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EDITORIAL

COVID-19, Vaccination, and Heart Transplantation

Forest W. Arnold, DO MSc[1]*

[1]Division of Infectious Diseases, School of Medicine, University of Louisville, Louisville, KY, USA

*f.arnold@louisville.edu

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See original article by Belur *et al.*

Operation Warp Speed was an inter-agency partnership program involving the U.S. government and pharmaceutical companies to create and distribute a vaccine for COVID-19 as fast as safely possible. The pursuit is continuing as variants become moving targets of vaccines much like influenza virus and its need for an updated vaccine. The learning curve to develop vaccines has been just as steep as for developing treatments and defining the best management approach to the pandemic. Great progress has been made. Consider the mortality difference noted with the introduction of COVID-19 vaccines (**Figure 1**).[1]

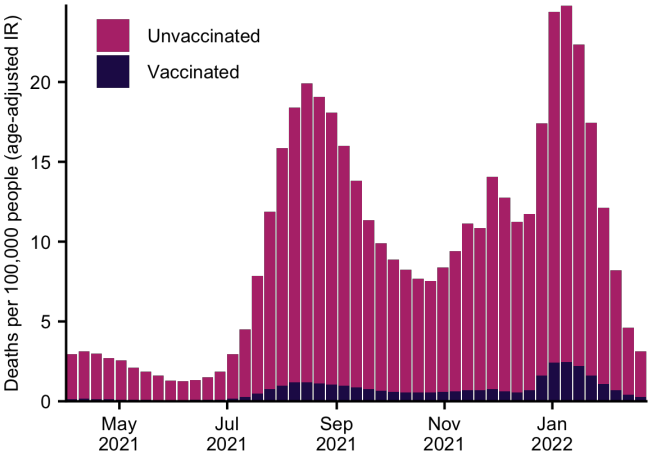

Figure 1. Difference in incidence of mortality between vaccinated and unvaccinated individuals, April 2021–February 2022. Data from the Centers for Disease Control and Prevention, last updated April 15, 2022. **Abbreviations:** IR, incidence rate.

In this issue of the *ULJRI*, Belur *et al.* report a case of COVID-19 in a heart transplant patient. As a case report, it represents how new knowledge is amassed by disseminating and assimilating one study at a time. Certainly, randomized control trials are the preferred standard, but those are only funded after preliminary studies point toward a possible association of an intervention with an outcome.

For this topic of COVID-19, vaccination, and heart transplantation, timing is everything. COVID-19 data from the pandemic are relevant, but to benefit from them, one must know when the case occurred since management and treatment have been evolving and vaccines have been phased into the population. Knowing at what time during the pandemic a patient was treated is critical in interpreting what took place. This particular case occurred in March 2021 when vaccines were available, but prior to the approval of booster doses. At that time, the Centers for Disease Control and Prevention (CDC) guidelines recommended either two mRNA (BNT 162b2 [Pfizer and BioNTech] or mRNA-1273 [Moderna and the National Institutes of Health]) doses or one adenovirus (Ad26.COV2.S [Janssen Pharmaceuticals, Inc.]) dose. Since boosters had not yet been recommended, the patient in the present case was considered "fully vaccinated" at the time.[2]

The protection and efficacy provided by any vaccine in an immunosuppressed person is always a question, but the benefit of the COVID-19 vaccine, as with many vaccines, is that if it does not prevent one from acquiring an infection, it may still prevent hospitalization or death from the infection. As one might imagine, solid organ transplant recipients require immunosuppressive regimens, with heart transplant recipients typically requiring the most aggressive regimen.[3]

The length of treatment of a regimen is tied to the need for immunosuppressives to prevent rejection of a transplanted organ and graft *versus* host disease balanced with susceptibility to opportunistic infection or malignancy that may ensue with a compromised immune system. Tolerance may develop to some degree, and it may be possible to discontinue individual components of a regimen, but lifetime suppression is usually necessary to prevent rejection after transplantation.

The present case represents a heart transplant recipient with a "breakthrough" infection as he had received two mRNA vaccines prior to acquiring COVID-19. Belur *et al.* review the immunosuppression of the patient and discuss the efficacy—or lack thereof—of the vaccination he had received.

Qin *et al.* found that among 101 million adults in the US who were vaccinated, 0.01% had a COVID-19 breakthrough infection while 0.83% of 18,215 transplant recipients had a breakthrough infection.[4] The mortality difference of breakthrough infections between the general population and the transplanted was much more significant at 0.00016% *vs.* 9.3%, respectively. Outcomes among unvaccinated transplant recipients were even worse with 5% acquiring COVID-19 [5] and 20% dying.[6] The patients in these studies were fully vaccinated, and despite being a high-risk group, experienced decreased breakthrough infections and decreased mortality.

In a study of ∼48,000 solid organ recipients, mortality from COVID-19 in those who did not receive a vaccine, or who only received one dose, was 12.6% and 12.0%, respectively, but for those who received two doses, the mortality was only 7.7%.[7] The transplanted are obviously a significantly vulnerable group. Their lack of humoral and cellular immunity makes them more susceptible, and they then struggle to clear infection once they have it, but it appears that vaccination offers some protection for them.

Belur *et al.* chose to obtain IgG antibodies to assess the vaccination status of their patient who had received Pfizer's BNT162b2 vaccine and had been on mycophenolate and tacrolimus. They checked a qualitative test for antibodies to SARS-CoV-2, which was negative. A cohort of heart transplant patients who had received the Pfizer vaccine also did not respond well.[8] Among 77 heart transplant patients, only 14 had detectable levels of IgG anti-receptor binding domain antibodies after a mean of 41 days from the second injection. None of the patients who were on mycophenolate and tacrolimus, like the patient in the present case report, had antibodies detected. There has been at least one call for a study to evaluate holding mycophenolate mofetil in order to prevent immune paresis—a suboptimal humoral and cellular response to an antigen.[9] However, just because antibodies are not detected, does not mean that the vaccine is unsuccessful as demonstrated above with improved outcomes in spite of low antibody responses.

Despite the outcome in the present case, physicians should not be deterred from vaccinating their heart transplant patients based on an anecdotal experience of a poor outcome in a vaccinated patient. No doubt, updated vaccines that adjust for variants will further improve outcomes in all populations, especially heart transplant recipients.

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