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Supplementary Materials for

Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial

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The PDF file includes:

Materials and Methods
Supplementary Text
Figs. S1 to S30
Tables S1 to S9
Immune Assays Team Collaborator List
Moderna, Inc. Team Collaborator List
CoVPN/COVE Team Collaborator List
USG/CoVPN Biostatistics Team Collaborator List
References

Other Supplementary Material for this manuscript includes the following:

MDAR Reproducibility Checklist
Statistical Analysis Plan

Table of Contents

Materials and Methods **6**

Composition of Research Teams **6**

Immune Assays Team 6

Moderna, Inc. Team 6

Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team 7

CoVPN/COVE Team (cont'd): COVE Trial Investigators and Study Teams 10

United States Government (USG)/Coronavirus Prevention Network (CoVPN) Biostatistics Team 20

Trial design and COVID-19 endpoint evaluated for correlates **20**

Laboratory methods **20**

Solid-phase electrochemiluminescence S-binding IgG immunoassay (ECLIA) 20

Neutralization assay 21

Ethics 22

Bridging of binding antibody assay readouts and neutralizing antibody assay readouts to the WHO International Standard for anti-SARS-CoV-2 immunoglobulin 22

Summary values for WHO anti-SARS-CoV-2 IgG (20/136) 23

Statistical methods **24**

Case-cohort sets included in correlates analyses 24

Covariate-adjustment 25

Correlates of risk in vaccine recipients 25

Correlates of protection: controlled vaccine efficacy and mediation 25

Hypothesis testing 26

Calibration of ID50 and ID80 titers between the Duke neutralization assay on COVE trial samples and the Monogram PhenoSense neutralization assay performed on AstraZeneca COV002 samples 26

Sensitivity analysis comparing correlate of protection results between COV002 and COVE 26

Software and data quality assurance 27

Research reproducibility approach 27

Table S1. Demographics and clinical characteristics of baseline SARS-CoV-2 negative per-protocol trial participants in the immunogenicity subcohort and thus have Day 1, 29, 57 antibody marker data. **28**

Table S2. Sample sizes of baseline SARS-CoV-2 negative per-protocol vaccine recipients included in immune correlates analyses, by baseline sampling strata and case/non-case strata. **29**

Fig. S1. (A) Day 29 marker case-cohort set and (B) Day 57 marker case-cohort set. 30

Fig. S2. Flowchart of study participants from enrollment to the Day 29 and Day 57 case-cohort sets of baseline SARS-CoV-2 negative per-protocol participants. 31

Fig. S3. Phases of the COVE trial, timing of mRNA-1273 doses and blood sampling, and the two time periods for diagnosis of COVID-19 endpoints ("Intercurrent" and "Post Day 57"). 32

Table S3. Meso-Discovery (MSD) and pseudovirus neutralization assay limits of the four antibody markers evaluated as immune correlates. 33

Fig. S4. For each antibody marker, correlations of Day 29 levels with Day 57 levels in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. 34

Fig. S5. Correlations of Day 29 antibody markers in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. 35

Fig. S6. Correlations of Day 57 antibody markers in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. 36

Fig. S7. A) Anti-RBD IgG concentration and B) pseudovirus neutralization ID80 titer by COVID-19 outcome status. 37

Fig. S8. Marker values (spike IgG, RBD IgG, ID50, ID80) by COVID-19 outcome status in placebo recipients. 38

Fig. S9. Day 29 marker data points from baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 29 marker case-cohort set. 39

Fig. S10. Day 57 marker data points from baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 57 marker case-cohort set. 40

Fig. S11. Inverse probability sampling (IPS)-weighted empirical reverse cumulative distribution function curves for each Day 57 marker (spike IgG, RBD IgG, ID50, ID80) and application of the Siber (2007) method (*27*) for estimating a threshold of perfect vs. no protection. 41

Fig. S12. Inverse probability sampling (IPS)-weighted empirical reverse cumulative distribution function curves for each Day 29 marker (spike IgG, RBD IgG, ID50, ID80) and application of the Siber (2007) method (*27*) for estimating a threshold of perfect vs. no protection. 42

Fig. S13. Day 29 and Day 57 antibody markers (spike IgG, RBD IgG, ID50, ID80) vs. number of days from Day 29 visit until COVID-19 primary endpoint diagnosis for per-protocol baseline SARS-CoV-2 negative vaccine recipient breakthrough cases. 43

Fig. S14: Covariate-adjusted cumulative incidence of COVID-19 by Low, Medium, High tertile of Day 57 IgG concentration or pseudovirus neutralization titer. (A) Anti-RBD IgG concentration; (B) ID80 titer. 44

Supplementary Text S1 45

Baseline covariates adjusted for in immune correlates analyses, including the baseline COVID-19 risk score 45

Table S4. Individual baseline variables input into the Superlearner model for predicting occurrence of COVID-19 in baseline SARS-CoV-2 negative per-protocol placebo recipients.[1] 45

Table S5. Learning algorithm-screen combinations (14 in total) used as input to the Superlearner model in baseline negative per-protocol placebo recipients. 46

Table S6. Weights assigned by Superlearner to each individual learner in the COVID-19 prediction modeling of the placebo arm 47

Table S7. Predictors in learners assigned positive weight by Superlearner in the COVID-19 prediction modeling of the placebo arm. 48

Fig. S15. (A) Cross-validated receiver operating characteristic curve for the two top-performing learners, Superlearner, and the Discrete Superlearner models classifying COVID-19 outcome occurrence in baseline SARS-CoV-2 negative per-protocol placebo recipients, with cross-validated area under the curve (CV-AUC) summarizing classification performance. (B) Receiver operating characteristic curve for the Superlearner upon applying the model built from placebo recipients to baseline SARS-CoV-2 negative per-protocol vaccine recipients, with AUC in parentheses summarizing classification performance. 50

Fig. S16. Superlearner model predicted probabilities of the COVID-19 endpoint starting 7 days post Day 57 visit by case vs. non-case (i.e., control) status, for baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 57 marker case-cohort set..... 51

Fig. S17. Covariate-adjusted hazard ratios of COVID-19 per 10-fold increase in each Day 29 antibody marker in baseline SARS-CoV-2 negative per-protocol vaccine recipients overall and in subgroups..... 52

Figure S18. Covariate-adjusted cumulative incidence of COVID-19 by Low, Medium, High tertile of Day 29 IgG concentration or pseudovirus neutralization titer in baseline SARS-CoV-2 negative per-protocol participants..... 53

Fig. S20. Covariate-adjusted risk of COVID-19 by the level of each Day 57 marker (spike IgG, RBD IgG, ID50, ID80), estimated with a generalized additive model, in baseline SARS-CoV-2 negative per-protocol vaccine recipients. 55

Fig. S21. Covariate-adjusted risk of COVID-19 by the level of each Day 29 marker (spike IgG, RBD IgG, ID50, ID80), estimated with a generalized additive model, in baseline SARS-CoV-2 negative per-protocol vaccine recipients. 56

Fig. S22. Further analyses of Day 29 ID50 level as a correlate of risk and as a correlate of protection. 57

Fig. S23. Further analyses of Day 57 ID80 level as a correlate of risk and analysis as a correlate of protection. 58

Fig. S24. Further analyses of Day 57 anti-spike IgG level as a correlate of risk and as a correlate of protection. 59

Fig. S25. Further analyses of Day 57 anti-RBD IgG level as a correlate of risk and as a correlate of protection. 60

Fig. S26. Further analyses of Day 29 ID80 level as a correlate of risk and as a correlate of protection. 61

Fig. S27. Further analyses of Day 29 anti-spike IgG level as a correlate of risk and as a correlate of protection. 62

Fig. S28. Further analyses of Day 29 anti-RBD IgG level as a correlate of risk and as a correlate of protection. 63

Supplementary Text S2: Controlled vaccine efficacy sensitivity analysis and mediation analysis ... 64

Controlled vaccine efficacy sensitivity analysis to assess robustness of the effect of antibody marker on preventing COVID-19 to unmeasured confounding..... 64

Table S8. Sensitivity analysis to assess Day 57 and Day 29 antibody markers categorized as upper vs. lower tertiles as controlled vaccine efficacy CoPs against COVID-19..... 65

Mediation analysis 66

Table S9. Table of mediation effect estimates for quantitative markers with 95% confidence intervals..... 66

Fig. S29. Vaccine efficacy with sensitivity analysis by Day 57 (A) anti-spike IgG level, (B) anti-RBD IgG level, (C) ID50 level, or (D) ID80 level. 68

Fig. S30. Vaccine efficacy with sensitivity analysis by Day 29 (A) anti-spike IgG level, (B) anti-RBD IgG level, (C) ID50 level, or (D) ID80 level. 69

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Principal Investigator	Study Team	Institution	Location
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Trial design and COVID-19 endpoint evaluated for correlates

From July 27 2020 to October 23 2020, 30 415 participants were randomized (1:1 ratio) to receive two injections of mRNA-1273 (100 μg) or placebo, one at Day 1 and one at Day 29 (*6*). (We use "Day 1", "Day 29", and "Day 57" to denote the Day 1, 29, and 57 study visits, respectively). Correlates were evaluated against the protocol-specified primary endpoint, hereafter "COVID-19": first occurrence of acute symptomatic COVID-19 with virologically-confirmed SARS-CoV-2 infection in participants with no evidence of previous SARS-CoV-2 infection (*6*). Correlates analyses included COVID-19 endpoints diagnosed starting 7 days post antibody marker measurement through completion of the blinded phase of follow-up (fig. S3). COVID-19 endpoints less than 7 days post antibody measurement were not included because the antibody levels may have been influenced by natural SARS-CoV-2 infection, complicating the interpretation of immune correlates. The data cutoff date was March 26, 2021.

Laboratory methods

Solid-phase electrochemiluminescence S-binding IgG immunoassay (ECLIA)

Serum IgG binding antibodies to spike and to RBD were quantitated using a validated solid-phase electrochemiluminescence S-binding IgG immunoassay. The ECLIA assay enables simultaneous quantitative detection of IgG antibodies to three distinct SARS-CoV-2 antigens in human serum. For this validated assay, custom MSD SECTOR® plates were precoated by Meso

Scale Discovery (MSD; Rockville, Maryland) with SARS-CoV-2 spike (S-2P), receptor binding domain (RBD) protein, Nucleocapsid (N) protein and a Bovine Serum Albumin (BSA) control in each well in a specific spot-designation for each antigen. The assay was performed with a Beckman Coulter Biomek based automation integration platform including the Biotek 405TS Plate Washer. Serum samples were heat-inactivated for 30 minutes at 56°C prior to assay. Plates were blocked for 60 minutes at room temperature (RT) with MSD blocker A solution without shaking. Plates were washed and MSD reference standard (calibrator), QC test sample (pool of COVID-19 convalescent sera) and human serum test samples were added to the precoated wells in duplicates in an 8-point dilution series. Reference standard was added in triplicates. MSD Control sera (low, medium and high) were added undiluted in triplicates as per validated assay format. Additional assay controls might be added in triplicates. Samples were incubated at RT for 4 hours with shaking on a Titramax Plate shaker (Heidolph) at 1500 rpm. SARS-CoV-2 specific antibodies present in the sera or controls bound to the coated antigens. Plates were washed to remove unbound antibodies. Antibodies bound to the SARS-CoV-2 viral proteins were detected using an MSD SULFO-TAG™ anti-human IgG detection antibody incubated for 60 minutes at RT and with shaking. Plates were washed and a read solution (MSD GOLD™ read buffer) containing electrochemiluminescence (ECL) substrate was applied to the wells, and the plate was entered into the MSD MESO Sector S 600 detection system. An electric current was applied to the plates and areas of well surface which form antigen-anti human IgG antibody SULFO-TAG™ complex emitted light in the presence of the ECL substrate.

The MSD MESO Sector S 600 detection system quantitates the amount of light emitted and reports the ECL unit response as a result for each test sample, control sample and reference standard of each plate. Analysis was performed with the MSD Discovery Workbench software, Version 4.0. Calculated ECLIA parameters to measure binding antibody activities include interpolated concentrations or assigned arbitrary units (AU/mL) read from the standard curve.

Neutralization assay

Serum neutralizing antibodies were measured in a validated pseudovirus-based assay as a function of reductions in luciferase reporter gene expression after a single round of infection with SARS-CoV-2.D614G spike-pseudotyped virus in 293T/ACE2 cells (293T cell line stably overexpressing the human ACE2 cell surface receptor protein, obtained from Drs. Mike Farzan and Huihui Mu at Scripps) as detailed in Shen et al. (*39*). Briefly, spike-pseudotyped virus was prepared by transfection in 293T cells (human embryonic kidney cells in origin; obtained from American Type Culture Collection, cat. no. CRL-11268) using a lentivirus backbone vector, a spike-expression plasmid, a TMPRSS2 expression plasmid and a firefly Luc reporter plasmid. A pre-titrated dose of pseudovirus was incubated with eight serial 5-fold dilutions of serum samples (1:10 start dilution) in duplicate in 96-well flat-bottom poly-L-lysine-coated culture plates (Corning, cat. no. 354516) for 1 hr at 37° C prior to adding 293T/ACE2 cells. One set of eight wells received cells + virus (virus control) and another set of eight wells received cells only (background control), corresponding to technical replicates. Luminescence was measured after 66-72 hr of incubation using Promega 1X lysis buffer (Promega, cat. no. E1531) and Bright-Glo luciferase reagent (Promega, cat. no. E2650). Neutralization titers are the inhibitory dilution of serum samples at which relative luminescence units (RLUs) were reduced by either 50% (ID50)

or 80% (ID80) compared to virus control wells after subtraction of background RLUs. Serum samples were heat-inactivated for 30 min at 56°C prior to assay.

Ethics

The Institutional IRB approval number for the use of human sera in the neutralization assay as described here is Pro00105358 (DUHS Institutional Review Board, 2424 Erwin Rd, Durham, NC, 919.668.5111, Federalwide Assurance No: FWA 00009025 Suite 405).

Bridging of binding antibody assay readouts and neutralizing antibody assay readouts to the WHO International Standard for anti-SARS-CoV-2 immunoglobulin

All serological assay readouts assessed as immune correlates were first expressed in assay values relative to the WHO International Standard for anti-SARS-CoV-2 immunoglobulin (*40*): spike bAbs and RBD bAbs were converted to Binding Antibody Units per ml (BAU/ml) and ID50 and ID80 nAb titers were calibrated to International Units/ml (IU/ml), yielding calibrated ID50 and ID80 titers expressed in units IU50/ml and IU80/ml, respectively (*40, 41*). Further details are provided below.

Conversion of AU/ml binding antibody readouts to BAU/ml. Recently the arbitrary units were bridged to the WHO International Standard (*41*) and a conversion factor was calculated and confirmed (see the Statistical Analysis Plan). Parallelism was established for all three antigens between the MSD provided reference standard and the WHO provided international standard. Concentration assignments were performed and then confirmed both at MSD and as part of a multi-site confirmation study. Sample results reported here have been converted to binding antibody units (BAU) per ml.

Calibration of ID50 and ID80 neutralization titers to International Units/ml (IU50/ml and IU80/ml). Results from the neutralization assay are reported as calibrated ID50 and calibrated ID80 titers, expressed in International Units/ml (IU50/ml and IU80/ml, respectively). The calibration was conducted for the First WHO International Standard for Anti-SARS-CoV-2 Immunoglobulin (20/136) in the SARS-CoV-2 spike-pseudotyped virus neutralization assay in 293T/ACE2 cells. The reagent is intended to be used in part to normalize neutralization titers across multiple SARS-CoV-2 neutralization assays (SOP CFAR02-A0026 "Measuring Neutralizing Antibodies Against SARS-CoV2 Using Pseudotyped Virus and 293T/ACE2 Cells" from the Duke Montefiori lab). The calibration work was performed by the "Neutralizing Antibody Core" Laboratory in the Surgical Oncology Research Facility, under the GCLP oversight of the Quality Assurance for Duke Vaccine Immunogenicity Programs (QADVIP).

Reagent description**.** In December 2020, the WHO released a well-characterized international standard for the purpose of improving comparability of results among different assays in different laboratories and reducing interlaboratory variability of anti-SARS-CoV-2 antibody assays (*40*). As described in the user instructions provided by the National Institute for Biological Standards and Controls (NIBSC): "The First WHO International Standard for anti-SARS-CoV-2 immunoglobulin is the freeze-dried equivalent of 0.25 mL of pooled plasma obtained from eleven individuals recovered from SARS-CoV-2 infection. The preparation was evaluated in a WHO International Collaborative study. The intended use of the International Standard is for the calibration and harmonization of serological assays detecting anti-SARS-

CoV-2 neutralizing antibodies. The preparation can also be used as an internal reference reagent for the harmonization of binding antibody assays. The preparation has been solvent-detergent treated to minimize the risk of the presence of enveloped viruses" (*41*).

Reagent preparation and storage**.** The reagent was shipped as a lyophilized powder by the NIBSC on December 23, 2020 and was received at Duke on January 4, 2021. A second shipment of the lyophilized reagent was received from the NIBSC on March 15, 2021. The reagent was stored at -80°C upon arrival. Each vial of lyophilized reagent was reconstituted with 0.25 mL of sterile distilled water (Invitrogen, Cat No. 10977015, Ultra-pure DNase, RNase free, Lot 2186762, Exp 30-Aug-2022) as described in the instruction packet (*41*) and stored at 4°C until use (no longer than 4 weeks).

Protocol and assay results**.** Neutralization assays were conducted in accordance with SOP CFAR02-A0026 "Measuring Neutralizing Antibodies Against SARS-CoV2 Using Pseudotyped Virus and 293T/ACE2 Cells" using the spike pseudotyped virus CoV-2 VRC7480.D614G.1[CMVΔR8.2]/293T/17. The assays were performed between January 5, 2021 and April 16, 2021 by four operators. All assays used either a 1:20 or 1:30 start dilution and a 5-fold dilution series for a total of 8 dilutions. One vial of the standard was reconstituted on January 5 and assayed once on each of 10 plates in a single setting by a single operator (EY) on January 5, 2021; the plates were read on January 8, 2021 (Exp ID EY18-134). These 10 assay results were described in Duke-02-MVR-COVID0001.2. In response to FDA/CBER recommendations (MF 026862, comments dated March 1, 2021), additional assays were performed over different operators and days to yield more precise estimates of the calibration factors. Additional vials of the reagent were reconstituted on March 20, 2021 and assayed in quadruplicate by two operators on two days, corresponding to technical replicates. A third operator assayed the reconstituted standard in quadruplicate on 3 days. All assays were set up within 24 days of reconstitution. The WHO assigned an arbitrary unitage of 250 IU/ampoule (1000 IU/mL) for neutralizing activity. For calibration purposes, ID50 and ID80 titers may be converted to IU50s and IU80s, respectively, by dividing 1000 IU/mL by either the mean, median or geometric mean ID50 and ID80 titer as a dilution factor. Thus, the calibration factor for mean ID50 is 1000 ÷ 4135 = 0.242. The calibration factor for mean ID80 is 1000 ÷ 666 = 1.502. The calibration factor for median ID50 is 1000 ÷ 2422 = 0.413. The calibration factor for median ID80 is 1000 ÷ 489 = 2.045. The calibration factor for geometric mean ID50 is 1000 ÷ 3047 = 0.328. The calibration factor for geometric mean ID80 is 1000 ÷ 567 = 1.764. The calibration factors are summarized below:

Summary values for WHO anti-SARS-CoV-2 IgG (20/136)

Virus: SARS-CoV-2 D614G Variant		**Calibration Factor**
Arithmetic mean ID50	4135	0.242
Arithmetic mean ID80	666	1.502
Median ID50	2422	0.413
Median ID80	489	2.045
Geometric Mean ID50	3047	0.328
Geometric Mean ID80	567	1.764

The three types of calibration factors (based on arithmetic mean, median, and geometric mean) were compared head-to-head on validation data from Day 29 and Day 57 ID50 and ID80 values from 30 recipients of the mRNA-1273 vaccine, with the common samples conducted by both the Duke Montefiori neutralization assay used for the COVE trial immune correlates study and the Monogram PhenoSense neutralization assays. The results showed that using arithmetic mean of the WHO IS sample for calibration yielded the highest agreement between the calibrated vaccine responses from the two labs, based on the concordance correlation coefficient (manuscript in preparation). Based on this validation experiment, the arithmetic mean calibration factors were selected for use in reporting results in terms of ID50 and ID80 (expressed in IU50/ml and IU80/ml, respectively).

Statistical methods

All data analyses were pre-specified in the Statistical Analysis Plan (SAP), available in the Supplementary Material. Two separate correlates analyses were done, which assessed the antibody markers measured at Day 29 or at Day 57 as correlates. These time points were selected for antibody measurement in both being scheduled 28 days post previous dose, and Day 57 was presumed to be when antibodies approximately peak and have wide inter-vaccinee variability.

Case-cohort sets included in correlates analyses

Through a case-cohort sampling design, participants were randomly sampled for antibody marker measurement at Day 1, 29, 57 (*42*). Without replacement stratified sampling was used, with 24 strata defined by randomization arm cross-classified by baseline SARS-CoV-2 positivity, protocol randomization strata (age below 65 years at risk, age below 65 years not at risk, age above 65 years), and minority status. "At risk" refers to participants believed to be at increased risk of severe COVID-19 illness and comprised six self-reported health/comorbidities, as in Baden et al (*6*). "Minority" includes Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders. Non-Minority includes all other races with observed race (Asian, Multiracial, White, Other) and observed ethnicity Not Hispanic or Latino. The sampling design oversampled baseline negative vaccine recipients and minorities, to improve power and ensure characterization of immunogenicity in minorities (see the SAP for details). In addition, the antibody markers were measured at Day 1, 29, 57 in all vaccine recipients with a breakthrough COVID-19 endpoint. Data analyses restricted to participants with no immunologic or virologic evidence of prior COVID-19 (negative nasopharyngeal swab test and/or anti-nucleocapsid binding antibodies below the limit of detection or the lower limit of quantification at Day 1; see table S3 for assay limits), as in Baden et al. (*6*), and per-protocol, i.e. received both doses without major protocol violations (see footnote 3 of fig. S2); we refer to these qualifying participants as baseline negative per-protocol participants. The "immunogenicity subcohort" is the subset of the randomly sampled participants who have antibody marker data at Day 1, 29, and 57 (N = 1010 vaccine recipients, N = 137 placebo recipients), which is almost 100% of sampled participants (fig. S1).

Correlates analyses for each marker time point were based on segregating vaccine recipients into non-cases vs. vaccine breakthrough cases, where the two analyses used the same set of non-cases: the subset of the immunogenicity subcohort who were baseline negative per-protocol and never had any evidence of SARS-CoV-2 infection (N=1005 vaccine recipients). The vaccine breakthrough case sets differed, defined based on "intercurrent endpoints" that start 7 days post Day 29 through 6 days post Day 57 and "post Day 57 endpoints" that start 7 days post Day 57 (fig. S3). Day 29 marker analyses included all intercurrent endpoints and all post Day 57 endpoints with antibody data at Day 1 and 29 (N=46 cases), and Day 57 marker analyses included all post Day 57 endpoints with antibody data at Day 1, 29, and 57 (N=36 cases) (fig. S1). The "Day 29 case-cohort set" included in Day 29 marker analyses comprised baseline negative per-protocol vaccine recipients in the immunogenicity subcohort plus the qualifying baseline negative per-protocol vaccine breakthrough cases, and the "Day 57 case-cohort set" included in Day 57 marker analyses was the same except intercurrent endpoints were excluded (table S2). The correlates analyses included follow-up through to the last pre-unblinding vaccine breakthrough endpoint post Day 29 and post Day 57, which were 126 and 100 days, respectively.

For each antibody marker, values below the assay limit of detection (LOD) were set to LOD/2, and values above the upper limit of quantitation (ULOQ) were set to ULOQ. Positive response for each marker is defined in Fig. 1 and table S3. Positive response rates were estimated by an IPS-weighted average, with 95% confidence interval (CI) calculated with an IPS-weighted Clopper-Pearson method. Differences in response rates with 95% CIs were calculated by the Wilson-Score method without continuity correction (*43*). Geometric mean concentration (GMC) or titer (GMT) and their ratios between cases vs. non-cases were estimated with 95% CIs based on the t-distribution with IPS weighting.

Covariate-adjustment

All correlates analyses adjusted for baseline variables prognostic for COVID-19: at risk status, membership in a community of color (all persons other than White Non-Hispanic), and the logit of predicted COVID-19 risk score built from machine learning of placebo arm participants (supplementary text S1).

Correlates of risk in vaccine recipients

For each marker, IPS-weighted Cox regression was applied to estimate the covariate-adjusted hazard ratio of COVID-19 across marker tertiles or per 10-fold increase in the quantitative marker level with 95% CIs and Wald-based p-values. The Cox model fits were used to estimate marker-conditional cumulative incidence of COVID-19 in the population of per-protocol baseline negative vaccine recipients, with 95% CIs computed using the bootstrap. The Cox models were fit using the *survey* R package (*44*). Additional analyses estimated the same quantity with a generalized additive model with degrees of freedom selected by generalized cross-validation (*45*), and by nonparametric targeted minimum loss-based threshold regression (*46*).

Correlates of protection: controlled vaccine efficacy and mediation

Vaccine efficacy by marker level was estimated by a causal inference approach implemented using the same IPS-weighted Cox regression described above for the vaccine arm, combined with unweighted Cox regression for the entire baseline SARS-CoV-2 negative per-protocol placebo arm (details in SAP Section 12.1.1). The analysis of the placebo arm ignored

antibody marker data given that all values were negative / undetectable given the absence of exposure to SARS-CoV-2 antigens (*28*) (see SAP). A sensitivity analysis was conducted to assess robustness of the results to unmeasured confounding of the effect of the antibody marker on COVID-19 (supplementary text S2 and SAP Section 12.1.2) (*28*). In addition, for each antibody marker with at least 10% of vaccinated participants with value the same as for placebo recipients, i.e., negative for IgG markers or undetectable for neutralization markers, the proportion of vaccine efficacy mediated by the antibody marker was estimated (*30*). (Availability of sufficient overlap in the vaccine and placebo arms is technically required for feasibility of median analysis, as detailed in the SAP.)

Hypothesis testing

All p-values were two-sided. For each set of hypothesis tests for Day 29 and Day 57 marker correlates of risk separately, Westfall-Young multiplicity adjustment (*47*) was applied to obtain false-discovery rate adjusted p-values and family-wise error rate adjusted p-values.

Calibration of ID50 and ID80 titers between the Duke neutralization assay on COVE trial samples and the Monogram PhenoSense neutralization assay performed on AstraZeneca COV002 samples

Using the WHO First Anti-SARS CoV-2 Immunoglobulin International Standard (20/136): 1000 IU/mL, PhenoSense SARS CoV-2 nAb titers can be converted to IU50/ml or IU80/ml by multiplying the nAb titer (ID50 or ID80) by the appropriate conversion factor, where conversion factors were estimated both for the D614 pseudovirus vaccine strain and for the D614G pseudovirus mutation strain. For each strain, conversion factors were calculated using the mean, geometric mean and median based on 24 replicate tests of the 20/136 standard (6 replicates per day x 4 days). Based on the validation data noted above the arithmetic mean conversion factor was used. For the D614 strain, the conversion factors for ID50 and ID80 were 0.1428 and 0.4585, respectively. For the D614G strain, the conversion factors for ID50 and ID80 were 0.0653 and 0.2281, respectively. In the main article, these conversion factors were first applied as follows: the ID50 values reported in Table 2 of Feng et al. (*19*) (COV002 immune correlates results) corresponding to 70% and 90% estimated vaccine efficacy were multiplied by 0.1428, where the D614 strain factor was used because the AZD12222 performed the Monogram PhenoSense pseudovirus neutralization assay on participant samples using the D614 strain. Specifically, the ID50 values 57, 183, 982, 303 reported in Table 2 of Feng et al. were each multiplied by 0.1428 to obtain ID50 values (in IU50/ml) 8, 26, 140, 43, respectively; these values are reported in the main article.

Sensitivity analysis comparing correlate of protection results between COV002 and COVE

The neutralization assays employed for COV002 and COVE used the D614 and D614G pseudovirus, respectively, such that this comparison is affected by any difference in neutralization sensitivity of these two strains. Therefore, we also performed a sensitivity analysis that assumes that D614G is more sensitive to neutralization by vaccine recipient sera than D614. The multiplicative factor defining more sensitive was taken to be (0.1428/0.0653) = 2.19, the ratio of conversion factors (D614 vs. D614G) calculated in the Monogram study that defined the conversion factors. This factor was applied to each ID50 value from the AZD12222 study, which means that each AZD12222 ID50 value on its original scale was multiplied by 0.1428*2.19 = 0.31. Therefore, in this sensitivity analysis, the ID50 values 57, 183, 982, 303

reported in Table 2 of Feng et al. were each multiplied by 0.31 to obtain the ID50 (in IU50/ml) values 18, 57, 307, 95, respectively. According to this sensitivity analysis, estimated AZD1222 vaccine efficacy in COV002 was 70% and 90% at ID50 titer of 18 (< LOD = 2.42, 57) and 307 (95, NC) IU50/ml, respectively.

Software and data quality assurance

The analysis was implemented in R version 4.0.3; code was verified using mock data.

Research reproducibility approach

All analyses were done reproducibly based on R scripts hosted at the Github code repository, which are publicly available with application to a mock COVE trial data set. The code is available at: https://zenodo.org/record/5593130#.YXLhQ0X3bDs (*38*).

Table S1. Demographics and clinical characteristics of baseline SARS-CoV-2 negative per-protocol trial participants in the immunogenicity subcohort and thus have Day 1, 29, 57 antibody marker data.

Characteristics	Vaccine (N = 1010)	Placebo (N = 137)	Total (N = 1147)
Age			
Age < 65	670 (66.3%)	91 (66.4%)	761 (66.3%)
Age ≥ 65	340 (33.7%)	46 (33.6%)	386 (33.7%)
Mean (Range)	54.6 (18.0, 87.0)	53.4 (19.0, 85.0)	54.4 (18.0, 87.0)
BMI			
Mean ± SD	30.9 ± 7.6	31.3± 9.0	30.9± 7.8
Risk for Severe COVID-19			
At-risk	396 (39.2%)	57 (41.6%)	453 (39.5%)
Not at-risk	614 (60.8%)	80 (58.4%)	694 (60.5%)
Age, Risk for Severe COVID-19			
Age < 65 At-risk	291 (28.8%)	40 (29.2%)	331 (28.9%)
Age < 65 Not at-risk	379 (37.5%)	51 (37.2%)	430 (37.5%)
Age ≥ 65	340 (33.7%)	46 (33.6%)	386 (33.7%)
Sex Assigned at Birth			
Female	476 (47.1%)	63 (46.0%)	539 (47.0%)
Male	534 (52.9%)	74 (54.0%)	608 (53.0%)
Hispanic or Latino Ethnicity			
Hispanic or Latino	322 (31.9%)	44 (32.1%)	366 (31.9%)
Not Hispanic or Latino	685 (67.8%)	93 (67.9%)	778 (67.8%)
Not reported and unknown	3 (0.3%)	0 (0.0%)	3 (0.3%)
Race			
White	735 (72.8%)	99 (72.3%)	834 (72.7%)
Black or African American	182 (18.0%)	24 (17.5%)	206 (18.0%)
Asian	25 (2.5%)	6 (4.4%)	31 (2.7%)
American Indian or Alaska Native	17 (1.7%)	2 (1.5%)	19 (1.7%)
Native Hawaiian or Other Pacific Islander	5 (0.5%)	0 (0.0%)	5 (0.4%)
Multiracial	12 (1.2%)	4 (2.9%)	16 (1.4%)
Other	25 (2.5%)	2 (1.5%)	27 (2.4%)
Not reported and unknown	9 (0.9%)	0 (0.0%)	9 (0.8%)
White Non-Hispanic	468 (46.3%)	61 (44.5%)	529 (46.1%)
Communities of Color	542 (53.7%)	76 (55.5%)	618 (53.9%)

This table summarizes the baseline SARS-CoV-2 negative per-protocol immunogenicity subcohort, which was randomly sampled within 12 strata defined by enrollment characteristics: Assigned treatment arm × Baseline SARS-CoV-2 naïve vs. non-naïve status (defined by serostatus and NAAT testing) × Randomization strata (Age < 65 and at-risk, Age < 65 and not at-risk, Age ≥ 65)× Minority status (Minority vs. Non-minority) defined by White Non-Hispanic vs. all others [same as in (*6*)]. "At Risk" refers to participants believed to be at increased risk of severe COVID-19 illness and comprised six self-reported health/comorbidities, as in (*6*). "Minority" includes Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders. Non-Minority includes all other races with observed race (Asian, Multiracial, White, Other) and observed ethnicity Not Hispanic or Latino. Numbers and percentages are based on inverse probability of sampling weighting.

Table S2. Sample sizes of baseline SARS-CoV-2 negative per-protocol vaccine recipients included in immune correlates analyses, by baseline sampling strata and case/non-case strata.

Day 29 marker case-cohort set = Baseline negative per-protocol vaccine recipients included in Day 29 marker correlates analyses (in the immunogenicity subcohort and/or an intercurrent case or a post Day 57 case)

Day 57 marker case-cohort set = Baseline negative per-protocol vaccine recipients included in Day 57 marker correlates analyses (in the immunogenicity subcohort and/or a post Day 57 case)

	Baseline Sampling Strata[1] of SARS-CoV-2 Negative Per-Protocol Vaccine Recipients Included in Correlates Analyses						
	1	2	3	4	5	6	Total
Intercurrent Cases	0	2	0	0	4	4	10
Post Day 57 Cases	1	4	2	8	5	16	36
Breakthrough cases included in Day 29 marker correlates analyses	1	6	2	8	9	20	46
Breakthrough cases included in Day 57 marker correlates analyses	1	4	2	8	5	16	36
Non-Cases in Immunogenicity Subcohort	171	168	143	146	188	189	1005

[1]Demographic covariate strata: 1. Age ≥ 65 Minority; 2. Age ≥ 65 Non-Minority; 3. Age < 65 At-risk Minority; 4. Age < 65 At-risk Non-Minority; 5. Age < 65 Not At-risk Minority; 6. Age < 65 Not At-risk Non-Minority. Minority includes Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders. Non-Minority includes all other races with observed race (Asian, Multiracial, White, Other) and observed ethnicity Not Hispanic or Latino. Participants not classifiable as Minority or Non-Minority because of unknown, unreported, or missing information were not included.

Cases for Day 29 marker correlates analyses are baseline SARS-CoV-2 negative per-protocol vaccine recipients with the symptomatic infection COVID-19 primary endpoint diagnosed starting 7 days after Day 29 through the end of the blinded phase. Cases for Day 57 marker correlates analyses are baseline SARS-CoV-2 negative per-protocol vaccine recipients with the symptomatic infection COVID-19 primary endpoint diagnosed starting 7 days after Day 57 through the end of the blinded phase. Non-cases are baseline SARS-CoV-2 negative per-protocol participants sampled into the immunogenicity subcohort with no COVID-19 endpoint through the end of the blinded phase and no evidence of SARS-CoV-2 infection up to six days post Day 57.

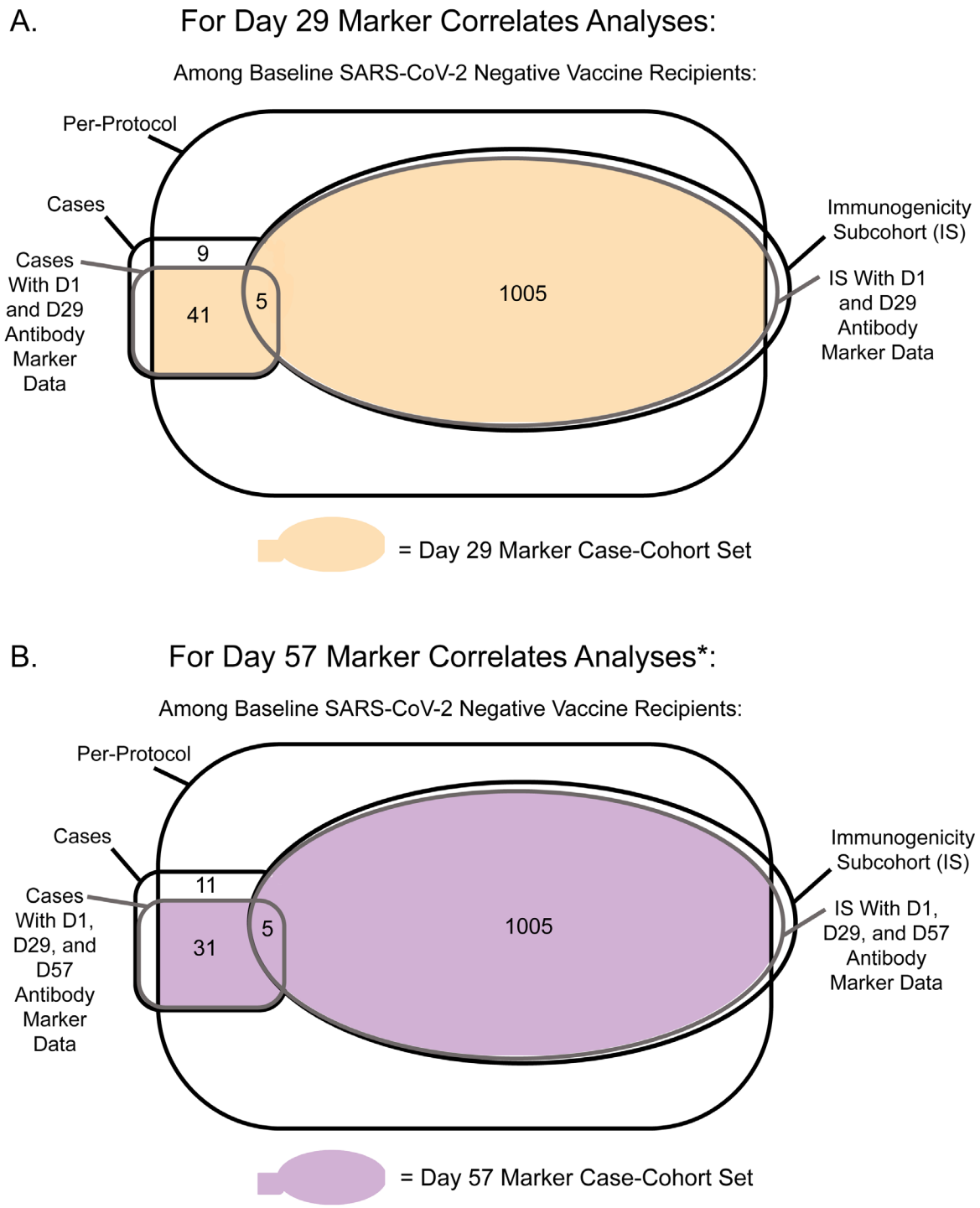
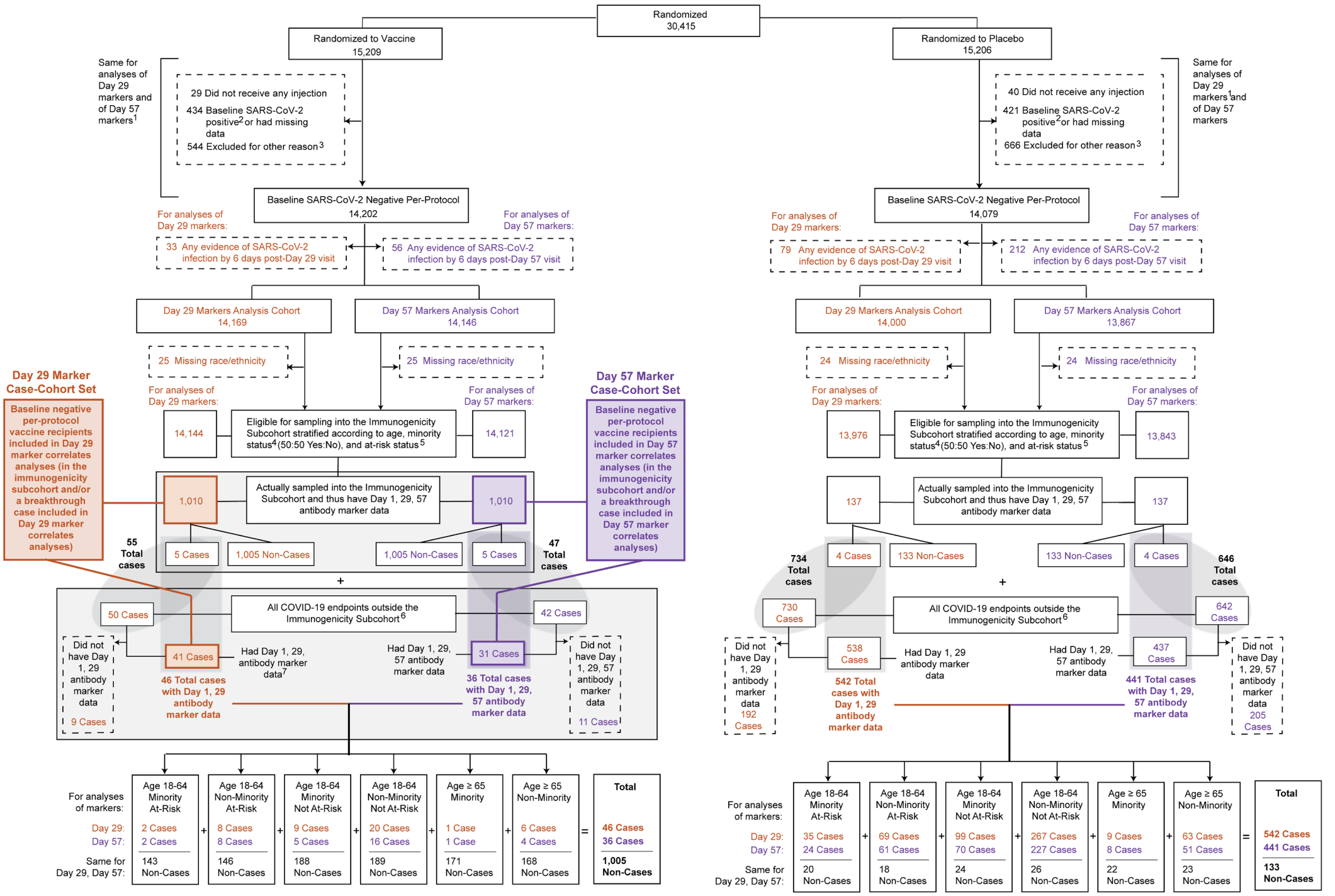


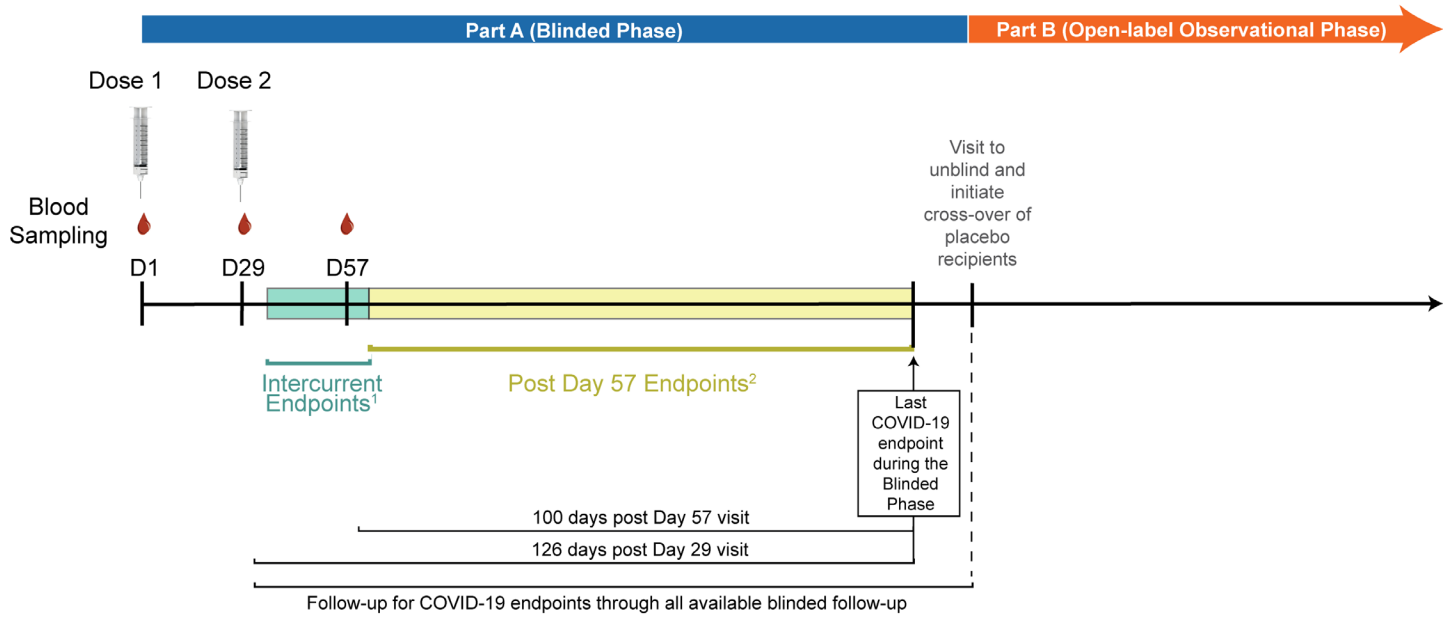
Fig. S1. (A) Day 29 marker case-cohort set and (B) Day 57 marker case-cohort set.



1 If a participant had multiple reasons for exclusion from the Per-Protocol Set, they were only counted in the earliest-listed reason.
2 Baseline SARS-CoV-2 positive is defined as immunologic or virologic evidence of prior COVID-19 (i.e. a positive nasopharyngeal swab and/or binding antibodies against SARS-CoV-2 nucleocapsid above the limit of detection or above the lower limit of quantification) at Day 1 before the first dose of investigational product (same definition as in Baden et al. 2021).
3 The other reasons for exclusion were: did not receive second dose; received incorrect vaccine; received dose 2 out of window; other major protocol deviations; were living with HIV; adjudicated COVID-19 cases up to Day 29 visit (dose 2 date).
4 Minority includes Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders. Non-Minority includes all other races with observed race (Asian, Multiracial, White, Other) and observed ethnicity Not Hispanic or Latino.
5 Participants 18-64 were categorized as "At-Risk" (of severe COVID-19 illness) if they had at least one of the following risk factors: chronic lung disease (e.g., emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, cystic fibrosis, or moderate-to-severe asthma); cardiac disease (e.g., heart failure, congenital coronary artery disease, cardiomyopathies, or pulmonary hypertension); severe obesity (BMI ≥40); diabetes (type 1, type 2, or gestational); liver disease; or HIV infection (same as in Baden et al. 2021).
6 Correlates analyses of Day 29 markers start counting COVID-19 endpoints at 7 days post Day 29 visit, and correlates analyses of Day 57 markers start counting COVID-19 endpoints at 7 days post Day 57 visit.
7 For Day 29 marker correlates analyses, intercurrent cases may not have Day 57 antibody data, as Day 57 antibody data are not used.

Fig. S2. Flowchart of study participants from enrollment to the Day 29 and Day 57 case-cohort sets of baseline SARS-CoV-2 negative per-protocol participants. Antibody data from the placebo arm are not used in correlates analyses, given no variability in values; they were only used to verify low false positive rates of the immunoassays.

For Baseline Negative Per-Protocol recipients of two doses of mRNA-1273:



[1]Intercurrent Endpoints: ≥ 7 days post Day 29 visit through 6 days post Day 57 visit; used in Day 29 marker correlates analyses only

[2]Post Day 57 Endpoints: ≥ 7 days post Day 57 visit through the end of the Blinded Phase (last COVID-19 endpoint in the Blinded Phase occurred at 126 days Post Day 29 visit); used in Day 29 and in Day 57 marker correlates analyses

Counting of Intercurrent Endpoints started ≥ 7 days post Day 29 visit to help ensure that the endpoint did not occur before Day 29 antibody measurement; counting of Post Day 57 Endpoints started ≥ 7 days post Day 57 visit to help ensure that the endpoint did not occur before Day 57 antibody measurement.

Fig. S3. Phases of the COVE trial, timing of mRNA-1273 doses and blood sampling, and the two time periods for diagnosis of COVID-19 endpoints ("Intercurrent" and "Post Day 57"). The schematic applies to baseline SARS-CoV-2 negative per-protocol recipients of two doses of mRNA-1273. During Part A (Blinded Phase) of the trial, participants were blinded to treatment assignment. After issuance of the Emergency Use Authorization from the US FDA on Dec 18, 2020, the trial entered Part B (Open-Label Observational Phase), where participants could choose to be unblinded; those assigned to placebo could opt to receive two doses of mRNA-1273 vaccine.

Table S3. Meso-Discovery (MSD) and pseudovirus neutralization assay limits of the four antibody markers evaluated as immune correlates.

	MSD Binding Assay (VRC)			PsV nAb (Duke)	
Reported units	BAU/ml*			IU50/ml (ID50); IU80/ml (ID80)**	
	Spike	RBD	N	ID50	ID80
Positivity Cutoff	10.8424	14.0858	23.5	2.42	15.02
LOD	0.3076	1.5936	0.09	2.42	15.02
LLOQ	1.7968	3.43	4.49	4.477	21.4786
ULOQ	10,155.95	16,269	575	10919	15368

*AU/ml units converted to BAU/ml units for all data analysis.

**Original titers calibrated to the WHO anti-SARS-CoV-2 immunoglobulin International Standard (NIBSC code: 20/136) for all data analyses (*41*). ID50 = ID50 titer in IU50/ml; ID80 = ID80 titer in IU80/ml.

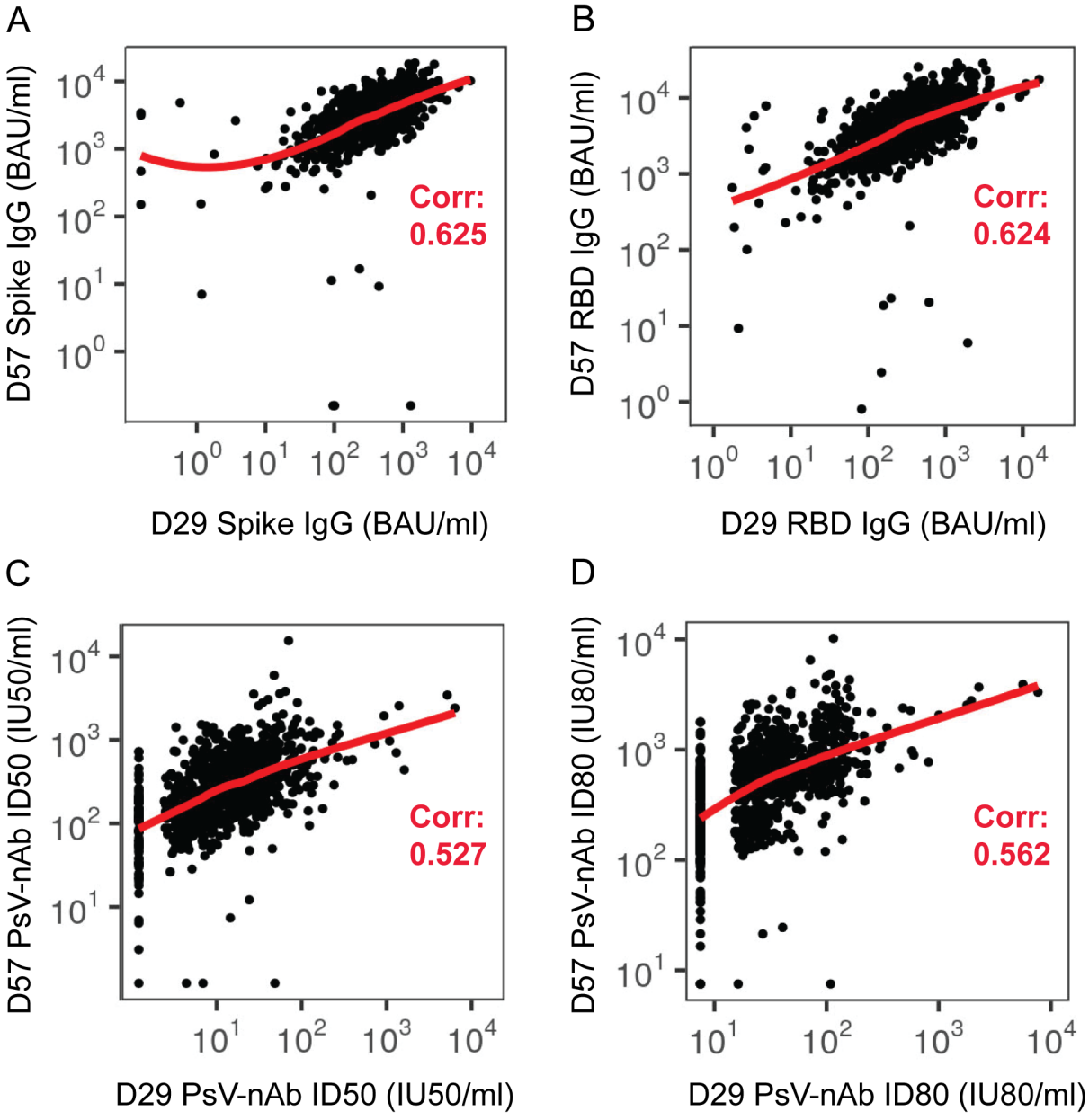


Fig. S4. For each antibody marker, correlations of Day 29 levels with Day 57 levels in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. Corr = baseline variable adjusted IPS-weighted Spearman rank correlation. PsV, pseudovirus.

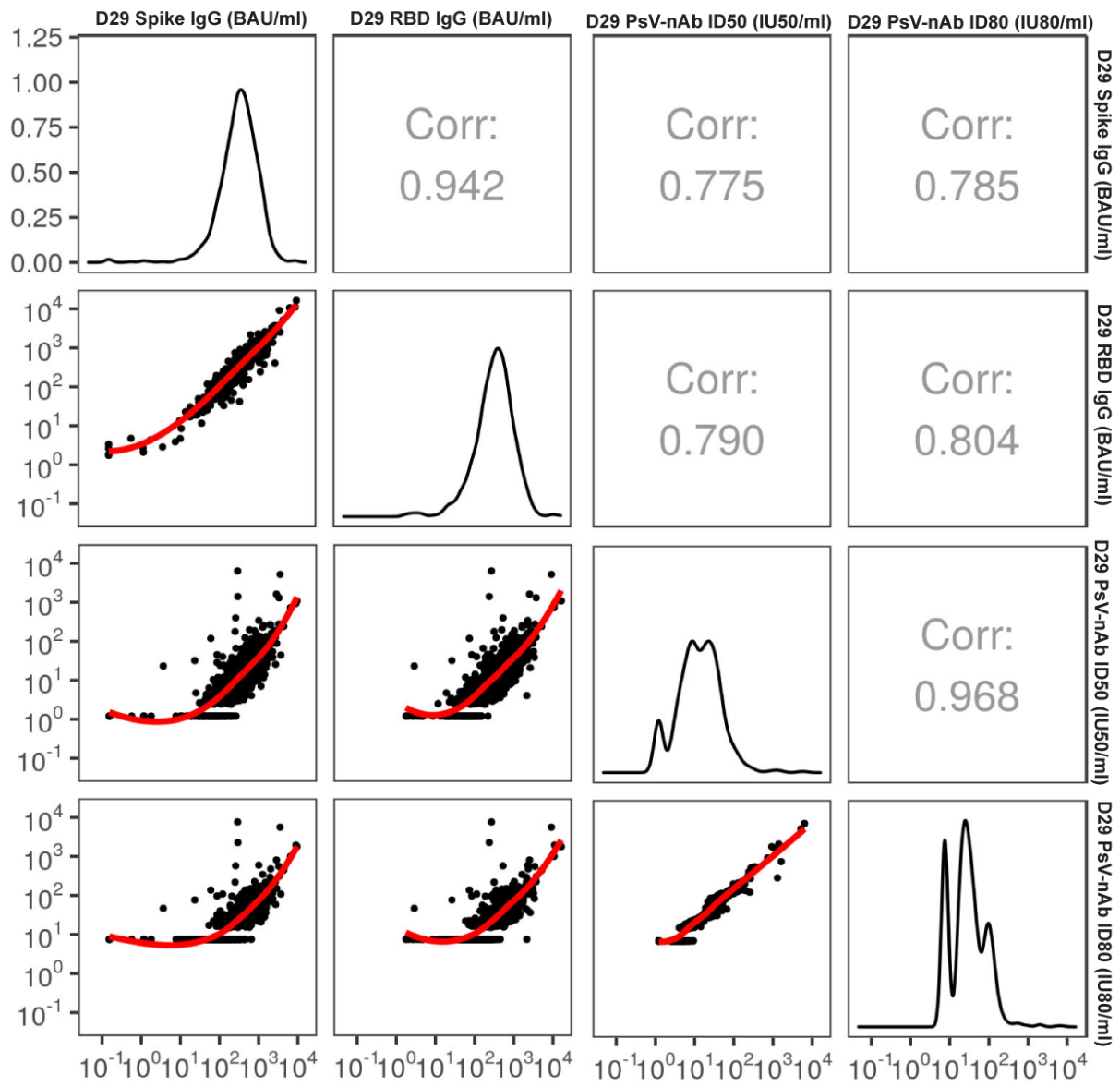


Fig. S5. Correlations of Day 29 antibody markers in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. Corr = baseline variable adjusted Spearman rank correlation. PsV, pseudovirus.

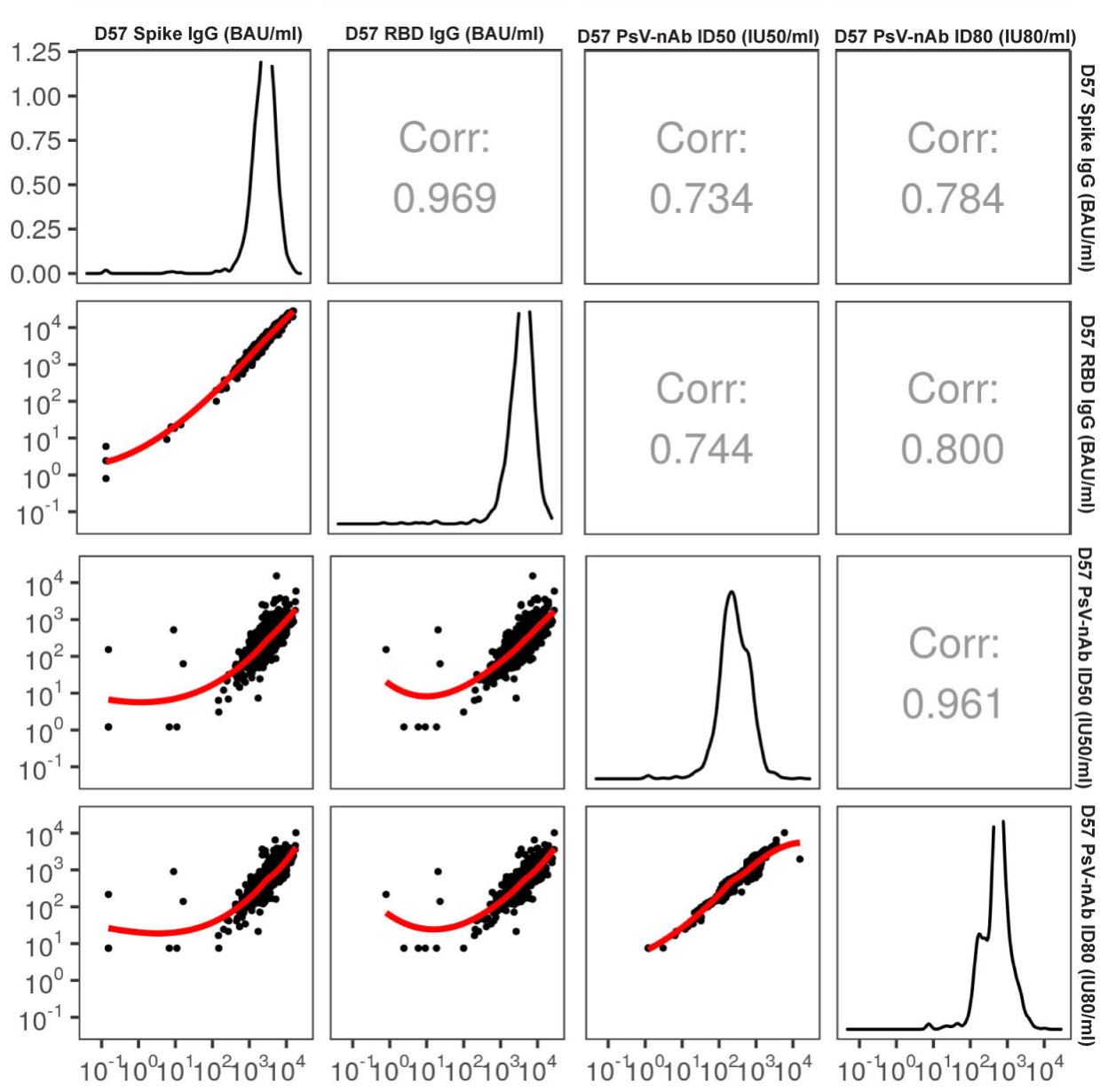


Fig. S6. Correlations of Day 57 antibody markers in baseline SARS-CoV-2 negative per-protocol vaccine recipients in the immunogenicity subcohort. Corr = baseline variable adjusted Spearman rank correlation. PsV, pseudovirus.

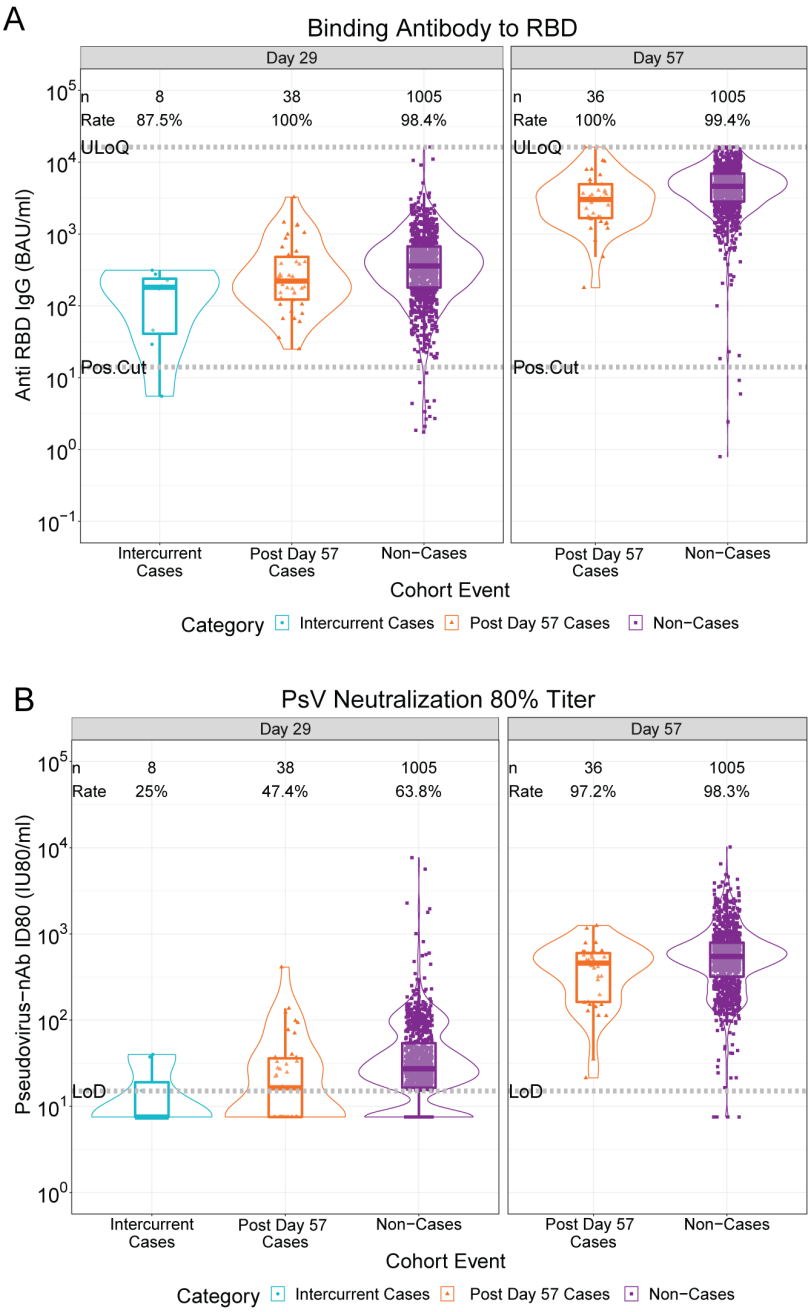


Fig. S7. A) Anti-RBD IgG concentration and B) pseudovirus neutralization ID80 titer by COVID-19 outcome status. Data points are from baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 29 marker or Day 57 marker case-cohort sets. Pos.Cut, Positivity cut-off. LoD, limit of detection. ULoQ, upper limit of quantitation; ULOQ = 15,368 for ID80 (above all data points). Post Day 57 cases are COVID-19 endpoints starting 7 days post Day 57; Intercurrent cases are COVID-19 endpoints starting 7 days post Day 29 through 6 days post Day 57.

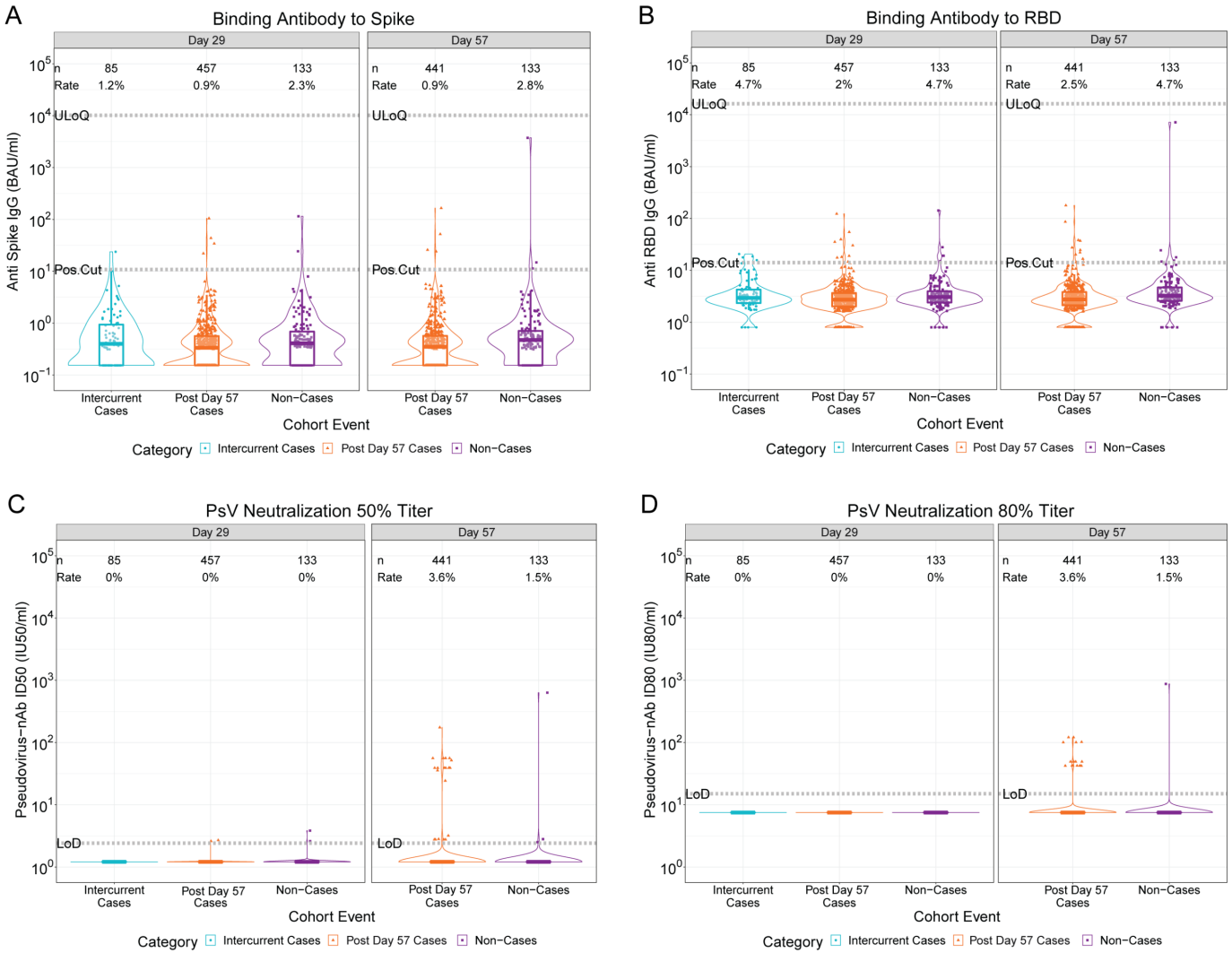


Fig. S8. Marker values (spike IgG, RBD IgG, ID50, ID80) by COVID-19 outcome status in placebo recipients. Data points are from baseline SARS-CoV-2 negative per-protocol placebo recipients in the Day 29 marker or Day 57 marker case-cohort set. Positive response rates are computed with Inverse Probability Sampling (IPS) weighting. Pos.Cut, Positivity cut-off. LoD, limit of detection. ULoQ, upper limit of quantitation.

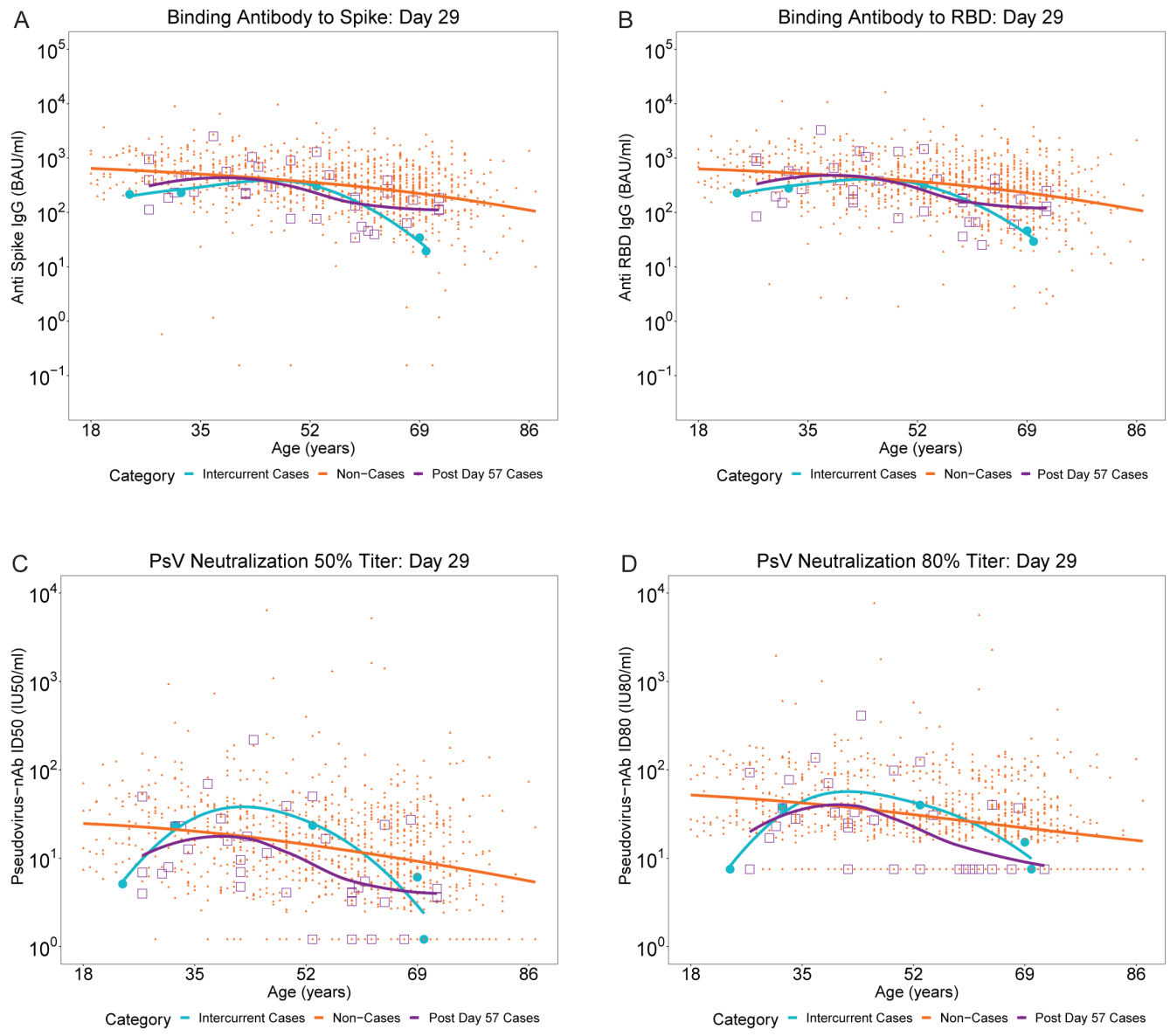


Fig. S9. Day 29 marker data points from baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 29 marker case-cohort set. Non-cases are represented by orange dots, intercurrent cases by large blue circles, and post Day 57 cases by large purple squares.

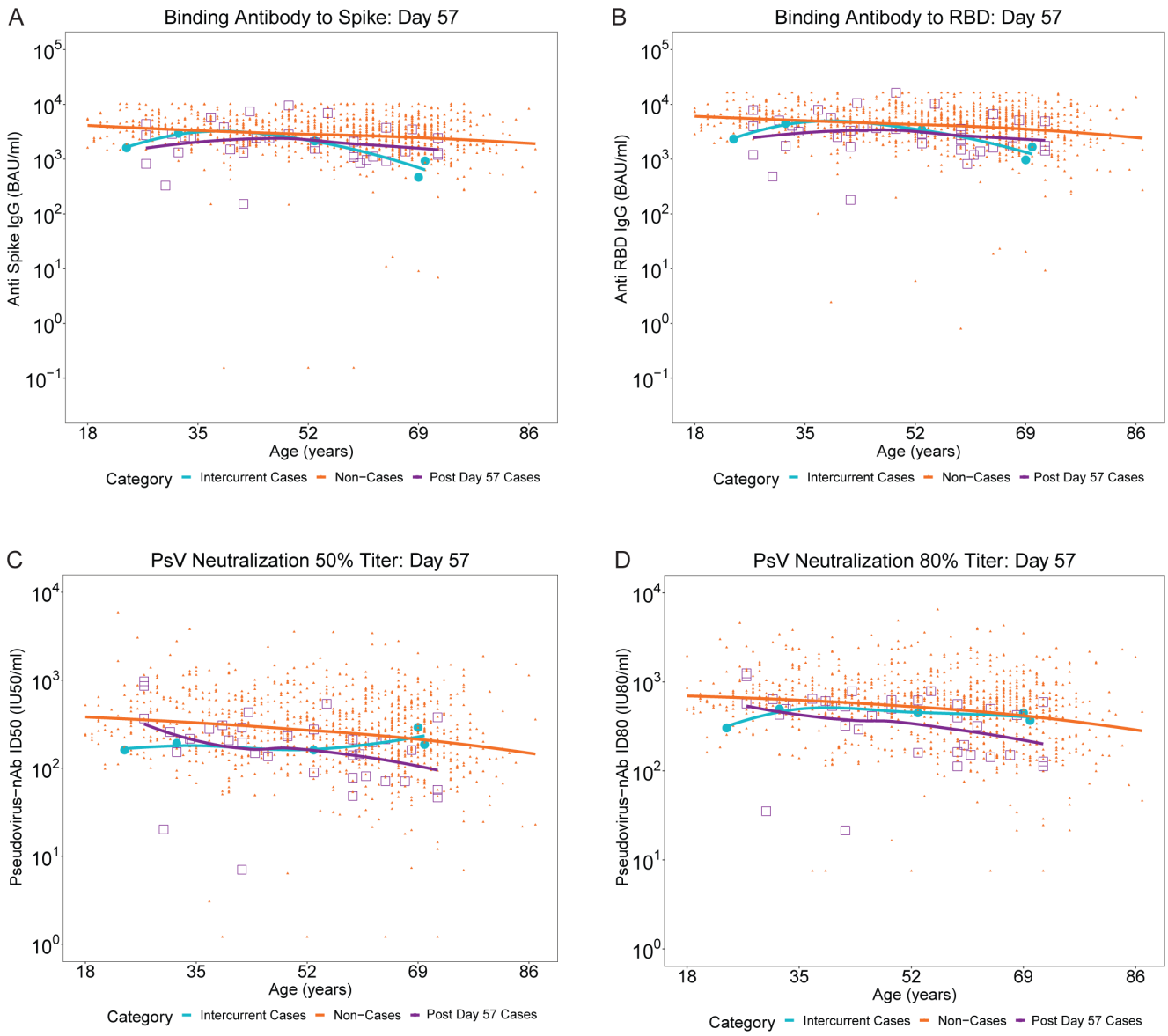


Fig. S10. Day 57 marker data points from baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 57 marker case-cohort set. Non-cases are represented by orange dots, intercurrent cases by large blue circles, and post Day 57 cases by large purple squares.

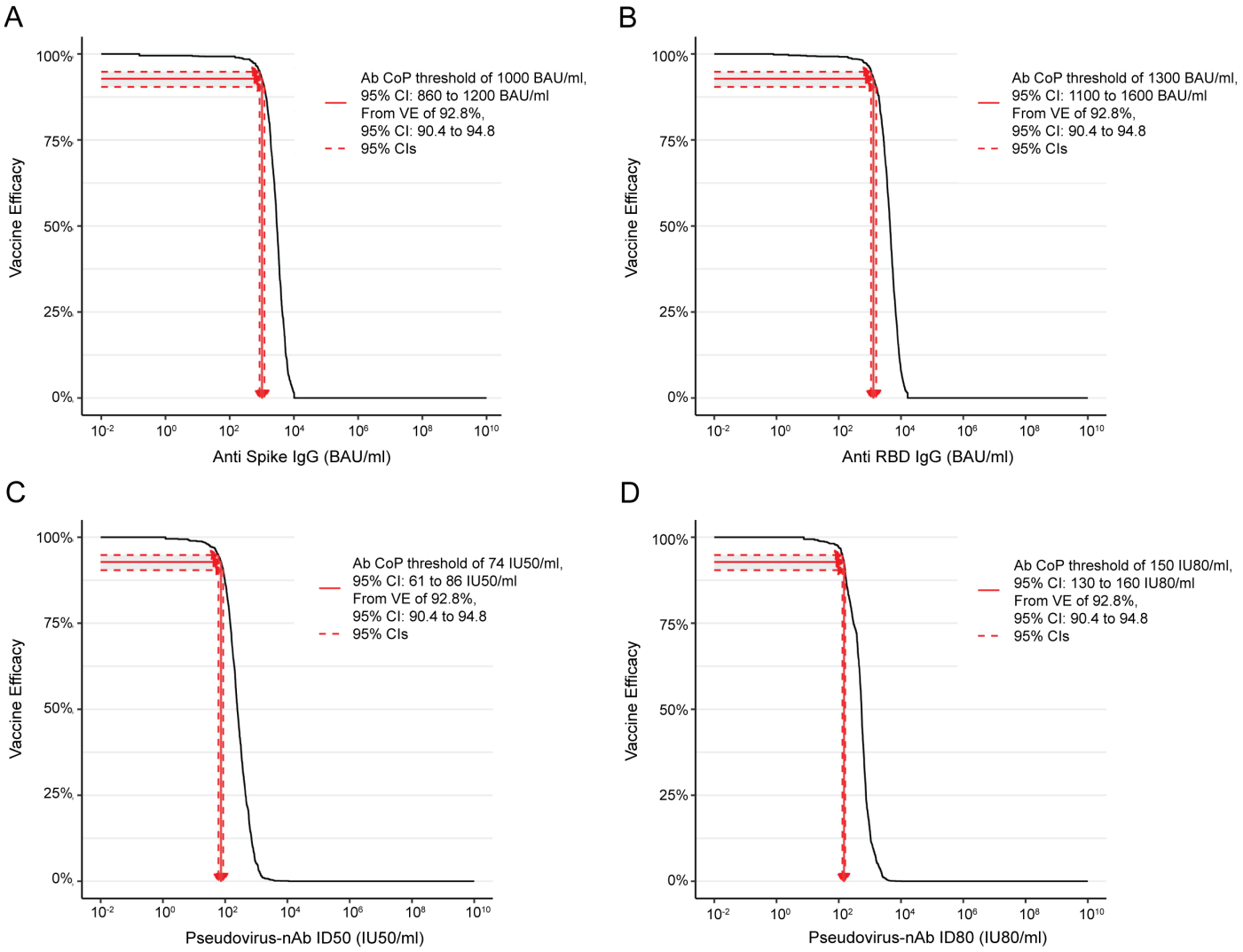


Fig. S11. Inverse probability sampling (IPS)-weighted empirical reverse cumulative distribution function curves for each Day 57 marker (spike IgG, RBD IgG, ID50, ID80) and application of the Siber (2007) method (*27*) for estimating a threshold of perfect vs. no protection.

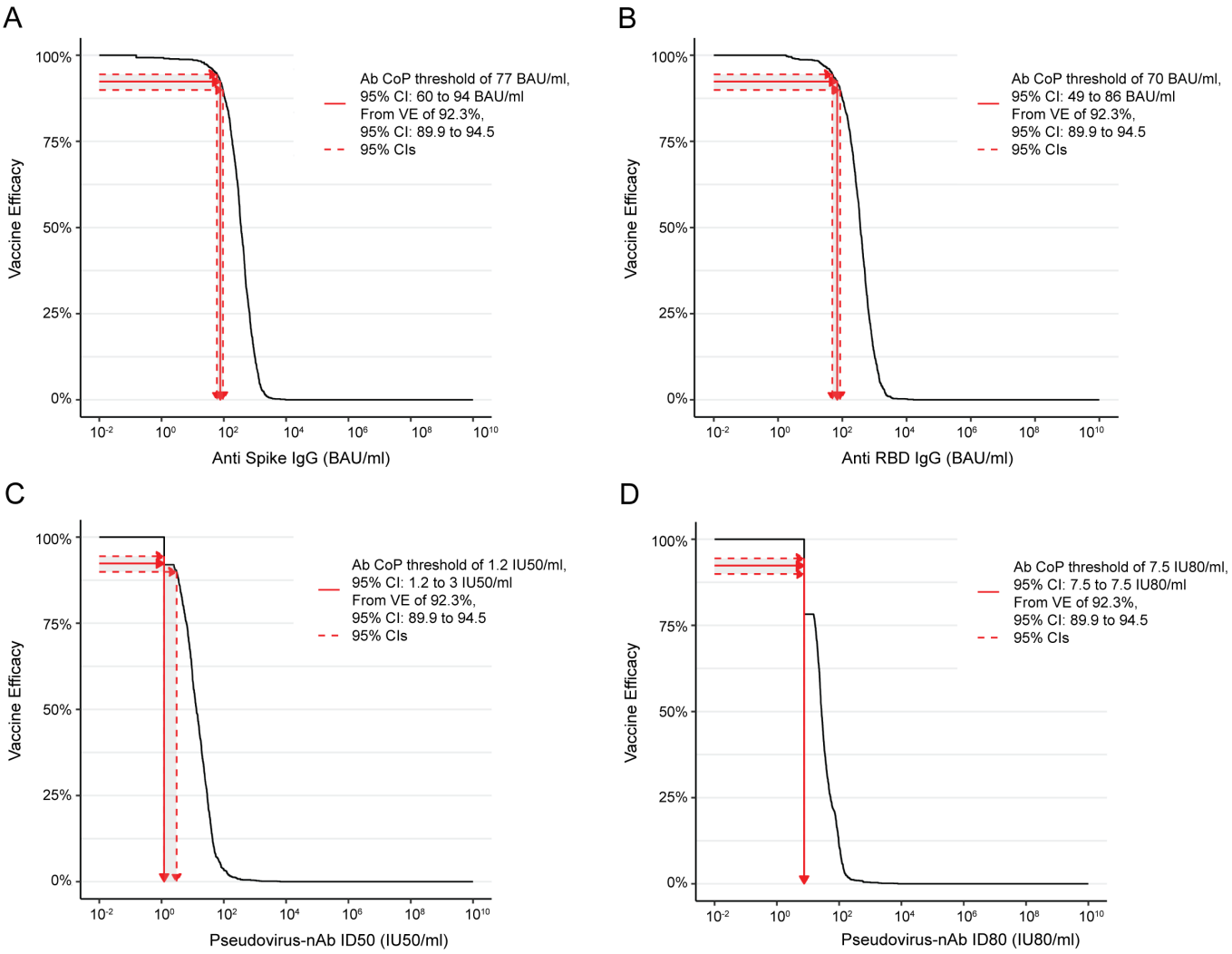


Fig. S12. Inverse probability sampling (IPS)-weighted empirical reverse cumulative distribution function curves for each Day 29 marker (spike IgG, RBD IgG, ID50, ID80) and application of the Siber (2007) method (*27*) for estimating a threshold of perfect vs. no protection.

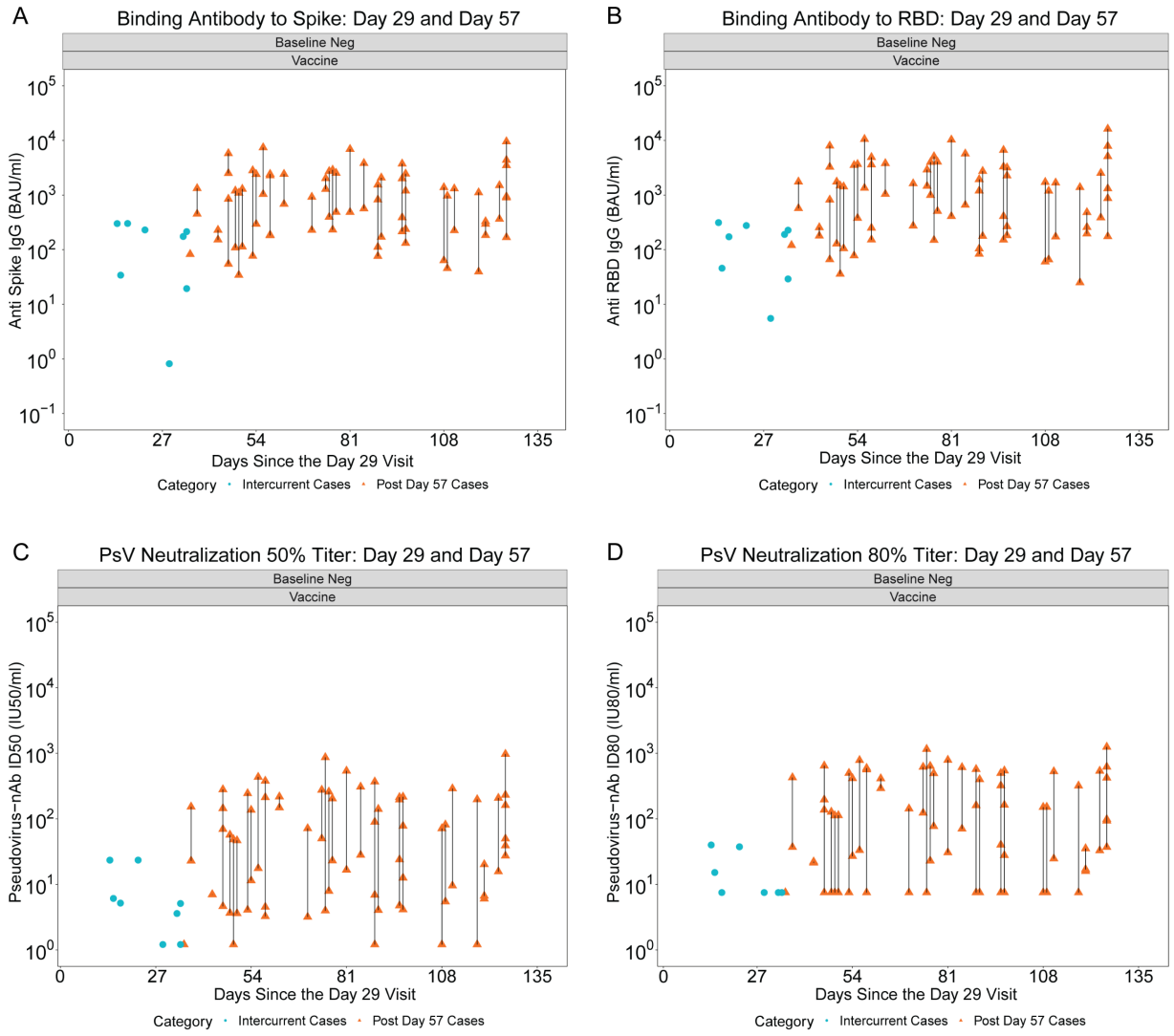
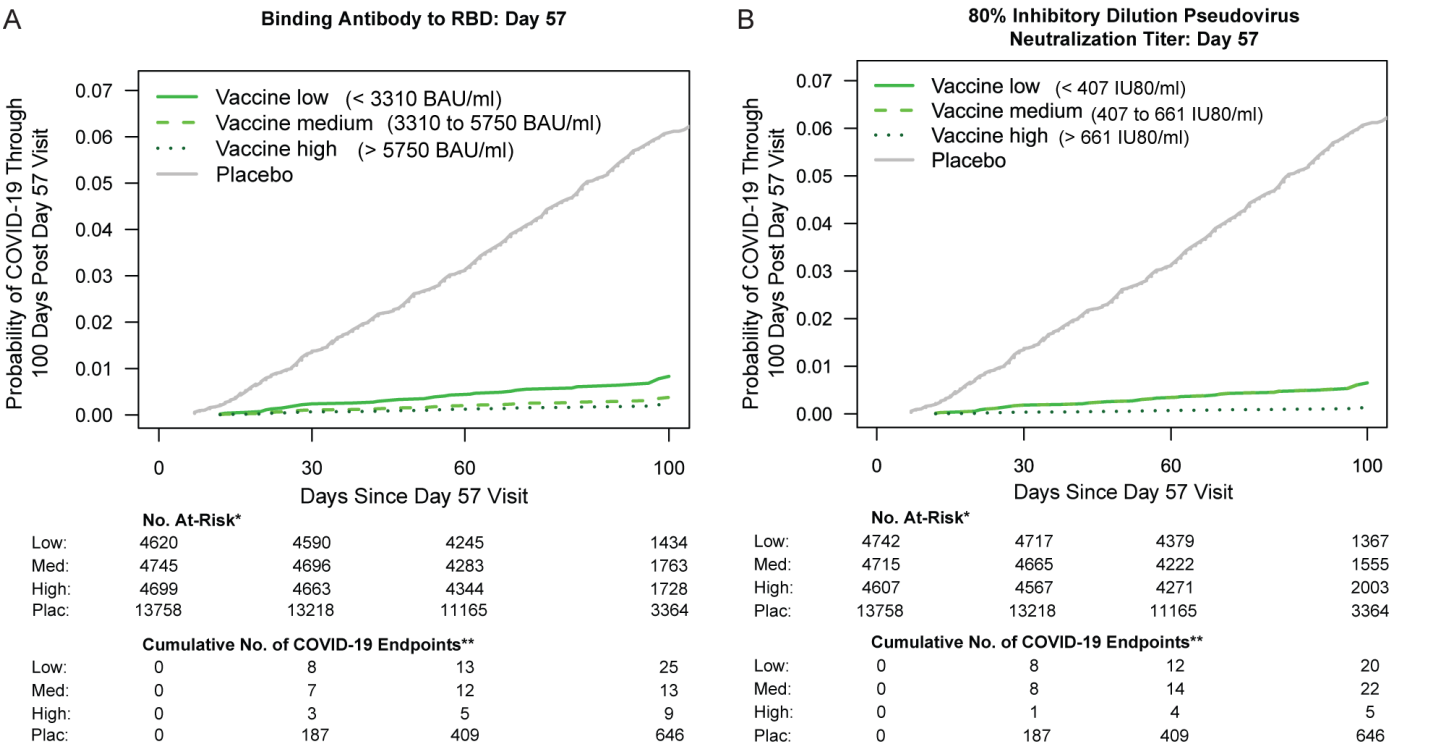


Fig. S13. Day 29 and Day 57 antibody markers (spike IgG, RBD IgG, ID50, ID80) vs. number of days from Day 29 visit until COVID-19 primary endpoint diagnosis for per-protocol baseline SARS-CoV-2 negative vaccine recipient breakthrough cases. Blue circles are Day 29 marker values for Intercurrent Cases. Orange triangles are Day 29, Day 57 marker values for Post Day 57 cases, with paired marker values from the same participant joined by a vertical line segment, with Day 57 marker value always the top triangle.



*No. At-Risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 57 visit.
**Cumulative No. of COVID-19 Endpoints = estimated cumulative number of this cohort with a COVID-19 endpoint.

Fig. S14: Covariate-adjusted cumulative incidence of COVID-19 by Low, Medium, High tertile of Day 57 IgG concentration or pseudovirus neutralization titer. (A) Anti-RBD IgG concentration; (B) ID80 titer.

Supplementary Text S1

Baseline covariates adjusted for in immune correlates analyses, including the baseline COVID-19 risk score

In addition to adjusting for the at-risk indicator (a stratification factor used in the COVE trial randomization) and the indicator of membership in community of color, all correlates analyses adjust for a baseline COVID-19 risk score that was developed through machine learning of the baseline SARS-CoV-2 negative per-protocol placebo arm data in the COVE trial. This supplementary text summarizes the COVID-19 risk score, with the Statistical Analysis Plan providing additional details.

Table S4 lists the input variables that were included in the machine learning to build a model predicting the COVID-19 endpoint, where cases are COVID-19 endpoints starting 7 days post Day 57 visit and non-cases are participants with follow-up beyond 7 days post Day 57 visit and that never registered a COVID-19 endpoint. The risk score is defined as the logit of the predicted COVID-19 outcome probability from the predictive regression model, estimated using the ensemble algorithm superlearner (i.e. stacking), where this logit predicted outcome is scaled to have empirical mean zero and empirical standard deviation one.

Table S4. Individual baseline variables input into the Superlearner model for predicting occurrence of COVID-19 in baseline SARS-CoV-2 negative per-protocol placebo recipients.[1]

Variable Name	Definition	Total missing values
MinorityInd	Baseline covariate minority status (1=minority, 0=non-minority)	0/14079 (0.0%)
EthnicityHispanic	Indicator ethnicity = Hispanic (0 = Non-Hispanic)	0/14079 (0.0%)
EthnicityNotreported	Indicator ethnicity = Not reported (0 = Non-Hispanic)	0/14079 (0.0%)
EthnicityUnknown	Indicator ethnicity = Unknown (0 = Non-Hispanic)	0/14079 (0.0%)
Black	Indicator race = Black (0 = White)	0/14079 (0.0%)
Asian	Indicator race = Asian (0 = White)	0/14079 (0.0%)
NatAmer	Indicator race = American Indian or Alaska Native (0 = White)	0/14079 (0.0%)
PacIsl	Indicator race = Native Hawaiian or Other Pacific Islander (0 = White)	0/14079 (0.0%)
Multiracial	Indicator race = Multiracial (0 = White)	0/14079 (0.0%)
Other	Indicator race = Other (0 = White)	0/14079 (0.0%)
Notreported	Indicator race = Not reported (0 = White)	0/14079 (0.0%)
Unknown	Indicator race = unknown (0 = White)	0/14079 (0.0%)
HighRiskInd	Baseline covariate high risk pre-existing condition (1=yes, 0=no)	0/14079 (0.0%)
Sex	Sex assigned at birth (1=female, 0=male)	0/14079 (0.0%)
Age	Age at enrollment in years, between 18 and 85	0/14079 (0.0%)
BMI	BMI at enrollment (kg/m^2)	79/14079 (0.6%)

[1]The per-protocol group for immune correlates analysis is slightly different than that for the primary vaccine efficacy analysis (*6*), due in part to a data cutoff for the primary vaccine efficacy analysis of November 25, 2020 (*6*) vs a data cutoff for the immune correlates analysis of March 26, 2021, and also in part due to the inclusion of participants with HIV in the per-protocol set for vaccine efficacy analysis (*6*) vs. the exclusion of participants with HIV from the per-protocol set for the immune correlates analysis

The following details were used in the implementation of superlearner of the baseline SARS-CoV-2 negative per-protocol placebo arm:

- All of the selected learners (i.e., regression methods for classifying whether a participant has a COVID-19 outcome or not) were coded into the SuperLearner R package available on CRAN, and the analysis was done using this R package.
- Each quantitative and ordinal variable was pre-scaled to have empirical mean 0 and standard deviation 1.
- 5-fold cross-validation was used with no more than max(20,floor(np/20)) input variables included in each model, where np is the number of evaluable placebo arm cases.
- High-correlation variable screening was used, not allowing any pair of input variables to have Spearman rank correlation $r > 0.9$.
- Two levels of cross-validation (CV) were used. The outer level computed CV-AUC over 5-fold cross-validation, and the inner level used 5-fold CV.
- Results for comparing classification accuracy of different models were based on point and 95% confidence interval estimates of cross-validated area under the ROC curve (CV-AUC) (*48, 49*). Results are presented as forest plots of point and 95% confidence interval estimates similar to those used in Figure 3B of Neidich et al. (*50*) and in Figure 2 of Magaret, Benkeser, and Williamson et al. (*51*). CV-AUC was estimated using the *vimp* R package (*52*) available on CRAN.

Table S5 lists the learning algorithms that were applied to estimate the conditional probability of the COVID-19 outcome based on the input variables listed in **table S4**. Some of the algorithms are non-data-adaptive type learning algorithms, such as parametric regression models (e.g., generalized linear models [glms]), which are simple and stable. Data-adaptive type algorithms are also included, for increasing flexibility of modeling and reducing the risk of model misspecification: SL.randomForest, SL.gam, SL.polymars, and SL.xgboost. All of the selected learners are coded into the SuperLearner R package.

Table S5. Learning algorithm-screen combinations (14 in total) used as input to the Superlearner model in baseline negative per-protocol placebo recipients.

Learner	Screen*
SL.mean	All
SL.glm	all
	glmnet
	univar_logistic_pval
	highcor_random
SL.glm.interaction	glmnet
	univar_logistic_pval
	highcor_random
SL.glmnet	All
SL.gam	glmnet
	univar_logistic_pval
	highcor_random
SL.xgboost	All
SL.ranger.imp	All

*Screen details:
all: includes all variables
glmnet: includes variables with non-zero coefficients in the standard implementation of SL.glmnet that optimizes the lasso tuning parameter via cross-validation
univar_logistic_pval: Wald test 2-sided p-value in a logistic regression model < 0.10
highcor_random: if pairs of quantitative variables with Spearman rank correlation > 0.90, select one of the variables at random

Table S6 shows the weights that the Superlearner ensemble model applied to each of the individual prediction algorithms in the modeling of the placebo arm.

Table S6. Weights assigned by Superlearner to each individual learner in the COVID-19 prediction modeling of the placebo arm

Learner	Screen	Weight
SL.gam	screen_highcor_random	0.369
SL.gam	screen_univariate_logistic_pval	0.291
SL.ranger.imp	screen_all	0.165
SL.mean	screen_all	0.112
SL.xgboost	screen_all	0.062
SL.glm	screen_all	0.000
SL.glmnet	screen_all	0.000
SL.glm	screen_glmnet	0.000
SL.glm	screen_univariate_logistic_pval	0.000
SL.glm	screen_highcor_random	0.000
SL.glm.interaction	screen_glmnet	0.000
SL.glm.interaction	screen_univariate_logistic_pval	0.000
SL.glm.interaction	screen_highcor_random	0.000
SL.gam	screen_glmnet	0.000

To inform about which individual input variables were most important for the risk score, **table S7** shows the predictors used in the learners that were assigned positive weight by the Superlearner model, with multiple metrics reported that can be used for ranking variable importance. BMI and age were ranked as the two most important variables for predicting COVID-19.

Table S7. Predictors in learners assigned positive weight by Superlearner in the COVID-19 prediction modeling of the placebo arm.

Learner	Screen	Weight	Predictors	Coefficient	Odds Ratio	Importance	Feature	Gain	Cover	Frequency
SL.gam	screen_highcor_random	0.369	(Intercept)	-3.109	0.045	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	s(Age,2)	-0.280	0.756	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	s(BMI,2)	0.174	1.190	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	MinorityInd	-0.042	0.959	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	EthnicityHispanic	0.027	1.028	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	EthnicityNotreported	-0.046	0.955	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	EthnicityUnknown	-0.056	0.945	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Black	-0.250	0.779	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Asian	-0.047	0.954	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	NatAmer	-0.059	0.943	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	PacIsl	-0.442	0.643	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Multiracial	-0.143	0.866	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Other	0.018	1.018	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Notreported	0.033	1.034	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Unknown	0.029	1.030	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	HighRiskInd	0.007	1.007	NA	NA	NA	NA	NA
SL.gam	screen_highcor_random	0.369	Sex	0.054	1.056	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	(Intercept)	-3.084	0.046	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	s(Age,2)	-0.274	0.761	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	s(BMI,2)	0.183	1.201	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	EthnicityHispanic	0.010	1.010	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	Black	-0.268	0.765	NA	NA	NA	NA	NA
SL.gam	screen_univariate_logistic_pval	0.291	Multiracial	-0.150	0.861	NA	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	MinorityInd	NA	NA	3.296	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	EthnicityHispanic	NA	NA	3.844	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	EthnicityNotreported	NA	NA	1.069	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	EthnicityUnknown	NA	NA	0.433	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Black	NA	NA	2.608	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Asian	NA	NA	2.318	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	NatAmer	NA	NA	0.971	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	PacIsl	NA	NA	0.133	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Multiracial	NA	NA	1.394	NA	NA	NA	NA

SL.ranger.imp	screen_all	0.165	Other	NA	NA	2.155	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Notreported	NA	NA	1.390	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Unknown	NA	NA	1.682	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	HighRiskInd	NA	NA	4.380	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Sex	NA	NA	6.329	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	Age	NA	NA	50.511	NA	NA	NA	NA
SL.ranger.imp	screen_all	0.165	BMI	NA	NA	109.263	NA	NA	NA	NA
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	BMI	0.664	0.796	0.75
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Age	0.238	0.153	0.17
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Sex	0.025	0.006	0.01
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Black	0.022	0.018	0.01
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	MinorityInd	0.018	0.009	0.01
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	HighRiskInd	0.014	0.006	0.01
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	EthnicityHispanic	0.011	0.004	0.00
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Multiracial	0.007	0.004	0.00
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Asian	0.001	0.003	0.00
SL.xgboost	screen_all	0.062	NA	NA	NA	NA	Other	0.000	0.001	0.00

Figure S15 Panel A shows the cross-validated receiver operating characteristic curve for the 2 top-performing learners, Superlearner, and the Discrete Superlearner models classifying COVID-19 outcome status in baseline SARS-CoV-2 negative per-protocol placebo recipients, with predictive performance summarized by cross-validated area under the receiver operating characteristic curve (CV-AUC). The point estimate of CV-AUC for the Superlearner was 0.612 with 95% CI 0.591, 0.633.

Figure S15 Panel B shows the receiver operating characteristic curve for the Superlearner model built from baseline SARS-CoV-2 negative per-protocol placebo recipients applied to baseline SARS-CoV-2 negative per-protocol vaccine recipients, for which the point estimate of AUC for classifying COVID-19 outcome status was 0.614.

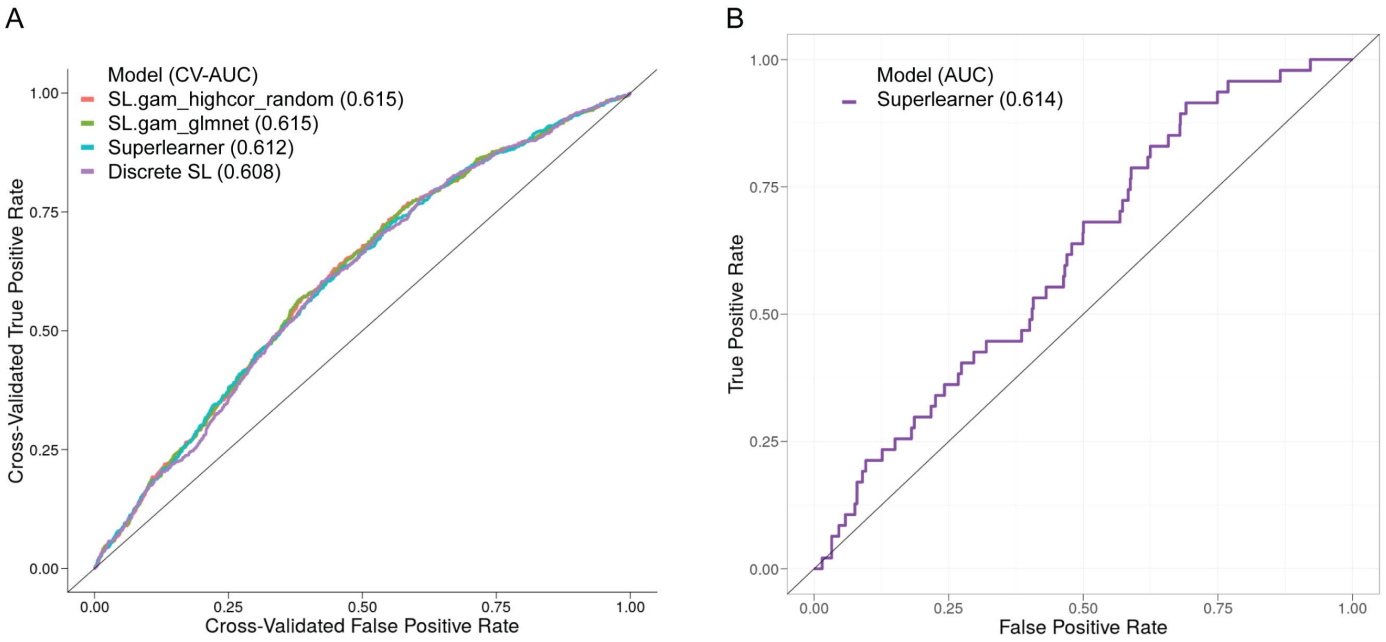


Fig. S15. (A) Cross-validated receiver operating characteristic curve for the two top-performing learners, Superlearner, and the Discrete Superlearner models classifying COVID-19 outcome occurrence in baseline SARS-CoV-2 negative per-protocol placebo recipients, with cross-validated area under the curve (CV-AUC) summarizing classification performance. (B) Receiver operating characteristic curve for the Superlearner upon applying the model built from placebo recipients to baseline SARS-CoV-2 negative per-protocol vaccine recipients, with AUC in parentheses summarizing classification performance.

Figure S16 shows Superlearner model predicted probabilities of the COVID-19 endpoint starting 7 days post Day 57 visit by case vs. non-case status, for baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 57 marker case-cohort set.

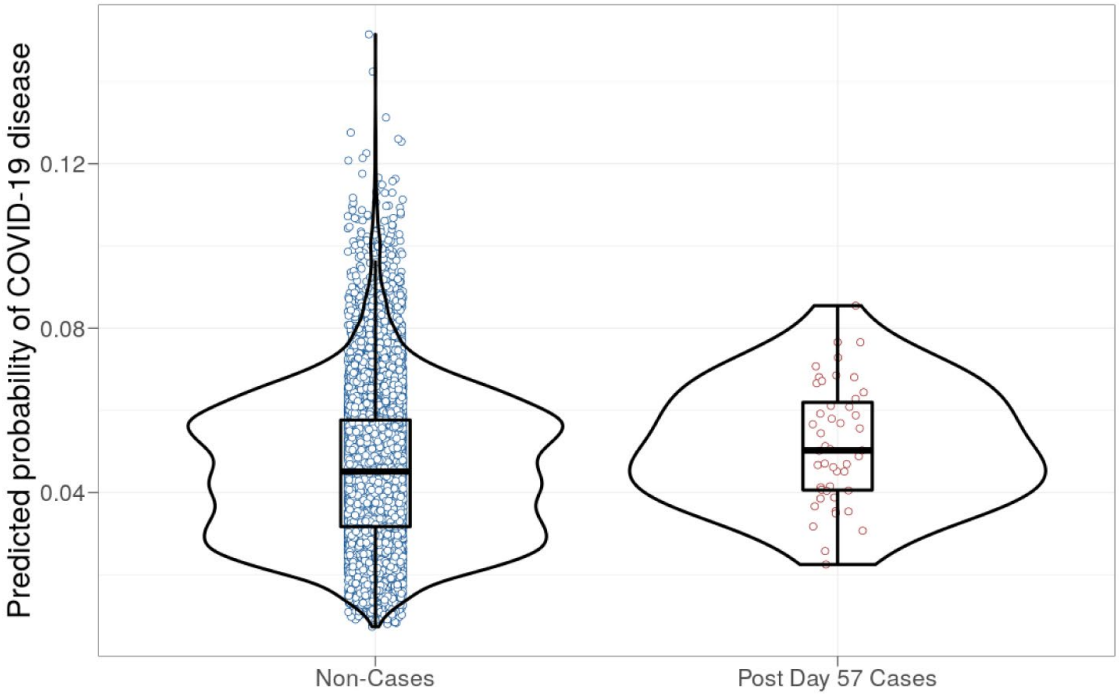


Fig. S16. Superlearner model predicted probabilities of the COVID-19 endpoint starting 7 days post Day 57 visit by case vs. non-case (i.e., control) status, for baseline SARS-CoV-2 negative per-protocol vaccine recipients in the Day 57 marker case-cohort set.

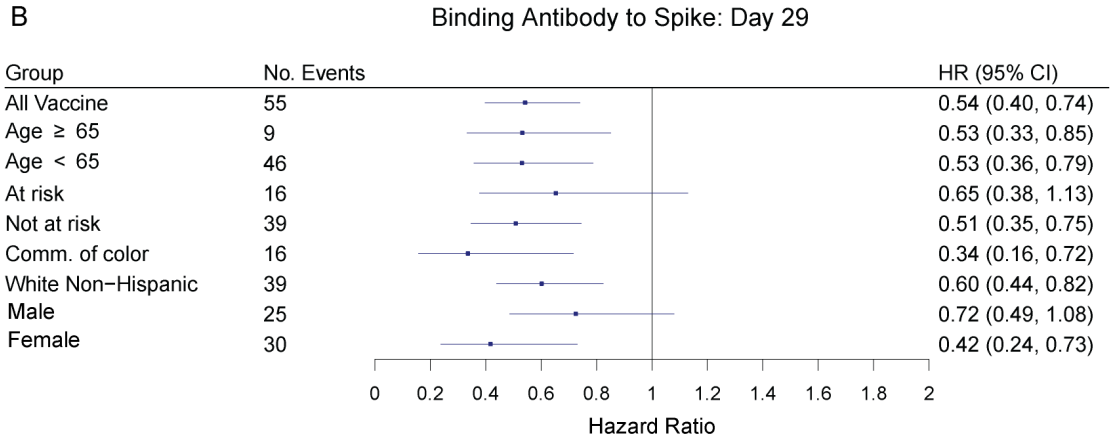
A

COVE Immunologic Marker	No. cases / No. at-risk*	HR per 10-fold incr. Pt. Est.	95% CI	P-value (2-sided)	FDR-adjusted p-value**	FWER-adjusted p-value
Anti Spike IgG (BAU/ml)	55/14,141	0.54	(0.40,0.74)	<0.001	<0.001	<0.001
Anti RBD IgG (BAU/ml)	55/14,141	0.46	(0.30,0.70)	<0.001	0.001	0.001
PsV-nAb ID50 (IU50/ml)	55/14,141	0.33	(0.17,0.65)	0.001	0.003	0.002
PsV-nAb ID80 (IU80/ml)	55/14,141	0.19	(0.07,0.56)	0.003	0.004	0.003

*No. at-risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 29 visit; No. cases = estimated number of this cohort with an observed COVID-19 endpoint starting 7 days post Day 29 visit. The count 55 differs from 46 (Figure 1, Table 1) because the 55 includes all vaccine breakthrough cases including the 9 without Day 1, 29, 57 antibody marker data.

** FDR (false discovery rate)-adjusted p-values and FWER (family-wise error rate)-adjusted p-values are computed over the set of p-values both for quantitative markers and categorical markers (Low, Medium, High) using the Westfall and Young permutation method (10,000 replicates).

B



C

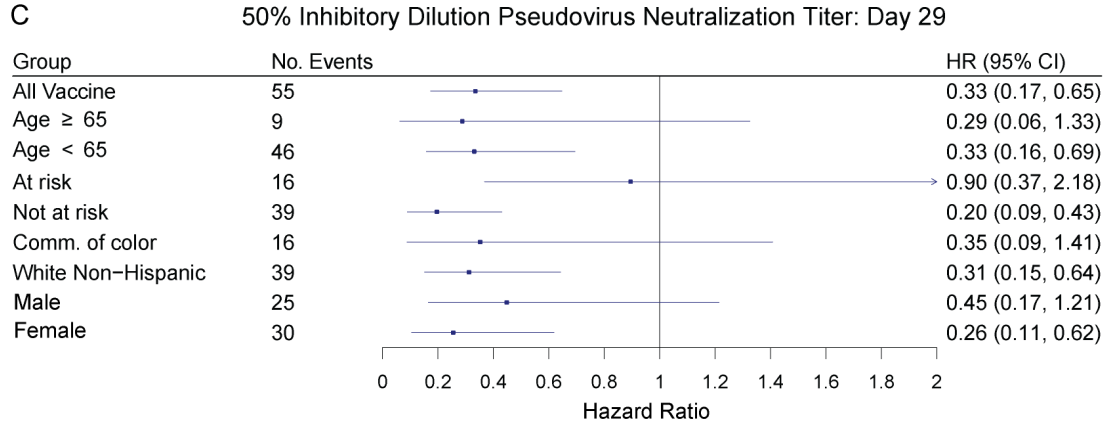
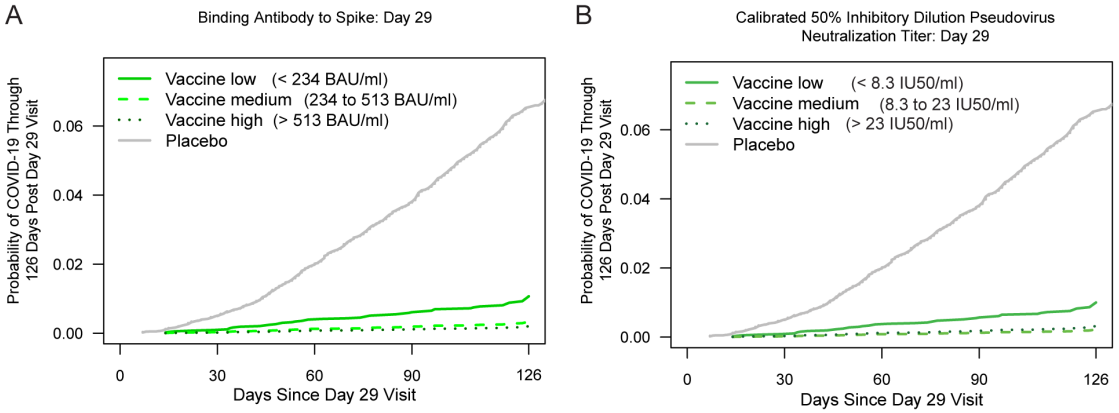


Fig. S17. Covariate-adjusted hazard ratios of COVID-19 per 10-fold increase in each Day 29 antibody marker in baseline SARS-CoV-2 negative per-protocol vaccine recipients overall and in subgroups. (A) Inferences for IgG (spike, RBD) and (ID50, ID80); (B) Forest plots for anti-spike IgG concentration; (C) Forest plots for ID50. Community of color is the complement of White Non-Hispanic (different from Minority because missing values are included in Community of color).



No. At-Risk*

Low:	4509	4506	4462	4182	1664
Med:	4897	4894	4878	4434	1926
High:	4735	4735	4688	4207	1939
Plac:	13972	13856	13250	11117	3963

Cumulative No. of COVID-19 Endpoints**

Low:	0	4	18	24	33
Med:	0	2	5	8	13
High:	0	0	2	6	8
Plac:	0	71	278	507	734

No. At-Risk*

Low:	4688	4684	4635	4371	1687
Med:	4778	4778	4737	4185	1917
High:	4675	4673	4656	4266	1925
Plac:	13972	13856	13250	11117	3963

Cumulative No. of COVID-19 Endpoints**

Low:	0	4	18	25	33
Med:	0	0	4	5	8
High:	0	2	4	8	13
Plac:	0	71	278	507	734

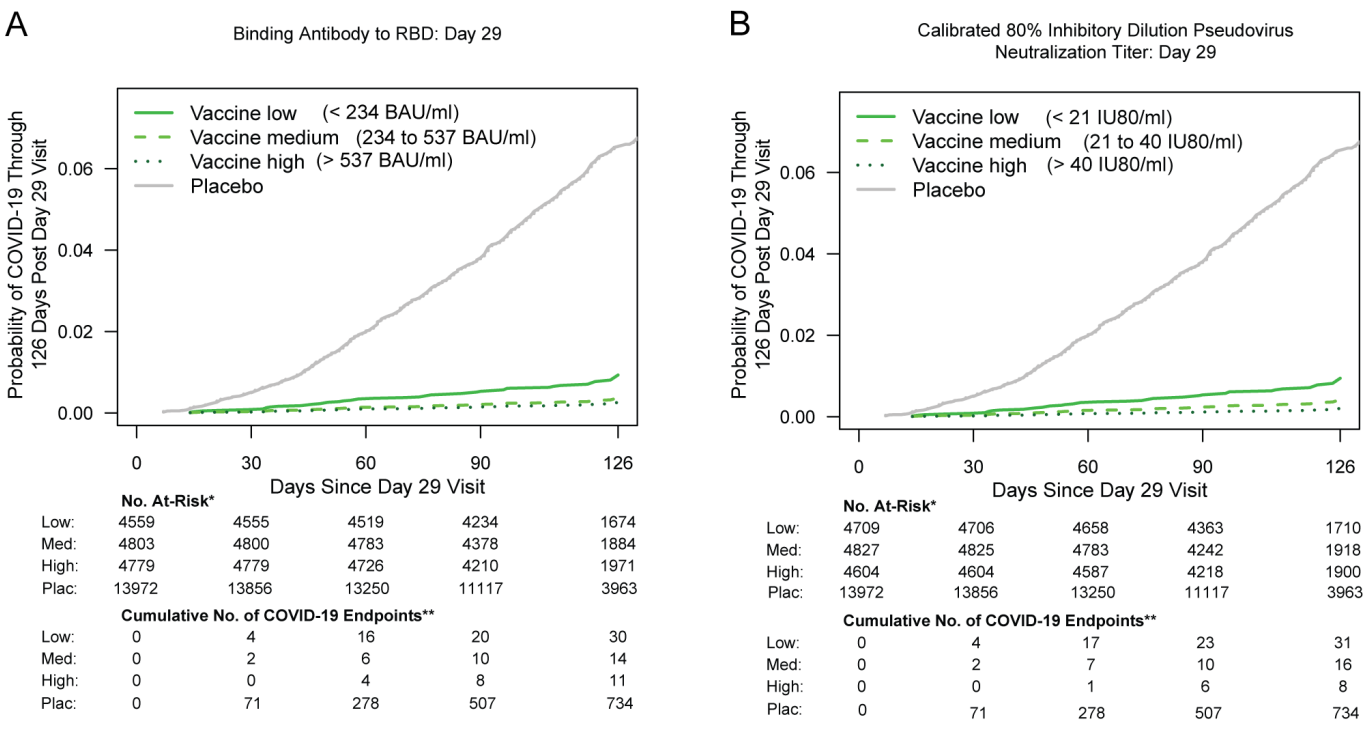
*No. At-Risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 29 visit.
**Cumulative No. of COVID-19 Endpoints = estimated cumulative number of this cohort with a COVID-19 endpoint.

C

COVE Immunologic Marker	Tertile¶	No. cases / No. at-risk§	Attack rate	Haz. Ratio Pt. Est.	Haz. Ratio 95% CI	P-value (2-sided)	Overall P-value	FDR-adjusted p-value†	FWER-adjusted p-value†
Anti Spike IgG (BAU/ml)	Low	33/4,509	0.0073	1	N/A	N/A	<0.001	<0.001	<0.001
	Medium	13/4,897	0.0027	0.31	(0.15,0.65)	0.002			
	High	8/4,735	0.0017	0.19	(0.08,0.44)	<0.001			
Anti RBD IgG (BAU/ml)	Low	30/4,559	0.0066	1	N/A	N/A	0.002	0.004	0.003
	Medium	14/4,803	0.0029	0.40	(0.19,0.84)	0.016			
	High	11/4,779	0.0023	0.28	(0.13,0.60)	0.001			
Pseudovirus-nAb ID50 (IU50/ml)	Low	33/4,688	0.0070	1	N/A	N/A	<0.001	0.001	0.001
	Medium	8/4,778	0.0017	0.22	(0.09,0.53)	<0.001			
	High	13/4,675	0.0028	0.32	(0.15,0.69)	0.003			
Pseudovirus-nAb ID80 (IU80/ml)	Low	31/4,709	0.0066	1	N/A	N/A	0.001	0.003	0.002
	Medium	16/4,827	0.0033	0.44	(0.21,0.90)	0.025			
	High	8/4,604	0.0017	0.22	(0.09,0.51)	<0.001			
Placebo		734/13,972	0.0525						

Baseline covariates adjusted for: baseline risk score, At Risk status, Community of color status.
Maximum failure event time 126 days post Day 29 visit.
¶Tertiles:
Spike IgG: Low is < 234 BAU/ml, Medium is 234 to 513 BAU/ml, High is > 513 BAU/ml.
RBD IgG: Low is < 234 BAU/ml, Medium is 234 to 537 BAU/ml, High is > 537 BAU/ml.
ID50: Low is < 8.3 IU50/ml, Medium is 8.3 to 23 IU50/ml, High is > 23 IU50/ml.
ID80: Low is < 21 IU80/ml, Medium is 21 to 40 IU80/ml, High is > 40 IU80/ml.
§No. at-risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 29 visit; No. cases = estimated number of this cohort with an observed COVID-19 endpoint. The total count (55) across all tertiles for each marker differs from 46 (Figure 1, Table 1), because the 55 includes all vaccine breakthrough cases including the 9 without Day 1, 29, 57 antibody marker data.
† FDR (false discovery rate)-adjusted p-values and FWER (family-wise error rate)-adjusted p-values are computed over the set of p-values both for quantitative markers and categorical markers (Low, Medium, High) using the Westfall and Young permutation method (10,000 replicates).

Figure S18. Covariate-adjusted cumulative incidence of COVID-19 by Low, Medium, High tertile of Day 29 IgG concentration or pseudovirus neutralization titer in baseline SARS-CoV-2 negative per-protocol participants. (A) Anti-spike IgG concentration; (B) ID50 titer; (C) IgG (spike, RBD) and (ID50, ID80). The overall p-value is from a generalized Wald test for whether the COVID-19 hazard differed across Low, Medium, and High subgroups.



*No. At-Risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 29 visit.
**Cumulative No. of COVID-19 Endpoints = estimated cumulative number of this cohort with a COVID-19 endpoint.

Figure S19: Covariate-adjusted cumulative incidence of COVID-19 by Low, Medium, High tertile of Day 29 IgG concentration or pseudovirus neutralization titer. (A) Anti-RBD IgG concentration; (B) ID80 titer.

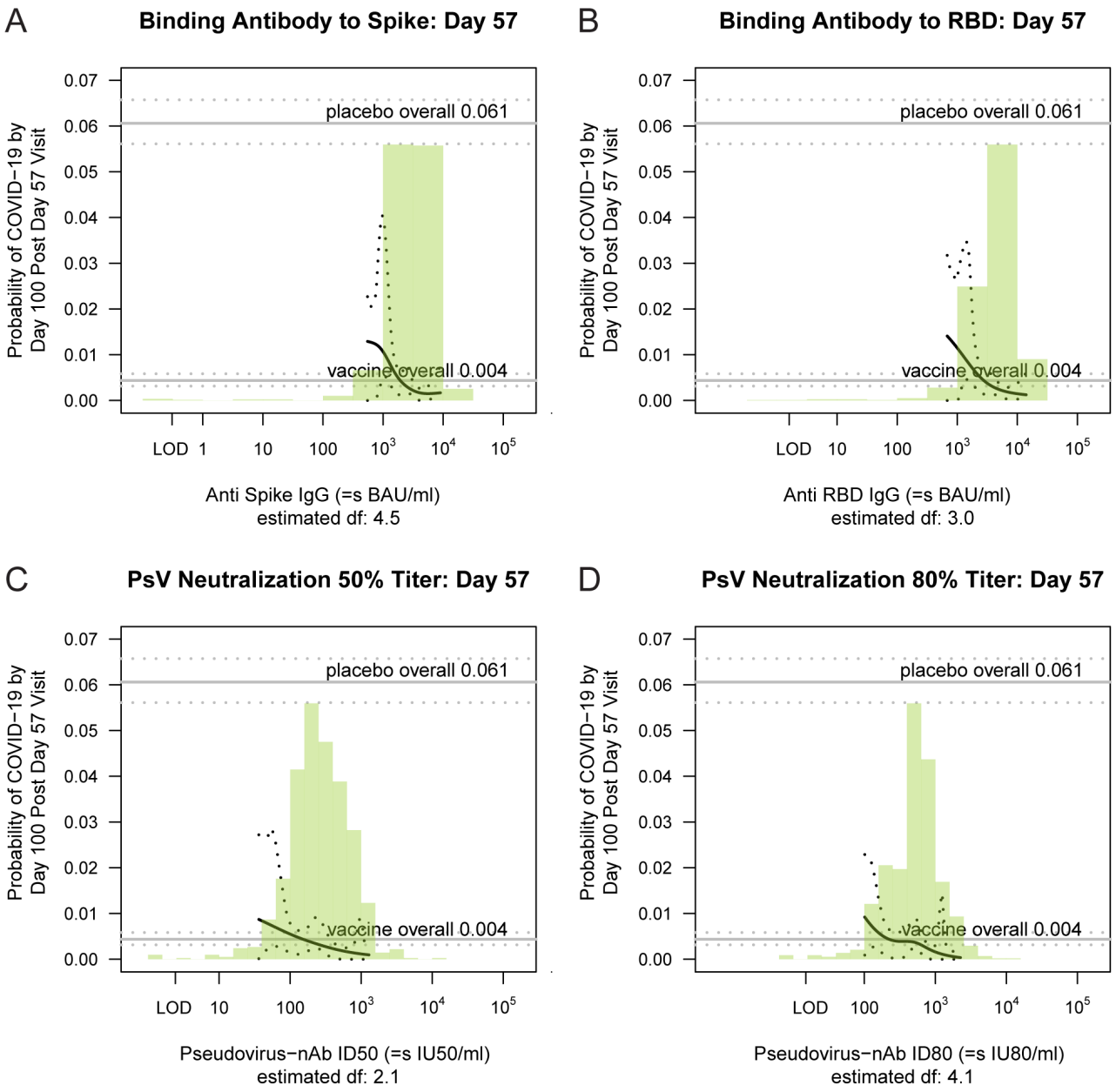


Fig. S20. Covariate-adjusted risk of COVID-19 by the level of each Day 57 marker (spike IgG, RBD IgG, ID50, ID80), estimated with a generalized additive model, in baseline SARS-CoV-2 negative per-protocol vaccine recipients.

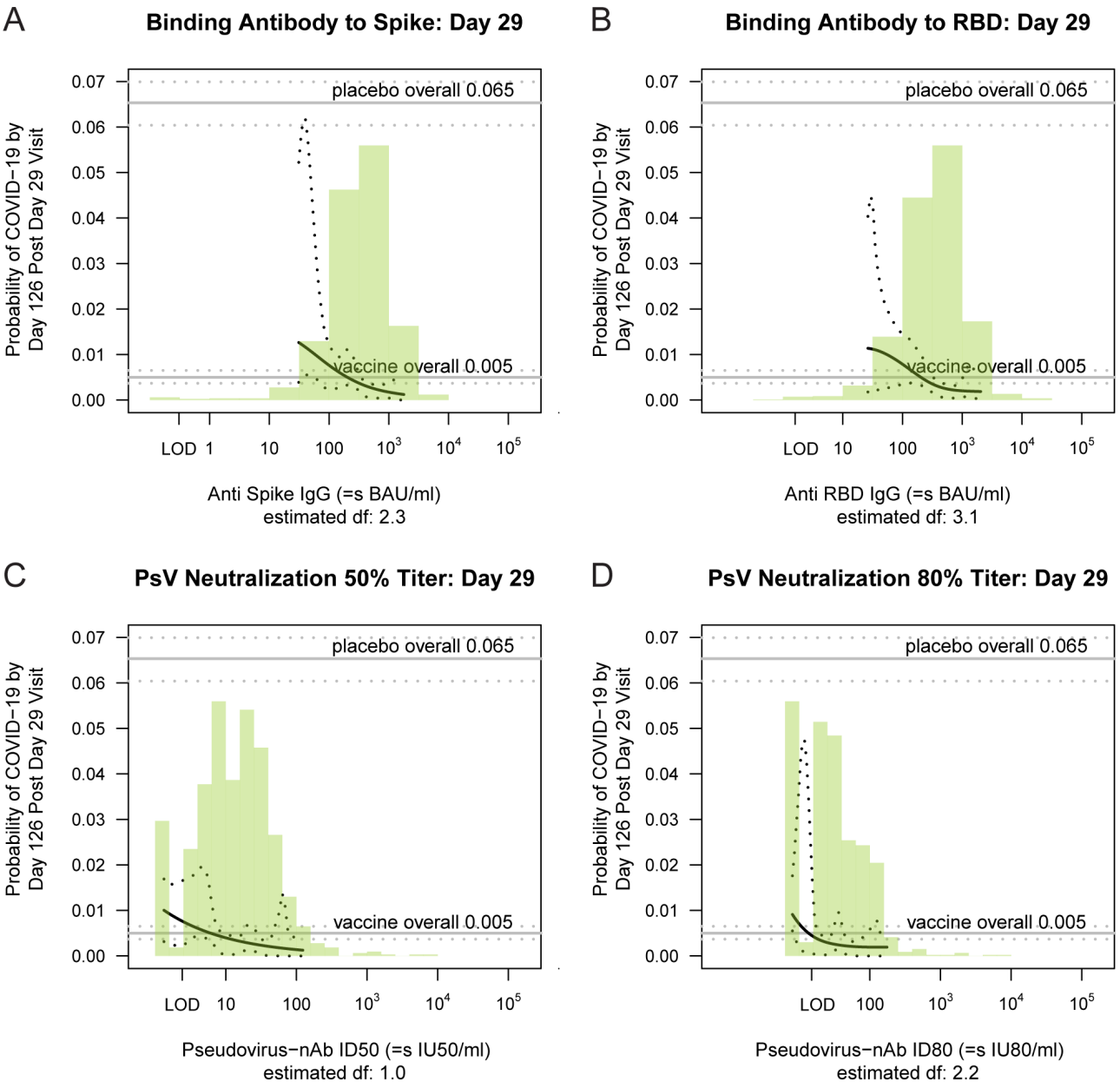


Fig. S21. Covariate-adjusted risk of COVID-19 by the level of each Day 29 marker (spike IgG, RBD IgG, ID50, ID80), estimated with a generalized additive model, in baseline SARS-CoV-2 negative per-protocol vaccine recipients.

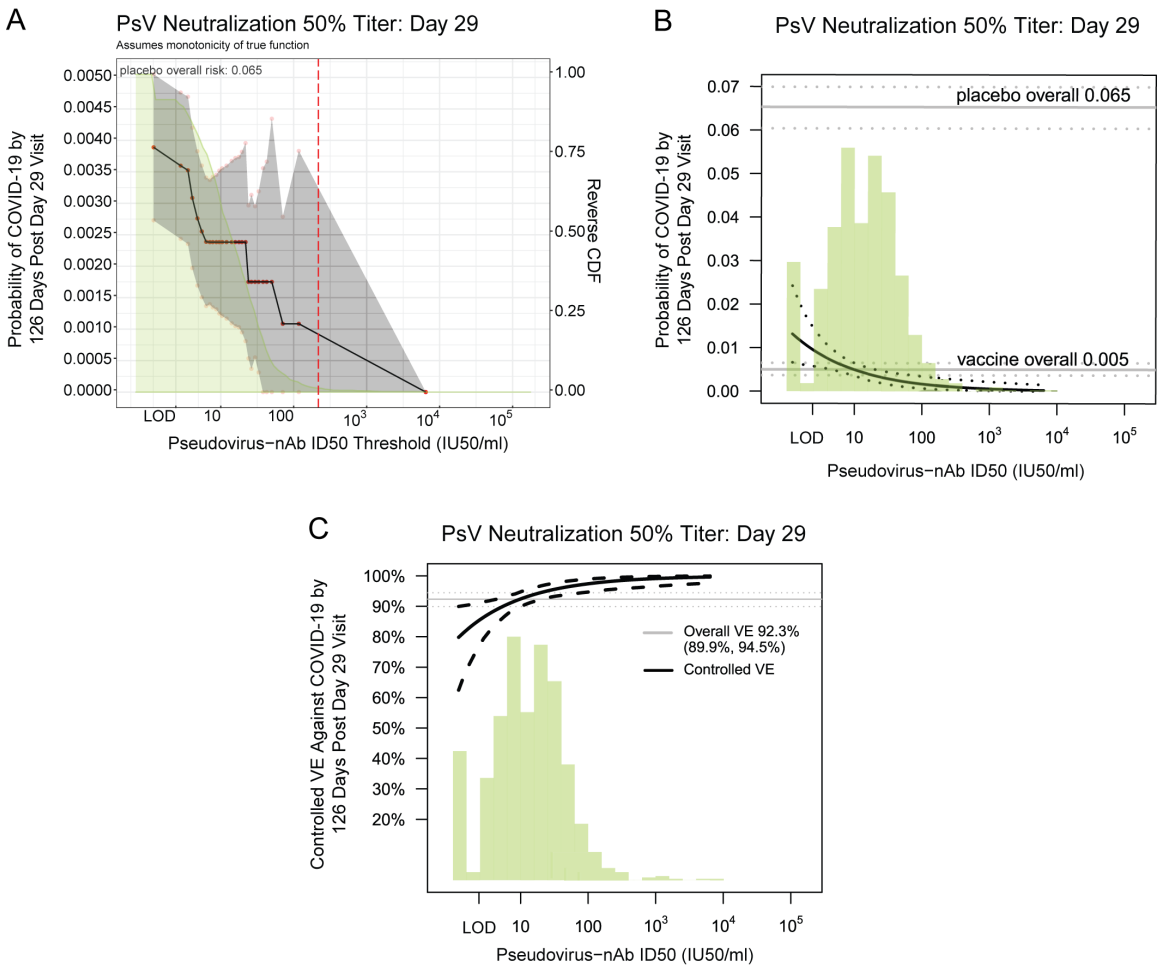


Fig. S22. Further analyses of Day 29 ID50 level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 29 ID50 level above a threshold, with reverse cumulative distribution function (CDF) of Day 29 ID50 level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 29 ID50 level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 29 ID50 threshold above which no post Day 29 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by Day 29 ID50 level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 126 days post Day 29 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 29 ID50 level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 126 days post Day 29, with the dotted gray lines indicating the 95% CIs (this number 92.3% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 29 ID50 level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

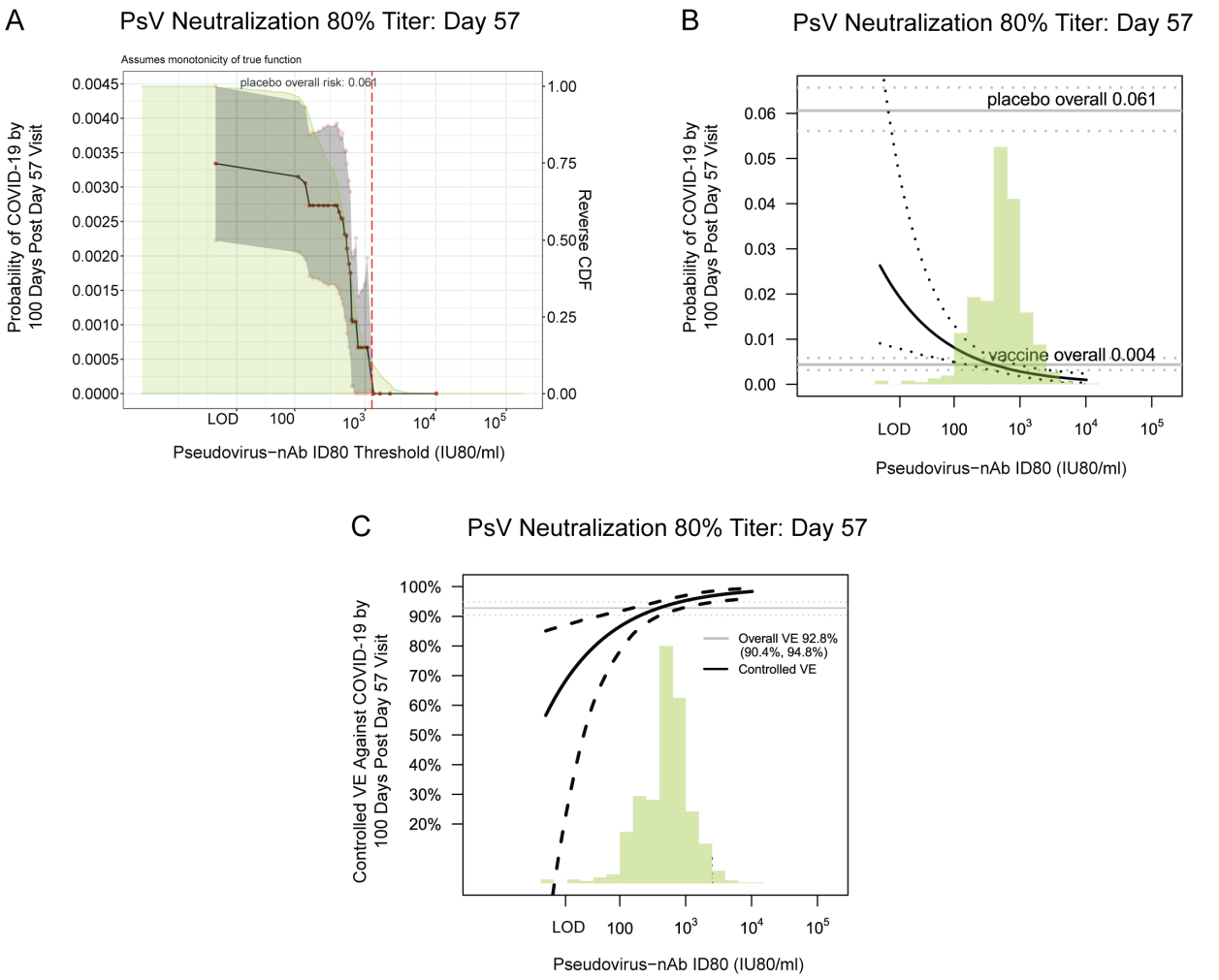


Fig. S23. Further analyses of Day 57 ID80 level as a correlate of risk and analysis as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 57 ID80 level above a threshold, with reverse cumulative distribution function (CDF) of Day 57 ID80 level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 57 ID80 level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 57 ID80 threshold above which no post Day 57 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by Day 57 ID80 level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 100 days post Day 57 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 57 ID80 level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 100 days post Day 57, with the dotted gray lines indicating the 95% CIs (this number 92.8% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 57 ID80 level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

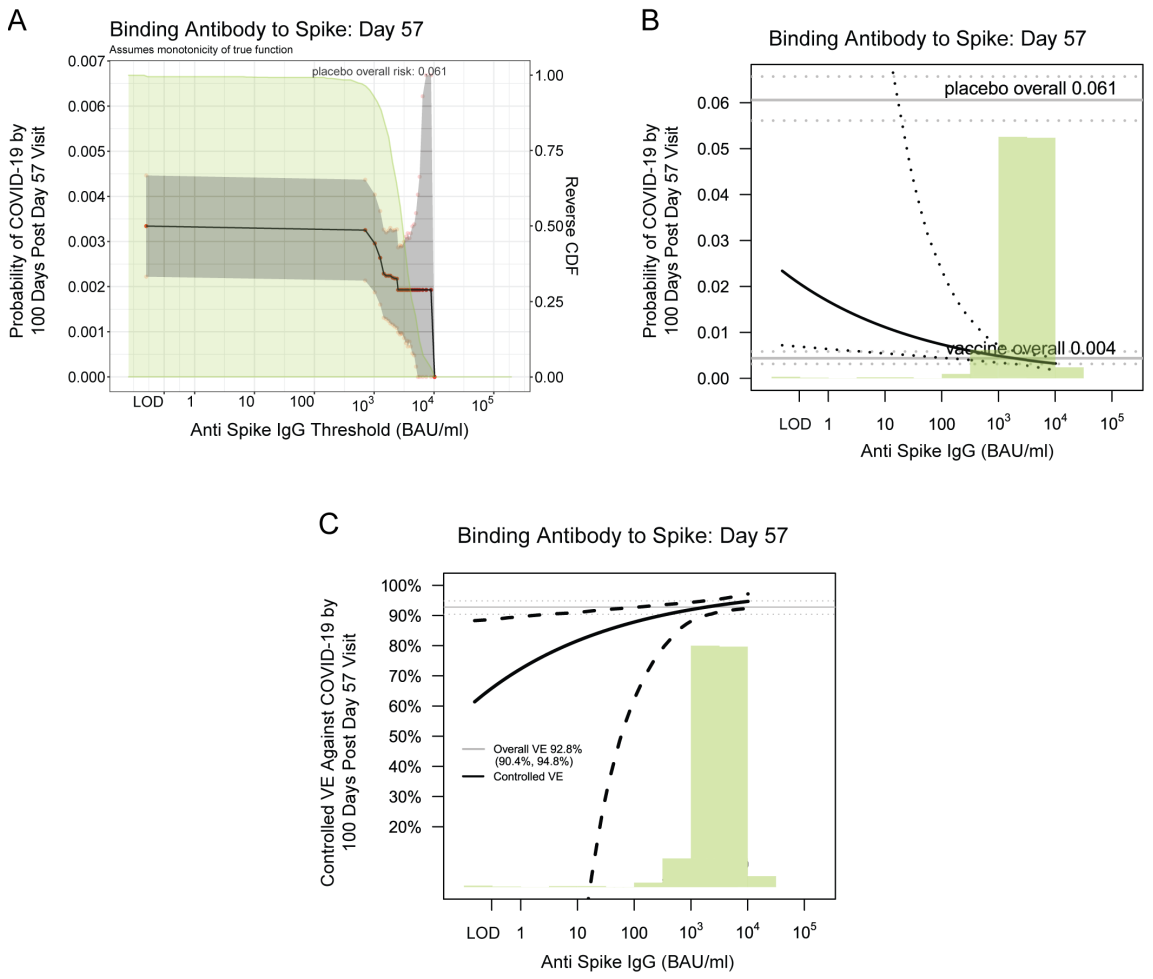


Fig. S24. Further analyses of Day 57 anti-spike IgG level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 57 anti-spike IgG level above a threshold, with reverse cumulative distribution function (CDF) of Day 57 anti-spike IgG level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 57 anti-spike IgG level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 57 anti-spike IgG threshold above which no post Day 57 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by Day 57 anti-spike IgG level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 100 days post Day 57 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 57 anti-spike IgG level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 100 days post Day 57, with the dotted gray lines indicating the 95% CIs (this number 92.8% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 57 anti-spike IgG level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

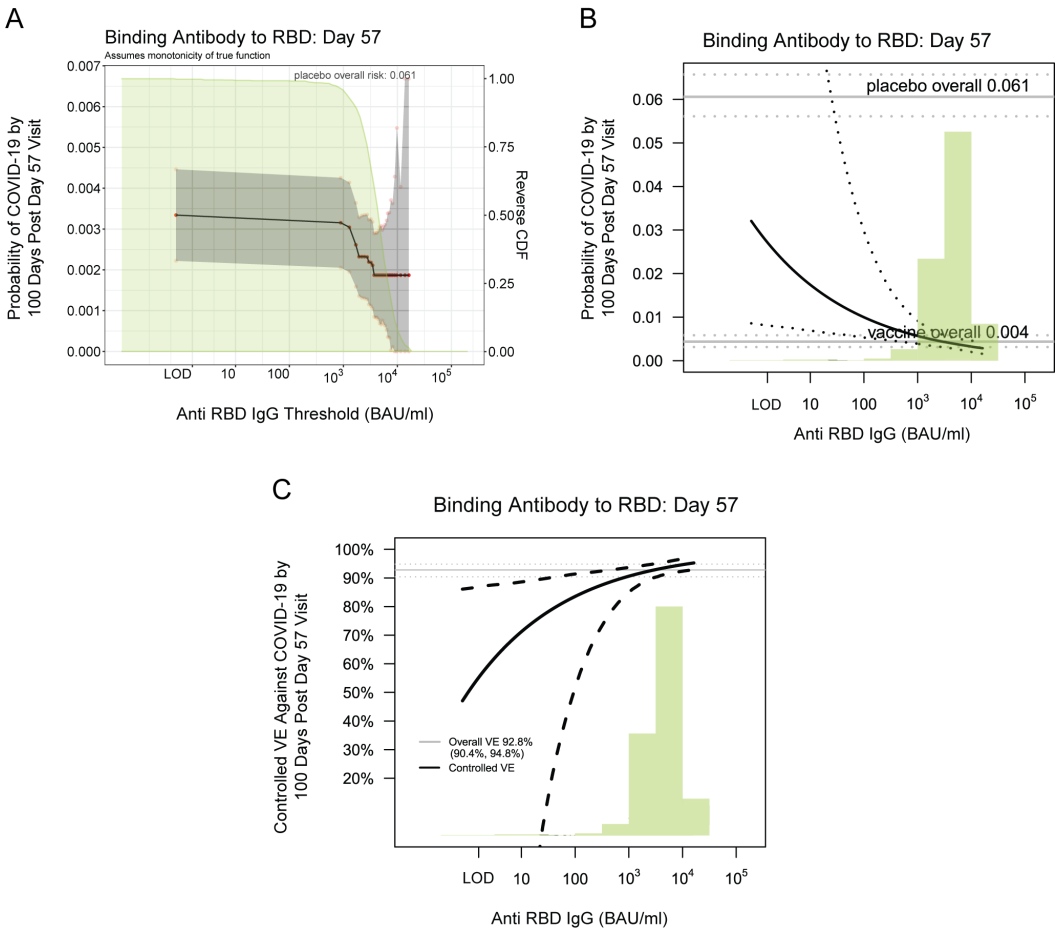


Fig. S25. Further analyses of Day 57 anti-RBD IgG level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 57 anti-RBD IgG level above a threshold, with reverse cumulative distribution function (CDF) of Day 57 anti-RBD IgG level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 57 anti-RBD IgG level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 57 anti-RBD IgG threshold above which no post Day 57 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 100 days post Day 57 by Day 57 anti-RBD IgG level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 100 days post Day 57 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 57 anti-RBD IgG level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 100 days post Day 57, with the dotted gray lines indicating the 95% CIs (this number 92.8% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 57 anti-RBD IgG level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

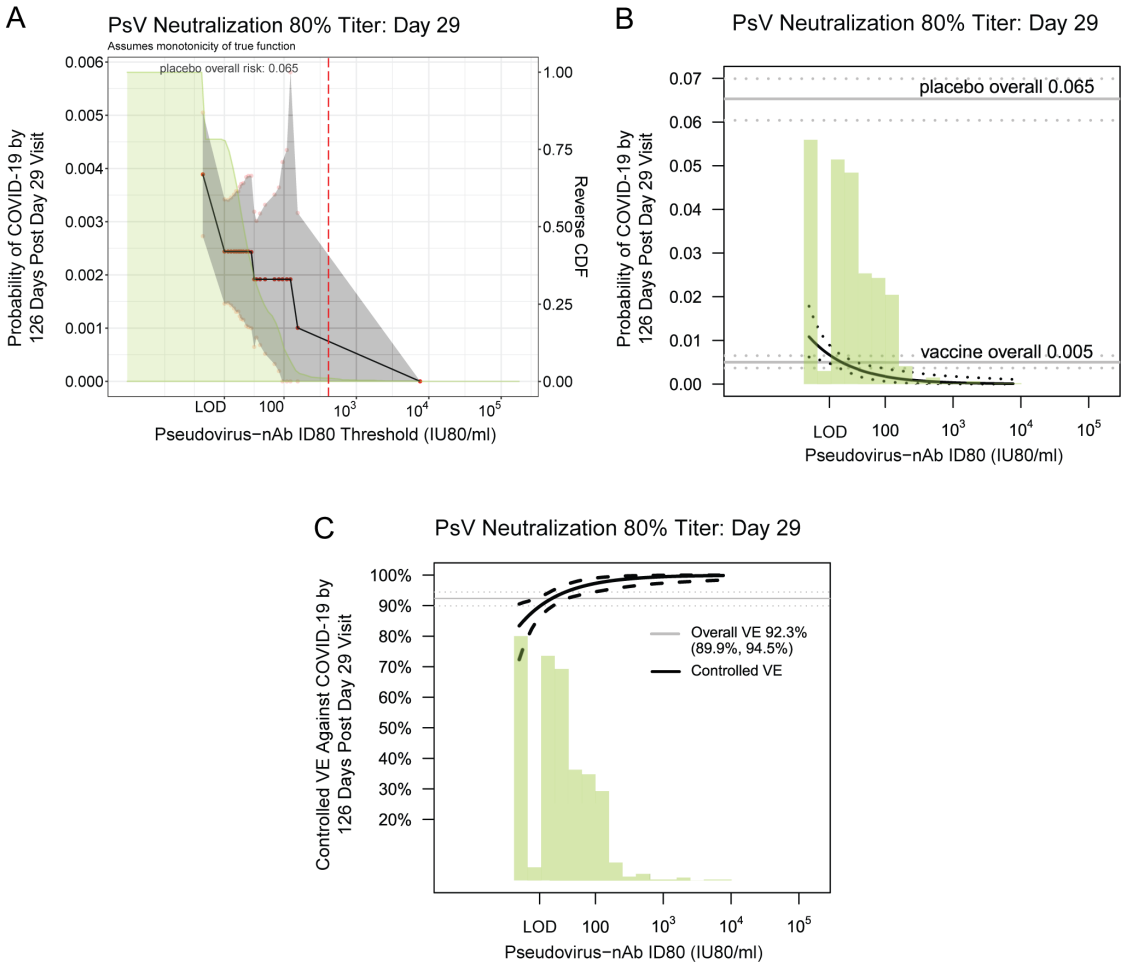


Fig. S26. Further analyses of Day 29 ID80 level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 29 ID80 level above a threshold, with reverse cumulative distribution function (CDF) of Day 29 ID80 level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 29 ID80 level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 29 ID80 threshold above which no post Day 29 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by Day 29 ID80 level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 126 days post Day 29 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 29 ID80 level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 126 days post Day 29, with the dotted gray lines indicating the 95% CIs (this number 92.3% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 29 ID80 level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

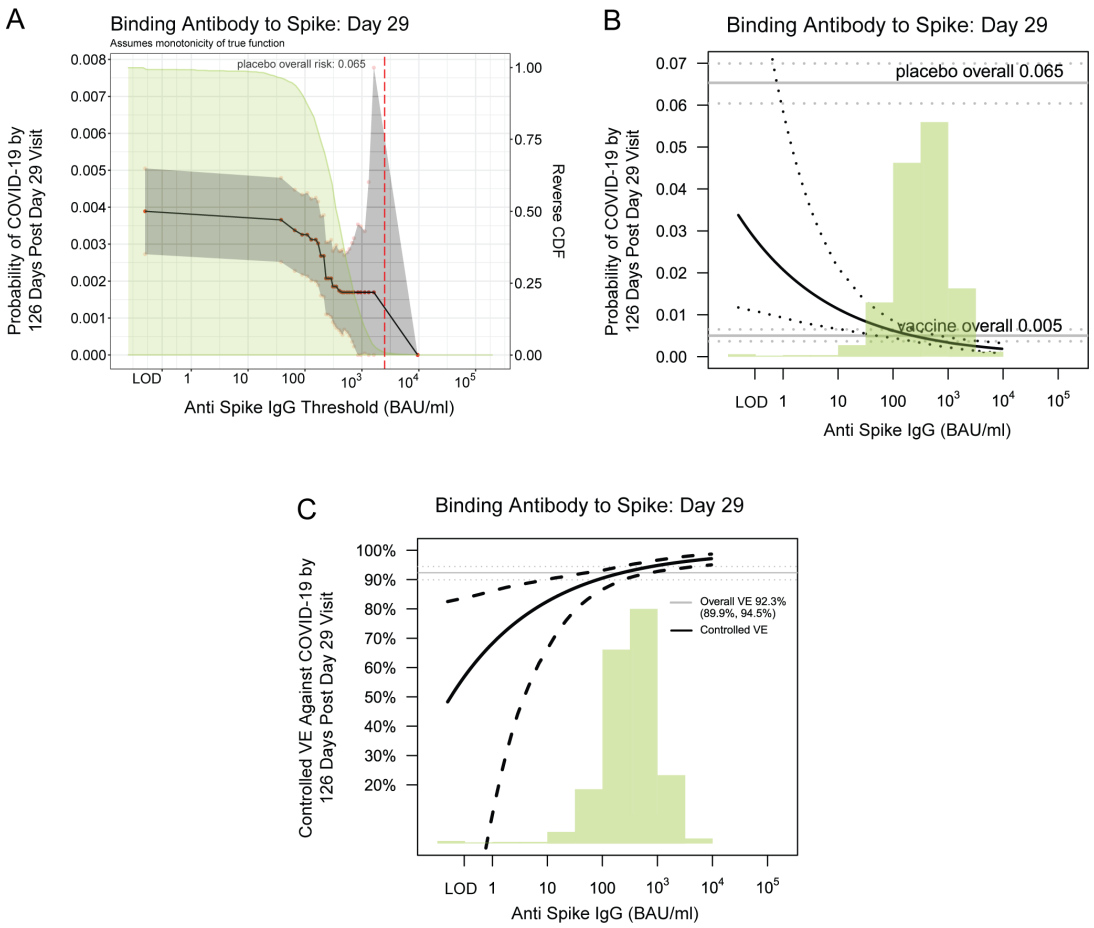


Fig. S27. Further analyses of Day 29 anti-spike IgG level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 29 anti-spike IgG level above a threshold, with reverse cumulative distribution function (CDF) of Day 29 anti-spike IgG level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 29 anti-spike IgG level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 29 anti-spike IgG threshold above which no post Day 29 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by Day 29 anti-spike IgG level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 126 days post Day 29 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 29 anti-spike IgG level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 126 days post Day 29, with the dotted gray lines indicating the 95% CIs (this number 92.3% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 29 anti-spike IgG level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

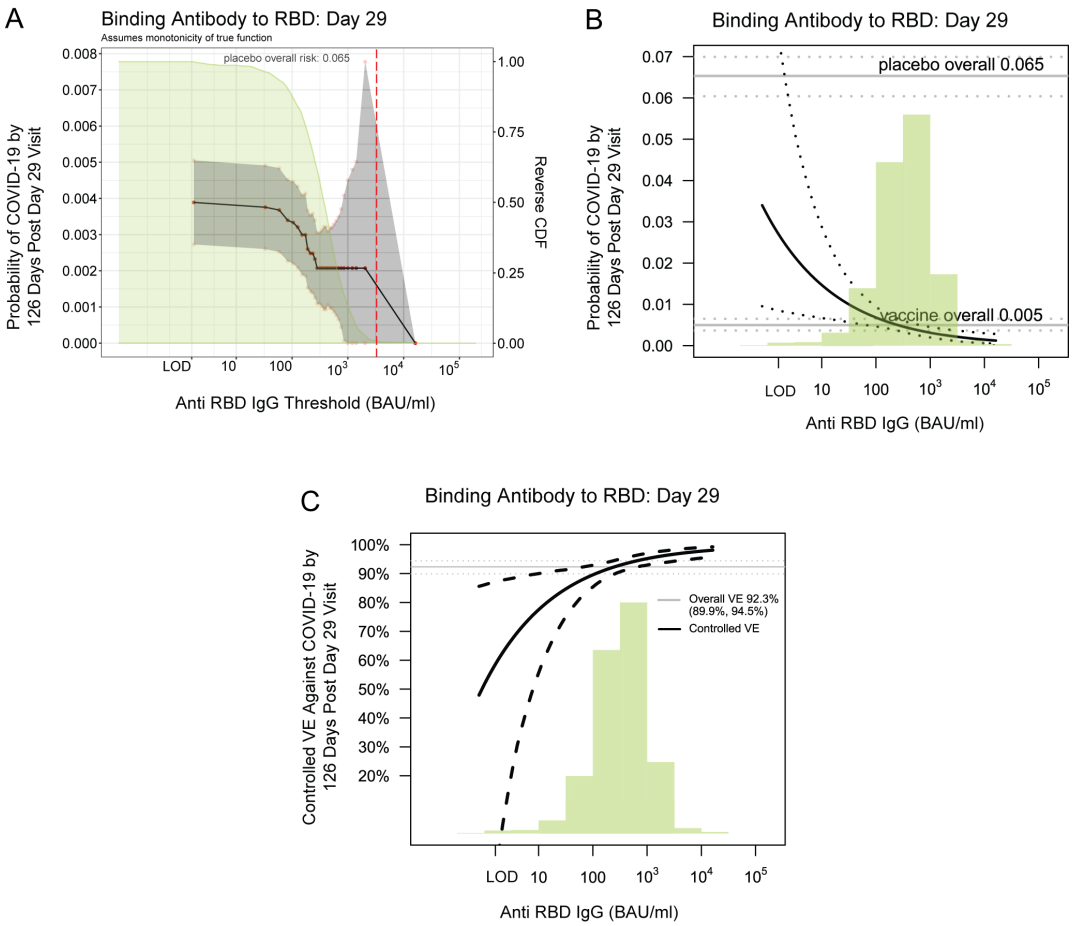


Fig. S28. Further analyses of Day 29 anti-RBD IgG level as a correlate of risk and as a correlate of protection. (A) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by vaccinated baseline SARS-CoV-2 negative per-protocol subgroups defined by Day 29 anti-RBD IgG level above a threshold, with reverse cumulative distribution function (CDF) of Day 29 anti-RBD IgG level overlaid in green. The red dots are point estimates at 35 threshold values equally spaced over quantiles of the observed marker values, linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of Day 29 anti-RBD IgG level in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The vertical red dashed line is the Day 29 anti-RBD IgG threshold above which no post Day 29 COVID endpoints occurred. (B) Covariate-adjusted cumulative incidence of COVID-19 by 126 days post Day 29 by Day 29 anti-RBD IgG level. The dotted black lines indicate bootstrap point-wise 95% CIs. The upper and lower horizontal gray lines are the overall cumulative incidence of COVID-19 from 7 to 126 days post Day 29 in placebo and vaccine recipients, respectively. (C) Vaccine efficacy (solid black line) by Day 29 anti-RBD IgG level, estimated using the method of Gilbert, Fong, and Carone (*28*). The dashed black lines indicate bootstrap point-wise 95% CIs. The horizontal gray line is the overall vaccine efficacy from 7 to 126 days post Day 29, with the dotted gray lines indicating the 95% CIs (this number 92.3% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). In (B) and (C), the green histograms are an estimate of the density of Day 29 anti-RBD IgG level in baseline negative per-protocol vaccine recipients. LOD, limit of detection. Baseline covariates adjusted for: baseline risk score, at risk status, community of color status.

Supplementary Text S2: Controlled vaccine efficacy sensitivity analysis and mediation analysis

Controlled vaccine efficacy sensitivity analysis to assess robustness of the effect of antibody marker on preventing COVID-19 to unmeasured confounding

Fig. 2 reports results for estimation and inference for baseline covariate-marginalized COVID-19 risk ratios comparing vaccine recipients with Day 57 antibody marker in the third tertile vs. in the first tertile; denote this marginalized risk ratio by $RR_M(0,1)$, where 1 indicates the third tertile and 0 indicates the first tertile. As described in the SAP and Gilbert, Fong, and Carone (*28*), under the assumption of no unmeasured confounding of the effect of the antibody marker on COVID-19, the COVID-19 risk ratio $RR_M(0,1)$ equals a causal effect parameter $RR_C(0,1)$, the controlled effects risk ratio, which in turn equals $(1 – CVE(1))/(1 – CVE(0))$, where CVE(1) is controlled vaccine efficacy for vaccine recipients with third tertile marker level and CVE(0) is controlled vaccine efficacy for vaccine recipients with first tertile marker level. In sensitivity analysis, we allow for some unmeasured confounding that makes $RR_M(0,1) < RR_C(0,1)$. In particular, as specified in the SAP the first part of the sensitivity analysis reports E-values, both for the point estimate of $RR_C(0,1)$ and for the upper 95% confidence limit of $RR_C(0,1)$. The E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the antibody marker (exposure) and the COVID-19 outcome in order to fully explain away a specific observed exposure-outcome association, conditional on the measured covariates (*29*). Here 'fully explain away' means that $RR_C(0,1) =1$, or equivalently CVE(0)=CVE(1), i.e., controlled vaccine efficacy does not differ by upper vs. lower tertile, which means no correlate of protection. Many epidemiologists recommend that E-values are always reported (or alternative sensitivity metrics) for causal inferences, given that it is not possible to guarantee that all confounders are controlled for in the analysis; thus by using E-values we are implementing best practice.

In addition, we apply the sensitivity analysis technique developed by Ding and Vanderweele (2016) (*53*), as implemented in the SAP and in Gilbert, Fong, and Carone (*28*) for the COVE trial correlates application, to estimate $RR_C(0,1) = (1 – CVE(1))/(1 – CVE(0))$ under a specified scenario of unmeasured confounding that makes it harder to conclude a correlate of protection. This sensitivity analysis specifies an amount of unmeasured confounding defined by $RR_{UD}(0,1)=RR_{EU}(0,1)=2$, where these parameters are defined in Ding and Vanderweele (2016) (*52*) and in our SAP and Gilbert et al. If the 95% confidence interval for $RR_C(0,1) = (1 – CVE(1))/(1 – CVE(0))$ is less than 1 after accounting for this confounding that pushes the confidence interval upwards, it provides evidence for a correlate of protection with a degree of robustness to possible unmeasured confounding.

Table S8 shows results for the eight Day 57 and Day 29 antibody markers categorized by upper vs. lower tertile that were assessed as correlates. For example, the E-value of 9.3 for the Day 57 ID80 marker means that a marginalized risk ratio $RR_M(0,1)$ at the observed value 0.20 could be explained away (i.e., $RR_C(0,1) = 1.0$) by an unmeasured confounder associated with

both the exposure and the outcome by a marginalized risk ratio of 9.3-fold each, after accounting for the measured potential confounders (risk score, at-risk status, community of color indicator), but that weaker confounding could not do so. In addition, the E-value of 3.3 for the upper confidence limit UL indicates the strength of unmeasured confounding at which statistical significance of the inference that CVE(1) > CVE(0) would be lost.

Table S8. Sensitivity analysis to assess Day 57 and Day 29 antibody markers categorized as upper vs. lower tertiles as controlled vaccine efficacy CoPs against COVID-19

	Marginalized Risk Ratio $RR_M(0,1)$[1]		Controlled Risk Ratio = (1-CVE(1))/(1-CVE(0))[2]		E-values[3]	
Antibody Marker	Point Est.	95% CI	Point Est.	95% CI	For Point Est.	For 95% CI UL
Day 57 Spike IgG	0.24	0.06, 0.56	0.32	0.09, 0.75	7.9	3.0
Day 57 RBD IgG	0.28	0.08, 0.62	0.38	0.11, 0.83	6.5	2.6
Day 57 PsV ID50	0.31	0.08, 0.72	0.42	0.11, 0.96	5.9	2.1
Day 57 PsV ID80	0.20	0.03, 0.51	0.27	0.05, 0.68	9.3	3.3
Day 29 Spike IgG	0.19	0.06, 0.40	0.26	0.08, 0.53	9.8	4.5
Day 29 RBD IgG	0.29	0.10, 0.59	0.38	0.13, 0.79	6.5	2.8
Day 29 PsV ID50	0.33	0.13, 0.65	0.44	0.17, 0.86	5.5	2.5
Day 29 PsV ID80	0.22	0.07, 0.46	0.30	0.10, 0.61	8.5	3.8

[1]This analysis estimates the Controlled Risk Ratio under the no-unmeasured confounding and positivity assumptions.
[2]Conservative (upper bound) estimate assuming unmeasured confounding at level $RR_{UD}(0, 1) = RR_{EU}(0, 1) = 2$ and thus $B(0, 1) = 4/3$ (notation as in Ding and vanderWeele (2016)).
[3]E-values are computed for upper tertile ($s = 1$) vs. lower tertile ($s = 0$) biomarker subgroups after controlling for baseline risk score, at risk or not, community of color or not; UL = upper limit.

A second sensitivity analysis was conducted to assess robustness of findings on correlates of vaccine efficacy as a function of the quantitative antibody marker level varying over its whole range, which builds on the analyses that assumed no-unmeasured confounding that were reported in **Fig. 4C** for ID50 titer and in **figs. S22-S28** for the other seven antibody markers. With details in the SAP and Gilbert, Fong, and Carone (*28*), the sensitivity analysis was done similarly to the analysis above for categorized markers, except now instead of specifying $RR_{UD}(0,1)$ and $RR_{EU}(0,1)$ for third tertile vs. first tertile, we specified $RR_{UD}(s^{15}, s^{85}) = 2$ and $RR_{EU}(s^{15}, s^{85}) = 2$ for s^{15} the 15th percentile of the antibody marker and s^{85} the 85th percentile of the antibody marker. We then specified unmeasured confounding across the whole range of antibody marker levels through the model

$$\log(RR_{UD}(s1, s2)) = [(s2 - s1)/ (s^{85} – s^{15})] \log(RR_{UD}(s^{15}, s^{85})) \text{ for all } s1 \leq s2,$$

with the same model used for $RR_{EU}(s1, s2)$. The result of the sensitivity analysis is point estimates of controlled vaccine efficacy CVE(s) over the range s of antibody marker levels, with 95% bootstrap pointwise confidence intervals, which build in robustness to unmeasured confounding by supposing bias that makes the estimate of the curve CVE(s) flatter. **Figures S29** and **S30** show the sensitivity analysis results for the eight antibody markers, for the markers at Day 57 and at Day 29, respectively. We interpret the results as follows. For both binding antibody markers at each time point (top panels), the point estimate of the CVE(s) curve with measured confounding is considerably flatter than under no unmeasured confounding (solid red curve vs. solid pink curve), and it is possible to draw a horizontal line between the lower and upper 95% confidence limits without intersecting either limit curve. This suggests that at the specified amount of unmeasured confounding for this quantitative marker analysis, the evidence for a CoP is not robust. In contrast, for the Day 29 ID50 and ID80 titer markers, the point estimate of the CVE(s) curve with posited measured confounding varies markedly, from 85% at the left-most point and 98% at the right-most point, constituting a 7.5-fold difference in efficacy level (7.5 = (1-.85)/(1-0.98)), and a horizontal line cannot be drawn between the lower and upper 95% confidence limits without intersecting either limit curve (where preferably the analysis would use simultaneous 95% confidence intervals). We conclude that the sensitivity analysis shows robustness of the Day 29 ID50 and ID80 neutralization titer markers as CoPs. The Day 57 ID50 and ID80 titer marker sensitivity analyses show less robustness of results compared to the Day 29 markers.

Mediation analysis

Table S9. Table of mediation effect estimates for quantitative markers with 95% confidence intervals.

Direct VE = VE comparing vaccine vs. placebo with marker set to distribution in placebo.
Indirect VE = VE in vaccinated comparing observed marker vs. hypothetical marker under placebo.
Prop. mediated = fraction of total risk reduction from vaccine attributed to antibody response.

Time	Assay	Direct VE	Indirect VE	Prop. mediated
Day 29	PsV Neutralization 50% Titer (ID50, IU50/ml)	0.560 (0.422, 0.665)	0.832 (0.769, 0.878)	0.685 (0.585, 0.784)
Day 29	PsV Neutralization 80% Titer (ID80, IU80/ml)	0.739 (0.601, 0.829)	0.717 (0.597, 0.801)	0.485 (0.345, 0.624)

In the main text, it was claimed that "Yet, under the reasonable assumption that the vaccine's effect on the risk of COVID-19 operating through the Day 57 ID50 marker is non-negative, 68% may be a lower bound on the proportion of vaccine efficacy that is mediated through ID50 levels

at both Day 29 and Day 57." The mathematical statement of this assumption is that beta >= 0, where

beta = E[Y(1, M1(0), 1, M2(1, M1(0), 1))] - E[Y(1, M1(0), 1, M2(0, M1(0), 0))].

Here Y(1, m1, 1, m2) is the potential COVID-19 outcome under assignment to both doses of the vaccine and if the Day 29 ID50 marker is set to m1 and the Day 57 ID50 marker is set to m2; M1(0) is Day 29 ID50 marker under assignment to placebo (and hence equals LOD/2); and M2(a1, m1, a2) is Day 57 ID50 marker under assignment of vaccine dose one to a1 and vaccine dose two to a2. The parameter beta measures an effect of the vaccine operating only through the Day 57 antibody marker, with Day 29 antibody marker held fixed to what it would have been under assignment to placebo.

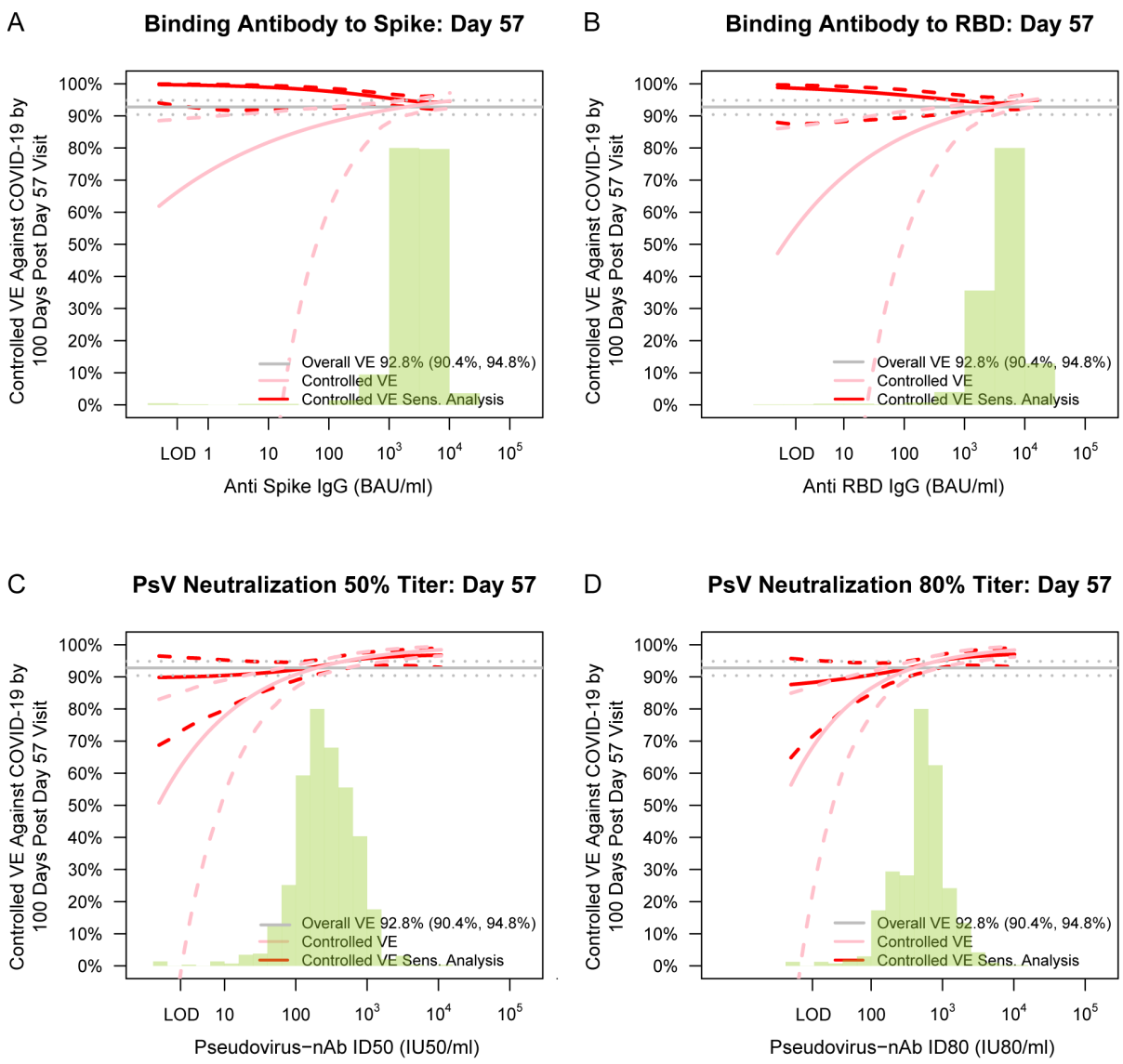


Fig. S29. Vaccine efficacy with sensitivity analysis by Day 57 (A) anti-spike IgG level, (B) anti-RBD IgG level, (C) ID50 level, or (D) ID80 level. Vaccine efficacy estimates were obtained using the method of Gilbert, Fong, and Carone (*28*). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function of the marker in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The pink solid line is point estimates assuming no unmeasured confounding; the dashed lines are bootstrap point-wise 95% CIs. The red solid line is point estimates assuming unmeasured confounding in a sensitivity analysis (dashed lines are bootstrap point-wise 95% CIs); see supplementary text S2 and the SAP (Section 12.1.2) for details of the sensitivity analysis. The horizontal gray line is the overall vaccine efficacy from 7 to 100 days post Day 57, with the dotted gray lines indicating the 95% CIs (this number 92.8% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). LOD, limit of detection.

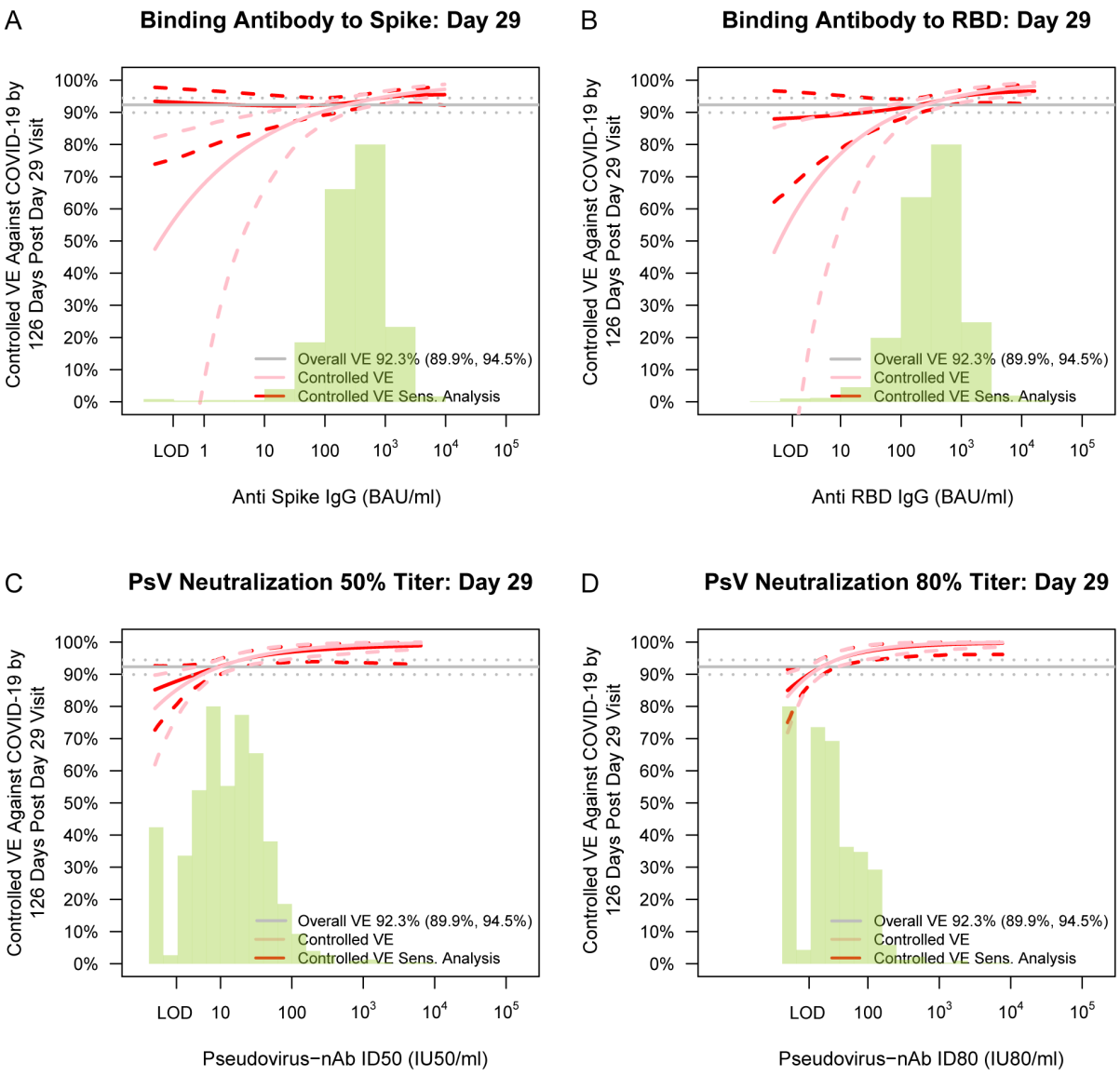


Fig. S30. Vaccine efficacy with sensitivity analysis by Day 29 (A) anti-spike IgG level, (B) anti-RBD IgG level, (C) ID50 level, or (D) ID80 level. Vaccine efficacy estimates were obtained using the method of Gilbert, Fong, and Carone (*28*). The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function of the marker in baseline SARS-CoV-2 negative per-protocol vaccine recipients. The pink solid line is point estimates assuming no unmeasured confounding; the dashed lines are bootstrap point-wise 95% CIs. The red solid line is point estimates assuming unmeasured confounding in a sensitivity analysis (dashed lines are bootstrap point-wise 95% CIs); see supplementary text S2 (and the SAP Section 12.1.2) for details of the sensitivity analysis. The horizontal gray line is the overall vaccine efficacy from 7 to 126 days post Day 29, with the dotted gray lines indicating the 95% CIs (this number 92.3% differs from the 94.1% reported in (*6*), which was based on counting COVID-19 endpoints starting 14 days post Day 29). LOD, limit of detection.

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