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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Commentary

Anaphylactic reactions to novel mRNA SARS-CoV-2/COVID-19 vaccines

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Recent approval of two novel mRNA SARS-CoV-2/COVID-19 vaccines by various regulatory agencies has provided hope that we may finally be able to end the pandemic that has claimed hundreds of thousands of lives. The vaccines come not a moment too soon as the numbers of COVID-19-related hospitalizations and deaths reach record, horrifying numbers.

Administration of the first vaccine approved to prevent COVID-19 (Pfizer-BioNTech) began in the United Kingdom in December 2020. Within days, there were reports of two or possibly three anaphylactic reactions that occurred following vaccination [1]. The same vaccine was subsequently given emergency use authorization (EUA) by the United States Food and Drug Administration (FDA) [2] and again within days, there were reports of at least two anaphylactic reactions [3]. A second, similar vaccine (Moderna) has also now been approved [4].

In general, anaphylactic reactions to vaccinations are very rare, occurring at a rate of about 1 per million [5]. These reports indicate that the rate may be higher with these vaccines. The vaccine manufacturers and regulatory agencies are investigating these cases in an attempt to confirm that they were in fact anaphylactic events and to determine the cause. These investigations will likely include performing immediate-type allergy skin tests on the patients who suffered these apparent reactions as well as control subjects. If such tests are positive on the patients and negative on controls, it would imply an IgE-mediated mechanism but would not identify the culprit allergen. In vitro assays would also be performed to search for serum specific IgE directed against specific vaccine components.

Anaphylaxis is a multisystem, potentially life-threatening event that occurs due to widespread release of histamine and other mediators from mast cell granules [6]. It is typically triggered by an IgE-mediated mechanism whereby prior exposure to an allergen in a genetically predisposed person can lead to the production of allergen-specific IgE antibodies. These allergic antibodies then coat the surface of mast cells by means of high-affinity IgE Fc receptors. With subsequent exposure, the allergen cross-links adjacent IgE antibody molecules on the surface of the mast cells, leading to "degranulation" and the release of these mediators into the local tissues and circulation. Other substances such as opioids and radiocontrast media can lead to non-IgE-mediated, so-called "direct" mast cell degranulation through other mast cell receptors. Mast cells are found most prominently in the skin, respiratory tract and gastrointestinal tract. Histamine causes vasodilatation and increases vascular permeability and is also a potent bronchoconstrictor. The signs and symptoms of anaphylaxis stem from the effects of histamine and other substances on the target organs to include dermatologic (urticaria, flushing, angioedema), respiratory (stridor, cough, wheeze, shortness of breath) and gastrointestinal (nausea, emesis, abdominal pain, diarrhea). Systemic vasodilatation and vascular leakage can also lead to hypotension (usually preceded by a reflex tachycardia) which can lead to syncope and vascular collapse. Fatalities from anaphylaxis are either due to asphyxiation from upper airway angioedema or severe bronchospasm or to hypotension. A case definition of anaphylaxis as an adverse event following immunization (AEFI) has been developed and is useful in diagnosis and pharmacovigilance [7].

The first step in determining whether or not a patient has suffered an anaphylactic reaction to a vaccine is to determine that the nature and timing of the event are consistent with this diagnosis [8]. IgE-mediated reactions are also called immediate-type hypersensitivity because such reactions typically occur within minutes to an hour or so after exposure to an allergen. Reactions to an injected substance such as a vaccine would be expected to occur within minutes. The nature of the reaction should include some combination of the symptoms described above, typically urticaria with respiratory and/or cardiovascular symptoms. There are other reactions to vaccines that could mimic an anaphylactic reaction including vasovagal reactions which can also cause syncope but are preceded by bradycardia and pallor as opposed to the tachycardia and flushing that would be typical of anaphylaxis. Similarly, vocal cord spasm can cause stridor and dyspnea and panic attacks can cause dyspnea and other symptoms.

If the nature and timing of an adverse event following immunization are in fact consistent with anaphylaxis, the next step would be to determine if the patient has IgE antibody to some component of the vaccine. The two COVID-19 vaccines approved thus far are novel mRNA vaccines, and the reactions are being reported after the first dose which would seem to exclude the patients having had the prior exposure necessary for the production of IgE antibodies. However, it is possible that the patients were sensitized to some component of the vaccine to which they had been previously exposed. The vaccines consist of modified messen-

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ger RNA (mRNA) encoding the spike protein of the SARS-CoV-2 virus inside a lipid nanoparticle. The vast majority of allergens are proteins, and the vaccines do not contain any protein. One of the components of the lipid particle, polyethylene glycol (PEG) has been reported to cause IgE-mediated anaphylactic reactions and is being considered as a possible culprit allergen [9,10]. PEG allergy is very rare, but is sometimes implicated in patients who have had reactions to multiple medications. PEG is widely usedin oral and injectable medications and bowel preps, and also in non-medicinal products such as cosmetics and foods. Such exposure could potentially explain how a patient may be sensitized to PEG prior to COVID vaccination. As with all vaccines, the EUA prescribing information for the vaccines indicate that a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine is a contraindication to vaccination [2,4]. Thus, for those very rare patients who have been identified as being allergic to PEG, this history would be a contraindication to receiving the vaccine.

Also as with all vaccines, the EUAs indicate that appropriate treatment required to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration. Thus, the vaccines should be administered in a setting where patients can be observed after vaccination. Epinephrine (adrenaline) is a potent bronchodilator and vasoconstrictor and may slow further mast cell degranulation and is the first-line treatment for anaphylaxis in all patients, including those with underlying cardiovascular of pulmonary disease [11]. Injectable epinephrine should be available to treat an anaphylactic reaction should it occur, which could either be epinephrine 1 mg/mL (may also be labeled 1:1000) 0.3–0.5 mL = 0.3–0.5 mg, or a 0.3 mg epinephrine autoinjector, administered IM in the thigh. Response to epinephrine is usually prompt and complete, however additional doses may be administered as frequently as every 5 min if required as well as other therapies to include oxygen and intravenous fluid resuscitation [11]. Although antihistamines may help with urticaria, they do not reverse bronchospasm or hypotension and are therefore not appropriate for the first-line treatment of anaphylaxis. Corticosteroids are frequently used to treat anaphylaxis, but there is no evidence to support their benefit, and they should not be used in place of epinephrine [12]. Following emergency treatment, a blood sample should be obtained for measurement of mast cell tryptase. An elevated mast cell tryptase level obtained within several hours after a suspected anaphylactic event confirms the diagnosis, although a normal level does not exclude it [13]. Depending on the severity of the initial anaphylactic event, it may be appropriate to monitor the patient for several hours for recurrent or biphasic anaphylaxis [12].

Any suspected anaphylactic reaction after receipt of any vaccine should be reported to appropriate regulatory and monitoring agencies, such as the Vaccine Adverse Event Reporting System (VAERS) in the US. It is critical that the report include details on the nature and timing of the reaction and response to therapy as well as vaccine brand/manufacturer and lot number to assist with investigation of the reaction. Referral to an allergist is appropriate to confirm the diagnosis, identify possible culprit allergens, exclude a mast cell disease, advise on re-vaccination and if so, do this under controlled conditions [14].

When the initial reports of apparent anaphylactic reactions to COVID-19 vaccines appeared, it was certainly appropriate for regulatory agencies to make recommendations to try to prevent such reactions by excluding patients from vaccination who may be prone to such reactions. Given how little is known about which patients might be at risk, it was difficult to make decisions about appropriate precautions. After the reported anaphylactic reactions to the Pfizer/BioNTech vaccine in the UK, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued guidance indicating that "any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer/BioNTech vaccine." [15] The Centers for Disease Control and Prevention (CDC) in the United States has proposed less restrictive guidance indicating that patients with a history of a severe allergic reaction due to any cause be observed for 30 min after vaccination, while all others should be observed for 15 min [16]. A history of food, pet, insect, venom, environmental, latex, etc., allergies, history of allergy to oral medications (including the oral equivalent of an injectable medication) and non-serious allergy to vaccines or other injectables (e.g., no anaphylaxis) are specifically listed as not being precautions or contraindications.

Attempts to confirm that the reactions reported thus far are anaphylactic and if so to determine a culprit allergen are appropriate. While the early focus thus far has been on PEG as a possible allergen, alternative allergens or mechanisms of these reactions may be revealed. If risk factors can be determined, such as rare patients with previously established IgE-mediated PEG allergy, this could potentially be a contraindication to receipt of COVID-19 vaccines that contain this and deferral of vaccination until additional vaccines that do not are available. It should be noted regarding the evaluation of possible PEG allergy that anaphylactic reactions to skin testing with PEG itself has caused anaphylactic reactions and should be undertaken only by allergists or others skilled in such testing [17]. Given how rare PEG allergy is, and that patients may have been sensitized through prior exposure but never suffered a reaction, if it turns out to be the culprit allergen, it is unlikely that patients who react to the substance in the vaccine would have thought of themselves as being PEG-allergic. Thus, it may be that we are not able to identify risk factors ahead of time and the first sign of the allergy may be a reaction to the vaccine. Patients who have suffered an anaphylactic reaction to dose one of a COVID-19 vaccine that requires 2 doses should not receive the second dose of the suspect vaccine or vaccines with similar components. Although the 2 vaccines approved thus far are similar in components, other COVID-19 vaccines likely to be approved in the near future contain very different components that may allow vaccination of those who were unable to receive the mRNA vaccines due to a prior reaction.

While anaphylaxis is a potentially life-threatening event, it is almost always successfully treated and its risk must be weighed against leaving patients unvaccinated and therefore susceptible to a potentially life-threatening disease, COVID-19. We have examples where we have been overly cautious in such situations in the past. Based on an early report of anaphylactic reactions to measles, mumps and rubella vaccine (MMR) in 2 egg-allergic children and the notion that the vaccine was "grown in eggs", egg allergy was considered a contraindication to receipt of MMR for many years. However, the vaccine is actually grown in chick embryo fibroblast cultures and subsequent evaluation revealed that virtually all egg-allergic patients receive MMR uneventfully and that virtually all patients who had anaphylactic reactions to MMR were not egg-allergic. The culprit allergen was determined to be another vaccine ingredient, namely gelatin, which was also responsible for anaphylactic reactions to other gelatin-containing vaccines [18]. Thus, now allergy to gelatin, which is very rare, is listed as a contraindication to receiving MMR, while egg allergy, which is very common, is not. Most influenza vaccines are in fact grown in eggs and contain residual egg protein (ovalbumin). It was assumed that injection of this egg protein into egg-allergic patients would cause anaphylactic reactions and egg allergy was therefore considered a contraindication to influenza vaccination. However, studies revealed that patients with egg allergy are at no greater risk for reaction to influenza vaccination then those without egg allergy because the vaccine does not contain enough egg protein to provoke a reaction even in the most severely egg-allergic patients

[19]. Thus, current guidelines from the American Academy of Pediatrics state that it is not necessary to inquire about egg allergy prior to the receipt of any influenza vaccine [20]. The prior recommendations to not provide MMR and influenza vaccines to egg-allergic patients left them susceptible to these vaccine-preventable diseases. Given the large number of patients, mostly children, with egg allergy, this undoubtedly led to unnecessary morbidity and likely mortality. Thus, it is imperative that investigations into the apparent anaphylactic reactions to these novel mRNA COVID-19 vaccines proceed in a timely and thorough manner to narrow down the group of patients for whom the vaccine will be contraindicated to the smallest appropriate number and not to exclude those who could receive the vaccine uneventfully and be protected against this life-threatening disease.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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