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A doctor administers a dose of the AstraZeneca vaccine against COVID-19 in Dippoldiswalde, Germany, on 15 March—the day the German government said it would temporarily halt the use of the vaccine because of safety concerns. JENS SCHLUETER/GETTY IMAGES

## 'It's a very special picture.' Why vaccine safety experts put the brakes on AstraZeneca's COVID-19 vaccine

By [Gretchen Vogel](#), [Kai Kupferschmidt](#) | Mar. 17, 2021 , 1:30 PM

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

The decision this week by more than 20 European countries to temporarily stop using AstraZeneca's COVID-19 vaccine has opened a rift between vaccine safety experts, who say the cases of serious clotting and bleeding that triggered the pause are alarming and unusual, and public health officials concerned that the immunization pause on a continent in the grip of the pandemic's third wave could take a heavy toll.

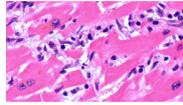
"The harm caused by depriving people of access to a vaccine will likely vastly outweigh even the worst case scenario if any link to the clotting disorders is eventually found," University of Leeds virologist Stephen Griffin told the United Kingdom's Science Media Centre. The European Medicines Agency (EMA) and the World Health Organization have

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recommended that countries continue immunizations while they investigate the reports.

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Scientists don't know whether the vaccine causes the syndrome, and if so, what the mechanism is.

"Everyone's scratching their heads: Is this a real signal?" says Robert Brodsky, a hematologist at Johns Hopkins University. But vaccine safety officials say they did not take the decision lightly, and that symptoms seen in at least [13 patients, all between ages 20 and 50 and previously healthy, in at least five countries are more frequent than would be expected by chance. The patients, at least seven of whom have died, suffer from widespread blood clots, low platelet counts, and internal bleeding—not typical strokes or blood clots.](#) "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."

A [somewhat similar blood disorder, called immune thrombocytopenia \(ITP\), has been seen in at least 36 people in the United States who had received the Pfizer and Moderna vaccines against COVID-19, The New York Times recently reported.](#) The U.S. Food and Drug Administration said it was investigating these cases, but also said the syndrome did not appear to be more common in vaccinated people, and

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immunizations in the United States have continued. But Madsen says the cases seen in Europe in recent weeks are distinct from ITP, which lacks the widespread blood clots seen in the European patients.

The United Kingdom, which has administered the AstraZeneca vaccine to more than 10 million people, has so far not reported similar clusters of unusual clotting or bleeding disorders.

In Europe, a 49-year-old intensive care nurse in Austria was one of the first cases. She died last week from what officials called "clotting disorders" that culminated in internal bleeding. (A colleague at the same hospital who received the vaccine developed lung embolisms, but was expected to recover.) A similar constellation of symptoms has been identified in four patients in Norway, two of whom have died, Madsen says.

German officials said Monday they had received seven reports of cerebral venous thrombosis (CVT), three of them fatal, in patients who had recently been vaccinated with the AstraZeneca vaccine. In this rare type of stroke, the vein that drains blood from the brain is blocked, which can result in massive, deadly bleeding in the brain. All of the patients also had low levels of platelets, which aid in clotting, a possible sign of more widespread clotting. One affected patient had blood clots "from head to toe," says Clemens Wendtner, a hematology and infectious disease specialist at the Munich Clinic, Schwabing. The symptoms remind Wendtner of a syndrome called disseminated intravascular coagulation (DIC), in which blood clots form throughout the body, depleting its platelet supply. When the clots cause blood vessels to burst, the body is less able to stop the internal bleeding, which can damage the brain or other organs.

Arnold Ganser, a hematologist at Hannover Medical School, says he is treating another patient who developed CVT within days of vaccination. He says that patient appears to be suffering from another condition called atypical hemolytic uremic syndrome (HUS). (The patient, a woman older than 60, is not yet

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counted in the seven cases announced in Germany on Monday.) Although it can look similar to DIC, HUS develops from damage to the vascular walls. It is usually caused by a bacterial toxin, but can also arise from unknown factors. The condition can be treated with an antibody targeting the complement system, a cascade of molecular interactions that aids immune clearance of pathogens or diseased cells, and Ganser says the patient appeared to be responding to that treatment.

Germany paused vaccinations on Monday on the recommendation of the Paul Ehrlich Institute (PEI), the country's agency in charge of vaccine safety. PEI head Klaus Cichutek says all seven cases of CVT had occurred between 4 and 16 days after vaccination, and that an analysis suggested only a single case would normally be expected among the 1.6 million people who received the vaccine in that time window. A group of experts convened on Monday "agreed unanimously that there seemed to be a pattern here and that a link to the vaccine was not implausible and that this should be investigated," Cichutek says.

Other factors played a role in the recommendation, including the fact that the syndrome is so severe and difficult to treat, and that it affects relatively young people who are at low risk of dying from COVID-19. It was also an opportunity to urge people to seek medical attention immediately if they develop persistent headaches or unusual bruising in the week following vaccination, Cichutek says.

But the decision put PEI at odds with EMA, which says vaccinations should continue for now. "When you vaccinate millions of people, it's inevitable that you have rare or serious incidences of illnesses that occur after vaccination," EMA head Emer Cooke said at a press conference yesterday. EMA will convene a panel on Thursday to help figure out whether there was a causal relationship between the vaccinations and the highly unusual syndrome. For the moment, the agency is "firmly convinced" that the vaccine's benefits outweigh any risks, Cooke said.

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**“ If possible, we need to have a European decision this week on the basis of what we know. ”**

*Klaus Cichutek, Paul Ehrlich Institute*

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Madsen believes the unusual symptoms may be the result of “a very strong immunological reaction.” Acute infections can trigger clotting and bleeding, sometimes culminating in DIC, Wendtner notes. But abnormal clotting is also a feature of COVID-19. It’s possible, Wendtner says, that the unusual cases had a COVID-19 infection before they got vaccinated; many were health care workers and teachers who may have been exposed at work. Coming on top of the infection, the vaccine might somehow have triggered an overreaction by the immune system, sparking the clotting syndrome. Ganser thinks patients suffering from CVT may be the tip of the iceberg and that more people may suffer similar, but milder, symptoms.

If there really is a link between the vaccine and the blood disorders, Brodsky says a lot of evidence points to a crucial role for the complement system. Dysregulation of that system can lead to diseases that Brodsky terms “complemenopathies.” “What complementopathies have in common is: They all have thrombosis as part of it, they all have thrombocytopenia as part of it, they all have relative resistance to traditional anticoagulants and they all have triggers such as infections, inflammation, pregnancy, cancer, vaccines.”

In a paper published in October in *Blood* Brodsky and colleagues showed that the spike protein of SARS-CoV-2, by binding to the inner surface of blood vessels, can activate the complement system. In some people that leads to the cells lining the vessel being attacked, which in turn can lead to blood clotting and ultimately cause severe disease. Brodsky says he has had several patients with a complement disorder called paroxysmal nocturnal hemoglobinuria whose symptoms worsened after receiving a COVID-19

vaccine. "It doesn't prove anything, but there is a lot of smoke here."

Some have instead speculated that specific batches of the vaccine caused the problem, for instance because they were contaminated or contained a higher dose. That's unlikely, Cooke said yesterday, because across Europe, the patients received doses from many different batches. AstraZeneca supplies Europe with vaccine from several plants, however, and EMA could not say whether all of the batches involved came from the same facility.

AstraZeneca said in a statement that "a careful review of all available safety data of more than 17 million people vaccinated in the European Union and UK with COVID-19 Vaccine AstraZeneca has shown no evidence of an increased risk of pulmonary embolism, deep vein thrombosis or thrombocytopenia, in any defined age group, gender, batch or in any particular country. ... The Company is keeping this issue under close review but available evidence does not confirm that the vaccine is the cause."

The pause is quickly developing into a full-blown crisis for Europe, where vaccination has been sluggish compared with the United States and the United Kingdom while cases have raced upward, thanks in part to more transmissible variants. Several hundred thousand people per day were receiving the AstraZeneca vaccine across Europe until last weekend. That puts enormous pressure on regulatory agencies to resolve the issue quickly.

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

[Paul Hunter, an infectious disease expert at the University of East Anglia, noted in a statement that even if the risk of CVT is raised by the vaccine to five or more cases per million people vaccinated, the](#)

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Given the rarity of the syndrome and the vaccine’s enormous benefits, it might be worth restarting immunizations even if the complications are connected to the vaccine, but with precautions, Cichutek says, such as informing people about what to do if certain symptoms appear or excluding some groups of people from the vaccinations. “If possible, we need to have a European decision this week on the basis of what we know,” Cichutek says.

Brodsky says the people to watch might be the same people who are at very high risk from COVID-19, which could mean that the risk of getting the virus still exceeds that of developing these blood issues.

Karl Lauterbach, a German politician and epidemiologist, says he would have let the vaccinations continue while the safety concerns are investigated. But Wendtner says officials had little choice given the severity of the reactions. In communicating about vaccine or drug safety, he says, “there is nothing worse than trying to sweep things under the rug.” If the investigations show there was no connection to the vaccine, he says, “then we can be even more certain that the vaccine is safe.”

*\*Update, 17 March, 4:55 p.m.: This story has been updated to add comments from Robert Brodsky.*

Posted in: [Health](#), [Coronavirus](#)

doi:10.1126/science.abi5259



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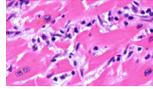
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