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Infection by SARS-CoV-2 with alternate frequencies of mRNA vaccine boosting

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Abstract

One of the most consequential unknowns of the COVID-19 pandemic is the frequency at which vaccine boosting provides sufficient protection from infection. We quantified the statistical likelihood of breakthrough infections over time following different boosting schedules with messenger RNA (mRNA)-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech). We integrated anti-Spike IgG antibody optical densities with profiles of the waning of antibodies and corresponding probabilities of infection associated with coronavirus endemic transmission. Projecting antibody levels over time given boosting every 6 months, 1, 1.5, 2, or 3 years yielded respective probabilities of fending off infection over a 6-year span of >93%, 75%, 55%, 40%, and 24% (mRNA-1273) and >89%, 69%, 49%, 36%, and 23% (BNT162b2). Delaying the administration of updated boosters has bleak repercussions. It increases the probability of individual infection by SARS-CoV-2, and correspondingly, ongoing disease spread, prevalence, morbidity, hospitalization, and mortality. Instituting regular, population-wide booster vaccination updated to predominant variants has the potential to substantially forestall—and with global, widespread uptake, eliminate—COVID-19.

KEYWORDS

BNT162b2, mRNA-1273, mRNA vaccines, SARS-CoV-2 variant evolution, updated COVID-19 vaccine, vaccination schedule

1 | INTRODUCTION

The unprecedented development of efficacious vaccines against SARS-CoV-2 was hailed as a triumph in the global effort to control the ongoing COVID-19 pandemic. Vaccines were shown to provide short-term protection from infection and major adverse health outcomes of hospitalization and death.^{1–4} However, protection from infection by SARS-CoV-2 wanes over the short term,⁵ and breakthrough infections are increasingly frequent,^{6,7} raising the question of how often vaccine boosters should be administered. The FDA and the CDC have been working to keep booster recommendations

current in the face of serial, somewhat unpredictable variant-driven waves of infection.⁸ As COVID-19 becomes an endemic disease, regular boosting of vaccination is likely advisable.⁹ Consequently, rigorous prediction of the immunity over time that would be conferred by candidate boosting schedules against SARS-CoV-2 infection is essential for personal and public health decision-making. Such predictions regarding the ability of regular boosting to fend off infections have major implications worldwide.^{10,11}

Short-term longitudinal studies of SARS-CoV-2 neutralizing antibodies in vaccinated and boosted individuals^{12–14} indicate that antibody-mediated protection against infection wanes after

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vaccination,¹⁵ and after vaccine boosting.¹⁶ Long-term longitudinal reinfection data have not been collected for SARS-CoV-2 and insufficient information has been gathered from direct studies of protection against infection by vaccination and boosting to identify the consequent long-term protection conferred by candidate boosting schedules. However, data on antibody responses, their waning, and corresponding probabilities of infection have been collected for a diversity of closely related coronaviruses.^{17–22} Here, we quantify the effect of boosting by pairing antibody responses and their waning consequent to booster vaccination with corresponding infection probabilities. The aim of this study is to assess these probabilities of infection over the long term to evaluate alternate serial boosting schedules.

2 | ONLINE METHODS

2.1 | Study design

We expanded on a comparative evolutionary framework for inference of infection probability associated with antibody level after natural infection.²³ This framework enabled us to estimate the typical peak antibody response to vaccination with mRNA-1273 and BNT162b2, relative to natural infection. We obtained published empirical antibody waning profiles following vaccination with mRNA-1273 and BNT162b2 and supplemented them with subsequent waning dynamics inferred from an ancestral and descendent states analysis incorporating observed antibody waning of the six human-infecting coronaviruses HCoV-OC43, HCoV-NL63, and HCoV-229E, SARS-CoV-1, SARS-CoV-2, and MERS. We then used ancestral and descendent states analysis to infer parameters for logistic regression models of the endemic probabilities of infection based on antibody level. Projecting waning and boosting over 6 years at intervals ranging from every 6 months to every 3 years, we quantified probabilities of boosted breakthrough infection.

2.2 | Data acquisition

2.2.1 | Phylogenetic tree topologies

Phylogenetic tree topologies for the relationships of SARS-CoV-2 and the endemic human-infecting coronaviruses were obtained from Townsend et al.²³ These tree topologies are based on data from 58 *Alphacoronavirus*, 105 *Betacoronavirus*, 11 *Deltacoronavirus*, and 3 *Gammacoronavirus* that were analyzed by multiple maximum-likelihood analyses of concatenated DNA sequence alignments of the S, M, and ORF1b genes. Resulting topologies were found to be robust to alternative maximum-likelihood search algorithms,^{24,25} to alternative divergence time estimation approaches,^{24,26–28} and to a potential history of recombination.²⁹

2.2.2 | Waning antibody data

To obtain data that would provide relative peak antibody levels comparing BNT162b2 with natural infection and mRNA-1273 occurring at a known time relative to antibody measurement, we conducted literature searches using the PubMed and Google Scholar databases. Searches were conducted between July 1, 2021 and October 24, 2022, using combinations of the terms “SARS-CoV-2,” “BNT162b2,” “mRNA-1273,” “antibodies,” “antibody response,” “ELISA,” “IgG,” “longitudinal,” “optical density,” “naive,” “seropositive,” “natural infection,” or “convalescent.” There were no language restrictions imposed. Studies were included when they reported ELISA anti-S, anti-S1, or anti-RBD data that covered the peak antibody response for naive individuals vaccinated with mRNA-1273 or BNT162b2 compared to those with natural infection and no prior vaccination.

The relative peak antibody levels comparing mRNA-1273 and BNT162b2 booster vaccination with the first series of mRNA-1273 and BNT162b2 vaccination were obtained by searches of PubMed and Google Scholar databases between January 1, 2022 and October 24, 2022. Searches used combinations of the terms “SARS-CoV-2,” “BNT162b2,” “mRNA-1273,” “antibodies,” “antibody response,” “ELISA,” “IgG,” “longitudinal,” “optical density,” “naive,” “booster,” or “second dose” without language restrictions. Inclusion criteria necessitated that studies reported ELISA anti-S, anti-S1, or anti-RBD data that covered the peak antibody response for naive individuals vaccinated and subsequently boosted with mRNA-1273 or vaccinated and subsequently boosted with BNT162b2. Additionally, optical density measures of antibody levels subsequent to the first vaccination series and after boosting had to be measured by the same lab using the same assay to ensure standardized measurements.

This antibody-waning data set was then supplemented by further analysis of a data set assembled by Townsend et al.²³ on waning antibody levels following natural infection by SARS-CoV-2 and its closest human-infecting relatives. To supplement the natural infection data gathered by Townsend et al.²³ we incorporated data assembled by Townsend et al.⁹ that included alternative SARS-CoV-2 data from two studies^{30,31} that met the criteria of having sufficient ELISA optical density data on anti-S1 IgG antibody levels beyond the anti-S1 IgG antibody level data set provided by Townsend et al.²³ These natural infection studies used a consistent antibody type (Euroimmun S1) and provided longitudinal sampling, thereby ensuring that our comparative phylogenetic analyses were conducted on a common scale of immunological measurement.³² We used the six comparative data sets assembled in Townsend et al.⁹ to assess the robustness of our findings to data selection. Data set 1 comprised anti-S1 data from a population sample of 1797 individuals extending over 125 days after diagnosis of infection by SARS-CoV-2,³³ nine individuals (five male and four female; age: 27–54 years) infected by MERS-CoV with symptoms ranging from asymptomatic to severe, monitored up to 18 months,¹⁷ and putative endemic coronavirus anti-S1 IgG antibody waning data from our linear model relating

anti-N and anti-S1 IgG that included 10 adult males aged 27–75 years who were assayed for antibody response to infection by HCoV-OC43, HCoV-NL63, and HCoV-229E over 28 years spanning two periods: 1984–1997 and 2003–2020.¹⁸ Data sets 2 and 3 included alternate SARS-CoV-2 data from two sources: (Data set 2) 264 individuals over 28 weeks whose positive status was validated by two or more assays in addition to the Euroimmun anti-S1 assay,³⁰ and (Data set 3) 145 seropositive health care workers who experienced infection over the course of 21 weeks.³¹ Data sets 4–6 were replicates of Data sets 1–3 with the supplementation of MERS-CoV data from 11 individuals (five with severe disease; six with mild disease) monitored over 1 year after symptom onset.²⁰

To obtain data for antibody-waning profiles following vaccination that are an alternative to the antibody-waning profile following natural infection, we conducted additional PubMed and Google Scholar database searches between 1 September, 2021 and 24 October, 2022 using as terms combinations of “BNT162b2,” “mRNA-1273,” “antibodies,” “antibody response,” “coronavirus,” “ELISA,” “IgG,” “immunity,” “immune response,” “longitudinal monitoring,” “optical density,” “Euroimmun,” “S protein,” “Spike protein,” “reinfection,” “serological,” and “titer.”

2.3 | Waning antibody profiles and baselines

We constructed profiles of SARS-CoV-2 anti-S1 IgG antibody waning through time as in Townsend et al.⁹ We extracted postpeak infection antibody levels for human-infecting coronaviruses, normalized the postinfection peak antibody level, and calculated typical antibody waning profiles, using phylogenetic ancestral and descendent analysis³⁴ to estimate baseline anti-Spike IgG values for SARS-CoV-2, SARS-CoV-1, and MERS-CoV. We projected the time course for each typical antibody waning profile to 4393 days postpeak infection to match the duration of the longest full typical antibody waning profile. For each virus, antibody waning was related to its probability of infection using logistic regression of daily probability of infection against antibody level, $(1 + e^{-(a_v + b_v g)})^{-1}$. Parameters a_v (intercept) and b_v (slope) for each endemic coronavirus v , dependent on g , the peak-normalized antibody level, were fit to data from Edridge et al.¹⁸ analyzed as in Townsend et al.⁹ We estimated the a_v and b_v parameters for SARS-CoV-2, SARS-CoV-1, and MERS-CoV as in Townsend et al.²³ Using the antibody waning time course and the logistic infection functions inferred for each virus, we calculated the probabilities of infection on each day under endemic conditions. Mathematica notebooks and data used to conduct our approach have been deposited on Zenodo (DOI:10.5281/zenodo.6968130).

To connect these results on the durability of immunity against natural infection to durability of immunity against breakthrough infection following booster vaccinations, we quantified four ratios: (1) the ratio of the typical peak anti-RBD IgG antibody levels associated with the first BNT162b2 vaccination series to the peak anti-RBD IgG antibody levels associated with natural infection, (2) the ratio of the typical peak anti-RBD IgG antibody levels associated with the first

mRNA-1273 vaccination series to the peak anti-RBD IgG antibody levels associated with the first BNT162b2 vaccination series, (3) the ratio of typical peak anti-RBD IgG antibody levels associated with booster vaccination by mRNA-1273 to peak anti-RBD IgG antibody levels associated with the first mRNA-1273 vaccination series, and (4) the ratio of typical peak anti-RBD IgG antibody levels associated with booster vaccination by BNT162b2 to peak anti-RBD IgG antibody levels associated with the first BNT162b2 vaccination series. We then projected waning beginning at the product of ratios (1) and (3) for mRNA-1273, or at the product of (2) and (4) for BNT162b2. These products quantify antibody level relative to natural infection normalized at 1.0. Above 1.0, antibody waning postpeak followed the concave form inferred from Gudbjartsson,^{9,23,33} scaled to match the 5-month postpeak decline quantified in Pajon et al.³⁵ Antibody waning at level 1.0 and below was projected based on our analysis of empirical data supplemented by results from the comparative evolutionary analysis.

We replicated the sensitivity analyses conducted in Townsend et al.,⁹ including using a nonrecombinant alignment for phylogenetic inference, using alternate phylogenetic inference methods, and using alternate sources of anti-Spike IgG antibody data. Additional phylogenetic ancestral and descendent state analyses³⁴ were conducted to assess the impact of method of phylogenetic inference on our phylogenetic trait estimation of the baseline antibody level ω and the logistic infection function parameters a_v and b_v . To assess the impact of phylogenetic uncertainty on our analyses, we compared all results conditioned on the phylogenetic chronogram estimated in IQ-TREE to results conditioned on phylogenetic chronograms estimated using RelTime and TreeTime, molecular phylogenies from IQ-TREE and RAxML, and also phylogenies derived from those same methods using only the nonrecombinant alignment.

Using each of these alternate phylogenetic trees, the impact of using alternate anti-Spike IgG antibody data on our estimates was assessed through five additional analyses, designated 2–6. Analyses 2 and 3 substituted two alternate SARS-CoV-2 anti-S1 IgG longitudinal datasets,^{30,31} but otherwise were identical to analysis 1. For analyses 4 through 6, we repeated analyses 1–3, substituting an alternate anti-S IgG data set for MERS-CoV.²⁰ In total, these analyses resulted in 84 postpeak estimates of the median times to breakthrough infection following mRNA-1273 or BNT162b2 booster vaccination.

To quantify the statistical likelihood that no breakthrough infections would occur over a specified time following either the mRNA-1273 or BNT162b2 vaccination series, we projected the antibody waning time in the context of boosters administered every 6 months, 1, 1.5, 2, 3, or 6 years. Boosters were specified to elevate antibody levels on the day administered to their known peak at the first booster subsequent to vaccination,³⁶ and waning of antibody levels was projected to proceed as stated above. Applying the logistic infection function for SARS-CoV-2 (inferred from evolutionary ancestral and descendent states analysis) to that antibody-waning time course provided daily probabilities of no breakthrough infection following peak antibody response. These probabilities of infection given antibody level reflect the decreasing defense against

infection over time as a consequence of decreasing antibody level, as well as the average decrease in antibody efficaciousness against successive evolved variants in endemic coronaviruses.²³

From these daily probabilities of no breakthrough infection for each boosting schedule, we calculated the individual probabilities that no breakthrough infection would occur by 6 months, 1, 1.5, 2, 3, and 6 years after a booster. Using those individual probabilities, we determined the cumulative probabilities of no breakthrough infections over a 6-year time period with scheduled boosting upon the close of each interval.

3 | RESULTS

3.1 | Collection of data on waning of antibodies following vaccination and boosting

Literature search yielded one study meeting all inclusion criteria that reported peak antibody levels following the first series of BNT162b2 vaccination in comparison to natural infection (Table 1). This study included 272 individuals infected with SARS-CoV-2 sampled at an average of 40 days after symptom onset and 1256 SARS-CoV-2

naive individuals sampled 37 days after BNT162b2 vaccination.³⁷ Literature search yielded one study meeting all inclusion criteria that compared peak antibody levels following BNT162 booster vaccination to the first series of BNT162b2 vaccination. This study included 110 SARS-CoV-2 naive individuals vaccinated and boosted with BNT162b2 who were sampled 30 days after both BNT162b2 primary vaccination and boosting.³⁶

For mRNA-1273, literature search yielded six studies meeting all inclusion criteria that reported peak antibody levels following the first series of mRNA-1273 vaccination in comparison to peak antibody levels following the first series of BNT162b2 (Table 1). These studies ranged from 8 to 199 SARS-CoV-2 naive individuals sampled at an average of 24.5 days after mRNA-1273 vaccination.^{38–43} As for mRNA-1273 booster vaccination, our literature search yielded one study meeting all inclusion criteria that compared boosted peak antibody levels with the first series of mRNA-1272 vaccination. This study included 142 SARS-CoV-2 naive individuals vaccinated and boosted with mRNA-1273 who were sampled 28 days after both mRNA-1273 primary vaccination and boosting.⁴⁴

3.2 | Estimation of long-term antibody waning rates

Projection of the waning antibody levels postpeak in response to natural infection by SARS-CoV-2 exhibited consistent estimates of half-life to baseline, ranging from 36 to 156 days between data sets (Supporting Information: Table 1).

3.3 | Risk of breakthrough infection associated with each boosting schedule

Results for each mRNA vaccine were highly similar. In the absence of updated boosting, the probability of remaining free of infection for 6 years was 13% for either mRNA vaccine (Figure 1). A schedule specifying boosting at 3-year intervals resulted in only a marginal attenuation of the risk of breakthrough infection by 6 years (mRNA-1273: 87% with cessation of boosting to 76% with boosting every 3 years, Figure 1A; BNT162b2: 87% with cessation of boosting to 77% with boosting every 3 years, Figure 1B). Annual boosting resulted in a substantial reduction in 6-year risk (to 25% for mRNA-1273, Figure 1A; to 31% for BNT162b2, Figure 1B). Boosting every 6 months induced the highest level of protection, with a risk of breakthrough infection over 6 years that is less than 7% for mRNA-1273, compared with 11% for BNT162b2. These results were consistent regardless of SARS-CoV-2 waning antibody data set used (Table 2). Alternate compositions of the antibody-waning data sets for related viruses provided consistent results with respect to relative decreases in probability of no breakthrough infection at the close of these intervals, but differed modestly in the scale of risk associated with each booster schedule (Supporting Information: Figure 1).

TABLE 1 Peak antibody levels subsequent to vaccination and natural infection

Stimulus	Subjects	IgG antibody	Days ^a	Peak ^{b,c}	Study
Infection	1797	anti-S1	34	1.00 ^c	[33]
Infection	264	anti-S1	28	1.00 ^c	[30]
Infection	145	anti-S1	56	1.00 ^c	[31]
Infection	272	anti-S	40	1.00 ^c	[37]
<i>Means (across studies)</i>			39.5	1.00 ^c	—
BNT162b2 ^d	1256	anti-S	37	1.50	[37]
BNT162b2 ^e	110	anti-S1-RBD	30	1.54	[36]
mRNA-1273 ^d	10	anti-S1	35	1.59	[38]
mRNA-1273 ^d	52	anti-S	28	1.42	[39]
mRNA-1273 ^d	8	anti-RBD	14	1.42	[40]
mRNA-1273 ^d	29	anti-RBD	14	1.48	[41]
mRNA-1273 ^d	40	anti-S1-RBD	28	1.53	[42]
mRNA-1273 ^d	199	anti-S	28	1.55	[43]
<i>Means (across studies)</i>			24.5	1.50	—
mRNA-1273 ^e	142	anti-S	28	1.68	[44]

^aNumber of days after second dose of BNT162b2 or mRNA-1273 vaccination, or average number of days post symptom onset for natural infection.

^bRelative values versus natural infection.

^cIn every analysis, the peak value for natural infection was assigned to equal 1.

^dPostvaccination peak antibody levels.

^ePostbooster peak antibody levels.

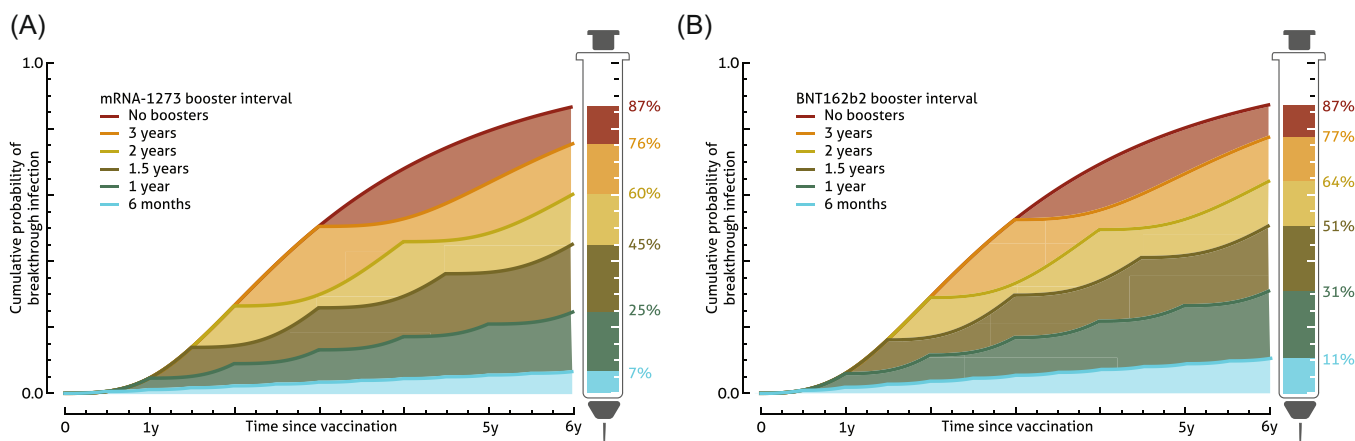


FIGURE 1 Probabilities of remaining free of infection under endemic conditions over 6 years at a range of intervals of updated boosters. Probabilities were quantified for no boosting and for updated boosting every 6 months, 1, 1.5, 2, and 3 years, for (A) vaccination and boosting by mRNA-1273 and (B) vaccination and boosting by BNT162b2.

TABLE 2 Probabilities of no breakthrough infection after vaccination with no boosting at different time points for alternative SARS-CoV-2 waning data sets

	Boosting every					
	6 months	1 year	1.5 years	2 years	3 years	6 years
mRNA-1273						
Gudbjartsson ³³	0.93	0.75	0.55	0.40	0.24	0.13
Harris ³⁰	0.97	0.69	0.47	0.36	0.28	0.21
Manisty ³¹	0.86	0.43	0.31	0.26	0.22	0.18
BNT162b2						
Gudbjartsson ³³	0.89	0.69	0.49	0.36	0.23	0.13
Harris ³⁰	0.96	0.66	0.45	0.35	0.28	0.21
Manisty ³¹	0.82	0.42	0.30	0.25	0.21	0.18

For each antibody waning data set, results were consistent regardless of the method of phylogenetic inference and were consistent whether a chronogram or a molecular evolutionary tree was used (Supporting Information: Table 2).

4 | DISCUSSION

Here we have quantified the probability of breakthrough infection under alternate mRNA-1273 or BNT162b2 booster vaccination schedules. We leveraged a data-driven model that incorporates the waning of antibodies, the probability of infection given antibody level under endemic conditions, and the distribution of likely times to breakthrough infection following vaccination. This approach enables forecasting of the risk of infection attributable to alternate timings of booster administration. Delaying boosting beyond 2 years is found to yield cumulative risks of future infection that are nearly as high as foregoing boosting entirely. Our analysis strongly supports boosting on an annual or more frequent cycle to markedly diminish the long-term risk of infection. These results provide a quantitative basis for

the specification of regularized booster vaccination policies and encourage their implementation.

We have here quantified the benefits of boosters as though each immunizes against the coincident circulating strain. We are only beginning to comprehend the dynamics of how antigenic drift of the SARS-CoV-2 virus promotes the evolution of immune evasion.¹⁶ However, our projection of the benefits of each booster schedule does incorporate the effect of virus variation and consequent antigenic drift on immunity. The probabilities of infection given antibody levels were calculated by an evolutionary analysis of long-term antibody and infection data responsive to infections by endemic coronaviruses that share antigenic drift characteristics with SARS-CoV-2. The use of long-term infection and antibody data naturally includes the evolution of endemic coronaviruses variants. To obtain the predicted levels of protection, booster vaccinations have to be updated to keep in lock-step with the ongoing evolution of the virus.⁴⁵ Accordingly, mRNA boosters that target predominant new strains of SARS-CoV-2 have been produced.^{46,47}

Globally equitable access and uptake of booster vaccination is essential to the long-term control of COVID-19 infection in defiance

of viral variant evolution. Repeated boosting that targets ancestral strains instead of currently circulating variants has thus far retained at least partial utility in preventing infection, hospitalization, and death.⁴⁸ However, the benefit of boosters that target ancestral strains inevitably diminishes as new variants evolve. The rate of new variant evolution will be proportional to the viral population size, which in turn is proportional to global infection rate. Infection rate can be lowered by booster vaccination.^{49,50} Therefore, vaccination on an efficacious schedule that successfully suppresses disease will be essential to the persistence of immunity consequent to booster vaccination, to the suppression of viral infection and reproduction, and to the minimization of opportunities for viral evolution of immunoevasion.

For the average individual, receiving booster vaccinations on this optimized schedule provides maximal protective benefit in consideration of the costs of vaccination. However, the benefit of booster vaccination will depend upon specific aspects of individual context. Some individuals will acquire a boost to their immunity from asymptomatic or symptomatic infection. The durability of protection from viral infections has been estimated to be lower than mRNA vaccination.⁹ Depending on the antibody response mounted during viral infection boosting could reasonably be slightly delayed in cases where an individual has recently recovered from infection. In some individuals, T-cell or other adaptive immune responses may be a better determinant of the benefits of boosting than antibody responses would be.⁵¹ More long-term data on these additional adaptive immune responses in diverse viral lineages would refine these quantitative analyses of effective booster frequencies.

Regular vaccinations with updated mRNA-1273 and BNT1262b2 boosters under endemic conditions are predicted in our analysis to yield similar suppression of infection. This result is consistent with similar short-term antibody responses observed following primary vaccination^{52–54} and consistent with long-term projections based on vaccination alone.⁹ However, other vaccines may require higher frequencies of boosting to achieve similar results. The ChAdOx1-S and Ad26.CoV2.S vaccines evoke substantially lower peak antibody responses,^{42,55,56} confer lower levels of short-term protection from infection,^{2,57,58} and provide at best half as much durability of immunity.⁹ Based on these performances as primary vaccines, ChAdOx1-S or Ad26.CoV2.S boosters could be crudely presumed to require at least twice the frequency of dosing to achieve an equivalent suppression of infection. Durability of immunity based on primary vaccination with the Novavax vaccine has not been assessed. The durability of the immune response following other vaccinations has largely been commensurate with antibody levels.⁹ Nearly equivalent antibody responses between Novavax NVX-CoV2373/TAK-019 and mRNA vaccination⁵⁹ imply that suppression of infection with the NVX-CoV2373/TAK-019 vaccine could be similar to that indicated for mRNA vaccines. Regardless of vaccine type, the efficacy of boosting will also depend on an individual's immune status. For example, among cancer patients, there are substantial differences in the elicitation of antibody responses following various

immuno- or- chemotherapies.^{60,61} A proportion of cancer patients would likely require more frequent immune boosting to maintain protection against infection over time. As data on the immune response to vaccination within disease- or treatment-specific cohorts of immunocompromised individuals become available, our approach can be deployed to quantify appropriate booster frequencies.

Our assessment of the protection provided by alternate booster schedules provides knowledge for personal and policy-relevant decision-making that can have substantial impact on the mitigation of future transmission of SARS-CoV-2. Not only does updated booster vaccination have direct impact on SARS-CoV-2 transmission in individuals, but global vaccination and boosting could further aid in extending the durability of vaccine-mediated immunity—partly by suppressing levels of infection below that expected in a circulating coronavirus, but also by decreasing the evolving viral population and thus the rate of variant evolution.

AUTHOR CONTRIBUTIONS

Jeffrey P. Townsend and Hayley B. Hassler conceived the project and designed the study with Alex Dornburg; Hayley B. Hassler, Jeffrey P. Townsend, and Alex Dornburg performed literature review and assessed suitable data sets; Hayley B. Hassler accessed and processed antibody data for each virus; Hayley B. Hassler performed analyses with guidance from Jeffrey P. Townsend and Alex Dornburg; Hayley B. Hassler, Alex Dornburg, and Jeffrey P. Townsend designed and implemented data visualizations; Jeffrey P. Townsend and Alex Dornburg wrote the manuscript with contributions from Hayley B. Hassler; and all authors reviewed the manuscript before submission. Jeffrey P. Townsend and Alex Dornburg were responsible for the decision to submit the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Data were verified by Hayley B. Hassler, Alex Dornburg, and Jeffrey P. Townsend.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data and code are public: supplemental tables, alignments, phylogenies, and code used to generate these analyses are available on Zenodo:10.5281/zenodo.6968130.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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