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SARS-CoV-2 Vaccination in Heart and Lung Transplantation, MCS and PH

Recommendations from the ISHLT COVID-19 Task Force

May 21, 2021

Several SARS-CoV-2 vaccines are approved for administration in various countries (Table 1) 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 as noted in Table 1 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 1.59 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.

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.[16-20] One study in lung transplant recipients noted a T-cell response in a third of vaccinated recipients with no detectable anti-spike IgG.[20] While the rate of immunogenicity appears lower than that noted in the general population, we do not yet have clinical effectiveness data on rates of protection against severe illness or death in those transplant recipients that are fully vaccinated with longer term follow up. However, these vaccines overall demonstrate safety in the transplant population with no concern for rejection or

other serious adverse events in the early period following administration.[21] We expect that the risk of rejection will likely remain low and not dissimilar to that observed in previous vaccine studies of adjuvanted zoster vaccine or high dose influenza vaccine in transplant recipients.[22, 23]

Serological correlates of immunity against COVID-19 as a measure of vaccine efficacy are unknown at this time. 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.[24] 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 needed.

In aggregate, we believe that the benefits of receiving SARS-CoV-2 vaccination outweigh the risk and endorse 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

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.
8. **Additional vaccination strategies including a booster dose or use of a different vaccine for the second dose should be studied in a clinical trial setting.**

Choice of SARS-CoV-2 vaccine:

1. All currently available vaccines, as noted in Table 1, 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.**

Serological testing:

1. We recommend against routine testing of SARS-CoV-2 serology following vaccination as correlates of immunity are unclear. 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.

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.**

Table 1. SARS-CoV-2 vaccinations available globally, as of May 21, 2021.

Manufacturer	Type	Vaccine efficacy reported in clinical trials	Prevention of severe disease leading to hospitalization or death in clinical trials
Pfizer/BioNTech	mRNA	95%	100%
Moderna	mRNA	94.5%	100%
Sputnik V	Ad26/Ad5	91.4%	100%
AstraZeneca	ChAdOx1	60-85%	100%
Johnson & Johnson	Ad26	57-72%	100%
Cansino	Ad5	66%	100%
Sinopharm	inactivated	79.6-86%	100%
Sinovac	Inactivated	50.1%	100%
Sinopharm-Wuhan	inactivated	?	?
Bharat	inactivated	?	?
Vector Institute	protein	?	?
Novavax	protein	86-96%	100%

References:

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Perez Marc G, Moreira ED, Zerbini C *et al*: **Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine**. *N Engl J Med* 2020.
2. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Borat QE *et al*: **Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK**. *Lancet* 2020.
3. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB *et al*: **Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine**. *N Engl J Med* 2020.
4. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, Kovyryshina AV, Lubenets NL, Grousova DM, Erokhova AS *et al*: **Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia**. *Lancet* 2021, **397**(10275):671-681.
5. **Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial. Accessed 3/13/2021** [<https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3>]
6. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernan MA, Lipsitch M, Reis B, Balicer RD: **BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting**. *N Engl J Med* 2021.
7. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, Bedston S, Beggs J, Bradley D, Chuter A *et al*: **Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study**. *Lancet* 2021, **397**(10285):1646-1657.
8. Pritchard E MP, Stoesser N, Eyre DW, Gethings O, Vihta K, Jones J, House T, VanSteenHouse H, Bell I Bell JI, Newton JN, Farrar J, Diamond A, Rourke E, Studley R, Crook D, Peto T, Walker AS, Pouwels KB, Coronavirus Infection Survey team: **Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK's COVID-19 Infection Survey**. *medRxiv Posted April 23, 2021*.
9. **NYT Vaccinations Tracker. Accessed 3/13/21** [<https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html>]
10. Shimabukuro TT, Cole M, Su JR: **Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021**. *JAMA* 2021.
11. Blumenthal KG, Robinson LB, Camargo CA, Jr., Shenoy ES, Banerji A, Landman AB, Wickner P: **Acute Allergic Reactions to mRNA COVID-19 Vaccines**. *JAMA* 2021.
12. Chan BT BP, Odutayo A, Pai M: **Meta-Analysis of Risk of Vaccine-Induced Immune Thrombotic Thrombocytopenia Following ChAdOx1-S Recombinant Vaccine**. *medRxiv Posted May 8, 2021* 2021.
13. Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattor TH, Tjonnfjord GE *et al*: **Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination**. *N Engl J Med* 2021.
14. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S: **Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination**. *N Engl J Med* 2021.
15. Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, Zhang B, Licata C, Clark TA, Shimabukuro TT: **Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19**

- Vaccine - United States, March-April 2021.** *MMWR Morb Mortal Wkly Rep* 2021, **70**(18):680-684.
16. Brian J. Boyarsky WAW, Robin K. Avery, Aaron A. R. Tobian, Allan B. Massie, Dorry L. Segev, Jacqueline M. Garonzik-Wang: **Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients.** *JAMA* 2021.
 17. Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, Katchman E, Halperin T, Turner D, Goykhman Y *et al*: **Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus.** *Am J Transplant* 2021.
 18. **Impaired Humoral and Cellular Immunity after SARS-CoV2 BNT162b2 (Tozinameran) Prime-Boost Vaccination in Kidney Transplant Recipients**
 19. Peled Y RE, Lavee J, Sternik L, Segev A, Wieder-Finesod A, Mandelboim M, Indenbaum V, Levy I, Raanani E, Lustig Y, Rahav G: **BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response.** *J Heart Lung Transplant* 2021.
 20. Havlin J SM, Dvorackova E *et al*. : **Immunogenicity of BNT162b2 mRNA COVID19 Vaccine and SARS-CoV-2 Infection in Lung Transplant Recipients.** . *Journal of Heart and Lung Transplantation* 2021.
 21. Boyarsky BJ, Ou MT, Greenberg RS, Teles AT, Werbel WA, Avery RK, Massie AB, Segev DL, Garonzik-Wang JM: **Safety of the First Dose of SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients.** *Transplantation* 2021.
 22. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, Kim SJ, Kim SI, Zaltzman J, Ortiz F, Campistol Plana JM, Fernandez Rodriguez AM, Rebollo Rodrigo H *et al*: **Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial.** *Clin Infect Dis* 2020, **70**(2):181-190.
 23. Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, Rotstein C, Lilly L, Schiff J, Singer L *et al*: **A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients.** *Clin Infect Dis* 2018, **66**(11):1698-1704.
 24. Sette A, Crotty S: **Adaptive immunity to SARS-CoV-2 and COVID-19.** *Cell* 2021, **184**(4):861-880.