

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Vaccinations could limit further mutations.

As more of the population is vaccinated, an increasing number of people have antibodies against SARS-CoV-2, either via infection or, more safely, via inoculation. Many experts have pointed to vaccination as a way to limit future evolution of the coronavirus into new and possibly more dangerous variants. The overall immune status of an entire population can in essence serve as an evolutionary selection pressure; but that assumes there is enough replication going on for mutations to be under positive selection—meaning that mutations don't just occur but that there are conditions that either favor or disfavor that new version of virus by virtue of some change in its structure and therefore its "behavior." This means that we might see a greater number or more effective so-called escape variants (i.e. variants that evade vaccines). That could happen if one or both of the following scenarios occur:

1. Widespread community transmission persists with slow vaccine uptake.
2. The vaccines don't provide any protection against infection and transmission continues unchecked after vaccination.

Currently, our trajectory is most akin to the first scenario. We need to get transmission under control as we ramp up immunization. The second scenario is far less likely, as several lines of evidence suggest that the existing vaccines in use protect at least partially against infection and thus transmission.

Mutation is a relatively constant process. It happens randomly whenever a virus replicates. Selection pressures themselves don't increase mutation or make the virus mutate differently. They simply refer to the conditions in which mutations occur. For example, if an animal has a mutant that makes its neck longer, that won't give it an advantage if it does not allow it to reach food in trees that other animals can't also reach. So there would be no selection pressure in that circumstance to "select" for the animal with the long neck mutation. But if there were higher branches with food that only long-necked animals could reach, then a selection pressure would exist, and other time, animals with that mutation would have an advantage and perhaps survive while other animals did not.

Similarly, positive selection is when a randomly acquired mutation changes a virus in a way that gives it an advantage based on the prevailing circumstances. In this case, evading the human immune system's weapons would be an advantage. But acquiring mutations is a numbers game, because it happens randomly. When it does happen, it has to be "meaningful" (i.e. there has to be a selection pressure) or else that mutation won't be favored or disfavored; it simply would not even be "noticed." The process is akin to buying lottery tickets. Buy one? Chances of winning are very low. Buy millions of tickets? Your chances go up. Depending on how many millions or billions you buy, your odds increase. Because transmission is so high right now, SARS-CoV-2 is, by analogy, out there buying unlimited Powerball tickets. Thus, as the population's immunity to some variants grows, a selective pressure that favors the occasional new variant amount to some jackpots for the virus. By doubling down on efforts to reduce transmission while simultaneously ramping up vaccination, we can cut the virus off from its supply of chances to win. Immunization is a major way out of the pandemic. It won't automatically select for vaccine-resistant variants, especially if we do everything we can to knock down transmission now. [17 February 2021](#).
—Angela Rasmussen, PhD

New hope for tocilizumab.

For months now, doctors have been operating with the knowledge that [dexamethasone](#), a frequently used steroid, has been the only true success story in the treatment of covid-19. That insight came from a large study conducted by the RECOVERY research group in the United Kingdom, which showed that dexamethasone decreased mortality for patients requiring oxygen. Now the RECOVERY group has released a new [preprint](#) of a study showing promising outcomes for the monoclonal antibody drug, tocilizumab (*TOE-see-liz-you-mab*). Monoclonal antibodies, or mAbs, are proteins that can be designed to target certain molecules, and in the case of tocilizumab it blocks an inflammatory cascade performed by the body's natural immune system (as opposed to the SARS-CoV-2-specific monoclonal antibodies that have been hyped to [mixed if not disappointing](#) results).

The data in this new study included over 4,000 hospitalized patients who had an oxygen levels of less than 92 percent, or were already required supplemental oxygen, as well as a positive test for a marker of inflammation known as c-reactive protein. The trial participants were then randomized to receive tocilizumab, or standard of care (which included a steroid like dexamethasone for 82 percent of patients).

The crux of the results is that when given tocilizumab, patients had decreased mortality and decreased progression to the need for mechanical ventilation in the following 28 days. The caveat is that the signal effectively disappeared for those patients who received tocilizumab but did not receive steroids. In other words, patients who received tocilizumab and steroids did better than those who received steroids alone (27 versus 33 percent mortality)—but when removing steroids from the comparison, the patients who got tocilizumab actually did *worse* (39 versus 35 percent mortality). However, since most patients get steroids anyway, the overall effect in the study favored the group receiving the monoclonal antibody.

Although previous studies of tocilizumab were [disappointing](#) (after initial enthusiasm from some [retrospective analyses](#), as we covered here in *Brief19*), the RECOVERY trial and another recent trial REMAP-CAP, seem to have found a particular population of covid-19 patients in whom tocilizumab appears to add a benefit on top of steroids alone.

Nevertheless, there are several issues with the RECOVERY trial. Notably, at the time of this analysis, not all patients had completed follow-up. In addition, not all patients who were randomized to receive tocilizumab actually received it. Regardless, enthusiasm for tocilizumab now on the rise again in the wake of this trial. That said, the currently limited supply of the drug and the expense of the medication signal a need for equitable distribution. [16 February 2021](#).
—Lauren Westafer, DO MPH

PTSD rates elevated in patients who survived covid-19.

For many people, surviving a life-threatening event may lead not only to long-term physical consequences, but significant psychological difficulties as well. Past research has found that among survivors of medical conditions including stroke and heart attacks, posttraumatic stress disorder (PTSD) symptoms were seen in almost one out of eight survivors of [heart attacks](#) and nearly one in four survivors of [stroke](#). Now we have emerging data for people who have survived covid-19.

Outlined in a new research letter in *JAMA Psychiatry*, researchers followed a group of 381 patients who were diagnosed with covid-19 between April and October 2020 at a hospital in Italy. The researchers found that over 30 percent of the participants met criteria for PTSD, and approximately another 17 percent were noted to have developed other mental health conditions including depression.

While this finding is certainly concerning for clinicians and patients alike, the authors' conclusions are tempered by several methodological issues. First, this was a study conducted at a single site, as opposed to multiple hospitals. In addition, the researchers used a cross sectional design, meaning that the post-covid-19 patients were not compared to a non-covid-19 control group and that the data captured a single snapshot of the patients, but not over time. Based on knowledge from past pandemics, it's likely that many recovered individuals would be expected to exhibit psychological symptoms in the wake of an acute event, but that a significant number will recover or have only [minimal](#) long-term effects. Furthermore, the participants in this study had a number of pre-existing individual factors such as a past history of mental health conditions that could also significantly influence the odds that PTSD would develop after infection.

Nevertheless, this study contributes to our understanding of the short and long-term mental health effects of the pandemic, and adds to information from [other studies](#) on the “long haul” effects. Future work looking at the longitudinal mental health of recovered patients may help us identify at-risk persons and develop targeted interventions that supports patients in their psychological recovery. [18 February 2021](#).

—Bernard Chang MD, PhD

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Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.