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TESTING FRACTIONAL DOSES OF COVID-19 VACCINES

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ABSTRACT

Millions of people are being vaccinated against SARS-CoV-2 every day, but the virus is also mutating and spreading fast. Vaccine production is increasing, but supply still constrains vaccinations worldwide. Using lower doses of vaccines could dramatically accelerate vaccination. Available evidence on efficacy is not dispositive but suggests half- or even quarter-doses of some vaccines could be almost as effective as currently-used doses. Even if fractional doses are less effective than standard doses, an epidemiological model suggests they could significantly reduce total infections and deaths. The social value of testing dwarfs the costs. However, firms do not internalize the full social value, a market failure that could be addressed with public funding. Governments could support either experimental or observational evaluations of fractional dosing.

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1. Introduction

Millions of people are being vaccinated against SARS-CoV-2 every day, but the virus is also mutating and spreading fast. Vaccine production is increasing and could be accelerated further, but supply still constrains vaccinations worldwide, and many countries do not expect to vaccinate large shares of their populations until 2023 (Padma 2021). Until shortages can be alleviated by other means, it is vital that we explore options for using existing vaccine supplies more efficiently.

Using fractional doses of vaccines is one such option, employed successfully in 2016-2018 when several countries used 1/5-doses of yellow fever vaccine to combat epidemics, based on advice from the WHO (World Health Organization 2017). For COVID-19 vaccines, available evidence on efficacy is not dispositive but suggests half- or even quarter-doses of some vaccines could be almost as effective as currently-used doses and more effective than the current standard of care in many countries. They might also reduce side effects. Even if fractional doses are less effective than standard doses, an epidemiological analysis suggests that increasing the speed of vaccination would reduce total infections and deaths under a wide range of conditions. This is true even with minimal impact on disease transmission.

Governments could support either experimental or observational evaluations of fractional dosing. The social value of testing dwarfs the costs. However, firms do not internalize the full social value, a market failure that could be addressed with public funding.

2. Individual impact of changing doses

Efficacy of fractional doses of COVID-19 vaccines has not been tested (except for AstraZeneca's ChAdOx1 nCoV-19, where a low dose-full dose regimen appears to have worked well). 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 Moderna's mRNA-1273, four doses were tested) (see Table 1 in Więcek et al. 2021 for a compilation of clinical trials). More recently, NAb titers for standard doses were found to be remarkably predictive of efficacy against infection (Khoury et al. 2021). We use that relationship together with data on NAb titers in fractional doses to derive their predicted effectiveness (Figure 1). This section reproduces the analysis presented in Więcek et al. (2021).

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 larger doses and greater than those of standard doses of many other, currently-approved vaccines. For example, 50μg and 25μg of Moderna's mRNA-1273 vaccine produce immune responses very similar to those of the standard 100μg doses; all three are associated with 90-95% efficacy. For Pfizer's BNT162b2, 10μg and 20μg have NAb responses associated with efficacy of 70-85%, versus roughly 95% for 30μg, the standard dose.

Extant data also suggest fewer side effects from fractional doses (e.g. Ramasamy et al. 2020). This could be helpful in combating vaccine hesitancy, as vaccine safety and side effects remain a concern for many (e.g. Africa CDC 2021). Additionally, given large variation in immune response with age (see Table 2 in Więcek et al. 2021), a dose that is optimal for the elderly may be unnecessary for younger adults.

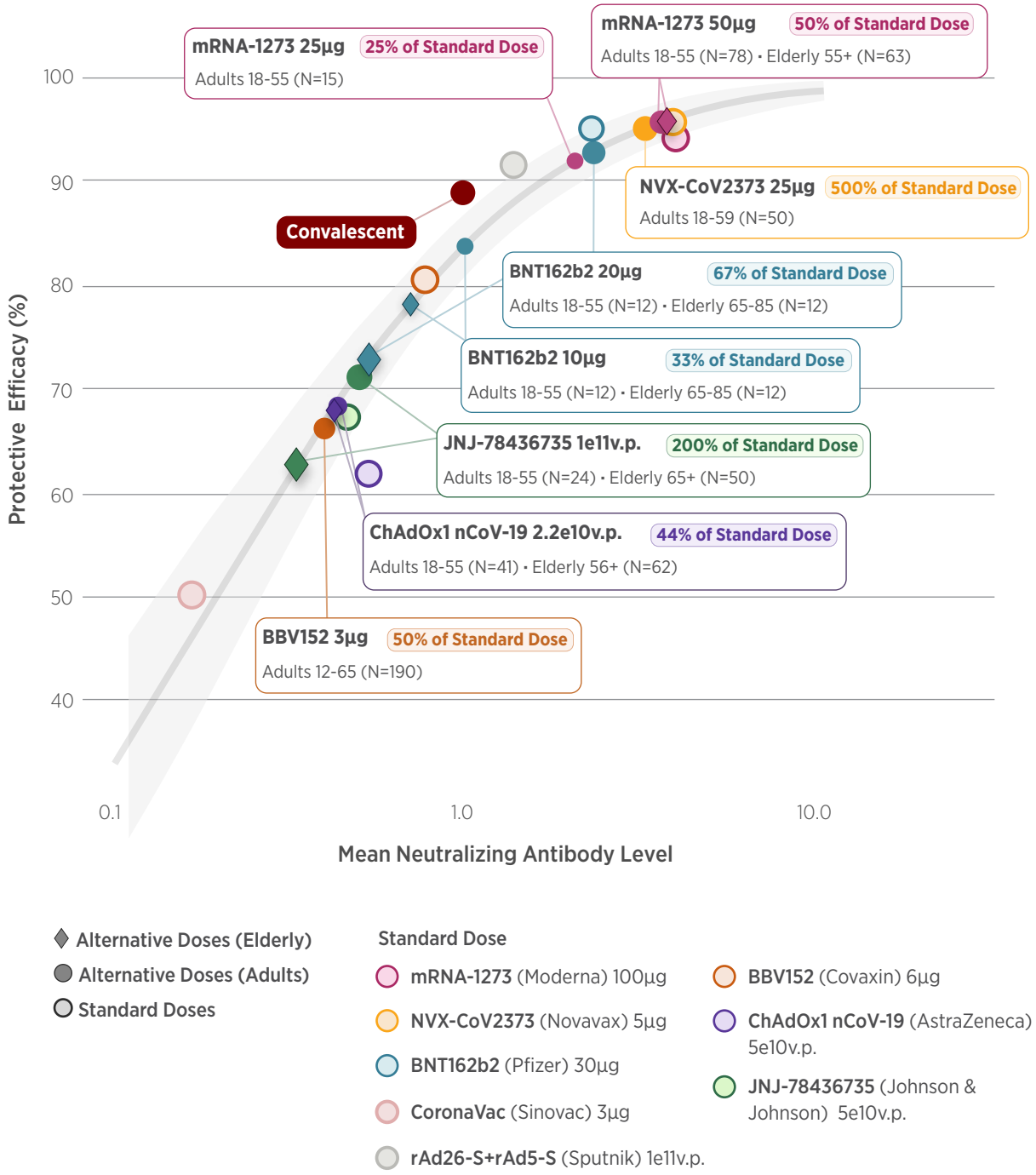

Figure 1: Efficacy Associated with Mean Neutralization Levels for Alternative Doses. The curve follows the model derived in Khoury et al. (2021) linking NAb levels to protection from symptomatic infection for standard doses of eight vaccines and in convalescents, with the shaded area corresponding to the 95% confidence interval of the model. Lighter data points represent the mean (normalized) immune response and clinical efficacy of specific vaccines (referred to by colors) at standard doses, following Khoury et al. (2021); 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 alternative versus standard doses using data from clinical trials that tested different doses. We then plot the alternative doses on Khoury et al.'s 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.

3. Simulating public-health benefits of fractional dosing

Figure 1 suggests that changing doses may produce only minor reductions in efficacy. What if the reductions were larger? Fractional doses might still be beneficial for the population if they enable faster vaccinations. To investigate this, we use an epidemiological model to account for the age-varying effect of vaccination on infections and deaths. We simulate vaccination across a range of efficacy levels and epidemic scenarios in a modified susceptible-exposed-infected-recovered (SEIR) model with a single epidemic peak (to focus on the immediate impact of vaccination). More details are provided in Więcek et al. (2021).

To account for the emergence of more transmissible viral variants which evade some of the vaccine protection, we consider base cases of both 95% and 70% effectiveness. The former is comparable to efficacy against the wild-type virus; the latter is lower than observed effectiveness of BNT162b2 against the Delta variant (Appendix A). In both cases we assume a vaccination rate of 0.25% of the population per day, approximately the global median (Mathieu et al. 2021) as of early May 2021 (when we ran the simulations), and that older individuals are vaccinated first. We consider ranges of losses of immune response (ratios of NAb levels) and use the model from Figure 1 to calculate associated efficacy loss. We consider the case in which vaccination rates are constrained by supply, rather than demand, and therefore inversely proportional to dose.

If there is no loss in efficacy, switching to half-doses would reduce deaths by 20-47% compared to using a standard dose, depending on base case and epidemic scenario (Table 1). Even if half-dose has NAb levels 5-fold lower than a 95% effective full dose, it is still beneficial to switch (or approx 2.5-fold reduction if base case is 70% effective). Additional scenarios are considered in Więcek et al. (2021), with similar reductions in infections.

	Dose			
	1	**1/2**	**1/3**	**1/4**
NAb ratio (efficacy)	**% deaths averted relative to 95% effective full dose**			
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	16 to 22	23 to 44	29 to 60
NAb ratio (efficacy)	**% deaths averted relative to 70% effective full dose**			
1.0 (70%)	0	20 to 32	30 to 52	35 to 64
0.8 (65%)	-6 to -3	18 to 25	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 12

Table 1: Deaths Averted by Switching to Hypothetical fractional dosing Regimens. 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.

Thus, our modeling suggests that even when new variants dominate and vaccine efficacy is significantly lower than that suggested by Figure 1, using fractional doses of the more effective vaccines would save lives. The benefits derive from vaccinating quickly in the face of a growing epidemic.

4. Risks of using lower doses

A possible critique is that it is more difficult to break virus transmission with a less effective vaccine. However, a simple epidemiological analysis shows that, at the vaccination rates typical in many low- and middle-income countries, even a vaccine that is very effective at reducing transmission does not prevent large outbreaks, simply because not enough people are vaccinated in time

(Appendix B). As the recent experience of the UK shows, it is difficult to stop some variants even with high uptake of the most effective vaccines. What faster vaccination can do, however, is protect more people from hospitalization and death.

Relatedly, our modeling does not consider the rate of immunity loss, which may vary by dose size. However, we expect vaccine shortages to ease over time. Therefore, overall mortality is likely to be substantially reduced by addressing shortages quickly. Moreover, 7-month data on people vaccinated with a 25μg dose of mRNA-1273 suggests immunity is indeed durable (Mateus et al. 2021). Some have also argued that alternate dosing might increase the risk of new variants arising due to a prolonged period of partial immunity increasing the risk of immune escape. However, many epidemiologists now believe that faster vaccination may instead reduce the probability of immune escape, and that the greatest risk to immune escape likely comes from the unvaccinated (Cobey et al. 2021).

Lastly, switching to lower dosing now could be criticised as inequitable. However, if there is little efficacy loss and a reduction in side effects, lower doses may actually be superior to standard doses. Even vaccinating more people with a less effective vaccine would still be more equitable than the status quo. Second, reduced doses of vaccines such as the mRNA vaccines are likely more efficacious than the standard of care in many low- and middle-income countries; 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. If fractional dosing could cut time to vaccination in half, the benefits are the largest for those at the end of the queue.

5. Private and social incentives

Some vaccine manufacturers are studying fractional dosing for children and as booster doses (Miller 2021). However, their private incentives to accelerate production are far below the social incentives, creating a critical role for public investment (Ahuja et al. 2021). The value of an additional course of vaccine is estimated to be on the order of $500-1000 (Castillo et al. 2021); in comparison, vaccine manufacturers typically receive $6-40 per course. Hence, pharmaceutical companies have too little incentive to test fractional doses, even if they may improve safety or accelerate vaccinations.

Government investment in accelerating the first-generation vaccines created benefits in the trillions of dollars (Castillo et al. 2021). Similar investments in testing fractional dosing could also have extremely high payoffs: a simple calculation suggests that it is reasonable to expect a boost in vaccine supply ranging from 400 million to 1.5 billion doses per month in 2021 with fractional dosing (Appendix C). Even national incentives are below global incentives, however. For example, the UK's experimentation with increased delay between doses provided valuable information to the rest of the world. Similarly, information on optimal dosing would have tremendous global value, suggesting a role for global institutions.

6. The high value of testing

Despite a global shortage of vaccines, promising clinical trial data available since autumn of 2020, and high expected value of testing, we are aware of only one ongoing efficacy trial, testing half-doses of ChAdOx1 nCoV-19 in Brazil (Universidade Federal do Espírito Santo 2021).

To date, no regulatory agency or immunization advisory group has recommended fractional dosing for COVID-19 vaccines. But given recent progress in establishing correlates of protection against infection (Khoury et al. 2021; Krammer 2021), immunogenicity trials may be sufficient evidence for some policymakers. They can be conducted for many doses in a matter of weeks, at low cost, with few participants and even in places where the risk of COVID-19 infection is low. Pharmacologic models could help combine data from multiple studies and extrapolate a dose-response function over doses and ages.

Where risk of infection is high, governments could instead decide to conduct rapid clinical trials of efficacy or randomize fractional doses as part of wider national vaccination campaigns (Kominers and Tabarrok 2020; Haushofer and Metcalf 2020). Alternatively, to save the most lives in expectation, the policy with the highest expected value could be implemented and outcomes evaluated in real time. 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 (UK Department of Health 2020). Real-world evidence has since emerged supporting this and several countries opted to delay second doses. If evidence suggests that changing doses is not effective or if supply increases rapidly, policy can be adjusted, just as the UK reduced the interval between doses for some adults to maximize protection against the Delta variant. For fractional dosing, this could mean increasing the second dose size or providing booster shots.

Existing vaccines were also used at standard dose against the Delta variant, before there was evidence of effectiveness against this variant, or that the currently prescribed dose (rather than, say, a higher dose) was optimal. As viral evolution outstrips the pace of vaccine trials, decisions will have to be made under uncertainty.

While most of our discussion has focused on the value of testing fractional doses for the un-

vaccinated, the approach is also relevant for booster shots and vaccinations in children and young adults. Lower doses could also be tried for heterologous prime-boost vaccination.

Together, the reversibility and large potential benefits of fractional doses suggest there is tremendous option value in testing them. Given the substantial risks of status quo policies, as recent outbreaks in India, Brazil, and elsewhere have illustrated, the expected value of testing is high even with only a modest chance that they will be effective. We also note that any risk of changing doses is reduced when the unvaccinated population is young or has a higher share of natural immunity, as is increasingly the case amongst those who remain unvaccinated around the world.

7. Conclusion

Clinical evidence and epidemiological modeling both suggest that using fractional doses of some COVID-19 vaccines could accelerate global vaccination and save lives. Fractional doses may be more effective than current standard of care in many countries and may also have fewer side effects.

Any method of increasing supply will require changes in the supply chain and in distribution; changing doses is perhaps the least disruptive and quickest available. Some vaccines could potentially be used off-label in their current formulations, although requiring different syringes or needles for accurate delivery of fractional doses; others may need changes in fill and finish. Modifications to supply chains and delivery systems can proceed in parallel to testing.

The question we face now is not whether there are complications to changing dosing (there are), but what additional information available quickly could resolve the most uncertainty? Testing - either via immunogenicity studies or via rigorously evaluated roll-outs of fractional dosing

regimens - has tremendous option value. If lower doses are found to be effective, they will save lives. If not, the policy can be reversed. The social value of such testing is enormous, but it may not be carried out without public funding.

Appendix A: 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. 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 fold-reductions in NAb levels we described above; second, to motivate choice of parameters in the simulations.

Wall et al. (2021b) and Wall et al. (2021a) 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 efficacy for different variants. Bernal et al. (2021) reports estimates of efficacy against symptomatic infection using observational data on vaccinated individuals in the UK and conclude that efficacy against the Alpha variant for BNT162b2 was 93%, dropping to 88% for the Delta type, for ChAdOx1 nCoV-19 (AstraZeneca/Oxford) the drop is from 66% to 60%. Sheikh et al. (2021) analyses data from Scotland and report the decrease in efficacy against confirmed infection from 92% with the Alpha variant to 79% with the Delta variant for BNT162b2, and from 73% to 60% 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

79% (Sheikh et al. 2021) is associated with a 2.8-fold drop in NAb levels; a decrease from 93% to 88% (Bernal et al. 2021) is associated with a 1.7-fold drop. We can see that these values are comparable to the 2.2-fold drop reported in (Wall et al. 2021b). Moreover, focusing on the Delta variant alone, Wall et al. (2021a) reports a 2.5-fold drop in NAb levels from ChAdOx1 nCoV-19 when compared to BNT162b2. Sheikh et al. (2021) reports a 79% efficacy for BNT162b2 against Delta while ChAdOx1 nCoV-19 has a 60% efficacy. In Khoury et al.'s model, this is associated with an exact 2.5-fold drop in NAb levels.

Appendix B: Differential Impact on Mortality and Infection

The initial SEIR model (Więcek et al. 2021) assumes that effectiveness 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 is available at https://github.com/wwiecek/covstretch, together with all code used in this study.

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 vacci-

nations 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 2, where we assume 95% effectiveness against mortality and varying effectiveness against infection from 0% to 95% (differently coloured lines) and speed of vaccination (x axis). For simplicity we use a fast growing epidemic scenario where infections are increasing, but the overall result carries across all scenarios we simulate (see more details in Więcek et al. 2021).

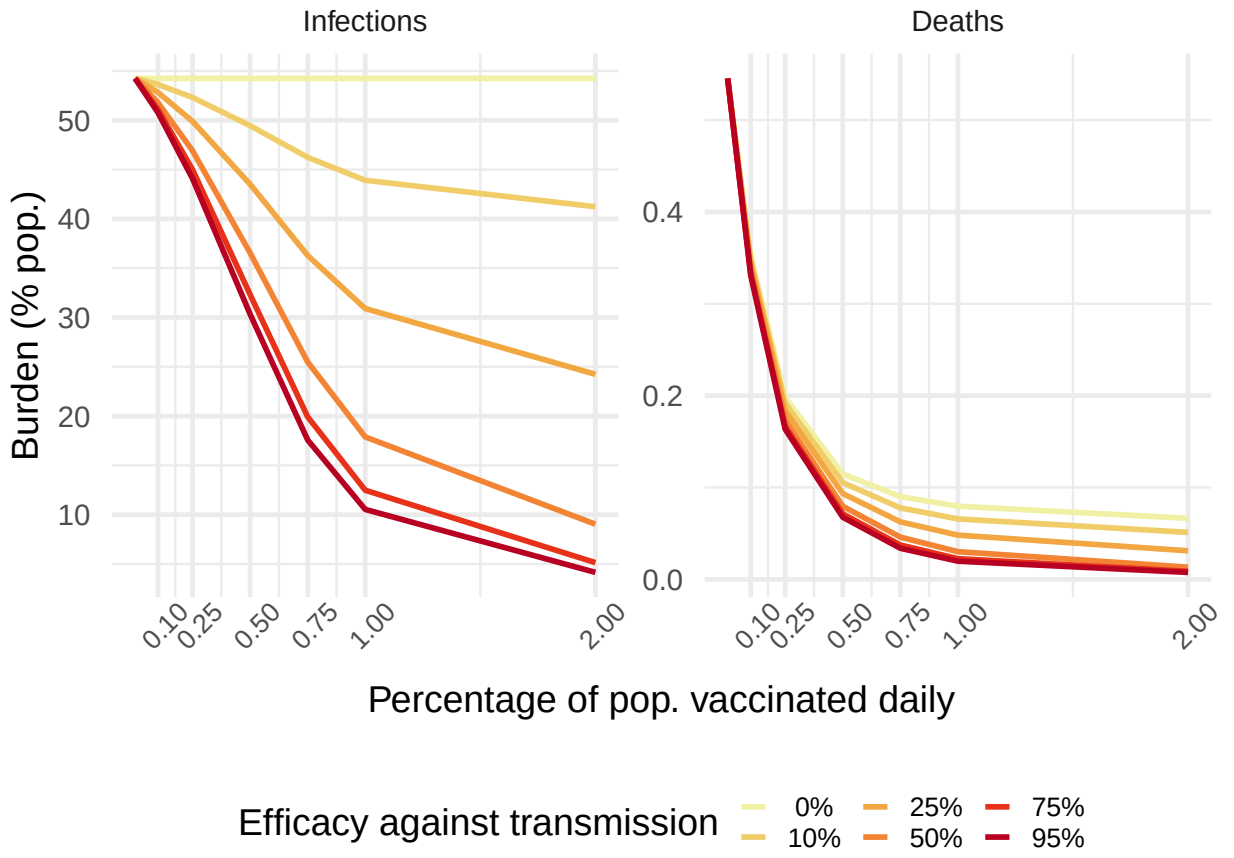

Figure 2: Burden of Infections and Deaths Depending on Effectiveness Against Infection. We assume 95% effectiveness against mortality; different levels of protection from infection are given by differently coloured lines. Horizontal axis varies vaccination speed.

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 2 (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% effectiveness 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.

Appendix C: Increase in Supply from Alternative 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 distributed (or expected to be approved soon – e.g Novavax). The results are shown in Table 2.

We use the best projections currently available for vaccine supply in 2021. This includes data from financial reports (Novavax, Inc. 2021), press releases (Pfizer Inc. 2021; Moderna, Inc. 2021), and third-party publications (Duke Global Health Innovation Center 2021; Zimmer, Corum, and Wee 2021) 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), 2.1 billion doses for ChAdOx1 nCoV-19 (Oxford/AstraZeneca), 1 billion doses for JNJ-78436735 (Johnson & Johnson), and 300 million doses for NVX-CoV2373 (Novavax). For the latter, the manufacturer expects to be able to supply 100 million doses per month starting in the fourth quarter of 2021.

We combine the projected supply with the number of doses already delivered according to UNICEF (UNICEF 2021) (as of July 12, 2021). We subtract doses delivered from projected supply and assume that the remaining quantity will be delivered uniformly during the last 6 months of the year. The exception is NVX-CoV2373 (Novavax), which will become available only in October. 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 2.

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). The exceptions are JNJ-78436735 (Johnson & Johnson) and NVX-CoV2373 (Novavax), for which there is no data on immunogenicity of reduced doses. For those, we adopt an alternative dose corresponding to 2/3 of the standard, which is an intermediate but still conservative level. We observe that for the scenarios considered here, it is possible to produce 400 million to 1.4 billion extra doses globally in each month starting in July, and 440 million to 1.5 billion extra doses starting in October.

BNT162b2 (Pfizer)	mRNA-1273 (Moderna)	ChAdOx1 nCoV-19 (Oxford/AstraZeneca)	NVX-CoV2373* (Novavax)	JNJ-78436735 (Johnson & Johnson)	Total
1. Projected Supply in 2021 (billions of doses)					
3.00	0.80	2.10	0.30	1.00	7.20
2. Doses Delivered by July 2021					
0.56	0.23	0.39	0.00	0.04	1.22
3. Projected Baseline Monthly Supply (billion doses/month) = $\frac{[1]-[2]}{6}$					
0.41	0.10	0.29	0.10	0.16	1.06
4. Dose Regimen (relative to standard)					**5. Extra Doses (billions/month)**
1/3	1/4	1/2	2/3	2/3	1.51
1/3	1/4	1/2	2/3	1	1.41
1/3	1/4	1/2	1	1	1.38
2/3	1/2	1/2	2/3	1	0.63
2/3	1/2	1/2	1	1	0.58
2/3	1/2	3/4	2/3	1	0.44
2/3	1/2	3/4	1	1	0.39

Table 2: Increase in Supply from Alternative 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 6 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.
*For NVX-CoV2373 (Novavax), we use the projected supply capacity expected to be available by the end of the third quarter of 2021, therefore the extra doses would only come in effect starting in October. For this reason, line 3 shows a projected monthly supply of 0.1 billion doses for NVX-CoV2373. For the other vaccines, capacity should be readily available, so extra doses could come in effect already in July, 2021.

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