections and deaths. Methods are described in SM2.

To fix ideas, we start by considering a base case of a vaccine with 95% efficacy against infection, comparable to efficacy against symptomatic disease of the best vaccines measured in phase 3 trials (SM1). We assume a vaccination rate of 0.25% of the population per day, approximately the recent global

median (SM2), and that older individuals are vaccinated first. We consider a range of losses of immune response, which we define through ratios of NAb levels. We then use the model from Figure 1 to calculate predicted efficacy loss.[4] We consider the case in which vaccination rates are constrained by supply, rather than demand or distribution, and therefore inversely proportional to dose size (as a fraction of the current dose).

To account for the emergence of VOCs, we also consider a vaccine with 70% efficacy against infection, comparable to reported effectiveness of ChAdOx1 against symptomatic infection with the Delta variant (SM1). We hold other assumptions constant.

As discussed, real-world data for COVID-19 suggest that vaccines have higher effectiveness against severe outcomes than against infection, especially for less effective vaccines and in the presence of VOCs. To address this, we run a third analysis varying efficacy against infection while holding efficacy against death fixed at 95%.

The results for cases with 70% and 95% efficacy against infection are given in Table 1. We find that if half doses are as efficacious as full doses, then switching would reduce deaths by 22-47% for a baseline 95% efficacious vaccine and 20-35% for a 70% efficacious vaccine, compared to using a standard dose. (The range of outcomes represent different epidemic scenarios.) Even if a half dose leads to a 5-fold reduction in NAb titres relative to a 95% efficacious full dose, the lower dose would reduce total mortality. For a baseline 70% effective vaccine, the threshold is a 2.5-fold reduction. We show reductions in infections (which are similar in magnitude) and additional scenarios in SM2. Thus, our modeling suggests that even when new variants dominate and lower-dose efficacy is significantly lower than suggested by Figure 1, using fractional doses of the more efficacious vaccines would save lives.

The results for the model varying efficacy against infection are presented in SM3. We find that at the vaccination rates typical in many low- and middle-income countries, even a vaccine with high efficacy against infection does not prevent large outbreaks, simply because not enough people are vaccinated in time. Moreover, as the recent experience of the UK shows, it is difficult to stop the spread of Delta VOC even with high uptake of the most efficacious vaccines (22, 23). However, in these settings, accelerating vaccination is still beneficial, as it confers direct protection against hospitalization and death to more people. As shown in Table S4, effectiveness against these outcomes is high for all vaccines where data are available.

Fractional doses and booster shots

In discussing health benefits we have so far focused on primary vaccination, where more data are available. Optimizing dose size for booster shots could also have public health benefits. At the individual level, existing experimental data suggest that a 50ug dose booster of mRNA-1273 (half of the standard primary series dose) produces a strong immune response, comparable to peak response after the primary vaccination with a standard dose (24).

From global health and social perspectives, despite a recommendation by the WHO to delay administering boosters until primary vaccinations have been delivered to more people in low and middle income countries, it is likely that some high income countries will seek to deliver booster doses to many people in the coming months, further constraining already limited supply of vaccines to developing countries (25, 26). Using low doses for boosters would put less strain on the global supply of vaccines. In the UK, the Joint Committee for Vaccination and Immunisation is reported to be considering recommending use of fractional doses of currently used vaccines for boosters (27).

[4] We use fold-reductions rather than simply reducing efficacy by a set amount, as this allows us to appropriately account for the shape of the curve in Figure 1. For example, a 2.5-fold reduction in mean neutralization level has a very small impact on efficacy for a 95% effective vaccine (drop to 87% efficacy) than for a 70% effective vaccine (drop to 49%).

Risks of using lower doses

Our modeling does not consider the rate of immunity loss, which has been established for currently used vaccines (e.g., 28, 29) and will likely be impacted by modifying dose size. Protection from severe outcomes of COVID-19 may be longer lasting (30). However, even assuming duration of immunity is proportional to dose, it will likely be optimal to improve vaccine coverage in the short-term by switching to lower doses and then using future supply as boosters. Moreover, shortages are likely to ameliorate over time as more production comes online, production techniques are optimized, and more countries will have made primary vaccination available to those who seek it, decreasing the infection risk.

Another potential risk is that fractional dosing would increase the probability of new variants arising due to a prolonged period of partial immunity increasing the risk of immune escape. However, many epidemiologists now believe that accelerating vaccination may instead reduce the probability of immune escape, since the greatest risk to immune escape likely comes from the unvaccinated (31, SM1.3). The mutation rate of the Delta variant has also been lower in countries that have vaccinated faster (32).

Vaccination programs that make use of lower doses could also be criticized as inequitable. However, if there is little efficacy loss and a reduction in side effects, lower doses may actually be superior to standard doses from the standpoint of individuals who would be vaccinated in either case. Even if not, vaccinating a greater number of people with a somewhat less efficacious vaccine is still more equitable than the status quo. Moreover, reduced doses of some vaccines, such as the mRNA vaccines, are likely more efficacious than the standard of care in many low- and middle-income countries. As suggested by the analysis depicted in Figure 1, existing evidence suggests that a ½ dose of mRNA-1273 may be more efficacious than a standard dose of ChAdOx1, and similarly that a ½ dose of ChAdOx1 could be more efficacious than a standard dose of CoronaVac. Hence, fractional dosing may improve the quality of care by increasing supply of more effective vaccines. Third, increased supply will cut wait times the most for those who have the longest to wait to receive vaccinations. (For example, doubling the speed of a year-long vaccination program cuts the wait time by a week for someone two weeks from the front of the queue, but by six months for the person at the end of the queue.)

Another risk would be that switching to fractional doses could contribute to vaccine hesitancy. However, if lower doses of high-efficacy vaccines are safer, reduce side effects relative to existing standard doses, and are more effective than the low-efficacy vaccines currently used in many countries with short supply, fractional dosing might even be helpful in combating vaccine hesitancy. Surveys suggest that while vaccine acceptance in low- and middle-income countries is higher than in many high-income countries, side effects remain the most common concern among individuals who remain undecided or opposed to vaccination (9). For the yellow fever outbreak in the DRC and Angola in 2016, the WHO concluded that the rationale for switching to lower doses was well-understood by the target population: while there were questions raised, there was no significant resistance or misinformation specific to fractional dosing observed, and overall uptake was high (98% of the target population) (33).

Testing fractional doses

To date, no regulatory agency or immunization advisory group has recommended fractional dosing for COVID-19 vaccines. The recent WHO SAGE interim statement on fractional dosing (10 August 2021) encourages more research (34). However, despite the global shortage of vaccines, high expected value of testing, and promising clinical trial data being available since autumn of 2020, very few studies of fractional dosing have been conducted since. One exception is the mRNA-1273 vaccine, where we are

aware of three results suggesting safety, strong immune response to primary and booster doses, and durability of protection in lower doses.[5]

As of September 2021, a few studies of fractional doses are ongoing. We are aware of an observational study of efficacy of primary vaccination with half-doses of ChAdOx1 nCoV-19 in Brazil (37)[6] and two randomized trials of immunogenicity comparing low doses with full doses for BNT162b2 (39) and mRNA-1273 (35). A randomized evaluation of several low-dose boosters is ongoing in the United Kingdom (40). None of these studies are sponsored by vaccine makers.

Large sample size trials of efficacy against disease were needed for the initial regulatory approvals for COVID-19 vaccines. However, given recent advances in establishing correlates of protection against infection (11, 41), data on immunogenicity of fractional doses may provide sufficient evidence for some policymakers (in particular, national immunization advisory groups) to recommend their use in national vaccination campaigns, especially for younger adults or other low-risk groups. Considering small sample sizes of existing dosing trials and lack of data on protection from VOCs, decision makers are likely to request additional data.

Additional immunogenicity trials can be conducted for many doses in a matter of months, at low cost, and even when risk of COVID-19 infection is low (as is the case for the three ongoing immunogenicity trials we cited).[7] Given this time frame, immunogenicity trials may be optimal for policymakers looking to reduce global shortages or to improve the safety profile of vaccines in the medium term. In the longer term, randomized trials of efficacy may also offer useful data to the policymakers, but they are more time-consuming to run and require much larger sample sizes, which, given recent difficulties in procuring vaccines for clinical research (42) may also contribute to delays.

Alternatively, where short-term supply is limited and infection risk is high, some policy-makers may decide to roll out the vaccine dose which offers the highest expected health benefit based on the latest available data and use data from the rollout to assess effectiveness and safety (43, 44). The UK did something similar when they extended the gap between doses of BNT162b2 and ChAdOx1 nCoV-19 to twelve weeks in December 2020 based on limited data (45).[8] The roll-out can be limited to certain areas or to lower-risk age groups. Observational data can then be collected in prospective cohort or case-control studies, used to estimate effectiveness and guide further decisions. In parallel, immunogenicity data can also be collected for a smaller subset of the population. If evidence suggests that changing doses is not effective or if supply increases rapidly, the approach can be adjusted or even reversed, just as the UK reduced the interval between doses for some adults to maximize protection against the Delta variant. For fractional dosing, reversibility would mean increasing the second dose size or providing booster shots.

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[5] The studies find that intradermal administration of 10ug dose induces antibody responses comparable to that of convalescent individuals (35); a 50ug booster shot induces antibody levels similar or higher than those observed after primary vaccination with the standard dose (24); and primary vaccination with two 25ug doses elicits antibody and cellular protection comparable to that of convalescent individuals, with the cellular protection persisting even after 6 months (36).

[6] Preliminary results show that 88% of the subjects with no previous exposure to the virus that received half a dose developed neutralizing antibodies (38). Additionally, NAb titres among subjects that received half and full doses were similar (findings still need to be confirmed by ongoing tests).

[7] Both primary vaccination and boosters can be studied. The primary endpoint can be measured within weeks of completing primary vaccination or receiving booster and immunological assays can be conducted in another few weeks. Since small sample size (on the order of 100 subjects per study arm) is sufficient to precisely measure immune responses, it is easy to study subpopulations of interest, e.g. further stratifying the subjects by age, immunocompromised status or, in the case of booster studies, vaccination history. Meta-analysis (including hierarchical mechanistic modeling) can be used to synthesise data across multiple studies, including combining new data with previous phase 1-2 studies.

[8] Real-world evidence, including observational studies of effectiveness which we cited earlier and immunogenicity data, has since emerged supporting the UK decision; this led several countries to delay second doses. Relatedly, existing vaccines were also used at standard dose against the Delta variant, before there was evidence of effectiveness of standard doses against this variant. As viral evolution outstrips the pace of vaccine trials, more such decisions will have to be made under uncertainty.

Ultimately, the decisions will depend on factors that are unique to each country. Between June and August 2021, we reached out to clinical researchers, decision makers in individual countries, and vaccine manufacturers to better understand prospects for testing fractional doses and changing of current recommendations. There was substantial interest from policymakers and researchers in lower and middle-income countries. Different groups expressed interest in pursuing different approaches, depending on their countries' current vaccination rates and expected future supply. In some cases, where the majority of a country's population might have received a low-efficacy vaccine, policymakers wanted to explore fractional dosing for booster shots. In other cases, where vaccine supplies are very low, they were interested in exploring fractional dosing for primary vaccination. There was also variation in preferred approach to testing, with some policy makers considering proceeding with limited roll-outs and collecting observational data while others looked to first sponsor immunogenicity trials, but all agreed that more data should be collected. We are aware of several more immunogenicity trials that are being planned in middle-income countries, but no efficacy studies.

In addition to testing efficacy and safety of alternative doses, logistical questions regarding their administration will also have to be answered through validation studies. Some vaccines could potentially be used off-label in their current formulations. In that case studies must test how many times a vial can be punctured and whether smaller volumes of vaccine can be administered consistently and with which syringes. In all of the studies so far, the same vials and dilution procedure were used as in general practice, and lower doses were obtained by drawing less volume into syringes. Other vaccines may need changes to fill and finish processes. Any modifications to supply chains and delivery systems can proceed in parallel to testing.

Gaps between commercial incentives and social value

In previous research, we estimated the social value of an additional course of vaccine to be $500-1000 (depending on when it was available), which dwarfs the $6-$40 price that manufacturers receive in current contracts (3). We have argued in previous work that this gap leads to significant underinvestment by private companies in manufacturing capacity, compared to the social optimum (3). It may also lead to private underinvestment in research on other ways to accelerate vaccination. This suggests that such research may not be carried out without public funding (46).

Our limited outreach to manufacturers suggests low enthusiasm for testing lower doses. Although some vaccine manufacturers are studying fractional doses of vaccines for children and as boosters (21, 47, 48), private companies may even have disincentives to conduct research on fractional dosing for primary vaccination. First, if countries decided to use lower doses off-label and they paid the same amount per vial, total demand would decrease. Switching doses while maintaining current prices could create communications or public relations risks, so a switch to lower doses would likely result in lost revenue. Second, manufacturing vials with specific doses involves substantial sunk costs. Seeking regulatory approval for a new dose is also a costly and slow process. Manufacturers may prefer to focus on products that can be sold at much higher prices in high-income countries, such as booster shots that have been modified to address variants, or combination COVID-19 and flu vaccines. Manufacturers may see testing of lower doses of existing products as interfering with this strategy. Finally, firms face a reputational risk if something goes wrong with a lower dose.

Government investment in accelerating the development of first-generation COVID-19 vaccines created benefits in the trillions of dollars (3). Similar investments in testing fractional dosing could also have extremely high payoffs: for a rough sense of the magnitude of the effect, a simple calculation based on manufacturer's production estimates suggests that implementing fractional dosing globally for the most promising vaccines could potentially increase vaccine supply by 450 million to 1.55 billion doses per month in the last quarter of 2021 (Supplementary Materials, SM4).

Even at the government level, no single country internalizes the total global benefit of testing, because the information generated by testing is a global public good. For example, following the UK's successful

experimentation with a longer delay between first and second doses, many other countries adopted the same dosing schedule (49). Likewise, evidence on fractional dosing could inform decision-making in multiple countries, suggesting a role for global institutions to invest in and coordinate studies.

Conclusion

There are risks to using fractional doses, and logistical questions that remain to be answered. However, the reversibility and large potential benefits of fractional doses suggest that testing - in the short term most likely achieved either via immunogenicity studies or rigorously evaluated rollouts of fractional dosing regimens - has tremendous informational value. Clinical data and epidemiological modeling suggest that switching to fractional doses of some COVID-19 vaccines could potentially save lives by accelerating vaccination in countries still facing supply constraints. Fractional doses may be more efficacious than the current standard of care in many countries and may also have weaker side effects.

Given the substantial risks of status quo policies, as recent outbreaks in Southeast Asia and elsewhere have illustrated, the expected value of testing fractional doses is high even with only a modest chance that they will be effective. Furthermore, the risk of changing doses is lower when the unvaccinated population is young or when a higher share of the population has already acquired immunity through infection, as is increasingly the case around the world. If lower doses are found to be effective, they have the potential to save lives. If not, the policy can be reversed. The social value of such testing is significantly greater than the private value, suggesting a role for public funding.

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Figures and Tables

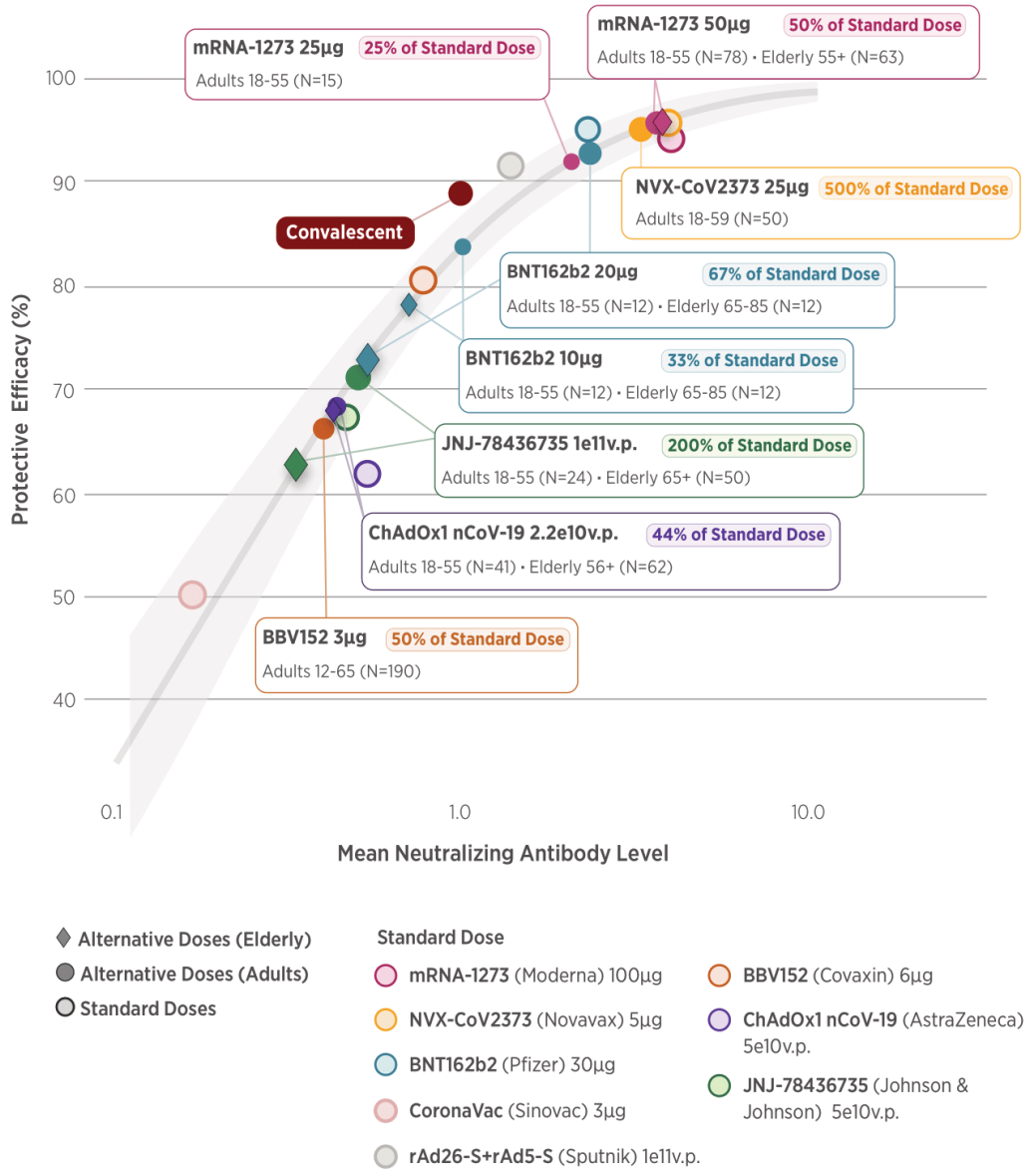

Figure 1. Efficacy associated with mean neutralization levels for fractional doses. The curve follows the model derived by Khoury et al. (10) linking NAb levels (horizontal axis) to protection from symptomatic infection (vertical axis) for standard doses of eight vaccines and in convalescents, with the shaded area corresponding to the 95% confidence interval of the model. Lighter data points represent the mean (normalized) immune response and clinical efficacy against symptomatic infection of specific vaccines (referred to by colors) at standard doses, collected by Khoury et al. (10); response in convalescents is also plotted. NAb levels for vaccines are normalized to those of convalescents using clinical trial data for each vaccine. We calculate the ratios of mean NAb responses for fractional versus standard doses using data from clinical trials that tested different doses. We then plot the fractional doses on the immunogenicity-efficacy curve as darker shapes. Doses for the elderly are represented by diamonds while doses for non-elderly adults (or all adults, where data is not available by age) are represented by circles. For consistency, if multiple age groups were compared, we use the immune response to the

standard dose in younger adults to normalise mean NAb levels. We note small sample sizes, typical of early stage trials, and do not include measures of uncertainty.

Switching from 95% effective full dose				
	Dose			
NAb ratio (efficacy)	**1**	**1/2**	**1/3**	**1/4**
1.0 (95%)	0	22 to 47	32 to 69	37 to 80
0.8 (94%)	-2 to -1	21 to 45	31 to 67	37 to 79
0.4 (87%)	-12 to -4	18 to 34	28 to 59	34 to 73
0.2 (76%)	-29 to -10	13 to 22	23 to 44	29 to 60
Switching from 70% effective full dose				
1.0 (70%)	0	20 to 35	30 to 52	35 to 64
0.8 (65%)	-6 to -3	18 to 31	27 to 45	33 to 57
0.4 (49%)	-27 to -13	-1 to 15	17 to 32	24 to 40
0.2 (34%)	-52 to -24	-26 to -5	-12 to 12	-3 to 21

Table 1. Deaths averted by switching to hypothetical fractional dosing regimens. Values are $1 - (\#\ deaths\ with\ fractional\ dose / \#\ deaths\ with\ standard\ dose)$. Ranges correspond to different epidemic scenarios (see SM2) from R=0.99 to R=2. Positive values (white background) favour switching to the lower dose. Vaccination rate is proportional to reciprocal of dose.

Supplementary Information for Testing Fractional Doses of COVID-19 Vaccines

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1. Summary of Available Evidence

1.1. Clinical Trial Data

Table S1 lists clinical trials for vaccines discussed in the paper.

In early stage clinical trials, lower dosages of COVID-19 vaccines were often found to stimulate a strong NAb response, at least in non-elderly patients. Evidence on the immunogenicity of a range of dose sizes of each vaccine is summarized in Table S2. Note that in some later trials, such as those for JNJ-78436735 (Johnson & Johnson) and NVX-CoV2373 (Novavax), Phase 3 clinical trials proceeded with the smaller of two dose options tested in early trials after those trials found no statistically significant difference in immune response between the doses.

As discussed in the paper, Khoury *et al.* (*10*) find a "remarkably predictive" logistic relationship between neutralizing antibody (NAb) levels and vaccine efficacy against symptomatic infection, with Spearman ρ of 0.905 (*10*). Authors base their analysis on publicly available data from phase 1-2 clinical trials for NAb data and from phase 3 for vaccine efficacy for subsequently approved vaccines. We assume the relationship between immune response and efficacy holds for all doses tested in phase 1-2 trials and plot additional points based on immune response for all doses of currently used vaccines (Figure 1 in the main text). We use immunogenicity data from phase 1-2 trials that tested different doses (Table S2). Where available, we use the same studies referenced by Khoury *et al.* (*10*). The exceptions were: the 25µg dose of mRNA-1273 (Moderna) (*34*); BBV152 (the vaccine developed and manufactured by Bharat Biotech, sold under brand name Covaxin) (*35*); ChAdOx1 nCoV-19 (AstraZeneca-Oxford) (*14*).

We use the data from those trials to calculate the ratio of mean NAb levels for alternative versus standard doses in each study. In some of the trials multiple age groups were tested, so for consistency we always use in the denominator the NAb levels for standard doses among non-elderly adults (under 55, 59 or 65 years old depending on the study). We then multiply the ratio of alternative versus standard doses by the ratio of standard doses versus convalescents (reported

by Khoury *et al.* (*10*)) for each vaccine to make our estimates of efficacy comparable to those calculated by the authors of the original study.

Our results show that for some vaccines, immune responses associated with high efficacy can be obtained even with much smaller doses. For mRNA-1273 (Moderna), for example, doses 1/2 and 1/4 of the standard both have immune response levels associated with 90-95% efficacy, compared to 94.1% initially reported in phase 3 trials (*36*) for the standard dose. For BNT162b2 (Pfizer) there is no significant decrease in NAb level for a 2/3 dose in non-elderly populations (albeit with a very small sample size), while NAb levels are associated with efficacy between roughly 70% and 85% for other dose-age combinations, compared to 95% initially reported in phase 3 trials (*37*) for the standard dose. For other vaccines, we also sometimes observe unexpected trends, where lower doses lead to NAb levels associated with higher efficacy (e.g., NVX-CoV2373 (the vaccine developed by Novavax and not yet approved for distribution) and ChAdOx1 nCoV-19 (AstraZeneca-Oxford). While these results are not necessarily unrealistic, they may be a consequence of limitations of the modeling approach or of uncertainty inherent in early-stage clinical trials (especially the small sample sizes), or both.

1.2. Viral Variants

Recent studies have found a significant decrease in immune response from vaccines for newer variants such as the Delta variant of concern, first detected in India in December 2020. A summary of effectiveness studies is presented in Table S4. Here, we briefly summarise existing evidence on effectiveness of vaccines against variants.

The purpose of this is two-fold: first, to provide a basic validation of the approach of deriving effect based on reductions in NAb levels we described above; second, to motivate choice of parameters in the simulations.

Wall *et al.* (*4*, *38*) use a live-virus SARS-CoV-2 neutralisation assay to determine NAb titres for different variants in 250 participants from the Legacy study. They report a 5.8-fold reduction in NAb levels after two doses of BNT162b2 (Pfizer) when comparing the wild type to the Delta variant and 2.6-fold decrease when comparing Alpha to wild type. This implies a 2.2-fold reduction between Alpha and Delta (5.8/2.6=2.2).

Other studies report the variation in vaccine effectiveness for different variants. Bernal *et*

al. (*11*) report estimates of effectiveness against symptomatic infection using observational data on vaccinated individuals in the UK and conclude that effectiveness against the Alpha variant for BNT162b2 was 94%, dropping to 88% for the Delta type, for ChAdOx1 nCoV-19 (AstraZeneca/Oxford) the drop is from 75% to 67%. Sheikh *et al.* (*39*) analyse data from Scotland and report a decrease in effectiveness against symptomatic infection from 92% with the Alpha variant to 83% with the Delta variant for BNT162b2, and from 81% to 61% for ChAdOx1 nCoV-19.

Combining both types of data provides some measure of external validation of Khoury *et al.*'s model from Figure 1. For example, according to the model, a decrease in efficacy from 92% to 83% (*39*) is associated with a 2.2-fold drop in NAb levels; a decrease from 94% to 88% (*11*) is associated with a 2.0-fold drop. We can see that these values are comparable to the 2.2-fold drop reported in (*4*). Moreover, focusing on the Delta variant alone, Wall *et al.* report a 2.5-fold drop in NAb levels from ChAdOx1 nCoV-19 when compared to BNT162b2 (*38*). Sheikh *et al.* report a 83% effectiveness for BNT162b2 against Delta while ChAdOx1 nCoV-19 is 61% effective. In Khoury *et al.*'s model, this is associated with an 3.1-fold drop in NAb levels, once again comparable to the decrease reported in observational studies.

1.3. Immune Escape Risk

One serious concern about modified vaccination approaches is that they might lead to weak immune responses and immune escape through mutation (*40*). In considering such risks it is important to also consider the risks of the status quo. Without a modified vaccination approach there is a higher probability of more infections. A non-vaccinated person who becomes infected goes through a period of "partial immunity" when there is also a higher risk of immune escape. Indeed, variants of the SARS-CoV-2 virus are already circulating that are more transmissible and might be less vulnerable to vaccines but these arose before widespread vaccination (*41*). Additionally, we should also take into account the fact that there is some indication that alternative doses of some vaccines can lead to immune responses comparable to that of currently approved vaccine-dosage combinations, as presented above, and that milder and less symptomatic infections lead to less transmission (*42*). Thus, it isn't clear whether the balance of probabilities on immune escape favors or disfavors the modified approach.

2. Epidemiological Simulations

2.1. Epidemiological Model

Since the evidence on alternative dose efficacy is not dispositive, we model the potential impact on the pandemic of a range of efficacy levels using a standard epidemiological model. The model we use extends the canonical susceptible-exposed-infectious-recovered (SEIR) model, which is widely used in mathematical epidemiology to characterize the spread of an infectious disease in a closed population (*43*, *44*). The SEIR model assumes individuals flow between disease and vaccination states over time, with sizes of population in each state changing according to a set of differential equations. We extend the canonical SEIR model to allow for death and vaccination (which is ineffective for some individuals), yielding the following equations:

$$\dot{S}_i(t) = -\lambda_i(t)S_i(t) - v_i(t)\delta_i\tilde{S}_i(t) \tag{1}$$

$$\dot{E}_i(t) = \lambda_i(t)[S_i(t) + N_i(t)] - \gamma' E_i(t) \tag{2}$$

$$\dot{I}_i(t) = \gamma' E_i(t) - \gamma_i'' I_i(t) \tag{3}$$

$$\dot{D}_i(t) = p_i\gamma'' I_i(t) \tag{4}$$

$$\dot{R}_i(t) = (1-p_i)\gamma'' I_i(t) - v_i(t)\delta_i\tilde{R}_i(t) \tag{5}$$

$$\dot{P}_i(t) = v_i(t)\delta_i\left[e\tilde{S}_i(t) + \tilde{R}_i(t)\right] \tag{6}$$

$$\dot{N}_i(t) = v_i(t)\delta_i(1-e)\tilde{S}_i(t) - \lambda_i(t)N_i(t). \tag{7}$$

Dots denote derivatives with respect to time. Uppercase letters denote population compartments (i.e., the fraction of the population in a given state): S for susceptible, E for exposed (individuals carrying the virus, but who are not yet contagious), I for infectious, R for recovered, D for dead, P for protected by vaccine, and N for vaccinated but not protected. The population is divided into G age cohorts, indexed by $i = 1, \ldots, G$, with respective sizes n_i. Subscripting compartments by i allows for different epidemic evolution across age cohorts. Tildes denote the size of the compartment in proportion to both compartments receiving vaccines (susceptible and recovered) i.e.,

$$\tilde{S}_i(t) = \frac{S_i(t)}{S_i(t) + R_i(t)} \tag{8}$$

$$\tilde{R}_i(t) = \frac{R_i(t)}{S_i(t) + R_i(t)}. \tag{9}$$

Figure S1 depicts the population flows between the compartments described in equations (1)–(7). For simplicity, we consider the case of either a single dose vaccine or a two-dose vaccine where efficacy does not change between doses. Lowercase letters denote model parameters governing the evolution of compartments. All parameters except e are age-specific, as denoted by subscript i. γ' and γ'' are, respectively, the hazard rates of moving from exposed to infected and from infected to recovered or dead. These are estimated as the reciprocals of the durations of the virus's incubation period and of the infectious period, respectively. The rate of new infections equals $\lambda_i(t)$, described in further detail below. Parameter p_i is the mortality risk. Vaccine efficacy, denoted e, is the probability the vaccine protects from infection. The model makes no distinction between the vaccine's *efficacy* (performance measured in clinical trials) and *effectiveness* (performance in practice in the population); e is used to denote both interchangeably. We assume recovered individuals (compartment R) are perfectly protected by vaccination and that exposed or infectious individuals (compartments E and I) are not vaccinated.

To account for vaccine prioritization, we introduce an indicator variable $v_i(t)$, switching from 0 to 1 on the day age cohort i becomes eligible for vaccination and to 0 again at the point where all willing members of the cohort have been vaccinated. Reflecting common practice, we assume older cohorts must finish vaccinations before the next cohort becomes eligible. When $v_i(t) = 1$, age cohort i is vaccinated at a constant rate δ_i, drawing on a continuous stream of vaccine production from a given capacity. To keep track of cumulative doses distributed, we introduce the auxiliary compartment V, where $\dot{V}_i(t) = \delta_i v_i(t)$, and where $V(t)$ is the proportion vaccinated in the entire population.

The rate of new infections, $\lambda_i(t)$, depends on the number of daily contacts a susceptible individual has with currently infectious individuals. To reflect differences in interaction across age cohorts, we use a contact matrix C, where entry $c(i, j) \geq 0$ denotes the number of contacts made by an individual in cohort i with an individual in cohort j. To derive the proportion of each age group infected at time t, each contact is scaled by the probability of virus transmission on contact,

q, and probability that the contacted person is infected, $I_j(t)$, yielding

$$\lambda_i(t) = q \sum_{j=1}^{G} c(i,j) I_j(t). \tag{10}$$

For a given C, q can be adjusted to match any desired reproductive number $\mathcal{R}$ for the virus (i.e., the number of secondary cases produced by a single infection).

The initial conditions of the system (1)–(7) require specifying the proportion of the population that is susceptible $S(0)$, immune $R(0)$, and infectious $I(0)$ at the outset of the epidemic. We generally take $I(0)$ to be small and for simplicity take $E(0) = I(0)$. We assume that the proportion of each age cohort in each initial compartment is the same as in the overall population.

2.2. Initial Conditions

We run simulations for three illustrative epidemic scenarios designed to span a range of cases. The *slow decrease* scenario sets the initial effective reproduction rate to $\mathcal{R} = 0.99$ and initial infectious proportion to $I(0) = 1\%$. Since we assume 20% of pre-existing protection in people aged 20 and over, the initial effective reproductive number $\mathcal{R}$ is lower than $\mathcal{R}_0$, the basic reproductive number in a fully susceptible population. The *slow decrease* scenario may capture a situation in which non-pharmaceutical interventions (NPIs) are introduced following an epidemic wave but are only effective enough to decrease cases slowly. The *slow growth* scenario sets $\mathcal{R} = 1.1$ and $I(0) = 0.5\%$, perhaps reflecting a situation in which NPIs are not effective enough to prevent a subsequent wave of infections, such as the one experienced by the United States in late 2020. The *fast growth* scenario sets $\mathcal{R} = 2$ and $I(0) = 0.1\%$, e.g., a case when a new virus strain suddenly emerges, thwarting previously effective NPIs (such as the one observed in the United Kingdom in December 2020, or the emergence of the P.1 variant in Brazil in late 2020 (*45*). In both growth scenarios, $I(0)$ is adjusted so that the peak of infections occurs three to four months from the start of vaccinations.

We choose parameters for initial immunity that broadly reflect the state of the COVID-19 pandemic in early 2021. We assume 20% of people aged 20 and over have immunity acquired from infection, leaving 80% susceptible. To reflect the lower clinical case rate in the younger population (*46*, *47*), we assume only 50% of under 20s are susceptible.

2.3. Parametrization

Each simulation runs for $T = 365$ days. This is sufficient time for the epidemic to die out in the scenarios considered but, we assume, not long enough for unmodeled factors to come into play, such as the alleviation of supply constraints with expanded capacity or the waning of vaccine protection from initial doses, perhaps warranting booster shots. Similarly, we assume that there is no natural loss of immunity (no flow from recovered to susceptible) during the simulation period.

We use a social contact matrix $c(i, j)$ based on a large cross-country study of contacts between different age groups, primarily in European countries (*48*). Our matrix is therefore more representative of high-income countries, but we are not aware of comparable data on social mixing in low-income countries. Cohort size (n_i) and mortality risk (p_i) for different age cohorts is consistently based on data for high-income countries. Throughout the age distribution, the risk of death from COVID-19 increases rapidly with age, about three-fold per decade (*49*).

The model assumes that contact frequencies are independent of infection risk, precluding behavioral changes in response to changes in infection risk as the epidemic progresses. We also assume that epidemics always have a single peak and fade out when the virus's effective reproductive number satisfies $\mathcal{R} \leq 1$, which happens when a sufficiently high fraction of population is protected, either by vaccination or recovery from natural infection.

The base case for vaccination is a 95% effective vaccine, when used as tested in Phase 3 trials (standard dosing, with a delay between two doses). We assume that those under 20 (constituting 22% of population in our base case simulations) receive no vaccination. To account for vaccine hesitancy, we assume 20% in each age group refuse vaccination. We assume that the vaccine becomes effective 10 days after it is administered. We achieve this by treating vaccinated compartments in the model as "effectively vaccinated". Hence if vaccinations in a given age group start of day t_1 and end of t_2, we start the flow into vaccinated compartments on date $t_1 + 10$ and stop it on $t_2 + 10$.

As of early May 2021, countries were vaccinating at a median rate of approximately 0.25% of the population per day (*50*), our base case immunization speed. At the high end, countries such as the United Kingdom, United States, Canada, Chile, and Israel have all managed to vaccinate at rates well above 0.8% of the population per day; however, the current median global rate of

vaccination (as of July 10, 2021) is approximately 0.31% of the population per day, up from exactly 0.25% in May 2021 when we ran our simulations (*50*). Thus, at a global level, supply rather than delivery logistics or demand (e.g., vaccine hesitancy) seem likely to constrain full vaccination well into 2022, and perhaps for considerably longer.

Accordingly, our model is intended to apply to contexts in which vaccination rates are constrained primarily by the available supply. While this may not apply for some countries, this seems broadly to be the case globally in the sense that increases in vaccine supply could effectively be used. The model could be extended to consider other scenarios where, for example, delivery constraints might at some point be binding.

Additionally, while we treat efficacy as a scalar, in reality it is multidimensional: vaccines may differ in efficacy against different variants, in duration of protection, or in their protection against infection and disease.

2.4. Simulation Method

We generate a simulation run for each configuration of parameters by finding the deterministic solution of the differential-equation system consisting of these equations (1)–(7) using standard numerical methods. We solve all differential-equation systems using the odin package, version 1.0.8, and generate exhibits using R, version 4.0.2. All code used in this project is available at https://github.com/wwiecek/covstretch.

Figure S2 illustrates the evolution of vaccinations and infections for the various epidemic scenarios and vaccination rates analyzed. With no vaccination, we find that from 8% (slow decrease scenario) to 55% (fast growth scenario) of the population get infected during the simulation period. Individuals aged 20 to 49 are responsible for between 55% and 59% (depending on the scenario) of all infections, assuming no vaccine. This is consistent with recent estimates (*51*) that three quarters of infections in the US originated from individuals in that age bracket (albeit in a period with school closures).

The outcome variables for our simulations are the burden of infection, defined as the proportion of the total population that develop new infections during the simulation period, and the burden of death, defined as the proportion of the total population that die during the simulation period.

2.5. Simulations

We consider the case in which the pace of immunization is subject only to a supply constraint, therefore the vaccination rate is proportional to the reciprocal of dose size. So, for example, using half rather than full doses would double the vaccination rate. We analyze the impact of alternative dosing on the burden of infections and deaths while varying three variables: dose fractions, efficacy reductions associated with moving to alternative dosing, and epidemic scenarios.

We run scenarios with two different baseline assumptions for vaccine efficacy with full dose vaccine efficacy. First we assume that a full dose has 95% efficacy, compatible with the verified efficacy of mRNA vaccines. Second, to account for the overall drop in effectiveness against some viral variants we repeat our analysis assuming a 70% efficacy for full doses. (This case can also be used to evaluate less effective vaccines in general.)

In order to make the 95% and 70% cases comparable, we define alternative doses efficacy in terms of relative reduction in NAb levels compared to the baseline. To do this, we follow the previously-cited model by Khoury *et al.*. This allows us to make a "fair" comparison, since comparable fold-reductions in NAb titres will have different impacts on efficacy, due to the concave shape of the curve in Figure 1 in the main text. For example, if starting from the base case of 95% efficacy, a 5-fold reduction in NAb titres is associated with a drop of efficacy to 76%. If starting from 70%, a 5-fold reduction in NAb is associated with efficacy of 34%.

We use ratios of 1, 0.8, 0.4 and 0.2 (1.25, 2.5, 5-fold reductions respectively) to derive the new results. For comparison with measured data, the NAb ratios for fractional doses among non-elderly adults range from 0.43 (1/3 dose of BNT162b2) to 0.91 (1/2 dose of mRNA-1273), the exact values are presented in Table S2. Therefore, despite the exploratory nature of this approach, we find it illustrative to consider a ratio of 0.8 (1.25-fold reduction) with 1/2 dose and a ratio of 0.4 (2.5-fold reduction) with 1/3 dose to guide intuition on expected impact of using alternative doses. 5-fold reduction may correspond to using much lower doses than what was previously tested in dose ranging studies. The results are shown in Figure S3 and summarised in Table 1 of the main text.

We find that for a 95% efficacious vaccine the burden of mortality relative to status quo (risk ratio) is 0.55-0.79 with 1/2 dose and 0.8 NAb ratio and 0.41-0.72 with 1/3 dose and 0.4 NAb ratio,

suggesting large benefits of switching to fractional dosing. The ranges correspond to different epidemic scenarios. With 70% baseline efficacy we find a higher but still lower than the status quo relative burden, of 0.69-0.82 with 1/2 dose and 0.8 NAb ratio and 0.68-0.83 with 1/3 dose and 0.4 NAb ratio (drop to 49% efficacy).

3. Differential Vaccine Impact on Mortality and Infection

The initial SEIR model assumes that efficacy of the vaccine against mortality was the same as against infection. However, observational data for multiple vaccines (including mRNA) suggests a differential impact on deaths and infection (and therefore transmission). Therefore we modify the model by adding extra compartments, allowing for differential efficacies against infection and death. A reproducible version of this simple calculation are available in the code repository we referenced earlier.

Let us focus on reducing mortality as the primary objective of a vaccination programme and use the fast growth scenario from earlier simulations. In an extreme (and purely theoretical) case, vaccines have no impact on infection, while providing very good protection against death. In other words, there are no indirect benefits of vaccination and herd immunity can never be achieved. Conversely, when the impact on infection is high, indirect benefits eventually start to outweigh the direct ones.

However, in the current pandemic setting the indirect benefits also depend on speed of vaccinations in relation to infection risk. If only a low proportion of the population can be vaccinated during the exponential growth phase of the epidemic, the impact of infection is low. We illustrate this in Figure S4, where we assume 95% efficacy against mortality and varying efficacy against infection from 0% to 95% (differently coloured lines) and speed of vaccination (x axis). For simplicity we use the fast growing epidemic scenario, but the overall result carries across all scenarios.

We find that at lower vaccination speeds like 0.1 to 0.25% per day (similar to the speed in many lower and middle income countries) the direct effects will outweigh indirect effects. This can be seen in the right panel of Figure S4 (mortality rate), where the lines (corresponding to different levels of sterilising immunity) do not diverge until higher vaccination rates (>= 0.50%) are reached. For example, at 0.25% vaccinated per day we have 54% infected if there is no impact on infection and 45% if the level of protection is 95%. In terms of mortality, we find 17 deaths per

10,000 if there is 50% efficacy against infection, 16 if 95%, and 20 if 0%. We should note that the absolute benefits are very sensitive to the assumption of how far in the future the peak of infections is: here we assume that it is about 3 months as per the fast epidemic growth scenario depicted in Figure S2.

4. Increase in Vaccine Supply from Fractional Doses

While it is hard to predict with precision the increase in supply resulting from the adoption of alternative doses, we present a range of estimates based on the projected supply in 2021 for some of the main vaccines being currently distributed. The results are shown in Table S3.

We use the best projections currently available for vaccine supply in 2021. This includes data from press releases (*52*, *53*) and third-party publications (*54*, *55*) when updated information directly from the manufacturers is not available. This leads to an expected supply for 2021 of 3 billion doses for BNT162b2 (Pfizer), 800 million doses for mRNA-1273 (Moderna), and 2.1 billion doses for ChAdOx1 nCoV-19 (Oxford/AstraZeneca).

We combine the projected supply with the number of doses already delivered according to official statements from vaccine developers UNICEF (*56*–*58*) (as of September 3, 2021). We subtract doses delivered from projected supply and assume that the remaining quantity will be delivered uniformly during the remaining months of the year. Based on these values, we estimate the number of extra doses that would be generated with the adoption of alternative dosing regimens, as shown in Table S3.

The dosing regimens represented here capture a range of scenarios with varying degrees of optimism. We include only dose sizes that demonstrate NAb levels correlated with high efficacy or comparable to the efficacy of the standard dose in our initial analysis (Figure 1). We observe that for the scenarios considered here, it is possible to produce 450 million to 1.55 billion extra doses per month in the last quarter of 2021.

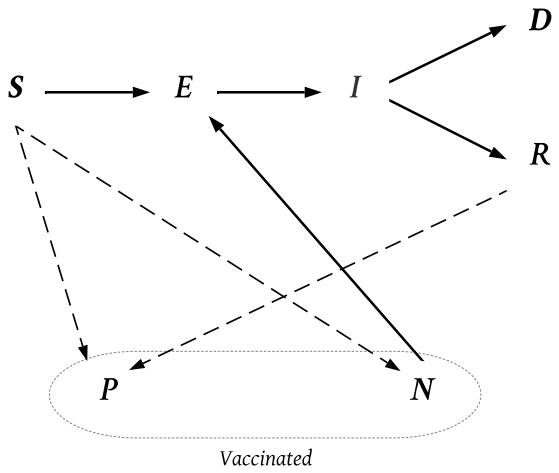

Figure S1: Compartment Flows in Epidemiological Model. Model described by Equations (1)–(7). Solid black lines reflect virus model and dashed lines vaccination. The full model has separate compartments for each age group *i*.

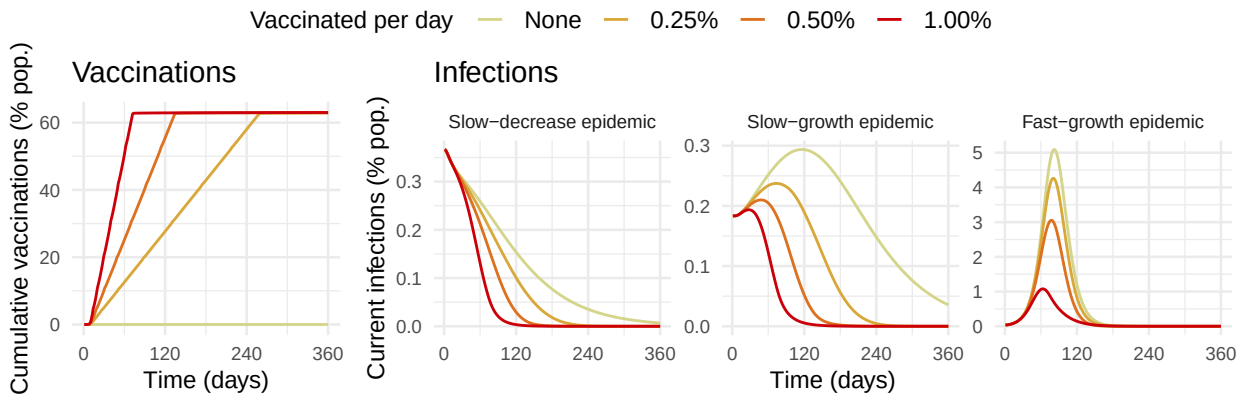

Figure S2: Evolution of Vaccinations and Infections under Baseline Epidemic Scenarios. Colors indicate different vaccination rates δ with a 95% efficacious vaccine. While the population is vaccinated at a constant rate, age prioritization leads different age cohorts to start being vaccinated at different times. Cohorts aged 20 and above achieve 80% vaccination coverage by time $T = 365$ days. Please note that the scales of the vertical axes vary according to the epidemic scenario.

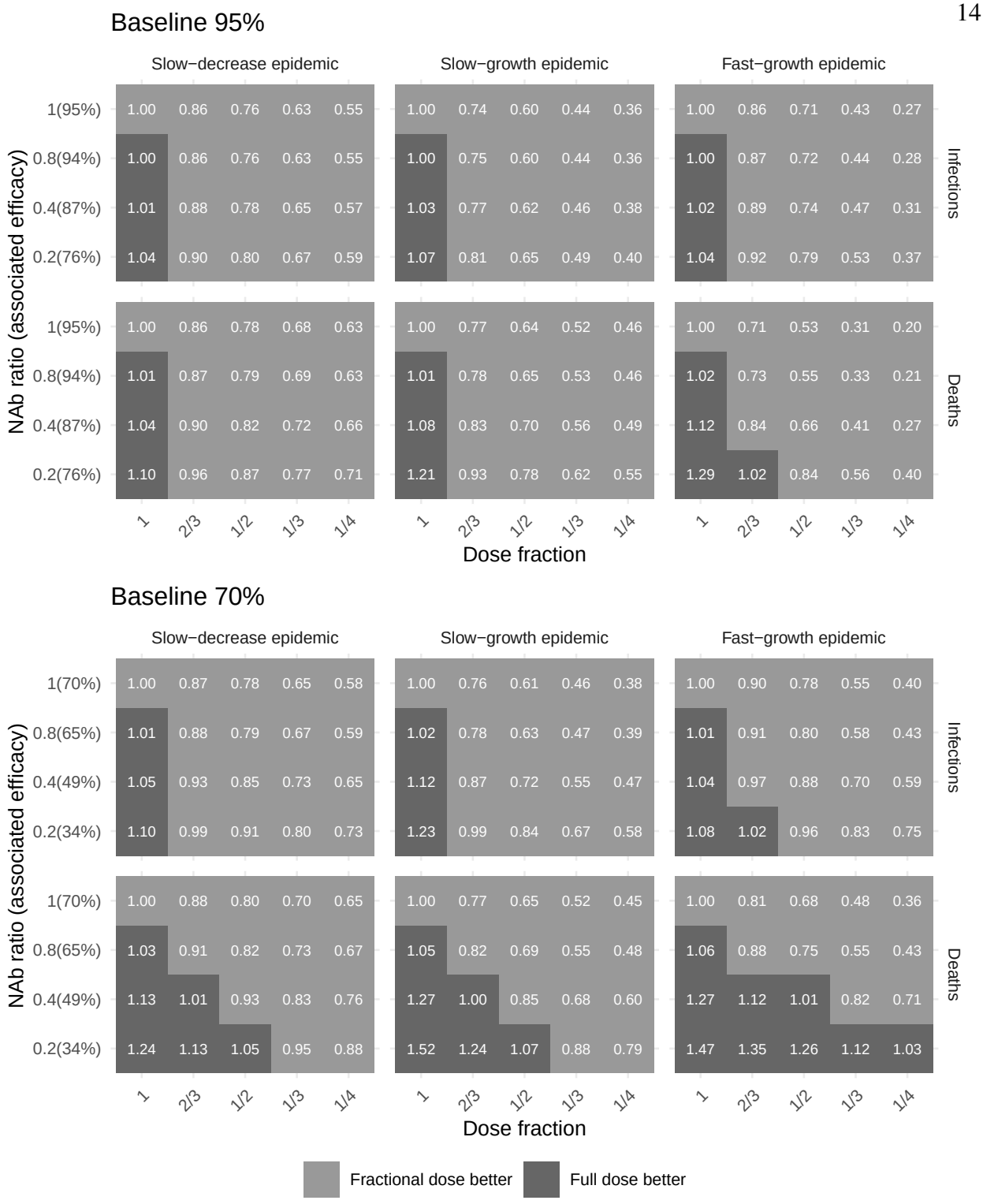

Figure S3: Burden Averted under Full Relative to Alternative Dosing for Different Baselines Entries are burden ratios; greater than 1 (emphasized by darker background) favors full dosing and less than 1 (emphasized by lighter background) favors alternative dosing. Each tile represents a different combination of epidemic growth, level of efficacy of alternative dose, and size of alternative dose, proportional to reciprocal of vaccination rate. The upper figure represents the case for 95% efficacy baseline and the bottom figure represents 70% baseline efficacy. The labels on the vertical axis represent the NAb ratio in relation to baseline followed by the vaccine efficacy estimated using the model by Khoury *et al.* (*10*).

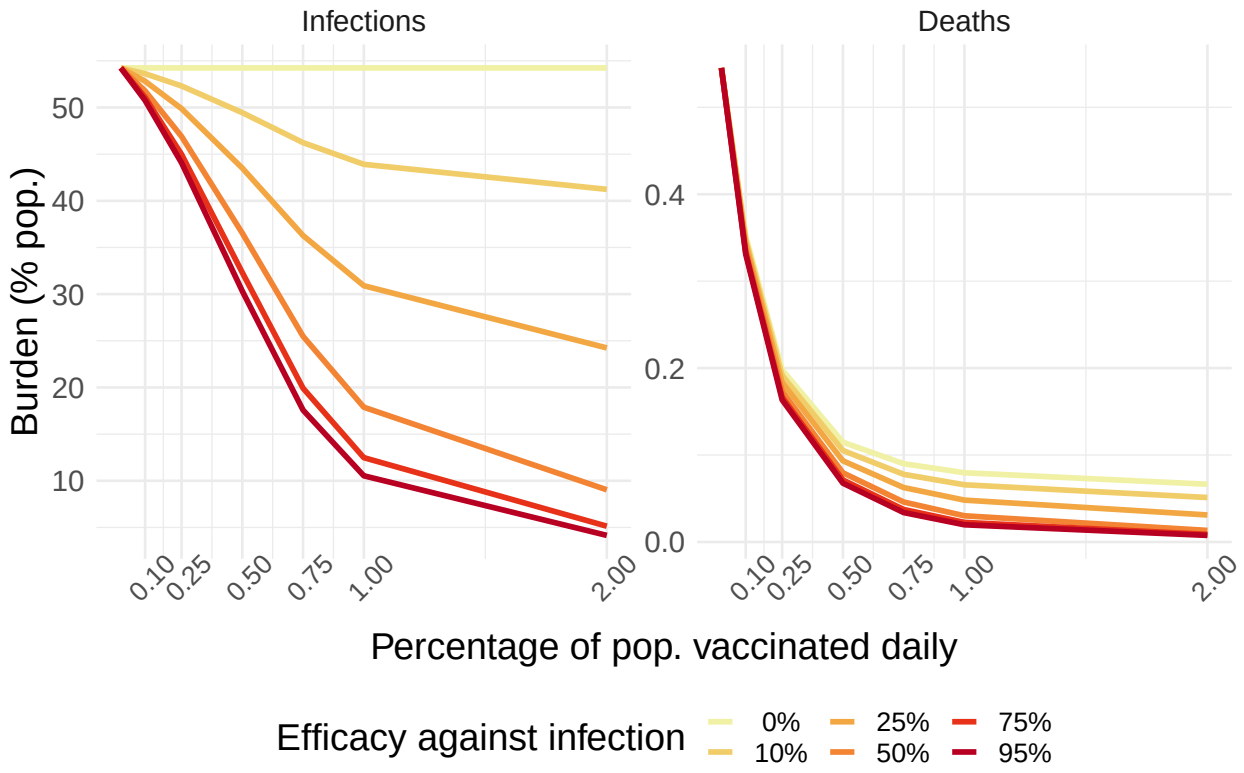

Figure S4: Burden of Infections and Deaths Depending on Efficacy Against Infection. We assume 95% efficacy against mortality; different levels of protection from infection are given by differently coloured lines. Horizontal axis varies vaccination speed.

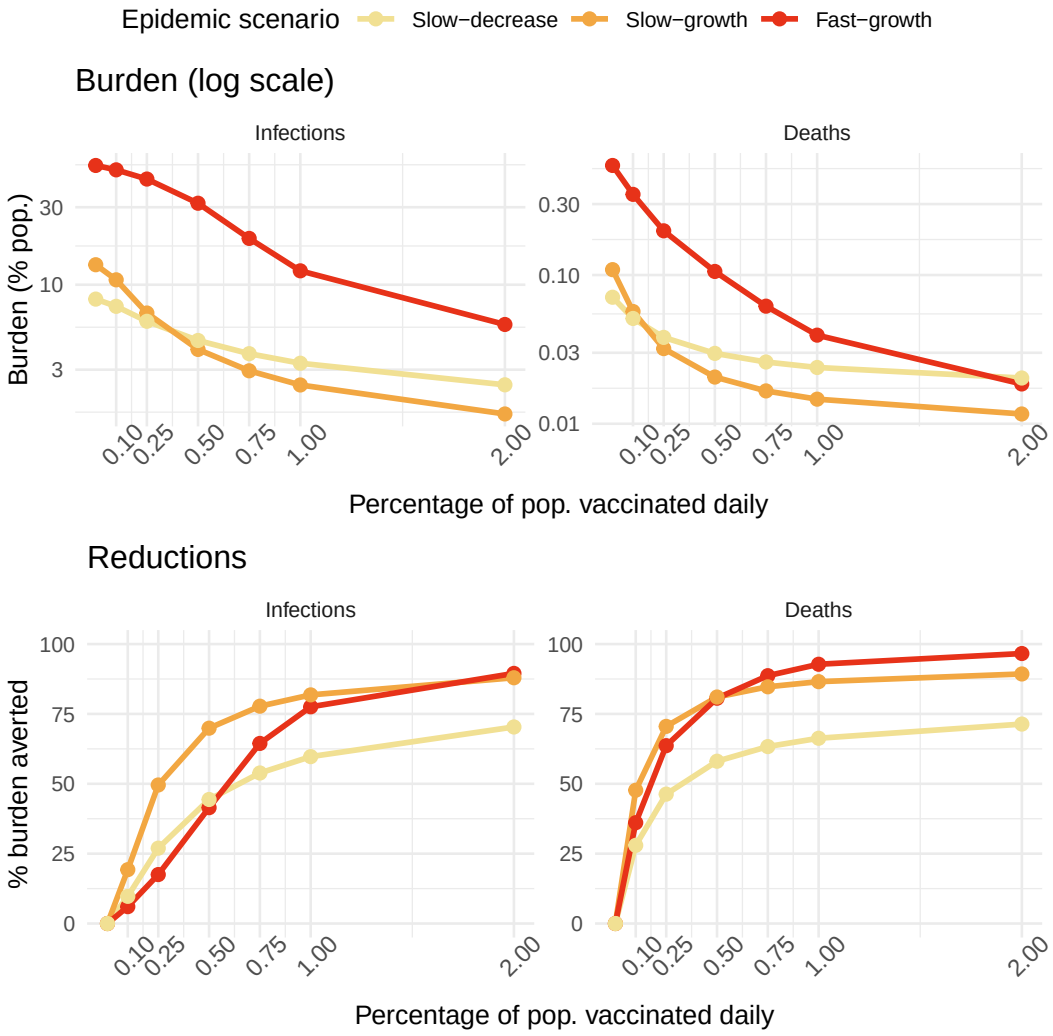

Figure S5: Benefits of Faster Vaccination. The top panels show simulation results for burdens under various vaccination rates for the fast growth epidemic scenario. The bottom panels show simulation results for the percentage reduction in burdens relative to no vaccination. In the left panels, we refer to the burden from infection, while in the right panels we refer to the burden from death. In all scenarios we assume a 95% efficacious vaccine and sequential age prioritization.

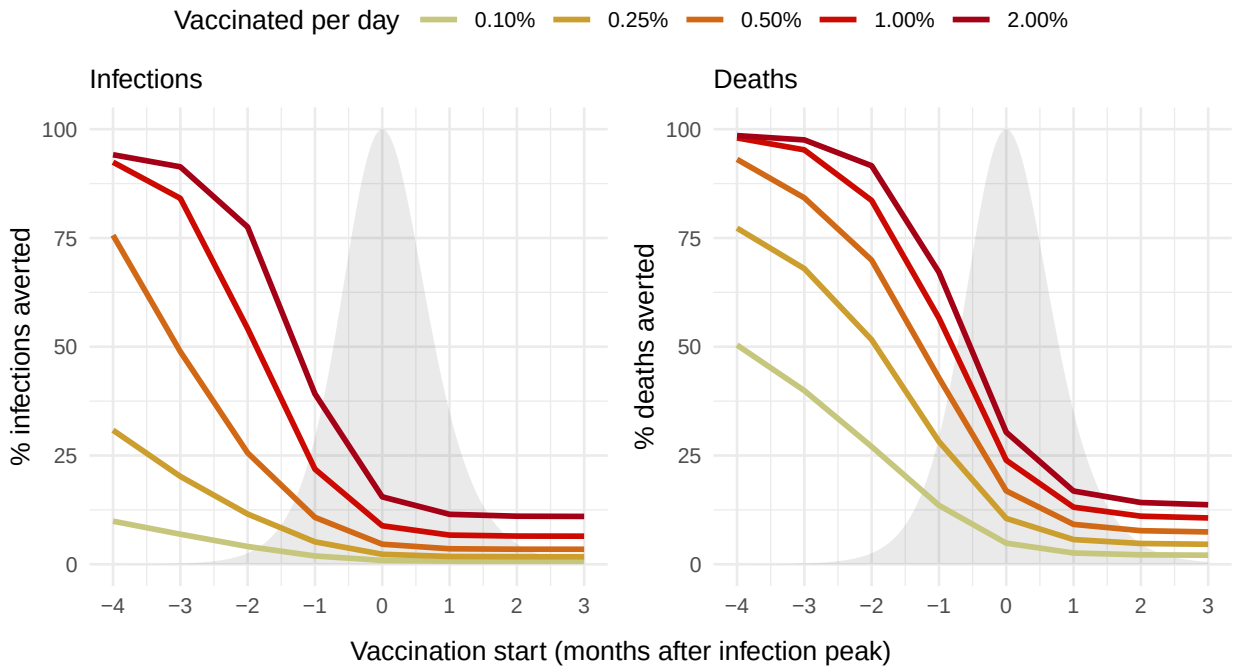

Figure S6: Burden Averted Varying Start of Vaccine Campaign. Simulation results for burden averted relative to no vaccine with vaccination campaign having start dates before or after infection peak (horizontal axis). Different curves correspond to different vaccination speeds. Maintains baseline assumptions including 95% efficacious vaccine. Results consider a fast growth epidemic scenario.

Table S1: Summary of Clinical Trials for COVID-19 Vaccines.*Trial reports immunogenicity at least three weeks after dose administration, before a second dose (if planned) has been administered, and has a comparable outcome (in terms of age group, dose, and day measured) for second doses. **Treatment arms also included groups in which each vaccine dose arm was administered with and without 50µg of Matrix-M adjuvant.

Vaccine	Phase	Date posted	1st dose results*	Doses	Dose interval (days)	Treatment arms	Age group	N	Clinical trials.gov number
ChAdOx1 nCoV-19	1/2	3/27/2020	Yes	2	28, 56	• 1× 5e10 v.p. • 2× 5e10 • 5e10, 2.2e10 • 5e10, 3.5-6.5e10	18-55	1090	NCT04324606
	1/2	6/23/2020	No	2	28	2× 5-7.5e10 v.p.	18-65	2130	NCT04444674
	2/3	5/26/2020	Yes	2	28-42	• 1× 5e10 v.p. • 2× 3.5-6.5e10 • 5e10, 2.2e10 • 5e10, 3.5-6.5e10	18-70+	12390	NCT04400838
	3	9/2/2020	Yes	2	28-84	• 1× 5e10 v.p. • 5-10, 3.5-6.5e10	18+	10300	NCT04536051
JNJ-78436735	1	6/18/2020	Yes	1	n/a	• 1× 5e10 v.p. • 1× 1e11	18-55	25	NCT04436276
	1/2a	6/18/2020	Yes	2	56	• 1× 5e10 v.p. • 2× 5e10 • 1× 1e11 • 2× 1e11	18-55, 65+	1085	NCT04436276
	3	8/10/2020	Yes	1	n/a	1× 5e10 v.p.	18+	44325	NCT04505722
mRNA-1273	1	2/25/2020	No	2	28	• 2× 25µg • 2× 50 • 2× 100 • 2× 250	18+	120	NCT04283461
	2a	5/28/2020	No	2	28	• 2× 50µg • 2× 100	18+	660	NCT04405076
NVX-CoV2373**	1/2	4/30/2020	Yes	2	21	• 2× 5µg • 2× 25 • 5, 25	18-59/ 18-84	131/ 1500	NCT04368988
BNT162b2	1	4/20/2020	No	2	21	• 2× 10µg • 2× 20 • 2× 30 • 2× 100	18-55, 65-85	195	NCT04368728
	2/3	4/20/2020	No	2	21	30µg	12-15, 16-55, 55+	43548	NCT04368728

Table S2: Immunogenicity Data from Phase 1/2 Trials. Neutralizing antibody (nAb) responses listed are the peak levels recorded in published trial data. Sources: ChAdOx1 nCoV-19 (Oxford/AstraZeneca) (*14*), BBV152 (Covaxin) (*35*), JNJ-78436735 (Johnson & Johnson) (*59*), mRNA-1273 (Moderna) - 25 µg (*60*), mRNA-1273 (Moderna) - 50µg (*34*), NVX-CoV2373 (Novavax) (*61*), BNT162b2 (Pfizer) (*62*). *"Standard dose" is what is being used in vaccine roll-outs thus far (v.p.=viral particles). **Both doses were administered together with 50µg of adjuvant. ***Sample size was too small to determine significance.

Vaccine	nAb assay	Day of 2nd dose	Age group	N	Measured on day	Standard dose*	Dose tested	Dose fraction	NAb response	Standard dose NAb response	NAb response as fraction of standard dose	Difference is significant (at 95% level)?
ChAdOx1 nCoV-19	MN_{80}	14	18-55	41	42	5e10 v.p.	2.2e10 v.p.	0.44	161	193	0.83	no
			56-69	28	42			0.44	143	144	0.99	no
			70+	34	42			0.44	150	161	0.93	no
BBV152	$PRNT_{50}$	28	12-65	190	56	6µg	3µg	0.5	100	197	0.51	yes
JNJ-78436735	PRNT IC_{50}	n/a	18-55	24	56	5e10 v.p.	1e11 v.p.	2	310	288	1.08	no
			65+	50	28			2	212	277	0.77	no
mRNA-1273	$PRNT_{80}$	28	18-55	15	42	100µg	25µg	0.25	340	654	0.52	no
	MN_{50}		18-55	78	42		50µg	0.5	1733	1909	0.91	no
			55+	63	42		50µg	0.5	1827	1686	1.08	no
NVX-CoV2373**	MN $IC_{>99}$	21	18-59	50	35	5µg	25µg	5	3305	3906	0.85	no
BNT162b2***	$PRNT_{50}$	21	18-55	12	28	30µg	10µg	0.33	157	361	0.43	n/a
			65-85	12	35		10µg	0.33	111	206	0.54	n/a
			18-55	12	28		20µg	0.67	363	361	1.01	n/a
			65-85	12	28		20µg	0.67	84	206	0.41	n/a

Table S3: Increase in Vaccine Supply from Fractional Doses. Panel 1 shows the total supply projected for 2021. Panel 2 shows the number of doses already delivered by July 2021. Based on the previous values, panel 3 shows the projected baseline supply per month for the remaining 4 months of the year. Finally, panel 4 shows the size of the alternative dose relative to the standard used to estimate the number of extra doses shown in panel 5, where we assume fractional doses would be adopted starting in October.

BNT162b2 (Pfizer)	**mRNA-1273 (Moderna)**	**ChAdOx1 nCoV-19 (Oxford/AstraZeneca)**	**Total**
1. Projected Supply in 2021 (billions of doses)			
3.00	0.80	2.10	5.90
2. Doses Delivered by September 2021			
1.30	0.20	1.10	2.60
3. Projected Baseline Monthly Supply (billion doses/month) = $\frac{[1]-[2]}{4}$			
0.43	0.15	0.25	0.83
4. Dose Regimen (relative to standard)			**5. Extra Doses (billions/month)**
1/3	1/4	1/2	1.55
2/3	1/2	1/2	0.61
2/3	1/2	3/4	0.45

Table S4: Comparison of Efficacy and Effectiveness Data for COVID-19 Vaccines. Values represent point estimates of efficacy and effectiveness. Efficacy against symptomatic infection is derived from phase 2/3 trials data. Estimates of effectiveness against symptomatic infection, hospitalization and death come from various observational studies. Viral variants referred to as "non-VOC" includes all variants that are not classified as Variant of Concern, therefore excluding B.1.617.2, B.1.1.7, and B.1.351.
*Study combines data from individuals vaccinated with both BNT162b2 and mRNA-1273.
**Estimates include occurrences of either hospitalization or death.
***Estimates include occurrences of any severe, critical or fatal disease.

Vaccine	**Efficacy**		**Effectiveness**					
	Symptomatic Infection	Source	Location	Variant	Symptomatic Infection	Hospitalization	Death	Source
ChAdOx1 nCoV-19	64%	(*63*)	UK	B.1.1.7	75%			(*11*)
				B.1.617.2	67%			
				B.1.1.7		86%		(*12*)
				B.1.617.2		92%		
			Scotland	B.1.1.7	81%			(*39*)
				B.1.617.2	61%			
CoronaVac	51% 84%	(*64*) (*65*)	Chile	Various	66%	88%	86%	(*13*)
BNT162b2	95%	(*37*)	UK	B.1.1.7	94%			(*11*)
				B.1.617.2	88%			
				B.1.1.7		95%		(*12*)
				B.1.617.2		96%		
			Scotland	B.1.1.7	92%			(*39*)
				B.1.617.2	83%			
			Israel	Various	97%	97%	97%	(*66*)
			Qatar	B.1.1.7	90%	100%	100%	(*67*)
				B.1.351	75%	100%	100%	
mRNA-1273	94%	(*68*)	USA	Various	94%			(*69*)*
			Canada	B.1.1.7	91%	94%**		(*70*)
				Non-VOC	91%	96%**		(*70*)
			Qatar	Various	99%	96%***		(*71*)
				B.1.617.2	86%	100%	100%	(*72*)

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