Super Immunity!

Vaccination plus infection creates super immunity against Covid-19

We have seen a huge increase in Covid-19 cases over the past two months. Here in Wisconsin, the incidence of the Omicron variant went from 0.1% of cases at Thanksgiving to 95% of cases by New Year's Day. As a result, we saw a lot more infections in people who had previously been vaccinated and even boosted. What does this mean for us going forward? Does everyone need another "booster"? Should people who got infected get "boosted" and if so, when? Should our young children who have contracted the virus get vaccinated and then "boosted"? We have heard conflicting reports about infection-induced (natural) immunity throughout the pandemic. What does the research show? When you informed me of your positive Covid test, why did I respond "welcome to hybrid immunity"?

Abstract

Current COVID-19 vaccines significantly reduce overall morbidity and mortality and are vitally important to controlling the pandemic. Individuals who previously recovered from COVID-19 have enhanced immune responses after vaccination (hybrid immunity) compared to their naïve-vaccinated peers; however, the effects of post-vaccination breakthrough infections on humoral immune response remain to be determined. Here, we measure neutralizing antibody responses from 104 vaccinated individuals, including those with breakthrough infections, hybrid immunity, and no infection history. We find that human immune sera following breakthrough infection and vaccination following natural infection, broadly neutralize SARS-CoV-2 variants to a similar degree. While age negatively correlates with antibody response after vaccination alone, no correlation with age was found in breakthrough or hybrid immune groups. Together, our data suggest that the additional antigen exposure from natural infection substantially boosts the quantity, quality, and breadth of humoral immune response regardless of whether it occurs before or after vaccination.

When the Covid-19 vaccines came out in late 2020, the early numbers were incredible; 95% prevention from severe disease AND symptomatic infection. Over the past few months with the arrival of the Delta variant and now the Omicron variant we are seeing much less protection from symptomatic infection. We initially termed these "breakthrough" infections but as time has gone on, we now realized that while the vaccines are still great at protecting from severe outcomes (hospitalization and death) in most people they are not as good at protecting from contracting the virus as they were initially. Because of this, we now have a lot of people who have been vaccinated and have had an infection, either before vaccination or after vaccination. What does this mean?

This study followed 104 Pfizer vaccinated health care workers and divided them into three groups. Forty-two were vaccinated with no infection, 31 were vaccinated after they had an infection, and 31 had a "breakthrough" infection after vaccination. Blood samples were collected and exposed to three Covid-19 variants. Both groups with "hybrid" immunity (vaccine + infection) generated greater levels of immunity compared to the vaccination-only group. There was no significant difference in whether the infection occurred before or after vaccination. What does this mean? While we shouldn't seek out an infection, when we do get infected, and it is likely we will all eventually get infected regardless of vaccination status, we should be comforted by the fact that vaccination will protect the vast majority of us from a severe outcome requiring hospitalization and when we recover we will have hybrid "super immunity"! What extra immunity does contracting the virus give us? The vaccines make us form spike protein antibodies. An infection also gives us antibodies to other parts of the virus (nucleocapsid) so we have more triggers that we can respond to and will in the long-term give us a very adaptable immune response to any forthcoming variants.

Early in the pandemic, our public health leadership proclaimed that there was no protection from reinfection from natural immunity. A big part of this messaging was likely because we didn't have data to know the strength and durability of naturally acquired immunity. We now have this data. Natural immunity is real and durable but may be variable. Those who only get mild symptoms may not generate as robust a response as those who have more symptoms,

but it does appear that humoral immunity (long-term memory immunity) is triggered which will provide protection. Additionally, contracting the virus provides us antibodies to other parts of the virus besides the spike protein. During the Delta surge, people with hybrid immunity had significantly better outcomes than vaccine-induced immunity alone.

What does this mean moving forward? People hospitalized because of Covid are virtually all unvaccinated (personal communication with local hospitalists). I ***recommend*** *vaccination for anyone who has no immunity to this virus. It is the best way to provide excellent protection from severe outcomes with the lowest risk. I recommend a longer period between doses of the mRNA vaccines than 3-4 weeks as this has been shown to provide a better immune response. I recommend a minimum of 8 weeks between doses and preferably closer to 12 weeks.*

Should everyone get a booster? Boosters have been shown to boost antibody levels and lower infection rates in people over 60 years of age in the short term. Are they of benefit to the general population? I am skeptical that it makes much difference, especially in light of Omicron. The booster shots are showing a period of significantly increased circulating antibodies that may temporarily protect from symptomatic infection for 10-12 weeks, but do not look to provide any long-term benefits. Based on potential risks to teens and children (very low but present) and the extremely low risk of severe outcomes in this group, including long-Covid, I see no reason to give boosters to teens and children in the general population. It may make sense for individuals in these groups based on personal medical history, but high schools and colleges mandating booster vaccinations for their students are simply not following outcomes data. My clinical experience has been that vaccinated and even boosted people are contracting Omicron. I am also for the first time seeing significant numbers of people getting the virus for a second time (even if vaccinated). The good news is that the outcomes are good for people with previous immunity.

Will a 4th "booster" be needed? At this point, I would not recommend the 4th booster for anyone except possibly severely immunocompromised. In the immunocompromised, a 4th dose may be helpful to try to "run out the clock" on a surge in circulating virus but unless we have a variant-specific booster for a much different variant it makes no sense for the general population. Training our immune system to respond to the same ancestral strain with the same mRNA formulation is not helpful when you have adaptive immunity of your own.

What about a "booster" for a vaccinated person after contracting the virus? I think this depends on the individual situation. In general, for people with no risk (especially < 40 yrs), in my opinion, a booster is not needed. For those with risk factors, including BMI > 30, diabetes, lung disease, heart disease, age > 65, or any immunocompromised status, I would say yes to a booster but wait for at least 8-12 weeks after the infection. This will provide the best immune response, similar to spacing out doses of the original vaccine series.

Based on antibody seroprevalence among blood donors, it is estimated that as of November 2021 94% of Americans had some protection against Covid-19, either through vaccination or prior infection. This is great news! The Delta and Omicron waves have also given a large number of people hybrid immunity. Based on my reading of the data, I believe that Covid-19 will be with us in some form for the long term, likely as a circulating, possibly seasonal flu-like illness based on the emergence of different variants. The durable, adaptable immunity we have acquired through vaccine and eventual infection will serve us well.

Vaccination before or after SARS-CoV-2 infection leads to robust humoral response and antibodies that effectively neutralize variants. *Sci Immunol*. 2022 Jan 25;eabn8014. doi: 10.1126/sciimmunol.abn8014. Online ahead of print.