Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines

Two messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines were granted emergency use authorization by the US Food and Drug Administration in December 2020.[1,2] Although no anaphylactic reactions were reported in their research trials, during the first few weeks of clinical use, such reactions have been reported at 2.5 to 11.1 per million first doses administered.[3,4] It was surprising that anaphylaxis could occur because the patients had not previously been exposed and because the vaccines contain no protein. The lipid nanoparticles that surround the mRNA do contain polyethylene glycol (PEG),[1,2] to which patients may have been previously exposed and which has rarely been implicated in immunoglobulin E (IgE)–mediated allergic reactions,[5,6] although the amount of PEG in the vaccines is very small and there is no evidence to date that PEG is responsible for the vaccine reactions. An adenovirus vector COVID-19 vaccine recently granted emergency use authorization[7] does not contain PEG, but it does contain the structurally related polysorbate-80.

We have had the opportunity to evaluate 4 patients who suffered early onset reactions after their first doses of mRNA COVID vaccines and who were diagnosed and treated for presumed systemic allergic reactions. However, further evaluation suggested that the reactions were not allergic (Table 1). Although notes were not generated regarding physical examination at the vaccine clinics, all patients had only subjective complaints with normal vital signs and physical examination results when subsequently evaluated in the emergency department or urgent care center, including 1 patient subsequently admitted to the intensive care unit. Subsequent vaccine skin testing suggested that the reactions were not IgE-mediated, and 3 of 4 have received their second doses either without symptoms or with only mild transient symptoms. Despite negative skin testing results, 1 patient declined her second dose. The skin test results and subsequent vaccination outcomes in these patients indicate that their initial reactions were not allergic. The patients had symptoms that were triggered by the vaccination, but not by an allergic mechanism.

Other early onset reactions to vaccination can mimic anaphylaxis. Vasovagal reactions can also cause lightheadedness or syncope. Vocal cord spasm can cause stridor and dyspnea. Panic attacks can cause a globus sensation, palpitations, dyspnea, and other symptoms. It is likely that our patients' initial reactions represent some variation of such reactions. Patients and providers are sometimes reluctant to believe that physical reactions and sensations can be triggered by something other than an allergic reaction. However, the somatic element of a psychosomatic response is in fact a real physical phenomenon, and conversely, symptoms can be present without physical findings. It has proved helpful to review with these patients other circumstances in which this may be the case. For example, embarrassment can cause obvious flushing (vasodilatation) triggered only by a thought. The sensation of throat or tongue swelling when none is present (globus sensation) is also common. Most patients are familiar with the experience that after local anesthesia for a dental procedure, they often have the distinct sensation that their lip or tongue is swollen, but looking the mirror reveals that it is not. Patients being able to see negative skin test results in contrast to positive histamine control tests can also provide reassurance that they are not allergic to the vaccine.

Although it is important for providers overseeing vaccination clinics to recognize and treat anaphylaxis after vaccine administration, they should also be aware that there is a differential diagnosis. Epinephrine should certainly not be delayed or withheld if anaphylaxis is suspected, but in the setting of minor and more subjective symptoms, observation may be appropriate. Patients with possible allergic reactions after immunization should evaluated by an allergist rather than simply being labeled "allergic" or recommending that they not receive additional doses.[8]

In patients who may have had a reaction to the first dose of an mRNA COVID vaccine, an alternative to second-dose administration could be to assess for the presence of anti-severe acute respiratory syndrome coronavirus 2 spike protein IgG antibody as evidence of immune response, but no data exist that a single dose provides the same level or duration of protection from the disease as the 2 dose series. Another approach might be to suggest that the patient forego the second dose of an mRNA vaccine and receive an alternative vaccine with different technology or ingredients, such as the adenovirus vector vaccine.[7] However, there are no data on the immune response or protection that this might provide.

Thus, the more appropriate approach would seem to be for patients who have had possible immediate-type allergic reactions to an mRNA COVID vaccine to undergo an allergy evaluation to determine if the nature and timing of the patient's symptoms are consistent with an anaphylactic reaction and to perform vaccine skin testing. The stability of any potential allergens in the COVID vaccines is not known, and so skin testing should be performed within the same 6-hour time frame from reconstitution used for vaccine administration, using residual volume from the multidose vials so as not to waste doses. Negative vaccine skin test results argue strongly that a reaction was not IgE mediated, and consideration can be given to administration of the second dose in the usual manner under observation as in the cases described.

Other reported anaphylactic reactions attributed to the mRNA COVID vaccines[3,4] may not have been systemic allergic reactions, but

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Table 1
Four Patients Misdiagnosed as Having Systemic Allergic Reactions After Messenger RNA Coronavirus Disease 2019 Vaccines

Patient age (y) sex	Vaccine brand	Time to onset of symptoms (min)	Symptoms	Level of care: treatment after first dose	Vaccine skin test results[a]	Symptoms with second dose[b]	Treatment after second dose
47 Female	Pfizer-BioNTech	5	Sensation of throat swelling, shortness of breath	Emergency department, intensive care unit: prednisone, cetirizine, epinephrine, famotidine methylprednisolone	Negative	Sensation of throat swelling, shortness of breath	None
56 Female	Pfizer-BioNTech	2	Hot and sweaty, headache, disoriented, pruritus	Emergency department: diphenhydramine, dexamethasone, hydroxyzine	Negative	Headache	Acetaminophen
43 Female	Pfizer-BioNTech	15	Itching, flushing	Urgent care: diphenhydramine, epinephrine (self-administered), dexamethasone, famotidine	Negative	None	None
42 Female	Moderna	1	Sensation of throat swelling, puffy eyelids, hives	Ambulance: diphenhydramine, intravenous epinephrine (which caused nausea, shaking, and paranoia) Emergency department: diazepam	Negative	Refused owing to fear of epinephrine to treat a reaction should one occur	Not applicable

[a]Using residual vaccine from multidose vials within 6 hours of reconstitution. Prick full strength, if negative intradermal diluted 1:100 with normal saline with positive (histamine) and negative (saline) controls. Prick test considered positive if greater than or equal to 3 mm wheal and greater than or equal to 10 mm flare. Intradermal test considered positive if greater than or equal to 3 mm larger than initial wheal and greater than or equal to 10 mm flare.
[b]Administered in the usual manner with 1-hour observation period.

rather vasovagal or panic reactions. Whatever risk may be posed by receiving a second dose of COVID vaccine when the first dose may have triggered a reaction must be weighed against the risk of remaining inadequately vaccinated against a potentially fatal disease. The former risk in most cases is small and manageable, whereas the latter is substantial. For most patients, weighing the relative risks of these options will favor careful evaluation and subsequent vaccination.

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