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REVIEW ARTICLE

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Vaccination and allergy: EAACI position paper, practical aspects

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Abstract

Immunization is highly effective in preventing infectious diseases and therefore an indispensable public health measure. Allergic patients deserve access to the same publicly recommended immunizations as non-allergic patients unless risks associated with vaccination outweigh the gains. Whereas the number of reported possible allergic reactions to vaccines is high, confirmed vaccine-triggered allergic reactions are rare. Anaphylaxis following vaccination is rare, affecting <1/100 000, but can occur in any patient. Some patient groups, notably those with a previous allergic reaction to a vaccine or its components, are at heightened risk of allergic reaction and require special precautions. Allergic reactions, however, may occur in patients without known risk factors and cannot be predicted by currently available tools. Unwarranted fear and uncertainty can result in incomplete vaccination coverage for children and adults with or without allergy. In

Dedicated to Christoph Grüber and Isil Barlan

addition to concerns about an allergic reaction to the vaccine itself, there is fear that routine childhood immunization may promote the development of allergic sensitization and disease. Thus, although there is no evidence that routine childhood immunization increases the risk of allergy development, such risks need to be discussed.

KEYWORDS

adjuvant, adverse event, allergy, anaphylaxis, vaccination

1 | AIMS

This position paper provides expert advice on how to prevent and manage allergic reactions to vaccines against infectious diseases, and immunization in relation to the development of allergic diseases. Because systemic reactions can cause greater harm than local reactions, this paper focuses on the former.

2 | METHODS

Evidence and recommendations provided are based on currently available published data. In January 2013, articles in English, German, and Italian with data on hypersensitivity reactions to vaccines were identified by searching the Medline (National Library of Medicine) database. Additional articles were found through the reference lists of the identified articles, textbooks, publications of national registries or organizations, existing guideline articles, and a Medline search update covering January 2013-September 2016. Relevant articles were identified on the basis of title and abstract, retrieved, and analyzed. Evidence was discussed, and statements were adopted or amended by consensus among the authors.

3 | Basic information

3.1 | Allergic reactions to vaccines

Statement: Allergic reactions to vaccines are rare, mostly directed to additives. Knowledge of all ingredients is of importance when vaccinating an allergic individual.

Documented allergic reactions have been reported for all vaccines but account only for a minority of all adverse events following immunization (AEFI, abbreviations; see also Table 1). In addition to microbial antigens, vaccines may include stabilizers, adjuvants, preservatives, and residual contaminants from the production process. (http://www.vaccinesafety.edu/components.htm and http://www.cdc.gov/vaccines/pubs/pinkbook/appendix/index.html).[1,2] Although microbial antigens rarely cause allergic reactions, they have been described in recent papers for anaphylaxis associated with influenza vaccine and for a mutant diphtheria toxin (CRM197) in pneumococcal conjugated vaccine (PCV).[3,4] Knowledge of all the ingredients in a vaccine is crucial to identifying the culprit allergen. The principal allergens in vaccines are listed below.

Gelatine, a vaccine stabilizer of bovine or porcine origin, has been reported to be responsible for anaphylaxis to some brands of measles, mumps, and rubella (MMR) and varicella vaccines, and also earlier in Japanese encephalitis and influenza vaccines.

Residual ovalbumin from hen's egg can be present in yellow fever (YF), influenza, MMR, tick-borne encephalitis (TBE), and some rabies vaccines in various concentrations (Figure 1). Chicken protein in YF vaccine has been reported to be a potential severe problem in chicken-allergic recipients. Very low concentration of cow's milk proteins may

TABLE 1 Abbreviations

AEFI	Adverse event following immunization
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
D	Diphtheria
DTaP	Diphtheria - Tetanus - Acellular pertussis
DTP	Diphtheria - Tetanus - Pertussis
EAACI	European Academy of Allergy and Clinical Immunology
HBV	Hepatitis B vaccine
Hib	*Haemophilus Influenzae type b*
IIV	Trivalent and quadrivalent inactivated influenza vaccine
IPV	Inactivated polio vaccine
RIV	Recombinant subunit influenza vaccine
LAIV	Live attenuated trivalent and quadrivalent influenza vaccine
MCT	Mast cell tryptase
MMR	Measles-mumps-rubella
OPV	Oral polio vaccine
P	Pertussis
PCV	Pneumococcal conjugated vaccine
T	Tetanus
TBE	Tick-borne encephalitis
TIV	Trivalent inactivated influenza vaccine
WAO	World Allergy Organization
WHO	World Health Organization
YF	Yellow fever

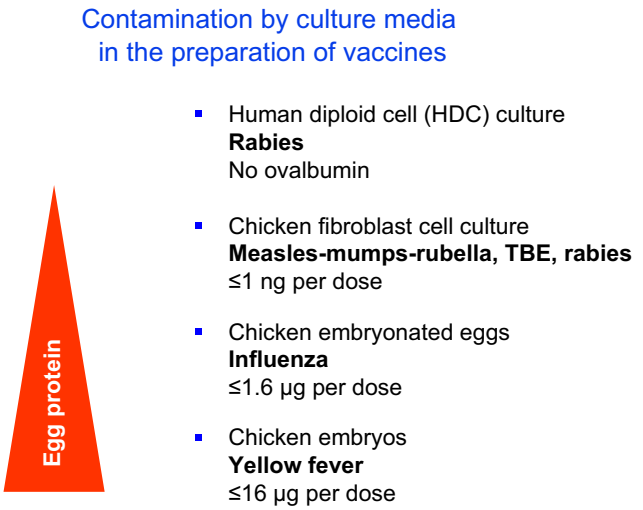

FIGURE 1 Contamination by culture media in the preparation of vaccines. [Colour figure can be viewed at wileyonlinelibrary.com]

be present in some brands of diphtheria, tetanus and pertussis (DTP) vaccines, and oral polio vaccine (OPV).[5]

Thiomersal, aluminum, and phenoxyethanol can cause local reactions (mostly delayed-type hypersensitivity such as contact allergy and maculopapular rash), but have not been reported as a cause of proven anaphylaxis. Nowadays, thiomersal is rarely used as a preservative in vaccines, and its clinical importance as an allergen is doubtful.[6] Local reactions can nevertheless be more frequent among sensitized recipients.[7] Formaldehyde is still used in vaccine preparation,[8] but no IgE-mediated reactions to formaldehyde have been recently described.

Trace amounts of antimicrobials could theoretically cause anaphylaxis in sensitized patients; however, few reports are found in the literature. Although the association of neomycin sensitization and IgE-mediated allergic reactions to vaccines is poorly supported by the literature, a history of anaphylaxis to neomycin is considered a contraindication for immunization with vaccines containing neomycin.[9] Contact dermatitis with neomycin is more frequent.[9]

Vaccine vial stoppers or syringe plungers may contain natural latex rubber and pose a theoretical risk to latex-allergic patients.[10] Incidence is, however, low; only one report of an anaphylactic reaction in a latex-allergic patient was attributed to rubber in the stopper [11] of an hepatitis B (HB) vaccine. Human papillomavirus vaccines (HPVs) may contain residual yeast protein (*Saccharomyces cerevisiae)* from the production process. Rarely, an immediate reaction can happen after vaccination in yeast-allergic patients.[12] Yeast is also used in the production of the carrier CRM197 and could theoretically be contained in PCV-13 and some meningococcal and oral typhoid vaccines.[1] Dextran has been implicated in allergic reactions to some vaccines that have been withdrawn from the market.[1] Alpha-gal anaphylaxis minutes after immunization with zoster vaccine (OKA VZV) has recently been suggested in a patient with a documented history of red meat allergy. It has been postulated that the patient has reacted to alpha-gal from porcine gelatin or bovine calf serum in the vaccine.[13]

3.2 | Immune response to vaccines in relation to allergy

Statement: Determination of vaccine antigen-specific IgE is not recommended in the work-up of allergic reactions to vaccines, because IgE production can be part of the normal vaccine immune response and it is mainly not commercially available.

Specific IgE response to vaccine antigens can frequently be observed alongside IgG responses.[14] After primary immunization, about 50% of infants have detectable IgE against D and T toxoids[14]; after booster, more than 90% of vaccines have detectable IgE against the vaccine antigens.[15] The IgE response to vaccine antigens, mediated by a Th2-type immune response, seems more pronounced among atopic individuals.[14] It has therefore been hypothesized that immunization of atopic children may be associated with clinical vaccine allergy. However, no relevant clinical allergic reaction to microbial antigens in vaccines has been reported before two recent papers (see 3.1).[3,4] In young children, Th1-/IFN-associated and Th2-associated gene networks coexist in an apparent state of dynamic equilibrium, but atopic individuals have Th2-dominant allergen-specific responses, and their Th1/IFN networks are disrupted and downregulated.[16] Therefore, the optimal immunogenicity/reactivity balance of new vaccines will have to be specifically defined in this population.

3.3 | Systemic and local reactions

Statement: Anaphylaxis following vaccination is rare and has to be distinguished from vasovagal reaction. Local reactions are common and mainly due to non-allergic immune reaction.

Classification of hypersensitivity reactions to vaccines is challenging as the underlying mechanisms are poorly understood, and no consensus exists in the literature. Several classifications have been proposed, based on the extent, severity and timing of the reaction.[17] In this paper, reactions after vaccination are categorized as systemic and local reactions according to WHO.[18]

Systemic reactions

Among AEFI, systemic severe allergic reactions are rare but important. Anaphylaxis is an acute severe, potentially life-threatening emergency[19] (Table 2). Symptoms usually start within the first hour after immunization.[17] Reactions occurring more than 2 hours after exposure have been described, but are uncommon, and the causal relationship is unclear.[20] The incidence of anaphylactic reactions to certain vaccines is listed in Table 3. In typical cases with multi-organ

TABLE 2 Clinical criteria for diagnosing anaphylaxis (NIAID and EAACI)

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. 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
   a. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% decrease in systolic BP[a]
   b. Adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.
[a]Low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 y, less than (70 mm Hg + [2× age]) from 1 to 10 y, and <90 mm Hg from 11 to 17 y.
From: Hugh Sampson, and used in the position paper in Allergy 2014.[19]

TABLE 3 Anaphylaxis after vaccination, rates; adapted from NcNeil et al., 2016.[20] Brighton Collaboration case definition

Vaccine	Rate/Million doses	Total doses administered (in millions)
Hib	0	1.14
Hepatitis B	0	1.29
Influenza (TIV)	1.59	8.83
MMR	5.14	0.58
Pertussis (Tdap)	2.89	3.12
Pertussis (DTaP)	2.07	1.45
Pneumococcal (PCV13)	0	0.74
IPV	1.65	1.22
All vaccines*	1.31	25.17

*All vaccines described in the McNeil paper

involvement and objectively measurable signs in the four organ systems (skin, gastrointestinal tract, respiratory tract, and cardiovascular system), diagnosis can be easy and certain. In other cases, diagnosis may be difficult, and anaphylaxis has to be differentiated from vasovagal reaction after immunization (Table 4).

Anaphylactic reactions can be IgE-mediated or non-IgE-mediated; these can be difficult to differentiate clinically.

Non-allergic systemic reactions should be distinguished from systemic IgE-mediated reactions. Fever and non-specific systemic symptoms, such as skin rash, irritability, malaise, diarrhea, headache, muscle pains, and syncope are the most common systemic events after vaccination. Skin rashes, delayed urticaria, and/or angioedema or maculopapular skin rash often occur a few hours after vaccine administration. Non-specific activation of the immune system and non-specific degranulation of mast cells may be the cause.[21]

Local reactions

Local reactions include pain, redness, and/or swelling at injection site. Mild local reactions are attributed to non-specific inflammation due to the injection itself and injection of foreign materials. Large local reactions are less common and usually occur within 24-72 hours after vaccine administration. However, after a fifth dose of DTaP vaccine in four- to five-year-olds, about 1/4 of the children will get a large local reaction, usually well tolerated and resolving within 1-2 weeks.[22] Typical large local reactions and chronic subcutaneous nodules with itching and eczema are considered type IV reactions. Local reactions could also be Arthus type, that is, type III hypersensitivity. For these, the administration technique is important; deeper injection is associated with a lower rate of local reactions, especially in children younger than 3 years.[23] Injection in the arm is associated with higher incidence of reactions than injection in the thigh.[24] Traces of antibiotics, thiomersal, and formaldehyde can contribute to local reactions. The incidence of local reactions for certain vaccines is shown in Table 5.

3.4 | Possible development of allergy by immunization

Statement: Routine childhood immunization does not promote the development of allergic sensitization to common inhalant or food allergens or the development of allergic disease.

Immunizations have been widely suspected of promoting the development of allergies, with related concerns contributing to delayed or incomplete immunization.[25]

Epidemiologic studies have addressed a possible effect of immunization on allergy development in general. However, immunizations had no effect on allergic disease in several studies.[26,27] Higher cumulative vaccine antigen doses were associated with less allergic sensitization, allergic disease,[28] and less severe infant eczema.[29] In concordance, regional immunization rates were inversely associated with allergic disease.[30] Pertussis immunization has been suspected as pro-allergic because P toxin, included in cellular and acellular vaccines, can enhance IgE formation. However, data from a randomized intervention trial failed to show an increased risk of allergic sensitization or allergic disease up to 7 years of age.[31] In a large ecologic study, there

TABLE 4 Differentiation of anaphylaxis and vasovagal reaction

Possible symptoms	Anaphylactic reaction	Vasovagal reaction
Onset from time of immunization	Few minutes delay, typically within 30 min	During or shortly after injection
Respiratory	Wheezing, stridor	Normal or hyperventilation
Cardiovascular	Tachycardia, hypotension	Self-limited bradycardia, hypotension
Skin	Flushing, itchy rash, angioedema, urticaria	Pale, sweaty, cold, clammy
Gastrointestinal	Abdominal cramps	Nausea, vomiting
Neurologic	Loss of or altered consciousness, little response to prone positioning	Self-limited loss of consciousness, good response to prone positioning

Adapted from the Green Book August 2013, chapter 8, available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147868/Green-Book-Chapter-8-v4_0.pdf.

TABLE 5 Common, minor local vaccine reactions

Vaccine	Local adverse events (pain, swelling, redness)
Measles/MR/MMR	1 of 20 (mild rash)
Pertussis (DTaP)	Up to 1 of 4[a] (redness or swelling)
Pneumococcal conjugate (PCV 13) Pneumococcal unconjugated	1 of 3 (swelling) 1 of 2 (redness or pain)
Tdap	1 of 5 (redness or swelling) (3 of 4 pain)
Varicella	1 of 5 (soreness or swelling)
HPV (quadrivalent)	1 of 3 (redness or swelling)

[a]More often after the 4th and 5th dose.
Source: http://www.cdc.gov/vaccines/vac-gen/side-effects.htm

was no increased risk of requiring asthma medication in adolescents whether they had had P vaccination in infancy or not.[32]

Lower rates of allergic symptoms and allergic sensitization have been found among children with measles, but no association was found between measles vaccination and allergic symptoms.[33] DT immunization was associated with asthma in one study,[34] but not in others. Importantly, several further studies could not find any effect of MMR,[28,35] *Haemophilus influenzae* type b[36] or DTP[27] vaccinations on allergic sensitization or allergic disease. Mycobacterial lipoproteins elicit particularly strong Th1 responses. Consequently, it has been suggested that BCG vaccine administered in infancy might protect against the development of Th2-mediated allergic disease. A systematic review and meta-analysis[37] suggested that BCG vaccination is unlikely to be effective in preventing allergic sensitization or eczema, but might offer transient benefits against developing asthma.

4 | SPECIFIC VACCINES AND ADVERSE EVENTS

4.1 | Diphtheria, tetanus, pertussis vaccines

True allergic or immediate hypersensitivity reactions to routine vaccines are rare, estimated as 2 per million doses for DTaP.[20] In Japan (1994-2004), the total incidence of anaphylaxis was 0.95 per million doses of DTaP, but the authors were unable to identify a causal relationship to any vaccine component.[38] Neither skin prick tests (SPT) nor specific IgE analyses could predict these reactions.

Specific IgE antibodies to D, T, and P vaccines are common after booster doses if primary vaccination was with an acellular P vaccine; this response was exaggerated in atopic children with clinical manifestations.[39] Elevated P toxin IgE levels are associated with local reactions.[40] As the adjuvant effect of aluminum on IgE production is well known, controversy exists regarding the extent to which the toxoids cause the local reactions.[22]

Casein, a cow's milk protein, has been implicated as a cause of anaphylaxis to DTP-containing vaccines in children with severe milk allergy and high specific milk IgE levels.[41] Whereas these data need to be confirmed, trace amounts of casein have been demonstrated in some brands of DTaP or Tdap-containing vaccines prepared in a medium derived from cow's milk protein. However, it is important to recognize that most patients with even severe milk allergy tolerate childhood vaccines, so no changes to vaccine recommendations have resulted from these case reports.[42]

4.2 | Influenza vaccination

Vaccines for influenza prevention include the trivalent and quadrivalent inactivated influenza vaccines (IIVs), recombinant subunit vaccine

(RIV), and live attenuated three and quadrivalent influenza vaccines (LAIVs). According to the Centers for Disease Control and Prevention (CDC) and WHO, individuals from 6 months of age should be vaccinated against seasonal influenza [http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm?s_cid=rr6505a1_w; August 26, 2016].

IIVs have generally been found to be safe for adults and children with asthma,[43,44] including those with severe disease.[44] Medically significant wheezing was increased in children aged 6-23 months who had received LAIVs but not in children aged 2-5 years.[45] Moreover, a recent Cochrane review did not show any significant increase in acute asthma exacerbations immediately following IIVs in adults or children older than 3 years of age.[46] In addition, data support the safety and efficacy of LAIVs among children aged 2-17 years with mild to moderate asthma or with a history of wheezing,[47] but data regarding individuals with severe asthma/active wheezing are limited.

Recent studies provide robust evidence that IIVs with low ovalbumin content (<0.12 μg/mL) can be administered safely in egg-allergic patients, even in those with severe reactions.[48-50] Data regarding the safety of LAIVs in egg allergy are emerging. The upper ovalbumin content of LAIVs is, reported on the package insert, 0.24 μg per 0.2 mL dose, but independent laboratories found it to be very low, between 0.00013 and 0.0017 μg per 0.2 mL dose.[17] The ovalbumin content is published prior to the influenza season each year (https://www.gov.uk/government/collections/vaccine-update). The recent SNIFFLE studies combined found no systemic vaccine reactions and only 17 (1.6%) mild self-limiting reactions in 1242 LAIV doses given to 1061 egg-allergic children, including 335 with previous anaphylaxis to egg.[49,50] Based on these results, UK immunization recommendations no longer consider egg allergy a contraindication to LAIV, unless a child has had life-threatening anaphylaxis requiring intensive care treatment.[51]

4.3 | MMR vaccine

MMR vaccination has been considered a problem in egg-allergic children because the attenuated viruses are cultured in hen's embryonic fibroblasts, and the vaccines could contain traces of ovalbumin. However, several studies revealed that MMR vaccination is safe in infants and children with egg allergy.[52] There are, however, reports of allergic reactions to gelatine.[53]

Recent data confirm that infants and children allergic to hen's egg can be vaccinated in GP settings and do not have to be referred to specialized centers. A review of the Irish pediatric emergency department vaccination program for patients at risk of allergy/anaphylaxis analyzed the clinical outcome of 374 children referred due to a history of allergy or anaphylaxis after 446 vaccine doses, including 310 (69.5%) MMR doses. Only six patients (1.3%) experienced a minor immediate reaction to a vaccination.[54] In the Danish Childhood Vaccination Programme, 32 patients with sensitization to hen's egg displayed no reaction to MMR vaccine (Priorix® GlaxoSmithKline, London, UK).[55]

The British Society for Allergy and Clinical Immunology (BSACI) guidelines for the management of egg allergy recommend that children with egg allergy should receive routine MMR vaccination in primary care.[56]

4.4 | Pneumococcal and meningococcal vaccines

There are no contraindications to pneumococcal or meningococcal vaccines for patients with allergy except for those with other known hypersensitivity to vaccine components including D (or CRM 197) or T toxoids present as carriers in conjugated vaccines, or previous severe reaction to the vaccine.

4.5 | BCG vaccine

Most adverse reactions after BCG vaccination are infectious. Hypersensitivity reactions are mostly mild injection site reactions and lymphadenitis, whereas systemic reactions, such as the immune reconstitution inflammatory syndrome, are rare.[57]

4.6 | Polio vaccination

A theoretical risk of hypersensitivity reactions exists due to trace amounts of streptomycin, neomycin, and polymyxin B in both injectable and oral polio vaccine. The latter may also contain cow's milk proteins [5] (see 3.1). Confirmed anaphylaxis is extremely rare. Data from the UK, Canada, and the USA indicate rates of 0.65-3 anaphylaxis events per million doses of vaccine administered.[58]

4.7 | Hepatitis B vaccination

Hepatitis B (HB) vaccines are manufactured in yeast cells, and residual *Saccharomyces cerevisiae* antigens can be present in the product. Anaphylaxis in children with HB vaccine has been rarely reported; it has been related to possible hypersensitivity to yeast.[52] Anaphylaxis has been reported in a further HB vaccine recipient with the causative agent most likely being latex.[11]

4.8 | Yellow fever vaccine

Demand for the vaccine is increasing, with more than 60 million doses administered annually.[59] The YF vaccine Stamaril (UK) contains 0.13-0.61 ug/mL of egg protein,[60] and YF-VAX contains 2.43-4.42 ug/mL of egg protein,[59] used in USA. Compared to the recommendations for egg protein in TIV, egg protein in Stamaril is not high. However, no large studies about egg allergy in YF vaccines exist. Anaphylaxis risk from YF vaccine ranges from 0.42 to 1.8/100 000 doses.[60] With the low ovalbumin content in the present YF vaccine, desensitization will probably not be necessary henceforth. However, egg-allergic persons should be evaluated by an allergist before YF vaccination (see 5.3).

4.9 | HPV

IgE-mediated anaphylaxis to quadrivalent HPV vaccine is rare, 2.6/100 000.[61,62] An expert panel classifying suspected cases using the Brighton Collaboration (BC) case definition of anaphylaxis found eight cases. The panel rejected the possibility that these could have

been vasovagal episodes or somatic conversion disorder misdiagnosed as anaphylaxis. The anaphylaxis rate was higher than in previous vaccination programs. However, there was no anaphylactic shock.

Allergenicity of the vaccine is biologically plausible for HPV virus-like particles, which are highly immunogenic when injected.[63] Any residual amounts of yeast proteins might cause allergic reactions[12]; the quadrivalent vaccine also contains polysorbate 80 as a stabilizer, which might trigger anaphylaxis.[64]

4.10 | TBE - tick-borne encephalitis vaccine

In the 1990s, the TBE vaccine (Encepur, Chiron Vaccines) caused an immediate allergic reaction in approximately 1/50 000 doses and was modified in 1998. The stabilizer polygeline (a gelatine) was replaced with human serum albumin, and the immediate reactions decreased to 0.08-0.24/100 000 doses.[65]

5 | DIAGNOSTIC ASPECTS OF SEVERE REACTIONS

In the setting of vaccination reactions, different definitions and grading systems for anaphylaxis have been proposed. Our group prefers the case definition of anaphylaxis established at an NIH consensus conference and subsequently endorsed by WAO and EAACI (Table 2, NIH criteria for anaphylaxis). The definition is widely accepted by allergists.

5.1 | Diagnostic tests of severe reactions

Serum mast cell tryptase (MCT) levels have been used as a marker of anaphylaxis,[66] although its predictive value for vaccine-associated anaphylaxis has not been formally established. We recommend MCT level determined within 2 hours after a systemic vaccine reaction, as well as serum baseline tryptase evaluated at least 48 hours afterward. A significant increase in MCT level from baseline is a strong indicator of a systemic mast cell-mediated hypersensitivity reaction.

If a patient has had a suspected allergic reaction to a vaccine, identification of the culprit allergen is important, because it may permit the use of a vaccine formulation without the offending allergen for subsequent doses and also to avoid other products containing these allergens.

> Statement: Pre-immunization allergy tests (skin test, specific serum IgE) as screening do not reliably predict or exclude future allergic vaccine reactions and are not recommended.

Testing serum IgE to microbial components is frequently unhelpful in preventing allergic vaccine reactions because the IgE response is part of the regular immune response and does not predict an allergic reaction to a vaccine (see section 3.2). Specific IgE tests are not commercially available for most microbial components. For some other constituents (eg, ovalbumin and gelatin), the predictive capacity for reaction to vaccines is rather low. False-positive tests may occur as many more individuals are allergic and sensitized to a given allergen than those reacting clinically on exposure to the minute amounts of this allergen encountered during immunization.

> Statement: After a vaccine reaction, preferably specific IgE to egg/gelatin/latex/yeast should be analyzed when suspected; otherwise skin test is recommended. However, lack of data on the sensitivity and specificity of skin test to vaccines in different concentrations makes them unreliable in predicting or excluding future allergic vaccine reactions.[48] More studies are needed to establish thresholds for the prediction of anaphylaxis to a vaccine.

Skin testing can provide additional information about sensitization and the probability of a hapten/allergen being the culprit. This could help evaluate severe vaccine reactions. Skin testing should start with SPT (undiluted), a positive reaction being a sign of an allergic reaction. Skin prick testing sensitivity to vaccines itself is low. If negative, intradermal testing (0.02 mL) should follow (1:100 dilution, 1:10 dilution, see Figure 2). Undiluted intradermal testing is discouraged because of the high rate of irritant (non-relevant) reactions. False-positive reactions may also occur at 1:10 dilution especially with influenza, MMR, and varicella vaccines and were even described for 1:100 dilutions in 5% of controls for DT and DTaP, and 15% for influenza.[67] Thus, positive reactions should be regarded as indicative rather than confirmatory, and further studies are needed. Positive and negative controls are mandatory.

In non-immediate local reactions, contact dermatitis or subcutaneous nodules, type IV hypersensitivity to preservatives, aluminum, or antibiotics may be assessed by patch testing. Although patch testing is not essential for therapeutic decisions, it could help in choosing alternative vaccines if available.

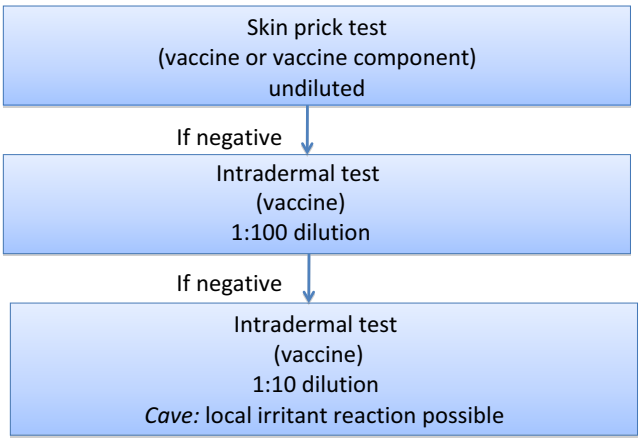

FIGURE 2 Diagnostic algorithm in case of suspected allergic reaction to vaccine or vaccine component. [Colour figure can be viewed at wileyonlinelibrary.com]

5.2 | Local aluminum reactions

Statement: Aluminum-allergic persons can be vaccinated with aluminum-containing vaccines without inducing severe reactions, although new itching nodules may appear.[68]

Aluminum compounds, such as aluminum phosphate and aluminum hydroxide, are used as vaccine adjuvants and can induce type IV hypersensitivity (contact allergy).[69] Contact hypersensitivity to aluminum was demonstrated in 77% of the children with itching nodules and in 8% of the symptomless siblings who had received the same vaccines, that is, not a specific test for symptoms. Subcutaneous nodules may develop and persist for months to years before they gradually disappear.[68] Risk factors for aluminum sensitization at vaccination seem to be the dose of aluminum, the number of vaccinations, and the aluminum compound, where aluminum hydroxide seems more liable to induce sensitization than aluminum phosphate.

In a prospective study of 4758 children, 0.66% (n = 38) developed an itching granuloma after Pentavac® (DTaP-Hib-Polio vaccine). When Prevenar® (conjugated pneumococci vaccine) was added, the percentage was 1.2%, and most of them had positive patch tests to aluminum.[70] Patch tests with aluminum chloride hexahydrate 2% and elemental aluminum have been suggested, but some cases may be missed unless tested with aluminum chloride hexahydrate 10%.[71] Patch tests should be read after 3 or 4 days and after 1 week.[72] An itching granuloma and a positive epicutaneous test are illustrated in Figures 3 and 4.

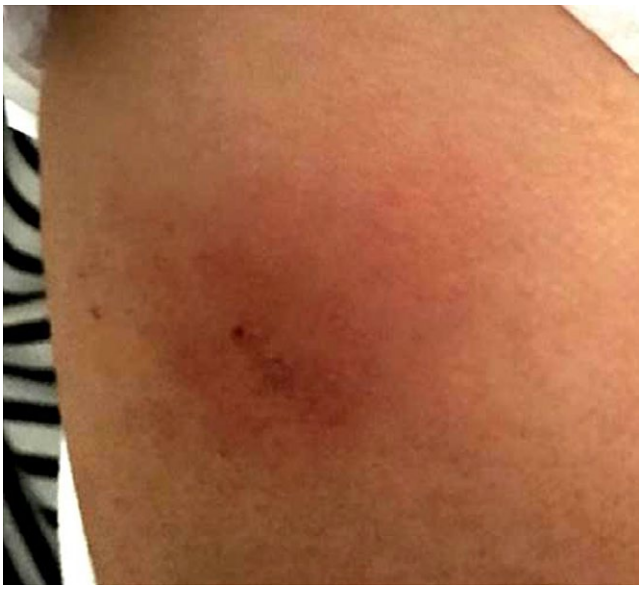

FIGURE 3 Local reaction after vaccination at 3, 5, and 12 mo of age with DTaP-Hib-polio

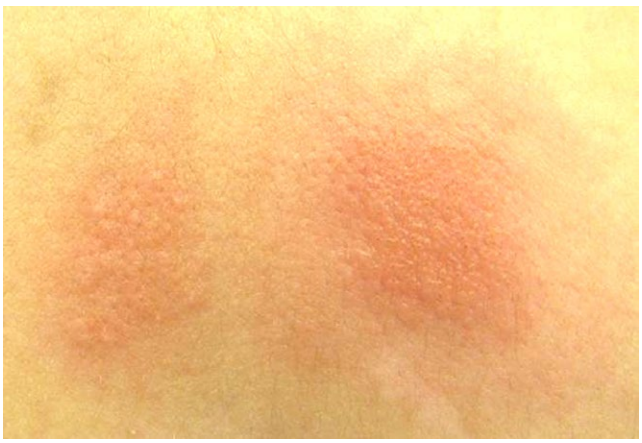

FIGURE 4 Epicutaneous test with aluminum 2% in a 2-y-old child

5.3 | Identification of patients at risk and contraindications to immunization

Currently available tools cannot predict most of the severe allergic reactions following immunization. Patients who manifested a severe allergic reaction following immunization are considered at high risk of the next immunization and merit special precautions[73] (see 6.2).

Patients who reacted clinically to an allergen contained in the vaccine are at increased risk of allergic vaccine reactions. Although specific sensitization can increase the risk of allergic reaction to vaccines, atopy in general does not seem an important risk factor.[74]

Statement: Atopy and family history of allergy or asthma are not per se contraindications for immunization.

Few real contraindications for routine immunizations exist. Patients are often falsely labeled as allergic although, in most cases, administration of another dose is well tolerated. Patients with anaphylaxis or other severe (life-threatening) adverse events following immunization should not be re-immunized with the same vaccine before allergological investigations are completed. Most patients can be immunized safely (see abstract).

Statement: Local reactions to antibiotics are not a contraindication for immunization.

Previous localized delayed-type reactions to thiomersal, neomycin, or aluminum are not considered absolute reasons for withholding vaccines because the risks of not being immunized outweigh problems caused by local reactions.

Patients with mastocytosis, particularly children, are at increased risk of mast cell-mediated reactions after various triggers including routine vaccination. Therefore, we recommend administering vaccines in single injections, avoiding co-administrations, under medical supervision for at least 30 minutes.[75]

6 | PRACTICAL ASPECTS

As it is important to evaluate whether there is an evident risk of allergic reactions, patients should be asked whether they experienced allergic symptoms following previous vaccinations. Also, underlying uncontrolled diseases must be ruled out.

Statement: Expertise and equipment for treating anaphylaxis should always be available when immunizing.

All vaccinating units need to have adrenaline, antihistamine, and oral steroids at hand and in most countries beta-2-inhalers. For patients at risk, also parenteral steroids, oxygen, and a defibrillator should be available close to where the vaccinations are administered.

6.1 | Immunization of patients at increased risk

Statement: A history of a previous allergic reaction to a vaccine or to one of its constituents should be ascertained before immunization.

Identification of increased risks through clinical history is essential for risk minimization. Patients with a positive history should be investigated for type I hypersensitivity to the vaccine and its ingredients, and vaccination should be managed following specific recommendations for subjects allergic to vaccine components (see 5.1).

Statement: Immunization under standard conditions (standard vaccine, full dose, no mandatory observation time) is recommended for patients with:
-Allergic sensitization but without a clinical reaction to an allergen contained in the vaccine;
-Allergic disease not related to a vaccine;
-Family history of allergy.

Statement: If, based on a positive benefit/risk balance, an additional dose is needed after an anaphylactic vaccine reaction, a vaccine preparation without the offending ingredient should be preferred.

Statement: Egg-allergic patients can be MMR-immunized under standard conditions.

Data from clinical studies suggest that the small amount of residual egg protein in MMR vaccines represents an exceptionally uncommon risk of egg-allergic patients.[76]

Statement: Patients with manifest egg allergy who intend to be influenza-immunized should only be vaccinated with low egg (<0.12 μg/mL) vaccines:
(A). Previous non-anaphylactic reactions to egg: can be influenza-vaccinated under standard conditions
(B). Previous anaphylaxis to egg: single-dose vaccination with a personal staff experienced in recognizing and treating anaphylactic reactions under observation (minimum 1 hour).

Gelatine-allergic patients could most often receive an alternative vaccine without gelatine as a stabilizer. Otherwise, SPT with the vaccine should be performed and, if positive, fractionated vaccine doses administered.[17]

6.2 | Fractionated immunization or graded desensitization. Management of allergic reactions to vaccines

Patients sensitized to a vaccine or its components with previous anaphylaxis to this vaccine should be revaccinated only if absolutely necessary. If at all possible, a vaccine without the offending allergen should be chosen. Where this is not possible, two pragmatic (not evidence-based) approaches have been used:

Assuming that a smaller vaccine dose does less harm than a full dose, patients with negative skin tests to the vaccine but with a history of anaphylaxis or other severe allergic reaction can be immunized with split-dose vaccination. Initially, 10% of the dose is given, followed 30 min later by the remaining 90% provided that no allergic reaction has occurred after the initial dose.

As in rapid desensitization, immunization in graded doses may reduce the risk of anaphylaxis. Increasing vaccine doses are administered every 15-30 minutes provided that there are no signs of allergic reaction (0.05 mL of 1:10 dilution, then 0.05 mL, 0.1 mL, 0.15 mL, 0.2 mL, of a 0.5 mL full-strength vaccine).[17] Importantly, this protocol only leads to transient desensitization, and patients undergoing this protocol successfully must still be considered allergic to the vaccine. These vaccination approaches must only be used in a controlled setting where prompt treatment of anaphylaxis by experienced staff is available (see Table 6).

6.3 | Delay of routine immunization

Statement: Delay of routine immunizations is not recommended. Delay withholds protection from vaccine preventable disease, and there is no justifiable evidence that it would prevent allergic reactions or development of allergic disease.

TABLE 6 Pre-immunization testing and immunization in patients who had a suspected previous allergic reaction to a vaccine

Allergic reaction to previous vaccine dose	Skin test result	Vaccine administration	Precautions
Local reaction	Not needed	Full dose	No observation period
Anaphylaxis, systemic reaction	Negative	Allergen avoidance[a] if possible, split dose	60 min observation, IV line
Anaphylaxis, systemic reaction	Positive	Allergen avoidance[a] if possible, graded doses	60 min observation, monitoring, IV line

[a]Allergen avoidance does not mean no vaccination, but using an allergen-free vaccine or a low allergen content vaccine, if available.

One study reported that delaying primary DTP immunization beyond 2 months of age was associated with a 50% risk reduction of recorded asthma by age 7 years.[77] This effect could not be replicated [78] and may have been reporting bias. A further study of children with ≥2-month delay in the third DTP dose reported a 20% risk reduction in hay fever at school age.[79] In contrast, a recent large Swedish study did not show any increased risk of requiring asthma medication whether the first DTaP vaccine was administered at 2 months or at 3 months of age.[32] Studies on the effects of delaying other immunizations are lacking. The risk of vaccine-preventable disease outweighs a doubtful risk reduction in allergic disease.

7 | STRATEGIC ASPECTS

7.1 | Surveillance

Statement: EAACI should make efforts to register severe vaccine adverse events.

Strategies to monitor AEFI need to be developed, particularly those that may have an underlying allergic etiology. Here, EAACI can play an important role by encouraging the sharing of best practice and insights gained within and between member countries, and through fostering common surveillance approaches to assess beneficial and adverse impacts of immunization strategies. Greater use of electronic health record systems is likely to be the key to such efforts in the future.

Concerning pediatric patients, adverse reactions to vaccines are already the most common reactions reported to pharmacovigilance systems.

7.2 | Risk communication

Public interest in the field of risk communication and vaccines is growing, fuelled by contemporary debate about perceived adverse events and easy access to information via the Internet, which, however, increases the risk of misinformation. Although public confidence in vaccines may be decreasing,[80,81] the public's trust in healthcare workers remains well documented. Therefore, it is important to properly educate and train vaccine providers to maintain public acceptance of immunizations.[82]

The extensive scientific literature on risk communication includes several publications on immunization and allergy, but apart from advice on egg allergy,[56] few studies on risk communication specifically address allergy in connection with immunization. The general literature on risk communication highlights the value of transparency, sensitivity, and respect, with trust and confidence as essential elements.[81,83] There is no reason for other strategies when communicating risks concerning immunizations and allergy. Denying or diminishing known risks is unethical and can lead to a higher risk perception among the target group.[84]

7.3 | Education and information for health professionals

To communicate effectively with patients/carers and members of their teams, healthcare professionals need accurate, authoritative, and accessible information on the potential benefits and risks of immunizations. It is unrealistic to expect busy professionals to read, digest, and interpret the substantial body of epidemiologic and health services research on this subject. They also need tools to communicate these benefits/risks in an open, non-coercive way to foster relationship-building and trust between health providers and patients/carers. As a respected professional body throughout Europe, EAACI can play an important leadership and coordinating role by ensuring the consistency of key messages being transmitted to health professionals throughout Europe and by eliciting information on professional concerns and hitherto unanswered questions.

7.4 | Future vaccine development and use

Vaccination stimulates different types of Th cells and IgE production. Immunologic effects can be considerable, particularly when adjuvants are used. When trials of new vaccines or vaccine components

are planned, aspects of clinical allergy and its immunologic features should be integrated into research protocols. Also, both stabilizers and adjuvants in new vaccine compositions should be evaluated. New vaccines without egg protein and gelatine would be preferable.

7.5 | Research needs

A validated test predicting clinical reactions following vaccination would be of major benefit. Such a study could examine whether graded desensitization has a role in these situations, and the results could be further studied, potentially through a network within EAACI.

Aluminum gives local itchy granuloma from pediatric vaccinations in approximately 1% of cases. A change of adjuvant might be advisable.

Although extensive scientific research has not concluded that vaccination promotes allergic diseases, new data from ongoing studies, and new environmental factors and vaccine constituents will require us to conduct retrospective and prospective studies in the future.

CONFLICT OF INTEREST

See COI for the authors, respectively.

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