Abstract

IMPORTANCE Recipients of solid organ transplant (SOT) experience decreased immunogenicity after COVID-19 vaccination.

OBJECTIVE To summarize current evidence on vaccine responses and identify risk factors for diminished humoral immune response in recipients of SOT.

DATA SOURCES A literature search was conducted from the existence of databases through December 15, 2021, using MEDLINE, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov.

STUDY SELECTION Studies reporting humoral immune response of the COVID-19 vaccines in recipients of SOT were reviewed.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data from each eligible study. Descriptive statistics and a random-effects model were used. This report was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. Data were analyzed from December 2021 to February 2022.

MAIN OUTCOMES AND MEASURES The total numbers of positive immune responses and percentage across each vaccine platform were recorded. Pooled odds ratios (pORs) with 95% CIs were used to calculate the pooled effect estimates of risk factors for poor antibody response.

RESULTS A total of 83 studies were included for the systematic review, and 29 studies were included in the meta-analysis, representing 11,713 recipients of SOT. The weighted mean (range) of total positive humoral response for antispike antibodies after receipt of mRNA COVID-19 vaccine was 10.4% (0%-37.9%) for 1 dose, 44.9% (0%-79.1%) for 2 doses, and 63.1% (49.1%-69.1%) for 3 doses. In 2 studies, 50% of recipients of SOT with no or minimal antibody response after 3 doses of mRNA COVID-19 vaccine mounted an antibody response after a fourth dose. Among the factors associated with poor antibody response were older age (mean [SE] age difference between responders and nonresponders, 3.94 [1.1] years), deceased donor status (pOR, 0.66 [95% CI, 0.53-0.83]; $I^2 = 0%$, antimetabolite use (pOR, 0.21 [95% CI, 0.14-0.29]; $I^2 = 70%$), recent rituximab exposure (pOR, 0.21 [95% CI, 0.07-0.61]; $I^2 = 0%$), and recent antithymocyte globulin exposure (pOR, 0.32 [95% CI, 0.15-0.71]; $I^2 = 0%$).

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, the rates of positive antibody response in solid organ transplant recipients remained low despite multiple doses of mRNA (continued)
vaccines. These findings suggest that more efforts are needed to modulate the risk factors associated with reduced humoral responses and to study monoclonal antibody prophylaxis among recipients of SOT who are at high risk of diminished humoral response.


**Introduction**

Individuals with COVID-19 who have undergone solid organ transplant (SOT) experience higher mortality and prolonged viral shedding compared with the general population.\(^1\)\(^5\) Multiple vaccine platforms have been proven successful in reducing viral spread and preventing poor outcomes in the general population.\(^6\)\(^8\) Unfortunately, recipients of SOT were excluded from the initial licensing trials of these vaccines, and accumulating data have shown reduced immunogenicity among recipients of SOT.\(^9\)\(^14\)

The US Food and Drug Administration (FDA) has approved the COVID-19 mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) and has granted emergency use authorization (EUA) for the adenoviral vector vaccine Ad26.COV2.S (Janssen).\(^15\)\(^18\) In response to emerging SARS-CoV-2 variants and evidence of a mortality benefit from booster or additional doses, the US Centers for Disease Control and Prevention (CDC) recommended a booster or additional dose after completion of the primary COVID-19 vaccination series for all adults who received BNT162b2, mRNA-1273, or Ad26.COV2.S.\(^19\)\(^21\) For patients who are immunocompromised, including recipients of SOT, the CDC recommended an additional primary shot (third dose of mRNA COVID-19 vaccine for those receiving BNT162b2 or a booster dose of mRNA-1273) and a subsequent dose (fourth dose of BNT162b2 or second booster dose of mRNA-1273 for those receiving mRNA COVID-19 vaccine or second dose for those receiving Ad26.COV2.S).\(^22\) Despite this strategy, there are concerns for inadequate protection and risks of breakthrough infections among recipients of SOT because of diminished immunogenicity. We conducted this systematic review and meta-analysis to summarize the current evidence on vaccine responses and identify risk factors associated with diminished humoral immune response among recipients of SOT.

**Methods**

**Data Sources and Searches**

A systematic search was conducted independently by 2 of us (N.C. and K.M.) in MEDLINE, Embase, Web of Science (Clarivate), Cochrane Library, and ClinicalTrials.gov databases for research available through December 15, 2021. Complete search terms are included in the eMethods in the Supplement. Studies from different databases were combined, and duplicates were excluded. We did not limit our search by language. We conducted the study according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021277109).

**Study Selection and Quality Assessment**

Two authors (N.C. and K.M.) independently reviewed all studies and selected studies that reported the immunogenicity of COVID-19 vaccines in recipients of SOT, described as study participants in the methods and results. We included clinical trials and observational studies consisting of prospective cohort, retrospective cohort, and case-control studies. We excluded studies of humoral immunity after COVID-19 infection in study participants. Corresponding authors were contacted for immunogenicity testing or vaccination information if needed. We used Google Translate (Alphabet) to translate non-English studies during title and abstract screening. The Newcastle-Ottawa scale was
used for assessing the risk of bias of the studies (eTable 1 in the Supplement). Conflicts were resolved by mutual consensus between reviewers.

Data Extraction
The checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies was used. Our primary outcome was the seroconversion rate after COVID-19 vaccine administration. We extracted the numbers of responders and total participants to calculate the seroconversion rates. Responders were defined as participants whose humoral response met definitions and cutoffs of antibody testing in each primary study. The numbers of responders, total participants, and odds ratios (ORs) with 95% CIs of factors associated with vaccine response were extracted. If ORs were not available, crude numbers were extracted for OR calculation.

Statistical Analysis
Descriptive statistics were used to characterize humoral immune response, the primary outcome, for each COVID-19 vaccine platform and for each number of doses. We then performed a meta-analysis with Comprehensive Meta-Analysis software version 3.3 (Biostat) to identify risk factors associated with poor humoral immune response. To determine the factors associated with humoral immunogenicity, pooled ORs (pORs) with 95% CIs for binary variables and differences in means (with SEs) for continuous variables were calculated using meta-analysis with the random-effects model. If the study provided both adjusted and unadjusted ORs, we used adjusted ORs for calculations. If the primary study provided ORs of the factors associated with vaccine nonresponse, we used log transformation to calculate ORs associated with vaccine response of those specific factors. We performed sensitivity analyses using a leave-1-out method. If the P value of Egger regression was P < .1, the publication bias was considered significant. Factors with concerns of publication bias were further adjusted by the Duval and Tweedie trim-and-fill method. We assessed the heterogeneity of effect size estimates of each study using the $I^2$ statistic. The $I^2$ statistic ranged from 0% to 100%, with $I^2$ less than 25% indicating low heterogeneity; $I^2$ of 25% to 60%, moderate heterogeneity; and $I^2$ greater than 60%, substantial heterogeneity. $P$ values were 2-sided, and statistical significance was set at $P = .05$. Data were analyzed from December 2021 to February 2022.

Results

Study and Patient Characteristics
Our initial search generated 2832 studies; 896 studies were removed because they were duplicates, and 1748 studies were excluded by screening through the titles and abstracts. We performed full-study reviews on 188 articles. After review, 105 articles were excluded owing to being a review article, case report, preprint, incorrect patient population, or duplicate cohort or having no outcomes of interest. A total of 83 studies were included in the systematic review, of which 29 studies were included in the meta-analysis (Figure 1). The characteristics of 83 included studies are described in eTable 2 in the Supplement. There were 11713 study participants across all studies, including heart, lung, heart-lung, liver, kidney, pancreas, kidney-pancreas, and other combined transplantation. Grading of recommendation assessment, development and evaluation for potential factors associated with seroconversion was reported in eTable 3 in the Supplement.

Humoral Immune Responses

mRNA Vaccines
A total of 83 studies of immunogenicity of the mRNA COVID-19 vaccines in study participants were identified. Of these, 18 studies reported antibody response after 1 dose, 54 studies after 2 doses, 11 studies after 3 doses, and 2 studies after 4 doses of the mRNA COVID-19 vaccines.
Among the studies analyzed, the weighted mean (range) seroconversion rate after 1 dose of mRNA vaccine was 10.4% (0%-37.9%) for antispike antibodies (18 studies) and 4.1% (0%-5.9%) for neutralizing antibodies (2 studies) (Figure 2). The mean (range) antibody testing time was 25.5 (21-28) days after the first dose.

The weighted mean (range) total seroconversion rate after 2 doses of mRNA COVID-19 vaccines was 44.9% (0%-79.1%) for antispike antibodies (53 studies) and 22.6% (0%-47.5%) for neutralizing antibodies (8 studies) (Figure 2). Among studies reporting seroconversion rates after 2 doses of mRNA COVID-19 vaccines, we reviewed the rates of positive antibody response by types of the mRNA COVID-19 vaccines. The BNT162b2 vaccine had a weighted mean (range) seroconversion rate of 44% (range 0%-79.1%) for antispike antibodies (36 studies) and 15.3% (0%-35%) for neutralizing antibodies (5 studies).

Figure 1. Study Selection Flowchart

Figure 2. Antibody Response of mRNA Vaccines

Total seroconversion includes all seroconversion regardless of humoral immune response from the previous dose. New seroconversion only includes seroconversion from patients with no or minimal immune response from the previous dose. Dark lines indicate medians; dots, means; boxes, IQRs; whiskers, ranges. * Box plot cannot be graphed because fewer than 5 studies were included.
The mRNA-1273 vaccine demonstrated a weighted mean (range) seroconversion rate of 51.4% (29.9%-76.2%) for antispie antibodies (7 studies \textsuperscript{10,12,32,48,79,103,105}) and a mean of 26.9% for neutralizing antibodies (1 study\textsuperscript{19}). The mean (range) antibody testing time after the second dose was 31.9 (8-81) days for all vaccines, 33.8 (8-81) days for the BNT162b2 vaccine, and 25.2 (14-28) days for the mRNA-1273 vaccine. Humoral immune response rates after 2 doses of mRNA vaccines by the different testing modalities are summarized in eTable 4 in the Supplement.

Three doses of mRNA vaccines showed higher total seroconversion rates (including all seroconversion regardless of humoral immune response from the second dose) with a weighted mean (range) of 63.1% (49.1%-69.1%) for antispie antibodies (8 studies\textsuperscript{31,41,52,56,72,78,81,85,99}) and a mean of 60% for neutralizing antibodies (1 study\textsuperscript{12}) (Figure 2). Two studies reported new seroconversion (ie, only study participants with no or minimal immune response after the second dose), with the weighted mean (range) seropositivity rate of 32% (13.3%-60%) for antispie antibodies (Figure 2). The mean (range) antibody testing time was 26.3 (14-30) days after the third dose. A study by Schrezenmeier et al\textsuperscript{104} reported a 36% antispie antibodies response rate and a 35% neutralizing antibodies response rate after 2 doses of BNT162b2 followed by either 1 dose of BNT162b2 or AZD1222 (University of Oxford and Vaccitech).

A study by Alejo et al\textsuperscript{30} reported high positive antibody response rates after 4 doses of mRNA vaccines, with a mean response rate of 83.3% for antispie antibodies; however, the study also included study participants with positive antibody response after the third dose. A study by Kamar et al\textsuperscript{98} included only study participants with negative or low positive antibody response after the third dose, and reported a seropositivity rate of 48.7% after 4 doses of the BNT162b2 vaccine for antispie antibodies.

Other Vaccine Platforms
For study participants vaccinated with the viral-vectored vaccine platform, Boyarsky et al\textsuperscript{9} reported that 16.7% had positive antispie antibodies after 1 dose of Ad26.COV2.S, and Prendercki et al\textsuperscript{86} reported 43.6% had positive antispie antibodies after 2 doses of AZD1222. Masset et al\textsuperscript{100} reported that either 2 doses of AZD1222 followed by 1 dose of mRNA vaccine or 1 dose of AZD1222 followed by 2 doses of mRNA vaccine resulted in antispie antibody seroconversion in 75% of participants. Among inactivated COVID-19 vaccine platforms, only CoronaVac (Sinovac Biotech) has been studied in recipients of kidney transplants, and the seroconversion rate for antispie antibodies was 15.2% after 1 dose (1 study\textsuperscript{59}) and 40.8% (range, 18.8%-43%) after 2 doses.\textsuperscript{58,89} There were no studies available for other vaccine platforms response in recipients of SOT at the time of our data search. Humoral immune response rates by the COVID-19 vaccine types and doses are summarized in eTable 5 in the Supplement.

Factors Associated With Reduced Humoral Immune Responses After 2 Doses of mRNA Vaccines

Host Characteristics
Increased age was associated with lower seroconversion rates. The pooled difference in means (SE) of 10 studies showed study participants with antibody response were 3.94 (1.1) years younger than those without antibody response ($P = .001$)\textsuperscript{45-47,49,53,56,59,64,103} (Table; eFigure 1 in the Supplement). Male sex was associated with higher seroconversion rates (pOR, 1.16 [95% CI, 1.01-1.33]); $P = .04$; $I^2 = 0$%) (26 studies\textsuperscript{32,45-47,49,50,53,56,57,59,62-64,66,70,74,79,80,82,84,86,88,92-94,103}) (Table, Figure 3; eFigure 1 in the Supplement). Body mass index (BMI) and absolute lymphocyte count were not associated with differences in antibody response based on differences of means that were not statistically significant (Table; eFigure 1 in the Supplement).

Transplant Characteristics
Receipt of a deceased donor organ was associated with lower seroconversion rates compared with living donor status (pOR, 0.66 [95% CI, 0.53-0.83]; $P < .001$; $I^2 = 0$%)}
(10 studies) (Table, Figure 3; eFigure 1 in the Supplement). Time from transplantation to vaccination was associated with seroconversion rate. The pooled difference in means (SE) from 9 studies showed study participants with positive antibody response had 2.17 (0.71) years longer from transplantation to vaccination compared with those without antibody response ($P = .002$) (Table; eFigure 1 in the Supplement).

**Immunosuppression**

A total of 25 studies reported on antimetabolite use at the time of vaccine administration, which was associated with lower seroconversion rates (pOR, 0.21 [95% CI, 0.14-0.29]; $P < .001$; $I^2 = 70\%$) (Table, Figure 3; eFigure 1 in the Supplement). A total of 21 studies reported active use of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors, which was associated with higher seroconversion rates (pOR, 1.46 [95% CI, 1.02-2.08]; $P = .04$; $I^2 = 42\%$) (Table, Figure 3; eFigure 1 in the Supplement). Furthermore, 17 studies reported calcineurin inhibitor (CNI) use at the time of vaccine administration, which was not associated with antibody response (pOR, 0.92 [95% CI, 0.65-1.30]; $P = .64$; $I^2 = 21\%$) (Table, Figure 3; eFigure 1 in the Supplement).

Both rituximab exposure and antithymocyte globulin (ATG) exposure within 12 months of vaccination were associated with lower seroconversion rates (rituximab: pOR, 0.21 [95% CI, 0.07-0.61]; $P = .005$; $I^2 = 0\%$; ATG: pOR, 0.32 [95% CI, 0.15-0.71]; $P = .005$; $I^2 = 0\%$) (Table, Figure 3; eFigure 1 in the Supplement). All data extraction of potential risk factors are summarized in eTable 6 and eTable 7 in the Supplement.

<table>
<thead>
<tr>
<th>Table. Summary of Factors Associated With Immunogenicity After 2 Doses of mRNA Vaccines</th>
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<tbody>
<tr>
<td><strong>Risk factor</strong></td>
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<tr>
<td><strong>Host characteristics</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Male</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Lymphocyte count</td>
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<tr>
<td><strong>Transplant characteristics</strong></td>
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<tr>
<td>Time from transplant, y</td>
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<tr>
<td>Deceased donor status</td>
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<tr>
<td><strong>Maintenance IS</strong></td>
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<tr>
<td>Antimetabolites</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
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<tr>
<td>Augmented IS in 12 mo</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
</tr>
<tr>
<td>Rituximab</td>
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</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IS, immunosuppression; mTOR, mammalian (mechanistic) target of rapamycin; NA, not applicable; pORs, pooled odds ratios.
**Sensitivity Analysis and Publication Bias**

Results of sensitivity analysis are reported in eFigure 2 in the Supplement. The pORs of male sex and seroconversion lost significance after removing 1 of the following studies: Cholankeril et al,92 Davidov et al,93 Ducloux et al,80 Haskin et al,67 Kantauskaite et al,82 Masset et al,56 Rozen-Zvi et al,66 Sanders et al,103 or Villanego et al.74 The pORs of rituximab exposure and seroconversion lost significance after removing Haskin et al67 from the analysis. The pORs of mTOR inhibitor use and seroconversion lost significance after removing any 1 of the following studies: Benotmane et al,32 Cucchiari et al,10 Grupper et al,46 Kantauskaite et al,82 Korth et al,53 Peled et al,62 Rabinowich et al,63 Rashidi-Alavijeh et al,64 Sanders et al,103 or Villanego et al.74

We found evidence of publication bias for age, BMI, lymphocyte count, antimetabolite use, mTOR inhibitor use, and ATG exposure (eFigure 3 in the Supplement). After accounting for publication bias by the Duval and Tweedie trim-and-fill method, antimetabolites (adjusted pOR, 0.31 [95% CI, 0.21-0.46]) and ATG (adjusted pOR, 0.41 [95% CI, 0.20, 0.82]) remained significantly associated with lower seroconversion rates (Figure 4; and eFigure 4 in the Supplement). After adjusting, the association of mTOR inhibitors was no longer significant (adjusted pOR, 1.09 [95% CI, 0.77-1.55]) (Figure 4; and eFigure 4 in the Supplement). The adjusted pooled difference in means of age remained significant, while those of BMI and lymphocyte count remained not statistically significant (eFigure 4 in the Supplement).

**Discussion**

This systematic review and meta-analysis summarizes the cumulative evidence of immunogenicity of COVID-19 vaccines and risk factors associated with poor humoral response in recipients of SOT. Despite receiving multiple doses of mRNA vaccines, approximately 20% to 40% of recipients of SOT...
did not mount an antibody response. Although the correlation between positive humoral immune response with the clinical efficacy of COVID-19 vaccines in recipients of SOT has yet to be determined, the rates of humoral immune response in these populations after 3 or 4 doses of the mRNA COVID-19 vaccines are lower than those found in the general populations of the phase III clinical trials, and the rates of COVID-19 vaccine breakthrough infection in recipients of SOT are higher than those of the general public. COVID-19 breakthrough infection rates before the emergence of the Omicron variant in recipients of SOT who had received at least 2 doses of an mRNA vaccine or 1 dose of an adenovirus vaccine varied from 0.23% to 2.5%, as reported among transplant centers in the US. The breakthrough infection rate was up to 5% among recipients of kidney transplant treated with belatacept in a French cohort study, which is much higher than the general public.

Our study has identified several risk factors associated with the lower seroconversion rate after 2 doses of mRNA COVID-19 vaccines in recipients of SOT. Recipients of SOT who were older, had recent transplants, or received deceased donor organ transplants had lower seroconversion rates. Unfortunately, we cannot determine specific cutoffs of age or time after transplantation associated with poor antibody response based on our study design. Similarly, recipients of SOT who were actively using antimetabolite immunosuppression (e.g., mycophenolate mofetil, mycophenolic acid, or azathioprine) or who had recent exposure to rituximab or ATG within 12 months had lower seroconversion rates. We hypothesize that lower seroconversion with these agents could be caused by direct suppression of B-lymphocyte function or suppression of T-lymphocyte-dependent B-lymphocyte activation. Currently, there are ongoing clinical trials in Israel (NCT04961229), the US (NCT04969263), and the Netherlands (NCT05030974) to evaluate immunogenicity in solid organ transplant recipients after modulation of immunosuppression.

Despite higher seroconversion rates with progressively higher numbers of vaccine doses in recipients of SOT, the durability of the antibody response to repeated vaccination and the clinical outcomes in infection rates, disease severity, and mortality remain unknown. As of December 20, 2021, the US FDA has issued an EUA for tixagevimab-cilgavimab, a combination of long-acting monoclonal antibodies (mAb), for preexposure prophylaxis in patients who are immunocompromised, including recipients of SOT. Although the EUA states that mAb preexposure prophylaxis should not be considered an alternative to vaccination, there is inherent tension between the strategy of active immunization through vaccination and passive immunization with mAbs. Long-acting mAb preexposure prophylaxis is a valuable resource to add protection for recipients of SOT who have received all available and recommended doses of COVID-19 vaccines but who have demonstrated poor humoral immunity or who have the risks factors associated with lower seroconversion rates identified in our study. But for recipients of SOT who have not received all available doses of COVID-19 vaccines, there are now 2 options: to proceed with vaccination according to the recommended schedule or to postpone vaccination and pursue mAbs. The risk factors

### Table 1. Unadjusted and Adjusted Pooled Odds Ratios (ORs) Accounting for Publication Bias

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>OR (95% CI)</th>
<th>Favors negative humoral immune response</th>
<th>Favors positive humoral immune response</th>
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<tr>
<td>Antimetabolites</td>
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<tr>
<td>Unadjusted</td>
<td>0.21 (0.14-0.29)</td>
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<tr>
<td>Adjusted</td>
<td>0.31 (0.21-0.46)</td>
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<tr>
<td>mTOR inhibitor</td>
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<tr>
<td>Unadjusted</td>
<td>1.46 (1.02-2.08)</td>
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<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.09 (0.77-1.55)</td>
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<td>Antithymocyte globulin</td>
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<tr>
<td>Unadjusted</td>
<td>0.32 (0.14-0.71)</td>
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<tr>
<td>Adjusted</td>
<td>0.41 (0.20-0.82)</td>
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identified in this study for lower seroconversion rates after 2 vaccine doses may also help to inform transplant professionals who must advise their patients on time-sensitive decisions about active vs passive immunization by weighing the likelihood of benefit from vaccination compared with the likelihood of benefit from mAbs.

Additional unanswered questions include the optimal number of doses for a primary vaccination series, particularly in recipients of SOT with risk factors associated with lower seroconversion rates. Additionally, the role of antibody testing to determine strategies for additional doses or mAbs, the appropriate antibody cutoff level or other tests to ascertain immunity, and the most just allocation of scarce vaccine supply toward first doses or additional and booster doses at the global level are questions worthy of investigation and discussion.

Limitation
This study has some limitations. One limitation of COVID-19 vaccine immunogenicity research in recipients of SOT to date is the overrepresentation of the mRNA platform. Many recipients of SOT, particularly those living outside the US, may not have been fully vaccinated against COVID-19 or may not have access to mRNA vaccines owing to vaccine scarcity. Second, several techniques of SARS-CoV-2 antibody testing were used in the studies, and there is no criterion standard at this time. Third, the correlation between humoral immune response and the clinical efficacy of COVID-19 vaccines in recipients of SOT remains unclear. Fourth, most study participants were recipients of kidney transplant, with relatively fewer other organ transplant types. Fifth, the data regarding other vaccine platforms, including the heterologous prime-boost strategy, in recipients of SOT are extremely limited.

Conclusions
In this systematic review and meta-analysis of 29 studies and 11,713 recipients of SOT, seroconversion rates among recipients of SOT vaccinated with mRNA vaccines were higher with successive doses but remained lower than those among the general population. The availability of long-acting mAbs for preexposure prophylaxis presented an additional option for solid organ transplant recipients who have been vaccinated but may still be at inordinate risk for COVID-19, and mAbs are an additional consideration for recipients of SOT who have not yet been vaccinated and who may have multiple risk factors associated with a lower immune response to vaccination.
Author Contributions: Drs Manothummetha and Permpalung had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Manothummetha and Chuleerarux contributed equally to this study.

Concept and design: Manothummetha, Chuleerarux, Kates, Torvorapanit, Worasilchai, Plongla, Chindamporn, Thaniyavarn, Nematollahi, Permpalung.

Acquisition, analysis, or interpretation of data: Manothummetha, Chuleerarux, Sanguankeo, Hirankarn, Thongkam, Dioverti-Prono, Langsiri, Moonla, Plongla, Garneau, Nissaisorakarn, Thaniyavarn, Permpalung.

Drafting of the manuscript: Manothummetha, Chuleerarux, Thongkam, Worasilchai, Plongla, Thaniyavarn, Nematollahi, Permpalung.

Critical revision of the manuscript for important intellectual content: All authors.

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Obtained funding: Torvorapanit.

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Supervision: Dioverti-Prono, Plongla, Chindamporn, Nissaisorakarn, Permpalung.

Conflict of Interest Disclosures: Dr Torvorapanit reported receiving grants from Health Systems Research Institute during the conduct of the study. Dr Garneau reported receiving personal fees from DKBmed and the Society of Hospital Medicine during the conduct of the study and owning stock in Abbott, Avantor, Danaher, Eli Lilly, Ecolab, Iqvia, Johnson & Johnson, Stryker, United Healthcare, and AstraZeneca outside the submitted work. Drs Worasilchai, Plongla, and Chindamporn reported receiving grants from the Health Systems Research Institute (Thailand) and Rachadapiseksompotch Fund, Chulalongkorn University outside the submitted work. Dr Permpalung reported receiving grants from Health Systems Research Institute, Fisher Center Discovery Program, Cystic Fibrosis Foundation, and National Institutes of Health, and personal fees from Shionogi and Pulmocide outside the submitted work. No other disclosures were reported.

REFERENCES


SUPPLEMENT.
eMethods. Search Strategies
eTable 1. Newcastle-Ottawa Quality Assessment Scale of Included Studies in Meta-Analysis
eTable 2. Study Characteristics
eTable 3. Grading of Recommendation Assessment, Development and Evaluation (GRADE) for Potential Factors Associated With Diminished Humoral Immune Response
eTable 4. Humoral Immune Response Rates After 2 Doses of mRNA Vaccines by the Different Testing
eTable 5. Humoral Immune Response by the COVID-19 Vaccine Types and Doses
eTable 6. Participants and the Effect Estimates of Potential Risk Factors for Diminished Humoral Immune Response in Each Study
eTable 7. Continuous Data of Potential Risk Factors for Diminished Humoral Immune Response
eFigure 1. Forest Plots of Studied Risk Factors
eFigure 2. Sensitivity Analysis of Studied Risk Factors
eFigure 3. Publication Bias of Studied Risk Factors
eFigure 4. Funnel Plots and Adjusted Effect Estimates Accounting for Publication Bias
eReferences.