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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary analysis

Analysis of data on neutralisation against variants

In this study we aimed to determine the factors that influenced the loss of recognition against SARS-CoV-2 variants of concern (VOC), and more specifically, whether different vaccines varied in their recognition of VOC. The loss of recognition of vaccines to VOC is typically measured as the 'drop in neutralisation titre' against the variants (ie: the change in the concentration of serum needed for 50% neutralisation in vitro). Therefore, we obtained data from 16 published studies which directly compared neutralisation titre against ancestral (Wuhan-like / D614G strains) and the VOC. This included data provided in the original publications or sent by authors (see Supplementary table 1). We focused primarily on assays using live SARS-Cov-2 virus (to reduce the potential variability that might arise from different pseudoviral constructs[1]), with the exception of the NVX-CoV2373 vaccine, for which only data from neutralisation assays using a spike-expressing pseudovirus was available. Neutralisation level is defined as the neutralisation titre estimated in a particular assay, normalised to the average neutralisation titre (against ancestral virus) observed in convalescent sera in the same assay. All means of neutralisation titres are reported as geometric means and all regression and modelling that contains neutralisation titres (or levels) or fold-changes in neutralisation titres use log base 10 transformed neutralisation titres (or levels).

When combining data from multiple studies, an important caveat is that different laboratories used distinct in vitro assays to measure neutralisation of SARS-CoV-2 (Supplementary table 1) [1]. These assays differ considerably in the mean neutralisation titres and fold-change to variants reported, even when considering notionally similar groups of subjects, such as convalescent serum against the ancestral virus (Figure 1a). To test the extent to which a given vaccine platform affects antibody cross reactivity, we calculated the mean drop in neutralisation titre across different vaccines and variants (comparing to ancestral virus), while accounting for censoring at the assay specific limit of detection (censoring to estimate means and in regression analysis is described in supplementary methods). We found a large variation in drops in titres in vaccine serum between variants, vaccines and laboratories. For example, comparing 7 studies reporting the change in neutralisation titre of vaccine sera against the beta (B.1.351) variant (compared to ancestral virus) following vaccination, the estimated decrease in neutralisation titre ranges from 6-fold[2] to 16-fold[3], depending on the study and the vaccine considered. Superficially, these differences might suggest the vaccines

elicit antibody responses with different levels of cross-reactivity to the VOC. However, many studies also included a direct comparison of convalescent sera or included sera from different vaccines. When the change in neutralisation titre in vaccinees is compared with the change seen in convalescent subjects in the same study, this is usually very similar (Figure S1a, b). The same is true when using a vaccine comparator group instead of convalescent subjects (Figure S1c).

The variability in results between assays means that we observe several estimates for the extent of antibody cross-reactivity against a given variant (Figure 1a). It is not clear if one assay is more accurate than another in capturing the biologically relevant change in neutralisation. Therefore, we estimated the mean drop in neutralisation titre for a given variant across the available studies by aggregating all individual data (convalescent and vaccine) from each study, and using censoring to account for the differing limit of detections of each assay (supplementary methods). We find the mean drop in neutralisation titre is 1.6-fold for the alpha/B.1.1.7 variant (95% CI = 1.5 -1.7, average of n= 9 studies), 8.8-fold (95% CI = 8 -9.7, n= 9 studies) for the beta/B.1.351 variant, 3.5-fold (95% CI = 3.1 - 4, n= 3 studies) for the gamma/P.1 variant and 3.9-fold (95% CI = 3.5 - 4.4, n= 3 studies) for the delta/B.1.617.2 variant (Figure S3).

We then performed censored regression to assess the impact of vaccine type on cross-reactivity. We accounted for both variant and laboratory specific effects. The variant specific effect was incorporated by including the mean drop in neutralisation titre seen between ancestral virus and each variant virus across all studies as described above (Δ_V). A laboratory specific effect was incorporated by including a factor for each laboratory (L). We also allowed for an additional categorical variable for serum type to be included (S). S was a factor that determined whether the serum came from a convalescent or vaccinated individual, and if it was the latter, which vaccine was used. Thus the model was:

$$Variant\ Neut \sim \alpha_0 + \alpha_1 Ancestral\ Neut + \Delta_V + \alpha_2 L + \alpha_3 S \quad \text{(Eq S1)}$$

We found that in this model laboratory was a highly significant factor (p<.0001), but after including laboratory, serum type (S) was not a significant factor in the model (p=0.256) (detailed in supplementary methods). Additionally, the best model (as judged by the model

with the lowest AIC was one that included L but not S. This does not mean that vaccine sera all neutralise VOC equally. That is, vaccinee sera vary considerably in their ability to neutralise ancestral virus. However, they all tend to *lose recognition* of a given VOC to a similar extent (ie: comparing the drop in titre between ancestral and VOC). This demonstrates that the neutralisation titre of ancestral virus is a very good predictor of neutralisation of a variant (Figure 1b, S1a, S2), and that once the initial neutralisation level and variation between labs is considered the vaccine platform itself is not a factor in the model.

We additionally performed censored regression to determine the best predictors of the *drop* in neutralization against a variant (compared to ancestral virus) for each vaccine used. For this we modelled

$$Fold\ Drop_v \sim \alpha_0 \Delta_V + \alpha_1 L + \alpha_2 \mu_{conv_L} + \alpha_3 S \quad \text{(Eq S2)}$$

Where μ_{conv_L} was defined as the mean fold-drop in convalescent sera against each variant for each laboratory, L was once again a categorical factor for the laboratory and S was a categorical factor for the serum used (however here only vaccinated individuals were considered in the model, as convalescent individuals were used to normalise the fold-drop by laboratory). For this model we allowed only one of α_1 or α_2 to be non-zero (so that there was only one laboratory specific effect). We found that once again, after accounting for laboratory specific effects, the vaccine used was not a significant factor, regardless of whether α_1 or α_2 (or neither) were included in the model ($p>.07$ in all cases, likelihood ratio test). Additionally, we found that the best model (i.e. the model with the lowest AIC) was one that included μ_{conv_L} but did not include L or S. This means that a combination of (i) the mean drop in neutralisation titre seen between ancestral virus and each variant virus across all studies and (ii) the mean drop in neutralisation titre seen in convalescent sera in the current study are the best predictors of the fold drop in neutralisation titre for the serum under consideration.

Together, these results suggests that any one study of neutralisation of a variant does not provide a reliable estimate of the cross-reactivity of serum to variants, but the best estimate of neutralisation against current VOC is obtained from the neutralisation observed against the ancestral virus, combined with the average fold drop in neutralisation to the particular variant observed across multiple studies.

We note that since the 30 June cut-off of study acquisition, more studies have continued to be published on variant recognition. However, our current analysis is limited by the lack of a standardised neutralisation assay more than low data availability (since between lab variation is much greater than within lab variation), and there is yet no direct comparison across a panel of serum from all existing vaccines. Thus, we cannot exclude minor variations in cross-reactivity between vaccines and more standardised data rather than large quantities of data is likely to be necessary to identify any difference in cross-reactivity.

Estimating neutralisation after boosting

To estimate the neutralisation level achieved in individuals after boosting, we used data from studies of boosting of previously infected individuals or previously vaccinated individuals. Studies were included if they contained a comparison with naïve vaccinated individuals within the same study or if a similar comparison of vaccination in naïve individuals could be made with a separate study by the same laboratory using the same assay (detailed in Supplementary table 4). This allowed us to determine the fold increase in neutralisation level in previously infected/vaccinated individuals compared with naive individuals who received the standard two-dose vaccine regimen. All boosted individuals received either BNT162b2, mRNA-1273 or CoronaVac. To calculate the neutralisation level in individuals after boosting (Figure 3), the neutralisation level reported in naïve individuals in the phase I/II trials for each vaccine (as reported in the Supplementary table S3 from reference[4]) were multiplied by the fold increase reported in the boosting studies in Supplementary table 3. For some studies – naïve or previously infected individuals were reported to have received either BNT162b2 or mRNA-1273 - and data on which individuals received which vaccines was not paired with the neutralisations titres [5-7]. In these cases the geometric mean of the neutralisation reported in the phase I/II trials for BNT162b2 and mRNA-1273 was calculated (geometric mean: 3.13 fold of convalescent plasma) and the fold-increase between vaccination in previously infected individuals and naïve individuals was multiplied by this geometric mean level for naïve individuals receiving one of the two vaccines. This provided a range of estimates of the neutralisation level (as a fold of convalescent plasma) after boosting of previously infected individuals of between 6.1-28.7, with geometric mean of 12.0 (red shaded region and dashed line, Figure 3).

Estimating decay in vaccine efficacy

In this study we aimed to estimate the efficacy against variants over the first year (with and without boosting). Modelling the decay in efficacy was performed by determining (from the inverse of the model in Equation S8 below), the neutralisation titres expected to give an initial target efficacy (ie: 95%, 90%, 80% or 70%) against infection with the ancestral virus. Neutralisation was assumed to decay over the first 360 days with a half-life of 108 days (as estimated in [4], using data from [8]). The efficacy at each time point was then determined from the neutralisation level after decay until that time point (using Equation S8). Neutralisation to variants was assumed to be reduced by the same fold change (Figure S3), as titres decayed. Boosting was modelled as an increase in the neutralisation level to the mean level determined

from studies in previously infected or vaccinated individuals (red dashed line in Figure 3), assuming decay rate in neutralisation was the same after boosting as before, and assuming that loss of neutralisation to variants was the same fold-change as prior to boosting. The lower bound on efficacy estimates from the model was determined using the bootstrapping approach described in the supplementary methods.

Supplementary Methods

In this section we describe the methods used to estimate the average fold-drop in neutralisation against each variant and how this was used to predict the efficacy of vaccines against each variant. A major focus of these methods is in accounting for censoring of neutralisation measurements when they fell below the limit of detection, and standard censoring models cannot be used because different assays had different limits of detection. Another major focus of these methods is to explain how bootstrapping was used to determine the error in predictions of vaccine efficacy.

To aid reading of these methods it is worth noting that throughout these methods we will use subscripts to refer to the serum type under consideration and superscripts to refer to the virus type under consideration. A superscript of either *a* or *0* refers to the special case of ancestral virus. Appendix A outlines the variables used in the model, and they are also described below.

The following letters are paired with these subscripts and superscripts: (i) Neutralisation titre for serum i against variant v is depicted by $\mathrm{N_i^v}$; (ii) Fold change in neutralisation titre from variant $\mathrm{v_j}$ to variant v for serum i is depicted by $\mathrm{F_i^{v,v_j}}$. Where variant $\mathrm{v_j}$ is ancestral virus (i.e. $\mathrm{F_i^{v,a}}$) this is shortened to $\mathrm{F_i^v}$; (iii) The limit of detection for serum i against variant v is depicted by $\mathrm{L_i^v}$; (iv) Left and right censoring variables for serum i against variant v are denoted by $\mathrm{c_{L_i}^v}$ and $\mathrm{c_{R_i}^v}$, respectively.

Estimating the mean fold-change in neutralisation against each variant with censoring at the limit of detection

When estimating the mean fold-change in sera neutralisation of ancestral virus versus a SARS-CoV-2 variant (F_i^v) it was important to adjust for the censoring of data when neuralisation against the variant or ancestral virus fell below the limit of detection. When the neutralisation titres for a serum sample against the ancestral virus (N_i^a) and a variant (N_i^v) were both above the limit of detection the fold-change in neutralisation was calculated as $F_i^v = \frac{N_i^v}{N_i^a}$. When the neutralisation titre declined from a value above the limit of detection against the ancestral virus, to below the limit of detection against the variant (L_i^v), the fold-change in neutralisation was $F_i^v \leq \frac{L_i^v}{N_i^a}$ (this occurred in 98 samples). In this case we set the

left censoring variable, $c_{L_i}^{v}$ to be 1. In the uncommon case (2 samples) where the neutralisation against the ancestral virus was below the (L_i^a), but the neutralisation against the variant was above the limit of detection the fold change was $F_i^v \geq \frac{N_i^v}{L_i^a}$, and this possibility accounts for the times when there is a detected increase in neutralisation titre against variant compared with ancestral. In this case we set the right censoring variable, $c_{R_i}^{v}$ to be 1. In all other cases the left and right censoring variables were set to 0. When the neutralisation titre against the ancestral virus and variant were below the limit of detection these data were excluded as they provided no information on neutralisation change (29 samples). To estimate the mean fold-change in neutralisation against a particular variant (v) we assumed a normal distribution for the log-transformed fold changes observed in sera samples against that variant, (i.e. $\log_{10} F_i^v$), and fitted this using maximum likelihood estimation. The likelihood function for fitting this normal distribution (including censoring) was,

$$\mathcal{L}_v(\boldsymbol{F^v}, \boldsymbol{N^v}, \boldsymbol{N^a}, \boldsymbol{L^v}, \boldsymbol{L^a}\boldsymbol{C_L^v}, \boldsymbol{C_R^v} \mid \mu^v, \sigma^v) = \prod_{i=1}^{S^v} g(\log_{10}(F_i^v), \mu^v, \sigma^v)^{1-C_{L_i}^v - C_{R_i}^v} G\left(\log_{10}\left(\frac{L_i^v}{N_i^a}\right), \mu^v, \sigma^v\right)^{C_{L_i}^v} \left(1 - G\left(\log_{10}\left(\frac{N_i^v}{L_i^a}\right), \mu^v, \sigma^v\right)\right)^{C_{R_i}^v} \quad \text{(Eq S3)}$$

where the i[th] elements of the vectors $\boldsymbol{F^v}, \boldsymbol{N^v}, \boldsymbol{L^v}, \boldsymbol{C_L^v}$ and $\boldsymbol{C_R^v}$ vectors are F_i^v, N_i^a, N_i^a, L_i^v, L_i^a, c_i^L and c_i^R, respectively. The function $g(x, \mu, \sigma)$ is the probability density at x of a normal distribution with mean μ and standard deviation σ. The function $G(x, \mu, \sigma)$ is the cumulative density at x of a normal distribution with mean μ and standard deviation σ. The mean (μ^v) and standard deviation (σ^v) of the normal distribution that minimise the negative log of this likelihood function were found using the *nlm* function in the R statistical package (version 4.0.2).

Creating a censored regression model to predict neutralisation against variant virus

In order to predict neutralisation titre against variant virus using the multiple regression model in Equation S1, we set up a custom censored regression model. The purpose of this custom model is to allow for both neutralisation titre against the variant virus and

neutralisation titre against the ancestral virus to potentially be below the limit of detection for a study. Existing censored regression packages (e.g. *CensReg*[9]) were not used as the limit of detection was different for different laboratories – though *CensReg* produced similar results in a parallel analysis.

We set up a likelihood function to estimate the neutralisation against each variant using the neutralisation against ancestral virus. We considered n_v different variants, and, using Equation S3 we estimated the mean fold change in neutralisation titre against each variant (compared to ancestral virus) across all serum samples available, and denoted this, $\bar{F}^v$. Here we denote ancestral virus by $v=0$. The vector of these fold changes across all variants is denoted $\overline{\boldsymbol{F}}$. We also stored the neutralisation titres and limits of detection for each variant / serum (including convalescent serum) combination in matrices $\boldsymbol{N}$ and $\boldsymbol{L}$ respectively, with $\boldsymbol{N} = (N_i^v)$ and $\boldsymbol{L} = (L_i^v)$. For each serum sample we recorded the study (A_i) and serum type (T_i) and stored these in vectors $\boldsymbol{A}$ and $\boldsymbol{T}$ respectively. Finally, the lower and upper bounds for censoring (due to either variant neutralisation being below the limit of detection or ancestral virus neutralisation titre being below the limit of detection, as described above) were stored in matrices $\boldsymbol{C_L} = \left(C_{L_i}^v\right)$ and $\boldsymbol{C_R} = \left(C_{R_i}^v\right)$, respectively. We define a vector of parameter estimates $\boldsymbol{\alpha}$ as $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \alpha_2, \alpha_3, \alpha_4)$; corresponding to the coeffcients in the regression model.

The likelihood function (including censoring) that we used was

$$\mathcal{L}_v(\boldsymbol{N}, \overline{\boldsymbol{F}}, \boldsymbol{L}, \boldsymbol{A}, \boldsymbol{T}, \boldsymbol{C_L C_R} | \, \boldsymbol{\alpha}, \sigma) = \prod_{v=1}^{n_v} \prod_{i=1}^{S^v} g(\log_{10}(N_i^v), h_i^v, \sigma^v)^{1-C_{L_i}^v-C_{R_i}^v} \, G(\log_{10}(L_i^v), h_i^v, \sigma^v)^{C_{L_i}^v} \left((1 - G(\log_{10}(L_i^0), h_i^v, \sigma^v)\right)^{C_{R_i}^v}. \quad \text{(Eq S4)}$$

Where h_i^v is defined as:

$$h_i^v = \alpha_0 + \alpha_1 N_i^0 + \bar{F}^v + \alpha_2 A_i + \alpha_3 T_i. \quad \text{(Eq S5)}$$

We minimised the negative log of the likelihood function in Equation S4 for models where neither, one or both of α_3 and α_4 were set to zero using the *optim* function in the *stats* package of R (version 4.0.2). We then compared models using the likelihood ratio test.

Creating a censored regression model to predict fold drop in neutralisation titre for variant virus

In a similar way to that described above, we set up a censored regression model to predict the fold change in neutralisation titre for each variant. In this case, and using the same notation outlined above, the likelihood function (including censoring) that we used was

$$\mathcal{L}_v(\boldsymbol{F}, \overline{\boldsymbol{F}}, \boldsymbol{L}, \boldsymbol{A}, \boldsymbol{T}, \boldsymbol{C_L C_R} | \, \boldsymbol{\alpha}, \sigma) =$$

$$\prod_{v=1}^{n_v} \prod_{i=1}^{S^v} g(\log_{10}(F_i^v), k_i^v, \sigma^v)^{1-C_{L_i}^v - C_{R_i}^v} \, G\left(\log_{10}\left(\frac{L_i^v}{N_i^0}\right), k_i^v, \sigma^v\right)^{C_{L_i}^v} \left(\left(1 - G\left(\log_{10}\left(\frac{N_i^v}{L_i^0}\right), k_i^v, \sigma^v\right)\right)^{C_{R_i}^v}. \right.$$

(Eq S6)

Where k_i^v is defined as:

$$k_i^v = \alpha_0 + \bar{F}^v + \alpha_1 \overline{FC_{A_\iota}^v} + \alpha_2 A_i + \alpha_3 T_i.$$

(Eq S7)

and $\overline{FC_{A_\iota}^v}$ represents the average fold drop in convalescent sera for variant *v* in the lab from which serum *i* comes. As in Equation S2, at most one of α_1 or α_2 were allowed to be non-zero.

Predicting the efficacy for variants based on previously developed model

Previously, we developed and fitted a model of vaccine efficacy to data on the immunogenicity and protective efficacy (against symptomatic and severe COVID-19) of 7 vaccines from phase I/II and phase III trials, respectively [4]. Here we use this model, as originally published and parameterised, to predict the efficacy of vaccines against each variant, using the fold-change in neutralisation titre estimated against each variant in this study (Figure S3). The model estimates protective efficacy of a vaccine as,

$$P(n_{50}, k, \mu_s^v, \sigma_{all}) = \int_{-\infty}^{\infty} E(n \mid n_{50}, k) \, f(n \mid \mu_s^v, \sigma_{all}) \; dn$$

(Eq S8)

where μ_s^v is the ($\log_{10}$) mean neutralisation titre of a vaccine (s) against variant (v) (normalised to the mean of convalescent sera against ancestral virus), σ_{all} is the standard deviation in the neutralisation titres across individuals, f is the probability density of a normal distribution with mean μ_v and standard deviation σ_{all}, and E is a logistic function of the form,

$$E(n \mid n_{50}, k) = \frac{1}{1 + e^{-k(n-n_{50})}}. \quad \text{(Eq S9)}$$

The parameter n_{50} is the ($\log_{10}$) neutralisation level that provides an individual with 50% protective efficacy of COVID-19, and k is the parameter determining the steepness of the logistic relationship. A number of these parameters were estimated previously for symptomatic and severe COVID-19 (Supplementary table 4) [4].

To investigate the ability of the previously published model to predict vaccine efficacy against variants, we compared our models prediction of vaccine efficacy with the observed efficacy for each variant and vaccine combination we identified in the literature (Figure 2). To estimate the mean neutralisation level of each vaccine against each variant (where efficacy data was available), we calculated

$$\mu_s^v = \mu_s + \bar{F}^v$$

where $\bar{F}^v$ is the ($\log_{10}$) mean fold-change in neutralisation titres for each variant (calculated above) and μ_s is the neutralisation level reported for each vaccine (ratio of neutralisation titre in vaccinated individuals compared with convalescent individuals) that was reported in Phase I/II trials against ancestral virus [4] (Figure 2).

Determining the confidence and lower bound of predicted efficacy using parametric bootstrapping

During vaccine development it is useful to know the uncertainty in efficacy predictions as measured by the confidence interval for the efficacy estimate. In particular, the lower confidence bound for efficacy for a given neutralisation level is useful as an estimate of the minimum expected level of achieved efficacy (Figure 2). Confidence intervals (and lower bounds) of predicted efficacies (shaded regions) in Figures 2, 4 and S4 were generated using parametric bootstrapping on the parameters with uncertainty in their estimation (Supplementary table 4) as follows. For any neutralisation ratio (i.e. position on the x-axis in Figure 2 and S4), Equation S8 was first used to estimate the mean corresponding protective

efficacy against a particular variant. Then the distribution of likely efficacies was estimated by repeating the efficacy calculation with Equation S8, using parameter values chosen randomly from distributions according to their standard error or covariance matrix (normal and bivariant normal distributions respectively, Supplementary table 4). The sources of uncertainty include the model parameter uncertainty estimated in the previous study [4], as well as the uncertainty in estimates of the neutralisation level and the fold drop in neutralisation to each variant (Figure S3). It should be noted that when estimating the neutralisations level for each vaccine there is between laboratory uncertainty (i.e. due to differences in laboratory and assays used), and within laboratory uncertainty. The between laboratory variability in estimates of neutralisation level (standard error in estimates 0.18) was determined in this study and found to be less than the maximum within laboratory uncertainty (standard error in estimates, 0.20). Therefore, we used the largest within study uncertainty as the measure of uncertainty in the efficacy estimates (Supplementary table 4). The distribution in efficacy was generated from 10,000 bootstraps for each neutralisation level and the 95% confidence limits estimated using the percentile method (2.5 and 97.5 percentile for a regular 95% confidence interval, Figure 2, 4 and S4).

Appendix A – List of Variables Used in the Censored Regression Modelling

Symbol	Interpretation	Variable Type	Explanation / Possible Categories
v	Variant Type	Categorical	VOCs/VOIs $\alpha, \beta, \gamma, \delta, \lambda$
i	Serum Type	Ordinal	Index of sample
N_i^v	Neutralisation titre for serum i against variant v	Numerical – extracted from publication	This is the dependant variable used in the main regression model.
F_i^v	Fold change in neutralisation titre from ancestral virus to variant v for serum i – determined as	Numerical – calculated form data extracted from publication	This is the dependant variable used in the fold change regression model.

	$F_i^v = \frac{N_i^v}{N_i^a}$ where *a* is ancestral virus.		
L_i^v	The limit of detection for serum *i* against variant *v*	Numerical – taken from publication	
$c_{L_i}^v$	Left variable for serum *i* against variant *v*	Categorical	Takes a value of 1 if $F_i^v \leq \frac{L_i^v}{N_i^a}$ and 0 otherwise.
$c_{R_i}^v$	Right censoring variable for serum *i* against variant *v*	Categorical	Takes a value of 1 if $F_i^v \geq \frac{N_i^v}{L_i^a}$, and 0 otherwise.
A_i	Study/Laboratory for serum *i*	Categorical	Laboratory 1 – Laboratory 11
T_i	Serum Type	Categorical	Convalescent or Vaccine Sera. Vaccine Sera are: BNT162b2, ChadOx1 nCov-19, mRNA-1273, NVX-CoV2373, BBV152.

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Supplementary Table 1:

Reference	Serum type	Dosage	Measured on day	Assay	Variants tested	Data derived from:	Figure Lab Number
1	Convalescent	n/a	> 1 month post recovery (severe and non-severe)	Live virus end point microneutralisation assay, ID50	Ancestral (WA1) Alpha/B.1.1.7 Beta/B.1.351	Fig 3b and Fig 4b, raw data kindly provided	Laboratory 1
	mRNA-1273	100 μg	15 days post second dose				
	BNT162b2	ns	> 7 days post second dose				
2	Convalescent	n/a	> 1 month post recovery (severe and non-severe)	Live virus end point microneutralisation assay, ID50	Ancestral (WA1) Gamma/P.1	Fig S1C and D, raw data kindly provided	Laboratory 1
	mRNA-1273	100 μg	15 days post second dose				
	BNT162b2		>7 days post second dose				
3	Convalescent	n/a	4-9 weeks post infection	Live virus focus reduction neutralisation test, FRNT50	Ancestral (Victoria) Beta/B.1.351	Fig 2c/Table S1a	Laboratory 2
	BNT162b2	30 μg	7-17 days post second dose			Fig 3c/Table S2	
	CHAdOx1/AZD1222	Standard or half dose	14 or 28 days post second dose			Fig 3d/Table S2	
4	Convalescent	n/a	4-9 weeks post infection	Live virus focus reduction neutralisation test, IC50	Ancestral (Victoria) Gamma/P.1	Table S4A	Laboratory 2
	BNT162b2	30 μg	4-17 days post second dose			Table S5	
	CHAdOx1/AZD1222	Standard or half dose	14 or 28 days post second dose				
5	Convalescent	n/a	4-9 weeks post infection	Live virus focus reduction neutralisation test FRNT50	Ancestral (Victoria) Alpha/B.1.1.7	Fig5a, raw data kindly provided	Laboratory 2
	BNT162b2	30 μg	7-17 days post second dose			Fig5b, raw data kindly provided	
	CHAdOx1/AZD1222	Standard dose (5×10^{10}) or half dose	14 or 28 days post second dose			Fig5c, raw data kindly provided	
6	Convalescent	n/a	4-9 weeks post infection	Live virus focus reduction neutralisation test, FRNT50	Delta/B.1.617.2	Table S4	Laboratory 2
	BNT162b2	30 μg	7-17 days post second dose				
	CHAdOx1/AZD1222	Standard or half dose	14 or 28 days post second dose				
7	Convalescent	n/a	168-197 days post symptom onset. Mild/moderate, severe and critical disease	Live virus, GFP-split reporter system, IC50	D614G (hCoV-19/France/GE1973/2020) Alpha/B.1.1.7 Beta/B.1.351	Fig 2b, raw data kindly provided	Laboratory 3
8	Convalescent	n/a	6 months post symptom onset	Live virus, GFP-split reporter system, IC50	D614G (hCoV-19/France/GE1973/2020) Alpha/B.1.1.7 Beta/B.1.351 Delta/B.1.617.2	Fig 4a, raw data kindly supplied	Laboratory 3
	BNT162b2	ns	Ave 36 days (32-46)				
9	Convalescent	n/a	~ 1 month post mild infection	Live virus focus reduction	Ancestral WA1with D614G (recombinant) Alpha/B.1.1.7- isolate	Fig 2a,e, raw data kindly provided	Laboratory 4

	BNT162b2	ns	7 days post second dose	neutralisation test, EC50	Beta/B.1.351 spike (recombinant)	Fig 4a,d, raw data kindly provided	
10	Convalescent	n/a	10-102 days post infection	Live virus Plaque reduction neutralisation test PRNT50	Ancestral Gamma/P.1	Supplementary table 4	Laboratory 5
11	Convalescent	n/a	6-43 days post symptom onset/first PCR test positive	Live virus focus reduction neutralisation test, IC50	Ancestral (hCoV-19/England/02/2020) Alpha/B.1.1.7 Beta/B.1.351	2b, raw data kindly provided	Laboratory 6
12	BBV152	ns	ns	Live virus Plaque reduction neutralisation test PRNT50	Ancestral Alpha/B.1.1.7	Fig 1b	Laboratory 7
13	Convalescent	n/a	1 to 8 weeks after resolution of infection or 2 to 10 weeks after the most recent positive SARS-CoV-2 test.	Lentivirus based pseudovirus assay, ID50	Ancestral with D614G Alpha/B.1.1.7	Fig 2a/Table S1	Laboratory 8
	mRNA-1273	100 µg	28 days post second dose				
	NVX-CoV2373	5 µg protein + Matrix M	14 days post second dose				
14	Convalescent	n/a	1 to 8 weeks after resolution of infection or 2 to 10 weeks after the most recent positive SARS-CoV-2 test.	Lentivirus based pseudovirus assay, ID50	Ancestral with D614G Beta/B.1.351	Fig 1a/Table S2	Laboratory 8
	mRNA-1273	100 µg	28 days post second dose				
	NVX-CoV2373	5 µg protein + Matrix M	14 days post second dose				
15	Convalescent	n/a	2-85 days post + PCR test	Live virus focus reduction neutralisation test, ID50	B.1.126 ('WT') Beta/B.1.351	Fig 4a	Laboratory 9
	BNT162b2	ns	7-16 days post second dose				
16	Convalescent	n/a	31-91 days post symptom onset	Live virus focus reduction neutralisation test, FRNT50	Ancestral (WA1) Kappa/B.1.617.1	Fig 1a/Supplementary table 2	Laboratory 10
	BNT162b2	ns	7-27 days post second dose			Fig 1c/ Supplementary table 3	
	mRNA-1273	ns	35-51 days post second dose			Fig 1b/ Supplementary table 4	
17	BNT162b2	ns	Median: 28 days post second dose	Live virus focus reduction neutralisation test, IC50	Ancestral (hCoV19/England/02/2020) D614G Alpha/B.1.1.7 Beta/B.1.351 Delta/B.1.617.2	https://github.com/davidlvb/Crick-UCLH-Legacy-VOCs-2021-05	Laboratory 11

ns. Not specified

Supplementary Table 2:

Study	Vaccine	Trial Started (Day)	Variants compared			Measure of effectiveness	Efficacy / effectiveness against severe disease			Trial design	Data derived from
			Alpha/B.1.1.7	Beta/B.1.351	Delta/B.1.617.2		Alpha/B.1.1.7	Beta/B.1.351	Delta/B.1.617.2		
18	BNT162b2	14 days post 2nd dose	89.5%*	75%#	N/A	Any documented infection	100% (95% CI: 81.7-100)	100% (95% CI: 73.7-100)	N/A	Test negative case control	Table 1
19	BNT162b2	14 days post 2nd dose	93.4%		87.9%	Symptomatic disease	ND			Test negative case control	Table 2
	ChAdOx1 nCoV-19	14 days post 2nd dose	66.1%		59.8%	Symptomatic disease	ND				
20	ChAdOx1 nCoV-19	14 days post 2nd dose		10.4%		Symptomatic disease	Not able to report.			Randomized controlled trial	Table 2
21	NVX-CoV2373	7 days post 2nd dose		51%^		Symptomatic disease	Not able to report			Randomized controlled trial	In text
22	NVX-CoV2373	7 days post 2nd dose	86.3%			PCR confirmed symptomatic COVID, mild, moderate or severe	Not specifically reported (only 5 cases of severe disease, all in placebo group)			Randomized controlled trial	Fig 4
23	Ad26.COV2.S	28 days post dose		64%		Moderate/ severe disease		81.7%		Randomized controlled trial	Table 3
24	BNT162b2	14 days post 2nd dose	92%*		79%δ	PCR confirmed infection	Not reported			Test negative case control	Text
	ChAdOx1 nCoV-19	14 days post 2nd dose	73%*		60%δ						

*S-gene "target failure" PCR used as indicator of B.1.1.7, # Assumed to be B.1.351 if not B.1.117, δ S-gene positive PCR assumed to be B.1.617.2
^ HIV-negative population

Supplementary Table 3:

Source of uncertainty		Parameter in model	Estimated value	Standard error in value	Reference
Model parameters ($\log_{10}$ of the 50% protective neutralisation titre and natural log of the logistic slope parameter)	Symptomatic	n_{50}, k_{log}	-0.697, 1.13	Covariance matrix from fit	25
	Severe	n_{50}, k_{log}	-1.509, 1.12	Covariance matrix from fit	25
Standard deviation of neutralisation titres for each vaccine		σ_{all}	0.46	0.022	25
Mean ($\log_{10}$) neutralisation level of a vaccine against ancestral virus		μ_s	Table S4 of reference (Ref)	Max. value across studies, 0.20	25
Fold-change ($\log_{10}$) in neutralisation titre against each variant		$\log_{10} \bar{F}^v$	Fig. S3	0.015-0.029	Current study

Table S3: Sources of uncertainty in model predictions of vaccine efficacy against variants. In this table we use k_{log} to denote $\log_e(k)$.

Supplementary Table 4:

Reference	Vaccine	Reference Group	Boosted Group (days post-infection)	Measured on day post-dose	Assay	Fold change (Boosted/ Reference) for ancestral virus	Neutralisation titre (fold convalescent) in reference group (Phase I/II trials)[25]	Predicted mean neutralisation level after boosting (fold convalescent)	Date derived from	Data on Variants
26	BNT162b2	Naïve, 2 doses	Convalescent, 1 dose (mean:111)	10	Live virus Microneutralisation test, 50% endpoint titre	4.8	2.4	11.4	GMT titres in text	
27	BNT162b2	Naïve, 2 doses	Convalescent, 2 doses (median: 53)	>14	Live virus, Focus reduction neutralisation test (FRNT50)	3.4	2.4	8.0	Extracted from Figure 2	Alpha, Beta, Gamma
28	BNT162b2 or mRNA-1273	Naïve, 2 doses	Convalescent, 2 doses (median: 247)	19/13 (reference/ convalescent)	Pseudovirus neutralisation	5	3.1*	15.7	Mean value given in text	Beta
29	BNT162b2 or mRNA-1273	Naïve, 2 doses	Convalescent, 2 doses (65-275)	7	Pseudovirus neutralisation	9.2	3.1*	28.7	Raw data in supplement appendix	Beta
30	BNT162b2 or mRNA-1273	Naïve, 2 doses	Convalescent, 2 doses	28	Live virus, Plaque reduction neutralisation assay (PRNT50)	2	3.1*	6.1	Raw data kindly supplied	Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, Kappa
31 and 32	mRNA-1273 (50 μg)	Naïve, 2 doses	mRNA-1273 boosted (177-226 post second dose)	7/15 (reference/boost)	Pseudovirus neutralisation	2.5	4.1	10.1	Figure 3 (31) and Figure 1 (32)	Beta, Gamma
33	CoronaVac	Naïve, 2 doses	CoronaVac 3rd dose, (180 post-second dose)	14	Live virus, microneutralisation test	4.9	0.17	0.82	Figure 2	

* Geometric mean of neutralisation levels for BNT162b2 and mRNA-1273 reported in Phase I/II trials as summarised in reference 25

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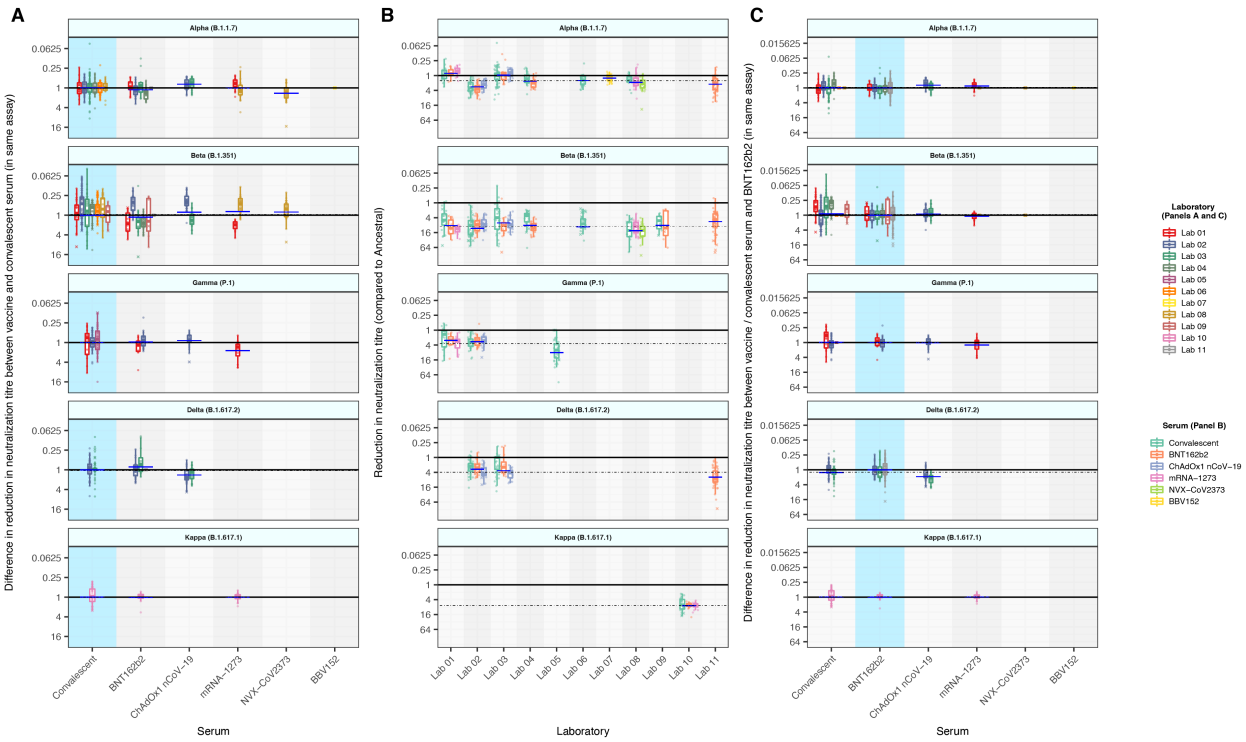

Figure S1: In vitro neutralisation of SARS-CoV-2 variants.
(A) Change in neutralisation titre of all vaccinees normalised against the change in neutralisation titre seen in convalescent individuals in the same study. For convalescent subjects, the mean for each study is one (since titres are normalised to convalescent). For different vaccination groups, the difference between the drop in titre in convalescent individuals in the same study is shown. Horizontal blue bars indicate the censored mean for that vaccine / variant combination. The boxes extend between the first and third quartiles, and the whiskers extend out to up to 1.5×IQR (interquartile range). Vaccination groups show changes in neutralisation titre that closely match that of convalescent subjects in the same study. (B) For each laboratory the mean change in neutralisation titre observed in convalescent subjects and different vaccine groups is shown. Although estimates of change in neutralisation vary between laboratories, within a given laboratory the change in neutralisation titre is congruent between convalescent and different vaccine groups. (C) Normalisation against BNT162b2 vaccinee sera; Panel A normalises vaccine responses against convalescent sera (which are not consistently defined across different studies). To check that our conclusions are robust to the reference serum used, we also analysed the subset of studies in which sera from individuals vaccinated with BNT162b2 was available and normalised against the change in neutralisation titre seen in BNT162b2-vaccinated subjects. As can be seen, the dominant effect of laboratory is still evident when normalised against BNT162b2 sera.

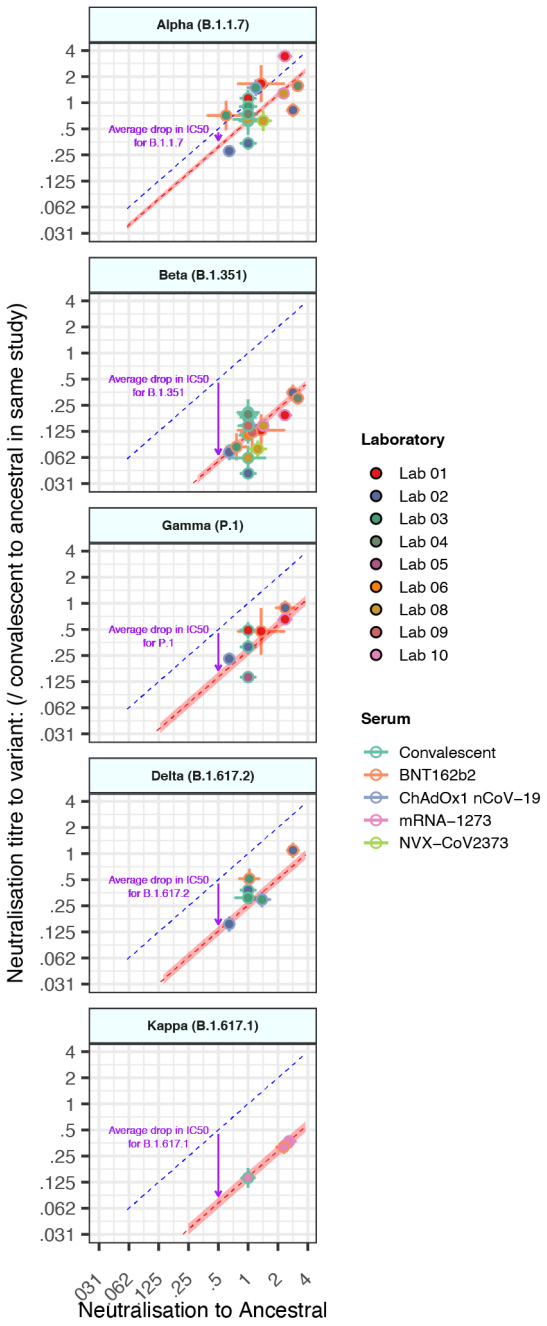

Figure S2: Neutralisation of ancestral virus predicts neutralisation of variants.
The mean neutralisation titre against the ancestral virus (x-axis) and the mean neutralisation titre against the VOC (y-axis) is shown for individual studies. The predicted line for a 1:1 relationship is indicated (dashed blue line). The observed mean drop in neutralisation titre across all vaccines and convalescent subjects is indicated by an arrow, and the predicted levels of variant neutralisation are indicated by a dashed red line (shading indicates 95% CI) are shown. The results for individual studies are variable because of differences between assays and Figure 2 reports the mean across all studies for each vaccine / variant combination.

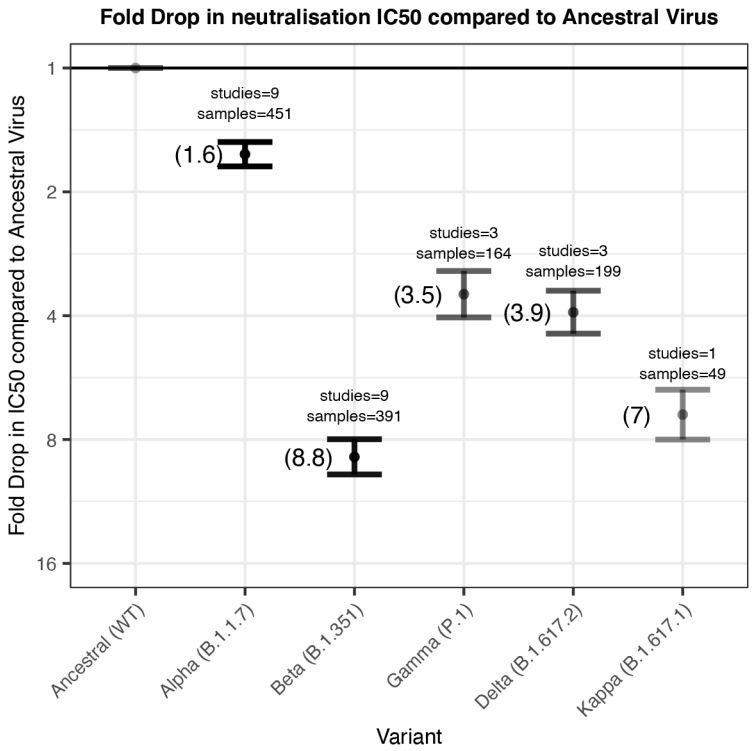

Figure S3: Mean drop in neutralisation titre against SARS-CoV-2 variants.
The mean fold-drop in neutralisation titre reported for different SARS-CoV-2 variants is shown (with 95% CI). The number of subjects and studies contributing to this is also indicated.

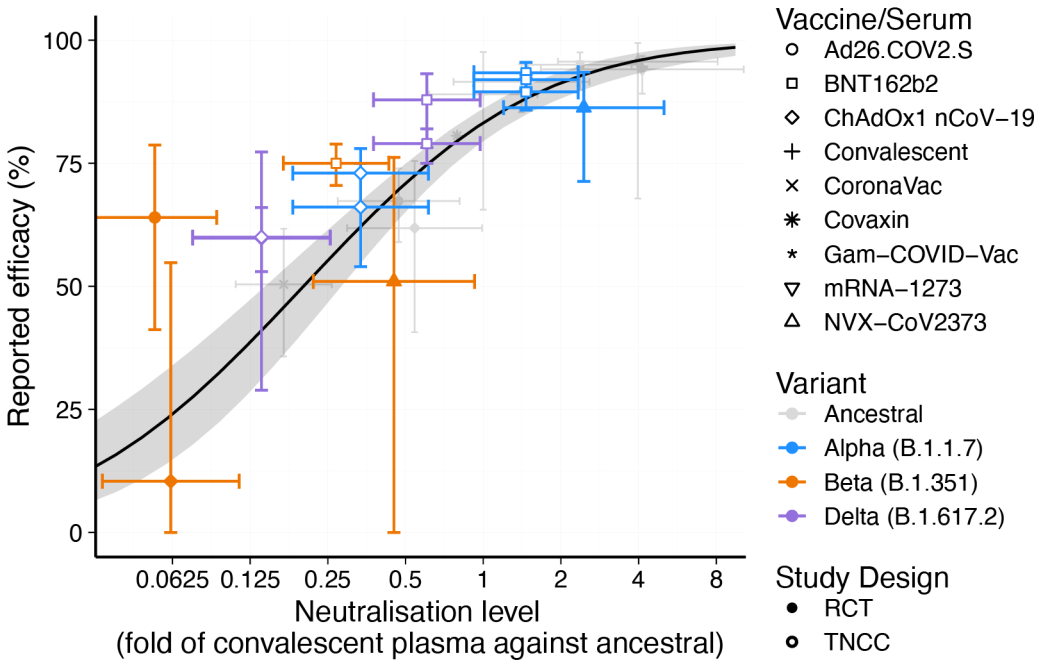

Figure S4: Correlation between in vitro neutralisation and observed protection.
The relationship between neutralisation and protection derived from data on ancestral virus is shown (mean as solid line, shading is 95% CI). The in vitro neutralisation titres against variants (based on the titres reported against ancestral virus in phase I/II studies, and adjusted for the mean drop in neutralisation titre to variants reported in supplementary Figure S3) are shown for each vaccine, along with the observed efficacy (effectiveness) against VOC (see supplementary table 2). Note that whereas in Figure 2 the model curve is adjusted by the mean drop in neutralisation to VOC, here the mean neutralisation titres for each vaccine / variant combination are adjusted for this drop. Open shapes indicate effectiveness reported in a TNCC study design, and the shaded shaped and other marker types indicate vaccine efficacy reported from RCT.