

Clinical & Experimental Allergy / Early View

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Specialist allergy advice allows vaccination in patients with reactions to COVID-19 vaccines

Verah Harper MBBS, MRCP , Padmalal Gurugama MD, MRCP, FRCPath, Pamela Ewan MB, FRCP, FRCPath, Shuaib Nasser MBBS, MD, FRCP, Priya Sellaturay MBBS, MRCP

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Key Messages

We evaluated 60 adult patients with adverse reactions to a COVID-19 vaccine.

75% of patients with adverse reactions to COVID-19 vaccines were managed with written advice only.

One patient had PEG allergy, second vaccine doses were advised for all, but 9 declined.

To the Editor,

Vaccination remains the most effective means out of the COVID-19 pandemic. Data from randomized clinical trials demonstrated that COVID-19 vaccines, reduce severe COVID-19 infections and prevent deaths.¹ However, there was initially an unexpectedly high rate of suspected allergic reactions to COVID-19 vaccines (for anaphylaxis 2.5–11.1 cases/million doses for the mRNA vaccines) compared with non-COVID-19 vaccines (1.3 cases/million doses) which caused considerable alarm,^{2,3} placing significant pressure on allergy centres. It also perpetuated fears circulating in the media about COVID-19 vaccines resulting in vaccine scepticism and hesitancy. Allergic reactions following vaccination may be due to any of the excipients (adjuvants, preservatives, emulsifiers, stabilizers etc.).³ Polyethylene glycol (PEG)

in mRNA COVID-19 vaccines (Pfizer-BioNTech, Moderna) remains the only likely IgE-mediated allergenic suspect, but investigation has so far confirmed this in only one case.⁴ Other mechanisms are likely implicated, accounting for the majority of hypersensitivity reactions.³ Although cases of PEG allergy have been increasingly reported to the medical literature in the recent decade,⁵ PEG allergy remains rare. PEG has not been an excipient in vaccines until the development of COVID-19 mRNA vaccines.⁴ Typically, PEG allergic reactions are rapid-onset immediate reactions, seen with drugs/products containing higher molecular weight (MW) PEGs, administered parenterally and usually dose-dependent.⁵ Lipid nanoparticles (LNP) encapsulating mRNA and used as a carrier system to prevent rapid mRNA enzymatic degradation are also potentially allergenic.³

We describe a retrospective analysis of 60 patients referred to the Allergy Clinic, Cambridge University Hospital between December 2020 and April 2021 following systemic adverse reactions to COVID-19 vaccines. We discuss management strategies employed and outcomes. The objectives are twofold: 1. To provide evidence that allergy to COVID-19 vaccines are rare, and most reactions are not a contraindication for further doses, 2. To help meet the public health aim of vaccinating all adults safely, by de-mystifying widespread COVID-19 vaccine scepticism and fears perpetuating vaccine hesitancy.

The analysed cohort included sixty patients referred for either outpatient review or for written advice. Clinical data were extracted manually from electronic healthcare records. A pre-clinic COVID-19 vaccine questionnaire was completed by the referring clinician. The questionnaire captured the index COVID-19 vaccine, reaction history, historical drug/vaccine reactions, the brand and excipients of each culprit drug/vaccine and drugs tolerated which contain PEG and/or polysorbate 80 (PS80).

The reactogenicity profile for each referral was analysed and clinical phenotype categorized as: (a). low risk: if symptoms were subjective e.g., lip tingling or felt transiently unwell and resolved spontaneously or treated in the vaccine hub; (b). medium-risk: throat constriction, sensation of tongue or lip swelling or breathlessness without objective signs and with normal vital signs; visible urticaria or angioedema and unlikely allergic to PEG or PS80 e.g., tolerated PEG (MW $\geq$ 2000) and PS80 in a medication; or the reaction was delayed in onset; or immunogenic. (c). high risk, if the history contained objective features of anaphylaxis and/or history of known/suspected PEG allergy and/or history of multiple drug/vaccines allergies. Figure one demonstrates the triage pathway and the criteria for risk stratification.

Written advice was provided for both low- and medium-risk patients. Where a patient was tolerating both PEG (MW $\geq$ 2000) and PS80, in a medication, we recommended any of the age-appropriate licenced vaccines after anti-histamine pre-dosing. And after ensuring that any pre-existing allergic and multi-system disorders were optimally controlled. Where allergy to PEG was suspected, but the patient tolerated PS80 in medications, the AstraZeneca vaccine was recommended for those aged over 40 and without a history of thrombosis. Further assessment to evaluate possible PEG allergy was recommended.

High-risk patients were followed up via telephone for a detailed medical, drug and allergy history. History of immediate reactions to most common drugs containing PEG such as laxatives, antacids (Gaviscon Double Action), injectable corticosteroids (depo-methylprednisolone), depo medroxyprogesterone and phenoxymethylpenicillin tablets were checked on direct questioning. Patients with a convincing history of vaccine anaphylaxis with objective symptoms or with suspected PEG and/or PS80 allergy were invited for allergy skin testing.

Skin prick tests (SPT) to PEGs of different MW, other Pfizer vaccine excipients (1,2-distearoyl-sn-glycero-3-phosphocholine and cholesterol; Sigma-Aldrich Co), PS80 and the vaccines were undertaken.⁴ Intradermal skin tests were not undertaken. If SPT was negative, vaccination with the second dose of the index vaccine was recommended. An alternative vaccine was offered if the index vaccine was declined. All patients were discussed at the drug allergy multi-disciplinary meeting (MDT).

Of the 60 analysed cohort, the mean age was 49.3 (range, 21 – 92) and the majority were female, 48 (80.0%). Fifty-eight of 60 (96.7%) reacted to the first dose (35-AstraZeneca, 22-Pfizer, 1-Moderna) and 2/60 (3.3%) to the second dose (Pfizer). Baseline demographics, reaction characteristics and the outcome of allergy advice/skin testing are shown in Table 1. Three (5%) had a history of suspected PEG allergy, 19 (31.7%) anaphylaxis, 7 (11.7%) allergy/adverse reactions to previous vaccines, 20 (33.3%) multiple drug allergies, 29 (48.3%) atopic diseases, 9 (15%) food allergy, 21 (35%) mental health disorders, 16 (26.7%) autoimmunity and 20 (33.3%) urticaria and angioedema.

TABLE 1. Characteristics of cases with systemic reactions after 1st or 2nd COVID-19 vaccine dose and outcome of allergy specialist advice/investigations

Characteristic	Overall (<i>n</i> = 60)	Immediate (<i>n</i> = 33) (onset ≤1 h)	Delayed (<i>n</i> = 27) (onset ≥1 h)
Age (years) Mean			
Mean (±SD)	49.3 (±15.7)	44.1 (±14.0)	55.7 (±15.6)
Min	21	21	31
Max	92	83	92
Sex			
Male	12 (20.0%)	4 (6.7%)	8 (13.3%)
Female	48 (80.0%)	29 (48.3%)	19 (31.7%)

Characteristic	Overall (n = 60)	Immediate (n = 33) (onset ≤1 h)	Delayed (n = 27) (onset ≥1 h)
Relevant comorbidities ^a			
Atopy (seasonal & perennial rhinitis, asthma, eczema)	29 (48.3%)	21 (35.0%)	8 (13.3%)

Abbreviations: COVID-19, coronavirus disease 2019; LOC, loss of consciousness; PEG, polyethylene glycol; PS80, polysorbate 80.

^a Patients may have more than one comorbidity.

^b Patients presented with more than 1 symptom which included: *Cutaneous (hives, angioedema, itch, rash, flushing, tongue and/or throat swelling); [†]Upper resp (stridor, globus, cough, hoarseness, throat constriction, itchy and/or sore throat, dyspnoea); [‡]Lower resp tract (chest tightness, difficulty breathing, dyspnoea, cough, wheeze, tachypnoea, desaturation); [§]Cardiovascular (tachycardia, hypotension, palpitations, chest pain, feeling faint, dizziness, collapse without LOC, LOC, hot, clammy, sweaty, pallor); [¶]GIT (nausea, retching, vomiting, abdominal pain, diarrhoea); ^{‡‡}Neurological (headache, voice alteration/disphonia, peripheral paraesthesia, involuntary jerking movements, seizure, ringing in ears).

^c Culprit vaccines: Swine flu, Small pox, Influvac, Flucelvax Tetra(contains traces of PS80), Sanofi Pasteur Quadrivalent (non polysorbate containing), Twinrix, Revaxis, Typherix, Pneumovax, Hepatitis B, Yellow fever, MMR, BCG (Bacillus Calmette-Guerin), HPV (human papillomavirus).

^d Acute tryptase all normal.

^e Paroxysms of cough, burning sensation in throat, generalized itch reported after 5 min of placebo intramuscular injection with normal saline. Patient was reassured symptoms were non-allergic and tolerated the vaccine with gradual improvement in symptoms.

^f Opted (n = 4); Advised (n = 4).

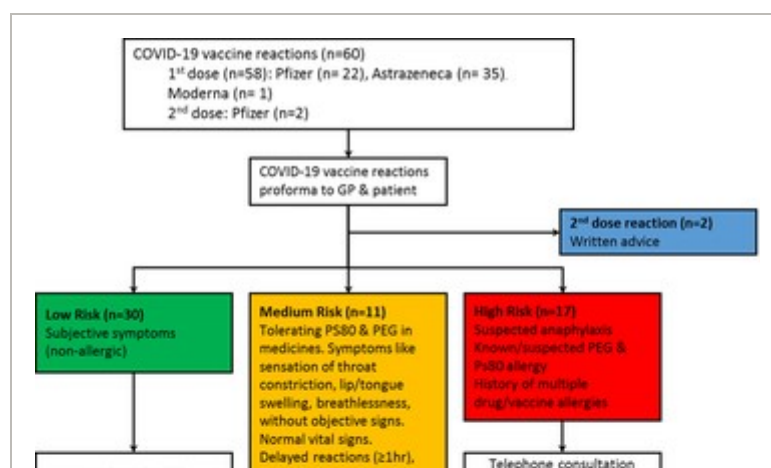
Of the 58/60 (96.7%) with reactions to the first dose, the majority, 32(55.2%) reported immediate reactions (19 received adrenaline, 31 managed in emergency department, 3 required intensive care unit (ITU) admission, 18 had acute tryptase testing with normal results). Fifteen patients with immediate reactions to the first dose were invited for allergy skin testing (1 positive to PEG 2000, 10 negatives, 3 declined, 1 awaiting skin test). Only 1/60 patients was diagnosed with allergy to PEG in the Pfizer vaccine with a positive SPT and tolerated the AstraZeneca vaccine for the second dose.

All patients with delayed reactions (1st dose [n = 26], 2nd dose [n = 2]) were managed with written advice and two (1-Bell's palsy, 2-erythema multiforme) following the first dose were advised to avoid their index vaccine (Pfizer).

Overall, 45/60 (75%) patients received written advice. Among the 32 patients who reported immediate reactions to the first dose, over 60% ($n = 37$) and 8 (13.3%) tolerated the second dose of the index vaccine and alternative vaccine (4-opted, 4-advised), respectively without adverse reaction under anti-histamine cover. One patient reported subjective symptoms immediately after receiving the second dose (resolved on reassurance only). One patient died from unrelated causes prior to the second dose. One patient is awaiting skin testing and 10 (16.7%) declined the second dose (1-history of mast cell activation syndrome, 7 fear/anxiety, 1 developed menstrual changes and breast lumps weeks after vaccination, 1 allergy work-up cancelled due to logistical challenges [Table 1]). No patient was advised against having a second dose.

Like all medicines, vaccines can cause adverse reactions which are either immune- or non-immune-mediated and allergic or non-allergic.³ The key finding of our study was that almost all of COVID-19 vaccine reactions were non-allergic or related to immunogenic effects, as a consequence of innate immune system activation.³ Patients in our cohort were predominantly female (80%), a finding similar to those reported in the literature.^{2, 6} Over a third (35%) of our analysed cohort had a history of mental health disorders. Previously published reports show that some non-allergic vaccine reactions are likely related to immunization stress-related responses.⁷ In an individual with underlying anxiety, pandemic-related fears and vaccine-induced anxiety may be exacerbated by the misconceptions/myths surrounding COVID-19 vaccines.

A systematic review with meta-analysis reported incidence of anaphylaxis with COVID-19 vaccines to be 7.91 cases per million.⁸ Other studies have reported anaphylaxis based on symptom survey.^{2, 6} The majority of our patients (75%) were managed through written advice (Table 1). Patients who tolerated the second COVID-19 vaccine dose with anti-histamine cover included some patients whose initial reaction was treated with adrenaline or who required care in an emergency department. We demonstrate that anaphylaxis and allergy to COVID-19 vaccines is rare – a finding similar to other reported data.⁹ The pre-clinic COVID-19 vaccine questionnaire, detailed telephone consultation in high-risk cases and the triage algorithm (Figure 1), facilitated effective management of patients with suspected allergy to COVID-19 vaccines. This helped free capacity within the drug allergy service.



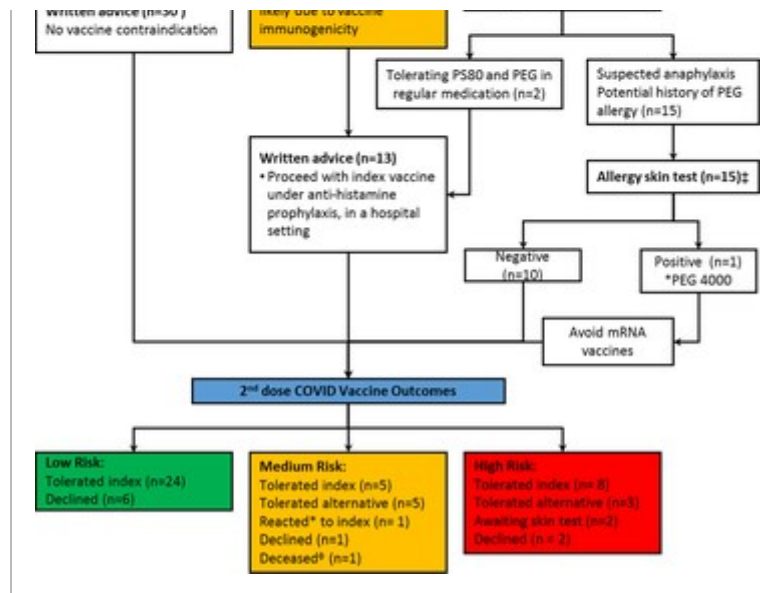


FIGURE 1

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Risk stratification algorithm for patients referred with suspected anaphylaxis/allergy or systemic adverse reactions to COVID-19 vaccines. *PS80*, polysorbate 80, *PEG*, polyethylene glycol. *subjective symptoms, non-allergic; †unrelated to the vaccine

Almost half (48.3%) of our cohort had a history of atopic diseases, an interesting finding as atopic individuals are reported to have a twofold higher anaphylaxis risk.³ Recent published data support this finding.^{2, 6}

Our findings highlight the importance of risk stratification based on patient's clinical phenotype. A thorough clinical history is essential for evaluation of vaccine reactions. Allergy to excipients in vaccines, although rare, should be considered if the history is convincing, especially in a patient with previous immediate reactions to unrelated drugs+/-cosmetics. To confirm or refute PEG allergy, a thorough drug history should be elicited and each drug checked for excipients to determine if PEG or PS80 are tolerated. If the index of suspicion is high, PEG testing should be considered with PEG of both low and higher MW as reactivity thresholds to PEG vary between patients.⁵

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Verah Harper contributed to investigation, writing original draft, data collection, resources and review and editing; Padmalal Gurugama contributed to resources and review and editing; Pamela Ewan contributed to data collection, resources and review and editing; Shuaib Nasser contributed to data collection and review and editing and Priya Sellaturay contributed to conceptualization, project administration, data collection and review and

editing. All are accountable and gave final manuscript approval.

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