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Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized

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Abstract

Background: The most common immediate hypersensitivity to macrogols is associated with PEG 3350, however the epidemiology, mechanisms and cross-reactivity are poorly understood. Thousands of medications contain either PEGs or structurally similar polysorbates.

Objective: Our objective was to better understand the mechanism, cross-reactivity and scope of PEG hypersensitivity.

Methods: Two cases with a past history of immediate hypersensitivity to PEG-containing medications were used to study potential mechanisms and cross-reactivity of immediate reactions to PEG 3350. Skin testing and oral challenges with PEG and polysorbate-containing agents were employed to determine clinical reactivity and cross-reactivity between the two allergens. Enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescent immunoassay were used to detect anti-PEG specific IgG and IgE respectively, using PEGylated protein or PEG alone as antigens in two cases and six PEG 3350 tolerant controls. We searched FDA adverse event reports for immediate reactions to PEG 3350 to determine the potential scope of this problem in the United States.

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Results: Skin and provocation testing demonstrated symptomatic reactivity in both cases to PEG 3350 and polysorbate 80. Plasma samples were positive for anti-PEG specific IgE and IgG antibodies only in cases and binding increased directly proportional to the molecular weight of PEG tested. FDA adverse event reports revealed 53 additional cases of possible PEG 3350 anaphylaxis.

Conclusions: Immediate hypersensitivity to PEG 3350 with cross-reactive polysorbate 80 hypersensitivity may be under recognized in clinical practice and can be detected with clinical skin testing. Our studies raise the possibility of an IgE mediated Type I hypersensitivity mechanism in some cases.

Keywords

polyethylene glycol; PEG; immediate hypersensitivity; allergy; polysorbate

Background:

Macrogols, including polyethylene glycols (PEG) and the structurally related polysorbates (Figure 1), are compounds whose primary feature includes polyether groups. They have wide ranging use in medical and commercial settings, with molecular weights (MW) that range from 200 to 35,000g/mol.[1] PEG of MW between 3350 and 6000 are frequently used as excipients in many liquid and solid formulations of medications.[2, 3] PEG of MW 5000 is used in conjugated enzyme therapeutics, such as PEG-asparaginase and PEG-adenosine deaminase, to improve drug pharmacokinetics and lower immunogenicity. PEG of MW 3350 is the primary ingredient in commonly used oral bowel preparations for colonoscopy procedures in the United States.[1, 4] Recently, PEGs of this MW range have been receiving attention as a cause of anaphylaxis to preparations used for colonoscopies,[5] and as an immunogenic epitope in PEGylated asparaginase (Oncaspar and Pegcrisantaspase).[6, 7] There is only limited awareness of their role in reactions to medications where they are present as an excipient.[4, 8–10] Many patients report repeated cutaneous exposures[11–14] or local reactions to PEG-containing topical items[15] prior to the onset of systemic reactions to high molecular weight PEG containing medications, suggesting a cutaneous mode of sensitization. Gastrointestinal sensitization has been theorized in PEG allergic patients with an impaired epithelial barrier.[16–18] However, the scope to which macrogol hypersensitivity might be a problem in the United States and the mechanism for PEG and polysorbate reactions are not well understood.[8, 19, 20] After encountering two cases of life threatening immediate hypersensitivity to macrogols in our clinic, we sought to further understand the mechanism and scope of immediate hypersensitivity to PEG.

Methods:

Clinical Surveillance:

Cases were recruited through a dedicated drug allergy clinic at Vanderbilt University Medical Center. A detailed clinical case description was obtained from patients whose history suggested an immediate reaction to PEG 3350 containing colonoscopy preparations, laxatives, or injected corticosteroids during a 3 year period.

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Skin Testing and Challenges:

To determine clinical reactivity to macrogols, including polyethylene glycols and polysorbate containing products, we used a combination of skin prick, intradermal and challenge testing with standard methodologies.[21]

Controls:

Two healthy adult volunteers served as negative controls for the skin testing protocol. Six additional healthy adult volunteers with previous exposure to PEG 3350 during colonoscopy preparation or use of laxatives during the last 5 years provided blood samples used as controls during laboratory assays.

Laboratory Methods:

To better understand the mechanism of macrogol hypersensitivity in the two cases, we next sought to detect the presence of polyethylene glycol specific antibodies. Enzyme-linked immunosorbent assay (ELISA) was used for the detection of anti-PEG antibodies. Briefly, Corning 96-well EIA/RIA assay microplates were coated with 5,000g/mol methoxy-PEG-*E.coli* asparaginase (Oncaspar) at 10 μg/ml. For anti-PEG IgG detection, plasma obtained from the aforementioned 2 cases 2~3 months after their last anaphylaxis episodes were incubated at 1:400 dilution. For anti-IgE detection, the same plasma samples were pretreated with Protein G Plus Agarose (Thermo Fisher Scientific) at 1:1 ratio to remove IgG, then incubated at 1:10 dilution. HRP-conjugated goat anti-human IgG (Sigma) or anti-human IgE (BioRad) antibodies were added at 1:1000 and 1:10,000 dilution respectively. Plates were read at dual wavelengths of 490 nm and 630 nm on an ELx808 microplate reader (BioTek). Plasma samples from 6 patients with similar exposure to colonoscopy preparations containing macrogols were used as controls.

To better determine the presence or absence of PEG specific IgE, we next used an electrochemiluminescent method with greater sensitivity for detection. Standard MULTI-ARRAY 96-well SECTOR plates were coated with Oncaspar and 5,000g/mol methoxy-PEG-bovine catalase at 10 μg/ml. Samples were processed with Protein G Plus Agarose as described above, then incubated at 1:10 dilution. Biotin-conjugated goat anti-human IgE (BioRad) antibody was added at 1:10,000 dilution. SULFO-TAG labeled Streptavidin was used as the detection reagent. Plates were read with a Sector Imager 6000 Analyzer (Meso Scale Discovery).

Furthermore, to investigate the effect of the molecular size of unconjugated PEG on anti-PEG specific IgG binding, we coated Nunc Maxisorp 96-well microplates (Thermo Fisher Scientific) with 5μg/ml HO-PEG-NH_2 of MW ranging from 1kDa to 10 kDa (Creative PEGWorks). Case and control samples were incubated at 1:100 dilution. Other steps were the same as the anti-Oncaspar IgG detection ELISA aforementioned.

Public Data Review:

To evaluate the scope to which polyethylene glycol 3350 might be associated with anaphylaxis in the United States, we next undertook a review of the publicly available FDA Adverse Event Reporting System (FAERS) database from 1989 through 2017. Using the

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search terms “polyethylene glycol” and “anaphylactic shock” or “anaphylactic reaction” we reviewed the number of these complaints for polyethylene glycol containing colonoscopy preparations and laxative products. We evaluated cases associated with branded and generic colonoscopy and laxative products whose primary ingredient was PEG 3350, including colonoscopy products both with and without electrolytes.

Medication Excipient Review:

To evaluate the degree to which immediate hypersensitivity to PEG 3350 or polysorbate 80 might affect medication or vaccine safety for affected patients, we next reviewed publicly available data in the searchable “DailyMed” database provided by the National Library of Medicine,[4] which allows for search queries targeting both active and inactive ingredients of all FDA approved and over-the-counter (OTC) medications in the United States. Searches conducted on the advanced search feature of this database will return reviewable information on the first 1000 hits. Using this database, we searched with the terms “polyethylene glycol 3350” and “polysorbate 80”, selecting that these ingredients must be either an “active” or “inactive” ingredient. We then classified the first 1000 hits by route of administration and indication for the medication. We also reviewed vaccine excipient summaries provided by the CDC for vaccines containing either of the two ingredients.[22]

Results:

Description of Cases:

During our 3 year period of surveillance, we encountered two patients with a history of anaphylaxis during preparation for colonoscopy and after methylprednisolone acetate injections.

The first such patient was a 57 year old white male with an occupational history as a mechanic and electrician, who presented to our clinic for evaluation of suspected medication allergies causing anaphylaxis. 5 years prior to presentation, he noted that while preparing for a colonoscopy, taking oral Colyte® brand colonoscopy preparation (active ingredient PEG 3350[23]) he developed severe itching of his palate and throat, which was alleviated by diphenhydramine. Two years prior to presentation, he underwent injection of methylprednisolone acetate (excipient PEG 3350[24]) into his neck as treatment of radicular pain from a bulging disk. Within seconds of receiving this medication, he developed urticaria, burning all over the body, throat tightness, wheezing, and hypotension. He was immediately given epinephrine, and transferred via emergency medical services to the emergency department, where he received additional epinephrine and IV fluid therapy. One year prior to presentation, he was scheduled for routine follow up of his initial colonoscopy. During his first few sips of Moviprep® brand colonoscopy preparation (active ingredient PEG 3350[25]) he developed severe itching of his palate and throat, along with diffuse urticaria. Symptoms resolved over a couple of hours with immediate cessation of the bowel preparation and diphenhydramine. Three months prior to presentation, he attempted once again to undergo colonoscopy, using oral Gavilyte™-G generic preparation (active ingredient PEG 3350[26]). He consumed approximately 10–12 ounces and subsequently developed itching, burning urticarial rash along with the urge to defecate. He went to the

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bathroom where he experienced syncope and fell, knocking a hole in the drywall with his head. Upon hearing the fall, his son, a nurse, arrived and checked his father's blood pressure, which was 60/20, and administered 0.3mg of 1:1000 concentration intramuscular epinephrine. EMS was called, and administered additional intramuscular epinephrine on arrival, taking the patient to the emergency department where he received diphenhydramine, famotidine, and intravenous fluids. He was observed overnight and discharged the next day.

The second patient was a 51 year old with an occupational history as a mechanic exposed to glycol containing hydraulic fluids, presenting for evaluation due to concern for peri-operative anaphylaxis. Four months prior to presentation, he was to receive an outpatient c-spine epidural steroid injection for cervical spine degeneration. He received lidocaine followed by omnipaque and methylprednisolone acetate. Within 5 minutes after the procedure he became itchy, red, hypotensive and a code was called. He was given ondansetron and methylprednisolone sodium succinate in addition to IV fluids. He was taken to the emergency department where he noted swelling in his hand, itching, difficulty swallowing, and hoarseness. He was given epinephrine as well as IV diphenhydramine and famotidine. He was admitted to the ICU for observation. One month prior to presentation, he began to develop a reaction just prior to a scheduled colonoscopy after use of a polyethylene glycol 3350 colonoscopy preparation. He became hypotensive and flushed and was treated with diphenhydramine, epinephrine, and IV fluids.

Skin Testing and Challenges:

The three bowel preparations and methylprednisolone acetate to which the patients had experienced immediate hypersensitivity reactions all share the ingredient PEG 3350. Both patients subsequently underwent prick and intradermal skin tests with serial dilutions of common corticosteroids, including methylprednisolone acetate (containing PEG 3350), methylprednisolone succinate (containing neither PEG nor polysorbate 80), betamethasone (containing neither PEG nor polysorbate 80), dexamethasone (containing neither PEG nor polysorbate 80), and triamcinolone acetonide (containing polysorbate 80, which shares significant structural homology to PEG) (Table I). During intradermal testing to the steroid preparations, patient 1 developed a sensation of throat and body itching, with a visible urticarial rash expanding from testing sites which was alleviated with 10 mg of cetirizine and 300 mg of ranitidine, without necessitating further treatment with epinephrine (Figure 2). Patient 1 was subsequently demonstrated to have skin test positivity to other polysorbate 80 containing products, including eye drops and conjugated pneumococcal vaccine, but was able to asymptomatically tolerate a low molecular weight PEG oral challenge with PEG 300. While Patient 2 had negative prick testing to PEG 3350 containing products and negative intradermal skin testing to methylpredisolone acetate, he did have positive testing to triamcinolone acetonide containing polysorbate 80. Upon challenge with PEG 3350 he developed diffuse urticaria, respiratory distress and hypotension requiring epinephrine and emergency department transfer. Both patients were able to tolerate challenge with parenteral steroids that did not contain macrogols.

Two healthy adult controls underwent polyethylene glycol testing on the same day as Patient 2, with negative testing and no irritation at testing sites.

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Laboratory Results:

Anti-PEG specific antibody concentrations were measured as optical density (OD) from the ELISA assay using methoxy-PEG-*E.coli* asparaginase as the antigen source. Anti-PEG specific IgG (sIgG) ODs in plasma samples from the 2 cases (0.50 for Patient 1 and 0.31 for Patient 2) were significantly higher than that of the 6 PEG-exposed controls (99% CI = 0.025 ± 0.019), indicating that both cases were positive for anti-PEG sIgG in these samples obtained 2~3 months after the last reaction (Table E1, Online Only). Anti-PEG specific IgE readings for the patients were negative by this method: ODs were 0.045 and 0.020 respectively for Patient 1 and Patient 2 compared to controls of 0.019 ± 0.0037, none of which were above the uncoated well background signal (99% CI = 0.050 ± 0.011).

Using the more sensitive Meso Scale Discovery electrochemiluminescence method we were then able to detect specific IgE directed against PEG in our two cases, but not our controls. Luminescence intensity from the two cases against Oncaspar (88 for Patient 1 and 77 for Patient 2) was significantly higher than that of the controls (99% CI = 55.9 ± 4.1). Similarly, luminescence intensity from the two cases against PEG-bovine catalase (246 for Patient 1 and 194 for Patient 2) was significantly higher than that of the controls (99% CI = 54.3 ± 9.3). The increase in luminescence intensity against both PEG containing reagents, when tested with sufficient sensitivity indicates that both cases were positive for anti-PEG sIgE (Table E1, Online Only).

Using unconjugated PEG molecules of different sizes as the antigen source, samples from both cases showed strong preference towards PEGs of larger molecular weights (Figure 3). Although patients in both cases reacted clinically to PEG 3350, anti-PEG sIgG antibodies in their plasma samples displayed even higher binding for higher molecular weight PEG 5k and PEG 10k, and almost no binding towards the lowest molecular weight PEG 1k (ODs were 0.021 and 0.014 respectively) compared to controls (99% CI = 0.014 ± 0.006) who did not demonstrate binding at any molecular weight of PEG.

Public data review results:

Using the preferred search term “anaphylactic” to capture both “anaphylactic shock” or “anaphylactic reaction”, we encountered 25,905 reports to the FDA between 1989 and the end of 2017. When the additional term “polyethylene glycol” was applied, we were left with 133 reports associating polyethylene glycol with anaphylaxis. Of these, we encountered 53 reports with unique case identifiers described as either anaphylactic shock or an anaphylactic reaction in which PEG containing bowel preparations or laxatives were the primary or sole agent suspected as causal. (Table II) The average age at reaction was 48.9 years (23% missing data), and 51% of those who reacted were male (15% missing data). At the time of reaction, 51% reported the PEG containing product was the sole agent they had ingested prior to anaphylaxis and were not using any other concomitant therapies. The other 49% were taking other concomitant therapies at the time of reaction, but their reports indicated primary suspicion was on PEG containing products. In terms of the clinical context, 72% of the reactions occurred prior to colonoscopy preparation, and 28% occurred during treatment of constipation. Reported reactions were distributed across the time period from 2005–2017,

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with an average of 4 cases reported per year during this time period. (Figure 4) We did not encounter any reports of PEG-related reactions prior to 2005.

Medication Excipient Review:

Using the search term “polyethylene glycol 3350” as an active or inactive ingredient returned 1155 FDA approved medications. A summary of the first 1000 hits can be found in Table E2 (Table E2, Online Only). This list demonstrates that polyethylene glycol 3350 can more commonly be found in film coated tablets, topical gels, and parenteral steroids. Using the search term “polysorbate 80” as an active or inactive ingredient returned 6821 FDA approved medications. A summary of the first 1000 hits can be found in Table E3 (Table E3, Online Only). This list demonstrates that polysorbate 80 can more commonly be found in film coated tablets, parenteral steroids, and vaccines.

Discussion:

The most commonly known clinical use of macrogols such as PEG 3350 is in colonoscopy preparation or constipation treatment.[5, 23, 25, 26] However, a review of common products and the literature demonstrates that polyethylene glycol and structurally similar polysorbate compounds can be found in vascular graft materials[10], surgical gels[27], PEGylated medications,[28–30] household and industrial compounds,[1] and as an excipient in a multitude of other medications both injectable and oral,[4, 31] In these settings, PEGs and polysorbates are not consistently described in ingredient lists.[8] The NIH DailyMed online resource through the National Library of Medicine is a useful resource for determining an individual product’s excipient content of macrogols such as PEGs and polysorbates: https://dailymed.nlm.nih.gov/.[4] Though cutaneous and systemic reactions to film coated tablets has been reported in patients with PEG hypersensitivity,[8] both of our patients were otherwise healthy and taking no daily medications that contained PEG. Neither one is known to have reacted to any products other than what we have described in this report.

A recent review of published case reports and case series in the literature by *Garvey et al.* found 37 cases of PEG hypersensitivity since 1977.[8] Our review of the FDA data adds a large number of additional cases that may not have been noticed in the medical literature. Our data suggests an average of 4 cases per year of PEG-associated anaphylaxis during colonoscopy preparation or laxative use are reported to the FDA. However, it is clear that relying on patient or physician initiated reports to the FDA will understate the true volume of the problem. Our review of FDA adverse event data focused only on drugs that contained pure polyethylene glycol 3350 at concentrations of grams per dose. Therefore we can not currently offer much additional data on whether drugs containing PEG or polysorbate 80 as an excipient at milligram or microgram concentrations can precipitate reactions in sensitized patients. We can only report that both of our patients have had anaphylaxis upon parenteral exposure to methylprednisolone acetate, formulations of which typically contain around 29 mg/ml of PEG 3350.[4]

The mechanism for macrogol hypersensitivity has been poorly understood. Anti-PEG sIgG has been detected in patients receiving PEG-conjugated protein therapeutics[6], but was not studied in unconjugated macrogol anaphylactic cases, while anti-PEG sIgE has not been

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directly measured in any human studies.[32] Our findings of skin test reactivity and coexisting polyethylene glycol-directed sIgE and sIgG antibodies suggest an IgE mediated Type I hypersensitivity could be possible in clinical reactions to unconjugated macrogols. These cases may represent a separate phenotype of immediate hypersensitivity from what has been previously shown during reactions to PEG-asparaginase and other PEGylated compounds.[7, 33] Of note, the absence of binding between patient IgG antibodies and lower MW PEGs also coincided with the tolerance of PEG 300 in both skin and oral challenges *in vivo*, supporting the involvement of antibodies specific for higher MW PEGs in the clinical reactions. The stronger reactivity of the patient samples against PEGs of higher molecular weight suggests that sensitization and risk of future reactions may depend partially on the molecular weight of PEG antigen exposures, and suggest that PEG may act as the primary antigen even when not conjugated to drug molecules. Detection of sIgE directed against PEG required use of the more sensitive Meso Scale Discovery electrochemiluminescence method and polysorbate-free testing reagents. Our results suggest that development of blood testing as a modality in diagnosis of macrogol hypersensitivity may be possible.

Conclusions:

High molecular weight polyethylene glycols are common excipients in a wide variety of medications, household products and industrial products which may provide a vehicle for sensitization in a subset of susceptible individuals. Allergists should be aware that cross-reactive immediate hypersensitivity to polyether containing compounds such as macrogols/PEGs and polysorbates can occur, that they may occur via a Type I hypersensitivity mechanism, and that they may be underrecognized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MW	molecular weight(s)
PEG	polyethylene glycol

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OTC	over-the-counter
OD	optical density
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention

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Highlights:

What is already known about this topic?

The most common immediate hypersensitivity to macrogols is associated with PEG 3350, however the epidemiology, mechanisms and cross-reactivity are poorly understood. Thousands of medications contain either PEGs or structurally similar polysorbates.

What does this study add to our knowledge?

In vivo and *ex vivo* testing of two cases suggest an IgE mediated, Type I hypersensitivity mechanism to polyethylene glycol 3350 anaphylaxis. This hypersensitivity, while rare, may be more common than we recognize.

How does this study impact current management guidelines?

Immediate hypersensitivity to PEG 3350 with cross-reactive polysorbate 80 hypersensitivity may be under recognized in clinical practice and can be evaluated with clinical skin testing.

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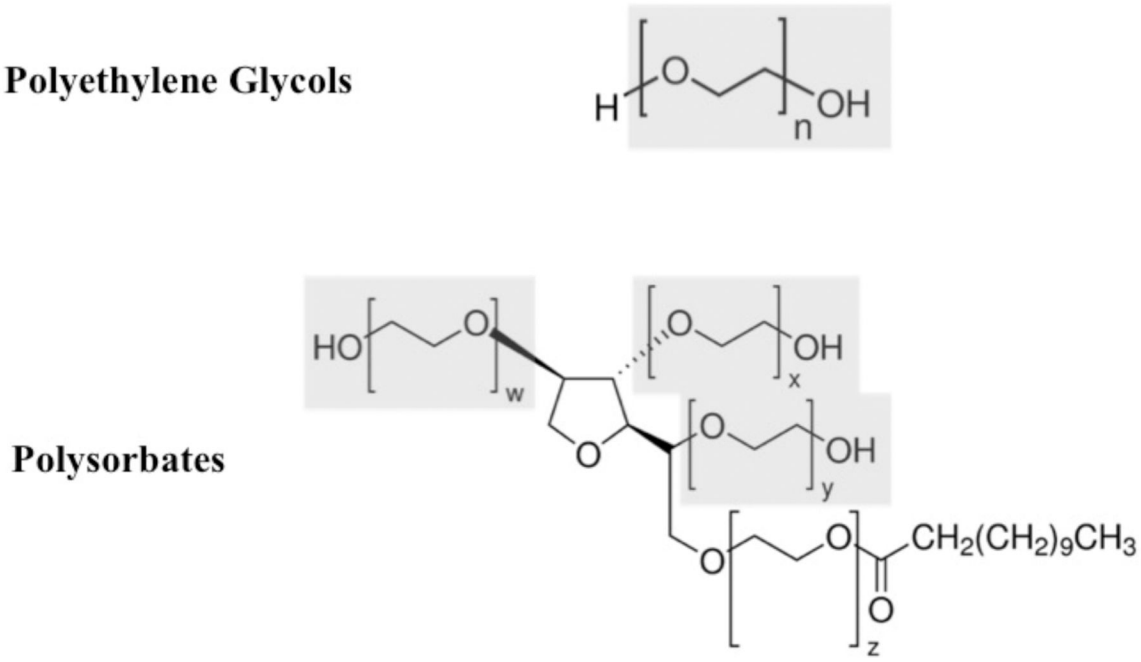

Figure 1:
Chemical structure of polyethylene glycols and polysorbates. Polysorbate 20 shown. Note the repeating polyether domains contained in both molecules, highlighted in gray. Source of chemical structure images: sigmaaldrich.com, accessed 5-15-2018. Highlights and labels added by authors to demonstrate similarity.

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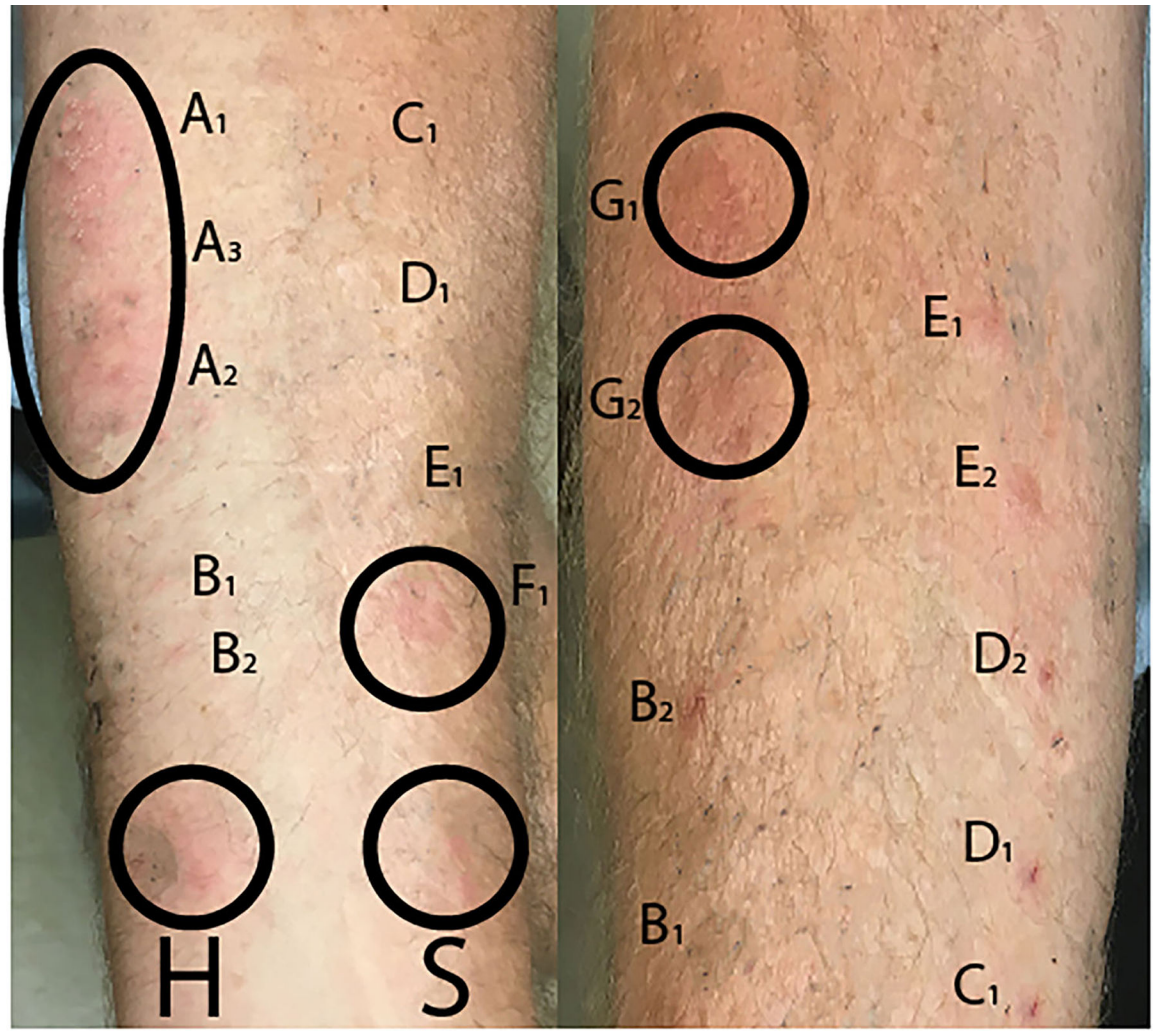

Figure 2:
Selected skin testing images for patient 1: In the left panel is skin prick testing demonstrating positive responses to methylprednisolone acetate (MP acetate), and polyethylene glycol 3350 (PEG 3350). Other tested corticosteroids were negative. In the right panel is intradermal testing, which demonstrates a positive response to triamcinolone acetate (T) at 1mg and 0.1mg. Other tested corticosteroids were interpreted as negative. (Measurements recorded in TABLE I).

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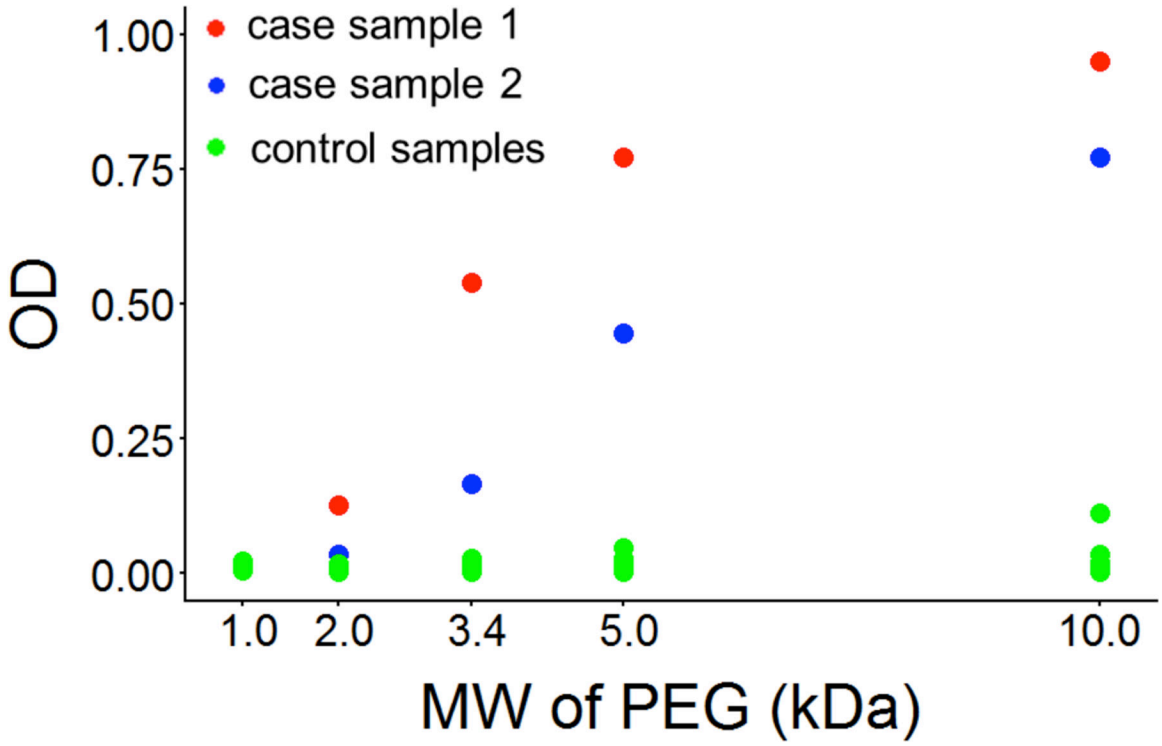

Figure 3:
IgG optical densities (ODs) of case and control plasma samples against HO-PEG-NH_2 of different molecular sizes.

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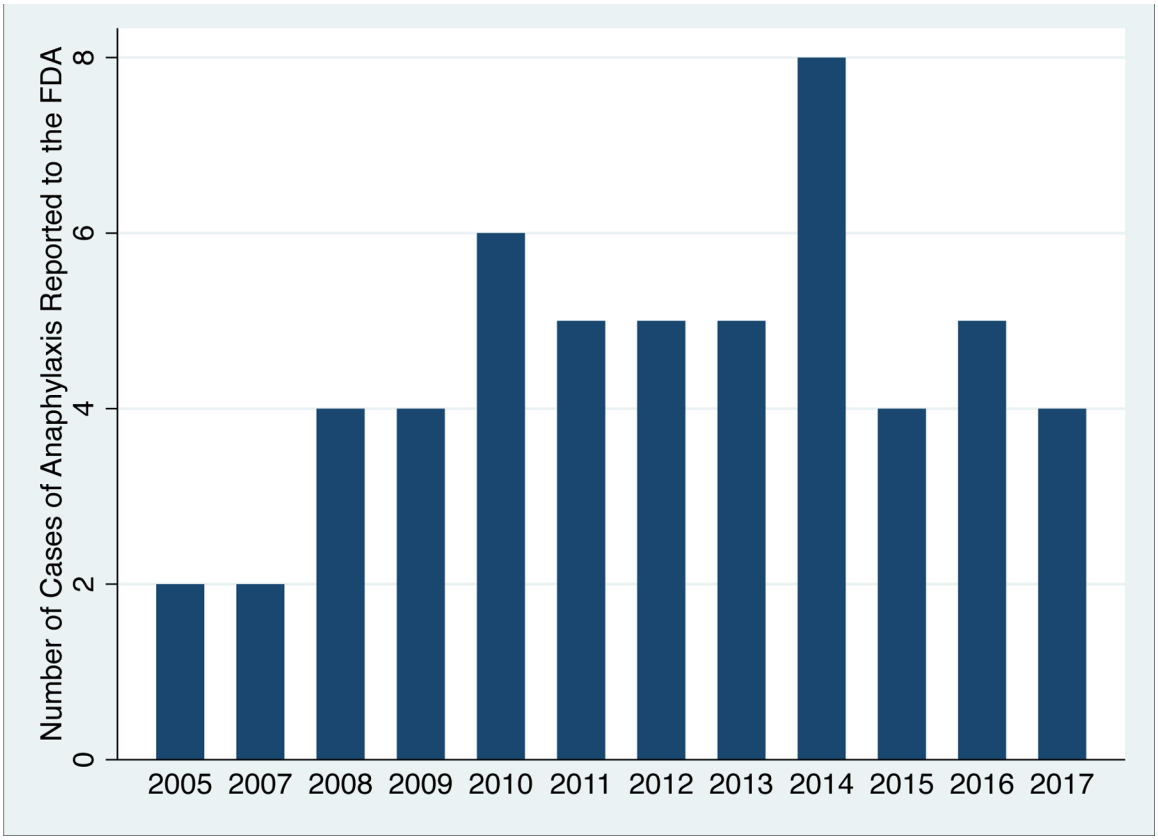

Figure 4:
Cases of anaphylaxis reported to the FDA (FAERS) implicating PEG containing bowel preparations or laxatives, by year.

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Table I:

Skin Prick and Intradermal Testing with Corticosteroids and Polyethylene Glycols

Skin Prick Test Results						
	Patient 1			**Patient 2**		
Agent (Concentration)	**Wheal (mm)**	**Flare (mm)**	**Inter-pretation**	**Wheal (mm)**	**Flare (mm)**	**Interpretation**
Histamine Control (0.1mg/ml)	6	26	Positive	7	20	Positive
Saline	0	0	Negative	0	0	Negative
PEG 3350	10	26	Positive	0	0	Negative
PEG 3350 (1:10 dilution)	11	22	Positive	0	0	Negative
PEG 3350 (1:100 dilution)	11	29	Positive	0	0	Negative
PEG 300 (1:10 dilution)	0	0	Negative			
PEG 300 (1:100 dilution)	4	5	Negative			
Methylprednisolone Acetate	5	12	Positive	0	0	Negative
Methylprednisolone Sodium Succinate	3	3	Negative	0	0	Negative
Intradermal Skin Test Results						
	Patient 1			**Patient 2**		
Agent (Concentration)	**Wheal (mm)**	**Flare (mm)**	**Inter-pretation**	**Wheal (mm)**	**Flare (mm)**	**Interpretation**
Betamethasone (6 mg/ml)	6	6	Negative	0	0	Negative
Betamethasone (0.6mg/ml)	5	5	Negative	0	0	Negative
Dexamethasone (0.4mg/ml)	5	0	Negative	0	0	Negative
Dexamethasone (0.04mg/ml)	7	0	Negative	0	0	Negative
Methylprednisolone Sodium Succinate (5mg/ml)	5	6	Negative	0	0	Negative
Methylprednisolone Sodium Succinate (0.5mg/ml)	0	0	Negative	0	0	Negative
Methylprednisolone Acetate (4mg/ml)				0	0	Subacute response developed at 20 hours, with 14mm raised wheal
Methylprednisolone Acetate (0.4mg/ml)				0	0	Negative
Triamcinolone Acetonide (1mg/ml)	10	19	Positive	10	30	Positive
Triamcinolone Acetonide (0.1 mg/ml)	15	24	Positive			
Conjugated pneumococcal vaccine (w/ polysorbate 80)	20	35	Positive			
Conjugated pneumococcal vaccine (1:10 dilution)	21	30	Positive			
Polysorbate 80 containing eye drop (1:10 dilution)	15	30	Positive			

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Table II:

Cases of Anaphylaxis Reported to the FDA from 2005 to 2017 Where Polyethylene Glycol 3350 Containing Formulations of Colonoscopy Preparation or Laxatives Were the Primary Drug Suspected

FAERS Report ID Number	Age	Sex	Year of Report	Formulation of PEG	Patient taking any other medications concomitantly	Indication (Colonoscopy Preparation vs. Constipation)
4852819-0	N/A	N/A	2005	Golytely	No	Preparation
4885400-8	30	Male	2005	Colyte	No	Preparation
5347102-3	42	Male	2007	Moviprep	No	Preparation
5326935-3	33	Female	2007	Polyethylene Glycol 3350-Brand not specified	No	Constipation
5792732-8	68	Male	2008	Golytely	No	Preparation
5829663-0	N/A	N/A	2008	Moviprep	No	Preparation
5909593-6	N/A	N/A	2008	Miralax	Yes	Constipation
5923262-8	64	Male	2008	Miralax	Yes	Constipation
6187140-4	52	Male	2009	Moviprep	Yes	Preparation
6262262-8	N/A	N/A	2009	Miralax	Yes	Preparation
6301790-3	52	Male	2009	Moviprep	Yes	Preparation
6446535-1	30	Female	2009	Moviprep	Yes	Preparation
6567457-1	N/A	N/A	2010	Polyethylene Glycol 3350-Brand not specified	Yes	Preparation
6583005-4	N/A	N/A	2010	Moviprep	No	Preparation
6625930-1	N/A	N/A	2010	Moviprep	No	Preparation
6649325-X	55	Female	2010	Golytely	Yes	Preparation
6681659-5	4	Male	2010	Miralax	No	Constipation
6784081-6	73	Male	2010	Miralax	No	Constipation
7610318-7	19	Male	2011	Moviprep	Yes	Preparation
7429359-8	59	Female	2011	Polyethylene Glycol 3350-Brand not specified	Yes	Preparation
7444601-5	55	Male	2011	Miralax	No	Preparation
7636123-3	64	Female	2011	Moviprep	No	Preparation
7759201-7	33	Female	2011	Polyethylene Glycol 3350-Brand not specified	No	Preparation
8274426-2	67	Female	2012	Moviprep	Yes	Preparation
8289679-4	57	Female	2012	Polyethylene Glycol 3350-Brand not specified	Yes	Constipation
8456637-6	46	Female	2012	Polyethylene Glycol 3350-Brand not specified	Yes	Constipation
8712178	N/A	Female	2012	Miralax	No	Constipation
8814458	24	Male	2012	Polyethylene Glycol 3350-Brand not specified	Yes	Constipation
9321913	16	Female	2013	Miralax	No	Preparation
9417033	56	Female	2013	Golytely	Yes	Preparation

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FAERS Report ID Number	Age	Sex	Year of Report	Formulation of PEG	Patient taking any other medications concomitantly	Indication (Colonoscopy Preparation vs. Constipation)
9420162	N/A	Female	2013	Miralax	Yes	Constipation
9607762	50	Male	2013	Golytely	No	Preparation
9782506	70	Female	2013	Moviprep	No	Preparation
9828607	34	Female	2014	Miralax	Yes	Preparation
9894648	N/A	Female	2014	Miralax	Yes	Constipation
9934430	54	Male	2014	Miralax	Yes	Constipation
10235381	87	Female	2014	Moviprep	Yes	Preparation
10242352	13	Male	2014	Miralax	No	Constipation
10335513	54	Female	2014	Glycolax	No	Preparation
10428179	65	Male	2014	Moviprep	Yes	Preparation
10682474	59	Male	2014	Moviprep	No	Preparation
10710219	19	Female	2015	Moviprep	Yes	Preparation
11362693	N/A	N/A	2015	Miralax	No	Preparation
11573598	N/A	Female	2015	Moviprep	No	Preparation
11617696	74	Male	2015	Moviprep	No	Preparation
12787790	62	Male	2016	Polyethylene Glycol 3350-Brand not specified	Yes	Preparation
12849324	39	Male	2016	Colyte	Yes	Preparation
12865113	59	Male	2016	Polyethylene Glycol 3350-Brand not specified	No	Preparation
13243846	46	Male	2016	Moviprep	Yes	Preparation
13268930	64	Male	2016	Polyethylene Glycol 3350-Brand not specified	No	Preparation
13747359	68	Female	2017	Miralax	Yes	Constipation
13854981	73	Female	2017	Golytely	No	Preparation
13870252	61	Female	2017	Moviprep	No	Preparation
13896629	2	Male	2017	Golytely	Yes	Constipation

Data marked as N/A indicate that the information was not contained in the primary report to the FDA.

JAMA Insights

Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021

Tom T. Shimabukuro, MD, MPH, MBA; Matthew Cole, MPH; John R. Su, MD, PhD, MPH

In December 2020, the US Food and Drug Administration (FDA) issued Emergency Use Authorizations for 2 mRNA-based vaccines for prevention of coronavirus disease 2019 (COVID-19): Pfizer-BioNTech COVID-19 vaccine (EUA issued December 11; 2 doses, 3 weeks apart) and Moderna COVID-19 vaccine (EUA issued December 18; 2 doses, 1 month apart). Shortly after each authorization, the Advisory Committee on Immunization Practices issued interim recommendations for use.[1,2]

Multimedia

Following implementation of vaccination, cases of anaphylaxis after administration of the Pfizer-BioNTech and Moderna vaccines began to be reported.[3,4] Anaphylaxis is a life-threatening allergic reaction that can occur after vaccination, with onset typically within minutes to hours.[5] The initial estimated reporting rates for anaphylaxis in the US were 11.1 cases per million doses administered of the Pfizer-BioNTech vaccine (December 14-23, 2020) and 2.5 cases per million doses administered of the Moderna vaccine (December 21, 2020-January 10, 2021).[3,4] Since these early estimates were generated, millions more doses of both vaccines have been administered and safety monitoring has detected additional cases of anaphylaxis. This analysis updates the reporting rates of anaphylaxis in individuals following receipt of either the Pfizer-BioNTech or Moderna vaccine.

The Vaccine Adverse Event Reporting System (VAERS), the national passive surveillance (spontaneous reporting) system for adverse events after immunization,[6] captured notifications and reports of suspected anaphylaxis following vaccination. Physicians at the Centers for Disease Control and Prevention (CDC) evaluated these reports and applied the Brighton Collaboration case definition for anaphylaxis to classify cases.[7]

During December 14, 2020 through January 18, 2021, a total of 9 943 247 doses of the Pfizer-BioNTech vaccine and 7 581 429 doses of the Moderna vaccine were reported administered in the US (CDC unpublished data, February 2021). CDC identified 66 case reports received by VAERS that met Brighton Collaboration case definition criteria for anaphylaxis (levels 1, 2 or 3): 47 following Pfizer-BioNTech vaccine, for a reporting rate of 4.7 cases/million doses administered, and 19 following Moderna vaccine, for a reporting rate of 2.5 cases/million doses administered. Cases occurred after receipt of doses from multiple vaccine lots. Characteristics of reported cases of anaphylaxis following these vaccines are described in the **Table**.

CDC physician reviewers concluded that the clinical characteristics of anaphylaxis cases following both vaccines were similar. Furthermore, there were no apparent clinical differences between anaphylaxis cases with symptom onset within 30 minutes and those with symptom onset after 30 minutes (a 15-minute postvaccination observation period is recommended for all persons and a 30-minute period is recommended for those with a history of certain allergic reactions).[8] Common signs and symptoms in anaphylaxis cases were generalized urticaria, diffuse erythematous rash, angioedema, respiratory and airway obstruction symptoms, and nausea. Twenty-one (32%) of the 66 case reports noted a prior episode of anaphylaxis from other exposures; prior exposures included vaccines (rabies, influenza A[H1N1], seasonal influenza, unspecified), contrast media (gadolinium-based, iodine-based, unspecified intravenous), unspecified infusions, sulfa drugs, penicillin,

Table. Characteristics of Reported Cases of Anaphylaxis Following Receipt of Pfizer-BioNTech (9 943 247 Doses) and Moderna (7 581 429 Doses) COVID-19 Vaccines—Vaccine Adverse Events Reporting System (VAERS), US, December 14, 2020-January 18, 2021

Characteristics	No. (%) of cases	
	Pfizer-BioNTech (n = 47)	Moderna (n = 19)
Age, median (range), y	39 (27-63)[a]	41 (24-63)
Female sex	44 (94)	19 (100)
Minutes to symptom onset, median (range)	10 (<1-1140 [19 h])[b]	10 (1-45)
Symptom onset, min		
≤15	34 (76)[b]	16 (84)
≤30	40 (89)[b]	17 (89)
Reported history[c]		
Allergies or allergic reactions	36 (77)	16 (84)
Prior anaphylaxis	16 (34)	5 (26)
Vaccine dose		
First	37	17
Second	4	1
Unknown	6	1
Brighton Collaboration case definition level[d]		
1	21 (45)	10 (52)
2	23 (49)	8 (43)
3	3 (6)	1 (5)
Anaphylaxis reporting rate (cases per million doses administered)	4.7	2.5

Abbreviation: COVID-19, coronavirus disease 2019.

[a] Age missing in 1 Pfizer-BioNTech report.

[b] Time to symptom onset missing in 2 BioNTech reports.

[c] To rabies vaccine, influenza A(H1N1) vaccine, seasonal influenza vaccine, unspecified vaccines, gadolinium- and iodine-based contrast media, unspecified intravenous contrast media, unspecified infusions, sulfa drugs, penicillin, prochlorperazine, latex, walnuts, unspecified tree nuts, jellyfish stings, unspecified multiple environmental and food allergens, unspecified exposure.

[d] The Brighton Collaboration case definition uses combinations of symptoms to define levels of diagnostic certainty. Brighton level 1 represents the highest level of diagnostic certainty that a reported case represents anaphylaxis; levels 2 and 3 are successively lower levels of diagnostic certainty. Level 4 is a case reported as anaphylaxis but that does not meet the Brighton Collaboration case definition, and level 5 is a case that was neither reported as anaphylaxis nor meets the case definition.

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prochlorperazine, latex, walnuts, unspecified tree nuts, jellyfish stings, and unspecified exposures.

In 61 (92%) of the anaphylaxis cases, patients received epinephrine as part of emergency treatment. All 66 persons were treated in health care settings; 34 (52%) were treated in an emergency department and 32 (48%) were hospitalized (including 18 in intensive care, 7 of whom required endotracheal intubation). As determined by medical record review and follow-up with treating health care facilities and clinicians, of the 7 patients who required endotracheal intubation, median time to symptom onset was 6 minutes (range, <1-45 minutes), with all but one patient having onset within 11 minutes. All 7 of those intubated received epinephrine, 6 received corticosteroids, and 5 received antihistamines; facial, tongue, or laryngeal angioedema was present in 4 of these patients; and hospitalization ranged from 1 to 3 days. Sixty-one individuals (92%) with follow-up information available are known to have been discharged from care or had recovered at the time of report to VAERS. No deaths from anaphylaxis after vaccination with either product were reported.

Continued safety monitoring of mRNA COVID-19 vaccines in the US has confirmed that anaphylaxis following vaccination is a rare event, with rates of 4.7 cases/million Pfizer-BioNTech vaccine doses administered and 2.5 cases/million Moderna vaccine doses administered, based on information through January 18, 2021. When considered in the context of morbidity and mortality from COVID-19,[9] the benefits of vaccination far outweigh the risk of anaphylaxis, which is treatable. Because of the acute, life-threatening nature of anaphylaxis, immediate epinephrine administration is indicated for all cases. CDC guidance on use of mRNA COVID-19 vaccines[8] and management of anaphylaxis is available.[10] All facilities administering COVID-19 vaccines should have the necessary supplies and trained medical personnel available to manage anaphylaxis.

ARTICLE INFORMATION

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Maintaining Safety with SARS-CoV-2 Vaccines

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To date, the development of mRNA vaccines for the prevention of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a success story, with no serious concerns identified in the ongoing phase 3 clinical trials.[1] Minor local side effects such as pain, redness, and swelling have been observed more frequently with the vaccines than with placebo. Systemic symptoms such as fever, fatigue, headache, and muscle and joint pain have also been somewhat more common with the vaccines than with placebo, and most have occurred during the first 24 to 48 hours after vaccination.[1] In the phase 1–3 clinical trials of the Pfizer–BioNTech and Moderna mRNA vaccines, potential participants with a history of an allergic reaction to any component of the vaccine were excluded. The Pfizer–BioNTech studies also excluded participants with a history of severe allergy associated with any vaccine (see the protocols of the two trials, available with the full text of the articles at NEJM.org, for full exclusion criteria).[1,2] Hypersensitivity adverse events were equally represented in the placebo (normal saline) and vaccine groups in both trials.[1]

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom was the first to authorize emergency use of the Pfizer–BioNTech mRNA vaccine. On December 8, 2020, within 24 hours after the start of the U.K. mass vaccination program for health care workers and elderly adults, the program reported probable cases of anaphylaxis in two women, 40 and 49 years of age, who had known food and drug allergies and were carrying auto-injectable epinephrine. On December 11, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the Pfizer–BioNTech mRNA vaccine, and general vaccination of health care workers was started on Monday, December 14. On December 15, a 32-year-old female health care worker in Alaska who had no known allergies presented with an anaphylactic reaction within 10 minutes after receiving the first dose of the vaccine. The participants who had these initial three reported cases of anaphylaxis would not have been excluded on the basis of their histories from the mRNA vaccine clinical trials.[1,2] Since the index case in Alaska, several more cases of anaphylaxis associated with the Pfizer mRNA vaccine have been reported in the United States after vaccination of almost 2 million health care workers, and the incidence of anaphylaxis associated with the Pfizer SARS-CoV-2 mRNA vaccine appears to be approximately 10 times as high as the incidence reported with all previous vaccines, at approximately 1 in 100,000, as compared 1 in 1,000,000, the known and stable incidence of anaphylaxis associated with other vaccines. The EUA for the Moderna mRNA vaccine was issued on December 18, and it is currently too soon to know whether a similar signal for anaphylaxis will be associated with that vaccine; however, at this time a small number of potential cases of anaphylaxis have been reported, including one case on December 24 in Boston in a health care worker with shellfish allergy who was carrying auto-injectable epinephrine.

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In response to the two cases of anaphylaxis in the United Kingdom, the MHRA issued a pause on vaccination with the Pfizer–BioNTech SARS-CoV-2 mRNA vaccine, to exclude any person with a history of anaphylactic reaction to any food, drug, or vaccine. The Centers for Disease Control and Prevention (CDC) has issued advice pertaining to administration of either the first or the second dose of the Pfizer–BioNTech or Moderna mRNA vaccine, recommending exclusion of any person who has a history of a severe or immediate (within 4 hours) allergic reaction associated with any of the vaccine components, including polyethylene glycol (PEG) and PEG derivatives such as polysorbates.[3]

Anaphylaxis is a serious multisystem reaction with rapid onset and can lead to death by asphyxiation, cardiovascular collapse, and other complications.[4] It requires prompt recognition and treatment with epinephrine to halt the rapid progression of life-threatening symptoms. The cause of anaphylactic reactions is the activation of mast cells through antigen binding and cross-linking of IgE; the symptoms result from the tissue response to the release of mediators such as histamine, proteases, prostaglandins, and leukotrienes and typically include flushing, hives, laryngeal edema, wheezing, nausea, vomiting, tachycardia, hypotension, and cardiovascular collapse. Patients become IgE-sensitized by previous exposure to antigens. Reactions that resemble the clinical signs and symptoms of anaphylaxis, previously known as anaphylactoid reactions, are now referred to as non-IgE–mediated reactions because they do not involve IgE. They manifest the same clinical features and response to epinephrine, but they occur by direct activation of mast cells and basophils, complement activation, or other pathways and can occur on first exposure. Tryptase is typically elevated in blood in IgE-mediated anaphylaxis and, to a lesser extent, in non–IgE-mediated mast-cell activation, a feature that identifies mast cells as the sources of inflammatory mediators. Prick and intradermal skin testing and analysis of blood samples for serum IgE are used to identify the specific drug culprit, although the tests lack 100% negative predictive value.[5] The clinical manifestations of the two U.K. cases and the one U.S. case fit the description of anaphylaxis: they occurred within minutes after the injections, symptoms were typical, and all responded to epinephrine. The occurrence on first exposure is not typical of IgE-mediated reactions; however, preexisting sensitization to a component of the vaccine could account for this observation.[4]

Anaphylaxis is a treatable condition with no permanent effects. Nevertheless, news of these reactions has raised fear about the risks of a new vaccine in a community. These cases of anaphylaxis raise more questions than they answer; however, such safety signals are almost inevitable as we embark on vaccination of millions of people, and they highlight the need for a robust and proactive "safety roadmap" to define causal mechanisms, identify populations at risk for such reactions, and implement strategies that will facilitate management and prevention (Fig. 1).[6]

Figure 1 (facing page). Assessing Reactions to Vaccines.
SARS-CoV-2 mRNA vaccines are built on the same lipid-based nanoparticle carrier technology; however, the lipid component of the Pfizer-BioNTech vaccine differs from that of the Moderna vaccine. Operation Warp Speed has led to an unprecedented response to the study of the safety and effectiveness of new vaccine platforms never before used in humans and to the development of vaccines that have been authorized for use less than a year after the SARS-CoV-2 viral sequence was discovered. The next few months could see the authorization of several such vaccines, and inevitably, adverse drug events will be recognized in the coming months that were not seen in the studies conducted before emergency use authorization. Maintenance of vaccine safety requires a proactive approach to maintain public confidence and reduce vaccine hesitancy. This approach involves not only vigilance but also meticulous response, documentation, and characterization of these events to heighten recognition and allow definition of mechanisms and appropriate approaches to prediction, prevention, and treatment. A systematic approach to an adverse reaction to any vaccine requires clinical recognition and appropriate initial treatment, followed by a detailed history and causality assessment. Nonimmune immediate reactions such as vasovagal reactions are common and typically manifest with diaphoresis, nausea, vomiting, pallor, and bradycardia, in contrast to the flush, pruritus, urticaria, angioedema, tachycardia, and laryngeal edema seen with anaphylaxis. Post-reaction clinical assessment by an allergist–immunologist that includes skin testing for allergy to components of the vaccine can be helpful. Use of other laboratory information may aid in clinical and mechanistic assessment and guide future vaccine and drug safety as well as management, such as rechallenge with alternative vaccines if redosing is required. A useful resource for searching the excipients of drugs and vaccines is https://dailymed.nlm.nih.gov/dailymed/. A useful resource for excipients in licensed vaccines is https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf.

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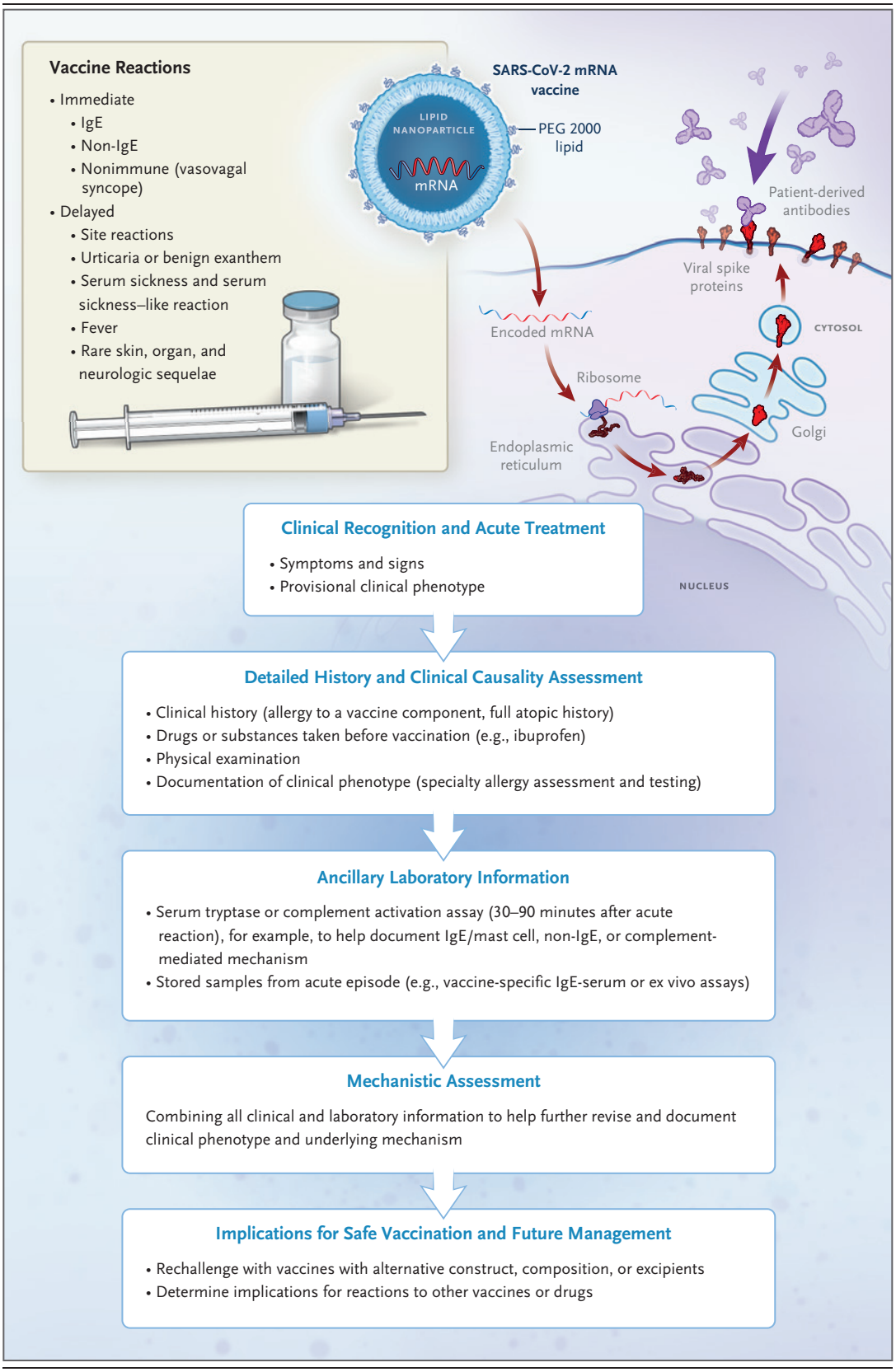

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We can be reassured that vaccine-associated anaphylaxis has been a rare event, at one case per million injections, for most known vaccines.[6] Acute allergic reactions after vaccination might be caused by the vaccine antigen, residual nonhuman protein, or preservatives and stabilizers in the vaccine formulation, also known as excipients.[6] Although local reactions may be commonly associated with the active antigen in the vaccine, IgE-mediated reactions or anaphylaxis have historically been more typically associated with the inactive components or products of the vaccine manufacturing process, such as egg, gelatin, or latex.[6]

The mRNA vaccines developed by Pfizer–BioNtech and Moderna use a lipid-based nanoparticle carrier system that prevents the rapid enzymatic degradation of mRNA and facilitates in vivo delivery.[1,2,7] This lipid-based nanoparticle carrier system is further stabilized by a polyethylene glycol (PEG) 2000 lipid conjugate that provides a hydrophilic layer, prolonging half-life. Although the technology behind mRNA vaccines is not new, there are no licensed mRNA vaccines, and the Pfizer–BioNtech and Moderna vaccines are the first to receive an EUA. There is therefore no prior experience that informs the likelihood or explains the mechanism of allergic reactions associated with mRNA vaccines. It is possible that some populations are at higher risk for non–IgE-mediated mast-cell activation or complement activation related to either the lipid or the PEG-lipid component of the vaccine. By comparison, formulations such as pegylated liposomal doxorubicin are associated with infusion reactions in up to 40% of recipients; the reactions are presumed to be caused by complement activation that occurs on first infusion, without previous exposure to the drug, and they are attenuated with second and subsequent injections.[8]

PEG is a compound used as an excipient in medications and has been implicated as a rare, "hidden danger" cause of IgE-mediated reactions and recurrent anaphylaxis.[9] The presence of lipid PEG 2000 in the mRNA vaccines has led to concern about the possibility that this component could be implicated in anaphylaxis. To date, no other vaccine that has PEG as an excipient has been in widespread use. The risk of sensitization appears to be higher with injectable drugs with higher-molecular-weight PEG; anaphylaxis associated with bowel preparations containing PEG 3350 to PEG 4000 has been noted in case reports.[9,10] The reports include anaphylaxis after a patient was exposed to a PEG 3350 bowel preparation; anaphylaxis subsequently developed on the patient's first exposure to a pegylated liposome microbubble, PEGLip 5000 perflutren echocardiography contrast (Definity), which is labeled with a warning about immediate hypersensitivity reactions.[11] For drugs such as methylprednisolone acetate and injectable medroxyprogesterone that contain PEG 3350, it now appears that the PEG component is more likely than the active drug to be the cause of anaphylaxis.[9,12] For patients with a history of an anaphylactic reaction to the SARS-CoV-2 Pfizer–BioNTech mRNA vaccine, the risk of anaphylaxis with the Moderna SARS-CoV-2 mRNA vaccine — whose delivery system is also based on PEG 2000, but with different respective lipid mixtures (see Table 1) — is unknown. The implications for future use of SARS-CoV-2 vaccines with an adenovirus carrier and protein subunit, which are commonly formulated with polysorbate 80, a nonionic surfactant and emulsifier that has a structure similar to PEG, are also currently unknown.[6,13] According to the current CDC recommendations, all persons with a history of an anaphylactic reaction to any component of the mRNA SARS-Cov-2 vaccines should avoid these vaccines, and this recommendation would currently exclude patients with a history of immediate reactions associated with PEG. It would also currently exclude patients with a history of anaphylaxis after receiving either the BioNTech–Pfizer or the Moderna vaccine, who should avoid all PEG 2000–formulated mRNA vaccines, and all PEG and injectable polysorbate 80 products, until further investigations are performed and more information is available.

We are now entering a critical period during which we will move rapidly through phased vaccination of various priority subgroups of the population. In response to the cases of anaphylaxis associated with the Pfizer–BioNTech vaccine in the United Kingdom and now several cases of anaphylaxis in the United States, the CDC has recommended that only persons with a known allergy to any component of the vaccine be excluded from vaccination. A systematic approach to the existing hypersensitivity cases and any new ones will ensure that our strategy will maintain safety not only for this

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Table 1. SARS-CoV-2 Vaccines under Emergency Use Authorization (EUA) or in Late-Phase Studies.

Vaccine Platform	Type of Vaccine and Immunogen	Developer (Name of Vaccine)	Dose Schedule and Administration	Phase*	Excipients†
RNA-based vaccine	mRNA encoding spike protein (30 μg)	BioNTech–Pfizer (BNT162b2)	Two doses (day 0, day 21) Intramuscular	Post-EUA	0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(**polyethylene glycol**)-**2000**]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol, 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% sodium chloride Injection) contributes an additional 2.16 mg sodium chloride per dose
RNA-based vaccine	mRNA encoding spike protein (100 μg)	Moderna (mRNA-1273)	Two doses (day 0, day 28) Intramuscular	Post-EUA	Lipids (SM-102; 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [**PEG 2000**-DMG]; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose
Adenovirus vector (nonreplicating)	ChAdOx1-Sn Cov-19 Nonreplicating chimpanzee AdV5 expressing spike protein	AstraZeneca and University of Oxford (AZD1222)	One (day 0) or two (day 0, day 28) doses Intramuscular	Phase 3	10 mM histidine, 7.5% (w/v) sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) **polysorbate 80**, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6
Adenovirus vector (nonreplicating)	Ad26.COV2.S Adenovirus 26 vectored vaccine using AdVac and PER.C6 technology	Janssen	One (day 0) or two (day 0, day 56) doses Intramuscular	Phase 3	Sodium chloride, citric acid monohydrate, **polysorbate 80**, 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol (absolute), sodium hydroxide
Protein subunit	Full-length recombinant SARS-CoV-2 glycoprotein nanoparticle with Matrix M adjuvant Spike prefusion protein	Novavax	Two doses (day 0, day 21) Intramuscular	Phase 3	Matrix M1 adjuvant Full-length spike protein formulated in **polysorbate 80** detergent and Matrix M1 adjuvant
Protein subunit	SARS-CoV-2 vaccine formulation with adjuvant (S-protein) (Baculovirus production) Spike protein	Sanofi Pasteur and GSK	Two doses (day 0, day 21) Intramuscular	Phase 1–2	Sodium phosphate monobasic monohydrate, sodium phosphate dibasic, sodium chloride **polysorbate 20**, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride

* Phase information was current as of December 21, 2020. In all cases, the placebo was normal saline.

† Bold entries are excipients potentially related to vaccine reaction that may be cross-reactive to other excipients (e.g., PEG 2000 and polysorbate 80). SM-102, a component of the Moderna vaccine, is a proprietary ionizable lipid.

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vaccine but for future mRNA and SARS-CoV-2 vaccines with shared or similar components (Fig. 1 and Table 1).[6]

The next few months alone are likely to see at least five new vaccines on the U.S. market, with several more in development (Table 1).[13] Maintaining public confidence to minimize vaccine hesitancy will be crucial.[14,15] As in any post-EUA program, adverse events that were not identified in clinical trials are to be expected. In addition, populations that have been studied in clinical trials may not reflect a predisposition to adverse events that may exist in other populations.[16] Regardless of the speed of development, some adverse events are to be expected with all drugs, vaccines, and medicinal products. Fortunately, immune-mediated adverse events are rare. Because we are now entering a period during which millions if not billions of people globally will be exposed to new vaccines over the next several months, we must be prepared to develop strategies to maximize effectiveness and safety at an individual and a population level. The development of systematic and evidence-based approaches to vaccination safety will also be crucial, and the approaches will intersect with our knowledge of vaccine effectiveness and the need for revaccination. When uncommon side effects that are prevalent in the general population are observed (e.g., the four cases of Bell's palsy reported in the Pfizer–BioNTech vaccine trial group), the question whether they were truly vaccine-related remains to be determined.[1]

If a person has a reaction to one SARS-CoV-2 vaccine, what are the implications for the safety of vaccination with a different SARS-CoV-2 vaccine? Furthermore, what safety issues may preclude future vaccination altogether? Indeed, mRNA vaccines are a promising new technology, and demonstration of their safety is relevant to the development of vaccines against several other viruses of global importance and many cancers.[7] For the immediate future, during a pandemic that is still increasing, it is critical that we focus on safe and efficient approaches to implementing mass vaccination. In the future, however, these new vaccines may mark the beginning of an era of personalized vaccinology in which we can tailor the safest and most effective vaccine on an individual and a population level.[17] Moreover, postvaccination surveillance and documentation may present a challenge. On a public health level, the Vaccine Adverse Event Reporting System (VAERS; https://vaers.hhs.gov) is a national reporting system designed to detect early safety problems for licensed vaccines, but in the case of Covid-19 vaccines, the system will serve the same function after an EUA has been issued. On an individual level, a system that will keep track of the specific SARS-CoV-2 vaccine received and will provide a means to monitor potential long-term vaccine-related adverse events will be critical to individual safety and efficacy. V-safe (https://cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html) is a smartphone application designed to remind patients to obtain a second dose as needed and to track and manage Covid-19 vaccine–related side effects.

In the world of Covid-19 and vaccines, many questions remain. What are the correlates of protective immunity after natural infection or vaccination? How long will immunity last? Will widespread immunity limit the spread of the virus in the population? Which component of the vaccine is responsible for allergic reactions? Are some vaccines less likely than others to cause IgE- and non-IgE–mediated reactions? Careful vaccine-safety surveillance over time, paired with elucidation of mechanisms of adverse events across different SARS-CoV-2 vaccine platforms, will be needed to inform a strategic and systematic approach to vaccine safety.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Lab Tests to Collect Shortly After Severe Allergic Reaction/Anaphylaxis Following COVID-19 Vaccination

For Healthcare Providers

There are no specific lab tests that can definitively diagnose the cause of a severe allergic reaction (e.g., anaphylaxis) following COVID-19 vaccination. In the United States, two commercially available lab tests can be ordered by healthcare providers and processed through healthcare facilities to better characterize a severe allergic reaction.

This document provides an overview of the timing and procedure for collecting blood samples for these lab tests. These samples should only be collected after medically stabilizing a patient who has experienced a severe allergic reaction.

The two commercially available lab tests are:

- Tryptase (a mast cell marker)
- SC5b-9 (terminal complement complex)

Tryptase is released from mast cells during anaphylaxis. SC5b-9 (terminal complement complex) is a measurement of complement system activation. These lab tests can be transiently elevated shortly after a severe allergic reaction. Elevations in these test results can help characterize the severe allergic reaction. Therefore, the timing of the blood sample collection for these tests can affect interpretation of the results.

The ideal time window to collect blood for these two tests is between 30 minutes and 90 minutes after the reaction began. However, these blood tests might still remain elevated up to 6 hours after the reaction began.

- Collecting blood earlier than 30 minutes after the reaction began could yield results that would be more difficult to interpret.
- If unable to collect this blood within the ideal 30–90 minute time window after the reaction began, healthcare providers can collect the blood samples as soon as possible, up through 6 hours after the reaction.
- These results are unlikely to be affected by epinephrine, antihistamines, and other treatments used to manage anaphylaxis.

Healthcare providers can consult with the laboratory in their healthcare facility to determine their site-specific practice for processing samples for tryptase and SC5b-9 tests. Typically, immediately flash-freezing the serum sample for SC5b-9 at -80 degrees C can maximize the accuracy of this test. The resources below provide more information about specimen processing requirements for some commercial laboratories. CDC does not endorse a particular laboratory.

A second sample for tryptase could be obtained 24 hours or more after the severe allergic reaction, or even weeks after the reaction. This tryptase level obtained 24 hours or more after the severe allergic reaction reflects the patient's typical tryptase level and can aid in the assessment of the allergic reaction.

Interpreting test results

Interpretation of these test results can be challenging. Consultation with a specialist (e.g., allergist-immunologist) within the weeks after the severe allergic reaction can help healthcare providers further evaluate potential factors that might have contributed to the development of the allergic reaction in these individuals. Also, healthcare providers or health departments in the United States can request a consultation from **CISA COVIDvax** for a complex COVID-19 vaccine safety question that is (1) about an individual patient residing in the United States or vaccine safety issue and (2) not readily addressed by CDC or Advisory Committee on Immunization Practices (ACIP) guidelines. More information about how to request a CISA COVIDvax consultation is available here: Clinical Immunization Safety Assessment (CISA) Project.

Reporting errors and adverse events

Vaccination providers are required by the Food and Drug Administration to report vaccination administration errors, serious adverse events, cases of Multisystem Inflammatory Syndrome, and cases of COVID-19 that result in hospitalization or death following COVID-19 vaccination under Emergency Use Authorization. Reporting is encouraged for any other clinically significant adverse event even if it is uncertain whether the vaccine caused the event. Information on how to submit a report to Vaccine Adverse Event Reporting System (VAERS) or call 1-800-822-7967.

Additional Resources

Tryptase | ARUP Lab Test Directory

Tryptase | Labcorp

Tryptase | Quest Diagnostics

SC5b-9 Level Terminal Complement Complex | Quest Diagnostics

SC5b-9 Level – Terminal Complement Complex | Diagnostic Testing | Clinical Laboratory (nationaljewish.org)

Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States | CDC

Interim Considerations: Preparing for the Potential Management of Anaphylaxis at COVID-19 Vaccination Sites | CDC

Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States

Interim considerations: preparing for the potential management of anaphylaxis after COVID-19 vaccination

Summary of recent changes (last updated February 10, 2021):

- New recommendations for preventing, reporting, and managing mRNA COVID-19 vaccine administration errors (Appendix A).
- Clarification on contraindications and precautions. Persons with a known (diagnosed) allergy to PEG, another mRNA vaccine component, or polysorbate, have a contraindication to vaccination. Persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG, another mRNA vaccine component or polysorbate, but in whom it is unknown which component elicited the immediate allergic reaction have a precaution to vaccination.
- Updated information on delayed, local injection-site reactions after the first mRNA vaccine dose. These reactions are neither a contraindication or precaution to the second dose.
- Updated quarantine recommendations for vaccinated persons. Fully vaccinated persons who meet criteria will no longer be required to quarantine following an exposure to someone with COVID-19. Additional considerations for patients and residents in healthcare settings are provided.
- Additional information and updated recommendations for testing for TB infection. TB testing can be done before or at the same time as mRNA COVID-19 vaccination, or otherwise delayed for ≥4 weeks after the completion of mRNA COVID-19 vaccination.

Background

The Advisory Committee on Immunization Practices (ACIP) has issued interim recommendations for the use of Pfizer-BioNTech and Moderna COVID-19 vaccines for the prevention of coronavirus disease 2019 (COVID-19) in the United States. Both vaccines are lipid nanoparticle-formulated, nucleoside-modified mRNA vaccines encoding the prefusion spike glycoprotein of SARS-CoV-2, the virus that causes COVID-19.

These interim CDC clinical considerations are informed by data submitted to the Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) of the vaccines, other data sources, general best practice guidelines for immunization, and expert opinion. These considerations for mRNA vaccines only apply to the currently authorized vaccine products in the United States (i.e., Pfizer-BioNTech and Moderna COVID-19 vaccines). Considerations will be updated when additional information becomes available and/or if additional vaccine products are authorized.

In addition to the following considerations, the EUA conditions of use and storage, handling, and administration procedures described in the prescribing information should be referenced when using the Pfizer-BioNTech and Moderna COVID-19 vaccines.

Authorized age groups

Under the EUAs, the following age groups are authorized to receive vaccination:

- Pfizer-BioNTech: ages ≥16 years
- Moderna: ages ≥18 years

Children and adolescents outside of these authorized age groups should not receive COVID-19 vaccination at this time.

Administration

The mRNA COVID-19 vaccine series consist of two doses administered intramuscularly:

- Pfizer-BioNTech (30 µg, 0.3 ml each): 3 weeks (21 days) apart
- Moderna (100 µg, 0.5 ml): 1 month (28 days) apart

Persons should not be scheduled to receive the second dose earlier than recommended (i.e., 3 weeks [Pfizer-BioNTech] or 1 month [Moderna]). However, second doses administered within a grace period of 4 days earlier than the recommended date for the second dose are still considered valid. Doses inadvertently administered earlier than the grace period should not be repeated.

The second dose should be administered as close to the recommended interval as possible. However, if it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of Pfizer-BioNTech and Moderna COVID-19 vaccines may be administered up to 6 weeks (42 days) after the first dose. There are currently limited data on efficacy of mRNA COVID-19 vaccines administered beyond this window. If the second dose is administered beyond these intervals, there is no need to restart the series.

Information on preventing, reporting, and managing mRNA COVID-19 vaccine administration errors is found in Appendix A. Vaccine administration errors should be reported to the Vaccine Adverse Event Reporting System (VAERS) .

Interchangeability with other COVID-19 vaccine products

Either of the currently authorized mRNA COVID-19 vaccines can be used when indicated; ACIP does not state a product preference. However, **these mRNA COVID-19 vaccines are not interchangeable with each other or with other COVID-19 vaccine products**. The safety and efficacy of a mixed-product series have not been evaluated. Both doses of the series should be completed with the same product.

Strategies to help ensure that patients receive the second dose with the appropriate product and interval between doses include:

- Providing COVID-19 vaccination record cards to vaccine recipients, asking recipients to bring their card to their appointment for the second dose, and encouraging recipients to make a backup copy (e.g., by taking a picture of the card on their phone).
- Encouraging vaccine recipients to enroll in VaxText[SM], a free text message-based platform to receive COVID-19 vaccination second-dose reminders.
- Recording each recipient's vaccination in the immunization information system (IIS).
- Recording vaccine administration information in the patient's medical record.
- Making an appointment for the second dose before the vaccine recipient leaves, to increase the likelihood that patients will present at the same vaccination site for the second dose.

Using the above strategies, every effort should be made to determine which vaccine product was received as the first dose, in order to ensure completion of the vaccine series with the same product. In exceptional situations in which the first-dose vaccine product cannot be determined or is no longer available, any available mRNA COVID-19 vaccine may be administered at a minimum interval of 28 days between doses to complete the mRNA COVID-19 vaccination series. If two doses of different mRNA COVID-19 vaccine products are administered in these situations (or inadvertently), no additional doses of either product are recommended at this time.

Recommendations may be updated when further information becomes available or other vaccine types (e.g., viral vector, protein subunit vaccines) are authorized.

Coadministration with other vaccines

Given the lack of data on the safety and efficacy of mRNA COVID-19 vaccines administered simultaneously with other vaccines, the vaccine series should routinely be administered alone, with a minimum interval of 14 days before or after administration with any other vaccine. However, mRNA COVID-19 and other vaccines may be administered within a shorter period in situations where the benefits of vaccination are deemed to outweigh the potential unknown risks of vaccine coadministration (e.g., tetanus toxoid-containing vaccination as part of wound management, rabies vaccination for post-exposure prophylaxis, measles or hepatitis A vaccination during an outbreak) or to avoid barriers or delays to mRNA COVID-19 vaccination (e.g., in long-term care facility residents or healthcare personnel who received influenza or other vaccinations prior to/upon admission or onboarding). If mRNA COVID-19 vaccines are administered within 14 days of another vaccine, doses do not need to be repeated for either vaccine.

Booster doses

The need for and timing of booster doses for mRNA COVID-19 vaccines has not been established. No additional doses beyond the two-dose primary series are recommended at this time.

Vaccination of persons with a SARS-CoV-2 infection or exposure

Persons with a current or prior history of SARS-CoV-2 infection

Data from clinical trials indicate that mRNA COVID-19 vaccines can safely be given to persons with evidence of a prior SARS-CoV-2 infection. Vaccination should be offered to persons regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection. Viral testing to assess for acute SARS-CoV-2 infection or serologic testing to assess for prior infection for the purposes of vaccine decision-making is **not** recommended.

Vaccination of persons with known current SARS-CoV-2 infection should be deferred until the person has recovered from the acute illness (if the person had symptoms) and criteria have been met for them to discontinue isolation. This recommendation applies to persons who experience SARS-CoV-2 infection before receiving any vaccine doses as well as those who experience SARS-CoV-2 infection after the first dose but before receipt of the second dose.

While there is no recommended minimum interval between infection and vaccination, current evidence suggests that the risk of SARS-CoV-2 reinfection is low in the months after initial infection but may increase with time due to waning immunity. Thus, **while vaccine supply remains limited**, persons with recent documented acute SARS-CoV-2 infection may choose to temporarily delay vaccination, if desired, recognizing that the risk of reinfection, and therefore the need for vaccination, might increase with time following initial infection.

For vaccinated persons who subsequently experience COVID-19, prior receipt of an mRNA COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment, or corticosteroid administration) or timing of such treatments.

Persons who previously received passive antibody therapy

Currently, there are no data on the safety and efficacy of mRNA COVID-19 vaccines in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. Based on the estimated half-life of such therapies and evidence suggesting that reinfection is uncommon in the 90 days after initial infection, vaccination should be deferred for at least 90 days, as a precautionary measure until additional information becomes available, to avoid potential interference of the antibody therapy with vaccine-induced immune responses. This recommendation applies to persons who receive passive antibody therapy before receiving any vaccine doses and those who receive passive antibody therapy after the first dose but before the second dose, in which case the second dose should be deferred for at least 90 days following receipt of the antibody therapy.

For persons receiving antibody therapies not specific to COVID-19 treatment (e.g., intravenous immunoglobulin, RhoGAM), administration of mRNA COVID-19 vaccines either simultaneously with or at any interval before or after receipt of an antibody-containing product is unlikely to substantially impair development of a protective antibody response. Thus, there is no recommended minimum interval between other antibody therapies (i.e., those that are not specific to COVID-19 treatment) and mRNA COVID-19 vaccination.

Vaccinating persons with a known SARS-CoV-2 exposure or during COVID-19 outbreaks

mRNA vaccines are not currently recommended for outbreak management or for post-exposure prophylaxis, which is vaccination to prevent the development of SARS-CoV-2 infection in a person with a specific known exposure. Because the median incubation period of SARS-CoV-2 is 4–5 days, it is unlikely that the first dose of COVID-19 vaccine would provide an adequate immune response within the incubation period for effective post-exposure prophylaxis. Thus, vaccination is unlikely to be effective in preventing disease following an exposure.

Persons in the community or outpatient setting who have had a known COVID-19 exposure should not seek vaccination until their quarantine period has ended to avoid potentially exposing healthcare personnel and other persons to SARS-CoV-2 during the vaccination visit.

Residents with a known COVID-19 exposure living in congregate healthcare settings (e.g., long-term care facilities), where exposure and transmission of SARS-CoV-2 can occur repeatedly for long periods of time, may be vaccinated. In these settings, healthcare personnel are already in close contact with residents (e.g., entering patient rooms for evaluation and treatment). Vaccinators should employ appropriate infection prevention and control procedures.

Residents of other congregate settings (e.g., correctional and detention facilities, homeless shelters) with a known COVID-19 exposure may also be vaccinated, in order to avoid delays and missed opportunities for vaccination given the increased risk for outbreaks in these settings. However, where feasible, precautions should be taken to limit mixing exposed individuals with other residents or staff (except those essential for the provision of vaccination services, who should employ appropriate infection and control procedures).

Persons residing in congregate settings (healthcare and non-healthcare) who have had an exposure and are awaiting results of SARS-CoV-2 testing may be vaccinated if the person does not have symptoms consistent with COVID-19.

In situations where facility-wide testing is being conducted to identify SARS-CoV-2 infections, facilities should attempt to complete facility-wide testing within a period that allows for test results to be received prior to vaccination in order to isolate those patients with SARS-CoV-2 infection. However, it is not necessary to wait for test results if this would create delays in vaccination. In such situations, persons without symptoms consistent with COVID-19 may be vaccinated. Although not contraindicated, vaccination may be deferred pending outcome of testing in persons with symptoms consistent with COVID-19. Viral testing for acute SARS-CoV-2 infection solely for the purposes of vaccine decision-making is not recommended.

Vaccination of persons with underlying medical conditions

mRNA COVID-19 vaccines can administered to persons with underlying medical conditions who have no contraindications to vaccination (see 'contraindications' section below). Clinical trials demonstrated similar safety and efficacy profiles in persons with some underlying medical conditions, including those that place them at increased risk for severe COVID-19, compared to persons without comorbidities. Information on groups with specific underlying medical conditions is included below.

Immunocompromised persons

Persons with HIV infection or other immunocompromising conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19. Data are not currently available to establish vaccine safety and efficacy in these groups. Persons with stable HIV infection were included in mRNA COVID-19 vaccine clinical trials, though data remain limited. Immunocompromised individuals can receive COVID-19 vaccination if they have no contraindications to vaccination. However, they should be counseled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, and the potential for reduced immune responses and the need to continue to follow all current guidance to protect themselves against COVID-19 (see below). Antibody testing is not recommended to assess for immunity to COVID-19 following mRNA COVID-19 vaccination.

At this time, re-vaccination is not recommended after immune competence is regained in persons who received mRNA COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs. Recommendations on re-vaccination or additional doses of mRNA COVID-19 vaccines may be updated when additional information is available.

Persons with autoimmune conditions

No data are currently available on the safety and efficacy of mRNA COVID-19 vaccines in persons with autoimmune conditions, though these persons were eligible for enrollment in clinical trials. No imbalances were observed in the occurrence of symptoms consistent with autoimmune conditions or inflammatory disorders in clinical trial participants who received an mRNA COVID-19 vaccine compared to placebo. Persons with autoimmune conditions who have no contraindications to vaccination may receive an mRNA COVID-19 vaccine.

Persons with a history of Guillain-Barré syndrome

To date, no cases of Guillain-Barré syndrome (GBS) have been reported following vaccination among participants in the Pfizer-BioNTech or Moderna COVID-19 vaccines clinical trials. With few exceptions, ACIP's general best practice guidelines for immunization does not include history of GBS as a contraindication or precaution to vaccination. Persons with a history of GBS may receive an mRNA COVID-19 vaccine unless they have a contraindication to vaccination. Any occurrence of GBS following mRNA COVID-19 vaccination should be reported to VAERS.

Persons with a history of Bell's palsy

Cases of Bell's palsy were reported following vaccination in participants in both the Pfizer-BioNTech and Moderna COVID-19 vaccines clinical trials. However, the FDA does not consider these to be above the frequency expected in the general population and has not concluded that these cases were causally related to vaccination. Post-authorization safety surveillance will be important to further assess any possible causal association. In the absence of such evidence, persons with a history of Bell's palsy can receive an mRNA COVID-19 vaccine unless they have a contraindication to vaccination. Any occurrence of Bell's palsy following mRNA COVID-19 vaccination should be reported to VAERS.

Persons with a history of dermal filler use

Infrequently, persons who have received dermal fillers might experience swelling at or near the site of filler injection (usually face or lips) following administration of a dose of an mRNA COVID-19 vaccine. This appears to be temporary and can resolve with medical treatment, including corticosteroid therapy. mRNA COVID-19 vaccines can be administered to persons who have received injectable dermal fillers who have no contraindications to vaccination (see 'contraindications' section below). No additional precautions are needed. However, these persons should be advised to contact their healthcare provider for evaluation if they experience swelling at or near the site of dermal filler following vaccination.

Vaccination of pregnant or lactating people

Pregnant people

Observational data demonstrate that while the absolute risk is low, pregnant people with COVID-19 have an increased risk of severe illness, including illness resulting in intensive care admission, mechanical ventilation, or death. Additionally, they might be at an increased risk of adverse pregnancy outcomes, such as preterm birth.

There are currently few data on the safety of COVID-19 vaccines, including mRNA vaccines, in pregnant people. Limited data are currently available from animal developmental and reproductive toxicity studies. No safety concerns were demonstrated in rats that received Moderna COVID-19 vaccine prior to or during gestation in terms of female reproduction, fetal/embryonal development, or postnatal development. Studies in pregnant people are planned and the vaccine manufacturers are following outcomes in people in the clinical trials who became pregnant. Based on current knowledge, experts believe that mRNA vaccines are unlikely to pose a risk to the pregnant person or the fetus because mRNA vaccines are not live vaccines. The mRNA in the vaccine is degraded quickly by normal cellular processes and does not enter the nucleus of the cell. However, the potential risks of mRNA vaccines to the pregnant person and the fetus are unknown because these vaccines have not been studied in pregnant people.

If pregnant people are part of a group that is recommended to receive a COVID-19 vaccine (e.g., healthcare personnel), they may choose to be vaccinated. A conversation between the patient and their clinical team may assist with decisions regarding the use of a mRNA COVID-19 vaccine, though a conversation with a healthcare provider is not required prior to vaccination. When making a decision, pregnant people and their healthcare providers should consider the level of COVID-19 community transmission, the patient's personal risk of contracting COVID-19, the risks of COVID-19 to the patient and potential risks to the fetus, the efficacy of the vaccine, the side effects of the vaccine, and the lack of data about the vaccine during pregnancy.

Side effects can occur with COVID-19 vaccine use in pregnant people, similar to those expected among non-pregnant people. Pregnant people who experience fever following vaccination can be counseled to take acetaminophen because fever has been associated with adverse pregnancy outcomes. Acetaminophen can be offered as an option for pregnant people experiencing other post-vaccination symptoms.

There is no recommendation for routine pregnancy testing before receipt of a COVID-19 vaccine. Those who are trying to become pregnant do not need to avoid pregnancy after mRNA COVID-19 vaccination.

Lactating people

There are no data on the safety of COVID-19 vaccines in lactating people or the effects of mRNA COVID-19 vaccines on the breastfed infant or milk production/excretion. mRNA vaccines are not thought to be a risk to the breastfeeding infant. A lactating person who is part of a group recommended to receive a COVID-19 vaccine (e.g., healthcare personnel) may choose to be vaccinated.

Vaccination of children and adolescents

Adolescents aged 16–17 years are included among persons eligible to receive the Pfizer-BioNTech COVID-19 vaccine under the EUA. While vaccine safety and efficacy data in this age group are limited, there are no biologically plausible reasons for safety and efficacy profiles to be different than those observed in persons 18 years of age and older. Adolescents aged 16–17 years who are part of a group recommended to receive a COVID-19 vaccine may be vaccinated with the Pfizer-BioNTech COVID-19 vaccine with appropriate assent. Children and adolescents younger than 16 years of age are not authorized to receive the Pfizer-BioNTech COVID-19 vaccine at this time.

Children and adolescents younger than 18 years of age are not authorized to receive the Moderna COVID-19 vaccine at this time.

Patient counseling

Vaccine efficacy

Preliminary data suggest high vaccine efficacy in preventing COVID-19 following receipt of two doses of mRNA COVID-19 vaccine (Pfizer-BioNTech: 95.0% [95% CI: 90.3%, 97.6%]; Moderna: 94.1% [95% CI: 89.3%, 96.8%]). Limited data are currently available regarding the efficacy of a single dose. Patients should be counseled on the importance of completing the two-dose series with the same vaccine product to optimize protection.

Reactogenicity

Before vaccination, providers should counsel mRNA COVID-19 vaccine recipients about expected local (e.g., pain, swelling, erythema at the injection site, localized axillary lymphadenopathy on the same side as the vaccinated arm) and systemic (e.g., fever, fatigue, headache, chills, myalgia, arthralgia) post-vaccination symptoms. Depending on vaccine product (Pfizer vs. Moderna), age group, and vaccine dose, approximately 80–89% of vaccinated persons experience at least one local symptom and 55–83% experience at least one systemic symptom following vaccination.

Most systemic post-vaccination symptoms are mild to moderate in severity, occur within the first three days of vaccination, and resolve within 1–3 days of onset. These symptoms are more frequent and severe following the second dose and among younger persons compared with older persons (i.e., ages >55 or ≥65 years [for Pfizer-BioNTech or

Moderna vaccines, respectively]). Unless persons experience a contraindication to vaccination (see below), they should be encouraged to complete the series even if they experience local or systemic symptoms following the first dose to optimize protection against COVID-19.

In clinical trials, hypersensitivity-related adverse events were observed in 0.63% of participants who received the Pfizer-BioNTech COVID-19 vaccine and 1.5% of participants who received the Moderna COVID-19 vaccine, compared with 0.51% and 1.1%, respectively, in the placebo groups. Anaphylaxis following vaccination was not observed in the Pfizer-BioNTech or Moderna COVID-19 vaccines clinical trials. However, anaphylactic reactions have been reported following receipt of mRNA vaccines outside of clinical trials.

Management of post-vaccination symptoms

Antipyretic or analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs) can be taken for the treatment of post-vaccination local or systemic symptoms, if medically appropriate. However, routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, because information on the impact of such use on mRNA COVID-19 vaccine-induced antibody responses is not available at this time.

In addition, administration of antihistamines to COVID-19 vaccine recipients prior to vaccination to prevent allergic reactions is not recommended. Antihistamines do not prevent anaphylaxis, and their use might mask cutaneous symptoms, which could lead to a delay in the diagnosis and management of anaphylaxis. See section below ("contraindications and precautions to vaccination") and interim considerations for anaphylaxis management for more information on management of anaphylaxis.

Infection prevention and control considerations are available for healthcare personnel and long-term care facility residents (e.g., populations included in phase 1a of vaccine allocation) with systemic signs and symptoms following COVID-19 vaccination. Considerations may be updated as additional information becomes available or additional groups are prioritized for vaccine allocation.

Contraindications and precautions

While rare, anaphylactic reactions have been reported following vaccination with mRNA COVID-19 vaccines. Although investigations are ongoing, persons with a history of an immediate allergic reaction (of any severity) to an mRNA COVID-19 vaccine or any of its components might be at greater risk for anaphylaxis upon re-exposure to either of the currently authorized mRNA COVID-19 vaccines. For the purposes of this guidance, an immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms such as urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.

Recommendations for contraindications and precautions are described below and summarized in Appendix B. The following recommendations may change when further information becomes available.

Contraindications

CDC considers a history of the following to be a contraindication to vaccination with both the Pfizer-BioNTech and Moderna COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components
- Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])*
- Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)*

* These persons should not receive mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna) at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available). See Appendix C for more information on ingredients included in mRNA COVID-19 vaccines.

Providers should attempt to determine whether reactions reported following vaccination are consistent with immediate allergic reactions versus other types of reactions commonly observed following vaccination, such as a vasovagal reaction or post-vaccination side effects (which are not contraindications to receiving the second vaccine dose) (Appendix D).

Healthcare personnel or health departments in the United States can request a consultation from the Clinical Immunization Safety Assessment COVIDvax project for a complex COVID-19 vaccine safety question about an individual patient residing in the United States not readily addressed by CDC guidance.

Precautions

CDC considers a history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies [excluding subcutaneous immunotherapy for allergies , i.e. "allergy shots"] not related to a component of mRNA COVID-19 vaccines or polysorbate) as a precaution but not a contraindication to vaccination for both the Pfizer-BioNTech and Moderna COVID-19 vaccines. This includes persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG, another vaccine component, or polysorbate, but in whom it is unknown which component elicited the immediate allergic reaction.

Persons with a precaution to vaccination should be counseled about the unknown risks of experiencing a severe allergic reaction and balance these risks against the benefits of vaccination. Deferral of vaccination and/or consultation with an allergist-immunologist may be considered until further information on the risk of anaphylaxis is available. The following considerations can be used to help the provider conduct a risk assessment for mRNA COVID-19 vaccination in these individuals:

- Risk of exposure to SARS-CoV-2 (e.g., because of residence in a congregate setting such as a long-term care facility, occupation)
- Risk of severe disease or death due to COVID-19 (e.g., because of age, underlying medical conditions)
- Whether the patient has previously been infected with SARS-CoV-2 and, if so, how long ago
    - Note: Vaccination is recommended for persons with a history of COVID-19; however, because reinfection is uncommon in the months following infection, persons with a precaution to vaccination and recent COVID-19 may choose to defer vaccination until further information is known about the risk of anaphylaxis following vaccination.
- The unknown risk of anaphylaxis (including fatal anaphylaxis) following mRNA COVID-19 vaccination in a person with a history of an immediate allergic reaction to other vaccines or injectable therapies
- Ability of the patient to be vaccinated in a setting where appropriate medical care is immediately available for anaphylaxis

Neither contraindications nor precautions to vaccination

Allergic reactions (including severe allergic reactions) not related to vaccines, injectable therapies, components of mRNA COVID-19 vaccines (including PEG), or polysorbates, such as allergic reactions related to food, pet, venom, or environmental allergies, or allergies to oral medications (including the oral equivalents of injectable medications) are **not** a contraindication or precaution to vaccination with either mRNA COVID-19 vaccine. The vial stoppers of these mRNA vaccines are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, because the mRNA COVID-19 vaccines do not contain eggs or gelatin, persons with allergies to these substances do not have a contraindication or precaution to vaccination.

Persons with only a delayed-onset local reaction (e.g., erythema, induration, pruritus) around the injection site area after the first vaccine dose do not have a contraindication or precaution to the second dose. Delayed-onset local reactions have been reported in some individuals, including in Moderna clinical trial participants, beginning a few days through the second week after the first dose, and are sometimes quite large. It is not known whether persons who experienced a

delayed-onset injection site reaction after the first dose will experience a similar reaction after the second dose. However, these delayed-onset local reactions are not felt to represent a risk for anaphylaxis upon receipt of the second dose. Thus, individuals with such delayed injection site reactions after the first mRNA COVID-19 vaccine dose should receive the second dose using the same vaccine product as the first dose and at the recommended interval, and preferably in the opposite arm.

Observation periods following vaccination (for persons without contraindications to mRNA COVID-19 vaccines)

CDC recommends an observation period following vaccination with mRNA COVID-19 vaccines. Persons with a history of an immediate allergic reaction of any severity to a vaccine or injectable therapy and persons with a history of anaphylaxis due to any cause should be observed for 30 minutes. All other persons should be observed for 15 minutes.

Management of anaphylaxis after mRNA COVID-19 vaccination

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of mRNA COVID-19 vaccine. Further information on anaphylaxis management can be found in the interim considerations for the management of anaphylaxis following COVID-19 vaccination and laboratory evaluation of persons who experience anaphylaxis after vaccination.

Public health recommendations for vaccinated persons

While mRNA COVID-19 vaccines have demonstrated high efficacy at preventing severe and symptomatic COVID-19, there is currently limited information on how much the vaccines might reduce transmission and how long protection lasts. In addition, the efficacy of the vaccines against emerging SARS-CoV-2 variants is not known. At this time, vaccinated persons should continue to follow **current guidance** to protect themselves and others, including wearing a mask, staying at least 6 feet away from others, avoiding crowds, avoiding poorly ventilated spaces, covering coughs and sneezes, washing hands often, following CDC travel guidance, and following any applicable workplace or school guidance, including guidance related to personal protective equipment use or SARS-CoV-2 testing.

However, vaccinated persons with an exposure to someone with suspected or confirmed COVID-19 are not required to quarantine if they meet all of the following criteria[†]:

- Are fully vaccinated (i.e., ≥2 weeks following receipt of the second dose in a 2-dose series, or ≥2 weeks following receipt of one dose of a single-dose vaccine)
- Are within 3 months following receipt of the last dose in the series
- Have remained asymptomatic since the current COVID-19 exposure

Persons who do not meet all 3 of the above criteria should continue to follow current quarantine guidance after exposure to someone with suspected or confirmed COVID-19.

Although the risk of SARS-CoV-2 transmission from vaccinated persons to others is still uncertain, vaccination has been demonstrated to prevent symptomatic COVID-19; symptomatic and pre-symptomatic transmission is thought to have a greater role in transmission than purely asymptomatic transmission. Additionally, individual and societal benefits of avoiding unnecessary quarantine may outweigh the potential but unknown risk of transmission, and facilitate the direction of public health resources to persons at highest risk for transmitting SARS-CoV-2 to others. This recommendation to waive quarantine for people with vaccine-derived immunity aligns with quarantine recommendations for those with natural immunity, which eases implementation.

Fully vaccinated persons who do not quarantine should still watch for symptoms of COVID-19 for 14 days following an exposure. If they experience symptoms, they should be clinically evaluated for COVID-19, including SARS-CoV-2 testing, if indicated. In addition, vaccinated persons should continue to follow **current guidance** to protect themselves and others, including all other SARS-CoV-2 testing recommendations and requirements, and state, territorial, tribal, and local travel recommendations or requirements. For additional considerations regarding quarantine or work restrictions for fully vaccinated healthcare personnel, patients, or residents in healthcare settings, please see section below.

These quarantine recommendations for vaccinated persons, including the criteria for timing since receipt of the last dose in the vaccination series, will be updated when more data become available and additional COVID-19 vaccines are authorized.

[†] CDC has not systematically evaluated the efficacy of COVID-19 vaccines from manufacturers that have not sought an EUA in the United States. For the purposes of these quarantine criteria, considerations for accepting a vaccination series that is not FDA-authorized include whether the vaccine product has received emergency approval from the World Health Organization or authorization from a national regulatory agency.

Vaccinated healthcare personnel, patients, and residents in healthcare settings

These criteria could also be applied when considering work restrictions for fully vaccinated healthcare personnel with higher-risk exposures, as a strategy to alleviate staffing shortages. Of note, exposed healthcare personnel would not be required to quarantine outside of work.

As an exception to the above guidance no longer requiring quarantine for fully vaccinated persons, **vaccinated inpatients and residents in healthcare settings should continue to quarantine following an exposure** to someone with suspected or confirmed COVID-19; outpatients should be cared for using appropriate Transmission-Based Precautions. This exception is due to the unknown vaccine effectiveness in this population, the higher risk of severe disease and death, and challenges with social distancing in healthcare settings. Although not preferred, healthcare facilities could consider waiving quarantine for vaccinated patients and residents as a strategy to mitigate critical issues (e.g., lack of space, staff, or PPE to safely care for exposed patients or residents) when other options are unsuccessful or unavailable. These decisions could be made in consultation with public health officials and infection control experts.

CDC's healthcare infection control guidance contains additional considerations regarding the need to protect healthcare personnel, patients, and residents while also alleviating any staffing shortages.

Reporting of vaccine adverse events

Adverse events that occur in a recipient following mRNA COVID-19 vaccination should be reported to VAERS. Vaccination providers are required by the Food and Drug Administration to report the following that occur after mRNA COVID-19 vaccination under Emergency Use Authorization:

- Vaccine administration errors
- Serious adverse events
- Cases of Multisystem Inflammatory Syndrome
- Cases of COVID-19 that result in hospitalization or death

Reporting is encouraged for any other clinically significant adverse event even if it is uncertain whether the vaccine caused the event. Information on how to submit a report to VAERS is available at https://vaers.hhs.gov or by calling 1-800-822-7967.

In addition, CDC has developed a new, voluntary smartphone-based tool, v-safe. This tool uses text messaging and web surveys to provide near real-time health check-ins after patients receive COVID-19 vaccination. Reports to v-safe indicating a medically significant health impact, including pregnancy, are followed up by the CDC/v-safe call center to collect additional information to complete a VAERS report, if appropriate.

Laboratory testing

Interpretation of SARS-CoV-2 test results in vaccinated persons

Prior receipt of an mRNA COVID-19 vaccine will not affect the results of SARS-CoV-2 viral tests (nucleic acid amplification or antigen tests). Currently available antibody tests for SARS-CoV-2 assess IgM and/or IgG to one of two viral proteins: spike or nucleocapsid. Because both the Pfizer-BioNTech and Moderna COVID-19 vaccines contain mRNA that encodes

the spike protein, a positive test for spike protein IgM/IgG could indicate either prior infection or vaccination. To evaluate for evidence of prior infection in an individual with a history of mRNA COVID-19 vaccination, a test specifically evaluating IgM/IgG to the nucleocapsid protein should be used. Antibody testing is not currently recommended to assess for immunity to COVID-19 following mRNA COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person.

Use of immune-based tests for tuberculosis infection, such as the tuberculin skin test and interferon-gamma release assay

The mRNA COVID-19 vaccine should not be delayed because of testing for TB infection. Testing for TB infection with one of the immune-based methods, either the tuberculin skin test (TST) or an interferon release assay (IGRA), can be done before or during the same encounter as the mRNA COVID-19 vaccination. When testing with TST or IGRA cannot be done at the same time as mRNA COVID-19 vaccination, these tests should be delayed ≥4 weeks after the completion of mRNA COVID-19 vaccination but generally should not be cancelled.

Patients who have active TB disease or an illness that is being evaluated as active TB disease can receive an mRNA COVID-19 vaccine (note: the presence of a moderate or severe acute illness is a precaution to administration of all vaccines). Whereas a TST or IGRA test is part of a comprehensive evaluation for TB disease, positive TST or IGRA results are not required to diagnose active TB disease .

When considering a tuberculin skin test or interferon-gamma release assay:

- The TST is not expected to have an effect on the safety or the effectiveness of the mRNA COVID-19 vaccine. IGRAs are blood tests and thus do not affect vaccine safety or effectiveness.
- The reliability of a positive TST or IGRA result after mRNA COVID-19 vaccination is expected to be the same as without the vaccination. mRNA COVID-19 vaccination is not expected to cause false positive results from a TB test that is done at the same encounter as or after mRNA COVID-19 vaccination.
- The reliability of a negative TST or IGRA result after mRNA COVID-19 vaccination has not been studied.
- The TST is not a vaccine. The guidance for separating other vaccines from mRNA COVID-19 vaccination by at least 2 weeks in time does not apply to the TST because the TST is not a vaccine.

When a tuberculin skin test or interferon gamma release assay is required by policy:

- A TST or IGRA to meet administrative requirements, (for example, for healthcare employment or for admission to long-term care), can be done prior to mRNA COVID-19 vaccination or at the same encounter. The mRNA COVID-19 vaccine should not be delayed because of testing for TB infection.
- A TST or IGRA should be deferred until ≥4 weeks after the completion of mRNA COVID-19 vaccination. If testing requirements or policies cannot be modified for the COVID-19 pandemic to accept this delay in TST or IGRA testing, it should be understood that a false negative TST or IGRA cannot be excluded, and consideration should be given to repeating negative TST or IGRA tests at least 4 weeks after the completion of COVID-19 mRNA vaccination. If TST was the initial test, boosting could be a factor if the result of the repeat test is positive.

When a tuberculin skin test or interferon gamma release assay is indicated for medical care:

- The decision as to whether a TST or IGRA that is being done for medical diagnosis of latent TB infection, (for example, during a contact investigation after exposure to contagious TB disease) should be delayed for 4 weeks after completion of COVID-19 mRNA vaccination is at the discretion of the responsible medical provider and local tuberculosis program overseeing the contact investigation. Medical providers and local tuberculosis programs may not wish to delay testing for persons at high risk for progression to TB disease. However, patients who have a negative result in this context should be considered for retesting ≥4 weeks after the completion of mRNA COVID-19 vaccination.
- Patients who have symptoms or diagnostic findings consistent with active TB disease should receive further medical evaluation, for example, with chest radiography and sputum bacteriology for *Mycobacterium tuberculosis*, regardless of TST or IGRA results.

Appendix A. Vaccine administration errors and deviations

A vaccine administration error is any preventable event that may cause or lead to inappropriate use of vaccine or patient harm. This appendix provides resources for preventing and reporting mRNA COVID-19 vaccine administration errors, as well as actions to take after an error has occurred. For completeness, this includes additional scenarios that deviate from CDC recommendations for vaccine intervals but are not considered administration errors. This document is intended to assist providers with handling exceptional situations in which a vaccination error or deviation has already occurred and may be updated when additional information becomes available.

The FDA-issued Emergency Use Authorization and Fact Sheet for Healthcare Providers Administering Vaccines should be referenced for detailed information on storage and handling, dosing and schedule, dose preparation, and administration of mRNA COVID-19 vaccines. The information provided below on managing vaccine administration errors should not be interpreted as a recommendation or promotion of unauthorized use of the vaccines.

For all vaccine administration errors:

- Inform the recipient of the vaccine administration error.
- Consult with the state immunization program and/or Immunization Information System (IIS) to determine how the dose should be entered into the IIS, both as an administered dose and to account for inventory.
- Report the error to the Vaccine Adverse Event Reporting System (VAERS), unless otherwise indicated in the table. Providers are required to report all COVID-19 vaccine administration errors—even those not associated with an adverse event — to the VAERS. To file an electronic report, please see the VAERS website .
- Determine how the error occurred and implement strategies to prevent it from happening again. A discussion on strategies to prevent errors can be found in the Vaccine Administration chapter of the *Epidemiology and Prevention of Vaccine-Preventable Diseases* (Pink Book). Additional resources can be found on CDC's vaccine administration web page, including a job aid for preventing errors.

Type	Administration error/deviation	Interim recommendation
Site/route	• Incorrect site (i.e., site other than the deltoid muscle [preferred site] or anterolateral thigh [alternate site])	• Do **not** repeat dose.*
	• Incorrect route (e.g., subcutaneous)	• Do **not** repeat dose.*
Age	• Unauthorized age group	• If received first dose at age less than 16 years, do not give second dose at this time∞. • If age 16 to 17 years and Moderna vaccine inadvertently administered instead of Pfizer-BioNTech as the first dose, may administer Moderna vaccine as the second dose (as off-label use, because Moderna vaccine is not authorized in this age group).
Intervals	• Second dose administered fewer than 17 days (Pfizer-BioNTech) or fewer than 24 days (Moderna) after the first dose (i.e., administered earlier than the 4-day grace period)	• Do **not** repeat dose.
	• Second dose administered more than 42 days after the first dose	• Do **not** repeat dose. This deviation from CDC guidance does **not** require VAERS reporting.

Type	Administration error/deviation	Interim recommendation
	• Dose administered within 14 days before or after another (i.e., non-COVID-19) vaccine	• Do **not** repeat COVID-19 vaccine* or other vaccine(s) doses. This deviation from CDC guidance does **not**require VAERS reporting.
Mixed series	• Incorrect mRNA COVID-19 vaccine product administered for second dose in 2-dose series	• Do **not** repeat dose. §
Dosage	• Higher-than-authorized dose volume administered	• Do **not** repeat dose. *† Inform the recipient of the potential for local and systemic adverse events.
	• Lower-than-authorized dose volume administered (e.g., leaked out, equipment failure, recipient pulled away)	• If more than half of the dose was administered, do **not**repeat dose.* • If less than half of the dose was administered or the proportion of the dose cannot be estimated, administer the authorized dose immediately (no minimum interval) in the opposite arm.#
Storage and handling	• Dose administered after improper storage and handling (e.g., temperature excursion, more than 6 hours after first vial puncture)	• Contact the manufacturer for guidance. If the manufacturer provides information supporting that the dose should be repeated, the repeated dose may be given immediately (no minimum interval) in the opposite arm.
	• Dose administered past the expiration/beyond use date	• Contact the manufacturer for guidance. If the manufacturer provides information supporting that the dose should be repeated, the repeated dose may be given immediately (no minimum interval) in the opposite arm.
Diluent (Pfizer-BioNTech only)	• ONLY diluent administered (i.e., sterile 0.9% sodium chloride)	• Inform the recipient that no vaccine was administered. Administer the authorized dose immediately (no minimum interval) in the opposite arm.#
	• No diluent, resulting in higher than authorized dose (i.e., 0.3 ml of undiluted vaccine administered)	• Do **not** repeat dose*† Inform the recipient of the potential for local and systemic adverse events.
	• Incorrect diluent type (e.g., sterile water, bacteriostatic 0.9% NS)	• Contact the manufacturer for guidance. If the manufacturer provides information supporting that the dose should be repeated, the repeated dose may be given immediately (no minimum interval) in the opposite arm.
	• Incorrect diluent volume (i.e., the vial contents were diluted with a diluent volume other than 1.8 ml, but a 0.3 ml dose was still administered)	• For doses administered with diluent volume less than 1.8 ml, Inform the recipient of the potential for local and systemic adverse events. * † • For doses administered with diluent volume greater than 1.8 ml, do **not** repeat dose. * (Note: dilution with a volume up to 4.0 ml [which exceeds vial capacity] results in more-than-half of the authorized dose administered).

[*] If the dose given in error is the first dose, a second dose should be administered at the recommended interval (21 days [Pfizer-BioNTech] or 28 days [Moderna]). If this dose is the second dose, the series is complete and no additional doses are needed.

[#] If the dose given in error is the first dose, the second dose should be administered at the recommended interval (21 days [Pfizer-BioNTech] or 28 days [Moderna]) from the date of receipt of the valid dose (not the date of receipt of the erroneous dose).

[∞] Do not administer the second dose until the person becomes eligible to receive vaccination (either by reaching the authorized age or if the authorization is extended to include additional age groups), even if this results in the second dose being administered after the recommended interval between doses.

[†] If the administration error resulted in a higher-than-authorized vaccine dose, in general the second dose may still be administered at the recommended interval. However, if local or systemic side effects following vaccination are clinically concerning (outside of the expected side effect profile), lead to serious adverse reactions, or are ongoing at the time of the second dose, the decision to administer the second dose may be assessed on a case-by-case basis.

[§] Although CDC provides considerations for a mixed series in exceptional circumstances, this is still considered an administration error that requires VAERS reporting (as a mixed series is not authorized under the vaccine Emergency Use Authorizations).

Appendix B: Triage of persons presenting for mRNA COVID-19 vaccination

	CONTRAINDICATION TO VACCINATION	PRECAUTION TO VACCINATION	MAY PROCEED WITH VACCINATION
ALLERGIES	History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines[*]: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components • Immediate allergic reaction[‡] of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components[^] (including polyethylene glycol)[#] • Immediate allergic reaction of any severity to polysorbate[^#]	Among persons without a contraindication, a history of: • Any immediate allergic reaction[‡] to other vaccines or injectable therapies[*]	Among persons without a contraindication or precaution, a history of: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies
ACTIONS	• Do not vaccinate[#] • Consider referral to allergist-immunologist	• Risk assessment • 30-minute observation period if vaccinated • Consider deferral of vaccination for further risk assessment and possible referral to allergist-immunologist	• 30-minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15-minute observation period: All other persons

[*] PEG and polysorbate are common excipients in many vaccines, injectable therapies, and other products. Persons with a known (diagnosed) allergy to PEG, another mRNA vaccine component, or polysorbate, have a contraindication to vaccination. Persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG, another mRNA vaccine component or polysorbate, but in whom it is unknown which component elicited the immediate allergic reaction have a precaution to vaccination.

[‡] Immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms consistent with urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.

[^] See Appendix B for a list of ingredients. Note: Polyethylene glycol (PEG), an ingredient in both mRNA COVID-19 vaccines, is structurally related to polysorbate and cross-reactive hypersensitivity between these compounds may occur. Information on ingredients of a vaccine or medication (including PEG, a PEG derivative, or polysorbates) can be found in the package insert.

[#] These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available)

Appendix C: Ingredients included in Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines

An immediate allergic reaction to any component or previous dose of an mRNA COVID-19 vaccine is a contraindication to vaccination with both the Pfizer-BioNTech and Moderna vaccines. The following is a list of ingredients for the Pfizer-BioNTech and Moderna COVID-19 vaccines reported in the prescribing information for each vaccine.

Description	Pfizer-BioNTech COVID-19 vaccine	Moderna COVID-19 vaccine
mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
Lipids	2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol
	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
	Cholesterol	Cholesterol
	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
Salts, sugars, buffers	Potassium chloride	Tromethamine
	Monobasic potassium phosphate	Tromethamine hydrochloride
	Sodium chloride	Acetic acid
	Dibasic sodium phosphate dihydrate	Sodium acetate
	Sucrose	Sucrose

* Neither vaccine contain eggs, gelatin, latex, or preservatives

Note: Both the Pfizer-BioNTech and Moderna COVID-19 vaccines contain polyethylene glycol (PEG). PEG is a primary ingredient in osmotic laxatives and oral bowel preparations for colonoscopy procedures, an inactive ingredient or excipient in many medications, and is used in a process called pegylation to improve the therapeutic activity of some medications (including certain chemotherapeutics). Additionally, cross-reactive hypersensitivity between PEG and polysorbates (included as an excipient in some vaccines and other therapeutic agents) can occur.

Information on whether a medication contains PEG, a PEG derivative, or polysorbates as either active or inactive ingredients can be found in the package insert. The National Institutes of Health DailyMed database can also be used as a resource. As of January 21, 2021, mRNA COVID-19 vaccines are the only currently available vaccines in the United States that contain PEG, though several vaccines contain polysorbate (more information can be found in CDC's vaccine excipient summary). Some medications that contain PEG and/or polysorbate are also described in the supplementary materials of Stone CA, et al. "Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized." *The Journal of Allergy and Clinical Immunology: In Practice* 7.5 (2019): 1533-1540. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6706272/pdf/nihms-1019221.pdf

Appendix D: Potential characteristics of allergic reactions, vasovagal reactions, and vaccine side effects following mRNA COVID-19 vaccination

In patients who experience post-vaccination symptoms, determining the etiology (including allergic reaction, vasovagal reaction, or vaccine side effects) is important to determine whether a person can receive additional doses of mRNA COVID-19 vaccines. The following table of signs and symptoms is meant to serve as a resource but might not be exhaustive, and patients might not have all signs or symptoms. Providers should use their clinical judgement when assessing patients to determine the diagnosis and management.

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reaction	Vaccine side effects (local and systemic)
Timing after vaccination	Most occur within 15-30 minutes of vaccination	Most occur within 15 minutes	Median of 1 to 3 days after vaccination (with most occurring the day after vaccination)
Signs and symptoms			
Constitutional	Feeling of impending doom	Feeling warm or cold	Fever, chills, fatigue
Cutaneous	Skin symptoms present in ~90% of people with anaphylaxis, including pruritus, urticaria, flushing, angioedema	Pallor, diaphoresis, clammy skin, sensation of facial warmth	Pain, erythema or swelling at injection site; lymphadenopathy in same arm as vaccination
Neurologic	Confusion, disorientation, dizziness, lightheadedness, weakness, loss of consciousness	Dizziness, lightheadedness, syncope (often after prodromal symptoms for a few seconds or minutes), weakness, changes in vision (such as spots of flickering lights, tunnel vision), changes in hearing	Headache
Respiratory	Shortness of breath, wheezing, bronchospasm, stridor, hypoxia	Variable; if accompanied by anxiety, might have an elevated respiratory rate	N/A
Cardiovascular	Hypotension, tachycardia	Variable; might have hypotension or bradycardia during syncopal event	N/A
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea might occur
Musculoskeletal	N/A	N/A	Myalgia, arthralgia
Vaccine recommendations			

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reaction	Vaccine side effects (local and systemic)
Recommended to receive 2nd dose of mRNA COVID-19 vaccine?	No	Yes	Yes