

Vaccine hypersensitivity – update and overview

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Summary

Concerns about possible reactions to vaccines or vaccinations are frequently raised.

However, the rate of reported vaccine-induced adverse events is low and ranges between 4.8–83.0 per 100 000 doses of the most frequently used vaccines. The number of true allergic reactions to routine vaccines is not known; estimations range from 1 per 500 000 to 1 per 1 000 000 doses for most vaccines. When allergens such as gelatine or egg proteins are components of the formulation, the rate for serious allergic reactions may be higher. Nevertheless, anaphylactic, potentially life-threatening reactions to vaccines are still a rare event (~1 per 1 500 000 doses). The variety of reported vaccine-related adverse events is broad.

Most frequently, reactions to vaccines are limited to the injection site and result from a non specific activation of the inflammatory system by, for example, aluminium salts or the active microbial components.

If allergy is suspected, an accurate examination followed by algorithms is the key for correct diagnosis, treatment and the decision regarding revaccination in patients with immediate-type reactions to vaccines.

Key words: vaccine allergy; vaccine-induced adverse events; immediate type vaccine allergy; delayed type vaccine allergy; egg protein; gelatine; antibiotics; toxoids; macrophagic myofasciitis; revaccination

Introduction

From the mid of the 20th century and since the propagation of vaccination schedules in various countries, many infectious diseases have been effectively reduced or eliminated and many sequelae of infections could be avoided [1, 2]. Vaccines represent the most effective measures in public health by controlling and preventing the spread of infectious diseases [3, 4]. Vaccines and vaccine components, however, may cause adverse events (AE) which provide arguments for opponents of vaccinations against national vaccination recommendations [5, 6]. Nonetheless, the rate of vaccine-induced side effects is low. Post-marketing surveillance data of the national vaccination programs in children from the Netherlands, Australia and the US report 4.8 to 83 AE per 100 000 given doses for the most frequently used vaccines [7–9]. Similarly, the Vaccine Adverse Event Reporting System (VAERS) of the US collected only few reports of AE after administration of commonly used vaccines (table 1). From 1991 to 2001, the number of reported mild and even severe AE remained relatively steady (1991: 7.2/100 000 given doses; 2001: 5.8/100 000 given doses) [8].

After routine vaccinations, the most common adverse side effects are symptoms at the injection site [8]. Local pain, erythema and swelling are the most frequently reported local side effects [5–7, 10–12]. With respect to systemic adverse reac-

Abbreviations

AE	adverse events
DT	diphtheria-tetanus
DTaP	diphtheria-tetanus-acellular pertussis
DTR	delayed-type reaction
HBV	hepatitis B virus
HPV	human papilloma virus
ITR	immediate-type reaction
JEV	Japanese encephalitis virus
MMF	macrophagic myofasciitis
MMR	measles-mumps-rubella
SPT	skin prick test
TBE	tick-borne encephalitis
VAERS	Vaccine Adverse Event Reporting System
2-PE	2-phenoxy-ethanol

tions, fever and irritability are often registered [10, 11, 13]. These usually mild post-vaccination reactions mainly reflect a non-specific stimulation of the inflammatory system by harmless inactivated or altered viral or bacterial particles [14–17]. A number of diseases like asthma, autism, multiple

sclerosis, Guillain-Barré syndrome, inflammatory bowel disease or sudden infant death have been assumed to be related somehow to vaccinations. However, none of these associations are based on scientific or clinical evidence [18–23, 24–28]. For atopic patients, there is no current evidence for an increased risk of allergic reactions after vaccination [29].

Allergies to vaccines only account for a limited number of all vaccination associated AE. Table 2 lists potential types of immune-mediated side effects associated with vaccination.

This review focuses on immediate and delayed type allergic reactions of commonly used vaccines in Switzerland.

Table 1
Reported AE per 100 000 doses of vaccine (VAERS 1991–2001, [108]).

Vaccine	Reported AE per 100 000 doses
Influenza	3
Hepatitis B	11.8
MMR	16.3
D'TaP	12.5

Table 2
Synopsis of potential immune-mediated reactions to vaccines.

Immune mediated reaction	Frequent clinical manifestation
IgE mediated	Urticaria, angioedema, rhinoconjunctivitis, bronchospasm, anaphylaxis, gastrointestinal disorders (diarrhea, abdominal cramping, vomiting)
Immune complex (IgG)	Vasculitis, myocarditis
T-cell mediated	Maculopapular exanthema, eczema, acute generalised exanthematous pustulosis (AGEP), erythema multiforme [109, 110]
Non-IgE mediated (pseudoallergic)	Urticaria, angioedema, anaphylactoid reactions, gastrointestinal disorders
Autoimmune/inflammatory	Thrombocytopenia, vasculitis, polyradiculoneuritis, macrophagic myofasciitis, rheumatoid arthritis, Reiter's syndrome, sarcoidosis (juvenile), bullous pemphigoid, lichen planus, Guillain-Barré syndrome, polymyalgia

Immediate type/IgE mediated vaccine allergy

Signs of immediate allergic reactions after vaccination are predominantly systemic and comprise of cutaneous symptoms such as flushing, urticaria, angioedema, respiratory signs such as rhinoconjunctivitis or bronchospasm, and cardiovascular complications with severe vertigo, faintness, drop of blood pressure and shock starting within minutes after vaccination.

Immediate, systemic reactions – allergic or not – following vaccination with frequently used vaccines are very rare. The average reporting rate for immediate type reactions (ITR) in children and adolescents is 0.22 per 100 000 doses of vaccines. 31% of these patients reported an ITR after the first vaccination [29]. This observation suggests either a pre-sensitization to a vaccine component or non-immunologically mediated reaction.

According to Bohlke et al., reported cases of potential anaphylaxis after vaccination amount to 0.065 per 100 000 given doses of vaccines. None of the episodes resulted in death [30]. This underlines that life-threatening reactions after routine vaccination are exceptional events. Table 3 summarises the rate of anaphylactic reactions of commonly used vaccines.

Table 3
Estimates for the incidence of anaphylaxis: 1994–1996 [111].

Vaccine	Anaphylactic reactions per 100 000 doses
Measles	0.68
Rubella	0.73
Mumps	0.44
Varicella	1.30
HPV	2.60

Table 4
Components of vaccines [112–114].

Vaccine	Attenuated virus
Culture media	Protein/peptides Hen's egg, horse serum, murine and simian cells, kidney cells of dog
Additives	Antibiotics Neomycin, chlortetracycline, gentamycin, streptomycin, polymyxin B, amphotericin B
	Preservatives Formaldehyde, thiomersal, natriumtmerfonat, aluminum, 2-PE
	Stabilizers Gelatine, lactose, polysorbate 80/20, polygelines
Contamination	Latex
Active agent	Toxoids, attenuated pathogens

Almost all components of a vaccine may be considered as potential triggers of an allergic reaction (table 4). Of particular importance are culture derived proteins from egg, yeast and gelatine.

Other sources are antibiotics and vaccination antigens. In terms of severe ITR, egg constituents, gelatine and latex are the most relevant and allergenic proteins [31, 32].

Delayed-type vaccine allergy and reactions at the site of vaccine injection

Delayed-type reactions (DTR) following vaccinations are generally local and confined to the site of injection. This form of reaction is usually not considered as an allergy. Such reactions probably result from non-specific activation of the inflammatory system by, for example, high doses of aluminium salts or microbial components (active agent) [33].

Rarely, patients hyperimmunized by previous injections of the vaccine (e.g., tetanus vaccination) might develop a local immune complex mediated, so called, Arthus-type reaction at the site of vaccine injection [12, 34].

T-cell mediated reactions usually manifest in the form of local eczema, starting from 2–8 hours up to 2 days after vaccination. Sometimes the reaction may extend beyond the injection area or may even become generalised [35–37].

Even an extensive swelling is usually self-limiting and disappears without complications within one to four days. Swellings at the injection-site are no contraindication for further vaccinations [11]. The following vaccines are commonly quoted as triggers of strong local reactions: polyvalent pneumococcal, influenza, acellular pertussis particularly combined with diphtheria and tetanus toxoid as well as hepatitis B [34].

Active immunization with tetanus leads to local side effects in approximately 80% of adults [38]. About 2% of child vaccines have, after the 4th or 5th booster dose or after a short injection interval (<5 to 10 years) with combined diphtheria-tetanus-acellular pertussis (DTaP), local side effects [39, 40].

Allergenic components in vaccines and their allergenic relevance

Proteins

Egg protein (ovalbumin)

Hen's egg allergy is a major issue and the most frequent discussed constituent, in terms of allergic reactions to vaccines. Egg allergy affects 1.6 to 2.4% of children [41, 42].

Due to cultivation in avian cell lines, vaccines like measles, mumps and rubella (MMR), influenza, yellow-fever, tick-borne encephalitis (TBE), herpes simplex (type 1 and 2) and rabies may contain low amounts of ovalbumin. Ovalbumin has been thought to be responsible for allergic or even anaphylactic reactions in egg-allergic individuals [43–46]. Several publications have demonstrated that allergy to hen's egg protein is not a contraindication for MMR vaccination, even in case of a severe egg protein hypersensitivity [43, 46, 47].

Whilst MMR, TBE and rabies vaccines are developed on fibroblasts of chick embryos, herpes simplex, influenza and yellow fever viruses need to be cultured in embryonated hen's eggs. Therefore, these vaccines may contain higher amounts of egg proteins (table 5), and are usually contraindicated for subjects with severe hen's egg allergy. However, several case series have demonstrated safe administration of the influenza vaccine (<0.6 µg egg protein/0.5 ml dose) in patients with anaphylaxis to egg [48–50].

Gelatine

Gelatine is an animal protein derived from the connective tissue of swine and cattle. It is used as a stabilizer in attenuated viral containing vaccines.

Gelatine may be added to many vaccines such as MMR (single or combined), Japanese encephalitis virus (JEV), DTaP and varicella. The amount of gelatine varies from vaccine to vaccine from

Table 5

Content of ovalbumin/dose in Switzerland (Arzneimittelkompendium der Schweiz).

Vaccine	Content of ovalbumin/dose
MMR	≤0.001 µg [119]
Influenza vaccines in Switzerland	
Fluarix®	≤1 µg
Influvac®	≤1 µg
Influvac plus®	≤0.5 µg
Fluad®	≤0.2 µg
Inflexal V®	≤0.05 µg
Mutagrip®	≤0.05 µg
H1N1 vaccines in Switzerland	
Pandemrix®	Traces (no quantity specified)
Focetria®	Traces (no quantity specified)
Yellow fever vaccine in Switzerland	
Stamaryl®	≤1600 µg (!)
Herpes simplex (1 and 2) vaccine in Switzerland	
Lupidon H/G®	≤50 µg (!)

<30 µg to >15 500 µg per dose [51]. Gelatine containing vaccines in Switzerland are listed in table 6.

Severe IgE mediated reactions after vaccination with gelatine containing compounds are very rare but have been described after MMR, varicella, and JEV [52]. The first vaccine-associated IgE-mediated reaction was reported after a MMR vaccination [53]. The rate of anaphylactic reactions after measles vaccination was 0.18 per 100 000 given doses [51]. IgE antibodies to gelatine have been demonstrated in 10/36 (28%) subjects with ITR after MMR vaccination [54], in 93% of 206 patients with anaphylaxis, and in 56% with urticaria [55]. In contrast, none of the patients with local reactions and none of the control group without AE showed IgE antibodies to gelatine [55]. These findings were linked to the use of gelatine containing DTaP vaccines as a primary sensitizer in these patients [55, 56]. Nowadays, all available DTaP vaccines in Switzerland are free of gelatine (table 6).

Yeast proteins

Hepatitis B (HBV) and the human papilloma virus (HPV) vaccines are prepared by harvesting the antigens from cell cultures of recombinant strains of *Saccharomyces cerevisiae* (common bakers' yeast). In the HBV vaccine, no detectible yeast DNA and only traces of yeast proteins may be found [57, 58]. Evidence from the post-marketing surveillance for vaccine safety suggests that recombinant yeast derived HBV and HPV vaccines pose minimal risk of allergic reactions to yeast sensitive individuals [59, 60].

Antibiotics

Many vaccines contain traces of antibiotics like aminoglycosides, polymyxin, chlortetracycline, and the fungicide amphotericin B, to avoid bacterial and fungal contamination during the manufacturing process.

To date, there are only few reports on allergic reactions induced by antibiotics in vaccines.

Neomycin sulphate is widely used in the production process of all kind of vaccines. On the Swiss market, vaccines contain only traces of less than 25 µg of neomycin per dose [61] (table 7). To date, one single case of anaphylaxis has been linked to a neomycin-containing vaccine [62]. It is a general agreement that patients with anaphylactic reactions to topical or systemic neomycin should not be vaccinated with neomycin containing vaccines [63].

In contrast, topical neomycin is known to elicit a high rate of contact dermatitis [64]. However, the amount of neomycin found in vaccines is not believed to trigger DTR [64]. Thus, all these vaccines may be given to patients with delayed type sensitization to neomycin [63, 65].

Other antibiotics like streptomycin, gentamicin, polymyxin B sulphate and chlortetracycline (table 8) have been reported to trigger mild to life-threatening allergic reactions caused by topical and/or systemic clinical use [66–71, 72–73], whilst in term of vaccination they have not yet been identified as a causative agent of severe allergic reactions [37, 74].

Preservatives and stabilizers

Preservatives in vaccines like thiomersal and 2-phenoxyethanol (2-PE) have been identified in single case reports to trigger allergic reactions after vaccination [39, 75].

Table 6

Gelatine containing vaccines in Switzerland 2008.

Brand name	Addressed disease(s)	Gelatine content/dose
MMR-II	Measles, mumps, rubella (trivalent)	14.5 mg/0.5 ml
Vivotif	Typhus	Capsule contains gelatine
Varivax	Varicella	12.5 mg/0.5 ml
Zostavax	Herpes zoster	15.58 mg/0.5 ml

Table 7

Neomycin containing vaccines in Switzerland.

MMR plus	M-M-RVaxPro®, Priorix®, Priorix-Tetra®
DTP plus	Infanrix DTPa-IPV®, Infanrix DTPa-IPV + Hib®, Infanrix hexa®, Pentavac®, Revaxis®, Td-Virelon®, Tetravac®
TBE	Encepur N®, Encepur N Kinder®, FSME-Immun 0.25ml Junior®, FSME-Immun CC®
Hepatitis	Twinrix 720/20®, HBVAXPRO (5/10/40)®, Havrix 1440/720®
Cholera	Dukoral®
Rabies	Rabipur®, Tollwut Impfstoff Mérieux®
Varicella	Varilrix®, Varivax®
Zoster	Zostavax®
Influenza	Mutagri®
H1N1	Focetria®
Polio	Poliorix®

Table 8

Antibiotic containing vaccines [61].

Streptomycin	Pentavac®, Tetravac®, Revaxis®, Td-Virelon®
Gentamicin	Fluarix®, Influvac®, Influvac plus®
Polymyxin B sulfate	Infanrix DTPa-IPV®, Infanrix DTPa-IIPV + Hib®, Infanrix hexa®, Pentavac®, Revaxis®, Td-Virelon®, Tetravac®, Poliorix®
Chlortetracyclin	Ecepur N®, Encepur Kinder® (TBE) and Rabipur®

Thiomersal

For all officially recommended vaccinations in Switzerland, vaccines without thiomersal are available [76]. In clinical vaccine-studies, it has been found that thiomersal is safe even in thiomersal patch-test positive subjects [77–79]. Recently, one ITR to thiomersal after influenza vaccination has been reported [75].

Although the anxiety of thiomersal causing autism could not be substantiated; thiomersal continuously disappears from many vaccines [80, 81].

Aluminium

In vaccines, aluminium salts are used as adjuvants to enhance the immune response [82]. The most frequent clinical manifestation of a reaction to aluminium in vaccines is the development of painful and pruritic nodules at the site of injection [83]. There are only a few case reports about patients with hypersensitivity reactions to aluminium developing dermatitis, either localised or generalised [35].

In recent years, several studies have provided scientific evidence that there is an association between aluminium exposure and Alzheimer's disease [84, 85]. However, the link between Alzheimer's disease and aluminium exposure from vaccination remains unclear, since aluminium uptake by food is much higher than by vaccination [61, 86, 87].

Macrophagic myofasciitis (MMF) is an aluminium related disease but is not considered to be an allergy. MMF was first reported in 1998. In France over 200 cases have been identified, and isolated cases have been recorded in Germany, the US, Spain and Australia. By histopathology, MMF is characterised by infiltration of muscle tissue by PAS-positive macrophages loaded with aluminium hydroxide salts [88, 89]. The condition manifests by diffuse myalgias, arthralgias, asthe-

nia, muscle weakness and fever. The World Health Organisation (WHO) comments that, to date, there is no evidence of a health risk from aluminium containing vaccines or any justification for changing current vaccination practices [90].

Toxoids

Toxoids are bacterial toxins whose toxicity is suppressed either by chemical or temperature (heat) conditions, while immunogenicity is maintained.

Challenges suggest that most toxoid induced mild to moderate reactions result from a non-specific activation of the inflammatory system by high doses of bacterial components [14–17]. That assumption has been supported by good tolerance of subsequent booster injections of the suspected vaccines [15–17, 33].

However, in patients with severe urticaria and angioedema, positive skin and CAP test results to toxoids have been identified following booster injections of toxoid containing vaccines [33]. Anaphylactic reactions to toxoids, however, are very rare [91–93]. In patients with generalised skin reactions, such as immediate and accelerated urticaria and angioedema, an allergological examination using the skin prick test (SPT) and determination of serum specific IgE to anti-toxoid antibodies (diphtheria and tetanus) should be performed, following booster injections of toxoid-containing vaccines.

Rare allergenic components in vaccines

Vaccine components like polysorbate (Tween) [94–96], polygelines [52], amphotericin B [97, 98], protamine sulphate [99–102] and phenol red [103] are rarely known to elicit hypersensitivity reactions. In the literature, there is no evidence for hypersensitivity reactions of these substances linked to vaccination.

Diagnostic approach in patients with vaccine allergy

The Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network presented, in September 2008, an algorithm for the treatment of patients with hypersensitivity reactions to vaccines [104].

Table 9 summarises important questions that have to be addressed during the interview with the patient to facilitate the classification of the vaccine induced reaction. The differentiation of an ITR from a DTR is essential since the allergy testing is

different. Whereas in ITRs the SPT or determination of specific IgE in serum may be helpful to identify the causative agent, in DTR patch tests may be performed.

Therefore, particularly in patients with symptoms consistent with IgE-mediated reactions, allergy testing is indicated, if future doses of the suspect vaccine will be needed. However, it is important to mention that the testing in vaccine hypersensitivity is not standardised and not validated. It is necessary to use the intact vaccine for skin testing preferably from the same manufacturer and in some instances it might be helpful to test with specific vaccine components when available. Skin tests are performed according to the general guidelines as for other allergic diseases (fig. 1). Due to a high incidence of false positive reactions due to inherent vaccine irritation, intra-

Table 9
Patient's history
and clinic.

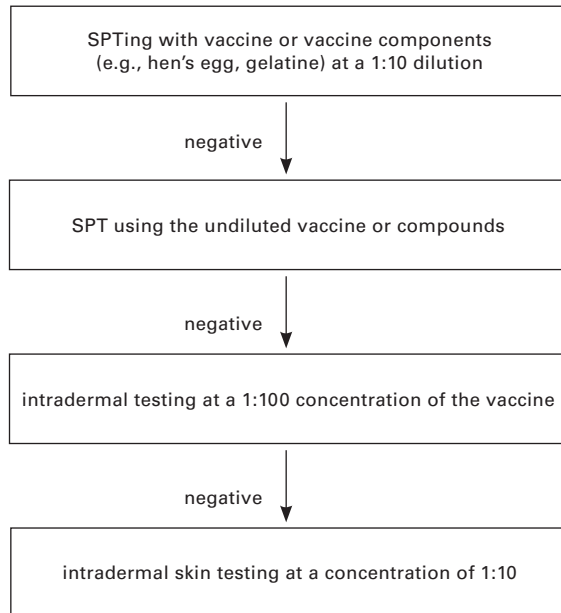
Timing of the symptoms relative to vaccine administration
(immediate, delayed, not allergic)

Characteristic symptoms (urticaria, angioedema, rhinoconjunctivitis, bronchospasm, eczema, maculopapular rash)

Localisation of the lesion (local at the injection site, generalised)

Figure 1

Diagnostic course of SPTing with vaccines.



Cave: intradermal skin testing at a 1:10 concentration might elicit irritative skin reactions (false positive such as for instance influenza vaccine).

dermal skin testing with undiluted compounds should be omitted. Furthermore, it is important to recognize that localised DTRs are common after testing with undiluted and 1:10 concentrations of many vaccines and are not diagnostic for an allergy.

In case a sensitization to vaccine compounds could be excluded, patients with ITR can be revaccinated, however, under controlled conditions in an appropriate setting.

Revaccination of patients with suspected hypersensitivity reactions

Decisions about revaccination should be made on the basis of a case-by-case risk/benefit analysis. For patients with an **ITR** and in need of revaccination, the following procedure may be considered [104]:

1. Alternative preparations without suspected allergens should always be used when available.
2. If testing has been inconclusive and multiple vaccines are potentially implicated, the vaccines should be given individually, on separate days.
3. If SPTs are negative, and there is no history of anaphylaxis, the vaccine can be given in a single dose followed by observation of the patient for one hour.
4. If SPTs are negative but the history is suggestive for anaphylaxis or other serious reactions, 10% of the dose of the full-strength of the vaccine could be administered followed by observation of the patient for at least 30 minutes. If there are no signs of any reaction, the remaining part of the vaccine can be given and the patient must be observed for another hour.
5. If SPTs are positive for the vaccine and/or one of its components and there is absolute need

for vaccination, fractionate vaccination according to the recommendation of the American Academy of Pediatrics [105] (table 10) may be considered. Doses are given at intervals of 15 to 30 minutes until the full dose has been applied or until the first signs of an AE is observed. For some cases, and according to the history, the time interval may be extended. In case of AE two options may be followed:

- a. Withhold additional doses of the vaccine,
- b. Pre-medication with antihistamines and oral corticosteroids before further up-dosing.

For patients with **DTRs**, the approach to revaccination will be based on the nature of the previous reaction, because patch testing will not be helpful in predicting future risk. The decision to revaccinate should be made on an individual basis, depending on the importance of revaccination and the nature of the previous reaction. Patients with previous DTRs can generally receive the full dose of the vaccine

Alternative algorithm for revaccination of patients with suspected hypersensitivity to egg (ovalbumin)

Lavi et al. showed that egg allergic children with a negative SPT to the suspected vaccine, tolerated a complete dose of ovalbumin-containing vaccines [106]. If SPTing is positive, a risk-benefit analysis is indicated or, if necessary, a two-dose protocol should be administered when the available vaccine preparation contains more than 1.2 µg/mL of egg protein (see table 5): Under pre-medication (antihistamines, steroids) injection of 1/10 of the total load, is followed after 30 minutes

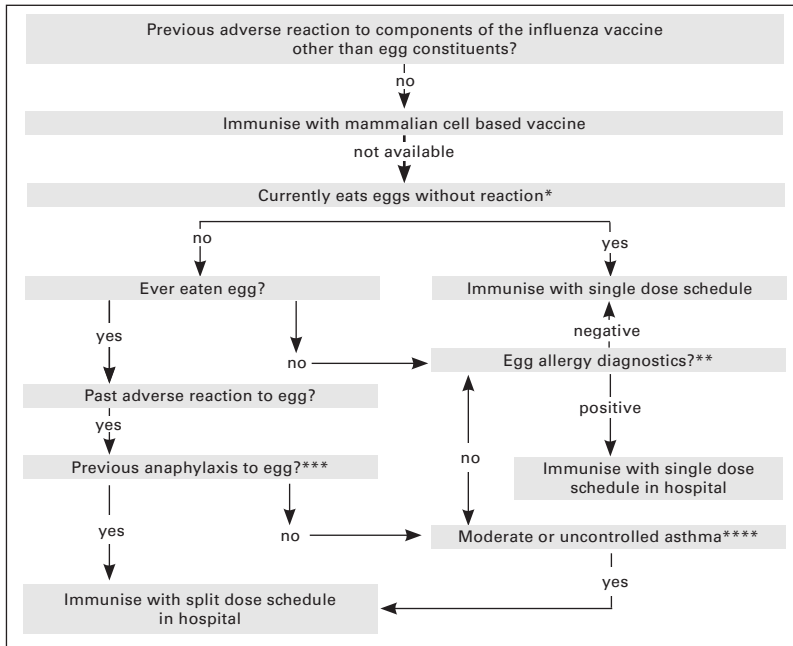
Table 10

Proposal of administration of vaccines in patients with positive SPT for the respective vaccine and absolute need for vaccination [105].

a) 0.05 mL of 1:10 dilution
b) 0.05 mL of full strength
c) 0.10 mL of full strength
d) 0.15 mL of full strength
e) 0.20 mL of full strength
f) for vaccines that require a volume of 1.0 mL, the remaining 0.5 mL dose can be added

Figure 2

Algorithm for the immunisation of individuals allergic to egg with influenza vaccine by Erlewyn-Lajeunesse et al. [107].



* Able to eat a portion of eggs (not just egg when baked in foods such as in cakes and biscuit) without immediate allergic reactions

** A positive SPT, specific IgE, food challenge

*** A history of a severe allergic reaction affecting at least one of the following areas: airway (throat tightness, sensation of closure, stridor, hoarseness), breathing (tachypnoea, respiratory distress, dyspnoea, wheeze, hypoxia), circulation collapse, hypotension, shock with or without loss of consciousness, severe abdominal pain)

**** Uncontrolled asthma or using preventative drugs

by the administration of the remaining dose [42, 48]. In a recently published review by Erlewyn-Lajeunesse, an algorithm for the immunisation of individuals allergic to hen's egg white with influenza vaccine has been presented [107]. This algorithm helps the clinician to safely administer egg protein containing vaccines in egg allergic patients (fig. 2).

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