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Diagnosis and management of hypersensitivity reactions to vaccines

Lucrezia Sarti[1], Guillaume Lezmi[2,3], Francesca Mori[1], Mattia Giovannini[1], Jean-Christoph Caubet[4]

1. Allergy Unit, Department of Pediatrics, Anna Meyer Children's University Hospital, Florence, Italy
2. Service de Pneumologie et Allergologie Pédiatriques, Hôpital Necker-Enfants Malades, AP-HP, Paris, France.
3. Université Paris Descartes, Paris, France
4. Division of Pediatric Allergy, Department of Pediatrics, University Hospitals of Geneva, Geneva, Switzerland

Corresponding Author

Lucrezia Sarti,

Address: AOU Meyer Viale Pieraccini 24, 50139, Florence, Italy

E-mail: lucrezia.sarti@gmail.com

Telphone: +39-05556621

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Lucrezia Sarti[1]*, Guillaume Lezmi[2,3], Francesca Mori[1], Mattia Giovannini[1], Jean-Christoph Caubet[4]

[1]Allergy Unit, Department of Pediatrics, Anna Meyer Children's University Hospital, Florence, Italy
[2]Service de Pneumologie et Allergologie Pédiatriques, Hôpital Necker-Enfants Malades, AP-HP, Paris, France.
[3]Université Paris Descartes, Paris, France
[4]Division of Pediatric Allergy, Department of Pediatrics, University Hospitals of Geneva, Geneva, Switzerland

***Corresponding Author:**
Lucrezia Sarti, AOU Meyer Viale Pieraccini 24, 50139, Florence, Italy
Telephone: +39-05556621
E-mail: lucrezia.sarti@gmail.com

Abstract

Introduction: Many countries in Europe now recommend and enforce mandatory vaccinations to improve vaccination coverage. Thus, the number of adverse events following immunization (AEFI) may show an increase. Among these events, severe hypersensitivity reactions to vaccines are rare. However, it is important that they be identified and recognized so that they may be adequately managed.

Areas covered: The literature search was undertaken through PubMed and Embase to identify English-language papers focusing on hypersensitivity to vaccines.

Expert opinion: Hypersensitivity reactions following vaccinations are rare and are classified according to their chronology and extension: immediate when they occur within the first 4 hours following administration and non-immediate when they occur later. Local reactions are the most common adverse event following injection of vaccines and generally do not require any allergy workup. Immediate reactions, however, are potentially IgE-mediated and require an allergy workup. In general, a previously known food allergy (i.e. egg or milk) is not a contraindication to immunizations. Patients with a known allergy to gelatin, yeast, latex, antibiotics or other specific components of vaccines require an allergy workup before administration of the vaccine.

Key words: vaccine, hypersensitivity reactions, vaccine allergy, systemic reactions, local reactions, hypersensitivity, egg allergy, gelatin.

Article highlights

- Local reactions to the vaccine are the most frequent adverse events following vaccinations. They are benign, not at risk of anaphylaxis, and generally require no allergy workup. Further vaccines can be administered safely without precaution.
- All immediate reactions after vaccine administration should be assessed by an allergist.
- Immediate reactions (<4 hours) are potentially IgE-mediated and require an allergy workup to prevent the occurrence of anaphylaxis after further administration.
- Egg allergy is not a contraindication to influenza vaccine. In the case of previous anaphylaxis to egg, some guidelines recommend administering the vaccine without specific precaution, while others recommend that an experienced staff administers the vaccine. In the absence of a prior history of anaphylaxis after egg consumption, influenza vaccines can be administered without precaution in egg-allergic patients.
- Allergy to gelatin, yeast, latex and antibiotics or other specific components of vaccines require an allergy workup before administration of the vaccine.

1. Introduction

Vaccines are a cornerstone of pediatric healthcare. The introduction of immunizations for the prevention of life-threatening infections was an important driver of improvements in infant and childhood morbidity and mortality in the 20th century. For this reason, nowadays in the vast majority of developed countries, vaccines on the National Immunization Program are free of charge for children, adults or both and are given in local council immunization sessions, primary healthcare provider clinics and some public hospitals. Enforcing mandatory vaccinations or strongly recommending vaccinations is one of the strategies that some countries in Europe have adopted to protect the community when vaccination coverage was not satisfactory. A recent study [1] showed that 35.4% of European countries had policies of mandatory vaccinations for at least one vaccine.

The success of immunization programs in eliminating vaccine-preventable diseases depends on the community knowledge and acceptance of the balance between the benefits of immunization and the potential vaccine risks. Parents are the ones who commonly perceive that their child has experienced an adverse event following immunization (AEFI), and within this group, the subsequent expectation of an AEFI and vaccine safety concerns may be heightened [2]. In this context, the allergist has a key role in identifying the potential reactions to investigate, in order to give patients a practical answer to their concerns.

The literature search was undertaken through PubMed and Embase. English-language papers focusing on hypersensitivity to vaccines were identified, using the keywords “vaccine hypersensitivity”.

2. Definition

An adverse drug reaction (ADR) is defined as a harmful and unintended effect occurring at doses normally used in humans for the prevention, diagnosis and treatment of diseases or, in general, for the modification of a physiological function [3]. An allergic reaction is defined as a harmful idiosyncratic response produced by a specific immune mechanism [4]. When drug reactions resembling allergy occur, they are called drug hypersensitivity reactions (DHRs) before showing the evidence of either drug-specific antibodies or T cells mediation. DHRs may be allergic or nonallergic in nature. These reactions are typically unpredictable [5]. For general communication, when an allergic drug reaction is suspected, DHR is the preferred term, because it may be difficult to differentiate between true drug allergy and nonallergic DHR based on the clinical presentation alone, especially in cases of acute severe DHR [5].

The definition of the type of reaction after immunizations is vitally important and often challenging. An AEFI includes any untoward medical occurrence following immunization, which does not necessarily have a causal relationship with the administration of the vaccine. Reported adverse events

can either be true adverse events, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization [6].

Any type of vaccine can cause an allergic reaction; however, in many cases, a suspected allergy to a vaccine is not conclusively confirmed [7-8]. Allergic reactions to vaccines have been reported with an incidence ranging from 1 case per 50.000 doses to 1 per 1.000.000 doses [9]. Hypersensitivity can occur as a result of the immunizing antigen or most often one of the other components of the vaccine (suspension fluid, preservatives, stabilizers, antibiotics and adjuvants).

3. Classification of the adverse reactions to vaccines

Immune reactions to drugs and vaccines, can be grouped into four types according to the Gell and Coombs classification [10]: type I or immediate reactions; type II or cytotoxic reactions; type III or reactions mediated by immune complexes; and type IV or delayed hypersensitivity reactions. Hypersensitivity reactions to vaccines are commonly classified by their clinical extension (local or systemic reaction) or according to the timing of the symptoms (immediate ~~and~~ or delayed) [11].

Distinguishing the type of reaction to a vaccine based on time of onset of symptoms and with different organ involvement is essential to prevent a re-exposure to a vaccine that can precipitate systemic and immediate reactions, which could potentially be life-threatening.

Local reactions or injection site reactions are the most frequent adverse events following immunization and have an important impact on clinical practice. Indeed, patients that manifest these reactions are often falsely labeled as allergic [6, 11-14]. Systemic reactions range from fever, headache, myalgia, generalized urticaria to anaphylaxis, that can affect potentially two or more systems: skin (i.e. erythema, pruritus, urticaria, angioedema, maculopapular rash), respiratory tract (i.e. stridor, wheezing, dyspnea), gastrointestinal (i.e. vomiting, diarrhea, abdominal pain) and cardiovascular systems (i.e. weakness, syncope, palpitations, tachycardia and hypotension) [4]. These reactions are less common, but their adequate identification and management are crucial because they include anaphylaxis [11].

Immediate reactions to vaccine are defined as occurring within minutes of exposure to the allergen and generally within 4 hours [9]; however, it is rare for an anaphylaxis reaction to occur beyond the first hour. Immediate reactions include injection site reactions and, rarely, systemic reactions. Delayed reactions to vaccines are defined as occurring within hours or days after exposure [4,6]. Most delayed reactions are limited and do not contraindicate the administration of future doses of the same vaccine [6]. Delayed reactions include [4]: cytotoxic reactions (type II), i.e. thrombocytopenia after administration of the measles-rubella vaccine [15-17]; reactions mediated by immune complexes (type III), i.e. serum sickness [18-20], Arthus reaction [21-22], erythema nodosum [23-24] or Henoch-

Schönlein purpura [25]; cellular reactions or delayed hypersensitivity reactions (type IV), i.e. contact dermatitis and subcutaneous nodules. Delayed urticaria and/or angioedema, or maculopapular rashes, are relatively common symptoms that can occur after vaccinations [11,28]. The pathogenesis of these reactions is not fully understood; however, the role of basophils' activation [26] and a reaction to circulating immune complexes [27] has been proposed in cases of reaction to Hepatitis B vaccine [11, 28].

3.1 Injection site reactions to vaccines

Injection site reactions are the most frequent adverse reactions following immunization [11,13,14]. Injection site reactions include two major patterns: a) pain, redness, and/or swelling and b) persistent subcutaneous itchy nodules at the injection site [11-29]. Their frequency depends on the composition of the vaccine, the number of injections previously administered, and the immunological and inflammatory responses of the host [30,31]. Injection site reactions are particularly frequent with acellular Pertussis (aP)-containing vaccines [32, 33]. Other reactions, such as sterile abscesses, morphea and nevi, with or without hypertrichosis are anecdotal [11].

Pain, redness, and/or swelling at the injection site are the most common local reactions and are generally mild. They are observed in 23 to 81% and 44 to 84% of infants and toddlers following vaccinations with 7 or 13 valent-pneumococcal conjugate vaccines, respectively [30], and in more than 75% of children between four and six years of age following a booster vaccination for diphtheria-tetanus-pertussis-poliomyelitis [34]. These reactions could result from non-specific inflammation induced by microbial or other components used as adjuvants [14]. Large injection site reactions typically occur within 24 to 72 hours following immunization and disappear in two to three days [11,14]. Reactions extending beyond the nearest joint or lasting more than three days are sometimes defined as severe local reactions [13]. Large injection site reactions most frequently occur after injections of toxoid-containing vaccines but may be observed after the injection of any vaccine [11, 13]. They may result from toxoid or aluminum hydroxide-induced inflammation and may occur after any injections of a vaccine [11,35]. Large injection site reactions may also result from an Arthus reaction in previously immunized patients who have developed high titers of specific IgG against the microbial components of the vaccine [11]. In this case, IgG antibodies may bind to vaccine antigens at the injection site and form antigen/antibody complexes, which are thought to activate complement, leading to non-specific mast-cell degranulation and neutrophil recruitment. Arthus reactions develop only in previously immunized patients and typically occur after the fourth or fifth injection [11].

Extensive limb swelling (ELS) is generally characterized as extending beyond the elbow or knee [11]. ELS can occur at any age after administration of a wide variety of vaccines, especially after polyvalent pneumococcal vaccine, diptheria, tetanus toxoids and aP-containing vaccines [36]. ELS is

defined as swelling that measures at least 10 cm and it was observed in 1.3% of children following the fourth dose of aP-containing vaccines [37]. ELS occurs commonly within the first 24 hours after vaccination [36], and is usually painless [11, 37, 38]. Ultrasound examination of 12 children with ELS suggested the potential implication of extravasation mechanisms [39].

Injection site reactions, both mild and large, are benign, resolve spontaneously, and most patients with previous large injection site reactions tolerate subsequent vaccine doses [40]. No allergy workup is generally required, and injection site reactions should not delay subsequent vaccination [9,14]. However, high titers of specific IgG to the vaccine in patients with large injection site reactions are strongly suggestive of an Arthus reaction. In this case, future administration may be delayed as long as IgG titers are protective [11]. In children up to six years of age, injection site reactions may be less frequent but more pronounced if the vaccine is injected in the thigh rather than the arm [41,42].

Persistent (> 6 months) subcutaneous itchy nodules are observed in approximately 1% of children following injection of vaccines containing aluminum, such as diphtheria-tetanus-pertussis-polio-hemophilus influenza type b, pneumococcal, or meningococcal conjugate vaccines [43, 44]. They typically develop weeks after injection [44]. They may increase and become itchier during infections and are often associated with local hypertrichosis and eczema [45]. Patch tests for aluminum salts are positive in 77 to 95% of patients, suggesting delayed type IV hypersensitivity to aluminum [43, 45-49]. However, 8% of control subjects without persistent nodules also have positive patch tests for aluminum salts [44]. The nodule may persist for several years before disappearing. Positivity for the patch tests often disappears over time, suggesting a loss of hypersensitivity [50]. Persistent subcutaneous itchy nodules are benign but may lead to unnecessary investigations and postponement of further vaccination [45, 47]. In clinical practice, persistent subcutaneous itchy nodules do not require any investigation and do not contraindicate vaccination.

No allergy workup is needed for most injection site reactions. These reactions have not been associated with subsequent anaphylactic reactions. Determination of specific IgG concentrations in large injection site reactions may be useful. Prevention of relapses is based on intramuscular injection of the vaccines [45, 51, 52].

3.2 Systemic reactions to vaccines

Very rarely do vaccines cause immediate hypersensitivity reactions, and among these, severe systemic reactions are even less frequent.

Anaphylaxis, the most severe form of acute IgE-mediated reactions, can involve multiple organ systems and can present with variable severity. The rate of anaphylaxis to vaccines has been estimated to be approximately 1 per million vaccine doses [9,53]. Current data are limited to estimating the risk of anaphylaxis associated with vaccination. The majority of studies that estimate the rate of

anaphylaxis to vaccines used passive surveillance systems that lacked an unvaccinated comparison group [9,54]. Passive surveillance systems depend on voluntary reports and cases of anaphylaxis are generally identified based on the presence of suggestive symptoms (Brighton criteria)[57] without confirmation of causality. In addition, several vaccines are often administered together. For these reasons, the exact rate of anaphylaxis for each vaccine is difficult to estimate.

In a recent study, Su et al. [55] searched the VAERS database (Vaccine Adverse Event Reporting System) [56] for reports of anaphylaxis after vaccination in the US for a period of 27 years and focused their analysis on 828 reports that met the Brighton Collaboration case definition for anaphylaxis [57] or included a diagnosis of anaphylaxis by a physician and in addition described symptoms within one day of receiving the vaccine. The most vaccine-induced anaphylaxis in children and young adults (< 19 age) were found to be MMR, Varicella and DTaP/Tdap vaccines, while the influenza vaccine was most commonly reported for adults [55]. The authors estimated a rate of anaphylaxis during the 27 year period to be 0.6 per million doses distributed of MMR and 0.2 per million doses distributed of PCV23. In a shorter test period of 10 years, the estimated rate of anaphylaxis was 1.2 per million doses distributed of Varicella vaccines and in a further test period of 6 years the median estimated annual rate of anaphylaxis due to influenza vaccines was 0.2 per million doses distributed. The authors suggested that the low rate of anaphylaxis in respect to previous studies was due to the fact that VAERS does not collect data on doses administered but estimates rates based on doses distributed which consequently creates a large denominator [55].

McNeil et al. [58], using Vaccine Safety Datalink (VSD) to enroll patients in a three year period (2009-2011), estimated that the rate of anaphylaxis was 1.31 (95% CI, 0,90-1,84) per million vaccine doses administered [58,59]. The advantage of using VSD is that the sites maintain a linked database of health care encounters, including immunization registers with detailed information on vaccines administered.

In both studies [55,58] the most frequently implicated vaccine in anaphylactic reactions was influenza. However, this might reflect its greater frequency of administration. The two studies mentioned above [55,58] are in agreement about the demographic characteristic of patients with anaphylaxis. In particular they found that the anaphylaxis reaction to vaccines in the adult population is more frequent in females and that the median age of patients who experienced anaphylaxis was similar: 12 years in Su's study [55] and 17 years in McNeil's study [58]. Finally, in both studies, atopy was present in the clinical history of patients with anaphylaxis reaction to vaccines: 59% in Su et al. [55] and 85% in McNeil et al. [58].

In the management of patients with suspected anaphylaxis to vaccines, it is important to remember that there are many immediate and systemic adverse events that could be misdiagnosed as anaphylaxis and many of these occur more frequently than vaccine related anaphylaxis [9]. For example, vasovagal syncope and hypotonic hyporesponsive episodes following immunization may be confused with anaphylaxis [9].

There are other systemic reactions to vaccines that are more frequent than anaphylaxis, including fever, headache, myalgia delayed or immediate skin symptoms (i.e. urticaria and/or angioedema, or maculopapular or other nonspecific rashes) and respiratory symptoms (i.e. rhinitis, wheezing). Other systemic reactions are extremely rare, such as Guillain-Barré Syndrome, Immune Thrombocytopenic Purpura, vasculitis and Serum Sickness. These reactions are not discussed in this review. The "Institute for vaccine safety, Johns Hopkins Bloomberg School of public health" provides an updated discussion and revision of the literature about these rare systemic reactions to vaccine [60].

3.2.1 Diagnostic workup (Figure 1)

In the case of suspected IgE-mediated reaction (i.e. urticarial rashes or anaphylaxis occurring within 4 hours from vaccine administration) where further doses of vaccine are required, a complete allergy workup is mandatory in order to avoid future reactions with the same vaccine or the possibility of cross-reactivity with components of other vaccines or foods. Skin tests (Skin Prick tests and Intradermal Tests) are recommended at least 3 weeks, but no more than one year, after the suspected IgE-mediated reaction [61], although ideally, they should be conducted within six months. In case of positive skin tests, the diagnosis of allergy is confirmed. However, positive and negative predictive values of skin tests to vaccines have not yet been established.

From a practical point of view, the occurrence of immunization could be assessed through the evaluation of disease-protecting antibody titers [12]. In case of a confirmed protective immunity induced by the first dose of vaccination, further vaccine doses could be delayed, always being aware that the duration of protection may be shorter than that of a standard administration schedule.

3.2.2 Scheme of vaccination of patients with immediate systemic reactions.

In the case of non-anaphylactic immediate systemic reactions, if the allergy workup (skin tests and specific IgE) is negative, the vaccine can be administered as usual and the patients observed for at least 30 min [4].

In the presence of severe immediate and systemic reactions (suggestive of being IgE-mediated), if the allergy work-up is negative, the vaccine should be administered in two doses: 1/10 of the total amount followed 30-60 minutes later by the remaining dose with a subsequent observation period of at least 30 minutes and even better if observed for one hour [14, 63]. So far, there have been no reports of patients with negative ID testing with the vaccine followed by a serious anaphylactic reaction upon revaccination.

If the skin tests or serum specific IgE titers are found to be positive in a patient with a history consistent with IgE-mediated reactivity to one of the components of the vaccine, it is advisable to use a vaccine lacking that component.

In any cases of a positive allergy workup in patients with suggestive history of severe immediate and systemic reaction to a vaccine or its component and vaccination is considered essential, the suspect vaccine or another vaccine containing the suspect component should be administered with a graded desensitization protocol. The scheme most commonly used is the one proposed by the American Academy of Pediatrics [14, 64]:

1. 0.05 ml of the 1:10 dilution in physiological saline solution
2. 0.05 ml of full-strength vaccine
3. 0.10 ml of full-strength vaccine
4. 0.15 ml of full-strength vaccine
5. 0.20 ml of full-strength vaccine
6. For vaccines requiring a volume of 1 ml, we can add a last dose of 0.5 ml

Each dose is administered every 15 minutes and at the end of the procedure the patient remains under observation for at least 30-60 minutes. This procedure is performed in patients considered at risk of severe reactions because they have been diagnosed as "allergic" to a vaccine or its components. For this reason, the desensitization or fractionated doses administration needs to be performed by trained personnel in a hospital setting with lifesaving facilities available.

The approach to the investigation and subsequent revaccination of patients who reacted after administration of multiple or combined vaccines is more time-consuming. Indeed patients need to be skin tested for all the suspected vaccines in a single session and, if the clinical history of the reaction is suggestive of an IgE mediated reaction and the skin tests are inconclusive, all the individual vaccines should be administered separately in different sessions.

In regard to the management of patients with risk factors, it is important to emphasize that for patients with mastocytosis it is recommended that vaccinations are performed with single vaccines and that observation time is 30 minutes at least, but a controlled setting is not usually required [14]. The management of patients with possible allergies to any component of vaccines as a risk factor is discussed in the specific section below.

4. Hypersensitivity reactions to vaccine components

Vaccine antigens are rarely the cause of hypersensitivity reaction in the vaccinated individual. They have been reported, however, particularly with tetanus toxoids [65], pneumococcal antigens [66] and hepatitis B [26-27]. In a recent study CRM (197) the non-toxic mutant form of diphtheria toxin) has been identified as an allergen that can elicit anaphylaxis reaction in patients immunized with PCV 13 [67].

Many other vaccine components have been hypothesized as being possibly responsible for hypersensitivity reactions to vaccines, but the reactions involving other vaccine components are more frequent than one involving the microbial component [6,12]. However, for some of them the direct causality between the component and the reaction has not been demonstrated, or it is not clear. In these cases, the management of the patient must be evaluated on a case-by-case basis, always remembering that most patients who develop a delayed reaction can receive the vaccine with a low risk of a mild reaction which is usually outweighed by the benefit of the vaccination [11].

Vaccine components that are known to cause hypersensitivity reactions are reported in Table 1, 2.

It is important to note that in the table some components of vaccines which have previously been described as responsible for delayed and injection site reactions (phenol, formaldehyde and 2-phenoxyethanol) are not listed, because they are mentioned only in outdated and single-case reports, without any recently confirmed data [120-122]. In only one recent study of Nagao et al. [123] the potential implication of 2-phenoxyethanol in anaphylaxis following influenza vaccine was suggested, although not confirmed.

4.1 Potential allergens in vaccines

4.1.1 Egg proteins

Literature underlines the rarity of severe reactions following vaccines potentially contaminated with egg proteins [79,82, 124, 125]. Recent data [4,6, 8,9,11-14, 61, 126, 127] confirm that no precaution is necessary for egg-allergic children who must undergo MMR or MMRV, even in those with a history of anaphylaxis to egg, because the safety of these vaccines depends on the minimum amounts of ovalbumin which is the agent that potentially contaminates the vaccines (0-1 ng / ml) [125]. However, an allergist should evaluate those children who have experienced a reaction with a previous MMR/MMRV vaccine, in order to exclude the possibility that the reaction occurred as a result of an hypersensitivity to some other components of the vaccine (especially gelatin). The same recommendation can be given for the tick born encephalitis vaccine. This vaccine is also grown on chicken embryo fibroblast and therefore contains low amounts of ovalbumin (< 1ng/ml) [14].
Some precautions are required in egg allergic patients who must be subjected to YF vaccination. Considering the number of children with egg allergy that undergo the administration of YF vaccine compared to the other vaccines (i.e. anti-influenza vaccination and anti MMR/MMRV), data on its safety in these patients are still lacking [9]. The concentrations of ovalbumin in YF vaccines are higher than in MMR/MMRV or influenza vaccines [14], ranging from 0,13 to 4,42 ug/ml, depending on the study and product batches [80,128]. Therefore, in egg allergic patients, skin testing including a skin prick test and, if negative, an intradermal test is recommended before the administration of YF

vaccine [9,11]. If skin testing is positive, the vaccine must be administered in graded doses under hospital observation. If the tests are negative, vaccination can be carried out as usual [9].
For the management of patients with allergies to egg and anti-influenza vaccinations, see specific sections below.

4.1.2 Milk

Hypersensitivity reactions possibly related to the presence of milk derivatives were described for MMR [117] and more recently for OPV [114] and DTaP or Tdap vaccines [113]; although these studies are debated and have not been confirmed.
There is a general consensus in literature to remark that no precautions are required when administering these vaccines to milk-allergic patients, even in those with history of anaphylaxis to milk. However, if a patient known to be allergic to milk suffers an allergic reaction to one of these vaccines, the possibility of milk protein contaminating should be considered [4,6, 9, 14]. It is noted that milk proteins are not included in the table of vaccine allergens from the "Institute for vaccine safety, Johns Hopkins Bloomberg School of public health" updated on December 2018 [68].

4.1.3 Gelatin

Gelatin, an animal protein used widely in foods and medication as a stabilizer in vaccines, was previously recognized as the principal cause of hypersensitivity reaction to MMR/MMRV vaccines and to tick-borne encephalitis vaccine [11,14].
In particular, a hypersensitivity reaction to vaccines is attributed to porcine or bovine gelatin, in that they show important cross-reactivity. The exact mechanism for patients to become sensitized to gelatin is unknown. However, recent studies have proposed galactose-a-1,3-galactose (alpha-gal), an allergen involved in hypersensitivity reactions to red meat and after exposure to tick bites, as a potential cross-reactive allergen responsible for hypersensitivity reactions to gelatin contained in vaccines [92,97,103,130]. Another possible cross-reactive allergen proposed in a recent study was bovine serum albumin, a major allergen (Bos d 6) in beef and a minor allergen in cows' milk [131]. Finally, Bogdanic J et al. showed that 16% and 38% respectively of beef and pork meat sensitized children, have IgE antibodies to gelatins that are cross-reactive [132].
It should be noted that in some countries, such as Japan and Germany, vaccine manufacturers have removed gelatin from vaccines or changed to a less allergenic gelatin (thoroughly hydrolyzed), with a resultant decrease in allergic reactions [133-137].
Thus, in patients allergic to gelatin, a gelatin-free vaccine should be preferred, because the content of gelatin in vaccine is not negligible (ranging from 500ug/0,5 ml to 12 mg/0,5 ml). If a gelatin-free vaccine is unavailable and the vaccination is required, a skin test with the vaccine itself should be performed before vaccine administration. Patients with negative skin tests can receive the full

vaccine dose, whereas patients with positive skin tests should receive the vaccine in fractionated doses [11, 12, 14].

4.1.4 Yeast protein

While yeast protein is present in HepB and HPV vaccines, only a few studies have demonstrated a possible relationship between the hypersensitivity reaction after immunization and the rare cases of yeast allergy, especially in HepB vaccines [110- 111]. Because the amount of yeast protein can reach 25 mg per dose (in HepB vaccine) [138] and because of the limited data present in literature, patients with suspected or confirmed yeast allergies should undergo a preliminary allergic evaluation with a skin prick test or serum specific IgE with S. cervisiae. If the tests are negative, vaccination can be performed as usual, ~~instead~~ however, if they are positive a skin test with the vaccine needs to be performed. If positive, vaccine administration can proceed in fractionated doses [4,9]. It should be noted that the amount of yeast protein in the quadrivalent HPV vaccine is less than 7 ug/dose [138].

4.1.5 Natural rubber latex

Natural rubber latex (NRL) can be present in the rubber stopper of some vaccine vials and plungers in some prefilled syringes. Even if it has been rarely reported as responsible for hypersensitivity reaction [118,119], it is a potential cause of anaphylactic reaction in NRL allergic patients. For this reason, it should be suggested that patients with a confirmed allergy to NRL be vaccinated with caution with latex-free equipment, such as gloves [4]. In case of a hypersensitivity reaction occurring in a patient immunized with a vaccine that contains latex in its packaging, latex allergy should be excluded. It is worth noting that if clinical manifestations of the patients are indicative of contact allergy, immunization can be performed without precaution [4].

4.1.6 Antibiotics

Some antibiotics, such as neomycin, gentamycin, streptomycin and polymyxin B, used during the production process for vaccines in order to avoid bacterial contamination are considered potential allergens because these antimicrobial agents can cause contact or, rarely, systemic hypersensitivity reactions when used in clinical settings for disease therapy. However, hypersensitivity reactions associated with trace amounts of antibiotics present in vaccines have not been well documented [9]. There is only one ancient reported case of anaphylaxis associated with neomycin in an MMR vaccine [139]. Even though rare, if a patient provides a history of an immediate-type reaction to neomycin or other antibiotics, it is appropriate to investigate with skin testing before immunization with a vaccine containing these constituents. Most patients who develop a non-immediate reaction can receive the vaccine with a low risk of mild reaction outweighed by the benefit of the vaccination [11, 14].

5. Focus on influenza vaccine

5.1 General considerations

Influenza immunization is recommended annually for individuals at risk of severe influenza disease, including young children, pregnant women, people with chronic medical conditions, and the elderly [140-143]. The vaccine formulation changes yearly, based on the strains of influenza anticipated to circulate in the upcoming season [9]. The risk of adverse events following immunization with influenza vaccines (IVs) is therefore a common concern in clinical practice.

IVs are generally prepared by propagation of the virus in embryonated chicken's eggs and thus contain variable and very low amounts of the egg protein ovalbumin. Currently available IVs include the adjuvanted or non-adjuvanted trivalent and quadrivalent inactivated influenza vaccines (IIVs) and live attenuated intranasal trivalent and quadrivalent influenza vaccines (LAIVs). Cell culture-based IIVs (ccIIVs), in which the viruses are grown in animal cells and liquid culture rather than eggs, have been recently developed. However, ccIIVs may contain egg protein, because some of the viruses provided to the manufacturer at the beginning of the process are egg-derived [141]. The only IVs considered to be egg-free are the recombinant trivalent and quadrivalent hemagglutinin influenza vaccines (RIV3, RIV4) [141].

5.2 Epidemiology of anaphylaxis following IVs

The risk of anaphylaxis following administration of trivalent inactivated influenza vaccines (IIV3s) was estimated to be 1.35/million doses between 2009 and 2011 in the United States (US) [58]. The incidence of anaphylaxis following vaccination with a high-dose IIV3, containing four times the standard concentration of hemagglutinin to improve the immune response in adults ≥ 65 years of age, was estimated to be one/million distributed doses [144]. However, all distributed doses are not necessarily administered to the patients and thus this figure may be underestimated. The incidence of anaphylaxis following immunization by quadrivalent IIVs (IIV4) for the 2013-2015 seasons in the US was estimated to be 0.17/million distributed doses [145]. In a post licensure analysis of the 521 adverse events reported following the new MF59-adjuvanted trivalent IIV (aIIV3), approved for adults ≥ 65 years of age in the US, there were no cases of anaphylaxis, whereas anaphylaxis accounted for 0.2 to 0.4% of adverse events reported for the non-adjuvanted IIVs during the same period [146]. Accordingly, in clinical trials, vaccination with the MF59-adjuvanted trivalent and quadrivalent IIVs was not associated with any particular risk of allergic reaction in the pediatric population relative to vaccination with the non-adjuvanted IIV3s and IIV4s [147, 148]. Seven cases of anaphylaxis were reported after the first two seasons of trivalent LAIV use in the US, during which approximately 2.5 million patients were immunized [149]. In a study assessing a total of 782,125 doses of intranasal LAIVs administered during the 2013-2014 season, no cases of anaphylaxis were reported, whereas more than 6.6 million doses of IIV3 were administered and 15 cases of anaphylaxis

recorded during the same period [150]. Anaphylaxis and hypersensitivity reactions after immunization with RIV3 were reported at a similar frequency as those reported after vaccination with IIV3s [151, 152]. Anaphylaxis following influenza vaccination is a rare event and may occur with all types of IVs.

5.3 IV and chicken's egg allergy

There has been a longstanding concern about the risk of anaphylaxis following administration of IVs to patients with egg allergy, particularly those with previous anaphylactic reactions to egg. This led to changes in manufacturing processes, resulting in vaccines with only trace amounts of ovalbumin and the development of egg-free vaccines. In the US, the ovalbumin content of IVs from 2011 through 2015 was ≤ 1 µg/0.5 mL dose for injectable vaccines and 0.24 µg/0.2 mL dose for the nasal LAIV [153]. In 1998, James *et al.* demonstrated that children with egg allergy, including those reporting anaphylaxis to egg, could be safely immunized with IIVs containing 0.02-1.2 µg/ml of egg protein, either in two graded doses or in one single dose [154]. Since then, the safety of IIV3s has been investigated in more than 4,000 children and adult patients with egg allergy, including patients with previous anaphylaxis, resulting in no reported cases of anaphylaxis following immunization with IIV3s [84-87, 155,156]. In a study evaluating the safety of IIV3s possibly containing higher concentration of ovalbumin than the 1.2 µg/ml usually deemed to be safe, none of the 152 egg-allergic patients receiving 292 doses developed anaphylaxis or mild allergic reactions [88]. During the 2009 influenza pandemic, the risk of anaphylaxis following immunization with the AS03-adjuvanted H1N1 vaccine, containing less than 0.03 µg/ml of ovalbumin, was compared between 830 children and adult patients with egg allergy and 393 control subjects [83]. None of the patients with egg allergy or the control subjects developed anaphylaxis and the proportion of patients with possible mild allergic reactions was similar in both groups. Overall, these studies showed that injectable IIVs are safe in egg-allergic recipients, even in those with previous severe reactions to egg, and that the risk of allergic reaction following immunization with IIVs appears to be similar between individuals with and without egg allergy. These studies also showed that pre-vaccine skin tests with the vaccines are unnecessary, since they do not predict the occurrence of an allergic reaction following influenza vaccination. However, in these studies, many patients with previous severe allergic reaction to egg and considered to be at high risk of anaphylaxis following IVs were vaccinated in two or more divided doses in a graded approach and not with a single dose. In addition, these studies included both patients naïve for previous IVs and others who received IVs in the past and were thus previously sensitized. The risk of a hypersensitivity reaction following influenza vaccination may differ between these two groups.

The safety of LAIVs has been assessed in 1,129 children with egg allergy, including 412 children with anaphylaxis to egg, receiving 1,330 doses [89,90,157]. Seventeen children experienced mild reactions post immunization, and no anaphylaxis was observed. In these studies, the concentration of

ovalbumin in the LAIVs was < 0.24 µg/dose. Interestingly, during intranasal challenges with egg protein performed in eight children, no symptoms were elicited at 1 µg/ml and the concentration of egg protein found to trigger nasal symptoms was 10 µg/ml or higher [158]. The risk of anaphylaxis following immunization with LAIVs in patients with egg allergy is therefore expected to be lower than with IIVs.

5.4 Other IV components and anaphylaxis

As for other vaccines, IVs contain various components that may cause allergic reactions. IgE antibodies against viral antigens, such as hemagglutinins were shown to be potential triggers of anaphylaxis after influenza vaccination of children in Japan during the 2011 season [123]. In addition, although very rare, latex present in the vial stopper or syringe plunger was associated with anaphylaxis following influenza vaccination of patients with a latex allergy [118]. Several cases of anaphylaxis have been reported in adults with and without egg allergy after vaccination with RIV3, which does not contain egg proteins, preservatives, or antibiotics, suggesting that other components may be involved [152, 159].

The causal relationship between vaccine components and allergic reactions is however difficult to confirm. For example, the generation of specific IgE antibodies against H1N1, H3N2, and B influenza vaccine components is part of the normal immune response to the vaccine, especially in young children [160]. Among patients from Canada who presented allergic symptoms within 24 hours following immunization with the AS03-adjuvanted monovalent pandemic H1N1 vaccine in 2009, an IgE-mediated mechanism was rarely demonstrated [161]. Skin-prick tests (SPTs) and intradermal tests (IDTs) with the vaccine and its components were positive in only 4% of cases, 3% of control subjects, and 9% of patients with anaphylaxis. Of note, the diagnostic value of skin testing is considered to be low for IVs. In healthy adult volunteers, IDTs to IIV3 were found to be falsely positive for 3 of 20 subjects at a 1:100 dilution, 11/20 subjects at a 1:10 dilution, and 13/20 at full strength [162]. Finally, data from a case-control study performed to determine risk factors for anaphylaxis and allergic-like events following immunization with the AS03-adjuvanted monovalent pandemic H1N1 vaccine in Canada identified food allergies and acute respiratory illness at the time of the vaccination as potential risk factors [163].

5.5 Allergy workup

5.5.1 Egg allergy

There is now strong evidence that individuals with egg allergy can receive any licensed age appropriate IV. Patients with non-severe egg allergy can be immunized under the same conditions as nonallergic patients, without specific precautions [14, 141, 142]. A single dose of IVs is recommended for patients who have experienced anaphylaxis after egg consumption [14, 141, 142].

In this case, some guidelines recommend administering IV without any additional precautions, given that standard vaccination practice includes the ability to recognize and manage severe hypersensitivity reactions [142]. Other guidelines [14, 141] state that IVs should be administered to patients with previous anaphylaxis to egg by an experienced staff in an inpatient or outpatient setting with 15 minutes [141], or a minimum of one hour post vaccination surveillance period [14].

5.5.2 Previous immediate reactions following influenza vaccination

For systemic reactions occurring within the two to four hours following influenza vaccination, an allergic workup, including an SPT with the undiluted vaccine and, if negative, IDT with the vaccine (1:100 and, if negative, 1:10 dilutions) is indicated to show evidence of an IgE-mediated mechanism. If skin-tests are positive, the diagnosis of allergy is confirmed, and further administration should be performed in a clinical setting with graded doses in one day using an intravenous line and the patient should be observed for two hours post-immunization [14].

If skin-tests are negative, the diagnosis of allergy is not excluded, and management depends on the severity of the previous reaction to vaccine. In case of a previous anaphylaxis following influenza vaccination, the patient should be immunized in a clinical setting in two divided doses of 10% of the total vaccine dose and then the other 90% 30 minutes later. If there is a non-severe reaction (urticaria), the patient should be immunized with a single dose in a clinical setting. In both cases, a two-hour post-vaccination surveillance period is required [14].

6. Conclusion

Severe hypersensitivity reactions to vaccines are a very rare eventuality and even rarer are the subsequent contraindications to the second dose of the same vaccine or especially to other vaccines. In patients without a history of allergy, with an allergic disease not related to a vaccine, or with a family history of allergy, no precaution prior to immunization with all types of vaccines is necessary. On the other hand, all patients with prior suspected hypersensitivity reaction to a vaccine have to be evaluated by an allergist to formulate the best approach for subsequent immunization and to avoid having children labeled as “allergic to vaccine” before a certain diagnosis. In all cases, routine vaccinations need to be administered in an adequate setting with trained personnel, medications and equipment needed to treat hypersensitivity reactions.

7. Expert opinion

With policies strengthening the indications for vaccination in Europe, the problem of adverse events following immunization is becoming more stringently identified and regulated in clinical practice.

The main concern is the occurrence of anaphylaxis. Recent data showed that the incidence of anaphylaxis is approximately 1 case per million injected doses, and death is exceedingly rare. In

patients with a suspicion of IgE-mediated reaction, an allergy workup is required if further immunizations are needed, both to avoid further potentially life-threatening reactions and to identify the causal agent that might lead to a hypersensitivity reaction in other situations (i.e. latex, gelatin). It is important to note that even in the case of positive allergy workup, the vaccine is not contraindicated, and can be administered according to a desensitization protocol, under medical supervision. From another point of view, injection site reactions are the most common adverse event following injection of vaccines and constitute one of the main post-vaccination issues. Although most of these reactions are benign, there are clearly associated with decreases in the vaccination rate. This is mainly due to fear of anaphylactic reaction during recall injection.

Insufficient understanding and knowledge of the real risk of severe hypersensitivity reactions to vaccines is responsible for the fact that too many patients are still needlessly referred to hospital for vaccine injection because of the fear of potential severe reactions. For the same reason, vaccinations are too often delayed even in the case of non-immediate or local reactions. Improving knowledge of side effects and their management is therefore crucial in the promotion of vaccinations to protect both the individual and the community at a time when anti-vaccination movements are very active. Communication skills need to be upgraded, improved and targeted to patients and their families in order to fully explain the different scenarios associated with hypersensitivity reactions to vaccines.

Moreover, the aim of successful management of suspected vaccine hypersensitivity reactions, at least in the case of the most frequently used vaccines in European countries (MMR/MMRV, influenza, DTP), is to reduce hospital admissions for the administration of vaccinations in a protected environment and to therefore stimulate the practice and belief that vaccines can be safely administered directly by local doctors.

In our opinion, future research should be aimed at identifying adverse reactions to lesser-known vaccines, such as yellow fever and Japanese encephalitis, increasingly needed due to the prevalence of travel in a globalized world. Studies in this area are still limited to date.

Furthermore, there has been a longstanding concern about the risk of anaphylaxis following administration of vaccines containing small amounts of egg proteins to patients with egg allergy, particularly those with previous anaphylactic reactions to egg. It is now clear that egg allergy is not a contraindication to influenza and MMR/MMRV vaccination. However, further large and multicentric studies are urgently needed to assess the real diagnostic value of skin test in egg allergic patients who need to be vaccinated with YF vaccine and the necessity of performing a graded dose administration versus full dose, as has been recently performed for influenza vaccine in egg allergic children.

In addition, more data are needed to provide correct definition of the incidence of anaphylaxis to vaccines with studies based on a confirmatory allergy work-up, especially in patients allergic to foods

such as milk and egg. At the same time, it is important to try limiting specific allergy tests to patients who have a clinical history of a reaction to a specific vaccine. Specifically, pediatric data are needed in order to focus on specific issues that could be associated with the hypersensitivity reactions management in this age group.

Changes in manufacturing processes of vaccines continue to increase their safety profiles.

In fact, to minimize the risk of hypersensitivity reactions the development of newer vaccines which use new manufacturing processes is crucial. For example, the use of new adjuvants in order to decrease the frequency of local reactions that have been responsible for a decreased vaccine coverage rate. An example of recent vaccines associated with low risk of hypersensitivity reaction are the recombinant trivalent and quadrivalent hemagglutinin influenza vaccines, which are considered to be egg-free, and devoid of preservatives and antibiotics.

In this regard, there is still a need for more research on newer adjuvants used in vaccines also taking into account that some adjuvanted vaccines are administered together with a potential additional risk which is not something evaluated in clinical trials.

Other routes of immunization such as the intranasal route have also demonstrated their safety for annual immunization against influenza. Recent development strategies have targeted specific populations which seems to be a productive path for more research. For example, the elderly population is a high-risk group for developing severe influenza disease. and aging is associated with a decreased immune response to vaccine. Influenza vaccines containing higher titers of hemagglutinin or adjuvant to increase the immune response in this age-group have now been developed and used in the US since the 2016-2017 season, with a good safety profile.

To summarize, the ultimate goal in this field is to establish unique guidelines to help identify potential patients who might require specific allergy workup and vaccination in a hospital setting while trying to guarantee a safe and desirable level of vaccination coverage for the entire population. In terms of clinical practice, this knowledge could lead to the definition and establishment of a network between first level vaccination centers and specialized referral centers, in order to formulate a shared management environment for selected cases of potential hypersensitivity reactions to vaccines. This would help immensely to maximize the efficiency and optimize the cost-benefit ratio of the vaccination process.

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Figure 1: Diagnostic workup for Immediate systemic reactions to vaccines.

§ 1/10 concentration for SPT with vaccine is recommended in cases of severe anaphylaxis (63)

Useful information for the management of vaccine allergy can be obtained by checking the following links (62):

1. http://www.vaccinesafety.edu/components-Allergens.htm: list of allergens and where they are contained;
2. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/ appendices/B/latex-table.pdf : list of vaccines at risk for latex allergic patients
3. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/ appendices/B/excipient-table-2.pdf: media used for vaccines and excipients.

Table 1: Potential vaccine allergens: adjuvant, preservatives, antibiotics, carrier proteins (modified 68)

Excipient	Type	Vaccine type	Type of hypersensitivity reaction	References
Aluminium	Adjuvant	DTaP/Tdap/DT/MEN B/HepB/HepA/HPV/DTaP+IPV/DTaP+IPV+HepB/Hib+HepB/ DTaP+IPV+Hib/PCV 13.	Delayed type hypersensitivity reactions (contact allergy, small granulomas, nodules)	43, 45, 47, 48, 69-73
Thimerosal	Preservative	DT/Td/influenza/Japanese encephalitis/ Menigococcal	Contact allergy, systemic allergic reaction (rare)	6, 74, 75
ASO-3	Adjuvant	AS0-3 adjuvanted A/H1N1 pandemic influenza vaccine	Anaphylaxis and other immediate hypersensitivity reaction	74, 76, 77
Neomycin	Antimicrobial	Influenza/HepA/IPV/DTaP+IPV/MMR/DTaP+HepB+IPV/DTaP+IPV+Hib/MMRV/ DTaP+IPV/Rabies/HepA/Varicella/Influenza/HepA+HepB	comment in the main text	
Polymixin B	Antimicrobial	Influenza/Polio/DTaP+IPV/DTaP+HepB+IPV	comment in the main text	
Polysorbate 80	Surfactant	HPV/influenza/HepB/DTaP/JapaneseEncephalitis/ DTaP+IPV/ DTaP+HepB+IPV/ DTaP+IPV+Hib/PCV13/Rotavirus/MEN B	Anaphylaxis and other immediate hypersensitivity reaction	78

Abbreviation: DTaP- diphtheria, tetanus and acellular pertussis; Tdap- tetanus, reduced diphtheria and acellular pertussis; DT- diphtheria, tetanus; Td- Tetanus and Diphtheria Toxoids adsorbed; MEN B- Meningococcal group B; HepB- Hepatitis B; HepA- Hepatitis A; HPV- Human papillomavirus; IPV- inactivated polio vaccine; Hib- Haemophilus influenzae type b; PCV13- Pneumococcal 13-valent; AS0-3- trade name for a squalen-based adiuvant; MMR- Measles, Mumps, Rubella; MMRV- Measles, Mumps, Rubella, Varicella;

Table 2: Other potential vaccine allergens (modified 68)

Excipient	Type	Vaccine type	Type of hypersensitivity reaction	References
Potential allergens				
Egg (ovoalbumin, egg protein)*	Residual medium	Influenza, MMR, YF, TBE.	Minor/local hypersensitivity reaction (macular rash, urticarial rash), anaphylaxis (rare)	79-91
Gelatin	Manufacturing residue/ stabilizer	YF/MMR/MMRV/Varicella/influenza/Varicella Zoster/Japanese encephalitis/TBE	Immediate-type (anaphylaxis) and delayed-type (localized erythema, induration at the injection site) hypersensitivity reactions.	92-109
Yeast (Saccharomyces cerevisiae)	Medium nutrient	Hib+HepB/HepB/HPV/Meningococcal/DTaP+HepB+IPV/PCV13/HepB/HepA+HepB/ Typhoid	Anaphylaxis and other immediate hypersensitivity reaction	110-112
Milk	Medium nutrient	DTaP/Td/Tdap/OPV/Typhoid fever (oral)/MMR	Anaphylaxis and other immediate hypersensitivity reaction	113-117
Latex**	Pharmaceutical closure	Tdap/Menigococcal/Hip+HepB/HepB/Influenza/HepA/HepB+HepA/DTaP/DTaP+IPV/ DTaP+HepB+IPV/Rotavirus/Td	Anaphylaxis and other immediate hypersensitivity reaction	118-119

Abbreviation: DTaP- diphtheria, tetanus and acellular pertussis; Tdap- tetanus, reduced diphtheria and acellular pertussis; DT- diphtheria, tetanus; Td- Tetanus and Diphtheria Toxoids adsorbed; MEN B- Meningococcal group B; HepB- Hepatitis B; HepA- Hepatitis A; HPV- Human papillomavirus; IPV- inactivated polio vaccine; Hib- Haemophilus influenzae type b; PCV13- Pneumococcal 13-valent; AS0-3- trade name for a squalen-based adiuvant; MMR- Measles, Mumps, Rubella; MMRV- Measles, Mumps, Rubella, Varicella; YF- yellow fever; OPV- oral polio vaccine; TBE- thick born encephalitis.

* Different vaccines are at risk of contain small amounts of residual egg proteins from the vaccine manufacturing process, concentrations are usually higher in vaccines cultured on embryonated chicken eggs (influenza, yellow fever, and rabies) and lower for vaccines cultured on fibroblasts of chicken embryos (MMR/MMRV, TBE).

** Latex may be present in the rubber stopper of some vaccine vials and plungers in some prefilled syringes

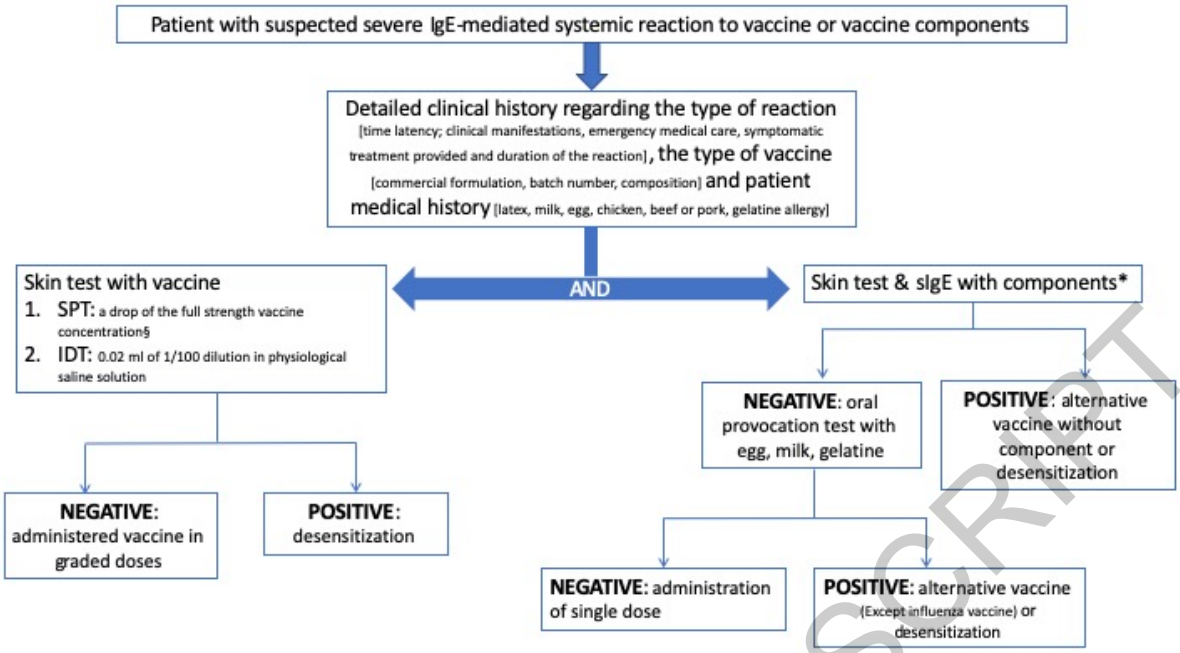

Fig 1