



Vaccine allergy: evidence to consider for COVID-19 vaccines

Lennart Nilsson^a, Ágnes Csuth^a, Jann Storsaeter^b, Lene H. Garvey^{c,d}, and Maria C. Jenmalm^e

Purpose of review

Whereas the COVID-19 pandemic has changed our lives worldwide, we hope that vaccination can combat the disease. We propose how to evaluate suspected severe allergic reactions to the vaccines so that as many as possible may be safely vaccinated.

Recent findings

Rare cases of severe allergic reactions after COVID-19 vaccination have been observed, seemingly at a higher frequency than for other vaccines. Few excipients are likely to have caused these reactions. IgE-mediated reactions to polyethylene glycol (PEG) and its derivatives are the most suspected, albeit hitherto unproven, causes. We suggest to make a diagnosis based on skin tests with PEG and PEG derivatives and that these be considered in relation to the decisions required before the first and the second vaccine dose. A vaccine without these excipients is available, but published data about its side effects are limited.

Summary

The underlying immunological mechanisms of the rare severe allergic reactions to the COVID-19 vaccines are poorly understood and need to be clarified. Identifying those who have an undiagnosed allergy to PEG and PEG derivatives is crucial before vaccination, and these substances are found in laxatives, cosmetics and in 30% of all our medications today.

Keywords

allergic reactions, anaphylaxis, COVID-19 vaccines, polyethylene glycol

INTRODUCTION

During the ongoing mass vaccination against SARS-CoV-2, rare cases of immediate allergic reactions of anaphylaxis have been observed [1***]. It is important that these patients are evaluated by an allergologist to obtain specific diagnoses and advice concerning future vaccinations. This article aims to facilitate evaluation of suspected serious allergic reactions to COVID-19 vaccines, including a thorough medical history and skin testing, with standard steps and guidelines.

The most severe allergic reaction to vaccines is anaphylaxis and different diagnostic criteria have been suggested. The widely used NIAID/FAAN criteria were published in 2006 [2] and has been updated by the World Allergy Organization (WAO) [3,4] for use in anaphylaxis of all causes. The Brighton Collaboration specifically developed guidelines, published in 2007, for adverse events after vaccinations. This guideline for anaphylaxis has three levels using a combination of symptoms to determine levels of diagnostic certainty rather than severity [5]. This is different from NIAID/FAAN and WAO's description, where the severity and the grading of

the severity are determined. While the Brighton Collaboration system has now been widely adopted worldwide in the assessment of reactions to the COVID-19 vaccines, information on sensitivity and specificity of this approach is lacking.

^aDepartment of Biomedical and Clinical Sciences, Allergy Center, Linköping University, Linköping, ^bDepartment of Vaccines, Public Health Agency of Sweden, Solna, Sweden, ^cAllergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital Gentofte, ^dDepartment of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark and ^eDivision of Inflammation and Infection, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

Correspondence to Lennart Nilsson, MD, PhD, Department of Biomedical and Clinical Sciences, Allergy Center, Linköping University, 581 85 Linköping, Sweden. Tel: +46 703 663125; e-mail: Lennart.J.Nilsson@regionostergotland.se

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KEY POINTS

- Rare cases of severe allergic reactions have been observed after COVID-19 vaccination, possibly at a higher frequency than for other vaccines.
- Reactions to, and possible allergenic excipients in, the vaccines from Pfizer/BioNTech, Moderna and AstraZeneca are described.
- We propose an evaluation strategy for patients with suspected severe allergy to excipients in COVID-19 vaccines.
- This evaluation is based on skin prick testing with PEG and derivatives, including polysorbate and poloxamer.
- We describe an approach to the patients who have reacted to the first dose of COVID-19 vaccine.

HISTORY OF VACCINATION AGAINST CORONAVIRUS INFECTION

Various coronaviruses cause symptomatic infections in domestic species such as dogs, cats, calves, pigs and chicken. Live and inactivated animal vaccines against coronaviruses have long been used in veterinary medicine, proving the feasibility of vaccination [6].

In humans, four different pathogenic human coronaviruses were identified in archived nasopharyngeal aspirates before 2002. The patients were typically reported to exhibit the mild respiratory symptoms known as the seasonal common cold. The viral strains are named HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 [7,8]. Successful human vaccines against these viruses have not been developed due to common mutations in these viral strains [9].

In 2002, a novel coronavirus, later named SARS-CoV, was reported from China in patients with atypical pneumonia and acute respiratory distress

syndrome (ARDS). This virus had high mortality and spread worldwide, but the disease was contained with public health measures only. A number of vaccine companies started research and development programmes against SARS, but these were generally terminated when SARS was eradicated from the human population in 2004 [9]. Immunological studies in SARS survivors have shown lasting T-cell immunity after 17 years [10].

In 2012, another pathogenic novel coronavirus appeared in the Middle East region. This virus – known as MERS-CoV, it is linked to high mortality due to atypical pneumonia, ARDS and renal failure. It is still circulating locally, but human-to-human transmission is limited.

SARS-CoV-2 virus causes the COVID-19 infection and is the seventh coronavirus known to infect humans and Chinese investigators released the genomic sequences of SARS-CoV-2 isolates on 10 January 2020. As some research groups had already established MERS-CoV or SARS-CoV as prototype pathogens to optimize vaccine design, delivery mechanisms and correlates of protection work on a vaccine was initiated almost immediately. In this way, the first human clinical trials on mRNA-vaccine formulated in lipid nanoparticles started as early as 16 March 2020 [11]. In the following months, clinical trials commenced with replication-incompetent adenovirus vector vaccine candidates and inactivated virus vaccines, and in May 2020 a recombinant spike-protein-based vaccine candidate was evaluated in clinical trials [9] (Table 1).

SERIOUS ADVERSE AND ANAPHYLAXIS EVENTS IN MASS VACCINATION PROGRAMMES

After UK emergency approval of the mRNA vaccine produced by Pfizer/BioNTech, BNT16262, BioNTechManufacturing GmbH Mainz Germany and

Table 1. COVID-19 vaccines mentioned in the text and used for mass vaccination in Europe

Product type	Manufacturer and name	Suspected culprit allergen
mRNA vaccine	Pfizer/BioNTech, BNT16262, BioNTechManufacturing GmbH Mainz Germany and Pfizer Manufacturing GmbH Puurs, Belgium, 'Comirnaty' COVID-19 Vaccine Moderna, Moderna Biotech Spain, Madrid, Spain	Polyethylene glycol (PEG-2000)
Adenovirus vector vaccine	AstraZeneca, AZD1222, AstraZeneca AB, Södertälje, Sweden, 'Vaxzevria' COVID-19 Vaccine Janssen, Ad26.COVS-S, Janssen-Cilag International NV, Beerre, Belgium Sputnik V, Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia	Polysorbate 80
Inactivated virus	BBIBP-CorV, Beijing Institute of Biological Products, Beijing, China, 'Sinopharm'	
Recombinant spike protein	Novavax COVID-19 Vaccine, NVX-COV2373, Novavax Inc, Gaithersburg, Maryland, USA	Polysorbate 80

Note: BBIBP-CorV does not contain polyethylene glycol or polysorbate 80. PEG, polyethylene glycol.

Pfizer Manufacturing GmbH Puurs, Belgium, “Comirnaty” (Table 1), mass vaccination of healthcare workers (HCWs) and high-risk patients against COVID-19 started on 8 December 2020. The next day two cases of anaphylaxis were reported among two female HCW. On 11 December, emergency use authorization was issued in the United States for Comirnaty, and six further cases were reported in the following week (<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/slides-12-19/05-COVID-Clark-508.pdf>; [12²²,13]). Before the start of the mass vaccine programmes against COVID-19, serious allergic reactions and anaphylaxis in connection with vaccines were regarded as extremely rare adverse events, with an overall risk estimate of 1.31 per million doses and with rather narrow 95% confidence intervals of 0.9–1.8, defined by Brighton level 1 and 2. Reactions occurred most often in women with 80% being women [14,15]. Increased rates of severe reactions in women were also observed for the COVID-19 mRNA vaccines [12²²]. The severe hypersensitivity symptoms mostly started within 10–30 min of exposure. The most common symptoms were urticaria, itching, flushing, general discomfort, angioedema, breathlessness, burning sensation and fainting [12²²].

Studies have confirmed initial suspicions and suggested that the incidence of anaphylaxis after mRNA vaccine against COVID-19 is somewhat higher than previously expected, but with very low mortality. The initial Vaccine Adverse Event Reporting System (United States) estimate for Comirnaty using the international standard case definition from Brighton Collaboration [5] is 4.7 cases per 1 million vaccine doses [12²²]. Initial safety signals were based on spontaneous reports influenced by awareness of a potential safety concern for the vaccines, potential underestimation of the denominator but also increased focus on this first vaccine. Even for a more recently licensed mRNA vaccine against COVID-19 produced by Moderna, the incidence of anaphylaxis immediately postvaccination appears higher than expected, at 2.5 per million doses [16,17].

As of end of March 2021, the United Kingdom had vaccinated 10.9 million people with Pfizer’s vaccine and had administered 13.7 million doses of AstraZeneca’s (AstraZeneca, AZD1222, AstraZeneca AB, Södertälje, Sweden) chimpanzee adenovirus vaccine, containing double-stranded DNA coding for the spike protein of SARS-CoV-2 (Vaxzevria). For 9 December 2020 to 8 April 2021, no evident significant differences existed in the reporting rate for anaphylaxis (spontaneous reports); 259 reports for the Pfizer vaccine (24 per million doses) and 455 reports for the AstraZeneca’s vaccine (23 per million

doses) [18]. Information of side effects of the vaccines have been given by healthcare professionals.

The Russian adenovirus vector vaccine, Sputnik V, is based on a similar platform to the AstraZeneca vaccine (using two human adenoviral vectors, Ad5 and Ad26), and is currently being used for mass vaccination in Serbia and Hungary. Both countries have also used an inactivated whole virus vaccine, Sinopharm, BBIBP-CorV. The two latter vaccines have been used consistently for many months in mass vaccination programmes in Russia, Middle East and China, but hitherto no vaccine-specific data on serious adverse events and anaphylaxis post vaccination has been presented.

A recently licensed single-dose adenovirus vector (Ad26) vaccine from Janssen Vaccine will be used in European mass vaccination programs from April 2021. The vaccine is reported to be less reactogenic than the two mRNA vaccines used in the United States, and no reports of anaphylaxis have emerged from the clinical phase 2/phase 3 studies. However, no such reactions were reported in the phase 2/phase 3 trials for the mRNA vaccines from Pfizer/BioNTech and Moderna. Of note, in the phases 1–3 clinical trials of the Pfizer/BioNTech and Moderna mRNA vaccines, anyone with a history of allergic reaction to any component of the vaccine was excluded, as were those with a history of severe allergy associated with any vaccine [19,20]. Similar exclusion criteria were used in the Janssen and AstraZeneca phase 3 trials (<https://www.jnj.com/coronavirus/ensemble-1-study-protocol>; [https://www.thelancet.com/cms/10.1016/S0140-6736\(20\)32661-1/attachment/87a97e27-03d4-40c9-8498-7e513e08d265/mmc2.pdf](https://www.thelancet.com/cms/10.1016/S0140-6736(20)32661-1/attachment/87a97e27-03d4-40c9-8498-7e513e08d265/mmc2.pdf)).

EXCIPENTS IN THE VACCINES POTENTIALLY CAUSING ANAPHYLAXIS

Allergic reactions to vaccines are usually caused by an inactive ingredient or excipient [21]. It is still unclear whether excipients caused the anaphylactic reactions observed after administration of the COVID-19 vaccines [1²²]. However, polyethylene glycol (PEG, in mRNA vaccines) and its derivatives including polysorbate 80 (in viral vector vaccines) have been suggested as potential culprit allergens (Table 1), possibly leading to more frequent anaphylactic reactions than to vaccines against other infectious diseases [22²³]. Recently, a group from the United Kingdom demonstrated PEG allergy in one of the first cases developing anaphylaxis to the Pfizer/BioNTech COVID-19 vaccine in the United Kingdom [24²²]. The patient had a previous history of anaphylaxis to other medication and milder reactions on exposure to other products suggestive of an

undiagnosed PEG allergy. While PEG has not been used in vaccines before, many widely used vaccines contain polysorbate 80 [25[■]].

Two of the seven vaccines presented in Table 1 are mRNA vaccines and contain PEG 2000 (Pfizer/BioNTech and Moderna). Other components are less likely to be allergenic [26[■]]. Polysorbate 80 is used in most other COVID vaccines in the market, that is, AstraZeneca's Vaxzevria, Janssen's vaccine, Sputnik V and the Novavax COVID-19 Vaccine (NVX-COV2373, Novavax Inc, Gaithersburg, Maryland, USA) [1[■],25[■]]. Polysorbates show cross-reactivity with PEG and structurally related polymers due to shared moieties [27]. However, Sinopharm, a Chinese inactivated virus vaccine, contains neither PEG nor PEG derivatives [25[■]].

Polyethylene glycols and other excipients that might cause anaphylaxis

PEGs are polymers of ethylene oxide and have varying molecular weights, between 200 and 35 000 g/mol. PEGs have many names, such as Macrogol and Laureth-9, and are found in a multitude of pharmaceutical and cosmetic products. In cosmetics, the number refers to its number of ethylene oxide units whereas molecular weight is referred to in pharmaceuticals. PEG 3350 is currently contained in more than 1000 FDA-approved medications and can be found in many tablets, topical gels, laxatives and parenteral steroids [27]. PEGylation is the conjugation of PEGs to drugs, leading to prolonged half-life in plasma and less immunogenicity without compromising clinical efficacy [28,29]. Polysorbate 80 is contained in nearly 7000 FDA-approved medications and is more commonly found in vaccines, parenteral steroids, immunoglobulin replacement and tablets [30]. The formulation of PEG in the mRNA vaccines is different from the PEG used most commonly in other healthcare products, both in molecular weight and due to its coformulation as a stabilizing portion of a liposome [31–33].

Severe reports of allergies to PEG have been published [27,33,34,35[■],36[■],37,38]. A review from 2016 reports 37 cases of anaphylaxis, describing the allergen as 'hidden' and overlooked, that is, people have had allergic reactions with severe symptoms to several unrelated products but connection to a seemingly inert excipient is not made. The main products containing PEG that cause anaphylaxis have been oral medications, such as analgesic tablets, antibiotic tablets, antacids and laxatives, followed by injections of depot steroids. Patients with drug allergy do not normally have an adrenaline autoinjector, however, for patients

with PEG allergy there is a risk of re-exposure and severe reactions, as it is not easy to avoid PEG. The patient should therefore get a written emergency plan and be issued with an adrenaline autoinjector [35[■],36[■]].

Due to low awareness of PEG allergy, patients reacting to healthcare, cosmetic or hygiene products or with severe reactions to, for example, antibiotics or laxatives have been misdiagnosed with idiopathic anaphylaxis or drug allergy to specific products [35[■],36[■],37,38]. Before being diagnosed with PEG allergy, 76–80% of the patients had experienced one or more episodes of anaphylaxis requiring adrenalin treatment [27,35[■]].

The vaccine from Moderna also contains tromethamine, an organic amine widely used in several medications for topical, enteral or parenteral administration. It is also used in cosmetics as an emulsifier. One case of anaphylaxis to tromethamine in a gadolinium-based contrast agent was reported in a 23-year-old woman; IgE-mediated trometamol allergy was detected in the patient [39]. Moreover, chlorhexidine, used to sterilize vaccine injection sites, may elicit allergic reactions. Specific IgE for chlorhexidine and skin testing may be used to establish a diagnosis [40–42].

Allergic reactions to polyethylene glycol with low and high molecular weight

Allergenicity to PEG seems to increase with increasing molecular weight and higher concentration [27,31,35[■],36[■],43[■],44,45,46[■]].

Patients diagnosed with PEG allergy find it challenging to avoid products containing PEG as PEG is very widely used. Establishing PEG molecular weight thresholds would be valuable, but presently there is not enough knowledge to provide general advice on this and patients should be warned against PEGs of all molecular weights unless they have tolerated exposure to lower molecular weights [35[■],46[■]].

An IgE-mediated mechanism for PEG allergy has been suggested [47]. Standardized tests to determine circulating IgE to PEGs are not commercially available, although detection of serum IgE to PEG 10 000 in patients with documented PEG-associated anaphylaxis was recently reported using a cytometric bead assay. PEG was linked to the beads with mouse anti-PEG IgG mAbs and IgE to PEG was not detected in healthy controls [43[■]]. Positive basophil activation tests or histamine release tests have also been reported in a few patients with documented anaphylaxis reactions to products containing PEG with varying results [35[■],46[■],48–50]. However, standardized methods are lacking. Whereas an

alternative mechanism underlying reactivity to PEG has also been proposed, that is, complement activation-related pseudo-allergy [51], evidence of complement activation as a mechanism for acute allergic reactions to PEG in humans is inconclusive [25^{27,33}]. Direct non-IgE-mediated activation and granulation of mast cells, via binding of the lipid nanoparticles to for example Mas-related G protein-coupled receptor X2 receptors, have also been proposed as potential mechanisms that require further investigation [52].

Investigation of patients suspected of an undiagnosed polyethylene glycol allergy or patients with severe allergic reactions to first dose of a COVID-19 vaccination

In case of immediate type reactions to the first dose of COVID-19 vaccine a blood sample taken 1.5–2 h after the reaction should be analysed for serum tryptase. Comparison with a baseline sample taken more than 24 h after resolution of symptoms should be performed. An elevation of serum tryptase more than $(\text{baseline} \times 1.2) + 2$ supports an IgE-mediated mechanism [53]. There are no data specifically addressing the use of serum tryptase in vaccination reactions, but it is used in other parts

of allergology, for example, when investigating insect venom, food allergy and perioperative allergy.

PEG and PEG derivatives such as polysorbate are testable components of the mRNA and adenovirus vector vaccines. Published data shows skin testing to be the investigation of choice to determine IgE-mediated allergy to these agents ([35³⁶,46⁴⁷]; <https://www.allergyandasthmacare.com/2021/04/updated-guidance-on-risk-of-allergic-reactions-to-covid-19-vaccines.html>). Although skin prick tests and intradermal tests have been used [27,36³⁷], due to the very low prevalence of PEG allergy their predictive value is still undefined, and standardized protocols are lacking. Severe allergic reactions have been described after intradermal testing with compounds containing PEG [36³⁷], and currently intradermal testing is not recommended [27]. Systemic reactions such as generalized urticaria, facial flushing and coughing, and rarely anaphylaxis, have been described during skin prick testing, especially with higher molecular weights [24²⁵,27,35³⁶,36³⁷,46⁴⁷].

Skin testing with undiluted vaccines might be another method of evaluating the patients, but its predictive value is unknown.

Hesselbach *et al.* [54] showed proportionality between molecular weight and skin prick test

Table 2. Skin prick test protocol for patients suspected to have a polyethylene glycol/polyethylene glycol derivative allergy

Skin prick test protocol. Low index of suspicion for allergy to PEG/PEG derivatives based on Ref. [46⁴⁷]

Positive/negative control

PEG 300 (100%)

PEG 3000 (50%)

PEG 6000 (50%)

Polysorbate 80 (20%)

Poloxamer 407 (10%)

Reading after 20 min for each SPT, all SPTs can be done the same time

Skin prick test protocol. High index of suspicion for allergy to PEG/PEG derivatives based on Ref. [46⁴⁷]

If any SPT is clearly positive further testing with higher MW is not necessary. Patients with positive SPT against PEG/PEG derivatives should avoid all medicines and other products containing PEG/PEG derivatives

Positive/negative control

PEG 300 (100%)

PEG 3000 (50%)

PEG 6000 (50%)

Polysorbate 80 (20%)

Poloxamer 407 (10%)

PEG 20 000 (0.01%)

PEG 20 000 (0.1%)

Stepwise method is recommended. Reading after 20 min for each step

MW, molecular weight; PEG, polyethylene glycol; SPT, skin prick test.

(SPT) reactivity. Other groups [27,46¹¹,47,55] indicate a need for testing several molecular weight PEGs. Moreover, SPT with lower molecular weight PEGs may require greater test concentrations to elicit a response [27,46¹¹,56]. Due to the risk of systemic allergic reactions on skin prick testing several groups recommend using a stepwise method, with gradually increasing molecular weights and concentrations of PEG; however, the data behind these recommendations originate from only few patients [27,36¹¹,37,46¹¹].

Wenande and Garvey [27] published a proposed algorithm for skin testing in 2016 which was very recently updated based on repeated skin testing over time in ten patients with verified PEG allergy [46¹¹]. This new algorithm is based on stepwise testing with increasing molecular weight PEGs starting with PEG 300 and stopping testing when a positive test is found. If testing on lower molecular weight PEGs is negative, increasing to using dilute solutions of PEG 20 000 has been shown to increase sensitivity of testing [46¹¹]. The study showed that skin test reactivity declines over time, so that the lower molecular weight PEGs may test negative, but higher

molecular weight PEGs in increasing concentrations can be used to make the diagnosis. To assess cross-reactivity to PEG derivatives skin prick testing with polysorbate 80 and poloxamer 407 is also recommended [46¹¹]. Intradermal tests should only be performed in SPT-negative patients and using diluted solutions [46¹¹].

Patients with a positive SPT against PEG or PEG derivatives are advised to avoid mRNA vaccines. The positive predictive values of SPT with PEGs and PEG derivatives is not known (<https://www.allergyandasthmacare.com/2021/04/updated-guidance-on-risk-of-allergic-reactions-to-covid-19-vaccines.html>), but suspected to be high based on a high number of negative controls (>350) from one centre [46¹¹].

Based on the limited evidence available in the literature, an approach to cases of probable PEG hypersensitivity suggested by the authors is described in Table 2 and for the patients who reacted to the first dose of COVID-19 vaccine in Table 3.

The guidelines of the Swedish Association for Allergology for COVID-19 vaccinations are described in Table 4 as an example of a national approach.

Table 3. A suggested approach to the patients who reacted to the first dose of COVID-19 vaccine

Mild side effects	
In case of mild side effects regardless of the interval after the first dose of COVID-19 vaccine such as headache, fever, tenderness in muscle, mild gastrointestinal symptoms etc.	Dose 2 of the same vaccine can be administered in any setting
Immediate reactions (within 4 h)	
Documentation of vital signs, blood pressure, saturation, chest auscultation, cutaneous symptoms, ear, nose and throat status is essential. Control tryptase	
Local reaction regardless of the size of the lesion	Dose 2 be administered in any setting
Verified anaphylaxis convincing clinical symptoms ± elevated serum tryptase	Dose 2 of the same vaccine is contraindicated. Should be referred for allergy evaluation. Dose 2 can be considered according to skin tests result and medical history in a setting with full resuscitation facilities; observation for at least 30 min is advised. Evaluate risk and benefit
Possible anaphylaxis or systemic symptoms such as urticaria, angioedema, severe gastrointestinal symptoms, rhinoconjunctivitis	Consider referral to allergologist/immunologist. Dose 2 can be considered according to skin tests result and medical history in a setting with full resuscitation facilities; observation for at least 30 min is advised. Evaluate risk and benefit
Delayed reactions (after 4 h)	
Documentation of vital signs, cutaneous and mucosal lesions, signs of organ failure, physical examination of the joints is advised. Skin biopsy can be considered in case of severe cutaneous/mucosal symptoms	
Delayed local reactions, even large exanthemas are described. Dose 2 can be administered in any setting, oral antihistamine or local steroid products can be used if itching and/or local tenderness occurs	
Mild systemic reactions such as urticaria, angioedema or maculopapular exanthema can be treated with antihistamine once or twice a day (e.g. desloratadine 5–10 mg). If the symptoms resolve, dose 2 can be administered in any setting. Observation for at least 30 min is advised. Premedication with antihistamine before dose 2 (e.g. desloratadine 5–10 mg) can be considered	
Patients with severe delayed systemic reactions such as extensive urticaria, angioedema, maculopapular exanthema, mucosal symptoms, arthralgia, suspected severe haematological differences, kidney or liver failure due to the vaccine should be referred to an allergologist/immunologist	

Table 4. Guidelines by Swedish Association for Allergology 30 April 2021

The following guidelines apply for evaluation and routines at vaccination with the three approved vaccines Comirnaty (Pfizer) and COVID-19 Vaccine Moderna (Moderna) and COVID-19 Vaccine Vaxzevria (AstraZeneca)

For all vaccinations	Remain at least 15 min after vaccination. Preparedness for anaphylaxis in place
For those with a severe allergic reaction to allergens such as food, insect stings, latex, contrast media, local anaesthetics or per oral medication (e.g. antibiotics)	Remain at least 30 min after vaccination. In addition to preparedness for anaphylaxis, emergency treatment should be available, including oxygen and access to peripheral venous catheterization (e.g. at a primary care centre)
For those with a severe allergic reaction to vaccines or other injected medication, or previous repeated anaphylaxis reactions to medications: evaluate/consider whether the person can have reacted to PEG or PEG derivative such as polysorbate or polyoxyl 35, castor oil. If no hypersensitivity exists to PEG or PEG derivatives	Consider the risk–benefit estimate for vaccination against COVID-19. Vaccination should be done at the hospital or specialist clinic with access to advanced hospital care if needed (including anaesthesia preparedness). Individual assessment of time for observation postvaccination
For those with a severe allergic reaction to PEG/polysorbate or polyoxyl 35 castor oil	Consider vaccination with a vaccine that does not contain PEG or PEG derivatives
Patient with systemic mastocytosis	Vaccination should be done at the hospital or specialist clinic with access to more advanced care if needed (including anaesthesia preparedness). Individual assessment for observation time after vaccination

*Severe allergic reaction relates to an adverse reaction in the patient's medical history that has required treatment at an emergency ward or hospitalization

PEG, polyethylene glycol.

CONCLUSION

COVID-19 vaccines have become available just a year after COVID-19 was first described, providing hope that vaccination can combat this pandemic. Although not yet proven, some rare adverse anaphylaxis events after vaccination may be attributed to PEG and PEG derivatives. Vaccines without PEG and polysorbate, for example, Sinopharm, are already being used for mass vaccination within the European Union and could be used for those with positive skin test to PEG or its derivatives if the adverse event profile is acceptable.

In the light of increased exposure to PEGs and polysorbates in our environment and increased awareness of this rare allergy, a greater incidence of PEG hypersensitivity could be expected in the next years. It is important to investigate patients with severe allergic reactions of unknown cause to identify the rare patients with PEG allergy. Impact on daily life was shown to be better after diagnosis.

As COVID-19 can cause such severe symptoms and vaccination against COVID-19 is a key global intervention, as many people as possible need to be safely vaccinated. The underlying immunological mechanisms of severe allergic reactions to the vaccines are poorly understood and urgently need clarification.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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