Vaccine Allergy

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KEYWORDS

• Vaccine allergy • Vaccine components • Toxoids • Hypersensitivity • Egg • Gelatin • Children

KEY POINTS

- Overdiagnosis of vaccine allergy is common and is considered a major public health problem.
- Usually, no allergy test is required in patients developing local reactions after vaccine administration as they are not associated with a higher rate of systemic reactions.
- In patients with a history suggestive of an immediate IgE-mediated hypersensitivity, a complete allergic work is mandatory to confirm or exclude an allergy.
- Egg allergic patients can received safely the influenza vaccine with some precautions and skin test to the influenza vaccine is no longer recommended before.
- In almost all cases, the vaccines can be administered using adapted protocols, even if the allergy tests are positive.

INTRODUCTION

Adverse events after vaccine administration are commonly reported in the general population and constitute a common problem in clinical practice. The most frequent reactions after immunization are local reactions and nonimmediate skin eruptions (ie, delayed urticaria or maculopapular or nonspecific skin rashes), particularly after injection of vaccines containing toxoids[1–5] and hepatitis B virus (HBV) vaccine.[6–9] The literature data strongly suggest that most of these clinical manifestations do not result from a hypersensitivity reaction but, instead, from a nonspecific inflammation as reflected by the usual tolerance of booster doses.[10,11] In the study by Gold and colleagues,[11] only 10% of children reporting generalized allergic reactions developed a reaction on reexposure but most of these reactions were not suggestive of a hypersensitivity reaction. A correct management of these reactions is an essential

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component of health care because they are clearly associated with a decreased vaccination rate in the general population. Indeed, most of these patients are falsely labeled as allergic, with a major impact on health, both individual and public. In addition, the economic impact is very important.

True allergic reactions to vaccines are rare but their identification is important because they can be life-threatening. Rarely, the vaccine itself is responsible for immediate hypersensitivity reactions, especially vaccines containing toxoids[2,12–14] and pneumococcal antigens.[15,16] In addition to microbial components, residual components of the culture medium, as well as preservatives, stabilizers, and adjuvants added to vaccines, may elicit hypersensitivity reactions in susceptible individuals. Particularly, gelatin used as a stabilizer in many vaccines has been incriminated in allergic reactions to vaccine.[17–22] Several recent studies led to a major change in paradigm. They showed that most patients with egg allergy, even those with severe egg allergy, can safely receive influenza vaccine under certain conditions.[23,24] Finally, local and generalized nonimmediate reactions can result from hypersensitivity to the excipient,[25–27] adjuvant,[28–31] stabilizer,[19,32–34] and microbial component itself.[35]

This article discusses the different types of allergic reactions after immunization based on the timing (immediate vs nonimmediate) and the extent of the reaction (local vs systemic). The different vaccine components potentially responsible for an allergic reaction are discussed, as well as the management of patients with a history of reaction to a specific vaccine and those with a history of allergy to one of the vaccine components.

LOCAL REACTIONS TO VACCINES

Local reactions are the most frequent adverse event after immunization and have an important impact in clinical practice. Indeed, these reactions are often associated with major discomfort, particularly pain, and patients are often falsely labeled as allergic.

Different Types of Local Reactions and Pathomechanisms

Based on the clinical aspect and the timing of reaction, different types of local reactions can be distinguished:

- Mild local reactions are the most frequent type of local reaction after vaccine administration and are benign. These mild local reactions result from a nonspecific inflammation due to the injection itself as well as injection of foreign material.
- Large local reactions are less common and are characterized by pain, swelling, and redness at the injection site, usually occurring within 24 to 72 hours after vaccine administration and regressing typically in 2 to 3 days.[36–42] Important local inflammatory reactions are particularly encountered after injection of vaccines containing toxoids but can occur after administration of other vaccines, particularly HBV, pneumococcal, and *Hemophilus influenzae* vaccines.[6–8,43,44] These reactions may represent an Arthus reaction (ie, important local inflammatory reaction) in patients with preexisting IgG antibodies from earlier immunizations.[3,45,46] Of note, although receiving multiple doses of vaccine has been identified as a risk factor, shorter interval between the doses was not associated with higher rates of Arthus reactions.[47,48] Nevertheless, these typical large local reactions can occur at the first vaccine injection or during booster doses made with batches of vaccines containing high concentrations of toxoids or aluminium hydroxide, independent of the concentrations of serum antibodies to tetanus, diphtheria, or *Bordetella pertussis*.[41,42] The relationship between the content of toxoids or aluminium hydroxide in the vaccine and the frequency of local

inflammatory reactions is inconstant. A recent study showed that the frequency of large local reactions to Diphtheria-Tetanus (DT) vaccines was significantly increased in mice preimmunized with combined vaccines containing vaccine acellular pertussis; however, the pathomechanisms explaining this adjuvant effect is far from clear.[49] Based on these data, it is likely that most of these accelerated large local reactions result from a nonspecific inflammation induced by a variety of factors, including a high content of aluminium hydroxide and/or substances of microbial origin. In most cases, boosters injected sequentially with monovalent vaccines containing limited number of vaccine antigens are well tolerated.[11,13,50]

- Extensive limb swelling is less common but may be impressive for the patients. It looks like a benign edema (ie, swelling and mild redness) and is usually painless. It probably results from extravasation mechanisms still poorly understood.[51–53] By definition, these reactions extend at least to the elbow or knee.
- Subcutaneous nodules have been described in up to 19% of patients receiving vaccines containing aluminium hydroxide.[28,54–58] Although these lesions usually regress spontaneously within a few weeks, few cases of persistent nodules have been reported.[54,56–58] Patch tests with aluminium salts are often negative. Most of these reactions result from a nonspecific foreign body inflammation as demonstrated by a significant positive correlation between the concentration of aluminium hydroxide and the frequency and size of nodules.[58,59] However, Bergfors and colleagues[57] found that most subjects who developed persistent nodules had positive patch tests to aluminium.[60] Finally, the positivity of delayed-reading intradermal tests to tetanus toxoid suggested a nonimmediate hypersensitivity to toxoids in children developing sterile abscesses.[35] However, a relatively high number of positive responses in skin tests to toxoids were also observed in control subjects.[45,61–63]
- Local eczema lesions have been mainly reported in adults immunized with vaccines containing aluminium hydroxide,[29–31] thimerosal,[26,64] and formaldehyde.[27] A nonimmediate hypersensitivity has been suggested by positive patch tests to these components.[28–30,64–66] Of note, generalized eczema has also been reported after vaccine administration.[67,68]
- Nevi associated with hypertrichosis are rarely reported after administration of various vaccines (eg, bacille Calmette-Guérin [BCG], tetanus, and smallpox), as well as after allergenic extracts used for desensitization.[69–71] The causal components responsible for the reaction, as well as the exact pathomechanisms of such reaction, remain unknown.

Diagnosis and Management of Local Reactions After Vaccine Administration

Management of patients with history of local reaction after vaccine injection is described in **Fig. 1**. Usually, no allergy test is required in patients developing local reactions after vaccine administration because they are not associated with a higher rate of systemic reactions on reexposure. However, measurements of serum vaccine-specific antibodies (IgM or IgG) are indicated in patients with suspicion of Arthus reaction.[24] Indeed, levels of antibodies associated with protection from vaccine-preventable disease has been proposed.[24] If patients reach the established level associated with protection from disease, consideration can be given to withholding additional doses, although the induced immunity might be lower than if all doses were injected.[24] From another point of view, positive late responses to intradermal tests have been reported in adult subjects who developed an Arthus reaction after receiving a booster dose of DT vaccine[45] but these results were not found in

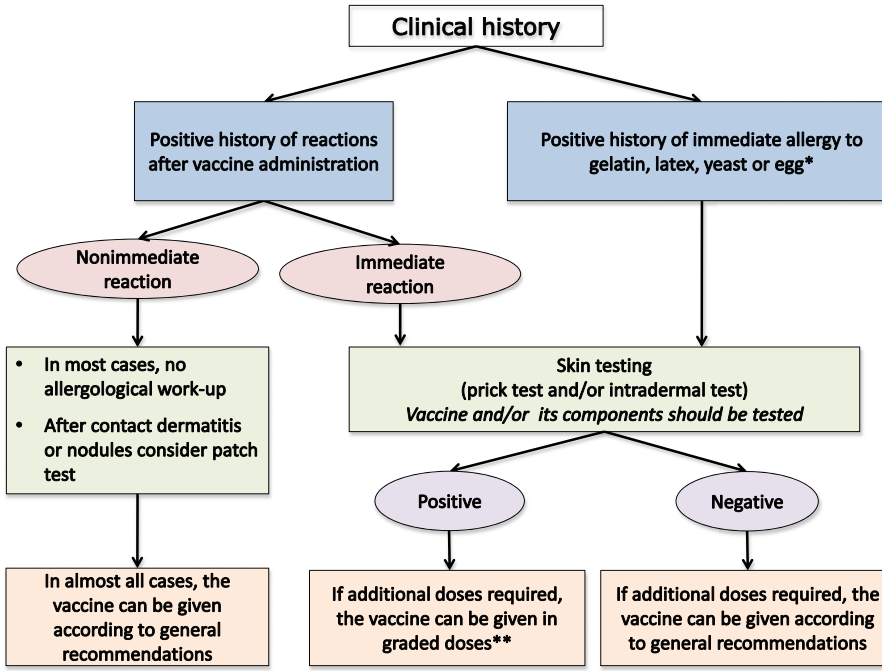

Fig. 1. Management of patients with suspected hypersensitivity to a vaccine and of patients with known allergy to a vaccine component. * for egg allergic patients, see text; ** Ref[110] (*Form* Caubet JC, Rudzeviciene O, Gomes E, et al. Managing a child with a possible allergy to vaccine. Pediatr Allergy Immunol 2013 http://dx.doi.org/10.1111/pai.12132. [Epub ahead of print]; with permission.)

children.[13] In patients reporting important local inflammatory reactions after injection of combined vaccines, sequential injections of single or limited numbers of vaccinating agents, every few days, preferably intramuscularly, are usually well tolerated.[72,73]

In patients developing eczema or persistent nodules after vaccine administration, patch tests may be useful to demonstrate a delayed hypersensitivity to preservatives or adjuvants and to guide the physician to avoid vaccine and other products containing these incriminated components. However, a positive patch test is not accurate for the purpose of assessing a patient's ability to tolerate a vaccine and is not a contraindication to administer the vaccine following a risk-benefit analysis.[74]

Prevention

The risks of developing a local reaction after immunization are not well defined. However, decreasing the frequency of local reactions would clearly improve the vaccination rate in the general population. Recently, it was demonstrated that reactogenicity is reduced by using a correct needle length because a longer needle is associated with a lower rate of local reactions.[72,73] Similarly, the site of injection may influence the development of local reactions. Injection in the thigh in children less than 3 years is associated with fewer local reactions, which supports current recommendations.[75] On the other hand, patients with known sensitization to one of the vaccine components should receive a vaccine free of this component, if available. All these preventive measures will help improve the vaccination cover of the population.

SYSTEMIC REACTIONS TO VACCINES

Systemic reactions are far less common, with an estimated incidence between one and three reactions per million vaccine doses.[76,77] However, identification of these reactions is of major importance because they carry the risk of life-threatening anaphylaxis if the patient is exposed again.

Different Types of Systemic Reactions and Pathomechanisms

Different types of systemic reactions can be discerned, mostly based on the clinical characteristics and the timing of the reaction:

- Delayed urticaria and/or angioedema, or maculopapular or other nonspecific rashes, occurring a few hours after vaccine administration, are relatively common. The pathomechanisms of these reactions is not fully understood; however, a nonspecific activation of the immune system as well as a nonspecific degranulation of mastocytes has been proposed.[65]
- Immediate reactions usually occur within 1 hour after immunization and manifest as various combinations of IgE-mediated symptoms, mainly urticaria and/or angioedema, rhinitis, or wheezing and/or hypotension.
- Rarely, other serious reactions have been linked with some vaccines, including Guillain-Barré syndrome with swine flu influenza vaccine, transient rash with measles vaccine, and encephalopathy with *B pertussis* vaccine. These reactions are not discussed in this article.[24]

Patients with a History of Systemic Reaction to Vaccine

The main cause of consultation with an allergist regarding vaccine allergy is an adverse event following vaccine administration,[78] including systemic immediate or nonimmediate hypersensitivity reactions.

Systemic reactions due to hypersensitivity to microbial components

Rarely, hypersensitivity to a microbial component itself has been incriminated in patients who develop systemic allergic reactions after immunization. Although the most well known example is hypersensitivity to tetanus and diphtheria toxoids, specific hypersensitivity to other microbial components, such as pneumococcal or *B pertussis* antigens, has been described, mostly in single-case reports.

Hypersensitivity to toxoids Delayed urticaria and/or angioedema, as well as nonspecific skin rashes, have been reported in 5% to 13% of patients receiving vaccines containing toxoids.[3,5] Several studies, including skin tests (both immediate- and delayed-reading) and measurement of specific antibodies (IgE, IgM, IgG), 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 reexposure to the same vaccine.[11–13]

Although rare, real anaphylactic reactions to vaccines containing toxoids have been reported. Since the introduction of highly purified toxoids, the incidence of those reactions has decreased, ranging from 0 to 1 per 10,000.[79–85] Ponvert and colleagues[13] reported four subjects with positive skin tests to toxoids (one to diphtheria and three to tetanus toxoids) among six children with a history of severe anaphylactic reactions to vaccines containing toxoids. In addition, an immediate hypersensitivity to tetanus and diphtheria toxoids has been suggested by positive skin tests and/or specific IgE in six patients who developed an immediate urticaria. These results confirmed results from other investigators based on single-case reports.[2,3,13,14,79,86] However, Jacobs and

colleagues[3] reported on 95 adults with history of anaphylactoid reactions occurring within 2 hours after immunization. Only one subject had a positive immediate skin test to tetanus toxoid and tolerated the challenge without reaction. These discrepancies are probably explained by differences in subject selection, based on positive clinical history. On the other hand, false-positive specific IgE to these toxoids have been reported in many patients tolerating injections of vaccines containing tetanus toxoids (higher levels found in atopic subjects).[86–89]

Hypersensitivity to *B pertussis* antigen Urticaria and/or angioedema, as well as anaphylactic reactions after immunization, have been attributed to specific hypersensitivity to *B pertussis* antigen.[90,91] However, most of these studies did not include an allergic workup. Up to 65% of children immunized with *B pertussis* vaccines produce specific IgE to the microbial antigen, particularly atopic children immunized with acellular vaccines.[91–94] The concentrations of specific IgE to *B pertussis* are positively correlated with IgG responses and primarily reflect the immunogenicity of *B pertussis* antigens, instead of the allergenicity. In fact, no correlation has been demonstrated between IgE levels and the number of adverse reactions to vaccines, with the exception of inflammatory local reactions.[91] In animal experiments, the antigens of *B pertussis* have been shown to be potent adjuvants for IgE responses to unrelated antigens.[95,96] However, in humans, simultaneous administration of *B pertussis* vaccine and DT vaccine tends to inhibit IgE responses to toxoids.[88] The frequency of allergic reactions has been shown to be similar in subjects vaccinated with DT and DT combined with *B pertussis* (DTaP).

Hypersensitivity to pneumococcal antigens Except relatively frequent mild-to-moderate local reactions, pneumococcal vaccines are generally well tolerated. In the literature, most case reports of anaphylactic reactions to pneumococcal vaccine do not include an allergic workup.[43] However, immediate responses to skin tests and specific IgE were positive in two children reporting a severe anaphylactic reaction after injection of a pneumococcal vaccine.[15,16] Of note, skin tests and specific IgE were negative with the vaccine solvent (phenol) and the vaccine itself in 10 and 9 controls, respectively. Only one negative control (unvaccinated) had a positive skin test to the vaccine, suggesting a sensitization to *Streptococcus*, either through portage or unknown infection. These results support the good diagnostic value of these tests in patients with positive history of allergic reaction to pneumococcal vaccines.

Systemic reactions due to hypersensitivity to other vaccine components

In addition to microbial components, residual components of the culture medium, as well as preservatives, stabilizers, and adjuvants added to vaccines, may be responsible for allergic reactions to vaccines.

Gelatin and egg Gelatin and egg are among the most frequently incriminated components in hypersensitivity to vaccine. Although reactions to vaccine administration can be the revealing factor of an allergy to these components, the clinician is more often confronted with patients with a known allergy to these components who need to receive a vaccine containing these (see later discussion).

Yeast HBV and human papilloma virus (HPV) vaccines may contain traces of yeast proteins derived from cell cultures,[97] with a potential risk of allergic reactions in patients sensitized to yeast. However, anaphylactic reactions to these vaccines are rare and after-marketing surveillance data suggest that recombinant yeast-derived HBV and HPV vaccines pose minimal risk of allergic reaction in yeast-sensitized

individuals.[98,99] Sensitization to *Saccharomyces cerevisiae*, shown by positive skin tests and specific IgE, has been found in a patient with a history of allergy to hepatitis B vaccine.[100] Although the diagnostic value of these tests is not well defined, international guidelines recommend performing skin tests with yeasts in the rare patients reporting reactions to yeast-containing vaccines.[24]

Dextran Dextran hypersensitivity is rare and has been mainly implicated in allergic reactions to particular brands of measles-mumps-rubella (MMR) vaccine and BCG, both no longer available on the market.[101–103] However, dextran is found sporadically in other vaccines, such as some rotavirus vaccines. These allergic reactions were related to the presence of IgG antibodies to dextran and the mechanism was hypothesized to be complement activation and anaphylatoxin release.[101–103] In newborns, these antibodies are believed to derive from a placental transfer from the mother. In older children and adults, the origin of these antibodies remains obscure and may result from a previous sensitization by sugars expressed on infectious microorganisms or saprophytes. These could explain the presence of specific antibodies (IgM or IgG) to dextran found in 70% to 80% of the patients in the general population.[104] Nonimmediate reactions to dextran are rarely reported in the literature.[65]

Preservatives and adjuvants Preservatives are added to a large variety of vaccines and can be responsible for allergic reactions. Although thimerosal is one of the most effective preservatives, it has been used less often during the last few years because of its mercury content.[105] On the other hand, phenoxyethanol and formaldehyde have been increasingly used. As shown by several single-case reports, these preservatives might trigger allergic, mainly nonimmediate, reactions (contact dermatitis and generalized maculopapular rash).[27,67,106,107] Some vaccines require an adjuvant, such as aluminium, to become immunogenic. In addition to local reactions discussed above, patients sensitized to aluminium can rarely develop generalized contact dermatitis after vaccine administration.[29]

Antibiotics MMR, polio, and influenza vaccines are likely to contain small amounts of antibiotics, including neomycin, gentamicin, polymyxin B, and streptomycin. These are used to avoid contamination of the culture with bacteria or fungus. Although not confirmed by a complete allergic workup, an antibiotic allergy has been incriminated as a potential cause of nonimmediate reactions, such as contact dermatitis, and of immediate reactions (more rare) to a vaccine.[108,109] The rare patients with a confirmed immediate allergy to these antibiotics should avoid a vaccine containing them,[97] whereas most patients who develop a nonimmediate reaction can receive the vaccine with a low risk of mild reaction outweighed by the benefit of the vaccination.[97,109]

General management of patients with a history of systemic reaction to vaccine

Systematic approaches have been proposed for the management of patients with a suspicion of vaccine allergy (see **Fig. 1**). Although essential, the clinical history is not sufficient and a complete allergic workup is required in all patients with a suspicion of vaccine allergy, even if no further dose of the suspected vaccine is needed because of the potential for cross-reaction with common components in other vaccines or foods.[24,74] Allergy tests will be adapted, depending whether an immediate or a nonimmediate reaction is suspected. In patients with a suspicion of immediate hypersensitivity, the workup should include immediate-reading skin tests (prick tests full dose, or 1/10 in case of severe anaphylactic reaction) as well as intradermal tests (1/100) and/or specific IgE to the vaccine itself and the related vaccines (i.e. DTaP, DT, T and Polio vaccine in suspected allergy to DTaP-Polio vaccine), but also to the potential

single components that may have cause the reaction (egg, gelatin, yeast, formaldehyde and latex). In the decision to administer a vaccine, the ratio between risk and therapeutic benefit should be assessed. The physician should determine whether subsequent doses of the suspected vaccine, or other vaccines with similar components, are required. Measurement of vaccines antibodies to determine whether they are at protective levels can help determine whether booster injection can be withheld. The discussion should always involve the primary care physician, the allergist, and the patient and/or family. If the allergic workup confirms a hypersensitivity to one of the vaccine components, the vaccine can still be administered following the protocol proposed by the American Academy of Pediatrics.[110] Of note, monovalent vaccine should be preferred.[111] Regarding patient reporting generalized nonimmediate reaction, the diagnostic value of skin tests, particularly delayed-reading intradermal tests, remains highly uncertain.

Patients with History of Allergy to Vaccine Components

The other circumstance that often brings a patients to the allergist regarding vaccine allergy is that a patient needs a vaccine but has a positive history of allergy to one or several vaccine components.[78]

Patients allergic to eggs

Owing to manufacturing process, MMR vaccines, as well as influenza, yellow fever, and tick-borne encephalitis vaccines, may contain various amounts of ovalbumin and are, therefore, associated with a potential risk of anaphylactic reactions in patients who are allergic to egg.[112–116] Since the 1990s, the production methods of MMR and influenza vaccines have been modified. MMR vaccines are prepared on fibroblasts from chicken embryo and, therefore, contain no to trace ovalbumin (0–1 ng/mL). Several studies have confirmed the safety of this vaccine in patients allergic to egg.[115,117] In consequence, skin tests are not required and these patients can receive full-dose MMR regardless of the nature and severity of their allergy.[24,65,97]

The administration of influenza vaccine in patients allergic to egg has been a major concern for a long time. However, a major change of paradigm recently occurred.[118–127] Several studies have assessed the safety of influenza vaccine in these patients, including patients with severe egg allergy. More than 4800 subjects have been evaluated, including nearly 600 subjects with severe egg allergy.[23,24] Although some subjects developed mild cutaneous reaction (ie, generalized urticaria), no anaphylactic reaction has been reported in these studies. Also, it has been shown that skin tests with influenza vaccines may provide false-positive responses and that the risk of reaction was similar in subjects with positive skin tests compared with subjects who tested negative.[118,119,124] Based on these data, the current consensus indicates that skin testing to influenza vaccine is useless in egg allergic patients.[23,24] Recently, the ovalbumin content of currently used influenza vaccines was evaluated in several studies and three categories can be distinguished:

- Influenza vaccine obtained by genetic engineering do not contain ovalbumin, so they can be administered safely in patients allergic to egg.
- Influenza vaccines produced on chicken egg embryo contain very small amounts of ovalbumin (less than 1 μg/0.5 mL), even if the manufacturers often mention higher content. These vaccines can be administered full dose with some precaution (in the primary care office for patients with mild egg allergy [urticaria] and in the allergist office for patients with more severe egg allergy).[23,24] However, some investigators recommend administering the vaccine in two doses in patients with more severe egg allergy (1/10, then 9/10 30 minutes later).[65,111] In this case, if the

patient reacts to the first dose, the risk-benefit ratio should be evaluated. If the vaccine is absolutely required, it can be administered in graded dose.[110]
- Other influenza vaccines containing significant amounts of ovalbumin (>1.2 μg/mL) are potentially associated with a risk of reaction in patients allergic to egg[128,129]; therefore, administration of these vaccines in these patients should be avoided.

Regarding other vaccines containing egg proteins, such as yellow fever vaccines, unfortunately only a few studies have assessed their safety in patients allergic to egg. Skin tests to the vaccine before administration are recommended.[24] A recent study proposed a desensitization protocol in patients with positive skin tests.[130] However, a safe administration of influenza vaccine with an ovalbumin content much higher than yellow fever vaccine has been recently reported in patients allergic to egg.[131] Further studies are needed to evaluate the safety of yellow fever vaccine in these patients, particularly to determine the usefulness of skin tests and the optimal protocol to administer the vaccine (comparison of graded dose with full dose administration).

Patients allergic to gelatin

Anaphylactic reactions have been reported in patients without egg allergy after injection of vaccines containing gelatin used as a stabilizer, including MMR, Japanese encephalitis, and chickenpox vaccines.[17–22,132,133] Recently, gelatin hypersensitivity has been incriminated in a child allergic to egg who developed an anaphylactic reaction after receiving an influenza vaccine.[134] In these patients, the diagnosis of allergy to gelatin was based on positive skin test and/or specific IgE to gelatin. A history more or less suggestive of food allergy to gelatin was subsequently found in several of these patients. On the other hand, a study showed that food allergy to gelatin developed secondarily to vaccine administration in 20% to 25% of subjects.[20,21] Of note, a negative history of reaction to gelatin on ingestion should not exclude a hypersensitivity to gelatin.[20,135] Since gelatin was removed from several vaccines and hydrolyzed gelatin was used in others, anaphylactic reactions to vaccines have decreased significantly.[136–138] In patients with suspicion of hypersensitivity to gelatin, the first step is to confirm the allergy by a complete allergic workup, including skin tests and/or specific IgE to gelatin. In patients with a confirmed gelatin allergy, a gelatin-free vaccine should be preferred. If unavailable, the risk-benefit ratio to administer the vaccine should be discussed. If the vaccine is required, a skin test with the vaccine itself should be performed before vaccine administration. Patients with negative skin tests can receive the vaccine full dose, whereas patients with positive skin tests should receive the vaccine following the protocol proposed by the American Academy of Pediatrics.[110]

Of note, nonimmediate urticaria and/or angioedema, as well as nonspecific rashes have also been reported after injection of vaccine containing gelatin.[32] Some of these reactions may result from a nonimmediate hypersensitivity to gelatin, as suggested by high levels of serum specific IgG gelatin found in many of those subjects.[33] Another study showed that most subjects reporting nonimmediate reactions to vaccines containing gelatin had positive delayed-reading responses to an intradermal test and/or lymphocyte transformation test (LTT), supporting the hypothesis that these reactions may also result from an hypersensitivity to gelatin.[34] However, other studies have shown that LTT gelatin were positive in many subjects tolerating vaccine containing gelatin.[139]

Patients allergic to milk

DT vaccines are prepared on milk proteins and may contain nanoscale quantities of milk proteins. A recent case series incriminated casein in allergic reaction to DT vaccines in subjects with severe milk allergy and high levels of specific IgE to cow's

milk.[140] Similarly, allergy to cow's milk has been incriminated in an allergic reaction to Sabin vaccine.[141] However, these data must be confirmed by further study.

Patients allergic to antibiotics

To the authors' knowledge, there is no case report of immediate allergic reactions to vaccine attributed to antibiotic. However, regarding the rare patient with a confirmed immediate allergic reaction to antibiotics added to vaccine (ie, neomycin, gentamicin, polymyxin B, and streptomycin), it is recommended to avoid vaccines containing them. If the vaccine is really needed, skin tests with the vaccine itself and the antibiotics (if validated) are recommended. If the skin tests are negative, the vaccine can be administered full dose. If antibiotic hypersensitivity is confirmed (skin or provocation tests) or highly likely, based on clinical history, a graded protocol should be used to administer the vaccine.

General management of patients with an allergy to vaccine components

In patients with a suspected allergy to vaccine components, the first step is to confirm this allergy by skin tests, specific IgE measurement, and/or a provocation test, which is considered the gold standard. If an allergy is confirmed, skin tests with the vaccine itself are recommended. If negative, the vaccine can be administered full dose, whereas if the skin test is positive, the vaccine should be administered in graded dose following the protocol proposed by the American Academy of Pediatrics.[110] The decision to administer the vaccine should be based on risk-benefit assessment and should be discussed between the primary care physician, the allergist, and the patient and/or family. Usually, measurements of vaccine antibodies to determine if the patient already reaches the protective antibodies levels are needed before making this decision. As mentioned above, patients with egg allergy can be managed differently. Skin tests with the vaccine itself and graded-dose administration are no longer recommended.[23,24,111] However, the vaccine should be administered with some precautions (ie, in the primary care office in patients with mild egg allergy and in the allergist office or in the hospital in patients with severe egg allergy). Of note, skin test to the influenza vaccine is still recommended in patients who reacted after influenza vaccine administration.

SUMMARY

Overdiagnosis of vaccine allergy is common and is considered a major public health problem. The diagnosis of allergy to vaccine is complex and is often retained owing to fear of severe anaphylactic reactions. However, most patients labeled as allergic to a vaccine tolerate a subsequent injection of the vaccine without clinical reaction. This is particularly the case in patients who develop local reactions or delayed benign skin rashes. Regarding patients with a history suggestive of an immediate IgE-mediated hypersensitivity, a complete workup is mandatory. It should be primarily based on skin tests and/or specific IgE measurements. In almost all cases, the vaccines can be administered using adapted protocols, even if the allergy tests are positive. However, some vaccine administrations carry a relatively high risk of severe anaphylactic reactions and should always be performed by well-trained physicians and emergency equipment must be readily available.

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