

# Antibody Response to a Fourth Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: An Update

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Solid organ transplant recipients (SOTRs) have suboptimal antibody responses to 2-dose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, with some improvement after receiving a third dose.<sup>1,2</sup> Further boosting with a fourth dose (D4) has been suggested in small cohorts of SOTRs, but the evidence remains limited and restricted to kidney recipients with poor preceding seroresponse.<sup>3-5</sup> To expand on these early observations, we updated our original case series of 18 participants to a more granular evaluation of 128 participants, diverse in organ type and pre-D4 vaccine response.

One-hundred twenty-eight SOTRs without prior reported SARS-CoV-2 infection who reported 4 doses of SARS-CoV-2 vaccine were identified from a previously described national, prospective observational cohort.<sup>1</sup> Semiquantitative anti-spike (anti-S) serologic testing was performed using the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which tests for the receptor-binding domain (RBD), or the EUROIMMUN Anti-SARS-CoV-2 enzyme immunoassay, which tests for the S1 domain of the SARS-CoV-2 spike protein, 2–4 wk after D4. Using the pre-D4 antibody response (defined as most recent titer before D4), participants were stratified into 3 groups (negative [anti-RBD < 0.8 or anti-S < 1.1], low [anti-RBD < 250 U/mL or anti-S < 4 AU/mL], or high [anti-RBD ≥ 250 U/mL or anti-S ≥ 4 AU/mL] titer) based

on levels associated with in vitro neutralization.<sup>1</sup> Clinical characteristics were compared between the 3 groups using the Kruskal–Wallis test for continuous and Fisher exact test for categorical variables. This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540), and participants provided informed consent electronically.

The median (interquartile range [IQR]) age of participants at D4 was 62 y (49–69 y), 55% (n = 70) were female, and 59% (n = 75) were kidney transplant recipients. Pre-D4, 27% (n = 35) of SOTRs had negative titers, whereas 34% (n = 43) had low and 39% (n = 50) had high titers. The median (IQR) pre-D4 titers were 207.0 U/mL (11.6–1500.0 U/mL) (anti-RBD) and 2.1 AU/mL (0.5–6.0 AU/mL) (anti-S). Post-D4, 11% of SOTRs had persistently negative titers (nonresponders), whereas 14% had low and 75% had high titers (responders). The median (IQR) post-D4 titers were 2132.5 U/mL (96.9 to ≥ 2500.0 U/mL) (anti-RBD) and 8.8 AU/mL (5.3 to ≥ 8.94 AU/mL) (anti-S). Stratifying by pre-D4 antibody status, 61% (n = 21) of seronegative participants seroconverted and 84% (n = 36) of pre-D4 seroresponders boosted from low to high antibody titers post-D4 (Table 1). When stratified by post-D4 response, there were no statistically significant differences in any clinical factors between responders and nonresponders.

In this cohort of SOTRs receiving a D4 of SARS-CoV-2 vaccine, 89% of participants had positive

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**TABLE 1.**

**Demographics and antibody responses of solid organ transplant recipients who received 4 doses of SARS-CoV-2 vaccine, stratified by pre-dose 4 anti-spike antibody response**

Factor	Pre-dose 4 antibody levels <sup>a</sup>			P
	Negative	Low	High	
N	35	43	50	
Age, median (IQR)	63.5 (54.2–71.6) (n = 35)	62.3 (49.6–69.5) (n = 43)	58.4 (48.4–68.0) (n = 50)	0.54
Female, n (%)	20 (57)	24 (56)	26 (52)	0.90
Years since transplant, median (IQR)	4.6 (1.1–11.3)	4.9 (1.5–11.5)	7.2 (3.4–14.9)	0.11
Organ transplanted, n (%)				0.052
Kidney	27 (77)	23 (53)	25 (50)	
Liver	2 (6)	6 (14)	6 (12)	
Pancreas	0 (0)	0 (0)	2 (4)	
Lung	4 (11)	4 (9)	2 (4)	
Heart	1 (3)	4 (9)	11 (22)	
Multiorgan	1 (3)	6 (14)	4 (8)	
MMF, n (%)	30 (86)	31 (72)	37 (74)	0.33
Triple immunosuppression, n (%)	22 (63)	18 (42)	20 (40)	0.090
Initial vaccine series, n (%)				0.21
BNT162b2	22 (63)	28 (65)	24 (48)	
mRNA-1273	13 (37)	15 (35)	26 (52)	
Dose 3 vaccine type, n (%)				0.31
BNT162b2	16 (46)	15 (35)	17 (34)	
mRNA-1273	12 (34)	13 (30)	23 (46)	
Ad.26.CoV2.S	7 (20)	15 (35)	10 (20)	
Dose 4 vaccine type, n (%)				0.75
BNT162b2	15 (43)	14 (33)	17 (34)	
mRNA-1273	17 (49)	27 (63)	30 (60)	
Ad.26.CoV2.S	3 (9)	2 (5)	3 (6)	
Post-D4 antibody response category, <sup>a</sup> n (%)				<0.001
Negative	14 (40)	0 (0)	0 (0)	
Low	11 (31)	7 (16)	0 (0)	
High	10 (29)	36 (84)	50 (100)	
Pre-D4 anti-RBD titer, median (IQR)	<0.8 (<0.8 to <0.8) (n = 17)	103.3 (46.4–197.9) (n = 32)	1945.5 (1035.0 to >2500.0) (n = 34)	<0.001
Post-D4 anti-RBD titer, median (IQR) <sup>b</sup>	2.0 (<0.8 to 54.9) (n = 26)	2027.0 (475.0 to >2500.0) (n = 37)	>2500.0 (>2500.0 to >2500.0) (n = 35)	<0.001
Pre-D4 anti-S titer, median (IQR)	0.3 (0.1–0.6) (n = 18)	2.3 (2.0–2.9) (n = 11)	7.0 (5.4–8.8) (n = 16)	<0.001
Post-D4 anti-S titer, median (IQR) <sup>b</sup>	5.1 (2.0–8.2) (n = 9)	7.1 (5.1–8.9) (n = 6)	8.9 (8.6 to ≥8.94) (n = 15)	0.023

<sup>a</sup>Negative: Anti-RBD <0.8 U/mL anti-S <1.1 AU, low: anti-RBD <250 U/mL anti-S <4 AU high: anti-RBD ≥250 U/mL anti-S ≥4 AU.

<sup>b</sup>Titers were collected at a median (IQR) 28.5 d (17.0–32.0 d) post-D4.

anti-RBD, anti-receptor binding domain; anti-S, anti-spike; D4, dose 4; IQR, interquartile range; MMF, mycophenolate mofetil; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

anti-spike antibody post-D4 with a high rate of seroconversion among prior nonresponders. Additionally, titers were boosted in 75% to levels consistent with live virus neutralization. This is the largest study of SOTRs receiving 4 doses of SARS-CoV-2 vaccine, encompassing a breadth of organ recipients, and demonstrates the immunogenic potential of booster vaccination.<sup>3-5</sup> Limitations include the observational nature of the cohort, lack of formal neutralization against variants of concern including omicron, and the lack of cellular analyses.

These findings support recommendations for booster vaccination in SOTRs, with post-booster antibody testing to identify individuals who remain seronegative and may

be targeted for additional vaccination or passive immunoprophylactic interventions.

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