Supplemental materials

Table of Contents

SUPPLEMENTAL METHODS

Participants

Healthy volunteers (HVs) did not have any documented evidence of, and stated that they did not have, an immune disorder. The HV group included unaffected relatives of immune-deficient/disordered people (IDP) who participated in the study. While HVs were enrolled throughout the study period, blood samples could not be obtained for them at the six-month-post-dose-3 timepoint because HVs were not eligible to receive a third dose as soon as IDP, per contemporaneous vaccination guidelines from the Centers for Disease Control and Prevention. Thus, by the end of the study period, six months had not passed since the third dose for any HV. Pre-third dose samples were collected if vaccination occurred before the six-month timepoint.

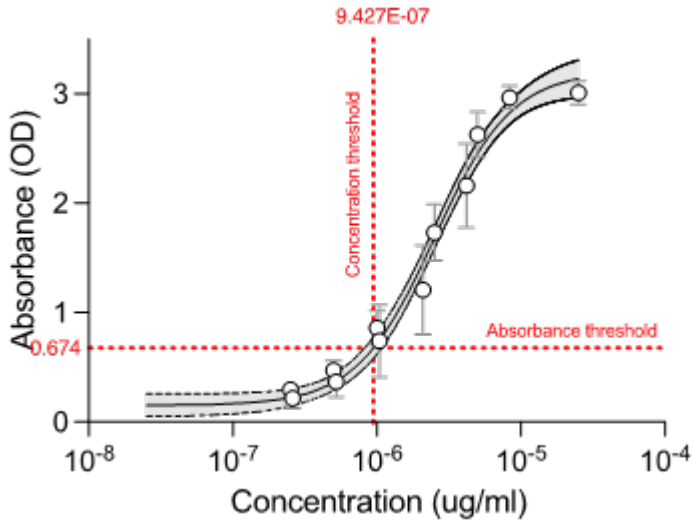
Blood collection methods

Blood was collected remotely via venous draw or by finger stick. Finger stick samples were collected as described previously[1,2] and directly stored at –80°C. Whole blood was collected from venous draw into EDTA and shipped overnight to the NIH for processing. Plasma was separated from peripheral blood samples (EDTA anticoagulant) by centrifugation for 10 min at 500 x *g*. The supernatant plasma was removed and spun a second time for 10 min to pellet residual platelets and leukocytes. The supernatant plasma was then transferred to 1.0 ml conical cryotubes and stored at –80°C.

Enzyme-linked immunosorbent assays (ELISA)

ELISAs were performed as previously described.[1–3] Whole blood was eluted from one microsampler, and the subsequent eluate was utilized in a 96-well ELISA. Briefly, 1 µg/ml ancestral SARS-CoV-2 spike antigen (NIAID VRC) was diluted in 1xPBS (Fisher) and added to each well of a 96-well plate (Nunc MaxiSorp) prior to incubation at 4°C overnight. All subsequent steps other than sample addition occurred on a BioTek EL406 with plate stacker to automate washing and blocking. Wells were washed with PBST (1xPBS + 0.05% Tween20; three cycles) and then blocked for two hours in PBST + 5.0% Nonfat Dried Milk. Wells were washed again, and eluate was diluted 1:10 in 1xPBS + 5.0% NFDM.

Samples were then added to the plates and incubated for one hour. Wells were washed with PBST, then 1:4000 dilution of horseradish peroxidase-conjugated goat anti-human IgG (H+L) secondary antibody in blocking buffer. Wells were washed then incubated with 1-Step Ultra TMB-ELISA Substrate Solution (ThermoFisher) for 10 minutes prior to stopping the reaction with 1 N sulfuric acid stop solution (ThermoFisher). Plates were read within 30 minutes of stopping the reaction on a BioTek Epoch2 Plate reader at 450 nm and 650 nm. Antibody concentration was calculated from the optical density as a function of a standard curve of a monoclonal anti-S-IgG antibody (GenScript). The detection cutoff value was OD = 0.674[1], which correlated to a concentration of 0.0009426984 ug/ml, as shown below.



Data in the figure above are means and 95% confidence intervals for points. The corresponding trendline was estimated with a sigmoidal four-parameter logistic regression model. The figure shows the mean regression trend with a 95% confidence band.

Electrochemiluminescence of anti-S-IgG and ACE2 pseudo-neutralization

Only post-dose 2 through six months post-dose 3 samples from whole blood were run on Meso Scale Discovery assays due to sample volume requirements. Serum samples run on VPLEX SARS-CoV-2 Panel 23 were diluted by 20,000; samples run on the corresponding pseudo-neutralization panel were diluted per manufacturer's instructions. All plates were prepared and samples run according to the kit instruction manual. A standard curve was run on each plate to allow for standardization across plates.

We used data from the following SARS-CoV-2 variant antigens on Panel 23: SARS-CoV-2 Spike (ancestral), B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron BA.1). Data were analyzed with the Meso Scale Discovery Workbench Application. Based on a comparison of IgG dynamics for the cohort, 100,000 antibody concentration units (AU/ml) as measured on the Meso Scale Discovery platform are approximately equal to 1 unit (ug/ml) of antibody concentration as measured by the ELISA.

SARS-CoV-2 PCR and sequencing

Viral RNA was extracted using the NucliSENS easyMag automated extraction system from 200ul of saliva in stabilizing solution and eluted in a total volume of 50ul. First strand cDNA synthesis was performed from 5ul of eluted RNA using SuperScript IV VILO Master Mix (Thermo Fisher). Tiled amplicon libraries were prepared using the Midnight panel and Rapid barcoding kit RBK-004 (Oxford Nanopore technologies) using previously published protocol.[4] Twelve sample pooled libraries were sequenced on a GridION X5 nanopore sequencer using Flongle adapters. The timing of breakthrough infections was used to assign the likeliest variant responsible for corresponding samples that could not be sequenced. This was accomplished by comparing the week of breakthrough infection with the most common SARS-CoV-2 variant at the time using data from CDC's laboratory-based national variant estimates, available here: https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp.

Participant surveys

Standardized surveys that participants were asked to complete contained questions regarding their demographics, medical history, immune disorders, related comorbidities, immunoglobulin replacement regimens, medications, previous and known SARS-CoV-2 infections (whether symptomatic or not), and post-vaccination adverse events[5] (as per the CDC's v-safe system). Survey instruments can be found here: https://doi.org/10.5281/zenodo.7529357

Statistical methods

Medians, interquartile ranges, and boxplots were primarily used to compare and visualize data, as some subgroup-by-timepoint strata had small sample sizes, rendering the arithmetic and geometric

means suboptimal measures of central tendency. A Wilcoxon signed-rank test was used to compare median titer levels for IDP from the post-dose 3 and six months post-dose 3 paired samples. Fisher's exact test was used to compare the percentage of seropositive IPD at the same timepoints. Wilcoxon rank-sum tests were used to compare titer levels for HV and IDP (considered collectively) across timepoints; pairwise Wilcoxon rank-sum tests of each IDP group and HVs for each timepoint were conducted. All Wilcoxon rank-sum tests used continuity corrections. For visualization purposes, figures were made with the ggplot2 R package[6], and data were pseudo-log10 transformed using the scales R package[7], where appropriate. Points were jittered for boxplots. Values below the limit of detection (LOD) for the anti-S IgG ELISA (0.0009426984 ug/ml), anti-S IgG electrochemiluminescence assay (21.05 AU/ml as previously reported)[8], and ACE2 pseudo-neutralization assay (5% as determined by NIAID's Laboratory of Virology) were substituted for the quotient of the LOD and the square root of 2.

Generalized additive mixed models (GAMMs)[9] were used to visualize the relationship between anti-S IgG antibody concentration and ACE2 pseudo-neutralization capacity, both of which were measured with the Meso Scale Discovery platform. GAMMs were built for variant-, time-, and subgroup-specific relationships. GAMMs used restricted maximum likelihood to estimate optimal smoothing parameters and thin plate regression splines.[10] Intra-participant correlation was accounted for using a random effect term at the individual level. The models used a quasibinomial distribution as the outcome variable was a percentage. GAMMs were constructed using the mgcv R package[11] and visualized using the ggplot2 R package by generalizing and correcting the plotting function found here: https://gist.github.com/richardbeare/b679c38dcb644ec50ea34ac061200504, which contained a simplified estimator for the standard errors. GAMM trend lines are visualized with their standard output, the mean and 95% confidence interval, unless noted otherwise.

The correlation between anti-S IgG antibody concentration and ACE2 pseudo-neutralization was measured with the Kendall rank correlation coefficient using the confintr R package.[12] Data were bootstrapped 9,999 times at the individual level to account for intra-participant correlation. Bias-

corrected and accelerated 95% confidence intervals were constructed from the bootstrap distributions. Comparisons of two correlation coefficients were facilitated by comparing the point estimate of one to the bootstrap distribution of the other and calculating one-sided empirical p-values. Bootstrapping was efficiently performed using the dplyr[13], purrr[14], and coxed[15] R packages.

SUPPLEMENTAL FIGURES

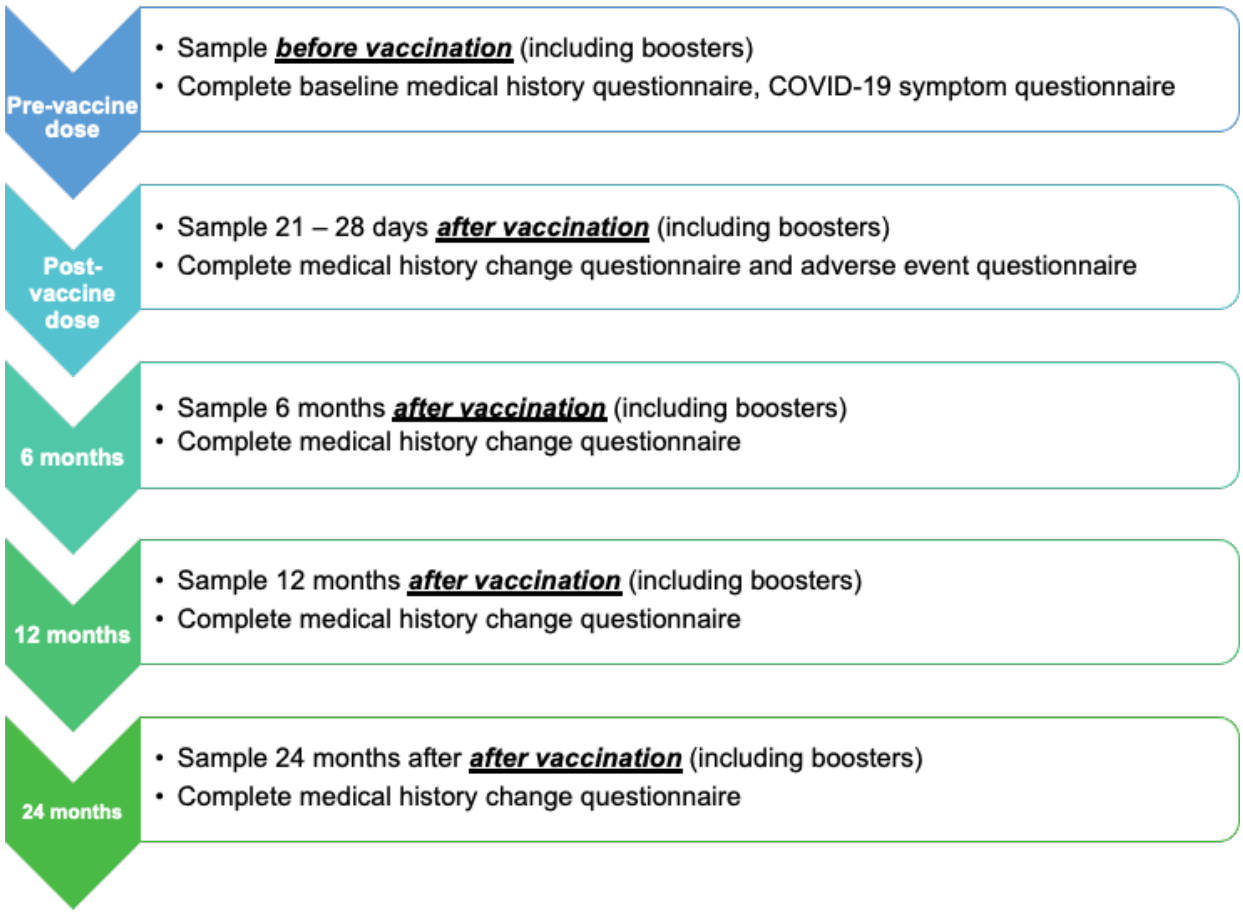


Figure S1. Sample collection timeline.

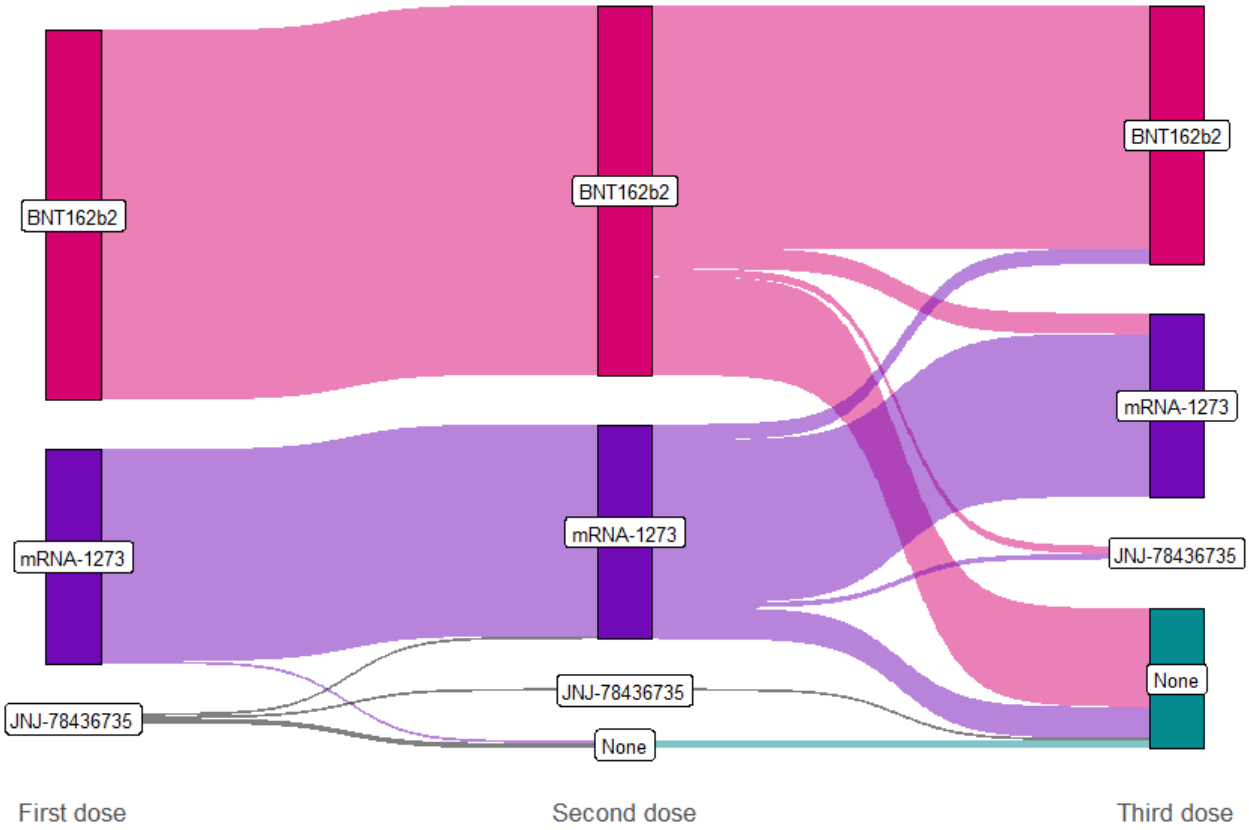


Figure S2. Sankey plot of vaccine brand received for all 230 participants during the study period.

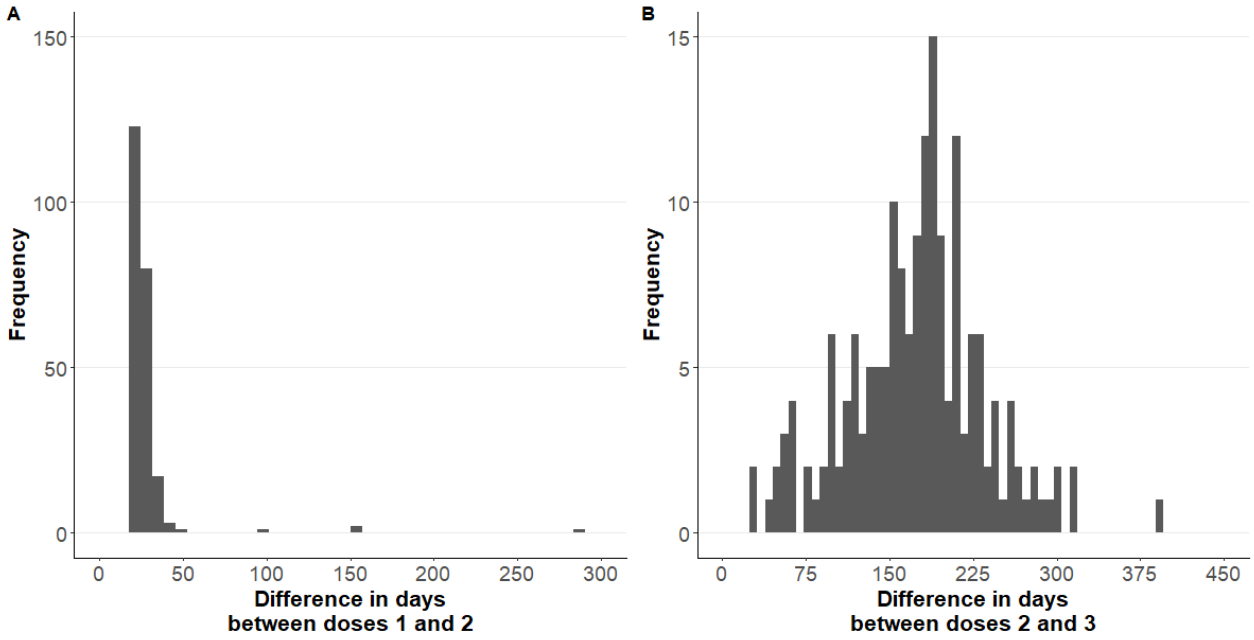


Figure S3. Histograms of the number of days between vaccinations. The histogram bandwidth is same across two panels. **A)** Distribution of the number of days between dose 1 and dose 2. The mean is 27.5 days and the median is 22 days. **B)** Distribution of the number of days between dose 2 and dose 3. The mean is 174.5 days and the median is 180.5 days.

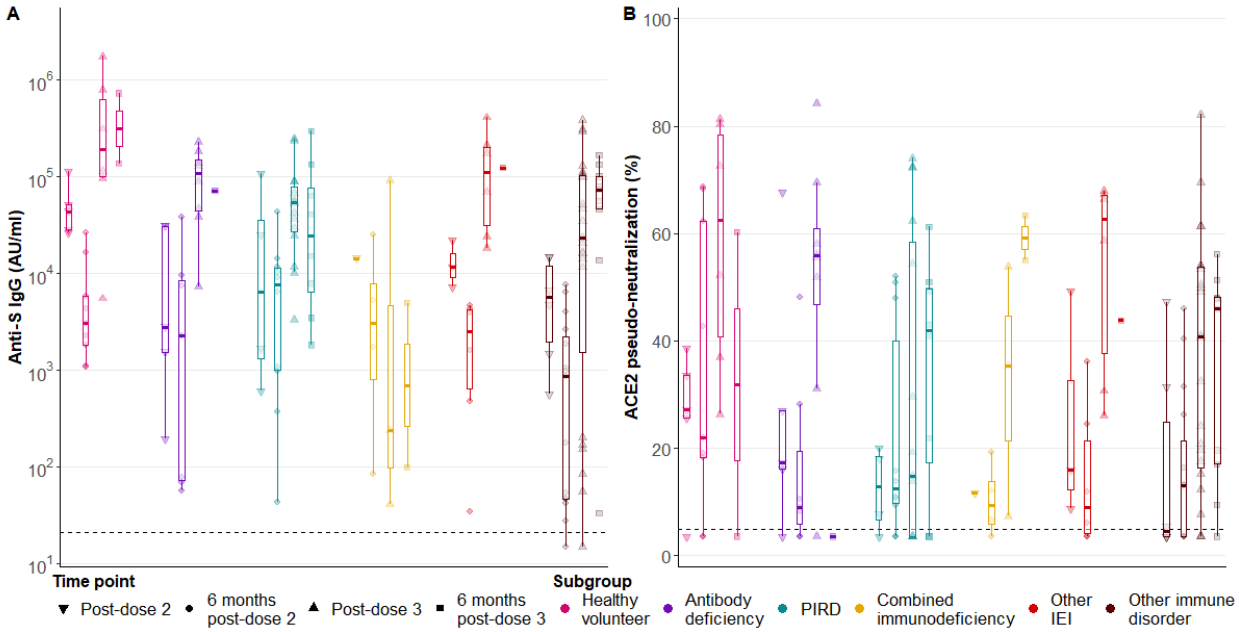


Figure S4. Anti-S IgG antibody concentration and ACE2 pseudo-neutralization for the Omicron BA.1 variant. Data shown are measured by electrochemiluminescence. Samples from participants with evidence of prior SARS-CoV-2 infection, those on immunoglobulin replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and post-breakthrough infection were removed to quantify the impact of the vaccines against an immunologically naïve background. The dashed line shows the assay limit of detection. **A)** IgG concentration against the Omicron BA.1 variant across timepoints and immunological subgroups. Comparable data for the ancestral strain is shown in Figure 2A. **B)** ACE2 pseudo-neutralization data against the Omicron BA.1 variant across time and immunological subgroups. Comparable data for the ancestral strain is shown in Figure 2B.

Abbreviations: ACE2, angiotensin converting enzyme 2; IEI, inborn error of immunity; IgG, immunoglobulin G; IgRT, immunoglobulin replacement therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PIRD, primary immune regulatory disorders

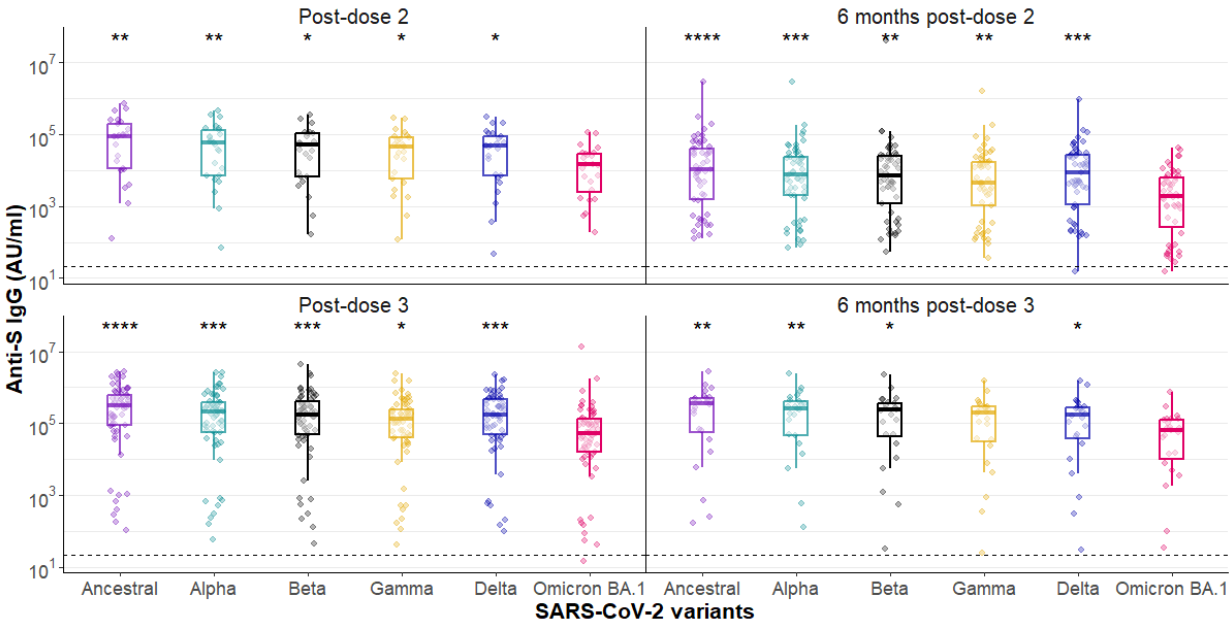


Figure S5. Anti-S IgG antibody concentration by SARS-CoV-2 variant and timepoint. Data shown are measured by electrochemiluminescence. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoint post-breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. The Wilcoxon rank-sum test was used to assess pairwise differences in medians, with all within-timepoint comparisons against Omicron BA.1. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the assay limit of detection.

Abbreviations: HV, healthy volunteer; IDP, immune-deficient/disordered persons; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

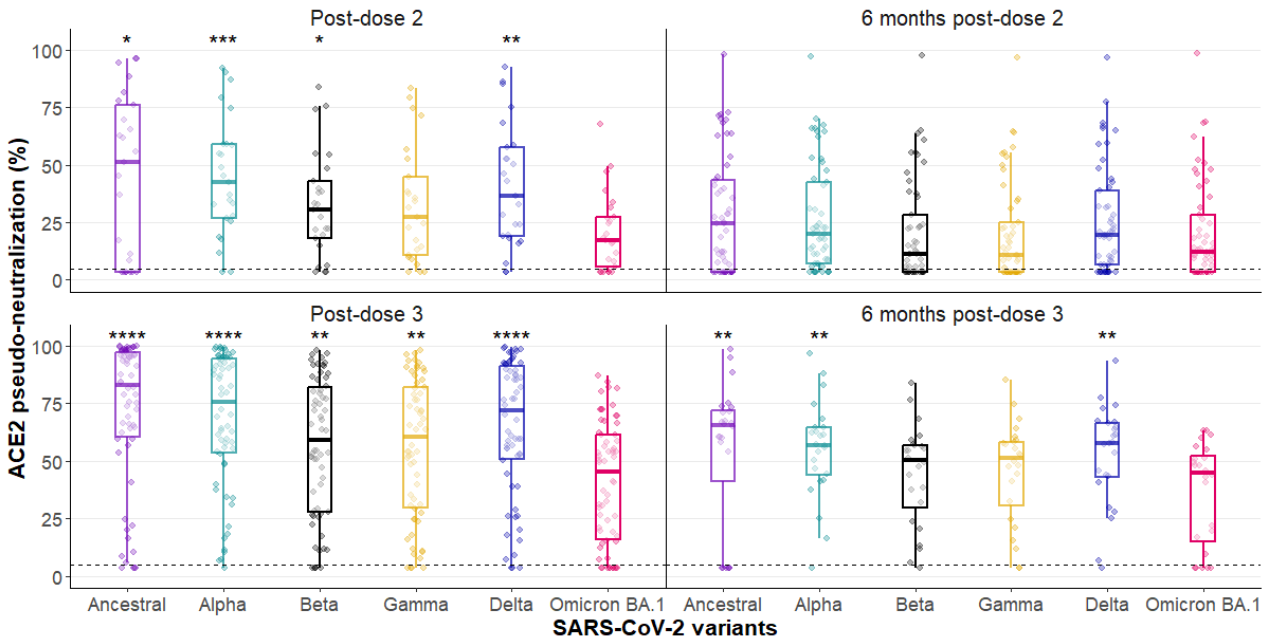


Figure S6. ACE2 pseudo-neutralization by SARS-CoV-2 variant and timepoint. Data shown are measured by electrochemiluminescence. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoint post-breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. The Wilcoxon rank-sum test was used to assess pairwise differences in medians, with all comparisons against Omicron BA.1. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the assay limit of detection.

Abbreviations: HV, healthy volunteer; IDP, immune-deficient/disordered persons; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

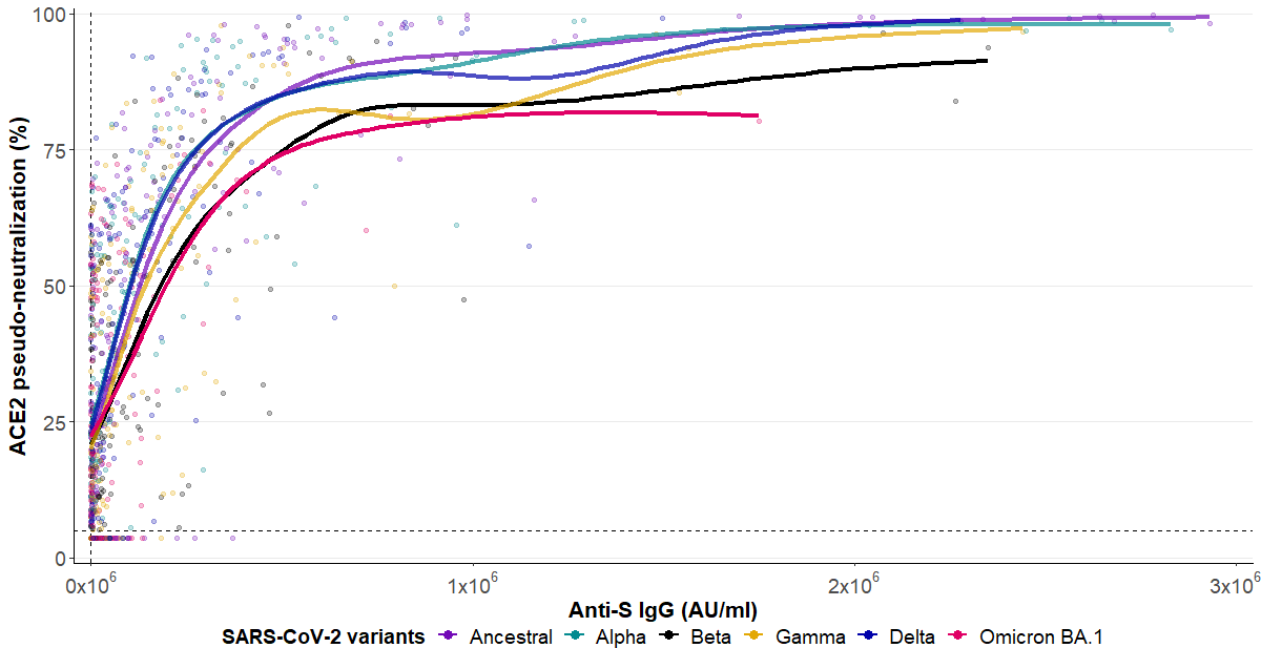


Figure S7. GAMM trendlines of ACE2 pseudo-neutralization capacity as functions of anti-S IgG concentration by SARS-CoV-2 variant. Points represent anti-S IgG concentration and pseudo-neutralization values for each SARS-CoV-2 variant of concern. Variant-specific GAMMs are used to show the mean variant-specific trend. For statistical convergence, the model aggregates over the six immunological subgroups (*i.e.*, healthy volunteers, antibody deficiencies, PIRD, combined immunodeficiencies, other IEI, other immune disorders) and four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3). The mixed model incorporates a random effect at the individual level to account for intra-person correlation. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoints post-breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. This figure plots and models the raw values shown in Figure 2C rather than showing the IgG concentration data on a log10 scale. Dashed lines correspond to assay limits of detection.

Abbreviations: ACE2, angiotensin converting enzyme 2; GAMM, generalized additive mixed model; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

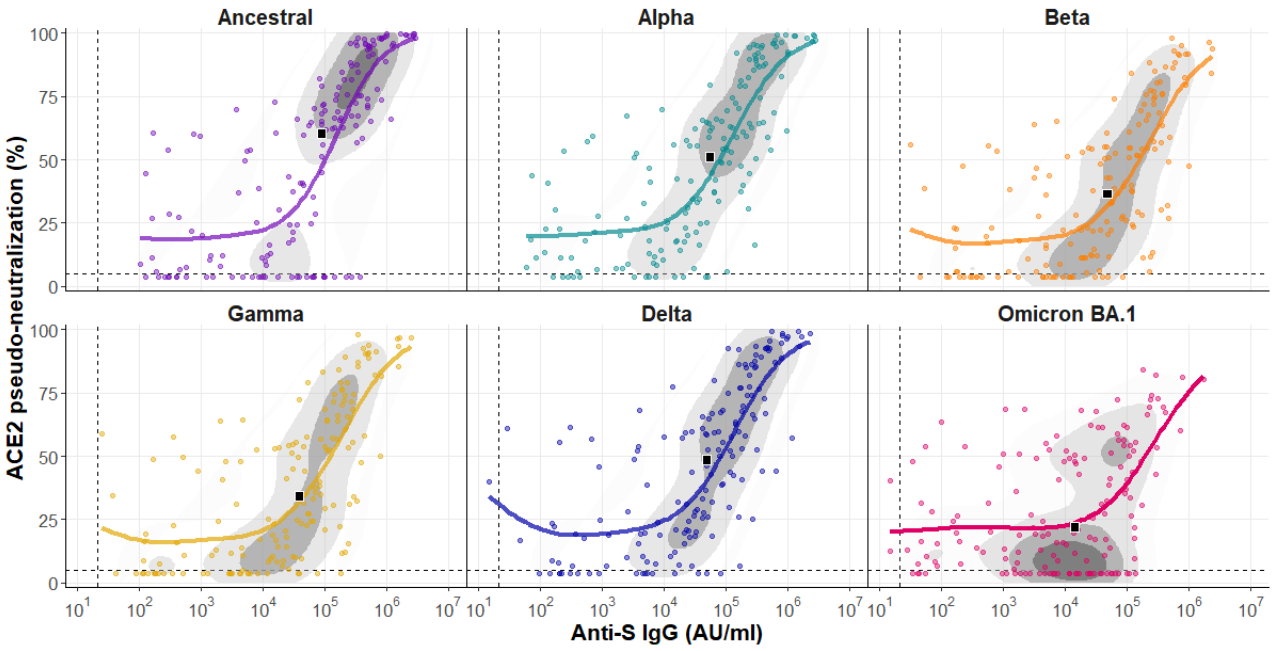


Figure S8. GAMM trendlines of ACE2 pseudo-neutralization capacity as functions of anti-S IgG antibody concentration SARS-CoV-2 variants with accompanying contours from a two-dimensional kernel density estimation. Points represent anti-S IgG concentration and pseudo-neutralization values for each SARS-CoV-2 variant of concern. A two-dimensional kernel density estimation was used, with the same settings across variants to generate contours, which show the density of the points. Darker contours indicate a higher concentration of points, and vice versa. For plotting purposes, anti-S IgG concentration values (on the x-axis) were transformed using a base-10 logarithm since the kernel density algorithm requires a reasonably regular grid to generate contour plots. A GAMM, which captures non-linear trend, shows the mean trend and is superimposed on the kernel density. For statistical convergence, the model aggregates over the six immunological subgroups (*i.e.*, healthy volunteers, antibody deficiencies, PIRD, combined immunodeficiencies, other IEI, other immune disorders) and four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3). These trendlines are the same as those in Figure 2C. The mixed model incorporates a random effect at the individual level to account for intra-person correlation. The confidence band is not shown to better visualize the underlying kernel density-based contours. The black squares indicate the median values for anti-S IgG concentration and ACE2 pseudo-neutralization. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoints post-breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. Dashed lines indicate the assay limits of detection.

Abbreviations: ACE2, angiotensin converting enzyme 2; GAMM, generalized additive mixed model; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

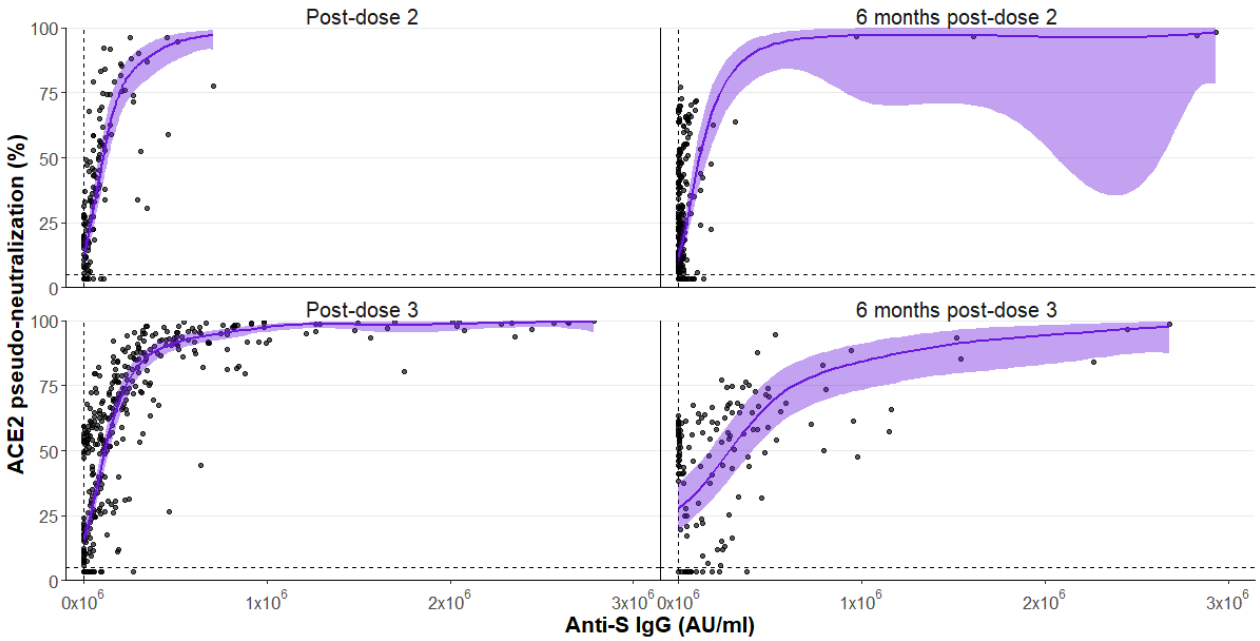


Figure S9. GAMM trendlines of ACE2 pseudo-neutralization capacity as functions of anti-S IgG antibody concentrations by sample timepoint. Each trend line is shown with a corresponding 95% confidence band. For statistical convergence, the model aggregates over the six immunological subgroups (*i.e.*, healthy volunteers, antibody deficiencies, PIRD, combined immunodeficiencies, other IEI, other immune disorders) and six SARS-COV-2 variants (*i.e.*, Ancestral, Alpha, Beta, Gamma, Delta, and Omicron BA.1). Individual values are shown as dots. The mixed model incorporates a random effect at the individual level to account for intra-person correlation. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoints post-breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. The dashed lines show the assay limits of detection.

Abbreviations: ACE2, angiotensin converting enzyme 2; GAMM, generalized additive mixed model; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome

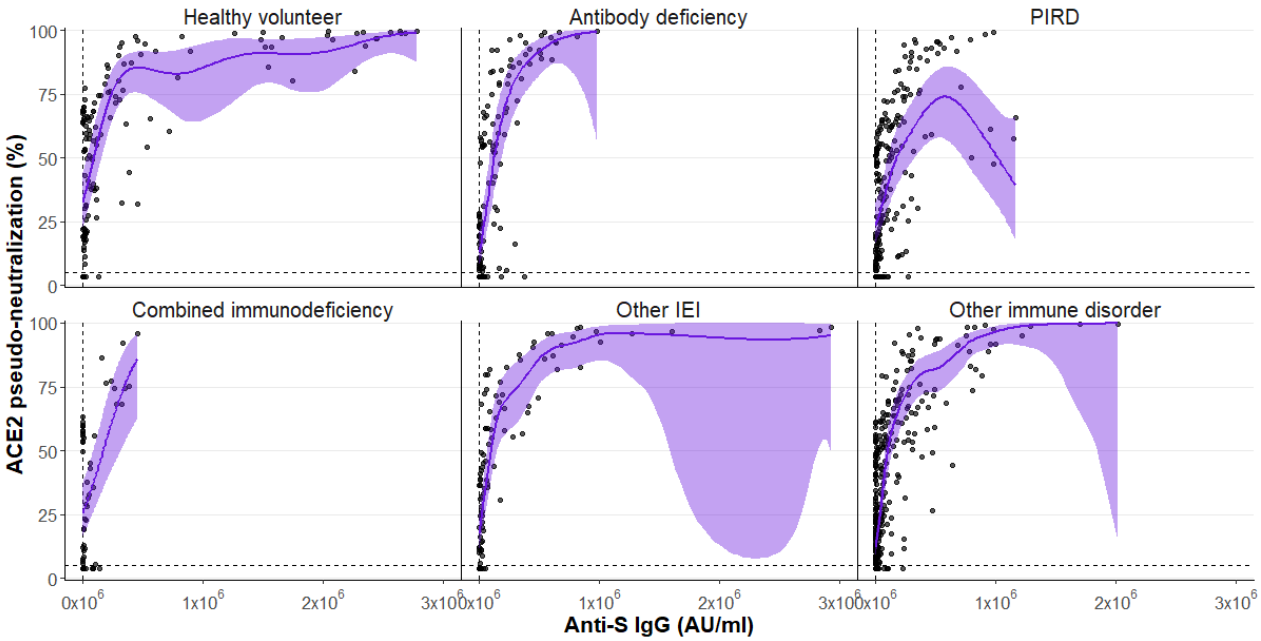


Figure S10. GAMM trendlines of ACE2 pseudo-neutralization capacity as functions of IgG anti-S IgG antibody concentrations by immunological subgroup. Each trend line is shown with a corresponding 95% confidence band. For statistical convergence, the model aggregates over four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3) and six SARS-COV-2 variants (*i.e.*, Ancestral, Alpha, Beta, Gamma, Delta, and Omicron BA.1). Individual values are shown as dots. The mixed model incorporates a random effect at the individual level to account for intra-person correlation. Samples corresponding to participants with evidence of prior SARS-CoV-2 infection, those on antibody replacement therapy, those on AZD7442 (tixagevimab-cilgavimab, AstraZeneca), and timepoints collected after breakthrough infections were removed to quantify the impact of the vaccines against an immunologically naïve background. The dashed lines show the assay limits of detection.

Abbreviations: ACE2, angiotensin converting enzyme 2; GAMM, generalized additive mixed model; IEI, inborn errors of immunity; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome; PIRD, primary immune regulatory disorders

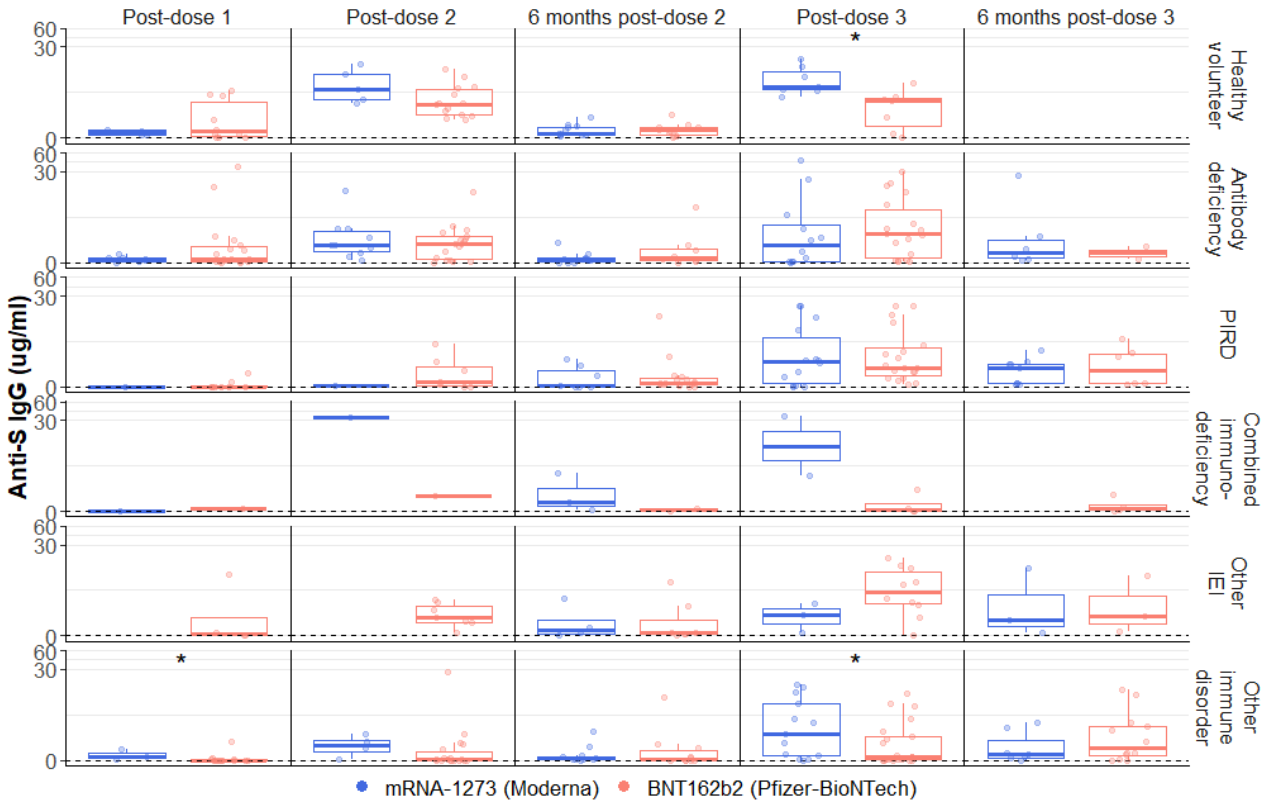


Figure S11. Boxplots of anti-S IgG antibody titers by vaccine brand across timepoints and immunological subgroups. The Wilcoxon rank-sum test was used to evaluate differences in titer levels across the multiple vaccine brands. Only participants who received the same vaccine brand across all doses were included. Participants who received JNJ-78436735 (Janssen) (n=9) at any point were excluded. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the assay limit of detection.

Abbreviations: IDP, immune-deficient/disordered people; IEI, inborn errors of immunity; HV, healthy volunteers; PIRD, primary immune regulatory disorders

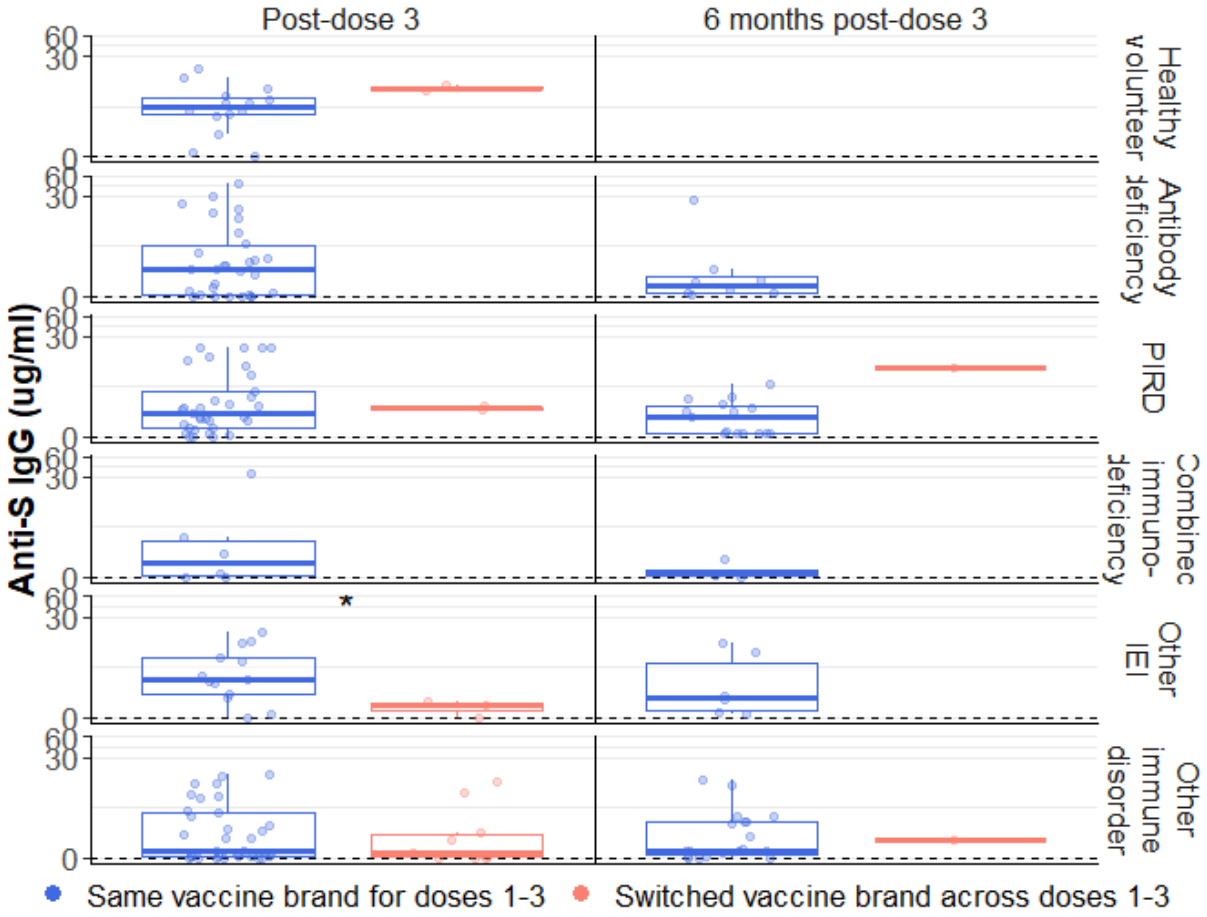


Figure S12. Boxplots of anti-S IgG titers of participants by timepoint, immunological subgroup, and vaccine switching status. The Wilcoxon rank-sum test was used to evaluate differences in median titer levels across vaccine brands by time. Only the post-dose 3 and six months post-dose 3 timepoints are examined because almost all participants received the mRNA-based vaccines, which have a two-dose primary series for immunocompetent participants, and no participant who received either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) at dose 1 switched vaccine brands at dose 2. As a result, only individuals with 3 doses are considered. While most participants switched between mRNA-based vaccines at dose 3, this analysis includes data for individuals who switched from BNT162b2 or mRNA-1273 to JNJ-78436735 (Janssen) for the third dose. However, removing the JNJ-78436735 recipients did not alter the conclusions. No data for individuals who received JNJ-78436735 for doses 1 or 2 are shown as no such participant received a third dose. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the limit of detection.

Abbreviations: IDP, immune-deficient/disordered people; IEI, inborn errors of immunity; HV, healthy volunteers; PIRD, primary immune regulatory disorders

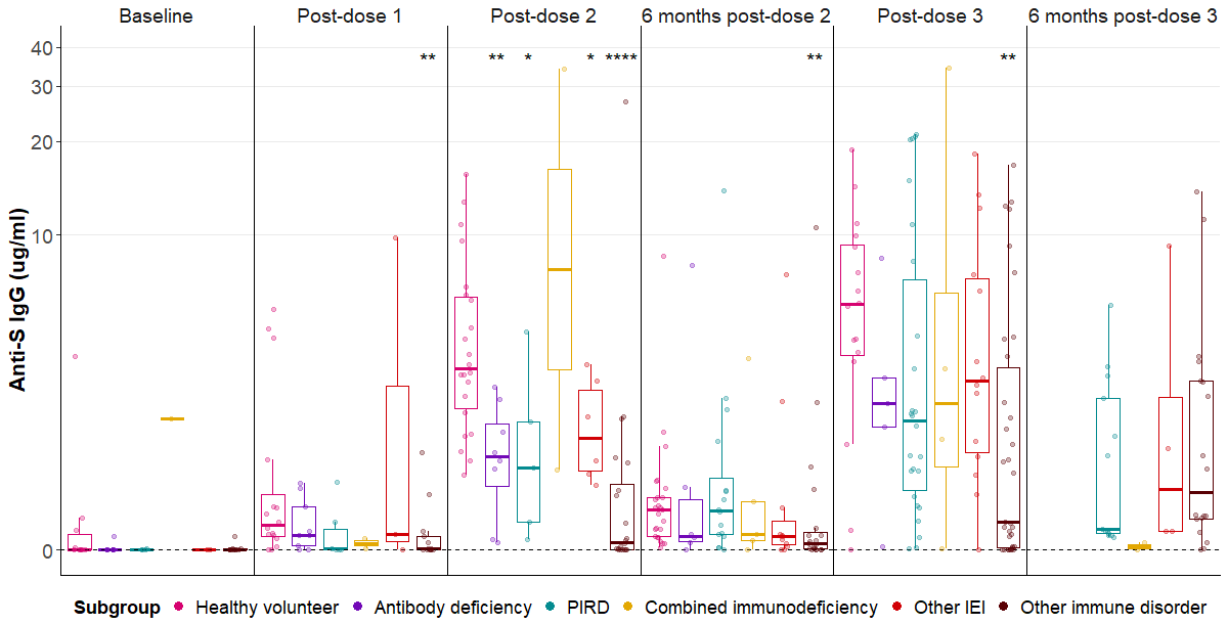


Figure S13. Boxplots of anti-S IgG titers of study participants not receiving IgRT. Data in the figure are restricted to participants not receiving IgRT during the study period and those who did not report whether they received IgRT (as in Figure 3a). However, restricting to only those not receiving IgRT led to very similar results. Pairwise comparisons between the HV control group and each IDP subgroup at each timepoint were made using the Wilcoxon rank-sum text. No comparisons were possible at the six months post-dose 3 timepoint as healthy volunteers were not eligible for a third dose until late in the study period, per vaccination guidelines from the Centers for Disease Control and Prevention. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the assay limit of detection.

Abbreviations: IDP; immune-deficient/disordered person; IEI, inborn errors of immunity; IgG, immunoglobulin G; IgRT, immunoglobulin replacement therapy; HV, healthy volunteer; PIRD, primary immune regulatory disorders

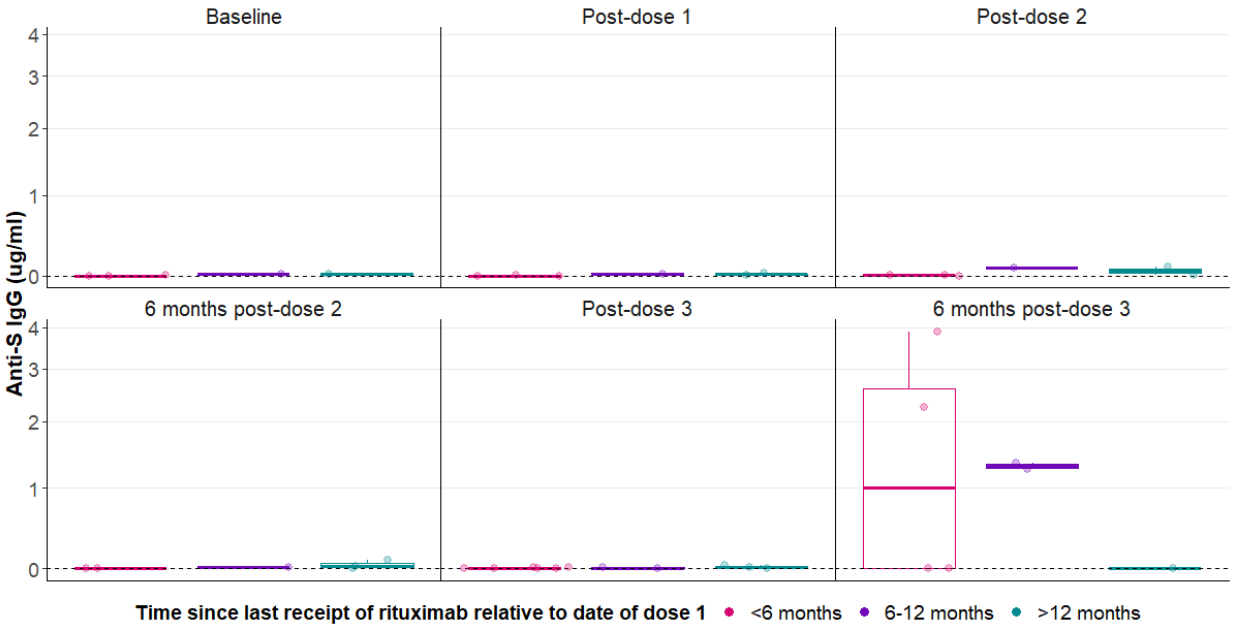


Figure S14. Boxplots of anti-S IgG titers of participants who received rituximab prior to vaccine dose 1. Data for the 15 participants who received rituximab before dose 1 are shown by timepoint. All data are grouped by time from last receipt of rituximab relative to the date of dose 1. Three of the four participants whose anti-S IgG titers are >1ug/ml at six months post-dose 3 received AZD7442 (tixagevimab-cilgavimab, AstraZeneca) before their six month post-dose 3 sample. The dashed line indicates the assay limit of detection.

Abbreviations: IgG, immunoglobulin G

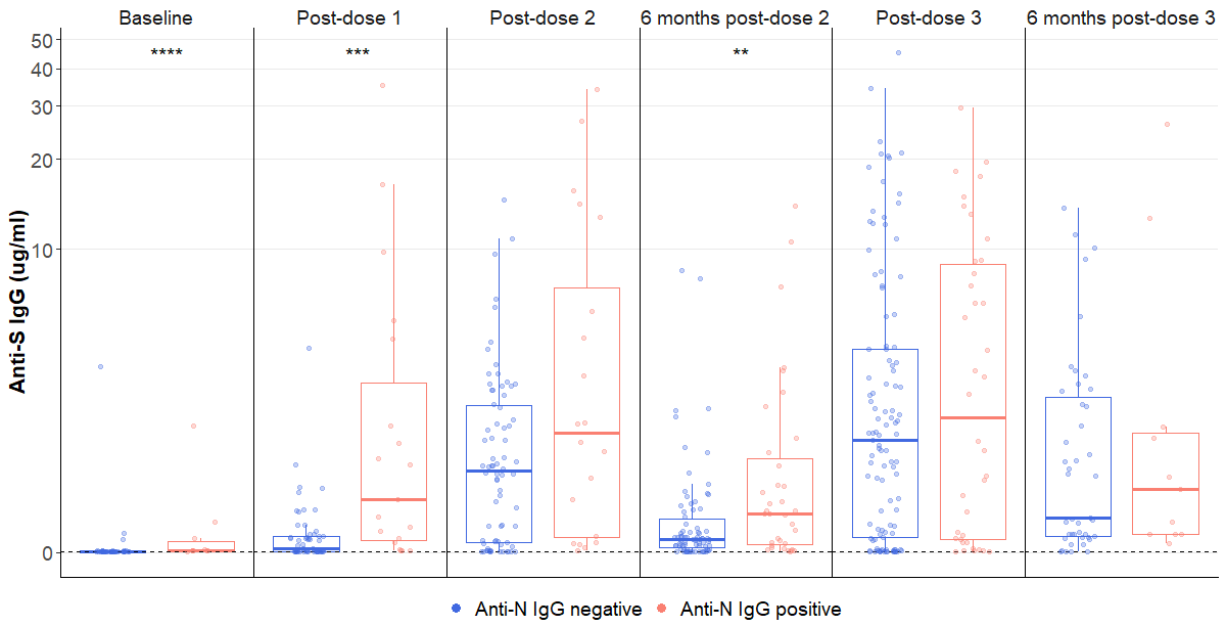


Figure S15. Boxplots of anti-S IgG titers by nucleocapsid-positive status by time. The Wilcoxon rank-sum test was used for all comparisons. In all cases, missing values were coded as "No." The figure shows all participants in the study, including IDP on IgRT. Nucleocapsid positivity was determined by ELISA and assessed at each timepoint. A lack of asterisks indicates a non-significant comparison. By convention, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, and **** = $p \leq 0.0001$. The dashed line indicates the assay limit of detection.

Abbreviations: IDP, immune-deficient/disordered people; IgG, immunoglobulin G; IgRT, immunoglobulin replacement therapy; ELISA, enzyme-linked immunosorbent assays

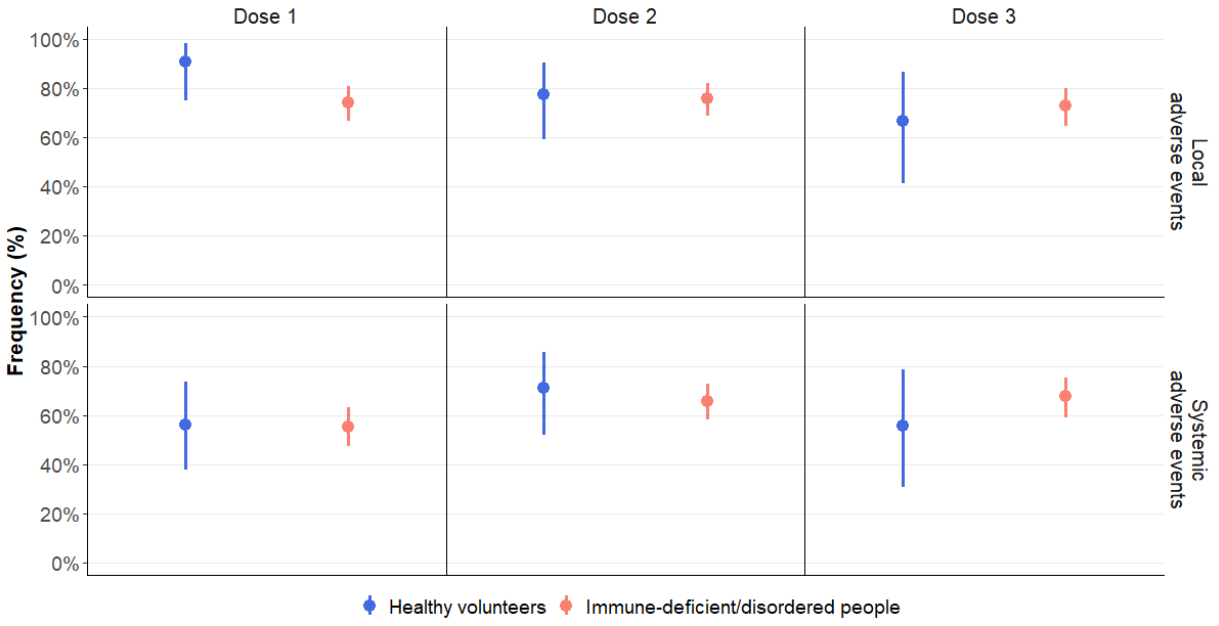


Figure S16. Proportion of vaccine-induced adverse events in IDP and HV. There was no significant difference in frequency of local or systemic events between IDP or HV. Means and 95% Clopper-Pearson confidence intervals are shown. Local adverse events were defined as the presence of pain, redness, itching, and swelling at the injection site. Systemic adverse events were defined as the presence of chills, headache, joint pain, muscle aches, fatigue, nausea, vomiting, diarrhea, abdominal pain, itching in the mouth, body rash, heart palpitations, or dizziness.

Abbreviations: IDP, immune-deficient/disordered people; HV, healthy volunteers

SUPPLEMENTAL TABLES

Table S1. Specific immunodeficiencies of IDP participants.

Immunological subgroup	Specific Immunodeficiency	N
Antibody deficiency	Common variable immunodeficiency	31
Antibody deficiency	Hypogammaglobulinemia	8
Antibody deficiency	NFkB1 haploinsufficiency	1
Antibody deficiency	Specific antibody deficiency	10
Antibody deficiency	X-linked agammaglobulinemia	2
Combined immunodeficiency	CD4 lymphocytopenia	4
Combined immunodeficiency	DiGeorge syndrome	1
Combined immunodeficiency	DOCK8 deficiency	1
Combined immunodeficiency	NEMO deficiency	1
Combined immunodeficiency	SASH3	1
Combined immunodeficiency	Severe combined immune deficiency	1
Primary immune regulatory disorders	Autoimmune lymphoproliferative syndrome	1
Primary immune regulatory disorders	Activated PI3K delta syndrome	6
Primary immune regulatory disorders	Autoimmune polyendocrinopathy-candidiasis-ecto-dermal dystrophy	16
Primary immune regulatory disorders	CTLA4 deficiency	3
Primary immune regulatory disorders	STAT1 autosomal dominant loss of function	1
Primary immune regulatory disorders	STAT1 gain of function	2
Primary immune regulatory disorders	STAT3 dominant-negative	17
Other inborn errors of immunity	Autoantibodies to GM-CSF	3
Other inborn errors of immunity	Autoantibodies to IFN-γ	1
Other inborn errors of immunity	C4 complement deficiency	1
Other inborn errors of immunity	Chronic granulomatous disease	5
Other inborn errors of immunity	COPA mutation	1
Other inborn errors of immunity	DADA2 deficiency	4
Other inborn errors of immunity	GATA2 haploinsufficiency	1
Other inborn errors of immunity	Hereditary angioedema	1
Other inborn errors of immunity	Autosomal dominant IFN-γ receptor deficiency	1
Other inborn errors of immunity	IRAK4 deficiency	1
Other inborn errors of immunity	Myhre syndrome	2
Other inborn errors of immunity	SCT/Rac2 exon 3	1
Other inborn errors of immunity	Thymoma/Good syndrome	4

Other immune disorders	Autoimmune	20
Other immune disorders	Bone marrow transplant	2
Other immune disorders	Severe combined immune deficiency post-bone marrow transplant/gene therapy	4
Other immune disorders	Chronic lymphocytic leukemia	13
Other immune disorders	Chronic myeloid leukemia	1
Other immune disorders	Hairy cell leukemia	1
Other immune disorders	Idiopathic membranous nephropathy	1
Other immune disorders	Lymphoma	1
Other immune disorders	Merkel cell carcinoma	1
Other immune disorders	Multiple myeloma	2
Other immune disorders	Myelofibrosis	1
Other immune disorders	Non-Hodgkin's lymphoma	4
Other immune disorders	T cell large granular lymphocytic leukemia	1
Other immune disorders	Solid organ transplant	7
Other immune disorders	Waldenström macroglobulinemia	3

Abbreviations: COPA, coatomer protein, subunit alpha; CTLA4, cytotoxic T-lymphocyte associated protein 4 ; DADA2, deficiency of the enzyme ADA2 (adenosine deaminase 2); DOCK8, dedicator of cytokinesis 8; IDP, immune-deficient/disordered people; IFN-γ, interferon gamma; IRAK4, interleukin 1 receptor associated kinase 4; GATA2, GATA-binding factor 2; GM-CSF, granulocyte macrophage-colony stimulating factor; NEMO, nuclear factor-kappa B essential modulator; NFB1, nuclear factor kappa B subunit 1; PI3K, phosphoinositide 3-kinases ; SASH3, SAM and SH3 domain containing 3; STAT 1/3, signal transducer and activator of transcription 1/3

Table S2. Number of samples available by timepoint and immunological subgroup.

Timepoint	Immunological subgroup	N
Baseline	Healthy volunteer	10
	Antibody deficiency	21
	PIRD	7
	Combined immunodeficiency	1
	Other IEI	2
	Other immune disorder	14
Post-dose 1	Healthy volunteer	16
	Antibody deficiency	29
	PIRD	9
	Combined immunodeficiency	2
	Other IEI	4
	Other immune disorder	16
Post-dose 2	Healthy volunteer	22
	Antibody deficiency	30
	PIRD	8
	Combined immunodeficiency	2
	Other IEI	7
	Other immune disorder	25
6 months post-dose 2	Healthy volunteer	25
	Antibody deficiency	21
	PIRD	24
	Combined immunodeficiency	5
	Other IEI	14
	Other immune disorder	24
Post-dose 3	Healthy volunteer	16
	Antibody deficiency	30
	PIRD	35
	Combined immunodeficiency	6
	Other IEI	16
	Other immune disorder	44
6 months post-dose 3	Healthy volunteer	0
	Antibody deficiency	8
	PIRD	16
	Combined immunodeficiency	4
	Other IEI	6
	Other immune disorder	20

Abbreviations: IEI, inborn errors of immunity; PIRD, primary immune regulatory disorder

Table S3. Vaccine brand received by immune status for all participants.

Immunological subgroup	Vaccine 1	Vaccine 2	Vaccine 3	N
Healthy volunteers	BNT162b2	BNT162b2	BNT162b2	7
	BNT162b2	BNT162b2	mRNA-1273	2
	BNT162b2	BNT162b2	None	11
	mRNA-1273	mRNA-1273	mRNA-1273	11
	mRNA-1273	mRNA-1273	None	2
	JNJ-78436735	mRNA-1273	None	1
	JNJ-78436735	None	None	1
Immune-deficient/disordered people	BNT162b2	BNT162b2	BNT162b2	87
	BNT162b2	BNT162b2	mRNA-1273	6
	BNT162b2	BNT162b2	JNJ-78436735	3
	BNT162b2	BNT162b2	None	27
	mRNA-1273	mRNA-1273	BNT162b2	6
	mRNA-1273	mRNA-1273	mRNA-1273	52
	mRNA-1273	mRNA-1273	JNJ-78436735	2
	mRNA-1273	mRNA-1273	None	9
	mRNA-1273	None	None	1
	JNJ-78436735	JNJ-78436735	None	1
	JNJ-78436735	None	None	1

Table S4. Median anti-S IgG antibody titers of PID IDP subgroups as a percentage of median antibody titers of HVs.[1-3]

Timepoint	HV	All IDP[4]		Antibody deficiency	Primary immune regulatory disorder	Combined immuno-deficiency	Other inborn errors of immunity	Other immune disorder
Post-dose 1	100.0	14.1		58.1	5.5	NR	NR	3.8
Post-dose 2	100.0	24.5		40.0	8.0	NR	40.2	3.9
6 months post-dose 2	100.0	33.3		34.4	40.1	39.9	29.8	18.1
Post-dose 3	100.0	29.0		35.3	35.4	17.1	50.4	6.3

[1] Percentages are calculated row-wise relative to the healthy volunteers.
[2] Data with fewer than five IDP at a given timepoint are not reported due to a lack of statistical confidence in the IDP-specific median.
[3] Data are not presented for the six months post-dose 3 timepoint as healthy volunteers were not eligible for a third dose during the study period, per vaccination guidelines from the Centers for Disease Control and Prevention.
[4] This column includes all IDP in the study.

Abbreviations: HV, healthy volunteer; IDP, immune-deficient/disordered people; IgG; immunoglobulin G; NR, not reported

Table S5. Median anti-S IgG antibody titers (ug/ml) by immunological subgroup.[1,2]

Timepoint	HV	All IDP[3]		Antibody deficiency	Primary immune regulatory disorder	Combined immuno-deficiency	Other inborn errors of immunity	Other immune disorder
Post-dose 1	0.365	0.052		0.212	0.020	NR	NR	0.014
Post-dose 2	3.525	0.863		1.408	0.283	NR	1.416	0.139
6 months post-dose 2	0.601	0.200		0.207	0.241	0.240	0.179	0.109
Post-dose 3	5.886	1.706		2.075	2.081	1.008	2.965	0.370
6 months post-dose 3	--	0.762		0.733	0.169	0.195	1.423	0.516

[1] Data with fewer than five IDP at a given timepoint are not reported due to a lack of statistical confidence in the IDP-specific median.
[2] Data are not presented for the six months post-dose 3 timepoint as healthy volunteers were not eligible for a third dose during the study period, per vaccination guidelines from the Centers for Disease Control and Prevention.
[3] This column includes all IDP in the study.

Abbreviations: HV, healthy volunteer; IDP, immune-deficient/disordered people; IgG; immunoglobulin G; NR, not reported

Table S6. Kendall correlation values of anti-S IgG antibody concentration and ACE2 pseudo-neutralization by immunological subgroups. The correlations summarize data across six SARS-CoV-2 variants (*i.e.*, Ancestral, Alpha, Beta, Gamma, Delta, and Omicron BA.1) and four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3)

Immunological subgroup	Correlation	95% BC_a CI[1]
Healthy volunteers	0.57	(0.44, 0.73)
Antibody deficiency	0.55	(0.34, 0.69)
PIRD	0.47	(0.31, 0.63)
Combined immunodeficiency[2]	0.33	(0.02, 0.57)
Other IEI	0.69	(0.57, 0.80)
Other immune disorder	0.49	(0.31, 0.61)

[1]Data were bootstrapped at the individual level to account for intra-participant correlation.
[2]Due to few participants with combined immunodeficiencies in the study, these CIs are wider than for other immunological subgroups.

Abbreviations: ACE2, angiotensin converting enzyme 2; BC_a, bias-corrected and accelerated; CI, confidence interval; IEI, inborn errors of immunity; IgG, immunoglobulin G; PIRD, primary immune regulatory disorder; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table S7. Kendall correlation values of anti-S IgG antibody concentration and ACE2 pseudo-neutralization by timepoints. The correlations summarize data across six immunological subgroups (*i.e.*, healthy volunteers, antibody deficiencies, PIRD, combined immunodeficiencies, other IEI, other immune disorders) and six SARS-CoV-2 variants (*i.e.*, Ancestral, Alpha, Beta, Gamma, Delta, and Omicron BA.1).

Timepoint	Correlation	95% BC_a CI[1]
Post-dose 2	0.57	(0.43, 0.68)
Six months post-dose 2	0.26	(0.09, 0.43)
Post-dose 3	0.67	(0.58, 0.74)
Six months post-dose 3	0.28	(0.06, 0.47)
One month after vaccination (Combining post-dose 2 and post-dose 3)	0.66	(0.58, 0.72)
Six months after vaccination (Combining six months post-dose 2 and six months post-dose 3)	0.32	(0.19, 0.44)

[1]Data were bootstrapped at the individual level to account for intra-participant correlation.

Abbreviations: ACE2, angiotensin converting enzyme 2; BC_a, bias-corrected and accelerated; CI, confidence interval; IEI, inborn errors of immunity; IgG, immunoglobulin G; PIRD, primary immune regulatory disorders; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table S8. Kendall correlation values of anti-S IgG antibody concentration and ACE2 pseudo-neutralization by SARS-CoV-2 variants. The correlations summarize data across six immunological subgroups (*i.e.*, healthy volunteers, antibody deficiencies, PIRD, combined immunodeficiencies, other IEI, other immune disorders) and four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3)

SARS-CoV-2 variant	Correlation	95% BC_a CI[1]
Ancestral	0.60	(0.53, 0.67)
Alpha	0.60	(0.54, 0.66)
Beta	0.52	(0.44, 0.59)
Gamma	0.53	(0.45, 0.61)
Delta	0.58	(0.51, 0.65)
Omicron BA.1	0.25	(0.14, 0.34)

[1]Data were bootstrapped at the individual level to account for intra-participant correlation.

Abbreviations: ACE2, angiotensin converting enzyme 2; BC_a, bias-corrected and accelerated; CI, confidence interval; IEI, inborn errors of immunity; IgG, immunoglobulin G; PIRD, primary immune regulatory disorders; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table S9. Kendall correlation values of anti-S IgG antibody concentration and ACE2 pseudo-neutralization by immunological subgroups and SARS-CoV-2 variants. The correlations summarize data across four timepoints (*i.e.*, post-dose 2, six months post-dose 2, post-dose 3, and six months post-dose 3).

Immunological subgroup	SARS-CoV-2 variant	Correlation	95% BC_a CI[1]
Healthy volunteers	Ancestral	0.68	(0.53, 0.87)
	Alpha	0.64	(0.48, 0.84)
	Beta	0.52	(0.32, 0.71)
	Gamma	0.61	(0.44, 0.82)
	Delta	0.55	(0.37, 0.74)
	Omicron BA.1	0.23	(0.01, 0.44)
Antibody deficiency	Ancestral	0.60	(0.30, 0.82)
	Alpha	0.63	(0.42, 0.81)
	Beta	0.56	(0.32, 0.74)
	Gamma	0.55	(0.29, 0.75)
	Delta	0.58	(0.29, 0.75)
	Omicron BA.1	0.33	0.02, 0.57)
Primary immune regulatory disorder	Ancestral	0.57	(0.40, 0.73)
	Alpha	0.54	(0.38, 0.72)
	Beta	0.45	(0.25, 0.62)
	Gamma	0.45	(0.24, 0.65)
	Delta	0.52	(0.33, 0.70)
	Omicron BA.1	0.11	(-0.20, 0.34)
Combined immunodeficiency[2]	Ancestral	0.32	(-0.43, 0.80)
	Alpha	0.45	(-0.32, 0.78)
	Beta	0.37	(-0.48, 0.76)
	Gamma	0.37	(-0.48, 0.76)
	Delta	0.37	(-0.48, 0.76)
	Omicron BA.1	-0.07	(-0.69, 0.50)
Other inborn error of immunity	Ancestral	0.75	(0.61, 0.93)
	Alpha	0.72	(0.55, 0.92)
	Beta	0.72	(0.58, 0.90)
	Gamma	0.77	(0.64, 0.92)
	Delta	0.7	(0.65, 0.94)
	Omicron BA.1	0.53	(0.23, 0.86)
Other immune disorder	Ancestral	0.55	(0.34, 0.69)
	Alpha	0.59	(0.41, 0.71)
	Beta	0.50	(0.29, 0.66)
	Gamma	0.49	(0.30, 0.64)
	Delta	0.56	(0.37, 0.71)
	Omicron BA.1	0.26	(0.03, 0.43)

[1]Data were bootstrapped at the individual level to account for intra-participant correlation.
[2]Due to the few participants with combined immunodeficiencies in the study, these data could not be bootstrapped. A bootstrap (at the sample level rather than at the individual level) 95% CI is therefore given. As a result of the few participants, these CIs are wider than for other immunological subgroups.

Abbreviations: ACE2, angiotensin converting enzyme 2; BC_a, bias-corrected and accelerated; CI, confidence interval; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table S10. The causative SARS-CoV-2 variant of breakthrough infections.

Variant	Variant identified by sequencing (N=11)	Variant assigned based on national CDC estimates at the time of infection (N=24)
Delta	1	3
Omicron BA.1	7	17
Omicron BA.2	3	4

Abbreviations: CDC, Centers for Disease Control and Prevention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table S11. Adverse events in IDP and HV.

Dose	Adverse event information	HV	IDP
1	N	32	162
	Any local adverse event	29	122
	Any systemic adverse event	18	90
	ER visits	0	1
	Time from vaccination to symptom onset (median, days)	1	1
	Symptom duration (median, days)	2	2
2	N	30	164
	Any local adverse event	24	125
	Any systemic adverse event	22	107
	ER visits	0	0
	Time from vaccination to symptom onset (median, days)	1	1
	Symptom duration (median, days)	2	2
3	N	17	130
	Any local adverse event	12	96
	Any systemic adverse event	10	88
	ER visits	1	3
	Time from vaccination to symptom onset (median, days)	1	1
	Symptom duration (median, days)	1	2

Adverse events data comes from self-reported surveys. Not all participants completed every adverse event survey after each dose.

Abbreviations: ER, emergency room; HV, healthy volunteer; IDP, immune-deficient/disordered people

REFERENCES

1. Klumpp-Thomas C, Kalish H, Drew M, et al. Standardization of ELISA protocols for serosurveys of the SARS-CoV-2 pandemic using clinical and at-home blood sampling. *Nat Commun*. 2021;12(1):113. doi:10.1038/s41467-020-20383-x

2. Kalish H, Klumpp-Thomas C, Hunsberger S, et al. Undiagnosed SARS-CoV-2 seropositivity during the first 6 months of the COVID-19 pandemic in the United States. *Science Translational Medicine*. 2021;13(601):eabh3826. doi:10.1126/scitranslmed.abh3826

3. Buckner CM, Kardava L, El Merhebi O, et al. Interval between prior SARS-CoV-2 infection and booster vaccination impacts magnitude and quality of antibody and B cell responses. *Cell*. 2022;185(23):4333-4346.e14. doi:10.1016/j.cell.2022.09.032

4. Freed NE, Vlková M, Faisal MB, Silander OK. Rapid and inexpensive whole-genome sequencing of SARS-CoV-2 using 1200 bp tiled amplicons and Oxford Nanopore Rapid Barcoding. *Biol Methods Protoc*. 2020;5(1):bpaa014. doi:10.1093/biomethods/bpaa014

5. Centers for Disease Control and Prevention. V-safe active surveillance for COVID-19 vaccine safety, Version 3. Published online May 20, 2021. https://www.cdc.gov/vaccinesafety/pdf/V-safe-Protocol-508.pdf

6. Wickham, Hadley. ggplot2: Elegant Graphics for Data Analysis. Published online 2016.

7. Wickham, Hadley, Seidel, Dana. scales: Scale Functions for Visualization. Published online 2022. https://CRAN.R-project.org/package=scales

8. Johnson M, Wagstaffe HR, Gilmour KC, et al. Evaluation of a novel multiplexed assay for determining IgG levels and functional activity to SARS-CoV-2. *Journal of Clinical Virology*. 2020;130:104572. doi:10.1016/j.jcv.2020.104572

9. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2011;73(1):3-36. doi:10.1111/j.1467-9868.2010.00749.x

10. Wood SN. Thin plate regression splines. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2003;65(1):95-114. doi:10.1111/1467-9868.00374

11. Wood SN. Modelling and smoothing parameter estimation with multiple quadratic penalties. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2000;62(2):413-428. doi:10.1111/1467-9868.00240

12. Mayer, Michael. confintr: Confidence Intervals. Published online 2022. https://CRAN.R-project.org/package=confintr

13. Wickham, Hadley, Francois, Romain, Henry, Lionel, Muller, Kirill. dplyr: A Grammar of Data Manipulation. Published online 2022. https://CRAN.R-project.org/package=dplyr

14. Henry, Lionel, Wickham, Hadley. purrr: Functional Programming Tools. Published online 2020. https://CRAN.R-project.org/package=purrr

15. Kropko, Jonathan, Harden, Jeffrey. coxed: Duration-Based Quantities of Interest for the Cox Proportional Hazards Model. Published online 2020. https://CRAN.R-project.org/package=coxed