

Rapid progress in our understanding of COVID-19 vaccine allergy: A cause for optimism, not hesitancy



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Anaphylaxis is a life-threatening condition and when associated with vaccination, leads to vaccine hesitancy. The concerns around vaccine-related anaphylaxis have become even more important during the coronavirus disease 2019 (COVID-19) pandemic where the COVID-19 vaccines remain one of our most important tools. Although rates of anaphylaxis to COVID-19 vaccines are not significantly different from those to other vaccines, Centers for Disease Control and Prevention guidance recommends avoidance of the same COVID-19 vaccine in individuals who had an allergic reaction or are allergic to a COVID-19 vaccine component. Fortunately, our understanding of COVID-19 vaccine allergic reactions has improved dramatically in the past year in large part due to important research efforts from individuals in the allergy community. Initially, researchers published algorithmic approaches using risk stratification and excipient skin testing. However, as our experience and knowledge improved with ongoing research, we have better data showing safety of repeat vaccination despite an initial reaction. We review our progress starting in December 2020 when the Food and Drug Administration approved the first COVID-19 vaccine in the United States through early 2022,

highlighting our success in understanding COVID-19 vaccine reactions. (*J Allergy Clin Immunol* 2022;150:12-6.)

Key words: COVID-19, vaccine, allergy, anaphylaxis, polyethylene glycol, mRNA

DECEMBER 2020 MESSENGER RNA CORONAVIRUS DISEASE 2019 VACCINE ROLLOUT

Anaphylactic reactions to the messenger RNA (mRNA) vaccines were reported within hours of their first rollout in December 2020, causing much public concern and media publicity (Fig 1).¹⁻¹⁰ These reactions, reported at a rate of 2.5 to 5 events per million, occurred within 15 minutes of vaccination and were more common in women and those with underlying histories of allergy and anaphylaxis (Table I).^{1,8,11-14} Active surveillance of the health care worker coronavirus disease 2019 (COVID-19) vaccine rollout at Mass General Brigham supported this epidemiology but showed that anaphylaxis to the first dose of mRNA COVID-19 vaccines occurred in up to 2.5/10,000.² Vaccine and vaccine component allergies had been excluded from the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccine phase 3 clinical trials, where anaphylactic reactions had not been reported. This led to the hypothesis that the polyethylene glycol (PEG)-2000 molecule, which stabilizes the lipid nanoparticle carrier of the active mRNA encoding the severe acute respiratory syndrome coronavirus 2 spike protein, could be the culprit antigen triggering these COVID-19 mRNA vaccines' immediate allergic reactions.¹⁵ The Centers for Disease Control and Prevention, the Food and Drug Administration, and other regulatory bodies internationally proposed the exclusion of individuals with potential PEG allergies from mRNA vaccination out of an abundance of caution.⁴ Drug and vaccine allergy experts responded by developing risk stratification algorithms to not only investigate these reactions but more importantly to provide safe vaccination strategies in the face of uncertainty.^{4,5}

MANY VACCINE SAFETY LESSONS WERE LEARNED

We have learned a considerable amount this past year with additional clinical experience and ongoing research (Fig 1). There is now evidence that individuals with previous anaphylactic reactions to PEG or PEG derivatives tolerate the mRNA vaccines.⁵ There are exceedingly rare reports of mRNA vaccine reactions

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Abbreviations used

COVID-19: Coronavirus disease 2019
mRNA: Messenger RNA
PEG: Polyethylene glycol

in patients with a prior history of PEG allergy confirmed by positive skin testing result.¹⁶ Conversely, there are now multiple reports of individuals previously known to have PEG anaphylaxis, with skin test results positive to both PEG and polysorbate 80, who have tolerated either the mRNA or adenoviral vector COVID-19 vaccines.^{7,17} In addition, there are reports of patients with histories of immediate reactions to pegylated drugs (ie, pegaspargase) or those containing PEG derivatives (ie, paclitaxel) who tolerated the mRNA vaccines.¹⁸⁻²¹ Current evidence suggests that those with presumed anaphylaxis to the first dose of the COVID-19 mRNA vaccines largely tolerate second and booster doses, which favors a non-IgE-mediated mechanism.^{13,14} Many immediate reactions were experienced without objective hypersensitivity. Symptoms documented were ultimately vasovagal, sympathetic stress reaction, reactogenic, or syncopal rather than allergic.¹⁵ Recent reports suggest that PEG skin testing after an mRNA COVID-19 vaccine reaction is not needed and may delay completion of vaccination. Many individuals with immediate allergic and in some cases anaphylactic reactions have tolerated

subsequent doses of mRNA vaccines, although overwhelmingly with allergist oversight.²²

There is an ongoing crucial need to decrease COVID-19 vaccine hesitancy despite an allergy history. First, for viral variants of concern such as Delta and Omicron, reduction in disease severity is dependent on boosting the primary mRNA vaccination.²³ COVID-19 vaccines provide a high degree of protection against hospitalization and death. Second, new mAbs active against Omicron for acute treatment or preexposure prophylaxis (tixagevimab/cilgavimab [Evusheld]) are currently in short supply; their use should be prioritized for immunocompromised patients at risk for an inadequate response to a COVID-19 vaccine, rather than those with a history of a reaction to a component of a COVID-19 vaccine or an immediate allergic reaction to the first dose of a COVID-19 vaccine who are incompletely vaccinated. Patient discussions should include the risk and benefits, noting published data from this past year showing tolerance of mRNA vaccines despite a prior COVID-19 vaccine reaction.

PATHOPHYSIOLOGY OF REACTIONS REMAINS UNCLEAR

Beyond IgE-mediated reactions, which appear to occur only rarely, there is some theoretical evidence that non-IgE-mediated mechanisms such as complement activation-related pseudoallergy could be caused by PEG IgM and IgG in vaccine reactors.²⁴ However, given that 5% to 10% of the population has preexisting IgM

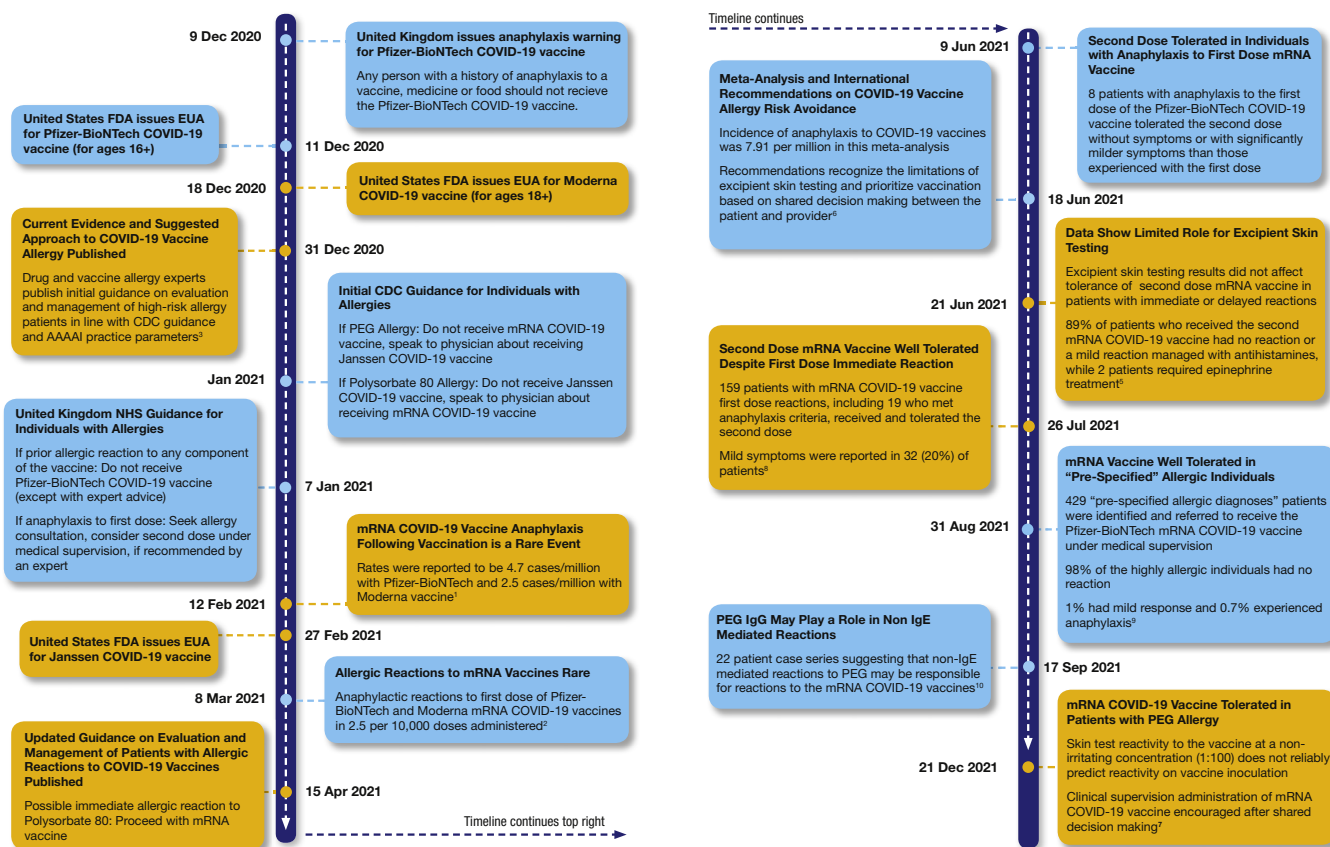


FIG 1. Rapid progress in our understanding of COVID-19 vaccine allergy. *CDC*, Centers for Disease Control and Prevention; *EUA*, Emergency Use Authorization; *FDA*, Food and Drug Administration; *NHS*, National Health Service.

TABLE I. The who, what, and when of allergic reactions to SARS-COV-2 vaccines vs other vaccines: Are they actually different?

Characteristic	Immediate allergic reactions to SARS-COV-2 vaccines	Immediate allergic reactions to other vaccines
Predisposition	<ul style="list-style-type: none"> ● History of allergies or allergic reactions ● About one-third have a prior history of anaphylaxis 	<ul style="list-style-type: none"> ● Preexisting allergy to excipient or component of vaccine ● History of alpha-gal or dairy allergy in a select few* ● History of chronic medical conditions
Demographics	<ul style="list-style-type: none"> ● <19 y old—unknown ● >19 y old—females > males 	<ul style="list-style-type: none"> ● <19 y old—males > females ● >19 y old—females > males
Symptom onset	<ul style="list-style-type: none"> ● Most within 20 min 	<ul style="list-style-type: none"> ● Most within 30 min
Reaction resulting in death	<ul style="list-style-type: none"> ● No peer-reviewed deaths reported 	<ul style="list-style-type: none"> ● 8 deaths reported from 1990 to 2016†
Possible mechanisms of immediate reactions when objective findings exclude anaphylactic mimickers	<ul style="list-style-type: none"> ● Anti-PEG IgG- or IgM- mediated CARPA ● Complement-mediated lipid reactions ● Nonspecific mast cell activation ● Autonomic instability ● Modifying effect of recent COVID infection ● IgE-mediated reaction to the vaccine or PEG 	<ul style="list-style-type: none"> ● IgE-mediated reaction to component or excipient of vaccine ● Nonspecific mast cell activation
Nonallergic mimics of anaphylaxis	<ul style="list-style-type: none"> ● Vasovagal symptoms ● Panic/anxiety (immunization stress-related response) ● Chronic urticaria ● Predisposition toward hives/dermatographism/nonspecific mast cell activation ● Autonomic instability ● Expected reactogenic effect of the vaccine misinterpreted as allergic reaction (mRNA vaccines) 	
Other adverse reactions (nonallergic)	<ul style="list-style-type: none"> ● Myocarditis reported in mRNA vaccines (typically in adolescent males) ● Thrombosis with thrombocytopenia (TTS) reported in Janssen vaccines ● Guillain-Barre syndrome (increased risk reported in Janssen) 	<ul style="list-style-type: none"> ● Encephalitis reported to whole-cell pertussis vaccine (not used in the United States since replaced by acellular vaccines in 1997) ● Myocarditis reported in smallpox vaccination ● Arthus reaction ● Disseminated infection with live virus vaccines in immune-compromised individuals ● Guillain-Barre syndrome—increased risk 1976 H1N1 flu vaccine; all others, unclear causality
Current CDC contraindications‡	<ul style="list-style-type: none"> ● Anaphylaxis after a previous dose or to a component of the COVID-19 vaccine§ ● Known diagnosed allergy to a component of the COVID-19 vaccine§ ● For the Janssen COVID-19 vaccine, TTS following receipt of a previous Janssen COVID-19 vaccine (or other COVID-19 vaccines not currently authorized in the United States that are based on adenovirus vectors) 	<ul style="list-style-type: none"> ● Immune-compromised and pregnant women should not receive live virus vaccines ● History of encephalopathy to a pertussis-containing vaccine ● Those with severe combined immune deficiency or history of intussusception should not receive the rotavirus vaccine

CARPA, Complement activation-related pseudoallergy; CDC, Centers for Disease Control and Prevention; VAERS, Vaccine Adverse Event Reporting System.

*Rare cases because egg allergy is no longer considered a risk or exclusion for reactions to flu vaccine and many egg-allergic individuals have safely received the yellow fever vaccine.¹¹

†The death rates to non-COVID vaccinations gathered from VAERS reports over a 26-y period before COVID-19 vaccines from the years 1990 to 2016.¹²

‡Current CDC contraindications last updated January 6, 2022.

§Current evidence suggests that many patients with anaphylaxis after the first dose will tolerate the second dose.^{8,13,14}

and/or IgG to PEG, this test is unlikely to be useful in predicting reactions to mRNA vaccines.²⁵ It is also possible that some individuals might have reactogenic symptoms associated with the active components of the vaccine that unmask an underlying tendency to non-IgE-mediated mast cell activation. There may also be diverse triggers of nonallergic symptoms including underlying anxiety around vaccination. Exacerbation of urticaria and the occurrence of chronic urticaria following both natural infection with COVID-19 and COVID-19 vaccination have been described.^{26,27} Although new insights on mechanism will come from studies currently in progress, it is now clear that the vast majority of individuals with a history of PEG allergy or COVID-19 vaccine reactions can safely receive subsequent doses of the mRNA vaccines.

A PEG CAVEAT

True immediate and anaphylactic reactions to PEG are fortunately very rare.²⁸ Unlike reactions to the mRNA vaccines that are predominantly in females, PEG anaphylaxis appears to be more

equal among males and females.^{28,29} Current reports are reassuring that many patients with histories of PEG anaphylaxis and positive skin test results to PEG3350 or higher tolerate mRNA vaccines.⁷ At this time, it is still prudent to manage these rare cases carefully and consider skin prick testing to PEG and the mRNA vaccines with physician-observed vaccination (Fig 2). Although it appears that the vast majority of those with anaphylaxis to PEG will tolerate COVID-19 mRNA vaccines, these individuals are still at risk and likely to have potentially fatal anaphylaxis to the higher molecular weight PEG (eg, PEG3350) products to which they initially reacted. All individuals with a history of PEG anaphylaxis regardless of whether they have tolerated an mRNA vaccine should still be worked up comprehensively by an allergist to determine the future safety of PEG-containing drug and products.³⁰

FUTURE DIRECTIONS

The approach to the COVID-19 pandemic has and will continue to require a global effort that should see its eventual retreat into

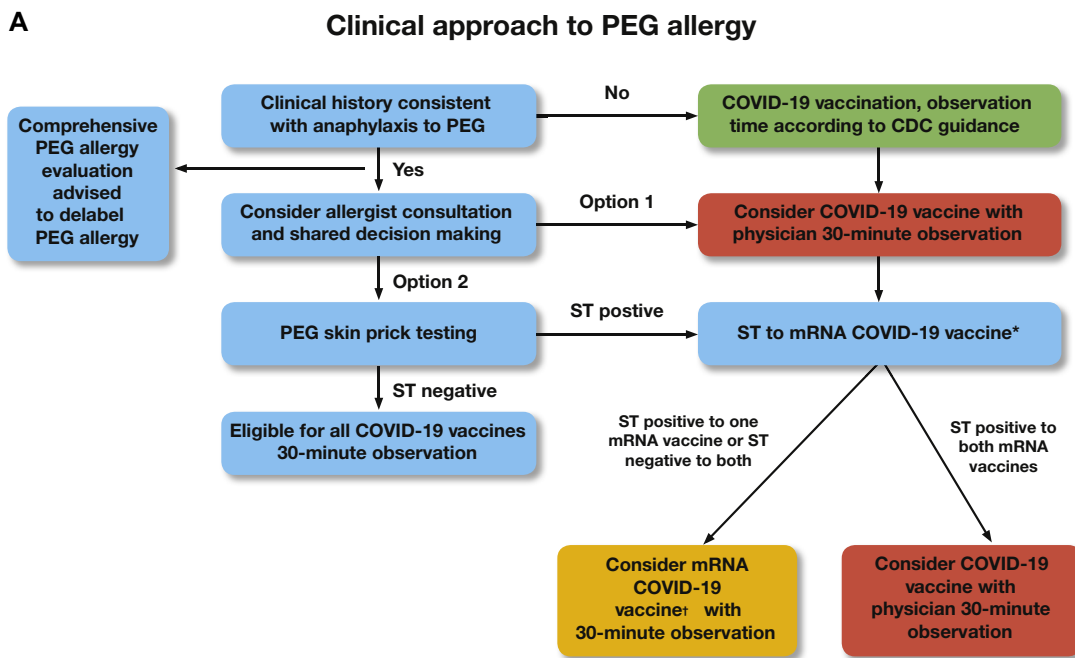


FIG 2. A, Clinical approach to PEG allergy. This algorithm can be used in individuals reporting a clinical history consistent with anaphylaxis to PEG including a PEG injectable or oral (eg, Miralax); tolerance of mRNA vaccines does not delabel a PEG allergy, and comprehensive PEG allergy evaluation is required following mRNA vaccination to guide the individual safety of PEG products.³⁰ When advising COVID-19 vaccination, current CDC recommendations are to receive mRNA vaccines if possible due to known risk of thrombosis with thrombocytopenia with adenoviral vector vaccine, Janssen. *CDC*, Centers for Disease Control and Prevention; *ST*, skin testing. *Use mRNA COVID-19 vaccine nonirritating skin testing concentration.⁶ †Consider proceeding with the mRNA COVID-19 vaccine that was not responsible for clinical vaccine reaction (eg, Moderna if clinical reaction was to Pfizer). Negative mRNA COVID-19 vaccine challenge has been described in the setting of positive skin prick testing result to the mRNA vaccines; full dose (0.3 mL/0.2 mL for Pfizer-BioNTech for ≥12 and children 5-11 years old and 0.5 mL for Moderna) is suggested because of lack of data on the efficacy of split-dose mRNA vaccination. Negative challenge to both the mRNA vaccines and the adenoviral vector vaccines has been described in the setting of a positive intradermal skin test result to polysorbate 80. **B,** Clinical approach to mRNA vaccine allergy. Excipient differences over time between mRNA vaccines: the original Pfizer-BioNTech vaccine distributed (purple cap) for the 12 years or older age group was PBS buffered (purple cap). These have now been replaced with a tris buffered (gray cap) version; the pediatric (orange cap) 10 µg, 0.2 mL intramuscular formulation is also tris buffered. Moderna vaccine is tris buffered. *There are no contraindications to receive subsequent COVID-19 mRNA vaccination for any other adverse events. Severe cutaneous adverse reactions or severe rash with systemic symptom has rarely been seen in temporal association with COVID-19 vaccinations. ‡Consider PEG skin prick testing if clinically relevant. If PEG skin prick testing result is positive, proceed with patient counseling regarding avoidance of medications containing PEG. †Consider proceeding with the mRNA COVID-19 vaccine not responsible for clinical vaccine reaction (eg, Moderna if clinical reaction was to Pfizer). Negative mRNA COVID-19 vaccine challenge has been described in the setting of positive skin prick testing result to the mRNA vaccines; full dose is suggested because of lack of data on the efficacy of split-dose mRNA vaccination. Negative challenge to both the mRNA vaccines and the adenoviral vector vaccines has been described in the setting of a positive intradermal skin test result to polysorbate 80.

endemicity. The rollout of COVID-19 vaccines has been a remarkable global safety success story because of exceptional clinical dedication and care, collaboration, and research efforts. Although patients are still seeking “exemption” from the first or subsequent COVID-19 vaccine doses for various reasons, data suggest that allergy is almost never a reason for COVID-19 vaccine “exemption.” We can be reassured 1 year following the COVID-19 vaccine rollout that there is no history of allergy, including to foods, drugs, vaccines, or other substances, that is a contraindication to receipt of any COVID-19 vaccine. With anaphylaxis or another adverse event to any dose of a COVID-19 vaccine, shared decision making is key although reassuringly patients appear to tolerate subsequent COVID-19 mRNA vaccination. The greatest contribution from the Allergy & Immunology community, in this challenging

period where we continue to strive toward achieving universal global COVID-19 vaccination, is consultation for vaccine counseling, which may enable the vaccine-hesitant or vaccine-resistant patient to get immunized. The experience of rolling out a global immunization effort against severe acute respiratory syndrome coronavirus 2 has been novel and challenging, and among those challenges was the need to adequately immunize patients who had experienced immediate vaccine reactions. In a matter of months, research from around the world improved our understanding of COVID-19 vaccine allergy and allowed large-scale vaccination efforts to succeed.

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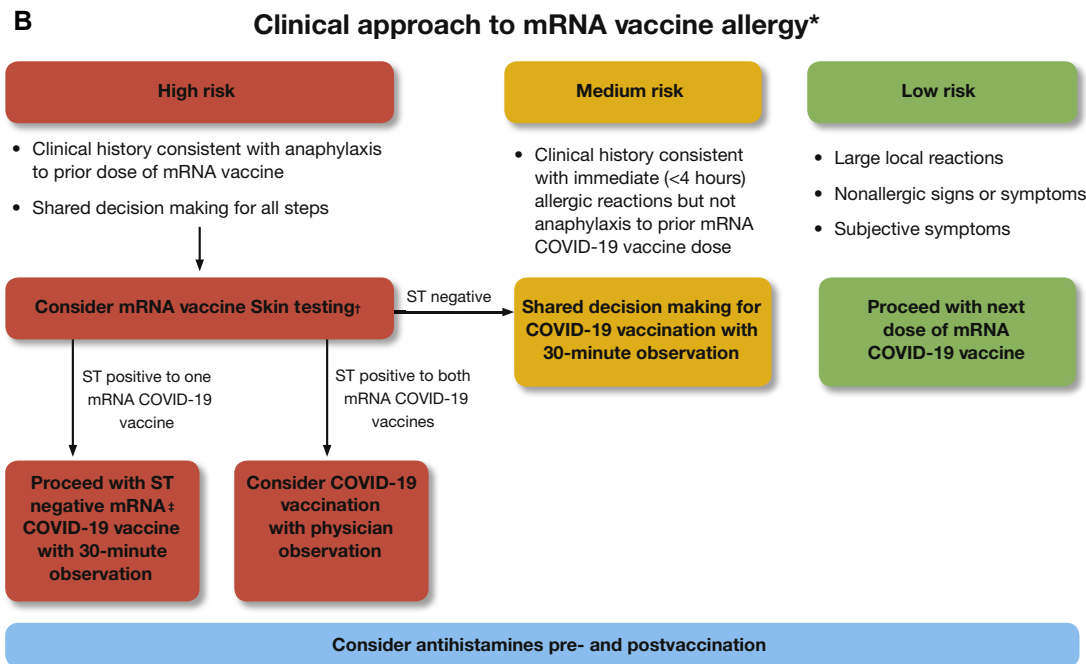


FIG 2. (Continued).

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