Outcomes of SARS-CoV-2 Infection in Unvaccinated Compared With Vaccinated Solid Organ Transplant Recipients: A Propensity Matched Cohort Study

Victoria G. Hall, MBBS,1 Ghadeer Al-Alahmadi, MBBS,1 Javier T. Solera, MD,1 Tina Marinelli, MBBS,1,2 John Matelski, MSc,13 Atul Humar, MD,1 and Deepali Kumar, MD1

Background. Solid organ transplant (SOT) recipients are at high risk for complications from coronavirus disease 2019 (COVID-19). Vaccination may mitigate this risk; however, immunogenicity appears to be significantly impaired, with reports of increased risk of breakthrough infection. It is unknown if vaccine breakthrough infections are milder or as severe as infections in unvaccinated patients. Methods. We performed a multicenter matched cohort study between March 2020 and September 2021 to assess influence of COVID-19 vaccination on outcomes of COVID-19 infection. Treatment characteristics and disease severity outcomes were compared on the basis of vaccine status; breakthrough infections versus unvaccinated infections. Variable ratio propensity score matching based on age, sex, transplant type, and number of comorbidities, was used to develop the analytic cohort. Logistic regression was used to assess the influence of vaccination status on the selected outcomes. Results. From a cohort of 511 SOT patients with COVID-19, we matched 77 partially or fully vaccinated patients with 220 unvaccinated patients. Treatment characteristics including use of dexamethasone, remdesivir, and antibiotics did not differ. Vaccinated participants were more likely to receive tocilizumab, 15 of 77 (19.5%) versus 5 of 220 (2.3%), P < 0.001. Disease severity outcomes including oxygen requirement, mechanical ventilation, and mortality were similar among medically attended vaccine breakthroughs compared with unvaccinated patients. Conclusions. SOT recipients who develop medically attended COVID-19 following 1- or 2-dose vaccination seem to have similar disease severity to unvaccinated patients who develop infection. This is consistent with the requirement that SOT recipients need 3 or more vaccine doses and emphasizes the importance of alternate strategies for this population.

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INTRODUCTION

Solid organ transplant (SOT) recipients are at high risk for complications from the coronavirus disease 2019 (COVID-19). This higher risk may be because of a combination of age and comorbidities coupled with potent immunosuppression in transplant recipients. To impede the spread of COVID-19, multiple vaccine platforms have been investigated, and demonstrated to be safe and successful in the general population. In contrast, humoral immune response has been shown to be significantly impaired in several studies by quantification of antibody against the receptor binding domain of the SARS-CoV-2 spike protein and neutralizing antibody capacity in SOT recipients. Cellular immunity, specifically the CD4+ T-cell response, has been less well assessed, although it appears to be discordant with B-cell responses and more preserved in SOT recipients. A third dose of vaccine for SOT recipients has now received regulatory approval based on the significant booster effect to both B- and T-cell response in published studies.

Currently, there is still no established humoral or cellular correlate of immunity in SOT recipients regarding vaccine-induced protection from SARS-CoV-2 infection or severity of disease. Despite the suboptimal immune response measured, studies have shown an overall reduction in the incidence of infection and death in fully vaccinated SOT recipients. The risk of breakthrough infection, however, appears to be increased in vaccinated SOT recipients and breakthrough COVID-19 severity has ranged from mild illness to severe pneumonia and death. The vast majority of studies that describe breakthrough infections are limited by small numbers and the lack of a suitable control population with which to compare disease severity. Some of these reports have been published before the delta variant, now recognized to be associated with a higher level of transmission, disease severity, and lowered vaccine neutralization capacity. We performed a matched cohort study to comprehensively assess the influence of vaccination status on the severity of SARS-CoV-2 infection in SOT recipients. Our primary hypothesis was that transplant patients who developed COVID-19 infection postvaccination (breakthrough infection) would in general have milder disease than unvaccinated patients who developed COVID-19.

MATERIALS AND METHODS

Study Population

This was a multicenter, matched cohort study of SOT recipients recruited from 9 tertiary care transplant programs in Canada. All transplant patients with PCR-confirmed SARS-CoV-2 infection from January 1, 2020, to September 21, 2021 were eligible to be included in the analysis. Patients were initially identified from a search of a COVID-19 diagnosis via the hospitals’ electronic medical records, as well as identification and referral from their transplant care team.

Participants entered the cohort after confirmation of SARS-CoV-2 infection. Two groups were then identified for comparative analysis based on vaccination status at the time of entry into the cohort. The “vaccinated” group included any participant who developed breakthrough infection after receipt of 1 or 2 doses of COVID-19 vaccine. Breakthrough infections were defined as transplant recipients who were diagnosed with PCR-confirmed SARS-CoV-2 infection ≥7 d after 1 dose of COVID-19 vaccination (partially vaccinated) or ≥14 d after 2 doses of COVID-19 vaccination (fully vaccinated). The “unvaccinated” group was defined as transplant recipients who contracted PCR-confirmed SARS-CoV-2 infection before any dose of COVID-19 vaccination or <7 d after first dose. The cohort was followed from the time of diagnosis of COVID-19 infection for at least 28 d until maximum 90 d postdiagnosis.

Unvaccinated participants were matched to vaccinated participants with SARS-CoV-2 infection by (i) age, (ii) sex, (iii) transplant type, and (iv) number of comorbidities. These factors were selected, as they have been found to be associated with increased disease severity in transplant patients with COVID-19. Comorbidities included hypertension, diabetes mellitus, body mass index >30, coronary artery disease, heart failure, chronic lung disease, chronic liver disease, chronic kidney disease, or active malignancy. The study received institutional ethics approval by each study site as part of a nationwide cohort registry of transplant recipients with COVID-19 in Canada.

Clinical Data

Data were systematically collected from the respective hospital’s electronic medical records. For all patients, date of diagnosis was determined by the first date of SARS-CoV-2 PCR positivity. This could be from nasopharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage specimens. If available, a distinction was made from microbiological records between wild-type or SARS-CoV-2 variants of concern, in particular the alpha (lineage B.1.1.7) and delta (lineage B.1.617.2) variants, which have been predominant in Canada.

Demographic data collected included age at infection, sex, organ type, date of transplant, comorbidities, induction therapy type if date of transplant was within 6 mo of COVID-19 diagnosis, receipt of antithymocyte globulin in the preceding 6 mo and treatment of rejection in the preceding 3 mo. For the vaccinated patients, vaccination dates were collected for dose 1 and dose 2, type of vaccine, and vaccination status at the time of COVID-19 diagnosis (ie, partially versus fully vaccinated). Immunosuppression factors at the time of COVID-19 diagnosis were collected for all patients, including lymphocyte count, current immunosuppression regimen, doses, and recent trough levels. Reduction of immunosuppression and the degree of reduction were recorded. Clinical presentation was detailed by symptomatology. The occurrence of pneumonia was based on symptomatology and compatible radiological evidence with plain chest radiograph or computed tomography of the chest. In 2020, the treatment for COVID-19 included dexamethasone and remdesivir for hospitalized and hypoxic patients. Starting February 2021, this remained the same except for the addition of tocilizumab to those with progressive pulmonary disease. Throughout the study period, no specific treatment was given to outpatients other than a reduction of immunosuppression as individually determined by the transplant
team. Complications such as invasive fungal infection, bacterial infection, and need for antibiotics or antifungal therapy were recorded.

Disease severity outcomes were defined by morbidity: hospitalization, length of stay, need for oxygen therapy, intensive care unit (ICU) admission, need for mechanical ventilation, and use of extracorporeal membrane oxygenation. If applicable, death, date of death, and cause of death were recorded.

Statistical Analysis
For both the unmatched and matched cohorts, demographic and treatment variables were compared for breakthrough versus unvaccinated cases using standard bivariate methods. Variable ratio propensity score matching (R package MatchIt)\(^{27}\) was performed by the nearest neighbor algorithm with a caliper width of 0.1 standard deviations, using age, sex, transplant type, and number of comorbidities as predictors of vaccination status (Figure S1, SDC, http://links.lww.com/TP/C433).

Outcomes were modeled using logistic regression within a generalized linear-mixed effects framework (R package lme4).\(^{27,28}\) A random intercept is included for each cluster of matched subjects. In addition to vaccination status, SARS-CoV-2 variant was included as a fixed effect of interest. For each outcome, we constrained and modeled vaccination status in 3 ways: (1) a binary categorical variable (any vaccination versus no vaccination); (2) 3 level categorical variable (unvaccinated, partially vaccinated, and fully vaccinated); and (3) as the numeric doses received (0, 1, 2). We then selected the best fitting model using the Akaike Information Criterion. Odds ratios were reported for the fixed effects from the best fitting model, with a 95% confidence interval (CI) and Wald test P value. The best model for each outcome was used in simulation-based sensitivity power analyses (R package simr) to assess the adequacy of our sample size in light of the minimum effect size needed for 80% power. Statistical analyses were performed using R version 3.6.2. A P value of <0.05 was considered to be statistically significant.

RESULTS
Patient Population
The total cohort population of SOT recipients infected with SARS-CoV-2 during the study period was n = 511 participants, with 78 participants in the vaccinated group and 433 participants in the unvaccinated group. After propensity score matching, the total cohort population was n = 297, with 77 participants in the vaccinated group and 220 in the unvaccinated group. Baseline demographics (Table 1) before and after matching are displayed in Table 1. Before matching, there were statistically significant differences in the frequency of diagnosis of SARS-CoV-2 variants of concern (P < 0.001), organ transplant type (P = 0.027) with trends toward significance for treatment for rejection in the preceding 3 mo (P = 0.075) and use of calcineurin inhibitor (P = 0.086) between the vaccinated and unvaccinated patients. After matching, only the frequency of SARS-CoV-2 variants of concern (P < 0.001) remained statistically significant between the 2 groups with a trend toward significance for treatment for rejection (P = 0.094).

Patient Population After Propensity Score Matching
After matching, cohorts were statistically balanced in terms of age, sex, transplant type, and number of comorbidities (Table 1). In addition, immunosuppression regimens and lymphocyte count at the time of COVID-19 diagnosis were similar. Regarding vaccination status, 51 of 77 (66.2%) and 26 of 77 (33.8%) were fully (2 doses) and partially (1 dose) vaccinated, respectively, at the time of COVID-19 diagnosis (Table 1), most commonly with mRNA vaccines. SARS-CoV-2 variants of concern were more common in those with breakthrough infections (vaccinated cohort), specifically the alpha (35 of 77, 45.5%) and delta (13 of 77, 16.9%) variants. In comparison, wild-type SARS-CoV-2 was mostly responsible for infection in the unvaccinated patients (150 of 220, 68.2%).

Treatment Characteristics of SOT Recipients With COVID-19 Infection After Propensity Score Matching
The treatment characteristics for the 77 vaccinated patients and 220 matched unvaccinated patients are shown in Table 2. Reduction in immunosuppression, including reduction in calcineurin inhibitor (P = 0.048) or antimetabolite (P = 0.065), occurred with greater frequency in the vaccinated patients. The frequency of patients that received dexamethasone and remdesivir were similar in the 2 groups. However, the vaccinated group had a greater proportion of patients treated with tocilizumab (15 of 77, 19.5% versus 5 of 220, 2.3%, P ≤ 0.001). Antibiotic and antifungal use was similarly distributed among both groups. Microbiologically confirmed bacterial infection occurred more frequently in vaccinated compared with unvaccinated patients, 10 of 77 (13.0%) versus 11 of 220 (5.0%), P = 0.036.

Disease Severity Outcomes of SOT Recipients With COVID-19 Infection After Propensity Score Matching
The disease severity characteristics for the 77 vaccinated patients and 220 unvaccinated patients are shown in Table 3. In univariate analyses, there were no significant differences in hospitalization, oxygen requirement, ICU admission, all-cause, and COVID-19-related mortality, between matched vaccinated versus unvaccinated transplant patients with COVID-19 infection. Once hospitalized, median length of stay was 11.0 d (interquartile range 6.25–28.8 d) in vaccinated patients and 10.0 d (interquartile range 5.75–16.5 d) in unvaccinated patients (P = 0.53). One partially vaccinated kidney transplant recipient who contracted delta variant required extracorporeal membrane oxygenation.

After logistic regression modeling (Table 4), there was no observed difference in the main disease severity outcomes examined between vaccinated versus unvaccinated SOT recipients with COVID-19 infection. In a simulation-based sensitivity power analysis (Table S1, SDC, http://links.lww.com/TP/C433), our study had an 80% power to detect a 2.5-fold reduction in need for any oxygen in vaccinated compared with unvaccinated participants.

We further performed a sensitivity analysis only for patients that had received 2 doses of mRNA vaccine and compared this with unvaccinated patients. The analysis was limited to infections diagnosed after March 2021, which is when vaccine became fully available to transplant recipients. This showed no significant differences...
| Characteristic | Before propensity score matching, n = 511 | After propensity score matching, n = 297 |
|---------------|------------------------------------------|------------------------------------------|
|               | Vaccinated patients (n = 78) | Unvaccinated patients (n = 433) | Vaccinated patients (n = 77) | Unvaccinated patients (n = 220) |
|               | Age, median, IQR, y | 58.00 (45.32–65.00) | 57.00 (47.00–66.00) | 0.686 | 58.00 (45.76–65.00) | 55.00 (45.00–64.00) | 0.517 | 0.028 |
|               | Male sex, n (%) | 52 (66.7) | 280 (64.7) | 0.832 | 52 (67.5) | 147 (66.8) | 1.00 | 0.015 |
|               | Time since transplant, median, IQR, y | 6.18 (2.75–12.86) | 6.21 (2.51–11.95) | 0.950 | 6.15 (2.63–12.83) | 5.84 (2.32–11.27) | 0.774 | 0.012 |
|               | Number of comorbidities, median (IQR) | 2 (2–3) | 2 (1–3) | 0.248 | 2 (2–3) | 2 (1–3) | 0.214 | 0.138 |
|               | Vaccination status | | | | | | | |
|               | Fully vaccinated, n (%) | 52 (66.7) | n/a | 51 (66.2) | n/a | | | |
|               | Partially vaccinated, n (%) | 26 (33.3) | n/a | 26 (33.8) | n/a | | | |
|               | Vaccine type | | | | | | | |
|               | mRNA-1273, n (%) | 20 (25.6) | n/a | 20 (26.0) | n/a | | | |
|               | BNT162b2, n(%) | 50 (64.1) | n/a | 49 (63.6) | n/a | | | |
|               | Astra Zeneca, n (%) | 5 (6.4) | n/a | 5 (6.5) | n/a | | | |
|               | Unknown, n (%) | 3 (3.8) | n/a | 3 (3.9) | n/a | | | |
|               | COVID-19 diagnosis, variant | <0.001 | <0.001 | 1.662 | | | | |
|               | No variant of concern detected, n (%) | 8 (10.3) | 298 (68.8) | 8 (10.4) | 150 (68.2) | | | |
|               | Alpha, n (%) | 35 (44.9) | 35 (8.1) | 35 (45.5) | 20 (9.1) | | | |
|               | Delta, n (%) | 14 (17.9) | 2 (0.5) | 13 (16.9) | 2 (0.9) | | | |
|               | Other or unknown, n (%) | 21 (26.9) | 98 (22.6) | 21 (27.3) | 48 (21.8) | | | |
|               | Transplant organ | 0.027 | | 0.152 | 0.365 | | | |
|               | Lung, n (%) | 12 (15.4) | 36 (8.3) | 12 (15.6) | 18 (8.2) | | | |
|               | Heart, n (%) | 4 (5.1) | 21 (4.8) | 4 (5.2) | 18 (8.2) | | | |
|               | Kidney, n (%) | 37 (47.4) | 291 (67.2) | 37 (48.1) | 131 (59.5) | | | |
|               | Kidney-pancreas, n (%) | 6 (7.7) | 17 (3.9) | 5 (6.5) | 6 (2.7) | | | |
|               | Liver, n (%) | 18 (23.1) | 63 (14.5) | 18 (23.4) | 42 (19.1) | | | |
|               | Kidney-liver, n (%) | 1 (1.3) | 5 (1.2) | 1 (1.3) | 5 (2.3) | | | |
|               | Immunosuppression | | | | | | | |
|               | Treatment for rejection in preceding 3 mo, n (%) | 5 (6.4) | 9 (2.1) | 5 (6.5) | 4 (1.8) | 0.094 | 0.236 |
|               | ATG in preceding 6 mo, n (%) | 0 (0.0) | 10 (2.3) | 0 (0.0) | 2 (0.9) | 0.976 | 0.135 |
|               | Prednisone, n (%) | 61 (78.2) | 356 (82.2) | 60 (77.9) | 170 (77.3) | 1.00 | 0.016 |
|               | Prednisone daily dose, median (IQR), mg | 5.00 (5.00–7.50) | 5.00 (5.00–5.00) | 5.00 (5.00–7.50) | 5.00 (5.00–5.00) | 0.358 | 0.036 |
|               | Mycophenolate mofetil/mycophenolate sodium, n (%) | 60 (76.9) | 315 (72.7) | 59 (76.6) | 160 (72.7) | 0.604 | 0.090 |
|               | Mycophenolate sodium daily dose, median (IQR), mg | 720 (360–1080) | 720 (0–1080) | 720 (360–1080) | 720 (0–800) | 0.239 | 0.139 |
|               | Azathioprine, n (%) | 6 (7.7) | 25 (5.8) | 6 (7.8) | 12 (5.5) | 0.644 | 0.094 |
|               | Sirolimus, n (%) | 4 (5.1) | 15 (3.5) | 4 (5.2) | 12 (5.5) | 1.00 | 0.016 |
|               | Lymphocyte count at diagnosis, median (IQR), 10^9 cells/μL | 0.90 (0.40–1.50) | 0.80 (0.46–1.30) | 0.85 (0.40–1.42) | 0.80 (0.40–1.20) | 0.613 | 0.096 |
|               | Calcineurin inhibitor | 0.086 | | 0.257 | 0.212 | | | |
|               | Tacrolimus, n (%) | 56 (71.8) | 351 (81.1) | 55 (71.4) | 177 (80.5) | | | |
|               | Cyclosporine, n (%) | 18 (23.1) | 58 (13.4) | 18 (23.4) | 35 (15.9) | | | |
|               | Tacrolimus trough level, median (IQR), ng/mL | 7.5 (5.8–24.8) | 7.0 (5.2–10.0) | 7.6 (5.7–30) | 7.2 (5.5–13.7) | 0.436 | 0.040 |

*Comorbidities include hypertension, diabetes mellitus, body mass index >30, coronary artery disease, heart failure, chronic lung disease, chronic liver disease, chronic kidney disease, or active malignancy.

ATG, antithymocyte globulin; COVID-19, coronavirus disease 2019; IQR, interquartile range; SMD, standardized mean difference.
DISCUSSION

We performed a matched cohort study to assess the characteristics and outcomes of medically attended COVID-19 infection in 1- or 2-dose vaccinated versus unvaccinated SOT recipients. After propensity score matching, we found no significant differences in disease severity outcomes including hospitalization, oxygen requirement, ICU admission, all-cause, and COVID-19-related mortality, between those with vaccine breakthrough infection and unvaccinated patients. This suggests that 1 or 2 doses of COVID-19 vaccine is not enough for protection from severe disease. Some differences in treatment factors were noted: vaccinated patients were more likely to receive tocilizumab and have their immunosuppression regimen reduced. There was no difference in remdesivir, dexamethasone, antibiotic, or antifungal therapy across both groups. There was considerable morbidity and mortality related to COVID-19 in both groups.

The difference in treatment characteristics likely reflects the era of COVID-19 diagnosis, as tocilizumab was more frequently used after March 2021 because of increased availability and incorporation into local guidelines. Similarly in the later era, clinicians became more adept at the management of COVID-19 and were more likely to reduce immunosuppression. Therefore, although both practices coincide with vaccination and breakthrough infections, they are not necessarily causal. The finding of increased frequency of microbiologically confirmed bacterial infection in vaccinated patients may be related to the increased use of tocilizumab during this time or reflect a change in clinician practice to be more diligent in investigating infections and not treat empirically. This is an area that requires further evaluation.

There have been mixed reports regarding vaccine effectiveness in SOT patients. Aslam et al found a reduction in the incidence of COVID-19 infection in vaccinated SOT recipients at their institution compared with unvaccinated, and Ravanar et al reported a reduction in mortality with 2 doses of vaccine (7.7% versus 12.6%) in an analysis of the UK Transplant registry. Despite the overall reduction in infections, a US study showed that the likelihood of breakthrough infections was 82-fold greater in the transplant versus the general population. Mortality among breakthrough infections was 9% consistent with our data, which show a 9.1% mortality. Although our study does not look at the incidence of infections with and without vaccine, it does show that medically attended vaccine breakthrough infections are just as severe as in unvaccinated patients. The lack of reduction in severity from up to 2 doses of vaccination seen in our cohort may be because of the known suboptimal immune response in SOT recipients. It may also be due to the increased proportion of infection with SARS-CoV-2 variants of concern in the vaccinated participants, which may cause more severe infection than wild-type SARS-CoV-2.

Breakthrough COVID-19 in SOT recipients has had limited description. Our hospitalization and mortality rates with breakthrough infections were similar to other case series that describe 30%–60% requiring hospitalization and 5%–10% mortality. It is important to acknowledge that we examined only medically attended breakthrough COVID-19 infections, and the true denominator of mild or asymptomatic infection, which may occur more frequently in vaccinated participants, is not known. In addition, none of our patients received

### Table 2

| Outcome | All-cause mortality | COVID-19-related mortality |
|---------|---------------------|---------------------------|
| OR      | (95% CI)            | OR                        |
| 1.25    | (0.39-2.28)         | 1.33 (0.680-2.633)        |

### Table 3

| Outcome | All-cause mortality | COVID-19-related mortality |
|---------|---------------------|---------------------------|
| OR      | (95% CI)            | OR                        |
| 1.25    | (0.39-2.28)         | 1.33 (0.680-2.633)        |

### Table 4

| Outcome | OR (95% CI) | P  |
|---------|-------------|----|
| Supplemental oxygen, anya | 1.207 (0.612-2.38) | 0.587 |
| ICU admissionb | 0.718 (0.457-1.129) | 0.151 |
| Mechanical ventilationb | 0.877 (0.519-1.483) | 0.625 |
| Acute kidney injury, anya | 1.487 (0.632-3.501) | 0.363 |
| All-cause mortalityb | 1.188 (0.635-2.224) | 0.590 |
| COVID-19 related mortalityb | 1.339 (0.680-2.633) | 0.398 |

aModel 1, any vaccination versus no vaccination.  
bModel 3, numeric predictor 0, 1, 2 doses to estimate an odds ratio for a 1 dose reduction. CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.
monoclonal antibodies and early data suggest that monoclonal antibodies may reduce severity of disease in transplant recipients.\textsuperscript{22,35}

Our study has some limitations. COVID-19 vaccination began later in the pandemic during the emergence of alpha and delta variants. Therefore, the majority of vaccinated patients were diagnosed with SARS-CoV-2 variants of concern, compared with wild-type virus in unvaccinated patients. Matching for this characteristic was not possible because of limited sample size. Although this may have led to an increased severity of disease in the vaccinated cohort, we would still expect vaccine to have some partial benefit. Management considerations also changed over time with increased use of tocilizumab and remdesivir for moderate-severe disease.\textsuperscript{10} Another limitation is that we used time of confirmed diagnosis to define the onset of infection, rather than time of symptom onset. This has the potential to affect case definition, as partially and fully vaccinated patients may have developed COVID-19 <7 d and <14 d after vaccine doses respectively. A major strength of our study is the propensity score matching on organ type, age, decade, sex, and number of comorbidities. This controls for several known factors that contribute to severity of disease. We also included a large dataset of patients from multiple sites across Canada, which provided a representative population. Our study had 80\% power to detect a 1.8- to 2.5-fold reduction for various severity outcomes. These numbers reflect clinically important end-points that would be expected from vaccination. Our study design did not allow for the determination of vaccine effectiveness and rather was meant to determine whether vaccine reduced disease severity in breakthrough infections. We did not include breakthroughs after third dose of vaccine, for which there is now robust data in terms of benefit to humoral and cell-mediated immunity against ancestral SARS-CoV-2 and the variants of concern.\textsuperscript{14,36} We acknowledge that 2 doses of vaccine is no longer recommended, and our data emphasize the current guideline recommendation that transplant recipients should receive 3 doses of vaccine as their primary course, with a fourth dose of vaccine considered the booster dose. Importantly, our study period was before the emergence of the omicron variant.

In conclusion, disease severity outcomes in medically attended breakthrough infection after 1 or 2 doses of vaccination in SOT recipients do not seem to be different to unvaccinated SOT recipients in our study. Therefore, transplant recipients should get at least 3 doses of vaccine for a primary series and potentially a fourth dose as a booster. Preventative measures such as additional vaccine doses or passive antibody prophylaxis should continue to be evaluated. In addition to our findings, the available literature emphasizes the importance for ongoing public health vigilance in SOT patients and vaccination of their close and household contacts.

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