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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

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.

—Joshua Niforatos, MD, MTS

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

Yesterday, 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.

Tuesday, 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.

—Jeremy Samuel Faust MD MS

POLICY BRIEFING

FDA streamlines path for screening of asymptomatic individuals.

On Tuesday, March 16, the US Food and Drug Administration announced plans to streamline the path for coronavirus screening for asymptomatic individuals in non-medical settings and provided information to groups establishing testing programs. This news comes at the one-year mark of the public health emergency of this pandemic.

The FDA will allow some developers of the tests to market their products for regular at-home use, with the aim of making it easier to screen Americans returning to school and work as sectors of the economy reopen. FDA medical device director Jeff Shuren and diagnostics director Tim Stenzel said in a joint statement, "We believe this effort will pave the way for further expanding the availability of tests authorized for screening asymptomatic individuals, help bolster existing and new testing programs and increase consumer access to testing."

While some rapid coronavirus tests are somewhat less accurate in identifying infected but asymptomatic individuals (as compared to symptomatic persons), the FDA's new policy aim is that with repeated testing over time, there can be improved overall accuracy of results.

The FDA also issued a fact sheet for those interested in setting up screening programs, offering a "streamlined path to emergency use authorization for these important screening tools," according to Shuren and Stenzel's joint statement. Companies will now be able to apply for permission to market an over-the-counter test for at-home use or at the "point-of-care," in public settings if there is evidence that any particular test performs well in symptomatic individuals and if repeated testing can help to avoid false results. The emphasis on repeat testing is the crux of an argument about rapid tests covered previously in *Brief19*: testing *regimens* should be evaluated for their ability to rule out infection, not one-off tests.

The FDA sees this streamlined path for test developers as a way to support the serial testing strategy recommended by the US Centers for Disease Control and Prevention, which recommends serial testing at least once per week along with other mitigation measures such as masking and social distancing to reduce transmission of SARS-CoV-2.

However, even as the FDA is now facilitating this serial testing strategy, its fact sheet emphasizes that even serial testing "is of limited value if it is not combined with appropriate mitigations for individuals who test positive (such as quarantine, good contact tracing, and behavioral protocols."

—Miranda Yaver, PhD

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