Allergies to mRNA-based COVID-19 vaccines rare, generally mild, study finds

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Allergic reactions to the new mRNA-based COVID-19 vaccines are rare, typically mild and treatable, and they should not deter people from becoming vaccinated, according to research from the Stanford

University School of Medicine.

The findings will be published online Sept. 17 in *JAMA Network Open*.

"We wanted to understand the spectrum of allergies to the new vaccines and understand what was causing them," said the study's senior author, Kari Nadeau, MD, Ph.D., the Naddisy Foundation Professor in Pediatric Food Allergy, Immunology, and Asthma.

The study analyzed 22 potential allergic reactions to the first 39,000 doses of Pfizer and Moderna COVID-19 vaccines given to health care providers at Stanford soon after the vaccines received emergency use authorization from the Food and Drug Administration.

Most of those in the study who developed reactions were allergic to an ingredient that helps stabilize the COVID-19 vaccines; they did not show allergies to the vaccine components that provide immunity to the SARS-CoV-2 virus. Furthermore, these allergic reactions occurred via an indirect activation of allergy pathways, which makes them easier to mitigate than many allergic responses.

"It's nice to know these reactions are manageable," said Nadeau, who directs the Sean N. Parker Center for Allergy and Asthma Research at Stanford. "Having an allergic reaction to these new vaccines is uncommon, and if it does happen, there's a way to manage it."

The study's lead author is former postdoctoral scholar Christopher Warren, Ph.D., now an assistant professor at Northwestern University Feinberg School of Medicine.

The research also suggests how vaccine manufacturers can reformulate the vaccines to make them less likely to trigger allergic responses, Nadeau said.

Delivery of protein-making instructions

The mRNA-based COVID-19 vaccines provide immunity via small pieces of messenger RNA that encode molecular instructions for making proteins. Because the mRNA in the vaccines is fragile, it is encased in bubbles of lipids—fatty substances—and sugars for stability. When the vaccine is injected into someone's arm, the mRNA can enter nearby muscle and immune cells, which then manufacture noninfectious proteins resembling those on the surface of the SARS-CoV-2 virus. The proteins trigger an immune response that allows the person's immune system to recognize and defend against the virus.

Estimated rates of severe vaccine-related anaphylaxis—allergic reactions bad enough to require hospitalization—are 4.7 and 2.5 cases per million doses for the Pfizer and Moderna vaccines, respectively, according to the federal Vaccine Adverse Event Reporting System. However, the federal system doesn't capture all allergic reactions to vaccines, tending to miss those that are mild or moderate.

For a more complete understanding of allergic reactions to the new vaccines—how common they are, as well as how severe—the research team examined the medical records of health care workers who received 38,895 doses of mRNA-based COVID-19 vaccines at Stanford Medicine between Dec. 18, 2020, and Jan. 26, 2021. The vaccinations included 31,635 doses of the Pfizer vaccine and 7,260 doses of the Moderna vaccine.

The researchers searched vaccine recipients' medical records for treatment of allergic reactions and identified which reactions were linked to the vaccines. Twenty-two recipients, 20 of them women, had possible allergic reactions, meaning specific symptoms starting within three hours of receiving the shots. The researchers looked for the following symptoms in recipients' medical records: hives; swelling of the

mouth, lips, tongue or throat; shortness of breath, wheezing or chest tightness; or changes in blood pressure or loss of consciousness. Only 17 of the 22 recipients had reactions that met diagnostic criteria for an allergic reaction. Three recipients received epinephrine, usually given for stronger anaphylaxis. All 22 fully recovered.

Of the 22 recipients, 15 had physician-documented histories of prior allergic reactions, including 10 to antibiotics, nine to foods and eight to nonantibiotic medications. (Some recipients had more than one type of allergy.)

The researchers performed follow-up laboratory testing on 11 individuals to determine what type of allergic reaction they had, as well as what triggered their allergy: Was it one of the inert sugar or lipid ingredients in the bubble, or something else in the vaccine?

The study participants underwent skin-prick tests, in which a clinician injected small amounts of potential allergens—the lipids, sugars (polyethylene glycol or polysorbates) or entire vaccine—into the skin. Skin-prick testing detects allergic reactions mediated by a form of antibody known as immunoglobin E, or IgE; these reactions are generally associated with the severest allergies.

None of the recipients reacted on skin-prick tests to the inert ingredients in the vaccines, and just one recipient's skin reacted to the whole COVID-19 vaccine. Follow-up blood tests showed that the vaccine recipients did not have significant levels of IgE antibodies against the vaccine ingredients.

Since the skin tests did not explain the mechanism of recipients' allergic reactions, the investigators proceeded to another type of diagnostic test. Vaccine recipients provided blood samples for tests of allergic activation of immune cells known as basophils. The blood samples from 10 of the

11 participants showed a reaction to the inert ingredient polyethylene glycol (PEG), which is used in both the Pfizer and Moderna vaccines. In addition, all 11 recipients had basophil activation in response to the whole mRNA vaccine when it was mixed with their own basophils.

All 11 subjects had high levels of IgG antibodies against PEG in their blood; IgG antibodies help activate basophils under some conditions, and this finding suggests the individuals were likely sensitive to PEG before receiving their vaccines.

"What's important is what we didn't find, as much as what we did find," Nadeau said. "It does not seem that the mRNA itself causes the allergic reactions."

In addition, the data suggest that reactions to the COVID-19 vaccines were generally not the most severe form of allergic reaction, which is good news in terms of vaccine safety, she said. Allergic reactions mediated by IgG and basophils can be managed with antihistamines, fluids, corticosteroids and close observation, meaning that many individuals who have had a reaction to their first vaccine dose can safely receive a second dose under medical supervision.

PEG is widely used as a stabilizer in household products, cosmetics and medications, with women more likely to be exposed to large quantities of the substance, possibly explaining why more vaccine allergies have been seen among women. (Repeated exposures to a substance can sometimes sensitize the immune system and provoke allergies.) Because most reactions were to PEG rather than the vaccine's active ingredients, it is likely that vaccine manufacturers can reformulate the vaccines with different stabilizers that are less likely to cause allergies, Nadeau said.

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