

ALLERGIES TO VACCINES IN CHILDREN

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Introduction

Allergic reactions to infectious disease vaccines are quite rare, as opposed to allergenic vaccines used in allergen immunotherapy. Despite the very low incidence estimates, the massive use of common vaccines in national immunization programmes makes this a relatively common clinical concern. Estimates of immediate hypersensitivity reactions to vaccines range from 0.65-1.53, 1-2 or 2.2 per 1 million doses (1, 2, 3). Therefore, allergic

The aim of this article is to review the allergic reactions to infectious disease vaccines in children and offer guidance on how to practically approach the question of a possible allergic reaction to a vaccine. Allergies to vaccines occur at an estimated rate of 1-2 in 1,000,000 vaccine doses. For the most part concerns over possible allergies to vaccines are usually not supported by the appropriate scientific facts and are exaggerated by ignorance, fear and irrational beliefs. If an allergic reaction to a vaccine is believed to have occurred, the first step is to link the clinical symptoms to the vaccine administration. Urticaria, angioedema, wheezing and hypotension occurring within 30 minutes after vaccine administration point to a probable severe IgE-mediated reaction. Most vaccine constituents may cause the immediate type allergic reaction: stabilizers (gelatin, dextran), remnants of culture media (ovalbumin, yeast), latex from vial stoppers, antimicrobial agents added to maintain sterility, the least common being microbial antigens and preservatives. Prick and intradermal testing with whole vaccine and with specific constituents should be performed within 3-12 weeks following the reaction. In vitro tests (specific IgE) should be done if available. Positive *in vivo* or *in vitro* tests do not necessarily preclude further vaccination, especially if it is considered vital or outweighing the potential risks. However, decision should be made on a case by case basis by a qualified allergist. Fractionated or graded dose protocols are available for implementation in day care or hospital settings. **Conclusion** – Systemic IgE mediated allergy to vaccines is rare in children. If it occurs a full list of vaccine constituents should be considered and appropriate allergological testing performed.

reactions to vaccines being very rare, it is important not to associate an allergic reaction to a vaccine without reliable objective evidence.

In this article we shall deal predominantly with immediate hypersensitivity reaction to antiinfectious vaccines.

Clinical presentation

Hypersensitivity can occur to any vaccine component. Vaccines contain microbial antigens, other proteins, adjuvants, preservatives,

antibiotics, stabilisers (e.g. albumin, gelatin), by-products remaining from the production process, or packaging contaminants, e.g. latex. Hypersensitivity reactions occur mostly to vaccine components other than the microbial antigen itself. Reactions are best classified by their clinical appearance and temporal association to vaccine administration. Immediate reactions occurring within moments to 30 minutes of vaccination that include several or all of the symptoms such as flushing, itching, urticarial eruption, angioedema, nasal and/or conjunctival congestion, stridor, wheezing, dyspnea, drop in blood pressure and altered mental status strongly suggest an IgE mediated mechanism.

However, anaphylaxis may appear hours after vaccine administration. A recent article has estimated the incidence of anaphylaxis to vaccines at 1.3 per 1 million doses, of which 55% affecting children 0-17 years of age. Atopy was found in 85% of cases. More than 50% of anaphylactic reactions were due to trivalent inactivated influenza vaccine (TIV), the other included common childhood combination vaccines or multiple vaccines given at the same visit [4-valent conjugate meningococcal vaccine (MCV4), varicella vaccine (Var), measles-mumps-rubella vaccine (MMR), hepatitis A vaccine (HAV), 4-valent human papillomavirus vaccine (HPV4), diphtheria-tetanus-acellular pertussis (DTaP), diphtheria-tetanus-acellular pertussis and inactivated polio (DTaP-IPV)]. Of note, only 25% presented within the first hour, and 55% presented within 1-4 hours, while the rest appeared later in the day of vaccination (4).

Delayed reactions appear >6 hours after vaccine administration and are usually not IgE dependent. They present as large local reactions that are thought of as „local reactive edema“ if present within 6-24 hours of vaccine administration, or Arthus type (immune complex mediated) inflammation if present at 24-72 hours after vaccination. The former

look rather benign with edema, pruritus, rather than pain, and absence of circulatory compromise distal to the swelling, while the latter may be difficult to clinically differentiate from cellulitis.

Systemic delayed hypersensitivity reactions appear within 24-72 hours of vaccination and include fever, maculopapular rash, delayed onset urticaria, erythema multiforme, lymph node enlargement. Although the mechanism is not always clear, they appear to be the expression of systemic Arthus type allergic reaction, similar to Arthus type local swelling. They may indicate that the organism is hyperimmunized and that further immunization with the same vaccine, if scheduled, may have to be reconsidered. It is useful to check the serologic titer to the vaccine antigen, if available. In general, however, these delayed reactions do not necessarily contraindicate the continuation of immunization at a later date, nor carry the risk of an IgE-mediated reaction (5).

Vaccine constituents most commonly involved in allergic reactions

As already stated, any vaccine component may cause a hypersensitivity reaction but the very vaccine antigen is the least common of all. When allergy to a vaccine is suspected, the full list of constituents should be available in order to plan a comprehensive diagnostic work-up.

Gelatin is a collagen derived protein and used as stabilizer in many vaccines. Its content ranges from as little as 20-250 µg (micrograms) per 0.5 ml vaccine dose in TIV, live attenuated influenza vaccine (LAIV) and DTaP based vaccines, up to 7-14.5 mg per 0.5 ml vaccine dose in yellow fever vaccine (YF), rabies, Var, zoster and MMR vaccines (6). Anaphylactic reactions have been noted following MMR, Japanese encephalitis, Var and some TIV vaccines. Increased susceptibility to gelatin allergy seems to be linked

to HLA-DR9 antigen, which is particularly prevalent in Japan (7). It has been hypothesized that severe reactions to MMR vaccination in Japanese children followed priming with minute gelatin content in DTaP vaccines in infancy (8).

Egg protein can be found in trace amounts (<1 ng) in MMR vaccines and some rabies vaccines. In influenza vaccines, both inactivated and live, the average ovalbumin content is about 350 ng per 0.5 ml dose, and the highest content is found in YF (9). The main risk is related to YF administration and persons who do not tolerate eggs. MMR and rabies vaccines can be administered to persons who tolerate eggs in food regardless of skin prick or specific IgE titers (10). In case of doubt, the author (DR) first administers 10% of the dose, followed in 30 minutes by the rest. Administration of influenza vaccine will be detailed later.

Casein originating from a cow-milk derived medium used in the production of DTaP vaccines can be found in trace amounts in DTaP based vaccines. There has been a report on 17 children with pronounced cow milk allergy (specific IgE 58.9 to >100 kU/L) that experienced anaphylactic reactions to DTaP vaccine (11). However, since the vast majority of children severely allergic to cow milk tolerate DTaP vaccines without side effects, these observations have not resulted in any change to official immunization recommendations regarding DTaP and cow milk allergy (12).

Yeast (*Saccharomyces cerevisiae*) is found in hepatitis B vaccine (HBV) and HPV4 vaccines which are produced by recombinant DNA technology in *Saccharomyces cerevisiae* culture. While allergy to yeast is a proven fact, hypersensitivity reactions due to yeast in vaccines appear to be quite rare (13). The potential presence of yeast allergy in the child dictates appropriate testing prior to vaccination with yeast containing vaccines.

Latex allergy may cause vaccine reactions through contamination of the vaccine dose

by latex found on vial stoppers and syringe plungers. In latex allergic patients syringes without rubber plungers should be used and rubber stoppers removed in order to draw the vaccine directly from the vial (14).

Antimicrobial agents - neomycin, polymyxin B, or streptomycin - are often added in trace amounts to vaccines to keep them sterile. Immediate hypersensitivity to these agents has been documented (15), but none linked to a vaccine administration. However, patients known to be allergic to these constituents, should undergo specialist allergist consultation and skin testing with the vaccine in question. Contact dermatitis (delayed hypersensitivity type IV-a) to these agents does not constitute a contraindication to immunization with vaccines containing them.

Preservatives like thiomersal and phenoxyethanol, and **adjuvants** like aluminium salts may be found in various vaccines. None have ever been implicated in immediate type hypersensitivity reactions. On the contrary, they can cause contact dermatitis and delayed type hypersensitivity, which in and of itself do not constitute a contraindication for a given vaccine. Thiomersal has been dropped from most childhood vaccines and is currently not even a theoretical risk. Aluminum-containing vaccines may rarely cause persistent nodules at the injection site, possibly because of delayed hypersensitivity or other inflammatory response to aluminum.

Dextran may be added to freeze dried vaccines as protein stabilizer (Bacillus Calmette-Guérin, monovalent rotavirus vaccine, and previously some MMR vaccines), and can cause severe immediate hypersensitivity reactions through specific IgG-complement-anaphylatoxin activation, including the neonatal period (16).

Microbial antigens are extremely rarely involved as allergens in hypersensitivity reactions to vaccines. Tetanus and diphtheria toxoids have been documented as causes of

allergic reactions to vaccines, including the diphtheria toxoid CRM[197] carrier protein in pneumococcal conjugate vaccines (17, 18).

Diagnostic work-up

If an allergic reaction to a vaccine is believed to have occurred, the first step is to link the clinical reaction to vaccine administration. General itching, angioedema, sudden tearing and nasal discharge, wheezing and hypotension are common typical clinical signs. An allergic reaction to a vaccine is most likely to occur within 30 minutes of vaccination, but

can also occur hours after vaccine administration. The diagnostic work-up should be initiated by performing skin tests to the whole vaccine and to the relevant specific constituents. Skin testing should be performed in a window of 3-12 weeks following the purported allergic reaction.

Skin prick test is performed with undiluted, full strength vaccine. In the event of a clinically probable severe immediate type hypersensitivity reaction to the vaccine, it can be diluted 1:10 or even 1:100 (19). If negative, skin prick test is followed by intradermal testing with 0.02 ml of a 1:100 dilution.

Table 1 Specific allergy testing in common vaccine allergic patients

Vaccine	Component	Prick [*]	Intradermal	IgE [§]
DTaP	DTaP	Undiluted	1:100	N/A
	DT	Undiluted	1:100	N/A
	Tetanus toxoid	Undiluted	1:100	N/A
	Gelatin	1 tsp gelatin powder in 5 ml normal saline [†]	?	Yes
	Cow milk	Commercial	No	Yes
	Latex	Commercial, or prick with sterile rubber glove coating the tip of the lancet [‡]	No	Yes
MMR	MMR	Undiluted	1:100	N/A
	Measles	Undiluted	1:100	N/A
	Mumps	Undiluted	1:100	N/A
	Rubella	Undiluted	1:100	N/A
	Gelatin	1 tsp gelatin powder in 5 ml normal saline [†]	?	Yes
	Egg	Commercial	No	Yes
	Latex	Commercial, or prick with sterile rubber glove coating the tip of the lancet [‡]	No	Yes
HBV	HBV	Undiluted	1:100	N/A
	Yeast	Commercial, or prick-prick with fresh yeast	No	Yes
	Latex	Commercial, or prick with sterile rubber glove coating the tip of the lancet [‡]	No	Yes
TIV/LAIV	TIV/LAIV	Undiluted	1:100	N/A
	Egg	Commercial	No	Yes
	Gelatin	1 tsp gelatin powder in 5 ml normal saline [†]	?	Yes
	Latex	Commercial, or prick with sterile rubber glove coating the tip of the lancet [‡]	No	Yes
Var	Var	Undiluted	1:100	No
	Gelatin	1 tsp gelatin powder in 5 ml normal saline [†]	?	Yes
	Latex	Commercial, or prick with sterile rubber glove coating the tip of the lancet [‡]	No	Yes

DTaP=Diphtheria-tetanus-acellular pertussis; MMR=Measles-mumps-rubella vaccine; HBV=Hepatitis B vaccine; TIV/LAIV=Trivalent inactivated influenza vaccine/Live attenuated influenza vaccine; Var=Varicella vaccine; N/A=Not available; If a severe hypersensitivity reaction has occurred, prick may be initiated at dilutions of 1:100 and 1:10; [†]See reference (5); [‡]Non-standardized procedure, as performed by author (DR): the tip of the lancet is covered with a piece of sterile surgical latex glove and the skin is pricked in the usual way; [§]Specific.

Appropriate positive and negative controls should be simultaneously performed. Diluting vaccines for intradermal testing is vital, because irritant reactions to full strength or 1:10 dilutions produce an unacceptably high rate of false positive results. Even at 1:100 dilutions there is a rate of 5% and 15% false positive findings for DTaP based vaccines and TIV, respectively; irritant reactions are also common with MMR and Var vaccines (20). A prick test is considered positive if the wheal is at least 3 mm greater than the negative control, and the intradermal test is positive if at least 7 mm in diameter, or 3 mm greater than the positive histamine prick control (21). Table 1 lists diagnostic tests to be performed in suspected immediate type allergy to common childhood vaccines.

Vaccine administration to children with prior vaccine allergy

If skin and in vitro testing is negative, the probability of a major hypersensitivity reaction is quite small. The usual dose of the vaccine can be administered at once or fractionated as 1/10 + 9/10 of the dose separated by 30-minute observation, under controlled conditions in day-care or hospital setting, with at least another 30-minute close monitoring following full dose administration (19, 22).

If any of the in vivo or in vitro test returned positive results, a decision how to proceed must be made on a case by case basis. Sometimes further vaccination may not be needed, or the patient may have evidence of valid serologic protection either by natural infection or prior vaccination. If vaccination is considered vital, then, taking into account all the historical and diagnostic data, a vaccination may be attempted in intensive care setting following a graded protocol approach: for a vaccine dose of 0.5 ml, administer graded doses in 15-minute intervals: 0.05 of 1:10 di-

lution, followed by full strength graded doses of 0.05 ml, 0.1 ml, 0.15 ml and 0.2 ml (23).

In individuals known to be allergic to a vaccine component, such as egg, gelatin or yeast, the risk of a severe allergic reaction depends on the the individual tolerance of the component and its quantity in a vaccine dose. In general, children who tolerate eggs in foods can safely receive MMR (usually <1 ng ovalbumin per 0.5 ml dose) and influenza vaccines [usually <1 mg (microgram) ovalbumin per 0.5 ml dose]. If there is a urticarial reaction to eggs, then vaccination may be undertaken under supervision of a qualified allergist, best by a fractionated regimen. More severe reactions need strict hospital ambience and a graded protocol. Prior skin prick testing with a vaccine has not proven useful, as it did not detect those who on vaccination with the full vaccine dose developed an allergic reaction (24).

Conclusion

Allergy to vaccines appears to be quite rare, but if anaphylaxis occurs, it is potentially life threatening and must be appropriately anticipated. The most severe allergic reactions occur within 30 minutes of injection, but reactions up to 4 hours and sometimes 24 hours of administration are known to have occurred. Any vaccine constituent may cause allergy, but gelatin, egg and latex seem to be the most common ones. A full list of vaccine constituents must be available and appropriate skin and in vitro testing performed within 3-12 weeks of a presumed vaccine hypersensitivity reaction. Children allergic to a vaccine should not receive that vaccine again, but, if protection is deemed vital, revaccination can be considered on a case by case basis and a graded vaccine administration protocol used by expert allergist in appropriate hospital setting.

Conflict of interest: The author declares that he has no conflict of interest.

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