

ALLERGIC REACTIONS TO VACCINES

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Vaccines have had a very significant impact in Human Health. Except for public water supply and sanitation measures, no other single public health intervention induced such a significant reduction in disease incidence and child mortality. In Portugal, a National Vaccination Program (NVP) began in 1965 and more recently, in January 2006, the new NVP was implemented.

However, it is important to recognize and understand adverse reaction to vaccines, since this therapy is intended to be administered to healthy individuals, a fact which considerably lowers the threshold of acceptability of adverse reactions by the general public. In such a way, better understanding of vaccine adverse reactions allows a correct diagnosis and a more appropriate selection of vaccines, increasing the acceptance of immunization in the community.

Allergy - Egg - Gelatine - Vaccines

INTRODUCTION

Vaccines are defined as pharmaceutical preparations that contain immunogenic substances capable of inducing specific immunity against a specific infectious agent. They are administered to healthy children or adults with the objective of protection of individual but also community health (1). The first reports of immunizations date back from 1000 BC, in India, where the content of smallpox pustules was inoculated into healthy individuals in order to confer protective immunity against this disease. This method was designated variolization and its use spread through the Middle East and Africa, arriving to Western Europe in the beginning of the XVIII century, by the action of Lady Mary Montagu, daughter of the British ambassador in Istanbul, who observed this immunization practice being performed by Turkish doctors. This method was widely used in the United Kingdom and in the United States. In 1798 Edward Jenner published his observations on the protective effect of cowpox immunization. After inoculation of the content of cowpox pustules, patients developed a benign condition named "vaccinia" and were effectively protected from smallpox infection. As a result of these findings, cowpox virus replaced smallpox virus in the immunization technique, with a great reduction

in the incidence of adverse effects and mortality that was associated with variolization (2).

One century later, Louis Pasteur was able not only to demonstrate the causal relationship between some infectious diseases and some microorganisms but also to show that a protective and long lasting immunity could be acquired through the contact with attenuated forms of these microorganisms. The term vaccine was then coined, in homage to Jenner, meaning any preparation of an attenuated pathogenic microorganism used for immunization against an infectious disease (3).

Between 1900 and 1956, vaccine use was almost restricted to the developed countries. The first worldwide vaccine program occurred in 1956, under the auspices of the World Health Organization, with the smallpox vaccination.

In Portugal the National Vaccination Program (NVP) started in 1965 with vaccination against poliomyelitis. In 1966 further vaccines were added: pertussis, diphtheria, tetanus. In 1974 and in 1987, vaccines against measles, rubella and mumps were included in the NVP. More recently, the present NVP was published, including vaccination against tuberculosis, hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* serotype b and *Neisseria meningitidis* serotype C infections, measles, mumps and rubella.

The impact of vaccination in Community Public Health is really remarkable. With the exception of sanitation measures, particularly the potable water

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supply and distribution, no other intervention has had, throughout the years, such an impact on disease and child mortality reduction (4). However, it is important to know that there can be some adverse reactions to vaccines. Although severe adverse reactions are so rare that a causal link is difficult to establish (5), it is important to be aware that since vaccines are intended to be administered to healthy and usually young people, the admissibility of adverse reactions by the general public is very much reduced when compared to therapeutic measures designed to treat already ill individuals.

ADVERSE REACTIONS TO VACCINES

Adverse reactions to vaccines can range from very mild local reactions to severe and potentially life-threatening reactions. Due to this possibility, vaccines should always be administered in places adequately equipped to treat anaphylaxis and vaccinated individuals should be kept under observation during 30 minutes (1, 4, 6).

Although in the last years many adverse reactions have been attributed to vaccines, most of these reactions are in fact not induced by vaccines. According to the WHO, adverse reactions occurring during vaccination procedures can be classified in: a) coincident reactions, b) reactions associated with errors in storage, handling or administration and c) reactions truly induced by the vaccines (7). The latter can be classified into local reactions (inflammatory signs in the site of administration, local abscess, lymphadenitis, etc), neurological reactions (acute paralysis, encephalopathy, meningitis, encephalitis, seizures, etc), other adverse systemic reactions (fever, osteomyelitis, arthralgias, etc) or hypersensitivity reactions, divided in four types according to Gell and Coombs classification.

➤ *Type I* hypersensitivity reactions. These are IgE dependent and constitute the most important mechanism, not only by their incidence but also by their potential severity. They may manifest as urticaria, angioedema, bronchospasm or anaphylaxis.

➤ *Type II* hypersensitivity reactions. Vaccine antigens can mimic tissular antigens and induce cross-reactivity but this type of reactions is very rare. One of these rare examples is the thrombocytopenia associated with DTP (diphtheria, tetanus and pertussis) vaccines.

➤ *Type III* hypersensitivity reactions. These involve the formation of antigen-antibody complexes, usually associated with repeated vaccinations, most frequently with diphtheria or tetanus toxoids. Cutaneous lesions are frequently seen in the hours following vaccination and sometimes fever, headaches and malai-

se can be also seen. Arthus reactions are also relatively common in adults receiving repeated doses of polyvalent anti-pneumococcal vaccine, although they are usually self-limited with complete resolution in a few days (8). Incidence and severity of these reactions can be reduced by increasing the interval between repeated immunizations.

➤ *Type IV* hypersensitivity reactions. These are cell-mediated, generally associated with delayed local reactions, appearing 24-72 hours after vaccination. Usually they are the result of a previous sensitization to contact dermatitis agents, such as neomycin, streptomycin or thimerosal. Normally they are mild and therefore a previous history of contact dermatitis to any of the vaccine constituents does not contraindicate vaccination.

HYPERSENSITIVITY REACTIONS TO VACCINE COMPONENTS

Although the main vaccine components are the antigens of the respective microorganisms, there are further constituents with the potential of inducing adverse reactions (9). These constituents (solvents, adjuvants, preservatives, etc) vary with the brand of the vaccine as well as with its manufacturing process. Additionally, vaccines can also contain small quantities of biologic particles from the materials used in the manufacturing process (proteins, cells from culture materials, etc). According to the causal agent, reactions to vaccines can be divided in 6 groups: i) reactions to infectious agent antigens, ii) reactions to adjuvants (e.g. aluminium hydroxide), iii) reactions to stabilizers (e.g. gelatine), iv) reactions to preservatives (e.g. thimerosal), v) reactions to antibiotics (e.g. neomycin) and vi) reactions to biological culture preparations (e.g. hen's egg embryo cells) (7).

The variety of possible causal agents, together with the huge diversity in manufacturing techniques makes very difficult a comparison between different studies on vaccine allergy. Regional factors are also important confounding factors since national vaccination programs differ in their schemes and in the vaccines used (1).

The most frequent hypersensitivity reactions to vaccines are:

- Reactions to biological culture preparations (hen's egg proteins).
- Reactions to yeasts.
- Reactions to stabilizers (gelatine).
- Reactions to preservatives (thimerosal).
- Reactions to antibiotics (neomycin).
- Reactions to adjuvants (aluminium salts).
- Reactions to bacterial antigens (tetanus toxoids).
- Reactions in latex-allergic patients.

■ Reactions to biological culture preparations (hen's egg proteins and related proteins).

In Portugal there are several commercial vaccines produced in biological culture preparations derived from chicken's embryo, namely vaccines against measles, mumps and rubella, vaccines anti-influenza, yellow fever vaccines and one brand of vaccine against rabies. However, the egg protein content is highly variable according to the manufacturing process: it is higher in those produced in chicken's embryo or in chicken's extra-embryonic liquid than in those produced in chicken's egg fibroblasts (1, 10, 11) (Table 1).

➤ **Vaccine against measles, mumps and rubella (MMR):**

The true incidence of systemic allergic reactions to MMR vaccines is hard to know since we have to rely on data from spontaneous notification because the number of cases in prospective studies is extremely low (5). In the USA, notification of adverse reaction to MMR vaccines was less than 1 case per one million doses administered (12). The first descriptions of immediate hypersensitivity to MMR vaccines date back from 1980 but despite its extensive use there are no more than 30 cases reported in the literature (13, 14, 15). Only 16 of these cases occurred in egg-allergic patients and in 8 of these 16 patients the allergic reactions occurred during the performance of skin tests or during tolerance induction protocols, procedures which are no longer recommended (10, 16, 17). On the other hand, only 5 of these 16 children performed tests to investigate possible hypersensitivity to other vaccine components, namely gelatine or neomycin. Interestingly all five children showed increased serum levels of gelatine specific IgE (18), which argues in favour of this allergy being the responsible for the clinical reactions observed.

Cutaneous tests with MMR vaccines as well as tolerance induction protocols were formerly used but are no longer recommended due to low positive and negative predictive values, low efficacy and to the potential of inducing severe allergic reactions (1, 6, 10). Presently the American Academy of Pediatrics (AAP) states that egg allergy is not an absolute contraindication for MMR vaccination (7).

Viral vaccines	Cultured in
Yellow fever	Embryonated chicken eggs
Influenza	Allantoic fluid of chick embryos
Rabies	Chick embryo fibroblasts culture *
Measles	Chick embryo fibroblasts culture
Mumps	Chick embryo fibroblasts culture

Table 1: Vaccines produced in chicken's egg preparations.

* Rabavert®

According to the guidelines of the British Society of Allergy and Clinical Immunology, the vast majority of children may receive MMR vaccine without need of any additional precautions, irrespective of the presence of egg allergy. Only children with cardio-respiratory symptoms related to egg ingestion or children with egg allergy and active chronic asthma should preferably receive MMR vaccination in a hospital setting, remaining under medical surveillance for 2 hours with cardiorespiratory monitoring during the first 20 minutes and a medical observation immediately before hospital discharge (Figure 1) (10).

In Portugal, the Ministry of Health recommends that individuals with history of egg-induced anaphylaxis should receive MMR vaccination only in a hospital setting (4), despite considering the unlikelihood of anaphylaxis to MMR vaccines. In the Immunoallergy Department of Hospital de Dona Estefânia, MMR vaccination has been regularly performed in children with egg allergy (19), as a single intramuscular dose without any previous tests, even in those with severe egg-induced reactions. We haven't registered any adverse reactions.

➤ **Influenza vaccines:** In the literature there is a report of one anaphylactic death after influenza vaccine administration in one egg-allergic child (20). Both the AAP and the Advisory Committee on Immunization Practices (ACIP) recommend that, in general, children with severe egg anaphylaxis should not receive influenza vaccines due to the risk of anaphylaxis and to the availability of effective chemoprophylaxis for

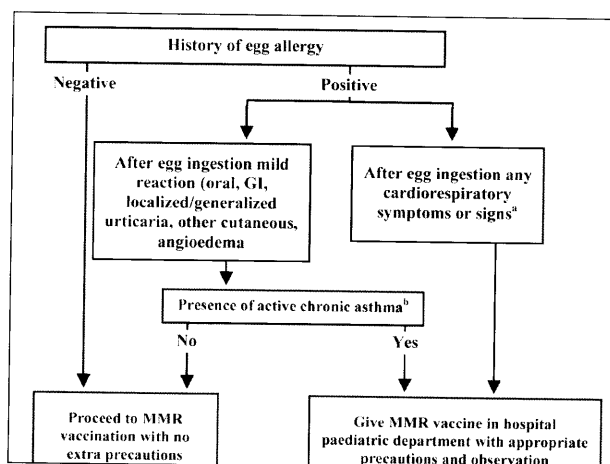


Figure 1: Decision criteria for MMR vaccination in egg-allergic individuals (Adapted from ref. 10).

a) Active chronic asthma defined as children with regular symptoms requiring inhaled steroid or other prophylaxis for symptom control - this does not include the majority of infants who have viral-induced wheeze.

b) Cardiorespiratory symptoms or signs include any difficulty in breathing, noisy breathing, stridor, hoarseness, cyanosis, change in consciousness level, pallor, hypotension.

this infection. However, they both recognize that this vaccine could be administered in some cases in which the benefit-risk ratio is favourable but in these cases a specialized allergological work-up should always be performed and safe administration protocols should be used. On the other hand, mild to moderate egg-allergic reactions do not contraindicate influenza vaccination, which can be carried out without any additional investigations (1, 21, 22, 23).

James *et al.* examined 83 egg-allergic patients, 27 with previous egg-induced anaphylaxis and 124 non-allergic controls. Egg allergic individuals were vaccinated in two injections (1/10 and 9/10), 30 minutes apart; non-allergic controls received a single administration of an influenza vaccine containing $\leq 1.2 \mu\text{g/mL}$ of egg proteins; no systemic reactions were documented (11). However, and since the content in egg proteins can be very variable and is not reported by the manufacturers of influenza vaccines, it has recently been proposed by Zeiger the use of the decision criteria shown in Figure 2 (22). Nevertheless, it should be stressed that annual influenza vaccination for asthmatic patients is recommended both by the American Academy of Pediatrics

and the Advisory Committee on Immunization Practices (ACIP), with numerous studies documenting its efficacy and safety (23, 24, 25, 26).

The protocol used in Immunoallergy Department of Hospital de Dona Estefânia for the administration of influenza vaccines in patients with egg allergy, follows the immunization scheme in two doses (1/10 e 9/10), without any previous skin tests with the vaccines, according to James *et al.* (11). In 1998, Moraes de Almeida *et al.* (19) performed influenza vaccination in 8 children with severe allergic reactions to egg, without any adverse reactions to influenza vaccine. Since then, many children have been vaccinated with this protocol, that has been shown safe (27).

Yellow fever vaccines

Yellow fever is caused by Flavivirus, transmitted to man through mosquito (*Aedes aegypti*) bite. It is endemic in some South American and African countries and has a high mortality rate. According to the WHO, yellow fever vaccination is advisable in all people travelling to South American or African countries located between 15° north and 15° south (28). Yellow fever vaccines are produced in chicken embryos and not only contain higher concentration of egg proteins than any other vaccine but also may contain chicken proteins (1, 10, 11, 29).

Kelso *et al.* reported one case of anaphylaxis after yellow fever vaccination in a woman who had no previous history of egg allergy but that on subsequent investigation was shown to have egg allergy but only to uncooked egg (30).

The AAP recommends performing skin tests with the vaccine itself (skin prick tests firstly with diluted (1/10) form and if negative with the undiluted solution and if both negative proceed with intradermal tests with diluted (1/100) solution), prior to its administration but only in individuals with previous history of egg anaphylaxis. If the skin tests are positive, the tolerance induction protocol shown in table 2 should be performed (1, 9).

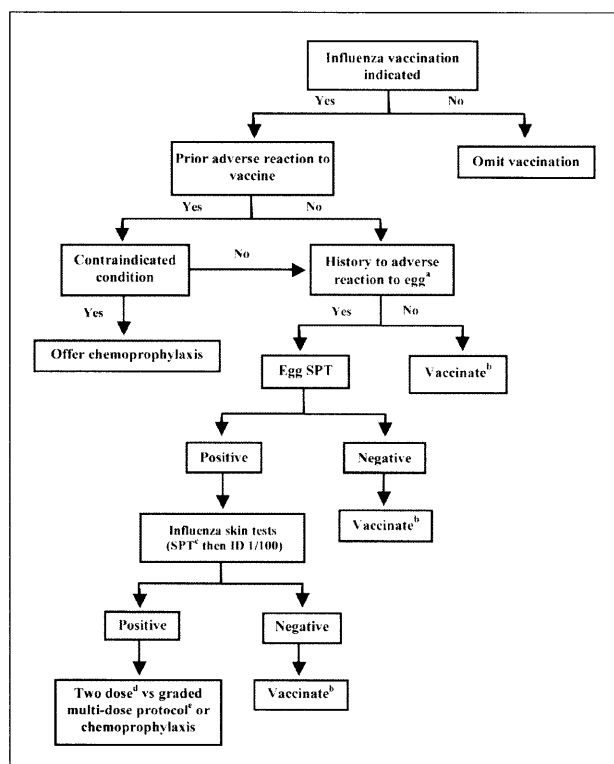


Figure 2: Decision criteria for the administration of influenza vaccines in egg-allergic patients (adapted from ref. 22).

SPT: skin prick tests; ID: Intradermal tests; **a**) if egg allergy has not already been definitively diagnosed, do so at a later evaluation; **b**) Single IM dose appropriate for age; **c**) start with 1/10 dilution if egg content unknown or $> 1.2 \mu\text{g/mL}$, otherwise full strength; **d**) egg content $\leq 1.2 \mu\text{g/mL}$; **e**) egg content unknown or $> 1.2 \mu\text{g/mL}$.

Volume administered *	Dilution
0,05 mL	1/10
0,05 mL	1/1
0,10 mL	1/1
0,15 mL	1/1
0,20 mL	1/1

Table 2: Yellow fever vaccine tolerance induction protocol in egg-allergic patients (Adapted from ref. 1).

*Subcutaneous administration in 15-20 minutes intervals.

■ **Reactions to yeasts:** Recombinant hepatitis B vaccine is produced in *Saccharomyces cerevisiae* cultures, and it is possible that it contains up to 5% of yeast proteins. However, there are very few cases of vaccine reactions due to yeast hypersensitivity (31, 32, 33). In the USA, DiMiceli found 11 reports of probable anaphylaxis after hepatitis B vaccination in patients with antecedents of yeast allergy (34). In the Portuguese NVP, severe hypersensitivity to yeasts is considered a contraindication for the administration of recombinant hepatitis B vaccines (4).

■ **Reactions to stabilizers:** gelatine. Gelatine of bovine or porcine origin is used as a thermal stabilizer in many vaccines (35). The highest concentrations of gelatine are found in MMR vaccines, isolated measles or rubella vaccines, as well as in rabies, varicella and yellow fever vaccines (Table 3). Lower concentrations can also be found in certain brands of influenza or tetanus vaccines (1,6).

Gelatine hypersensitivity is an important cause of anaphylaxis to some of these vaccines. Immediate reactions are caused by gelatine specific IgE, while delayed reactions are associated with specific T lymphocyte activation (36). Patients who are allergic to gelatine used in food (mostly from vegetal or porcine origin) are not necessarily allergic to gelatine used as stabilizer (mostly from porcine origin). In Japan, the substitution of a diphtheria, tetanus and poliomyelitis (DTP) acellular vaccine without gelatine by another DTP acellular vaccine containing gelatine, led to several anaphylactic reactions to the MMR vaccine which was administered afterwards, suggesting that gelatine contained in the DTP vaccine could have previously sensitized these patients (37).

Some American and European studies have documented gelatine specific IgE antibodies in 14 to 28% of patients with a history of post-vaccination anaphylaxis. However, Japanese studies have found much higher values, detecting gelatine specific IgE antibodies in up to 86-100% of patients with reactions to measles, mumps, rubella or varicella vaccination (38, 39). These geographical differences can be due to the

use in Japan, during the 1990's, of several viral vaccines that contained partly hydrolyzed gelatine of bovine origin or, in alternative, could be due to a genetic predisposition since HLA-DR9 positive individuals have a four fold relative risk of developing gelatine specific IgE antibodies (40). Nowadays only highly hydrolyzed gelatine of porcine origin, with a much lesser sensitizing potential, is used in vaccine production (6,41). However, the ideal would be not to use gelatine at all.

Approximately 25% of patients with a history of anaphylaxis after MMR vaccination can present gelatine hypersensitivity, thus being at risk for anaphylaxis if they receive subsequent gelatine-containing vaccines and therefore requiring an allergological work-up before any other immunization (1, 42). There are no consensual recommendations for performing skin prick tests or tolerance induction protocols to gelatine, although some authors suggest performance of skin prick tests with porcine gelatine used in food as well as measurement of serum specific IgE against porcine gelatine and if any of these are positive the patient should be vaccinated with an alternative vaccine, gelatine-free (1, 42).

The viral DTP vaccine Triviraten® (Berna Biotech Ltd, Switzerland) does not contain gelatine nor egg proteins, however some studies have shown a lesser immunizing potential, in comparison with conventional vaccines (43).

■ **Reactions to preservatives:** thimerosal. Thimerosal has been used since 1930 as an additive for biological products and vaccines, in order to prevent bacterial and fungal contamination. It is also found in contact lens solutions, topical preparations for eye or ear application and in cutaneous antiseptics. The prevalence of thimerosal hypersensitivity varies between 1 to 26%, being more frequent in countries where mercury-containing cutaneous disinfectants were widely used (44). Thimerosal hypersensitivity is also frequently found in patients with eczema, conjunctivitis or in those who were treated with allergenic extracts containing thimerosal (45, 46). Thimerosal containing vaccines include DTP, hepatitis B, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae* and rabies vaccines. However there are several thimerosal-free alternatives for all vaccines included in the Portuguese NVP. In 1999 the American Academy of Pediatrics (AAP) recommended the total elimination (or at least a significant reduction) of thimerosal use in vaccines, due to the theoretical risk of mercury intoxication. However, if this recommendation is not fulfilled we should proceed with vaccination since the infectious risk outweighs by far the potential risk of mercury intoxication (47).

Vaccine	Commercial denomination	Gelatine per dose (µg)
DTPa	Tripedia (Aventis Pasteur)	28
Influenza	Fluzona (Aventis Pasteur)	250
Measles	Attenuvax (Merck)	14500
Mumps	Mumpsvax (Merck)	14500
MMR	MMR II (Merck)	14500
Rabies	Rabavert (Chiron Corporation)	12000
Varicella	Varivax (Merck)	12500
Yellow fever	YF-Vax (Aventis Pasteur)	7500

Table 3: Gelatine content in some vaccines (adapted from ref. 42).

Despite the high prevalence of contact hypersensitivity to thimerosal, this preservative has an excellent safety profile, with only very few reports of generalized eczema or urticaria, without any report of anaphylaxis to this compound (46, 48). Thimerosal allergic individuals normally tolerate its presence in vaccines; reports of mild local reactions occur only in 1 to 20% of these patients; therefore thimerosal hypersensitivity does not constitute a contraindication for any vaccine administration (7, 31, 45).

■ **Reactions to antibiotics:** neomycin. Neomycin, streptomycin, polymixin B and tetracycline are antibiotics found in some vaccines. Nowadays no vaccine contains penicillin, sulphamids or any of their derivatives.

A previous history of anaphylaxis to one antibiotic is an absolute contraindication for the administration of any vaccine containing that antibiotic. In these patients, skin tests or tolerance induction protocols are not recommended (1, 6, 9, 12). Neomycin is the antibiotic most frequently associated with adverse reactions after vaccination. It is present, for instance, in MMR, poliomyelitis and varicella vaccines, in approximately 25 µg/dose, which correspond to a fourth of the dose necessary to elicit a cutaneous contact allergic reaction (49).

There is just one anaphylaxis report incriminating neomycin in the literature: a 7 year-old child with previous neomycin contact allergy, who developed anaphylaxis during MMR vaccine tolerance induction (50). However, in this case egg or gelatine allergies were not investigated and therefore it is not possible to exclude these possibilities. Neomycin contact dermatitis exists in about 1% of the general population and does not contraindicate immunization with neomycin containing vaccines (51). However, some neomycin allergic individuals may develop a delayed local hypersensitivity reaction in the 48-96 hours following vaccination, which generally tends to be mild (1).

■ **Reactions to adjuvants:** aluminium salts. Aluminium salts (aluminium hydroxide and aluminium phosphate) are largely used as vaccine adju-

vants, particularly in DTP, hepatitis A, hepatitis B and Haemophilus influenzae vaccines. Their role is to delay the release of vaccine antigens and attract immunomodulating cells to the site of injection (52, 53). Although there are no reports of anaphylaxis, aluminium salts are associated with local reactions: subcutaneous nodules containing aluminium crystals can be found in the injection site, particularly when using subcutaneous route, and can persist for weeks or even months. In rare instances they can be associated with persistent pain or pruritus, being necessary their surgical excision (54, 55, 56).

■ **Reactions to bacterial antigens:** tetanus toxoid. Tetanus toxoid vaccination, constituted by formaldehyde-treated tetanus toxin, is safe and effective. However there are local reactions in 13% and systemic reactions in 0,2% of the administrations (57). Local reactions usually appear in 2-8 hours following administration, some authors suggesting hyperimmunization as a presumptive mechanism since they correlate with the number of previous immunizations and with the protective antibody titers (58). Anaphylactic reactions are generally not IgE-mediated but there are already some reports of positive skin tests and specific IgE measurements to tetanus toxoid (59, 60). One case of co-sensitization to tetanus and diphtheria toxoids has also been reported (61). Despite being contraindicated the immunization of individuals with a history of anaphylaxis to tetanus toxoid, skin tests (table 4) and tolerance induction protocols have been used successfully in patients with protective anti-toxoid IgG antibody measurements below protective levels (0,02UI/ml), as shown in Table 5 (57, 59, 62, 63).

■ **Reactions in patients with latex allergy:** The contamination of vaccines by latex allergens contained in syringes and vial stoppers is possible and therefore the induction of allergic reactions in latex allergic patients can occur (64). Although this possibility seems very remote, there are reports in diabetic patients associated with insulin injections (65, 66, 67,

Method	Dilution	Interval (minutes)
Prick	1/10	10
Prick	1/1	10
Intradermal	1/10 000	15
Intradermal	1/1000	15
Intradermal	1/100	15
Intradermal	1/10	15
Intradermal	1/1	15
Intradermal	1/1	15

Table 4: Protocol of skin tests to tetanus toxoid (adapted from ref. 57).

Dilution 1/1000	Dilution 1/100	Dilution 1/10	Non diluted
0,05	0,05	0,05	0,05
0,10	0,10	0,10	0,10
0,20	0,20	0,20	0,20
0,30	0,30	0,30	0,30
0,50	0,50	0,50	0,50
Subcutaneous administration.			
Interval of 1 to 2 weeks between dilutions			
Interval of 30 minutes between each dose			

Table 5: Tetanus toxoid tolerance induction protocol (adapted from ref. 62).

68) and there is also a report of anaphylaxis in a latex allergic patient after hepatitis B vaccine (69). Russel *et al.* reported, in the USA, 28 cases of possible immediate hypersensitivity reactions to latex after vaccine administration in latex allergic patients (64). However, presently most syringes and vial stoppers are made of synthetic rubber, which does not contain any latex allergens and are the recommended materials for any injections in latex-allergic patients (1, 9).

ADVERSE REACTION TO VACCINES DIAGNOSTIC PROTOCOL

■ **Patients with previous systemic reaction to a vaccine** (Figure 3): Clinical history of a patient with an adverse reaction to a vaccine should always include detailed information on the exact date of the administration of the vaccine, commercial name of the vaccine and the number of the lot, the type of reaction (local or systemic), the time interval between injection and start of symptoms and their duration, as well as if there were, in the past, any antecedents of adverse reactions to the same or other vaccines or also history of allergy to hen's egg, chicken meat, gelatine, yeasts or to drugs, especially antibiotics. If this clinical inquiry is compatible with an IgE-mediated reaction, the need for administration of further

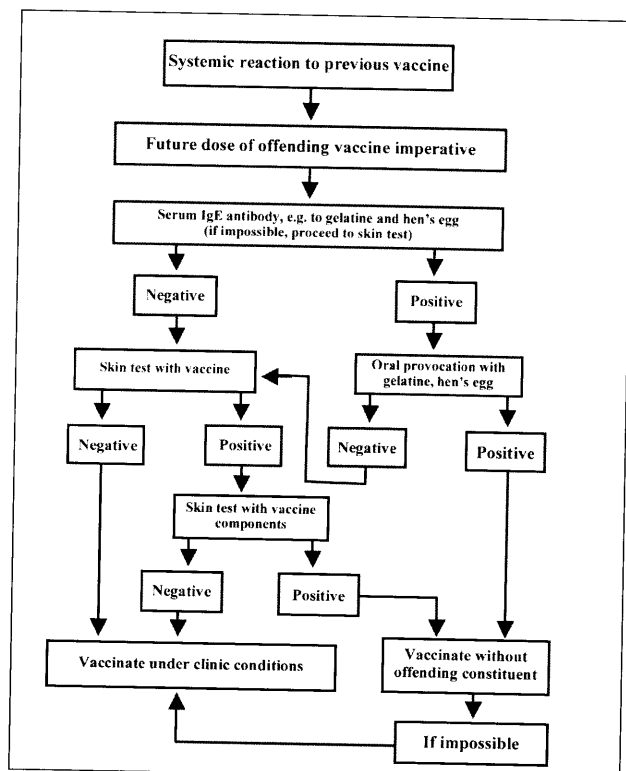


Figure 3: Decision criteria for the administration of vaccines in patients with previous systemic reactions to vaccines (adapted from ref. 6).

doses of this vaccine or of other vaccines that contain the same constituents should be carefully assessed, if necessary with regular measurement of serum levels of protective antibodies. Furthermore, it is generally recommended that screening tests to investigate allergy to gelatine, hen's egg or antibiotics are performed. If these are positive, a challenge test should be performed and if it is positive we should use a vaccine which does not contain the incriminated element. If that is not feasible we should administer the vaccine only in a hospital setting, eventually using a tolerance induction protocol.

If no specific IgE antibodies are detected or if oral challenge is negative, we should perform skin tests with the vaccine itself. Due to the fact that these tests may induce reactions, dilutions should be used initially in patients with a history of a severe reaction following vaccination. Patients with positive skin tests to a given vaccine should be investigated in order to try to identify the component to which they are allergic and to find an alternative vaccine without that component. Patients with negative skin tests should receive vaccination in a hospital setting, eventually using a tolerance induction protocol.

■ **Patients with allergy to a specific vaccine constituent** (Figure 4): If there is, in fact, a need for the administration of a vaccine containing this specific

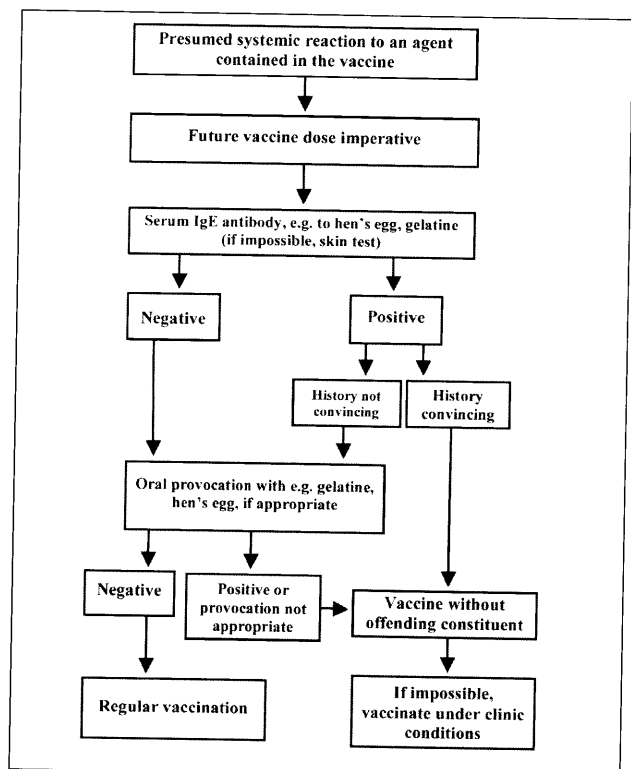


Figure 4: Decision criteria for the administration of vaccines in patients with allergy to a vaccine constituent (adapted from Ref. 6).

constituent, in the first place, investigation should start by specific IgE measurements or skin tests if the former measurements are not available. If both specific IgE and skin tests are negative, we should perform an oral challenge test to exclude the presumptive diagnosis. If this is excluded then the vaccine should be administered in a normal manner. However, if skin tests or specific IgE are positive, together with a very suggestive clinical history or with a positive provocation test, it is recommended the use of an alternative vaccine brand, not containing that specific constituent. If it is not available, then vaccination should be carried out in a hospital setting, eventually with tolerance induction protocols similar to those used for yellow fever vaccines in egg-allergic patients (table 2).

CONCLUSION

Vaccines are effective and safe tools in the prevention of severe infectious diseases such as poliomyelitis, tetanus or diphtheria, with a clearly favourable benefit-risk ratio.

On the other hand, although rare, adverse reactions to vaccines can occur, most frequently caused by components that are not related to microbial antigens. The knowledge of these reactions allows their investigation and the selection of safe alternatives in order to achieve or maintain infectious protection.

Allergic patients are more prone to infections and these infections, in turn, frequently are a cause of allergic disease exacerbation. Furthermore, several recent studies showed no increased susceptibility to adverse reactions to vaccines in atopic children in comparison to non-atopic children. Therefore, the allergic child should not be excluded from the normal vaccination schedule. Exceptions are, for obvious reasons, children with previous anaphylactic reactions to any vaccine or to any one of their components.

Most anaphylactic reactions to vaccines occur in individuals with no history of any previous reactions to vaccines. In view of this fact, vaccines should always be administered in places with appropriate means to treat an eventual anaphylactic reaction, making sure that the vaccinated individual stays in for at least 30 minutes after injection.

References

1. Madaan A., Maddox D. - Vaccine allergy: diagnosis and management. *Immunol Allergy Clin North Am* 2003;23:555-88.
2. Baxby D. - The genesis of Edward Jenner's Inquiry of 1798: a comparison of the two unpublished manuscripts and the published version. *Med Hist* 1985;29:193-199.
3. Pasteur L, Illo J. Pasteur and rabies: an interview of 1882. *Med Hist.* 1996;40:373-7.
4. Direcção Geral da Saúde: Programa nacional de vacinação 2006. Circular normativa nº 08/DT de 21/12/2005.
5. Crocket R.-E., Lockey R.-F. - Vaccine hypersensitivity. *Immunol Allergy Clin North Am* 2001;21:707-43.
6. Gruber C., Niggeman B. - A practical approach to immunization in atopic children. *Allergy* 2002;57:472-9.
7. American Academy of Paediatrics. In: Peter G, ed. 1997 Red Book: Report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Paediatrics Publications 1997:32-3.
8. Borgono J.-M., McLean A.-A., Vella P.-P. *et al.* - Vaccination and revaccination with polyvalent pneumococcal polysaccharide vaccines in adults and infants. *Proc Soc Exp Biol Med* 1978;157:148-54.
9. American Academy of Pediatrics. - Active and passive immunization. In: Pickering LK, editor. 2000 Red book: report of the committee on infectious diseases. 25th ed. Elk Grove Village (IL): American Academy of Pediatrics Publications 2003:46-9.
10. Khakoo G.-A., Lack G. - Guidelines for measles vaccination in egg-allergic children. *Clin Exp Allergy* 2000;30:288-93.
11. James J.-M., Zeiger R.-S., Lester M.-R. *et al.* - Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998;133:624-8.
12. Watson J.-C., Hadler S.-C., Dykewicz C.-A. *et al.* - Measles, mumps, and rubella-vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mort Wkly Rep* 1988;47:1-57.
13. Aukrust L., Almeland T.-L., Refsum D. *et al.* - Severe hypersensitivity or intolerance reactions to measles vaccine in six children. *Allergy* 1980;35:581-7.
14. Hermann J.-J., Radin R., Schneiderman R. - Allergic reactions to measles (rubeola) vaccine in patients hypersensitive to egg protein. *J Pediatr* 1983;102:196-9.
15. McEwen J. - Early-onset reaction after measles vaccination. *Med J August* 1983;2:503-5.
16. Lavi S., Zimmerman B., Koren G., Gold R. - Administration of measles, mumps and rubella virus vaccine (live) to egg-allergic children. *JAMA* 1990;263:269-71.
17. Baxter D.-N. - Measles immunization in children with a history of egg allergy. *Vaccine* 1996;14:131-4.
18. Sakaguchi M., Ogura H., Inouye S. - IgE antibody to gelatine in children with immediate-type reactions to measles and mumps vaccines. *J Allergy Clin Immunol* 1995;96:563-5.
19. Carvalho F., Agro J., Morais de Almeida M., Rosado Pinto J. - Imunizações e hipersensibilidade a proteínas de ovo. *Acta Pediatr Port* 1998;29:563-9.
20. Bierman C.-W., Shapiro G.-G., Pierson W.-E. *et al.* - Safety of influenza vaccination in allergic children. *J Infect Dis* 1977;136:S652-5.
21. Bridges C., Fukuda K., Uyeki T. *et al.* - Prevention and control of influenza: recommendations of the Advisory Committee on Immunizations Practices (ACIP). *Morb Mort Wkly Rep* 2002;51:1-31.
22. Zeiger R.-S. - Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol* 2002;110:834-40.
23. American Academy of Pediatrics Committee on Infectious Diseases. - Prevention of influenza: recommendations for influenza immunization of children, 2006-2007. *Pediatrics* 2007;119:846-51.
24. CDC. - Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mort Wkly Rep* 2002;51:1-31.
25. The American Lung Association Asthma Clinical Research Centers. - The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529-36.
26. Kramarz P., DeStefano F., Gargiullo P.-M. *et al.* - Does influenza vaccination prevent asthma exacerbations in children? *J Pediatr* 2001;138:306-10.
27. Godinho N., Martins P., Pires G. - Imunoterapia anti-infecciosa inespecífica e terapêutica anti-influenza na criança asmática. In: Rosado Pinto J, Morais de Almeida M, eds. A

- criança asmática no mundo da alergia. Miraflores: Euromédice Edições Médicas Lda; 2003:287-93.
28. Wilson ME. - Travel-related vaccines. *Infect Dis Clin North Am* 2001;15:231-51.
 29. O'Brien T.-C., Maloney C.-J., Tauraso N.-M. - Quantification of residual host protein in chicken embryo derived vaccines by radial immunodiffusion. *Appl Microbiol* 1971;21:780-2.
 30. Kelso J.-M. - Raw egg allergy - A potential issue in vaccine allergy [letter]. *J Allergy Clin Immunol* 2000;106:990.
 31. Goodwin H., Nash M., Gold M. *et al.* - Vaccination of children following a previous hypotonic-hyporesponsive episode. *J Paediatr Child Health* 1999; 35:549-52.
 32. Andre F.-E. - Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med* 1989;87:14S-20S.
 33. Hudson T.-J., Newkirk M., Gervais F. *et al.* - Adverse reaction to the recombinant hepatitis B vaccine. *J Allergy Clin Immunol* 1991;88:821-2.
 34. DiMiceli L., Pool V., Kelso J.-M. *et al.* - Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS). *Vaccine* 2006;24:703-7.
 35. Kelso J.-M., Jones R.-T., Yunginger J.-W. - Anaphylaxis to measles, mumps and rubella vaccine mediated by IgE to gelatine. *J Allergy Clin Immunol* 1993;91:867-72.
 36. Kumagai T., Osaki T., Kamada M. *et al.* - Gelatin-containing diphtheria-tetanus-pertussis (DTP) vaccine causes sensitization to gelatin in the recipients. *Vaccine* 2000;18:1555-61.
 37. Nakayama T., Aisawa C., Sakai K. - A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatine-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *J Allergy Clin Immunol* 1993;103:321-5.
 38. Patja A., Makinen-Kiljunen S., Davidkin I. *et al.* Allergic reactions to measles-mumps-rubella vaccination. *Pediatrics* 2001;107:27.
 39. Sakaguchi M., Nakayama T., Fujita H. *et al.* - Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin. *Vaccine* 2000;19:431-6.
 40. Kumagai T., Yamanaka T., Wataya Y. *et al.* - A strong association between HLA-DR9 and gelatin allergy in the Japanese population. *Vaccine* 2001;19:3273-6.
 41. Sakai Y., Yamato R., Onuma M. *et al.* - Non-antigenic and low allergic gelatine produced by specific digestion with an enzyme-coupled matrix. *Boil Pharm Bull* 1998;21:330-4.
 42. Pool V., Braun M.-M., Kelso J.-M. *et al.* - Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. *Pediatrics* 2002;110:71.
 43. Tischer A., Gerike E. - Immune response after primary and re-vaccination with different combined vaccines against measles, mumps, rubella. *Vaccine* 2000;18:1382-92.
 44. van't Veen A.-J., van Joost T. - Sensitization to thimerosal (Merthiolate) is still present today. *Contact Dermatitis* 1994;31:293-8.
 45. Schafer T., Enders F., Przybilla B. - Sensitization to thimerosal and previous vaccination. *Contact Dermatitis* 1995;32:114-6.
 46. Tosti A., Guerra L., Bardazzi F. - Hyposensitizing therapy with standard antigenic extracts: an important source of thimerosal sensitization. *Contact Dermatitis* 1989;20:173-6.
 47. Centers for Disease Control and Prevention. Notice to Readers: Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service. *Morb Mort Wkly Rep* 1999;48:563-565.
 48. Tosti A., Melino M., Bardazzi F. - Systemic reactions due to thimerosal. *Contact Dermatitis* 1986;15:187-8.
 49. Rietschel R.-L. - Neomycin sensitivity and the MMR vaccine. *JAMA* 2000;283:2104-5.
 50. Kwittken .-P.L, Rosen S., Sweinberg S.-K. - MMR vaccine and neomycin allergy [letter]. *Am J Dis Child* 1993;147:128-9.
 51. Watson J.-C., Peter G. - General immune practices. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. 3rd edition. Philadelphia: WB Saunders;1999:47-73.
 52. Cogné M., Ballet J.-J., Schmitt C. *et al.* - Total and IgE antibody levels following booster immunization with aluminium absorbed and nonabsorbed tetanus toxoid in humans. *Ann Allergy* 1985;54:148-51.
 53. Pauwels R., Bazin H., Platteau B., Van Der Straeten M. - The influence of different adjuvants on the production of IgD and IgE antibodies. *Ann Immunol Paris* 1979;130:49-58.
 54. Kaaber K., Nielsen A.-O., Veien N.-K. - Vaccination granulomas and aluminium allergy: course and prognostic factors. *Contact Dermatitis* 1992;26:304-6.
 55. Fawcett H.-A., Smith N.-P. - Injection-site granuloma due to aluminum. *Arch Dermatol* 1984;120:1318-22.
 56. Slater D.-N., Underwood JC, Durrant T.-E. *et al.* - Aluminium hydroxide granulomas: light and electron microscopic studies and X-ray microanalysis. *Br J Dermatol* 1982;107:103-8.
 57. Eserverri J.-L., Ranea S., Marin A. - Reacciones adversas a vacunas. *Alergol Immunopathol (Madr)* 2003;31:125-38.
 58. Bellanti J.-A., Fishman H.-J., Wientzen R.-L. - Adverse reactions to vaccines. *Immunol Allergy Clin North Am* 1987;7:423-45.
 59. Carey A.-B., Meltzer E.-O. - Diagnosis and desensitization in tetanus vaccine hypersensitivity. *Ann Allergy* 1992;69:336-8.
 60. Nagel J., Svec D., Waters T. *et al.* - IgE synthesis in man. Development of specific IgE antibodies after immunization with tetanus-diphtheria (Td) toxoids. *J Immunol* 1997;118:334-41.
 61. Gruber C., Nilsson L., Bjorksten B. - Do early childhood immunizations influence the development of and do they cause allergic reactions? *Pediatr Allergy Immunol* 2001;12:296-311.
 62. Cots P., Marin A., Juste C. *et al.* - Reacciones adversas a toxoide tetânico: pauta, desensibilización y seguimiento clínico inmunológico. *Alergol Immunol Clin* 1999;14:73-8.
 63. Silva A.-T., Fuentes M.-S., Rodriguez R. *et al.* - Reacção anafiláctica ao toxóide tetânico. *Rev Port Imunoalergologia* 2005;13:89-93.
 64. Russel M., Pool V., Kelso J., Tomazic-Jesic V. - Vaccination of persons allergic to latex: a review of safety data in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2004;23:664-7.
 65. Kearns C.-F., Norris A. - Latex allergy and plastic syringes. *Anesth Analg* 1996;82:429.
 66. Vassallo S.-A., Thurston T.-A., Kim S.-H. *et al.* - Allergic reaction to latex from stopper of a medication vial. *Anesth Analg* 1995;80:1057-8.
 67. MacCracken J., Stenger P., Jackson T. - Latex allergy in diabetic patients: a call for latex-free insulin tops. *Diabetes Care* 1996;19:184.
 68. Towse A., O'Brien M., Twarog F.-J. *et al.* - Local reaction secondary to insulin injection. A potential role for latex antigens in insulin vials and syringes. *Diabetes Care* 1995;18:1195-7.
 69. Lear T.-J., English J.-S. - Anaphylaxis after hepatitis B vaccination. *Lancet* 1995;345:1249.

