

Review

What have we learned about the allergenicity and adverse reactions associated with the severe acute respiratory syndrome coronavirus 2 vaccines: One year later



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Key Messages

- The current vaccines for severe acute respiratory syndrome coronavirus 2 currently approved for use by different international jurisdictions and in clinical phase I to III development are whole virus, protein subunit, nucleic acid (RNA and DNA), and viral vector vaccines.
- The adverse reactions associated with the coronavirus disease 2019 (COVID-19) vaccines can be broadly classified as reactogenic or allergic. They are further classified as local or systemic, immediate or non-immediate, and immune or non-immune-mediated reactions.
- Initial reports of allergic reactions led to a risk management strategy that triaged patients based on their prior history of a potential reaction to a vaccine or a component of the existing (messenger [m]RNA) vaccines.
- Now with a mature understanding of risk, and the reassurance of the very low risk of a preexisting allergy history affecting the safety of COVID-19 vaccination, we have pivoted to a different approach. This risk management approach focuses on those who have had an allergic or other serious reaction to a COVID-19 vaccine and provides support for the completion of primary and booster vaccinations.
- Anaphylaxis to excipients used in the manufacturing process of mRNA vaccines, such as polyethylene glycol used to stabilize the lipid nanoparticle, appears to occur rarely. This means that most individuals known to have allergy to polyethylene glycol (PEG) will usually tolerate mRNA vaccines. However, the flip side of this is that tolerance of mRNA vaccines does not confirm tolerance of PEG. Those that tolerate mRNA vaccines can still be susceptible to severe reactions to PEG, and caution should be applied to hidden ingredients in other products, such as bowel preparations and injectable corticosteroids.

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ABSTRACT

Objective: The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the most rapid response and scale-up in vaccine and therapeutic development in history. We highlight the history of these amazing achievements with a focus on the description of the classification and mechanisms of allergic reactions and adverse events relevant to the allergist and immunologist

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that have been associated with the SARS-CoV-2 vaccines. Finally, we offer a detailed management approach in the context of a possible allergic reaction.

Data Sources: Using defined search strategy, we identified peer-reviewed articles within PubMed that were published between January 1, 2019, and December 4, 2021.

Study Selections: All recent articles on COVID-19 published in English were reviewed with focus on the immunogenicity and allergenicity of the current existing COVID-19 vaccines.

Results: Following a detailed literature review, we discuss the evolution and development of the new vaccines for SARS-CoV-2. Furthermore, we provide evidence regarding the significance and mechanisms of allergic reactions associated with the vaccines and offer a management approach for those with an increased risk of presenting an allergic or other relevant vaccine reaction.

Conclusion: The international rollout of COVID-19 vaccination started with reports of immediate allergic reactions. Although we still need to understand the mechanisms of these reactions, we can be reassured that patients with underlying allergic disease will not need to avoid SARS-CoV-2 vaccination. In addition, the vast majority of those with a first-dose reaction will tolerate subsequent doses.

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Introduction

Since the first described case of coronavirus (COVID-19) disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) described in December 2019, the scientific community has united in a common battle against its associated global threats, morbidity, and the astounding 5 million deaths¹ (Fig 1). Supportive care, corticosteroids, monoclonal antibodies, and other immunosuppressive and antiviral medications are being trialed and used since the beginning of this pandemic.² Although patients who have recovered from the COVID-19 disease produce robust humoral and cellular responses, the appropriate memory CD4 cell response is most effectively attained with an optimal vaccination strategy.³ Currently, there are 139 SARS-CoV-2 vaccines in clinical development, and different types of vaccines have been developed and rolled out in the previous year using various strategies to generate an immune system response¹ (Table 1). We aim to describe the evolution and the development of the new vaccines for SARS-CoV-2. Furthermore, we will give the context of what is known about the background of vaccine allergy and propose and provide an understanding of the classification and mechanisms of allergic reactions associated with the COVID-19 vaccines. We will synthesize the known information to provide a risk-based management approach for those with immediate and delayed hypersensitivity reactions associated with vaccination and other vaccine-related adverse events.

Search Strategy and Selection Criteria

We searched PubMed for peer-reviewed articles published between January 1, 2019, and December 4, 2021 (date of previous search), with the following key terms: (“SARS-CoV-2” or “severe acute respiratory syndrome coronavirus 2” or “COVID-19”) and (“vaccine” or “mRNA” or “Pfizer-BioNTech” or “BNT162b2” or “Moderna” or “mRNA-1273” or “PEG” or “polyethylene glycol” or “AstraZeneca” or “AZD1222” or “Johnson & Johnson” or “Ad26.COV2.S” or “JNJ-78436735”) and (“allergy” or “anaphylaxis” or “allergenicity” or “adverse reaction” or “immune response” or “immunogenicity”). Articles published in English were selected and reviewed. We focused on articles classified as “clinical trials” and “meta-analysis.” This search provided 116 articles. The first screening was based on titles and abstracts followed by a second round of screening performed by reviewing the full-text articles for selected studies. This was performed by the first and last authors. We also identified several new references from the ones listed in the reviewed articles. Finally, we researched the ClinicalTrials.gov website to identify current trials on the allergenicity of the SARS-CoV-2 vaccines. The aim of this study was to provide a narrative review, and future systematic reviews are required to establish the allergenicity and adverse reactions associated with SARS-CoV-2 vaccines.

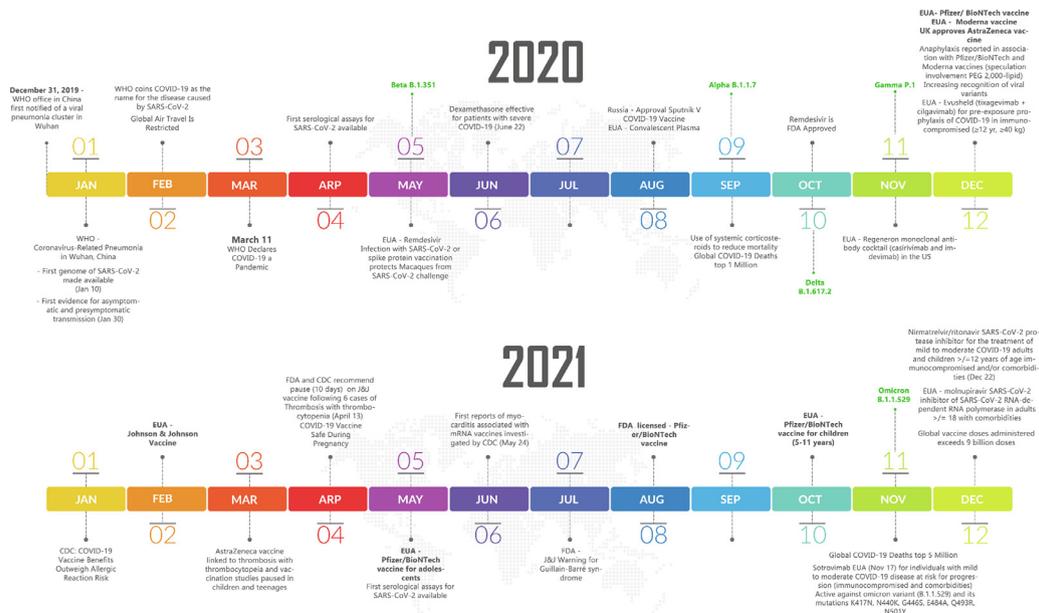


Figure 1. Timeline of COVID-19 vaccines and therapeutics. COVID-19, coronavirus disease 2019; EUA, emergency use authorization; FDA, Food and Drug Administration; PEG, polyethylene glycol; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Table 1
Approved Vaccines for SARS-CoV-2

Research name	Commercial name	Developer	Vaccine type	Active ingredient	Relevant details of excipients and formulation ^a	Dose	Number of doses	Interval doses	Booster dose ^b	Efficacy ^c	Age indication	Storage
BNT162b2 Tozinameran	Pfizer Comirnaty >17 y	Pfizer-BioNTech (and Fosun)	RNA based	Nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylacetamide	0.3 mL IM (30 µg)	2	21 d	≥ 5 mo	95% ¹²	18 y +	-80°C to -60°C (-112°F to -76°F)
BNT162b2 Tozinameran	Pfizer Comirnaty 12-17 y	Pfizer-BioNTech (and Fosun)	RNA based	Nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylacetamide	0.3 mL IM (30 µg)	2	21 d	≥5 mo	100% ⁷⁷	12-17 y	-80°C to -60°C (-112°F to -76°F)
BNT162b2 Tozinameran	Pfizer Comirnaty 5-11 y	Pfizer-BioNTech (and Fosun)	RNA based	Nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylacetamide Tromethamine	0.2 mL IM (10 µg)	2	21 d	n/a ^b	90.7% ⁷⁸	5-11 y	-80°C to -60°C (-112°F to -76°F)
mRNA-1273	Moderna Spikevax >17 y	Moderna and NIAID	RNA based	mRNA encoding the pre-fusion stabilized spike GP (S) SARS-CoV-2	PEG-2000-DMG Tromethamine	0.5 mL IM (100 µg)	2	28 d	50 mcg ≥6 mo	94.1% ⁷⁹	18 y +	-20°C (-4°F)
mRNA-1273	Moderna Spikevax 12-17 y	Moderna and NIAID	RNA based	mRNA encoding the pre-fusion stabilized spike GP (S) SARS-CoV-2	PEG-2000-DMG Tromethamine	0.5 mL IM (100 µg)	2	28 d	n/a	100% ⁸⁰	12-17 y	-20°C (-4°F)
AZD1222 ChAdOx1-S Vaxzevria	AstraZeneca vaccine COVISHIELD Vaxzevria	AstraZeneca and the University of Oxford	NR viral vector	Recombinant, replication-deficient chimpanzee adenovirus vector encoding SARS-CoV-2 spike GP	Polysorbate-80	0.5 mL IM (5 × 10 ¹⁰)	2	4-12 wk	n/a	62% ⁸¹	18 y +	2°C to 8°C (35.6°F to 46.4°F)
JNJ-78436735 Ad26.COVS.2.S	Johnson & Johnson	Janssen Pharma- ceutical com- panies (John- son & Johnson)	NR viral vector	Recombinant, replication-incompetent adenovirus type 26 expressing SARS-CoV-2 spike protein	Polysorbate-80	0.5 mL IM	1	n/a	≥2 mo	66% (overall) 72% (United States) 85% (severe disease) ⁸²	18 y +	-20°C (-4°F)
NVX-CoV2373	Nuvaxovid	Novavax	Protein	SARS-CoV-2 recombinant spike protein	Polysorbate-80	0.5 mL IM	2	21 d	n/a	89.7% ⁸³	18 y +	≤-60°C
BBIBP-CorV	Sinopharm	Sinopharm (Beijing)	Inactivated virus	SARS-CoV-2 virus (cultivated in Vero cell line)	n/a	0.5 mL IM	2	21-28 d	n/a	78.1% ⁸⁴	18 y +	2°C to 8°C
CoronaVac PiCoVacc	CoronaVac PiCoVacc	Sinovac	Inactivated virus	SARS-CoV-2 virus	n/a	0.5 mL IM	2	14-28 d	n/a	50%-91% ⁸⁵⁻⁸⁷	18 y +	Room temp.
BBV152 A, B, C	Covaxin	Bharat Biotech	Inactivated virus	SARS-CoV-2 virus	n/a	0.5 mL IM	2	28 d	n/a	77.8% ⁸⁸	18 y +	2°C to 8°C

Abbreviations: COVID-19, coronavirus disease 2019; GP, glycoprotein; IM, intramuscular; mRNA, messenger RNA; modRNA, modified messenger RNA; NIAID, National Institute of Allergy and Infectious Diseases; PEG, polyethylene glycol; PEG-2000-DMG, 1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NR, non-replicating; Temp, temperature.

^aThis column only contains the inactive lipids that are considered potential culprit for hypersensitivity reactions associated with these vaccines.

^bThe recommendation for immunocompromised hosts for the mRNA vaccines is to administer a third dose 28 d after the second dose and a fourth booster dose 5 mo after the third dose. For immunocompromised children, a third dose is also recommended 28 d after the second dose but only the Pfizer-BioNTech vaccine has an EUA for 5- to 11-year-old children should this be used. Booster dosing 5 mo following primary vaccination has not yet received a EUA. The American College of Rheumatology has recommended adjusting the timing of immunosuppression where possible (eg, rituximab initiated 4 wk before primary series or delaying rituximab until 2-4 wk after completion of the primary vaccination series).⁸⁹ Revaccination with the original series 3 mo following the intervention is recommended after hematopoietic cell transplant or CAR-T therapy.⁹⁰

^cRefers to efficacy in phase III clinical trials against symptomatic COVID-19 illness. All vaccines have reduced efficacy against the SARS-CoV-2 viral variants although the effectiveness against severe COVID-19 disease, hospitalization, and mortality has remained for the delta and omicron variants particularly in adults who have received a booster dose with mRNA vaccines. Measurement of SARS-CoV-2 antibody titer or neutralizing antibody should not be measured because there is poor correlation and cellular immunity is likely playing a key role in protection against severe disease associated with newer variants.

History of Allergic Reactions and Adverse Reactions Associated With Vaccines

In the last century of vaccine development, allergic reactions to vaccines have been an infrequent but measurable effect that may in some circumstances have led to exclusion from future vaccination.^{4–6} Most information gained about vaccine adverse events in the United States has been through the Vaccine Adverse Event Reporting System (VAERS) that was established in 1990 and is managed by both the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration. VAERS is a passive surveillance system and relies on individual reports of adverse experiences. A recent publication highlighted that from 1990 to 2016 and from 467,960 reports, 828 met Brighton collaboration case definition or a physician's diagnosis of anaphylaxis. Of the 42% of reports from adults, 80% were women, 41% had no history of hypersensitivity, and most were associated with influenza vaccination.⁷ One of the largest studies to date used health care data from vaccine safety datalink.⁸ The vaccine safety datalink is a collaborative effort between the CDC immunization safety organization and 9 health care organizations that is updated weekly since 1990 specifically to answer important vaccine safety questions in larger populations. This study confirmed 33 cases of anaphylaxis after 25,173,965 vaccine doses to give the vaccine rate of anaphylaxis that we most commonly quote today of 1.31 per million vaccine doses. Interestingly, this study also sets the context for events to follow with COVID-19 messenger RNA (mRNA) vaccines as it suggested that most (85%) of those who developed vaccine-associated anaphylaxis had preexisting atopic disease. Although there has been much interest in excipients being the culprits for vaccine-associated immediate reactions and anaphylaxis, there have only been a few case reports to support immunologic cross-reactivity between vaccines and drugs on the basis of shared common excipients, such as the polysorbates.^{4,9} For other vaccines, the rates of anaphylaxis have been modified by reduction or elimination of factors, such as gelatin and latex.⁴

Allergic Reactions Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines

Shortly after the first administered Pfizer-BioNTech COVID-19 mRNA vaccine in the United Kingdom, anaphylaxis and other allergic reactions were reported on December 8, 2020. This led to the initial recommendation of the Medicines and Healthcare Products Regulatory Agency in the United Kingdom to exclude from vaccination any person with a history of food, drug, or vaccine anaphylaxis and initiating the threat of a vaccine hesitancy movement for patients with known allergies worldwide. This recommendation was later lifted after an additional review on December 30, 2020, that recommended continued mRNA vaccine avoidance in anyone with a history of an allergic reaction to components of the vaccine but allowed those with unrelated allergies (eg, food allergy) to receive COVID-19 mRNA vaccines. In the United States, the first cases were reported in health care workers in December 16, 2020. This led the US Food and Drug Administration and CDC to reinforce the recommendation against vaccination in individuals with a history of allergic reactions to any of the vaccine components, a recommendation instigated by the Medicines and Healthcare Products Regulatory Agency and all the other allergy associations worldwide^{10,11} (Fig 1). Of note, the clinical trials performed for the mRNA vaccines had excluded patients with a possible allergic reaction to any vaccine component and a past medical history of a severe adverse reaction with any type of vaccine.^{12,13} In the initial report from the VAERS monitoring database of the Pfizer-BioNTech (BNT162b2) mRNA COVID-19 vaccine between December 14, 2020, and December 23, 2020, 1,893,360 doses of the vaccine were administered and 21 cases of anaphylaxis (Brighton criteria) were reported giving a rate of 11.1 per million.¹⁴ As a more diverse

group of individuals was vaccinated, the reported rates of anaphylaxis decreased to 2.5 to 5.1 events per million.^{11,15} One must also consider that there are various definitions of anaphylaxis and that the Brighton collaboration case definition has recently been reported to overestimate the prevalence of anaphylaxis compared with other criteria, such as the National Institute of Allergy and Infectious Disease 2005 and World Allergy Organization 2020.¹⁶ Various ongoing trials are aspiring to understand the mechanisms of these reactions focusing on possible risk factors, such as patients with multiple allergies or mast cell disorders (ClinicalTrials.gov Identifiers NCT04761822, NCT04977479). Furthermore, recent evidence reveals that patients who presented an allergic reaction to their first dose can safely tolerate their second dose.¹⁷

Epidemiology of Allergic Events and Vaccine Rollout of Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines

The initial anaphylaxis reactions reported occurred within 15 minutes of vaccination and primarily in women with a previous history of self-reported allergic reactions.¹⁴ Further insights came from individual health care systems that had full ascertainment of vaccine allergic reactions, such as the Mass General Brigham.¹⁸ Mass General Brigham employees receiving their first dose from December 16, 2020, to February 12, 2021, were studied through follow-up on February 18, 2021. Overall acute allergic reactions occurred within 15 minutes of vaccine administration in 2.10%; more typically with the Moderna vaccine and in women with prior histories of allergic reactions. Approximately one-third (31%) had a history of prior anaphylaxis. No individual who experienced anaphylaxis required resuscitation or endotracheal intubation. At Vanderbilt University Medical Center, 23,094 health care workers were screened for history in the vaccine hall before vaccination with Pfizer-BioNTech COVID-19 mRNA vaccine.¹⁹ Among the 31 identified with higher risk histories, 28 went onto safe vaccination based on tolerance of polyethylene glycol (PEG) or polysorbate-containing medications or vaccines. Shavit et al²⁰ conducted an 8-week prospective cohort study where they risk stratified patients with potential allergy before vaccination. Those considered highly to have allergy were monitored for 2 hours after vaccination in a specialized setting and those at low risk for 30 minutes in a routine setting.^{20,21} They did not vaccinate patients with a history of allergy to two or more injectable drugs or PEG. Of the 429 patients deemed highly to have allergy and observed for 2 hours, 9 patients, all women (2.1%), had immediate reactions, of which most were mild, and 3 (0.7% overall) experienced anaphylaxis, which resolved with epinephrine and without hospitalization.²⁰ A more recent study reviewed 391,123 members at the Kaiser Permanente Southern California who received at least 1 dose of a COVID-19 mRNA vaccine between December 15, 2020, and March 11, 2021.²² Overall, 104 (0.028%) with 85% women had a first-dose reaction and only 2 of these (0.00033%) were consistent with anaphylaxis. Less than 10% of those with first-dose reactions had any reaction to the second dose. Similar to other studies, those who received treatment for a first dose or a second dose reaction were more likely to be younger women with a preexisting history of another allergy. To date, no clear risk factors for the COVID-19 vaccines have been definitively proven considering that the group that has safely tolerated the vaccine has not been described in most of the studies and that the atopic comorbidity data derive from self-reports.

Classification of Allergic Reactions to Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines

The adverse reactions associated with the COVID-19 vaccines can be classified as immediate or non-immediate, local or systemic, and immune or non-immune-mediated reactions (Fig 2).⁵

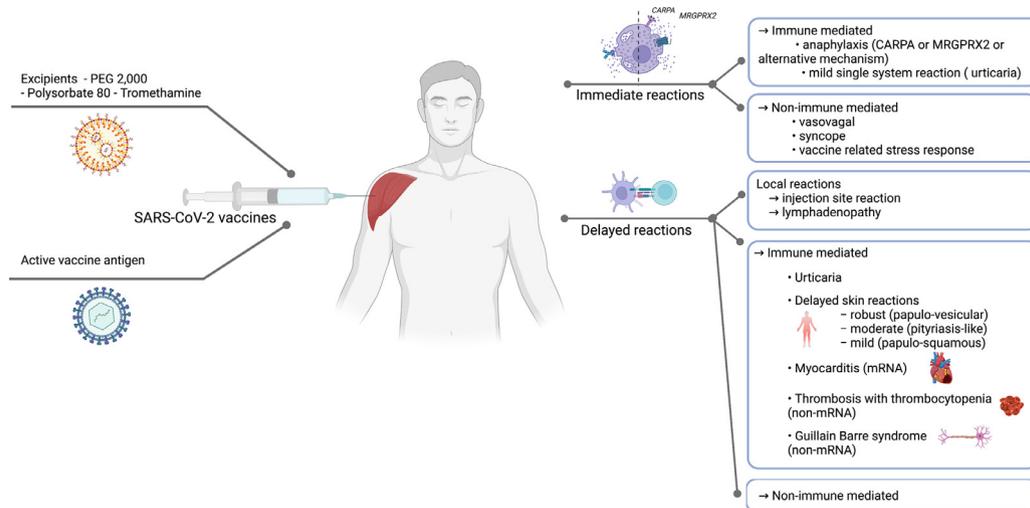


Figure 2. Classification of COVID-19 vaccine reactions. CARPA, complement activation-related pseudoallergy; COVID-19, coronavirus disease 2019; MRGPRX2, Mas-related G protein-coupled receptor-X2; mRNA, messenger ribonucleic acid; PEG, polyethylene glycol; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Immediate Reactions

Systemic Reactions—Immune Mediated

Various described cases fall into the category of anaphylaxis with multisystem involvement. This raised concern that these reactions could be immunoglobulin (Ig)E mediated with allergen crosslinking on mast cells and rapid improvement following epinephrine administration.⁵ If this was the case, reactions would be expected to repeat and intensify on subsequent reactions, which fortunately was not the case. However, at the time these reactions were initially reported, distinguishing between an IgE-mediated reaction and a non-IgE-mediated reaction on history alone was a complex task in the acute clinical setting vaccination rollout in the health care setting where allergist and immunologist were not in close proximity. Indeed, in the case of a mast cell activation not triggered by IgE linking, it is considered that the reactions are caused by direct and indirect mast cell and basophil degranulation by activation of Mas-related G protein-coupled receptor-X2²³ or complement activation-related pseudoallergy.²⁴ Mortality has not been reported following an allergic reaction associated with one of the SARS-CoV-2 vaccines,²⁵ with higher anaphylaxis rates for mRNA vaccines compared with adenoviral vector and inactivated virus vaccines.¹¹ As we will discuss in the allergenicity and management section, second-dose reactions in those with first-dose reactions are uncommon. This is evidence against an IgE-mediated mechanism.²¹

Systemic Reactions—Non-immune mediated

Vasovagal reactions are relatively common following vaccine administration and unless fastidiously documented can be confusing retrospectively. It is thus essential for a clinician to be able to recognize these reactions and to distinguish them from anaphylaxis. Important considerations for vasovagal reactions are (1) timing, with reactions occurring in the first seconds to minutes; (2) blood pressure that can transiently drop and pulse that is slow and weak; (3) slow breathing and possible apnea; and (4) marked pallor and diaphoresis that can be observed in the patient's skin.²⁶ The differential diagnosis for immediate reactions also includes the anxiety-related symptoms, such as vocal cord dysfunction and panic attacks, that can manifest by stridor and dyspnea and globus sensation.²⁷ In this context, the World Health Organization has defined a condition called “immunization stress-related response” and has defined this as a stress-related response that can include a variety of symptoms, such as fainting, hyperventilation, or a dissociative neurologic symptom reaction.²⁸ This is also confirmed by looking at reports of adverse

reactions to placebo where more than 35% of the participants in the placebo arms have reported systemic adverse reactions.²⁹ Furthermore, reports have indicated that among previously reported severe allergic reactions, up to 50% were non-anaphylactic in nature.²⁷ These can be challenging for allergists to recognize if the history is not well documented because allergists are typically not present to observe the initial vaccine reaction.

Delayed Reactions

Local Reactions

Local non-immediate reactions, which are not allergenic but possibly a consequence of an innate immune system activation, are common and may include swelling, soreness, and erythema at the injection site.^{10,30,31} Furthermore, delayed indurated-erythematous reactions have been reported following the administration of RNA vaccines.^{32,33} The manifestations known as “COVID-arm,” which have been more commonly associated with the Moderna mRNA-1273 SARS-CoV-2 vaccine, are considered based on supportive histopathology from the site of the reaction, possible T-cell-mediated cutaneous hypersensitivity reactions.^{34,35} These marked local reactions occurred in 0.8% after dose 1 of an mRNA vaccine and 0.2% after dose 2³² (Table 2).

Systemic Reactions—Immune Mediated

Various maculopapular and morbilliform benign skin eruptions have been reported both with mRNA and adenoviral vector vaccines.^{11,36} Although most of these are benign rashes (morbilliform and urticarial reactions), acute generalized exanthematous pustulosis, erythema multiforme, and other blistering rashes have been described. Furthermore, a full spectrum of delayed phenotypes described includes bullous-pemphigoid like, dermal hypersensitivity reactions, lichen planus, pernio, neutrophilic dermatosis, leukocytoclastic vasculitis, granuloma annulare, and tattoo and sarcoidal reactions.³⁷ Currently, it has been proposed that delayed reactions be divided into robust (papulovesicular), moderate (pityriasis-like), and mild (papulosquamous subphenotypes). In addition, a flare of chronic spontaneous urticaria, including new-onset acute urticaria, has been described in the days or weeks following the COVID-19 vaccine.^{31,36} Several case reports of reactivation of Varicella-Zoster virus (VZV) after the mRNA and adenoviral vector vaccines, including Herpes simplex virus reaction, have been described.^{38–42} Another article found no evidence of oropharyngeal shedding of human Herpes

Table 2
Immediate and Delayed Adverse Reactions to SARS-CoV-2 Vaccines

Clinical phenotype	Specific type of vaccine	Risk group	Prevalence	Acute management	Advice for future vaccination
Immediate reactions					
Anaphylaxis	mRNA vaccines	Women > men History of previous anaphylaxis is prevalent	2.5-5.1 events per million ¹¹	Intramuscular epinephrine Serum tryptase	Refer to allergy and immunology Increasing reports of tolerance of second and subsequent doses in the setting of anaphylaxis to the first dose suggests that a non-IgE-mediated mechanism may be prevalent. ^{61,62}
Mild single-system reaction	mRNA vaccines	Women > men	2.1% ²⁰	Symptomatic management with antihistamines ^{61,62}	Antihistamine premedication before subsequent dosing of mRNA vaccine. ^{61,62}
Delayed reactions					
Mild-to-moderate urticaria	mRNA vaccines	Individuals with underlying urticaria Women > men	Local reactions 0.8% (dose 1) 0.2% (dose 2) ³²	Symptomatic management with ice (for local reactions) topical steroids and antihistamines	No contraindication for second and subsequent doses of vaccine
Injection site		Women < 65 y			Consider antihistamine premedication
Lymphadenopathy		Third dose booster > others	Can be >50% lasting up to 10 wk when sensitive imaging is performed ⁴⁸	Symptomatic management	No contraindication for second and subsequent doses of vaccine (on side contralateral to tumor or other disease process if patient has known pathology for which they are being staged or followed)
Myocarditis	mRNA vaccines	Men < 30 y	More common on second dose (vs first dose or booster) Estimated risk 12- to 29-y-old males —41 cases/million ⁹¹ Moderna > Pfizer in Denmark (4.2/100,000 vs 1.4/100,000 vaccinated) ⁵¹	Symptomatic management	Consider subsequent dose with mRNA vaccine on full recovery of all signs and symptoms of myocarditis particularly if patient has comorbidities or is immunosuppressed. Benefit on resolution of all symptoms and signs associated with myopericarditis
Guillain-Barré or transverse myelitis	Adenoviral vector vaccines	-	8/million doses	Symptomatic management	Vaccinate with an alternative vaccine if the conditions is self-limited and resolved
Thrombosis with thrombocytopenia (multiple thrombotic episodes venous and arterial)	Adenoviral vector vaccines (AstraZeneca (ChAdOx1) > Johnson and Johnson (Ad26.COV2.S))	Women > men (69% for J&J; median age < 50 y for 48% with J&J vaccine) ⁹² Time course—median 9 d	3.8/million doses for J&J ⁹²	Avoid heparin Administer thrombin inhibitors Ivlg may be of benefit	Administer mRNA vaccine following occurrence. Since December 16, 2021, CDC recommends mRNA vaccines and the Johnson & Johnson vaccine for initial and booster dosing.

Abbreviations: IgE, immunoglobulin E; Ivlg, intravenous immunoglobulins; J&J, Johnson & Johnson; mRNA, messenger ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

viruses before or after vaccination with the Pfizer-BioNTech COVID-19 mRNA vaccine in Israel.⁴³ The potential mechanism of human herpesvirus (HHV) reactivation is not known. Furthermore, given that this HHV reactivation occurs soon after the first dose and infrequently after the second dose raises the question of whether cross-reactive HHV responses triggered with the initial vaccine dose cause a compensatory regulatory response leading to reactivation. A more recent study which was a retrospective cohort study using aggregated health records from 63 health care organizations that included more than 70 million patients and a control population without COVID-19 vaccination did not show a difference in VZV reactivation between those who had received a COVID-19 mRNA vaccine within 28 days and the historical control and contemporary cohort.^{44,45} Given that this may be affecting specific risk groups, the jury is still out as to whether this is a true association. In addition, clouding the picture is that COVID-19 infection itself has been associated with VZV reactivation in case reports.⁴⁵

Other Systemic Delayed Reactions

Other delayed reactions may range from those that interestingly mimic the symptoms and signs of COVID-19 disease, such as anosmia, fever, fatigue, headache, and musculoskeletal pain, 24 to 48 hours following a vaccine dose.^{12,46} Lymphadenopathy is now a prevalent reactogenic symptom that is more common following the third-dose booster and may last for up to 3 months. For patients with cancer, it is recommended that vaccination occurs contralateral to any known adenopathy or tumor pathology.^{47,48} Studies have also reported neuropsychiatric symptoms with important morbidity and mortality, such as depression, anxiety, and altered mental status.⁴⁶ In very rare instances (approximately 1%), ischemic and hemorrhagic strokes and seizures have been reported.⁴⁶ Guillain-Barré Syndrome (GBS) has been more prevalently linked to the viral vector vaccines such as the J&J (Janssen) COVID-19 vaccination at a rate of 305 preliminary reports of GBS identified in VAERS after more than 18.1 million doses.²⁵ Of note, GBS may be associated with other vaccines such as influenza and past GBS with influenza is not a contraindication to vaccination with a SARS-CoV-2 vaccine.⁴ Thrombosis with thrombocytopenia has been associated with the viral vector vaccines with AstraZeneca ChAdOx COVID-19 vaccine appearing to have a higher risk than the Janssen Ad26.COV2S (Johnson & Johnson). This appears to have an immunopathogenesis similar to heparin-induced thrombocytopenia in the absence of heparin. The case definition includes a COVID-19 adenoviral vector vaccine 4 to 42 days before symptom onset, any venous or arterial thrombosis (cerebral and abdominal prevalent), thrombocytopenia (platelets $< 150 \times 10^9/L$), positive platelet factor 4 ELISA (HIT assay), and elevated D-dimer ($>4 \times$ upper limit normal). This should be suspected when there are severe headaches, visual changes, abdominal pain, back pain, shortness of breath, leg swelling or pain, easy bruising, or petechiae occurring 4 to 42 days following vaccination.⁴⁹ A small case series of 20 patients with a prior history of heparin-induced thrombocytopenia tolerated the AstraZeneca ChAdOx COVID-19 adenoviral vector vaccine.⁵⁰ Myocarditis has been reported primarily after the second dose of the mRNA vaccines and more prevalently in men less than 30 years of age.^{51–53} One study of interest suggested that this might be more common with the traditional 3- or 4-week interval between mRNA vaccines vs the extended 12- to 16-week interval in the rollout in Canada. In addition, heterologous vaccination (eg, Moderna mRNA-1273 vaccine following another vaccine) may also be associated with a heightened risk. Myocarditis has also been a prevalent feature of COVID-19 natural infection.⁴¹ The incidence of COVID-19-associated myocarditis and cardiac injury is of 1000 to 4000/100,000 people vs 0.3 to 5.0/100,000 after COVID-19 mRNA vaccination.⁵⁵

Allergenicity of Vaccine Components

There are multiple vaccine components that could be responsible for allergic reactions, such as the active vaccine antigen, the residual nonhuman proteins, the excipients such as preservatives or stabilizers in the vaccine formulation, and other inactive products such as gelatin or latex.^{5,54} (Fig 2). Contrary to drug hypersensitivity reactions, most of the reactions to vaccines have traditionally been thought to be associated with excipients contained in the formulation and not by the active ingredient.⁴ For the mRNA vaccines, concern was initially raised about the PEG-2000 lipid component of the mRNA BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna vaccines that stabilizes the lipid nanoparticle that carries the mRNA spike protein construct.⁵ This concern led to special care being taken during the rollout to risk stratify individuals who historically may have had a history of reaction to a vaccine (many of which contain a PEG-like sorbitan polysorbate 80 but not PEG) or PEG itself.³¹ The PEGs are synthetic agents used as excipients in various medicinal and cosmetic products.^{27,55} Although this agent is typically associated with a good safety profile and pharmacokinetic studies of PEG-3350 following laxative administration reveal a minimal systemic absorption,⁵⁶ cases of anaphylaxis and severe immediate hypersensitivity reactions have been described.^{11,57} The mRNA-1273 Moderna mRNA vaccine and the newly formulated BNT162b2-Pfizer COVID-19 vaccine for more than 12 years of age (gray top vial) and that for children (5–11 years) (orange top vial) are tris rather than PBS buffered (contains tromethamine). The original adult BNT162b2-Pfizer COVID-19 mRNA equivalent vaccine is not PBS buffered (purple top vial) and did not contain tromethamine.⁵⁴ The allergenic potential of this excipient is not known at this time and has been reported as a possible cause of anaphylaxis in the following 2 patients: (1) a patient receiving a gadolinium-based contrast agent⁵⁸ and (2) a case report of a 45-year-old woman who presented an urticarial reaction following the Moderna mRNA-1273 vaccine and was positive on intradermal testing to an MRI contrast agent gadobutrol which contains tromethamine and negative to gadoteric acid which does not.⁵⁹ The viral vector vaccines contain polysorbate 80,²⁷ and this typically used excipient has also been linked to allergic reactions.⁵⁴ Despite polysorbate 80 being an excipient in many vaccines and monoclonal antibodies, including other injectable drugs, it causes surprisingly few adverse events. Because excipients are not strictly regulated, the specific concentration present in drugs and vaccinations is often not precisely stated. Polysorbate 80 contains a lower molecular form of PEG (880 g/mL), and the evidence of cross-reactivity is through skin testing only.⁵⁷

Lack of Evidence to Support Excipients as the Culprits of Allergic Reactions to Coronavirus Disease 2019 Messenger RNA Vaccines

Currently, there is a general lack of evidence to support that the prevalent immediate reactions associated with mRNA COVID-19 vaccines are related to an antigen-specific IgE-mediated reaction to an excipient component, such as PEG.⁶⁰ Most reactions were occurring on the first dose of the mRNA vaccines in primarily women with a history of other allergic reactions. The reactions have rarely recurred on the second or subsequent dose and most patients were tolerant.^{61,62} The vast majority of people who experience these reactions have mild-to-moderate reactions that resolve without epinephrine. Tryptase levels, when done, have been normal compared with baseline.⁶² Those who have been rechallenged with a second or subsequent vaccine dose were largely without symptoms, and antihistamine administration pre- and post-dosing seems to help.^{61,62} This tolerance of the second and subsequent doses is very reassuring and is strongly suggestive against PEG or another excipient being the culprit of an antigen-specific IgE-mediated reaction. However, there may be rare patients who warrant risk mitigation and specific workup. Several studies now suggest that specific testing for

excipients, such as PEG and PEG derivatives, is not helpful to risk stratify patients before first or second dosing.⁶⁰ Furthermore, several studies have suggested that patients with immediate reactions to specific drugs containing PEG or PEG derivatives, such as pegaspargase or taxanes, are tolerant of the mRNA vaccines.^{63–66} In addition, patients with known PEG anaphylaxis have tolerated the Janssen and AstraZeneca vaccines containing the PEG derivative polysorbate 80, despite being intradermal skin test positive to polysorbate 80 in 3 of 10 cases.^{67,68} Patients known to have PEG anaphylaxis have also tolerated the mRNA vaccines despite being skin test positive to polysorbate 80 or the mRNA vaccine.⁶⁹ Importantly, tolerance of an mRNA vaccine in those with histories of PEG anaphylaxis does not suggest tolerance of PEG reagents. It appears that following tolerance of an mRNA vaccine, patients can still have anaphylaxis to PEG 3350 and higher molecular weight PEG products.⁶⁹ Therefore, the role of detailed excipient testing in an individual who has a history of anaphylaxis to a non-COVID-19 vaccine-related PEG product is really to test the safety of administering PEG and other PEG derivatives and products unrelated to the COVID-19 vaccines in the future.^{55,57} It may be that the PEG 2000 in the vaccines is too low a molecular weight to be antigenic or that through the intramuscular injection of the vaccine, it is rapidly taken up by the reticuloendothelial system and not bioavailable to induce an immune response. Because mRNA technologies are now of great promise for vaccines and other therapeutics, this has great practical implications for the future. It is of interest that the epidemiology of PEG anaphylaxis, which occurs equally in men and women without prior allergic histories, is associated with PEG IgE and positive prick tests to PEG.^{57,70} PEG anaphylaxis intensifies over time and is often severe and initially requires repeat dosing of epinephrine. This is quite different from the COVID-19 vaccine allergy reactions that occur primarily in women with previous allergic histories and reactions typically remit with no treatment or antihistamines alone and do not intensify over time.⁵⁷

Summary of Management of Allergic Reactions Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines

Following the potentially life-threatening allergic reactions reported, allergists have responded rapidly during this period of high need to help risk stratify and manage patients based on the reported history of allergic reactions.²⁶ An abundance of caution was taken during the first few weeks to months of the rollout of the COVID-19 vaccines and, after the billions of doses now given globally, these have now proven to be safe. Months after the beginning of the vaccination campaign, we are now reassured that any allergic potential of the mRNA vaccines is largely benign and that the vast majority of patients can be safely redosed without fear of a repeat reaction. Despite the fear that a component of the vaccines could be an allergen, there is clear evidence that even for the rare individuals confirmed to have allergy to PEG, these vaccines can be safely administered.⁶⁹ In this context, investigations for possible PEG or polysorbate allergy before the vaccination are now not routinely suggested. Furthermore, we can be reassured that for those who tolerated the first and second doses of the vaccine, the chance of any subsequent reactions appears minimal and the longer observation periods initially recommended for those with an underlying allergy can now be relaxed for those with proven tolerance.

Overall, the confirmation of an allergic mechanism, such as an IgE-mediated reaction, should this occur rarely is suggested by *in vivo* investigations such as prick and intradermal testing or the detection of antigen-specific IgE antibodies.⁵⁷ In the acute setting, it is recommended to test for tryptase, a biomarker that is elevated in anaphylaxis, and repeat this at minimum 24 hours later or at baseline. A suggested management strategy is described in [Figure 3](#).

Skin Testing

The evolving literature on skin testing in the previous year has allowed us to progress from the recommendation of performing PEG skin testing,²⁷ despite absent information on sensitivity and specificity to avoiding routine skin testing with the vaccine or its excipients.¹¹ Some study protocols have involved skin testing with 1:1 mRNA vaccine dilution with negative results in all patients confirmed by a negative mRNA vaccine challenge result.^{71–73} The previous guidelines for vaccine allergy testing have recommended performing skin prick test (SPT) and the undiluted vaccine followed by intradermal with a 1:100 dilution if the initial SPT result was negative.⁷⁴ Despite the lack of international guidelines, non-irritating concentrations for vaccine excipients and standardization across different centers based on trialed concentrations, including for PEG testing, polysorbate 80, and tromethamine, are available.^{57,71} Currently, there is little evidence to support using excipient skin tests to risk stratify patients before vaccination, and it appears that most of the patients can go straight to first or subsequent mRNA vaccine dosing without testing. Indeed, the initial recommendation formulated for skin testing was based on a conservative expert recommendation derived from the 2012 vaccine anaphylaxis parameter guidance.⁶ Even if the positive predictive value of PEG SPT is not well described, this provides useful information in those with a high pretest probability of a PEG allergy in the context of a history of anaphylaxis to PEG.²⁷

The PEG derivatives should be tested in individuals who have underlying suspected PEG anaphylaxis despite having tolerated an mRNA vaccine because tolerance of an mRNA vaccine does not reassure that the patient will tolerate the wide array of PEG products.

Vaccine Challenge

For patients with a history of anaphylaxis to any allergen, the recommendation is to offer a 30-minute observation period following the administration of the COVID-19 vaccine in a monitored area. The vaccination sites should have the equipment necessary to treat possible anaphylactic reactions. A shared decision-making approach is favored, and, in most cases, it appears that a single-dose vaccine rechallenge can be carried out in the setting of an immediate reaction on the first COVID-19 vaccine dose.¹¹ Following previous cohort studies, it is now suggested that patients who are known for previous severe allergic reaction to a non-vaccine component can safely tolerate the COVID-19 vaccine.^{69,71} Various graded dosing⁷⁵ or desensitization⁷⁶ protocols have been suggested. As mentioned previously, oncology patients who presented immediate reactions to paclitaxel that contains polyoxyl-35 castor oil and pegaspargase, a multidrug chemotherapy regimen containing PEG 5000, have safely received the mRNA COVID-19 vaccines.^{64–66} Furthermore, evidence is emerging that patients who reported an immediate reaction and even anaphylaxis to the first mRNA vaccine dose can safely tolerate their second dose,^{17,61,62} supporting non-IgE-mediated mechanisms.

Follow-up and Long-term Advice

Currently, we have an incomplete understanding of the immune correlates of protection for SARS-CoV-2, and this affects our ability to understand the response to vaccines. It is clear that SARS-CoV-2 vaccines have the largest impact on reduction of illness severity, hospitalization, and death, and the very high effectiveness in preventing these primary outcomes in clinical trials has meant that it has not been easy to define the immune correlates of failure.

Newer therapies, such as tixagevimab co-packaged with cilgavimab (Evusheld), have been approved for preexposure prophylaxis with administration every 6 months. This agent is a SARS-CoV-2 monoclonal antibody combination reserved for the moderately to severely immune-compromised patients who may not mount an

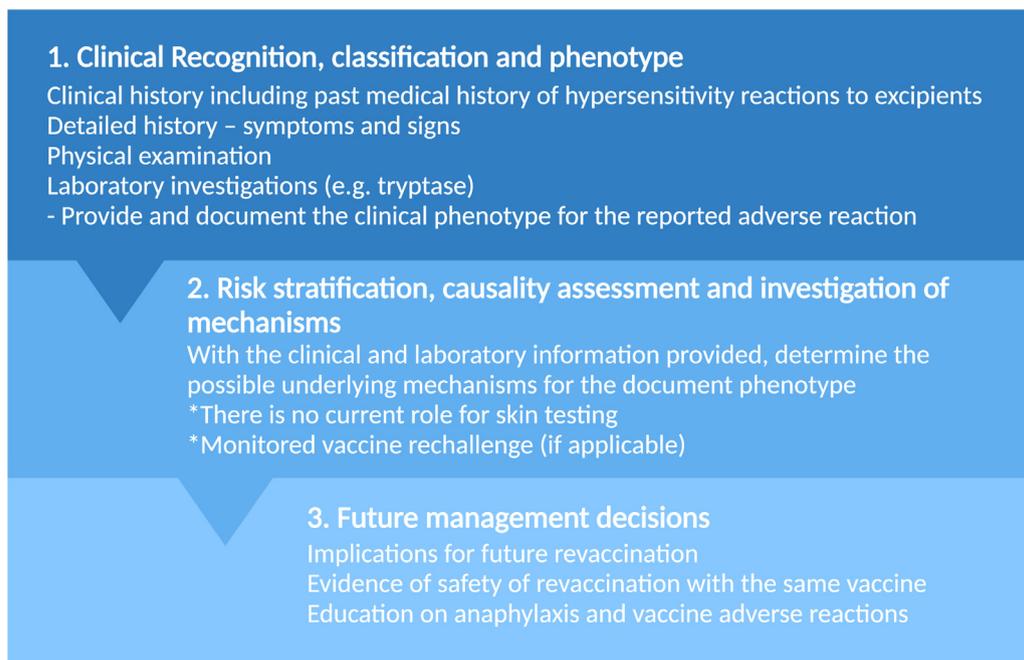


Figure 3. . Management approach.

adequate response to vaccines. However, this drug should not replace vaccination event in the immunocompromised individuals. Another use for this antibody cocktail is listed as being those who have had a severe adverse reaction to a SARS-CoV-2 vaccine where future vaccination is precluded. A severe allergic reaction is listed as an example; however, we now know that it would be an extremely rare event for an allergic reaction to preclude future vaccination. Ideally, all patients with suspected allergic reactions associated with SARS-CoV-2 vaccines, such as the mRNA vaccines, should be assessed by an allergist with workup and observed vaccination as indicated. Interventions such as prophylactic monoclonal antibodies, a precious resource, should ideally be reserved for immunocompromised patients, such as those with primary immunodeficiency or transplantation. Following vaccine assessment, the patient needs to be provided with a clear management plan regarding future same-type vaccine administration and the likelihood of safely receiving other vaccines. One year following vaccine rollout, it is clear that allergy consultations continue to represent important guidance for risk assessment and vaccine guidance. We would suggest that the role of the allergist and immunologist is not to provide vaccine exemptions but to provide evidence-based confidence and reassurance to the patient who may be hesitant because of a reaction to a previous vaccine, drug, or a

COVID-19 vaccine. Most immediate and delayed reactions seem to not recur on the second and subsequent doses. Over the next year, we will learn more about mechanisms; however, to date, the chance of tolerance with subsequent vaccination is excellent and the chance of harm is minimal.

Conclusion

Further research is needed to identify vaccine components that are responsible for immune-mediated hypersensitivity reactions and to understand the underlying mechanisms of vaccine reactions. This will shed light on the immunogenicity, reactogenicity, and allergenicity of current and future SARS-CoV-2 vaccine constructs. The use of effective vaccines is part of the long-time management strategy for SARS-CoV-2 and may continue to be important as the virus moves from a pandemic to an endemic infection. The risk of a reaction compared with the benefit of protection from severe illness and hospitalization is extremely small, and we can be reassured that although there are still many unanswered questions and controversies, there is already a very sound approach to ensure safe COVID-19 vaccination even in those with anaphylactic first-dose reactions (Table 3). As the pandemic and the number of SARS-CoV-2 viral variants evolve in the

Table 3
 Questions on How to Manage Those With a History of Anaphylaxis to a Vaccine Component or Anaphylaxis Following an mRNA Vaccine

Question	Pro	Con	General consensus
Is there a role of skin testing to PEG or PEG derivatives to guide initial or future doses of COVID-19 vaccines?	<ul style="list-style-type: none"> If anaphylaxis to PEG exists, this will help define what products might be safe and what should be avoided in the future (molecular weight threshold) 	<ul style="list-style-type: none"> Mounting evidence supports that PEG skin testing is not helpful to determine vaccine tolerance⁶⁹ Patients with PEG anaphylaxis and positive skin test results to PEG have been tolerant of mRNA vaccines 	<ul style="list-style-type: none"> There is no role for PEG skin testing before administration of a COVID-19 vaccine There is no role for PEG skin testing before administration of a COVID-19 vaccine in someone with a history of PEG allergy There is no role for PEG skin testing alone following anaphylaxis to the first dose of a COVID-19 vaccine to guide future vaccine dosing. It is recommended instead that vaccine skin testing be done

(continued)

Table 3 (Continued)

Question	Pro	Con	General consensus
Is there a role of skin testing to COVID-19 vaccines to guide initial or future doses of COVID-19 vaccines?	<ul style="list-style-type: none"> Prick testing to vaccines is an established procedure to help guide management.⁹³ Non-irritating concentrations (undiluted for mRNA vaccines) for prick and intradermal testing have been reported.^{72,73} If testing for more than one COVID-19 vaccine, a positive test result to one and a negative result to another may give a vaccination strategy. 	<ul style="list-style-type: none"> Negative vaccine responses have occurred in those with positive immediate skin test results raising the question of positive predictive value. Delayed responses (not relevant to an allergic response) at the skin test site may be relevant in those who have had at least dose 1 or prior natural infection. Does not give any indication of tolerance of PEG in drugs or injectables and patients with PEG anaphylaxis as they can be negative on skin testing to mRNA vaccines and require additional follow-up and PEG specific testing to determine PEG product avoidance. 	<ul style="list-style-type: none"> PEG skin testing should be used in an individual suspected to have PEG anaphylaxis regardless of COVID-19 vaccine exposure or tolerance to help guide PEG-containing drugs and products that the individual should avoid. There is no role for skin testing before administration of a COVID-19 vaccine It is recommended that COVID-19 vaccine challenge whether it be to the same or different mRNA vaccine or a different vaccine platform (eg, adenoviral vector) be done under the allergist observation.
Is there a role for administering a future dose with a different COVID-19 vaccine platform	<ul style="list-style-type: none"> Provides a strategy based on those used with vaccine allergy in the past. Some evidence in small studies to support robust immunologic response using heterologous vaccine platform. Can be an allergist observed procedure with the decision shared with the patient. 	<ul style="list-style-type: none"> Data on the efficacy and safety of such procedures have not been established and have typically favored better response with mRNA vaccine following adenoviral vector vaccine. Vaccination with a new platform or different vaccine (eg, adenoviral vector vaccine) could be associated with age- and demographic-related adverse events that are not as easily treated as anaphylaxis (eg, thrombosis with thrombocytopenia with adenoviral vector vaccines or myocarditis with mRNA vaccines). 	<ul style="list-style-type: none"> Increasing evidence supports that most patients with an mRNA vaccine reaction will tolerate repeat dosing with an mRNA and the decision of whether to administer an alternative mRNA vaccine vs the same mRNA vaccine vs a new platform (eg, Johnson & Johnson or AstraZeneca) should be shared with the patient.
Is there a role for graded dosing of a COVID-19 vaccine	<ul style="list-style-type: none"> This is an established approach that allergists have used with other vaccines to challenge in the face of a suspected component or previous vaccine reaction. 	<ul style="list-style-type: none"> mRNA vaccines are a new vaccine platform and the Pfizer-BioNTech vaccine in particular is low in volume. It is not known the impact that graded dosing might have on vaccine efficacy. 	<ul style="list-style-type: none"> Shared decision with the patient for challenge is recommended. Regardless of how the vaccine is administered in the setting of prior anaphylaxis, allergist-observed vaccination is recommended. Observed full-dose vaccination has been well tolerated even in the setting of first-dose anaphylaxis.
Is there a role to check SARS-CoV-2 antibodies to guide future dosing?	<ul style="list-style-type: none"> Antibodies may give some information about a response to vaccine (Spike) or natural infection (Nucleocapsid-RBD). 	<ul style="list-style-type: none"> Although our knowledge is advancing, the specific immune correlates of protection are not known and include a complex equation of both antibody and T-cell responses. An antibody response does not take into account the importance of T-cell responses. Antibody responses are not predictably helpful with the presence of new viral variants. 	<ul style="list-style-type: none"> Measuring antibody responses is generally not helpful to guide initial or future vaccination and could give false reassurance given the importance of booster doses for protection of new viral variants, such as omicron.
Should COVID-19 vaccination be deferred in someone who has had a history of a component reaction or first or second dose reaction?	<ul style="list-style-type: none"> COVID-19 monoclonal antibodies have been approved that provide passive immunity giving a buffer of time to make the decision on the safest management. 	<ul style="list-style-type: none"> COVID-19 monoclonal antibodies approved for preexposure prophylaxis (tixagevimab/cilgavimab [Evusheld]) are in short supply and ideally should be reserved for our patients with primary or secondary immunodeficiencies likely to have inferior vaccine response. In addition, they are not a replacement for vaccination and all patients who receive Evusheld should have had vaccination attempted. Monoclonal antibodies may not be active against future variants. Most patients with a component reaction tolerate COVID-19 mRNA vaccines. Most patients with a first or second dose anaphylactic reaction tolerate subsequent dosing. 	<ul style="list-style-type: none"> With careful allergist assessment, there should be no need to unnecessarily delay COVID-19 vaccination in either initial series or booster based on a prior reaction. This should be shared with the patient and follow the principles outlined previously.

near future, new vaccines are built on an adapted mRNA construct, but the same delivery method and platform will rollout. The Allergy and Immunology community plays an enormous role in the education, clinical care, and research outputs that will result in optimized individual and public health.

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