

# 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 post-vaccination is of paramount importance due to the risk of a potential serious reactions 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. Especially, in the light that 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 The patient assessment has to be done by an allergist or an immunologist expert in the vaccine field 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. Aim of this review is to provide a practical and safe management in the clinical settings of the allergic patient which have to undergo immunization practices, both to manage children with a suspected allergic reaction to a vaccine both children with history of allergy to a vaccine component.

## A practical guide to address reactions to vaccines in children

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## KEY WORDS

Allergic reactions; anaphylaxis; hypersensitivity reactions; vaccines allergy; vaccine components; vaccines.

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## KEY MESSAGE

The purpose of this review is to provide clinicians with a concise and practical review which summarize how to manage in the clinical settings allergic children which have to undergo immunization practices. 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 both of the children with a suspected allergic reaction to a previous vaccine and the need to continue the vaccination schedule, both of the children with a history of allergy to a vaccine component.

## INTRODUCTION

Although approved vaccines have been rigorously tested for safety, anaphylactic reactions, albeit very rare, can occur<sup>1</sup> and potentially, any vaccine can cause an allergic reaction. According to the Institute of Medicine, epidemiologic and mechanistic evidence support a causal relationship between anaphylaxis and several vaccines, including those for measles, mumps and rubella (MMR), varicella, influenza, hepatitis B, meningococcus, human papillomavirus, and the combined diphtheria, tetanus, pertussis vaccine<sup>2</sup>. 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<sup>3</sup>.

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 the almost 500,000 reports, only 828 were classified as anaphylaxis based either on physician's diagnosis or in according to the Brighton Collaboration case definition<sup>4</sup>. 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<sup>5</sup>. In children, Gold et al.<sup>6</sup>, demonstrated that only 10% of reported generalized allergic reactions developed a reaction on re-exposure and that most of these reactions were not suggestive for 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 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 labelled as allergic.

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

## *PART I – CLINICAL ASPECTS*

### **IMMEDIATE RECTIONS**

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

Anaphylaxis is defined, according to EAACI<sup>11</sup> 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<sup>12</sup>. 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 characterised 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 has always to be considered whenever an episode appears to coincide with vaccine administration<sup>13</sup>, see Tab 1.

Since post-vaccination anaphylaxis is very rare, usually it starts to be reported to passive pharmacovigilance during post-marketing surveillance and data are often influenced by under- and over-reporting, incomplete information and lack of denominators<sup>13</sup>. Recently, Miller et al. assessed current VAERS sensitivity for anaphylaxis ranging from 13% to 76%<sup>14</sup>, that highlights the need of a correct diagnostic framework performed by allergists or immunologists expert in vaccine allergy for a correct vaccination management. Being rare, the incidence varies among different studies: in a study population consisted of children and adolescents Bohlke et al.<sup>15</sup> 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.<sup>5</sup> identified 18 cases of anaphylaxis after administration of 12,403,201 vaccine doses to 0-17 age group, for an incidence rate of 1.45 cases per million vaccine doses.

Treatment of anaphylaxis in the setting of vaccine administration is reviewed in Castells et al.<sup>16</sup>.

Although rare, the precise diagnostic management of a suspected anaphylaxis post-vaccination is of paramount importance due to the risk of a potential serious reactions after re-exposure and, not secondly, because of 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 immune preventable diseases.

## DELAYED REACTIONS

Delayed reactions are defined as reaction that develop hours or days after vaccination, and are very unlikely to be mediated by IgE. Delayed urticaria and/or angioedema, as well as non-specific 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<sup>17</sup>.

Delayed reactions are usually self-limiting conditions that do not contraindicate the administration of future doses of the same vaccine<sup>18</sup>. Of these, local reactions are the most frequent and are commonly non-allergic such as pain, redness and swelling, that develops 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 hours after vaccination<sup>19</sup>.

Soreness, redness and/or swelling at the injection site are generally mild and could result from nonspecific inflammation induced by injection itself or other components used as adjuvants. Large injection site reactions are less common and usually occur within 24-72 hours following immunization and disappear in a few days<sup>17,20</sup>. Swelling that measure at least 10 cm and extend beyond the elbow or knee is defined as extensive limb swelling<sup>17</sup>, it is usually painless and occur commonly within the first 24 hours after vaccination and his 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 develop only in previously immunized patients occurring typically after the fourth or fifth injection<sup>20</sup>.

Subcutaneous nodules have been described in up to 19% of patients receiving vaccines containing aluminum hydroxide<sup>1</sup> 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<sup>21</sup>.

Patch testing with aluminum chloride hexahydrate 2% and/or elemental aluminium should be used to investigate the presence of a type IV hypersensitivity<sup>22</sup>. Positive results were demonstrated in 95% of children with persistent itching subcutaneous nodules and tend to disappear over time, suggesting a loss of hypersensitivity<sup>23</sup>. However, delayed-type hypersensitivity to Aluminum causing an injection site nodule, is not usually a contraindication to subsequent vaccination.

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<sup>1</sup>.

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<sup>17</sup>. 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.

Concurrent systemic viral infections that may predispose to delayed cutaneous reactions after immunization practice have been observed in children<sup>17</sup>. 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<sup>21</sup>.

### *PART II - MANAGEMENT / DIAGNOSTIC PROCEDURES*

#### **I) 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<sup>24</sup>, both to manage

subsequent administrations if further doses are needed avoiding unnecessary restrictions against vaccine use. A complete list of all potential allergens in vaccines can be found at the website of the Institute for Vaccine Safety of the John Hopkins University<sup>25</sup>.

An algorithm to select and manage vaccination of patients who refer a previous suggestive allergic reaction to a vaccine is proposed in Fig 1. If a vaccinee manifests an adverse event suggestive for a hypersensitivity reaction, it is mandatory to evaluate the clinical history to identify whether is present any risk factor as for e.g. food allergy, severe uncontrolled asthma, mastocytosis etc. It has to be evaluated 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 hours<sup>26</sup>. The allergy workup in case of a suspected immediate-hypersensitivity reaction provides for complete vaccine skin testing in a setting equipped to treat anaphylaxis. First, it has to be performed a prick test with full-strength vaccine 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<sup>27</sup>. Positive and negative control testing are recommended. The sensitivity and specificity of skin tests with vaccines in confirming or discarding 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<sup>17</sup>. In drug allergy, more than one year after an IgE-mediated reaction, there might be very little remaining circulating IgE with a consistent risk for false negative skin testing results<sup>28</sup> and the same should be taken into account for IgE reactions to vaccines.

The next step is to assess sensitisation to the components of the vaccine, with the aim of preventing reactions with other vaccines containing the same components<sup>17</sup>, in Tab 2 are listed the main vaccine components which can elicit an allergic reaction. 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, e.g. 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. In regards 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<sup>1</sup>.

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

Non-protected patients with negative skin testing results can be immunized with a full-strength dose. In case of history suggestive for anaphylaxis, a split dose strategy with initial 10% of the vaccine dose followed 30 minutes later by the remaining 90% of the dose is a more cautious option<sup>1</sup>.

Patients positive skin testing should undergo desensitization in graded doses. Increasing vaccine doses are administered every 15-30 minutes after providing that there are no signs of allergic reaction (0.05 ml of 1:10 dilution, following 0.05 ml, 0.1 ml, 0.15 ml and 0.2 ml of a 0.5 ml full strength vaccine)<sup>26</sup>. 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<sup>1</sup>.

In case of suspicion for a delayed reaction, the vaccine in most cases can be administered in a conventional manner<sup>29</sup>. Patch testing, although not essential for therapeutic decisions, might help in identifying the culprit component and avoiding it when alternative apten-free brands are available. Various vaccine aptens are commercially available for patch testing: aluminium chloride hexahydrate 2%, elemental aluminium (an

empty aluminium metal Finn chamber), polysorbate 80, formaldehyde 1%, kanamycin sulphate, polymyxin B, gentamycin, phenoxyethanol 1%, neomycin and phenol. Patch tests should be removed at 48 hours and read at 72 and/or 96 hours or 1 week (the latter might be necessary in case of sensitization to aluminium salts).

### Measles, mumps, rubella and varicella vaccines

Live attenuated measles, mumps and rubella (MMR) viruses contained in trivalent and measles, mumps, rubella and varicella (MMRV) in quadrivalent vaccines, are cultured in hen's 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<sup>1</sup>.

Some brands of MMR, MMRV and varicella vaccines may contain residual porcine or bovine gelatine as a stabilizer, which has been identified the responsible component in rare cases of anaphylaxis but also non-immediate systemic reactions such as skin symptoms are reported<sup>30</sup>. Consequently, in case of allergy to animal gelatine or to galactose-alpha-1,3-galactose ( $\alpha$ -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).

*Children with egg allergy, including those with immediate even severe reactions, can receive MMR and MMRV vaccine under standard condition in the usual vaccination centre.*

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### Influenza vaccines

Influenza vaccines include trivalent and quadrivalent inactivated vaccines (IIV), recombinant subunit vaccine (RIV) and live attenuated vaccine (LAIV) and mostly 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 these patients can safely be vaccinated.

In fact, there is strong evidence that children with egg allergy, including those reporting anaphylaxis, could be safely immunized with IIVs containing less than 1.2  $\mu$ g/ml of egg protein, either in two graded doses or in one single dose<sup>31</sup>, while a concentration of ovalbumin < 0.24  $\mu$ g/dose in LAIVs was assessed as safe for children with egg allergy including anaphylaxis<sup>32,33</sup>.

In the absence of a prior history of anaphylaxis after egg consumption influenza vaccines can be administered without precautions while, when history of anaphylaxis is reported, in some guidelines it is recommended administering the vaccine without specific precautions<sup>34</sup> while others recommend a prolonged observation period to 60 minutes and the presence of an equipped setting<sup>32,33</sup>.

A vaccine obtained from human diploid cells is also available as a safe alternative for egg allergic individuals<sup>26</sup>.

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

### Yellow fever vaccine

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

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

## Rotavirus vaccine

Since its introduction, hundreds of millions doses of Rotavirus vaccine have been administered and safety problems with regard to allergy have not been reported<sup>1</sup>. severe reactions suggestive for an allergic mechanism after a previous dose are to be considered contraindications for a booster dose and need to be evaluated<sup>35</sup>.

## Diphtheria, tetanus and pertussis vaccines

Confirmed allergic reactions to diphtheria, tetanus and pertussis vaccines are very rare comprising both urticaria or hives<sup>36</sup> both anaphylaxis<sup>37</sup>. Injection site reactions to DTaP have rarely been reported, some referred to delayed hypersensitivity to aluminum included in the vaccine as adjuvant<sup>38</sup>. DTaP and Tdap vaccines might include traces of cow's milk proteins, in particular casamino acids. 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<sup>39</sup> although most patients with severe milk allergy have tolerated such vaccines. Thus, vaccination of children allergic to cow's milk is considered safe<sup>1,17</sup>.

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

## 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<sup>40</sup>.

## 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<sup>41</sup>, 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<sup>1</sup>.

Traces of Aminoglycosides (Streptomycin, Neomycin and/or Polimixin B) could be contained in inactivated Polio vaccines, that 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<sup>1</sup>.

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

## Pneumococcal vaccines

Pneumococcal vaccines contain inactivated diphtheria toxin (CRM 197), used as carrier protein, and Polysorbate 80 (PS80) which are adsorbed on aluminum phosphate. CRM 197 was implicated as cause of anaphylaxis in one case after administration of pneumococcal conjugate vaccine<sup>42</sup>. Aluminum phosphate may be cause of injection site nodules<sup>38</sup>, 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.

## 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 vaccines administration, including anaphylaxis, have been reported<sup>43,44</sup>. Previous severe hypersensitivity reactions to the vaccine or to its components, mainly tetanus or diphtheria toxoid, are the only allergic contraindications to Meningococcal vaccines.

## Human papilloma virus 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 administration of this vaccine<sup>45</sup>. Therefore, in case of yeast allergy, it is recommended to perform a complete allergy evaluation.

Some brands of HPV vaccines contain PS80 as stabilizer, which might be responsible for hypersensitivity reactions<sup>46</sup>. 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 prescribe the protocol of vaccination as described in the diagnostic work-up.

### **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<sup>47,48</sup>. 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<sup>49</sup>. 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<sup>50</sup>. 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 then after the second dose and it might be possible that a non-IgE mediated mechanism could be implicated, such as complement activation<sup>13</sup>.

*No convincing evidence has demonstrated PEG and/or PS80 to be the causal allergens responsible for allergic reactions to SARS-CoV-2 vaccines, thus, PEG/PS80 skin testing are not indicated.*

## **II) 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<sup>51-53</sup> 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 expert in vaccine allergy, allergists or immunologists, because positive test results do not pose diagnosis of allergy but are only index of sensitization that has to be evaluated according to the clinical history.

In case of history of delayed reactions, as contact allergy to a vaccine component and patch testing positive results, are not considered absolute contraindications because of the risks of not being immunised outweigh issues caused by delayed reactions<sup>1</sup>.

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

### **Egg allergy**

Egg allergy is the most common type of food allergy in children with an estimated prevalence of 2.5% in the first two years of life<sup>54</sup> while reported allergic reactions to vaccines containing egg proteins traces are very rare.

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

### **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 experienced reactions with such vaccines<sup>17</sup>. Nowadays, vaccination of children allergic to cow's milk is considered safe<sup>1,17</sup>.

### **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 stabiliser in viral attenuated vaccines in order to protect them against unfavourable conditions<sup>52</sup>. Despite extremely rare, in case of allergy to animal gelatine or to galactose-alpha-1,3-galactose ( $\alpha$ -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 5g gelatine powder diluted in 5 ml saline<sup>52</sup> and mammalian meet extract; II) serological test with the determination of specific IgE to mammalian meet and galactose-alpha-1,3-galactose ( $\alpha$ -Gal).

### **Antibiotics allergy**

Vaccines, especially with live attenuated virus, may contain traces of antibiotics such as neomycin, gentamicin, streptomycin and polymixin 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<sup>17</sup>. 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<sup>1,24</sup>. Commercially available haptens are kanamycin sulphate, polymyxin B, gentamycin and neomycin.

### **Yeast allergy**

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

### **Dextran allergy**

Dextran has been implicated in serious immediate IgG-mediated hypersensitivity reactions to a brand of MMR vaccine subsequently withdrawn from the market<sup>55</sup>. This residual component is not present in MMR vaccines currently available.

### **Latex allergy**

Patients with latex allergy should be vaccinated with latex-free vaccines and equipment. The allergy workup in presence of a suspicion of sensitization to latex is as follow: 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).

### **Mastocytosis**

Children with mastocytosis have an increased risk of mast cell mediators release after various triggers including vaccination<sup>1,56</sup>. To minimize the risk of immediate reactions premedication with anti-H1 histamine the day before and five days after immunization and vaccine administration in single injections under medical supervision for 30 minutes is recommended<sup>57</sup>.

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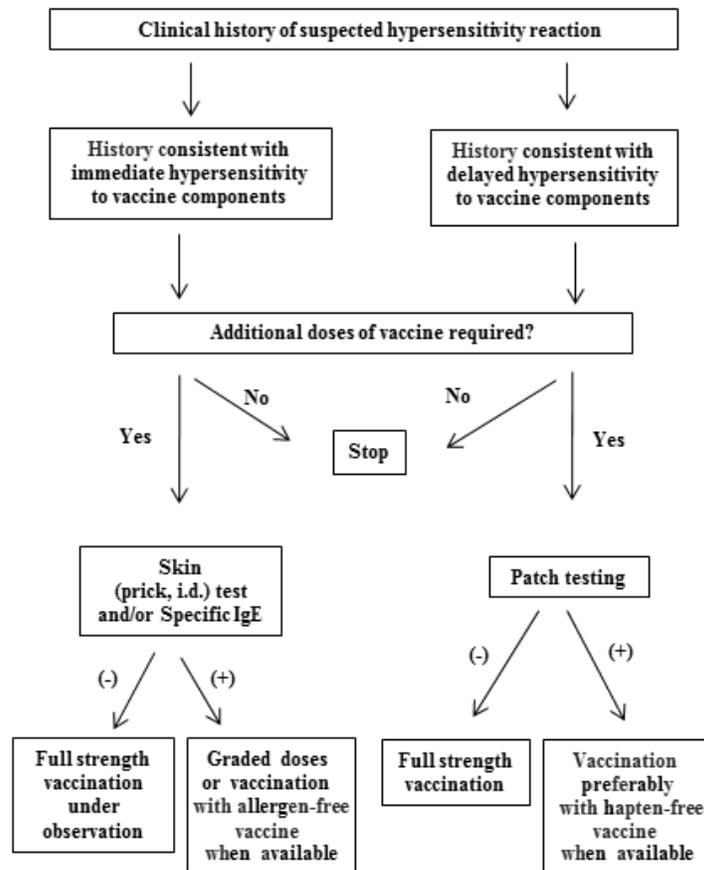
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**Figure 1:** Algorithm to select and manage vaccination of patients who refer a previous suggestive allergic reaction to a vaccine.



**Table 1:**

Differential diagnosis to consider in cases of suspected anaphylaxis in children

Differential diagnosis of anaphylaxis in children

Vasovagal syncope Hypotonia-hyporesponse syndrome Crying spasm Vocal cord dysfunction Hypoglycemia Skin rash (exant)

**Table 2:**

Vaccine components capable to elicit an allergic reaction.

COMPONENT	VACCINE	RECOMMENDATIONS
Egg (ovalbumine)	Yellow fever	Allergy assessment with skin tests and sIgE*. In case of positive results administer in graded doses in equipped setting.

COMPONENT	VACCINE	RECOMMENDATIONS
Gelatine ( $\alpha$ -Gal)	Influenza	Allergy assessment not recommended. Vaccinate with low albumin content.
	MMR**	Allergy assessment not recommended. Vaccinate under standard conditions.
	MMR** Varicella	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.
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.
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

\*sIgE, Specific IgE; \*\*MMR, measles, mumps and rubella;