IN DEPTH

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

COVID-19

New problems erode confidence in AstraZeneca's vaccine

Rare clotting disorders interrupt vaccination in Europe as U.S. expert panel rebukes company over efficacy data

By **Gretchen Vogel** *and* **Kai Kupferschmidt**

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's journey has been anything but smooth. The company's early efficacy claims were confusing and, in some cases, disappointing. And over the past 2 weeks, the waters got particularly choppy. 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.

Then, the company announced the long-awaited results of a large trial in the Americas that seemed to end lingering doubts about the vaccine's 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Monitoring Board (DSMB) overseeing the study, which, in a highly unusual clash, suggested the company had presented "outdated information" on efficacy.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 23 March statement. (The DSMB saw no safety concerns, however.)

The company promised to publish more up-to-date data by 25 March. But the drama 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."

The very rare hematological disorders seen in European recipients are perhaps the most worrisome development for the vaccine, but many scientists are still unsure what to make of them. 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. "It's a very special picture" of symptoms, says Steinar Madsen, medical director of the Norwegian Medicines Agency. "Our leading hematologist said he had never seen anything quite like it."

The problems appear to be more common among vaccinees than would be expected by chance. Germany's regulatory agency, the Paul Ehrlich Institute, recommended pausing vaccinations after receiving seven reports of what it called cerebral venous thrombosis, a rare type of stroke leading to massive, life-threatening bleeding in the brain, occurring in a 2-week window after vaccination; only one such case would have been expected among the 1.6 million vaccinees in that time period.

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 shots again. As *Science* went to press, most countries had done so, but five Nordic nations had not. (France decided to restrict its use to people 55 and over, because the suspected side effects appeared mostly in younger people.) Initial polls showed the public's confidence in the vaccine had been significantly dented, a worrying sign in countries that are facing rapidly increasing infections and sluggish vaccination campaigns.

A somewhat similar blood disorder, called immune thrombocytopenia (ITP), has been seen in at least 40 people in the United States who received the Pfizer or Moderna vaccines against COVID-19, but the U.S. Food and Drug Administration said that syndrome did not appear to be more common in vaccinated people.

PHOTO: MICHELE LAPINI/GETTY IMAGES

Published by AAAS

Madsen says the European cases are distinct from ITP, which does not result in widespread blood clots.

Just how AstraZeneca's vaccine could cause the problems seen in Europe is unclear. "The combination of thromboses and low platelet counts 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.

HIT can be treated with high doses of intravenous immunoglobulins and nonheparin blood thinners; the same approach works for VIPIT, says Greinacher, noting that a doctor whom the group advised successfully treated at least one case. He stresses that the AstraZeneca vaccine should remain in use, even if the rare syndrome occurs, "We know what to do: how to diagnose it, and how to treat it," he says.

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. The VIPIT hypothesis "may explain a few of the cases. I don't think this explains all of them," says Robert Brodsky, a hematologist at Johns Hopkins University.

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.

The data from the new phase 3 trial, in 32,000 people in the United States, Chile, and Peru, seemed to offer some good news for the vaccine. According to a 22 March press release from the company, the trial showed it 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 emergency use authorization.

But less than 24 hours later, NIAID issued a statement saying 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 reportedly said that when later trial data were included, the efficacy fell to between 69% and 74%.

Science's COVID-19 reporting is supported by the Heising-Simons Foundation.

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. That is not the case in Europe, where the AstraZeneca vaccine was envisioned as 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.

The speed of immunizations in the next 4 weeks will be crucial for how many people eventually get sick and die in Europe's third wave, says Dirk Brockmann, a disease modeler at the Robert Koch Institute. "We actually need to speed up vaccinations—a lot," he says. ■

GEOPHYSICS

Remains of Moon-forming impact may lie deep in Earth

Mysterious rocks at mantle's base tied to violent "Theia" strike 4.5 billion years ago

By **Paul Voosen**

Scientists have long agreed that the Moon formed when a protoplanet, called Theia, struck Earth in its infancy some 4.5 billion years ago. Now, a team of scientists has a provocative new proposal: Theia's remains can be found in two continent-size layers of rock buried deep in Earth's mantle.

For decades, seismologists have puzzled over these two blobs, which sit below West Africa and the Pacific Ocean and straddle the core like a pair of headphones. Up to 1000 kilometers tall and several times that wide, "they are the largest thing in the Earth's mantle," says Qian Yuan, a Ph.D. student in seismology at Arizona State University (ASU), Tempe. Seismic waves from earthquakes abruptly slow down when they pass through the layers, which suggests they are denser and chemically different from the surrounding mantle rock.

The large low-shear velocity provinces (LLSVPs), as seismologists call them, might simply have crystallized out of the depths of Earth's primordial magma ocean. Or they might be dense puddles of primitive mantle rock that survived the trauma of the Moon-forming impact. But based on new isotopic evidence and modeling, Yuan believes the LLSVPs are the guts of the alien impactor itself. "This crazy idea is at least possible," says Yuan, who presented the hypothesis last week at the Lunar and Planetary Science Conference.

The idea has rattled around lab corridors and conference halls for years. But Edward Garnero, a seismologist at ASU Tempe who was not involved in the work, says it's the first time anyone has marshaled multiple lines of evidence and mounted a serious case for it. "I think it's completely viable until someone tells me it's not."

Evidence from Iceland and Samoa sug-

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Science **371** (6536), 1294-1295.
DOI: 10.1126/science.371.6536.1294