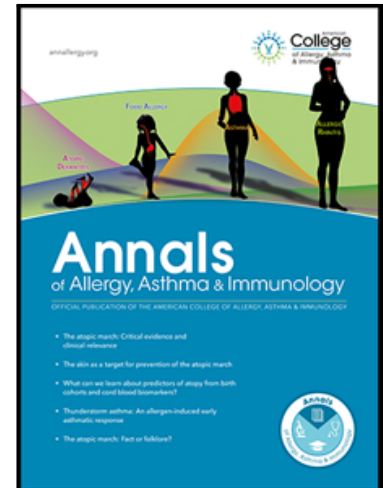


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Iris M. Otani MD , Lulu R. Tsao MD , Monica Tang MD

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COVID-19 Vaccine Administration in Patients with Reported Reactions to Polyethylene Glycol- and Polysorbate-Containing Therapeutics

Iris M. Otani, MD¹, Lulu R. Tsao, MD¹, Monica Tang, MD¹

¹Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine, UCSF Medical Center, San Francisco, CA

Corresponding Author:

Iris M. Otani, MD (iris.otani@ucsf.edu)

400 Parnassus Ave, Box 0336

San Francisco, CA 94143

Phone: 415-353-2725

Fax: 415-353-3529

E-mail: iris.otani@ucsf.edu

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COVID-19 vaccine, COVID-19 vaccine allergy, COVID-19 vaccine reaction, Polyethylene Glycol allergy, Polyethylene Glycol reaction, Polysorbate allergy, Polysorbate reaction, Vaccine Hesitancy, Vaccine Safety

Abbreviations

Coronavirus disease 2019 (COVID-19), electronic medical record (EMR), Johnson&Johnson (J&J), polyethylene glycol (PEG)

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Abstract

Background: Polyethylene glycol (PEG) and polysorbate reactions were initially implicated as a likely risk factor for reacting to COVID-19 vaccines and remain a source of vaccine hesitancy despite increasing evidence that they do not pose an increased risk for COVID-19 vaccine reactions.

Objective: To investigate COVID-19 vaccine safety outcomes in patients with reported reactions to PEG and polysorbate containing medications/vaccines.

Methods: COVID-19 vaccine safety was reviewed in patients identified with PEG/polysorbate reactions documented in their electronic medical records at a tertiary academic medical center (cohort 1) and patients referred to allergy/immunology with reported PEG/polysorbate reactions (cohort 2). COVID-19 vaccine safety was also reviewed following reported symptoms (onset ≤ 12 hours) to 1st dose PEG-containing mRNA COVID-19 vaccine (cohort 3).

Results: Of 252 patients in cohort 1 (n=202) and cohort 2 (n=50), 236 (94%) received mRNA COVID-19 vaccines (106 Pfizer, 130 Moderna); 235 received both doses and only 3 developed mild rash following vaccination. None of the 44 patients in cohort 3 with acute symptoms following 1st dose mRNA COVID-19 vaccine (27 Pfizer, 17 Moderna) had previously reported PEG/polysorbate reactions. Of these 44, 43 received 2nd dose and all 3 who developed symptoms following 2nd dose (one required epinephrine) had negative PEG skin testing.

Conclusion: Patients with reported reactions to PEG/polysorbate safely received COVID-19 vaccines. PEG/polysorbate skin testing did not identify patients at risk for 1st dose or recurrent reactions to COVID-19 vaccines. Screening for PEG/polysorbate allergy may only increase vaccine hesitancy without identifying patients at risk for COVID-19 vaccine reactions.

Introduction

Anaphylaxis to the mRNA COVID-19 vaccine has been reported to both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines, primarily after receipt of the 1st dose.¹⁻⁴ Allergic reactions to PEG and polysorbate were implicated as a risk factor for an allergic reaction to COVID-19 vaccines as PEG is the only known potentially allergenic component in the COVID-19 mRNA vaccines and polysorbate is the only known potentially allergenic component in the COVID-19 Johnson & Johnson (J&J) vaccine.⁵⁻⁸

Current CDC guidance highlights allergic reactions to PEG as a contraindication to receiving mRNA COVID-19 vaccine and allergic reactions to polysorbate as a contraindication to receiving J&J COVID-19 vaccine.⁹ Published guidance following CDC recommendations for 1st dose risk stratification has suggested that (1) patients with a possible PEG and polysorbate allergy be referred to an allergist for possible PEG/polysorbate skin testing, (2) patients with a possible PEG allergy receive the J&J COVID-19 vaccine or be referred to an allergist for possible PEG/polysorbate skin testing, and (3) patients with a possible polysorbate allergy

receive any COVID-19 vaccine if they have subsequently tolerated a polysorbate-containing vaccine or receive mRNA COVID-19 vaccine if they have not.⁴

While this strategy provides a vaccine option for most patients, vaccination sites are still left with the important but arduous task of screening for PEG and polysorbate allergy, as PEG and polysorbate can be found in numerous medications and vaccines.¹⁰ Differentiating between allergic and non-allergic reactions can also pose challenges. Furthermore, a national survey found that vaccine efficacy has the largest influence on people's reported likelihood of receiving a vaccine, and patients cleared to receive J&J COVID-19 vaccine may still prefer allergy evaluation for clearance to receive mRNA COVID-19 vaccines due to reports of higher efficacy with these vaccines.¹¹⁻¹⁴

As such, assessing COVID-19 vaccination safety in patients with history of PEG/polysorbate reactions has become a question that allergists face often. A recently published International Consensus document on the risk of allergic reactions to COVID-19 vaccines recommends that patients with past medical history of reaction to a COVID-19 vaccine excipient are referred to allergy for assessment of vaccination safety.¹⁵ A COVID-19 Vaccination Approach Survey found that 82% of allergists reported evaluating patients to clear them for their first dose of Pfizer or Moderna vaccine, with many performing PEG and polysorbate skin testing.¹⁶ Studies investigating the safety of COVID-19 vaccination in patients with a history of PEG/polysorbate reactions are needed.

To investigate COVID-19 vaccine safety outcomes in patients with reported reactions to PEG and polysorbate containing medications/vaccines, we reviewed vaccine safety outcomes in patients with reported reactions to PEG and polysorbate containing medications and vaccines.

Methods

We reviewed demographics, documented allergies, PEG/polysorbate reaction histories, allergy evaluations, and vaccine safety outcomes in 3 patient cohorts with possible PEG/polysorbate reactions. This study was approved by our institution's institutional review board (IRB #21-33623).

Cohort 1:

We queried the electronic health system database at a tertiary academic medical center for patients with PEG/polysorbate reaction(s) documented in their electronic medical record (EMR) between 5/4/11 to 8/23/21 who subsequently received COVID-19 vaccine. We excluded patients with documented reactions to mRNA COVID-19 vaccine and patients referred to allergy/immunology. Documented reaction symptoms obtained from the EMR were categorized as follows:

- Anaphylaxis: anaphylaxis
- Cutaneous: hives, itching, rash, swelling
- Respiratory: shortness of breath
- Neurological: lightheadedness
- Gastrointestinal: abdominal pain, diarrhea, nausea only, nausea and vomiting
- Other: other, unknown

Cohort 2:

Patients with a history of PEG, polysorbate, vaccine, or paclitaxel reactions already established in the allergy/immunology clinic or referred for COVID-19 vaccine clearance between 12/1/2020-8/31/2021 were included in this cohort. Patients with a history of reactions to any vaccine were included as it was not always clear which vaccine patients had reacted to. Patients with a history of paclitaxel reactions were included as paclitaxel contains a PEG derivative that is structurally similar to the excipient mRNA COVID-19 vaccines.¹⁷

Available reaction comments/descriptions of anaphylaxis, allergic reaction, erythema/redness, flushing, rash, urticaria/hives, angioedema/swelling, wheezing, shortness of breath, coughing, throat tightness, and difficulty swallowing were categorized as a history possibly consistent with allergy. Reaction comments/descriptions of body/muscle aches, chills, fever, Guillain-Barre Syndrome, hand-foot syndrome, injection site reactions, mania, migraine, nausea, neuropathy, and vasculitis were categorized as a history not consistent with allergy.

Cohort 3:

Patients referred between 12/1/2020-8/31/2021 to allergy/immunology for PEG/polysorbate testing after experiencing symptoms following 1st dose COVID-19 vaccine were included in this cohort. Patients with symptom onset <20 hours after vaccine receipt were included as a prior report of anaphylaxis cases from Vaccine Safety Datalink found that symptom onset when documented occurred within 20 hours.¹⁸ Patients referred for symptoms following 2nd dose COVID-19 vaccine were excluded from this review. Reported symptoms were categorized as follows:

- Cutaneous: diaphoresis, erythema, flushing, hives, itching, rash, swelling, warm sensation
- Lower respiratory: chest tightness, shortness of breath, wheezing
- Cardiovascular: chest pain, hypertension, palpitations, tachycardia
- Neurological: dizziness, headache, lightheadedness, numbness, tingling
- Gastrointestinal: dry heaving, nausea, vomiting
- Upper airway: difficulty swallowing, voice change
- Tongue/Throat Sensation: throat closing, throat sensation not otherwise specified, throat swelling, throat tightness, tongue pain, tongue swelling, tongue tingling

Medication/Vaccine Classification

Medications and vaccines were classified into those that contained PEG or polysorbate based on published FDA package inserts. Influenza, tetanus, pneumococcal, and meningococcal vaccines were considered to potentially contain polysorbate unless it was clearly documented that the patient had received a vaccine type that did not contain polysorbate.

Testing

PEG 3350 and polysorbate testing were performed closely following guidance outlined in Banerji et al.⁹ Triamcinolone IDT 40 mg/ml was not performed due to our prior clinical experience with false positives at that dilution. Testing with Refresh eyedrops was not performed. The highest dilutions used for testing are shown in **eTable 1**.

Results

Cohort 1:

There were 202 patients with PEG/polysorbate reactions documented in the EMR prior to receiving COVID-19 vaccines, and all (100%) did not have documented reactions to the COVID-19 vaccine received: 120 (59%) received Moderna, 82 (41%) received Pfizer, 188 (93%) received two doses. No patients were documented as having received J&J. No patients were documented as having received an allergy evaluation prior to receiving the COVID-19 vaccine. Characteristics are shown in **Table 1**.

The PEG/polysorbate reactions documented in the EMR prior to patients receiving COVID-19 vaccines were documented to PEG in 19% and to polysorbate in 85%. The specific PEG- and polysorbate-containing medications/vaccines documented as allergies are shown in **Table 1**. Reactions were documented a median of 1010 days (interquartile range 458-2059) prior to receipt of the 1st COVID-19 vaccine dose. A polysorbate-containing vaccine had been administered in 72% of patients after their PEG/polysorbate reaction was first documented and prior to receipt of the 1st COVID-19 vaccine dose. Although details regarding reaction history was not available for over half of the documented reactions, cutaneous symptoms were the most common documented symptom (**Table 1**).

Taken together, these findings suggest that patients with documented reactions PEG/polysorbate-containing medications/vaccines can receive mRNA COVID-19 vaccines safely.

Cohort 2

There were 50 patients referred to allergy/immunology with a history of PEG, polysorbate, vaccine, or paclitaxel reaction. There were 44 patients referred without any prior

PEG/polysorbate testing, 3 patients referred for repeat evaluation after positive PEG/polysorbate testing, and 3 patients who had a history of positive in-clinic testing/challenge to polysorbate-containing vaccines. All were cleared to receive COVID-19 vaccines. Of these patients, 37 received COVID-19 vaccines (24 Pfizer, 10 Moderna, 3 J&J). The only side effects reported were mild delayed rash (n=2; Pfizer 1, Moderna 1), mild immediate rash around the injection site (n=1; Pfizer), and hypertension (n=2; Pfizer 2) as described further below.

Of 44 patients referred without any prior PEG/polysorbate testing, 33 received COVID-19 vaccines. Demographics and vaccines received are shown in **Table 2**. There were 26 patients whose PEG/polysorbate reaction history was consistent with allergy and 18 patients whose PEG/polysorbate reaction was clearly inconsistent with allergy. Of 26 patients whose PEG/polysorbate reaction history was consistent with allergy, 20 patients received COVID-19 vaccines and none of them developed symptoms following vaccination (12 Pfizer, 5 Moderna, 3 J&J). Five patients with reaction history consistent with allergy to PEG-containing medications underwent Miralax (n=5), methylprednisolone acetate (n=5), methylprednisolone succinate (n=4), triamcinolone (n=1), and Prevnar-13 (n=1) skin testing; all negative. Among 18 patients with a history inconsistent with allergy, 13 subsequently received COVID-19 vaccines, of whom four reported symptoms. Two patients reported mild delayed rash: one after 1st dose only of Moderna and one after 2nd dose only of Pfizer. Two patients who reported experiencing hypertension, chest tightness, lightheadedness, dizziness, and tachycardia after receiving flu vaccines also reported hypertension after receiving COVID-19 vaccines (both Pfizer; one after 1st dose only, one after both doses).

Three patients were referred for repeat evaluation after positive PEG/polysorbate testing, as shown in **Table 3**. Two had negative testing at our clinic and one declined repeat PEG/polysorbate testing. Only one of these patients subsequently received COVID-19 vaccine.

Three patients who had positive in-clinic testing/challenge to polysorbate-containing vaccines (one had positive challenge to Tdap vaccine, one had positive challenge to influenza vaccine, and one had positive testing and history of urticaria following influenza vaccine) were able to receive both doses of mRNA COVID-19 vaccine (Pfizer). One patient developed an acute localized rash around the injection site after both doses of Pfizer vaccine.

Taken together, these findings suggest that patients with reported reactions to medication/vaccine containing PEG/polysorbate, even those with a history strongly suggestive of allergy to polysorbate-containing vaccines, can receive COVID-19 vaccines safely.

Cohort 3

There were 44 patients referred for evaluation of symptoms that occurred within the first 20 hours following 1st dose of Pfizer (n=27) or Moderna (n=17) COVID-19 vaccination.

Demographics, reaction history, and testing results are shown in **Table 4**. All 44 patients reported symptom onset within 12 hours. Although patients with symptom onset <20 hours after vaccine receipt were included per a prior report of anaphylaxis cases from Vaccine Safety Datalink, it is important to note that symptom onset <4 hours is considered immediate per CDC guidance and the 2 cases with symptom onset 5-12 hours after vaccination would be considered delayed.^{9,18} The 2 delayed cases occurred after Moderna (n=1) and Pfizer (n=1) vaccination. Of

note, although 57% reported at least one drug allergy at time of evaluation, none had a pre-existing documented PEG/polysorbate reaction. All received the 2nd dose.

Fourteen patients underwent testing for Miralax (n=14), methylprednisolone acetate (n=14), methylprednisolone succinate (n=9), triamcinolone (n=13), and Prevnar-13 (n=12). All testing was negative except for one questionable positive to methylprednisolone succinate (IDT 1:10 dilution) and two questionable positives to Prevnar-13 (IDT 1:100 dilution). One patient had a questionable irritant reaction to Miralax (SPT 17 mg/ml) but repeat negative testing to Miralax at a higher dilution (SPT 170 mg/ml) and negative methylprednisolone acetate testing, highlighting the fallibility of PEG 3350 testing.

Following the 2nd dose, 4 (9%, 4/44) patients reported symptoms that were visible or required treatment (Pfizer 3, Moderna 1). All occurred after negative PEG/polysorbate skin testing. All 4 patients had reported cutaneous symptoms with first dose and had received treatment with H1 antihistamines (**Table 4**). Additionally, 2 patients had reported lower respiratory and 3 tongue/throat sensation symptoms after 1st dose, and 2 had received epinephrine (**Table 4**). Reported symptoms following 2nd dose were (1) coughing and rashes treated with 2 doses of IM epinephrine, (2) acute throat tickling and difficulty swallowing treated with H1 antihistamines, (3) facial erythema and shaking for 10 minutes resolving without treatment, and (4) eyelid/facial angioedema, throat sensation, and difficulty swallowing for which 5 doses of intramuscular epinephrine was administered (2 initially and then 3 for ongoing throat tightness) and was admitted to the hospital for observation from the emergency department.

Taken together, these findings demonstrate that none of the patients who experienced symptoms following 1st dose COVID-19 vaccine had pre-existing PEG/polysorbate reactions and that PEG/polysorbate testing did not predict those who were able to safely receive a 2nd dose.

Discussion

Our study found that patients with documented reactions to PEG/polysorbate-containing medications/vaccines can indeed receive COVID-19 vaccines safely. This study adds to the growing body of evidence that screening for PEG/polysorbate allergy prior to administering COVID-19 vaccines only serves to increase vaccine hesitancy without identifying patients at risk for COVID-19 vaccine reactions.

A recently published study found that 8 patients with PEG/polysorbate-containing injectable medications or vaccines safely tolerated vaccine at a large academic hospital employee vaccination program. Seven of these patients were cleared by an allergist for vaccination based on their history of subsequently tolerating PEG/polysorbate.¹⁹ We add to this with our Cohort 1 data by specifically investigating 1st dose COVID-19 vaccine safety without any allergy evaluation in patients with reactions to multiple different PEG/polysorbate-containing medications/vaccines, 57 of whom had no documentation of tolerating polysorbate-containing vaccines prior to receiving a COVID-19 vaccine.

We found that both patients with PEG/polysorbate reactions documented in the EMR (cohort 1) and reported to patients' providers (cohort 2) received COVID-19 vaccines safely. No specific pattern of atopy was observed in cohort 2. Although EMR documentation and patient reports of

PEG/polysorbate reactions are not reliable indicators of a true allergy, they are the initial reference point for patients, providers, and vaccine administrators determining COVID-19 vaccine safety. Additionally, the finding that COVID-19 vaccines were safe remained true in the subset of patients with reaction histories consistent with potentially IgE-mediated allergic reactions, and even among patients who had positive challenges to polysorbate-containing vaccines. This finding is in line with prior reports of patients with PEG-asparaginase reactions who tolerated mRNA COVID-19 vaccines and PEG-allergic patients who tolerated both polysorbate-containing vaccines and PEG-containing COVID-19 vaccines.²⁰⁻²⁴ This suggests that patients do not need to be screened for PEG/polysorbate allergy prior to receiving COVID-19 vaccines.

PEG/polysorbate IgE-mediated allergy did not appear to be the cause of reactions to mRNA COVID-19 vaccines in our cohort. Patients with reactions to mRNA COVID-19 vaccines (cohort 3) did not have a pre-existing history of PEG or polysorbate allergy or any specific pattern of atopy. This finding is in line with the CDC reports of anaphylaxis to the mRNA COVID-19 vaccine occurring in patients without a history of PEG or polysorbate allergy.^{2,3} Additionally, as observed in prior reports, the results of PEG/polysorbate testing did not correspond with whether patients experienced symptoms with COVID-19 vaccines.^{25,26} Indeed, all of the patients who had a recurrent reaction to the 2nd dose, including those requiring epinephrine, had negative PEG testing.

A non-IgE-mediated mechanism may explain why most patients with symptoms following 1st dose COVID-19 vaccine are able to tolerate the 2nd dose, as observed in our patient cohort 3 as

well as in prior reports.²⁷⁻²⁹ There is evidence that PEGylated nanoparticles can activate the complement system depending on the form and structure of PEGylation.³⁰ Further investigation into the mechanism by which reactions occur to mRNA COVID-19 vaccines is needed.

Non-IgE-mediated anxiety-related adverse events have been reported to COVID-19 vaccines.³¹ In cohort 2, an anxiety diagnosis was the 2nd most commonly observed comorbidity following drug allergy, and in cohort 3, it was the 3rd most commonly observed after drug allergy and environmental allergy. This highlights the need for avenues to provide adequate patient reassurance prior to COVID-19 vaccine administration. These avenues would ideally extend beyond the allergy/immunology clinic, as general practitioners and vaccine administration sites are often first-line in discussing vaccine safety concerns with patients.

While negative PEG/polysorbate excipient allergy testing could provide reassurance for patients with histories of PEG/polysorbate reactions, it is not routinely recommended.¹⁵ Not only is IgE-mediated hypersensitivity to PEG/polysorbate likely not responsible for most mRNA COVID-19 vaccine reactions, but PEG/polysorbate testing is fraught with false positives. A prior report found that Refresh eyedrops are irritating.²⁵ Skin testing with COVID-19 vaccines has been studied but may carry similar risk for false positives.^{32,33} We additionally found that Prevnar-13 intradermal testing and possibly methylprednisolone succinate testing at 4mg/ml is likely irritating. Positive testing, even if followed by repeat negative testing, understandably increases vaccine hesitancy and we observed this in patients referred to our clinic. Taken together, our findings support the recommendation that PEG/polysorbate skin testing is not routinely performed to evaluate COVID-19 vaccine safety, even in patients with histories of

PEG/polysorbate reactions. Larger studies are needed to identify whether there are clinical factors that would more accurately identify patients at risk for developing symptoms COVID-19 vaccines.

There are limitations to our study. Chart review and data extracted from the EMR do not always accurately reflect true reaction history as documentation in the allergy section of the electronic medical record can be incomplete and inaccurate.³⁴ However, documented reactions to PEG/polysorbate are often the initial reference point for providers determining COVID-19 vaccine safety and we believe the information provided in this study will still be of use to vaccine administration sites. Additionally, in the cohort of patients with documented PEG/polysorbate reactions in the EMR, we were only able to capture COVID-19 vaccines administrations recorded at our institution. However, this would, if anything, underestimate the number of patients with documented PEG/polysorbate reactions who have received COVID-19 vaccines safely.

In summary, most patients with documented or reported reactions to PEG/polysorbate can safely receive COVID-19 vaccines. These findings do not negate the possibility that there are patients with PEG allergy who would react to PEG contained in COVID-19 vaccines. However, screening for PEG/polysorbate reactions may not be the optimal method for identifying those patients who experience reactions to COVID-19 vaccines and may only serve to increase vaccine hesitancy. To improve vaccine protocols, further investigation into what clinical factors identify patients at risk for COVID-19 vaccine symptoms is needed.

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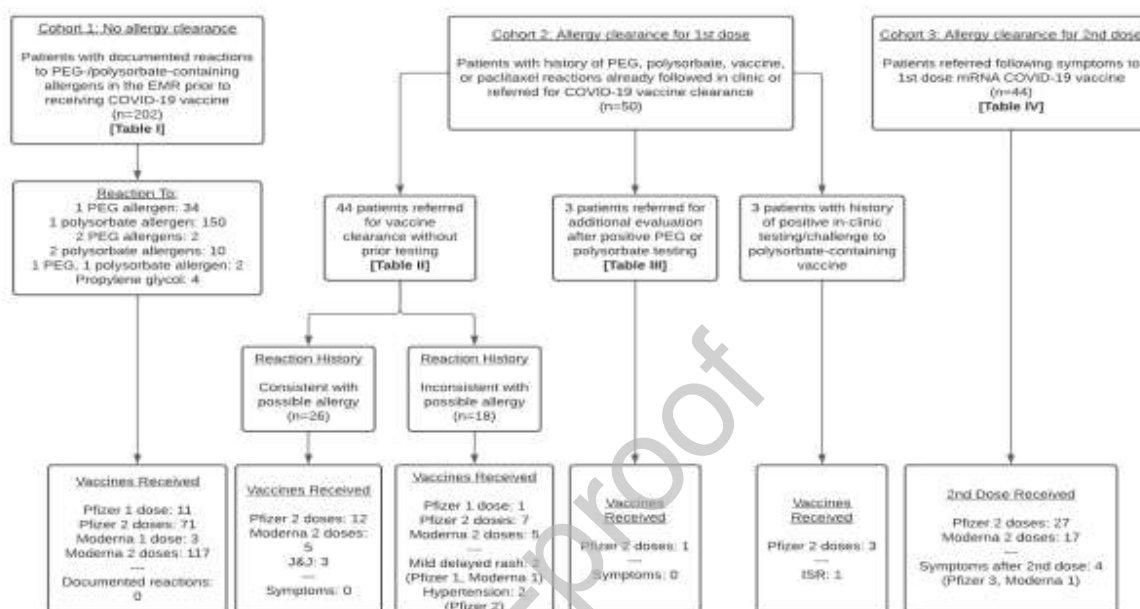
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Figure 1. Overview of 3 patient cohorts reviewed. The patient cohorts corresponding to the 4 tables are shown, as are the vaccines received in each patient cohort. Symptoms documented or experienced after vaccination are shown at the bottom underneath the '---'.



Abbreviations: ISR, injection site reaction

Table 1. Characteristics of patients in Cohort 1 with PEG/polysorbate reactions documented in the EMR prior to receiving COVID-19 vaccines who did not have documented reactions to the COVID-19 vaccine. Patients could have more than one reaction symptom documented to PEG/polysorbate as shown in “Documented Reaction(s)”, resulting in a combined total percentage of individual PEG/polysorbate allergens >100%.

Characteristics	Received COVID Vaccine (n=202)
Age in years, median [range]	75 [14-93]
Female sex at birth, n (%)	147 (73)
Race/Ethnicity, n (%)	
White	137 (68)
Hispanic/Latino	13 (6)
Black	7 (4)
Asian	33 (16)

American Indian	-
Multiracial	-
Other or Unknown	12 (6)
Documented Reaction(s), n (%)	
1 PEG allergen	34 (17)
1 Polysorbate allergen	150 (74)
2 PEG allergens	2 (1)
2 Polysorbate allergens	10 (5)
1 PEG, 1 Polysorbate allergen	2 (1)
Propylene glycol	4 (2)
# PEG allergens, n (%)	39 (19)
Bimatoprost (PEG, unspecified)	8 (4)
Doxorubicin* (PEG 2000)	4 (2)
Methylprednisolone acetate (PEG 3350)	1 (0)
Neulasta (20-kD monomethoxy PEG)	2 (1)
PEG, unspecified type	10 (5)
PEG 300	1 (0)
PEG 400	2 (1)
PEG 3350	4 (2)
PEG-asparaginase (PEG 5000)	3 (1)
Perflutren (PEG 5000)	1 (0)
Trastuzumab (PEG 3350)	3 (1)
# Polysorbate allergens, n (%)	172 (85)
Influenza vaccine, unspecified type	47 (23)
Influenza quadrivalent vaccine (polysorbate 80)	5 (2)
Hepatitis A vaccine (polysorbate 20)	2 (1)

Pneumococcal vaccine, unspecified type	17 (8)
Pneumococcal conjugated vaccine (Prevnar 13) (polysorbate 80)	12 (6)
Tetanus vaccine (polysorbate 80)	66 (33)
Zoster vaccine (polysorbate 80)	23 (11)
Documented Reaction Symptoms, n (%)	
Anaphylaxis	9 (4)
Cutaneous	72 (36)
Respiratory	1 (0)
Neurological	1 (0)
Gastrointestinal	7 (3)
Other / Unknown	21 (10)
Missing	105 (52)

*Included as doxorubicin can be pegylated in liposomal form.

Table 2. Characteristics of patients in Cohort 2 referred for COVID-19 vaccine clearance following a PEG (non-mRNA vaccine), polysorbate, vaccine, or paclitaxel reaction. Age in years is reported at time of referral. The number of documented allergies in the EMR range as low as zero as not all PEG/polysorbate reactions were documented as an allergy.

Characteristics	All (n=44)	Received vaccine (n=33)
Age in years, median [range]	51 [18-80]	48 [18-80]
Female sex at birth, n (%)	37 (84)	28 (85)
Race/Ethnicity, n (%)		
White	28 (64)	21 (64)
Hispanic/Latino	-	-
Black	2 (5)	2 (6)
Asian	3 (7)	3 (9)
American Indian	1 (2)	-
Multiracial	-	-
Other or Unknown	10 (23)	7 (21)
Primary language, n (%)		
English	42 (96)	32 (97)
Farsi	1 (2)	1 (3)
Russian	1 (2)	-
Documented allergies in EMR, median [range]	2 [0-52]	2 [0-25]
Co-morbidities, n (%)		
Drug Allergy	35 (80)	27 (82)
Food Allergy	8 (18)	8 (24)
Environmental Allergy	20 (46)	15 (46)
Asthma	14 (32)	12 (36)
History of Anaphylaxis	21 (48)	16 (49)
Atopic Dermatitis	7 (16)	6 (18)

Urticaria/Angioedema	7 (16)	7 (21)
Anxiety	30 (68)	22 (67)
Reaction history consistent with		
Allergy to medication containing PEG, n	9	8 (5 Pfizer, 2 Moderna, 1 J&J)
Allergy to vaccine/medication containing polysorbate, n	11	7 (4 Pfizer, 2 Moderna, 1 J&J)
Allergy to vaccine without polysorbate, n	3	2 (1 Pfizer, 1 J&J)
Allergy to paclitaxel, n	3	3 (2 Pfizer, 1 Moderna)
Inconsistent with allergy, n	18	13 (8 Pfizer*, 5 Moderna)

*One patient with history of GBS after influenza vaccine declined 2nd dose. All other patients received at least 2 doses of mRNA COVID-19 vaccine.

Table 3. Patients referred for evaluation after positive PEG/polysorbate testing.

Patient	Co-morbidities	Initial Reaction	1 st Positive Testing	2 nd Testing	COVID-19 Vaccine
1	Drug Allergy Environmental Allergy Urticaria Anxiety	Miralax prep complicated by vomiting and abdominal pain	(+) Miralax IDT 1:100 (+) Refresh eyedrops IDT 1:10	Declined	Declined
2	Drug Allergy Food Allergy Environmental Allergy Asthma Anaphylaxis Atopic Dermatitis Anxiety	Documented reactions to 52 allergens in EMR	Reportedly (+) PEG testing	(-) Miralax SPT 1:1 (170 mg/ml) (-) Methylprednisolone acetate IDT 1:10 (4 mg/ml)	Received Pfizer
3	Drug Allergy Anaphylaxis Anxiety	Syncope following methylprednisolone acetate, lidocaine, and bupivacaine injection	(+) Miralax SPT 1:100, 1:10, 1:1 (+) Methylprednisolone acetate SPT 1:10, 1:1	(-) Miralax SPT 1:1 (170 mg/ml) (-) Methylprednisolone acetate IDT 1:10 (4 mg/ml)	Declined

Negative local anesthetic
testing

Tolerated sequential
challenges with
methylprednisolone
acetate 16mg IM,
lidocaine 10mg SC,
bupivacaine 7.5mg SC

Table 4. Characteristics of patients in Cohort 3 referred for evaluation of symptoms following 1st dose mRNA COVID-19 vaccine. All received the 2nd dose. Characteristics, reaction history, and treatment are reported for symptoms following the 1st dose for both columns. Details regarding reaction history and treatment for 2nd dose symptoms are reported in the manuscript.

Characteristics	All patients (n=44)	Patients with symptoms after 2 nd dose (n=4)
Age in years, median [range]	45 [24-78]	44 [34-52]
Female sex at birth, n (%)	39 (89)	4 (100)
Race/Ethnicity, n (%)		
White	22 (50)	-
Hispanic/Latino	6 (14)	1 (25)
Black	1 (2)	-
Asian	10 (23)	2 (50)
American Indian	-	-
Multiracial	1 (2)	-
Other or Declined or Unknown	4 (9)	1 (25)
Primary language, n (%)		
English	43 (98)	4 (100)
Mandarin	1 (2)	-
Documented allergies in EMR, median [range]	2 [0-11]	6 [5-11]
Co-morbidities		
Drug Allergy	25 (57)	4 (100)
Food Allergy	16 (36)	3 (75)
Environmental Allergy	27 (61)	4 (100)
Asthma	22 (50)	4 (100)

History of Anaphylaxis	8 (18)	3 (75)
Atopic Dermatitis	8 (18)	2 (50)
Urticaria/Angioedema	5 (11)	1 (25)
Anxiety	24 (55)	4 (100)
Reaction onset	-	-
<30 min (Pfizer 19, Moderna 11)	30 (68)	4 (100)
30-60 min (Pfizer 5, Moderna 4)	9 (20)	-
1-4 hours (Pfizer 2, Moderna 1)	3 (7)	-
5-12 hours (Pfizer 1, Moderna 1)	2 (5)	-
Reaction symptoms	-	-
Cutaneous	31 (70)	4 (100)
Lower respiratory	10 (23)	2 (50)
Cardiovascular	5 (11)	-
Neurological	15 (34)	-
Gastrointestinal	6 (14)	-
Upper airway	3 (7)	-
Tongue/Throat Sensation	15 (34)	3 (75)
Treatment	-	-
Antihistamines (H1)	14 (32)	4 (100)
Corticosteroids	2 (5)	-
Intramuscular epinephrine	6 (14)	2 (50)
ED visit only	12 (27)	2 (50)
Hospitalization	1 (2)	1 (25)

eTable 1. Dilutions used for PEG and polysorbate skin prick and intradermal tests.

Medication	Skin Prick Test (highest dilution tested)	Intradermal Test (highest dilution tested)
Miralax (PEG 3350)	170 mg/ml	NA
Methylprednisolone acetate (PEG 3350)	40 mg/ml	4 mg/ml
Methylprednisolone succinate (control)	40 mg/ml	4 mg/ml
Triamcinolone acetate (polysorbate 80)	40 mg/ml	4 mg/ml
Pprevnar-13 (polysorbate 80)	1:10	1:100