



People line up to receive AstraZeneca's COVID-19 vaccine in Belfast, Northern Ireland.

COVID-19

Vaccine link to serious clotting disorder firms up

Rare symptoms seen in AstraZeneca recipients occur after Johnson & Johnson shot as well

By Kai Kupferschmidt and Gretchen Vogel

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. Researchers believe the problem, characterized by dangerous blood clots and low platelet counts, may be triggered by vaccines produced by AstraZeneca and Johnson & Johnson (J&J), which both contain a modified adenovirus. They have identified an errant immune reaction as the possible cause, but don't yet understand how it arises.

There are 222 suspected cases of the syndrome so far in Europe among 34 million people who have received their first dose of the AstraZeneca vaccine, recently named Vaxzevria; more than 30 have died. The European Medicines Agency (EMA) on 7 April acknowledged "a probable causal association" between the syndrome and the vaccine, and some countries have restricted Vaxzevria to older age groups at higher risks of severe COVID-19.

On 13 April, U.S. authorities said they would pause use of the J&J vaccine, which 6.8 million people have received so far, after six similar cases, including one death.

The move was out of "an abundance of caution," said Peter Marks of the U.S. Food and Drug Administration (FDA), and prompted in part by the similarity to the symptoms observed in Europe. In response, J&J said it would "proactively delay the rollout of our vaccine in Europe," where it was recently authorized for use.

As *Science* went to press, a joint committee of FDA and the Centers for Disease Control and Prevention was expected to meet on 14 April to assess the cases and advise on further use of the J&J vaccine. (FDA has not yet authorized use of the AstraZeneca vaccine.) The similar problems on both sides of the Atlantic Ocean "really increase the concern for a vaccine-related complication," says hematologist Gowthami Arepally of Duke University School of Medicine, who is an external consultant with AstraZeneca.

So far, no similar cases have been reported in people who received Russia's Sputnik V or China's CanSino Biologics vaccine, which are both based on an adenovirus as well. But data on those vaccines have been limited, and it isn't clear that regulators in regions where they have been used would either pick up on or report such safety sig-

nals, says Peter Hotez, a virologist and vaccine expert at Baylor College of Medicine. (Hotez is involved in the development of a protein-based COVID-19 vaccine.)

Researchers stress that the troubles by no means spell the end for the two vaccines. In the vast majority of cases, their benefits outweigh the risks, and the cheap and easy to store shots still offer the best hope for vaccinating large numbers of people in low- and middle-income countries.

On 9 April in *The New England Journal of Medicine*, one research team published its observations on 11 Vaxzevria recipients in Germany and Austria and another published data on five patients in Norway. Both found that symptoms resemble a

rare reaction to the drug heparin, called heparin-induced thrombocytopenia (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. They propose calling the syndrome vaccine-induced immune thrombotic thrombocytopenia.

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One of the groups, led by clotting expert Andreas Greinacher of the University of Greifswald, also speculates about a mechanism. Vaxzevria, the J&J shot, and similar vaccines consist of an adenovirus engineered to infect cells and prompt them to produce the pandemic coronavirus' spike protein. Among the 50 billion virus particles in each Vaxzevria dose, some may break apart and release their DNA, Greinacher says. Like heparin, DNA is negatively charged, which could cause it to bind to PF4, which has a positive charge. The complex might then trigger the production of antibodies, especially when the immune system is on high alert because of the vaccine.

Alternatively, the antibodies may already be present in the patients and the vaccine may just boost them. Many healthy people harbor antibodies against PF4, but they are kept in check by an immune mechanism called peripheral tolerance, Arepally says. "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?"

Several early ideas about a cause could not be substantiated. A past bout of COVID-19 is not the issue; none of the five patients in Norway had been infected. Others have suggested antibodies against the virus' spike protein—which many vaccines seek to elicit—also recognize PF4, which could spell trouble for many 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 in both the United States and Europe, are causing similar disorders.

For Vaxzevria, Greinacher and his collaborator Rolf Marschalek, a molecular biologist at Frankfurt University, are calling for tests of a simple solution: halving the 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 a reduced dose is also less likely to trigger the kind of strong inflammation that boosts PF4 antibodies, the researchers say. And unexpectedly, those people were slightly better protected, perhaps because high levels of inflammation can actually block the formation of antibodies. "Part of the problem might be that they just overdose" the vaccine, Greinacher says.

That remains to be seen, 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 protect twice as many people—with fewer side effects. ■

U.S. SCIENCE POLICY

Biden proposes a funding surge—and new agencies to manage it

White House floats three new ARPA-like research offices in 2022 spending request to Congress

By Jeffrey Mervis

President Joe Biden wants to go big and bold on science. The research community loves the big, but it has questions about the bold—especially Biden's plan for three new funding entities dedicated to health, technology, and climate.

Last week, in his 2022 budget request, Biden laid out a \$1.5 trillion blueprint that would increase discretionary spending by 8.4%. The \$118 billion bump would fund healthy boosts at many federal research agencies (see table, right), including 20% hikes at the two largest: the National Institutes of Health (NIH), to \$51 billion, and the National Science Foundation (NSF), to \$10.2 billion. Biden is also asking Congress to expand their missions, creating units that would build on their basic research portfolios to address pressing societal problems.

NIH would get \$6.5 billion to stand up an Advanced Research Projects Agency-Health (ARPA-H) initially focused on cancer, diabetes, and Alzheimer's disease. NSF would get a new technology directorate, of an unspecified size, that would lead the nation's efforts to outinnovate China (*Science*, 9 April, p. 112). Biden also wants to create an ARPA-Climate to take more aggressive steps against global warming, although he didn't say where it would be housed.

The model for all three entities is the military's Defense Advanced Research Projects Agency (DARPA). Created during the Cold War, DARPA has both developed high-tech weaponry and funded research on civilian technologies that have spawned trillion-dollar industries. In the past 2 decades, lawmakers have used DARPA's template to create three additional ARPAs tasked with combating bioterrorism, developing new energy technologies, and assisting the intelligence community.

Arati Prabhakar, a former DARPA director, calls the approach "solutions R&D." She's thrilled that the Biden administration wants to expand on it. "The president is asking the R&D community to help with some of the biggest problems facing the country," says Prabhakar, who in 2019

founded Actuate, a California-based non-profit working with private philanthropy to tackle some of those challenges.

Unlike most federal research agencies, which rely on scientists to submit ideas that fit into long-standing program areas and ask outside experts to judge their merit, DARPA gives its program managers the freedom to both solicit proposals and decide which should be funded. They are also quick to end projects that aren't making sufficient progress toward interim milestones. In contrast, other agencies that award basic research grants often give investigators considerable leeway to change course during the lifetime of the award.

Prabhakar says those features have helped DARPA be successful. But she warns against "tarnishing the brand [by] slapping the label on something that isn't

A rising tide

A White House outline of President Joe Biden's 2022 budget request included these highlights for research.

NIH	\$51 billion (20% increase)
NSF	\$10.2 billion (20% increase)
DOE science	\$7.4 billion (5.5% increase)
NASA earth science	\$2.25 billion (12.5% increase)
NOAA	\$6.9 billion (16% increase)
EPA	\$11 billion (21% increase)
NIST labs	\$916 million (16% increase)
ARPA-Energy and new ARPA-Climate	\$1 billion combined, up from \$427 million for ARPA-E alone

really DARPA." It's important, she says, that any new DARPA clone address a pressing national need that can be met with innovative technology.

The president's 9 April budget outline doesn't give many details about ARPA-H. But the idea has been around for decades, and advocates say it meets Prabhakar's test. They argue that not enough NIH-funded research leads to treatments and cures. "ARPA-H is recognition that funding basic research doesn't necessarily drive commercial innovation and that there are market

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