A physician prepares a dose of AstraZeneca's COVID-19 vaccine in Bologna, Italy, on 19 March. MICHELE LAPINI/GETTY IMAGES

Data concerns and safety worries fuel crisis of confidence in AstraZeneca vaccine

By **Gretchen Vogel**, **Kai Kupferschmidt** | Mar. 23, 2021 , 6:00 PM

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In the global battle against COVID-19, the vaccine made by British-Swedish firm AstraZeneca has been a source of great hope. It's easy to store—requiring only refrigeration, not a deep freeze—and the firm has partnered with several other manufacturers as part of its pledge to make the vaccine, developed by researchers at the University of Oxford, available to countries around the world at low cost.

But the vaccine keeps running into trouble. AstraZeneca's early efficacy claims were confusing and, in some cases, disappointing. In recent weeks, more than 20 European countries **suspended use of the shots** after more than a dozen recently vaccinated people developed unusual clotting disorders. (Immunizations **resumed in most countries** after the

European Medicines Agency [EMA] investigated the matter.)

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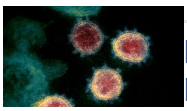

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Now, the vaccine has suffered a new blow. Yesterday, the company **announced the long-awaited results of a large trial** in the Americas that seemed to end lingering doubts about its efficacy—only to be rebuffed by the Data and Safety Monitoring Board (DSMB) overseeing the study, which, in a highly unusual clash, suggested the company had presented "outdated information" on efficacy.

"It appears that [AstraZeneca] may have been using the most favorable data, and the DSMB wanted to make sure they corrected that," says Anthony Fauci, director of the U.S. National Institutes of Allergy and Infectious Diseases (NIAID), which appointed the DSMB and made the discord public in a statement posted online late last night. (The DSMB saw no safety concerns, however.)

According to a **press release from the company**, the phase 3 trial, in 32,000 people in the United States, Chile, and Peru, showed that the vaccine had 79% efficacy at preventing symptomatic COVID-19. After the earlier, mixed results, the clear-cut finding excited public health experts and raised hopes that the vaccine might soon be used in the United States, where AstraZeneca has not yet filed a request for

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emergency use authorization. But the NIAID statement says AstraZeneca might have provided "an incomplete view of the efficacy data."

The company says the press release was based on data gathered until 17 February, when a prespecified cutoff point was reached. But the DSMB was "very concerned" that later data were excluded, Fauci says. The company said it would update its results "within 48 hours," but a letter from the DSMB to the company, **reported by *The Washington Post***, says that when later trial data were included, the efficacy fell to between 69% and 74%.

The company has promised to publish more up-to-date data by Thursday. But the drama has left public health experts reeling and raised fears that trust in the vaccine would erode further. "From everything I know, the AZ vaccine is a good vaccine that I would be comfortable having my family get," Ashish Jha, dean of the Brown University School of Public Health, **tweeted**. "From everything I know, AZ's incompetence at communicating trial results, working with regulatory agencies, etc. is stunning."

A delay in the vaccine's authorization in the United States is unlikely to slow that country's immunization campaign; the U.S. expects to have enough doses of three other vaccines for its entire population by the end of May.

In Europe, meanwhile, some scientists say they have come closer to understanding the rare hematological disorders seen in some vaccinees. Germany, Italy, Austria, Norway, and Denmark have all reported cases of people who developed widespread blood clots, low platelet counts, and internal bleeding; at least seven have died. The problems appear to be more common among vaccinees than would be expected by chance.

On 18 March, EMA said its experts could not rule out a connection to the vaccine and decided to add a warning to the product information. But it stressed that the vaccine's benefits outweighed the risks and urged European countries to start administering the

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shots again. Most countries have done so, but five Nordic nations have not. (France decided to restrict its use to people 55 and over because the suspected side effects appeared mostly in younger people.)

The combination of thromboses and low platelet counts seen in patients "immediately raises the possibility of an immune reaction," says Sabine Eichinger, a hematologist at the Medical University of Vienna who treated a 49-year-old intensive care nurse who died 11 days after receiving the vaccine. The timing of symptom onset—between 4 and 16 days following vaccination—was another clue that renegade antibodies might be playing a role, says hematologist Andreas Greinacher at the University of Greifswald in Germany.

Greinacher, Eichinger, and other scientists have found that blood samples from at least six patients tested positive for antibodies that react to platelet factor 4, a key molecule involved in clotting and inflammation. The finding led the researchers to conclude that the process resembles an autoimmune disorder called heparin-induced thrombocytopenia (HIT)—a rare side effect of the blood thinner heparin that leads to plummeting platelet counts and clotting. Something about the AstraZeneca vaccine seems to trigger a similar syndrome, the researchers say, which they dubbed vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). A research group in Norway has come to a similar conclusion.

Greinacher and his colleagues announced their findings in a 19 March press release—and have alerted AstraZeneca—but they have not published their data, leading other experts to reserve judgment. And some of the cases do not fit the VIPIT description. For instance, one vaccinee in Germany has been diagnosed with atypical hemolytic uremic syndrome, another disease that can show up as widespread blood clotting and low platelet counts but that's caused by damage to the endothelial lining of blood vessels.

In a statement, AstraZeneca emphasized that blood clots in general are no more common among people who have received its vaccine. But the statement did not address the unusual set of symptoms seen in Europe, or Greinacher's hypothesis.

In contrast to the United States, Europe badly needs AstraZeneca's vaccine, which is a key weapon in the pandemic arsenal. The European Union has ordered 400 million doses, which have arrived much more slowly than foreseen. Even as the safety questions developed, the European Commission charged that AstraZeneca has favored the United Kingdom over the European Union in deliveries and threatened to block doses made on the continent from being exported to the U.K. The pause in immunizations, and the dropping confidence, may cause further delays just as cases across the continent are soaring.

It is not yet clear, experts say, what impact the setbacks might have on global use of AstraZeneca's vaccine, a cornerstone of the World Health Organization's plan to help low-income countries beat the pandemic.

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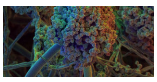

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