Supplementary Materials for "Immune Correlates Analysis of a Single Ad26.COV2.S Dose in the ENSEMBLE COVID-19 Vaccine Efficacy Clinical Trial" by Fong et al.

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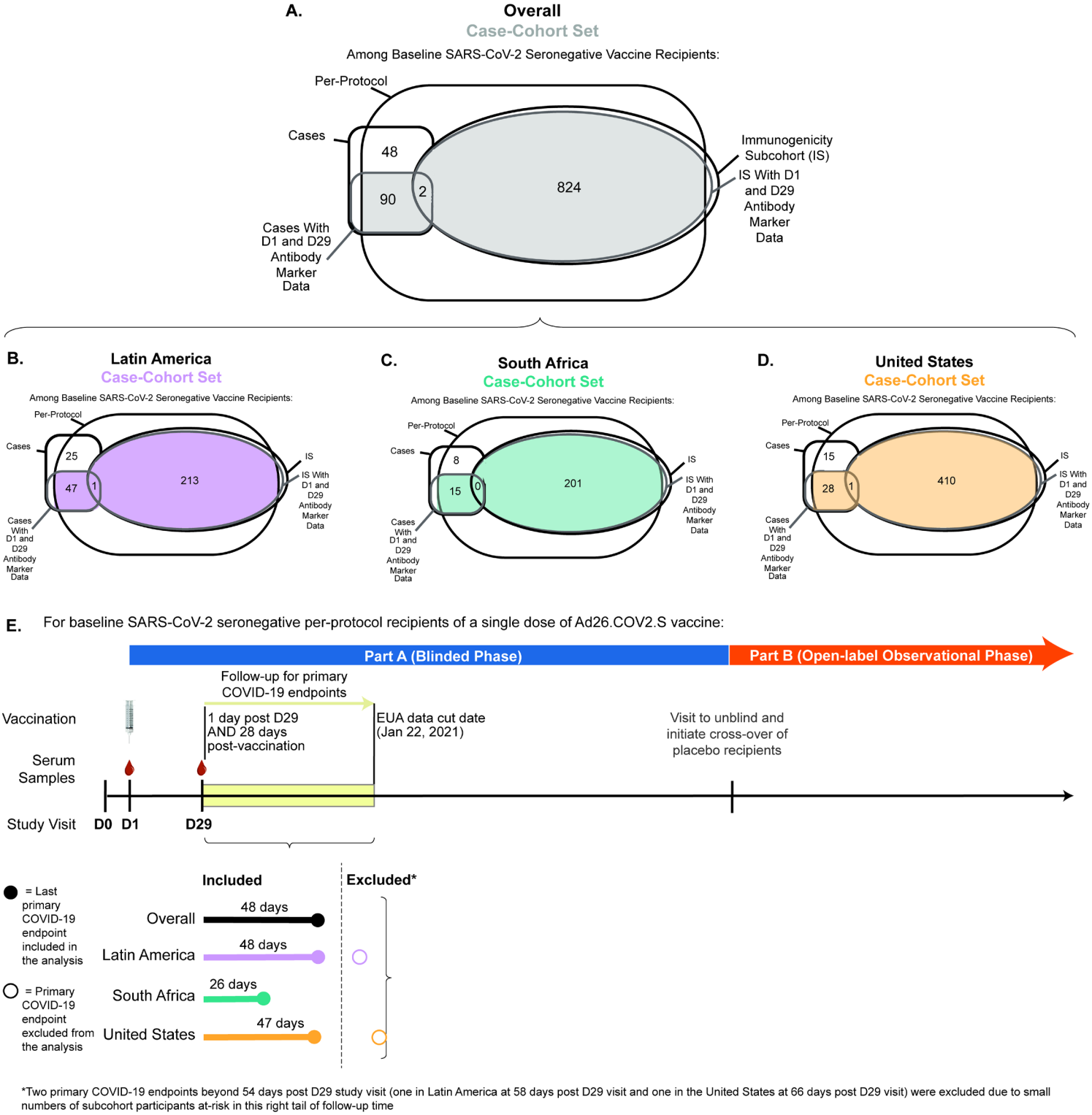
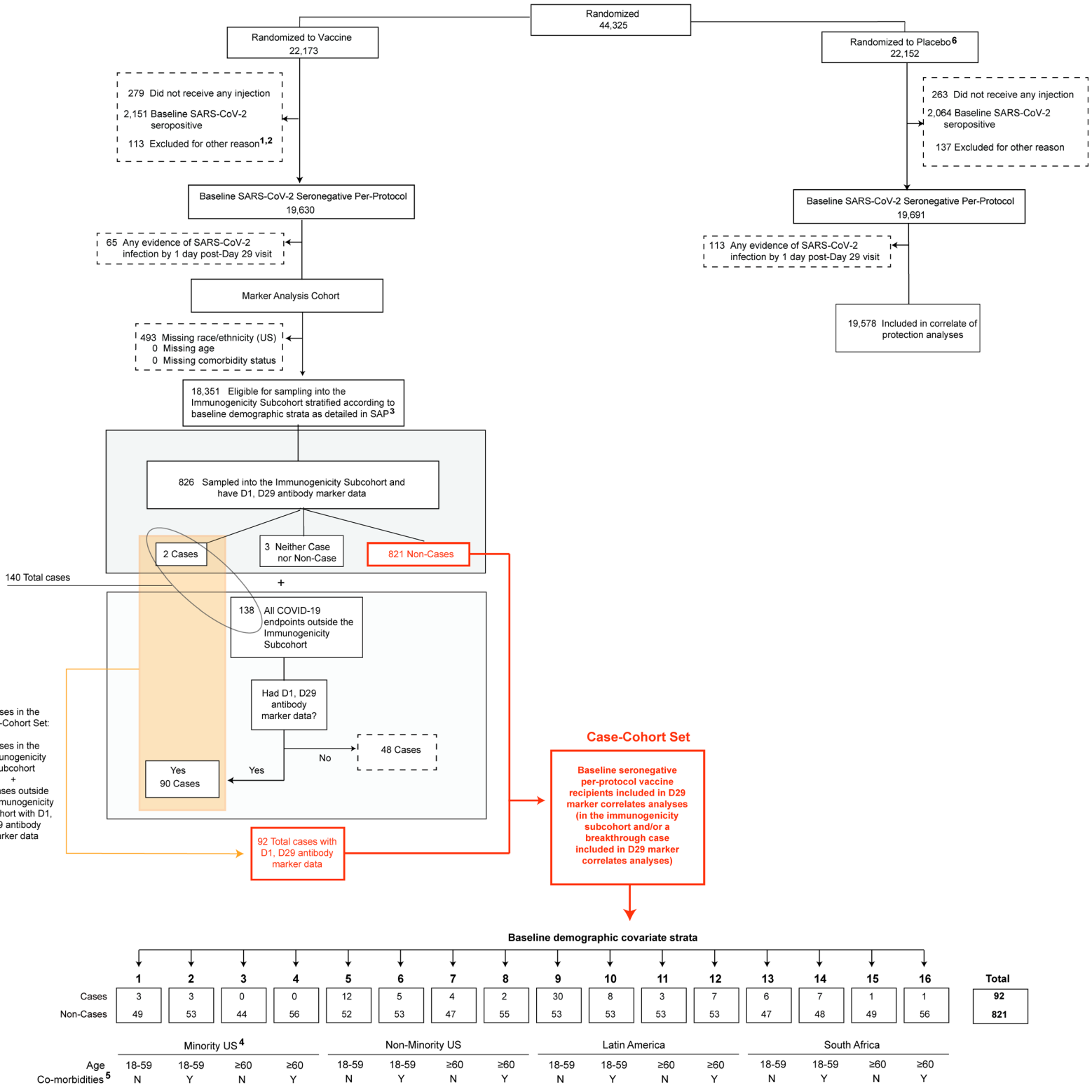
Extended Data Figure 1. Case-cohort set and trial timeline. A) Case-cohort set. **B-D)** Distribution of participants in the case-cohort set by geographic region: **B)** Latin America, **C)** South Africa, **D)** US. **E)** Phases of the ENSEMBLE trial, timing of Ad26.COV2.S dose and serum sampling, and time period for diagnosis of the COVID-19 endpoint.



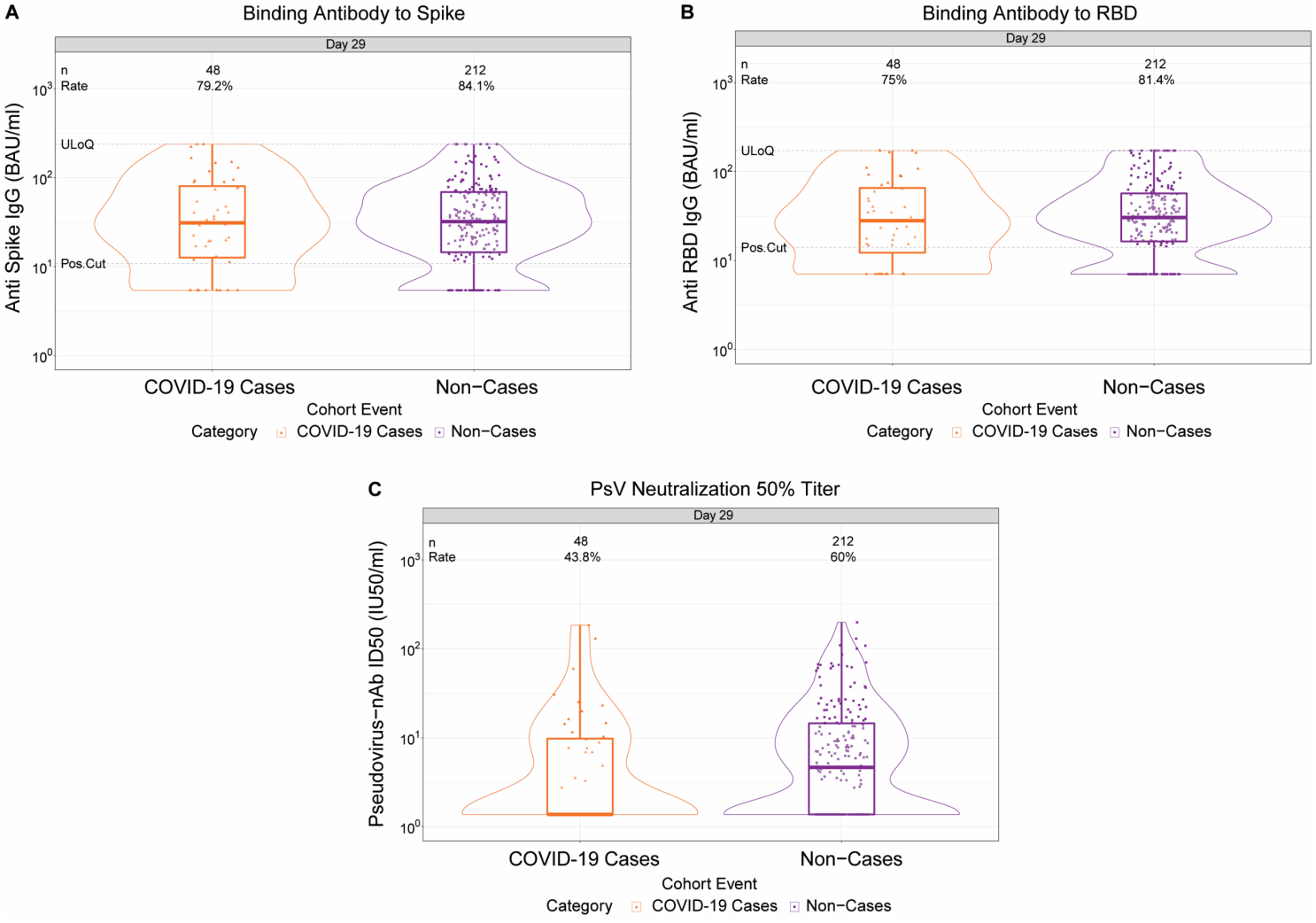
*Two primary COVID-19 endpoints beyond 54 days post D29 study visit (one in Latin America at 58 days post D29 visit and one in the United States at 66 days post D29 visit) were excluded due to small numbers of subcohort participants at-risk in this right tail of follow-up time

Extended Data Figure 2. Flowchart of study participants from enrollment to the case-cohort set of baseline SARS-CoV-2 seronegative per-protocol participants.

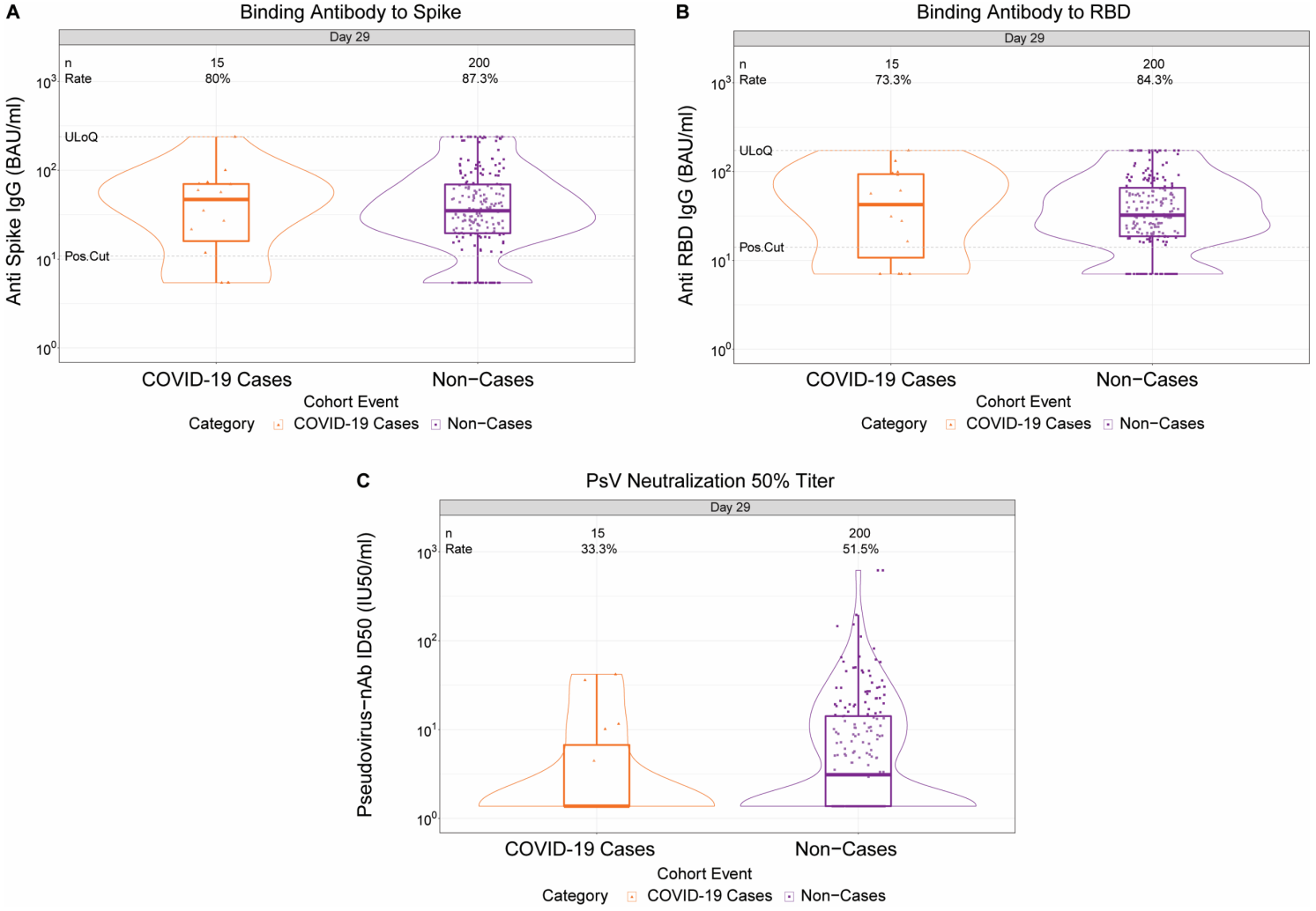


1 Participants could have been excluded for more than one reason.
2 Other reasons for exclusion included RT-PCR positive at baseline, violated inclusion or exclusion criteria, received wrong vaccine or incorrect dose, received disallowed concomitant medication, or other.
3 See the SAP for details.
4 Minority is defined as the complement of being known to be White Non-Hispanic. White Non-Hispanic is defined as Race=White and Ethnicity=Not Hispanic or Latino. All other Race subgroups are defined as Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Other, Not reported, or Unknown. (In Latin America, the American Indian or Alaska Native category was labeled as "Indigenous South American".) Minority status was only reported in the U.S.
5 Co-morbidities are listed in Table S4 of Sadoff et al. 2021, NEJM and consisted of conditions that have been associated with increased risk of severe COVID-19.
6 Placebo recipient ptids are used in the correlate of protection analyses. However, 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.

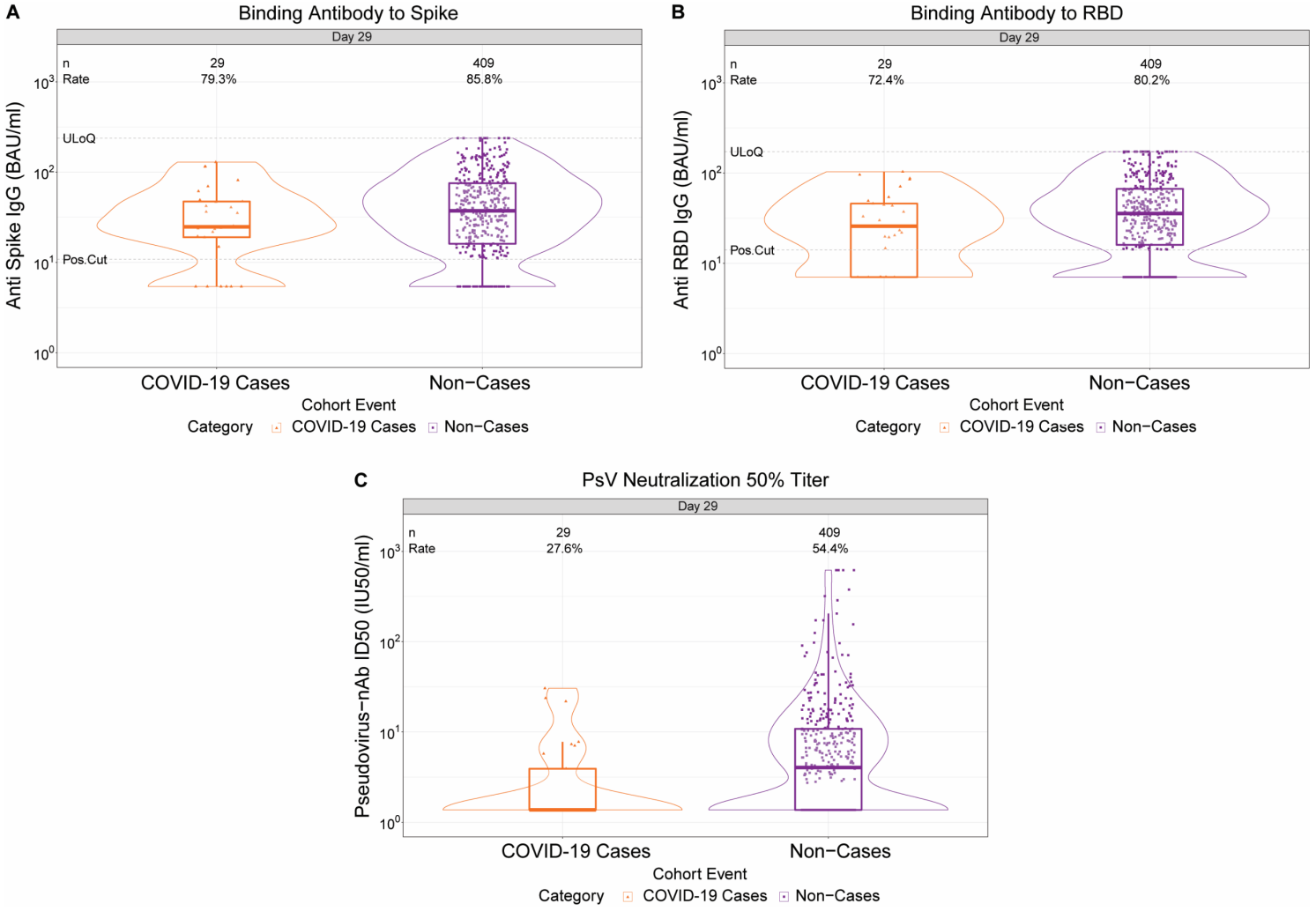
Extended Data Figure 3. D29 antibody marker level in participants in Latin America by COVID-19 outcome status. (A) Anti-spike IgG concentration, (B) anti-receptor binding domain (RBD) IgG concentration, and (C) pseudovirus (PsV) neutralization ID50 titer. Data points are from the Latin America subgroup of baseline SARS-CoV-2 seronegative per-protocol vaccine recipients in the set. The violin plots contain interior box plots with upper and lower horizontal edges the 25th and 75th percentiles of antibody level and middle line the 50th percentile, and vertical bars the distance from the 25th (or 75th) percentile of antibody level and the minimum (or maximum) antibody level within the 25th (or 75th) percentile of antibody level minus (or plus) 1.5 times the interquartile range. Each side shows a rotated probability density (estimated by a kernel density estimator with a default Gaussian kernel) of the data. Positive response rates were computed with inverse probability of sampling weighting. Pos.Cut, Positivity cut-off. Positive response for spike IgG was defined by IgG > 10.8424 BAU/ml and for RBD IgG was defined by IgG > 14.0858 BAU/ml. ULoQ, upper limit of quantitation. ULoQ = 238.1165 BAU/ml for spike IgG and 172.5755 BAU/ml for RBD IgG. LLoQ, lower limit of quantitation. Positive response for ID50 was defined by value > LLoQ (2.7426 IU50/ml). ULoQ = 619.3052 IU50/ml for ID50. Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset both ≥ 1 day post D29 and ≥ 28 days post-vaccination) up to 54 days post D29 but no later than January 22, 2021.



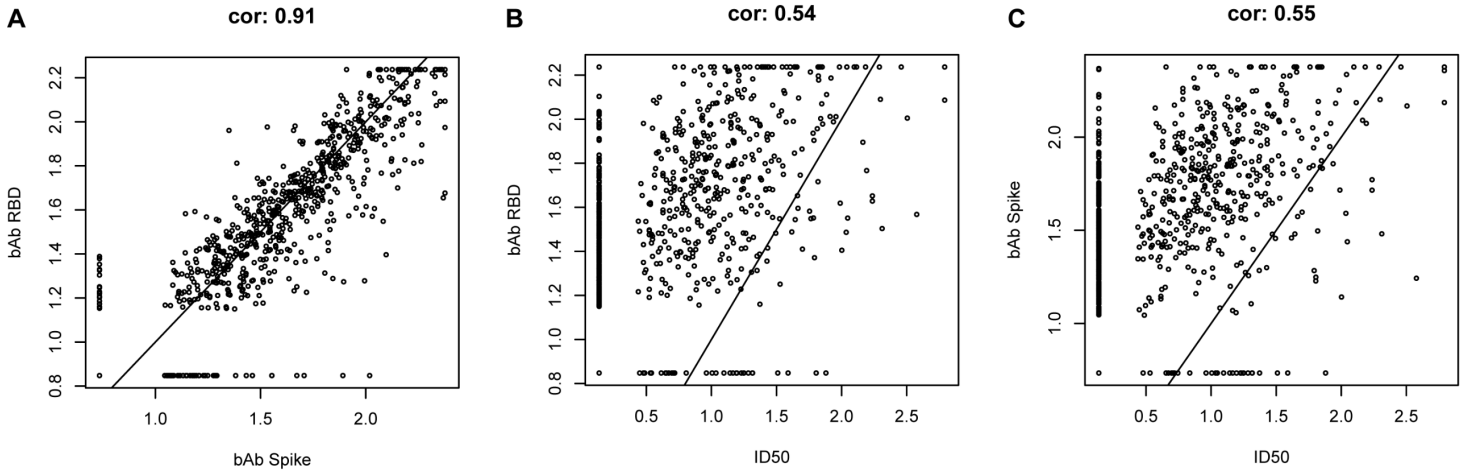
Extended Data Figure 4. D29 antibody marker level in participants in South Africa by COVID-19 outcome status. (A) Anti-spike IgG concentration, (B) anti-receptor binding domain (RBD) IgG concentration, and (C) pseudovirus (PsV) neutralization ID50 titer. Data points are from the South Africa subgroup of baseline SARS-CoV-2 seronegative per-protocol vaccine recipients in the set. The violin plots contain interior box plots with upper and lower horizontal edges the 25th and 75th percentiles of antibody level and middle line the 50th percentile, and vertical bars the distance from the 25th (or 75th) percentile of antibody level and the minimum (or maximum) antibody level within the 25th (or 75th) percentile of antibody level minus (or plus) 1.5 times the interquartile range. Each side shows a rotated probability density (estimated by a kernel density estimator with a default Gaussian kernel) of the data. Positive response rates were computed with inverse probability of sampling weighting. Pos.Cut, Positivity cut-off. Positive response for spike IgG was defined by IgG > 10.8424 BAU/ml and for RBD IgG was defined by IgG > 14.0858 BAU/ml. ULoQ, upper limit of quantitation. ULoQ = 238.1165 BAU/ml for spike IgG and 172.5755 BAU/ml for RBD IgG. LLoQ, lower limit of quantitation. Positive response for ID50 was defined by value > LLoQ (2.7426 IU50/ml). ULoQ = 619.3052 IU50/ml for ID50. Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset both ≥ 1 day post D29 and ≥ 28 days post-vaccination) up to 54 days post D29 but no later than January 22, 2021.



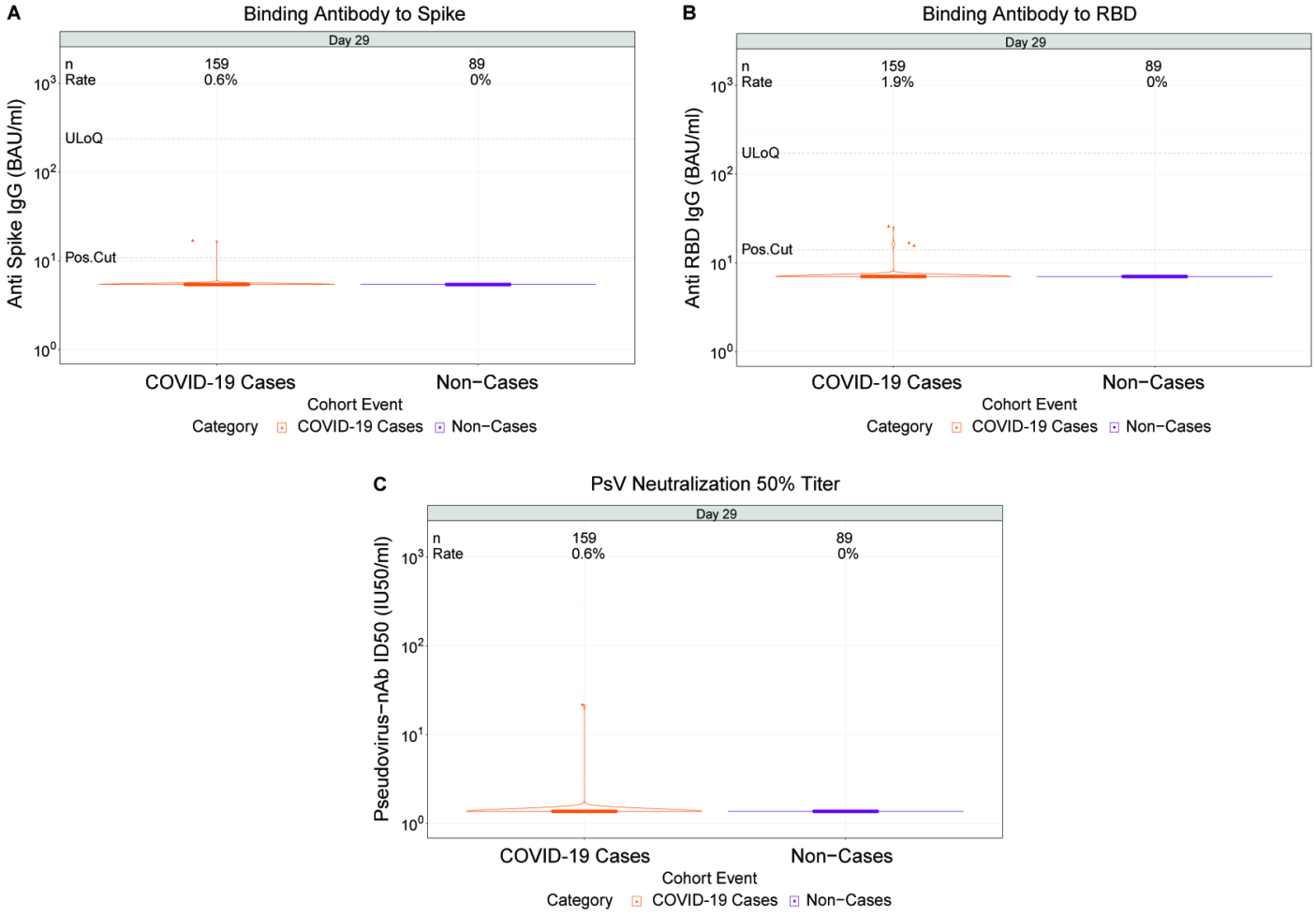
Extended Data Figure 5. D29 antibody marker level in participants in the United States by COVID-19 outcome status. (A) Anti-spike IgG concentration, (B) anti-receptor binding domain (RBD) IgG concentration, and (C) pseudovirus neutralization ID50 titer. Data points are from the United States subgroup of baseline SARS-CoV-2 seronegative per-protocol vaccine recipients in the set. The violin plots contain interior box plots with upper and lower horizontal edges the 25th and 75th percentiles of antibody level and middle line the 50th percentile, and vertical bars the distance from the 25th (or 75th) percentile of antibody level and the minimum (or maximum) antibody level within the 25th (or 75th) percentile of antibody level minus (or plus) 1.5 times the interquartile range. Each side shows a rotated probability density (estimated by a kernel density estimator with a default Gaussian kernel) of the data. Positive response rates were computed with inverse probability of sampling weighting. Pos.Cut, Positivity cut-off. Positive response for spike IgG was defined by IgG > 10.8424 BAU/ml and for RBD IgG was defined by IgG > 14.0858 BAU/ml. ULoQ, upper limit of quantitation. ULoQ = 238.1165 BAU/ml for spike IgG and 172.5755 BAU/ml for RBD IgG. LLoQ, lower limit of quantitation. Positive response for ID50 was defined by value > LLoQ (2.7426 IU50/ml). ULoQ = 619.3052 IU50/ml for ID50. Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset both ≥ 1 day post D29 and ≥ 28 days post-vaccination) up to 54 days post D29 but no later than January 22, 2021.



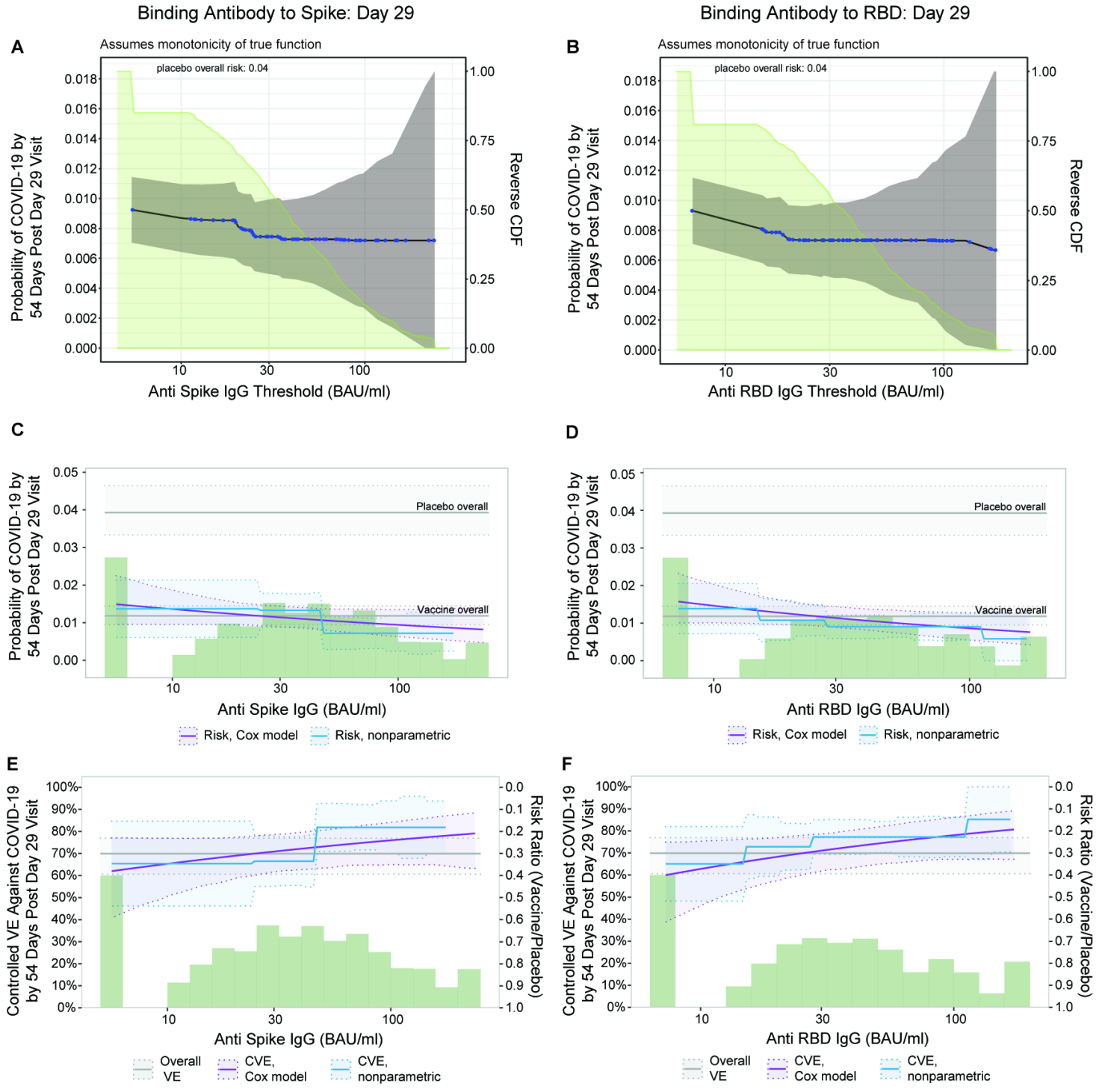
Extended Data Figure 6. Correlations of D29 antibody markers in baseline SARS-CoV-2 seronegative per-protocol vaccine recipients in the immunogenicity subcohort. A) Scatterplot of receptor binding domain (RBD) IgG and spike IgG; **B)** Scatterplot of RBD IgG and PsV-nAb ID50; **C)** Scatterplot of spike IgG and PsV-nAb ID50. Cor = Spearman rank correlation.



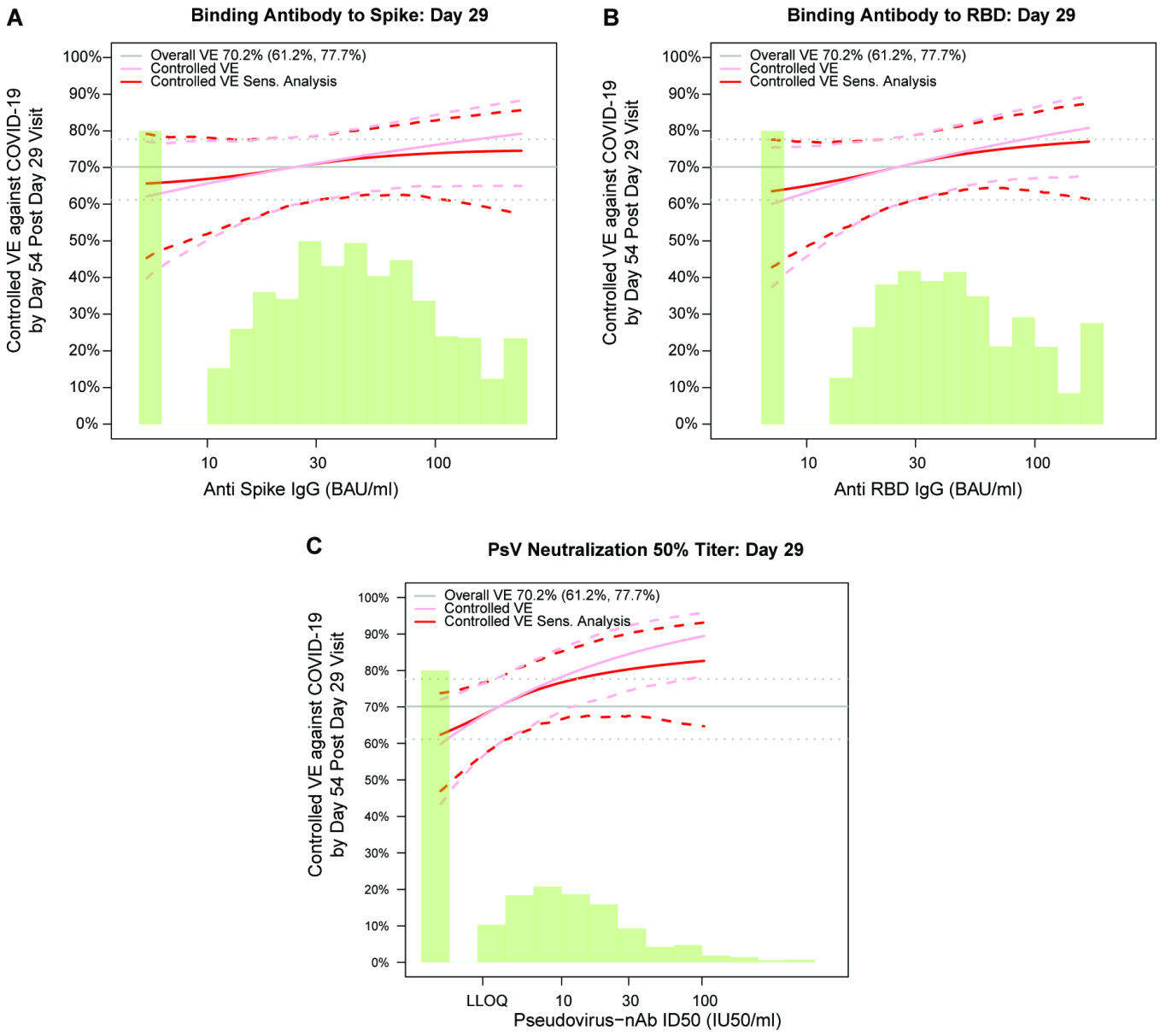
Extended Data Figure 7. Antibody marker values [spike IgG, receptor binding domain (RBD) IgG, ID50] by COVID-19 outcome status in placebo recipients. Data points are from baseline SARS-CoV-2 seronegative per-protocol placebo recipients in the case-cohort set. The violin plots contain interior box plots with upper and lower horizontal edges the 25th and 75th percentiles of antibody level and middle line the 50th percentile, and vertical bars the distance from the 25th (or 75th) percentile of antibody level and the minimum (or maximum) antibody level within the 25th (or 75th) percentile of antibody level minus (or plus) 1.5 times the interquartile range. Each side shows a rotated probability density (estimated by a kernel density estimator with a default Gaussian kernel) of the data. Positive response rates were computed with inverse probability of sampling weighting. Pos.Cut, Positivity cut-off. Positive response for spike IgG was defined by IgG > 10.8424 BAU/ml and for RBD IgG was defined by IgG > 14.0858 BAU/ml. ULoQ, upper limit of quantitation. ULoQ = 238.1165 BAU/ml for spike IgG and 172.5755 for RBD IgG. LLoQ, lower limit of quantification. Positive response for ID50 was defined by value > LLoQ (2.7426 IU50/ml). ULoQ = 619.3052 IU50/ml for ID50. Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset both ≥ 1 day post D29 and ≥ 28 days post-vaccination) up to 54 days post D29 but no later than January 22, 2021.



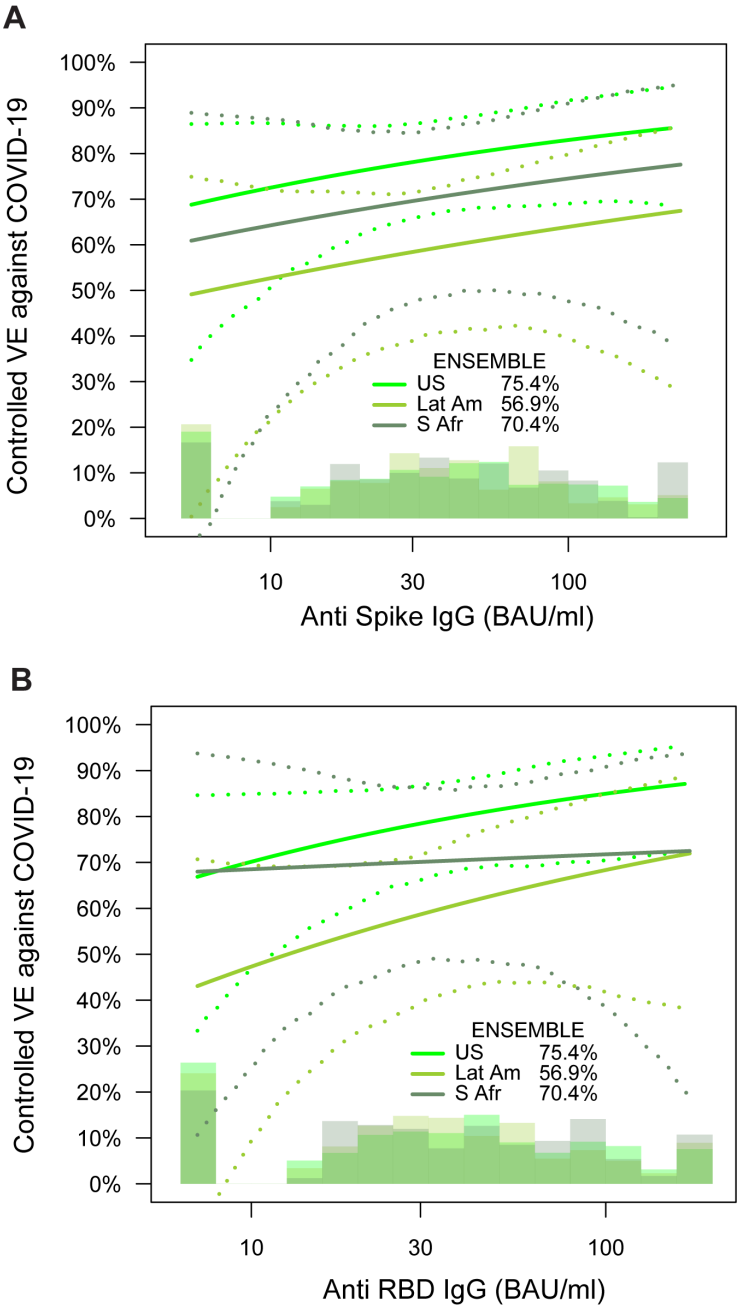
Extended Data Figure 8. Analyses of spike IgG and receptor binding domain (RBD) IgG as correlates of risk and as correlates of protection. Analyses were peformed in baseline SARS-CoV-2 seronegative per-protocol vaccine recipients. **A, B)** Covariate-adjusted cumulative incidence of COVID-19 by 54 days post D29 by vaccinated baseline SARS-CoV-2 seronegative per-protocol subgroups defined by D29 **(A)** anti-spike IgG or **(B)** anti-RBD IgG concentration above a threshold, with reverse cumulative distribution function (CDF) of D29 marker level overlaid in green. The blue dots are point estimates at each COVID-19 primary endpoint linearly interpolated by solid black lines; the gray shaded area is pointwise 95% confidence intervals (CIs). The estimates and CIs were adjusted using the assumption that the true threshold-response is nonincreasing. The upper boundary of the green shaded area is the estimate of the reverse cumulative distribution function (CDF) of D29 marker level in baseline SARS-CoV-2 seronegative per-protocol vaccine recipients. The vertical red dashed line is the D29 marker threshold above which no COVID-19 endpoints were observed (in the time frame of 1 through 54 days post D29). **C, D)** Covariate-adjusted cumulative incidence of COVID-19 by 54 days post D29 by D29 **(C)** anti-spike IgG or **(D)** anti-RBD IgG concentration, estimated using (solid purple line) a Cox model or (solid blue line) a nonparametric method. 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 1 to 54 days post D29 in placebo and vaccine recipients, respectively. **E, F)** Vaccine efficacy (solid purple line) by D29 **(E)** anti-spike IgG or **(F)** anti-RBD IgG concentration, estimated using a Cox proportional hazards implementation of [1]. The dashed black lines indicate bootstrap point-wise 95% CIs. Vaccine efficacy (solid blue line) by D29 **(E)** anti-spike IgG concentration or **(F)** anti-RBD IgG concentration, estimated using a nonparametric implementation of Gilbert et al.[1] (see SAP). The blue shaded area represents the 95% CIs. In **C**-**F**, curves are plotted over the range from Positivity Cut-off/2 to the 97.5th percentile = (**C**, **E**) 238 BAU/ml for Spike IgG or (**D**, **F**) 173 BAU/ml for RBD IgG; In **C**-**F**, the green histogram is an estimate of the density of D29 marker and the horizontal gray line is the overall vaccine efficacy from 1 to 54 days post D29, with the dotted gray lines indicating the 95% CIs. Baseline covariates adjusted for were baseline risk score and geographic region.


Binding Antibody to Spike: Day 29
Binding Antibody to RBD: Day 29
A
B
Assumes monotonicity of true function
placebo overall risk: 0.04
Probability of COVID-19 by 54 Days Post Day 29 Visit
Reverse CDF
Anti Spike IgG Threshold (BAU/ml)
Anti RBD IgG Threshold (BAU/ml)
C
D
Placebo overall
Vaccine overall
Anti Spike IgG (BAU/ml)
Anti RBD IgG (BAU/ml)
Risk, Cox model
Risk, nonparametric
E
F
Controlled VE Against COVID-19 by 54 Days Post Day 29 Visit
Risk Ratio (Vaccine/Placebo)
Overall VE
CVE, Cox model
CVE, nonparametric

Extended Data Figure 9. Vaccine efficacy with sensitivity analysis by D29 (A) anti-spike IgG concentration, (B) anti-receptor binding domain (RBD) IgG concentration, or (C) pseudovirus (PsV) neutralization ID50 titer. Vaccine efficacy estimates were obtained a Cox proportional hazards implementation of ref.[1]. 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 seronegative 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 the SAP section 15.1 for details of the sensitivity analysis. The horizontal gray line is the overall vaccine efficacy from 1 to 54 days post D29, with the dotted gray lines indicating the 95% CIs. All curves are plotted over the range from (A, B) Positivity Cut-off/2 to the 97.5th percentile = 238 BAU/ml for Spike IgG or 173 BAU/ml for RBD IgG; (C) LLOQ/2 to the 97.5th percentile = 96.3 IU50/ml for PsV nAb ID50.



Extended Data Figure 10. Vaccine efficacy (solid lines) in baseline SARS-CoV-2 seronegative per-protocol vaccine recipients by A) D29 spike IgG or B) D29 receptor binding domain (RBD) IgG in ENSEMBLE by geographic region (US, United States; Lat Am, Latin America; S Afr, South Africa), estimated using the Cox proportional hazards implementation of Gilbert et al.[1] The dashed lines indicate bootstrap point-wise 95% CIs. The follow-up periods for the VE assessment were: A) ENSEMBLE-US, 1 to 53 days post D29; ENSEMBLE-Lat Am, 1 to 48 days post D29; ENSEMBLE-S Afr, 1 to 40 days post D29. The green histograms are an estimate of the density of D29 marker level by geographic region. Baseline covariates adjusted for were baseline risk score and geographic region. Curves are plotted over the range from Positivity Cut-off/2 to the 97.5th percentile = (**A**) 238 BAU/ml for Spike IgG; (**B**) 173 BAU/ml for RBD IgG.



Supplementary Table 1. Sample sizes of baseline SARS-CoV-2 seronegative per-protocol vaccine recipients included in immune correlates analyses, by baseline sampling strata and case/non-case strata.

Case-cohort set = Baseline SARS-CoV-2 seronegative per-protocol vaccine recipients included in D29 marker correlates analysis [in the immunogenicity subcohort (IS) and/or a breakthrough COVID-19 case)]*

	Baseline Sampling Strata of Baseline SARS-CoV-2 Seronegative Per-Protocol Vaccine Participants Included in Correlates Analyses																			
																		Subtotals		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total	US	Lat Am	S Afr
Breakthrough COVID-19 cases (both within and outwith the IS) with Ab marker data	3	3	0	0	12	5	4	2	30	8	3	7	6	7	1	1	92	29	48	15
Non-cases in the IS with Ab marker data	49	53	44	56	52	53	47	55	53	53	53	53	47	48	49	56	821	409	212	200

Ab, antibody; IS, immunogenicity subcohort; Lat Am, Latin America; S Afr, South Africa; US, United States.

Demographic covariate strata:

1. Minority U.S., age 18-59, comorbidities N
2. Minority U.S., age 18-59, comorbidities Y
3. Minority U.S., age ≥ 60, comorbidities N
4. Minority U.S., age ≥ 60, comorbidities Y
5. non-Minority U.S., age 18-59, comorbidities N
6. non-Minority U.S., age 18-59, comorbidities Y
7. non-Minority U.S., age ≥ 60, comorbidities N
8. non-Minority U.S., age ≥ 60, comorbidities Y
9. Latin America, age 18-59, comorbidities N
10. Latin America, age 18-59, comorbidities Y
11. Latin America, age ≥ 60, comorbidities N
12. Latin America, age ≥ 60, comorbidities Y
13. South Africa, age 18-59, comorbidities N
14. South Africa, age 18-59, comorbidities Y
15. South Africa, age ≥ 60, comorbidities N
16. South Africa, age ≥ 60, comorbidities Y

Minority is defined as the complement of being known to be White Non-Hispanic. Minority status was only reported in the U.S.
White Non-Hispanic is defined as Race=White and Ethnicity=Not Hispanic or Latino. All other Race subgroups are defined as Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Other, Not reported, or Unknown. (In Latin America, the American Indian or Alaska Native category was labeled as “Indigenous South American”.)

Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset that was both ≥ 28 days post-vaccination and ≥ 1 day post-D29) through to the data cut (January 22, 2021).
Non-cases/Controls are baseline seronegative per-protocol vaccine recipients sampled into the immunogenicity subcohort with no evidence of SARS-CoV-2 infection up to the end of the correlates study period, which is up to 54 days post D29 but no later than the data cut (January 22, 2021).

Supplementary Table 2. Demographics and clinical characteristics of baseline SARS-CoV-2 seronegative per-protocol trial participants in the immunogenicity subcohort and thus have D1, D29 antibody data.

Characteristics	Vaccine (N = 826)	Placebo (N = 90)	Total (N = 916)
Age			
Age 18-59	412 (49.9%)	42 (46.7%)	454 (49.6%)
Age ≥ 60	414 (50.1%)	48 (53.3%)	462 (50.4%)
Mean (Range)	49.4 (18.0, 80.0)	51.8 (18.0, 80.0)	49.7 (18.0, 80.0)
BMI			
Underweight BMI < 18.5	18 (2.2%)	2 (2.2%)	20 (2.2%)
Normal 18.5 ≤ BMI < 25	230 (27.8%)	20 (22.2%)	250 (27.3%)
Overweight 25 ≤ BMI < 30	294 (35.6%)	34 (37.8%)	328 (35.8%)
Obese BMI ≥ 30	284 (34.4%)	34 (37.8%)	318 (34.7%)
Risk for Severe COVID-19			
At-risk	429 (51.9%)	45 (50.0%)	474 (51.7%)
Not at-risk	397 (48.1%)	46 (50.0%)	442 (48.3%)
Age, Risk for Severe COVID-19			
Age 18-59 At-risk	208 (25.2%)	21 (23.3%)	229 (25.0%)
Age 18-59 Not at-risk	204 (24.7%)	21 (23.3%)	225 (24.6%)
Age ≥ 60 At-risk	221 (26.8%)	24 (26.7%)	245 (26.7%)
Age ≥ 60 Not at-risk	193 (23.4%)	24 (26.7%)	217 (23.7%)
Sex Assigned at Birth			
Female	373 (45.2%)	37 (41.1%)	410 (44.8%)
Male	453 (54.8%)	53 (58.9%)	506 (55.2%)
Hispanic or Latino Ethnicity			
Hispanic or Latino	307 (37.2%)	32 (35.6%)	339 (37.0%)
Not Hispanic or Latino	492 (59.6%)	54 (60.0%)	546 (59.6%)
Not reported and unknown	27 (3.3%)	4 (4.4%)	31 (3.4%)
Race			
White	434 (52.5%)	48 (53.3%)	482 (52.6%)
Black or African American	245 (29.7%)	26 (28.9%)	271 (29.6%)
Asian	15 (1.8%)		15 (1.6%)
American Indian or Alaska Native	58 (7.0%)	6 (6.7%)	64 (7.0%)
Native Hawaiian or Other Pacific Islander	3 (0.4%)		3 (0.3%)
Multiracial	40 (4.8%)	7 (7.8%)	47 (5.1%)
Not reported and unknown	31 (3.8%)	3 (3.3%)	34 (3.7%)
Underrepresented Minority Status in the U.S.*			
White Non-Hispanic	208 (25.2%)	24 (26.7%)	232 (25.3%)
Communities of Color	203 (24.6%)	23 (25.6%)	226 (24.7%)
Country			
United States	411 (49.8%)	47 (52.2%)	458 (50.0%)
Argentina	33 (4.0%)	2 (2.2%)	35 (3.8%)

Brazil	89 (10.8%)	12 (13.3%)	101 (11.0%)
Chile	11 (1.3%)	3 (3.3%)	14 (1.5%)
Colombia	53 (6.4%)	5 (5.6%)	58 (6.3%)
Mexico	7 (0.8%)	2 (2.2%)	9 (1.0%)
Peru	21 (2.5%)	1 (1.1%)	22 (2.4%)
South Africa	201 (24.3%)	18 (20.0%)	219 (23.9%)
HIV Status			
Negative	798 (96.6%)	88 (97.8%)	886 (96.7%)
Living with HIV	28 (3.4%)	2 (2.2%)	30 (3.3%)

*Data on minority status was only gathered in the U.S.

This table summarizes characteristics of per-protocol participants in the immunogenicity subcohort, which was randomly sampled from the study cohort. The sampling was stratified by strata defined by enrollment characteristics: Assigned randomization arm × Baseline SARS-CoV-2 seronegative vs. seropositive × Randomization strata. The U.S. subcohort includes 8 baseline demographic strata; the Latin America and South Africa subcohorts each include 4 baseline demographic strata.

Supplementary Table 3. Demographics and clinical characteristics of baseline SARS-CoV-2 seronegative per-protocol trial participants in the United States subset of the immunogenicity subcohort (strata 1-8) and thus have D1, D29 antibody data.

Characteristics	Vaccine (N = 411)	Placebo (N = 47)	Total (N = 458)
Age			
Age 18-59	209 (50.9%)	24 (51.1%)	233 (50.9%)
Age ≥ 60	202 (49.1%)	23 (48.9%)	225 (49.1%)
Mean (Range)	48.9 (18.0, 80.0)	52.0 (18.0, 80.0)	49.3 (18.0, 80.0)
BMI			
Underweight BMI < 18.5	1 (0.2%)	1 (2.1%)	2 (0.4%)
Normal 18.5 ≤ BMI < 25	106 (25.8%)	11 (23.4%)	117 (25.5%)
Overweight 25 ≤ BMI < 30	153 (37.2%)	14 (29.8%)	167 (36.5%)
Obese BMI ≥ 30	151 (36.7%)	21 (44.7%)	172 (37.6%)
Risk for Severe COVID-19			
At-risk	217 (52.8%)	26 (55.3%)	243 (53.1%)
Not at-risk	194 (47.2%)	21 (44.7%)	215 (46.9%)
Age, Risk for Severe COVID-19			
Age 18-59 At-risk	106 (25.8%)	13 (27.7%)	119 (26.0%)
Age 18-59 Not at-risk	103 (25.1%)	11 (23.4%)	114 (24.9%)
Age ≥ 60 At-risk	111 (27.0%)	13 (27.7%)	124 (27.1%)
Age ≥ 60 Not at-risk	91 (22.1%)	10 (21.3%)	101 (22.1%)
Sex Assigned at Birth			
Female	191 (46.5%)	21 (44.7%)	212 (46.3%)
Male	220 (53.5%)	26 (55.3%)	246 (53.7%)
Hispanic or Latino Ethnicity			
Hispanic or Latino	104 (25.3%)	9 (19.1%)	113 (24.7%)
Not Hispanic or Latino	292 (71.0%)	36 (76.6%)	328 (71.6%)
Not reported and unknown	15 (3.6%)	2 (4.3%)	17 (3.7%)
Race			
White	268 (65.2%)	30 (63.8%)	298 (65.1%)
Black or African American	93 (22.6%)	13 (27.7%)	106 (23.1%)
Asian	13 (3.2%)		13 (2.8%)
American Indian or Alaska Native	11 (2.7%)	1 (2.1%)	12 (2.6%)
Native Hawaiian or Other Pacific Islander	2 (0.5%)		2 (0.4%)
Multiracial	7 (1.7%)	2 (4.3%)	9 (2.0%)
Not reported and unknown	17 (4.1%)	1 (2.1%)	18 (3.9%)
Underrepresented Minority Status in the U.S.			
White Non-Hispanic	208 (50.6%)	24 (51.1%)	232 (50.7%)
Communities of Color	203 (49.4%)	23 (48.9%)	226 (49.3%)
Country			
United States	411 (100.0%)	47 (100.0%)	458 (100.0%)
HIV Status			

Negative	406 (98.8%)	46 (97.9%)	452 (98.7%)
Living with HIV	5 (1.2%)	1 (2.1%)	6 (1.3%)

This table summarizes characteristics of per-protocol participants in the United States subset of the immunogenicity subcohort (strata 1-8), which was randomly sampled from the study cohort. The sampling was stratified by strata defined by enrollment characteristics: Assigned randomization arm × Baseline SARS-CoV-2 seronegative vs. seropositive × Randomization strata.

Supplementary Table 4. Demographics and clinical characteristics of baseline SARS-CoV-2 seronegative per-protocol trial participants in the Latin America subset of the immunogenicity subcohort (strata 9-12) and thus have D1, D29 antibody data.

Characteristics	Vaccine (N = 214)	Placebo (N = 25)	Total (N = 239)
Age			
Age 18-59	107 (50.0%)	12 (48.0%)	119 (49.8%)
Age ≥ 60	107 (50.0%)	13 (52.0%)	120 (50.2%)
Mean (Range)	49.2 (18.0, 80.0)	50.4 (18.0, 80.0)	49.3 (18.0, 80.0)
BMI			
Underweight BMI < 18.5	1 (0.5%)		1 (0.4%)
Normal 18.5 ≤ BMI < 25	53 (24.8%)	6 (24.0%)	59 (24.7%)
Overweight 25 ≤ BMI < 30	92 (43.0%)	12 (48.0%)	104 (43.5%)
Obese BMI ≥ 30	68 (31.8%)	7 (28.0%)	75 (31.4%)
Risk for Severe COVID-19			
At-risk	108 (50.5%)	11 (44.0%)	119 (49.8%)
Not at-risk	106 (49.5%)	14 (56.0%)	120 (50.2%)
Age, Risk for Severe COVID-19			
Age 18-59 At-risk	54 (25.2%)	5 (20.0%)	59 (24.7%)
Age 18-59 Not at-risk	53 (24.8%)	7 (28.0%)	60 (25.1%)
Age ≥ 60 At-risk	54 (25.2%)	6 (24.0%)	60 (25.1%)
Age ≥ 60 Not at-risk	53 (24.8%)	7 (28.0%)	60 (25.1%)
Sex Assigned at Birth			
Female	82 (38.3%)	8 (32.0%)	90 (37.7%)
Male	132 (61.7%)	17 (68.0%)	149 (62.3%)
Hispanic or Latino Ethnicity			
Hispanic or Latino	203 (94.9%)	23 (92.0%)	226 (94.6%)
Not Hispanic or Latino	7 (3.3%)		7 (2.9%)
Not reported and unknown	4 (1.9%)	2 (8.0%)	6 (2.5%)
Race			
White	128 (59.8%)	14 (56.0%)	142 (59.4%)
Black or African American	8 (3.7%)	1 (4.0%)	9 (3.8%)
Asian	1 (0.5%)		1 (0.4%)
Multiracial	21 (9.8%)	3 (12.0%)	24 (10.0%)
Not reported and unknown	9 (4.2%)	2 (8.0%)	11 (4.6%)
Country			
Argentina	33 (15.4%)	2 (8.0%)	35 (14.6%)
Brazil	89 (41.6%)	12 (48.0%)	101 (42.3%)
Chile	11 (5.1%)	3 (12.0%)	14 (5.9%)
Colombia	53 (24.8%)	5 (20.0%)	58 (24.3%)
Mexico	7 (3.3%)	2 (8.0%)	9 (3.8%)
Peru	21 (9.8%)	1 (4.0%)	22 (9.2%)
HIV Status			
Negative	207 (96.7%)	25 (100.0%)	232 (97.1%)

Living with HIV	7 (3.3%)	7 (2.9%)

This table summarizes characteristics of per-protocol participants in the Latin America subset of the immunogenicity subcohort (strata 9-12), which was randomly sampled from the study cohort. The sampling was stratified by strata defined by enrollment characteristics: Assigned randomization arm × Baseline SARS-CoV-2 seronegative vs. seropositive × Randomization strata.

Supplementary Table 5. Demographics and clinical characteristics of baseline SARS-CoV-2 seronegative per-protocol trial participants in the South Africa subset of the immunogenicity subcohort (strata 13-16) and thus have D1, D29 antibody data.

Characteristics	Vaccine (N = 201)	Placebo (N = 18)	Total (N = 219)
Age			
Age 18-59	96 (47.8%)	6 (33.3%)	102 (46.6%)
Age ≥ 60	105 (52.2%)	12 (66.7%)	117 (53.4%)
Mean (Range)	50.6 (18.0, 80.0)	53.3 (18.0, 80.0)	50.8 (18.0, 80.0)
BMI			
Underweight BMI < 18.5	16 (8.0%)	1 (5.6%)	17 (7.8%)
Normal 18.5 ≤ BMI < 25	71 (35.3%)	3 (16.7%)	74 (33.8%)
Overweight 25 ≤ BMI < 30	49 (24.4%)	8 (44.4%)	57 (26.0%)
Obese BMI ≥ 30	65 (32.3%)	6 (33.3%)	71 (32.4%)
Risk for Severe COVID-19			
At-risk	104 (51.7%)	8 (44.4%)	112 (51.1%)
Not at-risk	97 (48.3%)	10 (55.6%)	107 (48.9%)
Age, Risk for Severe COVID-19			
Age 18-59 At-risk	48 (23.9%)	3 (16.7%)	51 (23.3%)
Age 18-59 Not at-risk	48 (23.9%)	3 (16.7%)	51 (23.3%)
Age ≥ 60 At-risk	56 (27.9%)	5 (27.8%)	61 (27.9%)
Age ≥ 60 Not at-risk	49 (24.4%)	7 (38.9%)	56 (25.6%)
Sex Assigned at Birth			
Female	100 (49.8%)	8 (44.4%)	108 (49.3%)
Male	101 (50.2%)	10 (55.6%)	111 (50.7%)
Hispanic or Latino Ethnicity			
Not Hispanic or Latino	193 (96.0%)	18 (100.0%)	211 (96.3%)
Not reported and unknown	8 (4.0%)		8 (3.7%)
Race			
White	38 (18.9%)	4 (22.2%)	42 (19.2%)
Black or African American	144 (71.6%)	12 (66.7%)	156 (71.2%)
Asian	1 (0.5%)		1 (0.5%)
Native Hawaiian or Other Pacific Islander	1 (0.5%)		1 (0.5%)
Multiracial	12 (6.0%)	2 (11.1%)	14 (6.4%)
Not reported and unknown	5 (2.5%)		5 (2.3%)
Country			
South Africa	201 (100.0%)	18 (100.0%)	219 (100.0%)
HIV Status			
Negative	185 (92.0%)	17 (94.4%)	202 (92.2%)
Living with HIV	16 (8.0%)	1 (5.6%)	17 (7.8%)

This table summarizes characteristics of per-protocol participants in the South Africa subset of the immunogenicity subcohort (strata 13-16), which was randomly sampled from the study cohort. The sampling was stratified by strata defined by enrollment characteristics: Assigned randomization arm × Baseline SARS-CoV-2 seronegative vs. seropositive × Randomization strata.

Supplementary Table 6. D29 antibody marker response rates and geometric means (GMs) by COVID-19 outcome status, presented by ENSEMBLE geographic region. Analysis based on baseline SARS-CoV-2 seronegative per-protocol vaccine recipients in the case-cohort set. Median (interquartile range) days from vaccination to D29 was 29 (3) for Latin America, 29 (2) for South Africa, and 29 (2) for the United States. RBD, receptor-binding domain.

	COVID-19 Cases[1]			Non-Cases in Immunogenicity Subcohort[2]			Comparison	
D29 Marker	N	Positive Response Rate (95% CI)	GM (95% CI)	N	Positive Response Rate (95% CI)	GM (95 % CI)	Response Rate Difference (Cases – Non-Cases)	Ratio of GM (Cases/Non-Cases)
Latin America								
Anti Spike IgG (BAU/ml)	48	79.2% (65.0%, 88.6%)	29.90 (21.37, 41.83)	212	84.1% (78.1%, 88.7%)	32.62 (27.88, 38.16)	-4.9% (-19.9, 6.3%)	0.92 (0.69, 1.22)
Anti RBD IgG (BAU/ml)	48	75.0% (60.5%, 85.5%)	27.98 (20.74, 37.75)	212	81.4% (75.0%, 86.5%)	31.73 (27.54, 36.57)	-6.4% (-21.8, 5.9%)	0.88 (0.68, 1.14)
Pseudovirus-nAb ID50 (IU50/ml)	48	43.8% (30.2%, 58.3%)	3.91 (2.66, 5.73)	212	60.0% (52.3%, 67.3%)	5.62 (4.56, 6.93)	-16.3% (-31.7%, 0.2%)	0.70 (0.49, 0.98)
South Africa								
Anti Spike IgG (BAU/ml)	15	80.0% (49.8%, 94.2%)	32.70 (18.51, 57.78)	200	87.3% (81.2%, 91.7%)	37.90 (31.72, 45.28)	-7.3% (-37.8, 8.1%)	0.86 (0.59, 1.26)
Anti RBD IgG (BAU/ml)	15	73.3% (43.8%, 90.6%)	34.12 (19.30, 60.33)	200	84.3% (77.6%, 89.3%)	35.30 (30.12, 41.36)	-11% (-40.9, 7.6%)	0.97 (0.67, 1.40)
Pseudovirus-nAb ID50 (IU50/ml)	15	33.3% (13.3%, 62.0%)	3.05 (1.63, 5.70)	200	51.5% (43.3%, 59.7%)	4.99 (3.91, 6.37)	-18.2% (-39.9, 11.6%)	0.61 (0.37, 1.00)
United States								
Anti Spike IgG (BAU/ml)	29	79.3% (59.8%, 90.8%)	25.86 (18.15, 36.84)	409	85.8% (81.3%, 89.4%)	34.24 (30.35, 38.63)	-6.5% (-26.3, 5.8%)	0.76 (0.58, 0.99)
Anti RBD IgG (BAU/ml)	29	72.4% (52.7%, 86.1%)	24.00 (17.25, 33.38)	409	80.2% (75.2%, 84.4%)	32.49 (29.08, 36.30)	-7.7% (-27.9, 6.8%)	0.74 (0.57, 0.96)
Pseudovirus-nAb ID50 (IU50/ml)	29	27.6% (13.9%, 47.3%)	2.40 (1.68, 3.44)	409	54.4% (48.6%, 60.1%)	4.40 (3.83, 5.06)	-26.8% (-41.6, -6.3%)	0.55 (0.41, 0.72)

[1]Cases are baseline SARS-CoV-2 seronegative per-protocol vaccine recipients with the primary COVID-19 endpoint (moderate to severe-critical COVID-19 with onset that was both ≥ 28 days post-vaccination and ≥ 1 day post-D29) and before the end of the correlates study period, which is up to 54 days post D29 but no later than the data cut (January 22, 2021).

[2]Non-cases/Controls are baseline seronegative per-protocol vaccine recipients sampled into the immunogenicity subcohort with no evidence of SARS-CoV-2 infection up to the end of the correlates study period, which is up to 54 days post D29 but no later than the data cut (January 22, 2021). See Extended Data Figure 2. CI, confidence interval; GM, geometric mean.

Supplementary Table 7. Covariate-adjusted hazard ratios of COVID-19 per standard deviation (SD) increment in each D29 antibody marker in baseline SARS-CoV-2 seronegative per-protocol vaccine recipients.

D29 Immunologic Marker	No. cases/ No. at-risk*	HR per SD increment		P-value (2-sided)	FDR-adjusted p-value**	FWER-adjusted p-value
		Pt. Est.	95% CI			
Anti Spike IgG (BAU/ml)	140/18,395	0.84	(0.66, 1.07)	0.162	0.189	0.255
Anti RBD IgG (BAU/ml)	140/18,395	0.80	(0.62, 1.03)	0.079	0.150	0.144
Pseudovirus-nAb ID50 (IU50/ml)	140/18,395	0.65	(0.48, 0.88)	0.006	0.015	0.016

Baseline covariates adjusted for: baseline risk score, geographic region. RBD, receptor-binding domain.

*No. at-risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint and with no evidence of SARS-CoV-2 infection through D29; no. cases = estimated number of this cohort with an observed COVID-19 endpoint starting ≥ 1 day post D29 and ≥ 28 days post-vaccination. The count 140 differs from the number 92 (Figure 1, Table 1), because the 140 includes all vaccine breakthrough cases including those without D1, 29 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 (10000 replicates).

Supplementary Table 8. Sensitivity analysis to assess D29 antibody markers categorized as upper vs. lower tertiles as controlled vaccine efficacy correlates of protection against COVID-19.

	Marginalized Risk Ratio $RR_M(0,1)$[1]		Controlled Risk Ratio = (1-CVE(1))/(1-CVE(0))[2]		E-values[3]	
D29 Antibody Marker	Point Estimate	95% CI	Point Estimate	95% CI	For Point Estimate	For 95% CI Upper Limit
Anti-spike IgG (BAU/ml)	0.75	0.40, 1.31	1.00	0.53, 1.75	2.0	1.0
Anti-RBD IgG (BAU/ml)	0.61	0.33, 1.08	0.82	0.43, 1.43	2.6	1.0
ID50 (IU50/ml)	0.41	0.21, 0.69	0.55	0.28, 0.92	4.3	2.2

[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 and geographic region; UL = upper limit.

Supplementary Table 9. Assay limits of the three antibody markers evaluated as immune correlates. BAU = binding antibody units; IU = International Units; LLOQ, lower limit of quantification; RBD, receptor binding domain; ULOQ, upper limit of quantification.

MSD Binding Assay (VRC)		
Reported units	BAU/ml	
	Spike	RBD
Positivity Cutoff	10.8424	14.0858
LOD	0.3076	1.5936
LLOQ	1.8429	5.0243
ULOQ	238.1165	172.5755
All values < Positivity Cutoff were set to Positivity Cutoff/2		
All values > ULOQ were set to ULOQ (for immune correlates analyses)		

Pseudovirus neutralization ID50 titer (Monogram)	
Reported units	IU50/ml
LOD	2.612
LLOQ	2.7426
ULOQ	619.3052
All values < LLOQ were set to LLOQ/2	
All values > ULOQ were set to ULOQ (for immune correlates analyses)	

Supplementary Table 10. Individual baseline variables input into the Superlearner model for predicting occurrence of the COVID-19 primary endpoint in baseline SARS-CoV-2 seronegative per-protocol placebo recipients.

Variable Name	Definition	Total missing values
EthnicityHispanic	Indicator ethnicity = Hispanic (1 = Hispanic, 0 =complement)	0/18116 (0.0%)
EthnicityNotreported	Indicator ethnicity = Not reported (1 = Not reported, 0 =complement)	0/18116 (0.0%)
Black	Indicator race = Black (1=Black, 0=complement)	0/18116 (0.0%)
Asian	Indicator race = Asian (1=Asian, 0=complement)	0/18116 (0.0%)
NatAmer	Indicator race = American Indian or Alaska Native (1=NatAmer, 0=complement)	0/18116 (0.0%)
Multiracial	Indicator race = Multiracial (1=Multiracial, 0=complement)	0/18116 (0.0%)
Notreported	Indicator race = Not reported (1=Notreported, 0=complement)	0/18116 (0.0%)
Unknown	Indicator race = unknown (1=Unknown, 0=complement)	0/18116 (0.0%)
URMforsubcohortsampling	Indicator of under-represented minority (1=Yes, 0=No)	0/18116 (0.0%)
HighRiskInd	Baseline covariate indicating >= 1 Co-existing conditions	0/18116 (0.0%)
HIVinfection	(1=yes, 0=no, NA=missing) Indicator living with HIV at enrollment (1=living with HIV, 0=not living with HIV)	0/18116 (0.0%)
Sex	Sex assigned at birth (1=female, 0=male/undifferentiated/unknown)	0/18116 (0.0%)
Age	Age at enrollment in years (integer >= 18, NA=missing). Note that the randomization strata included Age 18-59 vs. Age >=60.	0/18116 (0.0%)
BMI	BMI at enrollment (Ordered categorical 1,2, 3, 4, NA=missing); 1 = Underweight BMI < 18.5; 2 = Normal BMI 18.5 to < 25; 3 = Overweight BMI 25 to < 30; 4 = Obese BMI >= 30	15/18116 (0.1%)
Country.X1	Indicator country = Argentina (1 = Argentina, 0 = complement)	0/18116 (0.0%)
Country.X2	Indicator country = Brazil (1 = Brazil, 0 = complement)	0/18116 (0.0%)
Country.X4	Indicator country = Colombia (1 = Colombia, 0 = complement)	0/18116 (0.0%)
Country.X6	Indicator country = Peru (1 = Peru, 0 = complement)	0/18116 (0.0%)
Country.X7	Indicator country = South Africa (1 = South Africa, 0 = complement)	0/18116 (0.0%)
Region.X1	Indicator region = Latin America (1 = Latin America, 0 = complement)	0/18116 (0.0%)

Region.X2	Indicator country = Southern Africa (1 = Southern Africa, 0 = complement)	0/18116 (0.0%)
CalDtEnrollIND.X1	Indicator variable representing enrollment occurring between 4-8 weeks periods of first subject enrolled (1 = Enrollment between 4-8 weeks, 0 = complement).	0/18116 (0.0%)
CalDtEnrollIND.X2	Indicator variable representing enrollment occurring between 8-12 weeks periods of first subject enrolled (1 = Enrollment between 8-12 weeks, 0 = complement).	0/18116 (0.0%)
CalDtEnrollIND.X3	Indicator variable representing enrollment occurring between 12-16 weeks periods of first subject enrolled (1 = Enrollment between 12-16 weeks, 0 = complement).	0/18116 (0.0%)

Note:
1. Binary input variable/s EthnicityUnknown, PacIsl, Country.X3, Country.X5 had <= 3 cases in the variable = 1 or 0 subgroup and were dropped from analysis.
2. No input variable had more than 5% missing values.
3. BMI had less than 5% missing values. The missing values were imputed using the mice package in R.

Supplementary Text 1.

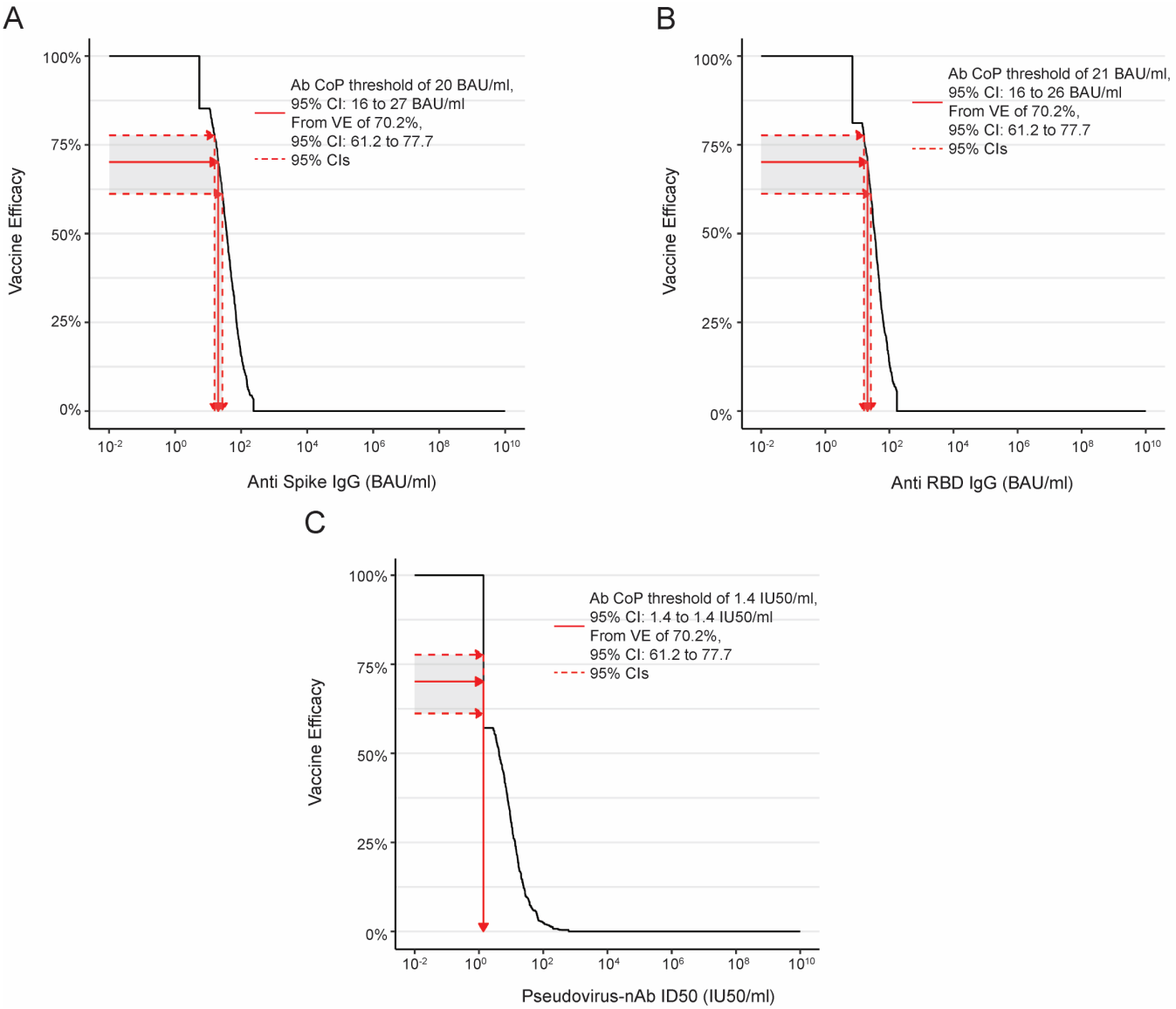
In addition to adjusting for geographic region, all correlates analyses adjust for a baseline COVID-19 risk score that was developed through machine learning of the baseline SARS-CoV-2 seronegative per-protocol placebo arm.
Supplementary Table 10 lists the input variables that were included in the machine learning to build a model predicting the COVID-19 endpoint, where cases are COVID-19 endpoints occurring at least 1 day post D29 and non-cases are participants with follow-up beyond 7 days post D29 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.

The receiver operating characteristic curve for the Superlearner model built from baseline SARS-CoV-2 seronegative per-protocol placebo recipients was applied to baseline SARS-CoV-2 seronegative per-protocol vaccine recipients, yielding an AUC of 0.670 for classifying COVID-19 outcome status.

Supplementary References:

1. Gilbert PB, Fong Y, Carone M. Assessment of Immune Correlates of Protection via Controlled Vaccine Efficacy and Controlled Risk. arXiv:2107.05734 [stat.ME]https://arxiv.org/abs/2107.05734. 2021.

Supplementary Figure 1. Inverse probability sampling-weighted empirical reverse cumulative distribution function curves for each D29 marker [(A) spike IgG, (B) receptor-binding domain (RBD) IgG, (C) ID50] in the vaccine arm and application of the Siber 2007 method for estimating a threshold of perfect vs. no protection.



Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 2007; **25**(19): 3816-26.