Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination

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Sarah Cobey[1]*, Daniel B. Larremore[2,3], Yonatan H. Grad[4], and Marc Lipsitch[4,5]

[1]Department of Ecology and Evolution, University of Chicago, Chicago, IL, USA
[2]Department of Computer Science, University of Colorado Boulder, Boulder, CO, USA
[3]BioFrontiers Institute, University of Colorado Boulder, Boulder, CO, USA
[4]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[5]Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

*Correspondence: cobey@uchicago.edu

Abstract

When vaccines are in limited supply, expanding the number of people who receive some vaccine can reduce disease and mortality compared to concentrating vaccines in a subset of the population. A corollary of such dose-sparing strategies is that vaccinated individuals may have less protective immunity. Concerns have been raised that expanding the fraction of the population with partial immunity to SARS-CoV-2 could increase selection for vaccine escape variants, ultimately undermining vaccine effectiveness. We argue that although this is possible, preliminary evidence instead suggests such strategies should slow the rate of vaccine or immune escape. As long as vaccination provides some protection against escape variants, the corresponding reduction in prevalence and incidence should reduce the rate at which new variants are generated and the speed of adaptation. Because there is little evidence for efficient immune selection of SARS-CoV-2 during typical infections, these population-level effects are likely to dominate vaccine-induced evolution.

Introduction

In an effort to reduce the number of COVID-19 cases, hospitalizations, and deaths as fast as possible, the UK has adopted a policy that prioritizes administering first doses of SARS-CoV-2 vaccines widely over giving second doses to those who have received one, and some in the US have discussed similar policies, including vaccination of twice the number of individuals with two half doses. These strategies are collectively known as “dose-sparing” strategies, intended to maximize the proportion of the population reached quickly with some vaccine. While much of the discussion of these strategies has been in high-income countries, it is an even more pressing question globally, where there remains an extreme vaccine shortage. Fewer than two billion doses are projected to be available by the end of 2021 through COVAX, which would cover about a quarter of the 6.4 billion residents of the countries targeted by COVAX, assuming two doses are

needed (COVAX 2021). There has been controversy about the scientific basis for dose-sparing strategies and whether they will result in better outcomes for the pandemic.

Opponents of dose-sparing strategies have raised concerns about the feasibility and legal status of dose-sparing efforts, noting that providing first doses without a short-term guarantee of a second dose could lead some individuals not to come back for a second dose, or to shortages if later vaccine supplies are delayed. Multiple modeling studies have suggested that dose-sparing strategies would reduce the burden of disease from COVID-19 (Tuite et al. 2021; Barnabas and Wald 2021; Paltiel, Zheng, and Schwartz 2021). To a first approximation, as previously observed in model-based considerations of dose sparing for other infections (Riley, Wu, and Leung 2007; J. T. Wu et al. 2016), if individuals given half as much vaccine (one versus two doses, or half the quantity of antigen per dose) get at least half the protection from clinical infection of those given a full regimen, then spreading the vaccine among more individuals will produce greater reductions in the number of clinical infections. These reductions will be even greater if the dose-sparing regimen is at least half as good as the full regimen in reducing transmission. The above-cited references make a similar point, with additional nuance specific to the present situation.

While the legal, logistical, and direct epidemiological impacts of dose-sparing strategies have received robust discussion and in the above-cited cases quantitative analysis, there has been another objection that is more speculative but, if correct, perhaps more important: that dose sparing will cause a more rapid emergence and spread of vaccine-resistant genetic variants (Bieniasz 2021; New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) 2021). Reports of lower vaccine efficacy against the B.1.351 variant in South Africa (Madhi et al. 2021) add urgency to this concern. In our view, there is an argument at least as strong to suggest that dose sparing could reduce the spread of vaccine-escape variants, rather than increase it. To be clear, we consider this to be a speculative issue on which no conclusive prediction can be made. Nevertheless, given the importance of making decisions about dose sparing with imperfect information, here we discuss how evolutionary considerations argue for, rather than militate against, dose-sparing strategies.

Dose sparing will likely reduce disease burden, infection prevalence, and incidence

Authorized mRNA vaccines against COVID-19 likely meet the criterion that a single dose gives at least half the protection of two doses. Direct evidence of the durability of protective immune responses months after a single dose is not yet available, but the data that do exist on the immune response after a single dose of mRNA vaccine are promising. The Phase 3 trials of the Moderna and Pfizer-BioNTech vaccines demonstrated high vaccine efficacy in the brief period starting approximately two weeks after the first dose to just before the administration of the second (Polack et al. 2020; Baden et al. 2020). Estimates of primary dose efficacy exclude the two weeks immediately after the first vaccination, as it takes approximately this long to develop a de novo antibody response to a new antigen. Moderna estimated the efficacy of the vaccine in this window

starting two weeks after the first dose to be 92.1% (68.8%, 99.1%) (ModernaTX, Inc. 2020), and the analogous estimate for the Pfizer-BioNTech vaccine is 92.6% (69.0%, 98.3%) (Danuta M. Skowronski and De Serres 2021). An observational study of early vaccination rollout in Israel estimates that one dose of the Pfizer-BioNTech vaccine reduces symptomatic infections and all documented infections, respectively, by 57% (50%, 63%) and 46% (40%,51%) (Dagan et al. 2021).

A reduction in disease in vaccine recipients is the first potential benefit of dose sparing. COVID-19 vaccines can attenuate disease severity when they do not stop infection (Voysey, Clemens, Madhi, Weckx, Folegatti, Oxford COVID Vaccine Trial Group, et al. 2021; Baden et al. 2020; Polack et al. 2020), a pattern sometimes observed in seasonal influenza vaccines (Tenforde et al. 2020; Thompson et al. 2018; C. S. Arriola et al. 2015; C. Arriola et al. 2017). As long as a single dose retains most of the effectiveness against disease of two doses, higher coverage via dose sparing should protect more people against clinical infection, hospitalization, and death (Tuite et al. 2021; Barnabas and Wald 2021; Paltiel, Zheng, and Schwartz 2021).

Another potential advantage of dose sparing is indirect protection of others, if the vaccine decreases transmission. Reduced rates of transmission would lower incidence and prevalence. Notably, the endpoint in most trials is symptomatic, PCR-confirmed COVID-19, and only limited data are available on the effects of vaccines on infection and viral replication. Early reports from the rollout of the Pfizer vaccine in Israel show lower nasopharyngeal viral loads in vaccine recipients (Levine-Tiefenbrun et al. 2021). Reductions in nasopharyngeal viral load are also observed in patients given systemically administered monoclonal antibodies (Chen et al. 2021) and antibody cocktails (Weinreich et al. 2021). Among those in the Moderna randomized controlled trial who were swabbed before their second vaccine dose, the first dose reduced nasopharyngeal PCR positivity by 61.5% (Baden et al. 2020), and it is reasonable to think that the reduction in infectiousness may be even greater given that vaccination might cause lower viral loads among the positives. This is by definition more than half of the maximum reduction one could hope to see (100%). If this (or a greater) level of protection is sustained for many weeks after a first dose, then dose sparing would certainly reduce the prevalence of infection more than vaccination with a two-dose regimen.

It is possible that protection against symptomatic or all infection could wane substantially in the weeks after the first dose. Although antibody responses typically fall from their peak several weeks after infection and vaccination, a study in animals suggests no reason to doubt the longevity of memory induced after a single dose of mRNA vaccine (Pardi et al. 2018). It is also possible, hypothetically, that the booster effect of a second dose of vaccine could be lower if given more than 3-4 weeks after the first dose. Again, there are few data from mRNA vaccines, but data from the chimpanzee adenovirus-vectored vaccine (AstraZeneca) indicates that, to the contrary, a longer dosing interval is associated with greater efficacy and better post-dose-2 antibody titers (Voysey, Clemens, Madhi, Weckx, Folegatti, Aley, et al. 2021).

One might ask if these reductions in disease and transmission from a dose-sparing strategy would persist in the face of variants that are less affected by the natural and/or vaccine-induced immune response. We argue that they should, because the evolution of complete escape from vaccine-induced immunity is exceedingly unlikely (Kennedy and Read 2017). Thus, vaccines that reduce disease against the original (wild-type) virus are still likely to reduce disease somewhat against the escape variant. Similar effects would hold for transmission: escape variants would transmit better than the wild-type virus in a vaccinated population, but they would not transmit as readily in a vaccinated population as the wild-type virus would in an unvaccinated population (Figure 1A, B). Vaccine-induced immunity includes an antibody response, which targets multiple conformational epitopes on the spike protein, and a T cell response, which targets a different set of linear epitopes. Mutations that attenuate the binding of some antibodies or T cell receptors will reduce but not eliminate individuals' protective immunity (Greaney et al. 2021; Wang et al. 2021; Liu et al. 2020). Consequently, it is extremely unlikely that the epidemic dynamics of a vaccine escape variant would be identical to the dynamics of original variants. Instead, the vaccine escape variants in vaccinated populations are likely to be transmitted more slowly than their ancestors were in unvaccinated populations, resulting in lower prevalence and incidence.

Taken together, these considerations argue that the protection against disease should be greater, and the reduction in prevalence of infection greater, in a dose-sparing approach where more individuals receive one dose than in a comparator scenario where half as many individuals receive two doses.

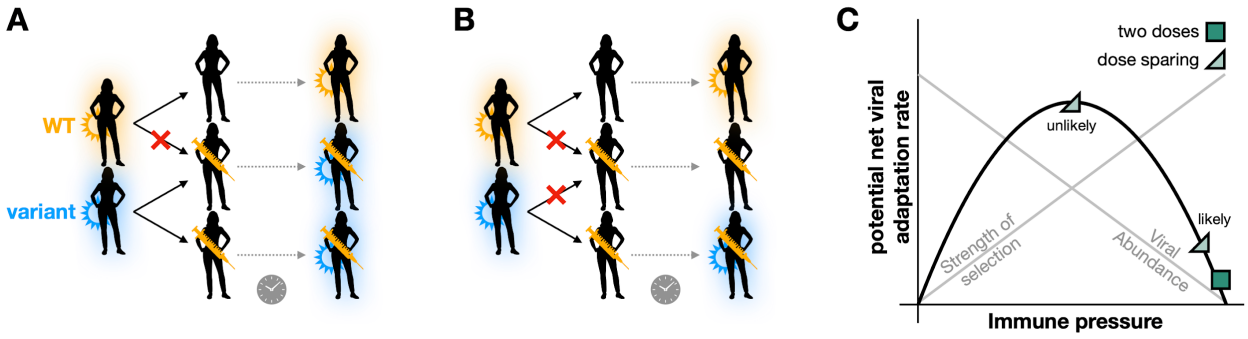

Figure 1. Potential vaccine-induced evolution. (A) Vaccination increases the transmission advantage of an escape variant compared to wild type. Here, vaccine escape is complete, allowing the variant to replace the wild type in vaccinated hosts. (B) If residual immune protection from vaccination slows the transmission of the variant, the variant cannot spread as readily in the vaccinated population, reducing prevalence and incidence. (C) Within hosts, "intermediate" immune pressure could in theory maximize the rate of adaptation. After two doses of vaccine, strong immune responses will likely inhibit viral replication and the emergence of escape mutations. Some have proposed that with just one dose, the rate of within-host adaptation could be high (triangle at top of the curve). We suggest that selection during COVID-19 infections is inefficient (triangle to lower right of curve).

Evolutionary considerations

Evolution by natural selection proceeds most quickly when it has more raw material, meaning more genetic variation to work with (Fisher 1999), and when it is stronger, meaning in this case that the immune responses promoting the growth or transmission of mutants resistant to these responses are stronger. Immunity can select for vaccine escape variants of a transmissible pathogen in two ways, during infection and during transmission. Both scales of selection determine the abundance of the pathogen in the population. Thus, evolutionary arguments about vaccination must consider both the propensity of immune-escape variants to spread between hosts and the rate at which these variants are generated.

Reduced prevalence and transmission reduce opportunities for emergence of resistance

The arguments above suggest that, thanks to at least some effect on transmission from one dose, widespread use of a single dose of mRNA vaccines will likely reduce infection prevalence compared to using the same number of doses to vaccinate half as many people, twice, at the recommended interval.

The reduced transmission and lower prevalence have several effects that individually and together tend to reduce the probability that variants with a fitness advantage such as immune escape will arise and spread (Wen, Malani, and Cobey 2020). The first is that with fewer infected hosts, there are fewer opportunities for new mutations to arise—reducing available genetic variation on which selection can act. Although substitutions that reduce antibody binding were documented before vaccine rollout and are thus relatively common, adaptive evolution is facilitated by the appearance of mutations and other rearrangements that increase the fitness benefit of other mutations (Gong, Suchard, and Bloom 2013; N. C. Wu et al. 2013; Starr and Thornton 2016). The global population size of SARS-CoV-2 is enormous, but the space of possible mutations is larger, and lowering prevalence helps constrain this exploration. Other benefits arise when a small fraction of hosts drives most transmission and the effective reproductive number is low. Selection operates less effectively under these conditions: beneficial mutations will more often be lost by chance, and variants with beneficial mutations are less certain to rise to high frequencies in the population (Desai, Fisher, and Murray 2007; Patwa and Wahl 2008; Otto and Whitlock 1997; Desai and Fisher 2007; Kimura 1957). More research is clearly needed to understand the precise impact of vaccination on SARS-CoV-2 evolution, but multiple lines of evidence suggest that vaccination strategies that reduce prevalence would reduce rather than accelerate the rate of adaptation, including antigenic evolution, and thus incidence over the long term.

In evaluating the potential impact of expanded coverage from dose sparing on the transmission of escape variants, it is necessary to compare the alternative scenario, where fewer individuals are vaccinated (but a larger proportion receive two doses) and more people recover from natural infection. Immunity developing during the course of natural infection, and the immune response

that inhibits repeat infection, also impose selection pressure. Although natural infection involves immune responses to a broader set of antibody and T cell targets compared to vaccination, antibodies to the spike protein are likely a major component of protection after either kind of exposure (Addetia et al. 2020; Zost et al. 2020; Steffen et al. 2020), and genetic variants that escape polyclonal sera after natural infection have already been identified (Weisblum et al. 2020; Andreano et al. 2020). Studies comparing the effectiveness of past infection and vaccination on protection and transmission are ongoing. If protective immunity, and specifically protection against transmission, from natural infection is weaker than that from one dose of vaccination, the rate of spread of escape variants in individuals with infection-induced immunity could be higher than in those with vaccine-induced immunity. In this case, an additional advantage of increasing coverage through dose sparing might be a reduction in the selective pressure from infection-induced immunity.

Within hosts, dose sparing is unlikely to promote immune escape

As has long been noted (Grenfell et al. 2004), immune responses reduce viral growth, which reduces genetic variation, creating a "Goldilocks" situation for adaptation: too little immune response means not much selective pressure to escape immunity, and too much immune response shuts down viral replication before escape variants can be generated. In theory, at intermediate levels of immunity, there is enough viral replication to generate escape variants and enough selection pressure to amplify those variants so that they grow to high frequency and may be transmitted to others (Figure 1C).

In the simplest terms, the concern that dose-sparing strategies will enhance the spread of immune escape mutants postulates that individuals with a single dose of vaccine are those with the intermediate, "just right" level of immunity, more likely to evolve escape variants than those with zero or two doses (Bieniasz 2021; Saad-Roy et al. 2021). Hypothetically this intermediate level of immunity could arise weeks to months after vaccination, after initial immune responses have waned, and would have been avoided had the second dose been received earlier. Similarly, for the half-dose strategy, the postulate is that an individual with two half-doses has immunity closer to "just right" levels than an individual with no doses or two full doses.

There is no particular reason to believe this is the case. Strong immune responses arising from past infection or vaccination will clearly inhibit viral replication, preventing infection and thus within-host adaptation. But it is unclear if weaker immune responses that do permit viral replication should impose much selective pressure. Unlike in chronic infections such as HIV, relatively few generations of replication and thus selection occur in hosts experiencing acute infections such as COVID-19. Most transmission occurs within a day or two of peak viral load, near the onset of symptoms (He et al. 2020; Li et al. 2021). The small founding populations and short time to peak load afford little time for escape variants to appear via mutation and rise to appreciable abundance, especially if viral loads are suppressed from residual immunity from vaccination (Morris et al. 2020; McCrone et al. 2018; Valesano et al. 2021; Martin and Koelle 2021). Past

work on influenza has found no evidence of selection for escape variants during infection in vaccinated hosts (Debbink et al. 2017). Instead, evidence suggests that it is immunocompromised hosts with prolonged influenza infections and high viral loads whose viral populations show high diversity and potentially adaptation (Xue et al. 2017, 2018), a phenomenon also seen with SARS-CoV-2 (Choi et al. 2020; Kemp et al. 2020; Ko et al. 2021). It seems likely, given its impact on disease, that vaccination could shorten such infections, and there is limited evidence already that vaccination reduces the amount of virus present in those who do become infected post-vaccination (Levine-Tiefenbrun et al. 2021).

The implication is that because within-host selection tends to be inefficient, the emergence by mutation and onward transmission of vaccine escape variants is not necessarily more likely in vaccinated hosts compared to unvaccinated ones, including individuals with immunity from natural infection. Instead, the strongest selection for vaccine escape mutants occurs via transmission.

Discussion

We have argued that dose sparing will not necessarily increase the risk of vaccine escape and might even lower it. Moreover, even under worst-case evolutionary scenarios, residual immunity from dose-sparing strategies should reduce the burden of COVID-19 disease. We propose that this residual immunity would in general not be expected to promote the evolution of escape variants because selection of de novo mutations is inefficient during individual infections, and residual immunity from expanded vaccination should slow transmission of all SARS-CoV-2. This, in turn, will slow the rate of adaptation and possibilities for further escape. This evolutionary logic implies that any measures to reduce the rate of transmission, not only dose sparing, could reduce the rate of vaccine or immune escape and the emergence of more transmissible variants.

Although they are based on the best available evidence, these conclusions are necessarily tentative. They rely on the notable assumptions that partial or delayed dosing can be at least half as effective as full dosing and that vaccines will continue to offer some protection against the transmission of escape variants. There is an urgent need for molecular epidemiological studies and quantitative modeling of SARS-CoV-2 to better understand the dynamics of immunity after infection and vaccination, including how immunity relates to protection against disease and transmission. Longitudinal studies that track natural infection among vaccinated and unvaccinated individuals are useful to evaluate the strength and durability of protection against disease and subclinical infections. By measuring shedding duration and intensity, such studies can also indirectly estimate the impact of immunity on transmission, although transmission is better studied in household studies and cluster randomized trials. A full understanding of the epidemiological and evolutionary impacts of vaccination requires reconciling individual observations with population patterns. Vaccine effectiveness against specific viral lineages can be measured by outpatient surveillance of clinical infections in vaccinated and unvaccinated subjects, as occurs for seasonal influenza (Flannery et al. 2019; D. M. Skowronski et al. 2016; Danuta M. Skowronski et al. 2020). Expanded genomic surveillance would also allow comparison

of lineage dynamics and disease rates in areas with different vaccination coverage (Wen et al. 2018). Combined, these measures could drive quantitative assessments of vaccination strategies and evaluate the truth of our assumptions.

An important caveat to our argument is that we assume that mutations that confer vaccine escape are not exclusively linked to other fitness-enhancing mutations. In other words, we assume that phenotypic traits are independent. For instance, if a mutation conferring a doubling in transmission rate, independent of immune recognition, arose in a vaccine escape variant, and if it only arose in this genetic background, then vaccination would accelerate the speed with which this variant displaced resident strains. Hitchhiking mutations conferring resistance to antivirals in influenza have spread unexpectedly through selection for faster replication (Bloom, Gong, and Baltimore 2010) or a putative immune escape variant. These situations are challenging to predict. But although vaccine escape variants such as B.1.351 are associated with mutations that might increase transmissibility, such as N501Y, other lineages such as B.1.1.7 also show high rates of transmission without comparable advantages against vaccines. Thus, we suspect vaccination will not accelerate the evolution of more transmissible variants—they are spreading regardless—and there are theoretical reasons to expect that vaccination will prevent their continued emergence. We note that the first putative vaccine escape variant, B.1.351, and a possible immune escape variant P1 spread in the presence of little or no vaccine-induced immunity.

The pandemic forces difficult choices under scientific uncertainty. There is a risk that appeals to improve the scientific basis of decision-making will inadvertently equate the absence of precise information about a particular scenario with complete ignorance, and thereby dismiss decades of accumulated and relevant scientific knowledge. Concerns about vaccine-induced evolution are often associated with worry about departing from the precise dosing intervals used in clinical trials. Although other intervals were investigated in earlier immunogenicity studies, for mRNA vaccines, these intervals were partly chosen for speed and have not been completely optimized. They are not the only information on immune responses. Indeed, arguments that vaccine efficacy below 95% would be unacceptable under dose sparing of mRNA vaccines imply that campaigns with the other vaccines estimated to have a lower efficacy pose similar problems. Yet few would advocate these vaccines should be withheld in the thick of a pandemic, or rollouts slowed to increase the number of doses that can be given to a smaller group of people. We urge careful consideration of scientific evidence to minimize lives lost.

Finally, limiting both the disadvantages cited by opponents of dose sparing and the advantages highlighted here is the global nature of the SARS-CoV-2 pandemic and continuing movement of variants across continents. It may be short-sighted to imagine that the policy of any one country can have a large influence on the global evolution of the virus.

Conclusion

We propose that dose-sparing strategies, which could have large public health benefits, not be dismissed out of concern that they might promote immune escape in SARS-CoV-2. In fact, multiple lines of evidence suggest that expanded vaccination coverage could reduce the rate of immune escape, providing an additional benefit of dose sparing beyond its immediate impact on disease. These beneficial effects hinge on the assumption that vaccination provides some protection against variants of SARS-CoV-2, or in other words, that vaccine effectiveness against the variants is not zero under dose sparing. Another requirement is that other fitness-enhancing mutations not be exclusively linked to vaccine escape mutations. Both of these assumptions appear currently met. We encourage research to refine understanding of vaccine effectiveness, immune pressure, and the evolutionary dynamics of SARS-CoV-2, and to investigate this problem more thoroughly.

Author contributions

SC, DBL, YHG, and ML wrote the manuscript.

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Competing interests

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