



Immunization practices and risk of anaphylaxis: a current update, comprehensive of COVID-19 vaccination data

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Purpose of review

This review aims to provide an updated report in regards to the correlation between vaccines and anaphylaxis and the related risk in the population.

Recent findings

Initial reports showed higher incidence of anaphylaxis following messenger RNA COVID-19 vaccines compared with 'routine' vaccinations, likely influenced by the great attention paid to these 'new' vaccines. However, anaphylaxis has still to be considered quite rare and its incidence will be systematically reconsidered in the light of additional data collected.

Summary

Adverse reactions to vaccines are commonly reported but most of them are nonspecific mild events, whereas vaccine-related anaphylaxis is considered a rare event, with an incidence rate equal to 1.3 cases per million vaccine doses administered. As anaphylaxis reports usually start to be reported to passive pharmacovigilance during postmarketing surveillance, the first data are used to be influenced by under- and over-reporting and lack of denominators and following studies are needed to confirm the causal relationship. This might create an initial overcautiously approach to new immunization practices but, being anaphylaxis a potential life-threatening event, every suspected contraindication has to be deepened to maximize effectiveness and safety profile and constantly redefined not to exclude an overestimated population group who could receive the vaccine uneventfully.

Keywords

anaphylaxis, COVID-19, vaccination, vaccine

INTRODUCTION

Routine immunization is one of the most effective public health interventions that has significantly reduced death and morbidity due to a variety of infectious diseases [1,2].

Nevertheless, vaccine hesitancy based on concerns about the decision to vaccinate oneself or one's children has risen up in the last decades [3,4] and clustering of vaccine refusal has contributed to outbreaks of vaccine-preventable diseases [4–7]. Controversies related to vaccine hesitancy have never been more actual than nowadays, due to the COVID-19 pandemic emergency and the need of immunizing the largest population in a short time. After the implementation of the COVID-19 vaccination programs, reports of many different adverse events following immunisation (AEFI) began to emerge, including anaphylactic reactions related mostly to messenger RNA (mRNA) vaccines. Consequently,

growing concerns about vaccine-safety and anaphylaxis risk raised both in the general and allergic population.

During the last decades, many Committees have analysed data and published recommendations, providing fundamental sources for safe vaccination practices. Such studies confirm the rarity of anaphylaxis after immunization, equal to 1.3 cases per million vaccine doses administered [8] and the need for a correct diagnostic framework in order to avoid inappropriate contraindications.

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KEY POINTS

- Adverse reactions to vaccines are commonly reported, but most of them are nonspecific mild events.
- Vaccine-related anaphylaxis is very rare, with an estimated rate of 1.3 cases per million 'routine' vaccines doses administered.
- Data from passive pharmacovigilance are influenced by under- and over-reporting, incomplete information and lack of denominators, hence, when safety signals are suspected, prospective studies are needed to confirm the causal relationship.
- Anaphylaxis rate after COVID-19 immunization has been reported higher when compared with routine vaccine rate but has still to be considered extremely rare.

This brief review aims to provide an update report in regards to the correlation between vaccines and anaphylaxis and the related risk in the population.

VACCINE-RELATED ANAPHYLAXIS

Adverse reactions to vaccines are commonly reported, but most of them are nonspecific mild events related to the immune response to injected material [9]. Hypersensitivity reactions following vaccination are not uncommon; however, these are often nonserious, and in many instances, they may not be IgE-mediated and not reproducible on re-exposure [8,10,11].

Anaphylaxis has been defined as a serious, generalized or systemic, allergic or hypersensitivity reaction that can be either life-threatening or fatal [12]. Nevertheless, the precise definition of anaphylaxis can vary between different Organizations, making comparison of data from different studies difficult. In 2007, the Brighton Collaboration (BC) published a standardized case definition to analyse data from epidemiologic studies and clinical trials for postvaccination anaphylaxis surveillance [13], which is considered the gold standard in vaccinovigilance. The BC criteria distinguish different levels of diagnostic certainty used primarily for epidemiologic studies and differ from the criteria for anaphylaxis

Table 1. The Brighton Collaboration case definition of anaphylaxis [13]

The Brighton Collaboration case definition of anaphylaxis			
Anaphylaxis is a clinical syndrome characterized by:			
•sudden onset AND •rapid progression of signs and symptoms AND • involving multiple (≥2) organ systems, as follow			
Level 1 of diagnostic certainty	Level 2 of diagnostic certainty		Level 3 of diagnostic certainty
•≥1 major dermatological and •≥1 major cardiovascular and/or ≥1 major respiratory criterion	•≥1 major cardiovascular and ≥1 major respiratory criterion or •≥1 major cardiovascular or respiratory criterion and •≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) or •(≥1 major dermatologic) and (≥1 minor cardiovascular and/or minor respiratory criterion)		•≥1 minor cardiovascular or respiratory criterion and •≥1 minor criterion from each of ≥2 different systems/categories
Major criteria			
Dermatologic or mucosal	•Generalized urticaria (hives) or generalized erythema •Angioedema, localized or generalized •generalized pruritus with skin rash		
Cardiovascular	•Measured hypotension •Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: •Tachycardia •Capillary refill time > 3s •Reduced central pulse volume •Decreased level of consciousness or loss of consciousness		
Respiratory	•Bilateral wheeze (bronchospasm) •Stridor •Upper airway swelling (lip, tongue, throat, uvula, or larynx) •Respiratory distress—2 or more of the following: •Tachypnoea •Recession •Increased use of accessory respiratory muscles •Cyanosis •Grunting		
Minor criteria			
Dermatologic or mucosal	•Generalized pruritus without skin rash •Generalized prickle sensation •Localized injection site urticaria •Red and itchy eyes		
Cardiovascular	•Reduced peripheral circulation as indicated by the combination of at least 2 of •Tachycardia •Capillary refill time > 3s without hypotension •Decreased level of consciousness		
Respiratory	•Persistent dry cough •Hoarse voice •Difficulty breathing without wheeze or stridor •Sensation of throat closure - Sneezing, rhinorrhea		
Gastrointestinal	•Diarrhoea •Abdominal pain •Nausea •Vomiting		
Laboratory	•Mast cell tryptase elevation upper normal limit		

Table 2. Clinical criteria for diagnosing anaphylaxis, Sampson *et al.* [14]**Anaphylaxis is highly likely when anyone of the following 3 criteria are fulfilled:**

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF^a, hypoxemia)
- Reduced BP^b or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

Reduced BP after exposure to known allergen for that patient (minutes to several hours):

- Infants and children: low systolic BP specific for age or greater than 30% decrease in systolic BP
- Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

^aPEF, Peak expiratory flow.

^bBP, blood pressure.

commonly used in clinical settings published by Sampson *et al.* in 2006 [14] and endorsed by other Organizations [15,16]. The BC and the Sampson *et al.* clinical criteria are summarized in Tables 1 and 2.

The first step in determining whether or not a patient has suffered an anaphylactic reaction due to a vaccine is to determine whether the nature and timing of the event are consistent with this diagnosis [17]. Most episodes of anaphylaxis occur with a sudden onset and rapid progression [12] and, although in most cases symptoms start within one hour from immunization [8], reactions occurring more than two hours after exposure have been described even if uncommon and the causal relationship is unclear [10]. The AAAAI and ACAAI Joint Task Force on Practice Parameters advised considering events with onset within 4 h of vaccine administration as possibly consistent with anaphylaxis [17], same timeframe reported from Dreskin *et al.* [8].

Despite expressing common clinical features, the underlying mechanisms of anaphylaxis may vary [18]. IgE-mediated anaphylaxis is considered the classic and most frequent mechanism. Non-IgE-mediated anaphylaxis may be either immunologic or nonimmunologic. The most relevant non-IgE-mediated immunologic mechanisms may involve the activation of pathways such as the complement system with anaphylatoxins, C3a, and C5a [19], the contact and coagulation system activation [20,21] or immunoglobulin G (IgG)-mediated anaphylaxis [22–25].

Since vaccine-related anaphylaxis is very rare, it usually starts to be reported to passive pharmacovigilance during postmarketing surveillance in which data might be influenced by under- and over-reporting, incomplete information and lack of denominators. Thus, when safety signals are suspected, prospective studies are needed to confirm the causal relationship,

identify the responsible component and delineate potential risk factors [26–27,28^{***}]. Recently, Miller *et al.* assessed current Vaccine Adverse Event Reporting System sensitivity for anaphylaxis ranging from 13% to 76% [29^{*}]. Consequently, a correct diagnostic framework performed by allergists or immunologists expert in vaccine allergy is of utmost importance and necessary for further vaccination management.

A number of immediate adverse events following immunization could be misdiagnosed as anaphylaxis as indicated in Table 3, differential diagnosis and alternative potential triggers should always be considered whenever an episode appears to coincide with vaccine administration. Typically, vasovagal symptoms might mimic an anaphylactic reaction causing syncope but are preceded by bradycardia and pallor as opposed to tachycardia and flushing typical of anaphylaxis instead, vocal cord spasm can cause stridor and dyspnoea, whereas panic attacks can cause dyspnoea and other symptoms [30^{***}]. In children, also hypotonic hyporesponsive episodes should be considered according to reported manifestations [8].

EPIDEMIOLOGY AND AETIOLOGY OF ANAPHYLAXIS AFTER IMMUNIZATION

In the USA, the rate of anaphylaxis from any causes is as high as 100 cases per 100,000 populations and is associated with as many as 1,000 deaths per year [31]. In contrast, serious postvaccination immunologically mediated reactions, including anaphylaxis, are considered exceedingly rare. In a comprehensive review, Dudley *et al.* [28^{***}] reported anaphylaxis as one of the AEFI in confirmed causal relationship with vaccines with an attributable risk after most commonly administered vaccinations estimated to

Table 3. Manifestations and disorders to be considered in case of suspected anaphylaxis**Differential diagnosis of anaphylaxis**

- Vasovagal reactions	- Neurologic diseases (seizure/stroke)
- Panic attacks	- Cardiovascular process (myocardial infarction, embolism)
- Vocal cord dysfunction	- Capillary leak syndrome
- C1 inhibitor deficiency syndromes (hereditary and acquired)	- Dehydration
- Pheochromocytoma	- Hypotonic Hyporesponsive Episodes (HHE) (in children)
- Hypoglycemia	

occur at a rate of 1 per 100,000 to 1 per 1,000,000 [8] depending from the considered vaccine. A study on healthcare data from the Vaccine Safety Datalink (VSD) [32] identified 33 cases that met BC case definition corresponding to an average rate of 1.3 cases per million vaccines doses administered, the most related to influenza vaccination, with a non-significant female predominance.

In regard to vaccine-specific anaphylaxis, limited data are available due to the scarcity of population-based studies and multiple co-administered vaccines make identification of causal component difficult. Any vaccine can potentially be the cause of anaphylaxis. Reports published after the introduction of new vaccines in mass vaccination campaigns provided specific data: an incidence rate of anaphylaxis after Human Papillomavirus vaccines (HPV) of 2.6/100,000 doses was estimated in Australian adolescents; for 2009 pandemic adjuvanted H1N1 vaccine a rate of 8/million doses in Canada and 1.4/million doses for unadjuvanted vaccine in the USA were reported [33]. McNeil *et al.* from the VSD study estimated the rates of anaphylaxis equal to 1.35 after trivalent influenza vaccine, 1.83 after monovalent influenza vaccine and 0.51 following tetanus-diphtheria-acellular pertussis per million doses administered [11].

Vaccines contain whole organisms or parts of them and/or inactivated toxins (toxoids) that induce protective immune responses. These microbial antigens are rarely cause of immediate hypersensitivity reactions, mostly directed to other components, which have been reported in the past years to be likely responsible for anaphylaxis to some brand of vaccines: residual media substances used to grow the organisms as porcine or bovine gelatine in some Measles, Mumps and Rubella, Varicella vaccines and others; traces of ovalbumin from hen's egg present in yellow fever, influenza, tick-borne encephalitis and some rabies vaccines; residual yeast proteins (*Saccharomyces cerevisiae*) in Hepatitis B (HBV) and

HPV vaccines, trace amounts of antibiotics or latex from vaccine vial stoppers or syringe plungers [8,10,17,34]. Hence, in evaluating a suspected allergic reaction to a vaccine, it is necessary to be aware of the components, excipients and the possible presence of latex [10]. Vaccine composition may vary over time and can be consulted on the summary of product characteristics and continuously updated online databases [35].

As regards immunization in patients with a history of allergic reactions to allergens also contained in vaccines, during the past decade alert signals about specific allergy and vaccine have been deepened and reconsidered and the actual recommended approaches for patients with a history of allergic reactions to principal allergens in vaccines are listed in Table 4.

COVID-19 VACCINE AND RISK OF ANAPHYLAXIS IN REAL SETTINGS

In the last months, scientific literature about immunization safety focused on new mRNA vaccine anti-SARS-CoV-2, highlighting concerns about the risk of allergic reactions including anaphylaxis [37]. Immediately after the introduction of the first vaccine approved to prevent COVID-19 (produced by Pfizer-BioNTech) began in UK in December 2020, two or possibly three anaphylactic reactions following vaccination were reported. The vaccine was subsequently given emergency use authorization by the US Food and Drug Administration and again within days, there were reports of at least two anaphylactic reactions [30²²], suggesting a provisional rate higher than that recorded with 'conventional' vaccines. Rare adverse events not identified during clinical trials have to be expected, regardless of the speed of development, with all drugs, vaccines, and medicinal products and, as stated before, when a potential signal for an AEFI is detected, controlled epidemiological studies are needed to determine if there is an increased risk in vaccinated subjects compared with those who did not receive the vaccine [28²²].

At the end of January 2021, the estimate rate of anaphylaxis after the first dose of the two mRNA vaccines in the USA were 4.7 and 2.5 per million Pfizer/BioNTech and Moderna vaccine doses administered, respectively [33,38,39]. Anaphylactic reactions to COVID-19 vaccines have also been reported to the Italian Pharmacovigilance System and out of 410 reports of immediate allergic reactions evaluated by experts, 80 cases met BC anaphylaxis case definition [40]. The estimated anaphylaxis rate for Pfizer/BioNTech product corresponded to 9.7 per million doses, with a rate of 10.9 after first dose and of 6.1 after the second dose. The overall reporting rate

Table 4. Recommended approaches for patients with a history of allergic reactions to principal allergens also contained in vaccines [9,17,36]

Components	Vaccines	Recommendations
Egg (ovalbumin)	Yellow fever	Skin test recommended with the vaccine and if positive, administer in graded doses under observation.
	Influenza	Egg allergy is actually not considered a contraindication due to the too small amount of egg protein contained (<1 µg). Skin test not recommended. Prolonged observation period (30 min).
	MMR	Skin test not recommended. Administer under standard conditions.
Gelatine	MMR Varicella	Potential contraindication. Allergy to mammalian-derived gelatine is considered the main cause of allergic reactions after MMR. When necessary, skin test with gelatine and vaccine and if positive, administer in graded doses under observation. Preparations without gelatine proteins to be preferred when available.
	Varicella Zoster live attenuated; Typhoid Vaccine live oral	Potential contraindication. When necessary, skin test with gelatine and vaccine and if positive, administer in graded doses under observation. Preparations without gelatine proteins to be preferred when available.
Yeast	Hepatitis B; Quadrivalent HPV	Contraindicated. When necessary, skin test with yeast and vaccine and if positive, administer in graded doses under observation.
Antibiotics (gentamicin, neomycin, kanamycin and streptomycin)	Varicella Zoster live attenuated; Hepatitis A; MMR; Varicella; Rabies; Inactivated polio vaccine; Tick-borne encephalitis.	If anaphylactic reaction is reported the vaccine is contraindicated. In case of previous history of contact dermatitis vaccines are not contraindicated when the antigen is present in trace amounts.

MMR, Measles, Mumps and Rubella.

after three months of use of Pfizer, Moderna, and lately AstraZeneca products was 8.8 per million doses.

The initial focus has been on the suspicion for an augmented risk of anaphylaxis in patients having a history of prior allergic reactions to any antigens in the majority of cases, due to early reports indicating presenting a high percentage of prior anaphylaxis episodes in such patients [33]; currently according to the Centers for Disease Control and Prevention (CDC) [41], a history of allergy to food, environmental, venom, latex and oral medications are listed as not being contraindications to Covid-19 vaccine administration. However, the precaution for a 30-min observation period in people who experienced anaphylaxis due to any cause has been recommended [41]. Early data also showed a gender unbalance, since over 90% of patients presenting with anaphylaxis to the mRNA vaccines were females [42], this is of uncertain significance considering that vaccination started in healthcare workers were female are predominant and more data from vaccine reactogenicity in general population are needed.

The first two COVID-19 vaccines approved were 'novel' mRNA vaccines, and reactions have been reported after the first dose, which would exclude the patients having had a prior exposure necessary for the production of IgE antibodies. However, it is possible that the patients were sensitized to some component of the vaccine to which they had been previously exposed [30²²]. Although COVID-19

mRNA vaccines are new, most of their ingredients have been used extensively in a wide variety of medical and nonmedical products, a fact that increases the likelihood of sensitization in the genetically predisposed population to some of these components [30²²]. Any component of a vaccine has the potential to cause adverse reactions and both vaccines contain mRNA, lipids, polyethylene glycol (PEG)-2000, electrolytes, sugar (sucrose), and a saline diluent, neither contain food products or preservatives and there is no latex in vial stoppers. Among the listed components, few clinical cases of hypersensitivity to PEG had been reported prior to the current pandemic era [43,44], thus, PEG has been suspected to be the primary culprit of the cases of severe allergic reaction to the vaccine [45–47]. It is widely used in oral and injectable medications and bowel preparations, cosmetics and foods and, although PEG allergy is very rare, such exposure could explain how a patient may be sensitized to PEG prior to COVID vaccination [30²²].

Although the early focus has been on PEG as a possible allergen, alternative substances or mechanisms of these reactions might be revealed [30²²]. The aetiology of anaphylaxis in these cases is not fully understood and is still an open area of active research. To note, in contrast to what would be expected in regards to a suspicion for an allergic IgE-mediated pathogenesis, reporting rate of anaphylaxis was higher after the first dose than after the

Table 5. Composition of COVID-19 vaccines authorized for emergency use by Food and Drug Administration (FDA) in US and authorized for use in EU by European Medicines Agency (EMA)^a. Potential allergens responsible for suspected hypersensitivity reactions are in bold

VACCINES AND MANUFACTURERS				
	Comirnaty - Pfizer/ BioNTech	mRNA 1273 -Moderna	Vaxzevria - Oxford/ AstraZeneca	Janssen - Johnson & Johnson
Composition	Single-stranded, 5'-capped messenger RNA (mRNA) encoding the viral spike (S) protein of SARS-CoV-2.	Single-stranded, 5'-capped messenger RNA (mRNA) encoding the viral spike (S) protein of SARS-CoV-2.	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S), not less than 2.5×10^8 infectious units (Inf.U).	Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S), not less than $8.92 \log_{10}$ infectious units (Inf.U).
Lipid nanoparticle	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315); 2-[[poly(ethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159); 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); Cholesterol.	Lipid SM-102; Cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG);	//	//
Excipients	Potassium chloride; Potassium dihydrogen phosphate; Sodium chloride; Disodium phosphate dihydrate; Sucrose; Water for injections.	Tromethamol; Tromethamol hydrochloride; Acetic acid; Sodium acetate trihydrate; Sucrose; Water for injections.	L-Histidine; L-Histidine hydrochloride monohydrate; Magnesium chloride hexahydrate; Polysorbate 80 (E 433); Ethanol; Sucrose; Sodium chloride; Disodium edetate (dihydrate); Water for injections.	2-hydroxypropyl- β -cyclodextrin (HBCD); Citric acid monohydrate; Ethanol; Hydrochloric acid; Polysorbate-80; Sodium chloride; Sodium hydroxide; Trisodium citrate dihydrate; Water for injections.

^aLast update on May 25th 2021.

second dose and it might be possible that a non-IgE mediated mechanism could be implicated, such as complement activation resulting in anaphylaxis-like symptoms as described to various liposomal drugs, most importantly pegylated liposomal doxorubicin [48], and to oversulfated chondroitin sulfate (OSCS) [49]. Reports of adverse reactions to heparin were linked to exposure to OSCS, which was found to induce kallikrein activity and activate the contact system that resulted in anaphylaxis-like symptoms [50]. Although these hypotheses are speculative, alternative mechanisms deserve further investigation. Furthermore, the implications for use of SARS-CoV-2 vaccines with an adenovirus carrier and protein subunit, which contain polysorbate 80, a non-ionic surfactant and emulsifier that has a structure similar to PEG, are also currently unknown [51[■]]. Table 5 shows the composition of COVID-19 vaccines actually approved in Europe and the USA with potential allergens responsible for hypersensitivity reactions. The higher rate of anaphylaxis from the early reports in respect to other 'conventional' vaccines, maybe influenced by the great attention paid to these new vaccines, has to be considered still quite rare and its incidence will be likely

reconsidered in the light of additional data collected and prospective studies. The reported cases of anaphylaxis raise more questions than they answer; however, such safety signals are almost inevitable as we embarked on vaccination of millions of people, and they highlight the need for a robust and proactive 'safety roadmap' to define causal mechanisms, identify populations at risk for such reactions, and implement strategies that facilitate management and prevention [51[■],52,53[■],54].

CONCLUSION

Routine immunization is a highly effective public health intervention which in the last decades has permitted to significantly reduce death rate and morbidity due to a variety of infectious diseases, whereas growing unwarranted fear and uncertainty can result in incomplete vaccination coverage for children and adults.

In real life settings, whereas the number of reported possible allergic reactions to vaccines may be high, confirmed vaccine-triggered allergic reactions are infrequent and anaphylaxis is considered a very rare event after immunisation practice.

Whereas by definition anaphylaxis is a life-threatening event, every potential contraindication has to be considered prior to immunisation and adequate management of subjects at increased risk must be planned according to existing recommendations. By the way, it has to be taken into account that is almost always successfully treated and its risk must be weighed against leaving patients unvaccinated and therefore susceptible to a potentially life-threatening disease, as COVID-19, with a much elevated risk of incidence. Nonetheless, expertise and equipment for treating anaphylaxis should always be available when immunizing.

First data from COVID-19 immunization safety profile reports refer a higher rate of anaphylaxis when compared with the anaphylaxis rate of 1.3 cases per million 'conventional' vaccines doses administered, rate that, however, remain quite low. Such safety signals are almost inevitable as we embark on mass vaccination. We are now into a critical phase of COVID-19 control: millions if not billions of people worldwide have been and will be exposed to new vaccines, starting from different priority subgroups of the population, and it is highly probable that at least a booster dose will be required. Thus, it is imperative to empower a systematic and evidence-based approach to vaccination to maximize effectiveness and safety at an individual and a population level. Investigations into the reported anaphylactic reactions to novel mRNA COVID-19 vaccines are crucial and need to proceed in a timely and thorough manner to narrow down the group of patients, for whom the vaccine is contraindicated or should be administered with special precautions, to the smallest appropriate number and not to exclude those who could receive the vaccine uneventfully and be protected against this life-threatening disease.

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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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- This article distinguishes patients into specific risk clusters for suspected allergy to PEG or polysorbate, with the aim of avoiding overdiagnosis of anaphylaxis risk while safely vaccinating.