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How Real Are Allergic Reactions to Vaccine Components in Children? – Experiences of Clinicians

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Abstract

Objective – Vaccine components have the potential to induce allergic reactions, although such reactions are infrequent, especially anaphylactic reactions, which are very rare (occurring at a rate of 1 per million vaccine doses). The objective of this study was to assess objectively the frequency of allergic reactions to vaccine components in children with suspected allergic reactions to vaccine components. **Materials and Methods** – We retrospectively analyzed the medical records of 209 patients aged 1 to 18 years with suspected allergic reactions to vaccine components, who underwent the standardized diagnostic procedures and tests to common allergens and vaccine components at Srebrnjak Children`s Hospital, Zagreb, Croatia. **Results** – Of the 209 children vaccinated in the hospital setting, only two (0.95%) developed side effects during their hospital stay, and 2.63% with a positive history of IgE mediated vaccine allergy were positive for one of the components of the vaccine. Local reactions to the vaccine were the most frequent adverse events in our patients. 62.6% of them were referred due to a positive history of egg protein allergy. **Conclusion** – Allergic reactions to vaccine components are rare and mild in most cases. In patients with a suggestive history, it is important to choose appropriate diagnostic tests to determine if vaccination can be performed safely. Only patients at risk of egg protein anaphylaxis generally require medically supervised vaccination in a hospital facility. Patients with a history or a documented and immediate allergic reaction (<4 h) require an allergy workup to avoid the risk of repeated anaphylaxis after further administration.

Key Words: Vaccine ▪ Allergy Reaction ▪ Vaccines Allergy ▪ Anaphylaxis.

Introduction

Vaccines have a favorable safety record and prophylactic efficacy. The primary goal of vaccination is to safeguard the vaccinated child and achieve herd immunity, diminishing the burden of an infectious disease in correlation to the population coverage (1). Like all other drugs, vaccines also have the potential to cause allergic reactions. Allergic reactions to vaccines are infrequent, and most reported cases are classified as suspected cases in which subsequent evaluation demonstrates no causal relation to immunization (2).

Vaccines consist of an active antigenic ingredient, and supplementary components. Antigens in vaccines may consist of entire organisms, organism components or subunits, inactivated toxins (toxoids), or a combination of these, all designed to elicit protective immune responses. Vaccine antigens themselves rarely, if ever, are the cause of hypersensitivity reactions (3). Hypersensitivity reactions following vaccination typically result from specific vaccine components, such as egg protein, gelatin, and potentially other additives. The World Allergy Organization (WAO) has recommended categorization of immunologic reactions to vaccines based

on the time of onset of symptoms (1). Two basic categories of reactions are defined: immediate or immunoglobulin E (IgE) mediated (type I immunologic reactions), and delayed or non-IgE mediated reactions.

IgE-mediated reactions are most likely immediate reactions and occur from within minutes to one hour after vaccination (4). IgE-mediated reactions carry the risk of life-threatening anaphylaxis if the patient is re-exposed to the same vaccine (5). Immediate, IgE-mediated allergic reactions to vaccines involve the skin, including flushing, itching, urticaria, and angioedema, the respiratory track, including nasal congestion, a sensation of throat closure or choking, stridor, cough, wheeze, and dyspnea, and/or the cardiovascular system, including faintness, syncope, altered mental status, palpitations, and hypotension (5). Delayed reactions may appear several hours to days after vaccination and these reactions are rarely mediated by IgE antibodies (4). Delayed urticaria and/or angioedema, as well as non-specific skin rashes, have been reported in 5% to 13% of patients receiving vaccines containing toxoids, but several studies suggest that most of these generalized reactions result from a nonspecific activation of the immune system by a significant amount of microbial substances, and usually do not occur on re-exposure to the same vaccine (6).

Most allergic reactions to vaccines are non-IgE mediated reactions to vaccine components rather than the microbial antigenic subunits (4). Allergic reactions after vaccination can be due to any of the vaccine components, such as adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, antibiotics, cell culture materials, and inactivating ingredients (7).

Confirmed vaccine-related allergic reactions are rare in children, ranging between 0.65-1.45 cases per million vaccine doses (8). Anaphylaxis following vaccination is rare, affecting <1/100 000, but it can occur in any patient (9). The vaccine specific risk for vaccines (DT, DTP, DTp-Hib, hepatitis B, MMR, OPV) are in the range of 1.1-3.5 cases per million doses (10).

In fact, a small percentage of these reactions is related to vaccine hypersensitivity, and even in cases of true IgE mediated allergic reactions most children can continue the vaccination schedule, providing that the subsequent vaccine administration is performed by expert medical personnel (11). Patient with anaphylaxis or other severe adverse events following immunization should not be re-immunized with the same vaccine before allergological investigations are completed (12). Most cases of suspected allergy to a vaccine are not effectively confirmed in up to 85% of the patients referred for an allergy evaluation, and patients can continue vaccination with the same formulation and tolerance of the booster doses (7). Although rare, the precise diagnostic management of suspected anaphylaxis post-vaccination is of paramount importance due to the risk of potentially serious reactions after re-exposure, and because over-diagnosis of severe allergic reactions to vaccines might lead to an increase in the number of children that interrupt the vaccination schedule, resulting in individual and collective risk of loss of protection against immune preventable diseases (7).

The aim of this study was to assess objectively the frequency of allergic reactions to vaccine components in children with suspected IgE-mediated vaccine allergy.

Methods

This was a retrospective analysis of the medical records of patients referred for suspected allergic reactions to vaccine components from June 2019 to September 2023, at Srebrnjak Children's Hospital, that is, its Referral Center for Clinical Allergology of the Ministry of Health of the Republic of Croatia. Data were collected on 209 children aged 1 to 18 years. Patients were referred for vaccination in a hospital setting by pediatricians, allergists, epidemiologists, specialists in school medicine, as well as clinical pharmacologists, due to suspected allergic reactions to previously administered vaccines, or known allergies, especially to food (most commonly eggs) and drugs. At the same hospital visit,

thirteen patients were vaccinated with two vaccines, while patients with a suspected allergic reaction to the SARS-Cov-2 virus vaccine were excluded from this analysis.

Upon admission, a thorough physical examination was conducted to rule out acute infections or other acute medical conditions. All children with suspected food allergy were tested (skin prick or prick to prick) for a standard range of food allergens (cow's milk, eggs, wheat flour, peanuts, sesame, tuna, trout, hake, hazelnut, walnut, almond, rice, and cocoa). All children with atopic background and/or a history of asthma, with or without allergic rhinitis, were tested (skin prick testing) for the standard range of inhalation allergens. Patients with a history of suspected allergy to other allergens, were additionally tested (e.g. latex, gelatin, drugs, preservatives). The standard method was applied: positive and negative controls, interpretation of the tests after 15 – 20 minutes of allergen application, and a positive result defined as a wheal ≥3 mm diameter. Spirometry, and fraction of exhaled nitric oxide (FeNO) measurement were performed using standardized methods and protocols. If the skin prick tests for vaccine components were negative, an intradermal test with the vaccine was performed. If the vaccine or vaccine component skin tests (prick or intradermal) were positive and if a vaccine was deemed necessary, the vaccine was administered using a graded-dose protocol (13). After vaccine administration, the patients were observed for a period of 24 hours to monitor for late reactions.

Results

Data were collected from the hospital information system and medical histories. For each patient, anamnestic data, age, gender, the type of vaccine received, information on clinical manifestations of previous reactions to the administered vaccine, results of in vitro diagnostic tests (total IgE, specific IgE, IgG, IgA, IgM, CRP), the results of Skin Prick Test (SPT), lung function tests, fraction of exhaled nitric oxide (FeNO), and the history of atopic diseases, including food allergies, were collected and analyzed (Table 1).

Table 1. Summary of Data of the Patients Referred for Vaccination in the Hospital Setting

Age (years); (mean, SD)	4.93±0.32
Gender N (%)	
Male	119 (56.9)
Female	90 (43.1)
Immunoglobulins and C reactive protein (mean, SD)	
Total IgE (kIU/l)	376.78±55.46
IgG (kIU/l)	7.57±0.21
IgA (kIU/l)	0.75±0.04
IgM (kIU/l)	0.83±0.03
CRP (mg/L)	1.85±0.38
Lung function parameters (mean, SD)	
% of FVC predicted	87.20±2.62
% of FEV1 predicted	101.83±1.75
FEV1/Vcmax (%)	106.52±1.29
% of MEF25 predicted	98.85±4.97
% of MEF50 predicted	93.52±3.95
% of MEF75 predicted	91.54±3.36
% of MEF25-75 predicted	98.75±3.96
% of PEF predicted- mean	88.86±2.57
FeNO (ppb)	20.24±2.93
Comorbidities- Atopic disorders (N, % positive)	
Asthma	30 (14.4)
Bronchitis	38 (18.2)
Atopic dermatitis	109 (52.2)
Allergic rhinitis	26 (12.4)
Broncho-obstruction	6 (2.9)
Caveats: Azithromycin and/or diclofenac	2 (1)
Laryngitis	6 (2.9)
Skin Prick Test allergen (N; % positive reaction [wheal ≥3mm])	
House Dust Mite- Dermatophagoides pteronyssius	33 (15.8)
House Dust Mite- Dermatophagoides farinae	23 (11
Dog epithelia	10 (4.8)
Cat epithelia	9 (4.3)
Hazel	19 (9.1)
Olive	3 (1.4)

Age (years); (mean, SD)	4.93±0.32
Grass mix	26 (12.4)
Artemisia vulgaris	11 (5.3)
Ambrosia elatior	18 (8.6)
Birch	20 (9.6)
Alternaria	7 (3.3)
Hazelnut	20 (9.6)
Walnut	16 (7.6)
Almond	18 (8.6)
Wheat flour	20 (9.6)
Soya bean	15 (7.2)
Corn flour	11 (5.3)
Tuna	10 (4.8)
Hake	8 (3.8)
Trout	6 (2.9)
Egg	59 (28.2)
Cow's milk	29 (13.9)
Peanut	15 (7.2)
Sesame	10 (4.8)

Of the 209 patients vaccinated (mean age 4.93±0.32 years) only two (0.95%) developed side effects during their hospital stay, and 2.63% with a positive history of IgE mediated vaccine allergy were positive for one of the components of the vaccine. Due to a suspected adverse reaction to specific vaccine components, 30.1% of patients were referred for vaccination in the hospital setting. The highest percentage of children referred for testing for vaccine components had egg protein allergy (28.2%).

Children vaccinated with the MMR vaccine (out of 155 children, 97 (62.6%) of them had a history of egg protein allergy) did not develop any clinical reaction (Table 2). All reactions to vaccine components were categorized as mild and localized at the site of application, with positive intradermal tests or delay local reactions.

None of the patients with a history of suspected allergic reactions to DTaP-IPV-HB- Hib vaccine, DTaP vaccine, Pneumococcal vaccine, Hepatitis B, and HPV vaccine had a positive skin test to the tested components from the same vaccine. Two children were referred for vaccination in hospital conditions at the insistence of their parents due to an allergy to egg proteins, and one child due to an allergy to cow's milk, and if they had a negative history of a previous allergic reaction to one of the components of the hepatitis B vaccine. Only one child with an allergic reaction to egg proteins was referred for testing and vaccination against influenza in hospital conditions.

None of the patients with a proven egg protein allergy, including patients with a severe egg protein allergy (28.2%), had any allergic reaction during the vaccination, which was carried out according to an adapted protocol (graded-dose protocol). Three of the referred patients who had a positive history

Table 2. Type of Vaccine with the Patients' Anamnestic Data (reason for Vaccination in Hospital Conditions)

Vaccine	Reason for vaccination in a hospital setting				
	Allergy to eggs	Nutritional allergy	Previous suspicious reaction after receiving the vaccine	Allergic to components of vaccines	Vaccinated
	N (%)				
MMR	97 (62.6)	41 (26.4)	17 (11.0)	-	155
Tetanus and diphtheria	-	-	14 (93.3)	1 (6.67)	15
Polio	-	-	14 (93.3)	1 (6.67)	15
DTaP-IPV-HB- Hib	-	-	13 (100)	-	13
DTaP	-	-	9 (100)	-	9
Pneumococcal	-	-	5 (100)	-	5
Hepatitis B	2 (40)	1 (20)	2 (40)	-	5
Tetanus	-	-	2 (66.7)	1 (33.3)	3
HPV	-	1 (100)	-	-	1
Influenza	1 (100)	0 (0)	-	-	1

of allergy to the antibiotics and antimycotics that are listed as components of vaccines (Neomycin, Polymyxin B, Gentamicin) had no allergic reaction after the vaccination, performed using standardized methods and protocols.

Delay and late-type sensitization to adjuvants, stabilizers, preservatives, tested with epicutaneous tests was not clinically relevant and was not a reason for postponing vaccination in the analysed patients.

Discussion

Patients were referred by pediatricians who refused to vaccinate children due to anamnestic data related to nutritional allergies or previous vaccine reactions. Before vaccination, the patients were referred to an allergist or clinical pharmacologist for examination and allergy assessment. The primary reason for vaccination in hospital conditions was nutritional allergy (mostly an allergy to eggs, in 28.2% confirmed by skin prick tests and sIgE). The rest of the children were referred due to a previous suspicious reaction after receiving a vaccine. Approximately 30% of the children were referred due to a suspected allergic reaction to a previous vaccine, manifesting as local redness and swelling, urticaria, or fever. Less than 2% were referred due to suspected reactions to anesthetics and muscle relaxants, neomycin sulfate and thimerosal.

In our study, of the total number of vaccinated children, only two of them developed side effects during their hospital stay. Two children, after receiving the DTaP-IPV-HB- Hib vaccine on the first night of their stay (around 10 hours post-vaccination), became febrile and a localized swelling with erythema occurred at the vaccination site. In a ten-year trial by Prymula et al., (14) involving a total of 3705 children, redness was the most frequently reported solicited local adverse event, followed by pain and swelling. Additionally, fever was the most frequently reported solicited general adverse event (15).

There have been concerns and discussions regarding the safety of administering vaccine to children with egg allergies, and whether vaccines should be given in pediatric departments equipped to manage anaphylaxis. Most of these components are present in minimal quantities that are generally inadequate to provoke allergic reactions in most individuals with potential hypersensitivity to the component.Top of Form However, patients with unusually high levels of IgE antibodies can theoretically react to very small amounts of these antigens, and experience severe reactions, including anaphylaxis (4). Concern exists over administration of vaccines prepared on embryonated chicken eggs (i.e. rabies, yellow fever, tick-borne encephalitis and influenza vaccine) to egg-allergic patients (16). The triple viral vaccine is an attenuated vaccine developed in chicken embryo fibroblasts, which do not contain egg antigens, while the influenza vaccine and the yellow fever vaccine must be cultured in embryonated hen's eggs, and thus may contain larger amounts of egg proteins (2, 17, 18).

In our study, out of the total number of patients, 155 children received the MMR vaccine, including 28.2% with a proven egg protein allergy and severe egg protein allergy, and none of them exhibited allergic reactions. Numerous studies have indicated that there is no link between egg allergy and anaphylactic reactions to MMR vaccination (17, 19, 20). In a study of 110 children who received the MMR vaccine, none had a significant reaction, and only one child had a reaction to the MMR vaccine, that is, transient local erythema around the injection site which did not require any treatment (20). Fasano et al., demonstrated 95% confidence that at least 97.5% of egg-allergic children will tolerate MMR vaccine without significant difficulty (21).

New studies show that egg allergy is no longer considered a contraindication to the administration of MMR vaccine, and recipients need not be screened for egg allergy. Most anaphylactic reactions to the MMR vaccine have been attributed to gelatin allergy (22, 23). All children with an egg allergy should receive their normal childhood immunizations, including the MMR, as a routine procedure in primary care (15).

From the data in the literature and our results, it is unquestionable that all patients with a proven allergy to egg proteins, without anamnestic data of anaphylaxis to egg proteins, can be vaccinated by their doctor, in primary health care offices. Only patients with a history of anaphylaxis to egg proteins should be referred for vaccination to a reference institution, where vaccination is carried out according to an adapted protocol, with monitoring and enhanced surveillance.

Gelatin (a stabilizer) can cause allergic reactions (0.5-1 case per million doses) and is probably responsible for most cases of allergy associated with the triple viral vaccine (measles, rubella and mumps) (Priorix® does not contain gelatin) (2). A retrospective case-control study, which interviewed and collected sera from individuals who had suffered anaphylaxis after receiving MMR, found that 27% of them had anti-gelatin IgEs (9). Vaccines, especially live attenuated virus, may contain traces of antibiotics-aminoglycosides (gentamicin, kanamycin), polymyxin, chlortetracycline and neomycin, in order to avoid bacterial contamination during the manufacturing process (2, 4). Children with a confirmed allergy to latex are to be vaccinated with caution in a latex-free environment, avoiding gloves, syringes and other medical materials containing this substance (2). We successfully vaccinated all the patients who were referred for testing due to a suspected allergy to one of the components in the vaccines.

If a child is presumed to have suffered an allergic reaction to a vaccine, subsequent immunizations will probably be suspended, and the patient becomes part of the population of individuals susceptible to diseases against which he or she is no longer to be vaccinated (2). It is crucial, therefore, to establish a definitive diagnosis of adverse reactions attributed to vaccines, and to ascertain whether there is a direct correlation between the reaction and the vaccination. The assessment of patients experiencing suspected vaccine reactions should commence by establishing whether the symptoms and timing align with a genuine allergic reaction. Subsequently, an evaluation is conducted to ascertain if the patient requires additional doses of the specific vaccine or similar vaccines in the future.

Allergic reactions to vaccine components are rare, and most reported cases are classified as suspected or mild (2). In clinical settings, we suggest vaccinating and monitoring the following due to the specific challenges involved:

- Children with an objective risk of a potential allergic reaction to vaccine components (additional testing to prove or rule out an allergy, and to decide on the suitable approach to completing the immunization schedule)
- Children with a documented history of allergy to a vaccine component require careful evaluation of the safety of administering that particular vaccine.

Since these can delay or even interrupt a regular vaccination plan, an allergological workup is required when a suspected immune-mediated AEFI occurs. The aims of the allergological evaluation are identifying or excluding hypersensitivity to vaccines, selecting those subjects who require immunization in specialized care settings, and ensuring access to the vaccination (24). A comprehensive diagnosis of allergic reactions to vaccines is crucial, not only to prevent life-threatening situations, but also to prevent unwarranted limitations of vaccine utilization.

The most effective approach to enhancing our understanding is to examine individuals who have experienced reactions, through a range of in vitro experiments and clinical testing. In vitro experiments, including the analysis of plasma IgE markers, as well as basophil and mast cell line activation tests, can aid in the more precise characterization of potential allergens, and identification of individuals at risk of anaphylaxis. Clinical examinations, including skin-prick and intradermal tests, can assist in identifying allergens in individuals at risk. All these tests may include examining the individual components of the vaccine to identify the antigen responsible for triggering the reaction. For patients with negative vaccine skin test results, it is recommended that the vaccine be administered

in a single dose under observation, and for patients with positive vaccine skin test results, it is recommended that the vaccine be administered in graded doses under observation (25). Immunization in graded doses may reduce the risk of anaphylaxis. These vaccination approaches must only be used in a controlled setting where prompt treatment of anaphylaxis by experienced staff is available (12).

The variables with the strongest supporting evidence for reducing reactogenicity include the site of injection (preferably the buttocks instead of the thigh), the tissue type (favoring intramuscular over subcutaneous administration), needle length (longer needles are linked to lower reactogenicity), and the angle of injection (a 90º angle shows less reactogenicity compared to a reduced angle) (26).

Advantage and Limitation of This Study

The advantage of the research is the objective evaluation of allergic reactions to vaccine components carried out by an expert team, headed by a subspecialist allergist and clinical immunologist, at the Department of Allergology and Clinical Immunology at Srebrnjak Children's Hospital, which is the Reference Center of the Ministry of Health of the Republic of Croatia for pediatric clinical allergology. A limitation of this research is that it is based on the experience of only one center. Another limitation is the inclusion in the analysis of all children referred for allergy testing to vaccine components (real-life study) who were not previously selected by a subspecialist allergist and clinical immunologist, and whose doctors did not want or refused to vaccinate them due to fear of allergic reactions or pressure of children's parents.

Conclusion

Local reactions following vaccinations are the most frequently observed adverse events. These reactions are generally benign, not prone to anaphylaxis, and typically do not necessitate an allergy workup. Further vaccines can be safely administered without additional precautions. All immediate reactions post-vaccination should be evaluated by an allergist. Immediate reactions occurring within four hours are potentially IgE-mediated, and require an allergy workup to prevent the occurrence of anaphylaxis upon further administration. Egg allergy is not a contraindication to MMR or influenza vaccines. In cases of previous anaphylaxis to egg, some guidelines suggest administering the vaccine without specific precautions, while others recommend having experienced staff administer the vaccine. In the absence of a prior history of anaphylaxis after egg consumption, influenza vaccines can be administered without precautions in patients with egg allergies. Allergies to vaccine components, including gelatin, yeast, latex, antibiotics, or other specific elements, necessitate an allergy workup before vaccine administration. Individuals experiencing a suspected allergic reaction to the initial vaccine dose should be monitored by an allergist. This ensures that subsequent doses can be administered safely under appropriate supervision, and that the second dose can be administered in a specialized setting equipped to manage potential anaphylaxis. Accurate diagnosis of vaccine allergies is important, not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary vaccine restriction (14).

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