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REVIEW ARTICLE

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A practical guide to address reactions to vaccines in children

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Abstract

Currently available vaccines are safe, but, potentially, any vaccine can cause an allergic reaction and, albeit very rare, anaphylaxis can occur. Although its rarity, the precise diagnostic management of a suspected anaphylaxis postvaccination is of paramount importance due to the risk of a potentially serious reaction after re-exposure, while a misdiagnosis might lead to an increase in the number of children that interrupt vaccinations resulting in an unjustifiably individual and collective risk of loss of protection against immune preventable diseases. In the light that most cases of suspected allergy to a vaccine are not effectively confirmed in up to 85% of the cases referred for an allergy evaluation, patients can continue the vaccination schedule with the same formulation and tolerance of the booster doses. The patient assessment has to be done by an expert in the vaccine field, usually an allergist or an immunologist depending on the country, to select subjects at risk of allergic reactions and to perform the correct procedures for vaccine hypersensitivity diagnosis and management, in order to guarantee safe immunization practices. The aim of this review is to provide a practical guidance for the safe management of allergic children undergoing immunization procedures. The guide is referred both to the evaluation of children who have previously experienced a suspected allergic reaction to a specific vaccine and their management in case of further booster doses, and to children allergic to a component of the vaccine to be administered.

KEYWORDS
allergic reactions, anaphylaxis, drug allergy, excipients, hypersensitivity reactions, vaccine components, vaccines, vaccine allergy

1 | INTRODUCTION

Although approved vaccines have been rigorously tested for safety, anaphylactic reactions, albeit very rare, can occur,[1] and potentially, any vaccine can cause an allergic reaction. According to the Institute of Medicine, epidemiologic and mechanistic evidence support a causal relationship between several vaccines and anaphylaxis, including those for measles, mumps, and rubella (MMR), varicella, influenza, hepatitis B, meningococcus, human papillomavirus, and the combined diphtheria, tetanus, pertussis vaccine.[2] Of note, most cases of suspected allergy to a vaccine are not effectively confirmed in up to 85% of the patients referred for an allergy evaluation, and patients can continue vaccination with the same formulation and tolerance of the booster doses.[3]

An analysis of reported anaphylaxis to the Vaccine Adverse Event Reporting System (VAERS) in the United States over a 26-year period found that out of almost 500,000 reports, only 828 were classified as anaphylaxis based either on physician's diagnosis or according to the Brighton Collaboration case definition.[4] Similarly, a 2016 study used health data from the Vaccine Safety Datalink

and found altogether 33 confirmed cases of anaphylaxis after 25,173,965 vaccine doses and an anaphylaxis rate of 1.31 per million vaccine doses.[5] In children, Gold et al.,[6] demonstrated that only 10% of reported generalized allergic reactions developed a reaction on re-exposure and that most of these reactions were not suggestive of a hypersensitivity reaction.

Allergic reactions after vaccination can be due to any of the vaccine components such as microbial antigens, adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, residual antibiotics, cell-culture materials and inactivating ingredients. Consequently, knowing all vaccine components is the starting point in evaluating the suspected adverse reaction.

In clinical practice we face two distinct situations, which pose specific related challenges: (I) children with a suspected allergic reaction to a vaccine: It is necessary to evaluate whether the reaction is allergic or not and how to manage the need to complete the immunization schedule; (II) children with a history of allergy to a vaccine component: It is necessary to assess the safety of administering that specific vaccine.

A correct management of suspected allergic reactions is crucial in terms of overall health care, both for the individual and for the community, constituting a potential risk of increased vaccine hesitancy, especially in light of that most of these patients are falsely labeled as allergic.

The aim of this review is to provide the means for a practical approach in the everyday clinical setting in regard to vaccines and allergy.

Key message

The purpose of this review is to provide clinicians with a concise and practical review, which summarizes how to manage allergic children who have to undergo immunization practices in the clinical setting. For this reason, the manuscript is divided into two parts: The first one concerns the clinical aspects of allergic reactions to vaccines, while the second is about the management of children with (a) a suspected allergic reaction to a previous vaccine and the need to continue the vaccination schedule, and (b) with a history of allergy to a vaccine component.

2 | PART I—CLINICAL ASPECTS

2.1 | Immediate reactions

Immediate hypersensitivity reactions to vaccines are rare, with a frequency that varies between 1 per 50,000 and 1,000,000 doses.[7,8] They typically occur between a few minutes and up to 4 h after vaccination, and immediate urticaria is the most frequent manifestation occurring four times more frequently than anaphylaxis.[9] Other skin reactions include erythema, isolated pruritus, and angioedema especially involving the face and lips. Respiratory symptoms, such as rhinoconjunctivitis, sensation of throat closure, dyspnea, and wheezing are less commonly reported.[10]

Anaphylaxis is defined, according to EAACI[11] as a life-threatening reaction characterized by acute onset of symptoms involving different organ systems and requiring immediate medical intervention and, when suspected to be vaccine-related, has to be evaluated according to the Brighton Collaboration Working Group Criteria recently reviewed with emphasis on objective symptoms and signs.[12] They define anaphylaxis as the involvement of at least two organs and provide a combination of major and minor criteria for classifying increasing levels of diagnostic certainty differing from Sampson et al. anaphylaxis clinical criteria commonly used in clinical settings.

Overall, being characterized by a broad range of possible symptoms, a number of immediate adverse events following immunization could be misdiagnosed as anaphylaxis and differential diagnosis, and alternative potential triggers have always to be considered whenever an episode appears to coincide with vaccine administration,[13,14] see Table 1.

Since post-vaccination anaphylaxis is very rare, it usually starts to be reported to passive pharmacovigilance during postmarketing surveillance and data are often influenced by under- and over-reporting, incomplete information, and lack of denominators.[13] Recently, Miller et al. assessed current VAERS sensitivity for anaphylaxis ranging from 13% to 76%,[15] which highlights the need for a correct diagnostic framework performed by allergists or immunologists expert in vaccine allergy for correct vaccination management. Being rare, the incidence varies among different studies: In a study population consisting of children and adolescents, Bohlke et al.[16] reported 5 cases of anaphylaxis after administration of 7,644,049 vaccine doses, for a risk of 0.65 cases/million doses; while, McNeil et al.[5] identified 18 cases of anaphylaxis after administration of 12,403,201 vaccine doses to 0–17 age groups, for an incidence rate of 1.45 cases per million vaccine doses.

Management of anaphylaxis in the setting of vaccine administration follows the same indications as anaphylaxis in any other clinical setting, and is thoroughly reviewed in the EAACI anaphylaxis guidelines.[11]

Although rare, the precise diagnostic management of a suspected anaphylaxis postvaccination is of paramount importance due to the risk of a potential serious reaction after re-exposure and, not secondly, because overdiagnosis of severe allergic reactions to vaccines might lead to an increase in the number of children that interrupt vaccinations, resulting in an individual and collective risk of loss of protection against immunization preventable diseases.

2.2 | Delayed reactions

Delayed reactions are defined as reactions that develop hours or days after vaccination, and are very unlikely to be mediated by IgE.

TABLE 1 Differential diagnosis to consider in case of suspected anaphylaxis in children.

Differential diagnosis of anaphylaxis in children
Vasovagal syncope
Hypotonia-hyporesponse syndrome
Crying spasm
Vocal cord dysfunction
Hypoglycemia
Nonallergic skin rash (exanthema in exanthematous diseases, etc.)

Delayed urticaria and/or angioedema, as well as nonspecific skin rashes, have been reported in 5% to 13% of patients receiving vaccines containing toxoids, but several studies suggest that most of these generalized reactions result from a nonspecific activation of the immune system by a significant amount of microbial substances and will not relapse on re-exposure to the same vaccine.[17]

Delayed reactions are usually self-limiting conditions that do not contraindicate the administration of future doses of the same vaccine.[18] Of these, local reactions are the most frequent and are commonly nonallergic such as pain, redness, and swelling, that develop within hours and days at the vaccination site after immunization and do not require any allergy workup. Instead, contact dermatitis, subcutaneous nodules, and maculopapular exanthema are local type IV hypersensitivity reactions and usually occur more than 12 h after vaccination.[19]

Soreness, redness, and/or swelling at the injection site are generally mild and could result from nonspecific inflammation induced by the injection itself or other components used as adjuvants. Large injection site reactions are less common and usually occur within 24–72 h following immunization and disappear in a few days.[17,20] Swelling that measure at least 10 cm and extend beyond the elbow or knee is defined as extensive limb swelling,[17] it usually occurs within the first 24 h after vaccination and the responsible mechanism is still poorly understood. They occur more frequently after polysaccharide pneumococcal vaccine, diphtheria, tetanus toxoids, and acellular pertussis (aP)-containing vaccines. Local reactions could also result from an Arthus reaction, a type III hypersensitivity, that develops only in previously immunized patients occurring typically after the fourth or fifth injection.[20]

Subcutaneous nodules have been described in up to 19% of patients receiving vaccines containing aluminum hydroxide,[1] and they typically develop weeks after injection. Although these lesions usually regress spontaneously within a few weeks, few cases of persistent nodules more than 6 months have been reported.[21] However, delayed-type hypersensitivity to aluminum causing an injection site nodule is not usually a contraindication to subsequent vaccination.

Aminoglycoside antibiotics (neomycin, gentamicin, streptomycin, and kanamycin) might be contained in many vaccines to avoid contamination of the culture with bacteria or fungi, including MMR, polio and influenza. Although they can theoretically cause immediate allergic reactions to containing vaccines, they are commonly implicated in delayed hypersensitivity reactions such as contact dermatitis.[17] Administration of vaccines containing gentamicin, neomycin, streptomycin, and kanamycin is contraindicated in case of anaphylaxis from such antibiotics, whereas patients suffering from allergic contact dermatitis can be safely vaccinated.[17,18]

Concurrent systemic viral infections that may predispose to delayed cutaneous reactions after immunization practice have been observed in children.[17] The mechanisms by which viral infections modify immune responses to drugs are not clear, widespread activation of T cells with a lower threshold of T cell reactivity and high cytokine levels may be involved.[21]

3 | PART II—MANAGEMENT/DIAGNOSTIC PROCEDURES

3.1 | Children with a suspected allergic reaction to a vaccine

Confirmation by allergy workup is recommended both to identify the culprit allergen from the vaccine components, in order to avoid the risk of cross-reactivity with other vaccines or foods,[22] and to manage subsequent administrations if further doses are needed to avoid unnecessary restrictions against vaccine use. A complete list of all potential allergens in vaccines can be found on the website of the Institute for Vaccine Safety of the John Hopkins University.[23]

An algorithm to select and manage vaccination of patients who refer a previous suggestive allergic reaction to a vaccine is proposed in Figure 1. If a vaccine manifests an adverse event suggestive of a hypersensitivity reaction, it is mandatory to evaluate the clinical history to identify whether any risk factor is present, as for example, food allergy, severe uncontrolled asthma, mastocytosis, etc. It has to be assessed the precise temporal relationship and thus the type of reaction (immediate or delayed), the brand of vaccine (necessary for the exact vaccine components list), the presence of comorbidities, and the need for further doses in order to evaluate the individual risks/benefits ratio.

As stated above, IgE-mediated reactions can be suspected on the basis of the short time interval between vaccination and the onset of symptoms, conventionally within 4 h.[24] The allergy workup in case of a suspected immediate hypersensitivity reaction includes complete vaccine skin testing in a setting equipped to treat anaphylaxis. First, a prick test with full-strength vaccine has to be performed followed, in case of negative result, by intradermal test with 0.02 mL of vaccine diluted 1:100 and, if negative, 1:10 dilution could follow, although some authors described irritant false-positive reactions with this concentration.[25] Positive and negative control testing are recommended. The sensitivity and specificity of skin tests with vaccines in confirming or ruling out allergy to a vaccine or its components have not been established; however, if skin testing proves negative, it is very unlikely for the patient to have IgE against the vaccine or its components.[17] In drug allergy, more than 1 year after an IgE-mediated reaction, there might be very little remaining circulating IgE with a consistent risk for false-negative skin testing results[26] and the same should be taken into account for IgE reactions to vaccines.

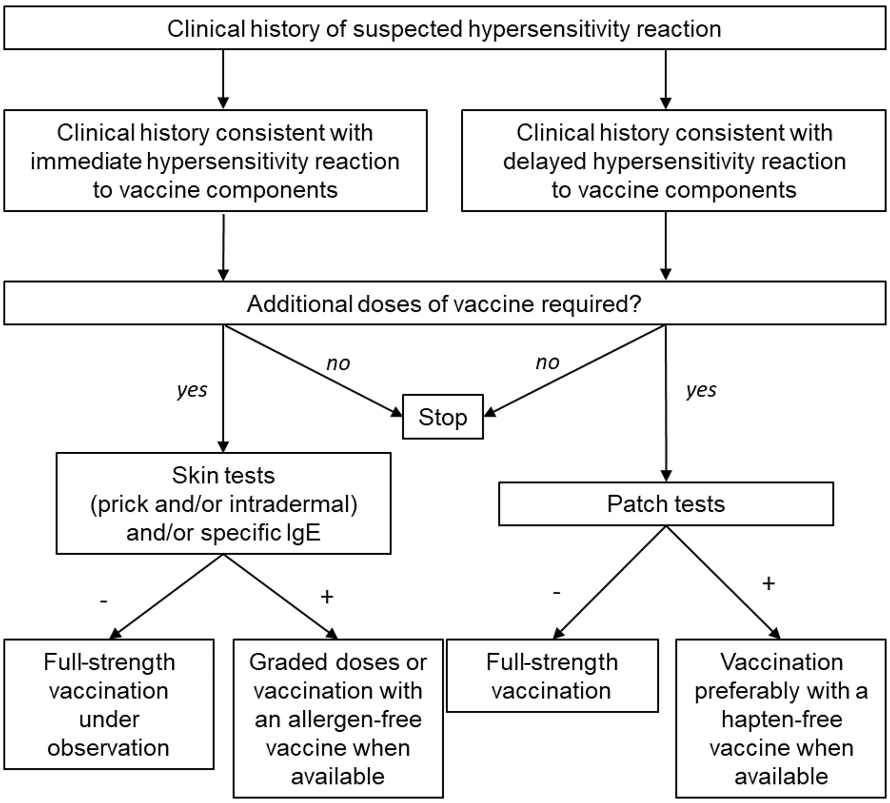

FIGURE 1 Algorithm to select and manage vaccination of patients who refer a previous suggestive allergic reaction to a vaccine.

TABLE 2 Vaccine components capable to elicit an allergic reaction.

Component	Vaccine	Recommendations	References
Egg (ovalbumin and egg white)	Yellow fever	Allergy assessment with skin tests and sIgE. In case of positive results administer in graded doses in equipped setting.	Nilsson et al.[1] Dreskin et al.[31]
	Influenza	Allergy assessment not recommended. Vaccinate with low albumin content.	Turner et al.[32] Des Roches et al.[33] Kelso et al.[34] https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine.2017-2018.html[36] Grohskopf, et al.[37]
	MMR	Allergy assessment not recommended. Vaccinate under standard conditions.	Nilsson et al.[1]
Gelatine (α-Gal)	MMR, MMRV MVaricella	Allergy assessment with skin tests and sIgE. In case of positive results prefer a gelatine-free vaccine as first choice, otherwise administer in fractionated doses in equipped settings.	Nilsson et al.[1] Dreskin et al.[31]
Yeast	Hepatitis B Human papilloma virus	Allergy assessment with skin tests and sIgE. In case of positive results prefer a yeast-free vaccine as first choice, otherwise administer in fractionated doses in equipped settings.	Dreskin et al.[31] Franceschini et al.[10]
Antibiotics (neomycin, gentamicin, streptomycin, and polimixin B)	MMR Varicella Inactivated polio	Vaccinate under standard conditions. Patch tests can be performed, in case of positive results vaccination is not contraindicated except for patients who report a history of anaphylaxis	Nilsson et al.[1]

Abbreviations: MMR, measles, mumps, and rubella; sIgE, Specific IgE.

The next step is to assess sensitization to the components of the vaccine, with the aim of preventing reactions with other vaccines containing the same components,[17] in Table 2 the main vaccine components that can elicit an allergic reaction are listed. Prick test and/or specific IgE to components present in the suspected vaccine are limited (food proteins and tetanus toxoid). To note, interpretation of specific IgE results needs expertise because for some constituents, for example, ovalbumin and gelatine, the predictive capacity for reaction to vaccines is rather low and false-positive results may occur. There are much more individuals allergic and sensitized to a given allergen, than those who react clinically on the exposure to a minute amount of the same allergen present in the vaccine composition. With regard to serum-specific IgE to vaccine microbial antigens production, this is mostly part of the regular immune response and has a limited predictive value for an allergic reaction.[1]

When the culprit allergen is identified, an alternative brand free from the offending ingredient should be preferred in case the patient needs additional doses.

Nonprotected patients with negative skin testing results can be immunized with a full-strength dose. In case of history suggestive of anaphylaxis, a split dose strategy with initial 10% of the vaccine dose followed 30 min later by the remaining 90% of the dose is a more cautious option.[1]

Patients with positive skin testing should undergo desensitization in graded doses. Increasing vaccine doses are administered every 15–30 min after providing that there are no signs of allergic reaction (0.05 mL of 1:10 dilution, following 0.05, 0.1, 0.15, and 0.2 mL of a 0.5 mL full-strength vaccine).[25] Patients who have successfully undergone this protocol still must be considered allergic to the vaccine and this procedure should be repeated in case of boosters. It is mandatory that patients suspected for an allergic reaction to a vaccine must only be managed in a controlled setting where prompt treatment of anaphylaxis by experienced staff is available.[1]

In case of suspicion for a delayed reaction, the vaccine in most cases can be administered in a conventional manner.[27] Patch testing, although not essential for therapeutic decisions, might help in identifying the culprit component and avoiding it when alternative hapten-free brands are available. Various vaccine haptens are commercially available for patch testing: aluminum chloride hexahydrate 2%, elemental aluminum (an empty aluminum metal Finn chamber), polysorbate 80, formaldehyde, kanamycin sulfate, polymyxin B, gentamycin, phenoxyethanol, neomycin, and phenol. Patch tests should be removed at 48 h and read at 72 and/or 96 h or 1 week (the latter might be necessary in case of sensitization to aluminum salts).

Patch testing with aluminum chloride hexahydrate 2% and/or elemental aluminum should be used to investigate the presence of a type IV hypersensitivity.[28] Positive results were demonstrated in 95% of children with persistent itching subcutaneous nodules and tend to disappear over time, suggesting a loss of hypersensitivity.[29]

In all these cases the administration technique is important and a deeper injection has been associated with a lower rate of local reactions, especially in children younger than 3 years.[1]

3.1.1 | Measles, mumps, rubella, and varicella vaccines

Live attenuated MMR viruses contained in trivalent and measles, mumps, rubella, and varicella (MMRV) in quadrivalent vaccines, are cultured in hen embryonic fibroblasts and might contain residual traces of ovalbumin. In the past, egg allergy has been suspected as a cause of hypersensitivity reactions to these vaccines but, currently, MMR and MMRV are considered safe for egg allergic patients and they can be administered in standard settings.[1]

Some brands of MMR, MMRV, and varicella vaccines may contain residual porcine or bovine gelatine as a stabilizer, which has been identified as the responsible component in rare cases of anaphylaxis but also nonimmediate systemic reactions such as skin symptoms are reported.[30] Consequently, in case of allergy to animal gelatine or to galactose-alpha-1,3-galactose (α-Gal) contained in mammalian meat, a gelatine-free vaccine is the first choice. When the latter is not available, in case of positive skin testing results, vaccines should be administered in fractionated doses (see above).[31]

Children with egg allergy, including those with immediate even severe reactions, can receive MMR and MMRV vaccines under standard conditions in the usual vaccination center.

Children with confirmed gelatine or α-Gal allergy should receive a gelatine-free vaccine as first choice; otherwise, vaccines should be administered in fractionated doses.

3.1.2 | Influenza vaccines

Influenza vaccines include trivalent and quadrivalent inactivated vaccines (IIVs), recombinant subunit vaccine (RIV), and live attenuated vaccines (LAIVs). Most are grown in embryonated chicken eggs and, consequently, might contain small amounts of egg proteins, most notably ovalbumin, the amounts of which vary by vaccine manufacturer and lot. In the past, egg allergy was considered a contraindication to the administration of influenza vaccines while, nowadays, it no longer contraindicates it and egg allergic patients can safely be vaccinated.

There is strong evidence that children with egg allergy, including those reporting anaphylaxis, could be safely immunized with IIVs containing less than 1 μg of ovalbumin per dose,[32] or with LAIVs containing a concentration of ovalbumin <0.24 μg per 0.2 mL dose.[33,34] Consequently, previously recommended precautions, at least in countries where the known ovalbumin content in all available IIV and LAIV is low, such as choice of a specific vaccine based on ovalbumin

content, skin testing with the vaccine, and divided or graded dosing, are unnecessary.[35,36]

In the absence of a prior history of anaphylaxis after egg consumption influenza vaccines can be administered without precautions while, when a history of anaphylaxis is reported, in some guidelines it is recommended administering the vaccine without specific precautions[37,38] while others recommend a prolonged observation period to 60 min and the presence of an equipped setting.[33,34]

A non-egg-based influenza vaccine obtained from human diploid cells is also available, even if its use in egg allergic individuals, in the age groups for which they are approved, is acceptable but not medically necessary or preferred.[32]

Children with egg allergy, including those who report anaphylaxis, can safely receive influenza vaccine with low ovalbumin content.

3.1.3 | Yellow fever vaccine

Yellow fever vaccine is obtained from chicken embryos and may contain residual ovalbumin in significant quantities, therefore precautions for vaccination of egg allergic subjects are necessary,[1] including evaluation by an allergist with vaccine testing and administration in graded doses in case of positivity.[31]

Children with egg allergy need a vaccine allergy consultation due to the possibility of high ovalbumin content in yellow fever vaccine and the potential risk for allergic reactions.

3.1.4 | Rotavirus vaccine

Since its introduction, hundreds of millions of doses of rotavirus vaccine have been administered and safety problems with regard to allergy have not been reported.[1] Severe reactions suggestive of an allergic mechanism after a previous dose have to be considered contraindications for a subsequent dose and need to be evaluated.[39]

3.1.5 | Diphtheria, tetanus, and pertussis vaccines

Confirmed allergic reactions to diphtheria, tetanus, and pertussis vaccines are very rare comprising both urticaria or hives[40] and anaphylaxis.[41] Injection site reactions to DTaP have rarely been reported, some referred to delayed hypersensitivity to aluminum included in the vaccine as adjuvant.[42] DTaP and Tdap vaccines might include traces of cow's milk proteins, in particular casaminoacids. Some cases of anaphylactic reactions to booster doses of DTaP or Tdap in children and adolescents with a documented history of severe milk allergy have been reported[43] although most of them have tolerated such vaccines. Thus, vaccination of children allergic to cow's milk is considered safe.[1,17]

Children with cow's milk allergy can receive diphtheria, tetanus, and pertussis vaccines under standard conditions in the vaccination center.

3.1.6 | Hepatitis B

Hepatitis B vaccines may contain viral proteins grown in the yeast Saccharomyces cerevisiae and rare anaphylactic reactions to HBV vaccine have been reported in children with a history of yeast allergy,[10,44] see Table 2.

3.1.7 | Polio vaccines

Some brands of oral Polio vaccine (Sabin) contain alpha-lactalbumin, and allergic reactions have been historically reported in four patients with a history of cow's milk allergy,[45] nevertheless the majority of milk allergic children receive these vaccines uneventfully suggesting that alpha-lactalbumin is not present in a quantity large enough to elicit a reaction. No special precautions are required when vaccinating milk-allergic patients.[1]

Traces of aminoglycosides (streptomycin and neomycin) and/or polimixin B could be contained in inactivated Polio vaccines, which should not be administered to individuals who experienced anaphylaxis to such components, while there are no contraindications in patients who refer allergic contact dermatitis to aminoglycosides or polimixin B.[1]

Children with history of allergic contact dermatitis to aminoglycosides or polimixin B can be safely vaccinated under standard conditions.

3.1.8 | Pneumococcal vaccines

Pneumococcal conjugated vaccines contain inactivated diphtheria toxin (CRM 197), used as a carrier protein, and Polysorbate 80 (PS80), which are adsorbed on aluminum phosphate. CRM 197 was implicated as a cause of anaphylaxis in one case after administration of pneumococcal conjugate vaccine.[46] Aluminum phosphate may be a cause of injection site nodules,[42] a delayed-type hypersensitivity, but it is not a contraindication to subsequent vaccination. Previous severe hypersensitivity reactions to the same vaccine or

its components, mostly CRM 197 are the only contraindications to pneumococcal vaccines.[1]

3.1.9 | Meningococcal vaccines

Meningococcal vaccines include Meningococcal Group B (MenB), Meningococcal C (MenC) and Quadrivalent Meningococcal ACWY (MenACWY) vaccines. The majority of MenC and MenACWY vaccines used in clinical practice contain modified diphtheria (CRM 197) or tetanus toxoid as carrier. Hypersensitivity reactions following MenACWY or MenB vaccine administration, including anaphylaxis, have been reported.[47,48] Previous severe hypersensitivity reactions to the vaccine or to its components, mainly tetanus or diphtheria toxoid, are the only allergic contraindications to Meningococcal vaccines.

3.1.10 | Human papillomavirus vaccines

HPV vaccines may contain residues of yeast. Individuals with a history of severe allergy to yeast could theoretically experience a severe allergic reaction after the administration of this vaccine.[49] Therefore, in case of yeast allergy, it is recommended to perform a complete allergy evaluation.

Some brands of HPV vaccines contain PS80 as a stabilizer, which might be responsible for hypersensitivity reactions.[50] Children that experienced a severe allergic reaction to this substance should be vaccinated with formulations that do not contain PS80 or should be addressed to a specialized allergy center to perform skin tests and receive the protocol of vaccination as described in the diagnostic workup.

3.1.11 | COVID-19 vaccine

Despite the high safety profile of COVID-19 vaccines, shortly after the start of the vaccination campaign, global health authorities, acting correctly in an overcautious way, had to contraindicate these vaccines among patients with a history of immediate allergic reaction to the first dose of the vaccine or to any of the vaccine excipients, polyethylene glycol (PEG) in mRNA vaccines and PS80 in adenovirus vector vaccines.[51,52] Thus, in an effort to provide guidance, skin tests for individuals with PEG/PS80 allergy or a reported allergic reaction to a prior vaccine dose were recommended.[53] Nowadays, instead, increasingly numerous data permit to refute the hypothesis that excipient skin testing could help to manage such patients not impacting tolerance of a second dose and that persons with first dose reactions can safely be re-vaccinated.[54–58] The etiology 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 regard to a suspicion for an allergic IgE-mediated pathogenesis, reporting rate of anaphylaxis was higher after the first dose than after the second dose[59] and it might be possible that a non-IgE-mediated mechanism could be implicated, such as complement activation.[14]

> *No convincing evidence has demonstrated PEG and/or PS80 to be the causal allergens responsible for allergic reactions to SARS-CoV-2 vaccines.*

3.2 | Children with a history of allergy to a vaccine component

There is no scientific evidence of an increased risk of allergic reactions after vaccination in atopic children and such patients should receive all the recommended vaccines[60,61] without any additional precautions. Children with a previous history of immediate allergic reaction to a vaccine or to any of its components might have an increased risk and a complete allergy evaluation of these patients is mandatory. The allergy assessment has to be performed by personnel experts in vaccine allergy, allergists, or immunologists because positive test results do not pose a diagnosis of allergy but are only an index of sensitization that has to be evaluated according to the clinical history.

In case of a history of delayed reactions, contact allergy to a vaccine component and patch testing positive results are not considered absolute contraindications because of the risks of not being immunized outweigh issues caused by delayed reactions.[1]

> *Atopic children do not have an increased risk of allergic reactions to vaccines and can be vaccinated under standard conditions.*

3.2.1 | Egg allergy

Egg allergy is the most common type of food allergy in children with an estimated prevalence of 2.5% in the first 2 years of life[62] while reported allergic reactions to vaccines containing egg protein traces are very rare.

To assess sensitization to egg proteins the allergy workup is based on: (I) skin prick testing with egg white and ovalbumin extracts; (II) serological test with the determination of specific IgE to egg white and ovalbumin (nGal d2). In both cases positive results indicate sensitization and do not pose a diagnosis of definite food allergy, thus, any result has to be evaluated by experts.

3.2.2 | Cow's milk allergy

Scarce traces of casein have been demonstrated in some vaccines. Cow's milk protein allergy is a common allergy in children but, during

the last decades, the vast majority of children with severe allergy to milk did not experience reactions to such vaccines.[17] Nowadays, vaccination of children allergic to cow's milk is considered safe.[1,17]

3.2.3 | Gelatine allergy

Gelatine is an animal protein derived from bovine and porcine connective tissue. It is used in amounts that range from micrograms to milligrams as a stabilizer in viral attenuated vaccines in order to protect them against unfavorable conditions.[60] Despite being extremely rare, in case of allergy to animal gelatine or to α-Gal contained in mammalian meat, a gelatine-free vaccine is the first choice. Anyway, to assess sensitization to gelatine the allergy workup is based on: (I) skin prick testing performed with 5 g gelatine powder diluted in 5 mL saline[60] and mammalian meet extract; (II) serological test with the determination of specific IgE to mammalian meat and α-Gal.

3.2.4 | Antibiotics allergy

Vaccines, especially with live attenuated virus, may contain traces of antibiotics such as neomycin, gentamicin, streptomycin, and polimixin B with the aim to avoid contamination among the manufacturing process. In case of allergy to such antibiotics, the most common clinical history regards local reactions as contact dermatitis, which require amounts of neomycin far higher than those normally found in vaccines to produce clinical manifestations, and which do not pose any contraindication to vaccinations.[17] In case of suspected allergy, patch tests are available and can be performed to confirm sensitization and choose alternative vaccines although re-vaccination is not contraindicated even in case of positive patch test results except for the very rare cases of anaphylaxis.[1,22] Commercially available haptens are kanamycin sulfate, streptomycin, gentamycin, and neomycin.

3.2.5 | Yeast allergy

Residual of yeast can be found in HBV and HPV vaccines produced by cell cultures of *Saccharomyces Cerevisiae*.[44,49] Allergy to yeast is very rare, especially in young individuals, and in case of allergy suspicion the workup is based on: (I) skin prick test with yeast extract; (II) specific IgE to yeast. In case of positive results vaccination with fractionated doses is necessary.

3.2.6 | Dextran allergy

Dextran has been implicated in serious immediate IgG-mediated hypersensitivity reactions to a brand of MMR vaccine subsequently withdrawn from the market.[63] This residual component is not present in MMR vaccines currently available.

3.2.7 | Latex allergy

Patients with latex allergy should be vaccinated with latex-free vaccines and equipment. The allergy workup in the presence of a suspicion of sensitization to latex is as follows: (I) skin prick testing performed with latex extract; (II) serological test with the determination of specific IgE to latex (rHev b1, rHev b3 and rHev b5), hevein (rHev b6.02), profilin (rHev b8), and class I chitinase (rHev b11).

3.2.8 | Mastocytosis

Children with mastocytosis have an increased risk of mast cell mediators release after various triggers including vaccination.[1,64] To minimize the risk of immediate reactions premedication with anti-H1 histamine the day before and 5 days after immunization and vaccine administration in single injections under medical supervision for 30 min is recommended.[65]

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CONFLICT OF INTEREST STATEMENT

All authors declare they do not have any conflict of interest related to the manuscript content.

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REFERENCES

1. Nilsson L, Brockow K, Alm J, et al. Vaccination and allergy: EAACI position paper, practical aspects. *Pediatr Allergy Immunol*. 2017;28(7):628-640.
2. Institute of Medicine (US). Committee to Review Adverse Effects of Vaccines, Stratton, K. R., & Clayton, E. W. (2012). *Adverse Effects of Vaccines: Evidence and Causality*. The National Academies Press.
3. Micheletti F, Peroni D, Piacentini G, et al. Vaccine allergy evaluation and management at the specialized Green Channel Consultation Clinic. *Clin Exp Allergy*. 2012;42(7):1088-1096.
4. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the vaccine adverse event reporting system, 1990-2016. *J Allergy Clin Immunol*. 2019;143(4):1465-1473.
5. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868-878.
6. Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child*. 2000;83(2):128-131.
7. Wood RA. Allergic reactions to vaccines. *Pediatr Allergy Immunol*. 2013;24(6):521-526.

8. Kimberlin DW, Brady MT, Jackson MA, Long SS, Academy A, of Pediatrics. Red book: 2015 report of the Committee on Infectious Diseases. *Am Acad Pediatr*. 2015;432:445.
9. Halsey NA, Griffioen M, Dreskin SC, et al. Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS. *Vaccine*. 2013;31(51):6107-6112.
10. Franceschini F, Bottau P, Caimmi S, et al. Evaluating children with suspected allergic reactions to vaccines for infectious diseases. *Allergy Asthma Proc*. 2018;39(3):177-183.
11. Muraro A, Worm M, Alviani C, et al. EAACI guidelines: anaphylaxis (2021 update). *Allergy*. 2022;77(2):357-377.
12. Gold MS, Amarasinghe A, Greenhawt M, et al. Anaphylaxis: revision of the brighton collaboration case definition. *Vaccine*. 2023;41(15):2605-2614.
13. Arcolaci A, Bronte V, Zanoni G. Immunization practices and risk of anaphylaxis: a current update, comprehensive of COVID-19 vaccination data. *Curr Opin Allergy Clin Immunol*. 2021;21(5):418-425.
14. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med*. 2021;384(7):643-649.
15. Miller ER, McNeil MM, Moro PL, Duffy J, Su JR. The reporting sensitivity of the Vaccine Adverse Event Reporting System (VAERS) for anaphylaxis and for GuillainBarre syndrome. *Vaccine*. 2020;38:7458-7463.
16. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003;112(4):815-820.
17. Caubet JC, Ponvert C. Vaccine allergy. Immunology and allergy. *Clinics*. 2014;34(3):597-613.
18. Echeverría-Zudaire LA, Ortigosa-del Castillo L, Alonso-Lebrero E, et al. Consensus document on the approach to children with allergic reactions after vaccination or allergy to vaccine components. *Allergol Immunopathol*. 2015;43(3):304-325.
19. Aytekin ES, Şekerel BE, Şahiner ÜM. Allergic reactions during childhood vaccination and management. *Turk J Pediatr*. 2021;63(6):941-954.
20. Sarti L, Lezmi G, Mori F, Giovannini M, Caubet JC. Diagnosis and management of hypersensitivity reactions to vaccines. *Expert Rev Clin Immunol*. 2020;16(9):883-896. doi:10.1080/1744666X.2020.1814745
21. Zanoni G, Migliorini M, Gallo T, Guidolin L, Schena D. Recurrent injection site reactions to vaccines: two clinical patterns of presentation. *Vaccine*. 2020;38(45):6985-6989.
22. Caubet JC, Rudzeviciene O, Gomes E, Terreehorst I, Brockow K, Eigenmann PA. Managing a child with possible allergy to vaccine. *Pediatr Allergy Immunol*. 2014;25(4):394-403.
23. https://www.hopkinsvaccine.org/cc-mmr.html
24. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130:25-43.
25. Wood RA, Setse R, Halsey N. Clinical immunization safety assessment (CISA) network hypersensitivity working group. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007;120:478-481.
26. Lopez-Serrano MC, Caballero MT, Barranco P, Martinez-Alzamora F. Booster responses in the study of allergic reactions to beta-lactam antibiotics. *J Investig Allergol Clin Immunol*. 1996;6(1):30-35.
27. Wood RA, Berger M, Dreskin SC, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008;122(3):e771-e777.
28. Bergfors E, Inerot A, Falk L, Nyström U, Trollfors B. Patch testing children with aluminium chloride hexahydrate in petrolatum: a review and a recommendation. *Contact Dermatitis*. 2019;81(2):81-88. doi:10.1111/cod.13303
29. Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines-prognosis and outcome after booster vaccination. *Eur J Pediatr*. 2013;172(2):171-177. doi:10.1007/s00431-012-1841-2
30. Miyazawa H, Inouye S, Sakaguchi M. Sensitization to gelatin in children with systemic non-immediate-type reactions to varicella vaccines. *Ann Allergy Asthma Immunol*. 2000;84(3):341-344.
31. Dreskin SC, Halsey NA, Kelso JM, et al. International consensus (ICON): allergic reactions to vaccines. *World Allergy Organization Journal*. 2016;9:32.
32. Greenhawt M, Turner PJ, Kelso JM. Administration of influenza vaccines to egg allergic recipients: a practice parameter update 2017. *Ann Allergy Asthma Immunol*. 2018;120(1):49-52.
33. Turner PJ, Southern J, Andrews NJ, et al. Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J Allergy Clin Immunol*. 2015;136(2):376-381.
34. Des Roches A, Samaan K, Graham F, et al. Safe vaccination of patients with egg allergy by using live attenuated influenza vaccine. *J Allergy Clin Immunol Pract*. 2015;3(1):138-139.
35. Kelso JM, Greenhawt MJ, Li JT. Update on influenza vaccination of egg allergic patients. *Ann Allergy Asthma Immunol*. 2013;111(4):301-302.
36. Committee on Infectious Diseases, & American Academy of Pediatrics. Recommendations for prevention and control of influenza in children, 2015-2016. *Pediatrics*. 2015;136(4):792-808.
37. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine.2017-2018.html
38. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2019–20 influenza season. *MMWR Recomm Rep*. 2019;68(3):1-21.
39. World Health Organization. Rotavirus vaccines: WHO position paper—January 2013. *Wkly Epidemiol Rec*. 2013;88(5):49-64.
40. Jackson LA, Carste BA, Malais D, Froeschle J. Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *Pediatr Infect Dis J*. 2002;21(8):781-786.
41. Cheng DR, Perrett KP, Choo S, Danchin M, Buttery JP, Crawford NW. Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. *Vaccine*. 2015;33(13):1602-1607.
42. Beveridge MG, Polcari IC, Burns JL, Adler A, Hendrickson B, Stein SL. Local vaccine site reactions and contact allergy to aluminum. *Pediatr Dermatol*. 2012;29(1):68-72.
43. Kattan JD, Konstantinou GN, Cox AL, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. *J Allergy Clin Immunol*. 2011;128(1):215-218.
44. DiMiceli L, Pool V, Kelso JM, Shadomy SV, Iskander J, VAERS Team. Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS). *Vaccine*. 2006;24(6):703-707.
45. Parisi CAS, Smaldini PL, Gervasoni ME, Maspero JF, Docena GH. Hypersensitivity reactions to the Sabin vaccine in children with cow's milk allergy. *Clin Exp Allergy*. 2013;43(2):249-254.
46. Arroabarren E, Anda M, Sanz ML. Anaphylaxis to pneumococcal vaccine; CRM (197): novel cause of vaccine allergy. *Pediatr Allergy Immunol*. 2016;27(4):433-437.
47. Myers TR, McNeil MM, Ng CS, Li R, Lewis PW, Cano MV. Adverse events following quadrivalent meningococcal CRM-conjugate vaccine (Menveo®) reported to the Vaccine Adverse Event Reporting system (VAERS), 2010–2015. *Vaccine*. 2017;35(14):1758-1763.
48. Perez-Vilar S, Dores GM, Marquez PL, et al. Safety surveillance of meningococcal group B vaccine (Bexsero®), Vaccine Adverse Event Reporting System, 2015–2018. *Vaccine*. 2022;40(2):247-254.

49. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep Recomm Rep*. 2014;63(5):1-30.
50. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012;2012:bcr0220125797.
51. Greenhawt M, Abrams EM, Shaker M, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. *J Allergy Clin Immunol Pract*. 2021;9(10):3546-3567.
52. Greenhawt M, Abrams EM, Oppenheimer J, et al. The COVID-19 pandemic in 2021: avoiding overdiagnosis of anaphylaxis risk while safely vaccinating the world. *J Allergy Clin Immunol Pract*. 2021;9:1438-1441.
53. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9:1423-1437.
54. Greenhawt M, Shaker M, Golden DB. PEG/polysorbate skin testing has no utility in the assessment of suspected allergic reactions to SARS-CoV-2 vaccines. *J Allergy Clin Immunol Pract*. 2021;9(9):3321-3322.
55. 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.
56. Picard M, Drolet JP, Masse MS, et al. Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: a case series. *J Allergy Clin Immunol Pract*. 2022;10(2):620-625.
57. Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell health experience. *Ann Allergy Asthma Immunol*. 2022;128(2):161-168.
58. Chu DK, Abrams EM, Golden DB, et al. Risk of second allergic reaction to SARS-CoV-2 vaccines: a systematic review and meta-analysis. *JAMA Intern Med*. 2022;182(4):376-385.
59. American Academy of Pediatrics. Active and passive immunization. In: Pickering LK, ed. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. American Academy of Pediatrics; 2009:48.
60. Kelso JM. Update on vaccination guidelines for allergic children. *Expert Rev Vaccines*. 2009;8:1541-1546.
61. Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations – a post-marketing surveillance review. *Eur J Pediatr*. 2002;161:21-25.
62. Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy*. 2001;56:403-411.
63. Zanoni G, Puccetti A, Dolcino M, et al. Dextran-specific IgG response in hypersensitivity reactions to measles-mumps-rubella vaccine. *J Allergy Clin Immunol*. 2008;122(6):1233-1235.
64. Zanoni G, Zanotti R, Schena D, Sabbadini C, Opri R, Bonadonna P. Vaccination management in children and adults with mastocytosis. *Clin Exp Allergy*. 2017;47(4):593-596.
65. Gallo G, Mel R, Ros E, Filia A. Guide to contraindications to vaccination (2018 update). *Rapporti ISTISAN-Istituto Superiore di Sanità*. 2019;19/3:111.

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