

Joint Statement about Vaccine Efficacy in Organ Transplant Recipients.

The recent reports of some transplant patients' failure to develop an antibody response to SARS-CoV-2 after vaccination has resulted in considerable concern and confusion within the transplant community. Our transplant societies are aware that clinical studies have not come to firm conclusions but feel that it is prudent to respond to these concerns.

Community spread of SARS-CoV-2 is waning in some parts of the world, especially in those areas with greater vaccine acceptance. Information about COVID-19 vaccine responses in transplantation is rapidly evolving. The impact of more easily transmissible variants is unknown but is likely to be less where greater numbers of individuals are vaccinated. Because vaccines are critical to containing further spread of the pandemic, there has been interest in optimizing vaccine responses in vulnerable populations, including solid organ transplant (SOT) recipients. To date, we have learned the following:

- Antibody responses to COVID-19 vaccines in transplant recipients are diminished compared with the general population (1-14). However;
 - The level of protective antibody has yet to be defined. Based on data derived from trials in the general population, there is a correlation between the level of neutralizing antibody to SARS-CoV-2 spike protein and symptomatic disease.
 - The threshold for protection against severe COVID-19 is significantly lower than that required to prevent viral infection (15).
 - Determination of protective levels of antibody is confounded by the wide variety of antibody tests that are commercially available, with no direct means to compare results from the different tests.
- The protective components of Cellular (T cell and NK T cells) and humoral responses (IgG/IgM vs IgA) may not be linked in individual SOT recipients; it is possible to have an active acquired or innate immune response in the absence of antibody and vice versa (3,6, 9,10). However, the clinical consequence of this divergence is not known nor measurable.
- Even in the absence of "protective antibody titers," there is likely some protection against more severe disease after vaccination (16-18).
- Clinical effectiveness studies in the setting of SOT are lacking.
- While the level of immunosuppression, specifically the use of antiproliferative agents, has been implicated as a factor in poor antibody response after vaccination, there is no reliable guide to immunosuppression management in anticipation of vaccine responses.
- Booster vaccines will likely become necessary after time, even for the general public to maintain immunity (19, 20). However, at this time, when booster vaccination should be administered is not clear. From the existing data/experience, there are no reliable recommendations for booster dosing in SOT recipients who have not generated an antibody response with the initial doses. Some SOT recipients will increase their antibody titers to SARS-CoV-2 after booster mRNA vaccination (21, 22); this includes people who developed a response to the standard series and those who were initially "non-responders." However, there are still a number of issues that remain unknown after booster vaccination. Because the majority of the available data examine kidney recipients and the most recent report examines the boosted response in patients who are beyond the first post-transplant year (median 99 months), it is unclear how to extrapolate these initial reports to the general SOT population. Despite 3 doses of mRNA vaccine, there are still non responders (up to a third in Kamar) and the cellular responses and neutralizing antibody to booster doses have not yet been reported in the studies of booster dosing. Safety data, in particular rejection, in SOT recipients are minimally reported at this time. Therefore,
 - It is suggested that recipients who are concerned about their ongoing Covid 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. 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.
- There are no data currently to support adjustment of immunosuppression in anticipation of booster vaccination.
- 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.

Based on the above information, we strongly recommend the following until further data are available:

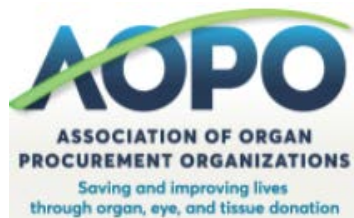
- All solid organ transplant recipients should be vaccinated against SARS-CoV-2, using locally approved vaccines.
- All eligible household and close contacts of SOT recipients should be vaccinated against SARS-CoV-2 to minimize risks to the recipient.
- Whenever possible, vaccination should occur prior to transplantation (ideally with completion of vaccine series a minimum of 2 weeks prior to transplant).
 - We support the development of institutional policies regarding pre-transplant vaccination as we believe that this is in the best interest of the transplant candidate, optimizing their chances of being safely transplanted, especially at times of greater infection prevalence.
- Routine antibody testing following vaccination is not recommended by the FDA. Considerations include:
 - Most commercially available tests do not examine neutralizing antibody to the spike protein receptor binding domain (RBD).
 - Many commercially available tests are qualitative.
 - The analytical cut-off values for antibody detection are not necessarily the same as clinically relevant values.
 - There is no commonly agreed upon titer that has been defined as protective against SARS-CoV-2 infection.
 - Cellular responses may occur in the absence of measurable antibody
- However, individual physicians and patients may decide that antibody testing is desirable following a discussion regarding the interpretation of the test results and the consequences/risks of acquiring COVID-19 infection. There are many additional issues relevant to the patient, such as local prevalence of SARS-CoV-2 and its variants, personal situations relating to immunosuppression and transplant infections and the vaccination level in the household.
- 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. Monitoring of long-term responses and adverse effects are important to clarify existing clinical uncertainties.
- It is strongly recommended that all health care providers be vaccinated against SARS-CoV-2 to foster a safer environment for our patients.
- While COVID-19 variants continue to circulate in the community and the extent of protection is still unknown in transplant recipients, it is recommended that SOT candidates and recipients continue to adhere to protective measures including masking in public spaces, social distancing, frequent hand washing, and avoiding indoor crowds. The “mixed messaging” of uncertainty of vaccine efficacy for certain populations is recognized and requires more counseling from the transplant providers.
- We recommend ongoing monitoring of the regulatory and health department websites to obtain up to date COVID-19 prevalence and vaccine updates.

- We STRONGLY urge funding agencies to invest in research evaluating vaccine immunogenicity, vaccine effectiveness, and strategies to enhance vaccine responses in vulnerable populations, including SOT candidates and recipients, who may fuel the perpetuation of the pandemic.





LEADING THE WAY
IN ORGAN
TRANSPLANTATION



References

1. Boyarsky BJ, Werbel WA, Avery RA, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM: Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 2021. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int 2021.
2. Sattler A SE, Weber U, Potekhin A, Bachmann F, Budde K, Storz E, Proß V, Bergmann Y, Thole L, Tizian C, Hölsken O, Diefenbach A, Schrezenmeier H, Jahrsdörfer B, Zemojtel T, Jechow K, Conrad C, Lukassen S, Stauch D, Lachmann N, Choi M, Halleck F, Kotsch K. MedRxiv. doi: <https://doi.org/10.1101/2021.04.06.21254963>. Accessed 4/19/2021. Impaired Humoral and Cellular Immunity after SARS-CoV2 BNT162b2 (Tozinameran) Prime-Boost Vaccination in Kidney Transplant Recipients. Available from:
3. Yi SG, Knight RJ, Graviss EA, Nguyen DT, Ghobrial RM, Gaber AO et al. Kidney Transplant Recipients Rarely Show an Early Antibody Response Following the First COVID-19 Vaccine Administration. Transplantation 2021.
4. 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.
5. 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.
6. Narasimhan M ML, Clark AE, Usmani A, Cao J, Raj E, Torres F, Sarode R, Kaza V, Lacelle C, Muthukumar A. Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines. medRxiv 2021.
7. Shostak Y SN, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, Amor SM, Yahav D, Zvi HB, Pertzov B, Kramer MR. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. The Lancet Resp Med 2021.
8. Miele M, Busa R, Russelli G, Sorrentino MC, Di Bella M, Timoneri F et al. Impaired anti-SARS-CoV-2 Humoral and Cellular Immune Response induced by Pfizer-BioNTech BNT162b2 mRNA Vaccine in Solid Organ Transplanted Patients. Am J Transplant 2021.

9. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant* 2021.
10. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect* 2021.
11. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol* 2021.
12. Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M 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.
13. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. *Eur J Heart Fail* 2021CHC Inc. (n.d.).
14. Khoury, D. S., Cromer, D., Reynaldi, A., Schlub, T. E., Wheatley, A. K., Juno, J. A., Subbarao, K., Kent, S. J., Triccas, J. A., & Davenport, M. P. (2021). Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Medicine*. <https://doi.org/10.1038/s41591-021-01377-8>
15. Basic-Jukic N, Jelacic I. SARS-CoV-2 infection after two doses of mRNA vaccine in renal transplant recipients. *Transpl Infect Dis* 2021:e13628.
16. Tsalouchos A, Rossolini GM, Magg L, Mazzoni A, Annunziato F, Dattolo PC. COVID-19 in a kidney transplant recipient after mRNA-based SARS-CoV-2 vaccination. *Transpl Infect Dis* 2021:e13649.
17. Tau N, Yahav D, Schneider S, Rozen-Zvi B, Abu Sneineh M, Rahamimov R. Severe consequences of COVID-19 infection among vaccinated kidney transplant recipients. *Am J Transplant* 2021.
18. *CDC Director Rochelle Walensky Talks Boosters, Masks and Health Equity*. Home - Community Health Center Presents Conversations on Health Care -. <https://www.chcradio.com/episode/Rochelle-Walensky/579>.
19. U.S. Department of Health and Human Services. (2021, June 1). NIH clinical trial evaluating mixed COVID-19 vaccine schedules begins. National Institutes of Health. <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-evaluating-mixed-covid-19-vaccine-schedules-begins>
20. Kamar, N., Abravanel, F., Marion, O., Couat, C., Izopet, J., & Del Bello, A. (2021). Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *New England Journal of Medicine*. <https://doi.org/10.1056/nejmc2108861>
21. Werbel, W. A., Boyarsky, B. J., Ou, M. T., Massie, A. B., Tobian, A. A. R., Garonzik-Wang, J. M., & Segev, D. L. (2021). Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Annals of Internal Medicine*. <https://doi.org/10.7326/l21-0282>