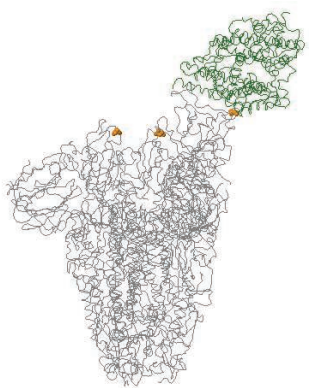
amino acids in the spike protein. It, too, had appeared before: It was found, together with another mutation named D796H, in the virus of a COVID-19 patient in Cambridge, U.K., who was given plasma from recovered patients as a treatment, but eventually died. In lab studies, the patient's strain was less susceptible to convalescent plasma from several donors than wild-type virus, says Ravindra Gupta, a virologist at the University of Cambridge who published the findings in a preprint in early December.

Gupta also engineered a lentivirus to express mutated versions of SARS-CoV-2's spike and found that the deletion alone made the virus twice as infectious for human cells. A third mutation, P681H, is one to watch as well, says virologist Christian Drosten of the Charité University Hospital in Berlin, because it changes the site where the spike protein is cleaved before it enters human cells.



The mutation N501Y affects amino acids (yellow) in the spike protein, which binds to a human receptor (green).

New virus strains are common in outbreaks and often spark alarm, but few are ultimately consequential. So U.K. scientists and others were initially cautious about concluding that B.1.1.7's mutations made the virus better at spreading from person to person. But the new variant is rapidly replacing other viruses, says Müge Çevik, an infectious disease specialist at the University of St. Andrews. Yet exactly what impact each mutation has is much more difficult to assess than spotting them or showing they're on the rise, says Seema Lakdawala, a biologist at the University of Pittsburgh.

Animal experiments can help show an effect, but they have limitations. Hamsters already transmit SARS-CoV-2 virus rapidly, for instance, which could obscure any effect of the new variant. Ferrets transmit it less efficiently, so a difference may be more easily detectable, Lakdawala says. "But does that really translate to humans? I doubt it." A definitive answer may be months off, she predicts.

The slew of mutations also raised worries that the South African or U.K. lineage might lead to more severe disease or even evade vaccine-induced immunity. So far there is little reason to think so. Whereas some mutations have been shown to let the virus evade monoclonal antibodies, vaccines and natural infections both appear to lead to a broad immune response that targets many parts of the virus, says Shane Crotty of the La Jolla Institute for Immunology. "It would be a real challenge for a virus to escape from that." The measles and polio viruses have never learned to escape the vaccines targeting them, he notes: "Those are historical examples suggesting not to freak out."

At a 22 December press conference, BioNTech CEO Uğur Şahin pointed out that the U.K. variant differed in only nine of more than 1270 amino acids of the spike protein encoded by the messenger RNA in the very effective COVID-19 vaccine his company developed with Pfizer. "Scientifically it is highly likely that the immune response by this vaccine also can deal with the new virus," he said. Experiments are underway that should soon confirm that, Şahin added.

Another major question is how the virus accumulated a host of mutations in one go. So far, SARS-CoV-2 typically acquired only one to two mutations per month. Scientists believe the new variant may have gone through a lengthy bout of rapid evolution in a chronically infected patient who then transmitted the virus. "We know this is rare but it can happen," says World Health Organization epidemiologist Maria Van Kerkhove.

Sébastien Calvignac-Spencer, an evolutionary virologist at the Robert Koch Institute, says the United Kingdom's new COVID-19 lockdown and other countries' border closures mark the first time such drastic action has been taken based on genomic surveillance in combination with epidemiological data. "It's pretty unprecedented at this scale," he says. But the question of how to react to disconcerting mutations in pathogens will crop up more often, he predicts. Most people are happy they prepared for a category 4 hurricane even if the predictions turns out to be wrong, Calvignac-Spencer says. "This is a bit the same, except that we have much less experience with genomic surveillance than we have with the weather forecast."

To Van Kerkhove, the arrival of B.1.1.7 shows how important it is to follow viral evolution closely. The United Kingdom has one of the most elaborate monitoring systems in the world, she says. "My worry is: How much of this is happening globally, where we don't have sequencing capacity?" Other countries should beef up their efforts, she says. And all countries should do what they can to minimize transmission of SARS-CoV-2 in the months ahead, Van Kerkhove adds. "The more of this virus circulates, the more opportunity it will have to change," she says. "We're playing a very dangerous game here." ■

COVID-19

Pfizer's vaccine raises allergy concerns

Polymer in mRNA's "packaging" may cause rare anaphylactic reactions

By **Jop de Vrieze**

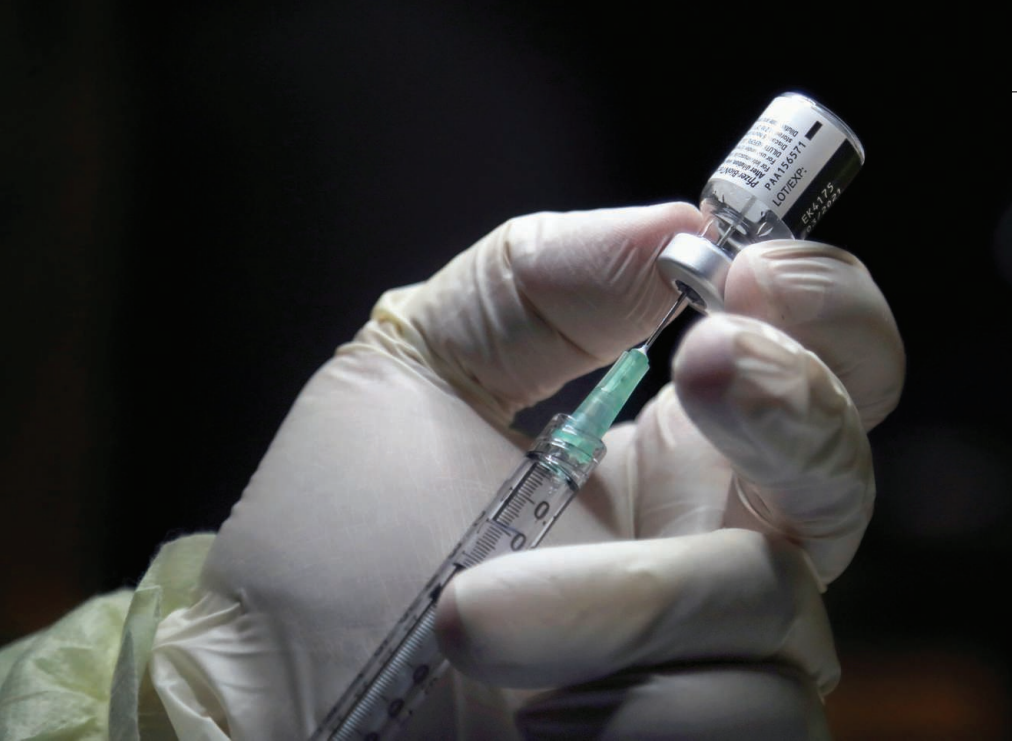
Severe allergy-like reactions in at least 12 people who received the COVID-19 vaccine produced by Pfizer and BioNTech may be due to a compound in the packaging of the messenger RNA (mRNA) that forms the vaccine's main ingredient, scientists say. A similar mRNA vaccine developed by Moderna also contains the compound, polyethylene glycol (PEG).

PEG has never been used before in vaccines but it is part of many drugs, some of which have occasionally triggered anaphylaxis—a potentially life-threatening reaction that can cause rashes, a plummeting blood pressure, shortness of breath, and a fast heartbeat. Some allergists and immunologists believe a small number of people previously exposed to PEG may have high levels of antibodies against it, putting them at risk of an anaphylactic reaction to the vaccine.

Others are skeptical of the link. Still, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) was concerned enough to convene several meetings last month to discuss the reactions with independent scientists, physicians, representatives of Pfizer and Moderna, and the Food and Drug Administration (FDA). NIAID is also setting up a study in collaboration with FDA to analyze the response to the vaccine in people who have high levels of anti-PEG antibodies or have experienced severe allergic responses to drugs or vaccines before. "Until we know there is truly a PEG story, we need to be very careful in talking about that as a done deal," says Alkis Togias, branch chief of allergy, asthma, and airway biology at NIAID.

Pfizer, too, says it is "actively seeking follow-up." A statement emailed to *Science* noted it already recommends that "appropriate medical treatment and supervision should always be readily available" in case a vaccinee develops anaphylaxis.

Reports about the allergic reactions have created anxiety among potential vaccine recipients. "Allergies in general are so common



At least 12 people suffered an anaphylactic reaction after receiving Pfizer's COVID-19 vaccine.

PHOTO: CARLOS OSORIO/POOL/AFP/GETTY IMAGES

in the population that this could create a resistance against the vaccines in the population," says Janos Szebeni, an immunologist at Semmelweis University in Budapest, Hungary, who has long studied hypersensitivity reactions to PEG.

Anaphylactic reactions can occur with any vaccine but are extremely rare—about one per 1 million doses. As of 23 December 2020, the United States had seen 10 cases of anaphylaxis among 614,117 people who received the COVID-19 vaccine; the United Kingdom had recorded two. Because the Pfizer and Moderna mRNA vaccines use a new platform, the reactions call for careful scrutiny, says Elizabeth Phillips, a drug hypersensitivity researcher at Vanderbilt University Medical Center who attended an NIAID meeting on 16 December. "This is new."

Clinical trials of the vaccines, which involved tens of thousands of people, did not find serious adverse events caused by the vaccine. But both studies excluded people with a history of allergies to components of the COVID-19 vaccines; Pfizer also excluded those who previously had a severe adverse reaction from any vaccine.

The two COVID-19 vaccines both contain mRNA wrapped in lipid nanoparticles (LNPs) that help carry it to human cells but also act as an adjuvant, a vaccine ingredient that bolsters the immune response. The LNPs are "PEGylated"—chemically attached to PEG molecules that cover the outside of the particles and increase their life span.

PEGs are also used in everyday products such as toothpaste and shampoo as thickeners, solvents, and softeners, and they've been used in laxatives for decades. An increasing number of biopharmaceuticals include PEGylated compounds as well.

The compounds were long thought to be biologically inert, but evidence is growing that they are not. As much as 72% of people have at least some antibodies against PEGs, according to a 2016 study led by Samuel Lai, a pharmaco-engineer at the University of North Carolina, Chapel Hill, presumably as a result of exposure to cosmetics and pharmaceuticals. About 7% have a level that may be high enough to predispose them to anaphylactic reactions, he found. "Some companies have dropped PEGylated products from their pipeline as a result," Lai says. But he notes that the safety record of many PEGylated drugs has persuaded others that "concerns about anti-PEG antibodies are overstated."

Szebeni says the mechanism behind PEG-conjugated anaphylaxis is relatively unknown because it does not involve immunoglobulin E (IgE), the antibody type that causes classical allergic reactions. Instead, PEG triggers two other classes of antibodies, IgM and IgG, involved in a branch of the body's innate immunity called the complement system, which Szebeni has spent decades studying.

In 1999, while working at the Walter Reed Army Institute of Research, Szebeni described a new type of drug-induced reaction he dubbed complement activation-related pseudoallergy (CARPA), a nonspecific immune response to nanoparticle-based medicines, often PEGylated, that are mistakenly recognized by the immune system as viruses. He believes CARPA explains the severe anaphylactoid reactions occasionally caused by some PEGylated drugs, including cancer blockbuster Doxil and pegnivacogin, an experimental coagulant whose phase III trial was halted in 2014 after some participants developed severe allergic responses and one died.

Some scientists believe PEGylated nanoparticles may cause problems through a mechanism other than CARPA. In November, Phillips and colleagues published a paper showing people who suffered an anaphylactic reaction to PEGylated drugs did have IgE antibodies to PEG after all, suggesting those may be involved, rather than IgG and IgM. Other scientists are not convinced PEG is involved at all. "There is a lot of exaggeration when it comes to the risk of PEGs and CARPA," says Moein Moghimi, a nanomedicine researcher at Newcastle University who suspects a more conventional mechanism is causing the reactions. "You are delivering an adjuvant at the injection site to excite the local immune system. It happens that some people get too much excitement, because they have a relatively high number of local immune cells."

Others note the amount of PEG in the mRNA vaccines is orders of magnitude lower than in most PEGylated drugs. And whereas those drugs are often given intravenously, the two COVID-19 vaccines are injected into a muscle, which leads to a delayed exposure and a much lower level of PEG in the blood, where most anti-PEG antibodies are.

Nevertheless, the vaccine companies were aware of the risk. In a 2018 stock market prospectus, Moderna acknowledged the possibility of "reactions to the PEG from some lipids or PEG otherwise associated with the LNP." And in a September paper, BioNTech researchers proposed an alternative to PEG for therapeutic mRNA delivery, noting: "The PEGylation of nanoparticles can also have substantial disadvantages concerning activity and safety.'" Katalin Karikó, an mRNA vaccine pioneer and senior vice president at BioNTech, says she discussed with Szebeni whether PEG in the vaccine could be an issue. They agreed that given the low amount of lipid and the intramuscular administration, the risk was negligible. Karikó emphasizes that based on what we know so far, the risk is still low. "All vaccines carry some risk. But the benefit of the vaccine outweighs the risk," she says.

Scientists who believe PEG may be the culprit agree, and stress that vaccination should continue. "We need to get vaccinated," Phillips says. "We need to try and curtail this pandemic." But more data on side effects are needed, she adds: "These next couple of weeks in the U.S. are going to be extremely important for defining what to do next." ■

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