Title: A Third Dose of SARS-CoV-2 Vaccine Increases Neutralizing Antibodies Against Variants of Concern in Solid Organ Transplant Recipients

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Abstract: Immunocompromised populations are at high risk for severe COVID-19. Vaccine-induced SARS-CoV-2 antibody responses are attenuated in solid organ transplant recipients (SOTRs), and breakthrough infections are more common. Additional SARS-CoV-2 vaccine doses may increase anti-spike antibody titers in some SOTRs, but whether this results in enhanced neutralizing capability, especially versus novel variants of concern (VOCs) that exhibit immune escape and higher infectivity (e.g., the Delta variant), is unclear. Here, we report that a third dose of a SARS-CoV-2 vaccine increases anti-SARS-CoV-2 spike and RBD IgG levels as well as plasma neutralizing capability versus VOCs, including Delta, in some SOTRs. However, anti-spike IgG and neutralizing capability remained significantly reduced compared to fully vaccinated healthy controls. These findings highlight the need for continued study of

strategies to improve protection from COVID-19 in immunosuppressed populations as more SARS-CoV-2 VOCs emerge.

Main Text: Solid organ transplant recipients (SOTRs) are at increased risk for severe COVID-19[1]. For example, case fatality ratios range from 10-30% in SOTRs, due to a combination of chronic disease and immunosuppressive medications[2]. Therefore, effective and optimized vaccines that prevent COVID-19 disease in this group are critical. Unfortunately, these patients were excluded from the Phase III trials of the mRNA based COVID-19 vaccines,[3,4] and recent publications suggest that breakthrough infections are more common among fully-vaccinated SOTRs than the general population[5,6]. Furthermore, it has been demonstrated that many SOTRs develop weak SARS-CoV-2 antibody responses after the recommended two doses of an mRNA-based vaccine[7–10]. This led to the hypothesis that a third dose of SARS-CoV-2 vaccine may improve the immune response and protection from COVID-19. While the number of SOTRs receiving a third dose remains small, preliminary data suggest that a subset of non-responders do mount higher antibody responses[11,12]. It is unclear, however, if this response will be protective, particularly against more transmissible variants of concern (VOCs) that exhibit immune escape, including the Delta variant which comprises >80% of new cases in the USA[13–15].

In an effort to assess whether a third dose of SARS-CoV-2 vaccine in SOTRs would improve the SARS-CoV-2 specific neutralizing response, we measured total SARS-CoV-2 specific IgG and neutralizing antibodies against the previously dominant D614G strain and four VOCs before and after a third dose of SARS-CoV-2 vaccine, and

compared this to IgG levels and neutralizing capacity of healthy controls who received a standard two-dose mRNA-based vaccine series.

Pre- and post-third dose samples were available for 31 SOTRs who were followed in our ongoing longitudinal observational cohort studying immunogenicity and safety of SARS-CoV-2 vaccination. Most of these participants had previously undergone anti-spike antibody testing using two clinically available assays[11]. The median age was 60 (interquartile range 49-67) years and 55% were female. Most SOTRs were kidney transplant recipients (61%) and all initially received two doses of an mRNA-based vaccine. Most were taking a calcineurin inhibitor-based maintenance immunosuppression regimen (81%). Among mRNA-vaccinated healthy controls (N=15), none had known medical conditions, and all received two doses of an mRNA-based vaccine. See **Supplemental Table 1** for full demographic and clinical data.

We measured anti-S1-RBD (RBD), anti-Spike (S), and anti-Nucleocapsid (N) total IgG in plasma using a research assay (Meso Scale Diagnostics) with FDA verified cutoffs for sero-positivity before and after a third dose of SARS-CoV-2 vaccine in SOTRs and healthy controls after two doses of an mRNA-based vaccine. No participants had a positive anti-N response at baseline (**Supplemental Figure 1**). Prior to a third dose of vaccine 12 (39%) and 8 (26%) SOTRs were positive for anti-RBD and anti-S respectively (**Figure 1A**). After the third dose, these numbers increased to 24 (77%), and 22 (71%) respectively and there was a significant increase in the median of total anti-S and anti-RBD IgG compared to matched pre-third dose samples (**Figure 1A**). The median of anti-RBD and anti-S IgG values of SOTRs receiving a third dose remained significantly lower than the median responses in fully vaccinated healthy

controls after the two-dose series (**Figure 1B**). When stratifying by type of third dose received (Ad26.COV2.S [n=12] or mRNA-based [n=19]), we observed a trend toward a greater increase in the median anti-S IgG value among those receiving a third mRNA-based vaccine dose, though this did not reach statistical significance (**Figure 1C**). Six (50%) of those receiving the Ad26.COV2.S as a third dose and 16 (84%) who received an mRNA-based vaccine as a third dose became sero-positive. In exploratory analysis, median IgG levels did not differ by key clinical or demographic parameters such as age, sex, or type of organ transplant, though subgroup sizes were small (**Supplemental Figure 2**).

Next, we investigated the neutralizing potential of SOTR plasma versus major SARS-CoV-2 VOCs after three vaccine doses with comparison to that of healthy individuals after two vaccine doses. There was a significant increase in the median pseudoneutralization (inhibition of S protein binding to the ACE2 receptor) of all variants after a third vaccine dose among SOTRs (**Figure 2A**). However, pseudoneutralization of all variants was significantly lower than that of healthy controls after two doses of an mRNA-based vaccine (**Figure 2B**). For example, only two (6%) SOTRs had pseudoneutralization values for the Delta variant above the first quartile of the healthy control pseudoneutralization values; the majority were below 25% inhibition for all variants. When stratified by type of third dose received, SOTRs receiving a third dose of an mRNA-based vaccine had greater pseudoneutralization than those receiving the adenovirus-based vaccine, but the difference did not reach statistical significance (**Figure 2C**). Stratification by age, sex, or type of graft received did not identify any significant differences in pseudoneutralization (**Supplemental Figure 3**). Finally, we

examined the correlation between anti-S IgG and pseudoneutralization for all the variants. We found a strong correlation between anti-S IgG and pseudoneutralization, but the relationship only became linear at approximately a value of 4 $\log_{10}$(AU) IgG, suggesting that values below this may not correlate with neutralizing response (**Figure 2D**).

Here, we provide the first evidence that a third dose of COVID-19 vaccine in SOTRs may increase neutralization against VOCs, including the highly transmissible and now dominant Delta variant. Further, our results are consistent with recent reports suggesting that a third dose of SARS-CoV-2 vaccine in SOTRs who fail to mount a positive antibody response to two doses of mRNA vaccine may increase the humoral immune response to SARS-CoV-2 based on measurement of IgG antibodies[12,16,17]. Additionally, pseudoneutralization capacity did increase after a third vaccine dose, which may indicate improved protection against COVID-19. However, the majority of SOTRs still did not demonstrate high-level ACE2 binding inhibition as was seen in nearly all healthy controls receiving the currently recommended two dose series. This was particularly true of the Gamma variant, known to cause vaccine breakthrough[18]. It is not yet certain whether this correlates with decreased protection from severe disease. We also found a trend on exploratory analysis of greater total IgG and pseudoneutralization with a third dose of an mRNA-based vaccine than with an adenovirus-based vaccine. This is consistent with prior work demonstrating somewhat lower humoral response to the one and two-dose Ad26.COV2.S series as compared to the two-dose mRNA series; a study in SOTRs also noted lower antibody levels after one dose of Ad26.COV2.s[19,20]. Regardless, a mixed-platform dosing strategy is of interest

given a recent study of healthy individuals who received an initial dose of an adenovirus-based vaccine demonstrated that an mRNA-based vaccine booster led to superior SARS-CoV-2 specific antibody production when compared to homologous adenovirus-based vaccine, leading to the hypothesis that a cross-platform approach may be an effective strategy for boosting the humoral response to the virus[21]. However, our preliminary data found higher anti-S IgG as well as pseudoneutralization with homologous mRNA boosting, which may suggest that the sequence (i.e., adenovirus followed by mRNA, instead of mRNA followed by adenovirus) may be important when considering an additional dose of vaccine in the SOTR population.

Although these data suggest that additional immunizations may increase protection from SARS-CoV-2 VOCs in vulnerable SOTRs, increases in antibody titers and pseudoneutralization were not observed in every SOTR. This suggests that additional strategies, such as immunosuppressive modulation or utilization of emerging vaccine platforms, may be necessary to induce a protective response to vaccination in SOTRs. Additional investigations are warranted to understand why some SOTRs respond to additional antigen exposure, while others do not.

This study was limited by its observational nature and small number of participants. Furthermore, while the pseudoneutralization assay employed correlates well with live-virus neutralization[22], it is possible that this assay either under or over estimates the true neutralization capacity of plasma. Despite these limitations, these results provide important and timely information regarding the potential to improve protection from SARS-CoV-2 variants in a highly vulnerable population amidst ongoing community surges.

Methods (online):

Cohorts:

SOTR participants were enrolled in a national prospective, observational cohort: COVID-19 Antibody Testing of Recipients of Solid Organ Transplants and Patients with Chronic Diseases, Johns Hopkins IRB00248540, as previously described[8,11]. SOTRs submitted blood samples to the investigators 0-4 weeks before and 2 weeks after third vaccine doses, which were independently obtained in the community. Healthy control participants were enrolled under Johns Hopkins IRB00027183. Blood was collected in Acid Citrate Dextrose (ACD) tubes and plasma was isolated by Ficoll centrifugation and stored at -80°C.

IgG Measurement:

Plasma was thawed and anti-N, anti-RBD, and anti-S IgG was measured using the multiplex chemiluminescent Meso Scale Diagnostics (MSD) V-PLEX COVID-19 Respiratory Panel 3 Kit according to the manufactures' protocol at a dilution of 1:5000. Two participants in the original SOTR cohort had N IgG values that rose above the cutoff after a third dose suggesting possible exposure to SARS-CoV-2 (**Supplemental Figure 1**), and they were subsequently excluded from analysis.

Pseudoneutralization/ACE2 Inhibition Measurement:

Plasma from study participants was thawed and ACE2 blocking was measured using the ACE2 MSD V-PLEX SARS-CoV-2 Panel 6 and Panel 14 kits according to the manufacturers' protocol at a dilution of 1:100.

Statistical analysis:

Only SOTRs with available demographic and immunological data on pre and post third dose of SARS-Cov-2 vaccine were included in the analysis. Wilcoxon signed rank test was used to compare the median of SARS-Cov-2 anti-Spike and anti-RBD IgG level and percent ACE2 inhibition before and after third dose of vaccine among SOTRs. The median of IgG level and ACE2 inhibition between SOTRs and HCs were compared using Wilcoxon rank sum test. Pearson correlation were used to evaluate the linear association between Spike IgG and percent ACE2 inhibition among SOTRs. A spline knot was added at 4 $\log_{10}$(AU) IgG. Bonferroni correction was conducted to control multiple comparison when analyzing variants ($p < 0.01$ was considered statistically significant). The analysis was also stratified by type of third dose vaccine, age, sex, and graft transplanted to evaluate effect measure modification. Missing values were treated using available case strategy in subgroup analysis.

Acknowledgements:

This work was supported by the Ben-Dov family, the Johns Hopkins COVID-19 Vaccine-related Research Fund, the National Cancer Institute (U54CA260491), grants 5T32DK007713 (JLA), F32DK124941 (BJB), and K23DK115908 (JMGW) from the National Institute of Diabetes and Digestive and Kidney Diseases, and grants K24AI144954 (DLS), K08AI156021 (AHK), and R01AI120938S1 (AART) from the National Institute of Allergy and Infectious Disease.

Author contributions:

AHK and WAW conceived of the study and design. OA and YE processed the samples and prepared them for the assays. AHK, KHW, and AGR performed the assays and collected the antibody data. AT, JLA, JNB, and BJB assisted with participant enrollment

and collection of clinical data. XZ and TL performed the analysis. AHK wrote the original manuscript. JMG, ALC, JNB, SLK, AP, JRB, DLS, AART, and WAW supervised the studies, provided material support, and contributed to the interpretation of results. All authors aided in editing the manuscript.

Competing Interests: DLS has the following financial disclosures: consulting and speaking honoraria from Sanofi, Novartis, CSL Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, Thermo Fisher Scientific. None of the other authors have any relevant competing interests.

FIGURE LEGENDS

Figure 1. Changes in SARS-CoV-2 Specific IgG After A Third Dose of SARS-CoV-2 Vaccine

a. Total SARS-CoV-2 S1 RBD (left) and Spike (right) specific IgG in SOTRs before and after a third dose of vaccine. The dashed line represents the assay manufacturer's cut-off for positivity based on convalescent samples.

b. Total SARS-CoV-2 S1 RBD (left) and Spike (right) specific IgG in fully mRNA vaccinated healthy controls (HCs) (n = 15) and SOTRs after a third dose of vaccine (n = 31).

c. Total SARS-CoV-2 Spike specific IgG in SOTRs who received a third dose consisting of either Ad26.COV2.S (n = 12) or mRNA-based vaccine (n = 19).

The boxplots represent the IQR. The median is represented by a horizontal line in the box. The lower and upper whiskers represent 1.5x the IQR beyond the quartiles. Each dot represents an individual sample. Statistical differences between groups were determined by Wilcoxon signed rank test for panel A, and Wilcoxon rank sum test for panel B and C. P-values of 0.05 were considered significant.

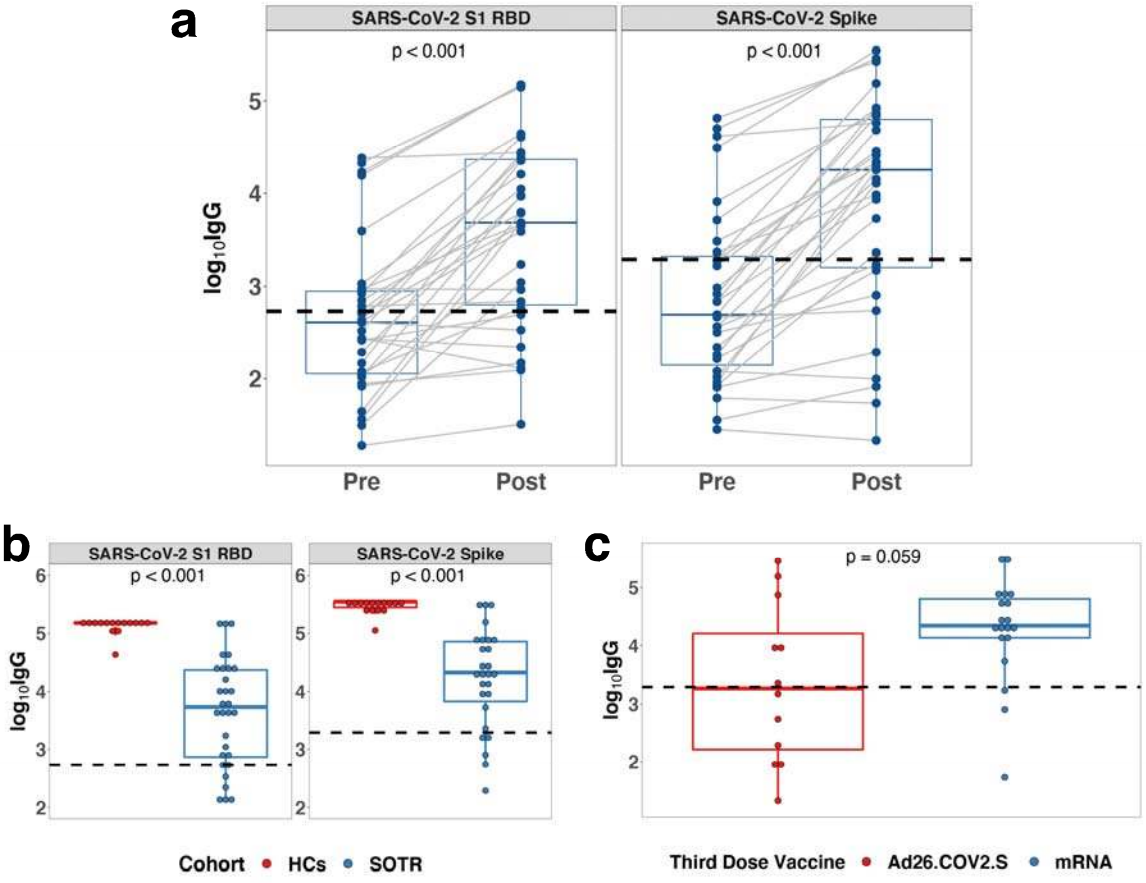


Figure 2. SARS-CoV-2 Pseudoneutralization After A Third Dose of COVID-19 Vaccine in SOTRs

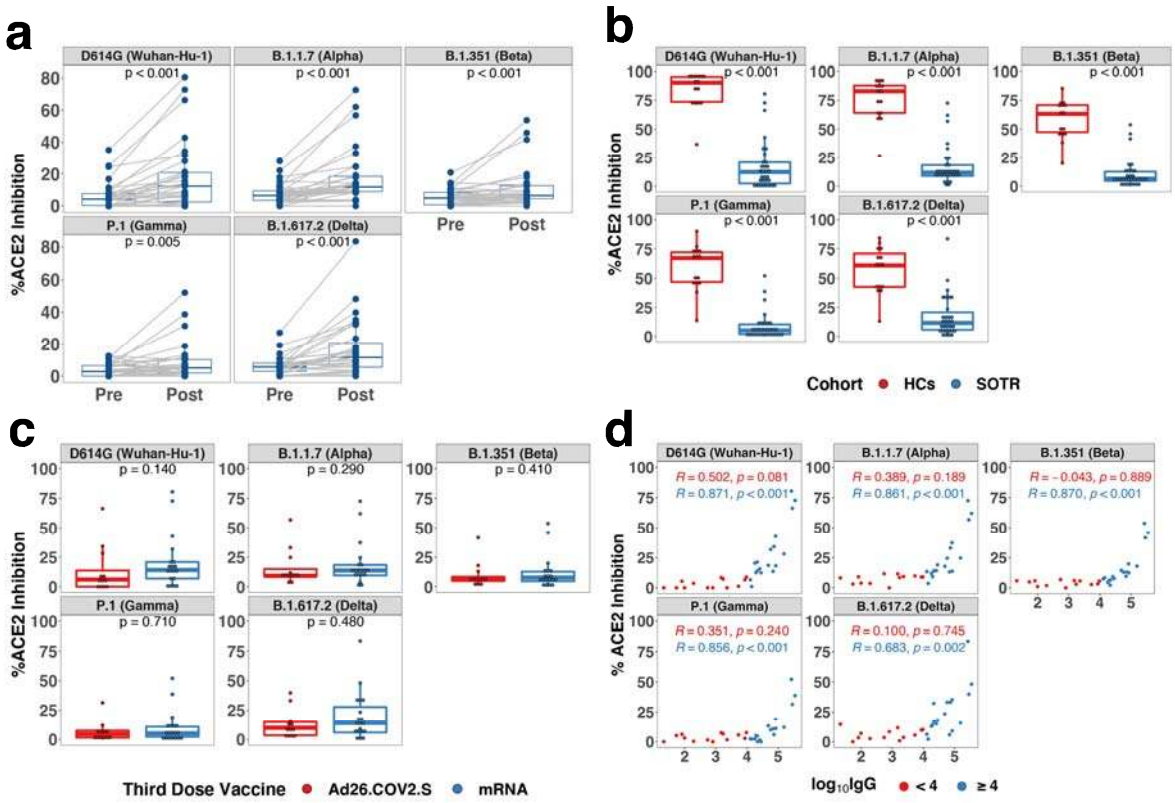
a. Pseudoneutralization of full-length SARS-CoV-2 Spike variants (indicated in top header of each panel) before and after a third dose of COVID-19 vaccine among SOTRs.

b. Pseudoneutralization of full-length SARS-CoV-2 Spike variants (indicated in top header of each panel) in SOTRs (n = 31) after a third dose of vaccine compared to fully vaccinated healthy controls (n = 15).

c. Comparison of pseudoneutralization of full-length SARS-CoV-2 Spike variants (indicated in top header of each panel) between SOTRs receiving a third dose of Ad26.COV2.S (n = 12) or mRNA-based vaccine (n = 19).

d. Correlation between total SARS-CoV-2 Spike IgG and pseudoneutralization of full-length SARS-CoV-2 Spike variants among SOTRs receiving a third dose of COVID-19 vaccine.

In panel A-C, the boxplots represent the IQR. The median is represented by a horizontal line in the box. The lower and upper whiskers represent 1.5x the IQR beyond the quartiles. Each dot represents an individual sample. Statistical differences between groups were determined by Wilcoxon signed rank test for panel A, and Wilcoxon rank sum test for panel B and C. Pearson correlation coefficient were generated for panel D. P-values of 0.01 were considered significant after Bonferroni correction.



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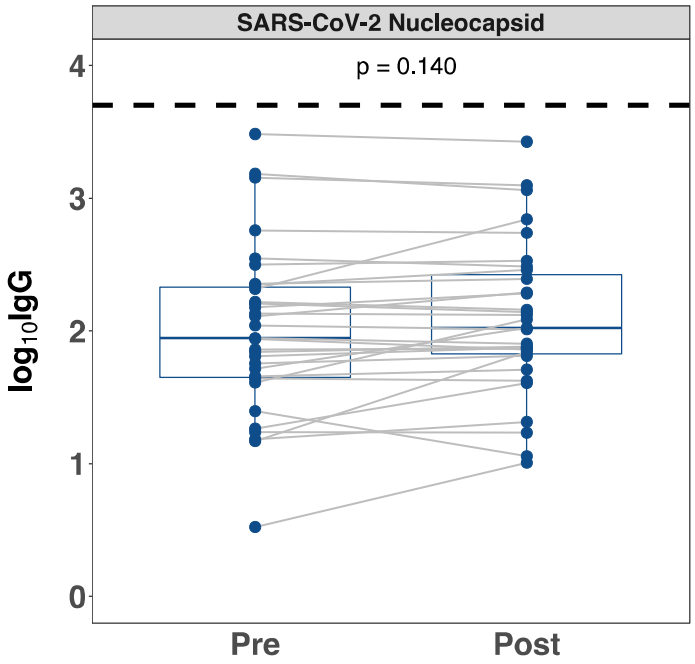
Supplemental Table 1. Clinical and Demographic Characteristics of SOTRs and Healthy Controls.

	Overall n = 46	SOTR n = 31	Healthy controls, n = 15
Age, years			
20-39	9 (20)	2 (7)	7 (47)
40-59	21 (46)	13 (42)	8 (53)
60-79	16 (35)	16 (52)	0 (0)
Sex			
Female	22 (48)	17 (55)	5 (33)
Male	21 (46)	11 (36)	10 (67)
Missing	3 (7)	3 (10)	0 (0)
Race			
White	39 (85)	28 (90)	11 (73)
Asian	3 (7)	0 (0)	3 (20)
African American	1 (2)	0 (0)	1 (7)
Missing	3 (7)	3 (10)	0 (0)
Graft transplanted			
Kidney	-	19 (61)	-
Other*	-	12 (39)	-
Anti-rejection medication†			
Prednisone	-	16 (52)	-
Calcineurin Inhibitors	-	25 (81)	-
mTOR inhibitors	-	3 (10)	-
anti-metabolites	-	20 (65)	-
Type of the third dose vaccine			
mRNA	-	19 (61)	-
Ad26.COV2.S	-	12 (39)	-
Days between second dose and third dose vaccine	-	83 (62 – 105)	-
Days between transplant and third dose vaccine	-	1778 (844 – 3954)	-
Days post second dose vaccine	-	-	8 (7 – 10)

Note: all study participants received mRNA vaccine for the first two doses. Categorical variables were presented in n (%), and continuous variables were presented in median (interquartile range). Other transplanted grafts includes , liver (n = 7), heart (n = 3), pancreas (n = 1) and lung (n = 1). 1 person had both kidney and pancreas transplanted and has been grouped into kidney category. †Anti-rejection medication use was not mutually exclusive.

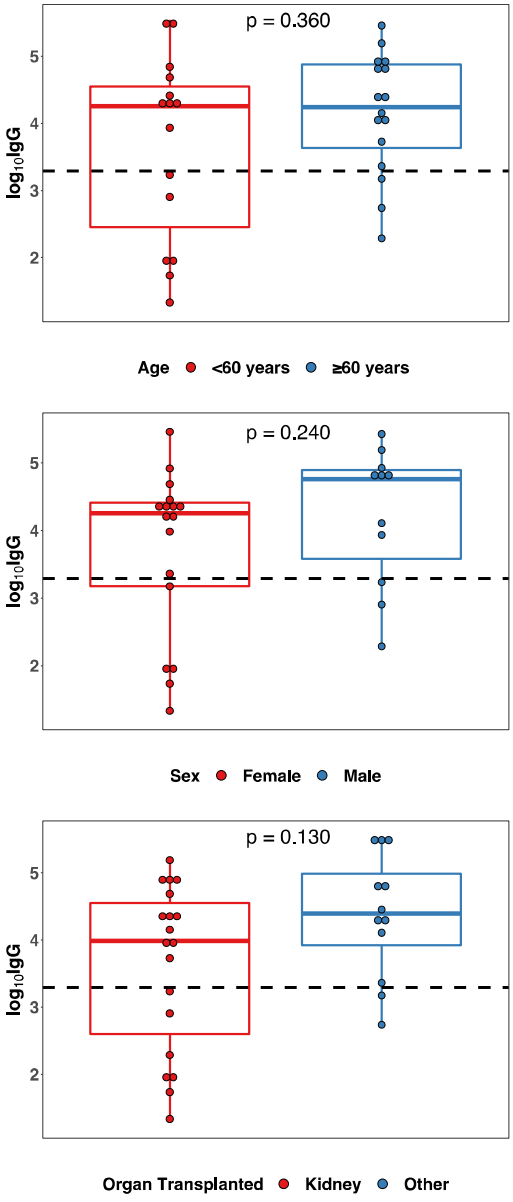
Supplemental Figure 1.

Total SARS-CoV-2 Nucleocapsid specific IgG in SOTRs before and after a third dose of vaccine. The dashed line represents the assay manufacturer's cut-off for positivity based on convalescent samples. P values were calculated using Wilcoxon rank sum test.



Supplemental Figure 2.

Total SARS-CoV-2 Spike specific IgG in SOTRs who received a third dose of COVID-19 vaccine stratified by age (<60 n = 15 and ≥60 years n = 16), sex (Female n = 17 and male n = 11), and graft received (Kidney n = 19 and other n = 12). P values were calculated using Wilcoxon rank sum test and should be considered exploratory given the small subgroups.



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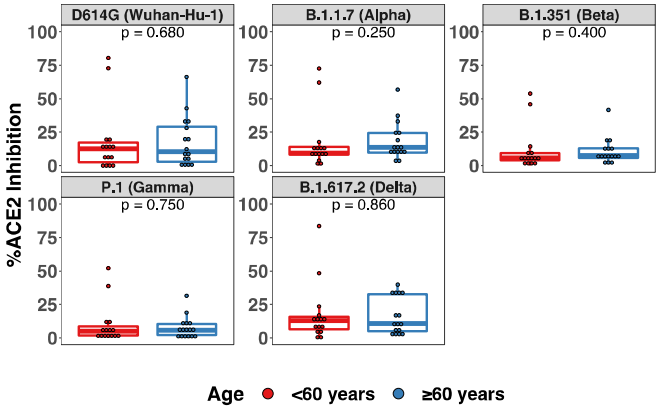
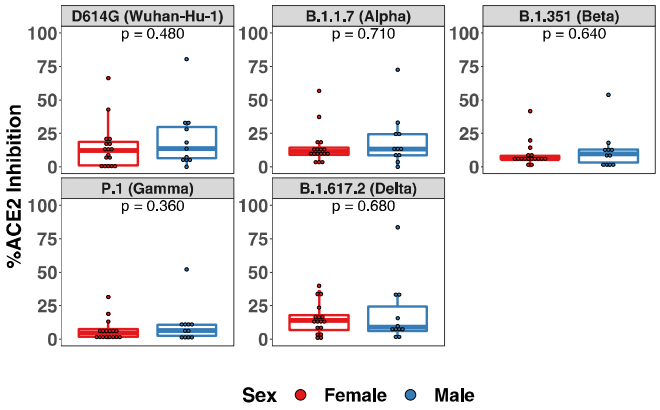
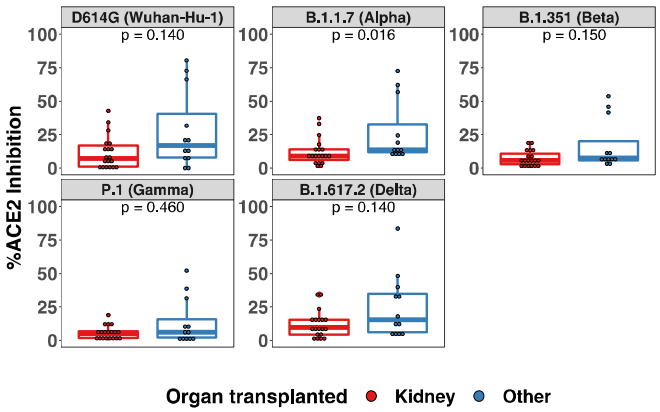
Supplemental Figure 3.

Pseudoneutralization of full-length SARS-CoV-2 Spike variants in SOTRs who received a third dose of COVID-19 vaccine stratified by age (<60 n = 15 and ≥60 years n = 16), sex (Female n = 17 and male n = 11), and graft received (Kidney n = 19 and other n = 12). P values were calculated using Wilcoxon rank sum test and should be considered exploratory given the small subgroups.







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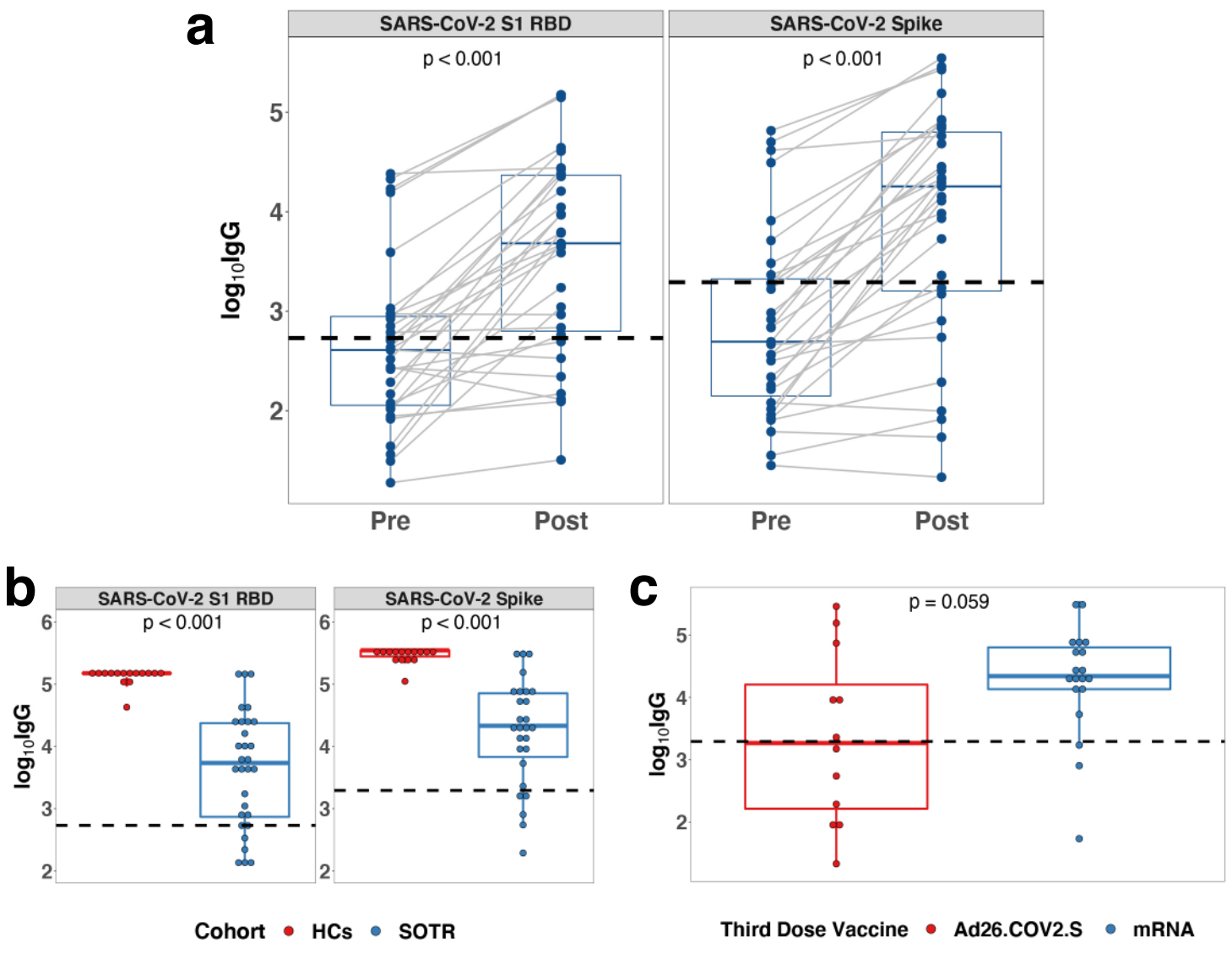
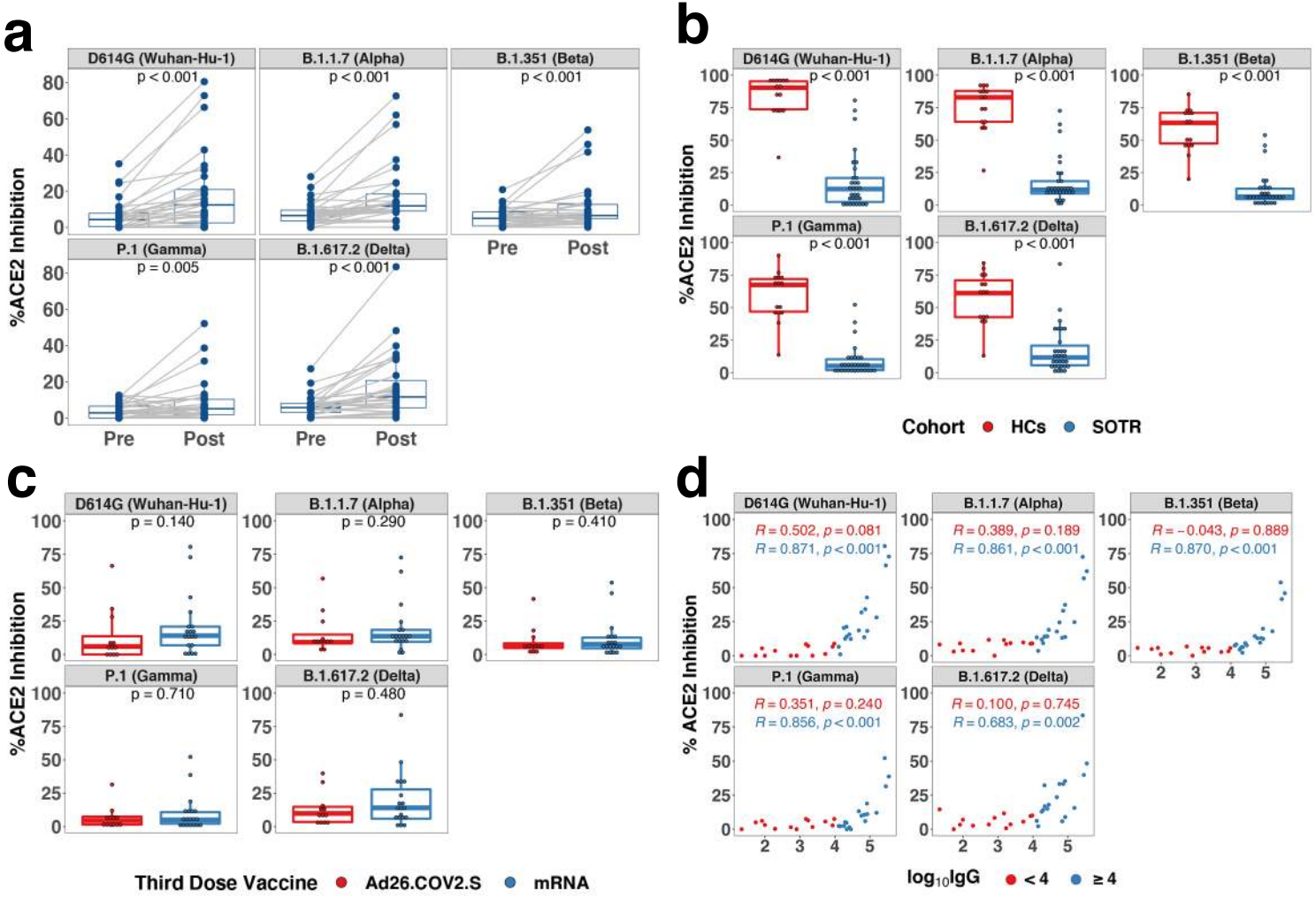

a
SARS-CoV-2 S1 RBD
SARS-CoV-2 Spike
p < 0.001
p < 0.001
log10IgG
Pre
Post
Pre
Post
b
SARS-CoV-2 S1 RBD
SARS-CoV-2 Spike
p < 0.001
p < 0.001
log10IgG
Cohort HCs SOTR
c
p = 0.059
log10IgG
Third Dose Vaccine Ad26.COV2.S mRNA


a
D614G (Wuhan-Hu-1)
p < 0.001
B.1.1.7 (Alpha)
p < 0.001
B.1.351 (Beta)
p < 0.001
P.1 (Gamma)
p = 0.005
B.1.617.2 (Delta)
p < 0.001
%ACE2 Inhibition
Pre
Post
b
D614G (Wuhan-Hu-1)
p < 0.001
B.1.1.7 (Alpha)
p < 0.001
B.1.351 (Beta)
p < 0.001
P.1 (Gamma)
p < 0.001
B.1.617.2 (Delta)
p < 0.001
%ACE2 Inhibition
Cohort HCs SOTR
c
D614G (Wuhan-Hu-1)
p = 0.140
B.1.1.7 (Alpha)
p = 0.290
B.1.351 (Beta)
p = 0.410
P.1 (Gamma)
p = 0.710
B.1.617.2 (Delta)
p = 0.480
%ACE2 Inhibition
Third Dose Vaccine Ad26.COV2.S mRNA
d
D614G (Wuhan-Hu-1)
R = 0.502, p = 0.081
R = 0.871, p < 0.001
B.1.1.7 (Alpha)
R = 0.389, p = 0.189
R = 0.861, p < 0.001
B.1.351 (Beta)
R = −0.043, p = 0.889
R = 0.870, p < 0.001
P.1 (Gamma)
R = 0.351, p = 0.240
R = 0.856, p < 0.001
B.1.617.2 (Delta)
R = 0.100, p = 0.745
R = 0.683, p = 0.002
% ACE2 Inhibition
log10IgG < 4 ≥ 4