ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Hypersensitivity reactions to vaccines

Reações de hipersensibilidade a vacinas

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ABSTRACT

The expansion of vaccine use and development in recent decades has contributed to the control and eradication of infectious diseases, causing a major impact on public health worldwide. Vaccine safety analysis, which involves careful processes and clinical study, is one of the essential pillars of regulatory approval and use in the population. In current terminology, events supposedly attributable to vaccination and immunization (ESAVI) are defined as any unwanted medical occurrence after vaccination that may or may not have a causal relationship with vaccines or other immunobiologicals. It is noteworthy that rare or unexpected adverse events, including hypersensitivity, can occur during the post-marketing phase, when vaccines are administered to millions of people. In this article, we will discuss the main aspects of post-vaccine hypersensitivity events of interest to specialists and challenges to recognizing the causal agent and appropriate clinical practice. Potential allergens in routine vaccines will also be reviewed to help health professionals identify patients with a potential risk of ESAVI due to such components. Updating health professionals' knowledge about the safety and benefits of vaccines, particularly in special populations, can contribute to more appropriate clinical practice regarding immunization, reducing the risk of exposure to possible allergens in people with allergies to vaccines or their components, avoiding unnecessary contraindications in coincidental or non-serious events.

Keywords: Hypersensitivity, vaccines, immunization.

RESUMO

O desenvolvimento e a ampliação do uso das vacinas durante décadas contribuíram para o controle e erradicação de doenças infecciosas, causando um grande impacto na saúde pública no mundo. A análise de segurança das vacinas percorre criteriosos processos e fases dos estudos clínicos, um dos pilares essenciais para aprovação regulatória e utilização do produto na população. O evento supostamente atribuído à vacinação e imunização (ESAVI), terminologia atual, é definido como qualquer ocorrência médica indesejada após a vacinação que possui, ou não, uma relação causal com o uso de uma vacina ou outro imunobiológico. Cabe ressaltar que eventos adversos mais raros ou inesperados, incluindo os eventos de hipersensibilidade, poderão ocorrer na fase pós-comercialização, quando as vacinas são aplicadas em milhões de pessoas. Neste artigo, serão discutidos os principais aspectos relacionados aos eventos adversos de hipersensibilidade pós-vacinais de interesse do especialista, e os desafios frente ao reconhecimento do agente causal e conduta a ser adotada. Além disso, serão revisados os potenciais alérgenos presentes nas vacinas de uso rotineiro para auxiliar o profissional de saúde na identificação de pacientes com potencial de risco de ESAVI por tais componentes. A atualização do conhecimento acerca da segurança e dos benefícios das vacinas pelos profissionais de saúde, sobretudo em populações especiais, contribui para condutas em imunização mais apropriadas, reduzindo o risco de exposição a um possível alérgeno em pessoas comprovadamente alérgicas às vacinas ou a alguns dos seus componentes, além de evitar contraindicações desnecessárias em eventos coincidentes ou não graves.

Descritores: Hipersensibilidade, vacinas, imunização.

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Submitted Nov 28 2022, accepted Feb 11 2023.

Arq Asma Alerg Imunol. 2023;7(1):3-22.

http://dx.doi.org/10.5935/2526-5393.20230002-en

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Introduction

Vaccination is one of the most successful public health interventions. By achieving high vaccination coverage, Brazil has greatly reduced the incidence of vaccine-preventable diseases.[1]

All vaccines available in Brazil through the public and private health systems have undergone extensive clinical testing for efficacy and safety before being approved by the relevant regulatory agencies; however, events supposedly attributable to vaccination and immunization (ESAVI) can still occur.[2,3]

An ESAVI is defined as any untoward medical occurrence which follows vaccination and which may or may not have a causal relationship with the vaccine or other immunobiological agent (immunoglobulin or heterologous sera). Any unfavorable or unintentional event, such as a sign, symptom, illness, or abnormal laboratory finding, can be classified as an ESAVI.[4,5] An ESAVI may be caused by several factors: I. Factors related to the vaccine product: including type (attenuated or inactivated), strain, culture medium, the inactivation or attenuation process, adjuvants, stabilizers, or preservatives, or a specific batch of vaccine; II. Factors related to the vaccine recipient: age, sex, number of vaccine doses and previous exposure to the vaccine, adverse reactions to previous doses, comorbid conditions, allergic conditions, autoimmunity, immunodeficiency; III. Administration-related factors: needle and syringe, site of inoculation, route of inoculation (intradermal, subcutaneous, or intramuscular).[5]

The cumulative experience acquired throughout the development of the National Immunization Program (NIP) has allowed Brazil to compile extensive knowledge about ESAVI, which can be classified as expected or unexpected, depending on their nature and the characteristics of the agent to which they are supposedly attributable. Among expected events, some are relatively trivial, such as fever, pain, and local swelling, while others can be severe, such as febrile seizures, hypotonic-hyporesponsive episode (HHE), anaphylaxis, etc. Unexpected events are those not previously identified, such as intestinal intussusception after administration of the rhesus rotavirus-based human rotavirus vaccine, or those known to occur but only rarely seen with older vaccines, such as viscerotropic disease and multiorgan failure after the yellow fever (YF) vaccine. Unexpected events also include those arising from issues related to the quality of the vaccine product, such as batch contamination (which can cause localized abscesses) or, in certain vaccines, presence of endotoxin (leading to febrile reactions and sepsis-like symptoms).[5]

Adverse events can also occur coincidentally after vaccine administration, in which case they are not directly related to the biological effects of the vaccine produce (i.e. they would have occurred even in the absence of vaccination).[6]

ESAVI can be further classified as serious or non-serious. *Serious* adverse events (SAEs) are those that require hospitalization for more than 24 hours or prolong an already existing hospitalization, cause significant dysfunction and/or persistent disability, result in a congenital anomaly, are life-threatening, and/or lead to death. All other events not meeting the SAE criteria are considered *non-serious*.[5]

Another important feature is whether reactions are *local* or *systemic*. Local reactions such as edema, erythema, and tenderness at the injection site are common after the administration of some vaccines. These symptoms do not contraindicate subsequent vaccinations.[7] Systemic reactions are mostly mild and can range from fever, myalgia, irritability, anorexia, drowsiness, persistent crying, and headache to more moderate and (rarely) severe events, such as

anaphylaxis, seizures, hypotonic-hyporesponsive episodes, and (with the yellow fever vaccine) acute viscerotropic and acute neurotropic disease.

This article will address the main aspects related to those adverse events following immunization of interest to the allergist/immunologist, the challenges posed by recognition of the causal agent, and key tenets of patient management. We will also review the main allergens present in routinely used vaccines to help clinicians identify patients at potential risk of ESAVI caused by these components.

Type I hypersensitivity reactions

Type I hypersensitivity reactions are mediated by preformed IgE antibodies against vaccine components. They rarely occur, but are considered potentially serious adverse events that require investigation and a keen understanding of the risk–benefit ratio for the administration of subsequent doses.[7] These reactions can occur after administration of any vaccine or serum, especially those of nonhuman (equine) origin.

Typically, reactions occur immediately or within 4 hours after exposure to the allergen, and can manifest as cutaneous or systemic symptoms (anaphylaxis).[7,8] The estimated rate of anaphylaxis ranges from 1 in 100,000 to 1 in 1,000,000 doses for most commonly administered vaccines.[9-11] One study evaluated cases of anaphylaxis reported to the United States Vaccine Adverse Event Reporting System (VAERS) from 1990 to 2016 and identified 8 fatal cases, of which 4 had no personal history of hypersensitivity.[12]

Another study showed the incidence of anaphylaxis to vaccines to be 1.31 cases per 1,000,000 vaccine doses administered (95% CI 0.90-1.84). Although anaphylaxis is a potentially serious reaction, it is treatable and recovery can be achieved with no sequelae or fatal outcome.[8]

During investigation of a potential allergic reaction to a vaccine, a detailed history is essential to rule out other etiologies unrelated to the vaccine components (e.g. exposure to latex in latex-allergic patients, anti-inflammatory medication).

The leading cause of immediate adverse reactions to vaccines is gelatin. Other components present in certain vaccines may also be involved in reactions, such as vaccine antigens, carrier proteins, egg, milk, yeast, latex, antimicrobials, and polyethylene glycol.[8,13] Allergic reactions to vaccines can be due to the active ingredient (the antigen) or to other components.[7,8] Vaccine antigens may consist of the microorganism in whole or in part, inactivated toxins (toxoids), or both, and are intended to elicit a protective immune response. These antigens are rarely the cause of hypersensitivity reactions. In most cases, vaccine hypersensitivity is actually caused by non-antigen components.[8] Table 1 summarizes the main vaccine components that can cause IgE-mediated reactions.

Vaccine components and immediate hypersensitivity reactions

Egg

Some commonly used vaccines contain small amounts of residual egg protein (ovalbumin) from the manufacturing process. Ovalbumin concentrations are generally higher in vaccines grown in embryonated chicken eggs (influenza, yellow fever, and rabies vaccines) and lower in those grown in chick embryo fibroblast cells, such as the measles/mumps/rubella (MMR) vaccine.[8]

The MMR vaccine is considered safe for patients with egg allergy, as it contains such small amounts of egg protein it is incapable of eliciting an allergic response.[7,13,14] Several studies have proven the safety of the vaccine in egg-allergic patients, and there is no contraindication to its use.[7,14,15] Most anaphylactic reactions to MMR vaccine have been attributed to gelatin allergy.[7]

The influenza vaccine was contraindicated in patients with egg allergy for many years, but it is now known to be safe for this patient population as well. A review of 28 studies in which influenza vaccine was administered to 4,315 egg-allergic patients, of which 656 had a history of anaphylaxis to egg, found no serious reactions to the vaccine.[16] Furthermore, in studies that included non-egg-allergic controls, the rate of mild reactions was similar in controls and in those with allergies.[16] Therefore, current recommendations hold that the influenza vaccine can be given to egg-allergic patients.[7,8]

The yellow fever vaccine contains higher amounts of protein, and whether or not it is indicated should be evaluated cautiously. Furthermore, the yellow fever vaccine is not heated at any time during the manufacturing process, so even patients who tolerate boiled/fried eggs may react to the vaccin.[17] A Brazilian study evaluated the safety profile of administering this vaccine to egg-allergic patients. In the study protocol, all patients underwent a skin prick test with undiluted

vaccine. If negative, an intradermal (ID) test was performed with the vaccine at a dilution of 1:100. If the ID test was negative, a full dose of the vaccine was given. If either the skin prick test or ID test was positive, the vaccine was applied in fractional (graded) doses according to the desensitization protocol. All 58 patients included in the study had a negative skin prick test; 10 had a positive ID test and were desensitized. Of these 10 patients, 4 had no hypersensitivity reaction whatsoever, 4 had local reactions (hives at the application site), and 2 had urticaria with subjective symptoms. Of the 48 remaining patients with a negative ID test, none had any reaction to the vaccine, which was given as a single dose.[18] Therefore, egg-allergic patients in whom yellow fever vaccination is indicated should be referred to a specialist for skin testing and, if necessary, desensitization.[18]

Milk

Patients with cow's milk allergy (CMA) should not receive the MMR vaccine manufactured by the Serum Institute of India Ltd., which may contain alpha-lactalbumin. Studies in Brazil and Chile reported cases of allergic reactions after exposure to this vaccine in patients with CMA.[19,20] In Chile, 9 cases of immediate hypersensitivity reactions after MMR vaccine were reported in milk-allergic patients. All had a diagnosis of CMA before administration of the first dose of the MMR vaccine, but none had a history of anaphylaxis.

Table 1
Major vaccine components associated with IgE-mediated reactions

Component	Vaccine	Recommendation
Egg	MMR	Administer vaccine without special precautions
	Influenza	Administer vaccine; no special precautions required
	Yellow fever	Assess on case-by-case basis. Consider skin testing with vaccine in patients with a history of anaphylactic reactions to eggs. If positive, administer in graded doses
Milk	MMR	MMR vaccine manufactured by the Serum Institute of India Ltd. is contraindicated; administer vaccine from any other manufacturer that does not contain milk
	DTaP Tdap	No contraindication. In patients with severe, low-threshold CMA, assess on case-by-case basis
Gelatin	Influenza, MMR, rabies, varicella, herpes zoster	Consider skin testing with vaccine. If positive, administer in graded doses
Yeast	Hepatitis B	Consider skin testing with vaccine
	Quadrivalent HPV	If positive, administer in graded doses
Latex	http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf	Administer vaccine. Vaccinator must not wear latex gloves

Adapted from Dreskin SC et al. [7].

All cases occurred within 2 hours of administration of Serum Institute of India MMR vaccine; 6 had anaphylaxis, 2 had only respiratory manifestations, and 1 developed only cutaneous manifestations.[20] Therefore, patients with CMA should receive MMR vaccine made by other manufacturers which does not contain milk proteins.

Milk proteins can also be used as a growth medium for tetanus-pertussis-diphtheria vaccines (DTaP and Tdap). A case series of 8 patients with severe CMA reported anaphylactic reactions with DTaP or Tdap vaccines. The study found that these vaccines contained casein derivatives, which could potentially explain the severe, immediate reactions elicited in patients with CMA.[21] However, the methodology used to identify the causality of the described reactions is controversial. Therefore, according to an EAACI position statement, vaccination with DTaP and Tdap vaccines is not considered to contribute to the pathogenesis of allergic diseases, and atopy does not contraindicate administration of these vaccines.[22]

Patients with IgE-mediated ALV, especially those with the severe form and with a low threshold for development of reactions, should be aware of medications and vaccines that potentially may contain traces or even minimal amounts of cow's milk protein. In these cases, an individual risk assessment is recommended, and vaccination in a supervised environment may be indicated.

Gelatin

Gelatin is added to vaccines – most often, attenuated virus vaccines – as a stabilizer, and is the component primarily responsible for most allergic reactions.[7] Studies have shown that gelatin was the triggering agent of anaphylactic reactions to the MMR[23-25] and chickenpox[26,27] vaccines.

A previous history of reaction to gelatin must be evaluated before indicating vaccines which contain this component, but the absence of such a history does not rule out the possibility of a reaction to these vaccines, since oral intake of gelatin allows digestion of gelatin into less allergenic peptide fragments.[7] Patients with alpha-gal allergy should also be approached with caution.[8]

Patients with a known history of allergy after oral gelatin intake or administration of a vaccine containing gelatin and who have indications for a vaccine containing this component should undergo testing. The workup may include gelatin-specific IgE measurement, a skin prick test with undiluted vaccine, and, if negative, an ID test with the vaccine at 1:100 dilution.[7] If both skin tests are negative, the vaccine can be given as a single dose with no further precautions except observation for 30 to 60 minutes after administration. If the skin tests are positive, a graded-dose can be administered in a facility equipped to respond in case of anaphylaxis.[7]

Yeast

The antigens of several vaccines, including hepatitis B, HPV, and one of the conjugated meningococcal vaccines, are recombinant proteins expressed in *Saccharomyces cerevisiae*.[8] In a review, DiMiceli et al. identified 180,895 adverse events, 15 of which were reports of probable or possible anaphylaxis, after vaccination in patients with a history of yeast or fungal allergy. Of these patients, 11 had received hepatitis B vaccine that contained traces of yeast protein, but in these cases no tests were performed to prove sensitization to the culprit protein.[28] Therefore, allergic reactions to vaccines allegedly caused by yeast or fungi are exceedingly rare. In some cases, skin testing may be performed in patients with a history of *S. cerevisiae* allergy; if positive, supervised administration of graded doses of the potentially yeast-containing vaccine may be considered.[8]

Latex

Exposure to latex during vaccination may be related to the packaging of the vaccine vial or syringe, but allergic reactions to such exposures are exceedingly rare. Unlike balloons and gloves, from which the latex allergen can be easily eluted, this component cannot be eluted from vaccine packaging. It is thus recommended that vaccinators wear latex-free gloves while administering vaccines to patients with latex allergy.[7] In case of multidose vials, one suggestion is to administer the first dose from a fresh vial to the latex-allergic patient.

Antimicrobials

Several antimicrobial agents, such as gentamicin, tetracycline, neomycin, streptomycin, and polymyxin B, are used to prevent bacterial or fungal growth during the vaccine manufacturing process. During the purification process, most of these antimicrobials are removed; although traces of these agents may still be present in some vaccines, they rarely cause

systemic reactions. People with a history of severe allergy (anaphylaxis) to antimicrobial agents contained in a given vaccine may benefit from an individualized immunization approach, and either replacement of the immunogen or vaccination under supervision may be considered.[8]

Polyethylene glycol (PEG) and Polysorbate 80 (PS80)

Polyethylene glycol, used as a stabilizer in drugs, cosmetics, and other product formulations, has recently been implicated as a possible cause of anaphylactic reactions following administration of COVID-19 mRNA vaccines. However, the evidence supporting this hypothesis is contradictory, and other factors may be involved in these immediate reactions.[29]

One study correlated an episode of anaphylactic reaction after administration of the Pfizer/BioNTech vaccine with the presence of anti-PEG antibodies, as determined by immediate-reading skin tests. However, the study also found that three other participants who experienced similar systemic adverse events did not have anti-PEG antibodies. Despite the small number of cases described in this study, the authors suggest that the role of PEG in eliciting anaphylactic reactions may be limited. Continuous monitoring of data on the rare potential risk of anaphylaxis and active surveillance of the population receiving COVID-19 vaccines may help identify risk factors for the development of severe allergic reactions following immunization. It bears stressing that people with a history of proven, severe allergy to PEG should not receive any vaccines containing this component. A better understanding of the frequency, characteristics, and mechanisms of reactions to PEG may aid in the development of increasingly safer vaccines for allergic patients.[29]

Polysorbate 80 (PS80) is a molecule structurally related to PEG which can be found in some vaccines. Some adverse events (including anaphylaxis) after vaccination with products containing PS80 have been described in the literature, which has led researchers to hypothesize a role for PS80 in inducing anaphylaxis.[30,31]

Adverse events consistent with type II (cytotoxic) hypersensitivity reactions

Type II hypersensitivity reactions are characterized by the formation of antibodies that attach to body cells, resulting in cell destruction by complement proteins and by lymphocytes that bind to the antibodies. This mechanism is probably involved in the demyelination (destruction of the nerve myelin sheath) that can occur after administration of certain live virus vaccines or nerve-tissue rabies vaccine, causing conditions such as acute disseminated encephalomyelitis (ADEM) or the Guillain-Barré syndrome (GBS). The yellow fever, influenza, DTP, and meningococcal vaccines have all been temporally associated with these reactions in the literature.[5]

Although cases of vaccine-associated idiopathic thrombocytopenic purpura (ITP) are rare, clinicians should bear in mind that the risk of ITP is increased for up to 6 weeks after MMR vaccination. In a 2010 systematic review, the median incidence of ITP after MMR vaccine administration was 2.6 cases per 100,000 doses given. This incidence is lower than that caused by natural measles and rubella infection, and similar to the incidence of ITP in the general population.[32]

Adverse events consistent with type III (immune complex) hypersensitivity reactions

These reactions are caused by the formation of immune complexes, which lead to vasculitis and tissue necrosis at the injection site (as can occur after multiple diphtheria-tetanus vaccine boosters – the so-called Arthus phenomenon) or to generalized manifestations, as in serum sickness. Arthus reactions have been reported after the administration of tetanus, diphtheria, hepatitis B, 23-valent pneumococcal, and meningococcal conjugate vaccines.[33]

Management of Arthus reaction is based on topical corticosteroids (to relieve discomfort caused by itching and rash), antihistamines (which also help relieve rash and itching), and non-steroidal anti-inflammatory drugs (to relieve joint pain when present).[5]

Serum sickness, characterized by the onset of rash, arthralgia or arthritis, fever, lymphadenopathy, and anorexia approximately 1 to 2 weeks after exposure to the antigen, may manifest after rabies vaccination and, more rarely, after administration of influenza, tetanus, and pneumococcal vaccines.[34]

Adverse events consistent with type IV (delayed) hypersensitivity reactions

Type IV hypersensitivity reactions are inflammatory reactions triggered by mononuclear leukocytes. The

term "delayed" is used to differentiate a secondary cellular response, which develops 48-72 hours after allergen exposure, from an immediate hypersensitivity response, which generally develops within 12 minutes. These reactions are mediated by T cells and monocytes/macrophages, not antibodies.[5]

Delayed hypersensitivity reactions can be localized, as in individuals who develop skin reactions to the neomycin and thiomersal used as preservatives in some vaccines.[5]

Vaccines containing aluminum adjuvants can induce formation of chronic subcutaneous nodules at the injection site.[35] Diphtheria-tetanus-pertussis vaccines (alone or in combination with other antigens), as well as human papillomavirus and hepatitis A and B vaccines, may contain aluminum. The risk of this complication is estimated at around 0.03% to 0.83%. Nodules usually appear approximately 3 months after vaccination, and can persist for many years (up to 3-4 years). Severe itching, local eczema, hypertrichosis, and discoloration may be present at the nodule site. Contact sensitivity to aluminum can be confirmed in clinical practice through patch testing.[36]

Severe manifestations such as the Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis have been reported as adverse events following immunization, although these reactions are vanishingly rare. The mechanisms putatively involved in delayed post-vaccination reactions are not well established, although preexisting allergy to vaccine components or possible genetic variations in antigen presentation or processing may be predisposing factors for the development of clinically severe reactions.[31]

Vaccines related to hypersensitivity events

Yellow fever vaccine

The yellow fever (YF) vaccine is grown in embryonated chicken eggs. Due to the manufacturing process, residual amounts of egg protein may be present in this vaccine. Two YF vaccines are available in Brazil. The amount of ovalbumin varies, ranging from 2.43 to 4.42 µg/mL depending on the batch. In addition to ovalbumin, the vaccine agent itself (live attenuated yellow fever virus), bovine gelatin, erythromycin, kanamycin, and latex (the last four being present only in some formulations) are potentially causative of hypersensitivity reactions.[5]

Inquiring as to severe allergy after ingestion or contact with eggs is considered appropriate for persons with a history of other severe allergies who will receive the yellow fever vaccine. For children without any clinical history consistent with egg allergy and in whom complementary feeds are being introduced, there is no evidence of a need to try eggs prior to yellow fever vaccination. Likewise, there is no recommendation for egg-specific IgE testing in children without a history of allergy after oral egg intake before the vaccine is administered.[37]

Individuals with a known diagnosis or clinical suspicion of egg allergy should be referred to a specialist for investigation of possible egg sensitization using immediate-reading skin tests or allergen-specific serum IgE. If these tests are negative, the vaccine can be administered at the standard dose and the individual kept under observation for 30 to 60 minutes. If a diagnosis of egg-mediated IgE allergy is confirmed by clinical or laboratory criteria by the allergist, the patient can receive the YF vaccine through desensitization protocols or fractional dosing, in an appropriate setting for the management of possible anaphylaxis.[16,17,37]

An important aspect to be considered is whether the patient reports tolerating boiled or fried eggs, but is not known to tolerate raw eggs. The YF vaccine is not subjected to high temperatures at any time during its manufacturing process, so even a patient who tolerates boiled or fried eggs may develop an immediate reaction after vaccine administration.[37]

Influenza vaccine

Influenza vaccine is grown in allantoic fluid from embryonated chicken eggs and contains varying amounts of ovalbumin depending on the manufacturer. In general, currently marketed influenza vaccines contain less than 1.2 µg/mL ovalbumin.

Egg allergy was once considered a contra-indication to influenza vaccination, but studies including 4,300 individuals with a history of egg allergy, of which 650 reported anaphylactic reactions, showed good tolerance to the vaccine. The current recommendation is that individuals with a history of severe allergy (anaphylaxis) to chicken eggs receive the influenza vaccine and remain under observation for 30 to 60 minutes. The American Academy of Pediatrics (AAP) advises that influenza vaccination in egg-allergic patients is safe and does not require additional precautions, since there is already a

formal recommendation on the need for standard precautions for all patients who receive any type of immunogen.[38]

MMR (measles, mumps, rubella) vaccine

The MMR vaccine contains negligible amounts of egg protein. In many studies, individuals with egg allergy – even those with a history of severe hypersensitivity – had an accordingly negligible risk of anaphylactic reactions. Skin testing with the MMR vaccine is not recommended, as it has no established predictive value.[16] Many reactions attributed to the MMR vaccine are possibly due to other components, such as gelatin.[37]

In 2014, some cases of children with CMA who developed anaphylaxis after receiving MMR vaccine manufactured by the Serum Institute of India were reported.[19,20] Upon investigation, the vaccine was found to contain traces of lactalbumin. Therefore, the Brazilian Ministry of Health advises that children with CMA receive MMR vaccine from another manufacturer that does not contain milk proteins; if a substitute vaccine is not available, vaccination should be deferred.[39]

Varicella vaccine

The varicella zoster (chickenpox) vaccine is a live attenuated virus vaccine (Oka strain) and may contain gelatin and traces of neomycin. The estimated rate of anaphylaxis to varicella vaccine reported to VAERS from 2006 to 2016 was 1.2 per 1 million doses deployed.[7,12] Ozaki et al. described 28 severe anaphylactic reactions and 139 non-severe allergic reactions following immunization with gelatin-containing varicella vaccine from 1994 to 1999 in Japan, out of 1.41 million doses administered (11.6/100,000). All nine available serum samples from children with anaphylaxis were gelatin-specific IgE-positive, whereas 55 of 70 available sera from children with non-severe allergy were positive. On the other hand, 5 non-serious allergic reactions and no serious reactions were described out of 1.3 million doses of gelatin-free varicella vaccine administered from 1999 to 2002 (0.38/100,000). The authors concluded that the gelatin-free vaccine was safer and provided data demonstrating comparable immunogenicity to that of the previous gelatin-containing vaccine.[40]

Serious and non-serious ESAVI reported in the literature for each vaccine are listed in Table 2.

Pneumococcal vaccines

Streptococcus pneumoniae is the leading cause of morbidity and mortality among children worldwide. It is the most common cause of otitis and invasive bacterial disease (including pneumonia, bacteremia, and meningitis) in children.[7]

More than 90 pneumococcal serotypes have been identified, but approximately 20 serotypes account for most infections worldwide.[8]

Two types of pneumococcal vaccine are currently commercially available in Brazil: the 23-valent polysaccharide vaccine (PPSV), available since the 1980s, and the 10- and 13-valent pneumococcal conjugate vaccines (PCV).[37]

The 23-valent pneumococcal polysaccharide vaccine covers the 23 most prevalent pneumococcal serotypes, and contains phenol as a preservative. The 13-valent pneumococcal conjugate vaccine contains polysorbate 80. In the 10-valent pneumococcal conjugate vaccine, the conjugate is nontypeable *Haemophilus influenzae* lipoprotein D for eight pneumococcal serotypes and the CRM_{197} protein for the remaining two. Overall, pneumococcal vaccines are well tolerated, with more local adverse events being reported.[41,42]

Two cases of anaphylaxis associated with the 23-valent pneumococcal polysaccharide vaccine were reported in children, in 2001 and 2010; in both, immediate-read skin tests demonstrated sensitization to pneumococcal polysaccharides. These cases highlight that hypersensitivity reactions to the vaccine antigen are rare events, and their confirmation is challenging in clinical practice.[43]

The first case of anaphylaxis to the 13-valent pneumococcal conjugate vaccine reported in the literature occurred in a 1-year-old child who received several vaccines at the same visit. Investigation by a specialist with skin testing and a basophil activation test concluded that CRM_{197} was the causative agent of anaphylaxis.[44]

Adult diphtheria toxoid-tetanus toxoid vaccine adsorbed (dT)

The adult diphtheria-tetanus vaccine is composed of diphtheria toxoid, tetanus toxoid, aluminum hydroxide, thiomersal, and buffered saline solution (pH 6.4). Hypersensitivity reactions are rare, with the majority being caused by thiomersal and aluminum.[5]

Table 2
Adverse events by vaccine

Vaccine	Adverse event			
	Site	General	Specific	Hypersensitivity reaction
Hepatitis B	Pain, induration, redness	Fever, irritability, fatigue, headache	ITP	Yes
DTP-HB/Hib	Pain, induration, redness	Fever, irritability, fatigue, headache, drowsiness	Apnea, encephalopathy, seizures, persistent crying, HHE	Yes
OPV		Rash, urticaria	Acute flaccid paralysis from vaccine-derived poliovirus, aseptic meningitis	Yes
Rotavirus		Nausea, vomiting	Intestinal intussusception	
Yellow fever	Pain, redness, induration	Fever, myalgia, headache	Encephalitis, acute viscerotropic disease, acute neurotropic disease	Yes
MMR (Measles, Mumps, Rubella)	Burning, hyperesthesia, redness, abscess, lymphadenopathy	Fever, headache, irritability, rash	Encephalitis, meningitis, subacute sclerosing panencephalitis, Guillain-Barré syndrome, orchitis, parotitis, ITP	Yes
IPV	Redness, induration, pain	Fever		Rarely
Hepatitis A	Redness, induration, pain	Fever, headache, malaise, fatigue		Rarely
Varicella	Redness, induration, pain	Fever, mild vesicular rash	Reactions are more common in immunosuppressed patients	Rarely
Pneumococcal, 10-valent	Redness, induration,	Irritability, drowsiness, excessive crying	Rarely	
Pneumococcal, 23-valent	Redness, edema, pain	Fever, myalgia, arthralgia, headache, listlessness	Local manifestations are more frequent in revaccinated patients	Rarely
Meningitis C	Redness, induration, pain	Fever and irritability		Rarely

ITP = idiopathic thrombocytopenic purpura.
HHE = hypotonic-hyporesponsive episode.

Vaccines with a pertussis component

Diphtheria-tetanus-pertussis vaccine acellular (DTaP)

Most allergic reactions to vaccines are reported in patients immunized against tetanus, diphtheria, and pertussis.[45] However, hypersensitivity reactions are exceedingly rare, at a rate of 2 per 1 million doses of DTaP.[35] When they do occur, they are often allergic reactions such as urticaria, or, in more severe cases, anaphylaxis.[45]

In addition to the active ingredients (diphtheria toxoid, tetanus toxoid, components of the *Bordetella pertussis* bacterial capsule, hemagglutinin, pertactin, phenoxyethanol), these vaccines contain excipients which vary (including in concentration) by manufacturer, and are the leading causes of allergic reactions. The excipients are: aluminum hydroxide, aluminum phosphate, sodium chloride, and water for injection. Traces of formaldehyde, polysorbate 80, glutaraldehyde, and glycine are likewise present.[5]

Aluminum may be present both as an excipient and as an adjuvant, to enhance the immunogenicity of the antigens, and may induce type IV hypersensitivity (contact allergy). Therefore, caution is warranted in individuals with a history of hypersensitivity to aluminum (most commonly to antiperspirants).[3] On rare occasions (< 1%), vaccinated children may develop pruritus and nodule formation at the application site due to the aluminum contained in the vaccine. The cause of this phenomenon is still poorly defined.[22] Contact hypersensitivity has been demonstrated in 77% of children with pruritic nodules and in 8% of asymptomatic siblings who received the same vaccines.[35] Subcutaneous nodules can develop and persist for months or years before gradually disappearing. Risk factors for aluminum sensitization during vaccination appear to be the amount of aluminum in the vaccine, the number of vaccinations administered, and the type of aluminum component, with aluminum hydroxide being more likely to induce sensitization than aluminum phosphate.[22]

Many manufacturers include glycine (gelatin) in their vaccines, which increases allergenic potential. The correlation of previous administration of DTaP doses with the development of gelatin hypersensitivity has been investigated, as it could explain the development of allergy to other glycine-containing vaccines, such as MMR. Most anaphylactic and urticarial reactions attributed to MMR are in fact related to elevated levels of gelatin-specific IgE, not to the vaccine antigens themselves.[46]

Whole-cell diphtheria-tetanus-pertussis vaccine (DTP)

The DTP vaccine, which contains whole *Bordetella pertussis* cells, is associated with a higher frequency of adverse reactions compared to the DTaP vaccine. However, the adjuvant composition of the two vaccines is similar, and the risk of allergic reactions may be the same. In some countries, whole-cell DTP vaccine does not contain aluminum[47]; therefore, allergic reactions are reported less frequently than with the acellular formulation.

DTaP-IPV-HepB+Hib (hexavalent) vaccine

The hexavalent vaccine is composed of diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentous hemagglutinin, pertactin, hepatitis B surface antigen, poliovirus, and *Haemophilus influenzae* type b polysaccharide as active ingredients. Hydrated aluminum hydroxide is the sole adjuvant. The excipients are lactose, sodium chloride, Medium 199 (M-199), aluminum hydroxide, aluminum phosphate, and water for injection. Traces of potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulfate, and polymyxin B sulfate may be present. Local reactions to antibiotics do not contraindicate vaccination. Reactions to aluminum and glycine are similar to those seen with DTaP.[37]

DTaP-IPV+Hib (pentavalent) vaccine

The active components of the pentavalent vaccine are diphtheria toxoid, tetanus toxoid, Bordetella pertussis antigens, pertussis toxoid (PT) 25 µg, filamentous hemagglutinin, pertactin, poliovirus type 1 strain Mahoney inactivated (IPV), *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate), and aluminum hydroxide as adjuvant. The excipients are lactose, sodium chloride, aluminum salts, medium 199 (M-199), and water for injection. Traces of potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 80, glycine, formaldehyde, neomycin sulfate, and polymyxin B sulfate may be present. Again, local reactions to antibiotics do not contraindicate vaccination.[46] Reactions to aluminum and glycine are similar to those seen with DTaP.

In a prospective study of 4758 children, 0.66% (n = 38) developed pruritic granuloma after administration of the pentavalent vaccine Pentavac® (DTaP-Hib-IPV). Patch testing for elemental aluminum and 2% aluminum hydrochloride hexahydrate has been suggested, but some cases may not be diagnosed and sensitization may fail to be identified. An alternative to improve the sensitivity of the test would be to use 10% aluminum hydrochloride hexahydrate as the antigen. To help confirm the diagnosis of hypersensitivity, it is recommended that patch testing performed with 10% aluminum hydroxide be read at 3 or 4 days and at 1 week.[47]

COVID-19

In the current coronavirus disease 2019 (COVID-19) pandemic, vaccines have been one of the most promising measures for controlling the spread of the virus and reducing severe cases and deaths. COVID-19 vaccines were developed using several different technologies, leveraging vast experience with previous platforms and due to the massive social and economic impact of the pandemic. The most common COVID-19 vaccines in use worldwide are inactivated virus, recombinant viral vector, nucleic acid (mRNA), virus-like particle, and protein subunit vaccines. Other vaccine platforms, such as attenuated virus and DNA vaccines, are at various stages of development.[48]

Anaphylaxis-like reactions following administration of the Moderna and Pfizer/BioNTech mRNA COVID-19 vaccines have been reported in the UK and U.S. The incidence of these reactions suggests that, while still rare, the rate may be higher with these vaccines than previously reported in the literature, at approximately 2.5 to 4.7 events per 1 million doses.[49]

Some cases characterized and treated as anaphylaxis subsequently resolved, and patients received the second dose of the vaccine uneventfully.[50] Other cases have been described that clearly resemble anaphylactic reactions, with rapid onset of symptoms and need for endotracheal intubation, although no investigation of the mechanism has been described.[49]

Occasionally, patients develop hives with or without mild angioedema within hours or days of receiving the vaccine. Most potentially serious systemic allergic reactions to mRNA COVID-19 vaccines reported to date have occurred within 30 minutes of vaccination (the majority within 15 minutes). This rapid onset of symptoms can assist recognition of anaphylaxis, and determines which precautionary measures must be taken at the vaccination facility.[37]

So-called persistent intermittent delayed swelling (PIDS) of the face in areas previously injected with cosmetic dermal fillers has been reported following administration of the Moderna mRNA vaccine. The pathophysiology remains unclear and may not involve allergic mechanisms, although local inflammation has been observed.[51]

Delayed local reactions are rare events and have been described with several vaccines. In phase III studies of the Moderna mRNA-1273 vaccine, delayed local reactions were seen in 0.8% of patients after the first dose and in 0.2% after the second dose.[52] Blumenthal et al. described 12 patients with extensive late local reactions after administration of the mRNA-1273 vaccine. Median time to reaction onset was 8 days (range, 4 to 11 days) after the first dose. Some patients had concomitant systemic symptoms, and two patients had other skin manifestations. Most patients were treated symptomatically (e.g. local ice and antihistamines). Symptoms resolved within a median of 6 days after onset (range, 2 to 11 days). All patients received the second dose of the vaccine, as this type of reaction does not contraindicate subsequent vaccination. Although half of the patients had no reaction, three patients had reactions similar to that observed after the first dose, and three patients had recurrence of the local reaction to a lesser degree compared to the first-dose reaction.[53]

Most reactions have occurred with the first dose, which suggests either that the patients were previously sensitized to some vaccine component or that the mechanism involved in these reactions could be different from known hypersensitivity mechanisms. As noted above, most allergic reactions to vaccines are usually not due to the antigen component, but rather to excipients. Table 3 lists available COVID-19 vaccines with their types, components, and hypersensitivity reactions reported up to January 2021.

Immediate hypersensitivity reactions have been more frequent with mRNA vaccines than with other commonly used vaccines, as described above. Therefore, efforts have been made to understand the mechanisms implicated in hypersensitivity to these vaccines. The Pfizer-BioNTech and Moderna vaccines do not contain any food or drug components nor latex, but both contain polyethylene glycol (PEG), which is used as an excipient with the aim of stabilizing the mRNA-containing lipid nanoparticles. The specific

type of PEG used in these vaccines was different from the PEG used in most other commercial products. Countless products contain PEG (also known as macrogol), including medicines, cosmetics, and foodstuffs.[54] Despite this widespread use, PEG allergy is very rare. Most reactions to PEG described in the literature are related to high-molecular-weight PEG, with low-molecular-weight PEG (more common in everyday products) being a less frequent cause of adverse reactions. The underlying pathophysiological mechanism of PEG allergy is still unclear, but the presence of anti-PEG IgE has been described in some patients with PEG-induced anaphylaxis. PEG also seems to induce complement activation mechanisms *in vitro*.[55] Most PEG allergies are usually discovered during evaluation of patients who have apparently had reactions to unrelated products, such as injectable corticosteroids, processed foods, cosmetics, drugs, and other substances.[54]

Polysorbate, like PEG, is an excipient used in multiple drug preparations (including vaccines), creams, lotions, and drug tablets. Polysorbates are derived from PEG, but have a very low molecular weight and are therefore much less likely to trigger an allergic reaction. The Oxford/AstraZeneca (ChAdOx1) vaccine is manufactured using a viral vector (non-replicating chimpanzee adenovirus) and contains histidine, sucrose, sodium chloride, magnesium chloride, polysorbate 80, disodium edetate (EDTA), and ethanol. Polysorbate 80 is present at a concentration of less than 100 µg per dose – the same amount found in other vaccines, such as the influenza vaccine, with which higher rates of allergic reactions have not been observed.[55]

The Janssen (Johnson & Johnson) vaccine also uses viral vector technology (recombinant adenovirus) and contains polysorbate 80. In phase III studies, hypersensitivity reactions (urticaria) were rare (1/10,000 to 1/1,000 doses) and anaphylactic reactions were reported, but the frequency could not be estimated from the available data.[56]

CoronaVac is an inactivated virus vaccine that contains aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, water for injection, and sodium hydroxide. In safety analyses of phase III studies including 5051 participants, 50.8% had adverse events within 7 days of administration, and 40.1% of the reactions were pain at the injection site. Hypersensitivity reactions were rare, occurring at a frequency of 1/1000 to 1/100.[57,58]

Of the 221 participants of a Turkish trial, 62 (28.1%) reported allergic or skin reactions (injection site pain and/or inflammatory reactions) temporally related to the CoronaVac vaccine. Of the 62 patients who had skin reactions, 25 (11.3%) had no personal or family history of allergy, while the remaining 37 reported a history of allergy. The 25 patients with no personal/family history reported the following events (some patients had more than one reaction): urticaria (n = 12, 5.4%); papulosquamous reactions (e.g. pityriasis rosea) (n = 8; 3.6%); herpes infection (n = 4; 1.8%), consisting of herpes zoster (HZ) (n = 2) and herpes simplex (HS) (n = 2); angioedema (n = 3; 1.4%), type IV hypersensitivity reactions, such as erythema multiforme, lichenoid drug eruption, and drug hypersensitivity syndrome (n = 3; 1.4%); palmar erythema (n = 2; 0.9%); anaphylaxis (n = 1; 0.5%); conjunctivitis (n = 1; 0.5%); and small-vessel vasculitis (n = 1; 0.5%). However, it should be noted that the events reported in this study were only temporally related to vaccination, with no further investigation or proof of causality.[59]

Rationale for investigation of hypersensitivity reactions following vaccination

When a patient is referred to an allergist/immunologist for assessment of a potential vaccine hypersensitivity reaction, the clinical reasoning process should always begin with the following questions:[7,17,22,37,60-62]

(a) Is the vaccination schedule incomplete? Are additional doses of the same vaccine still needed?

(b What is the risk–benefit ratio of continuing the vaccination schedule (i.e. weighed against the risk of disease)?

The workup should begin with a thorough clinical history, with particular attention to previous adverse drug reactions or reactions following immunization. Aspects important to assess include the extent of the reaction (local vs. systemic), the time to onset of the reaction (immediate vs. nonimmediate/delayed), and the need for rescue medication (H1 receptor antagonist, epinephrine). The manufacturer and batch of the vaccine suspected of causing the reaction must be ascertained and recorded. The vaccine package insert or prescribing information should be checked for components such as adjuvants

Table 3
COVID-19 vaccines and hypersensitivity reactions

Vaccine (manufacturer)	Legal status (as of January 2021)	Vaccine type	Excipients	Hypersensitivity reactions
CoronaVac (Sinovac, China)	EUA for use in China (essential workers and high-risk groups), Turkey Pending: Indonesia	Inactivated vaccine (formalin with alum adjuvant)	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride	No anaphylaxis events reported during Phase 3 trials (33,620 participants)
Convidicea Ad5-nCoV (CanSino Biologics, Beijing Inst. Biotech., NPO Petrovax)	EUA in China (limited to military use only) Pending: Mexico	Recombinant adenovirus type 5 vector against spike RBD protein	N/A	No anaphylaxis events reported during Phase 3 trials (40,000 participants)
BBIBP-CorV (Sinopharm, Beijing Institute & Wuhan Inst. of Biological Products)	Full authorization for use in China, EUA in Bahrain, Egypt, UAE.	Inactivated SARS-CoV-2 (vero cells) + aluminum hydroxide adjuvant	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium hydroxide, sodium bicarbonate, M199	No anaphylaxis events reported during Phase 3 trials (48,000 participants)
Pfizer-BioNTech BNT162b2	EUA in Argentina, Bahrain, Canada, Chile, Costa Rica, Ecuador, EU, Israel, Jordan, Kuwait, Mexico, Oman, Panama, Saudi Arabia, Singapore, Switzerland, UK, USA, WHO. Pending: Australia, India, Japan	mRNA-based vaccine encoding the viral spike (S) glycoprotein	(4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis (2-hexyldecanoate)] (ALC-0315), 2-[(polyethylene glycol)-2000]-N, N-ditetradecylacetamide (ALC-0159), 1,2-Distearoyl-sn-glycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection	No anaphylaxis events attributed to vaccine reported in clinical trials (~22,000 participants randomized to active dosing). Approximate incidence of anaphylaxis: 1:100,000 with routine use
Moderna mRNA-1273	EUA in Canada, EU, Israel, Switzerland, UK, USA	mRNA-based vaccine encoding the pre-fusion stabilized spike (S) glycoprotein	Lipids (SM-102, 1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-snglycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose	No acute anaphylaxis reactions reported in clinical trials (~15,000 participants randomized to active dosing)

Table 3 *(continued)*
COVID-19 vaccines and hypersensitivity reactions

Vaccine (manufacturer)	Legal status (as of January 2021)	Vaccine type	Excipients	Hypersensitivity reactions
ChAdOx1 (Oxford/ AstraZeneca; Covishield in India)	EUA in Argentina, Dominican Republic, El Salvador, EU, India, Mexico, Morocco, UK. Pending: Australia, Canada	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	L-Histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate, water for injection	No anaphylaxis events reported in clinical trials (~12,000 participants randomized to active dosing)
Covaxin (BBV152) (Bharat Biotech, India)	EUA in India	Inactivated vaccine	N/A	No events reported in Phase 1 studies (n = 300)
Sputnik V (Gamaleya Research Institute)	Russia, Palestine	Non-replicating, two-component vector (adenovirus) against spike (S) glycoprotein	Tris (hydroxymethyl) aminomethane, sodium chloride, sucrose, magnesium chloride hexahydrate, sodium EDTA, polysorbate 80, ethanol, water for injection	No events reported in Phase 1/2 studies (n = 76)
EpiVacCorona (Federal Budgetary Research Institution State Research Center, Russia)	Regulatory approval granted in Russia on basis of Phase 1/2 studies	Peptide vaccine with alum adjuvant	Aluminum hydroxide, potassium dihydrogen phosphate, potassium chloride, sodium hydrogen phosphate dodecahydrate, sodium chloride, water for injection	Unknown

Adapted from Turner PJ et al. [55].

(aluminium), preservatives (formaldehyde, thiomersal, 2-phenoxyethanol), stabilizers (lactose, gelatin), antibiotics, latex, and culture media (egg, yeast).[61,62] If the history is consistent with a hypersensitivity reaction to the vaccine, further workup should be directed by the hypersensitivity mechanism involved (Figure 1).

Skin tests with vaccines or their components, when recommended, should only be performed by a trained team in an appropriate environment, under the supervision of an allergist. All skin tests must be interpreted carefully, with both positive and negative controls. Positive results should be considered as indicative of sensitization, but not as proof of allergy, since false positives may occur in patients with no relevant clinical manifestations or may simply be due to the irritating effects of the antigen used for the test.

In patients who had an immediate hypersensitivity reaction, immediate-reading (skin prick or intradermal) tests with the vaccine and its components should be performed; if sensitization to a particular vaccine is demonstrated, vaccination can still be carried out in graded doses.[61,62] Premedication with antihistamines

after skin testing and before vaccination with graded doses is controversial, and is not recommended before an initial or booster dose.

A number of approaches to vaccine skin testing have been suggested, but current guidelines recommend that prick testing be initiated with undiluted vaccine (1:1) unless the patient has a history of severe anaphylaxis. In such cases, it is appropriate to dilute the vaccine to 1:10 or even 1:100, which are considered non-irritating concentrations.[63]

If the skin prick test is negative, an intradermal test with the vaccine at 1:100 dilution should then be performed.[7,60,62] Intradermal testing with undiluted vaccine is discouraged due to the high rate of irritation. False-positive results due to irritative reactions are more frequent with pure or 1:10 vaccine, especially with the influenza, MMR, and varicella vaccines. At 1:100 dilutions, irritability reactions are far less common: 5% for DT and DTaP and 15% for influenza.[7,22,55,63,64] Whenever possible, the test should be performed with the exact same vaccine (i.e. same manufacturer) suspected to have elicited the reaction.

If a hypersensitivity reaction is confirmed, another option to continue immunization is to switch to another vaccine for the same antigen but that does not contain the allergen putatively implicated in the reaction.[7,22,55,63] Local non-allergic reactions, such as redness, pain, and edema, do not contraindicate administration of subsequent vaccine doses; nor does fever.[7,22,55,63]

Immunization should not be delayed, and it is incumbent upon the allergist to carry out appropriate assessment and case management. With the decline in vaccination coverage observed in Brazil since the 1990s, the proportion of the population susceptible to infectious diseases – often highly communicable ones with high morbidity and mortality rates – has increased. In 2020, 8,000 cases of measles had already been confirmed in Brazil as of October. A specialist physician (allergist/immunologist) must be engaged to elucidate the case, together with the facility where vaccination took place or, in Brazil, the local referral center for special immunobiologicals (*Centro de Referência em Imunobiológicos Especiais*, CRIE).[65]

Once again, it bears stressing that severe reactions to vaccines are rare events. Nonetheless, all sites where vaccines are administered must have the necessary supplies on hand for management of immediate hypersensitivity reactions: epinephrine, antihistamines, corticosteroids, beta-2 agonists, and a supplemental oxygen source.[7]

Diagnostic workup

For assessment of a possible anaphylactic reaction to a vaccine, whenever possible, serum tryptase should be measured within 2 hours of the reaction and a baseline serum tryptase measurement should be obtained 48 hours after the reaction.[22]

If a severe allergic reaction to a vaccine is suspected, identification of the causative allergen is paramount, as this may allow the administration of another formulation of the same vaccine, as well as allow the patient to avoid other products that contain the same allergen in future. If additional doses of the vaccine should be administered, a skin test with the vaccine and/or its components should be performed. This process can be relatively simple if a single-antigen vaccine was administered, or more complicated if simultaneous or combined vaccination (e.g. MMR) was performed, as is common in pediatric practice.[7]

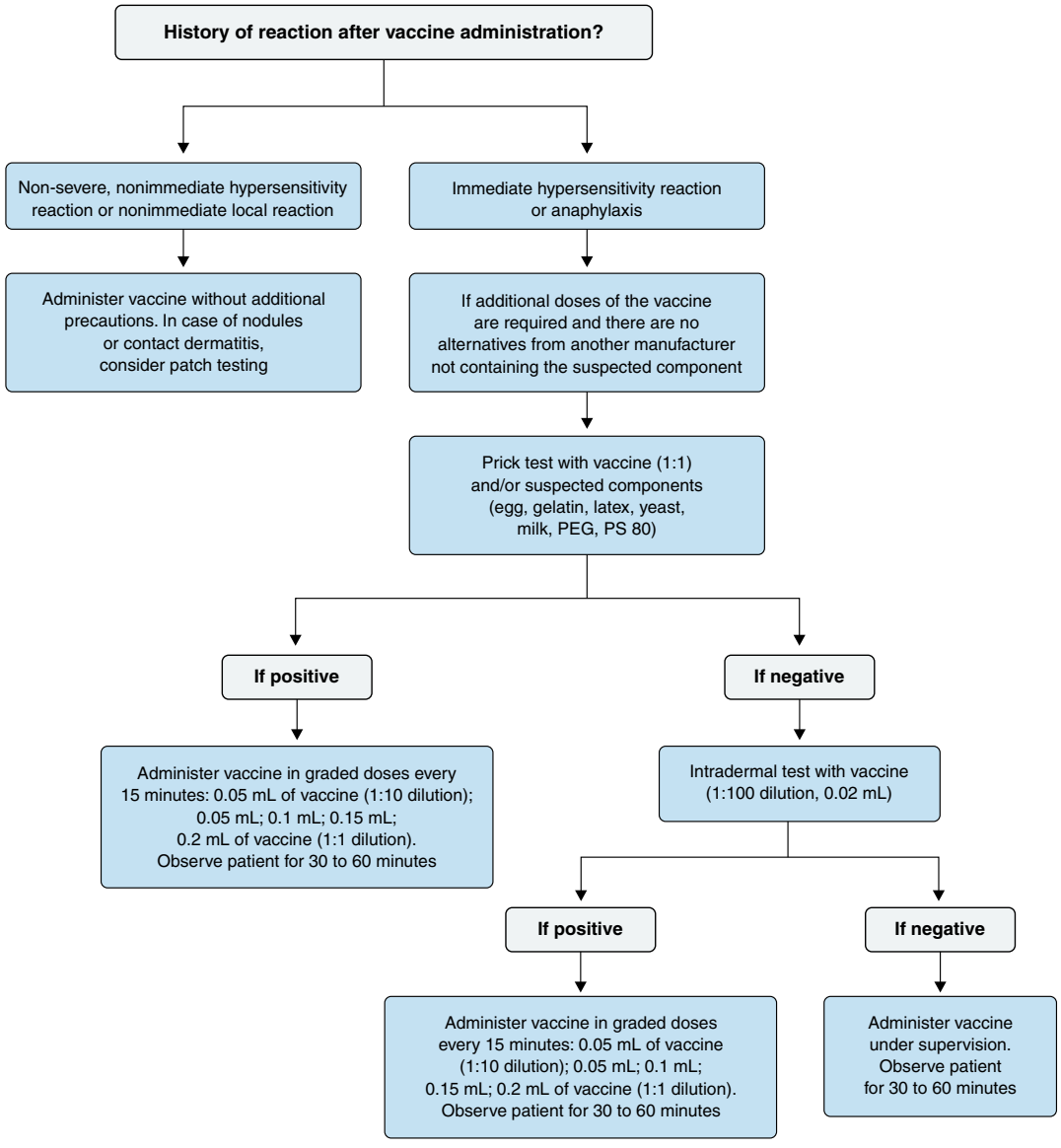
Investigation of potential allergens present in the vaccine can be performed *in vitro* and/or *in vivo*, depending on the availability of allergen extracts. Specific IgE tests for most antimicrobial components are not commercially available, and at any rate are often useless in predicting allergic reactions to vaccines. For some other components (e.g. ovalbumin and gelatin), the ability of tests to predict a vaccine reaction is very low.[22] Nevertheless, if the vaccine suspected to have caused the reaction contains specific components known to be potentially allergenic (e.g. egg, gelatin, latex or yeast), allergen screening should be conducted for these components. A simple gelatin prick test can be prepared by dissolving a teaspoon of powdered gelatin in 5 mL of normal saline solution.

Nonimmediate local reactions, such as contact dermatitis, subcutaneous nodules, or type IV hypersensitivity reactions to preservatives, aluminum, and antibiotics, can be evaluated through patch testing. Although patch testing is not essential for therapeutic decision-making, it can help in choosing alternative vaccines where these are available.[7]

Allergen-specific *in vitro* IgE tests for egg, gelatin, latex, and yeast are available at most commercial laboratories. Examples of skin and serology tests that would be appropriate in evaluating suspected reactions to specific vaccines are given in Table 4.[7]

Anaphylaxis and its management

Anaphylaxis is a rapidly progressive, life-threatening systemic hypersensitivity reaction involving at least two organ systems: *skin and mucosa* (most frequently involved, in >90% of cases, with erythema, pruritus, hives, and angioedema); *respiratory tract* (involved in 40% to 70% of cases, with hoarseness, cough, stridor, wheezing, dyspnea, chest tightness, asphyxia, death); *digestive tract* (affected in 30% of cases, with



Read at 15 min, consider positive if wheal = 3 mm. Positive (histamine) and negative (saline) controls. If skin test with vaccine negative: consider intradermal (ID) testing.

Consider test positive if the final wheal is twice as large as the initial wheal (ID). Obtaining written informed consent from the patient or guardian before the procedure is mandatory, as is a detailed explanation of the risks and benefits of desensitization.

Figure 1
Algorithm for investigation of hypersensitivity reactions to vaccines

nausea, vomiting, abdominal cramps, and diarrhea); *cardiovascular system* (tachycardia, hypotension, dizziness, syncope or presyncope, shock – in 10% of cases – and death); and/or *nervous system* (syncope, convulsions, coma). The estimated incidence of anaphylaxis is 10 to 20 cases per 100,000 person-years, with a documented upward trend in recent decades. With vaccines, the incidence is even lower, at approximately one case per million doses. Prompt treatment is critical for recovery, and delay in administration of epinephrine has been identified as a factor in unfavorable outcomes. It cannot be overstated that the first-line drug of choice in anaphylaxis is epinephrine IM, only later followed by antihistamines and corticosteroids.[37]

Other factors that may have a negative impact on the outcome of anaphylaxis are the use of inadequate doses or routes of administration for epinephrine (e.g. subcutaneous) and the concomitant use of other drugs, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, and antidepressants. After the acute episode, a second late phase may occur, with symptoms recurring after 6 to 12 hours. Therefore, patients must remain under close observation for at least 12 hours after an initial anaphylaxis event.[37]

Reporting

In 1992, to comply with World Health Organization (WHO) recommendations, the Brazilian Ministry of Health National Immunization Program (PNI/MS) began developing the Nationwide Surveillance System for Adverse Events Following Immunization (*Sistema Nacional de Vigilância de Eventos Adversos Pós-Vacinais*, SNVEAPV). Its objectives include standardizing recognition of suspected ESAVI and their management, providing in-depth knowledge on the nature of these events, and identifying potential breakdowns in transport, storage, handling, or administration (immunization errors) that result in adverse events. A careful analysis of the causality of the adverse event and its potential relationship with the administered product is conducted, and the resulting information – including incidence and severity of the observed reactions – is disseminated.[5]

Recognizing the importance of surveillance for this type of adverse event, the MoH Department of Health Surveillance (*Secretaria de Vigilância em Saúde*, SVS) has made all EAPVs notifiable events (Ordinance No. 33/SVS/MS of 2005, subsequently revoked by Ordinance No. 1.271/SVS/MS of 2014).[5]

Table 4
Examples of testing used to screen for sensitization to specific vaccines or components

Vaccine	Skin testing	Serum specific IgE testing
DTaP, Td, Tdap	DTaP, Td, Tdap, tetanus toxoid, gelatin, milk	Gelatin, milk, latex
Hepatitis B	Hepatitis B, yeast	Yeast, gelatin, latex
Influenza	Influenza, egg, gelatin	Egg, gelatin, latex
MMR	MMR, measles, mumps, rubella, gelatin	Gelatin, latex
Varicella or Zoster	Varicella or Zoster, gelatin	Gelatin, latex
Yellow fever	Yellow fever, egg, gelatin	Gelatin, latex

Adapted from Dreskin SC et al.[7]

To wit:

– Any adverse effect caused by immunization must be reported to the National Health Surveillance Agency (ANVISA) through the Health Surveillance Notification System (NOTIVISA). The time elapsed between vaccination and onset of symptoms should be considered.
– Local reactions such as abscess, cellulitis or nodulation at the site of administration; induration or swelling near or at the site of administration; granuloma; Arthus reaction; pain at the site of administration, at the time of administration or shortly after receiving the vaccine, must be reported.
– Systemic reactions such as anaphylaxis, as well as anaphylactoid reactions and anaphylactic shock, must also be reported. As must: inconsolable crying, lasting 3 hours or more, up to 48 hours after vaccine application; seizures, encephalitis, myelitis, acute disseminated encephalomyelitis; encephalopathy; hypotonic-hyporesponsive episode; fever; intestinal intussusception; aseptic meningitis; narcolepsy; optic neuritis; facial palsy; inflammatory polyradiculoneuropathies, such as the Guillain-Barré Syndrome; vasovagal syncope; Complex Regional Pain Syndrome; Early Systemic Reaction Syndrome; thrombocytopenia or low platelet count.
– Deaths temporally associated with adverse events following immunization, such as Sudden Unexplained Death in Childhood, Sudden Infant Death Syndrome, and all deaths with ill-defined causes, must also be reported. In these cases, reporting must be done in coordination with the medical examiner's office or coroner's office. Where available, it is recommended that a postmortem examination be performed within the first 72 hours, before tissue damage sets in which could hinder diagnosis.

Conclusions

It is part of health care providers' duty to assess the vaccination status of their patients and caregivers and formally recommend those vaccines indicated in the corresponding immunization schedule, considering age, special conditions (allergies and immunodeficiencies), and possible contraindications and precautions. In addition to recommending the necessary vaccinations, the allergist/immunologist must be prepared to address any vaccine-related adverse events, accurately establishing a diagnosis and providing the appropriate guidance and management.

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No conflicts of interest declared concerning the publication of this article.

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