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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

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."

—Jeremy Samuel Faust, MD MS

POLICY BRIEFING

An end to mask reuse? CDC and FDA move away from recycling guidance, as shortages end.

One of the earliest and most preventable failures of the coronavirus pandemic was the shortage of personal protective equipment (PPE). The distribution system was so convoluted that mere weeks into the pandemic, grassroots organizations were created to source and share even the most basic of supplies. Beyond competition for ready-to-ship PPE, the supply chain of materials was quickly overwhelmed, leading to global scarcity. Even the US Strategic National Stockpile's viability was at times in doubt.

To combat this, significant time and resources were poured into evaluating reuse and recycling of respirators (N95 in particular). A wide range of degradation of efficacy was reported, but given masks that *mostly* worked or *no masks at all,* reuse was the least bad option available.

It seems we may have finally turned a corner on this. On Friday, the US Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) issued joint guidance on pivoting away from strategy of crisis conservation due to increased availability of respirators. The FDA's website emphasizes acquiring more National Institute for Occupational Safety and Health (NIOSH)-approved devices, which have finally become more readily available, and reserving decontamination and reuse for crisis situations only. Similarly, the CDC's website outlines strategies for conventional, contingency, and crisis situations with regards to respirator use. *Various.*

—Brief19 Policy Team

Pfizer seeks expansion of emergency use authorization for its vaccine.

On Friday, Pfizer petitioned the US Food and Drug Administration (FDA) to expand the Emergency Use Authorization (EUA) for its SARS-CoV-2 vaccine to include children aged twelve to fifteen.

The initial EUA approved the vaccine for use in individuals aged sixteen and older in December. Since then, the pharmaceutical company has been conducting expanded clinical trials to evaluate safety and efficacy in previously-excluded populations, including minors.

Data from a new study released in early April by Pfizer supported its protection for adolescents aged twelve to fifteen, and it is based on these results that the petition has been made.

It should be noted that the new data has yet to be peer-reviewed, and the FDA review process is expected to take several weeks before a decision is rendered. Amidst this, Pfizer is continuing clinical trials of their vaccine in children aged six months to eleven years old, so we are likely to see more requests for EUA expansion in the future. *Various*.

—Brief19 Policy Team

Kimi Chernoby, MD, JD, Policy Section Founder, Joshua Niforatos, MD Research Section Editor, Frederick Milgrim, MD, Editor-at-Large, Joshua Lesko, MD Lead Policy Analysist, Barb Cunningham, Copy-editor, Benjy Renton, Thread-of-the-Week, Anna Fang, Week-in-Review. Megan Davis, social media. Kane Elfman PhD, Publishing and Design. 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 and public policy.