Week in Review: 12– 16 April 2021

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Past covid-19 infection does not fully protect against future infection; vaccines required.

Early in the pandemic, it seemed that reinfection with SARS-CoV-2 was unlikely. Then, case reports and anecdotal evidence started to indicate that this was not entirely the case. Now, a recent study out of Denmark, published in *The Lancet* suggests that fears of reinfection are not entirely unfounded.

Denmark presented a unique opportunity to obtain this kind of robust data, as an impressive 69 percent of its population has been tested for covid-19 at some point during the pandemic, many of whom were tested more than once. With this in mind, the authors of this new study wanted to know if a prior SARS-CoV-2 infection provided some ample immunity to preent reinfection.

The researchers compared individual reinfections between the first wave of the pandemic (March to May of 2020) and the second wave (September to December of 2020). Of the more than 11,000 people who tested positive during the first round, 72 individuals tested positive again. This means that 0.65 percent—or one out of around 153 people—was reinfected. When factored into infection rates later in the pandemic, this also implies that initial infection is about 80 percent effective at preventing reinfection, a rate which is notably worse than the protection afforded by both the Pfizer/BioNTech and Moderna vaccines.

But more worrisome were the data gleaned from individuals 65 years and older. Among that group, the data suggest just 47 percent protection against reinfection. Rates were similar between genders and there was no significant waning immunity after 7 months.

This study had some limitations, though. The study did not correlate symptoms with the risk of reinfection, so it's unclear if the infected individuals had mild, moderate or severe covid-19, which of course vastly changes the implication of a repeat infection. Additionally, there were no data regarding protection from the various covid-19 variants of concern.

Nevertheless, a national dataset that captured a significant proportion of the general population provides important information. Ultimately, it's clear that recovery from a SARS-CoV-2 infection affords some degree of immunity to the virus, but clearly not universally. The data certainly imply that protection from a prior infection is likely to be no better or inferior to that obtained by vaccination. In particular, older individuals with more vulnerable immune systems should not count on a prior infection to protect them going forward. We expect that more data will come out of other countries in the near future, and we hope that the people around globe will continue to get vaccinated, regardless of whether they previously had SARS-Cov-2. *16 April 2021*.

—Joshua Niforatos, MD MTS

Inhaled steroids may prevent disease progression in mild covid-19.

An important randomized clinical trial (RCT) recently published in *The Lancet* assessed the role of inhaled steroids in the treatment of covid-19. Of all of the proposed treatments for covid-19, inhaled steroids have been seen as among the most likely to be successful, since dexamethasone, another steroid taken by mouth of intravenously, was the first treatment to demonstrate improvement in mortality in patients with moderate to severe covid-19. Given that covid-19 pneumonia is a respiratory tract infection, researchers assessed whether inhaled steroids would have a net positive effect. The upshot is that the inhaled steroid that was studied, called budesonide, appears to have had a favorable effect in treating mild covid-19. But the reality is that this trial had some important methodologic issues that make this declaration a somewhat less definitive than we had hoped. So, while this is a moment for optimism—indeed positive randomized trials of old medications being

repurposed have been few-and-far-between, it's crucial that we understand the design and limitations of this particular trial.

In this study, 146 patients were randomized to receive either inhaled budesonide (a steroid medication) or no inhaled budesonide. Subjects were included if they sought medical attention within 7 days of the onset of mild covid-19 symptoms. Mild covid-19 symptoms were defined as new onset cough and fever, loss of smell, or both, without the need for supplemental oxygen. The primary outcome of the study was defined as subsequent covid-19-related urgent care visits, emergency departments visits, or hospitalizations.

Before we get to the results, a little digression on research methods is necessary. The authors shared the results of two distinct analyses: the per-protocol analysis and the intention-to-treat (ITT) analysis. Per-protocol analysis means that only data from the patients who actually completed the treatment as intended are considered. Conversely, ITT data includes *all* patients who were randomized to receive the treatment, regardless of whether or not they actually received or finished it. Per-protocol analyses are considered ideal for studying adverse events of medications. But when per-protocol data are used to assess whether a treatment "worked," potential biases can be introduced that muddy the picture. For example, a test subject who did not finish the treatment that they were assigned to receive is often not a random event. Meanwhile, ITT is considered the more ideal analysis for assessing the effectiveness of a treatment. That may seem strange; why include data from patients who may did not actually get the treatment in the treatment group? The reason is that doing it this way reduces bias. By keeping the patients in the groups that they were initially assigned to be in, the investigators maintain the comparability between groups that was achieved through the process by which the subjects were randomized to receive either the steroid, or not. In this study, the authors presented *both* analyses.

In the intention-to-treat analysis, 3 percent of participants randomized to receive budesonide needed further medical care compared to 15 percent of patients in the non-budesonide group; the difference was statistically significant. In the per-protocol analysis, however, inhaled budesonide failed to decrease the further need for medical care. Based on these data, the authors determined that the number of patients who would need to be treated in order for one patient to not need further medical care was 8. In medical trials, this is actually quite impressive.

Other ("secondary") outcomes in this study were maintained mostly through surveying the patients enrolled in the trial. Overall, patients in the inhaled budesonide group recovered on average one day faster, had fewer days with fevers, and were less likely to have symptoms at days 14 and 28 as compared to no inhaled budesonide group. Overall, only 7 percent of the study participants reported self-limited adverse events, suggesting that inhaled budesonide is safe.

As with all trials, there are some imperfections to acknowledge. In this case, the most important of these is that the primary outcome did not directly assess mortality but instead assessed needed for "further medical care." Another limitation of this study is that the patients enrolled were overall fairly healthy in comparison to the general population, which may limit generalizability of these results. It's possible the sicker patients—the very ones we are most interested in helping—may have smaller or larger benefits from budesonide.

Nevertheless, the lack of need for further medical care can be considered a surrogate for disease progression, and it appears that inhaled budesonide may prevent progression of covid-19 severity in otherwise fairly healthy patients presenting within the first seven days of mild illness.

13 April 2021. *—Joshua Niforatos, MD, MTS*

AstraZeneca/Oxford vaccine link to dangerous blood clotting disorder looks real and rare. Should it be avoided? Maybe in young adults in some circumstances.

The AstraZeneca/Oxford vaccine appears to be causing a rare immune reaction that can cause dangerous blood clots. The upshot is that despite this, for *most* adults in most situations, the AstraZeneca/Oxford vaccine remains far safer than risking a covid-19 illness. But a deep dive is in order, as this is the first time that *any* complexity surrounding vaccine choice has genuinely come up.

First, it's worth pointing out that amidst all the good news on vaccines in the past year, the AstraZeneca/Oxford effort has had the roughest ride of the major candidates. First, there were dosing mistakes in its trial. Ironically, the mistake seemed to have a fortuitous upside; subjects who accidentally received a half dose followed by a full dose later, appeared to have fared better. Later, a press release announcing updates on its efficacy was questioned publicly by regulators in the United States. But in the end, the daylight between what the company said initially and the final result was basically shrug-offable. The vaccine still works very well.

Now, two studies appearing in the *New England Journal of Medicine* describe a rare but apparently real connection between the AstraZeneca/Oxford vaccine and a blood clotting problem, some of which have proven to be fatal. This is the first time that a rare and important side effect has emerged *after* a clinical trial for one of the major vaccine options. This directly implies that the complication is rare, because it literally took millions of doses for enough cases to be noticed that researchers needed to investigate the phenomenon. The two studies describe 11 patients in Germany and Austria (6 of whom died) and 5 in Norway (3 of whom died). So far, over 200 cases of the clotting problem have been reported, out of over 34 million doses given in Europe. Many of those instances have not caused a serious problem. But a few of them indeed have, and these two papers provide important details.

The upshot is that in a few instances, the AstraZeneca/Oxford vaccine appears to be causing a condition now being called "vaccine-induced immune thrombotic thrombocytopenia," or VITT. That's science jargon for: the vaccine can cause an immune reaction that lowers platelet counts which can potentially cause or worsen dangerous blood clot formation. To some, this might sound paradoxical. After all, platelets help us *make* blood clots. Why would a condition that *lowers* platelet levels cause *more* clots? The answer is that when platelets are attacked by the immune system, the platelets release particles—a kind of molecular shrapnel—which then cause blood clots to form or worsen. These blood clots can be harmless and sub-clinical, or they occur or travel to areas of the body where they can do great harm by literally blocking the rest of the blood from reaching its intended destination. In the lungs, large blood clots inhibit the rest of the blood from getting oxygen. In the brain, blood clots stop blood from returning to the heart. The ensuing traffic jam first causes damage around the veins where they occur, but eventually cause a stroke, because oxygenated blood eventually can't reach that part of the brain. The reason that scientists worked this new vaccine-related phenomenon out so quickly is that this condition appears to be related to another similar and well-known problem, caused by a medication called heparin, a commonly used blood thinner.

That also means that scientists and clinicians already have a relatively easy way to test for the condition, and some treatment options which are likely to be effective, including blood thinners, immune globulin (which can raise platelet counts and decrease clots), and platelet transfusions. It is hoped that with earlier recognition and treatment, the few cases that do occur will be more quickly treated and have better outcomes.

The million (or billion) dollar question now is whether the risks and benefits of the AstraZeneca/Oxford vaccine calculation has changed. That hinges on how risky covid-19 is for any given person, how likely the vaccine is to cause VITT, and how likely that is to cause a genuine problem for the few who develop it. This in turn, hinges on the age of the person considering the question. As we know, age is the single greatest factor in determining a person's risk of developing severe or critical covid-19 after infection with SARS-CoV-2. While the statistics numbers are likely

to change with improved surveillance (and vigilance), the University of Cambridge has produced a reasonably credible readout on the risks and benefits of receiving the AstraZeneca/Oxford vaccine, given what we already have learned about VITT rates. The risk of VITT is so low that in areas were coronavirus is *moderately prevalent* (6 cases per 10,000 people per day) or *highly prevalent* (20 cases per 10,000 people per day), the vaccine remains safer than covid-19 risks by far. Even among people ages 20-29, in moderate-risk zones, the risk of an intensive care unit admission resulting from covid-19 is double that of any serious harms from the vaccine. In high-risk zones covid-19 is six times more dangerous for that age group. The balance tips in the vaccine's favor more and more with each decade, since covid-19 risk goes up with age, whereas vaccine-related risks appear to go *down* with age. For adults ages 60-69, covid-19 is over 638 times more dangerous than any vaccine-related risk. **The only scenario in which the risk-benefit balance currently leans away from the AstraZeneca/Oxford vaccine is for people younger than 30 years old, in low-risk covid-19 zones**, according to the University of Cambridge analysis. That means, that for the first time, many experts would specifically recommend that a particular subgroup avoid one vaccine product in favor of another. Until now, despite all the small statistical differences among the available options, experts have largely stuck to one message: get whichever vaccine you are offered first. That message remains true today, with the exception of persons under age 30 in low-risk areas.

So far there are no major concerns around the Moderna and Pfizer/BioNtech options, both of which use mRNA technology that is distinct from the AstraZeneca/Oxford adenovirus platform. This had led many people to wonder whether the Johnson & Johnson option, also an adenovirus vaccine, might carry the same risk. That remains unknown. Though a few possible cases of something similar to VITT have been reported, so far no official reports have been issued and United States regulators have not felt it necessary to stop the Johnson & Johnson rollout. In fact, yesterday, Dr. Rick Bright, the former head of the US Biomedical Advanced Research and Development Authority (BARDA), which ran Operation Warp Speed, tweeted images of himself getting his Johnson & Johnson shot. Dr. Bright indicated that he had a choice of which vaccine to receive, and that he decided to go with Johnson & Johnson. Asked about his decision, Dr. Bright told *Brief19* that he had confidence in all three of the options currently available in the United States. "All of them are very powerful at preventing hospitalization and death from SARS-CoV-2. I chose J&J because I really love the one-shot option. It's better for my schedule, easier to remember and, even though they can be mild, I don't have to think about a sore arm, or headache twice. I also wanted to demonstrate my confidence in this vaccine as some people have spread misinformation that it is inferior to others," Indeed, while Johnson & Johnson data have shown a slightly lower efficacy for preventing covid-19 as compared to the Moderna and Pfzier/BioNtech options overall, all three vaccines appear to be essentially 100 percent effective in preventing illnesses severe enough to require hospitalization or to cause death. "I trust the J&J vaccine to protect me," Bright added. "I wouldn't recommend something to other people that I wouldn't take myself." *12 April 2021*.

—Jeremy Samuel Faust, MD MS

Joshua Niforatos, MD, MTS, 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*

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