We Need to Talk About the AstraZeneca Vaccine

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The AstraZeneca COVID-19 vaccine is indispensable right now. As one of the first vaccines out of the gate, it's been at the center of the World Health Organization's plan to roll out some 2 billion doses to 92 nations by the end of the year. It's also one of just a handful of vaccines that are already being produced and distributed on such a massive scale that they might change the near-term course of the pandemic.

That's why the past few weeks have felt so catastrophic.

The run of bad news might have seemed, at first, to be short-lived. Earlier this month, regulators in more than 20 European countries suspended distribution of the AstraZeneca vaccine. The English-language media cited scattered reports of "blood clots" in recipients as the reason. A few days later, though, the European Medicines Agency's expert committee weighed in to recommend the vaccine's continued use. With COVID-19 case rates surging across Europe and more than 3,000 deaths a day, the group concluded that its benefits far outweighed any known or potential risks.

Just that short pause sparked despair and condemnation. Commentators and public-health experts called it "stupid, harmful, "quite dangerous," and a "magnificent example of European failure." The problem, they said, was that the actual evidence of harm had been very weak—and maybe even nonexistent. Writing in *The New York Times* on March 22, Heidi Larson, the director of the Vaccine Confidence Project at the London School of Hygiene & Tropical Medicine, noted that just 25 Europeans had developed blood clots, out of 20 million who received the AstraZeneca vaccine. That rate, she said, was *lower* than what you'd normally see among unvaccinated people. According to the statistician David Spiegelhalter, the furor over blood clots showed our "basic and often creative urge to find patterns even where none exist."

None of these critics said that potential risks should be ignored. They argued instead that, given the available data, the known harms from COVID-19 were clearly many orders of magnitude more significant. The cost of losing time from a temporary pause in vaccination was therefore disproportionate and unbearable; worse, it was likely to exacerbate concerns among vaccine-wary Europeans. Indeed, close to 60 percent of French adults now say they have little or no confidence in the AstraZeneca vaccine; similar poll numbers are turning up in Germany, Italy, and Spain. As Larson suggested in her op-ed last week, the AstraZeneca vaccine may now be back in distribution in many places, but the drama has "heightened anxieties and increased hesitancy." That effect could spread well beyond Europe, and beyond this particular vaccine.

But the challenges here are far deeper than this blizzard of commentary allows. The risk of a dangerous vaccine reaction could be very real, if also very rare—and major European vaccine authorities have not, in fact, been overcautious, political, or innumerate in

responding to this possibility. Rather, they've been faced with something of a nightmare scenario for vaccine communication. We're in the midst of a global public-health crisis, and regulators must address the possibility (still unproved) that perhaps one in every 1 million vaccinated people could have a potentially fatal drug reaction—as more than 1 million vaccine doses are being injected each day in Europe alone.

It seems as though anything the regulators say about this problem could serve to reduce trust in vaccination, and thus increase the toll of the pandemic. And yet if there does turn out to be a vaccine reaction, even a vanishingly infrequent one, keeping mum won't make the problem go away. Indeed, it could serve to worsen the effects of the fearmongering about vaccines that will surely grow from here.

The reason for the pause was never quite as simple as the critics made it sound. The AstraZeneca vaccine was first authorized for use in Europe at the end of January, then rolled out slowly in February. On March 7, Austrian authorities announced an investigation of a death that was potentially vaccine-related. A few days later, the Danish Health Authority announced that it was investigating a death as well, and then the same thing happened in Norway. On March 15, Germany suspended use of the AstraZeneca vaccine pending the investigation of three deaths and four other incidents.

According to the German vaccine authority, the sixth and seventh reports there "put the number of observed cases well above the expected number." All seven cases involved previously healthy people between ages 20 and 50. At that point, the German regulators advised the government that merely looking into this was not enough. If this weren't a coincidence—and again, that remains an "if"—then in the course of an investigation, more young people who are not generally at risk of dying from COVID-19 could end up being put at risk by the vaccine. If the regulators were able to identify any clear risk factors for this outcome, the medical community and the general public would need to know as soon as possible.

Two days later, on March 17, Gretchen Vogel and Kai Kupferschmidt of *Science* magazine reported that, across Europe, there had been to that point at least seven deaths from a similar condition, and six other people treated, among the 17 million people who had received the AstraZeneca vaccine. All were healthy before they developed a highly unusual, seemingly contradictory mix of blood disorders: clots throughout the body along with low numbers of platelets, the blood cells that help clots form. In a follow-up article published on Saturday, Vogel and Kupferschmidt cited a German researcher who has named the syndrome "vaccine-induced prothrombotic immune thrombocytopenia," or VIPIT. A hematologist from Johns Hopkins University told them he wasn't yet convinced by the "vaccine-induced" part, but he acknowledged that "these cases raise concern that this vaccine is potentially life-threatening in a small subset of patients."

By the time of Vogel and Kupferschmidt's first article, though, the prothrombotic immune thrombocytopenia problem had already been recast in the English-language media as simply one of "blood clots." Seen in that context, the decisions to suspend the AstraZeneca rollout were puzzling—and perhaps, as some maintained, driven more by emotions than

by data. The European Medicines Agency had helped create this impression, starting with a press release on March 10. In its statement, the agency compared the number of vaccinated people who had blood clots with the baseline rate across the population. Commentators quickly zeroed in on that comparison, or a similar one from an AstraZeneca press release, which stated that the number of events "is much lower than would be expected to occur naturally in a general population of this size."

These generic blood-clot data turned out to have little to do with the very specific, potential risks that several countries were confronting. The EMA said on March 18 that it had found, by then, a possible link to the AstraZeneca vaccine among 25 people who had developed the disturbing blood disorder, including nine who had died from it. All 25 had low platelet counts. Seven also had blood clots throughout their blood vessels—a condition known as disseminated intravascular coagulation, which showed up here at about five times the generally expected rate. The rest had blood clots that prevented blood from draining from their brain—a condition known as cerebral venous sinus thrombosis, which occurred at about nine times the expected rate. Also on March 18, the vaccine authority in the U.K. reported that it was investigating five cases of those cerebral clots in people with low platelets.

The original vaccination pause may be over in many countries, but investigations are continuing, and regulators around the world are taking further action. In France, for example, the National Agency for the Safety of Medicines and Health Products has identified nine cases of these blood disorders (including two deaths) out of 1.4 million injections, and described it as a vaccine reaction. In Australia, where there is, at the moment, essentially zero risk of COVID-19 infection, people who have had two very specific, rare blood disorders are now advised to defer any COVID-19 vaccination. Denmark's health authority just extended its blanket hold on the AstraZeneca vaccine for three more weeks, and so did Norway's. Since most cases have involved those under 50, several countries are limiting the vaccine's use to older people as a way to mitigate the risk.

We still can't be sure whether this blood disorder is triggered by vaccination, and we don't know yet whether the risk—if it's real—applies equally to all recipients, or only to a subset that might be predisposed. In light of these uncertainties, the balance here between vaccination's costs and benefits is obvious. Given the present context of COVID-19 transmission throughout Europe, and even assuming the very worst about the risk that the AstraZeneca vaccine might pose, the shot will save many more lives per million doses than it could ever possibly end.

It should be just as obvious that health authorities cannot simply look the other way. For these sorts of blood disorders, early diagnosis and appropriate action might be crucial for saving lives. Rajiv Pruthi, a hematologist at the Mayo Clinic, points out that the standard treatment for a cerebral clot—a blood thinner called heparin—could make things worse for patients with this syndrome. At the very least, doctors must be kept informed about potential risks.

It's certainly reassuring that so few safety issues have emerged from COVID-19 vaccination on a global scale. The AstraZeneca vaccine has not yet been approved for use in the U.S., but 145 million doses of other vaccines have been administered since December, and while lots of people have experienced headaches, fever, tiredness, and so on, according to the latest data from the CDC, reactions have almost always ended there. As is the case for vaccines in general, a small number of recipients—just a handful out of every million—have developed severe allergic reactions, which are easily treated. There's zero indication, at this point, that the Moderna, Pfizer-BioNTech, or Johnson & Johnson vaccines have caused any deaths at all.

In other words, the fact that a potential safety issue has emerged for the AstraZeneca vaccine is itself a rare exception. As of now, the EMA is continuing to investigate the blood-related syndrome, and another expert-committee meeting on the subject was scheduled for yesterday. In the meantime, the agency has added a warning to the vaccine's drug leaflet for the European Union. "Seek immediate medical attention if you develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain following vaccination," it says. "Also, seek immediate medical attention if you experience after a few days severe or persistent headaches or blurred vision after vaccination, or experience skin bruising or pinpoint round spots beyond the site of vaccination." Similar warnings have been issued in Canada and Australia.

Alerting people to that list of symptoms could save lives. But it might deter some people from vaccination. That's why even cautious actions like the one taken by the EMA might be seen as dangerously misguided. Any move that shakes confidence in the AstraZeneca vaccine could lead to broader, global harms, warns Paul Offit, the director of the Vaccine Education Center at Children's Hospital of Philadelphia. "While it's easy to scare people, it's very hard to unscare them," he told *USA Today*. "It creates the perception that these vaccines are dangerous."

But how far should this logic go? Does it matter that other COVID-19 vaccines are on the market—even if they're more expensive or in short supply? Should vaccine authorities adjust their approach to risk, with the goal of propping up the public's trust? These questions have no simple answers, and we shouldn't be surprised that highly qualified experts have come to different conclusions.

In fact, we saw something like the same debate unfold late last year, when AstraZeneca and Oxford University first announced their vaccine's success in clinical trials. The data contained numerous, serious shortfalls: Instead of judging efficacy from a single, large, placebo-controlled trial, the Oxford team merged results from different studies carried out in different ways. The research was so problematic, in fact, that regulators could not agree on whether the vaccine's demonstrated efficacy against symptomatic COVID-19 was closer to 70 percent, as England's drug regulator decided, or in the low 60s, per the EMA.

The lack of better data was a deal breaker for some health authorities. The U.S. Food and Drug Administration, for example, decided to await results from a large, rigorous trial; Switzerland's agency, Swissmedic, did the same. But regulators in Europe, along with those in many countries beyond the Continent, went the other way. The EMA

recommended authorization of the AstraZeneca vaccine, announcing that "the conduct of studies was sub-optimal" but also that, "given the emergency situation," the benefits of using it outweighed any risks.

In this case, the choice to loosen up paid off: The vaccine has reduced disease and death in recent months, and the more rigorous clinical-trial results—which have only just come in—showed an efficacy of 76 percent. But that doesn't tell us how regulators should handle the possibility of dangerous reactions to the same vaccine that are too rare to show up in a clinical trial, even one with 32,000 participants. And to some extent, the narrative about those reactions is no longer in their hands.

Stories linking people's deaths to vaccinations have been among the most popular vaccine-related stories on social media in recent months—and that was true long before there were any hints of a real association. Now that health authorities really are investigating a possible, fatal vaccine reaction, these narratives will increase their reach. The first face to be linked prominently to the blood disorders appeared on Facebook on March 22. More seem sure to follow.

It may be that at some point soon a non-vaccine cause will be established, or treatments will render the condition manageable. Until that happens, though, regulators must do their best to maintain calm, perspective, and transparency. Imagine if they'd reacted more conservatively from the start, and waited to say or do anything until the number of people who turned up with this condition had reached into the hundreds. More people would have been vaccinated along the way, but the eventual loss of trust in the monitoring system for vaccines could have been far more severe. Addressing concerns about vaccines is a long game, and the biggest challenges will come much later on, when all the eager people have been immunized and it's time to persuade the holdouts.

There are clear precedents for communicating effectively about very rare vaccine reactions. An ordinary flu shot, for example, may cause a tiny number of recipients—just one or two per million—to develop an autoimmune disorder called Guillain-Barré syndrome. The CDC describes this link as being "variable and inconsistent," but the slightly squishy facts are not concealed from the public.

We can recognize the painful ambiguity and uncertainty here, and steer clear of judging the decisions made by health authorities in different countries. While the controversy about European suspensions of the vaccine raged, a poll in Germany found that a narrow majority—54 percent—believed putting the vaccine on hold was the right decision. Norway's minister of health said that his constituents expected the government to do as it had promised, which was to be transparent about any problems. If the vaccine regulators are out of step with their communities' values, transparency will enable them to calibrate. They aren't being stupid. To argue otherwise invents an easy answer to a nearly impossible conundrum—and withers public confidence in authorities at the moment when we need it most.