COVID-19 vaccines and anaphylaxis—evaluation with skin prick testing, basophil activation test and Immunoglobulin E

To the Editor,

Allergic reactions, including anaphylaxis, have been reported from the second day of Pfizer-BioNTech's COVID-19 vaccine administration in the mass vaccination programme. Although the cause of these rare allergic reactions remains unclear, the excipient, polyethylene glycol (PEG), has been considered the culprit allergen. It is used as a stabilizer in the COVID-19 mRNA vaccines from Pfizer-BioNTech, 'Comirnaty', and Moderna, 'Spikevax'. A PEG-derivative polysorbate 80 is used in the adenovirus vector Oxford/AstraZeneca vaccine, 'Vaxzevria'. Our aim was to present our experiences of evaluating 27 patients with systemic acute reactions to the first dose of COVID-19 vaccine plus 10 patients with suspected PEG allergy diagnosed before administration of the first vaccine dose. Our results indicate that a systemic acute reaction to the first dose, or to PEG or PEG derivatives, does not necessarily contraindicate a second dose of COVID-19 vaccine.

Thirty-seven patients were referred to, and evaluated at, the Allergy Center in Linköping, Sweden. The study was approved by the Swedish Ethical Review Authority, Dnr 2021–01301. Seven patients had an acute onset systemic reaction to the first dose of COVID-19 vaccine from Oxford/AstraZeneca, Vaxzevria, one to Spikevax (Moderna) and nineteen after the Pfizer-BioNTech vaccine, Comirnaty. A second dose of Comirnaty was administered in 26 cases, and one patient refused to be vaccinated. Two doses of Comirnaty vaccine were administered to 10 patients with previously suspected PEG or PEG-derivative allergy (from guidelines of the Swedish Public Health Agency).

All 37 patients underwent skin prick testing according to Bruusgaard-Mouritsen et al. with PEG molecular weights from 300 to 20,000, poloxamer 407 and polysorbate 80 (Sigma-Aldrich, Stockholm, Sweden).

One of the patients had severe anaphylaxis after the first dose at our department and was evaluated with ImmunoCAP IgE to PEG 2,000 and 10,000 (Thermo-Fisher, Allerød, Denmark, with novel research use only tests) and basophil activation test (BAT) to PEG 4000, PEG 20,000, poloxamer 407 and the native vaccine (Comirnaty). Polysorbate 80 was also included, but the substance had a toxic effect on all cells, which made evaluation impossible.

Twenty-seven patients were referred from primary care due to a systemic acute reaction after COVID-19 vaccination with vaccines from Pfizer-BioNTech, Moderna or Oxford/AstraZeneca. The reactions were immediate (within 60 min) and systemic (Table 1). After evaluation, 26 patients were vaccinated with the second vaccine dose (Comirnaty, as Comirnaty was prioritized according to the county’s local vaccination policy).

Of these 27 patients, four had less pronounced or subjective symptoms such as shivering, sensation of swollen tongue or throat closure, anxiety, pruritus and dizziness (patient number 1–4/Table 1).

As anaphylactic reactions were initially suspected, epinephrine was injected and all four were reported to the Swedish Medical Products Agency (MPA) with a diagnosis of anaphylaxis. Tryptase was not taken during these reactions. The patients were referred to us for evaluation, underwent skin prick testing with PEG and PEG derivatives and tested negative. One patient refused to be vaccinated, and the other three received their second vaccine dose with no adverse events.

Five patients (patient number 5–9/Table 1) had an acute onset systemic reaction with at least two different organ systems involved. These patients were treated with epinephrine, oral antihistamine and oral steroid. Their symptoms are described in Table 1.

All patients tested negative in skin prick testing with PEG and PEG derivatives and were then vaccinated with the second vaccine dose with no adverse reactions.

Patient number 9 had an acute onset systemic reaction, clinically consistent with anaphylaxis (Level 2 according to Brighton Collaboration and to the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN)), including hypotension, vomiting, dizziness and decreasing saturation (from 95–96% to 91–93%). He was treated with intramuscular epinephrine, oral antihistamine, steroid tablets and oxygen. His tryptase level (14 µg/l) was not significantly elevated above his basal tryptase (13 µg/l). He was referred to a haematologist to evaluate suspected systemic mastocytosis, but the bone marrow biopsy did not show any evidence of such. Skin prick testing was carried out twice as a stepwise method, and all the SPTs were negative to PEG 300 (100%), /3000 (50%), /6000 (50%), /20,000 0.01%, 0.1%, 1%, 10% and 20%/ polysorbate 80 (20%/poloxamer 407 (10%). The SPT to the undiluted Comirnaty vaccine was negative as well. BAT showed positive results for PEG 20,000 and 4000, and for the Comirnaty vaccine. Circulating IgE antibodies to PEG 2,000 and
10,000 were not detectable with the novel ImmunoCAP assays. This patient had previously developed two suspected anaphylactic reactions after vaccinations, one of which contained polysorbate 80.

A new risk-benefit evaluation was done; due to his cardiovascular disease, diabetes and obesity, a second dose was administered. He had premedication with desloratadine 10 mg, betamethasone 1 mg the day before and desloratadine 10 mg, betamethasone 1 mg and promethazine 25 mg on the day of the vaccination. The patient did not have any adverse reaction to the vaccination.

Ten further patients (patient number: 10–19/Table 1) had different acute onset systemic reactions with at least two different organ systems involved or with swelling sensation in the upper airways. Nine of these patients were treated with oral antihistamine and oral steroids, but not with epinephrine, and were referred to us for evaluation. All tested negative in skin prick testing with PEG and PEG derivatives and were vaccinated with the second vaccine dose with no adverse reactions.

Two of the patients (20, 21) experienced shortness of breath without cardiovascular or dermatological symptoms after their first vaccine dose. The symptoms were described as asthma attacks. They used their previously prescribed short-acting beta- agonist inhalers to good effect. After negative skin prick testing, they received their second vaccine dose and tolerated it.

Six of the patients (patient number: 22–27/Table 1) reacted with acute onset (within 10–60 min after the first dose) skin symptoms such as urticaria or generalized erythema with or without pruritus with no other objective symptoms. Their skin prick tests for PEG and PEG derivatives were negative. One patient experienced generalized pruritus during skin prick testing, which did not worsen after the administration of the second vaccine dose. No severe objective symptoms were observed; one patient got slight redness on the chest. All six tolerated revaccination.

All patients with acute onset urticaria, pruritus and angioedema after the first dose of the vaccine were treated with 10 mg desloratadine as premedication. Patients with underlying uncontrolled asthma who experienced breathing difficulties after the vaccination were advised to take a double dose of their regular asthma medication for a few days before the revaccination was administered.

Ten patients were evaluated due to a previous severe reaction to medications, that is, injectable medicines containing PEG/PEG derivatives, which raised suspicion of a PEG/PEG-derivative allergy (patient number: 28–37/Table 2). All ten underwent skin prick testing with PEG and PEG derivatives, tested negative and were vaccinated with the Comirnaty vaccine with no severe allergic reactions.

We did not observe any severe reactions in patients who were revaccinated, although the symptoms after the first vaccination were consistent with Level 2 or 3 of diagnostic certainty according to the Brighton Collaboration. This concurs with a recently published study by Wolfson et al. Patients with acute onset urticaria, generalized erythema and pruritus also tolerated revaccination when allergy to PEG was ruled out. Patients with suspected severe PEG or PEG-derivative allergy were successfully vaccinated as well. The Brighton Collaboration scoring system seems to overestimate the number of patients with clinically significant anaphylaxis. One explanation may be that several subjective symptoms are included as minor criteria in the Brighton Collaboration scoring system. Although several patients experienced severe symptoms that were clinically consistent with anaphylaxis, revaccination could be administered without serious adverse events. Our findings suggest that anxiety-related non-immune factors may explain several of the reported anaphylaxis reactions.

To end the devastating COVID-19 pandemic and limit mortality, as many as possible need to be safely vaccinated. Patients with acute onset vaccine-related systemic reactions to the first COVID-19 vaccine dose, or suspected PEG allergy, should be referred to an allergist or allergy-interested physician. Risks and benefits should be carefully evaluated, with skin prick tests to PEG/PEG derivatives as promising aids. If allergy to PEG/PEG derivatives is ruled out and the benefits outweigh the risks, the first or second vaccine dose may

Key Messages
- Skin prick tests were negative in our patients with reported anaphylaxis to the first dose of mRNA vaccine against COVID-19.
- Although anaphylaxis according to the Brighton Collaboration Criteria was described after the first vaccination, the second dose was tolerated.
- As anxiety-related symptoms can mimic anaphylaxis, vaccinations in individuals with previous reactions should be performed in a peaceful, professional setting.
| No. | Age in years | Sex | History of allergy | 1st dose of vaccine | Symptoms after vaccination | Time to onset | Treatment | Vaccine outcome (2nd dose): all were vaccinated with Comirnaty vaccine | SPT with PEG and PEG derivatives |
|-----|--------------|-----|------------------|-------------------|---------------------------|--------------|----------|---------------------------------------------------------------|-------------------------------|
| 1   | 40–50        | F   | Systemic reaction: wheezing, shaking, chills during pollen allergen immunotherapy | Comirnaty         | Chills, shivering, anxiety, light-headedness | 20 min       | Epinephrine, antihistamine, oral steroid, oxygen | Negative                                      | No reaction                   |
| 2   | 30–40        | F   | Redness and skin irritation after exposure to different cosmetic products | Comirnaty         | Inconsistent history, Dizziness, nausea, giddiness. Unclear vital parameters | Within a few minutes after vaccination | Epinephrine, antihistamine | Negative                                      | Patient declined vaccination   |
| 3   | 20–30        | F (trans-gender) | None | Vaxzevria | Swelling sensation in the tongue, dizziness, giddiness, generalized pruritus. No objective symptoms | 15 min       | Epinephrine, antihistamine, oral steroid | Negative                                      | No reaction                   |
| 4   | 50–60        | F   | Severe angioedema to penicillin | Comirnaty         | Sensation of throat closure | 10 min       | Epinephrine, antihistamine, oral steroid | Negative                                      | No reaction                   |
| 5   | 40–50        | F   | None | Moderna | Generalized erythema (assessed as urticaria), nausea, tachycardia, hypertension | Within a few minutes | Epinephrine, antihistamine, oral steroid | Negative                                      | Hyperventilation, assessed as anxiety-related reaction |
| 6   | 20–30        | F   | Anaphylaxis to peanut | Vaxzevria         | Generalized pruritus, diplopia, dry throat, dyspnoea, anxiety | 10 min       | Epinephrine, antihistamine, oral steroid | Negative                                      | No reaction                   |
| 7   | 40–50        | F   | None | Comirnaty         | Shortness of breath. Generalized malaise. Sensation of throat closure | Within a few minutes | Epinephrine, antihistamine, oral steroid | Negative                                      | No reaction                   |
| No. | Age in years | Sex | History of allergy | 1st dose of vaccine | Symptoms after vaccination                                                                                                                                      | Time to onset | Treatment                                                | SPT with PEG and PEG derivatives | Vaccination outcome (2nd dose): all were vaccinated with Comirnaty vaccine |
|-----|---------------|-----|-------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------|
| 8   | 50–60         | F   | None              | Comirnaty           | Shortness of breath, generalized erythema, obstructive breathing sound over the lungs (Level 2 of diagnostic certainty according to Brighton Collaboration)             | 20 min       | Epinephrine, antihistamine, oral steroid, short-acting beta-agonist | Negative                      | No reaction                                                              |
| 9   | 50–60         | M   | Anaphylaxis to H1N1 influenza vaccine and to another vaccine (unclear) | Comirnaty           | Hypotension, vomiting, dizziness, decreasing saturation (from 95–96% to 91–93%) Tryptase 14 µg/l, not significantly elevated above baseline (13 µg/l) (Level 2 of diagnostic certainty according to Brighton Collaboration) | 15 min       | Epinephrine, antihistamine, oral steroid, oxygen         | Negative                      | No reaction                                                              |
| 10  | 30–40         | F   | None              | Comirnaty           | Flush, generalized pruritus, sensation of throat closure, shortness of breath. (Level 2 of diagnostic certainty according to Brighton Collaboration)                  | 10 min       | Antihistamine, oral steroid                             | Negative                      | No reaction                                                              |
| 11  | 10–20         | F   | None              | Comirnaty           | Nausea, generalized erythema, sensation of throat closure, abdominal discomfort. (Level 2 of diagnostic certainty according to Brighton Collaboration)               | 15 min       | Antihistamine, oral steroid                             | Negative                      | No reaction                                                              |
| 12  | 90–100        | M   | None              | Comirnaty           | Generalized pruritus, verbal and motoric distress, slight hoarseness                                                                                         | Within a few minutes after vaccination | Antihistamine, oral steroid                             | Negative                      | No reaction                                                              |
| No. | Age in years | Sex | History of allergy                           | 1st dose of vaccine | Symptoms after vaccination                                                                 | Time to onset    | Treatment                                      | SPT with PEG and PEG derivatives | Vaccination outcome (2nd dose): all were vaccinated with Comirnaty vaccine |
|-----|--------------|-----|---------------------------------------------|---------------------|------------------------------------------------------------------------------------------|-----------------|------------------------------------------------|----------------------------------|--------------------------------------------------------------------------------|
| 13  | 50–60        | F   | Generalized angioedema to wasp             | Comirnaty           | Paraesthesia in the scalp, soles, tongue and palms, sensation of swollen tongue           | Within a few minutes | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 14  | 50–60        | F   | None                                        | Comirnaty           | Sensation of swollen throat, dizziness, cold sweat                                        | Within a few minutes | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 15  | 20–30        | F   | Anaphylaxis to soya, peanuts, latex, NSAID | Comirnaty           | Urticaria, nausea, dizziness and headache, sensation of swollen throat (Level 2 of diagnostic certainty according to Brighton Collaboration) | Within a few minutes | None                                            | Negative                        | No reaction                                                                   |
| 16  | 6–70         | F   | Diverse food allergy, no anaphylaxis       | Vaxzevria           | Itching, angioedema, dyspnoea, (Level 2 of diagnostic certainty according to Brighton Collaboration) | Within 60 min   | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 17  | 50–60        | F   | Anaphylaxis to penicillin                  | Comirnaty           | Hoarse voice, sensation of swollen throat                                                 | Within a few minutes | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 18  | 40–50        | F   | Anaphylaxis to wasp                        | Comirnaty           | Hoarseness, generalized erythema, tachycardia Tryptase 10 microgram/l, not significantly elevated above basal tryptase (Level 2 of diagnostic certainty according to Brighton Collaboration) | 5 min            | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 19  | 40–50        | F   | Anaphylaxis to local anaesthetics          | Comirnaty           | Urticaria, itching throat, hoarseness, swollen sensation in the throat (Level 2 of diagnostic certainty according to Brighton Collaboration) | 15–20 min       | Antihistamine, oral steroid                      | Negative                        | No reaction                                                                   |
| 20  | 40–50        | F   | Worsening of asthma after NSAID exposure.  | Vaxzevria           | Dyspnoea, described as asthma attack by the patient                                     | 10 min           | Short-acting beta- agonist                      | Negative                        | No reaction                                                                   |
Table 1 (Continued)

| No. | Age in years | Sex | History of allergy | 1st dose of vaccine | Symptoms after vaccination | Time to onset | Treatment | SPT with PEG and PEG derivatives | Vaccination outcome (2nd dose): all were vaccinated with Comirnaty vaccine |
|-----|--------------|-----|-------------------|---------------------|---------------------------|--------------|----------|-------------------------------|---------------------------------------------------------------|
| 21  | 40–50        | F   | Nausea after exposure to radiocontrast agents. Anaphylaxis to peanut | Comirnaty           | Dyspnoea, sensation of swollen throat, prickling sensation in the feet and legs | 25 min       | Short-acting beta-agonist    | Negative.                      | No reaction                                                     |
| 22  | 50–60        | F   | Angioedema after NSAID exposure | Vaxzevria          | Acute systemic urticaria, paraesthesia in lips | Within a few minutes after vaccination | Antihistamine, oral steroid | Negative | No reaction |
| 23  | 50–60        | F   | Generalized flush to histamine-rich food and beverages | Vaxzevria          | Generalized erythema or urticaria. Two referrals for the same patient, inconsistent documentation | 20 min       | Antihistamine | Negative | No reaction |
| 24  | 50–60        | F   | None | Vaxzevria          | Itching throat, generalized erythema | 10 min       | Antihistamine, oral steroid | Negative | No reaction |
| 25  | 30–40        | F   | Anaphylaxis to peanut | Comirnaty          | Severe generalized pruritus with erythema. Prickling sensation in the fingers | Within a few minutes | Epinephrine, antihistamine, oral steroid | Negative | No reaction |
| 26  | 70–80        | M   | Anaphylaxis to wasp | Comirnaty          | Itching of the scalp, generalized urticaria | 1 h          | Antihistamine, oral steroid | Negative | No objective symptoms. Slight pruritus in the scalp during skin testing and after vaccination |
| 27  | 40–50        | M   | None | Comirnaty          | Generalized erythema and pruritus, prickling sensation in face and neck | 5 min        | Antihistamine, oral steroid | Negative | Slight redness on the chest |

Note: Abbreviations: F, female; M, male; SPT, skin prick test.
be administered in a peaceful, professional setting where immediate resuscitation can be performed. Further studies on the underlying immunological mechanisms of the rare severe true allergic reactions to the COVID-19 vaccines are needed.

**KEYWORDS**
anaphylaxis, basophil activation test, COVID-19, polyethylene glycol, skin prick test, vaccine

**ACKNOWLEDGEMENTS**
‘Special thanks to Mirjam Ydreborn, Allergy Center Linköping, for performing the skin prick tests and Zekiye Cansu, Research Center Södersjukhuset, Stockholm, for performing the basophil activation test’.

**CONFLICT OF INTEREST**
No conflict of interest to declare.

**AUTHOR CONTRIBUTIONS**
All authors provided critical feedback and helped shape the research, analysis and manuscript. À Csuth, M Jenmalm and L Nilsson conceived and planned the study and wrote the manuscript with input from all authors. À Csuth carried out the skin prick tests, decided whether the patients should receive the COVID-19 vaccines and organized the tables. A Nopp supervised the performance and evaluated the outcome of the basophil activation tests. All authors critically evaluated and revised the final manuscript.

**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

---

**TABLE 2** Evaluation of patients with previous severe reactions after PEG/PEG-derivative medications

| No. | Age in years | Sex | History of allergy                                                                 | SPT with PEG and PEG derivatives | Vaccination outcome (all patients were vaccinated with Comirnaty vaccine) |
|-----|--------------|-----|----------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------|
| 28  | 40–50        | F   | Suspected anaphylaxis to naproxen and omeprazole                                 | Negative                         | No reaction                                                           |
| 29  | 60–70        | F   | Anaphylaxis to steroid injection                                                 | Negative                         | No reaction                                                           |
| 30  | 80–90        | F   | Suspected anaphylaxis to radiocontrast agent; skin rash and swelling from make-up products | Negative                         | No reaction                                                           |
| 31  | 70–80        | F   | Anaphylaxis to paclitaxel                                                        | Negative                         | No reaction                                                           |
| 32  | 30–40        | F   | Anaphylaxis to paclitaxel                                                        | Negative                         | No reaction                                                           |
| 33  | 50–60        | F   | Anaphylaxis to tetanus vaccine                                                    | Negative                         | No reaction                                                           |
| 34  | 40–50        | F   | Anaphylaxis to muscle relaxant containing polyethylene glycol                    | Negative                         | No reaction                                                           |
| 35  | 50–60        | F   | Anaphylaxis to radio contrast media, omeprazole, penicillin, cephalosporin, erythromycin. Red eyes from eye drops containing PEG. Vomiting from laxative. | Negative                         | Late onset maculopapular exanthema (mild)                             |
| 36  | 70–80        | F   | Anaphylaxis to different vaccines (tetanus, polio, mumps)                        | Negative                         | No reaction                                                           |
| 37  | 50–60        | F   | Urticaria to penicillin, angioedema to influenza vaccine, large local reactions to ointments containing polyethylene glycol | Negative                         | No reaction                                                           |

Note: Abbreviations: F, female; M, male, SPT is skin prick test.
Correspondence
Âgnes Csuth and Lennart Nilsson, Department of Biomedical and Clinical Sciences, Allergy Center, Linköping University, Linköping.
Email: agnes.csuth@regionostergotland.se; lennart.j.nilsson@regionostergotland.se

ORCID
Âgnes Csuth https://orcid.org/0000-0003-0082-0431
Anna Nopp https://orcid.org/0000-0003-1389-8676
Lennart Nilsson https://orcid.org/0000-0002-5680-6367
Maria C. Jenmalm https://orcid.org/0000-0002-2117-5366

REFERENCES
1. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. N Engl J Med. 2021;384:643-649. doi:10.1056/NEJMr2035343
2. Turner PJ, Ansotegui IJ, Campbell DE, et al. Covid-19 vaccine-associated anaphylaxis: a statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J. 2021;14:100517. doi:10.1016/j.waojou.2021.100517
3. Nilsson L, Csuth Â, Storsaeter J, Garvey LH, Jenmalm MC. Vaccine allergy: evidence to consider for COVID-19 vaccines. Curr Opin Allergy Clin Immunol. 2021;21(4):401-409. doi:10.1097/ACI.0000000000000762
4. Rasmussen TH, Mortz CG, Georgsen TK, Rasmussen HM, Kjaer HF, Bindslev-Jensen C. Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. Clin Transl Allergy. 2021;11:e12044. doi:10.1002/cti.12044
5. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CAJr, Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: don’t give up on the second dose! Allergy. 2021;76:2916-2920. doi:10.1111/all.14958
6. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Johansen JD, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. J Allergy Clin Immunol. 2022;149:100517. doi:10.1016/j.jaci.2021.05.020
7. Zhou Z-H, Stone CAJr, Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. J Allergy Clin Immunol Pract. 2021;9:1731-33.e3. doi:10.1016/j.jaip.2020.11.011
8. Nopp A, Johansson SGO, Ankerst J, et al. Basophil allergen threshold sensitivity: a useful approach to anti-IgE treatment efficacy evaluation. Allergy. 2006;61:298-302. doi:10.1111/j.1398-9995.2006.00987.x
9. Wolfson AR, Robinson LB, Li L, et al. First dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. J Allergy Clin Immunol Pract. 2021;9(9):3308-3320.e3. doi:10.1016/j.jaip.2021.06.010
10. Sellaturay P, Nasser SM, Islam S, et al. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. Clin Exp Allergy. 2021;51:861-863.

How to cite this article: Csuth À, Nopp A, Storsaeter J, Nilsson L, Jenmalm MC. COVID-19 vaccines and anaphylaxis—evaluation with skin prick testing, basophil activation test and Immunoglobulin E. Clin Exp Allergy. 2022;52:812-819. doi:10.1111/cea.14143