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Predicting the efficacy of variant-modified COVID-19 vaccine boosters

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Booster vaccination for the prevention of Coronavirus Disease 2019 (COVID-19) is required to overcome loss of protection due to waning immunity and the spread of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. Studies have assessed the ability of existing ancestral-based vaccines as well as novel variant-modified vaccine regimens to boost immunity to different variants, and a crucial question is to assess the relative benefits of these different approaches. Here we aggregate data on neutralization titers from 14 reports (three published papers, eight preprints, two press releases and notes of one advisory committee meeting) comparing booster vaccination with the current ancestral-based vaccines or variant-modified vaccines. Using these data, we compare the immunogenicity of different vaccination regimens and predict the relative protection of booster vaccines under different scenarios. We predict that boosting with ancestral vaccines can markedly enhance protection against both symptomatic and severe disease from SARS-CoV-2 variant viruses, although variant-modified vaccines may provide additional protection, even if not matched to the circulating variants. This work provides an evidence-based framework to inform choices on future SARS-CoV-2 vaccine regimens.

Vaccination provides substantial protection from both symptomatic and severe Coronavirus Disease 2019 (COVID-19). However, the emergence of antigenically distinct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, such as Omicron and its subvariants, has markedly reduced the effectiveness of current vaccine regimens, which are based upon the ancestral (Wuhan-like) variant. This raises two major questions for future vaccine development. First, is there an advantage in switching from the current ancestral-based vaccines to incorporate variant spike proteins? Second, if switching to a variant-modified vaccine, how important is it that the immunogen in the variant-modified vaccine is antigenically closely related to the spike protein of the circulating variant? In the present study, we analyzed data from 14 reports[1–14] (three published papers, eight preprints, two press releases and notes from one advisory committee meeting) that directly compared neutralizing antibody titers against multiple SARS-CoV-2 variants elicited by an ancestral-based vaccine with those elicited by a variant-modified vaccine. The studies included data from Sanofi-GlaxoSmithKline, Moderna and Pfizer-BioNTech vaccine constructs, incorporating the ancestral, Beta, Delta, Omicron BA.1 or Omicron BA.4/5 spike proteins (either alone or in combination with each other or the ancestral variant spike proteins) and included mRNA vaccines (13 studies[2–14]) and an adjuvanted recombinant protein vaccine (one study[1]). We then used a validated model relating neutralization titers to vaccine effectiveness to estimate the changes in vaccine protection under different booster regimens[15–17]. The main findings and policy implications are presented in Extended Data Table 1.

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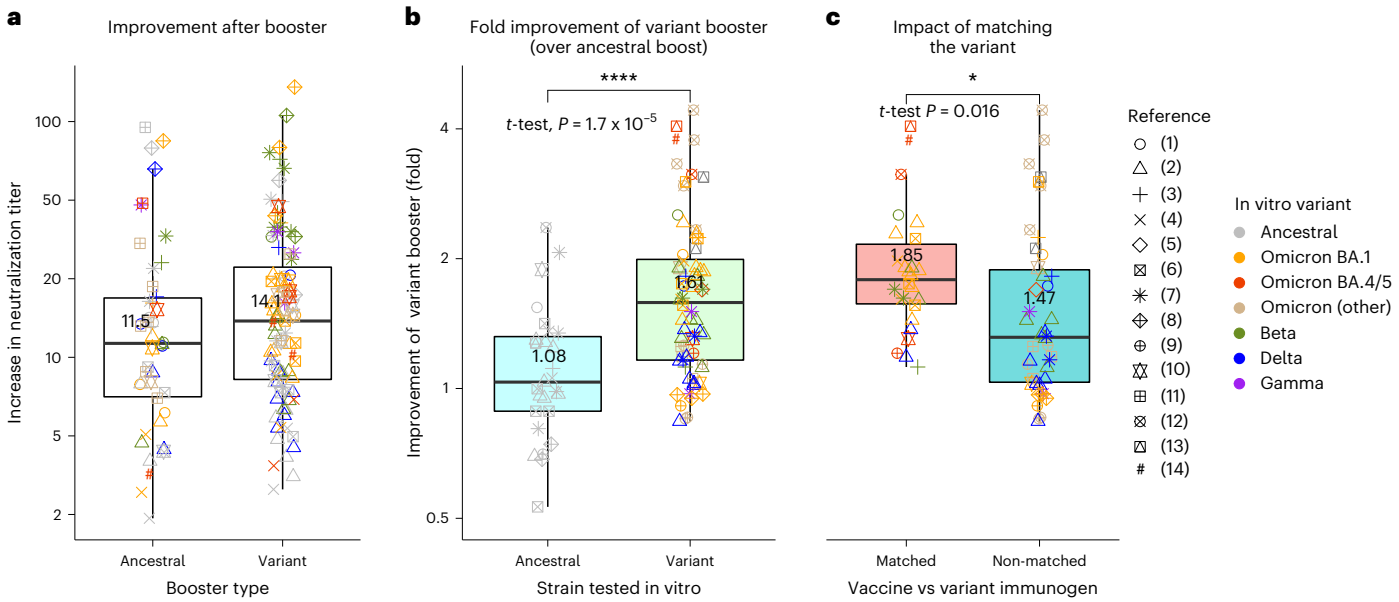

Fig. 1 | Aggregated neutralization data on boosting with both ancestral-based and variant-modified vaccines. a, Fold change in neutralization titers against all variants after boosting with an ancestral-based ($n = 46$ data points) or variant-modified ($n = 95$ data points) vaccine. Change in titers against different SARS-CoV-2 variants tested in vitro are depicted in different colors. **b**, Improvement in neutralization titers (shown as fold increase) when boosting with a variant-modified vaccine compared to an ancestral-based vaccine. Variant-modified boosters lead to similar in vitro neutralization titers to the ancestral strain (compared to ancestral-based boosters) (left, $n = 27$). However, variant-modified boosters lead to higher neutralization titers against other variants in vitro (right, $n = 68$). **c**, Fold increase in neutralization titers after boosting with a variant-modified vaccine compared to an ancestral-based vaccine depending on whether the variant tested in vitro matched the vaccine immunogen (red, left, $n = 26$) or did not match the vaccine immunogen (blue, right, $n = 42$). For **b** and **c**, two-sided t-tests were performed on the $\log_{10}$-transformed values. For all panels, **a**–**c**, the center line of the box shows the median; box limits show interquartile ranges; and whiskers show the range of the data (excluding outliers). Omicron (other) refers to other Omicron subvariants that were tested in vitro and includes BA.2, BA.2.75, BA.2.75.2, BA.4.6, BQ.1.1, BF.7 and XBB.1.

To compare the average magnitude of boosting between ancestral-based vaccines and variant-modified vaccines, we first compared the rise in neutralization titer between pre-booster and post-booster titers. Considering neutralization for all variants reported in the studies, we found that an ancestral-based booster increased neutralization titers by a mean of 11.5-fold compared to pre-booster titers (95% confidence interval (CI) 8.8–15.1; Fig. 1a). Although variant-modified vaccines showed similar neutralization toward ancestral SARS-CoV-2 compared to the ancestral-based vaccines ($P = 0.25$), the variant-modified vaccines produced higher levels of in vitro neutralization of the variants tested (compared to the ancestral-based vaccine) ($P < 0.001$; Fig. 1b) regardless of the variant composition within the vaccine (Extended Data Fig. 1). Considering only neutralization of SARS-CoV-2 variant strains, we found that variant-modified vaccines on average produced 1.61-fold (95% CI 1.5–1.8) higher titers than the equivalent ancestral-based vaccine ($P < 0.001$; Fig. 1b). To determine if this numerical superiority of the variant-modified vaccines was true only when the variant-modified vaccine matched the strain used in the neutralization assay, we compared the level of boosting to the homologous strains (that is, the same variant in vaccine and neutralization assay) versus non-homologous strains (neutralization of variants not included in the vaccine). Boosting was higher against homologous (1.85 (95% CI 1.6–2.1)) versus non-homologous (1.47 (95% CI 1.3-1.7)) strains ($P = 0.02$). The relative increase in neutralization titers conferred by a variant-modified vaccine over an ancestral-based vaccine was not significantly changed when stratifying data by vaccine valency (monovalent versus bivalent, $P = 0.64$), history of prior infection ($P = 0.08$) and the number of previous vaccines that individuals had received ($P = 0.17$) (Extended Data Figs. 2 and 3). It is important to note that the findings here do not imply that all variant-based vaccines in development will inevitably generate an improvement over the matched ancestral vaccine. Rather, from the available data (which are limited by the vaccine antigens, in vitro variants and populations tested), there is a high degree of confidence that, on average, across a population, variant-based vaccines produce higher variant-specific neutralizing antibody titers than ancestral-based vaccines, and, thus, a higher level of population protection is predicted. However, direct comparisons of the in vitro neutralizing antibody titers for specific vaccines, spike immunogens and circulating SARS-CoV-2 variants in randomized studies remains a critical tool in predicting future booster effectiveness.

To estimate the potential clinical benefits of the 1.6-fold improvement in neutralization titers resulting from switching from ancestral-based boosters to variant-modified boosters, we used a model that correlates neutralization titers with observed clinical protection[15]. This model was originally parameterized from phase 3 clinical trials of seven vaccines and has subsequently been validated for ancestral-based vaccines against the Beta, Delta and Omicron variants[16,17] as well as showing good agreement with individual-based studies of protective immunity[18]. This approach uses the correlation between neutralizing antibody levels measured in vitro and the level of protection observed in clinical studies to allow prediction of vaccine efficacy from the relative immunogenicity of different regimens. We first considered the effect of the prior level of immunity (mean pre-boost antibody titer) in the population, and then we considered a range of antibody titers spanning a very low and very high pre-existing immunity. We then applied the fold increase in neutralization titers resulting from the different interventions assessed in this study to predict the average population neutralization titers after boosting with the different vaccines. This predicted neutralization titer was then used in the existing model to predict vaccine efficacy[15]. We used the model to predict the relative protection conferred by booster vaccination with an ancestral-based vaccine compared to using different variant-modified vaccine regimens, based on the measured differences in neutralizing

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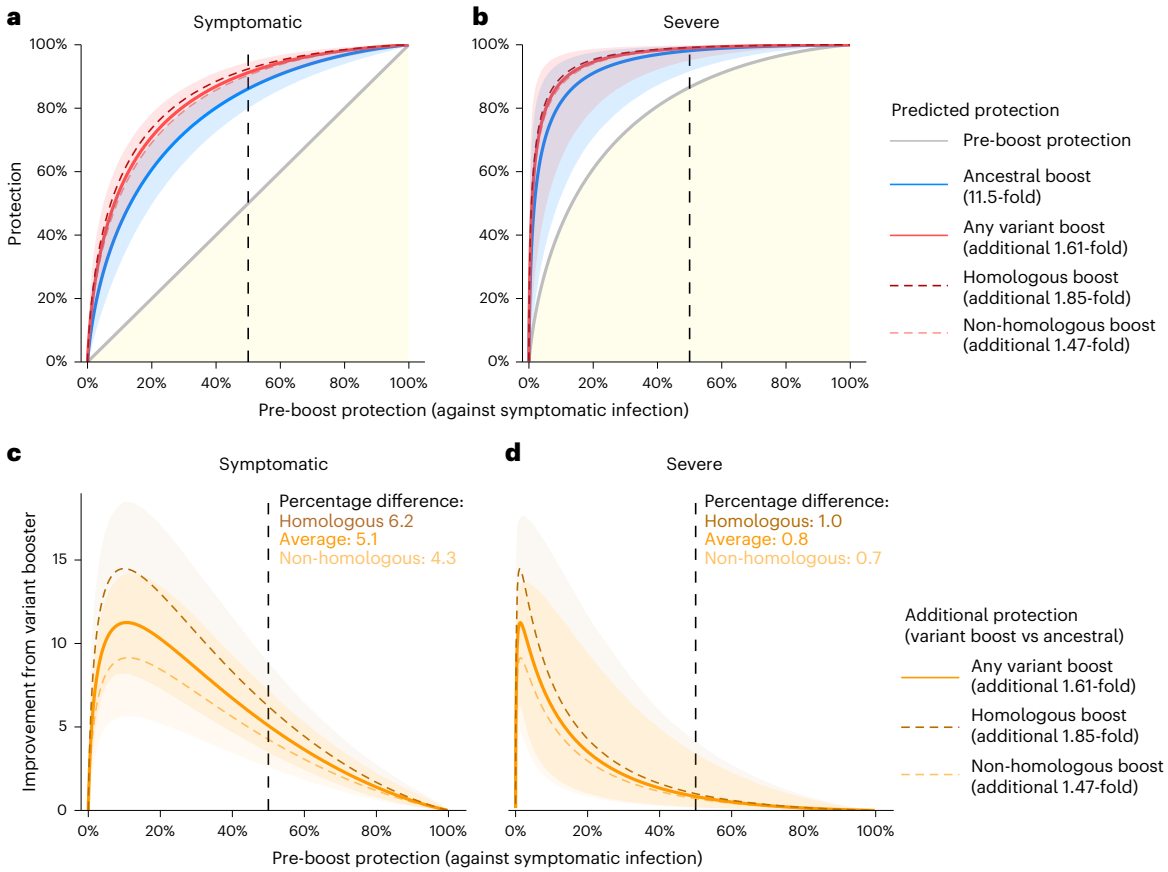

Fig. 2 | Estimated improved protection from a variant-modified booster over an ancestral-based booster. a,**b**, For different levels of pre-boost protection from symptomatic infection (gray), the levels of protection against symptomatic (**a**) and severe (**b**) COVID-19 after either an ancestral-based boost (blue) or a variant-modified boost (red) are shown. The solid red line shows protection after receiving any variant-modified vaccine; dashed red lines show protection for an antigenically matched variant-modified vaccine (dark red) and non-matched variant-modified vaccine (light red). **c**,**d**, Average improvement in protection from symptomatic (**c**) and severe (**d**) COVID-19 for a variant-modified vaccine over an ancestral-based vaccine over the 6 months after boosting. The solid line shows protection for any variant-modified vaccine; dashed lines show protection for a matched variant-modified vaccine (dark orange) and non-matched variant-modified vaccine (light orange). The text at the top of **c** and **d** indicate the percentage point improvement in protection over an ancestral-based booster when the pre-boost population protection against symptomatic disease is 50%. Shaded bands show 95% confidence bands of the correspondingly colored lines.

antibody titers. We considered the relative impact of an ancestral-based booster that delivers an 11.5-fold boost in neutralizing antibody titers and a variant-modified booster delivering a further 1.6-fold-higher titer than the ancestral booster (that is, an 18.5-fold increase in neutralizing antibody titers compared to pre-boost, consistent with the analysis above). We estimated the average protection against both symptomatic and severe COVID-19 provided by the different boosters over a 6-month period, assuming antibody titers decay at the same rate for both vaccines (with a half-life of 108 days[15,17,19]).

The relative benefits of a variant-modified vaccine are very dependent on the underlying (pre-booster) population immunity to infection for the currently circulating variant (Fig. 2). If we consider a previously vaccinated or infected population that already has 50% protection from symptomatic infection (compared to a naive population), we find that an ancestral-based booster giving an 11.5-fold boost (95% CI 8.8–15.1) in neutralizing antibody titers would increase the average protection over a 6-month period against symptomatic infection from 50% pre-boost to 86.1% (95% CI 80–90.6). Directly comparing the incremental benefit of a variant-modified booster versus an ancestral-based booster, a variant-modified booster is predicted to provide an additional 5.1 percentage points (95% CI 3.5–7.2) protection against symptomatic illness compared to the ancestral-based vaccine, resulting in 91.2% (95% CI 86.4–94.6) protection against symptomatic infection (Fig. 2a,c). Similar analyses can be used to predict comparative vaccine effectiveness against severe COVID-19 under the same assumptions. A population with 50% pre-boost protection from symptomatic infection is predicted to have 86.6% pre-boost protection from severe COVID-19. Boosting with an ancestral-based vaccine is expected to increase this to an average of 98.1% (95% CI 91.6–99.6) protection from severe COVID-19 over the 6-month period after boosting, and a variant-modified booster is predicted to provide an additional 0.8 percentage points (95% CI 0.2–3.4, P <0.001) of protection from severe COVID-19 compared to an ancestral-based booster, resulting in 99% (95% CI 95–99.8) protection against severe disease (Fig. 2b,d). This would correspond to eight additional severe cases (95% CI 2–34) averted for every 1,000 severe cases that would have occurred in a naive population over the 6-month period. However, in cases where the pre-boost immunity to the circulating variant is higher or lower (such as might occur in the context of an antigenically distinct variant or after waning of immunity), the relative benefits of a variant booster compared to an ancestral booster in protecting against symptomatic and severe COVID-19 can vary. In general, the lower the pre-boost immunity, the greater the relative benefit of a variant-modified booster compared to an ancestral-based booster, peaking with an additional 11.3 (95% CI 8.2–14.2) percentage points protection from symptomatic infection when the population has only 10.6% pre-boost protection against symptomatic infection (which corresponds to 44.1% protection against severe COVID-19 (Fig. 2d)). At this level of population immunity,

a variant-modified vaccine would provide an additional 6 percentage points (95% CI 2–12.1) protection from severe COVID-19 compared to an ancestral-based vaccine.

The analysis above considers the benefit of any variant-modified booster (regardless of whether it is antigenically similar to the circulating variant). Given that the relative advantage of variant-modified boosters was found to be higher to homologous than non-homologous variants (1.85-fold versus 1.47-fold), using the same approach we also estimated the relative advantage of a booster that did or did not match the antigenicity of the circulating variant over the first 6 months after boosting. We found that, for a population with 50% pre-boost protection from symptomatic SARS-CoV-2, antigenic matching of the booster is predicted to provide an additional 2 (95% CI 0.4–4) and 0.3 (95% CI 0.03–1.4) percentage points protection from symptomatic and severe COVID-19, respectively, when compared to an antigenically unmatched booster.

Our approach provides a method for predicting the comparative effectiveness of different booster vaccine formulations, informed by relative improvements in neutralization titers and changes in titers against different variants. Synthesis of the currently available data suggests that variant-modified booster vaccination can provide significantly higher (1.6-fold) neutralization titers to a diversity of current and historic SARS-CoV-2 variants compared to ancestral-based boosters. This is predicted to provide up to a maximum of an 11.3 percentage point increase in protection, dependent on the pre-boost level of population protection. An interesting question is whether increasing the dosage of the ancestral-based vaccines may bring them into line with a variant-modified vaccine[20]. However, although this may be possible in theory, within the currently available data there were an insufficient number of studies (only two (refs. [7,9])) that compared ancestral-based vaccines at different doses to draw a conclusion to this question.

This analysis includes several important caveats. First, it integrates data from studies of variant-modified boosters, which varied considerably in study design, and many of which were carried out largely by vaccine manufacturers. Studies differed in the number of previous vaccines that individuals had received, the number of prior SARS-CoV-2 infections and the time since last vaccination (Extended Data Tables 2 and 3), and they reported neutralization titers against a limited set of variants that were not the same across studies. In addition, only nine of 14 studies were clinical trials, and, of these, only four assigned participants between the arms of the studies in a randomized fashion. Non-randomized studies incorporated variable degrees of population matching (Extended Data Table 3). Finally, this work relies on predicting vaccine efficacy from neutralization titers. Although this approach has been validated in a number of contexts[15–17,21–24], it cannot replace clinical studies of vaccine effectiveness. This is especially true given that previous validation of this model's predictions has been for vaccines targeting the ancestral virus. Several other studies of correlates of protection have estimated a relationship between vaccine efficacy and neutralization[25–27], and these could represent a means of independently testing the model predictions reported here for variant-based booster vaccines. These studies have arrived at broadly consistent relationships between neutralizing antibodies and vaccine efficacy[18]. To predict average vaccine efficacy over the first 6 months after vaccination, we took into account waning of neutralizing antibodies over this period[15–17,19,28,29]. We estimated the difference in peak neutralization titers between different booster strategies from the data (Fig. 1) and assumed that antibodies waned at the same rate after ancestral-based and variant-modified boosters. Thus, it will be important to validate these assumptions and predictions in future clinical studies.

This work considers the impact that neutralizing antibodies have on protection against COVID-19. Although neutralizing antibodies have been shown to provide a very good correlate of protection against symptomatic[15,17,21] and severe[16] COVID-19, we cannot rule out an additional contribution of non-neutralizing antibody functions or cellular immunity to protection that may be impacted by these different vaccine formulations[30]. In addition, the study participants may not be representative of the populations at highest risk of severe COVID-19. Of the 11 studies considered here with documented participant demographics[1–4,7,8], participant gender was balanced in eight (40.4–58% female) but unbalanced in three (73–83% female) (Extended Data Table 2). The mean/median ages of participants ranged from 40.6 years to 71.1 years. The populations were also predominantly reported as 'white' (>67% in all studies that report participant race/ethnicity) and residing in the United States or France (ten studies and one study, respectively, of the 11 studies that report location).

Despite these limitations, this work provides a quantitative and evidence-based mechanism to estimate and compare the relative benefits of different vaccine modifications. Our findings suggest that a large proportion of the benefit comes from receiving any booster at all (including an ancestral-based booster). Indeed, variant-modified boosters may not be available in all regions, and this analysis supports the continued use of ancestral-based vaccines as an effective means of boosting immunity against SARS-CoV-2. Use of a variant-modified vaccine is expected to provide a modest increase in protection, which may be slightly greater in cases where the vaccine immunogen is more antigenically related to the circulating variant or if immunity has waned. However, even if the SARS-CoV-2 variant circulating at the time of vaccination is relatively antigenically distant from immunogen in the variant-modified booster, as may be the case for newly emerging variants, an elevated level of protection (when compared to either no booster or an ancestral-based booster) is still expected. Notably, the overall benefit of variant-modified vaccines will likely be determined by other factors, including the time since vaccination (waning of immunity), relative availability, cost and community acceptance of variant-modified vaccines over existing vaccines.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02228-4.

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Methods

Identifying studies to use in this analysis

We surveyed the academic literature (published works and preprints), manufacturer press releases and information provided to regulators for data on variant-modified vaccine immunogenicity. Where we identified multiple reports of the same underlying cohort or trial (for example, a preprint and a press release presenting the same information from a specific trial), we collected information from the report containing the most complete information only. We identified eight reports with unique information on variant-modified vaccine immunogenicity up to 15 July 2022 (refs. [1–8]). We further identified six reports containing data on the BA.5-containing vaccines from 24 October to 5 November 2022 (refs. [9–14]).

The studies identified for this analysis are shown in Extended Data Table 2.

Extracting data from relevant studies

For each study identified in Extended Data Table 2, we extracted information on the booster composition(s), the dose(s) administered and the variants against which neutralizing antibodies were tested in vitro. For each vaccine immunogen/dose/in vitro variant combination, we recorded the geometric mean neutralizing antibody titer (GMT) pre-vaccination and post-vaccination (for all reported assays). Where available, neutralizing antibody titers at 2 weeks after the booster dose were used. However, if these were not available, titers from up to 3.5 months after boost were used.

In the one case where exact neutralizing antibody levels were not reported[6], the ratio between neutralizing antibody levels against a variant of concern and against the ancestral virus was extracted instead. Data were processed using R version 4.0.2.

Statistical analysis and reproducibility

Unless otherwise stated, all tests performed were *t*-tests. The distribution of data was compared to a normal distribution using the Shapiro–Wilks test, and, if potential deviation from normality was detected, a sensitivity analysis was performed removing outliers according to their Cook's distance (that is, with Cook's $D > 4/n$), to verify that this did not change any interpretation of the findings. As an additional precaution, all *t*-tests were repeated as Mann–Whitney *U*-tests and verified to have the same interpretation. All tests were performed using R version 4.0.2. No data were excluded from the analyses. No statistical method was used to predetermine sample size.

Data were also analysed using custom code (details described below; code is directly available at GitHub links below) implemented in R version 4.0.2.

Fold rise in antibodies after boosting

To calculate the fold rise in neutralizing antibody titers after boosting (with either a variant-modified vaccine or an ancestral-based vaccine), we divided the reported GMT post-boost neutralizing antibody titers for each variant tested in vitro with the matched GMT pre-boost neutralizing antibody titers for the same in vitro variant (matching data by study, dose and assay). That is, the formula governing the fold change (*FC*) calculation is:

$$FC(v,m,d,s,a) = \frac{NAb_{post}(v,m,d,s,a)}{NAb_{pre}(v,m,d,s,a)} \quad (1)$$

where NAb_{post} is the GMT of the neutralizing antibody titers after booster dose; NAb_{pre} is the GMT of the neutralizing antibody titers before the booster dose; v is the variant tested; m is the makeup of the booster vaccine; d is the dose administered; s is the study; and a is the assay used.

Fold rise in neutralizing antibody titers for a specific booster vaccine

For a specific booster vaccine makeup m, we can determine the geometric mean fold rise in neutralizing antibody titers, $\overline{FC(m)}$, by taking the geometric mean of Eq. 1 over all available variants tested, doses administered, studies considered and assays used. Thus, the geometric mean fold rise in neutralizing antibody titers for a specific booster vaccine is given by:

$$\overline{FC(m)} = \left(\prod_{all\,v,d,s,a} FC(v,m,d,s,a)\right)^{\frac{1}{N_m}} \quad (2)$$

where N_m is the number of unique combinations available in our extracted data of v, d, s and a for vaccine makeup m.

Improvement for a variant-modified vaccine boost compared to an ancestral-based vaccine boost

To estimate the improvement gained by boosting with a variant-modified vaccine over boosting with an ancestral-based vaccine, we compared the neutralizing antibody titers after boosting with a particular variant-modified vaccine to the corresponding neutralizing antibody titers after boosting with an ancestral-based vaccine. Cohorts vaccinated with a variant-modified vaccine were always matched to a cohort of individuals receiving an ancestral-based vaccine from the same publication, and cohorts within the same study were matched by vaccine composition, assay and booster dose to control for non-vaccine-related differences in neutralization titers. The formula governing the improvement (I) is given by:

$$I(v,m,d,s,a) = \frac{NAb_{post}(v,m,d,s,a)}{NAb_{post}(v,m_A,d,s,a)} \quad (3)$$

where v, m, d, s and a are as defined above, and m_A refers to the ancestral-based vaccine.

We can then calculate the geometric mean improvement for a group K of variant-based boosters with different vaccine makeups, $\overline{I(K)}$, using the formula:

$$\overline{I(K)} = \left(\prod_{m\in K}\left(\prod_{all\,v,d,s,a} I(v,m,d,s,a)\right)^{\frac{1}{N_m}}\right)^{\frac{1}{N_k}} \quad (4)$$

where N_K is the size of the group K.

Matching of vaccine immunogen and variant tested

To assess the importance of matching the variant composition of variant-based booster vaccines with the circulating variant, we compared the improvement of variant-based boosters over ancestral boosters when immunogen in the vaccine and that used in the neutralization assay were matched or unmatched. We determined that the variant tested in vitro (v) was matched to vaccine immunogen (or vaccine makeup, m) if the variant tested was one of *any* of the variants that went into the vaccine makeup. Therefore, when testing neutralization of the Omicron BA.1 variant in vitro, this would have been considered to be matched with any of the following vaccines: (1) a monovalent BA.1 vaccine, (2) a bivalent vaccine containing BA.1 and ancestral virus spike or (3) a bivalent vaccine containing BA.1 and any other variant spike (for example, Beta or Delta). However, it would be considered non-matched to either an ancestral-based vaccine or a variant-modified vaccine that did not include the BA.1 variant spike. By a similar argument, when testing the neutralizing antibody titers against the ancestral virus in vitro, the ancestral variant would be considered to be matched with the ancestral-based vaccine as well as with any variant-modified

vaccine that also included the ancestral spike in its makeup. Thus, we determined the matching of vaccine antigen and neutralization antigen in a manner independent of vaccine valency.

Waning of neutralizing antibodies

After boosting, neutralizing antibodies are assumed to wane back to their pre-boost level with a half-life of 108 days[15,17,19]. Therefore, if the neutralizing antibody titers before boosting were given by n_0, then, at t days after an f-fold boost in neutralizing antibody titers due to vaccination, neutralizing antibody titers $n_{boost}(n_0, f, t)$ would be given by:

$$n_{boost}(n_0, f, t) = \max\left(f n_0 e^{-\frac{\ln(2)t}{108}}, n_0\right) \quad (5)$$

Calculating the average efficacy over a period of time, T, after boosting

To determine the average efficacy within a group of subjects over a fixed period of time after boosting (either by an ancestral-based or a variant-modified booster vaccine), we first need to know the pre-boost level of neutralizing antibody titers. This is equivalent to knowing the pre-boost symptomatic efficacy (labeled as VE_0) within the population from which the subjects are taken.

Given VE_0, the fold rise (f) in neutralizing antibody titers due to the vaccine boost and a period of time (T), we can follow the steps 1–4 below to calculate the average efficacy over the time period after boosting:

1. Establish the average baseline neutralizing antibody titers in the population.
   We can calculate the average neutralizing antibody titers within the population using our established relationship between neutralizing antibody titers and vaccine efficacy[15]. This is done by using the inverse of the relationship between neutralizing antibody titers and vaccine protection previously established in Khoury et al.[15]. For neutralizing antibody titers given by n, the original relationship takes the form:

$$VE(n) = \int_{-\infty}^{\infty} N(x, \log_{10}(n), \sigma) \frac{1}{1 - e^{-k(x - x_{50})}} dx \quad (6)$$

   where $VE(n)$ is the vaccine efficacy (compared to a naive population) for a population with GMTs of n, and $N(x, \mu, \sigma)$ is the probability density function of a normal distribution with mean μ and standard deviation σ, evaluated at a ($\log_{10}$) neutralization titer of x. A number of these parameters were previously estimated and reported in Khoury et al.[15] by fitting the model to data from randomized controlled trials—that is, $\sigma(0.46)$, $k(3.1)$ and x_{50} ($\log_{10}(0.20)$).

   Given a pre-boost level of protection from symptomatic disease of VE_0, we can numerically calculate the corresponding average neutralizing antibody titers in the population, n_0, by using the inverse of Eq. 6. We will represent these population average neutralizing antibody titers for a given pre-boost symptomatic efficacy, VE_0, as $\hat{n}(VE_0)$.
2. Calculate the neutralizing antibody titers at a given time, t, after boosting.
   For a given fold boost in neutralizing antibody titers due to a vaccine, we let n_0 be the neutralizing antibody titer determined in step 1 above and Eq. 5 to calculate the neutralizing antibody titers t days after boosting.
3. Establish the new efficacy (compared to a naive population) at a given time, t, after boosting.
   For the neutralizing antibody titers calculated in step 2 above, we use Eq. 6 to calculate the new efficacy t days after boosting. Therefore, efficacy at a given time, t, after an f-fold boost in a population with average neutralizing antibody titers of n_0, $VE_{boost}(n_0, f, t)$, is given by:

$$VE_{boost}(n_0, f, t) = \int_{-\infty}^{\infty} N(x, \log_{10}(n_{boost}(n_0, f, t)), \sigma) \frac{1}{1 - e^{-k(x - x_{50})}} dx \quad (7)$$

4. Determine the average efficacy over time period T after boosting.

We next integrate Eq. 7 from the time of boosting until the end of the time period T to determine the average efficacy over time period T after boosting with an f-fold boost in a population with average neutralizing antibody titers of n_0, $\overline{VE_{boost}}(n_0, f, T)$. This results in the following expression:

$$\overline{VE_{boost}}(n_0, f, T) = \frac{1}{T} \int_0^T VE_{boost}(n_0, f, t)\, dt \quad (8)$$

Average efficacy improvement for a variant-modified vaccine over an ancestral-based vaccine

To determine the efficacy improvement for a variant-modified vaccine over an ancestral-based vaccine, we first determine the fold change in neutralizing antibody titers for the ancestral-based vaccine, $\overline{FC(m_A)}$, using Eq. 2 and label this as f_A. The improvement for a group K of variant-modified vaccines is given in Eq. 4 by $\overline{I(K)}$.

Therefore, the average efficacy over time period T after giving an ancestral-based boost in a population with a pre-boost symptomatic efficacy of VE_0 is given by $\overline{VE_{boost}}(\hat{n}(VE_0), f_A, T)$, and the average efficacy over time period T after giving a variant-specific boost with a variant-specific vaccine from group K in a population with a pre-boost symptomatic efficacy of VE_0 is given by $\overline{VE_{boost}}\left(\hat{n}(VE_0), f_A \overline{I(K)}, T\right)$. Combining these expressions together, we find that the improvement in protection for a variant-modified vaccine (from a group K of variant-modified vaccines) over an ancestral-based vaccine (denoted by $IP(K)$) is given by:

$$IP(K) = \overline{VE_{boost}}\left(\hat{n}(VE_0), f_A \overline{I(K)}, T\right) - \overline{VE_{boost}}(\hat{n}(VE_0), f_A, T) \quad (9)$$

We note that the units of $IP(K)$, the improvement in protection, are in percentage points.

Determining CIs on using parametric bootstrapping

CIs of all estimates for predicted efficacies (shaded regions), and improvement of the variant-modified booster over the ancestral booster in Fig. 2, were generated using parametric bootstrapping on the parameters with uncertainty in their estimation (parameters given in Extended Data Table 4). This method of bootstrapping has previously been reported in ref. [17]; however, it is described in brief below.

For any starting population level of protection along the x axis in Fig. 2, the mean neutralizing antibody titer corresponding to that level of protection was first estimated using the inverse of Eq. 6 and mean parameters from ref. [15]. Then, the corresponding efficacy after

a. Ancestral boosting
b. Variant-modified boosting
c. Boosting with a homologous variant-modified vaccine
d. Boosting with a heterologous variant-modified vaccine

was estimated by repeatedly using Eq. 8, and sampling parameters from the distributions given in Extended Data Table 4.

Sampling was performed 10,000 times. The lower confidence bound was estimated from the 2.5% percentile, and the upper confidence bound was taken from the 97.5% percentile.

Ethics statement

This work was approved under the University of New South Wales Sydney Human Research Ethics Committee (approval HC200242).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data used in this analysis is available at https://github.com/InfectionAnalytics/Predicting-Efficacy-Variant-Modified-Boosters.

Code availability

Code used in this analysis is available at https://github.com/InfectionAnalytics/Predicting-Efficacy-Variant-Modified-Boosters.

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Author contributions

D.C., M.P.D. and D.S.K. contributed to study design. D.C., D.S.K. and S.D. performed the data extraction, curation and analysis. D.C., D.S.K. and S.D. performed the data analysis. D.C., M.P.D., D.S.K., K.S. and S.J.K. contributed to shaping the direction of the work. All authors contributed to the writing and reviewed and approved the final report.

Competing interests

The authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02228-4.

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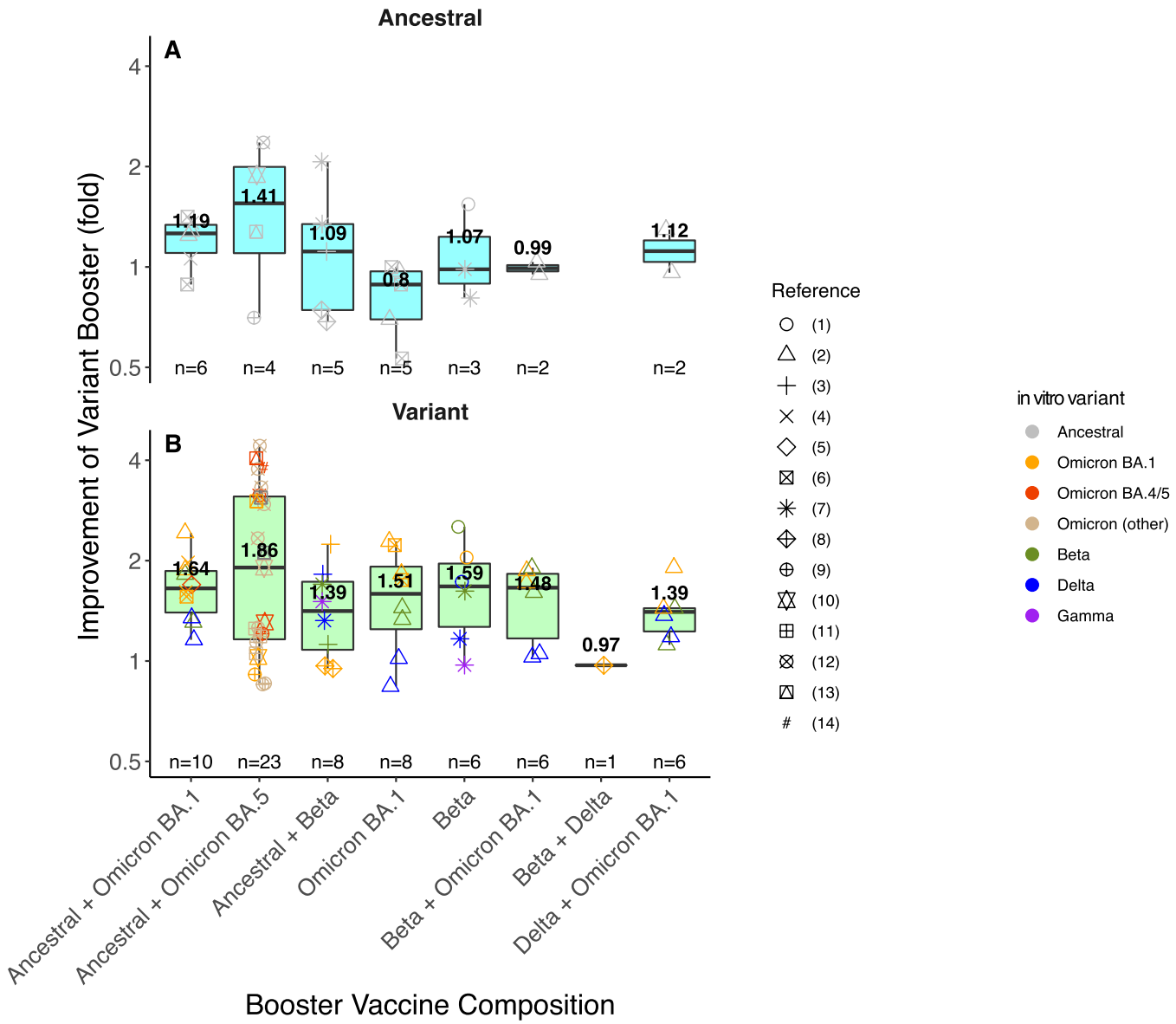
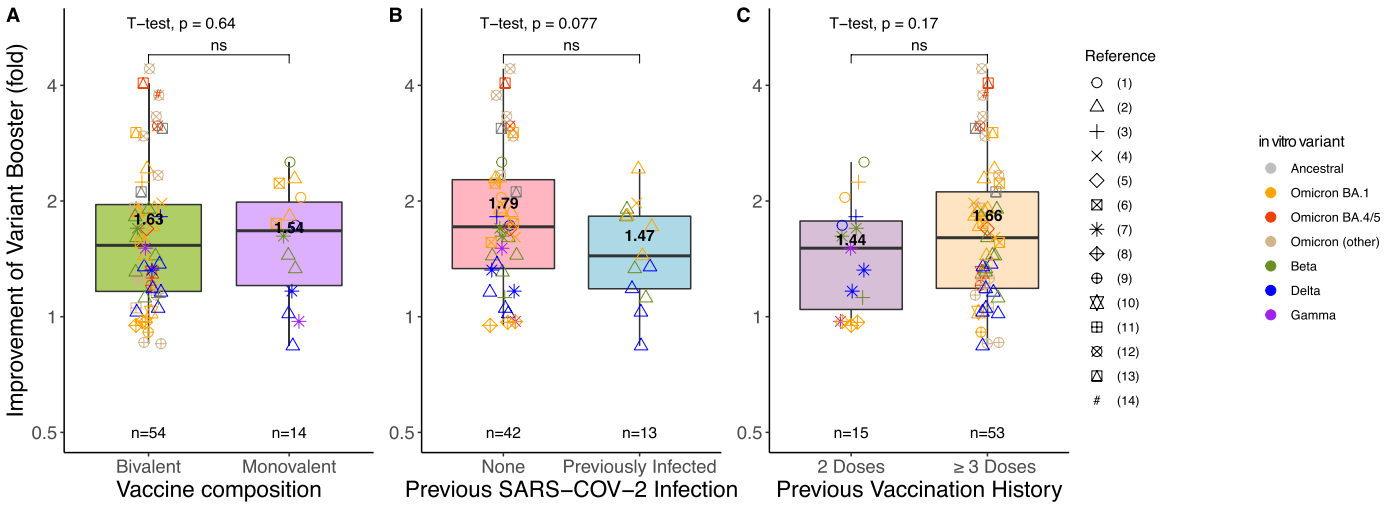


Extended Data Fig. 1 | Fold change in neutralization titers after boosting with variant-modified vaccines with different compositions against (A) the ancestral variant and (B) other variants. Change in titers against different SARS-CoV-2 variants tested in vitro are depicted in different colours. For all panels centre line of box shows median, box limits show interquartile ranges, whiskers show range of the data (excluding outliers). Number of data-points contributing to each box-plot is shown below the box plot.

https://doi.org/10.1038/s41591-023-02228-4



Extended Data Fig. 2 | Comparison of the improvement in neutralizing antibody titers for variant-modified boosters compared to ancestral-based boosters. Comparisons are split by either (**a**) monovalent and bivalent vaccine immunogens, (**b**) whether subjects had previously experienced SARS-CoV-2 infection or (**c**) whether subjects had previously received only a primary (two-dose) course of vaccination, or had also received a prior booster (third) vaccine dose. For all panels, two sided t-tests were performed on the log10-transformed values. For all panels centre line of box shows median, box limits show interquartile ranges, whiskers show range of the data (excluding outliers). Number of data-points contributing to each box-plot is shown below the box plot.

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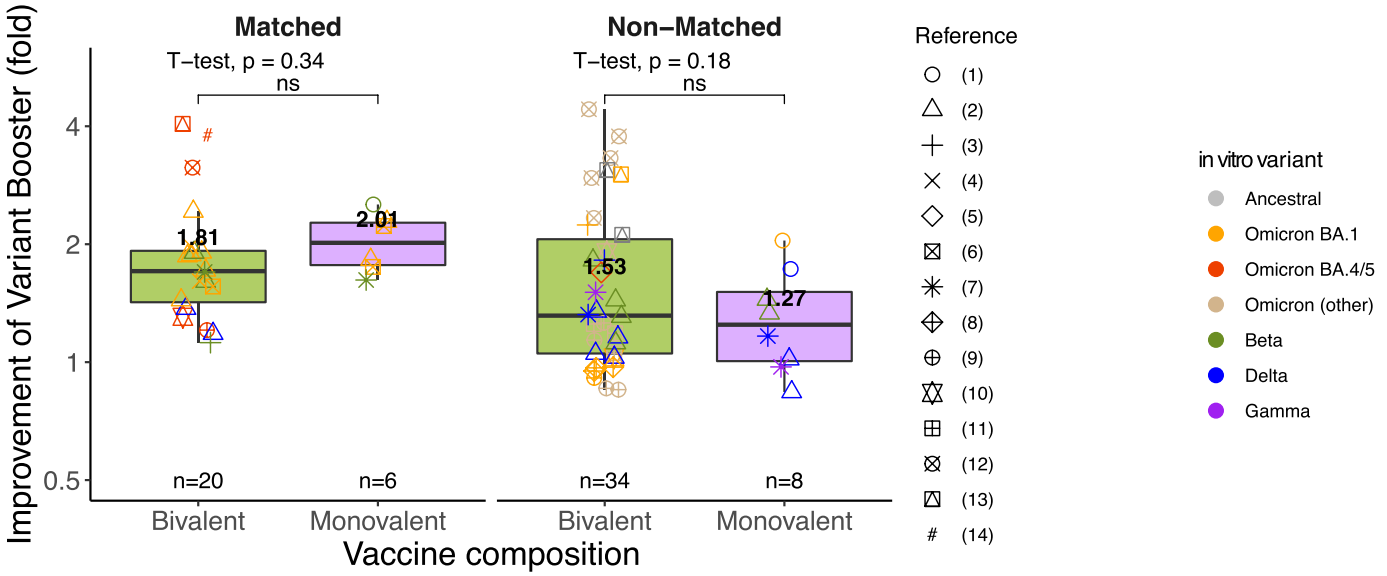

Extended Data Fig. 3 | Comparison of the improvement in neutralizing antibody titers for variant-modified boosters compared to ancestral-based boosters split by whether (A) the variant tested in-vitro matched the vaccine immunogen or (B) the variant tested in-vitro did not match the vaccine immunogen. Within each panel the vaccines are split into bivalent and monovalent vaccines. There is no significant difference in the improvement gained between monovalent or bivalent vaccines regardless of whether the variant tested in-vitro matched the vaccine immunogen or not (two-sided t-test performed on the $\log_{10}$-transformed values). For all panels centre line of box shows median, box limits show interquartile ranges, whiskers show range of the data (excluding outliers). Number of data-points contributing to each box-plot is shown below the box plot.

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Extended Data Table 1 | Policy summary

Background	Vaccination against COVID-19 has significantly reduced both morbidity and mortality from the SARS-CoV-2 virus, with early reports of vaccine efficacy suggested efficacies as high as 99% in preventing severe COVID-19 disease. However, booster doses of vaccine are required to maintain high efficacy due to waning of both vaccine and infection induced immunity, as well as the emergence of novel SARS-CoV-2 variants. Novel vaccines, that incorporate newer SARS-CoV-2 variants have now been developed. However the relative benefits of these variant-modified vaccines has not been fully assessed.
Main findings and limitations	We have used data from 14 reports of variant-modified vaccines to predict the average improvement in neutralising antibody titres after boosting with a variant-modified vaccine compared to using an ancestral-based vaccine to be 1.61 fold. Although on average variant modified boosters provide significantly higher neutralising antibody titres against emerging variants, the main benefit of a booster is derived from having any booster at all. An ancestral based booster has the capacity to boost protection against symptomatic disease from 50% up to 86.1%. while a variant-modified booster would increase this up by an additional 5.1 percentage points to 91.2%. This analysis is limited both by the fact that it incorporates data from a range of different reports, with different study designs, vaccines, randomization and prior immunological history of subjects, and that it predicts vaccine effectiveness using a model that relates neutralisation titres to vaccine effectiveness. Whilst this model has been proven to be accurate in a number of contexts, it cannot be verified in the same way as large scale clinical trials.
Policy implications	Using the results of our analysis, we can conclude that boosting with ancestral-based vaccines increases both neutralization titres towards, and protection against disease from SARS-CoV-2 variant viruses. Using variant-modified vaccines as boosters are likely to provide additional protection, however this improvement is likely to be a marginal one over an ancestral-based booster.

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Extended Data Table 2 | Reports of variant-modified vaccines used in this analysis

Reference	Previous immunological history of study participants	Dosage	Vaccines reported	Variants tested	Neutralisation measured after^	Data derived from	Demographics
1	BNT162b2 primary vaccination 3-7 months prior, no prior infections	nr	BNT162b2 (Ancestral) MVD614 (Ancestral) MVB.1.351 (Beta)	Ancestral, Beta, Delta, BA.1	15 d	Figure 1	Gender: 40.4% Female Mean age: 40.6 Race: nr Country: France
2	primary vaccination and booster (~95% received mRNA vaccines for both, remainder received Ad26.COV2.S for one or both of primary / booster doses). Booster given 112-333 days prior Grouped by either (A) no prior infections or (B) infection >=110 days prior	50µg	mRNA-1273 (Ancestral) mRNA-1273.529# (BA.1) combination of mRNA-1273.351 and mRNA-1273.529# (Beta+BA.1) combination of mRNA-1273.617.2# and mRNA-1273.529# (Delta+BA.1), combination of mRNA-1273 and mRNA-1273.529# (Ancestral+BA.1)	Ancestral, Beta, Delta, BA.1	15 d	Table S4	Sex: 53% Female Median age: 53 Race: 82%, 8%, 7% Country: United States
3	mRNA-1273 primary vaccination >6 months prior, no prior infections	50µg 100µg (mRNA-1273.211 only)	mRNA-1273 (Ancestral) mRNA-1273.211 (Ancestral + Beta)	Ancestral, Beta, Delta, BA.1*	28 d	Table S4	Gender: 56% Female Mean age: 52.2 Race: 88%, 5%, 3% Country: United States
4	mRNA-1273 primary vaccination and mRNA-1273 booster >3 months prior. Grouped by either (A) no prior infection and (B) infection >3 months prior	50µg	mRNA-1273 (Ancestral) mRNA-1273.214 (Ancestral + BA.1)	Ancestral, BA.1, BA.4/5*	28 d	Tables S7 and S8	Gender: 55% Female Mean age: 57.4 Race: 86%, 7%, 4% Country: United States
5	primary vaccination and booster§, no prior infection	50µg	mRNA-1273 (Ancestral) mRNA-1273.214 (Ancestral + BA.1)	BA.4/5	1 mo	Text	nr
6	BNT162b2 primary vaccination and BNT162b2 booster >4.7 months prior, no prior infections	30µg 60µg	BNT162b2 (Ancestral), BNT162b2 Omi (BA.1), BNT162b2 + BNT162b2 Omi (Ancestral + BA.1)	Ancestral, BA.1, BA.4/5*	1 mo	Slides labelled CC8-CC19	nr
7	mRNA-1273 primary vaccination >5 months prior, no prior infection	50µg 20µg (mRNA-1273.351 only)	mRNA-1273 (Ancestral) mRNA-1273.351 (Beta) mRNA-1273.211 (Ancestral + Beta)	Ancestral, Beta, Gamma, Delta*	15 d or 29 d	Figures 3, 4 and S1	Sex: 55% Female Mean age: 55.2 Race: 97.5%, 0%, 1.3% Country: United States
8	mRNA-1273 primary vaccination, no prior infections	100ug 50ug for mRNA-1273.211)	mRNA-1273 (Ancestral) mRNA-1273.211 (Ancestral + Beta), mRNA-1273.213 (Beta + Delta)	Ancestral, Beta, Delta, and BA.1*	29 d	Figure S6	Sex: 56% Female Mean age: 59.2 Race: 91%, 5%, 1.3% Country: United States
9	mRNA primary vaccination and up to 2 mRNA boosters, no prior infections	30µg (BNT162b2 and Pfizer bivalent) 50µg (mRNA-1273 and mRNA-1273.214)	mRNA ancestral (mix of BNT162b2 and mRNA-1273) mRNA bivalent (mix of Pfizer-BioNTech BA.4/BA.5 bivalent and mRNA-1273.214)	Ancestral, BA.1, BA.2, BA.4/5, BA.4.6, BA.2.75, BA.2.75.2	Range: 20 – 36 d	Figure 1	Gender: 83% Female Mean age: 45.4 Race: nr Country: United States
10	primary vaccination and up to 2 boosters (a mix of BNT162b2, mRNA-1273, Ad26.COV2.S), mix of infected and uninfected	30µg (BNT162b2 and Pfizer bivalent) 50µg (mRNA-1273 and mRNA-1273.214)	mRNA ancestral (mix of BNT162b2 and mRNA-1273) mRNA bivalent (mix of Pfizer-BioNTech BA.4/BA.5 bivalent and mRNA-1273.214)	Ancestral, BA.1, BA.2, BA.5	Range: 16 – 64 d	Figure 1	Gender: 73% Female Mean age: 45.6 Race: 79%, 6%, 12% Country: United States
11	primary vaccination and up to 2 boosters (a mix of BNT162b2, mRNA-1273, Ad26.COV2.S), mix of infected and uninfected	30µg (BNT162b2 and Pfizer bivalent) 50µg (mRNA-1273 and mRNA-1273.214)	mRNA ancestral (mix of BNT162b2 and mRNA-1273) mRNA bivalent (mix of Pfizer-BioNTech BA.4/BA.5 bivalent and mRNA-1273.214)	BF.7, BA.2.75.2, BQ.1.1	Range: 16 – 64 d	Figure 1	Gender: 73% Female Mean age: 45.6 Race: 79%, 6%, 12% Country: United States
12	mRNA primary vaccination and up to 2 mRNA boosters, no prior infections	30µg (BNT162b2 and Pfizer bivalent) 50µg (mRNA-1273 and mRNA-1273.214)	mRNA ancestral (mix of BNT162b2 and mRNA-1273) mRNA bivalent (mix of Pfizer-BioNTech BA.4/BA.5 bivalent and mRNA-1273.214)	Ancestral, BA.4/5, BF.7, BA.4.6, BA.2.75.2, BQ.1.1, XBB.1	Range: 14 – 94 d	Figure 1	Gender: 56% Female Mean age: 71.1 Race: 67%, 13%, 9% Country: United States
13	primary vaccination and 1 or 2 boosters, mix of infected and uninfected	30µg (BNT162b2 and Pfizer bivalent) 50µg (mRNA-1273 and mRNA-1273.214)	mRNA ancestral (mix of BNT162b2 and mRNA-1273) mRNA bivalent (mix of Pfizer-BioNTech BA.4/BA.5 bivalent and mRNA-1273.214)	Ancestral, BA.1, BA.5, BA.2.75.2, BQ.1.1	Range: 16 – 104 d	Figure 1	Gender: 58% Female Mean age: 51.7 Race: nr Country: United States
14	BNT162b2 primary vaccination and BNT162b2 booster, mix of infected and uninfected	30µg	BNT162b2 (Ancestral) Pfizer-BioNTech BA.4/BA.5 bivalent (Ancestral+BA.4/5)	BA.4/5	1 mo	Figure 1B,C	nr

nr, not reported; BA.1 and BA.4/5 refer to Omicron BA.1 and Omicron BA.4/5 variants, respectively. # Technical names not listed in reference but inferred from clinical trial number NCT05289037. * Results were not reported for all booster–variant combinations. ^ d, days; mo, months. § Details of primary and booster vaccine not listed. Race percentages listed for White, Black or African American and Asian, respectively.

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Extended Data Table 3 | Trial design and matching of comparator groups for each study

	Clinical Trial	Randomized Control Trial	Age (mean/median within 10 years)	Sample Collection Timing (mean/median within 2 weeks)	Vaccination History (same number of doses)	Prior infection history (% infected in each arm)
1	✓	✓	NA	NA	NA	NA
2	✓	✓	NA	NA	NA	NA
3	✓	X	✓	✓	✓	0/0/0
4	✓	X	✓	✓	✓	0/0/100/100
5	✓	X	✓	✓	✓	0/0
6	✓	✓	NA	NA	NA	NA
7	✓	X	✓	✓	✓	0/0/0/0
8	✓	X	✓	✓	✓	nr
9	X	X	X	✓	✓	nr
10	X	X	✓	✓	X	33/33
11	X	X	✓	✓	X	33/33
12	X	X	X	X	X	0/0
13	X	X	X	X	X	0/17
14	✓	✓	NA	NA	NA	NA

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Extended Data Table 4 | Model parameters used in estimating protection from COVID-19 after ancestral and variant-modified boosting

Parameter	Description	Endpoint	Mean Value	Distribution	Reference
σ		N/A	0.46	$N(0.465,0.022)$	15
k	Hill coefficient*	Symptomatic	$e^{1.13}$	$e^{N(1.13,.031)}$	15
		Severe	$e^{1.12}$	$e^{N(1.12,.03)}$	15
x_{50}	IC50 for protection against disease*	Symptomatic	$\log_{10} 0.20$	$N(\log_{10} 0.20\,, 0.006)$	15
		Severe	$\log_{10} 0.03$	$N(\log_{10} 0.03\,, 0.099)$	15
δ	Neutralising antibody decay rate	N/A	$\ln 2/108$	$N(6.42, .001) * 10^{-3}$	15,17,19
R	Fold-increase in Neutralising Abs from ancestral booster	N/A	$\log_{10} 11.5$	$N(\log_{10} 11.5\,, 3.6 * 10^{-3})$	This work
ϕ	Fold-increase in neutralising abs (over an ancestral boost) after a variant modified booster	N/A	$\log_{10} 1.61$	$N(\log_{10} 1.61\,, 4.77 * 10^{-4})$	This work
ϕ_m	Fold-increase in neutralising abs (over an ancestral boost) after a homologous variant modified booster	N/A	$\log_{10} 1.85$	$N(\log_{10} 1.85\,, 7.77 * 10^{-4})$	This work
ϕ_n	Fold-increase in neutralising abs (over an ancestral boost) after a heterologous variant modified booster	N/A	$\log_{10} 1.47$	$N(\log_{10} 1.47\,, 8.77 * 10^{-4})$	This work

*Note that the Hill coefficient and IC_{50} parameters are selected from a bivariate normal distribution with covariance matrix given by $C = \begin{pmatrix} 0.031 & 0.011 \\ 0.011 & 0.006 \end{pmatrix}$ for symptomatic protection and $C = \begin{pmatrix} 0.03 & 0.03 \\ 0.03 & 0.099 \end{pmatrix}$ for severe protection.

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Reporting Summary

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☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was extracted from publicly available papers or reports and processed using R version 4.0.2, and is available via https://gitfront.io/r/user-7600629/qP6gPJDERURt/Predicting-Efficacy-Variant-Modified-Boosters/
Data analysis	Data was analysed using custom code written in R version 4.0.2. Code is available on github via https://gitfront.io/r/user-7600629/qP6gPJDERURt/Predicting-Efficacy-Variant-Modified-Boosters/

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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https://gitfront.io/r/user-7600629/qP6gPJDERURt/Predicting-Efficacy-Variant-Modified-Boosters/

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Fourteen reports detailing neutralizing antibody titres were taken from public documents and the results from these reports were used in this analysis. No statistical method was used to predetermine sample size as sample sizes were taken from the original publications.
Data exclusions	No data was excluded
Replication	All results in the manuscript can be replicated using the data and code that has been made publicly available.
Randomization	All data used in this analysis were from previously published studies, therefore randomisation was not relevant
Blinding	All data used in this analysis were from previously published studies, therefore blinding was not relevant

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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging