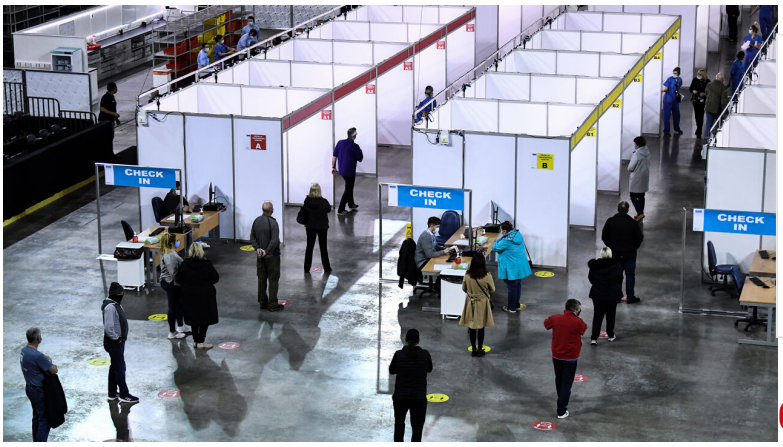

People line up to receive AstraZeneca's COVID-19 vaccine in Belfast, Northern Ireland. The United Kingdom has used the vaccine more than any other European country. CLODAGH KILCOYNE/REUTERS

Hard choices emerge as link between AstraZeneca vaccine and rare clotting disorder becomes clearer

By **Kai Kupferschmidt**, **Gretchen Vogel** | Apr. 11, 2021 , 7:15 AM

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What was a worrisome suspicion 4 weeks ago is now widely accepted: The AstraZeneca COVID-19 vaccine can, in very rare cases, cause a disorder characterized by dangerous blood clots and low platelet counts. In Europe, at least 222 suspected cases have been reported among 34 million people who have received their first dose of the vaccine. More than 30 have died.

"Causality is more of a journey to certainty than a binary decision," says Anthony Cox, an expert on pharmacovigilance at the University of Birmingham. But faced with accumulating cases, the European Medicines Agency (EMA), which had been careful not to point fingers, **acknowledged** on 7 April "a probable causal association" between the syndrome and the vaccine, recently named Vaxzevria.

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As the link has become clearer, a possible mechanism driven by an errant immune reaction has come into focus. Now, health officials face hard questions about who should and should not get Vaxzevria, which some countries have already restricted to older age groups, upending vaccination schedules.

Researchers stress that the troubles by no means spell Vaxzevria's end. In the vast majority of cases, its benefits outweigh the risks, and the cheap and easy to store vaccine is still the best hope for vaccinating large numbers of people in low- and middle-income countries. And some scientists suggest a simple strategy could reduce the risk while stretching supplies: Cut the vaccine dose in half.

Negative charge

On Friday, some of the first researchers to describe the condition published their observations in *The New England Journal of Medicine*. One team **describes 11 patients in Germany and Austria**; **the other** has observations on five patients in Norway. Both teams found the patients had unusual antibodies that trigger clotting reactions, which use up the body's platelets and can block blood vessels, leading to potentially deadly strokes or embolisms.

The symptoms resemble a rare reaction to the drug heparin, called heparin-induced thrombocytopenia

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(HIT), in which the immune system makes antibodies to a complex of heparin and a protein called platelet factor 4 (PF4), triggering platelets to form dangerous clots throughout the body. Sickened vaccine recipients also had antibodies to PF4, the researchers found.

The researchers who studied the German and Austrian patients, led by clotting expert Andreas Greinacher of the University of Greifswald, had **initially called the syndrome** vaccine-induced prothrombotic immune thrombocytopenia; both teams now suggest a slightly simpler name: vaccine-induced immune thrombotic thrombocytopenia (VITT).

In their paper, Greinacher and his colleagues also speculate about a possible mechanism. Vaxzevria consists of an adenovirus engineered to infect cells and prompt them to produce the virus' spike protein. Among the 50 billion or so virus particles in each dose, some may break apart and release their DNA, Greinacher says. Like heparin, DNA is negatively charged, which would help bind it to PF4, which has a positive charge. The complex might then trigger the production of antibodies, especially when the immune system is already on high alert because of the vaccine. An immune reaction to extracellular DNA is part of an ancient immune defense triggered by severe infection or injury, Greinacher notes, and free DNA itself can **signal the body** to increase blood coagulation.

Alternatively, the antibodies may already be present in the patients and the vaccine may just boost them. Many healthy people harbor such antibodies against PF4, but they are kept in check by an immune mechanism called peripheral tolerance, says Gowthami Arepally, a hematologist at the Duke University School of Medicine who is working as an external consultant with AstraZeneca on the issue. "When you get vaccinated, sometimes the mechanisms of peripheral tolerance get disrupted," she says. "When that happens, does that unleash any autoimmune syndromes that you are predisposed to, like HIT?"

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Early suggestions that the rare reactions may be the result of a COVID-19 infection before vaccination have not been substantiated. None of the five patients in Norway had been infected, for instance. Others have suggested that antibodies against the virus' spike protein—which many vaccines seek to elicit—somehow cross-react with PF4. That could spell trouble for nearly all COVID-19 vaccines. But so far, there is no evidence that the messenger RNA–based vaccines made by the Pfizer-BioNtech collaboration and Moderna, which tens of millions of people have received, are causing similar clotting disorders.

Initial studies by Greinacher's team, **posted as a preprint**, don't support that theory either. Among more than 200 patients who had recovered from COVID-19, they found only a few with antibodies that reacted to PF4, and those reacted relatively weakly. More importantly, Greinacher says, the platelet-activating antibodies isolated from VITT patients did not react to the coronavirus spike protein. At a press conference on Friday, Greinacher called the finding "fantastic news for the vaccination program."

Pinpointing the mechanism is crucial to understanding whether other vaccines made from a modified adenovirus, which include those from Johnson & Johnson and CanSino Biologics, as well as Russia's Sputnik V, do something similar. On 9 April, EMA said it was investigating four cases of similar clotting seen in U.S. patients who had received the Johnson & Johnson vaccine, which has been used in the United States since early March but has yet to make its debut in Europe. The cases could be coincidence, Greinacher says, but "it's at least very suspicious."

Weighing the risks

EMA emphasizes that Vaxzevria's benefits still outweigh the risks. Nevertheless, many countries have restricted its use in younger people. Germany is using the vaccine only in people over age 60, France in those older than 55. They reason that younger people are at lower risk of getting severely ill and dying from COVID-

19, making it harder to justify the risk of side effects. In the United Kingdom, a vaccine advisory panel has recommended that people younger than 30 be offered a different vaccine. (The country has used Vaxzevria more than any other European country, and on 7 April, the U.K. Medicines and Healthcare Products Regulatory Agency said it had been investigating **at least 79 cases of strokes and clotting events** tied to the vaccine, at least 18 of them fatal.)

EMA, however, does not recommend restricting the vaccine to particular age groups. And the ever-shifting COVID-19 statistics seem to support that position. Based on currently available data, the risk of serious harm because of the vaccine for people age 20 to 29 in the United Kingdom is about 1.1 in 100,000, says David Spiegelhalter, a statistician at the University of Cambridge. Their risk of being admitted to intensive care because of COVID-19 in the next 16 weeks ranges from 0.8 in 100,000 to about 6.9 in 100,000, depending on their risk of exposure to the virus.

“In this sort of gradual sliding curve of benefit-risk balance, there’s no sudden point at which it becomes safe or unsafe,” Spiegelhalter says. “This is a judgment.” But for now, the numbers suggest that even for young people, the vaccine is a net benefit for the vast majority. Getting vaccinated also provides protection to other people, Spiegelhalter says: “I think that’s an aspect that has not been emphasized enough.”

Local circumstances can change the picture. In Australia, where there is no COVID-19 at the moment, the calculation might go the other way than in Europe. (The country has recommended people under age 50 receive a different vaccine when possible.) The availability of alternatives is an important consideration as well. European countries have ordered doses from many different companies, but others do not have that luxury. More than 30 million doses of Vaxzevria have already been delivered to more than 100 countries through the COVID-19

Vaccines Global Access Facility, led by the World Health Organization and Gavi, the Vaccine Alliance.

Halving the dose

EMA has directed AstraZeneca "to look at their existing data from closed clinical trials to see if that can give any further information on possible mechanism, risk factors and so on," EMA's Peter Arlett told a 7 April press conference. It has also asked two academic groups, one led by Utrecht University and the other by the Erasmus University, Rotterdam, to look at risk factors for thrombosis in COVID-19 disease and after vaccination. "We would anticipate results starting to come in from those [studies] over the next couple of months," Arlett says.

Greinacher and his collaborator Rolf Marschalek, a molecular biologist at Frankfurt University, are also calling for tests of a simple solution: halving Vaxzevria's dose. In AstraZeneca's phase 3 trial in the United Kingdom, a small number of people accidentally received a lower dose and had fewer side effects in general; perhaps the lower dose is less likely to trigger the kind of strong inflammation that boosts PF4 antibodies as well, the researchers say. And unexpectedly, those people were slightly better protected, perhaps because high levels of inflammation can actually block the formation of antibodies, Marschalek says. "Part of the problem might be that they just overdose" the vaccine, Greinacher says.

The fact that more common side effects appear less frequently at half a dose does not mean the same is true for the very rare side effects, Cox cautions. But if the hunch proves correct, what looked like a terrible blow for one of the world's most important weapons against the pandemic might be good news in disguise: Supplies of the vaccine could vaccinate twice as many people—with fewer side effects.

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