Week in Review: 1 – 5 February 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Johnson & Johnson Janssen covid-19 vaccine 85% effective by Day 28 and 100 percent effective by Day 49.

Last week, headlines and stories circulated about the Johnson & Johnson (J&J)/Janssen vaccine based on a press release containing data from an interim analysis of their phase 3 clinical trial. The data made public at that time indicate that another weapon against SARS-CoV-2 could soon become available in the United States. This would be particularly helpful because in the effort to vaccinate more people, as the J&J vaccine does not require a second booster a.

The data released come from the ongoing ENSEMBLE Trial, a randomized, double-blind, placebo-controlled phase 3 study (i.e. meaning that thousands of patients are being enrolled) that assesses the safety and efficacy of vaccine. Unlike the Pfizer/BioNtech and Moderna vaccines, which rely on mRNA technology, the J&J vaccine is a so-called recombinant vector, meaning it uses a modified human adenovirus as a delivery mechanism for the genetic code for the spike protein of SARS-CoV-2.

Importantly, the J&J vaccine is a *single dose* vaccine as compared to the two currently authorized mRNA vaccines, which require 2 doses of the vaccine three to four weeks apart. Additionally, J&J reports that the "single-dose vaccine candidate is estimated to remain stable for two years at -20°C (-4°F), at least three months of which can be at temperatures of 2-8°C (36°F–46°F)," meaning that unlike the current options, refrigeration will suffice for the last few legs of the journey that any particular lot of the vaccine makes,

The results are impressive. The ENSEMBLE trial enrolled over 43,000 participants ages 18 years and older across three geographic regions, the United States, Latin America, and South Africa. Approximately 1 percent of patients enrolled in the study developed covid-19. The J&J single dose vaccine was 66 percent effective at preventing moderate *and* severe Covid-19 by day 28 after vaccination among all participants from the above-mentioned regions, including those regions with an emerging viral variant. Protection against SARS-CoV-2 was greatest in the United States (72 percent) and worst in South Africa (57 percent) where potentially more infectious variants have been reported recently. These results are likely to be further confounded by participant exposure to emerging viral variants; nearly 95 percent of all participants who developed covid-19 in South Africa were found to have been infected with SARS-CoV-2 from the B.1.351 lineage. That particular lineage has been found to resist at least to some degree antibodies generated by previous infections and other vaccines, as covered in *Brief19*.

However, with respect to the prevention of *severe* disease, the J&J vaccine was 85 percent effective across all regions by post-vaccination day 28. But most interestingly, J&J announced that there were *no cases* of severe covid-19 among participants after post-vaccination day 49. Does this mean the J&J vaccine is 100 percent effective at preventing severe covid-19 by day 49? We will only know that once the full data are released—but it is possible, based on these preliminary reports. In addition, no participants who received the J&J vaccine were either hospitalized for covid-19 nor died 28 days post-vaccination. This implies that one shot and one month of waiting could eliminate the most feared complications of SARS-CoV-2 infection, assuming that new variants do not render these findings obsolete.

Serious adverse events (i.e. side effects) were reportedly rare, with more participants in the placebo group reporting adverse events compared to those who received J&J vaccine. This implies that some of the adverse events reported by patients in the placebo arm may in fact be related to subsequently developing covid-19 itself, rather than as a result of anything in the vaccine or placebo shots themselves. The rates of fever were 9 precent, with Grade 3 fevers (greater than 39°C or 102.1°F) occurring just 0.2 percent of the time.

In light of this release, J&J announced it will file for Emergency Use Authorization in the U.S. in early February with plans to have the vaccine immediately available to ship when authorization is provided. Although these results were announced by press release, so far results from the large vaccine trials have had such impressive results, that even "science by press release" have ended up being borne out by the actual data when subsequently released. We hope the same is true for this vaccine. *2 February 2021*. *—Joshua Niforatos, MD, MTS*

Is one dose of the vaccine enough for people with evidence of prior coronavirus infection? New impressive data sheds light.

Around 8 hours after receiving my first dose of the coronavirus vaccine, I began to have mild body aches, in addition to the arm pain I'd been having all day. The arm pain had been expected, though as the hours passed the severity increased to the point where any lifting and ranging of the rotator cuff of my shoulder caused a substantial

amount of discomfort. Then the body aches, headache, and fatigue set in. By the late evening, I was shivering in a hoodie. Trying to smile my way through, I coined a term for what I was experiencing: manaphylaxis. Of the dozens of my colleagues who had already received their first dose and with whom I had spoken (or seen their reports on social media), I was the only one I knew of who had such a strong reaction.

I began seriously wondering whether my unusually strong reaction might be an indication that at some point in the last year I had, unbeknownst to me, contracted SARS-CoV-2 and that these side effects were an indication of that. Perhaps my body "recognized" the spike protein that my cells had just been co-opted into producing and rallied the antibody troops that my immune system had generated at some point in the past. As an aside, I will mention that in mid-to-late February, I was briefly ill, experiencing a fever and extreme fatigue for two days, but no other symptoms. Since uncontrolled spread became apparent, I've had nary a sniffle (turns out masks and our new enhanced hygiene regimens warded off the usual common colds that come and go).

A new paper on *medRxiv.com*, a preprint server where non-peer reviewed manuscripts are posted, makes me think that I really *might* have been infected with SARS-CoV-2 this year. That's because researchers in New York City tested vaccine recipients before receiving their first dose of a coronavirus vaccine in order to detect and quantify the presence of SARS-CoV-2 antibodies. They then tested all participants for antibody levels around every four days or so, to see how the antibody levels changed over time. Persons found to already have had antibodies before the first dose of either a Pfizer/BioNtech or Moderna vaccination mounted an impressive response within a 5-8 days. It took 9-12 days for those without evidence of prior infection ("seronegative") to have any response at all, and when they did, their levels ("titers") were noticeably lower than those who had previously been infected ("seropositive"). As of day 24, not a single person in the seronegative group had levels as high any any single person in the seropositive group. After the second dose, the levels did not change much; both group's levels rose some, but not a lot, albeit it is unclear how long after the 2nd dose these levels were checked. These data alone suggest that at least in the short term, for people who have evidence of a prior infection, a first dose of the vaccine may effectively be functioning as a booster, meaning a 2nd dose may not be needed for quite some time. In order to conclude this safely, we would need to see durability of these findings, which this paper does not present.

To my original question, the researchers noticed that seropositive vaccine recipients were far more likely to experience the "systemic symptoms" I had felt after my first (and second) injections. While a majority of people had some kind of pain near the injection site, regardless of evidence of prior infection, fatigue and headache were both around twice as common after the first dose in seropositive people. Chills and muscle pain showed even more pronounced differences, occurring around 5 to 6 times more often among seropositive people than seronegative. I'm beginning to think I really did have coronavirus this year. I'm going to try to get an antibody test that would not detect the vaccine-induced antibody and I'll report back. That said, when it is your turn to get vaccinated, it's safe to use products like Tylenol and Advil to manage symptoms, but don't take them *before* you have symptoms, as this theoretically could have a small impact on the vaccine's effectiveness. *5 February 2021.*

—Jeremy Samuel Faust, MD MS

Who got the vaccine? Demographic data released by CDC. Prepare to be *not* shocked.

The US Centers for Disease Control and Prevention released a detailed look at the demographics of those who have received coronavirus vaccinations in the first month of widespread rollouts across the United States. Data was obtained from information reported to the CDC by vaccinators around the country and the findings were published in *Morbidity and Mortality Weekly Report* (*MMWR*), the agency's medical journal.

The report covers just under the first 13 million people to receive at least 1 dose of the Pfizer/BioNtech or Moderna covid-19 vaccine, representing just 4 percent of the total US population and 5 percent of the US population 16 years of age or older. Most of the vaccinations have been in persons in the "Phase 1a group," as defined by the CDC's Advisory Committee on Immunization Practices (ACIP). ACIP has recommended priority to healthcare workers and long-term care facility staff and residents.

Thus far, more women (63 percent) have received the vaccine than men. The most vaccinated age group was 50 years and older (55 percent) followed next by those 18-39 years (28 percent). Information on race and ethnicity was known in a little over half of the recipients. A majority of those in whom the race or ethnicity was known have been White, at 60 percent of all recipient. While the White demographic makes up 76 percent of the US population overall, that is not necessarily the breakdown of the regions where vaccine rollout has occurred in the highest numbers. For example, in some regions, disparities have been noted, including in New York City, where just 25 percent of the people vaccinated so far have been Black or Latino, despite the fact that together, these two groups make up around 53 percent of the local population.

The Phase 1a group, which the published data reflect, is estimated to cover around 24 million people. But it is unlikely that 50 percent of the Phase 1a group actually received their first jabs. That's because some places, like

Florida and Texas, expanded vaccination to all persons 65 years of age or older, meaning that some people in lower priority groups have been vaccinated ahead of those in higher priority groups.

Regional data reporting under representation of vaccine recipients who are minorities in this first round of vaccination is concerning. While some of the low numbers could be due to a lack of complete data (the race or ethnicity were known in only around 52 percent of those vaccinated so far). Moving forward, the focus of vaccination rollout organizers should be to monitor these data, making sure to track emerging inequalities and to determine to the extent possible the reason for any such finding. Whether lower rates of vaccination are due to lack of access, outreach, or hesitancy will be important to measure so that the necessary policy adjustments are made. *3 February 2021*. *—Christopher Sampson, MD, FACEP*

Mix-and-match dosing regimens could ward off coronavirus variants.

Russian researchers released Phase 3 data from the Sputnik V vaccine trial (as per above), indicating an efficacy of 91.6 percent. Although this vaccine will not be available in the United States, these data underscore the importance of having more vaccines globally and the value of what scientists call "heterologous dosing regimens." A heterologous prime-boost is a "mix and match" vaccine dosing schedule, in which the immune response is primed with a first shot of one type of vaccine and then boosted with a different vaccine. In this case, researchers used two different vaccines based on adenoviruses.

Both the AstraZeneca/Oxford and Sputnik V vaccines use adenoviruses (which are a family of DNA viruses that cause common colds) as "vectors." Once injected, these vectors deliver the genetic code for the SARS-CoV-2 spike protein into our cells which then make that protein, eventually triggering an immune response. There are many different adenoviruses, and they can be engineered to safely deliver genes to a recipient via injection. However, it is important to understand that adenoviruses are *themselves* viruses. So, the immune system will also mount a response to the virus itself, not just the eventual spike protein it codes. Something called vector immunity can develop, meaning that the body creates a defense not just against the SARS-CoV-2 spike protein that has been engineered into the virus, but the rest of the virus itself. In effect, the virus is a trojan horse delivering the code for the SARS-CoV-2 spike protein, and the body's immune system does not let the trojan horse in a second time. This means that subsequent boosters that use the very same adenovirus vector to carry the SARS-CoV-2 spike might be blocked, thereby preventing the second round of spike protein production that is meant to trigger the body to make antibodies. This could also explain why the full two-dose regimen of the AstraZeneca/Oxford vaccine (also an Adenovirus-vector vaccine) performed less well than regimens in which a half-dose was given the first time.

The Sputnik V vaccine uses two different adenovirus-vector vaccines: Ad26 and Ad5. Any antibodies that develop against the prime Ad26 vector will not subsequently block a booster that is riding on an Ad5 adenovirus. This is notable because the Johnson & Johnson vaccine—which could soon receive an Emergency Use Authorization from the US Food and Drug Administration in the coming weeks—is an Ad26-based vaccine. Its efficacy might be improved with a boost. While a two-dose regimen is still in trials, we very well might anticipate potential issues with vector immunity.

As vaccine manufacturers have announced plans to develop boosters for the variants, we should begin to look at "mix-and-match" boosting strategies that use a combination of vaccine platforms. For example, it may be possible to mix the active components of the Pfizer or Moderna vaccines with a boost that uses another vaccine platform. Such an approach may also improve the side effect profile. This would also help with some logistical issues, as individuals may be able to get a boost from any number of options, allowing them to receive any appropriate vaccine that is available to them. Currently, these data for heterologous "mix-and-match" dosing across platforms and manufacturers are not available, but they have important implications for adapting to new emerging coronavirus variants, and for flexible and equitable vaccine access. *4 February 2021*. *—Angela Rasmussen, PhD*

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