Several SARS-CoV-2 vaccines are approved for administration in various countries and are available to select populations based on local recommendations and regulations, including children aged 12 years and above. These include mRNA-based vaccines (Moderna, Pfizer-BioNTech), those utilizing replication deficient viral vectors (Oxford-AstraZeneca, Johnson and Johnson, Sputnik V, Cansino), inactivated virus (Sinopharm, Sinopharm-Wuhan, Sinovac, Bharat) and protein subunits (Novavax, Vector Institute). Since none of the currently available vaccines are based on live replicating viral vectors, all are acceptable for transplant recipients. Thus, we recommend that transplant patients accept any of these vaccines made available to them.

Current efficacy data from clinical trials in immunocompetent hosts is variable based on the type of vaccine used; however, reported data in clinical trials thus far demonstrate 100% protection against severe COVID-19 related intensive care or death.[1-5] Real world observational data has demonstrated significant effectiveness of the vaccine in reducing symptomatic disease, hospitalization and death from COVID-19 in various countries ranging between 88-91%.[6-8] To date, nearly 3.57 billion vaccine doses have been administered worldwide.[9] Common adverse events are local to the injection site and related to reactogenicity of the vaccine; importantly anaphylaxis is very rare ranging between 2.47-4.7 cases/million doses administered for the mRNA vaccines; 60% with anaphylaxis had a prior history of allergic reactions and no related death was reported.[10, 11]

Vaccine-induced immune thrombotic thrombocytopenia (VITT) associated with thrombosis is a rare serious adverse event recently identified with adenovirus vector vaccines, with pooled incidence estimated at 0.73/100, 000 persons vaccinated with a single dose,[12-15] VITT is noted to be higher in persons aged <55 years with pooled incidence of 1.67/100,000 for the Oxford-AstraZeneca vaccine and 0.94-1.24/100,000 for the Johnson and Johnson (Janssen) vaccine, with a female preponderance. We do not anticipate additional safety concerns in the setting of mechanical circulatory support and pulmonary hypertension. There is emerging data regarding use of organ donors with VITT. Case series from the UK (n=27 allografts) and from France (n=10 allografts) note overall successful outcomes though allograft loss occurred in 3 cases (2 livers, 1 kidney).[16, 17] Three additional liver recipients had detectable anti-PF4 antibodies following transplant though none had allograft loss. Given limited experience, we urge caution in the use of such donors and recommend careful assessment of thromboses in the allograft and close monitoring of the recipient.

Efficacy data for SARS-CoV-2 vaccines in transplant recipients are emerging and demonstrate detectable serological response in up to 50% of transplant recipients following two doses of the
mRNA vaccines.[18-22] One study in lung transplant recipients noted a T-cell response in a third of vaccinated recipients with no detectable anti-spike IgG.[22] While the rate of immunogenicity appears lower than that noted in the general population, early clinical effectiveness data suggests <1% of breakthrough infections.[23] These vaccines overall demonstrate safety in the transplant population with low concern for rejection or other serious adverse events in the early period following administration.[24] Recently, data regarding a third booster dose has been reported;[25, 26] however only a minority of patients were cardiothoracic transplant recipients – 8/130 and 3/30. Administration of a third Pfizer booster dose at a median of 2 months following the previous dose increased detectable anti-spike antibody levels from 40% to 68% and boosted titers in the Kamar et al study of 101 patients and no serious adverse events were noted. In the Werbel et al paper, 24 patients had undetectable antibodies after a 2-dose series of an mRNA vaccine; only 6 (25%) developed high-positive antibody titers after the third vaccine dose but the majority (16, 67%) remained undetectable. In terms of safety, one heart transplant recipient developed rejection within a week following the booster dose in the Werbel et al study.

Commercially available serological tests measure antibody response against SARS-COV-2 test for presence or absence of antibodies to the nucleocapsid and/ or spike protein in a qualitative fashion. Tests measuring only anti-nucleocapsid antibodies will not show evidence of immunogenicity after administration of vaccines that target only the viral spike protein; immunogenicity in response to such vaccines requires testing for anti-spike antibodies. At this time, an optimal titer cut-off for neutralizing antibodies remains unknown and vaccine efficacy cannot be defined adequately by a simple presence or absence of antibodies, which may be misleading. Additionally, neutralizing antibodies as well as a Th1 CD4+ and CD8+ T cell response contribute to immunity against SARS-CoV-2.[27] Testing for the latter is not readily available and such vaccine-related response in transplant recipients is unknown currently. Due to these uncertainties, we recommend against routine serological testing of patients after SARS-CoV-2 vaccination at this time; more research in this area is ongoing.

In aggregate, we believe that the benefits of receiving SARS-CoV-2 vaccination outweigh the risk and continue to recommend COVID-19 vaccination for transplant recipients, once the early period (1-3 months) following transplantation has passed and immunosuppression is stabilized. Transplant patients should continue to use a face mask and maintain social distancing as recommended until further data on vaccine efficacy is available for this population. We recommend vaccination of transplant candidates and immunocompetent household members as a priority, particularly in those situations where a close care provider is needed for the transplant recipient. We also recommend the enrollment of cardiothoracic transplant recipients in vaccine trials or registries where available to assess vaccine efficacy, dosing intervals, need for booster shots, transplant-related adverse events such as rejection and potential change in circulating donor specific antibodies, and long-term effects of vaccination.
SPECIFIC RECOMMENDATIONS

Choice of SARS-CoV-2 vaccine:
1. All currently available vaccines do not use a live replicating viral vector and thus we consider these to be acceptable in transplant recipients.
2. We do not recommend any specific vaccine for transplant recipients. Patients should receive whichever vaccine is available to them based on local regulations and distribution policy. Where vaccine choice is available, individual risks and benefits of each vaccine for a specific patient may be considered by the transplant, PAH or MCS team, taking into account clinical and local epidemiologic factors.

Timing of SARS-CoV-2 vaccination:
1. We recommend vaccination of all transplant candidates based on age-appropriate availability to allow for development of an effective immune response to the vaccine prior to transplantation.
2. In the post transplantation setting, the ideal timing of vaccination is uncertain. We recommend delaying vaccination at least 1 month from transplant surgery and at least 3 months from use of T-cell depleting agents such as anti-thymocyte globulin or specific B-cell depletion agents such as rituximab (which may require a longer deferral period).
3. Patients who are transplanted in between vaccine doses should delay the 2nd dose until at least 1 month after the transplant surgery if no T-cell/B-cell depleting agent was used for induction, or at least 3 months after the transplant surgery if a T-cell/B-cell depleting agent was used for induction.
4. We recommend following manufacturer and/or local regulatory guidelines regarding dosing interval between the first and second vaccine doses until transplant specific data is available.
5. We recommend continuing stable maintenance immunosuppressive regimens, including anti-proliferative agents (such as mycophenolate mofetil) in patients that are receiving SARS-CoV-2 vaccination. We do not recommend alteration of immunosuppression specifically around vaccination as the risk of rejection may be greater with a reduction in immunosuppression.
6. Transplant recipients with prior COVID-19 should receive vaccination after clinical resolution of the infection or as per local regulations/guidelines.
7. Vaccination should be delayed by 3 months in patients that received monoclonal antibodies for COVID-19.

Booster doses:
1. It is suggested that recipients who are concerned about their ongoing COVID-19 risks after full vaccination discuss with their transplant physicians re: continued level of precautionary behavior to mitigate disease transmission/acquisition, testing and any new information about booster vaccination.
2. Information about viral variants, vaccine effectiveness and perceived/real risk is changing rapidly. The transplant recipient’s concerns need to be addressed. There has
been at least 1 report of rejection temporally following booster vaccination; the actual risk of rejection with additional doses of vaccine is unknown, however.

3. There are no data currently to support adjustment of immunosuppression in anticipation of booster vaccination.

4. While booster doses are not currently recognized under the EUA in the United States; international regulations may vary. We encourage people to follow clinical evidence and the local regulatory guidance regarding vaccine use/availability.

5. In order to clarify the potential benefit of booster vaccinations for transplant recipients with uncertain response to the SARS-CoV-2 vaccines, we recommend that booster dosing occur in the context of clinical research studies.

Prioritization:
1. We recommend vaccine prioritization for transplant candidates particularly those accepted on the waitlist.
2. We recommend prioritization of immunocompetent household members of transplant candidates and recipients.

Serological testing:
1. We recommend against routine testing of SARS-CoV-2 serology following vaccination as correlates of immunity are not well established. Additionally, many current serological assays test for nucleocapsid antibody only which will not detect anti-spike antibodies that are expected following vaccination with the vaccines that target the virus spike protein.

Daily Activities:
1. Fully vaccinated transplant recipients should continue to mask and practice social distancing based on local transmission rates of SARS-CoV-2 until more data on vaccine effectiveness are available. Vaccinated transplant recipients should continue to follow local guidelines as applicable to the highest-risk community members.

Organ Donors with Vaccine Induced Thrombotic Thrombocytopenia (VITT):
1. We recommend proceeding with caution when assessing organ donors with VITT and recommend careful assessment of the allograft as well as recipient following transplantation. Recipient monitoring should include measurement of anti-PF4 antibodies, platelet count, D-dimer and fibrinogen.
References:


20. Impaired Humoral and Cellular Immunity after SARS-CoV2 BNT162b2 (Tozinameran) Prime-Boost Vaccination in Kidney Transplant Recipients