Requested by: Anh Nguyen
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"I have a patient who was curious about COVID natural immunity vs. vaccine immunity and the data behind that. Which one lasting longer, stronger etc. It seems that they have read a study from Israel that showed that natural immunity seemed to be stronger than the vaccine immunity. Unsure which study he read but if you would look into this as well. The catch is that they don't want information from the manufactures themselves, believing in potential bias, but other sources if possible. Patient specifically wanted me to send linked article with summarized information for them. They also wanted some information about Israel's conducted study about natural immunity as well. Thanks!"

Relevant Patient Information:
Allergies:
Disease states: SARS-CoV-2
Medications:

Drug Information Response:

I want to preface this with the fact that the Israeli study that is getting attention regarding natural immunity is still in pre-print and has yet to be peer reviewed. With that said, this retrospective, observational study looks at comparing patients 16 years and older who have been vaccinated with the Pfizer vaccine to previously infected, unvaccinated individuals. The study period lasted from March 1, 2021, to August 14, 2021. The goal was to compare infection rates between those fully vaccinated and those who were unvaccinated. Ultimately, the authors determine that there was a 13.06-fold increased risk for breakthrough infection as opposed to reinfection (95% CI [8.08-21.11], p<0.001).[1] There are several issues with the study that I will try and address. First, when looking at Table 1a., there are vastly different characteristics between the groups when considering comorbidities as there are larger numbers of patients with comorbidities within the vaccinated group, specifically immunocompromised and cancer. The authors try to control for this by matching 16,215 patients from each group before their analysis, but there is still the potential for selection bias. Another concern with this data is that this analysis does not take mortality into account. Without accounting for mortality, there is a risk of survival bias, meaning that they show less patients with infection in the previously infected population. In the United States we know that majority of these breakthrough infections do not lead to hospitalizations or death. According to the CDC, as of September 13, 2021, more than 178 million Americans have been fully vaccinated against COVID-19. In total the CDC has received reports from 49 states and territories of 15,790 patients with breakthrough infections that have been hospitalized or died (0.0089%*).[2] Based off this information, we can assume that in Israel, during the study period, majority of their deaths due to COVID consisted of the unvaccinated population. The patients who died during this trial period were more than likely not vaccinated and therefore the true infection rate of the previously infected population is higher than analyzed leading to an overestimation of natural immunity.

A study published in the CDC's Morbidity and Mortality Weekly Report (MMWR) looked to evaluate antibodies among frontline health care workers with mild COVID-19 infection 60 days after initial testing. This took place across 12 states from April 2020 to August 2020. They found that 156 people initially tested positive for SARS-CoV-2 antibody in the Spring of 2020. Of these 156, 146 had a decline in antibody levels between baseline and follow up and 44 had complete seroreversion which is a decline to a level below the threshold for positivity. Within this group they noted that 64.9% had low baseline antibody levels.[3]

Furthermore, a study published in the CDC's Emerging Infectious Disease Journal evaluated 72 patients who had a previously positive RT-PCR test but were symptoms free for > 3 weeks before they had blood collected for testing. Of these 72, only 46 patients had detectable IgG responses, IgA responses, or both. Based off this information, they looked to see if they could determine a cause of nonseroconversion. They observed a trend for increasing antibody

positivity with increasing symptom severity, but overall did not find a statistically significant association with race/ethnicity, sex, or symptom severity. They did notice that seronegative patients were, on average, 10 years younger than seropositive patients (95% CI [3-17]) and had RT-PCT C_t values that were 11 cycles higher (95% CI [8-14]). After further analysis they determined that the higher the C_t value was, the further decline in the probability of seroconversion (e.g., C_t of 35 predicted 15% probability of seroconversion (95% CI [5%-37%]) indicating that the lower the viral load is, the less likely the patient will elicit an antibody response.[4]

Lastly, another study published in the CDC's Morbidity and Mortality Weekly Report (MMWR) analyzed Kentucky patients from May 2021 to June 2021. They were looking to determine the risk of reinfection in patients who were previously infected versus those have been vaccinated with either of the mRNA vaccines. They found 246 patients that met requirements and were matched to 492 controls. Overall, unvaccinated patients with previous infections were at a higher risk of reinfection than those who were fully vaccinated (OR 2.34, 95% CI [1.58-3.47]).[5]

*This is percentage of patients who have COVID-19 vaccination and were hospitalized or died. Of the 15,790, only 3,040 died of 178 million fully vaccinated (0.0017%)

Resources used (Package insert, primary literature, tertiary resource, etc.):
- Primary Literature

Citations:

1. Gazit S, Shlezinger R, Perez G, et al. Comparing sars-cov-2 natural immunity to vaccine-induced immunity: Reinfections versus breakthrough infections. *medRxiv*. August 2021. doi:10.1101/2021.08.24.21262415
2. COVID-19 Breakthrough Cases. Centers for Disease Control and Prevention. Updated September 13, 2021. Accessed September 21, 2021. https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html
3. Self WH, Tenforde MW, Stubblefield WB, et al. Decline in SARS-CoV-2 Antibodies After Mild Infection Among Frontline Health Care Personnel in a Multistate Hospital Network - 12 States, April-August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(47):1762-1766. Published 2020 Nov 27. doi:10.15585/mmwr.mm6947a2
4. Liu W, Russell RM, Bibollet-Ruche F, et al. Predictors of Nonseroconversion after SARS-CoV-2 Infection. *Emerg Infect Dis*. 2021;27(9):2454-2458. doi:10.3201/eid2709.211042
5. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination - Kentucky, May-June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(32):1081-1083. Published 2021 Aug 13. doi:10.15585/mmwr.mm7032e1

Search terms used:
- COVID-19 and Natural Immunity

Request Type:
☐Product availability   ☐Adverse reaction   ☐Compounding
☐Administration   ☐Drug interaction   ☐Pharmacokinetics
☒Therapeutics/efficacy   ☐Pregnancy/lactation   ☐Toxicity
☐Other:

Drug Information Response Form