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Third doses of COVID-19 vaccines reduce infection and transmission of SARS-CoV-2 and could prevent future surges in some populations — Source link

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Third doses of COVID-19 vaccines reduce infection and transmission of SARS-CoV-2 and could prevent future surges in some populations

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Summary

Background Vaccines have greatly reduced the impact of COVID-19 globally. Unfortunately, evidence indicates that immunity wanes following vaccination, especially with the Delta variant (B.1.617.2). Protection against severe disease and death remain high, but protection against milder disease and infection have dropped significantly. A third "booster" dose of two-dose vaccines has been approved in several countries to individuals at higher risk of severe disease to protect those individuals, but the benefit to boosting immunity in younger healthy individuals and the effects on transmission are less clear.

Methods Here we use relationships between neutralizing antibody titers and vaccine protection against infection and transmission, combined with data on waning and boosting of neutralizing antibody titers to examine the impact of a third dose of the Pfizer vaccine on infection and transmission and its impact on the pathogen effective reproductive number R_t.

Findings Eight months of waning reduced protection of the Pfizer vaccine against all infections from 80.0% (95% CI: 77% to 83%) to 60.4% (95% CI: 53% to 67%); a third dose (which increased neutralizing antibody titers 25.9- fold relative to levels after 8 months of waning) increased protection to 87.2% (95% CI: 83% to 91%). Increased protection against infection and transmission from third doses reduced R_t by 21% to 66% depending on vaccine coverage and previous infection and reduced R_t below 1 when vaccination coverage was high or contact rates were well below pre-pandemic levels.

Interpretation A third dose of the Pfizer vaccine could reduce transmission of SARS-CoV-2, which would reduce infection in unvaccinated individuals and breakthrough infections in vaccinated individuals. While vaccination of unvaccinated individuals, especially in developing countries, would be more effective for reducing disease than providing a third dose to vaccinated individuals, the benefit of a third dose in reducing transmission is sizeable and increases with vaccine coverage and contact rates among individuals.

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Introduction

The emergence of the Delta variant (B.1.617.2) of SARS-CoV-2 has caused a surge of infections globally, even in populations with high vaccination coverage [1]. This is due, in part, to the much higher infectiousness of this virus variant [2], moderate immune evasion [3-5], and, increasingly, waning vaccine immunity, based on both levels of neutralizing antibodies [6-9] and studies of vaccine effectiveness [10-12]. Several countries have recently offered third doses to individuals at higher risk of severe disease [13] because protection for these individuals, even against severe disease, has waned the most [10]. However, protection against severe disease for heathy individuals has waned far less and the need and benefit of providing third doses for young healthy individuals has been questioned [14]. Many populations, especially those in Africa, have received very few vaccine doses and many have argued that vaccinating these populations would provide a larger public health benefit than providing third doses to already vaccinated individuals [14] and for reducing the evolutionary potential of the virus [15].

While the direct benefit of providing third doses to elderly and other at-risk individuals is now clear [16], the indirect benefit for reducing transmission of SARS-CoV-2 is poorly understood. Most studies examining waning of vaccine effectiveness over time have focused on protection against symptomatic disease [10-12]. The impact of waning immunity and boosting on vaccine protection against all infections (symptomatic and asymptomatic) and against virus transmission has been mentioned [14], but not quantified, despite its potential importance for reducing infection in unvaccinated individuals and breakthrough infections in vaccinated individuals.

Here we extend a previous approach that showed strong correlations between a measure of immunity, neutralizing antibody titers and vaccine protection [17]. This study examined protection against symptomatic disease against non-Delta variants using data from randomized control trials [17]. We extend this approach by mapping neutralizing antibody titers to protection against both symptomatic disease and all infections for both Delta and non-Delta variants. We then use measurements of waning neutralizing antibody titers and boosting with a third dose to estimate the impact on protection against all infections, and the reproductive number of the virus, R_t which quantifies the average number of cases that each case goes on to infect.

Methods

Protection against infection, disease, and transmission

We collected data from the literature (including ongoing systematic reviews: [18, 19]) on protective efficacy and effectiveness of vaccines and convalescent sera for SARS-CoV-2 and categorized each study by variant type (Delta and non-Delta; estimates of protection against the Beta variant were excluded) and endpoint (symptomatic infections and all infections) (Table S1). We excluded studies of protection where the endpoint was “any infection” because these studies do not capture all infections; they include an unknown fraction of the asymptomatic infections. We also obtained a lower bound of the estimate of vaccine effectiveness against transmission (given infection) for Astrazeneca (ChAdOx1) and Pfizer-BioNTech (BNT162b2) for the Delta variant [20]. This study quantified secondary attack rates using qPCR tests of

contacts that were symptomatic or tested positive using lateral flow tests [20], but likely missed some asymptomatic or mildly symptomatic infected contacts, and thus provides a lower estimate of protection. We gathered neutralizing antibody titer data for each vaccine and ratios of titers to convalescent sera from [17]. Finally, we estimated the ratio of neutralizing antibody titers to the Delta variant relative to earlier variants (Table S2), and used these to adjust neutralizing antibody titer ratio estimates in analyses with vaccine effectiveness or protection from previous infection against the Delta variant (Table S1).

Estimating neutralizing antibody titers after waning and third doses

We obtained data on neutralizing antibody titers following vaccination for the Pfizer-BioNTech vaccine at several time points between 1 month after the second dose and 8 months post second dose, as well as 1 month after a third dose [9, 21]. One of these studies [21] reported data for two age groups separately (18-55 and 65+), so we weighted these estimates by the fraction of individuals in the age groups 18-60 and 60+ in the United States (71.0% and 29.0%), which is similar to the age distribution in the European Union [22]. We fit these data to a 3-parameter exponentially decaying function ($y = c_0 e^{c1*t} + c_2$) to estimate the neutralizing antibody titer on any day, t, post vaccination (Figure S1). We also fit similar relationships to data on neutralizing antibody titers over time for the Moderna vaccine [8] (Figure S2), and following infection with SARS-CoV-2 [6] (starting when titers peak at 25 days post symptom onset [23]) (Figure S3). Rates of waning for hybrid immunity following infection and vaccination with Pfizer-BioNtech and Moderna vaccines combined were statistically similar to rates of waning following vaccination with Pfizer-BioNtech [7], so we used the same relative rates of waning as for Pfizer-BioNtech (Figure S1) but adjusted titers for the much higher initial level in those with hybrid immunity [7]. We assumed that boosting individuals that had been infected and then vaccinated resulted in similar neutralizing antibody titers as people that had been vaccinated but not previously infected, because after 6 months of waning post-vaccination, these individuals with hybrid immunity had neutralizing antibody titers that had fallen below levels for newly vaccinated individuals [7].

Linking protection against infection and disease with neutralizing antibody titers

We modeled the relationship between protection from SARS-CoV-2 infections or disease and the ratio of neutralizing antibody titers relative to convalescent sera using logistic regression, following a previous approach [17]. In this analysis each data point is a single study of protection against SARS-CoV-2 infection or disease for a single virus variant. We included an interaction between neutralizing antibody titers and variant-endpoint to estimate separate relationships for each of four variant-endpoints (pairwise combinations of Delta and non-Delta, symptomatic disease, and all infections). We used the separate relationship for the Delta – all infections endpoint for all analyses described below.

The raw data for each estimate of protection (vaccine efficacy, vaccine effectiveness, or protection from previous infection) were unavailable, so we determined the effective sample sizes for a sample from a binomial distribution that matched the confidence intervals of the protection estimates (Table S1). We used the fitted model (Figure 1) to estimate protection against all infections for the Delta variant from Pfizer - BioNTech vaccination using neutralizing

antibody titers measured after eight months of waning and titers measured after a 3rd dose [21]. We performed a similar analysis using the limited data available to link neutralizing antibody titers to the minimum protection against transmission given infection [20] (Figure S4).

The impact of a third dose on the reproductive number, R_t

We used patterns of waning and boosting of neutralizing antibody titers and the relationships between neutralizing antibody titers and protection against all infections and transmission to estimate the impact of providing a third dose of the Pfizer – BioNTech vaccine to increasing fractions of vaccinated individuals on the reproductive number of SARS-CoV-2, R_t. The effective reproductive number, R_t, is the average number of secondary cases that each case infects. It is equal to the basic reproductive number for a fully susceptible population, R_0, multiplied by the fraction of the population that is still susceptible. We split the population based on vaccination and infection to determine the effective fraction susceptible: fraction previously infected and unvaccinated, f_{PU}, fraction previously infected and vaccinated, f_{PV}; fraction unvaccinated, f_U, fraction vaccinated (with two doses of either Pfizer-BioNtech or Moderna), f_V, and fraction boosted with a third dose, f_B ($f_U+f_V+f_B=1$). We estimated the susceptibility of each group using estimates of the protection against infection, VE_I, (Figure 1) and the minimum reduced probability of transmitting given infection, VE_T, (Figure S4) for each group using the subscripts above, except VE_{IH} and VE_{TH} which are estimates of protection from hybrid immunity from infection and vaccination. We used these estimates of protection to calculate R_t for five groups of people : fully susceptible unvaccinated $(1-f_P)f_U$, previously infected unvaccinated f_Pf_U, previously uninfected vaccinated $(1-f_P)f_V$, previously infected vaccinated f_Pf_V, and previously uninfected vaccinated and boosted with a third dose $(1-f_P)f_B$:

$$R_t= R_0 [(1-f_{PU})f_U + f_{PU}f_U(1-VE_{IP})(1-VE_{TP})+(1-f_{PV})f_V(1-VE_{IV})(1-VE_{TV})+ (f_{PV}f_V)(1-VE_{IH})(1-VE_{TH})+(f_B)(1-VE_{IB})(1-VE_{TB})]$$

We examined the effect of boosting vaccinated individuals with a third dose by considering five scenarios that differ in contact rates/R_0 (R_0 = 3.7 or 7 reflecting mid-summer 2021 levels in the USA and pre-pandemic behavior, respectively), vaccination coverage (56% similar to USA in mid-October [22]; 60%, 75% and 100%), and the fraction of the population previously infected (0.5%, 28.2% and 56.4%, with the last value being similar to estimates of the fraction of the USA population that had been infected by mid-October, based on 44 million cases and an infection to case ratio of 4.2 [24]). The scenarios and rationale were (Table S3):

1) R0 = 3.7, 56% vaccinated, 56.4% previously infected: approximates USA population in mid-October with contact rates similar to summer 2021, as might occur in winter 2021
2) R0 = 3.7, 60% vaccinated, 0.5% previously infected: approximates countries/populations that effectively suppressed transmission and haven't yet reached high vaccination levels and have somewhat reduced contact rates (e.g. New Zealand, Australia, Hong Kong, etc.)
3) R0 = 3.7, 75% vaccinated, 28.2% previously infected: approximates some populations with higher vaccination and lower fraction infected than scenario (1) (e.g. California)
4) R0 = 7, 100% vaccinated, 56.4% previously infected: a hypothetical optimistic scenario to compare to scenario (1) to determine if vaccination with or without boosting could limit transmission if behavior returns to pre-pandemic levels

5) R0 = 7, 56% vaccinated, 56.4% previously infected: a more realistic optimistic scenario to compare to scenario (1) to determine if boosting could limit transmission if behavior returns to pre-pandemic levels

For all scenarios we estimated the waning of vaccine-derived immunity as of October 15, 2021 using the timing of vaccination in the USA [25]; Figure S5) and patterns of waning neutralizing antibody titers over time for Pfizer-BioNtech (Figure S1) and Moderna vaccines (Figure S2) or hybrid immunity (Figure S1 with a higher initial starting value – see above). We estimated the waning of infection-derived immunity as of October 15, 2021 using the timing of deaths in the USA [22] shifted by 24 days [26] (Figure S6) and the rate of waning of infection-derived immunity (Figure S3). We estimated the number of infections in vaccinated and unvaccinated people using the ratios of cases in these two groups over time [27] (Figure S7). We used these data on the timing of vaccination and infection and rates of antibody waning to determine the protection against infection and transmission as of October 15, 2021 (Table S4). We calculated 95% CIs for predicted values of R_t that incorporated uncertainty in the relationships between neutralizing antibody titers and protection against infection and transmission (Figures 1 and S4). We drew 10,000 samples from a uniform distribution c(0,1) and used these as quantiles for a normal distribution to generate draws (on a logit scale) for values of protection VE for each value of neutralizing antibody titer adjusted for waning for the fraction of the population that was vaccinated or infected at each day in the past. This approach essentially drew a single line from the 95% CI of lines in Figure 1 and used that for all levels of waning. We then inverse-logit transformed these values of VE and used them to generate 10,000 values of R_t for that scenario. We took the 2.5% and 97.5% quantiles to estimate the 95% confidence intervals (CIs) for R_t for each point of each scenario.

Results

There were strong relationships between the ratio of neutralizing antibody titers to convalescent sera and protection against both symptomatic infection and all infections (Figure 1; Table S3). Protection was highest for symptomatic disease for non-Delta variants and lower for protection against all infections for both non-Delta and Delta variants (Figure 1; Table S3).

Neutralizing antibodies generated by vaccination with the Pfizer-BioNtech vaccine wane 8.06-fold after 8 months (Figure 1), with most of this waning occurring in the first 3 months (Figure S1). The strong relationship between protection and neutralizing antibody titers (Figure 1; Table S3) suggests that this waning of neutralizing antibody titers will reduce protection against all infections for the Delta variant from 80.0% (95% CI: 77.0% to 83.0%) to 60.4% (95% CI: 53.3% to 67.2%) (Figure 1, red line, compare points labelled “Pfizer 1 week” to “Pfizer 8 mo waning”). Similarly, this waning reduced the minimum protection against transmission given infection from 38% (95% CI: 28% to 47%) to 10.5% (95% CI: 6.6% to 16.4%) (Figure S4). A third dose of the Pfizer-BioNtech vaccine boosted antibody titers 25.9-fold relative to levels after 8 months of waning, or 25.9/8.06 = 3.22 higher than one week after dose 2 [21]. The fitted relationship (Figure 1; Table S3) suggests a third dose of the Pfizer-BioNtech vaccine would increase protection against infection from an eight-month waned value of 60.4% (95% CI: 53.3% to 67.2%) to a boosted value of 87.2% (95% CI: 82.8% to 90.7%) and would boost minimum protection against transmission given infection from 10.5% to 60.7% (95% CI: 42.3% to 76.5%).

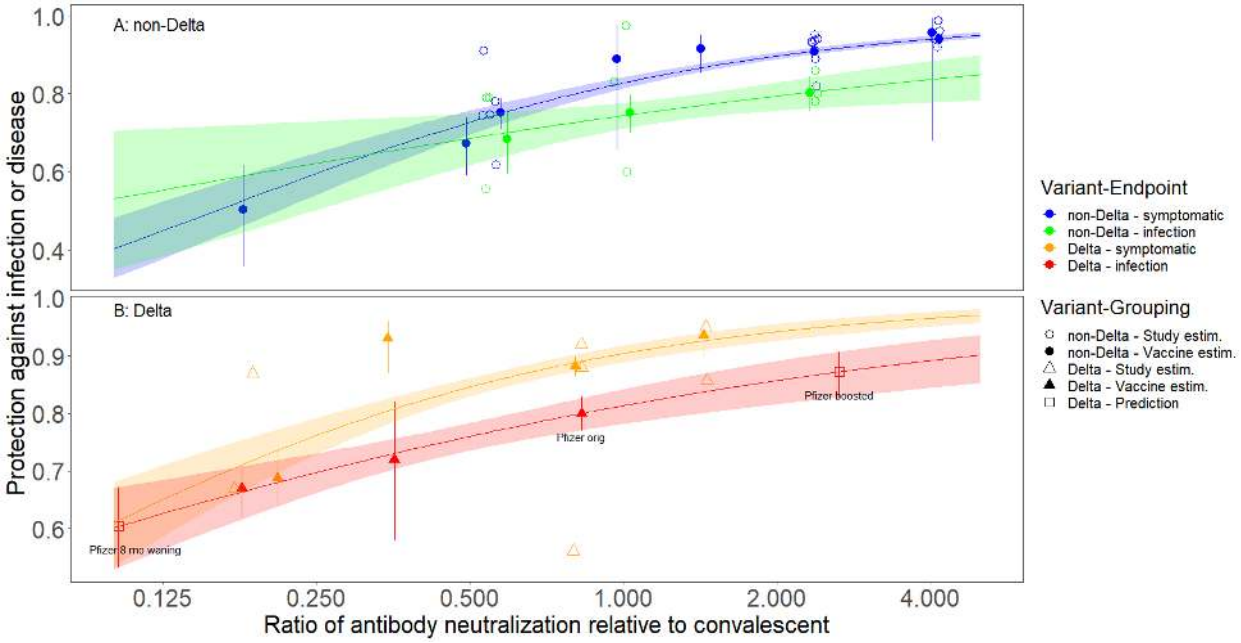

Fig. 1. Protection against symptomatic infections or all infections plotted against the ratio of neutralizing antibody titers relative to convalescent sera. Each point represents a single estimate of vaccine efficacy for a single vaccine & virus variant (from randomized control trials) or vaccine effectiveness (from observational studies) or an estimate of protection from previous infection from observational studies. Colors show the SARS-CoV-2 variant (Delta or non-Delta) and endpoint of the study (symptomatic infections or all infections). Closed symbols and 95% CIs show aggregated data for each vaccine-variant-endpoint. Open symbols show estimates from individual studies if there were more than one estimate for a vaccine-variant-endpoint. Points have been jittered along the x-axis to facilitate presentation; all points for the same vaccine-variant have the same x-value. Lines show a fitted logistic regression with protection as the response and an interaction between and neutralizing antibody ratio and variant-endpoint as predictors (Table S3). The lower panel shows relationships for the Delta variant, with all points shifted 2.88-fold along the x-axis to reflect the lower neutralizing antibodies observed with this variant across studies (Table S2). Although the fitted lines for symptomatic and infection endpoints cross at very low values on the x-axis, there is little data in this range of neutralizing antibody ratios.

Boosting immunity, by providing a third dose of the Pfizer-BioNtech to all doubly vaccinated individuals in the USA (56% of the total population), could reduce the reproductive number R_t by 22% from 1.26 to 0.98 and stop a surge (Figure 2, red line), assuming current levels of vaccination coverage (56%), estimated immunity from previous infection (56.4%), and behavior consistent with the summer Delta surge (R_0=3.7) (see Methods for further details). Unfortunately, in places where vaccination is slightly higher (60%), but previous infection is much lower, (0.5%; e.g. New Zealand), boosting with a third dose would be unable to prevent a surge with the same contact rates (Figure 2, grey line). Conversely, in populations where vaccination is higher (75%) and previously infection is lower (28.2%) (e.g. California), boosting

at least 45% of the population (60% of those vaccinated) could push R_t below 1 (Figure 2 blue line).

If contact rates return to pre-pandemic levels (R_0=7), with mid-October USA vaccine coverage (56%) and infection history (56.4%), then boosting could reduce R_t by a larger absolute amount (but the same relative amount, 21%) than with lower contact rates, from 2.37 to 1.85 (Figure 2, green line) but cases would still rise rapidly because 1.85 is still far above 1. Using the same number of 3rd doses to doubly vaccinate unvaccinated individuals would be more impactful, and could reduce R_t to 1.49 (Figure 2, compare right end of green line to black point labelled 84% vaccinated on left side). With contact rates return at pre-pandemic levels (R_0=7), then even if a population had 100% vaccination coverage and 56.4% previously infected, waning of vaccine and infection-derived immunity would cause cases to continue to grow without boosting (Figure 2, left end of yellow line: R_t=1.17 which is great than 1; without waning R_t would be 0.74, well below 1). However, boosting >21% of a fully (100%) vaccinated population could prevent a surge in cases even with pre-pandemic behavior (Figure 1, yellow line).

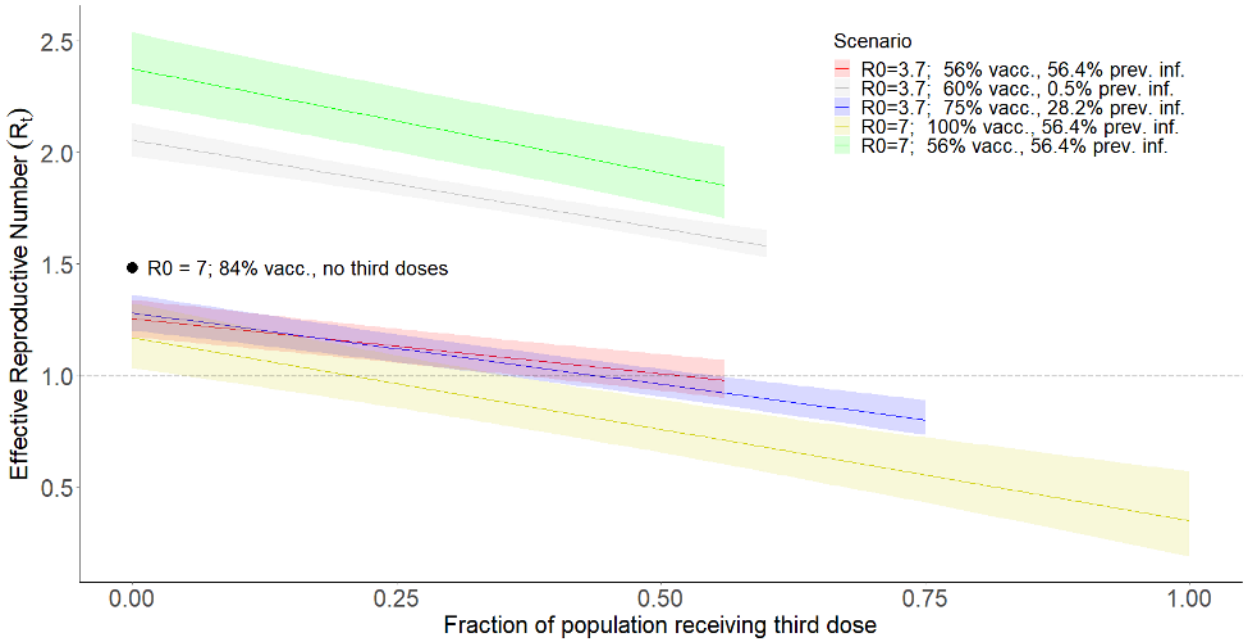

Figure 2. Relationship between third dose coverage and the pathogen effective reproductive number, R_t. Lines and 95% CIs show the estimated reproductive number for five scenarios (see Methods). The single black point shows the impact of using all third doses from the right end of the green line to doubly-vaccinate unvaccinated individuals, which would bring the vaccination coverage from 56% to 84%. Protection from vaccination and previous infection for all lines reflect waning, as described in the text (Table S3). The dashed horizontal line shows the threshold reproductive number R_t = 1, separating a growing from a shrinking epidemic.

Discussion

Vaccines have greatly reduced the impact of COVID-19 globally, but waning immunity and the emergence of the Delta variant have led to surges in cases despite high vaccination coverage in many populations [1, 6-9]. This has led to many countries recommending third doses to boost immunity to protect at-risk individuals [13]. However, the impact of third doses on transmission of SARS-CoV-2 has received far less attention [14].

We found that a third dose could substantially reduce transmission, especially in highly vaccinated populations and the effect was larger in populations with lower acquired immunity from infection and when contact rates (which scale R_0) were higher. We showed that neutralizing antibodies are strongly correlated not just with protection against symptomatic disease [3, 17], but also with protection against all infection and transmission given infection. This allowed us to estimate the effect of waning and boosting on transmission, and the pathogen reproductive number R_t. Boosting immunity by providing a third dose to individuals vaccinated more than three months ago (when most waning occurs: Figure S1, S2) could reduce transmission substantially and could prevent a winter surge in many populations where vaccination coverage is high, as long as contact rates and behavior don't fully return to pre-pandemic levels. In contrast, with pre-pandemic contact rates, only very high levels of vaccine coverage, and a combination of a moderate level of previous infection and boosting could prevent a surge.

We also show that despite the substantial potential impact of boosting on transmission, deploying vaccine doses to unvaccinated individuals has a larger effect on transmission (Figure 2, black circle versus the right end of the green line). In addition, the direct effect of vaccinating unvaccinated people is much larger than the benefit of providing a third dose for severe disease and death since protection against severe disease has barely waned except in older or at-risk individuals [10]. Unfortunately, vaccine hesitancy among those not vaccinated is quite high in many populations (e.g., USA, Russia, etc.) and many people are unwilling to get vaccinated despite strong incentives, often due to misinformation [28-30], making it difficult to increase vaccine coverage in some populations. In contrast, there other populations where vaccine coverage is very low, primarily due to poor availability, especially in Africa [31]. Clearly, limited vaccine doses would be most effectively used in these populations and should be deployed there until supplies are no longer limiting.

Our study has several limitations. First and foremost is the reliance on neutralizing antibody titers as a predictor of protection against infection and transmission. Although the analyses here, and elsewhere suggest a strong relationship between neutralizing antibody titers and protection at the population level [3, 17] and individual level [32], other parts of the immune system, such as T-cells, also play key roles in protection from infection and disease. Second, our analyses use population averages for estimates of protection against infection and transmission and ignore age-specific variation among individuals (as well as other factors). Third, the data available to estimate vaccine protection against all infections was very limited and we are unaware of any studies that have estimated the full impact of vaccination against transmission given infection from the Delta variant. Finally, we assume well-mixed populations in calculating reductions in the reproductive number R_t. Clearly a targeted vaccination approach would be more effective

than that outlined here if individuals that were highly connected to at-risk individuals could be targeted for third doses [33]. Finally, we focused on third dose boosters using the Pfizer vaccine, but third doses for other vaccines, including heterologous boosting [34], have also recently been approved in the USA and elsewhere.

In summary, many countries have already begun to deploy third doses to protect at-risk individuals, and some countries (e.g. Israel, [16]) have even deployed third doses to the general population to reduce transmission. However, uptake in most countries has been low, criteria for third doses are still vague [13], and only moderate effort has been deployed to deploy third doses widely. Our results suggest that widespread boosting of the general population could substantially reduce transmission. Polls in some countries suggest a large fraction of the population would be willing to get a third dose (e.g., 76% of Americans; [35]). If vaccine supplies can be increased to provide initial doses to populations with very low coverage, then offering third doses to the general public could play a significant role in reducing transmission. This would directly protect boosted individuals, indirectly protect unvaccinated and vaccinated individuals, and reduce the possibilities for viral evolution [15].

Contributors

AMK conceived the study. BJG and AMK performed the analyses and wrote the paper.

Declaration of interests

All authors declare no competing interests.

Data sharing

Code and data files to replicate the figures and analyses of this paper can be found at: https://github.com/marmkilpatrick/Vaccine-boosters

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References

1. Wadman M. Israel's grim warning: Delta can overwhelm shots. Science. 2021;373(6557):838-9.
2. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Eurosurv. 2021;26(24):2100509.
3. van Gils MJ, Lavell AHA, van der Straten K, Appelman B, Bontjer I, Poniman M, et al. Four SARS-CoV-2 vaccines induce quantitatively different antibody responses against SARS-CoV-2 variants. medRxiv. 2021:2021.09.27.21264163. doi: 10.1101/2021.09.27.21264163.
4. Davis C, Logan N, Tyson G, Orton R, Harvey W, Haughney J, et al. Reduced neutralisation of the Delta (B.1.617.2) SARS-CoV-2 variant of concern following vaccination. medRxiv. 2021:2021.06.23.21259327. doi: 10.1101/2021.06.23.21259327.

5. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.
6. Havervall S, Marking U, Gordon M, Ng H, Greilert-Norin N, Lindbo S, et al. Neutralization of VOCs including Delta one year post COVID-19 or vaccine. medRxiv. 2021:2021.08.12.21261951. doi: 10.1101/2021.08.12.21261951.
7. Goel RR, Painter MM, Apostolidis SA, Mathew D, Meng W, Rosenfeld AM, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. Science. 2021:eabm0829.
8. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med. 2021;384(23):2259-61.
9. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months. N Engl J Med. 2021.
10. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. medRxiv. 2021.
11. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman LS, Haas E, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. medRxiv. 2021.
12. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med. 2021.
13. Furlong A, Deutsch J. A country-by-country guide to coronavirus vaccine booster plans 2021. Available from: https://www.politico.eu/article/vaccine-booster-coronavirus-covid-19-europe-delta-varian-who/.
14. Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, et al. Considerations in boosting COVID-19 vaccine immune responses. Lancet (London, England). 2021;398(10308):1377-80. doi: 10.1016/S0140-6736(21)02046-8. PubMed PMID: 34534516.
15. Wagner CE, Saad-Roy CM, Morris SE, Baker RE, Mina MJ, Farrar J, et al. Vaccine nationalism and the dynamics and control of SARS-CoV-2. medRxiv. 2021.
16. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against covid-19 in Israel. N Engl J Med. 2021;385(15):1393-400.
17. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021:1-7.
18. Higdon MM, Wahl B, Jones CB, Rosen JG, Truelove SA, Baidya A, et al. A systematic review of COVID-19 vaccine efficacy and effectiveness against SARS-CoV-2 infection and disease. medRxiv. 2021:2021.09.17.21263549. doi: 10.1101/2021.09.17.21263549.
19. WHO. Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review 2021. Available from: https://view-hub.org/sites/default/files/2021-09/COVID19%20VE%20Studies_Forest%20Plots_1.pdf.
20. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, et al. The impact of SARS-CoV-2 vaccination on Alpha and Delta variant transmission. medRxiv. 2021:2021.09.28.21264260. doi: 10.1101/2021.09.28.21264260.

21. Falsey AR, Frenck Jr RW, Walsh EE, Kitchin N, Absalon J, Gurtman A, et al. SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3. N Engl J Med. 2021.
22. CDC. COVID Data Tracker 2021. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.
23. Arkhipova-Jenkins I, Helfand M, Armstrong C, Gean E, Anderson J, Paynter RA, et al. Antibody response after SARS-CoV-2 infection and implications for immunity: a rapid living review. Ann Intern Med. 2021;174(6):811-21. doi: doi.org/10.7326/M20-7547.
24. CDC. Estimated COVID-19 Burden 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html.
25. CDC. COVID-19 Vaccinations in the United States 2021. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.
26. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ-British Medical Journal. 2020;369:10. doi: 10.1136/bmj.m1923. PubMed PMID: WOS:000538336800001.
27. CDC. Rates of COVID-19 Cases and Deaths by Vaccination Status 2021. Available from: https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status.
28. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrachi M, Zigron A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol. 2020;35(8):775-9.
29. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. Vaccines. 2021;9(2):160.
30. Machingaidze S, Wiysonge CS. Understanding COVID-19 vaccine hesitancy. Nat Med. 2021;27(8):1338-9.
31. Acharya KP, Ghimire TR, Subramanya SH. Access to and equitable distribution of COVID-19 vaccine in low-income countries. npj Vaccines. 2021;6(1):1-3.
32. Gilbert PB, Montefiori DC, McDermott A, Fong Y, Benkeser D, Deng W, et al. Immune Correlates Analysis of the mRNA-1273 COVID-19 Vaccine Efficacy Trial. medRxiv. 2021:2021.08.09.21261290. doi: 10.1101/2021.08.09.21261290.
33. Firth JA, Hellewell J, Klepac P, Kissler S, Kucharski AJ, Spurgin LG. Using a real-world network to model localized COVID-19 control strategies. Nat Med. 2020;26(10):1616-22.
34. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. medRxiv. 2021:2021.10.10.21264827. doi: 10.1101/2021.10.10.21264827.
35. Aboulenein A, Kahn C. Most vaccinated Americans want COVID-19 booster shots - Reuters/Ipsos poll: Reuters; 2021. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/most-vaccinated-americans-want-covid-19-booster-shots-reutersipsos-poll-2021-09-01/.
36. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943. doi: 10.1136/bmj.n1943.
37. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412-23.
38. Emary KR, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.

1.1. 7): an exploratory analysis of a randomised controlled trial. The Lancet. 2021;397(10282):1351-62.
39. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. The Lancet. 2021;397(10286):1725-35.
40. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 vaccines against the B. 1.617. 2 (Delta) variant. N Engl J Med. 2021:585-94.
41. Martínez-Baz I, Miqueleiz A, Casado I, Navascués A, Trobajo-Sanmartín C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Eurosurv. 2021;26(21):2100438.
42. Narrainen F, Shakeshaft M, Asad H, Holborow A, Blyth I, Healy B. The protective effect of previous COVID-19 infection in a high-prevalence hospital setting. Clinical Medicine. 2021;21(5):e470.
43. Nasreen S, He S, Chung H, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern, Canada. Medrxiv. 2021.
44. Pouwels KB, Pritchard E, Matthews P, Stoesser NB, Eyre DW, Vihta K-D, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv. 2021.
45. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta K-D, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021:1-9.
46. Satwik R, Satwik A, Katoch S, Saluja S. ChAdOx1 nCoV-19 effectiveness during an unprecedented surge in SARS COV-2 infections. European Journal of Internal Medicine. 2021.
47. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane F, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B. 1.617. 2) variant in Qatar. MedRxiv. 2021.
48. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. The Lancet. 2021;397(10277):881-91.
49. Whitaker H, Tsang R, Byford R, Andrews N, Sherlock J, Pillai P. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups. Khub net Posted July. 2021.
50. Richardson JR, Goetz R, Mayr V, Lohse MJ, Holthoff H-P, Ungerer M. SARS-COV2 mutant-specific T cells and neutralizing antibodies after vaccination and up to 1 year after infection. medRxiv. 2021.
51. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B. 1.617. 2 and B. 1.351 by BNT162b2 vaccination. The Lancet. 2021;397(10292):2331-3.
52. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Ability of AZD1222 vaccination to elicit neutralising antibodies against SARS-CoV-2 VOC B. 1.617. 2 (Delta). Lancet (London, England). 2021;398(10296):207.

Supplemental Tables and Figures

Table S1. Data and studies used to estimate the relationship between protection (VE) against infection, disease and transmission endpoints and neutralizing antibody titer (NAT) ratios relative to convalescent sera (Figure 1). A single value of the neutralizing antibody titer ratio was used for each vaccine and variant; values for the Delta variant are 2.88-fold lower than for non-Delta variants (Table S2). N_{eff} are the effective sample sizes used for the logistic regression (Table S3).

Study	Vaccine or Convalescent	Variant	Endpoint	NAT Ratio	VE (95% CI)	N_{eff}
[12]	Moderna	non-Delta	Symptomatic	4.13	0.99 (0.92-1.00)	70
[36]	Moderna	non-Delta	Symptomatic	4.13	0.94 (0.86-0.97)	112
[36]	Pfizer	non-Delta	Symptomatic	2.37	0.91 (0.88-0.93)	550
[37]	Pfizer	non-Delta	Symptomatic	2.37	0.94 (0.87-0.98)	96
[38]	Astrazeneca	non-Delta	Symptomatic	0.54	0.75 (0.42-0.89)	16
[20]	Astrazeneca	Delta	Transmission	0.19	0.16 (0.12-0.21)	243
[20]	Pfizer	Delta	Transmission	0.82	0.38 (0.28-0.47)	109
[39]	Convalescent	non-Delta	All infections	1	0.83 (0.76-0.87)	168
[39]	Pfizer	non-Delta	All infections	2.37	0.86 (0.76-0.97)	49
[17]	Astrazeneca	non-Delta	Symptomatic	0.54	0.62 (0.41-0.76)	34
[17]	Convalescent	non-Delta	Symptomatic	1	0.89 (0.66-0.98)	18
[17]	CoronaVac	non-Delta	Symptomatic	0.17	0.50 (0.36-0.62)	60
[17]	JJ	non-Delta	Symptomatic	0.47	0.67 (0.59-0.74)	147
[17]	Moderna	non-Delta	Symptomatic	4.13	0.94 (0.89-0.97)	150
[17]	Novavac	non-Delta	Symptomatic	3.97	0.96 (0.68-0.99)	25
[17]	Pfizer	non-Delta	Symptomatic	2.37	0.95 (0.90-0.98)	200
[17]	Sputnik	non-Delta	Symptomatic	1.41	0.92 (0.85-0.95)	140
[40]	Astrazeneca	Delta	Symptomatic	0.19	0.67 (0.61-0.72)	330
[40]	Astrazeneca	non-Delta	Symptomatic	0.54	0.75 (0.68-0.79)	240
[40]	Pfizer	Delta	Symptomatic	0.82	0.88 (0.85-0.90)	750
[40]	Pfizer	non-Delta	Symptomatic	2.37	0.94 (0.92-0.95)	720
[41]	Pfizer	non-Delta	Symptomatic	2.37	0.82 (0.73-0.88)	110
[42]	Convalescent	non-Delta	All infections	1	0.97 (0.81-1.00)	25
[43]	Astrazeneca	non-Delta	Symptomatic	0.54	0.91 (0.62-0.98)	22
[43]	Astrazeneca	Delta	Symptomatic	0.19	0.87 (0.69-0.95)	32
[43]	Moderna	non-Delta	Symptomatic	4.13	0.92 (0.88-0.95)	225
[43]	Moderna	non-Delta	Symptomatic	4.13	0.96 (0.85-0.99)	50
[43]	Moderna	Delta	Symptomatic	1.44	0.95 (0.91-0.97)	220
[43]	Pfizer	non-Delta	Symptomatic	2.37	0.89 (0.86-0.91)	1440
[43]	Pfizer	Delta	Symptomatic	0.82	0.92 (0.90-0.94)	600
[43]	Pfizer	non-Delta	Symptomatic	2.37	0.93 (0.88-0.95)	210
[44]	Astrazeneca	Delta	All infections	0.19	0.67 (0.62-0.71)	420
[44]	Astrazeneca	non-Delta	All infections	0.54	0.79 (0.56-0.90)	25

[44]	Convalescent	Delta	All infections	0.35	0.72 (0.58-0.82)	53
[44]	Convalescent	non-Delta	All infections	1	0.60 (0.50-0.68)	125
[44]	Pfizer	Delta	All infections	0.82	0.80 (0.77-0.83)	780
[44]	Pfizer	non-Delta	All infections	2.37	0.78 (0.68-0.84)	100
[45]	Astrazeneca	non-Delta	All infections	0.54	0.79 (0.65-0.88)	50
[45]	Pfizer	non-Delta	All infections	2.37	0.80 (0.73-0.85)	185
[46]	Convalescent	Delta	Symptomatic	0.35	0.93 (0.87-0.96)	169
[47]	Moderna	Delta	Symptomatic	1.44	0.86 (0.71-0.94)	42
[47]	Pfizer	Delta	Symptomatic	0.82	0.56 (0.41-0.67)	64
[48]	Astrazeneca	non-Delta	All infections	0.54	0.56 (0.41-0.67)	63
[49]	Astrazeneca	non-Delta	Symptomatic	0.54	0.78 (0.70-0.84)	150
[49]	Pfizer	non-Delta	Symptomatic	2.37	0.93 (0.86-0.97)	100

Table S2. Ratios of neutralizing antibody titers to Delta or non-Delta variants of SARS-CoV-2 from vaccination or infection SARS-CoV-2.

Reference	non-Delta variant	Sample type	Ratio non-Delta to Delta
[3]	D614G	Pfizer-BioNtech	4.5
[3]	D614G	Astrazeneca	4.5
[21]	Wild Type	Pfizer-BioNtech	1.28
[4]	Wuhan	Pfizer-BioNtech	11.30
[4]	Wuhan	Astrazeneca	4.01
[50]	Wild Type	Pfizer-BioNtech	2.1
[50]	Wild Type	Astrazeneca	2.1
[51]	Wild Type	Pfizer-BioNtech	5.8
[52]	Wild Type	Astrazeneca	8.0
[6]	Wild Type	Pfizer-BioNtech	1.18
[6]	Wild Type	Astrazeneca	1.22
[5]	D614G	Pfizer-BioNtech	2.0
[5]	D614G	Astrazeneca	5.0
[3]	D614G	Convalescent	2.1
[5]	D614G	Convalescent	2.1
		Estimated ratio*	2.88

*There was no significant difference in the ratios among sample types (either vaccines or convalescent sera): mixed effects model of log-transformed ratio with Sample Type as a fixed effect and study as a random effect; likelihood ratio $\chi^2(df=2) = 2.6$; $P = 0.26$.

Table S3. Logistic regression analysis of protection (vaccine efficacy or effectiveness or protection from previous infection) with the log-transformed ratio of neutralizing antibody titers (NABT-Ratio) relative to convalescent sera, with an interaction with four groups for variant (Delta and non-Delta) and endpoint (symptomatic cases or all infections) as shown in Figure 1. Delta – infections was the reference level.

Predictor	Estimate	SE	Z-value	P-value
Intercept	1.47	0.10	14.49	<0.0001
$\log_2$(NABT-Ratio)	0.32	0.064	4.97	<0.0001
non-Delta - symptomatic	0.10	0.11	0.87	0.39
non-Delta - infection	-0.41	0.13	-3.00	0.0027
Delta - symptomatic	0.77	0.13	5.79	<0.0001
$\log_2$(NABT-Ratio):non-Delta - symptomatic	0.27	0.076	3.59	0.00034
$\log_2$(NABT-Ratio):non-Delta - infection	-0.035	0.12	-0.29	0.77
$\log_2$(NABT-Ratio):Delta - symptomatic	0.22	0.089	2.50	0.012

Table S4. Fraction of the population in each group for the five scenarios in Figure 2, using the case ratios in vaccinated and unvaccinated individuals and the timing of vaccinations and infections derived from COVID-19 deaths and vaccinations as of October 15, 2021 in the USA (Figures S5-S7).

Scenario	Fraction vaccinated and infected (f_{PV}*f_V)	Fraction vaccinated and not infected ((1-f_{PV})*f_V)	Fraction unvaccinated and infected (f_{PU}*f_U)	Fraction fully susceptible ((1-f_{PU})*f_U)
R0=3.7; 56% vacc., 56.4% prev. inf.	0.26	0.30	0.30	0.14
R0=3.7; 60% vacc., 0.52% prev. inf.	0.0012	0.60	0.004	0.40
R0=3.7; 75% vacc., 28.2% prev. inf	0.18	0.57	0.11	0.14
R0=7; 100% vacc., 56.4% prev. inf.	0.56	0.44	0	0
R0=7; 56% vacc., 56.4% prev. inf.	0.26	0.30	0.30	0.14

Table S5. Estimated protection (and 95% CI) against infection (VE_I) and transmission (VE_T) given waning of vaccine and infection derived immunity, as of October 15, 2021 in the USA, using case ratios in vaccinated and unvaccinated individuals and the timing of vaccinations and infections derived from COVID-19 deaths and vaccinations.

Endpoint	Estimate with waning (95% CI)
VE_{IP} (infected and unvaccinated)	0.627 (0.565-0.685)
VE_{TP} (infected and unvaccinated)	0.125 (0.086-0.181)
VE_{IV} (vaccinated and uninfected)	0.675 (0.637-0.712)
VE_{TV} (vaccinated and uninfected)	0.186 (0.152-0.226)
VE_{IH} (vaccinated and infected)	0.827 (0.792-0.857)
VE_{TH} (vaccinated and infected)	0.464 (0.341-0.583)
VE_{IB} (boosted with third dose)	0.873 (0.828-0.907)
VE_{TB} (boosted with third dose)	0.608 (0.428-0.764)

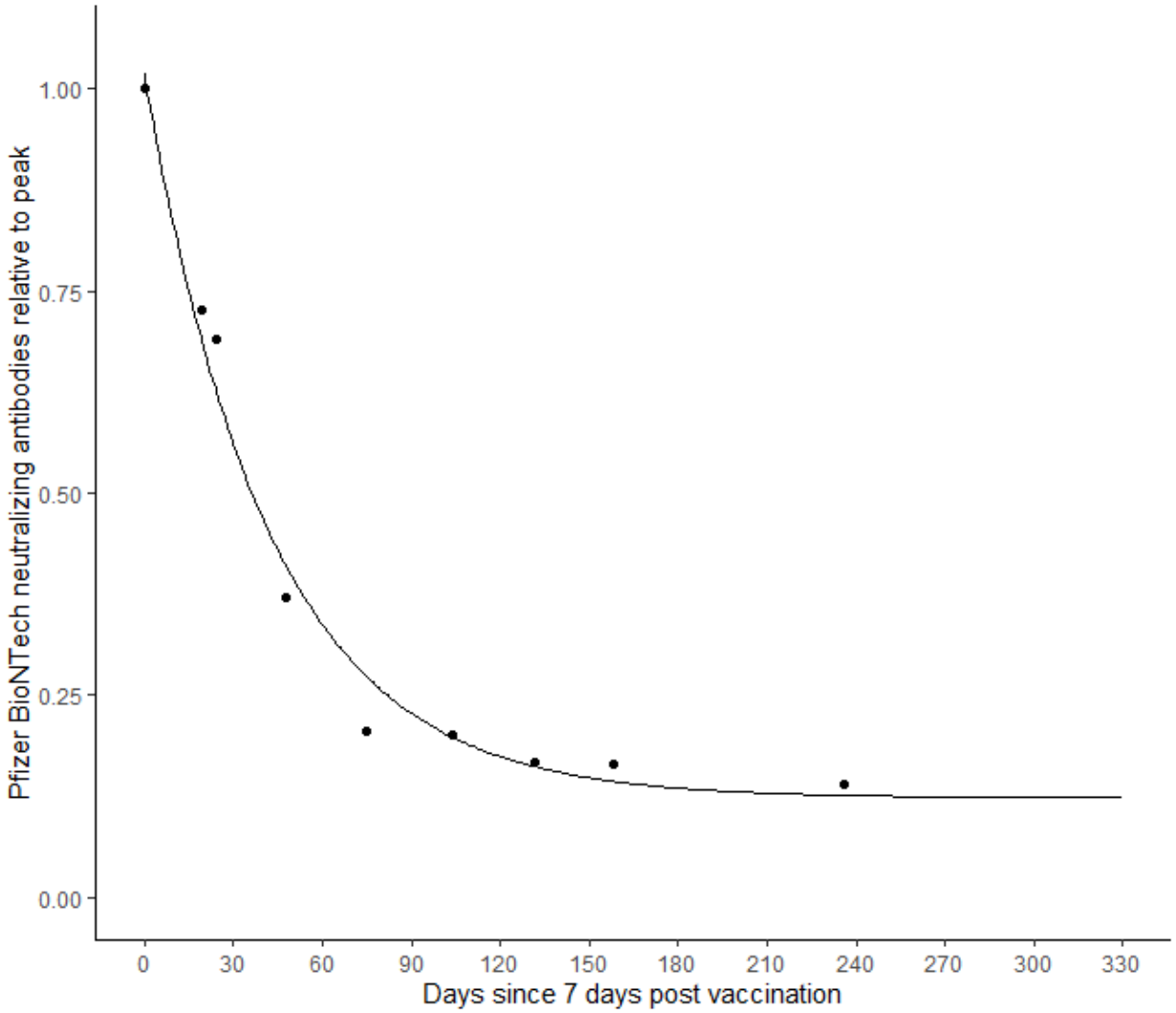

Fig S1. Decay in neutralizing antibody titers following vaccination with Pfizer-BioNtech based on two studies [9, 21]. Titers from the two studies were scaled to the maximum value observed in each study to account for differences among studies in methods used to measure antibody titers.

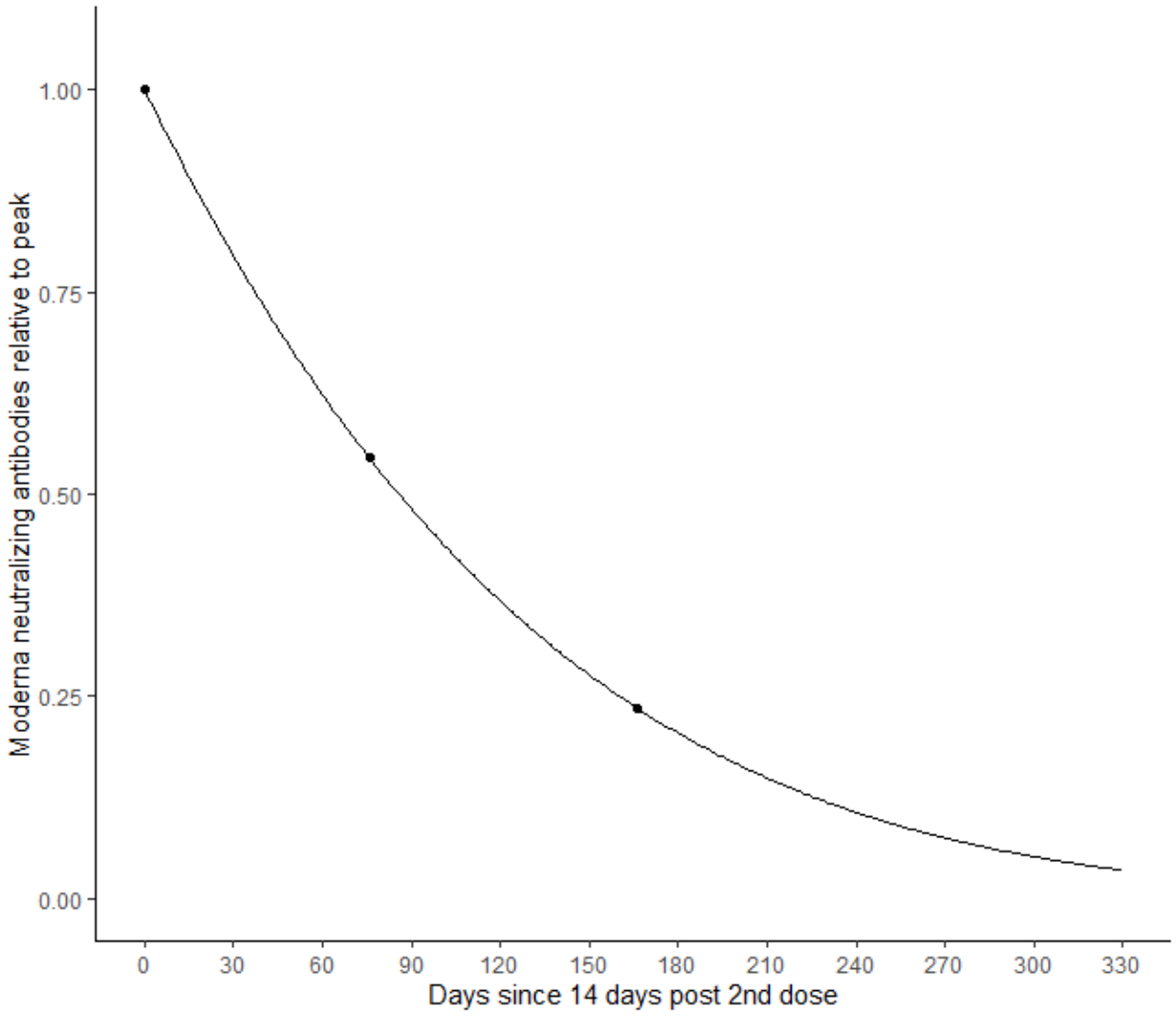

Fig S2. Decay in neutralizing antibody titers following vaccination with the Moderna vaccine [8]. Titers were scaled to the maximum value observed.

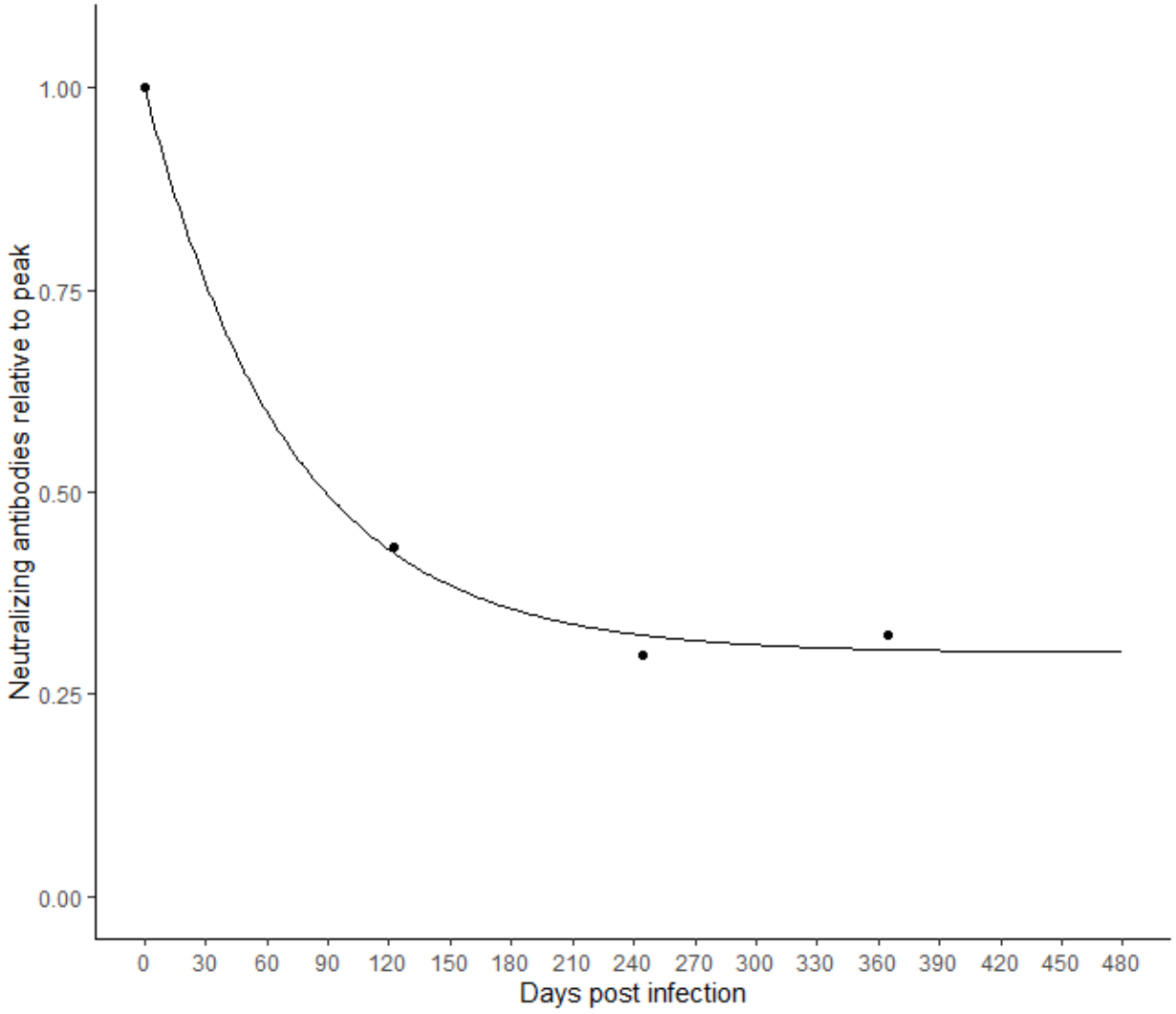

Figure S3. Decay in neutralizing antibody titers following infection with SARS-CoV-2 over time [6]. Titers are scaled relative to the peak shortly after infection.

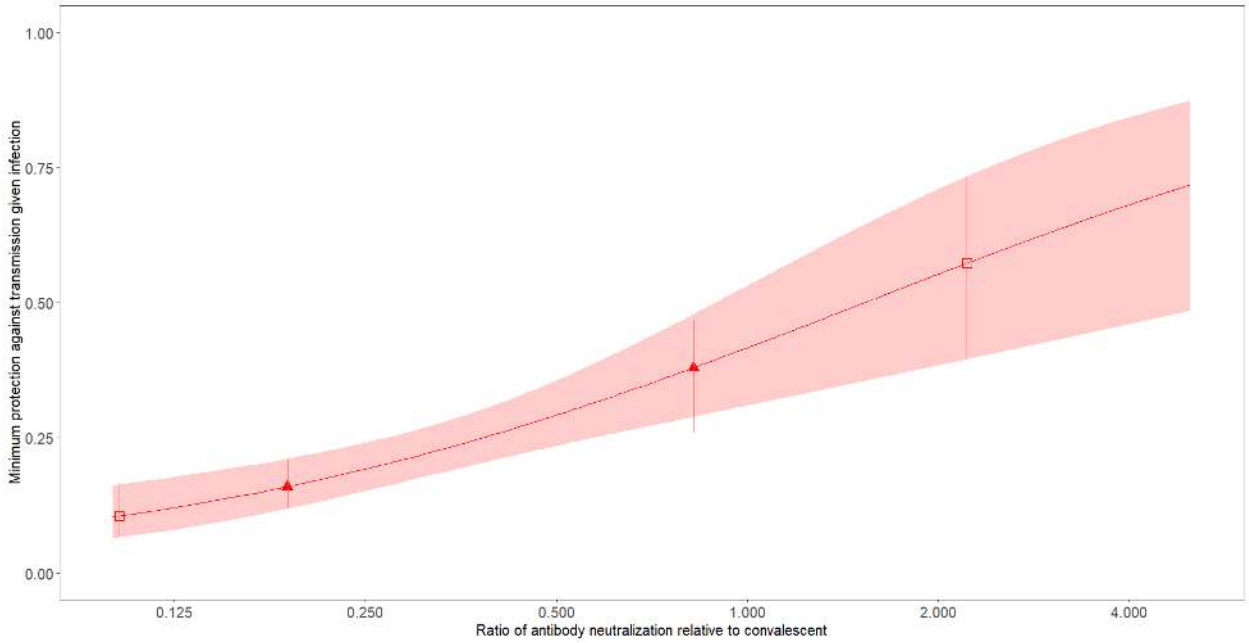

Figure S4. Minimum protection against transmission given infection plotted against the ratio of neutralizing antibody titers relative to convalescent sera from infection with SARS-CoV-2 for Astrazeneca (left filled triangle) and Pfizer (right filled triangle) [20]. Open squares show the estimated protection with waning (left open square) and boosting (right open square).

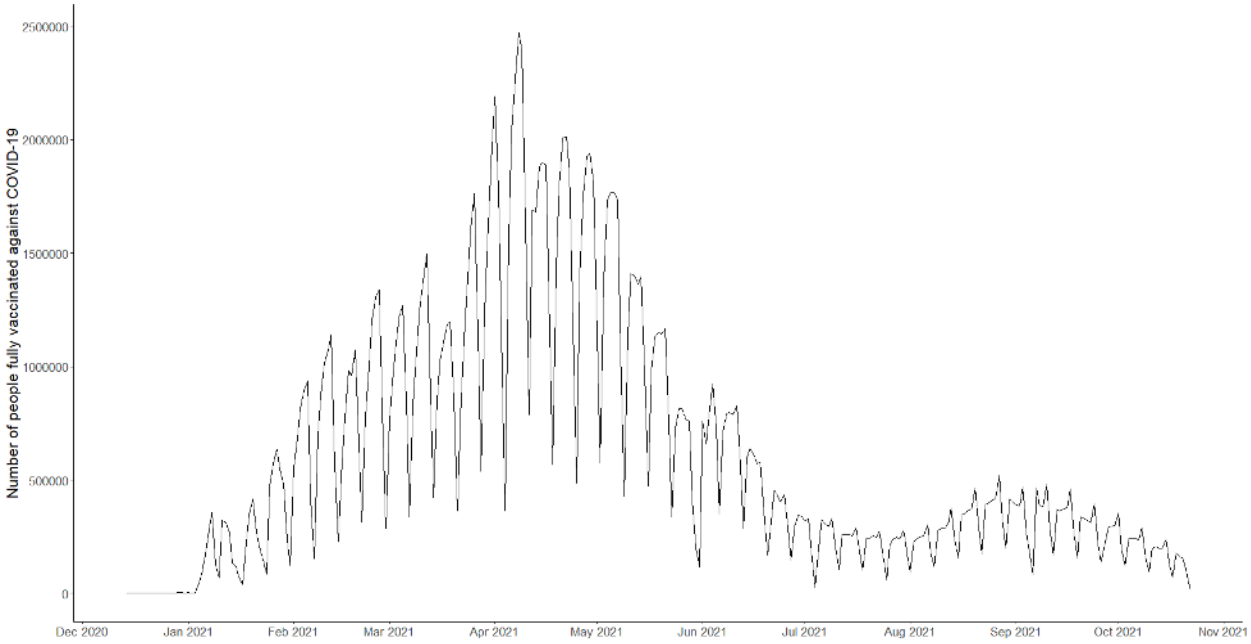

Figure S5. Number of people fully vaccinated in the USA [25].

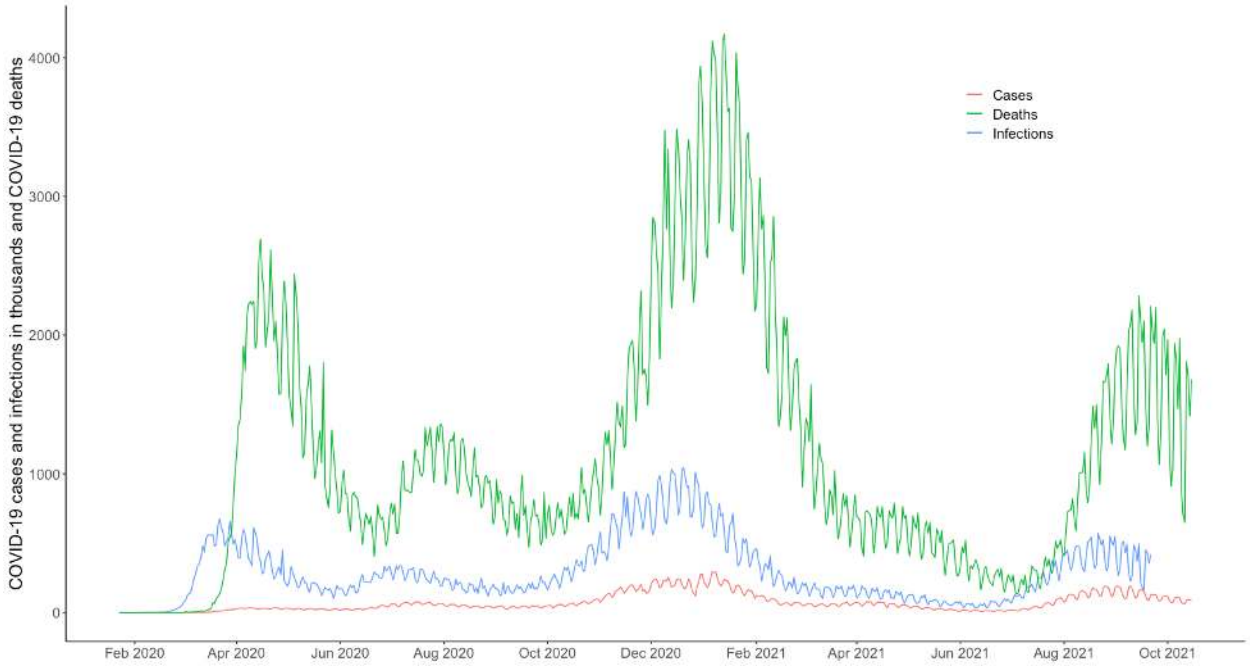

Figure S6. COVID-19 cases, deaths, and infections inferred from deaths in the USA [22].

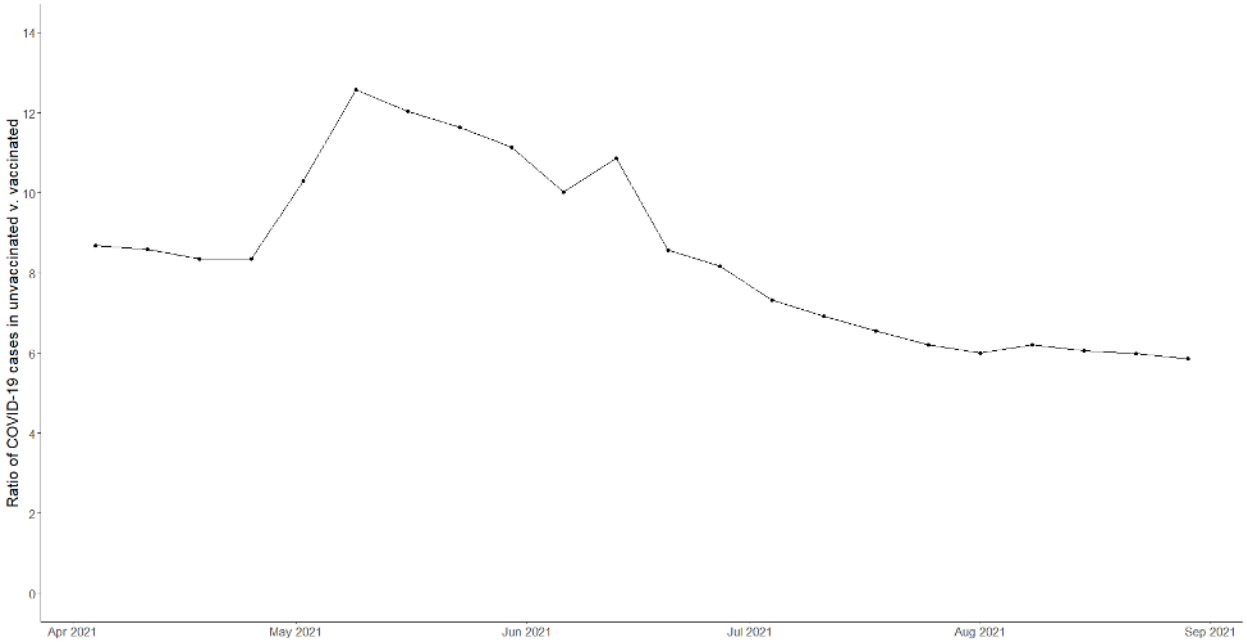

Figure S7. Ratio of COVID-19 cases in unvaccinated individuals relative to vaccinated individuals in the USA in 2021 [27].