A Systematic Review and Meta-Analysis of Serologic Response following Coronavirus Disease 2019 (COVID-19) Vaccination in Solid Organ Transplant Recipients

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Abstract: Solid organ transplant (SOT) recipients are at greater risk of coronavirus disease 2019 (COVID-19) and have attenuated response to vaccinations. In the present meta-analysis, we aimed to evaluate the serologic response to the COVID-19 vaccine in SOT recipients. A search of electronic databases was conducted to identify SOT studies that reported the serologic response to COVID-19 vaccination. We analyzed 44 observational studies including 6158 SOT recipients. Most studies were on mRNA vaccination (mRNA-1273 or BNT162b2). After a single and two doses of vaccine, serologic response rates were 8.6% (95% CI 6.8–11.0) and 34.2% (95% CI 30.1–38.7), respectively. Compared to controls, response rates were lower after a single and two doses of vaccine (OR 0.0049 [95% CI 0.0021–0.012] and 0.0057 [95% CI 0.0030–0.011], respectively). A third dose improved the rate to 65.6% (95% CI 60.4–70.2), but in a subset of patients who had not achieved a response after two doses, it remained low at 35.7% (95% CI 21.2–53.3). In summary, only a small proportion of SOT recipients achieved serologic response to the COVID-19 mRNA vaccine, and that even the third dose had an insufficient response. Alternative strategies for prophylaxis in SOT patients need to be developed. Key Contribution: In this meta-analysis that included 6158 solid organ transplant recipients, the serologic response to the COVID-19 vaccine was extremely low after one (8.6%) and two doses (34.2%). The third dose of the vaccine improved the rate only to 66%, and in the subset of patients who had not achieved a response after two doses, it remained low at 36%. The results of our study suggest that a significant proportion of solid organ transplant recipients are unable to achieve a sufficient serologic response after completing not only the two series of vaccination but also the third booster dose. There is an urgent need to develop strategies for prophylaxis including modified vaccine schedules or the use of monoclonal antibodies in this vulnerable patient population.

Keywords: COVID-19; vaccine; outcomes; meta-analysis; solid organ transplant; immunocompromised; kidney transplant; heart transplant; lung transplant

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global health emergency [1]. It has been reported that older individuals, patients with pre-existing comorbidities, and those that are immunosuppressed are at greater risk of COVID-19 and experiencing severe pneumonia [2–4]. Patients who have undergone organ transplants require lifelong immunosuppressive therapy. Long-term maintenance immunosuppression including the combinatory use of calcineurin inhibitors, antimetabolites, glucocorticoids (GCs), monoclonal antibodies, and inhibitors of T cell activation remains the mainstay in improving graft survival in transplant recipients [5,6]. In the United States, 39,000 organ transplants were performed in 2020 [7]. Renal transplants were the most commonly performed, followed by liver, heart, and lung transplantation [7]. Furthermore, more than 100,000 patients are on the national transplant...
waiting lists. Patients with solid organ transplants (SOT) are at risk for various infections because the immunosuppressive agents dramatically reduce immunity against viruses, bacteria, and other pathogens [8,9]. During periods of a pandemic, the protection of the safety or health of SOT patients is an important priority [10].

Salto-Alejandre et al., demonstrated that old age and a shorter interval between transplant and COVID-19 diagnosis showed an association with poor COVID-19 outcomes in SOT patients with a case fatality rate greater than 20% [4]. These reports suggest that there is a need for effective prophylaxis in SOT recipients. Due to the lack of efficacious therapies for COVID-19, vaccinations that could prevent infections are of importance in lowering the mortality risk [11]. COVID-19 vaccines were developed and a large number of studies demonstrated that mRNA COVID-19 vaccinations are efficacious and safe [12]. Patients who were on immunosuppressive drugs were excluded from initial vaccination trials, so the effectiveness of COVID-19 vaccinations in transplant recipients remains unclear [13]. Guideline recommendations are that transplant recipients should receive COVID-19 vaccination unless there is any contraindication. Studies of other infectious conditions have shown that SOT recipients have diminished humoral response to vaccinations [14]. Boyarsky et al., showed that kidney or liver transplant patients had decreased immunogenicity to mRNA-1273 and BNT162b2 vaccinations [15]. Most studies assessing the efficacy of COVID-19 vaccinations in transplant recipients are of limited sample size [16,17].

In order to improve clinical care and protect this vulnerable patient population, it is important to understand the efficacy of COVID-19 vaccinations in transplant recipients. We aimed to integrate data from various studies to evaluate the serologic response to COVID-19 vaccines in SOT patients.

2. Methodology
2.1. Search Strategy of Selecting Studies

We conducted the present meta-analysis according to a protocol that is in accordance with the PRISMA guideline [18]. We have submitted the protocol to the International Prospective Register of Systematic Reviews (PROSPERO) (pending approval) [19].

PubMed/MEDLINE, EMBASE, and medRxiv were electronically searched on 1 August 2021. Observational studies that reported the serologic response to COVID-19 vaccines in SOT recipients were included. No restrictions for country, language, age, or type of vaccine of the study were imposed. Two members (AS and AL) screened each potential study in an independent manner to assess the eligibility. When any issues or disagreements were found, they were resolved after discussion. We used the following terms to search for eligible studies: “SARS-CoV-2”, “COVID-19”, “vaccine”, “transplant”, “transplantation”, “liver”, “kidney”, “heart”, “lung”, “pancreas”, “multi-organ”, and “immunosuppressed”. We also searched bibliographies of eligible articles for any potential references. Manuscripts that were published in non-English language were translated if necessary. We excluded single case reports and studies that only reported adverse effects of COVID-19 vaccines. We contacted the corresponding author of studies to obtain missing data when necessary. Figure 1 shows the search strategy.
2.2. Extraction of Data and Assessment of Quality

The data of each eligible study were independently extracted in duplicate by the authors (AS and AL). Extracted data included study characteristics such as name of authors, publication year, country, administered vaccine, duration, sample size, transplanted organ, treatment, characteristics of patients, and results of serologic tests. The diseases were categorized into the following groups according to the transplanted organ: (1) kidney, (2) heart/lung, and (3) liver. Studies that reported outcomes in various organ transplant recipients without distinction were classified as (4) mixed.

The risk of bias of the studies was assessed by the Joanna Briggs Institute Critical Appraisal Checklist [20,21]. The quality of evidence obtained from the present meta-analysis was rated by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [22].

2.3. Assessment of Outcomes

Serologic response rate to COVID-19 vaccine was the primary outcome of the present meta-analysis. We separately assessed the rate of response following the first, second, and third vaccination. The rate of serologic response in transplant recipients compared to control population was the secondary outcome. The number of patients achieving antibody levels above the cut-off of the test method used in each study divided by the total number of patients was defined as the rate of serologic response [23]. A majority of studies used one of the three commercially available antibody tests (Roche, DiaSorin, and Abbott), so applying a common cut-off value between studies was not possible; however, they all have excellent sensitivity (98–100%) [21,24]. When response was tested at different timing, the time point closest to 4 weeks following the vaccine was chosen [21].

Meta-regression and subgroup analyses based on transplanted organs (kidney, heart/lung, liver, mixed group), patient’s age, and proportion of patients on immunosuppressive medications were performed. Immunosuppressive medications such as calcineurin inhibitors, mycophenolate, antimetabolites, monoclonal antibodies, and inhibitors of T cell activation were included, but were not assessed separately because a majority of studies did not report outcomes separately according to treatment.
2.4. Statistical Analysis

A meta-analysis of the serologic response rate to COVID-19 vaccine was undertaken by random effects model [21]. Heterogeneity across included studies was analyzed by $I^2$ statistic. Heterogeneity was defined as low, moderate, and high when $I^2$ value was <25%, 25–75%, and >75%, respectively [25]. Heterogeneity was also evaluated by Cochran’s Q-statistics ($p < 0.10$) [26]. Publication bias was analyzed with Begg’s and Egger’s tests. When more than 3 studies were included in the meta-analysis, funnel plots were created to assess asymmetry [27,28]. Subgroup analyses and random effects meta-regression models were used to evaluate the contribution of each risk factor to the response to vaccination [21]. When performing multivariate meta-regression, all variables included in the univariate meta-regression were included as they were all considered clinically important.

Preprint studies were included because they are a substantial part of the available COVID-19 literature [23]. However, we conducted sensitivity analyses by excluding preprint studies because they still lack peer-review [29]. One study included exclusively a non-mRNA vaccine (Ad26.COV2.S), so it was analyzed separately. One study removed analyses that were undertaken to assess whether the results of the meta-analyses were biased by a single study [21].

We used Comprehensive Meta-Analysis Software (version 3; Biostat, Englewood, NJ, USA) for all statistical analyses. We used a two-sided $p$-value of 0.05 for significance except for Q-statistics.

2.5. Data Sharing and Access

Data of the present study will be made available when requested from the corresponding author. All coauthors of the present study had access to the data of the study and approved final version of the manuscript.

3. Results

3.1. Study Characteristics

As shown in Figure 1, 1941 studies were identified through the literature search. We excluded 1833 studies after screening of title and abstract. We assessed 108 studies for eligibility and found 44 studies (6158 patients) that met the eligibility criteria. Twenty-two studies included only patients with kidney transplant, seven included patients with heart and/or lung transplant, and one included patients with liver transplant (Table 1). Fourteen studies included patients with various SOTs (mixed group), which included kidney, heart/lung, liver, and pancreas, but did not report outcomes separately. Twenty-six and five studies included patients vaccinated with only BNT162b2 and mRNA-1273, respectively. Eight studies included patients vaccinated with either BNT162b2 or mRNA-1273. One study only used AD26.COV2.S. One study used ChAdOx1 nCoV-19 as a third dose in patients who previously received two series of BNT162b2. Another study used AD26.COV2.S in patients who previously received two series of BNT162b2 or mRNA-1273.
| Author                        | Country   | Year | Patient Numbers and Description | Control Numbers and Description | Age of Patients (years) | Sex of Patients (% Female) | Cases, % of Patients on Steroids | Cases, % of Patients on Immunosuppression | Type of Vaccine | Number of Patients Receiving 1 Dose | Number of Patients Receiving 2 Doses | Number of Patients Receiving 3 Doses |
|------------------------------|-----------|------|----------------------------------|---------------------------------|-------------------------|---------------------------|-----------------------------------|----------------------------------------|----------------|--------------------------------------|--------------------------------------|--------------------------------------|
| 1. Grupper (Full paper)       | Israel    | 2021 | 136 (Kidney 100%)               | 25 (HCWs)                       | Cases mean: 59.6 (SD 12.7) | Controls mean: 52.7 (SD 11.5) | Cases 18.3%, Controls 68% | ATG last 12 months 7.9%, Rituximab last 12 months 29%, CNIs 25.3%, mTOR inhibitors 7.5%, MMF 79.5% | Triple maintenance immunosuppression 78.8% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 161                                  | NA                                  |
| 2. Boyarsky 1 (Letter)        | United States | 2021 | 458 (Kidney 100%, Liver 17.9%, Heart 3.3%, Lung 11.2%, Pancreas 1.1%, Multorgan 3.2%) | None                            | Median: 55.9 (IQR 41.3–67.4) | 61% | 100% (Tacrolimus 88%, MMF 66%, Azathioprine 9%, Sirolimus 4%, Everolimus 2%) | 54% | BNT162b2 (Pfizer-BioNTech) 52%, mRNA-1273 (Moderna) 48% | 436 | NA                                  | NA                                  | NA                                  |
| 3. Wadoi (Letter)             | United States | 2021 | 7 (Double lung 14.3%, Kidney 28.6%, Heart and kidney 14.3%, Kidney and pancreas 14.3%) | None                            | Mean: 59 (Range 42–69) | 0% | 100% (Tacrolimus 85.7%, MMF 100%, Belatacept 14.3%) | 100% | BNT162b2 (Pfizer-BioNTech) 57.1%, mRNA-1273 (Moderna) 42.9% | 2   | 5                                   | NA                                  | NA                                  |
| 4. Bonen-Axella (Full paper)  | Germany   | 2021 | 40 (Kidney 100%)               | 35 (Mainly HCWs)                | Cases mean: 62.4 (IQR 51.3–64.9) | Controls mean: 51.0 (IQR 43.0–68.5) | Cases 30%, Controls 42.9% | 100% (MMF 37.5%, Tacrolimus 37.5%, Cyclosporine 37.5%, Azathioprine 0.0%, mTOR inhibitors 5.7%) | 92.5% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 75                                  | NA                                  |
| 5. Benotmane 1 (Letter)       | France    | 2021 | 242 (Kidney 100%)              | None                            | 57.7 (49.3–67.6) | 35.50% | 100% (Induction treatment: ATG 59.5%, anti-CD20 37.5%, no induction 3.8%, CNIs Tacrolimus 59.5%, cyclosporine 34.2%, sirolimus 7.0%, Others: MMF 79.1%, Azathioprine 2.0%, mTOR inhibitors 9.8%, Belatacept 3.8%) | 58.9% | mRNA-1273 (Moderna) 100% | 242 | NA                                  | NA                                  | NA                                  |
| 6. Benotmane 2 (Letter)       | France    | 2021 | 305 (Kidney 100%)              | None                            | 57.7 (49.4–67.3) | 36.60% | 100% (Induction treatment: ATG 40.5%, anti-CD20 35.9%, no induction 3.6%, CNIs Tacrolimus 59.4%, Cyclosporine 35.0%, sirolimus 7.0%, Others: MMF 79.1%, Azathioprine 2.0%, mTOR inhibitors 13.2%, Tacrolimus + MMF/MPA 48%, Cyclosporine + MPA/stereoid 31.2%, Belatacept 2.5%) | 59.8% | mRNA-1273 (Moderna) 100% | NA                                  | 205 | NA                                  |
| 7. Rabinowitch (Full paper)   | Israel    | 2021 | 80 (Liver 100%)                | 25 (HCWs)                       | Cases mean: 61.1 (SD 12.6) | Controls mean: 52.7 (SD 11.5) | Cases 50%, Controls 48% | 100% (MPA 32.1%, MMF 22.1%, Everolimus 22.5%, Azathioprine 7.1%, MMF 50%) | High-dose steroids last 12 months 8.7%, prednisone 30% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 105 | NA                                  |
| 8. Xi (Letter)                | United States | 2021 | 149 (Kidney 100%)              | 31 (ESRD patients 4 on immunosuppression) | NA | NA | 100% | 100% (MPA 93.2%, MMF 22.1%, Everolimus 22.5%, Azathioprine 0.0%, Belatacept 14.3%) | 89.7–97.4% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 78 | NA                                  |
| 9. Pelid (Full paper)         | Israel    | 2021 | 77 (Heart 100%)                | 136 (healthy controls)          | NA | NA | 100% | 100% (MPA 93.2%, MMF 22.1%, Everolimus 22.5%, Azathioprine 0.0%, Belatacept 14.3%) | 81.7% | mRNA vaccine 100%: Of original cohort of 850, 942 retested BNT162b2 (Pfizer-BioNTech) and 8 received mRNA-1273 (Moderna) | 367 | 367 | NA                                  | NA                                  |
| 10. Sadik (Full paper)        | Germany   | 2021 | 39 (Kidney 100%)               | 39 (HCWs)                       | Cases mean: 57.3 (SD 16.1) | Controls mean: 53.0 (SD 17.5) | Cases 25.1%, Controls 48.72% | 100% (Tacrolimus 78.2%, Cyclosporine 7.1%, MPA 68.4%, mTOR inhibitors 29.2%, Belatacept 9.3%) | 56.3% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 39 | NA                                  |
| 11. Marion (Letter)           | France    | 2021 | 367 (Kidney 73.8%, Liver 15.8%, Thoracic-organs 9.0%, Pancreas 1.4%) (includes 5 patients with prior COVID-19 exposure) | None                            | Cases mean: 59 (Standard error 1) | 35.6% | 100% (Tacrolimus 78.2%, Cyclosporine 7.1%, MPA 68.4%, mTOR inhibitors 29.2%, Belatacept 9.3%) | 81.7% | mRNA vaccine 100%: Of original cohort of 950, 942 retested BNT162b2 (Pfizer-BioNTech) and 8 received mRNA-1273 (Moderna) | 367 | 367 | NA                                  | NA                                  |
| 12. Miele (Letter)            | Italy     | 2021 | 36 (Kidney 53.6%, Liver 15.8%, Heart 15.8%, Lung 7.2%) | 25 (HCWs)                       | Cases mean: 57 (SD 15.9) | Controls mean: 44 (SD 7.2) | Cases 18.8%, Controls 56.3% | Tacrolimus 93.7%, Everolimus 6.3%, MMF 62.9% | 56.3% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 39 | NA                                  |
| 13. House (Communication)     | Czech Republic | 2021 | 48 (Lung 100%)                | 10 (Healthy volunteers)         | Cases mean: 59 (SD 14.7) | Controls mean: 56.4 (SD 12.8) | NA | 100% (Tacrolimus 97.9%, Cyclosporine 2.1%, MMF 91.7%) | 97.9% | BNT162b2 (Pfizer-BioNTech) 100% | 46 | 30 | NA                                  | NA                                  |
| 14. Raus-Zvi (Full paper)     | Israel    | 2021 | 308 (Kidney 100%)              | None                            | Mean: 57.51 ± 13.84 | 35% | 100% (MMF 79.4%, Tacrolimus 90.3%, Cyclosporine 7.9%, mTOR inhibitors 8.4%, Sirolimus 1.4%, ATG 1.4%) | 8.4% | BNT162b2 (Pfizer-BioNTech) 100% | NA                                  | 308 | NA                                  |
| 15. Shohat (Letter)           | Israel    | 2021 | 168 (Liver 100%)               | None                            | Median: 60.5 (IQR 49.3–67.8) | 33% | 100% (Tacrolimus 97.9%, Cyclosporine 90.3%, MMF 62.9%, mTOR inhibitors 8.4%) | Mean prednisone dose 5.0 mg, IQR 5.0–10.0 | BNT162b2 (Pfizer-BioNTech) 100% | 168 | 168 | NA                                  | NA                                  |
### Table 1. Cont.

| Author | Country | Year | Patient Numbers and Description | Control Numbers and Description | Age of Patients (years) | Sex of Patients (% Female) | Cases, % of Patients on Immunosuppression | Cases, % of Patients on Steroids | Type of Vaccine | Number of Patients Receiving 1 Dose | Number of Patients Receiving 2 Doses | Number of Patients Receiving 3 Doses |
|--------|---------|------|----------------------------------|----------------------------------|-------------------------|--------------------------|----------------------------------------|----------------------------------|----------------|-------------------------------|----------------------------------|----------------------------------|
| 16. Betrcand (Full paper) | France  | 2021 | 45 (Kidney 100%) | None | Mean: 63.5 ± 16.3 | 48.9% | 50% (Celecoxib 31.6%, Cyclosporine 37.8%, MMF 62.2%, Azathioprine 8.9%, Everolimus 6.7%, Belatacept 22.5%) | 46.7% | BNT162b2 (Pfizer-BioNTech) 100% | 45 | 45 | NA |
| 17. Cacchiari (Full paper) | Spain  | 2021 | 117 (Kidney 10.2%, Kidney and pancreas 6.8%) | None | Mean: 59.00 ± 52.42 | 32.3% | 50% (Tacrolimus 83.8%, Cyclosporine 4.2%, MMF 61.3%, mTOR inhibitors 32.5%, Azathioprine 4.8%, Belatacept 6.8%, Eculizumab 1.2%) | 79.5% | mRNA-1273 (Moderna) 100% | NA | 148 | NA |
| 18. Husain (Letter) | United States | 2021 | 28 (Kidney 100%) (Includes 5 patients with prior COVID-19 exposure) | None | Median: 66 (Range 42–67) | 39% | Tacrolimus 75%, Belatacept 25%, MMF/MPA 61%, Azathioprine 11%, Leflunomide 4%, Sirolimus/everolimus 14% | 32% | BNT162b2 (Pfizer-BioNTech) 57%, mRNA-1273 (Moderna) 43% | NA | 28 | NA |
| 19. Korth (Communication) | Germany  | 2021 | 23 (Kidney 100%) | 23 (HCWs) | Cases mean: 57.7 ± 12.5 | Controls mean: 44.4 ± 9.2 | Cases 52%, Controls 61% | MMF 58.3%, Cyclosporine 69.9%, Cyclosporine 17.8%, Sirolimus 22.7%, Belatacept 4.3%, Azathioprine 4.2% | 60.8% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 46 | NA |
| 20. Royansky 2 (Letter) | United States | 2021 | 609 (Kidney 65.9%, Liver 19.6%, Heart 14.7%, Lung 10.8%, Pancreas 0.8%, Multigraft 4.0%) | None | Median: 60 (Range 18–960) | 56.7% | 50% (Antimetabolites 71.9%, Other 28.1%) | NA | BNT162b2 (Pfizer-BioNTech) 52.0%, mRNA-1273 (Moderna) 46.7% | 698 | 658 | NA |
| 21. Mazzola (Full paper) | France  | 2021 | 144 (Heart 80.0%, Kidney 40.3%, Heart 16.7%) (Includes 8 patients with prior COVID-19 exposure) | 25 (HCWs) | Cases mean: 61.0 (IQR 50.0–67.0) | Controls mean: 51.0 (IQR 38.0–62.0) | Cases 28.7%, Controls 27.2% | CNI 62.5%, MMF 72.0%, mTOR inhibitor 16.8%, Tri-therapy 50.4% | 62.2% | BNT162b2 (Pfizer-BioNTech) 100% | 125 | 158 | NA |
| 22. Tiflet (Letter) | Belgium  | 2021 | 10 (Kidney 100%) | 10 (Belgian vaccination program) | Cases mean: 49.7 (SD 13.8) | Controls mean: 51.3 (SD 10.5) | Cases 50.0%, Controls 30.0% | 50% (siRNA 52.0%, Antimetabolites 183%) | 40% | BNT162b2 (Pfizer-BioNTech) 100% | 20 | 20 | NA |
| 23. Dufresne (Communication) | France  | 2021 | 74 (Kidney 100%) | 7 (HCWs) | Cases mean: 68.8 ± 11.3 | Controls mean: 51.6 ± 6.8 | Cases 43.9%, Controls 42.5% | 50% (siRNA 91.0%, Belatacept 6.6%, Azathioprine 10.0%, MMF 70.0%, MP 9.5%, Azathioprine 2.7%) | 45.9% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 81 | NA |
| 24. Royansky 3 (Letter) | United States | 2021 | 12 (Kidney 99%, Liver 25%, Heart 9%, Lung 9%) | None (compared to mRNA cohort data) | Median: 56 (IQR 42–60) | 58.3% | 50% (siRNA 78.8%, Azathioprine 16.7%, Tacrolimus 83.1%, MMF 66.7%, Everolimus 8.3%) | 58.3% | mRNA-1273 (Janssen/Johnson & Johnson) 100% | 12 | NA | NA |
| 25. Matsnaki (Letter) | Greece  | 2021 | 34 (Heart 70.6%, Kidney 29.4%) | 116 (HCWs) | Cases mean: 60 (IQR 49.1–66.4) | Controls: Age and sex matched HCW | Case 20.6%, Controls: Age and sex matched HCW | 50% (CNI 94.9%, Antimetabolite therapy 44%, mTOR inhibitor 62%) | 15% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 150 | NA |
| 26. Chavant 1 (Letter) | France  | 2021 | 101 (Kidney 100%) | None | Cases mean: 64 (53–73) | 32.2% | 50% (Belatacept 100%, MPA 78.2%, mTOR inhibitors 11.9%, Tacrolimus 79.7%, Azathioprine 2.0%) | 96.0% | BNT162b2 (Pfizer-BioNTech) 100% | 101 | 35 | NA |
| 27. Ou (Full paper) | United States | 2021 | 609 (Kidney 100%), Pancreas 6%, Liver 4%, Heart 2%, Lung 2%, Pancreas 2% | None | Median: 58 (IQR 45–69) | 59.2% | 50% (Belatacept 3.3%, MMF 71.9%, Tacrolimus 72.2%, Azathioprine 9.5%, Sirolimus 8.4%) | 68.5% | BNT162b2 (Pfizer-BioNTech) 51.9%, mRNA-1273 (Moderna) 44.4% | 592 | 400 | NA |
| 28. Kamar (Correspondence) | France  | 2021 | 59 (Kidney 97.4%, LFR 11.9%, Lung 7.9%, Pancreas 3.1%) | None | Mean: 58 ± 2 | 30.3% | CNAs 79%, Antimetabolites 66%, mTOR inhibitors 30%, Belatacept 12% | 87% | BNT162b2 (Pfizer-BioNTech) 100% | 111 | 99 | 98 (Included in Del Bello) |
| 29. Hallat (Full paper) | United States | 2021 | 237 (Heart 57.5%, Lung 43%) | None | Median: 62 (48–69) | 58% (Heart 51%, Lung 56%) | 50% (Belatacept 86.0%, MMF 68.6%, Sirolimus 13.4%, Cyclosporine 8%, Azathioprine 8%, Everolimus 79%, Belatacept 15%) | 57% | BNT162b2 (Pfizer-BioNTech) 53%, mRNA-1273 (Moderna) 47% | 237 | 237 | NA |
| 30. Smirfi (Full paper) | Germany  | 2021 | 369 (Kidney 100%) | 144 (HCWs) | Cases mean: 57.7 ± 11.7 | Controls mean: 48 ± 11.9 | 54.8% | 50% (siRNA 47.6%, MPA 70.5%, mTOR inhibitor 16%, Belatacept 5.6%) | 48.4% | BNT162b2 (Pfizer-BioNTech) 28%, mRNA-1273 (Moderna) 40% | 144 | 333 | NA |
| 31. Zedek (Short report) | Israel | 2021 | 42 (Heart 100%) | None | Median: 61 (IQR 44–69) | 17% | 50% (siRNA 66.6%, Cyclosporine 10%, Steroids/mTOR inhibitor 39%) | 68% | BNT162b2 (Pfizer-BioNTech) 100% | 42 | NA | NA |
| 32. Schlesman (Full paper) | Germany  | 2021 | 50 (Heart 94%, Lung 14%, Heart/lung 2%) | 50 (HCWs) | Mean: 55 ± 10 | 56% | 50% (CNI 85.5%, Cyclosporine 10%, Steroids/mTOR inhibitor 39%) | NA | BNT162b2 (Pfizer-BioNTech) 100% | NA | NA | NA |
Table 1. Cont.

| Author                  | Country   | Year | Patient Numbers and Description | Control Numbers and Description | Age of Patients (years) | Sex of Patients (% Females) | Cases, % of Patients on Immunosuppression | Cases, % of Patients on Steroids | Type of Vaccine | Number of Patients Receiving 1 Dose | Number of Patients Receiving 2 Doses | Number of Patients Receiving 3 Doses |
|-------------------------|-----------|------|---------------------------------|---------------------------------|-------------------------|-----------------------------|----------------------------------------|-------------------------------|--------------------------------|------------------------------------|------------------------------------|----------------------------------|
| 23. Werbel (Letter)     | United States 2021 | 30 (Kidney 73.3%, Heart 6.7%, Lung 3.3%, Liver 10%, Pancreas 3.3%, Kidney and pancreas 3.3%) None | Median: 57 (IQR 44–62) | 56.7% | Tacrolimus or Cyclosporine + MMF 83.3%, Sirolimus 3.3%, Belatacept 3.3% | 80% | mRNA-1273 (Moderna) 43.3% | Third dose: BNT162b2 (Pfizer-BioNTech) 56%, mRNA-1273 (Moderna) 43.3% | mRNA-1273 (Moderna) 43.3% | 30 | 30 |
| 24. Hall (Correspondence) | Canada 2021 | 10 (Kidney 100%) None | (Randomized controlled trial contained all solid organ transplant patients) | Third dose median: 66.9 (IQR 64.9–70.5), Placebo median: 65.9 (IQR 62.9–70.5) | Third dose: 38.3%, Placebo: 30% | 100% (Tacrolimus 77.5%, Cyclosporine 20.8%, Sirolimus 9.2%, MMF 75%, Azathioprine 10%) | Third dose: 83.3%, Placebo: 70% | mRNA-1273 (Moderna) 100% | NA | 120 | 60 |
| 35. Karaba (Preprint)  | United States 2021 | 31 (Kidney 61.3%, Liver 22.6%, Heart 9.7%, Pancreas 3.2%, Lung 3.2%) None | (55 Healthy controls receiving 2 mRNA vaccine doses) | Median: 60 (IQR 49–67) | Cases: 54.8%, Controls: 33.3% | (CNI 80.6%, mTORi 9.7%, Anti-metabolites 64.5%) | 51.6% | None | NA | 46 | 46 |
| 36. Palad 2 (Full paper) | Israel 2021 | 96 (Heart 100%) None | | | | 100% (Tacrolimus 84.5%, Mycophenolate sodium 54.2%, MMF 24.0%, Cyclosporine 11.5%, Everolimus 21.9%) | 80.2% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 96 | 96 |
| 37. Benahmida 3 (Letter) | France 2021 | 139 (Kidney 100%) None | | | | 100% (Tacrolimus + MMF/MPA + steroid 52.8%, All other regimens 42.2%) | Tacrolimus + MMF/MPA + steroid 52.8%, All other regimens (7%, 42.2%) | mRNA-1273 (Moderna) 100% | NA | 159 | 159 |
| 38. Massel (Letter)     | France 2021 | 150 (Kidney 32.5%, pancreas 28.8%, Lung 9.4%, Liver 7.4%, Heart 9.4%, Pancreas 3.2%, Multiple organs 5.3%) None | | | | (CNI 86.6%, mTORi 14.7%, Anti-metabolites 74.5%, NA: 1.47%) | 31.6% | (NA: 1.47%) | BNT162b2 (Pfizer-BioNTech) 100% | NA | 456 | 136 |
| 39. Del Bello (Letter)  | France 2021 | 59 (SD 55) None | | | | 100% (CNI 96.5%, MPA 72.9%, mTORi 30.6%, Belatacept 16.1%) | 82.1% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 396 | 396 |
| 40. Charron 3 (Communication) | Canada 2021 | 66 (Kidney 100%) None | | | | 100% (CNI 92.4%, MPA 81.9%, mTORi 7.6%, Belatacept 1.5%) | 86.6% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 66 | 66 |
| 41. Weinfalk 2 (Letter) | Germany 2021 | 62 (Kidney 100%) None | | | | 100% (Belatacept 100%, Everolimus 12.9%, MPA 71.0%, Azathioprine 4.8%, CNI 3.2%) | 100% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 62 | 62 |
| 42. Marzella (Letter)   | Germany 2021 | 10 (Kidney 100%) None | | | | 100% (CNI 80%, MPA 10%, Belatacept 10%, MPA 90%) | 100% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 10 | 10 |
| 43. Massa (Preprint)    | France 2021 | 61 (Kidney 100%) None | | | | 100% (Antimetabolites 62.2%, CNIs 30.5%, mTORi 9.8%, Belatacept 1.6%) | 88.9% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 61 | 41 |
| 44. Schlechtwein (Preprint) | Germany 2021 | 25 (Kidney 100%) None | | | | 100% (Tacrolimus 96%, Cyclosporine 32%, MMF 96%, mTORi 16%) | 96% | BNT162b2 (Pfizer-BioNTech) 100% | NA | 25 | 25 | 25 |

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| Author       | Used to Check Antibody Response | Timing of Test After One Dose | After Two Doses | After Three Doses |
|--------------|---------------------------------|------------------------------|----------------|-----------------|
|              |                                 | Cases Responders             | Controls        | Cases Ab Titers  | Controls        | Cases Ab Titers  | Controls        | Cases Ab Titers  |
|              |                                 |                             | Responders      |                 | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       | Responders      | Ab Titers       |
| 1. Grupper    | DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay | 10–20 days after the second dose | -              | -               | 51/136          | 25/25           | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
|              | EURIBIO/ELISA anti-SARS-CoV-2 IgG assay or Roche Elecsys anti-RBD pan-Ig assay | 14–21 days after the first dose | 76/436         | NA              | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 2. Boyarsky | Antispike antibody, manufacturer NA | Medium 28 days (Range 6–48 days) after the first dose | 0/2             | NA              | 1/5             | 1.4 U/mL         | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 3. Wadei     | EUROIMMUN anti-SARS-CoV-2 ELISA, GenScript Surrogate SARS-CoV-2 virus neutralization ELISA | 7 ± 2 days after the second dose | -               | 4/40 (IgG 1/40, IgA 4/40, Neutralizing antibodies 1/40) | 35/35           | IgG median: 0.09 (IQR 0.07–0.15) | IgG median: 0.20 (IQR 0.15–0.40) | NC median: 0.07 (IQR 0.05–0.15) | -               | -               | -               | -               | -               | -               | -               |
| 4. Rincon-Arroyo  | -                                 | 28 days after the first dose | 26/242          | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 5. Benostane 1 | ARCHITECT IgG II Quant test | -                            | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 6. Benostane 2 | Abbott ARCHITECT IgG II Quant test | 1 month after the second dose | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 7. Rabinoobch | DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay | Cases: Mean 14.6 (±3.2) days after the second dose, Controls: Mean 15.8 (±2.9) days after the second dose | -               | -               | -               | -               | -               | -               | -               | -               | -               | -               |
| 8. Yi        | Anti-SARS-CoV-2 IgG and total antibody, anti-SARS-CoV-2 Nucleocapsid IgG, and anti-Spike IgG titer | At the time of second dose | 7/485            | 37/41           | -               | -               | -               | -               | -               | -               | -               | -               |
| 9. Peled 1    | An “in-house” ELISA that detects IgG antibodies against SARS-CoV-2 RBD | Transplant: 21 ± 10 days after the second dose, Control: 13.3 ± 14 days after the second dose | -               | -               | -               | -               | -               | -               | -               | 14/77           | 134/136          | NA              | NA              | -               | -               | -               | -               |

**Table 1.**
| Author               | Used to Check Antibody Response | Timing of Test                                                                 | After One Dose Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Two Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Three Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers |
|---------------------|---------------------------------|-------------------------------------------------------------------------------|---------------------------------|--------------------|-----------------|------------------|-------------------------------|--------------------|----------------|-------------------|-----------------------------|--------------------|----------------|-------------------|
| 10. Kallirri        | Euroimmun ELISA-based analysis of SARS-CoV-2 spike S1 domain-specific IgG and IgA | 8 ± 1 days after the second dose                                               | -                               | -                  | -               | -                | -                             | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 11. Marcon         | Beijing Wantai Biological Pharmacy Enterprise SARS-CoV-2 total antibodies ELISA or another validated anti-SARS-CoV-2 spike protein assay | 28 days after the first or second dose                                         | 23/367                          | -                  | NA              | 7/10             | 23/35                         | Median: 3.8 AU/mL | Mean: 5.72 AU/mL | Medium: 212 AU/mL | -                           | -                  | -              | -                 |
| 12. Miele          | Euroimmun ELISA-based analysis of SARS-CoV2 spike S1 domain-specific IgG and IgA | Causes: Median 20 days (Range 15-30) after the second dose, Controls: Median 15 days (Range 15-25) after the second dose | -                               | -                  | -               | 8/16             | -                             | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 13. Havlin          | Euroimmun anti-SARS-CoV-2 Spike S1 IgG ELISA, confirmed independently by Tensile Mesoarray Array COVID-19 IgG and Diurnal Lambda SARS-CoV-2 Trimeric S IgG | 0/46                            | -                               | NA                 | 8/16            | -                | 7 days after second vaccination: 0/10 (4-6 weeks after second vaccination: 0/21) | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 14. Rasul-Zvi       | ARCHITECT SARS-CoV-2 IgG II Quant assay | Median 28 days (IQR 22-34) days after the second dose                          | -                               | -                  | 12/83           | -                | -                             | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 15. Shostak         | Abbott SARS-CoV-2 IgG II Quant assay | Median 36 days (IQR 15-18) days after the second dose                          | 6/186                           | -                  | Geometric mean S-IgG titer: 3.12 (IQR 4.06) | -                | 31/168                        | Geometric mean S-IgG titer: 3.29 (SD 9.22) | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 16. Bertrand        | ARCHITECT SARS-COV2 IgG II Quant assay | Three weeks after the first dose and one month after the second dose       | 1/45                            | -                  | NA              | -                | Geometric median: 671 AU/mL (IQR 172-1325) | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 17. Carabelli       | A serological assay based on the Luminex technique measuring antibodies against the Receptor-Binding Domain (RBD) of the spike glycoprotein of SARS-CoV-2 | 2 weeks after the second dose                                                | -                               | -                  | 6/112           | -                | -                             | -                  | -              | -                 | -                           | -                  | -              | -                 |
| 18. Husain          | Euroimmun ELISA or Roche Diagnostics Elecsys anti-S IgG immunoassay | Median 29 days (Range 12-59) days after the second dose                     | -                               | -                  | 7/20            | -                | -                             | -                  | -              | -                 | -                           | -                  | -              | -                 |
Table 1. Cont.

| Author                | Used to Check Antibody Response | Timing of Test                                                                 | After One Dose Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Two Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Three Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers |
|-----------------------|---------------------------------|-------------------------------------------------------------------------------|---------------------------------|--------------------|-----------------|-------------------|-----------------------------|-------------------|-----------------|-------------------|-------------------------------|--------------------|-----------------|-------------------|
| Korth                 | DiaSorin LIAISON SARS-CoV-2 Trimeric S IgG assay | Cases: Mean 15.8 ± 3.0 days after the second dose Controls: Mean 15.7 ± 1.8 days after the second dose | -                               | -                  | -               | -                 | 35/105                      | 138.7 AU/mL         | -               | -                 | -                             | -                  | -               | -                 |
| Boyarsky 2            | ELROMMUN anti-S1 IgG assay 28.6%, Euro Diagnostics anti-RBD pan-IgG assay 71.4% | Median 19 days (IQR 19–25) after the first dose, Median 21 days (IQR 29–31) after the second dose | 36/128                         | -                  | NA              | -                 | -                           | -                 | -               | -                 | -                             | -                  | -               | -                 |
| Mazzola               | Abbott Diagnostics Alinity i chemiluminescent microparticle immunoassay | 28 days after the first and second dose | 9/125                           | -                  | Responder median: 150 AU/mL (IQR 120–160) | -                 | 36/133                      | 25/25                | -               | -                 | -                             | -                  | -               | -                 |
| Tokht                 | DiaSorin LIAISON SARS-CoV-2 Trimeric S IgG assay | At time of second dose, ~15 days after the second dose, ~50 days after the second dose for transplant patients | 10/10                          | 9/10               | Median: 7 AU/mL (Range 0–0 AU/mL) | -                 | 15 days after second dose 1/10 (50 days after second dose 3/10) | 10/10              | 15 days after second dose median: 0 AU/mL (0–60 AU/mL) 50 days after second dose median: 0 AU/mL (0–46 AU/mL) | 15 days after second dose median: 263 AU/mL (Range 155–2000 AU/mL) | -                  | -               | -                 |
| Dantha                | DiaSorin LIAISON SARS-CoV-2 Trimeric S IgG | 14, 28, 36, and 58 days after the first dose | -                               | -                  | -               | -                 | 3/74                        | 7/7                | NA (low number of responders) | Day 14: 99 AU/mL (IQR 265.5–216.9 AU/mL) Day 36: 1082 AU/mL (IQR 730.5–1662 AU/mL) Day 58: 925 AU/mL (IQR 657–963.5 AU/mL) | -                  | -               | -                 |
| Boyarsky 3            | Abbott Diagnostics anti-SARS-CoV-2 S enzyme immunoassay | Medium: 35 days (IQR 31–44 days) after the first dose | 2/15                           | -                  | -               | -                 | -                           | -                 | -               | -                 | -                             | -                  | -               | -                 |
| Marinski              | Abbott SARS-CoV-2 IgG II Quant anti-SARS-CoV-2-RBD IgG assay | Medium 19 days (IQR 19–25 days) after the second dose | -                               | -                  | -               | -                 | 20/14                      | 116/116             | -               | -                 | -                             | -                  | -               | -                 |
| Ekhaverd             | Abbott SARS-CoV-2 IgG II Quant antibody test or Beijing Wantai Biological Pharmacy Enterprise SARS-CoV-2 total antibody ELISA | 28 and 60 days after first dose | 2/101                          | -                  | NA              | -                 | 4/35                        | -                 | NA              | -                 | -                             | -                  | -               | -                 |
### Table 1. Cont.

| Author | Used to Check Antibody Response | Timing of Test | After One Dose | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Two Doses | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Three Doses | Controls Responders | Cases Ab Titers | Controls Ab Titers |
|--------|---------------------------------|----------------|---------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|---------------------|----------------|-------------------|----------------|-------------------|
| 27. Ou | EUROIMMUN anti-S1 IgG assay or Roche Elecsys anti-RBD pan-Ig assay | After 1 dose: Non-belatacept: Median 21 days (IQR 19–26) Belatacept: Median 22 days (IQR 19–26) After 2 doses: Non-belatacept: Median 29 days (IQR 28–32) Belatacept: Median 29 days (IQR 26–31) | - | - | 77/902 (Belatacept 0/74, Non-belatacept 77/766) | - | - | 101/400 (Belatacept 1/19, Non-belatacept 101/393) | - | - | - | - | - | - |
| 28. Kumar | Beijing Wanxin Biological Pharmacy Enterprise SARS-CoV-2 total antibodies ELISA Roche Elecsys for antibodies against the receptor-binding domain (RBD) or EUROIMMUN for antibodies to the S1 domain | 4 weeks after the third dose | 4/101 | - | NA | - | 40/99 | - | NA | - | - | 67/99 (Included in Del Bello) | - | - |
| 29. Hallett | Roche Elecsys for antibodies against the receptor-binding domain (RBD) or EUROIMMUN for antibodies to the S1 domain | Medium of 21 days (IQR 19–26 days) after the first dose, median of 29 days (IQR 28–32 days) after the second dose | 28/237 (Heart 19/134, Lung 9/103) | - | - | - | 120/237 (Heart 85/134, Lung 37/103) | - | Anti-spike RBD assay: 250 U/mL (IQR 174–250 U/mL) for first dose responders, 3.9–244.2 U/mL for second dose responders, 0 U/mL (IQR 0–0 U/mL) for non-responders | - | - | - | - | - | - |
| 30. Stumpf | SMAG-Cov-2-specific IgG or IgA antibody macromolecules (Euroimmun) against the Spike protein subunit S1 | 3–4 weeks after the first dose, 4–5 weeks after the second dose | 11/144 | 53/55 | NA | NA | 140/133 | 132/134 | NA | - | - | - | - | - |
| 31. Zadok | Anti-spike IgG (S-IgG) antibodies | 21–26 days and 35–40 days after the first dose | 6/39 | - | NA | - | 18/37 | - | NA | - | - | - | - | - |
| 32. Schaffzin | SMAG-Cov-2 IgG HI Quant assay (Adenov) which was used for the quantitative measurement of IgG antibodies against the spike receptor-binding domain (RBD) | 24 days after the first and the second dose | 2/56 | 49/86 | NA | Medium 50 (41;89) BAU/ml | 5/70 | 98/50 | NA | - | - | - | - | - |
| 33. Werbel | EUROIMMUN anti-S1 IgG assay or Roche Elecsys anti-RBD pan-Ig assay | Medium 9 days (IQR 2–33) before the third dose, Medium 14 days (IQR 14–17 days) after the third dose | - | - | - | - | 6/20 | - | - | - | - | - | - | - | - |

**Notes:**
- N/A denotes not available.
- BAU/ml: Baxter Units per milliliter.
| Author   | Used to Check Antibody Response | Timing of Test | After One Dose Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Two Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Three Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers |
|----------|--------------------------------|---------------|---------------------------------|--------------------|----------------|------------------|-------------------------------|---------------------|----------------|------------------|-------------------------------|--------------------|----------------|------------------|
| Hall     | Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay | 1 month after third vaccination | -                              | -                  | -              | -                | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
| Karaba   | Meso Scale Diagnostics (NDI) V-PLEX COVID-19 155 Respiratory Panel 3 multiplex chemiluminescent kit | 14 days after third vaccination | -                              | -                  | -              | -                | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
| Piled 2  | An “in-house” enzyme-linked immunosorbent assay that detects IgG antibodies against SARS-CoV-2 RBD | Mean 19.5 days (SD 3.35) after third vaccination | -                              | -                  | -              | -                | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
| Benotmane | Abbott ARCHITECT IgG II Quant test | Median 28 days (IQR 27–33) after third vaccination | -                              | -                  | -              | -                | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
| Mazzi    | Abbott Architect chemiluminescent microparticle immunoassay, Siemens Axilea chemiluminescence immunoassay, Roche Elecsys electrochemiluminescent immunoassay | Median 30 days (IQR 28–32) | -                              | -                  | 264/95 | -              | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
| Del Bello | Beijing Wantai enzyme-linked immunosorbent assay (228, 57.6%) or other anti-SARS-CoV-2 spike assay (168, 42.4%) | 4 weeks after third vaccination | -                              | -                  | -              | -                | -                                | -                           | -              | -                | -                                | -                           | -              | -                |
Table 1. Cont.

| Author                  | Used to Check Antibody Response | Timing of Test After Dose | After One Dose Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Two Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers | After Three Doses Cases Responders | Controls Responders | Cases Ab Titers | Controls Ab Titers |
|-------------------------|---------------------------------|---------------------------|---------------------------------|---------------------|-----------------|-------------------|-------------------------------|---------------------|-----------------|-------------------|-------------------------------|-------------------|-----------------|-------------------|
| 40. Charmetant         | Anti SARS-CoV-2 IgG test on a Maglumi 2000 analyser | 14 days after third vaccination | - | - | 27/93 | - | - | 28/93 (28/93 had no response after two doses) | - |
| 41. Chavarot 2         | Abbott SARS-CoV-2 IgG II Quant antibody test | Median: 25 (IQR: 18–38) days after third vaccination | - | - | - | 0/62 | - | - | 0/62 | - | - | Median: 542 AU/mL (IQR: 478–923) | - |
| 42. Westhoff           | Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay | 14 days after third vaccination | 0/10 | - | <142 BAU/mL | - | 28/66 (All 66 had no response after two doses) | - | - | - | - | - | - | - |
| 43. Massa              | Abbott ELISA on the Abbott Architect i1000 analyser | 28 days after third vaccination | - | - | - | 27/61 | - | - | - | 27/61 | - | GMT IgG: 528.5 AU/mL (95% CI: 380.0–930.1) | - | 38/61 | - | - | - | GMT IgG: 285 (95% CI: 121–423) | - |
| 44. Schrezenmeier      | Euroimmun ELISA-based analysis of SARS-CoV-2 spike S1 domain-specific IgG and IgA | 7±2 days after the second and third vaccination, and 19–27 days after each vaccination | 0/25 | - | NA | - | 0/25 | - | NA | - | 9/25 (BNT162b2: 3/14, AZD1222: 6/11) | - | - | - | NA | - | - | - |

HCW, health care worker; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mechanistic target of rapamycin; CNI, calcineurin inhibitor; ESRD, end stage renal disease; AU, arbitrary units; GMT, geometric mean titer; ELISA, enzyme-linked immunoassay; IQR, interquartile range; NA, not available.
Twenty-one and thirty-five studies were eligible for evaluation of serologic response after one and two doses, respectively. Four and fifteen studies compared serologic response after one or two doses of COVID-19 vaccination to controls with no history of transplant. Twelve studies reported outcomes in patients who received a third vaccine dose [16,17,30–37]. Most studies measured outcomes 3–5 weeks following the vaccine (Table 1). The summary of characteristics of the studies that were included in the meta-analysis is shown in Table 1. We evaluated the risk of bias in the studies with the Joanna Briggs Institute Critical Appraisal Checklist (Supplementary Table S1). Most of the studies were of medium–high quality.

3.2. Serologic Response following a Single Dose of COVID-19 Vaccination

There were 21 studies that evaluated the serologic response following the first vaccination in transplant recipients (20 mRNA vaccine and one AD26.COV2.S vaccine). The serologic response following a single dose of mRNA vaccine was extremely low at 8.6% (95% confidence interval [CI] 6.8–11.0) (Figure 2A). Subgroup analysis demonstrated that the rates were 7.0% (95% CI 3.3–14.0), 6.6% (95% CI 4.3–9.9), and 10.7% (95% CI 7.8–14.7) in heart or lung transplant recipients, kidney transplant recipients, and mixed transplant recipients, respectively. The one study that reported a serologic response following a single dose of AD26.COV2.S vaccination showed a rate of 16.7% (Supplementary Figure S1A). Heterogeneity was present ($I^2 = 74.2\%$) in the meta-analysis of mRNA vaccines possibly due to the differences in sample size and reported rates of the studies. Multivariate meta-regression showed that the proportion of patients on GCs (regression coefficient $-0.029$, 95% CI $-0.052$–$0.0061$, $p = 0.013$) was a source of heterogeneity. Studies that used both types of mRNA vaccines showed a greater response rate compared to studies that only included BNT162b2 vaccine (coefficient $1.08$, 95% CI $0.20$–$1.96$, $p = 0.016$) (Supplementary Table S2).

Visual evaluation of the funnel plot of the mRNA vaccine studies showed no asymmetry; however, we found publication bias with Egger’s test ($p < 0.001$), but not with Begg’s test ($p = 0.36$) (Supplementary Figure S2A).

We performed sensitivity analyses to evaluate whether any single study influenced the outcomes (Supplementary Figure S2B). The results were unchanged when each study was removed one at a time from the meta-analyses. Specifically, the removal of the one preprint study showed similar results [37]. Subgroup analysis stratifying based on the type of the vaccination demonstrated that the serologic response rates were 5.4%, 11.8%, and 10.7% in studies that used BNT162b2, mRNA-1273, or both types of vaccines, respectively (Supplementary Figure S2C).
Figure 2. (A) Meta-analysis of serological response after one dose of vaccine: mRNA vaccines.
(B) Meta-analysis of serological response after two doses of vaccine: mRNA vaccines.
3.3. Serologic Response following Two Doses of COVID-19 Vaccination

Thirty-five studies were available for the assessment of the serologic response following two doses of mRNA vaccination. There were no studies that used non-mRNA vaccines. The pooled serologic response rate was 34.2% (95% CI 30.1–38.7) (Figure 2B). Subgroup analysis demonstrated that the rates were 22.9% (95% CI 11.1–45.9), 28.3% (95% CI 22.6–34.8), and 35.5% (95% CI 29.4–44.2) in heart/lung transplant recipients, kidney transplant recipients, and mixed transplant group, respectively. The one liver transplant study reported a rate of 47.5%.

Heterogeneity was present ($I^2 = 88.9\%$) which was possibly due to the differences in the sample size and the response rates of the included studies. Multivariate meta-regression demonstrated that older age (regression coefficient $-0.10$, 95% CI $-0.19$–$0.020$), $p = 0.016$) and GC use (regression coefficient $-0.014$, 95% CI $-0.025$–$0.0024$), $p = 0.017$) were significant sources of heterogeneity. (Supplementary Table S3).

Visual evaluation of the funnel plot showed no asymmetry; however, we found publication bias with Egger’s and Begg’s tests ($p < 0.001$ and $p = 0.0038$, respectively) (Supplementary Figure S3A).

We performed sensitivity analyses to evaluate whether any single study influenced the outcomes (Supplementary Figure S3B). The results were unchanged when each study was removed one at a time from the meta-analyses. Removal of the three preprint studies showed similar results (Supplementary Figure S3C). Subgroup analysis stratifying based on the type of vaccine showed that the rates were 28.9%, 26.6%, and 40.6% in studies that used BNT162b2, mRNA-1273, or both types of vaccines, respectively (Supplementary Figure S3D).

A few studies that reported antibody titers or concentrations showed greater than ten-fold lower values in transplant recipients (Table 1).

3.4. Serologic Response following a Single Dose of COVID-19 Vaccination Compared to Controls

There were four studies that included control patients after one dose of the vaccine. Meta-analysis demonstrated that transplant recipients were less likely to achieve a serologic response compared to controls (6.3% vs. 94.5%; odds ratio [OR] 0.0049, 95% CI 0.0021–0.012, $p < 0.001$) (Figure 3A). Subgroup analysis demonstrated that both heart and/or lung and kidney transplant recipients achieved statistically significantly lower rates of response compared to control patients (4.0% vs. 98.0%; OR 0.0009, 95% CI 0.0001–0.0097, $p < 0.001$ and 6.7% vs. 92.8%; OR 0.0049, 95% CI 0.0021–0.012, $p < 0.001$, respectively).

Heterogeneity was absent ($I^2 = 16.0\%$). Visual evaluation of the funnel plot showed no asymmetry, and no publication bias was found (Begg’s $p = 0.73$, Egger’s $p = 0.51$) (Supplementary Figure S4A).
3.5. Serologic Response following Two Doses of COVID-19 Vaccination Compared to Controls

There were 15 studies that included control patients after two doses of vaccine. Meta-analysis demonstrated that transplant recipients were less likely to achieve a serologic response compared to controls (30.8% vs. 99.4%; OR 0.0057 [95% CI 0.0030–0.011], \( p < 0.001 \)) (Figure 3B). Subgroup analysis demonstrated that heart and/or lung and kidney transplant recipients as well as the mixed transplant group achieved statistically significantly lower response rates compared to controls (12.1% vs. 99.0%; OR 0.0024 [95% CI 0.0007–0.0084], 31.8% vs. 99.3%; OR 0.0063 [95% CI 0.0025–0.016], 35.5% vs. 100%; OR 0.011 [95% CI 0.0025–0.045], respectively, and all \( p < 0.001 \)).
There was no heterogeneity ($I^2 = 0\%$). Visual evaluation of the funnel plot showed no asymmetry, and no publication bias was found with Begg’s and Egger’s tests ($p = 0.20$, $p = 0.47$) (Supplementary Figure S4B).

3.6. Serologic Response following Three Doses of COVID-19 Vaccination

Ten studies reported the serologic response following a third dose of COVID-19 vaccination. Five studies used the same mRNA vaccine for all three doses (BNT162b2 or mRNA-1273) whereas three studies used a different mRNA vaccine for the third dose. Two studies used mRNA vaccines as the first two series followed by Ad26.COV2.S as the third dose. As can be seen in Figure 4A, the rate of serologic response was 65.5% (95% CI 60.4–70.2), which was nearly two-fold greater than the rate after two doses. Subgroup analysis demonstrated that the rates were 66.7% (95% CI 56.7–75.4), 66.9% (95% CI 60.1–73.2), and 59.9% (95% CI 47.9–70.8) in heart and/or lung transplant recipients, kidney transplant recipients, and mixed group, respectively. The rate was lower with Ad26.COV2.S as the third dose compared to using the same or different combination of mRNA vaccines (41.0% (95% CI 24.2–60.2%) vs. 66.1% (95% CI 62–69.9%)-70.1% (95% CI 43.7–87.6%), respectively) (Supplementary Figure S5B). The results were unchanged when each study was removed one at a time from the meta-analyses (Supplementary Figure S5C).

Heterogeneity was moderate ($I^2 = 44.7\%$) possibly due to the differences in the sample size and reported rates of the studies. Visual evaluation of the funnel plot showed no asymmetry, and no publication bias was found with Begg’s and Egger’s tests ($p = 0.37$, $p = 0.19$) (Supplementary Figure S5A).
3.7. Serologic Response following Three Doses of COVID-19 Vaccination in Non-Responders after Two Doses

There were six studies that reported the serologic response after a third dose of the COVID-19 vaccine in patients who did not show a response following two vaccination. All studies only included kidney transplant recipients. Four studies used the same mRNA vaccine for all three doses (BNT162b2 or mRNA-1273) whereas one study each used BNT162b2 as the first two series followed by AZD1222 or mRNA-1273 as the third dose. As can be seen in Figure 4B, the serologic response rate was 35.7% (95% CI 21.2–53.3), which was half of that seen among studies not restricted to two-dose non-responders (Figure 4A). Subgroup analysis demonstrated that the serologic response rates were 54.5% (95% CI 26.8–79.7) and 60.0% (95% CI 29.7–84.2) when AZD122 or mRNA-1273 were administered as the third dose following two doses of BNT162b2, but 27.9% (95% CI 13.3–49.4) when the same mRNA vaccines were used for all three doses (Supplementary Figure S6B). It should be noted that the number of studies that used a different type of the third vaccine was one.
each. The results were unchanged when each study was removed one at a time from the meta-analyses (Supplementary Figure S6C).

Heterogeneity was present ($I^2 = 82.1\%$) possibly due to the differences in the sample size and reported rates of the studies. Visual evaluation of the funnel plot showed no asymmetry, and no publication bias was found with Begg’s and Egger’s tests ($p = 0.71$, $p = 0.36$) (Supplementary Figure S6A).

### 3.8. Quality of Evidence Assessed by GRADE

The quality of evidence of this analysis was considered low because the data were derived mostly from observational or cohort studies (Supplementary Table S4).

### 4. Discussion

Our meta-analysis of the serologic response to the COVID-19 vaccine in SOT recipients showed that less than 10% of transplant recipients seroconverted following one dose of COVID-19 vaccination. The rate improved to 34% following the second dose. In comparison to controls, the seroconversion rates were lower following both doses. A third booster shot, which has recently been approved, improved the rate to 66%, but in a subset of patients who had not achieved a response after two doses, it remained low at 36%. The results of our study suggest that there is a need for a more effective prophylaxis strategy in SOT patients.

Patients with a history of SOT are at higher risk for COVID-19 and its mortality [38]. Transplant recipients are immunocompromised due to the long-term use of immunosuppressive medications. Immunosuppressive drugs may influence the functions of B and T cells that lower the response to vaccinations [21,23,39]. Furthermore, transplant recipients are generally older and may carry comorbidities that increase the risk of COVID-19.

The study by Shroti et al., reported that 96–99% of patients in the general community seroconverted following a single or two series of ChAdOx1 nCoV-19 or BNT162b2 vaccines. In their study, elderly individuals and those with cardiovascular disease, diabetes, or cancer were less likely to achieve antibody response [40]. In our study, the serologic response rates of SOT patients following one or two doses of COVID-19 vaccination was 9% and 34%, respectively, which were lower than those reported in a meta-analysis of immune mediated inflammatory disease patients receiving biologics [23]. When compared to controls, the odds of seroconversion among transplant recipients were lower after both doses. The proportion of patients on GC therapy was associated with lower response following one dose whereas advanced age was associated with lower response in addition to GC use following two doses. This suggests that additional patient and treatment factors may be associated with a weakened vaccine response in transplant recipients, which warrants further investigation.

The low serologic response rates to the two-dose mRNA vaccination strategy in transplant recipients led us to investigate the response to the booster (third) vaccination. The response rate after the third dose rose to 65%, but was still suboptimal. Furthermore, among a subset of patients who failed to seroconvert after two doses, merely a third seroconverted after the third dose. AD26.COV2.S mounted a weaker serologic response, but AZD1222 or mRNA-1273 induced a stronger response in subgroup analyses, so studies of different hybrid regimens or doses are warranted [41,42]. Future studies will need to assess strategies for prophylaxis including the use of monoclonal Antibody (mAb)-based immune prophylaxis as a substitute or as a complement to vaccines in SOT recipients.

### 5. Limitations

Although it has been more than a year since the first vaccine was approved against COVID-19, available reports on transplant recipients were rather limited and mostly consisted of studies of a small sample size. There are currently nine COVID-19 vaccinations available for use globally, but a majority of the studies included in our meta-analysis were of either mRNA-1273 or BNT162b2, and a small number of studies were of AD26.COV2.S or AZD-1222/ChAdOx1 nCoV-19. Our primary outcome was a humoral response to vaccines;
however, we could not evaluate the difference in T cell-mediated immune response due to the of data. Recent studies have reported that levels of antibodies can be predictive of the risk of infections in healthy individuals and that those who are immunocompromised were at greater risk of post-vaccination infections, so we consider that our meta-analysis focusing on serologic response provides meaningful information [43,44]. Further studies assessing whether the incomplete serologic response to vaccination would prevent symptomatic or severe COVID-19 in SOT patients are also warranted [45,46]. Due to the limited data, we were unable to undertake subgroup analyses according to different immunosuppressive therapies. Furthermore, the studies included in our meta-analysis were somewhat heterogeneous regarding transplanted organ(s), size of the sample, treatment, timing, and type of test used to measure antibody levels. A majority of studies included in our analysis used either the antibody test marketed by Abbott, DiaSorin, or Roche. They are all known to have a sensitivity of 98 to 100% [24]. Consequently, the results of antibody testing have an excellent correlation in regard to seroprevalence. Recent reports have shown declining antibody levels after 3–8 weeks of second vaccination in patients receiving ChAdOx1 nCoV-19 or BNT162b2 [47], so further research assessing the waning of antibodies in immunocompromised and transplant patients is warranted.

6. Conclusions

We have demonstrated that the rate of seroconversion to vaccinations against COVID-19 in SOT recipients was only 9% and 34% following the first and second dose. The rate improved to 66% following the third booster injection. However, in a subset of patients who had not achieved a response after two doses only a third achieved a response with the third dose. The results of our study suggest the urgent need for an improved prophylaxis strategy including the use of mAb-based immune prophylaxis as a substitute or as a complement to vaccines in this vulnerable patient population and that they need to continue following safety measures.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/v14081822/s1, Figure S1: A. Serologic response after one dose of vaccine: Ad26.COV2.S vaccine, Figure S2: A. Funnel plot of studies included in meta-analysis of serologic response after one dose of vaccine, Figure S3: A. Funnel plot of studies included in meta-analysis of serologic response after two doses of vaccine, Figure S4: A. Funnel plot of studies included in meta-analysis of comparison of serologic response after one dose of vaccine compared to controls, Figure S5: A. Funnel plot of studies included in meta-analysis of serologic response after three doses of vaccine, Figure S6: Funnel plot of studies included in meta-analysis of serologic response after three doses of vaccine among non-responders to two doses, Table S1: Risk of bias assessment by Joanna Briggs Institute Critical Appraisal Checklist, Table S2: Univariate and multivariate meta-regression models of variables associated with serologic response after one dose of mRNA vaccine, Table S3: Univariate and multivariate meta-regression models of variables associated with serologic response after two doses of mRNA vaccine, Table S4: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria for studies included in the meta-analysis.

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