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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

A new report suggests why convalescent plasma may harm some people, and possibly lead to new variants.

If there were ever a treatment that *should* work in treating covid-19, it is convalescent plasma. The idea is so tantalizing. A person who has recovered from covid-19 donates blood, and the antibodies that they generated while fighting the disease are transfused into another person now in the throes of their own illness.

As *Brief19* readers are well aware theory and reality have not meshed when it comes to convalescent plasma. At least not for the most part. The results from a series of [disappointing trials](#) did not stop the Trump administration from granting Emergency Use Authorization for the treatment in August, calling it a breakthrough (I called it [a low point for science](#)). The US Food and Drug Administration [amended that policy](#) late last week, limiting the EUA to those early in the disease course, and requiring that the plasma be “high titer,” meaning that the blood products are screened to assure that a high enough quantity of antibodies are in the transfusions. This more closely aligns with findings in the one positive [clinical trial](#) (among several negative ones) that showed a modest benefit for the treatment, limited to these parameters in older patients.

A new report in the journal *Nature* now suggests [a rationale](#) for why giving convalescent plasma to some patients could harm them and the community at large. The concept is simple: evolution.

This new report describes the case of a patient with a compromised immune system who was infected with SARS-CoV-2. As is the case with some immune-compromised persons, the patient had a protracted course of covid-19. Investigators tracked the case rigorously. They performed careful genetic analyses on the patient’s virus many times over. They did so after the patient received courses of remdesivir and after receiving plasma. What they found was striking. After plasma was given, many more mutant variants of the virus emerged. It’s as if the plasma knocked out one variant, making room for a tiny minority of mutant strains that had popped up over time to gain an edge and take over. By the time the patient died, there were several new variants that had in effect survived a type of natural selection process, akin to Darwinism. The variants survived because they were “fit” to evade the antibodies that doctors had introduced to the patient via convalescent plasma. Some of these new variants were more infectious than others. Some were “duds,” meaning they actually might be *less* infectious to other people, were the patient to have spread those viral particles near others. But the overall point is clear: giving plasma to some patients might turbo-charge the evolutionary process in unpredictable ways.

One case report, extraordinarily detailed though it is, does not count as definitive literature. But what I think is important about this particular paper is that it provides an important cognitive framework. Many physicians have made the mistake of thinking that unproven treatments like convalescent plasma are safe to give, and should be given even if they are not proven to work because, the thinking goes, “what’s the harm?” The answer is that physicians have a long and well-documented history of hyping the benefits of treatments and downplaying the risks and side effects. When something has not been studied sufficiently, it’s possible that “unknown unknowns” will crop up. This latest insight on convalescent plasma could turn out to be a dangerous example of a previously “unknown unknown” becoming a “known problem.” More research will be necessary to make any definitive statements on this, but we’ll be watching.

—Jeremy Samuel Faust, MD MS

POLICY BRIEFING

United States CDC recommends double masking.

Across many parts of the country, life in masks has become the norm for the better part of the past year. Now, the United States Centers for Disease Control and Prevention (CDC) is offering [new guidance](#). Yesterday the agency recommended that Americans wear tighter fitting mask—or even two masks—in order to slow the spread of covid-19. The guidance came with a study that demonstrated that improved masking can reduce exposure to potentially infectious aerosols (this was a study done in a simulated environment using mannequin-like constructs, known as “headforms.”)

The particular instructions specify that masks should fit tightly over the nose, mouth, and chin with a wire at the top to prevent air from leaking out along the top; the masks should contain at least two layers. If one only has access to loose-fitting surgical masks, the alternative of placing a tightly fitting cloth mask over the surgical one is suggested. The general idea is to reduce the ability of particles to escape around the edges of the mask. The new guidance goes so far as to recommend modifying medical procedure masks by knotting the ear loops and tucking in any extra material (see the link above for images). Indeed, in the aforementioned experiment, when both the source and receiver “headforms” wore masks modified to fit more tightly, the receiver’s exposure to projected particles (simulating a cough) were reduced by more than 95 percent as compared to no masks at all.

“The bottom line is this: masks work and they work best when they have a good fit and are worn correctly,” said CDC Director Dr. Rochelle Walensky in a White House briefing on Wednesday. John T. Brooks, chief medical officer for the CDC’s covid-19 response, added that with the circulation of three new variants, “whatever we can do to improve the fit of a mask to make it work better, the faster we can end this pandemic.”

As the death toll in the United States approaches 500,000 and as the nation rushes to vaccinate a larger swath of the population, the updated guidance emphasizes mask-wearing as one of the best defenses against more transmissible variants of the SARS-CoV-2 virus.

—*Miranda Yaver, PhD*

CDC says vaccinations mean quarantine not necessary for all, with caveats galore and incomplete evidence to back it up.

The United States Centers for Disease Control and Prevention has issued new guidance stating that the people who are fully vaccinated and are within 3 months of the last dose need not quarantine if they have had exposure to a person with suspected or confirmed covid-19, provided they have been asymptomatic since the exposure. The policy applies to both vaccines currently in use in the United States, as well as those authorized elsewhere (including one-dose regimens).

Evidence to support this is a bit lacking, as we do not know whether vaccinated people can acquire asymptomatic infection and transmit it to others who in turn could become gravely ill. However, there is mounting evidence that at least some spread will be inhibited by the vaccines, as we have covered in [Brief19](#), although the extent and timing of this vaccine benefit remains unknown.

To that end, the CDC guidance acknowledges that the evidence behind this policy is not ironclad. They overtly state that what is behind this policy is the notion that there are “societal benefits of avoiding unnecessary quarantine [which] may outweigh the potential but unknown risk of transmission, and facilitate the direction of public health resources to persons at highest

risk for transmitting SARS-CoV-2 to others.” In addition to that, the guidance slips in a fairly controversial statement regarding contagion, saying that “symptomatic and pre-symptomatic transmission is thought to have a greater role in transmission than purely asymptomatic transmission.” While this may be true, it’s unclear how a person would *know* that they are presymptomatic as opposed to merely asymptomatic. In sum, the policy seems to be suggesting that this approach could lead to some spread, but that taking this approach might on balance draw attention and resources to people most likely to spread the virus.

—*Jeremy Samuel Faust MD MS*

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