Anaphylaxis to vaccinations: A review of the literature and evaluation of the COVID-19 mRNA vaccinations

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ABSTRACT
Recent reports of allergic reactions to the Pfizer-BioNTech and the Moderna COVID-19 vaccines have resulted in questions about how and to whom they can be safely administered. Although anaphylaxis was not observed in clinical trials for either vaccine, there have been 21 reported possible cases of anaphylaxis associated with the Pfizer vaccine (11.1 cases per million doses administered) and 10 possible cases associated with the Moderna vaccine (2.5 anaphylaxis cases per million doses administered). The etiology of anaphylaxis in these cases is not fully understood and is an area of active research. The overall incidence of anaphylaxis to COVID-19 mRNA vaccines is very low. By following recommendations from the US Centers for Disease Control and Prevention, an overwhelming majority of the US population can be safely immunized.

INTRODUCTION
Vaccinations against infectious diseases are one of the most impactful public health measures in existence. The development of a vaccine against SARS-CoV-2 has been viewed as a tool to control the global COVID-19 pandemic and as a path toward recovery for our society. However, recent reports of allergic reactions to the COVID-19 vaccine have resulted in questions about how and to whom the vaccine can be safely administered. Here we provide a general discussion of vaccine-related reactions. We also discuss current knowledge on COVID-19 vaccine-related reactions and recommendations on COVID-19 vaccine administration with respect to potential for allergic reactions.

VACCINE-RELATED ADVERSE REACTIONS
Adverse reactions to vaccines are commonly reported, but most are not immunologically mediated. Non-immunologically mediated reactions are typically related to the pharmacology of the vaccine and consist of toxic reactions, side effects, and medication interactions. Immunologically mediated reactions include IgE-mediated and T-cell mediated reactions as well as other immunologic mechanisms that occur as a result of allergen exposure. These responses, particularly severe anaphylaxis, rarely occur. In the United States (US), anaphylaxis to vaccination is reported at an incidence of 0.7-1.3 per one million vaccinations, and are more common in atopic individuals. Nevertheless, those with no history of allergic disease may also experience severe adverse reactions.

Most acute-onset immunologically mediated reactions are IgE-mediated, meaning the patient has pre-formed IgE antibodies to a component of the vaccine. In this type of reaction, symptoms can begin within minutes of exposure to the allergen—generally within 30 minutes—and less commonly within several hours. Symptoms range from urticaria, swelling, and gastrointestinal upset, to respiratory distress and cardiovascular collapse associated with severe anaphylaxis. Delayed reactions typically occur hours to days after exposure to the antigen trigger, and most typically manifest as a cutaneous reaction. There are reports of delayed-onset reactions to rabies and Japanese encephalitis vaccines, although this is also rare.

Vaccines consist of antigens that elicit the desired immune response, and a variety of other components including adjuvants, carrier proteins, and preservatives. Most IgE-mediated reactions do not occur in...
response to the antigenic components. More commonly, other components are the culprit for allergic reactions.6

Often, food components of vaccines have been implicated in vaccine reactions. For instance, patients with anaphylaxis to the MMR vaccine had evidence of IgE-mediated hypersensitivity to gelatin, which is commonly used as a vaccine stabilizing agent.6 Milk and egg are common food allergens that are also found in vaccines. Some vaccines are cultured on chicken embryos. However, this typically results in such a small amount of possible egg exposure that even those with severe egg allergy can safely tolerate these vaccines.7 Some vaccines employ milk protein as a stabilizer; however, reports of adverse reaction in milk-allergic children are exceedingly rare.6

Adjuvants are vaccine components that improve the patient’s immune response to the antigen. The most common of these are aluminum hydroxide and aluminum phosphate. These more commonly cause injection site irritation, and there has not yet been a documented case of IgE-mediated hypersensitivity to these ingredients. However, other adjuvants have been implicated. There were reports in Canada of anaphylaxis occurring due to adjuvant system 03 (AS03), an adjuvant used in some influenza vaccines outside of the US.6

Latex exposure is another possible culprit of vaccine anaphylaxis. Rubber stoppers or plungers in some vaccine vials contain latex, exposing the patient to trace amounts of latex protein. There are reports of anaphylaxis associated with vaccine-mediated latex exposure.8 However, this is rare. Individuals with latex allergy should avoid vaccines packaged or administered with latex-containing products.6

Preservatives are an anti-microbial component of vaccines that are associated with adverse reactions. However, these are typically limited to local injection site swelling or delayed-hypersensitivity skin reactions. These reactions are rare and are primarily described in single case reports. Thus, even a history of delayed-hypersensitivity reaction to a preservative component, such as thimerosal, is not a contraindication to receiving a thimerosal-containing vaccine.6

**COVID-19 MRNA VACCINES**

There are currently two COVID-19 vaccines that have been granted emergency use authorization by the FDA: the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine. Anaphylaxis was not observed in the clinical trials for either vaccine. Outside of trials, there have been reports in the US and abroad of anaphylactic reactions occurring after COVID-19 vaccine administration. Based on US data of 1.8 million doses of the Pfizer vaccine administered, there were 175 cases of severe allergic reaction reported to the Vaccine Adverse Events Reporting System (VAERS). Twenty-one of these were deemed consistent with anaphylaxis. Of these, 17 cases occurred in people with a history of allergy or allergic reactions, and 70% of the reactions occurred within 15 minutes after vaccine administration.9 There are 10 reported cases of possible anaphylaxis to the Moderna vaccine (2.5 anaphylaxis cases per million doses administered).10 Notably, the Pfizer-BioNTech has a rate of anaphylaxis four times that of the Moderna vaccine. However, the vaccine components do not differ significantly and the reason for this observed increased reaction rate is unknown. This rate of anaphylaxis is significantly higher than the previously reported one per million vaccination doses seen with other vaccines, but is still quite rare (11.1 cases per million vaccine doses of the Pfizer vaccine).9

The etiology of anaphylaxis in these cases is not fully understood and is an area of active research. Any component of a vaccine has the potential to cause adverse reaction. Both COVID-19 vaccines contain mRNA, lipids, polyethylene glycol (PEG)-2000, electrolytes, sugar (sucrose), and a saline diluent. Neither contain food products or preservatives. There is no latex exposure because the vial stoppers are not made with natural rubber.

Notably, PEG has been associated with cases of anaphylaxis to other agents. Polyethylene glycol and related polysorbates are ingredients in colonoscopy preps, medications for constipation, vascular grafts, surgical gels, PEGylated medications, and household and industrial compounds and are used as excipients in oral and injectable medications, including vaccines. These components have previously been implicated in anaphylactic reactions.11 Currently, patients who exhibit signs of allergic reaction after COVID-19 vaccination are recommended to avoid new PEG exposure and to undergo further evaluation with a board-certified allergist/immunologist.

Another theoretical consideration is complement activation mediated by RNA exposure. In 2008, reports of adverse reactions to heparin were linked to exposure to oversulfated chondroitin sulfate (OSCS). This was found to induce kallikrein activity and activate the contact system that resulted in anaphylaxis-like symptoms.12 It is possible that a non-IgE mediated mechanism could be implicated such as
complement activation, resulting in anaphylaxis-like symptoms as described with the OSCS.\textsuperscript{13} Although this is speculative, alternative mechanisms such as this merit further investigation.

To further evaluate possible anaphylaxis associated with the COVID-19 vaccinations, all patients who experience symptoms that are consistent with the clinical criteria for diagnosis of anaphylaxis\textsuperscript{14,15} should have a serum tryptase level and complement components (CH50 and/or SC5b-9) obtained.\textsuperscript{16} These evaluate for mast cell activation seen in anaphylaxis as well as complement system activation. More extensive evaluation, including immediate hypersensitivity skin testing to PEG, can be performed at a later date by a board-certified allergist/immunologist. Patients who have had anaphylaxis with the first dose of the COVID-19 vaccine should be excluded from receiving the second dose.

At this time, there are no evidence-based recommendations for less severe reactions. In our practice, mild, self-limited symptoms (e.g., pruritus or urticaria) are not viewed as absolute contraindications for receiving subsequent dosing of the COVID-19 vaccines. Such patients are given the opportunity to voice their values and preferences via a shared decision making approach, and they may elect to cautiously proceed with receiving the second vaccine dose with antihistamine pre-treatment. These symptoms can be treated symptomatically with oral antihistamines. Allergy and immunology referral for further evaluation may be considered for these patients. Delayed rashes or delayed local reactions (onset > 24 hours after injection) are unlikely to represent an IgE-mediated allergy, and these individuals may receive the second COVID-19 vaccine dose with no precautions.

With limited data, the recommendations regarding who should and should not receive the vaccine will likely continue to evolve. Currently, the US Centers for Disease Control and Prevention (CDC) has made recommendations regarding the allergic potential of COVID-19 vaccination as outlined in Table 1.\textsuperscript{17}

The CDC further recommends that vaccination sites have equipment, supplies, and personnel...

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\textbf{Clinical history} & \textbf{Action recommended} \\
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History of immediate allergic reaction of any severity (including anaphylaxis) to mRNA COVID-19 vaccine or any component of the vaccine (including polyethylene glycol) & Vaccine should not be administered\footnote{Refer to allergist/immunologist for further evaluation and to determine if the patient can safely receive the vaccine.} \\
History of immediate allergic reaction of any severity to polyethylene glycol & Discuss risks/benefits with the patient, consider: \footnote{Risk of COVID-19 exposure} \footnote{Risk of COVID-19–related complications or death} \footnote{Prior history of COVID-19 infection} \footnote{Risk of anaphylaxis and availability of vaccination site equipped to treat anaphylaxis} \footnote{Consider deferring vaccination until further information is known or refer to allergist/immunologist} \footnote{If vaccine is given, the patient should be observed for 30 minutes after administration} \\
History of immediate allergic reaction to any other vaccine or injectable therapy (not related to COVID-19 vaccine component or polyethylene glycol) & Administer the vaccine\footnote{Patients with history of anaphylaxis from any cause should be observed for 30 minutes after administration} \footnote{All other patients should be observed for 15 minutes after administration} \\
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\caption{Current CDC recommendations on COVID-19 vaccination}
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\textsuperscript{17}Reprinted from reference 17
immediately available to manage anaphylaxis. For patients receiving a COVID-19 vaccine, the CDC recommends that those with any history of anaphylaxis should be observed for 30 minutes following vaccination. All other patients may be observed for 15 minutes.18

■ CONCLUSION

With the administration of increased numbers of the COVID-19 vaccines, cases of anaphylaxis have been reported. The mechanism of these reactions has not yet been fully elucidated. Further investigation should clarify this as we move forward with the vaccine rollout in 2021. Immunization is an important strategy for controlling the COVID-19 pandemic. By following CDC recommendations, an overwhelming majority of the US population can be safely immunized.

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

■ REFERENCES


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