COVID-19 Vaccination in Lung Transplant Recipients

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Abstract

Lung transplant patients are at increased risk of infection due to immunosuppression. Vaccination is a key source of protection; however, after transplant, patients tend to have diminished host response. This is an important concern given the ongoing coronavirus disease 2019 (COVID-19) pandemic. Less is known about how transplant patients respond to COVID-19 vaccination and how best to approach immunization in the setting of a global pandemic. Lung transplant patients, and solid organ transplant patients as whole, have a less robust immune response after COVID-19 vaccination. This article reviews the literature on vaccine immune response in transplant patients with a focus on COVID-19 vaccination and international society guidelines.

Keywords Transplant · Immunosuppression · COVID-19 · Vaccination

Introduction

Transplant patients are immunosuppressed and at increased risk of morbidity and mortality related to infection as compared to the immunocompetent population. This increased risk profile also holds true for coronavirus disease 2019 (COVID-19) infection [1–4]. Vaccination is an important strategy to prevent post-transplant complications.

Before the release of COVID-19 vaccines globally, transplant patients lacked targeted tools to prevent infection. COVID-19 vaccination dramatically changed the landscape for both immunosuppressed and immunocompetent hosts. This review will discuss the importance of understanding humoral and cellular impairments in solid organ transplant (SOT) patients, specific factors related to liver transplant (LT) recipients, the integral role vaccination plays in disease prevention, and transplant society guidelines on COVID-19 vaccination.

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Immunosuppressive Factors

The approach to immunosuppression in lung transplantation varies from center to center, but the utilization of potent induction immunosuppression is on the rise. A recent report found that 76% of adult lung transplant recipients received induction immunosuppression [5]. Agents utilized for induction immunosuppression include lymphocyte depleting therapy (anti-thymocyte globulin or alemtuzumab) and anti-interleukin-2α (anti-IL-2α or basiliximab), which are often used in combination with high-dose corticosteroids. Medications currently used for induction immunosuppression have significant effects on the number and function of lymphocytes, a key component of the immune response to vaccination.

Alemtuzumab is utilized in the treatment of multiple sclerosis in addition to its use as an induction agent in transplantation. In one study in multiple sclerosis patients assessing vaccine response after alemtuzumab therapy, 91% ($N = 21$) of patients were able to develop a protective response to a novel vaccine. Of the 21 patients who developed a response to vaccination, the majority were immunized greater than 6 months from receipt of alemtuzumab. In a subgroup of those immunized within 6 months of alemtuzumab, 40% ($N = 2$) of patients developed a protective antibody. Data from this study must be cautiously applied to transplant recipients since these patients were not on maintenance immunosuppression, but

this study does illustrate the reduced vaccine response to vaccines after receipt of alemtuzumab [6].

In addition to induction immunosuppression, LT recipients are typically on two or more classes of maintenance immunosuppression to regulate immune function. Commonly used immunosuppressive medications have multiple downstream effects impacting several facets of the immune system. For a review of this topic, readers are encouraged to seek a review specific to transplant immunosuppression [7, 8]. Commonly used medications come from a variety of classes of medications and exert their effect differently. Calcineurin inhibitors block T-cell activation and proliferation and impair IL-2 production. Mycophenolate derivatives reduce T and B lymphocytes through impaired proliferation and increased apoptosis. Corticosteroids impact T-cells through impaired development, survival, activation, and decreased migration [7]. Mammalian target of rapamycin (mTOR) inhibitors impairs T-cell proliferation and alters regulatory T-cells, but this pathway is also implicated in increased development of CD8 memory cells and preserved humoral response to vaccination, which is further discussed below [9]. In combination, the most frequently used maintenance immunosuppressive regimen impacts the ability to recognize and counteract foreign antigens. This is beneficial for preventing recognition of the allograft, but detrimental when trying to develop immunity from vaccination.

Retrospective studies examining transplant recipients' response to vaccine have identified factors associated with a poor response to COVID-19 vaccination. The use of an anti-metabolite such as a mycophenolic acid derivative results in a reduced response to COVID-19 vaccination [10, 11]. SOT recipients who did not develop antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after vaccination were those who were of a younger age, thoracic organ recipients, induction therapy recipients, and tacrolimus + mycophenolic acid ± steroids recipients (anti-metabolite group) [10].

Additional factors in SOT recipients that have been shown to impact response to COVID-19 vaccination were examined in a study of 393 transplant recipients at a center in France. Factors that resulted in higher humoral response to vaccination included male gender, a longer period between transplantation and vaccination, higher baseline lymphocyte count, higher baseline glomerular filtration rate (GFR), and utilization of tacrolimus + everolimus ± steroids combination (mTOR containing immunosuppressive regimen) [10]. Additional studies have shown that mTOR inhibitors, occasionally used as one of the immunosuppressive agents in organ transplantation, resulted in an improved response to COVID-19 vaccination over standard immunosuppression. In a study of renal transplant recipients, those on an mTOR inhibitor had higher anti-SARS-CoV-2 immunoglobulin (IgG) titers as well as measures of T-cell function to SARS-CoV-2 [12].

Vaccination (non-COVID) in Solid Organ Transplant Recipients

SOT recipients are immunosuppressed, which places them at increased risk of infections [13]. This is true for vaccine-preventable illnesses, to which SOT recipients have a variable response to vaccination. Previous literature studies of pneumococcal and influenza immunizations have noted that, due to a variety of external and internal factors, including humoral and cellular immunity, thoracic organ transplant recipients do not respond in the same way to vaccination as immunocompetent hosts [3, 14–16].

Humoral immune response has been studied for pneumococcal and influenza vaccines in heart transplant recipients. A small cohort of heart transplant patients was compared to an immunocompetent control group. For the 23-valent polysaccharide pneumococcal vaccine, the transplant patients and control group had similar median antibody titers after vaccination. However, for the influenza vaccination (trivalent), post-vaccination antibody titers were significantly lower in the transplant patients [15]. A separate research group measured pre- and post-pneumococcal vaccination antibody levels in heart transplant recipients and a control group without transplant. They found that the transplant recipients had a blunted IgG response compared to the healthy control group [16].

LT recipients have unique characteristics that make them more susceptible to infections, such as drug-related immunosuppression, postoperative anatomical changes to lung anatomy and physiology, retention of mucus due to poor clearance, and reactions to acute rejection [3]. LT patients are typically given pneumococcal conjugate and polysaccharide vaccines prior to transplant. Retrospective comparison of this vaccine series in LT candidates and recipients has been evaluated by measuring titers over time to assess a booster effect. Researchers found that after lung transplant, these patients had no significant increase in antibodies after sequential administration of both pneumococcal vaccinations [17].

A retrospective analysis of LT patients was undertaken in the Netherlands to assess response to pneumococcal vaccination. Antibodies from pneumococcal vaccination were measured before and after transplantation. The analysis found a progressive decline in titers after transplant and in subsequent visits, which represented a decrease in humoral immunity [18].

Influenza vaccination response in lung transplant recipients has also been assessed in relation to both humoral and cell-mediated immunity. An initial study in 2001 looked at humoral response with measurements of antibody titers before and after influenza vaccination in lung transplant patients at least 3 months after transplant. These values were compared to an immunocompetent control group. Titers for three serogroups represented in the vaccine were measured and found to be

significantly lower in the transplant group, with only five of the 43 patients (8.6%) developing protective levels to all three serogroups [3]. Later work by the same group looked at non-specific markers of cell-mediated immune response to influenza vaccination in lung transplant patients. This study measured IL-2, IL-10, interferon gamma, and granzyme B levels as markers of T-cell and B-cell function. The researchers again compared transplant recipients with an immunocompetent control group in relation to their pre- and post-vaccination cytokine levels. No significant rise in cell-mediated factors was observed after vaccination in the transplant group. These levels were also lower when compared to the healthy control group [14].

Influenza vaccine dosage also influences immunity. High-dose influenza vaccine has typically been reserved for patients over the age of 65, who often have lower immune response. A double-blind, randomized trial assessed the humoral (antibody) response in SOT recipients to either the high-dose (HD) or standard-dose (SD) influenza vaccine. Patients with any SOT (kidney, liver, heart, lung, pancreas, or combination) were randomized to either the HD or SD arm. Measurements of post-vaccination titers at approximately 4 weeks were higher in the patients who were administered the HD influenza vaccine [19].

Measurement of cell-mediated immunity may offer a different view of immunogenicity in transplant patients in relation to HD or SD influenza vaccination. A heterogeneous group of SOTs was randomized to either HD or SD influenza vaccine. Approximately 4 weeks after vaccination, blood samples were analyzed for specific CD4 and CD8 T-cell populations. The samples showed increased cellular response in the HD group as compared to SD. In combination, these studies argue for considering HD dosing for influenza vaccination in transplant recipients [2].

Humoral Immunity COVID-19 Vaccination

LT recipients are at increased risk of severe disease from COVID-19 [20, 21]. Similar to the impaired immune response seen in other vaccines, such as pneumococcal and influenza, solid organ transplant recipients have a diminished humoral response to COVID-19 vaccination.

Initial study of SOT recipients has identified significantly lower antibody response compared to immunocompetent patients after a single dose of messenger ribonucleic acid (mRNA) COVID-19 vaccination [11]. Further study by the same investigator looked at 658 solid organ transplant patients and demonstrated that, although a slight majority had detectable antibody levels after a second dose of mRNA COVID vaccine, 46% of patients had no antibody response after both doses [22].

In a study specific to heart and lung transplants, researchers examined whether patients developed a measurable antibody level after the first dose of COVID vaccine or only after the second dose of COVID vaccine. Results showed that 49% of recipients did not produce protective antibody levels after two doses of mRNA vaccine, 39% of recipients produced protective antibody response only after the second dose, and 12% had measurable response after the initial dose, which persisted when measured after the second dose. Young age and lack of anti-metabolite immunosuppression were considered statistically significant variables for positive antibody response. In addition, heart transplant patients were more likely to develop an immune response than lung transplant patients [1].

In a small cohort of 73 LT patients given a two-dose mRNA vaccine, only 25% had IgG (specific to spike protein) above the defined cutoff. Labs were drawn for this study at median time of 17.5 days after second Pfizer dose and 19 days after second Moderna dose. In this study, a majority of patients did not develop a robust humoral immune response [20]. Havlin et al. noted similarly low-level humoral measurements in a study of LT patients. For all 48 LT participants in the trial, none had measurable IgG levels after vaccination indicating immunity to COVID-19. That group was compared to "natural" immunity in LT patients who recovered from COVID-19 infection; 85% of these patients had measurable IgG levels [23].

Lack of humoral response to two-dose mRNA vaccination in transplant patients raises the question of whether additional doses or an alternate vaccination strategy is necessary. A systematic review of the literature undertaken by Efros et al. identified seven studies that examined immunologic response to a third dose of mRNA vaccine in SOT recipients. All but one study demonstrated improved response in transplant recipients who received a third vaccine dose [24].

In the case of heart transplants, one set of study patients had antibody levels measured before and after a third dose was administered. Improvement in antibody response from 23% of patients to 67% of patients was seen after the third dose, in this case the Pfizer-BioNTech series [25]. A small study of LT patients underwent third dose vaccination with Pfizer-BioNTech COVID-19 vaccine. Prior to the third dose, no patients had detectable antibody levels (IgG), and 3 weeks after the third dose, only 13% had measurable levels [26]. Larger study specific to lung transplantation and additional vaccine doses should be undertaken for this at-risk population.

The Omicron variant has been a cause of concern given known lower vaccine response in the immunocompetent population. One study in non-lung transplant recipients demonstrated lower neutralizing antibodies to Omicron as compared to wild type and Delta in transplant patients after a three-dose mRNA series [27]. More study is ongoing related to the current strain(s).

Non-mRNA-based COVID-19 vaccines are utilized internationally, including in India. These vaccines include the following: Covishield (adenovirus vector), Covaxin (inactivated

virus), Sinopharm (inactivated virus), and Sputnik V (adeno-virus vector). Limited data on these vaccines exists in the transplant community. Humoral immune response was assessed in renal transplant patients given the Sinopharm (BBIBP-CorV) vaccine. In renal transplant patients that had not had COVID-19 infection, 43% of participants had a measurable antibody response, as compared with 86% in the general population of immunocompetent patients [28].

It is difficult to compare the various vaccines to one another, let alone in the transplant population. Vaccine response in immunocompetent patients was comparatively evaluated in a study in Mongolia between Sinopharm, Sputnik V, AstraZeneca/Oxford, and Pfizer COVID vaccines. When measuring a surrogate antibody assay, the researchers found that the Sinopharm and Sputnik V vaccines elicited the lowest response, AstraZeneca/Oxford elicited an intermediate response, and Pfizer elicited the highest response [29]. When the Sinopharm (BBIBP-CorV) vaccine was compared to the Pfizer vaccine in immunocompetent patients, it was found to elicit lower antibody and interferon response. However given that this was not a trial with transplant patients, it would be difficult to extrapolate from these findings [30].

Fourth doses of mRNA COVID vaccine are currently being investigated. A small group of kidney transplant recipients in France was studied for a fourth dose. These patients were selected if, after three doses of COVID vaccine, they had an antibody level below a threshold that signaled lower immunity. At a median time of 29 days after the fourth dose, 50% of the 92 patients in the study had an increased antibody response that crossed the previously specified threshold [31]. In a case series of SOT recipients, researchers categorized patients as non-responders, low titer responders, or high titer responders after three doses of COVID vaccine based on antibody assay. Among those patients in the non-responder and low titer responder group who were given a fourth dose of COVID vaccine, five out of eight patients (63%) increased antibody levels into the high titer level [32]. Fourth doses of the Pfizer COVID vaccine have been more widely rolled out in Israel to immunosuppressed patients, healthcare workers, and individuals over 60 years old. Results from this rollout are forthcoming [33].

Cell-mediated Immunity

T-lymphocyte function is a key component of the overall immune state for patients on immunosuppression. Measurement of T-lymphocytes, when stimulated with SARS-CoV-2 antigens, may be a marker of protection against COVID-19 infection, particularly in those who lack a sufficient humoral response [20, 21, 25, 26, 31, 32, 34, 35]. T-cell activity is commonly assessed by measuring interferon or a cytokine released by intact T-lymphocytes when stimulated with an antigen of

interest. This technology is used worldwide in interferon gamma releasing assays, for example, in the diagnosis of latent tuberculosis utilizing the QuantiFERON or T-spot brand assay.

When T-lymphocytes identify an antigen they have previously encountered, the strength of that response can be measured and correlated with the degree of immune response. This correlated level of protection has been demonstrated in cytomegalovirus (CMV) cell-mediated immunity studies [36–38]. A commercially available assay for the measurement of cell-mediated immunity against cytomegalovirus presently available is the QuantiFERON CMV T-cell assay. This assay uses the same principles described above to measure T-cell response to an antigen of interest and a recent prospective trial in lung transplant recipients utilized this assay to identify patients capable of controlling CMV without anti-viral prophylaxis [39].

Cell-mediated immunity against SARS-CoV-2 21 days after second dose of the Pfizer-BioNTech vaccine was assessed in fifty thoracic organ transplant recipients utilizing a modified QuantiFERON-based interferon gamma releasing assay. Interferon gamma release in the transplant recipients was significantly reduced when compared to 50 immunocompetent controls ($p < 0.0001$). The majority of their 50 thoracic transplant recipients were heart transplant recipients ($N = 42$). No subgroup analysis was performed between heart and lung transplant recipients. Notably, they reported that eight transplant recipients without detectable antibodies had an interferon gamma response [35].

An additional study examined cell-mediated response in 12 lung transplant recipients without protective levels of SARS-CoV-2 antibodies 4 to 6 weeks after second Pfizer-BioNTech vaccination. Measurement of interferon-gamma, interleukin-2, and tumor necrosis factor (TNF)-alpha was performed after stimulation of intact T-cells in the presence of receptor-binding domain antigens. Of the 12 patients assessed, four had measurable T-cell responses. The identification of T-cell responses in the absence of detectable SARS-CoV-2 anti-spike antibodies emphasizes the complexities of the immune system in lung transplant recipients as well as the importance of vaccination [23].

Safety of Vaccines in Transplantation

Monitoring and safety of COVID-19 vaccines have been of utmost importance for acceptance in the transplant community and the public. To date, over ten billion doses of COVID-19 vaccines have been administered [40]. The COVID-19 pandemic marked the first widespread use of a mRNA-containing vaccine against an infectious disease. mRNA vaccines have had widespread acceptance in transplant recipients, and tens of thousands of doses are estimated to have been received by

solid organ transplant recipients. An early trial of 741 SOT recipients who received two doses of a mRNA vaccine found these vaccines were well tolerated with local reactions, most frequently pain at the injection site, and systemic reactions, most frequently fatigue and headache. No reported cases of anaphylaxis requiring epinephrine, nor development of neurologic conditions such as Guillain-Barré syndrome or Bell's palsy, were identified. One patient, a renal transplant recipient, developed acute rejection after the second mRNA vaccine [41].

Adenovirus-vectored vaccines, such as the Janssen/Johnson & Johnson vaccine or the Oxford/AstraZeneca vaccine, utilize an adenovirus vector that is replication deficient and cannot replicate in any host. This technology varies from live virus vaccines which must take up residence and replicate in a host for an immune response. No currently available COVID-19 vaccines utilize live viruses, which are contraindicated in immunocompromised patients. Other COVID-19 vaccine technology includes protein subunit vaccines and inactivated vaccines, both of which are based on long-standing vaccine technology with proven safety records in immunocompetent and immunocompromised individuals [42].

Society Guidelines

The American Society of Transplantation (AST) released an initial joint statement with the International Society of Heart and Lung Transplantation (ISHLT) on August 13, 2021, urging all transplant candidates and recipients to obtain vaccination against COVID-19. For those patients not yet transplanted, it was recommended that they attempt to complete the series at least 2 weeks prior to transplantation [43].

Further guidance has been released with additional detail. The guidance reiterated the need for three doses of mRNA COVID-19 vaccine, with the third dose occurring greater than 28 days after the second dose. For those patients who received a single-dose Johnson & Johnson/Janssen vaccine, a mRNA full-dose vaccine is the recommended second immunization greater than 2 months after the first immunization. Post-transplant, if the patient had not received all vaccinations, the COVID-19 series can be given 1 to 3 months after surgery. In addition, the AST recommends that all family members and close contacts greater than 5 years of age be fully immunized [44]. Guidance on additional COVID-19 vaccinations beyond the primary series and increased age eligibility is forthcoming, and it is recommended to seek out the most up-to-date guidance. The AST does not recommend adjustment of immunosuppression for vaccination purposes (outside of a clinical trial.) [45]

The ISHLT released their own guidance on February 1, 2021, concerning the vaccines available internationally, including mRNA (Moderna, Pfizer-BioNTech) and viral vectors (Johnson & Johnson/Janssen, Oxford/AstraZeneca). The ISHLT also recommended completing vaccination for COVID-19 before transplant but specified that, if not completed, at least one dose to be given 2 to 3 weeks prior to transplant, if possible. In terms of post-transplant timing, the ISHLT gave a wider range of time, with a minimum of 1 month after surgery or 3 to 6 months after surgery if a T-cell-depleting regimen was used [45]. Both the AST and ISHLT recommend that all persons in contact with the transplant recipient be vaccinated [43–45].

Conclusion/Current Recommendations

As COVID-19 continues to persist globally and remains a concern, vaccination against COVID-19 in transplant recipients provides reduced protective response when compared to immunocompetent hosts. However, COVID-19 vaccination remains beneficial in transplant recipients to reduce infection severity, hospitalizations, and death. The measurement of response to vaccination is complex and highly dependent on several dynamic factors. The authors agree with guideline writing societies and strongly recommend COVID-19 vaccination for all—including transplant recipients—with the optimal time for vaccination occurring prior to transplantation. The optimal number of COVID doses and timing remains unclear with emerging evidence citing the need for a fourth mRNA vaccine.

Declarations

References

1. Hallett AM, Greenberg RS, Boyarsky BJ, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. J Hear Lung Transplant. 2021. https://doi.org/10.1016/j.healun.2021.07.026.

2. L'huillier AG, Ferreira VH, Hirzel C, et al. Cell-mediated immune responses after influenza vaccination of solid organ transplant recipients: secondary outcomes analyses of a randomized controlled trial. J Infect Dis. 2020;221:53–62. https://doi.org/10.1093/infdis/jiz471.

3. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Schilz RJ, Maurer JR. The humoral immune response to influenza vaccination

in lung transplant patients. Eur Respir J. 2001;18:971–6. https://doi.org/10.1183/09031936.01.00215201.

4. Scharringa S, Hoffman T, van Kessel DA, Rijkers GT. Vaccination and their importance for lung transplant recipients in a COVID-19 world. Expert Rev Clin Pharmacol. 2021;14:1413–25. https://doi.org/10.1080/17512433.2021.1961577.

5. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. J Heart lung Transplant. 2018;37:1169–83. https://doi.org/10.1016/j.healun.2018.07.020.

6. McCarthy CL, Tuohy O, Compston DAS, Kumararatne DS, Coles AJ, Jones JL. Immune competence after alemtuzumab treatment of multiple sclerosis. Neurology. 2013;81:872–6. https://doi.org/10.1212/WNL.0b013e3182a35215.

7. Roberts MB, Fishman JA. Immunosuppressive agents and infectious risk in transplantation: managing the "Net State of Immunosuppression". Clin Infect Dis. 2021;73:e1302–17. https://doi.org/10.1093/cid/ciaa1189.

8. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351:2715–29. https://doi.org/10.1056/NEJMra033540.

9. Powell JD, Delgoffe GM. The mammalian target of rapamycin: linking T cell differentiation, function, and metabolism. Immunity. 2010;33:301–11. https://doi.org/10.1016/j.immuni.2010.09.002.

10. Marion O, Del Bello A, Abravanel F, et al. Predictive factors for humoral response after 2-dose SARS-CoV-2 vaccine in solid organ transplant patients. Transplant direct. 2021;8:e1248. https://doi.org/10.1097/TXD.0000000000001248.

11. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA. 2021;325:1784–6. https://doi.org/10.1001/jama.2021.4385.

12. Netti GS, Infante B, Troise D, et al. mTOR inhibitors improve both humoral and cellular response to SARS-CoV-2 messenger RNA BNT16b2 vaccine in kidney transplant recipients. Am J Transplant. 2022. https://doi.org/10.1111/ajt.16958.

13. van Kessel DA, Hoffman TW, van Velzen-Blad H, van de Graaf EA, Grutters JC, Rijkers GT. Immune status assessment in adult lung transplant candidates. Transpl Immunol. 2017;40:31–4. https://doi.org/10.1016/j.trim.2016.11.001.

14. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Mauer JR. Cell-mediated immune response to influenza vaccination in lung transplant recipients. J Heart Lung Transplant. 2004;23:1175–81. https://doi.org/10.1016/j.healun.2003.08.033.

15. Dengler TJ, Strnad N, Bühring I, et al. Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. Transplantation. 1998;66:1340–7. https://doi.org/10.1097/00007890-199811270-00014.

16. Blumberg EA, Brozena SC, Groover JE, Stutman P, Wood D, Musher DM. Immunogenicity of pneumococcal vaccine(PV) in heart transplant recipients (HTR). Clin Infect Dis. 1997;25:464.

17. Hoffman TW, Meek B, Rijkers GT, Grutters JC, van Kessel DA. Pneumococcal conjugate vaccination followed by pneumococcal polysaccharide vaccination in lung transplant candidates and recipients. Transplant Direct. 2020;6:e555. https://doi.org/10.1097/TXD.0000000000001003.

18. van Kessel DA, Hoffman TW, Kwakkel-van Erp JM, et al. Long-term follow-up of humoral immune status in adult lung transplant recipients. Transplantation. 2017;101:2477–83. https://doi.org/10.1097/TP.0000000000001685.

19. Natori Y, Shiotsuka M, Slomovic J, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult

20. Narasimhan M, Mahimainathan L, Clark AE, et al. Serological response in lung transplant recipients after two doses of SARS-CoV-2 mRNA vaccines. Vaccines. 2021. https://doi.org/10.3390/vaccines9070708.

21. Aslam S, Danziger-Isakov L, Mehra MR. COVID-19 vaccination immune paresis in heart and lung transplantation. J Hear Lung Transplant. 2021;40:763–6. https://doi.org/10.1016/j.healun.2021.04.018.

22. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA. 2021;325:2204–6. https://doi.org/10.1001/jama.2021.7489.

23. Havlin J, Svorcova M, Dvorackova E, et al. Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients. J Hear Lung Transplant. 2021;40:754–8. https://doi.org/10.1016/j.healun.2021.05.004.

24. Efros O, Anteby R, Halfon M, Meisel E, Klang E, Soffer S. Efficacy and safety of third dose of the COVID-19 vaccine among solid organ transplant recipients: A systemic review and meta-analysis. Vaccines. 2022;10:95. https://doi.org/10.3390/vaccines10010095.

25. Peled Y, Ram E, Lavee J, et al. Third dose of the BNT162b2 vaccine in heart transplant recipients: Immunogenicity and clinical experience. J Hear Lung Transplant. 2022. https://doi.org/10.1016/j.healun.2021.08.010.

26. Havlin J, Skotnicova A, Dvorackova E, et al. Impaired humoral response to third dose of BNT162b2 mRNA COVID-19 vaccine despite detectable spike protein-specific T cells in lung transplant recipients. Transplantation. 2021. https://doi.org/10.1097/TP.0000000000004021.

27. Kumar D, Hu Q, Samson R, et al. Neutralization against Omicron variant in transplant recipients after three doses of mRNA vaccine. Am J Transplant. 2022. https://doi.org/10.1111/ajt.17020.

28. Nafar M, Chehrazi S, Dalili N, et al. Humoral immunity of BBIBP-CorV (Sinopharm) in kidney transplant recipients: Is it time to revise vaccination strategies. Transpl Infect Dis. 2022;24:e13798. https://doi.org/10.1111/tid.13798.

29. Dashdorj NJ, Wirz OF, Röltgen K, et al. Direct comparison of antibody responses to four SARS-CoV-2 vaccines in Mongolia. Cell Host Microbe. 2021;29:1738–1743.e4. https://doi.org/10.1016/j.chom.2021.11.004.

30. Vályi-Nagy I, Matula Z, Gönczi M, et al. Comparison of antibody and T cell responses elicited by BBIBP-CorV (Sinopharm) and BNT162b2 (Pfizer-BioNTech) vaccines against SARS-CoV-2 in healthy adult humans. GeroScience. 2021;43:2321–31. https://doi.org/10.1007/s11357-021-00471-6.

31. Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: A case series. Ann Intern Med. 2022. https://doi.org/10.7326/L21-0598.

32. Alejo JL, Mitchell J, Chiang TP-Y, et al. Antibody response to a fourth dose of a SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. Transplantation. 2021;105:e280–1. https://doi.org/10.1097/TP.0000000000003934.

33. Burki TK. Fourth dose of COVID-19 vaccines in Israel. Lancet Respir Med. 2022. https://doi.org/10.1016/s2213-2600(22)00010-8.

34. Hall VG, Ferreira VH, Ierullo M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. Am J Transplant. 2021;21:3980–9. https://doi.org/10.1111/ajt.16766.

35. Schramm R, Costard-Jäckle A, Rivinius R, et al. Poor humoral and T-cell response to two-dose SARS-CoV-2 messenger RNA vaccine BNT162b2 in cardiothoracic transplant recipients. Clin Res

Cardiol. 2021;110:1142–9. https://doi.org/10.1007/s00392-021-01880-5.

36. Westall GP, Mifsud NA, Kotsimbos TC. Linking CMV serostatus to episodes of CMV reactivation following lung transplantation by measuring CMV-specific CD8+ T-cell immunity. Am J Transplant. 2008;8:1749–54.

37. Kumar D, Chernenko S, Moussa G, et al. Cell-mediated immunity to predict cytomegalovirus disease in high-risk solid organ transplant recipients. Am J Transplant . 2009;9:1214-1222. https://doi.org/10.1111/j.1600-6143.2009.02618.x.

38. Kumar D, Mian M, Singer L, Humar A. An interventional study using cell-mediated immunity to personalize therapy for cytomegalovirus infection after transplantation. Am J Transplant. 2017;17: 2468–73. https://doi.org/10.1111/ajt.14347.

39. Westall GP, Cristiano Y, Levvey BJ, et al. A randomized study of quantiferon CMV-directed versus fixed-duration valganciclovir prophylaxis to reduce late CMV after lung transplantation. Transplantation. 2019;103:1005–13. https://doi.org/10.1097/TP.0000000000002454.

40. Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald DB and MR. Coronavirus pandemic (COVID-19). OurWorldInData.org.

41. Ou MT, Boyarsky BJ, Motter JD, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. Transplantation. 2021;105:2170–4. https://doi.org/10.1097/TP.0000000000003780.

42. Danziger-Isakov L, Kumar D. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33:e13563. https://doi.org/10.1111/ctr.13563.

43. *AST Statement about Vaccine Efficacy in Organ Transplant Recipients*.; 2021. https://doi.org/10.1101/2021.04.06.21254963.

44. *Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic*.; 2021.

45. *COVID-19 Vaccine FAQ Sheet (Updated 11/14/2021)*.; 2021.