

HOME > NEWS > SCIENCEINSIDER > DO PRESERVATIVE AND STRAY PROTEINS CAUSE RARE COVID-19 VACCINE SIDE EFFECT?

SCIENCEINSIDER | EUROPE

Do preservative and stray proteins cause rare COVID-19 vaccine side effect?

Research team further details hypothesis for dangerous clotting cascade after analyzing contents of AstraZeneca's vaccine

22 APR 2021 • BY GRETCHEN VOGEL, KAI KUPFERSCHMIDT



The European Medicines Agency paved the way this week for Europe's use of a COVID-19 vaccine made by Johnson & Johnson, but questions persist about a rare clotting side effect linked to it and a similar vaccine made by AstraZeneca. ROB ENGLAAR/ANP/NEWSCOM

SHARE: [Twitter](#) [LinkedIn](#) [Facebook](#) [Reddit](#) [WhatsApp](#) [Email](#)

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

Researchers in Germany and Canada have added provocative new details to their proposal for how the COVID-19 vaccine made by AstraZeneca might be causing an unusual clotting disorder in a small number of recipients. The mechanism, involving stray human proteins and a preservative in the vaccine, remains speculative. And it is not clear whether their hypothesis explains similar reactions observed in recipients of the COVID-19 vaccine made by Johnson & Johnson (J&J).

The new data are "interesting but not a smoking gun by any means" for the group's hypothesis, says Gowthami Arepally, a hematologist at the Duke University School of Medicine who is working as an external consultant with AstraZeneca on the issue. But figuring out what in a COVID-19 vaccine might start the sometimes fatal combination of blood clotting and low platelets is crucial for developing better treatments for the side effect and possibly for understanding who might be most at risk, says Paul Offit, a vaccine researcher at the Children's Hospital of Philadelphia (CHOP). It could also be vital for modifying vaccines so they don't kick-start the reaction, which researchers are calling vaccine-induced immune thrombotic thrombocytopenia (VITT).

Vaccine regulators are struggling to balance the small risk of VITT versus the clear need to immunize people against the pandemic virus SARS-CoV-2. The European Medicines Agency (EMA) declared on Tuesday that the COVID-19 protection of the J&J vaccine significantly outweighs the danger of the rare side effect and recommended its use, with an addition to the warning label that alerts doctors and recipients to the clotting problem. That advice, which matches EMA's verdict on the AstraZeneca vaccine, cleared the way for vaccinations with the J&J shots to begin across Europe.

Both J&J and AstraZeneca use modified adenoviruses to deliver and express the spike protein gene of SARS-CoV-2. But new data posted Tuesday in a preprint on Research Square show that doses of the AstraZeneca vaccine also contain significant amounts of protein from human cells—presumably from the human cell line used to grow the virus during the manufacturing process. The preprint's authors, some whom were among the first to identify the VITT side effect, propose that these proteins, together with another component of the vaccine called ethylenediaminetetraacetic acid (EDTA), may set off a dangerous response by the immune system in some vaccine recipients.

EDTA is used in some vaccines as a preservative, but it is also known to make blood vessels a bit leaky, says Andreas Greinacher, an expert on clotting at the University of Greifswald who led the study. He said he was surprised at the concentration the group found in the AstraZeneca vaccine samples they examined: 100 micromoles, which is much higher than amounts listed for other common vaccines.



The group showed that in a mouse model, the vaccine did increase vascular leakage. Greinacher says this may make any free proteins in a vaccine dose more likely to encounter platelets, or thrombocytes, in a recipient's bloodstream. Platelet factor 4 (PF4), a protein secreted by these thrombocytes, could then form complexes with the residual human proteins and other components of the vaccine, thanks to its strong positive charge. Indeed, when the researchers added PF4 to the vaccine in the lab, large complexes formed. Greinacher notes that other vaccines contain human proteins, but the amount—between 70 and 80 micrograms per milliliter (mcg/mL) in the four batches they tested—was "surprisingly high," he says. Other vaccines list amounts of 5 mcg/mL or less, although many do not specify an amount.

In a tiny minority of people, Greinacher and his colleagues speculate, the combination of PF4 complexes and the strong inflammation triggered by the vaccine may turn on a specialized set of immune cells that can make antibodies to PF4. (This also happens in a similar clotting syndrome triggered by the blood thinner heparin. In that case, heparin forms the problematic complexes with PF4.) In an even smaller minority, the researchers say, the antibodies to PF4 are strong enough to fuel additional immune reactions in the blood that deplete platelets in the blood and cause potentially deadly clots to form in the brain, abdomen, or lungs.

Those PF4 antibodies can be useful if the body is fighting off severe infection—but they can get out of control, Greinacher says. "It's like waking a sleeping dragon," he says. "In most cases, we really want to keep the dragon sleeping, and the vaccine is like a guy coming into a cave and throwing stones at it." An AstraZeneca spokesperson said the company could not comment directly on the preprint, but that they "continue to work to understand the individual cases, epidemiology, and possible mechanisms that could explain these rare events."

Greinacher has asked J&J for doses of its vaccine so he can analyze its contents and see whether it might trigger the same cascade. The vaccine had not been used yet in Germany, which he says prevented him from using it in his initial experiments.

Offit notes that other vaccines are grown in cell culture and contain cellular debris, and it isn't clear that AstraZeneca's contains more or different remnants. EDTA may also not be needed to trigger VITT; J&J's COVID-19 vaccine doesn't include it, for instance. "Adenovirus has a notorious history of being a particularly inflammatory stimulating virus," says Mortimer Poncz, a pediatric hematologist at CHOP. "Whether the EDTA is involved, I think, is the softest part of the whole story."

Arepally agrees. "The virus itself, which has been given in such large amounts, is probably enough to cause an inflammatory response," she says. Arepally suggests PF4 simply binds to the adenovirus—which could, in theory, be why the J&J vaccine produces the same side effect. She speculates that a few unlucky people "simply have higher levels of PF4 for some reason and that's why they are forming these complexes when they get the vaccine."

Poncz, on the other hand, isn't convinced PF4 complexes are actually behind the clotting problems. The complexes may be innocent bystanders, he says, although he applauds Greinacher "for leading the field and providing thought-provoking and experiment-provoking questions."

Rolf Marschalek, a molecular biologist at Goethe University Frankfurt, suspects that additional spike-related mechanisms may play a role once a vaccinated person's cells start to make the viral protein, which happens in the same time frame as the clotting disorders appear, generally between 4 to 20 days following vaccination. These might then add to the PF4 antibody cascade which the Greifswald group describes, he says.

Even as the spotlight shines on the J&J and AstraZeneca vaccines, scrutiny is widening to two other COVID-19 vaccines that rely on adenovirus vectors: Sputnik V, developed by the Russian Gamaleya National Research Institute of Epidemiology and Microbiology, and another made by the Chinese company CanSino Biologics. CanSino CEO Yu Xuefeng told journalists the company is monitoring recipients more carefully after the clotting reports emerged. The Gamaleya Institute said in a press release there had been no reports of clotting disorders following its vaccine rollout in many countries, although it's not clear how many people have received it so far.

Hungary is already using Sputnik V, and several other European countries are considering purchases, but EMA has not yet approved it for use. EMA Director Emer Cooke says the agency's review of safety data for the vaccine "is at an early stage," and it has not yet looked carefully at data regarding possible side effects. "But now that we are aware of [VITT], will make sure it's part of the company's responsibility to report any of these events."

***Update, 22 April, 3 p.m.:** This story has been updated to include a statement from AstraZeneca.

***Clarification, 22 April, 3:40 p.m.:** This story originally said the AstraZeneca vaccine was grown in human kidney cells. Although they are grown in a cell line derived from an embryonic human kidney, recent studies suggest the cells have an adrenal identity.

doi: 10.1126/science.abj1373

RELEVANT TAGS:

[EUROPE](#) [HEALTH](#) [CORONAVIRUS](#)

ABOUT THE AUTHOR



Gretchen Vogel [✉](#) [T](#)
Author

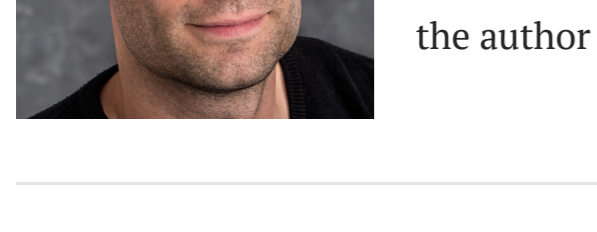
Gretchen Vogel is a contributing correspondent for *Science* magazine based in Berlin, Germany.



Kai Kupferschmidt [T](#)
Author

Kai is a contributing correspondent for *Science* magazine based in Berlin, Germany. He is the author of a book about the color blue, published in 2019.

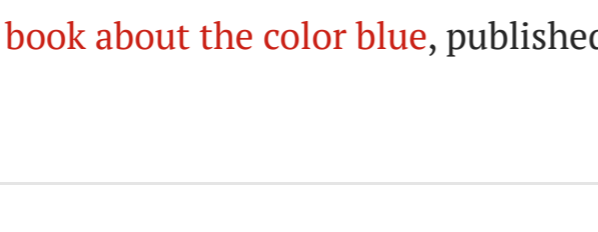
MORE FROM NEWS



24 AUG 2022

All-seeing telescope will snap exploding stars, may spy a hidden world

BY DANIEL CLERY



24 AUG 2022

Scientists exposed plants to a yearlong drought. The result is worrying for climate change

BY ELIZABETH PENNISI



24 AUG 2022

Human ancestors were walking upright 7 million years ago, ancient limb bone...

BY ANN GIBBONS

[VIEW MORE >](#)

Got a tip for Science's news department?

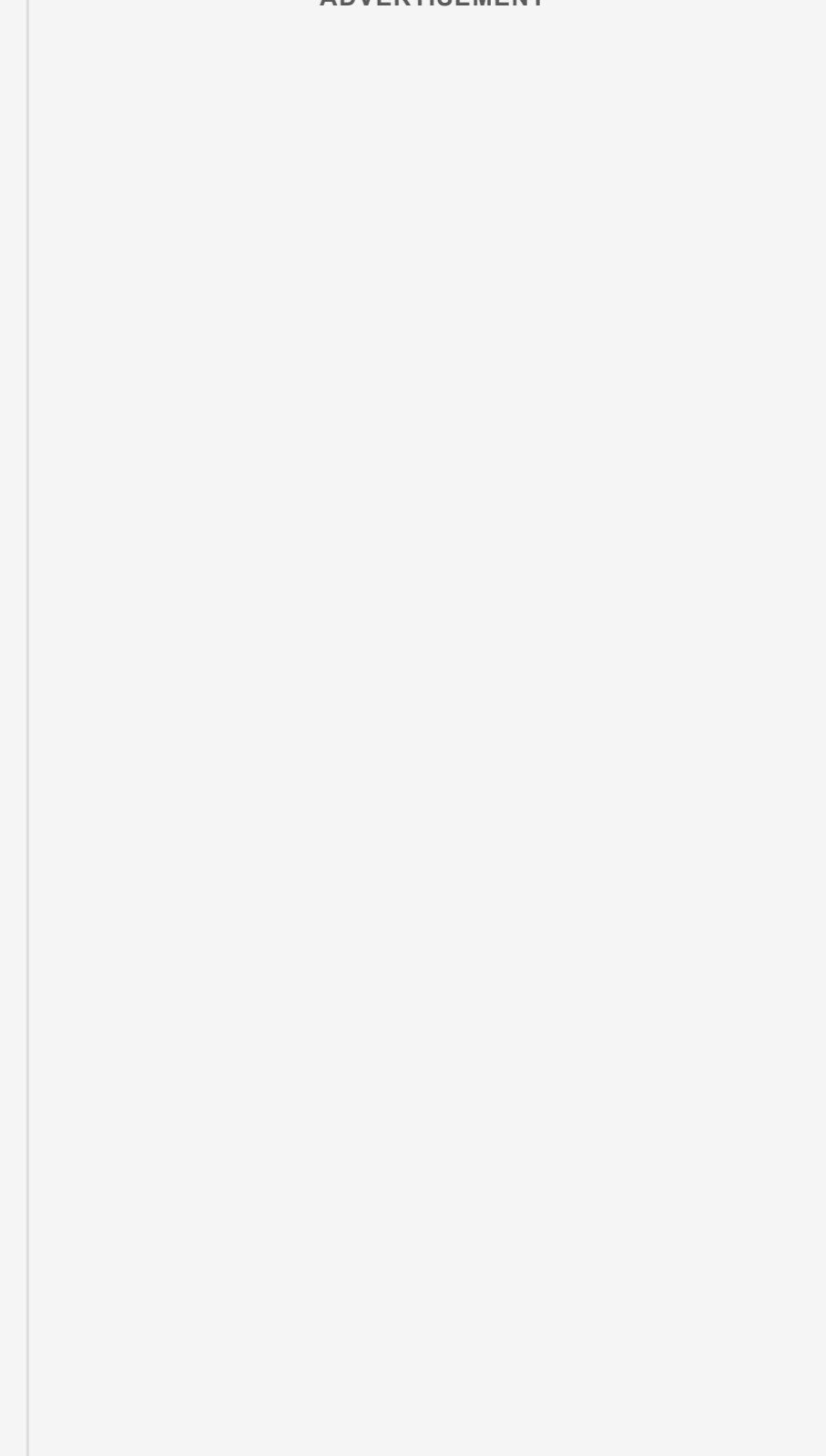
[CONNECT >](#)

Subscribe to News from Science

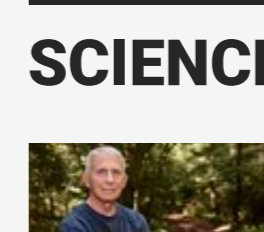
Don't yet have access? Subscribe to News from Science for full access to breaking news and analysis on research and science policy.

[SUBSCRIBE >](#)

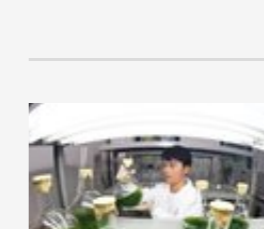
ADVERTISEMENT



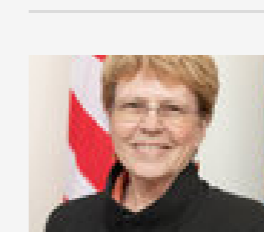
SCIENCEINSIDER 1



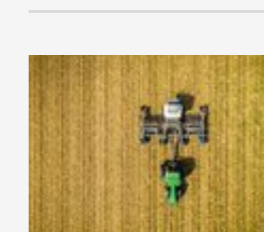
22 AUG 2022 BY JOCELYN KAISER
He battled AIDS, COVID-19, and Trump. Now, Anthony Fauci is stepping down



17 AUG 2022 BY JEFFREY BRAINARD, DENNIS NORMILE
China rises to first place in most cited papers



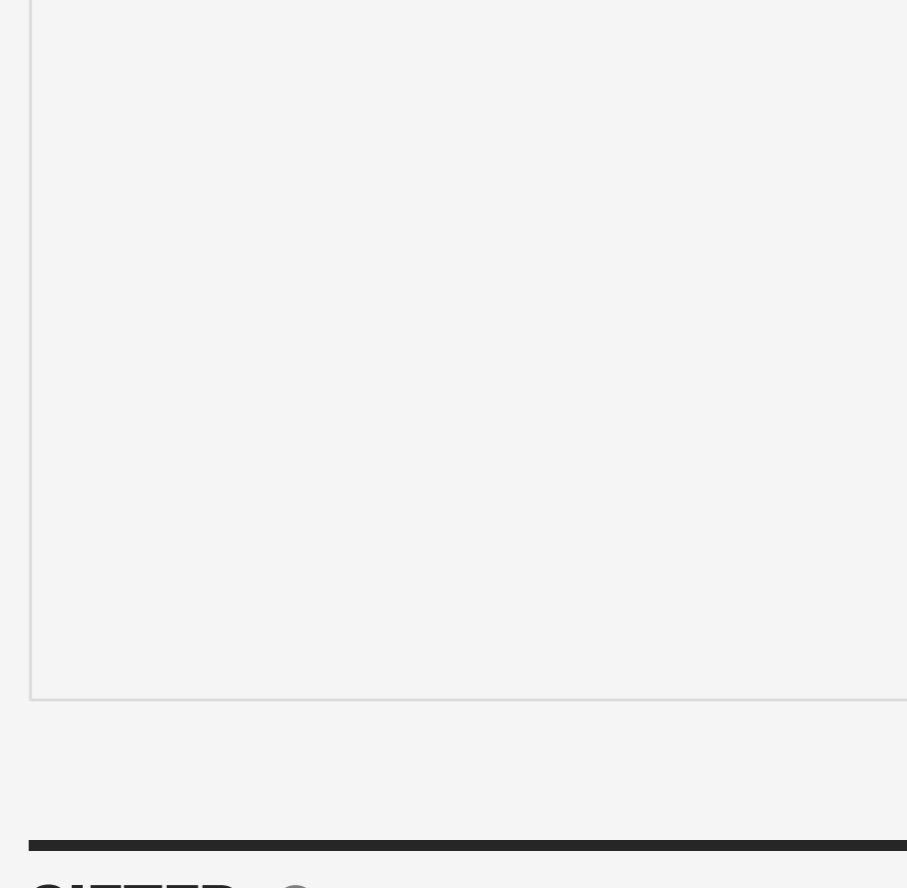
17 AUG 2022 BY JOHN TRAVIS, MEREDITH WADMAN
NAS sanctions White House official, changes bylaws to allow member suspensions



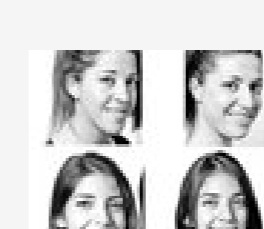
16 AUG 2022 BY ERIK STOKSTAD
Can farmers fight climate change? New U.S. law gives them billions to try

[VIEW MORE >](#)

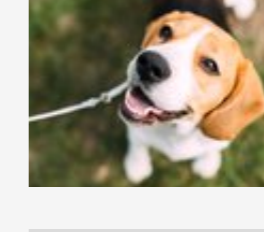
ADVERTISEMENT



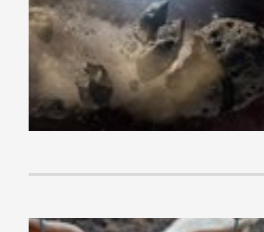
SIFTER 1



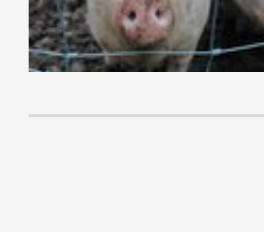
24 AUG 2022 BY JOCELYN KAISER
Those doppelgängers don't just look like you—they may share your DNA



22 AUG 2022 BY DAVID GRIMM
Do dogs cry 'happy tears' when reunited with owners?



18 AUG 2022 BY ZACK SAVITSKY
Dinosaur-killing asteroid may have had siblings



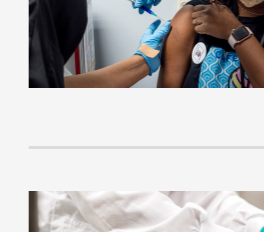
3 AUG 2022 BY JACKLIN KWAN
Pig organs revived 1 hour after animals' death

[VIEW MORE >](#)

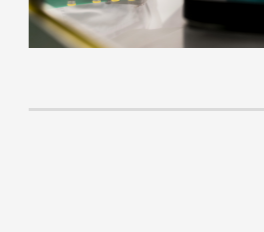
RECOMMENDED

IN DEPTH | APRIL 2020

Vaccine designers take first shots at COVID-19



14 JUN 2021 BY MEREDITH WADMAN
Powerful new COVID-19 vaccine shows 90% efficacy, could boost world's supply



29 JAN 2021 BY JON COHEN
One-dose COVID-19 vaccine offers solid protection against severe disease



13 APR 2021 BY GRETCHEN VOGEL, KAI KUPFERSCHMIDT
Concerns over rare clotting disorders halt use of Johnson & Johnson's COVID-19 vaccine

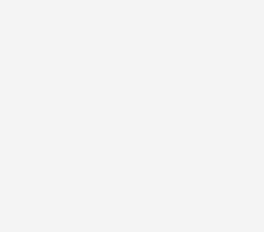
RECOMMENDED

IN DEPTH | APRIL 2020

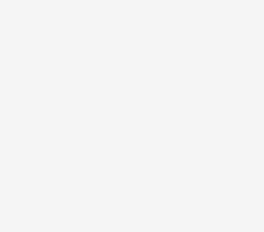
Vaccine designers take first shots at COVID-19



14 JUN 2021 BY MEREDITH WADMAN
Powerful new COVID-19 vaccine shows 90% efficacy, could boost world's supply



29 JAN 2021 BY JON COHEN
One-dose COVID-19 vaccine offers solid protection against severe disease



13 APR 2021 BY GRETCHEN VOGEL, KAI KUPFERSCHMIDT
Concerns over rare clotting disorders halt use of Johnson & Johnson's COVID-19 vaccine

ADVERTISEMENT

Science

Science Advances

Science Immunology

Science Robotics

Science Signaling

Science Translational Medicine

NEWS

All News
ScienceInsider
News Features
Subscribe to News from Science
News from Science FAQ
About News from Science

CAREERS

Careers Articles
Find Jobs
Employer Profiles

COMMENTARY

Opinion
Analysis
Blogs

JOURNALS

Science
Science Advances
Science Immunology
Science Robotics
Science Signaling
Science Translational Medicine
Science Partner Journals

AUTHORS & REVIEWERS

Information for Authors
Information for Reviewers

FOLLOW US

[Facebook](#) [Twitter](#) [Instagram](#)
[YouTube](#) [RSS](#) [WhatsApp](#)

LIBRARIANS

Manage Your Institutional Subscription
Library Admin Portal
Request a Quote
Librarian FAQs

ADVERTISERS

Advertising Kits
Custom Publishing Info
Post a Job

RELATED SITES

AAAS.org
AAAS Communities
EurekAlert!
Science in the Classroom

ABOUT US

Leadership
Work at AAAS
Prizes and Awards

HELP

FAQs
Access and Subscriptions
Order a Single Issue
Reprints and Permissions
TOC Alerts and RSS Feeds
Contact Us

AAAS

© 2022 American Association for the Advancement of Science. All rights reserved. AAAS is a partner of HINARI, AGORA, OARE, CHORUS, CLOCKSS, CrossRef and COUNTER.