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# Yes, It Does

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We live in strange times, but the questions are not strange or new. My colleagues and I in Infectious Diseases and related specialties have heard them all before with other vaccines. For those who have access to the vaccine but remain unvaccinated against COVID-19 and are open to that possibility, a reductionist version of those myriad questions is simply, Does the vaccine work? Pani and colleagues address this simple question elegantly in their manuscript published in this issue of *Mayo Clinic Proceedings*, and the findings are even more relevant in the setting of increasing COVID-19 vaccine mandates.[1] Their study is particularly noteworthy as it provides more "real-world" evidence of the effectiveness of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in frontline health care workers in Milan, Italy, which has been hard-hit by the pandemic. If an unvaccinated health care worker were to ask me now, "Does the vaccine work?" I would hand the person this article by Pani et al and say simply, "Yes, it does."

Does it generate an immune response? The primary outcome of this prospective, observational cohort study was the measurement of total anti-spike IgG antibody levels and neutralizing antibody levels 14 days after the second injection. Acknowledging that the critical immunologic determinants of immune protection against COVID-19 have not yet been established, these 2 orthogonal serologic markers are standard and reasonable surrogates of immunogenicity of the vaccine. Remarkably, of the 2569 medical staff tested, only 4 (0.16%; 95% CI, 0.04% to 0.4%) were immunologic nonresponders based on antibody detection. This robust and pervasive immunogenicity has been confirmed in health care workers in Belgium.[2] Does it work? Yes, it does.

Does it protect from infection, disease, and death? The secondary outcome of this study was the frequency of symptomatic, polymerase chain reaction–positive COVID-19 after vaccination. As this was not a randomized clinical trial, the authors compare the rates of COVID-19 in the study participants with the concurrent epidemiologic curve in the region at the time. Only 13 of 5023 health care workers (0.26%) had a laboratory-confirmed breakthrough infection within the first few months after vaccination. This rate of early breakthrough infections is remarkably similar to those reported in Germany,[3] the United Kingdom,[4] and New York.[5] Furthermore, the epidemiologic curves in Figure 3 of the manuscript by Pani et al demonstrate significantly reduced infection rates in vaccinated health care workers compared with the pre–vaccination period and compared with the general population in the third wave in Milan, similar to reports from Israel.[6] Does it work? Yes, it does.

Do the benefits outweigh the risks? All vaccines are subject to pharmacovigilance, or systemic monitoring of adverse effects on a population level. However, no vaccine has previously been scrutinized so thoroughly in so short a period as have the available COVID-19 vaccines, which have been administered in the billions of doses in less than a year. Comparatively, the sample of Pani et al of 1900+ vaccine recipient respondents reporting adverse events associated with the BNT162b2 vaccine is an almost insignificant drop in the ocean. However, consistent with much larger studies,[7] serious adverse events were rare after the vaccine was received (<0.5%) in this study. Given the benefit of reduced COVID-19 infection from the vaccine, the benefits of vaccinating health care workers clearly exceed the risk. Does it work? Yes, it does.

Will it work for me? This is the fundamental question for the vaccine-hesitant health care worker. Unfortunately, it is also fundamentally unanswerable. Pani et al describe several factors associated with reduced response to the BNT162b2 vaccine in health care workers, including age, sex,



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and immunosuppressed state. These are neither surprising nor modifiable and have been confirmed in other studies. It is notable that 22.7% of respondents self-reported 1 or more concomitant clinical conditions, reminding us that health care workers are susceptible to the same conditions that we treat in patients. The only difference is the degree of exposure to COVID-19. So, if a hesitant health care worker self-identifies a high personal risk of vaccine nonresponse, the logical conclusion should not be to avoid vaccination because of possible lack of benefit. The risk factors for vaccine nonresponse are the same for severe infection, and if there is increased risk of exposure, there is only one logical answer. Will it work for me? As the Magic Eight ball says, "Cannot predict now." But better safe than sorry.

Will it work forever? The study of Pani et al was not designed to address vaccine efficacy during a prolonged period. However, an affirmative answer to this very understandable question was never on the table. Viruses mutate and evolve. Immunity wanes. Babies are continuously born and are unprotected until vaccinated. Global and local disparities in access to vaccines persist. For these and other reasons, the SARS-CoV-2–susceptible pool is continually replenished. Infections continue, and the virus mutates to evade immunity. This is the same for all infections and vaccines. No vaccine works forever, individually or for a population. It is clear, though, that the BNT162b2 vaccine will not work forever. Despite persistence of detectable neutralizing antibodies up to 6 months after receipt of the related mRNA-1273 (Moderna) vaccine, the quantitative levels of these antibodies decline significantly.[8] This is likely the same with the BNT162b2 vaccine. With the emergence and dominance of the delta SARS-CoV-2 variant, breakthrough infections in vaccinated health care workers increase.[9] Will the available COVID-19 vaccines work forever? No, but that does not mean they are not useful in the present and for considerable but as yet unquantifiable periods into the future.

President Biden announced on September 9, 2021, a COVID-19 vaccine mandate for health care workers at facilities receiving funds from Medicare and Medicaid. Vaccine mandates are not without controversy, and questions abound. However, one question has an answer. Does it work? Yes, it does.

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**Potential Competing Interests:** Dr Cummins serves as a physician lead for international medical education collaboration for Pfizer Inc, co-manufacturer of the BNT162b2 vaccine. This activity is unrelated to COVID-19 or vaccine-related research. The opinions expressed in this editorial are solely of the author and do not reflect the official opinion of the Mayo Clinic or Pfizer Inc.

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