A nurse fills a syringe with the Johnson & Johnson COVID-19 vaccine at a pop-up vaccination site in New York City on 8 April. MARY ALTAFFER/AP

Concerns over rare clotting disorders halt use of Johnson & Johnson's COVID-19 vaccine

By **Gretchen Vogel**, **Kai Kupferschmidt** | Apr. 13, 2021 , 4:50 PM

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A rare but very serious side effect that has **complicated Europe's COVID-19 vaccination schedules** for the past month has now thrown a wrench into U.S. immunization efforts as well. In a **joint statement on Tuesday morning**, the U.S. Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) announced they were "recommending a pause" in the use of the COVID-19 vaccine made by Johnson & Johnson (J&J) "out of an abundance of caution."

The move came after six cases of a rare clotting disorder, also seen in some people vaccinated with AstraZeneca's vaccine, were reported among more than 6.8 million people vaccinated with the J&J vaccine in the United States. All cases occurred in

women between the ages of 18 and 48. One of them died.

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"While these events are very rare, we're recommending a pause in the use of the J&J COVID-19 vaccine in order to prepare the health care system to recognize and treat patients appropriately and to report severe events they may be seeing," FDA acting Commissioner Janet Woodcock said at a press conference. J&J announced it had decided "to proactively delay the rollout" of the vaccine in Europe, where it has not yet been used, as well. The European Medicines Agency (EMA) announced on Friday it was investigating reports of four clotting cases in the United States following use of the vaccine.

The U.S. move is warranted, says Gowthami Arepally, a hematologist at the Duke University School of Medicine, given that the constellation of symptoms, cerebral venous sinus thromboses and low platelet counts, is very unusual. "People don't come in off the streets, with clots at unusual places, and low platelets. It's just not a background signal that we have," she says. Seeing cases on both sides of the Atlantic Ocean with two similar vaccines "does really increase the concern for a vaccine-related complication."

When a similar safety signal was first noticed in Europe after vaccination with the AstraZeneca

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vaccine, named Vaxzevria, about 6 weeks ago, EMA did not recommend pausing use of the vaccine but **several countries suspended it for a while** and many are now vaccinating only older age groups with it, where the risk of severe COVID-19 is highest. Cases of unusual clotting with low platelets have not been seen in recipients of the messenger RNA–based vaccines made by Pfizer or Moderna.

Both Vaxzevria and the J&J vaccine are based on a modified adenovirus, so researchers are looking at whether something about that technology could be triggering the side effect. So far, no similar cases have been reported in people who received two other adenovirus-based vaccines: Russia's Sputnik V and China's CanSino Biologics vaccine. But data on both vaccines have been limited, and it isn't clear that regulators in regions where they have been used would either pick up or report such safety signals, says Peter Hotez, a virologist and vaccine researcher at Baylor College of Medicine. (Hotez is involved in developing a protein-based COVID-19 vaccine.)

Researchers who have been investigating the possible causes **have termed the rare complication** vaccine-induced immune thrombotic thrombocytopenia (VITT). Similar to a side effect called heparin-induced thrombocytopenia, the patients in Europe harbored antibodies against a protein called platelet factor 4 that appear to activate platelets, leading to widespread clotting. It is not yet clear whether these antibodies have also been found in the U.S. patients. How the vaccines could lead to VITT is being investigated.

For now, the number of cases in the United States appears to be much lower than in Europe, where more than 222 suspected cases have been reported among 34 million Vaxzevria recipients. But more cases may surface, says Anthony Cox, an expert on pharmacovigilance at the University of Birmingham: "There is probably some underreporting … and the FDA report will lead to more cases being reported as a result of raised awareness."

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The attention should also help ensure that patients are treated appropriately, FDA's Peter Marks said at the press conference. That includes avoiding heparin, which many doctors normally prescribe for clotting problems. "If you're treating this with heparin you are just throwing fuel on the fire," Arepally says.

The U.S. agencies' move increases concerns about both vaccines' global rollout. Because of their low cost and relatively easy transport and storage, Vaxzevria and the J&J vaccine, which requires only a single dose, have been a key part of plans to vaccinate billions of people in low- and middle-income countries. "I'm really worried how we're going to manage this outside wealthy countries that have access to multiple vaccines," Hotez says. "A lot of countries are going to be in a very difficult position now."

Woodcock today suggested the U.S. suspension might be short-lived: "The time frame will depend obviously on what we learn in the next few days. However, we expect it to be a matter of days for this pause." A joint FDA-CDC committee is expected to meet on Wednesday to assess the cases and advise on further use of the J&J vaccine.

An interruption may not have been necessary at all, Cox says. EMA never recommended a pause for Vaxzevria in spite of many more cases of the serious side effect, he points out. Pending further studies, "I think warnings as per EMA on overall risk-benefit would have been sufficient," he says.

But Paul Offit, a vaccine researcher at the Children's Hospital of Philadelphia, says suspending use of the J&J vaccine while more data is gathered was the right decision. "I think this was the only thing they could do," he says. Offit sees essentially three ways forward: Accept that this is a rare side effect and keep vaccinating because the benefits outweigh the risk, limit the vaccine to groups where the risk-benefit assessment is clearer, or stop using this vaccine altogether. Based on Europe's experience, he says, "I think the best route honestly would be to limit this, for instance to men over 55," where the risk of COVID-19

complications is much higher and the risk of side effects may be lower.

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