Simple Vaccination Is not Enough for the Transplant Recipient

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The outcome of SARS-CoV-2 vaccination in vulnerable populations has been a cause for especial concern among transplant patients and the medical teams responsible for advising them. The prospect that immunosuppressed patients would not respond to vaccines for COVID prevention was based on the known need to specifically tailor vaccines for this population, for example, Shingles.[1]

Thanks to the exemplary capacity of the UK National Health Service to collect and link data reliably on the English population, we now have the answer we feared from >40 000 solid organ and islet transplant recipients (SOT).[2] This analysis of the individually linked transplant, vaccination, infection, and mortality data, shows that the 2 vaccines studied (Pfizer-BioNTech BNT162b2 and Oxford-AstraZeneca ChAdOx1-S) do not protect patients from infection and only 2 doses of Oxford-AstraZeneca ChAdOx1-S provide a modest 31% reduction in mortality compared with being unvaccinated. Risk factors for death of SOT patients within 28 d of testing positive for SARS-CoV-2, include being over 50 y of age, having a lung transplant, being of Black ethnicity and living outside London. There are additional issues identified by this analysis including the implication that the unvaccinated protect themselves better from infection using nonpharmaceutical interventions (NPI), since the rate of infection was actually increased in the vaccinated patients by 29%, perhaps related to individuals' relaxation of mask use and other protective measures once vaccinated. There was a dramatic impact of age, with mortality rates of 2.1%–2.9% in those with a positive test either before or after vaccination under 50 y of age, compared with mortality of those 50 y and older at 12.2%–17.3%, depending on vaccination status.

The strengths of the study include comprehensive near real-time data collection and national coverage, which has delivered by far the largest experience of vaccine effectiveness (VE) in SOT to date with minimal ascertainment bias. What is missing is the granular detail of the immunosuppressive agents used and the humoral and cellular postvaccine responses in the patients. Asymptomatic and untested symptomatic patients with COVID were obviously not assessable and hospitalization rates will need an additional analysis. The effectiveness of mixing vaccine types is not assessed, and the study period preceded the appearance of the omicron strain and so nothing can be inferred about VE for SOT from this strain. The data, however, provide the best evidence available today on which to base future actions to protect the immunosuppressed.

Some of the many questions that arise have already been acted upon, based on early small cohort data. Third[3,4] and fourth[5] dose vaccine shots are clearly justified and already partly enacted in the target population in England and other comparable countries[6] though the effectiveness of this strategy for SOT must be tested. Vaccination after COVID infection is both justified and effective in raising antispike humoral responses. Study of mixed vaccines may deliver new options to improve VE. Vaccination before transplantation is important and though we do not know quite how important for the different organ transplants, lung transplant recipients are certainly at high risk from COVID once immunosuppressed.

The question remains open as to whether individualized or personalized strategies can be helpful in broadening the protection for SOT. Such strategies could be developed based on changing immunosuppression at vaccination. Belatacept is strongly associated with unresponsiveness, as its mode of action would have predicted[7] and early data from several small studies suggest that mycophenolate mofetil doses under 1 g/d are associated with better humoral response than doses >1 g. The importance for VE of cellular, as opposed to humoral, responses has yet to be understood.

Bigger and longer lasting questions arise from these data for policy makers, pharmaceutical companies, and vaccine regulators. Excluding high-risk immunosuppressed patients from early vaccine studies may seem to be commercially sound but is not acceptable to the millions taking immunosuppressive agents provided by those same companies and regulated by those same agencies.

The failure of the tested mRNA vaccine to protect SOT patients from infection is disappointing, but the apparent failure to protect from death is extremely worrying and unexpected and needs further research before this finding can be confirmed and a biological explanation identified. The SOT population must look to third and fourth doses of available vaccine to enhance protection, as they do in the general population.[8]

Finally, what is the message from these data for the most important people in this context, SOT recipients? We must be clear, consistent and accurate:

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- **The first and most important advice** is to talk to your transplant specialist.
- **If unvaccinated,** then get vaccinated to reduce mortality risk by up to 30%. Getting vaccinated, especially before a transplant and commencement of immunosuppression, is important and indeed critical for lung transplant recipients. The chance of a severe adverse reaction to a vaccine is around 70 000-fold less than the risk of severe, debilitating, or lethal COVID-19.
- **If vaccinated** with 2 doses, then seek out the third and fourth doses.
- **Use every reasonable nonpharmaceutical method** to protect yourself from infection—for example, masks, avoidance of crowded places, avoidance of contact with any symptomatic person, encourage your close contacts to be vaccinated. Use of regular lateral flow and screening tests in asymptomatic and minimally symptomatic people after potential contact may also assist.
- **If you become symptomatic**, treatments coming on stream in the near future and some available today, but yet to be trialed in immunosuppressed people, when used early in the course of COVID-19, may reduce your risk of death so do not wait at home to get sicker.[9]

This is an important study of a group of vulnerable individuals who had a 10.4% mortality rate within 28 d of testing positive for SARS-CoV-2 if unvaccinated, reduced by only 31% (to 8.2%) after 2 doses of Oxford-AstraZeneca ChAdOx1-S vaccine. We have much to understand before a semblance of normality can pervade the transplant programs of the world.

REFERENCES

1. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, et al; Z-041 Study Group. 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;70:181–190.
2. Callaghan CJ, Mumford L, Curtis RMK, et al. Real-world effectiveness of the Pfizer-BioNTech BNT162b2 and Oxford-AstraZeneca ChAdOx1-S vaccines against SARS-CoV-2 in solid organ and islet transplant recipients. *Transplantation*. [Epub ahead of print. January 4, 2022]. doi:10.1097/TP.0000000000004059
3. Munro APS, Janani L, Cornelius V, et al; COV-BOOST Study Group. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*. 2021;398:2258–2276.
4. Massa F, Cremoni M, Gérard A, et al. Safety and cross-variant immunogenicity of a three-dose COVID-19 mRNA vaccine regimen in kidney transplant recipients. *Ebiomedicine*. 2021;73:103679.
5. Alejo JL, Mitchell J, Chiang TP, 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–e281.
6. National Health Service. Booster dose of the coronavirus (COVID-19) vaccine. 2021. https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/. Accessed September 22, 2021.
7. Ou MT, Boyarsky BJ, Chiang TPY, et al. Immunogenicity and reactogenicity after SARS-CoV-2 mRNA vaccination in kidney transplant recipients taking belatacept. *Transplantation*. 2021;105:2119–2123.
8. Stuart ASV, Shaw RH, Liu X, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. *Lancet*. 2022;399:36–49.
9. Ahearn AJ, Maw TT, Mehta R, et al. A programmatic response, including bamlanivimab or casirivimab-imdevimab administration, reduces hospitalization and death in COVID-19 positive abdominal transplant recipients. *Transplantation*. 2022;106:e153–e157.