Week in Review: 23 – 27 November 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Trial of convalescent plasma for covid-19 falls flat, another setback for hyped treatment,

Is convalescent plasma the miracle treatment we were promised? The answer in the latest published clinical trial appears to be no. This is more worrisome news for a proposed treatment that has been bandied about and for which the US Food and Drug Administration granted emergency use authorization, despite the absence of compelling trial data to support its use (for more, see our prior coverage in March and August).

Released on November 24 in *The New England Journal of Medicine* is a multicenter randomized, double-blind, placebo-controlled clinical trial (RCT) of 228 patients hospitalized with severe covid-19 who received either standard-of-care and convalescent plasma therapy or standard-of-care plus placebo. The primary outcome the researchers tracked was "clinical status" during follow-up at day 30.

The average age of participants was 62 years, and the majority were identified as male. Over one-fourth of patients were in intensive care units. Importantly, 93 percent of patients were on steroids, such as dexamethasone—meaning that they were already receiving the one treatment that has been shown to improve mortality rates in covid-19 patients with severe illness.

Interestingly, 68.6 percent and 61.8 percent of patients given placebo and convalescent plasma, respectively, were discharged home in good condition, though that difference was not statistically significant. Unfortunately, by day 30 there were no significant differences noted between the convalescent plasma group and the placebo group with regard to clinical outcomes or mortality. Adverse events were similar in both groups. Previous retrospective studies have found that convalescent plasma can cause serious harms, despite the general talking point that "plasma is safe." But in a trial with just 228 patients, it is unlikely that many adverse events would occur.

The idea behind convalescent plasma makes sense: when fighting an infection, our bodies manufacture specific antibodies in bulk to combat an invading pathogen. After the infection, the body maintains a stock of "memory cells," meaning that in the event of a future infection by the same virus, bacteria, or other infectious disease, our response can be both rapid and specific. Some antiviral antibodies circulate in the blood, almost like molecular surveillance drones. If an infection re-appears those antibodies spring into action.

By mid-August it was announced that over 60,000 people had already received convalescent plasma therapy for covid-19, despite any high quality evidence of its ability to improve morbidity or mortality. Since that time, likely tens of thousands of additional patients have been given this medical therapy, largely owing to the FDA's emergency use authorization. This new study adds to a growing list of randomized trials that have failed to show a benefit for this treatment. So far, only retrospective studies have been "positive." When retrospective studies and randomized trials conflict, the trials should be seen as more definitive.

More trials are ongoing. While that is good, it is important to remember that if enough trials are conducted, one or two may find a marginal benefit, just as a result of statistical chance. Any positive findings would have to be weighed against the totality of the other existing evidence. At this time, we continue to believe that most patients should not be receiving convalescent plasma therapy outside of formal clinical trials. *24 November 2020.* *—Joshua Niforatos, MD, MTS*

US pediatric testing results for covid-19: The kids are…just ok. And not immune.

The number of children in the United States diagnosed with SARS-CoV-2 recently reached a grim milestone: 1 million. Most of the information we know about the infection rates in children come from local and regional data. US-level data has been difficult to find.

Now, a group of researchers from the Children's Hospital of Philadelphia have provided a high-quality assessment of infections and testing among children around the country in a new study in *JAMA Pediatrics*. Seven large children's hospitals—Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Children's Hospital of Colorado, Nationwide Children's Hospital, Nemours Children's Health System, Seattle Children's Hospital and St. Louis Children's Hospital—compiled data to gain insight.

First, they determined how many tests have been performed and tracked the number of positive tests. From there, they wanted to determine whether the presence of a complicated medical history had any association with the likelihood of developing covid-19. In short, do children with preexisting conditions get sick, hospitalized, or die? Lastly, they looked for rare but potentially dangerous cases of Multisystem Inflammatory Syndrome in Children (MIS-C) an inflammatory disease some children can develop.

A total of 135,794 "children" ages 0 to 25 (yes, people see pediatricians into their 20s) were tested. Of those tested, 4 percent (5,374 cases) tested positive. Though over half of the tests were done on White children (59 percent), the highest number of positive cases were in Black, Hispanic, and Asian children. This should surprise no one. It's an example of social determinants of health at work—the notion that your ZIP code is every bit as important as your genetic code, if not more so. This racial disparity in both testing and positivity is striking and mirrors findings in adult populations.

Unsurprisingly, children and young adults with chronic or underlying medical conditions were found to be more likely to get sick. Also, the older the patient, the more likely they were to be worse. That said, only 7 percent of the 5,374 children who tested positive had severe illness—meaning they required services such as hospitalization, respiratory support, and or admission to an intensive care unit. The death rate was 0.15 percent, or 8 of those 5,374 known to have the disease. While that is low, there are very few viral infections that cause death in one out of 672 people in this age range. It is likely that many milder cases go diagnosed in the communities where the data are from. So while scary, the real mortality rate may be better.

As for evaluating the rare and elusive MIS-C, this study found that rates of Kawasaki's disease (thought to be similar to MIS-C) were actually *lower* in 2020, according to hospital billing codes from January 1st to September 8th. The reason for this is unclear. One possibility is under-diagnosis; not all clinicians know how to document MIS-C, and not all hospital computer systems have well-defined codes for this new disease variant. An alternative explanation is that the lower rates of these inflammatory condition might be a result of increased physical distancing; some infections that lead to these conditions in children may have decreased this year. For example, Australia and New Zealand had *extremely* mild flu seasons this year, as they also controlled covid-19 impressively.

In sum, this study provides new insight on how frequently covid-19 infects, affects, and kills children. In short, no, they are *not* immune. However, they are less likely than adults to develop serious illness. Much remains unknown. Because of this, we should continue to evaluate children for infection, include them in vaccine trials, and address the disparities that are endemic to the way healthcare in America is delivered. *23 November 2020*. *—Joanna Parga-Belinkie, MD*