Week in Review: 15 – 19 March 2021

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Moderna vaccine shows reduced activity against South Africa B.1.351, Brazil (P.1), and California (B.1.427/B.1.429) coronavirus variants. However, it remains highly active against U.K. B.1.1.7 variant.

As vaccination rates go up and hospitalizations go down, there is finally reason for optimism in ending the covid-19 pandemic. But variants of SARS-CoV-2 could substantially impede our progress. Scientists are rushing to study whether antibodies generated by the currently authorized vaccines offer as much protection against emerging variants as they have been shown to provide against the original or "wild type" virus.

There are several ways to study this question. Three ways to study this are:

1. Laboratory experiments of cells and viruses.
2. Animal studies
3. Real-world data

Today, the *New England Journal of Medicine* released a paper by researchers at Moderna and their collaborators at the US National Institutes of Health. In it, scientists report data using the first approach; they measured how well antibodies taken from humans previously vaccinated with Moderna's mRNA-1273 shot (the one being rolled out to the public now) attach to and neutralize viral particles engineered to resemble the new coronavirus variants.

Antibodies taken from patients who received the Moderna vaccine showed reduced ability to neutralize the coronavirus variants found in South Africa (B.1.351), Brazil (P.1), and in California (B.1.427/B.1.429). The good news is that the B.1.1.7 (UK variant) response was not affected. This is good because this variant has been shown to have a small but real increase in mortality. Of these, the South Africa variant evaded neutralization the most, with a decrease by more than a factor of 6. The reduction in neutralization against the Brazil and California variants was a factor of 2.3 and 3.5, respectively.

However, the neutralizations were still well above detectable levels. This means that it takes a higher quantity of vaccine-derived antibodies to get the same amount of neutralizing that occurs when the antibodies confront the "wild type" virus.

We don't yet know whether these new data will translate to any clinical impact among vaccinated persons. Many scientists believe that as long as antibody activity remains above a certain level, that the vaccines will still provide broad clinical protection against serious disease. The data today show that the Moderna vaccine is still well above that threshold. One possibility is that those who received the Moderna vaccine would still be protected against serious disease caused by the South Africa B.1.351 variant, but not against mild infection or the ability to spread the virus, especially to unvaccinated individuals.

Yesterday, we learned that the Oxford/AstraZeneca vaccine does not protect against mild or moderate infections with the B.1.351 South Africa variant, though we do not know about whether that product still protects against more serious illness. On the hopeful side, the Johnson & Johnson vaccine, constructed similarly to the Oxford/AstraZeneca option, has indeed been shown to offer powerful protection against serious illness from the South Africa variant.

In the meantime, we await real-world data on hospitalizations and other markers of serious covid-19 in areas where the new variants are dominant. That will tell us, more than anything, just how the increasingly vaccinated population at large is responding to these new versions of

SARS-CoV-2. Finally, scientists are likely to study what happens to non-human primates who are vaccinated and then exposed to a novel variant. So far, data on these experiments, assuming they exist, have not been made public. In an email to *Brief19,* Darin Edwards, the Director for Infectious Diseases at Moderna said, "I can't comment specifically on the non-clinical research efforts that we are performing in the variant space, but I will say we are trying to be as comprehensive as possible, as we were in the original evaluation of mRNA-1273."

Competing companies like Pfizer/BioNtech, Johnson & Johnson, and others are also likely to be addressing these concerns using a combination of the various approaches described above. If and when such data become available, they would add important about what we can expect in the coming weeks and months. Any findings could determine the character of the next phase of the covid-19 pandemic. *17 March 2021*. *—Jeremy Samuel Faust MD MS*

Covid-19 reinfection is rare, though older adults are more at risk.

Can recovered covid-19 patients become reinfected with coronavirus? If so, the pandemic could extend for years. A new paper released in *The Lancet* describes data from the first large-scale study measuring SARS-CoV-2 reinfections at the population level.

Researchers from Denmark assessed data from the Denmark Microbiology Database that included all patients who had a SARS-CoV-2 test between February 26 and December 30, 2020. Residents of Denmark were excluded if they tested positive (by PCR) for the first time between Denmark's two main surges or who died before the second surge; the first covid-19 surge was defined as the time from February 26 to June 1, 2020, and the second surge was defined as the time from September 1 to December 30, 2020. The primary outcome of the study was infection rates of residents during the *second* surge of the pandemic.

During the first surge, 2.2 percent of all people in Denmark tested positive for SARS-CoV-2. Of the 525,339 residents who were eligible for follow-up during the second surge, 0.65 percent of citizens who had covid-19 during the first surge re-tested positive during the second surge. Furthermore, 3.27 percent of those who tested negative during the first surge subsequently tested positive in the second surge.

Based on these data, the authors estimate that prior infection with SARS-CoV-2 provides an estimated 80.5 percent protection against repeat infection. That protection seemed to remain strong in patients who were followed for greater than 7 months. In a subgroup analyses, previous covid-19 illness conferred slightly less protection (47.1 percent) for patients 65 years of age and older. This is concerning given the high rates of serious illness and mortality among this demographic.

While this study is the largest to look at reinfection rates we have to date, the results may not be applicable to other parts of the world. First, trends and risk factors for the spread of coronavirus in Denmark may differ substantially compared to the United States and elsewhere. Second, there was not enough granularity in this study to determine risk factors for reinfection beyond basic demographic information, including race/ethnicity, location, socioeconomic status, and other factors like local case prevalence. And as with any observational study, it is impossible to account for individual behaviors of those who did and did not have repeat infections. It could be that the infection rate is far lower among those who have already had the virus, but it is also possible that those who had the virus are more likely to have behaviors that confer protection against contracting the virus for a second time. Alternatively, those with a prior infection may have specifically dropped their guard, and therefore were willing to expose themselves to *higher* risks than most. Another limitation is that we do not know whether reinfections commonly caused serious illness.

In sum, this is a large, population-based study that provides some preliminary evidence that the risk of reinfection is significantly lower among those who have already had covid-19. *18 March 2021*. *—Joshua Niforatos, MD, MTS*

Vaccination appears to be safe for covid-19 long-haulers.

SARS-CoV-2 vaccines have been heralded as the best path to achieving herd immunity and ending the covid-19 pandemic. However, the appearance of "long-haulers" or Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)—that is, patients with persistent symptoms following infection lasting weeks to months and affecting various body systems—has threatened to extend things. Many have wondered what impact the new coronavirus vaccines might have on PASC patients and their symptoms. A preprint released last week on *medRxiv* from scientists in the United Kingdom looked at this previously unresearched topic.

Previously hospitalized covid-19 patients being followed in clinics for eight months were enrolled into the present study. These individuals received the either the Pfizer/BioNtech or Oxford/AstraZeneca (AZ) vaccine and were matched against non-vaccinated controls at a rate of two to one. A reassessment was performed one month after vaccination; in all there were forty-four vaccinated patients and 22 non-vaccinated subjects included in the analysis. The rates of persistent symptoms were extremely high in both groups; fatigue was most common PASC symptom (82 percent of subjects), followed by fatigue (61 percent), breathlessness (50 percent) and insomnia (38 percent). Quality of life and mental well-being were also assessed.

Following vaccination almost two-thirds of patients reported typical short-lived post-vaccination complaints such as fever, body aches, and headaches. Some degree of improvement in PASC symptoms was documented in the vaccinated group as compared to unvaccinated controls; among vaccinated persons, 5.6 percent reported worsening symptoms versus 14.2 percent among unvaccinated controls. In addition, an increase in symptom resolution was observed among the vaccinated (23.2 percent) as compared to unvaccinated individuals (15.4 percent). When comparing the pre- and post-vaccination periods, no effect was noted with respect to worsening of mental well-being or quality life. Also, the brand of vaccine did not affect the results despite one of the studied vaccines being a mRNA (Pfizer) product, and the other being an adenovirus vector vaccine (AZ).

In sum, this was a small but interesting study demonstrates the need for studies with larger numbers of test subjects in order to confirm what is likely the safety of vaccination in patients with persistent post-infection systems, More than that, we await larger datasets that confirm or refute what in this study appeared to be the vaccines' beneficial effects to people suffering from long-standing post-acute covid-19 symptoms. *17 March 2021*.

—Christopher Sampson, MD, FACEP

Oxford/AstraZeneca fails to prevent mild to moderate covid-19 from B.1.351 ("South Africa") variant.

The rise of variants of SARS-CoV with alterations at the key spike protein, notably the "South Africa" variant (B.1.351), has posed potential challenges to the covid-19 vaccines. Many have expressed worry regarding the possibility of reduced efficacy of the currently available coronavirus vaccines, which were developed to combat the "wild type" virus that became pandemic one year ago. With numerous variants emerging since, scientists have begun to assess whether the game-changing vaccines being rolled out globally will still work against them.

In a randomized trial published in the *New England Journal of Medicine* today, researchers tested the Oxford/AstraZeneca viral vector vaccine in participants ages 18-65 years

old in South Africa. Participants either received two "standard dose" vaccines or saline injections as placebo 28 days apart.

Among those that received the vaccine, 2.5 percent were diagnosed with mild-to-moderate covid-19 compared with 3.2 percent among those who received the placebo. Nearly all (93 percent) of those diagnosed with covid-19 were infected with the B.1.351 SARS-CoV-2 variant. Overall vaccine efficacy was quite low (at 22 percent) and even lower amongst those with confirmed cases of the B.1.351 variant (at 10.4 percent).

Yes, the results of this trial are disappointing. We would like to see good efficacy of the vaccine in protecting people from any degree of covid-19, asymptomatic or otherwise. However, we suspect that some headlines reporting this study to the mainstream media will present the findings as more doomsday than is owed. The results from this trial do not necessarily imply the Oxford/AstraZeneca vaccine is "useless" against this variant. While it is possible that this vaccine has reduced efficacy against more serious or critical covid-19, we simply do not know that from these data; there were no cases of severe covid-19 in either the placebo or vaccine group in the present trial. In fact, as the recent larger Johnson & Johnson trial in South Africa showed (which included many patients infected with the B.1.351 variant), at least one adenovirus vector vaccine constructed similarly to the Oxford/AstraZeneca vaccine has been shown to have good efficacy against the B.1.351 variant in achieving the overarching goal of reducing the number of people who get severely or critically with covid-19.

In sum, we now have data to suggest that adenovirus vaccines may not protect against mild and moderate covid-19 (Oxford/AstraZeneca) and data to suggest that this type of vaccine may yet still protect against serious and critical illness (Johnson and Johnson). If these data were to hold up, the pandemic would indeed eventually end even in places that only have access to these adenovirus options. We need to remember that the short-term goal of getting out of this pandemic is not eliminating mild and moderate disease; those cases we can live with. The way out of the pandemic is by eliminating the high number of hospitalizations and deaths; the high prevalence of such widespread and severe disease we can't continue to abide. *17 March 2021*.

—Lauren Westafer, DO MPH

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