Week in Review: 20-24 July 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Two SARS-CoV-2 vaccine trials report progress in world's first Phase II data.

As the covid-19 pandemic unfolds and spirals out of control, a two-part strategy remains our only hope in limiting mortality. The first, so-called non-pharmacologic interventions, aim to slow down the spread of the virus. These efforts include physical distancing, mask wearing, and improved hygiene. Taken to extremes, such measures could eradicate the virus. But most countries have not shown the willingness or capability of achieving that with these strategies alone. Therefore, in essence, non-pharmacologic interventions have two purposes. The first is to flatten the curve so that hospital capacity is not a factor in our ability to save lives using finite resources such as mechanical ventilators. The second is to buy time for the other major strategy in getting out of this crisis with the fewest deaths: pharmacologic interventions. While therapeutic drugs play a role—for example, the steroid dexamethasone was recently shown to improve mortality among covid-19 patients requiring mechanical ventilation by 11 percent—it is unlikely that a medicine or even a cocktail of them will be sufficient. No, the great hope remains in a vaccine.

While hundreds of potential candidate vaccines have been identified by researchers all over the world, fewer than a dozen are registered in active clinical trials. Of these, just two have posted results from phase I trials which by definition only assessed a handful of subjects, and with no control arms. The two studies appearing yesterday in *The Lancet* both describe results from Phase II trials, one conducted in the United Kingdom and one in China. Both studies reported on findings that utilize a similar technology—genetic material is introduced to the body via a weakened common cold virus (called an adenovirus). The "Ad5" virus is specially encoded with the genetic code for an important "spike" protein of SARS-CoV-2. It infects human cells which in turn read the genetic instructions and produce the viral protein. While the virus is not capable of replicating, the eventual protein the cells are co-opted into making is recognized by the body's immune system, which responds to by creating antibodies and, crucially, T cells, which remember the shape of the protein for far longer and, hopefully, ward off future infections. Adenovirus vaccines were not approved for widespread use until recently.

Both of these new trials randomized subjects to receive either the candidate vaccine or a control. Both reported encouraging responses. Signs of vigorous immune responses were observed in each of the trials. In the UK study, a smaller subset of subjects received a booster shot, which also appears to have strengthened the response. It is encouraging that the measured magnitudes of the immune responses found in subjects in both trials was similar in both trials, comprising a kind of immediate replication of the findings found in each study.

While side effects like feeling feverish were very common in both studies (slightly less in the study from China, but both hovering around 50%), the use of the European equivalent of Tylenol/ acetaminophen (known as paracetamol) lowered symptoms substantially without a loss in immune response (feeling feverish dropped from 51 percent to 36 percent in the UK study).

Several hurdles remain. While these studies show the overall safety and potential effectiveness of these vaccines, the reality is that there is no guarantee that the responses detected in cells means that the vaccine recipients will be immune or less likely to either experience a serious future infection by SARS-CoV-2 or be less contagious. That information will only be gleaned from Phase III trials, which are already underway. However, if bothersome side effects, non-serious though they may be, are as frequent as described in these studies, getting people to sign up to receive the vaccine may be another barrier to ending this pandemic. *21 July 2020. –Jeremy S. Faust, MD MS*

Another major trial finds hydroxychloroquine offers no covid-19-relatd benefit. A new randomized controlled clinical trial comparing hydroxychloroquine (HCQ) to control has been published in *The New England Journal of Medicine*. No benefit was found. In the study from Brazil, covid-19 patients with mild or moderate disease (either not requiring oxygen, or less than 4 liters per

minute) were randomized to one of three groups: 1. HCQ alone; 2. HCQ with azithromycin (an antibiotic) and; 3. No addition to the standard covid-19 treatments ("usual care"). The "primary" outcome was clinical status 15 days after entering the trial. To assess this, the investigators used a 7-point scale based on early guidance provided by the World Health Organization when this SARS-CoV-2. No significant changes in score were found. There were also no differences in "secondary" outcomes, including an analysis at 7 days, monitoring for blood clots, number of days alive and free from the need for breathing support (meaning no need for any extra oxygen, including by nose, face mask, high flow oxygen, or mechanical ventilation) up to day 15. HCQ was seen to increase the QT or QTc interval, which can predispose to life-threatening cardiac rhythms. This trial comes in the context of two recent important clinical trials assessing HCQ. One American study assessed whether persons with substantial exposure to patients with covid-19 could be prevented from becoming infected by taking HCQ as prophylaxis. It did not work. Another, out of the United Kingdom found no benefit in hospitalized patients. In the United States, HCQ prescriptions skyrocketed this Spring after President Trump and Elon Musk touted its benefit, without any quality evidence supporting the claims. *Abbreviated from Brief19 for 24 July 2020.* *–Jeremy S. Faust, MD MS*

Antibody levels fall after SARS-CoV-2 infection. What does that mean?

One of the important questions in covid-19 is whether we become immune after an infection. If so, for how long? A correspondence in the *New England Journal of Medicine* reports on the concentration of antibodies against SARS-CoV-2 over time in 34 subjects who recovered from mild covid-19. All participants had their antibody levels measured twice; once around a month after symptom onset and the second nearly 3 months after. Rather than just testing for the presence or absence of antibodies, the researchers quantified the amount of anti-SARS-CoV-2 antibody (Immunoglobulin G, or IgG) in each participant. After statistical modeling, they concluded that the concentration of antibodies quickly declined by approximately 50 percent in just over a month (36 days). At the individual level, there was variability. In fact, it appears 7 patients had at least some *increase* over time. A small number of participants had minimal decreases, and others had rapid declines.

Before we panic about lack of immunity, it is crucial to consider that the human immune response is much more complicated than the concentration of antibodies against a virus. First, it is not uncommon for antibodies to peak, decline, and then stabilize at lower levels. As a novel virus, we don't know what quantity of antibody provides protection. Additionally, while antibodies are produced by B cells, another line of cells, T cells, can identify and kill viruses and infected cells. This form of immunity was not evaluated here, but hopefully future research can determine if and how immunity to SARS-CoV-2 is generated by humans. *24 July 2020.* *–Lauren Westafer, DO, MPH*

Joshua Niforatos, MD Research Section Editor.
Kane Elfman PhD, Publishing and design. *Anna Fang, Week in Review.*
Jeremy Samuel Faust MD MS, Editor-in-Chief.

http://www.brief19.com/ *Twitter: @brief_19* *submissions@brief19.com*

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.