Allergic Reactions to mRNA COVID-19 Vaccines

Sean Brady, MD

Assistant Professor of Medicine

Allergy/Immunology Fellowship Associate Program Director

UBMD Internal Medicine & Subspecialties

Division Chief, Allergy/Immunology, Buffalo VAMC

Outline

- Vaccine allergy
  - Differential diagnosis
  - Treatment of anaphylaxis
  - Laboratory evaluation
- Rates of anaphylaxis to the mRNA vaccines
- Potential allergenic components of the mRNA vaccine
  - PEG and polysorbate allergy
- Treatment algorithm for patients with potential allergic reaction to the vaccine or one of its components


ALLERGY
CONCERNS
OVID-19
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Vaccine Reactions

Immediate Reactions

- Often IgE-mechanism
- Usually within 0-30 minutes
- Re-exposure could result in more severe reaction
- Subsequent doses should be held

Delayed Reactions

- Non-IgE mechanism
  - Immunologic and non-immunologic
- Hours to days after injection
- Often do NOT preclude future doses

Delayed Reactions

- Fever
- Local reactions
  - Swelling and redness
  - Axillary lymphadenopathy
  - Reported significantly later in mRNA vaccines
    - 1 weeks after vaccination
    - Robust local humoral and cellular immune response
    - Analgesic or antihistamine, avoid steroids
    - Opposite arm for next injection
- Serum sickness and serum sickness-like reactions
  - Rash
  - Fever
  - Malaise
  - Polyarthralgia and polyarthritis
- Rare reactions
  - Swelling at site of dermal fillers (Moderna)
  - Encephalopathy

Reactogenicity reported to v-safe

Local and systemic reactions, day 0-7*,†	All vaccines %	Pfizer- BioNTech dose 1 %	Pfizer-BioNtech dose 2 %	Moderna dose 1 %
Pain	70.7	67.7	74.8	70.1
Fatigue	33.4	28.6	50.0	29.7
Headache	29.4	25.6	41.9	26.0
Myalgia	22.8	17.2	41.6	19.6
Chills	11.5	7.0	26.7	9.3
Fever	11.4	7.4	25.2	9.1
Swelling	11.0	6.8	26.7	13.4
Joint pain	10.4	7.1	21.2	8.6
Nausea	8.9	7.0	13.9	7.7

* v-safe data lock point 1/14/2021, 5:00 AM ET

† Reported on at least one health check-in completed on days 0-7 after receipt of vaccine

Most commonly reported adverse events to VAERS after COVID-19 vaccines*

Pfizer-BioNTech COVID-19 vaccine (N = 7,307)

Adverse event†	N (%)
Headache	1,550 (21.2)
Fatigue	1,192 (16.3)
Dizziness	1,113 (15.2)
Nausea	1,014 (13.9)
Chills	983 (13.5)
Pyrexia	962 (13.2)
Pain	958 (13.1)
Injection Site Pain	716 (9.8)
Pain In Extremity	610 (8.4)
Dyspnoea	536 (7.3)

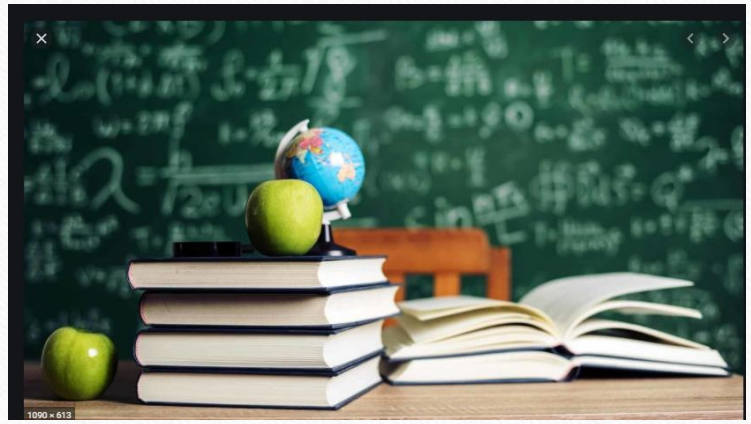
Moderna COVID-19 vaccine (N = 1,786)

Adverse event†	N (%)
Headache	430 (24.1)
Pyrexia	333 (18.6)
Chills	315 (17.6)
Pain	290 (16.2)
Dizziness	289 (16.2)
Fatigue	287 (16.1)
Nausea	281 (15.7)
Injection Site Pain	208 (11.6)
Pain In Extremity	189 (10.6)
Dyspnoea	172 (9.6)

* Reports received through January 18, 2021; †Adverse events are not mutually exclusive

Educate Patients

- Local (80-89% of patients)
  - Pain, swelling erythema at side of injection
  - Axillary lymphadenopathy
- Systemic (55-83% of patients)
  - Fever/chills
  - Fatigue
  - Headache
  - Myalgias/arthralgias



Immediate Reactions

- Usually within 0-30 minutes
- Skin (90%):
  - Flushing
  - Hives
  - Angioedema
- Respiratory:
  - Voice change (laryngeal edema)
  - Cough
  - Wheeze
- GI:
  - Nausea
  - Vomiting
  - Diarrhea
- Cardiovascular:
  - Hypotension
  - Syncope

Hypersensitivity Rates

- 0.63% in the Pfizer-BioNTech
- 1.5% in the Moderna
- Anaphylaxis
  - 0.00025%-0.0005% in post-licensure data

Mimics of Immediate (IgE-Mediated) Reactions

Vasovagal Reactions

- Pallor
- Bradycardia
- Hypotension
- Diaphoresis
- Nausea
- Vomiting

Anxiety-Related Symptoms

- Hypertension
- Tachycardia
- Vocal cord spasm
- Globus sensation
- Dyspnea
- Nausea

TABLE VI. Anaphylaxis compared with vasovagal reaction[43]

Signs and symptoms	Vasovagal reaction	Anaphylaxis
Interval (after injection)	Sometimes before, usually after a few seconds to a few minutes after the injection	Within 30 min after injection; the most severe reactions begin within the first 15 min
Consciousness	Fainting sensation, dizziness, loss of consciousness in some cases	Anxiety, which may progress into unconsciousness in severe cases
Breathing	Slow, with a few seconds of apnea in some cases	Respiratory difficulties; coughing, sneezing, wheezing, stridor
Pulse	Slow and weak, but regular	Rapid, weak and irregular
Skin	Diaphoresis, clammy skin, pallor	• Warm skin, progressing to clammy and pallor • Pruritis and urticaria (>90% of cases) • Swelling of face and tongue
Blood pressure	Transient hypotension	Hypotension (systolic pressure <90 mm Hg), which may progress to cardiovascular collapse
Gastrointestinal system	Nausea, vomiting	Nausea, vomiting, abdominal pains, diarrhea
Treatment	• Place client in a recumbent position and elevate legs above head (or have client sit with head between their knees) • Ventilate the room well • Place cold, damp cloth on face • Give reassurance	See Manitoba Health *Protocol for Management of Suspected Anaphylaxis*
Prevention	Do not vaccinate a standing person. Before vaccinating, ask if the person tends to faint; if so, ask patient to lie down	Before vaccinating, ask if the person has ever had an anaphylactic reaction to any product; if yes, ask for the name of the product and decide accordingly

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 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, may have an elevated respiratory rate	N/A
Cardiovascular	Hypotension, tachycardia	Variable; may have hypotension or bradycardia during syncopal event	N/A
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea may occur
Musculoskeletal	N/A	N/A	Myalgia, arthralgia

TABLE 1. Characteristics of reported cases of anaphylaxis (n = 21) after receipt of Pfizer-BioNTech COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 14–23, 2020

Return

Age (yrs)	Sex	Past history		Onset after receipt (mins)	Signs and symptoms	Treatment setting†	Epi received	Brighton level§	Outcome or disposition¶
		Allergies or allergic reactions*	Anaphylaxis						
27	F	Tropical fruit	No	2	Diffuse erythematous rash, sensation of throat closure	ED	Yes	2	Recovered at time of report
35	M	No	No	5	Diffuse erythematous rash, swollen tongue	ED	Yes	1	Discharged home
55	F	Rabies vaccine	Yes, rabies vaccine	5	Generalized urticaria, wheezing	Inpatient	Yes	1	Discharged home
52	F	Sulfa drugs	Yes, sulfa drugs	7	Wheezing, stridor, nausea	Inpatient	Yes	1	Discharged home
30	F	Bee sting	No	8	Generalized urticaria, wheezing	Inpatient	Yes	1	Recovered at time of report
32	F	No	No	10	Diffuse erythematous rash, difficulty breathing	Inpatient	Yes	2	Discharged home
60	F	Eggs, milk, sulfa drugs, jellyfish sting	Yes, jellyfish sting	10	Diffuse erythematous rash, hoarseness	ED	Yes	2	Recovered at time of report

29	F	Shellfish, eggs	No	10	Generalized urticaria, swollen lips and tongue	ED	Yes	1	Discharged home
52	F	Metoprolol, clarithromycin	No	10	Generalized urticaria, stridor, wheezing	ED	Yes	1	Recovered at time of report
49	F	Iodinated contrast media	No	13	Generalized urticaria, swollen throat	ED	Yes	1	Recovered at time of report
36	F	No	No	13	Generalized urticaria, nausea	ED	Yes	2	Not specified
40	F	Sulfa drugs, walnuts	Yes, walnuts	14	Generalized urticaria, nausea	ED	Yes	2	Discharged home
33	F	Wasp sting	No	15	Diffuse erythematous rash, swollen lip	ED	Yes	1	Recovered at time of report
41	F	Prochlorperazine	Yes, prochlorperazine	15	Diffuse erythematous rash, persistent dry cough	ED	No	2	Discharged home
57	F	Penicillin, azithromycin	Yes, unspecified	15	Diffuse pruritic rash, hoarseness	ED	Yes	2	Recovered at time of report
45	M	No	No	23	Generalized urticaria, swollen airway	ED	Yes	2	Discharged home
46	F	Hydrocodone, nuts	No	25	Diffuse erythematous rash, difficulty swallowing	ED	Yes	2	Discharged home
30	F	Cats, dogs	No	30	Generalized pruritis, wheezing	ED	No	2	Discharged home

30	F	Cats, dogs	No	30	Generalized pruritis, wheezing	ED	No	2	Discharged home
44	F	Influenza A(H1N1) vaccine	Yes, influenza A(H1N1) vaccine	34	Generalized urticaria, swollen lips	ED	Yes	1	Discharged home
29	F	Sulfa drugs	No	54	Generalized urticaria, persistent cough	ED	Yes	2	Recovered at time of report
29	F	Steroids	No	150	Diffuse pruritic rash, swollen lip	ED	Yes	1	Discharged home

Abbreviations: COVID-19 = coronavirus disease 2019; ED = emergency department; epi = epinephrine; F = female; M = male.

* As documented in the VAERS report or medical records, or through confirmation with the treating health care provider or the patients themselves.

† Inpatient = inpatient hospitalization.

§ 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 is indeed a case of 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. Level 5 is a case that was neither reported as anaphylaxis nor meets the case definition (https://doi.org/10.1016/j.vaccine.2007.02.064).

¶ As documented in the description of the adverse event in the VAERS report in Box 18 or as document in recovery status in Box 20.

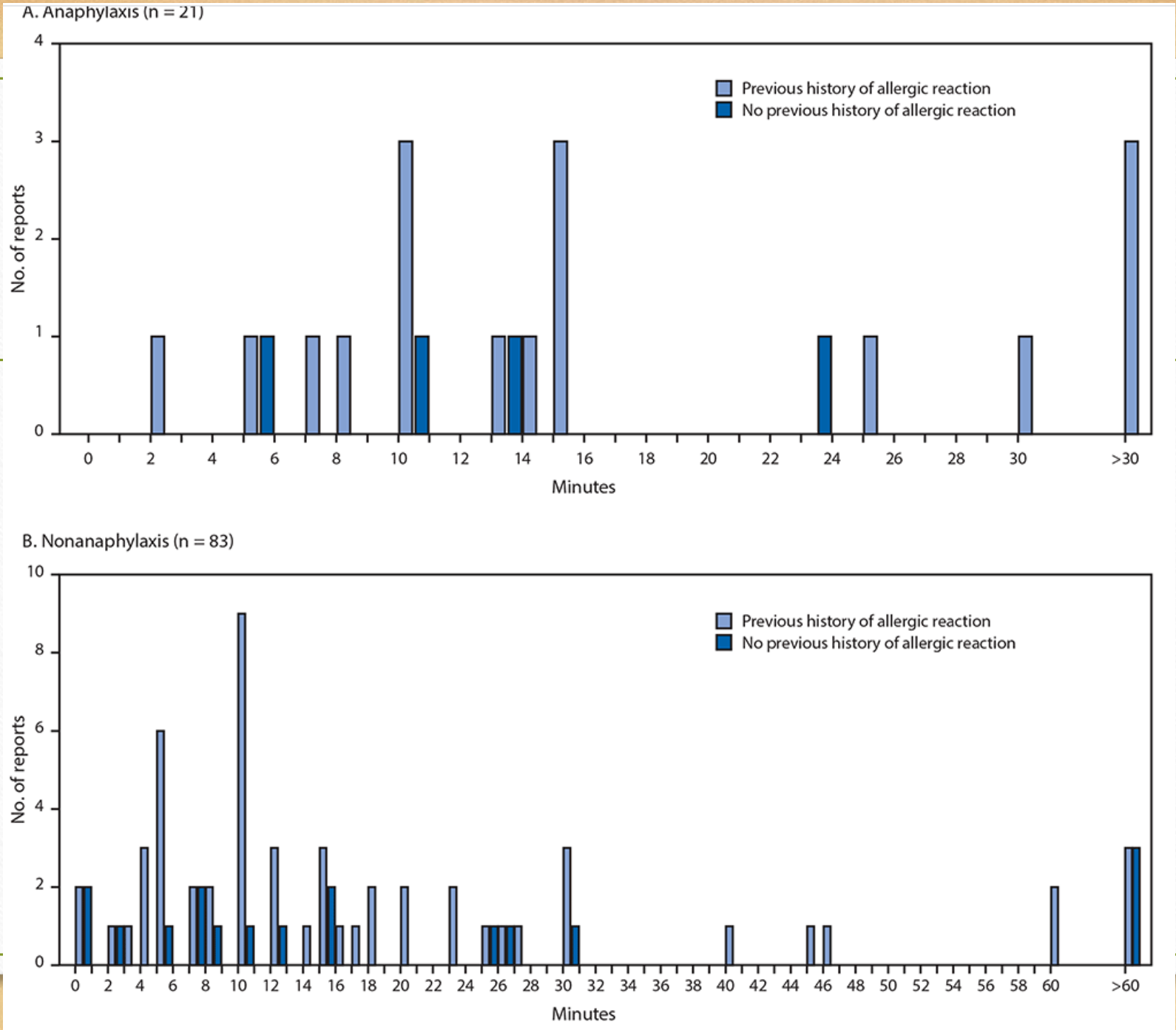

A. Anaphylaxis (n = 21)
No. of reports
Minutes
Previous history of allergic reaction
No previous history of allergic reaction
0
1
2
3
4
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
>30
B. Nonanaphylaxis (n = 83)
No. of reports
Minutes
Previous history of allergic reaction
No previous history of allergic reaction
0
2
4
6
8
10
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48
50
52
54
56
58
60
>60

TABLE 2. Characteristics of patients with report of anaphylaxis and nonanaphylaxis allergic reactions after receipt of Pfizer-BioNTech COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 14–23, 2020

Return

Characteristic	Type of reported reaction, no. (%)	
	Anaphylaxis (n = 21)	Nonanaphylaxis allergic reactions (n = 83)*
Median age, yrs (range)	40 (27–60)	43 (18–65)
Female	19 (90)	75 (90)
Mins to symptom onset, median (range)	13 (2–150)	12 (<1–1,200 [20 hrs])
Symptom onset ≤15 mins	15 (71)	44 (61)†
Symptom onset ≤30 mins	18 (86)	61 (85)†
Documented history of allergies or allergic reactions	17 (81)§	56 (67)

Abbreviation: COVID-19 = coronavirus disease 2019.

* Three of the initial 86 nonanaphylaxis allergic reaction reports were excluded from the final analysis because symptom onset occurred later than the day after vaccination (i.e., outside of the 0–1-day risk window).

† Eleven reports were missing information on time of symptom onset; percentage calculated among 72 patients.

§ Seven anaphylaxis patients reported a history of a previous anaphylaxis episode, including one after receipt of rabies vaccine and one after receipt of influenza A(H1N1) vaccine.

Takeaways from Pfizer-BioNTech

- 11.1 cases of anaphylaxis per million vaccinations
  - Updated number closer to 5 per million
- 86% happened within 30 minutes
- 81% had history of allergies or allergic reactions
  - 30% of general population has this….
- 90% of the cases happened in women
  - 64% of the vaccine doses given to women

TABLE 1. Characteristics of reported cases of anaphylaxis (n = 10) after receipt of the first dose of Moderna COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 21, 2020–January 10, 2021

Return

Age, yrs	Sex	Past history		Onset after receipt (mins)	Signs and symptoms	Treatment setting†	Epi received	Brighton level§	Outcome or disposition¶
		Allergies or allergic reactions*	Previous anaphylaxis episode						
37	F	Penicillin, phenytoin, ibuprofen	No	1	Respiratory failure, vomiting	Inpatient	Yes	2	Discharged home
39	F	Penicillin, aloe	Yes, penicillin	2	Decreased peripheral perfusion, persistent dry cough, nausea	Inpatient	Yes	3	Discharged home
63	F	Acetaminophen, azithromycin	No	4	Periorbital edema, nausea	ED	Yes	2	Not specified
55	F	Multiple unspecified environmental and food allergies	Yes, unspecified	5	Hypotension, wheezing	Inpatient	Yes	2	Not specified
31	F	No	No	5	Diffuse erythematous rash, throat swelling	ED	Yes	1	Discharged home
49	F	Gadolinium, iodine	Yes, gadolinium, iodine	10	Diffuse erythematous rash, tongue swelling, wheezing	ED	Yes	1	Recovered at time of report
37	F	Unspecified intravenous contrast dye, penicillin	Yes, intravenous contrast dye	11	Generalized urticarial rash, tongue swelling	Inpatient	Yes	1	Discharged home

37	F	Unspecified intravenous contrast dye, penicillin	Yes, intravenous contrast dye	11	Generalized urticarial rash, tongue swelling	Inpatient	Yes	1	Discharged home
50	F	Unspecified allergies or allergic reactions	Yes, unspecified	12	Diffuse erythematous rash, wheezing	Inpatient	Yes	1	Discharged home
57	F	Multiple drugs including penicillin and sulfa	No	13	Periorbital edema, tongue swelling	ED	Yes	1	Recovered at time of report
44	F	Morphine, codeine	No	45	Diffuse erythematous rash, marked tongue swelling	Inpatient	Yes	1	Discharged home

FIGURE. Minutes from vaccine receipt to onset of anaphylaxis (A)* and nonanaphylaxis allergic reactions (B)† after receipt of the first dose of Moderna COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 21, 2020–January 10, 2021

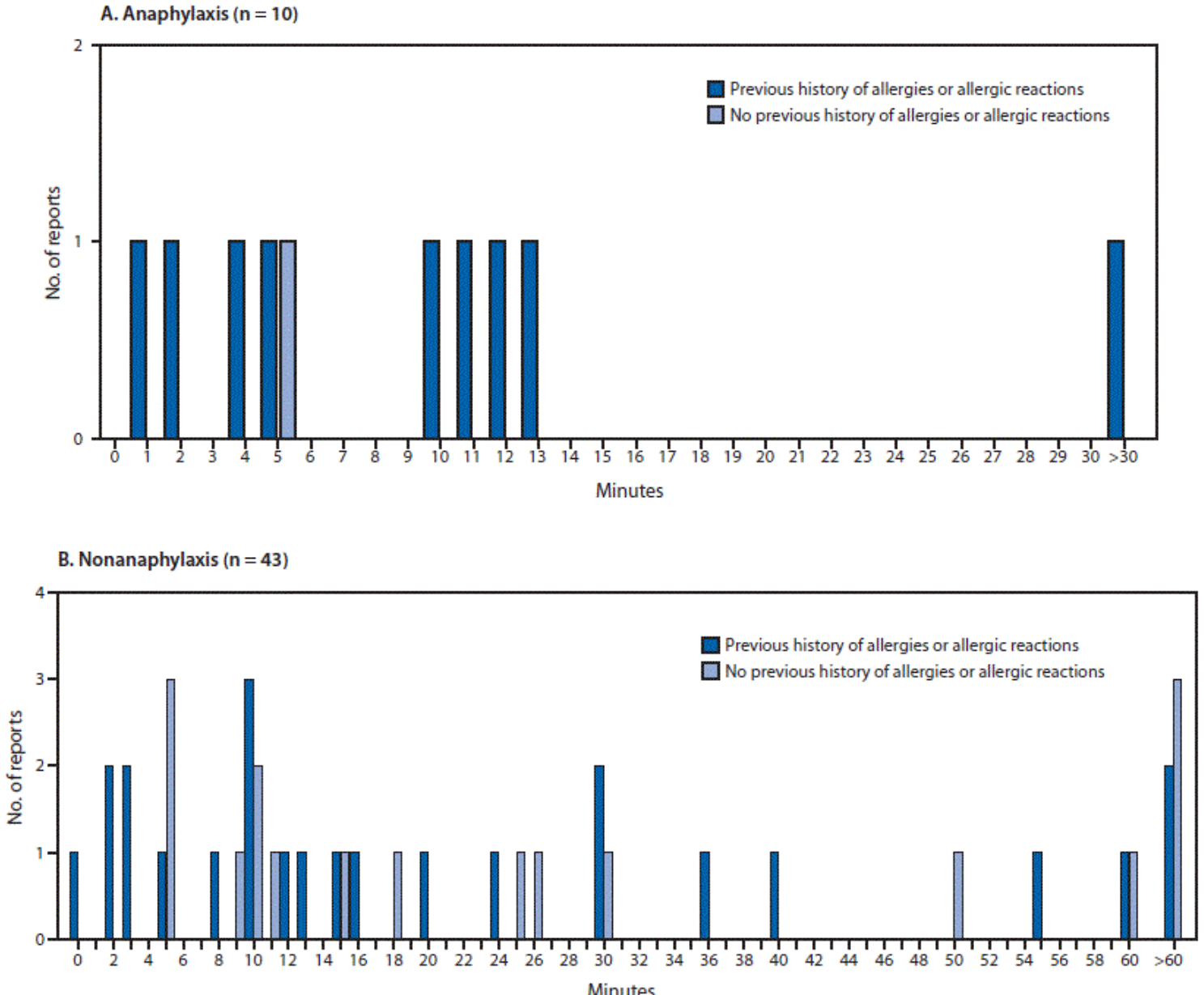


TABLE 2. Characteristics of patients with reported anaphylaxis and nonanaphylaxis allergic reactions after receipt of the first dose of Moderna COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 21, 2020–January 10, 2021

Return

Characteristic	Type of reported reaction, no. (%)	
	Anaphylaxis (n = 10)	Nonanaphylaxis allergic reactions (n = 43)*
Median age, yrs (range)	47 (31–63)	43 (22–96)
Female	10 (100)	39 (91)
Minutes to symptom onset, median (range)	7.5 (1–45)	15 (<1–1,440 [24 hrs])
Symptom onset ≤15 mins	9 (90)	21 (51)†
Symptom onset ≤30 mins	9 (90)	30 (73)†
Documented history of allergies or allergic reactions	9 (90)§	26 (60)

Abbreviation: COVID-19 = coronavirus disease 2019.

* Four of the initial 47 nonanaphylaxis allergic reaction reports were excluded from the final analysis because symptom onset occurred later than the day after vaccination (i.e., outside the 0–1-day risk window).

† Two nonanaphylaxis allergic reaction reports were missing information on time of symptom onset; percentage calculated among 41 case reports with onset documented.

§ Five anaphylaxis reports included a patient history of a previous anaphylaxis episode.

Takeaways from Moderna

- 2.5 cases of anaphylaxis per million vaccinations
- 9 of 10 cases happened within 30 minutes
- 9 of 10 cases had history of allergies/allergic reactions
  - 30% of the general population has allergies though…
- 10 of 10 cases happened in woman
  - 61% of doses given to women

Anaphylaxis reports to VAERS following COVID-19 vaccines*

Characteristics	Pfizer-BioNTech (N = 50)	Moderna (N = 21)
Median age, years (range)	38.5 (26–63)	39 (24–63)
Female (%)	47 (94)	21 (100)
Minutes to symptom onset, median (range)	10 (<1–1200 [20 hr])†	10 (<1-45)
Symptom onset ≤15 minutes (%)	37 (74)	18 (86)
Symptom onset ≤30 minutes (%)	45 (90)	19 (90)
Documented h/o of allergies or allergic rxns (%)	40 (80)	18 (86)
Documented h/o of prior anaphylaxis (%)	12 (24)	5 (24)
Dose number (1st, 2nd, unknown)	42, 3, 5	19, 1, 1

- Common allergies and allergic reactions included to drugs and foods
- Anaphylaxis cases occurred following drugs, foods, contrast media, vaccines, insect stings, unspecified

* Reports received through January 18, 2021; Includes case reports that met Brighton Collaboration case definition criteria for anaphylaxis at Levels 1, 2, or 3

†20 hour onset was an outlier, the remaining onset for cases with onset >30 minutes were 34, 54, 90, and 150 minutes

Estimated anaphylaxis reporting rates following COVID-19 vaccines based on VAERS reports and reported doses administered*

Reported vaccine doses administered	Anaphylaxis cases	Reporting rate (analytic period Dec 14-Jan 18)
Pfizer-BioNTech: **9,943,247**	50	5.0 per million doses admin.
Moderna: **7,581,429**	21	2.8 per million doses admin.

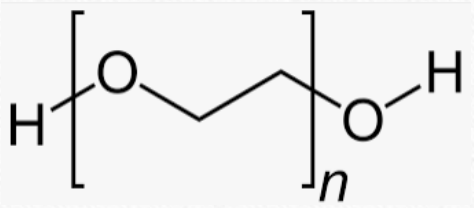
- Total COVID-19 vaccine doses administered thru Jan 18 by sex: Female 61%, Male 36%, Unk 3%
- Previously reported rate for Pfizer-BioNTech vaccine: 11.1 per million doses admin (Dec 14-Dec 23)
  https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm
- Previously reported rate for Moderna vaccine: 2.5 per million doses admin (Dec 21-Jan 10)
  https://www.cdc.gov/mmwr/volumes/70/wr/mm7004e1.htm

Potential culprits

- Vaccine allergies are often due to excipients
  - Latex
  - Egg
  - Gelatin
  - Casein
  - Yeast
  - ……Polyethylene glycol (PEG)???
  - ……Complement activation???

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



Polyethylene Glycol (PEG)

- Lipids provide a nanoparticle carrier
  - protective shield for the mRNA after injection
  - Facilitate cellular uptake
- Lipid nanoparticle (LNP) carrier
  - Cationic lipids coating the polyanionic mRNA
  - Zwitterionic lipids that mimic phospholipids of the cell membrane
  - Cholesterol stabilizes the lipid bilayer of the LPN
- Polyethylene glycol (PEG)
  - Polyether compound that improved the aqueous solubility of LNP

PEG and Polysorbate Allergy

- PEG molecular weights (200 to 35,000 g/mol)
- PEG MW 3350-6000 frequently used as excipients in medications
- PEG allergy
  - Extremely rare
  - May explain previously unexplained reactions to multiple unrelated medications
  - PEG reactions appear to be molecular weight specific
- PEG and Polysorbate are present in thousands of medications
  - Present in both mRNA vaccines
  - May explain why patient are reacting to the first dose of the COVID-19 vaccines

Original Article

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

Cosby A. Stone, Jr., MD, MPH[a], Yiwei Liu, PhD[b], Mary V. Relling, PharmD[b], Matthew S. Krantz, MD[c], Amanda L. Pratt, MD[a], Andrew Abreo, MD[a], Jonathan A. Hemler, MD[d], and Elizabeth J. Phillips, MD[e] *Nashville and Memphis, Tenn*

What is already known about this topic? The most common immediate hypersensitivity to macrogols is associated with polyethylene glycol (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 2 cases suggest an IgE-mediated type I hypersensitivity mechanism to PEG 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 underrecognized in clinical practice and can be evaluated with clinical skin testing.

J Allergy Clin Immunol Pract 2019;7:1533-40

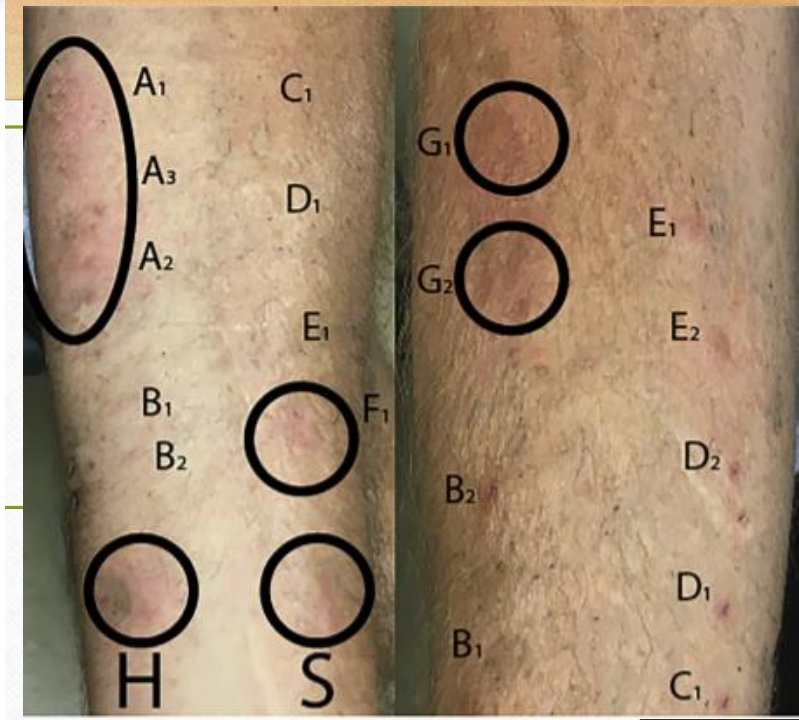
Case Report 1

- 57 yo male mechanic
  - Colyte (PEG 3350) – severe itching throat, palate
  - Meythlprednisolone acetate (PEG 3350) – hives, throat tightness, wheezing hypotension
  - Moviprep (PEG 3350) – itching of palate, throat, hives
  - Gavilyte-G (PEG 3350) – itching, hives, syncope, hypotension
- Positive skin testing to PEG 3350
- Positive skin testing to Polysorbate 80
- Negative skin testing to PEG 300
- Tolerated oral challenge to PEG 300

Case Report 2

- 51 yo mechanic (exposed to glycol-containing hydraulic fluids)
  - PEG 3350 for colonoscopy – hypotension, flushed skin
  - Epidural steroids injection, omnipaque and methylprednisolone acetate (PEG 3350) – itchy, red, hypotensive, hoarseness
- Negative Skin test to PEG 3350
- Positive skin test to Polysorbate 80
- Failed oral challenge to PEG 3350 (spectacularly)

Agent (concentration)	Patient 1 Wheal (mm)	Patient 1 Flare (mm)	Patient 1 Interpretation	Patient 2 Wheal (mm)	Patient 2 Flare (mm)	Patient 2 Interpretation
Skin Prick Test Results						
Histamine control (0.1 mg/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						
Betamethasone (6 mg/mL)	6	6	Negative	0	0	Negative
Betamethasone (0.6 mg/mL)	5	5	Negative	0	0	Negative
Dexamethasone (0.4 mg/mL)	5	0	Negative	0	0	Negative
Dexamethasone (0.04 mg/mL)	7	0	Negative	0	0	Negative
Methylprednisolone sodium succinate (5 mg/mL)	5	6	Negative	0	0	Negative
Methylprednisolone sodium succinate (0.5 mg/mL)	0	0	Negative	0	0	Negative
Methylprednisolone acetate (4 mg/mL)				0	0	Subacute response developed at 20 h, with 14 mm raised wheal
Methylprednisolone acetate (0.4 mg/mL)				0	0	Negative
Triamcinolone acetonide (1 mg/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			



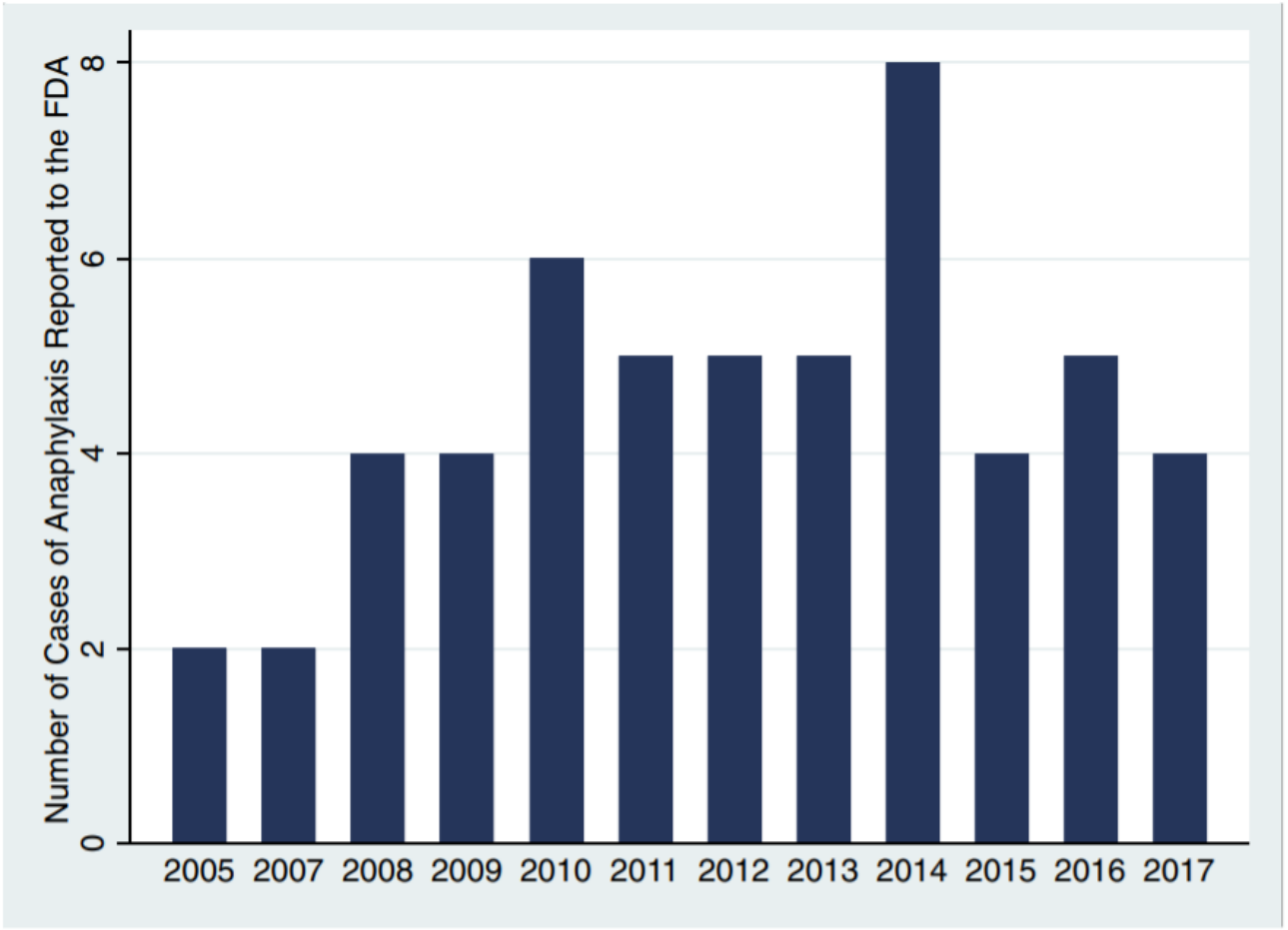


FIGURE 4. Cases of anaphylaxis reported to the FDA (FAERS) implicating PEG containing bowel preparations or laxatives, by year. *FAERS*, FDA Adverse Event Reporting System; *FDA*, US Food and Drug Administration; *PEG*, polyethylene glycol.

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

Clinical Communications

Anti-PEG IgE in anaphylaxis associated with polyethylene glycol

Zhao-Hua Zhou PhD [a], Cosby A. Stone Jr. MD, MPH [b], Baruch Jakubovic MD [c], Elizabeth J. Phillips MD [b], Gordon Sussman MD [d], JuMe Park MS [a], Uyen Hoang MS [a], Susan L. Kirshner PhD [a], Robert Levin MD [e], Steven Kozlowski MD [a]

- General population
  - 5% to 9% anti-PEG IgG
  - 3% to 6% anti-PEG IgM
  - 0.1% anti-PEG IgE

Zhou Z.H., Stone Jr., C.A., Jakubovic B., Phillips E.J., Sussman G., Park J. et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. ([published online ahead of print November 17, 2020]. J Allergy Clin Immunol Pract)https://doi.org/10.1016/j.jaip.2020.11.011

Common Medications that Contain PEG

- Polyethylene glycol 3350 (Miralax)
- Cetirizine Methylprednisolone acetate (Depo-Medrol)
- Sumatriptan
- Aleve
- Fluoxetine
- Nifedipine
- Xarelto
- Metoprolol
- Valsartan
- Amoxicillin
- Famotidine
- Omeprazole
- Mupirocin
- Topical lidocaine

Polysorbate

- Found in both medications and vaccines
- Has also been associated with allergic reactions
- Given structure, potential for cross-reactivity with PEG

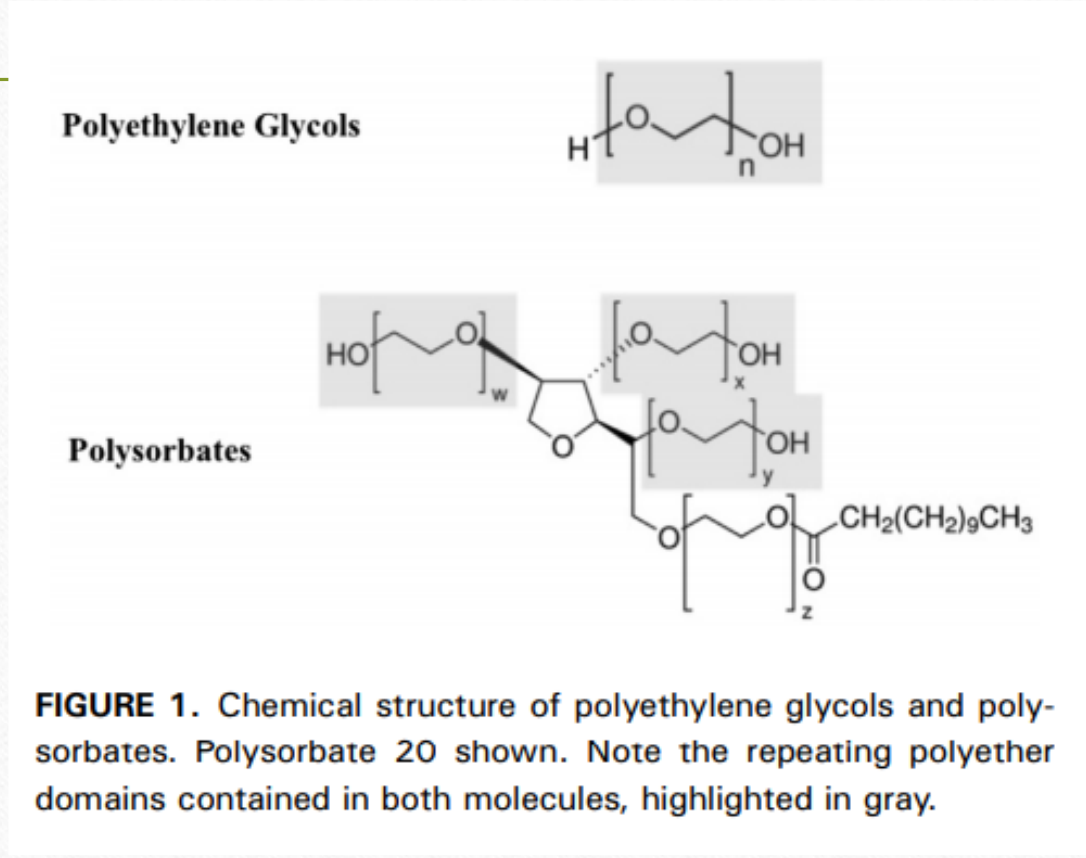


FIGURE 1. Chemical structure of polyethylene glycols and polysorbates. Polysorbate 20 shown. Note the repeating polyether domains contained in both molecules, highlighted in gray.

Common Medications Containing Polysorbate

- Amitriptyline
- Citalopram
- Kenalog-10,40
- Carvedilol
- Artificial tears
- Aspirin
- Valacyclovir
- Pantoprazole
- Diltiazem ER
- Triamterene-HCTZ
- Amoxicillin-clavulanate
- Sulfamethoxazole-trimethoprim

Vaccines with polysorbate

- Influenza
  - Flublok and Flubok quad
  - Fluad
  - Fluarix Quad
  - Flucelvax Quad
- Hepatitis A, B or A+B
  - Havrix
  - Twinrix
  - Heplisav-B
- HPV
  - Gardasil and Gardasil 9
- Meningococcal Group B
  - Trumenba
- Pneumococcal 13-valent
  - Prevnar 13
- Rotavirus
  - RotaTeq

Vaccines with Polysorbate

- DTaP
  - Infanrix
- DtaP +IPV
  - Kinrix
  - Quadracel
- DTaP+HepB+IPV
  - Pediarix
- DTaP+IPV+Hib
  - Pentacel
- Tdap
  - Boostrix
- Japanse Encephalitis
  - JE-Vax
- Zoster
  - Shingrix

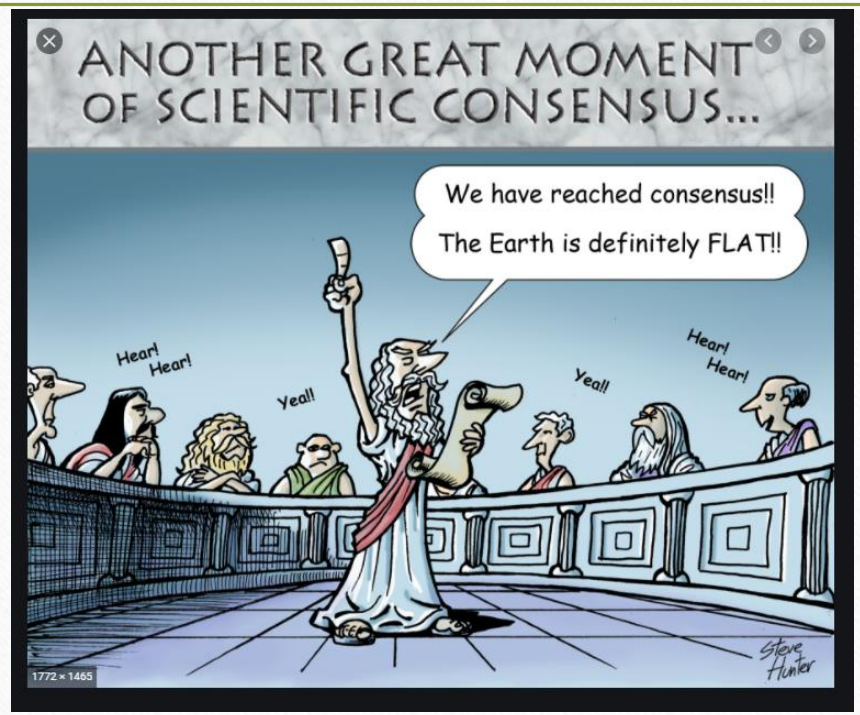
Vaccine Excipient Tables

- https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf

- https://www.vaccinesafety.edu/components-Excipients.htm

Different approaches

- There is no "consensus" on how to proceed for all patients



Neither Contraindications nor Precautions

- Non-anaphylactic allergic reactions to:
  - Food
  - Pets
  - Venom
  - Environmental
  - Oral medications
  - Latex

Precautions (not contraindications)

- Immediate allergic reaction to any other vaccine or injectable therapy
- History of anaphylaxis
- Can consider deferral of vaccination and/or consultation with an allergist-immunologist
- Considerations
  - Risk of exposure
  - Risk of severe disease
  - Recent infection with SARS-CoV-2
  - Risk of anaphylaxis
  - Ability to be vaccinated in a setting where appropriate medical care is immediately available

Contraindications

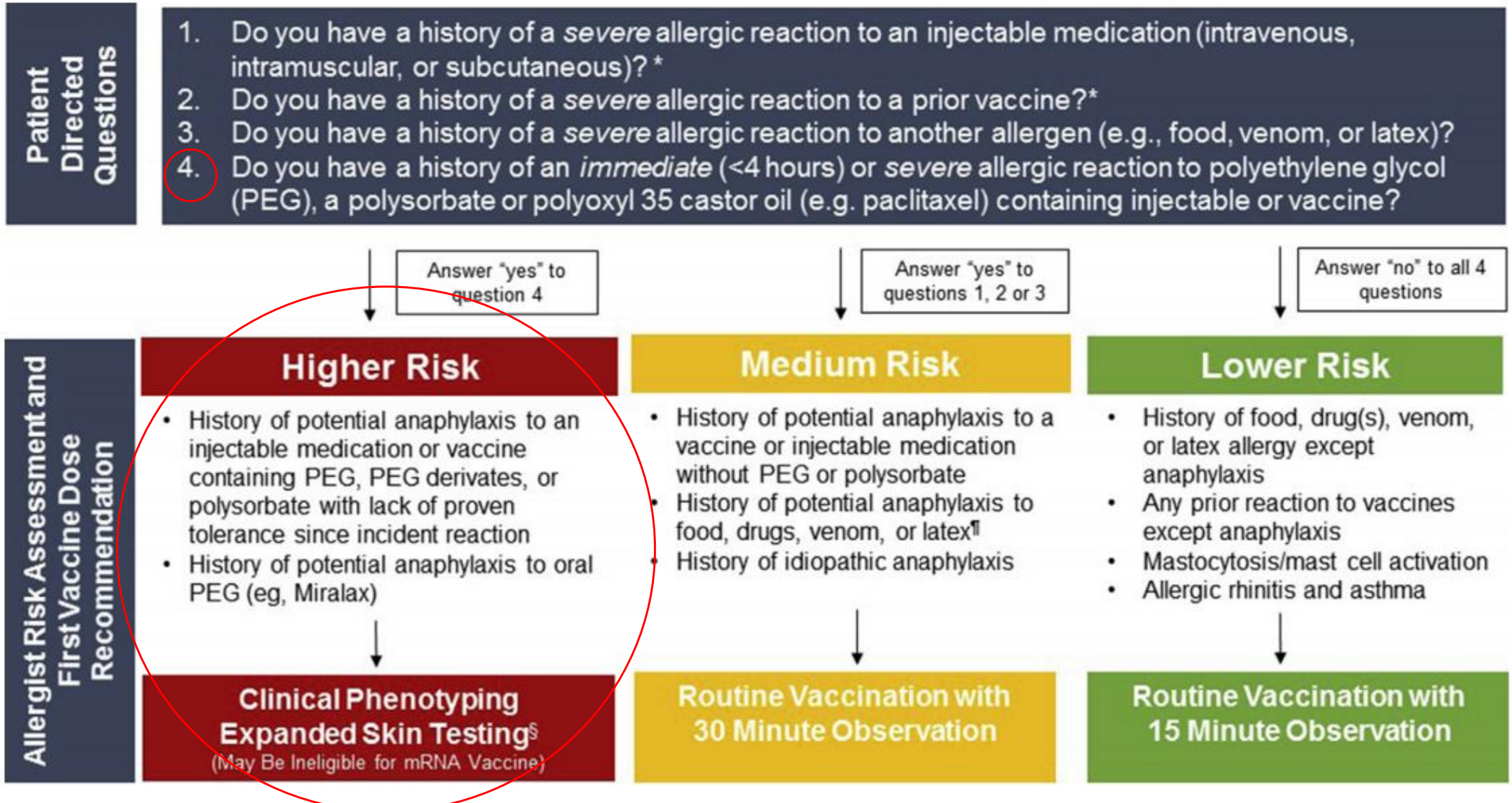
- Severe allergic reaction after previous dose of mRNA COVID-19 vaccine or any of its components (including PEG)
- Immediate allergic reaction of any severity to a previous dose of mRNA COVID-19 vaccine or any of its components (including PEG)
- Immediate allergic reaction to polysorbate

CDC Guidance

- Known (diagnosed) allergy to PEG or polysorbate have a ***contraindication*** to vaccination.
- 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*** (counseling, 30-minute observation).
- Deferral of vaccination and/or **consultation with an allergist** may be considered.

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

	MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
CONDITIONS	**CONDITIONS** • Immunocompromising conditions • Pregnancy • Lactation **ACTIONS** • Additional information provided* • 15 minute observation period	**CONDITIONS** • Moderate/severe acute illness **ACTIONS** • Risk assessment • Potential deferral of vaccination • 15-minute observation period if vaccinated	**CONDITIONS** • None **ACTIONS** • N/A
ALLERGIES	**ALLERGIES** History of allergies that are unrelated to components of an mRNA COVID-19 vaccine[†], other vaccines, injectable therapies, or polysorbate, such as: • 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** • 30-minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15-minute observation period: All other persons	**ALLERGIES** • History of any immediate allergic reaction[‡] to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines[†] or polysorbate, as these are contraindicated) **ACTIONS:** • Risk assessment • Consider deferral of vaccination and/or referral to allergist-immunologist • 30-minute observation period if vaccinated	**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[^#] **ACTIONS** • Do not vaccinate[#] • Consider referral to allergist-immunologist


Patient Directed Questions
1. Do you have a history of a severe allergic reaction to an injectable medication (intravenous, intramuscular, or subcutaneous)? *
2. Do you have a history of a severe allergic reaction to a prior vaccine?*
3. Do you have a history of a severe allergic reaction to another allergen (e.g., food, venom, or latex)?
4. Do you have a history of an immediate (<4 hours) or severe allergic reaction to polyethylene glycol (PEG), a polysorbate or polyoxyl 35 castor oil (e.g. paclitaxel) containing injectable or vaccine?
Answer "yes" to question 4
Answer "yes" to questions 1, 2 or 3
Answer "no" to all 4 questions
Allergist Risk Assessment and First Vaccine Dose Recommendation
Higher Risk
History of potential anaphylaxis to an injectable medication or vaccine containing PEG, PEG derivates, or polysorbate with lack of proven tolerance since incident reaction
History of potential anaphylaxis to oral PEG (eg, Miralax)
Clinical Phenotyping Expanded Skin Testing§
(May Be Ineligible for mRNA Vaccine)
Medium Risk
History of potential anaphylaxis to a vaccine or injectable medication without PEG or polysorbate
History of potential anaphylaxis to food, drugs, venom, or latex¶
History of idiopathic anaphylaxis
Routine Vaccination with 30 Minute Observation
Lower Risk
History of food, drug(s), venom, or latex allergy except anaphylaxis
Any prior reaction to vaccines except anaphylaxis
Mastocytosis/mast cell activation
Allergic rhinitis and asthma
Routine Vaccination with 15 Minute Observation

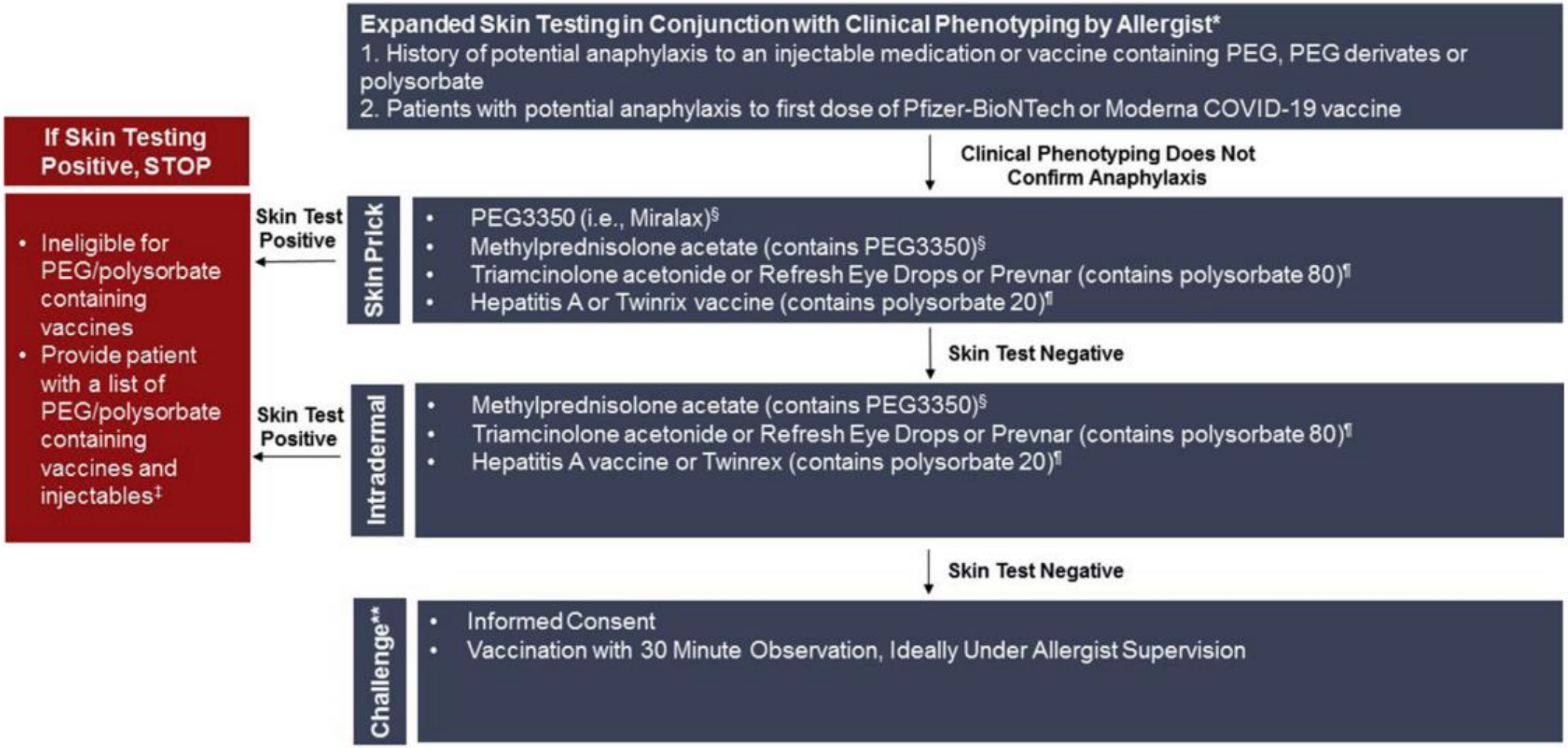


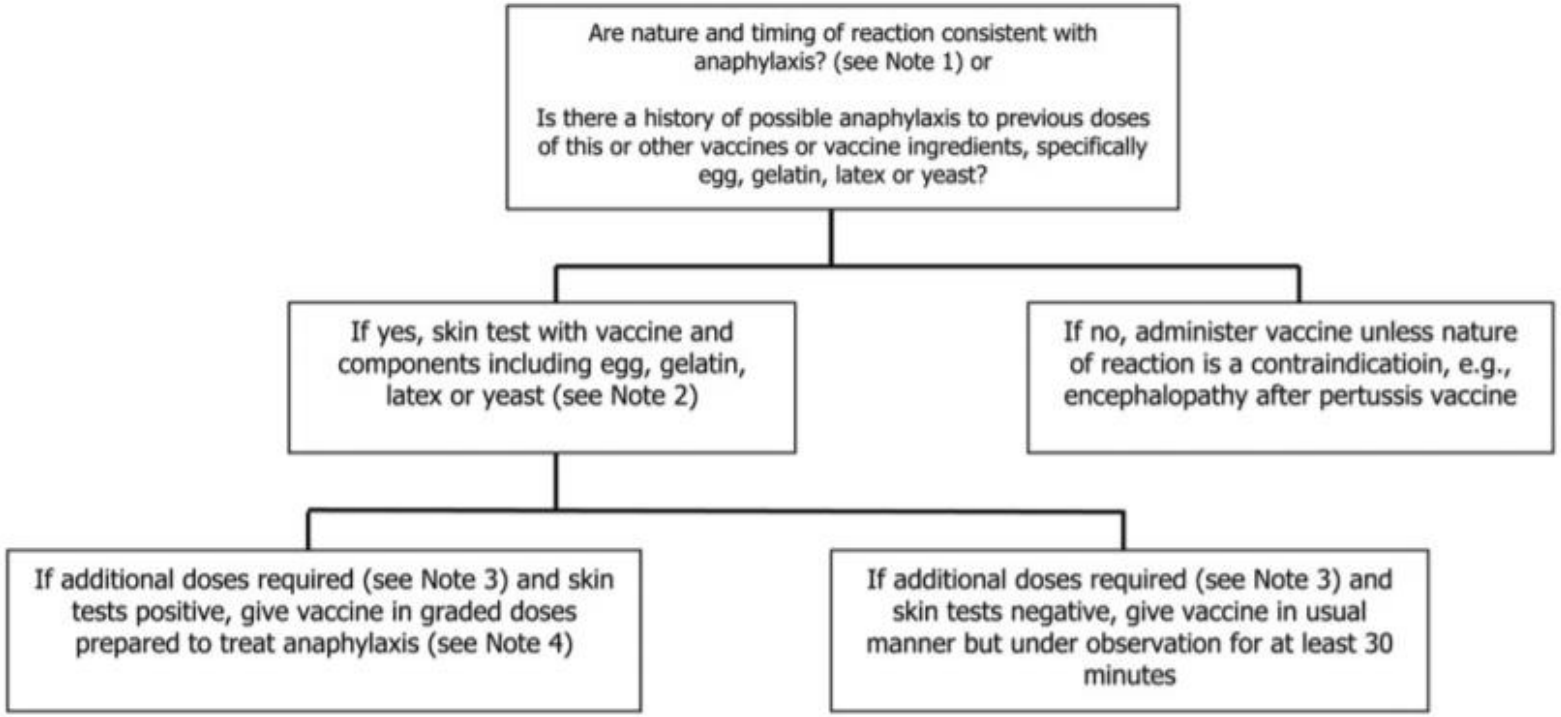
FIGURE 3. Expanded skin testing procedure. *Recommended skin testing to evaluate only known potential IgE mechanism (PEG allergy). ¶Skin testing for consideration to evaluate PEG and polysorbate allergy. In patients with positive PEG skin testing, the result of polysorbate 20 and 80 skin testing becomes important with regards to the safety of future SARS-CoV-2 vaccines in development. Therefore, based on clinical history, skin testing to both PEG and polysorbate during 1 clinic visit may be appropriate. §Anaphylaxis with intradermal skin testing in PEG allergic patients has been described. We recommend staff have anaphylaxis training and anaphylaxis kit available in close proximity. ‡Tables II, III, and IV contain a list of PEG/polysorbate containing vaccines and injectables that can be shared with patients. **Recommended only after shared decision making between allergist and patient.

	PEG3350		Control*	Polysorbate 20	Polysorbate 80¶		
	Miralax	Methyl-prednisolone Acetate (Depo-Medrol) §	Methyl-prednisolone Sodium Succinate (Solu-medrol)‡	Hepatitis A vaccine or Twinrix	Triamcinolone Acetonide (also contains carboxymethyl-cellulose)	Refresh - sterile eye drops	Prevnar 13
Step 1 Epicutaneous	1:100 (1.7mg/mL)	40 mg/ml	40 mg/ml	1:1	40 mg/ml	1:1	1:10
Step 2 Epicutaneous	1:10 (17 mg/mL)						
Step 3 Epicutaneous	1:1** (170 mg/mL)						
Step 4 Intradermal		0.4 mg/ml	0.4 mg/ml	1:100	0.4 mg/ml	1:10	1:100
Step 5 Intradermal		4 mg/ml	4 mg/ml	1:10	4 mg/ml		
Step 5 Intradermal					40 mg/ml		

FIGURE 4. Nonirritating skin testing concentrations for PEG3350 and polysorbate. *Methyl-prednisolone sodium succinate does not contain PEG or polysorbate 80 and can be used as an additional control. ¶Refresh Optive Advanced Lubricant eye drops and Prevnar are an alternate source for polysorbate 80 skin testing. §Some brands of methylprednisolone acetate contain polysorbate and PEG3350 while others only have PEG3350; use methylprednisolone acetate containing PEG3350 only. ‡Nonirritating skin testing concentrations for methyl-prednisolone sodium succinate and triamcinolone acetonide include a range of 10 to 40 mg/mL for initial skin prick testing with subsequent 10× dilutions.[37] One author (E.P.) has extensive experience using 50 mg/mL as a non-irritating skin testing concentration for methyl-prednisolone sodium succinate skin prick testing with subsequent 10× dilutions. **Dissolve 17 gram miralax packet in 100mL of sterile water for 1:1 solution (170 mg/mL).

Skin testing to the vaccine itself

- Currently not practical with current limitation in vaccine supply
- If it was possible:
  - Skin prick with full strength vaccine
  - Intradermal testing with 1:100 dilution
  - Consideration of intradermal testing with 1:10 dilution


Are nature and timing of reaction consistent with anaphylaxis? (see Note 1) or
Is there a history of possible anaphylaxis to previous doses of this or other vaccines or vaccine ingredients, specifically egg, gelatin, latex or yeast?
If yes, skin test with vaccine and components including egg, gelatin, latex or yeast (see Note 2)
If no, administer vaccine unless nature of reaction is a contraindicatioin, e.g., encephalopathy after pertussis vaccine
If additional doses required (see Note 3) and skin tests positive, give vaccine in graded doses prepared to treat anaphylaxis (see Note 4)
If additional doses required (see Note 3) and skin tests negative, give vaccine in usual manner but under observation for at least 30 minutes

EAACI

- "Even when severe, anaphylaxis can resolve with little or no sequelae with immediate and proper management."

- Whatever risk this may pose needs to be balanced against the risk of leaving persons susceptible to vaccine-preventable diseases is they do not receive subsequent doses

EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy. 2021 Jan 16. doi: 10.1111/all.14739. Epub ahead of print. PMID: 33452689.

Fillers

- Facial swelling reported in 3 patients with soft tissue fillers after receiving the Moderna vaccine
- All episodes of swelling started with in days of the vaccination and were transient
- A local, inflammatory reaction is proposed mechanism
- American Society for Dermatologic Surgery advised not discouraging or precluding vaccination for patients previously treated with soft tissue fillers

https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-vaccines-to-prevent-sars-cov-2-infection?search=covid-19%20fillers&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Risk of Anaphylaxis

- Allergy shots – 1 per 1000
- Oral food challenge- 3 per 100 challenges
- Omalizumab (Xolair)- 1 per 1000
- Beta-Lactam antibiotics – 1 per 200,000
- COVID-19 vaccine 2.5-5 per 1,000,000

Summary

- Severe allergic reactions to the COVID-19 vaccines are ***extremely rare***
  - 2.5-4.7 per million doses and dropping
- The cause of these apparent allergic reactions is unclear
  - PEG?
  - Complement activation?
  - Other?
- Delayed reactions to the first vaccine for the most part are not contraindications to the second dose of the vaccine
- The vast majority of patients should be able to get the vaccine without additional precautions
- When in doubt consider allergy/immunology referral

Questions?