Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

DOI: 10.1111/ajt.16788

Boosters and optimizing SARS-CoV-2 vaccine for transplantation: No time to wait

To the Editor:

We read with appreciation Ison and colleagues' thoughtful perspective regarding optimizing SARS-CoV-2 vaccination in solid organ transplant recipients (SOTRs).[1] However, we respectfully counter that waiting for clinical trials to guide vaccination strategies is divorced from the reality that SOTRs face in a society with increasingly adversarial attitudes toward masking and social distancing. Despite the proliferation of the SARS-CoV-2 delta variant in the United States, only eight states currently mandate masking for unvaccinated individuals, decreasing the feasibility of SARS-CoV-2 avoidance.

A strategy to wait for additional evidence also disregards that current recommendations themselves lacked empiric evidence. Based on reasonable inferences, we recommended standard SARS-CoV-2 vaccination to SOTRs as safe and effective despite SOTRs' exclusion from vaccine trials. Similarly, a strategy of empiric vaccine "boosters" should be pursued in the absence of trial data given the reasonable potential for benefit and minimal likelihood of harm, a scenario we believe exists given that:

1. It is likely that vaccine-induced immunity is lower in SOTRs than immunocompetent individuals.
   Although cellular immunity may offset the absence of post-vaccination neutralizing antibodies in SOTRs, among 148 kidney transplant recipients, 35% developed neither humoral nor cellular responses following vaccination.[2] Furthermore, while breakthrough COVID-19 is predominantly mild, a recent review of patients with kidney disease, including kidney transplant recipients, identified multiple reports of severe and fatal breakthrough infection in patients with suboptimal humoral responses.
2. It is plausible that additional vaccine doses increase the likelihood and/or degree of humoral immunity in SOTRs.
   Among 658 SOTRs, 39% had detectable antibodies only after two doses of mRNA SARS-CoV-2 vaccines and even those with antibodies detectable after dose 1 displayed higher titers following dose 2.[3] Among 101 SOTRs receiving a third vaccine dose, anti-SARS-CoV-2 antibody prevalence increased from 40% to 68%.[4] A lack of universal seropositivity does not negate the incremental benefit observed; achieved antibody level is highly correlated with protection from symptomatic disease. Furthermore, boosting using original or modified vaccines will likely be used going forward to achieve protective immunity against emerging variants of concern.
3. It is unlikely that booster doses carry a significant risk of adverse events.
   Although the authors quote a sixfold higher incidence of rejection in third-dose versus second-dose recipients, this is based on only one case of rejection per group (Fisher's exact $p = .28$) and the putative mechanism is unclear. De novo anti-HLA antibody development has been reported after seasonal influenza, H1N1, and even standard SARS-CoV-2 vaccination, and there are rare cases of acute rejection following influenza vaccination.[5] Rare rejection episodes after influenza vaccination have not led to withholding these vaccines from SOTRs, and the benefit:risk of vaccination against SARS-CoV-2 far outweighs that of seasonal influenza given higher SARS-CoV-2 vaccine effectiveness and more severe clinical spectrum of COVID-19 disease.

The unfortunate reality is that SARS-CoV-2 avoidance remains challenging as increasingly transmissible variants proliferate. It is imperative that we act urgently to improve transplant recipients' protection. In the absence of a reasonable expectation for harm, vaccine boosters should be pursued even if the potential benefit is uncertain.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

No data is analyzed in this letter.

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