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Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

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The antibody response after 2 doses of an mRNA SARS-CoV-2 vaccine is excellent in the general population but less robust in transplant patients.¹ Severe breakthrough infections in SOTRs have prompted debate on how to protect these individuals.^{2,3} We previously reported improved antibody responses in ~50% of SOTRs after a third vaccine.⁴ In this series we studied antibody responses to a 4th dose of SARS-CoV-2 vaccine in 18 SOTRs from April 24, 2021, through June 16, 2021.

Participants were enrolled in an observational study of SARS-CoV-2 vaccination outcomes in SOTRs.¹ 18 received a 4th dose (D4) of a COVID-19 vaccine and had no known history of COVID-19 infection. Semiquantitative anti-spike antibody testing was performed using the Roche Elecsys® anti-ARS-CoV-2 S or the EUROIMMUN® IgG enzyme immunoassays 2–6 weeks after D4. We categorized titers as negative, low-positive, and high-positive: low-positive titers were >0.8 U/mL but <50 U/mL (Roche), or >1.1 but <4 arbitrary units (AU) (EUROIMMUN). High-positive titers were 50 U/mL (Roche), or 4 AU (EUROIMMUN). This study was approved by the Johns Hopkins Institutional Review Board and participants provided informed consent electronically.

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The median age was 58 years (interquartile range [IQR] 50 to 65 years). Median time from transplant was 7.1 years (IQR 2.3 to 16.2 years). Median time from D3 to D4 was 28 (IQR 21 to 30) days. Eleven (61.1%) participants received kidney transplants. Sixteen (88.9%) were on mycophenolate mofetil at the time of vaccination. Pre-D4, there were 6 participants with negative titers, 2 low-positive, and 10 high-positive. Post-D4, 5/8 (63%) participants with negative or low-positive titers showed boosting to high-positive titers (Table 1). Additionally, among 11 SOTRs serially tested on similar assays, post-D4 titers rose in 7 (63%). Most participants with high-positive pre-D4 titers showed further boosting. The 3 participants with persistently negative titers after D4 were kidney transplant recipients less than 5 years posttransplant taking tacrolimus and mycophenolate mofetil, and 2/3 were additionally taking corticosteroids. Eleven of 16 participants (69%) receiving antiproliferative agents showed antibody boosting.

To our knowledge this is the first series describing the antibody response among SOTRs after 4 doses of vaccine against COVID-19. Given neutralizing antibody level may be the best correlate of vaccine-associated immunoprotection to date, it is encouraging that 50% of participants with negative and all with low-positive titers pre-D4 showed boosting to high-positivity post-D4.⁵ This echoes previous findings that one-third of negative and all low-positive patients after 2 doses were boosted to high-positive after receiving a third vaccine dose.⁴ These findings suggest immunogenic potential exists for these poor responders.

Limitations include small sample size, lack of formal neutralizing antibody, B-cell, or T-cell assays, durability of antibody levels, or safety information regarding the 4th dose given limited time to follow-up. We also lacked CD4 counts or hypogammaglobulinemia information in persistent suboptimal responders.

Though some patients may require additional measures such as immunosuppression modulation to achieve immunity, these data support continued exploration of subsequent vaccine doses in SOTRs.

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ABBREVIATIONS

D4	Dose 4
mRNA	messenger RNA

SOTRs Solid Organ Transplant Recipients**References:**

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Table 1.

Antibody titers after each vaccine.

Age, y	Sex	Organ(s)	Time since transplant, y	Anti-metabolite	Initial vaccine series	Post D2 titer	D3	Post D3 titer	Post D3 titer	D4	Post D4 titer	Post D4 titer
44	F	Kidney	4	Yes	Moderna	Negative	Pfizer	Negative	0.22 E	Pfizer	Negative	0.92 E
65	F	Kidney	0.5	Yes	Moderna	Negative	Moderna	Negative	0.06 E	Moderna	Negative	0.06 E
44	M	Kidney	3	Yes	Pfizer	Negative	Pfizer	Negative	0.09 E	J&J	Negative	0.4 R
63	M	Liver	11	Yes	Pfizer	Negative	J&J	Negative	0.46 R	Pfizer	High	54.9 R
57	M	Kidney	15	Yes	J&J	Negative	Moderna	Negative	0.97 E	Moderna	High	286.9 R
53	M	Kidney	21	Yes	Pfizer	Negative	Pfizer	Negative	(self-report)	J&J	High	343 R
61	F	Kidney	8	Yes	Pfizer	Negative	Moderna	Low	2.75 R	Moderna	High	>2500 R
49	F	Kidney	1	Yes	Moderna	Negative	Pfizer	Low	7.3 R	Pfizer	High	82.9 R
52	F	Kidney-Pancreas	20	Yes	Moderna	Negative	Pfizer	High	504.4 R	Pfizer	High	845 R
54	M	Liver	1	Yes	Pfizer	Low	Moderna	High	125.7 R	Moderna	High	>2500 R
69	M	Heart	16	Yes	Pfizer	Negative	Moderna	High	8.37 E	Moderna	High	>2500 R
68	M	Heart	2	Yes	Pfizer	Negative	Moderna	High	>250 R	Moderna	High	402.9 R
43	F	Pancreas	1	Yes	Pfizer	Negative	Moderna	High	4.72 E	Moderna	High	5.27 E
58	M	Kidney	3	Yes	Moderna	Low	Moderna	High	6.93 E	Moderna	High	4.16 E
42	F	Liver	5	No	Moderna	Negative	Pfizer	High	11.39 E	Pfizer	High	8.75 E
73	F	Kidney-Liver	18	Yes	Pfizer	Low	Moderna	High	4.45 E	Moderna	High	1691 R
67	F	Kidney	11	Yes	Moderna	Low	Pfizer	High	9.19 E	Pfizer	High	>2500 R
64	M	Liver	21	No	Moderna	Low	Pfizer	High	7.21 E	Pfizer	High	>2500 R

D, dose; E, EUROIMMUN assay (parameters: low-positive, 1.1 and <4; high-positive, 4 AU); F, female; J&J, Johnson & Johnson; M, male; R, Roche assay (parameters: low-positive, 0.8 and <50; high-positive, 50 U/mL).