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Adverse Reactions to Anti-Infective Vaccines: an Emerging Problem in the COVID-19 Era

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Abstract

Purpose of review Vaccines are an essential tool for preventing infectious diseases and reducing associated morbidity and mortality. Vaccination has a significant impact at both individual and community levels, and COVID-19 vaccination programs are a new example of the great value of this public health strategy. However, adverse reactions, especially severe reactions such as anaphylaxis, prevent these programs from progressing properly, thus limiting vaccination uptake in the population.

Recent findings The frequency of reactions and types of vaccine components, with special attention to COVID-19 vaccines studies, provides information on the magnitude and causes of adverse events. The understanding of mechanisms involved has made it possible to adequately guide diagnosis, especially to COVID-19 vaccine components, such as polyethylene glycol, trometamol, and polysorbate-80.

Summary This review focuses on adverse reactions to vaccines, with emphasis on allergic reactions. A diagnostic pathway is suggested that, on the one hand, enables to take the necessary precautions in persons with a history of allergy to vaccine components or allergic reactions to vaccines and, on the other, supports administration of subsequent doses. The overall objective is to ensure that people with allergy can be vaccinated in the same way as the rest of the population, and that they are offered alternatives where necessary.

Abbreviations

ADE	Antibody-dependent enhancement
AEFI	Adverse events following immunization
AstraZeneca	DNA & viral vector vaccine Vaxzevria (before COVID-19 Vaccine AstraZeneca ChAdOx1-S)
CARPA	Complement activation-related pseudoallergy
CDCs	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
CRM197	Cross-reacting material 197
DTaP	Diphtheria, tetanus, and acellular pertussis
DT	Diphtheria and tetanus
EAACI	European Academy of Allergy and Clinical Immunology
HBV	Hepatitis B virus vaccine
HPV	Human papillomavirus vaccine
Hib	Haemophilus influenzae type b
Ig	Immunoglobulin
Janssen	DNA & viral vector vaccine (JNJ-78436735, Janssen Pharmaceuticals Companies of Johnson & Johnson)
IPV	Inactivated poliovirus
MMR	Measles, mumps, and rubella vaccine
Moderna	Spikevax (formerly COVID-19 Vaccine Moderna m-RNA1273)
mRNA	Messenger ribonucleic acid
PEG	Polyethylene glycol
Pfizer	Comirnaty (formerly COVID-19 Vaccine Pfizer/BioNTech BNT162B2)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEAIC	Spanish Society of Allergy and Clinical Immunology
Tdap	Tetanus, diphtheria, and pertussis
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
YF	Yellow fever vaccine

Introduction

Vaccines are one of the most cost-effective tools in healthcare interventions. They prevent infectious diseases, reduce morbidity, and save innumerable lives. However, vaccines can cause adverse reactions, which may range from local and mild to systemic and severe. While severe adverse reactions can occur after the administration of the vaccine, for most people, the benefits of vaccination overcome the potential risk of experiencing such a reaction. Nevertheless, the fear of an adverse reaction may lead to reticence towards vaccination, thus leaving the individual in danger of not being protected against the disease and limiting collective immunity. Millions of vaccine doses are administered throughout the world every year, although the rate of reactions reported is low, especially anaphylaxis with only 1.3 cases per million vaccinations [1].

The development of new vaccines against severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) constitutes an unprecedented achievement in modern science, since these were the first vaccines created with messenger RNA (mRNA)-based technology. Once the first temporary authorizations were given by the regulatory agencies for BNT162b2, mRNA-1273, and AZD1222, from December 2020 to May 2022 it has been estimated that 11.9 billion doses have

been administered worldwide, and that 65.9% of the world's population has received at least one dose of COVID-19 vaccine [2]. Anaphylaxis after SARS-CoV-2 vaccination is rare, affecting 5 persons per million who receive the vaccination [3].

We review the type and frequency of adverse reactions associated with the administration of anti-infective vaccines, both traditional products and COVID-19 vaccines. Our study also provides guidelines for accurate diagnosis of these reactions and indications for controlled administration of new doses of the vaccine. Our objectives were to improve individual safety and ensure that as many people as possible can be vaccinated.

Immediate and non-immediate reactions

The WHO recommends classifying drug reactions based on the onset of symptoms. The two general types are immediate (< 1 h) and delayed reactions (> 1 h). Immediate reactions are generally IgE-mediated and carry a risk of systemic allergic reaction (anaphylaxis). Delayed reactions can be caused by various mechanisms, but are rarely IgE-mediated. Allergic reactions to vaccines are immune-mediated and account for a small percentage of AEFI [4].

Immediate reactions

Systemic allergic reactions are severe AEFI. Although uncommon, anaphylaxis is a severe and potentially life-threatening reaction [5]. It is highly probable when its signs appear rapidly (generally < 30 min after injection) [6], affecting various organs and systems (urticaria, erythema, bronchospasm, nausea, vomiting, diarrhea, hypotension with tachycardia, and/or loss of consciousness) [5]. It should be differentiated from other clinical presentations, such as vasovagal reactions (fainting) [7], and symptoms related to anxiety [8]. In these cases, symptoms appear during the injection or immediately after. They are characterized by pallor, cold, and clammy skin, sweating, hyperventilation or normal breathing, hypotension with bradycardia, and, occasionally, self-limiting loss of consciousness, with a favorable response to decubitus positioning. It is essential to differentiate between vasovagal reactions and anaphylaxis.

Non-immediate reactions

Fever, asthenia, myalgia, and/or headache are common non-immediate reactions, as are pain, reddening, and/or mild swelling at the injection site. These should not be a contraindication to future doses [9]. Extensive local reactions and chronic subcutaneous nodules appear 24–72 h after administration and are usually type-IV hypersensitivity reactions. Their frequency can be reduced by deep injection into the thigh [10]. Serum-like sickness (type-III), which progress with skin rash, fever, malaise, and polyarthralgia or polyarthritis, occur up to 1–2 weeks after vaccination if the patient has received the vaccine

more than once. In very rare cases, they have been associated with inactivated vaccines against influenza and HBV [11, 12].

Reactions to vaccine components

Reactions to vaccines may be due to the microbial antigen, residual proteins from production process, antimicrobial agents, stabilizers, preservatives, or any other element used during the packaging and administration processes [13]. Vaccine antigen is an infrequent cause of allergy. However, associated anaphylaxis has been reported, for example, with influenza vaccine and a nontoxic mutation of diphtheria toxin (CRM197) in the pneumococcal conjugate vaccine [14, 15]. Table 1 shows the main components, their function, vaccines that contain them, and reaction type [16].

Aluminum salts

Adjuvants used in vaccines to boost the immunogenic response, it do not cause anaphylaxis, although they trigger local reactions such as subcutaneous nodules or type-IV reactions. The latter occur 24–72 h after administration, and their risk increases with the number of doses received. Local reactions do not contraindicate administration of vaccines that contain aluminum [17]. Research is under way on the allergenicity of new adjuvants such as squalene derivatives (MF59, AS03, AF03) [18•].

Gelatin

Vaccine stabilizer is essentially porcine in origin and frequently cross-reacts with bovine gelatin. Patients who are sensitized to beef/pork also become sensitized to their gelatins, thus increasing the risk of experiencing reactions with vaccines that contain them [19]. Specific IgE (sIgE) has been detected in anaphylaxis induced by gelatin in the MMR [20]. Gelatin can also be a source of galactose-alfa-1,3-galactose (alfa-gal) [21]. Anaphylaxis has been reported after vaccination against MMR, varicella zoster virus, and DTaP/IPV in patients with a history of allergy to red meat [22•]. Hydrolysis/elimination of gelatin has reduced the frequency of systemic reactions [23]. Administration of gelatin-containing vaccines is contraindicated in patients who have previously experienced anaphylaxis to this component.

Thiomersal

Preservative synthetized from ethylmercuric chloride and thiosalicylic acid induces mild late local reactions (contact dermatitis). Positive patch test result

Table 1 Components, function, and allergic reactions of vaccines

Component	Function	Reaction	Vaccine
Aluminum hydroxide and aluminum phosphate	Adyuvant	Local: - Granulomas - Contact dermatitis	Adenovirus Anthrax DTaP/Tdap Haemophilus (Hib) Hepatitis A/B HPV Japanese Encephalitis Meningococcal Pneumococcal
Gelatin	Stabilizer	Local urticaria Anaphylaxis	Influenza MMR Rabies Typhoid YF Zoster
Alpha-gal	Stabilizer	Anaphylaxis	DTaP/IPV MMR Varicella
Thiomersal	Preservative	Contact dermatitis	Influenza Td
Beta-propiolactone	Inactivation of virus	Delayed local reaction	COVID-19 (Sinovac, Sinopharm) Rabies human diploid cell vaccine (HDVC)
Formaldehyde	Inactivation of virus Detoxification of bacterial toxin	Local: -Contact dermatitis -Systemic contact dermatitis	DTaP/Tdap Hepatitis B Hib Influenza Japanese Encephalitis Meningococcal Polio Typhoid
Neomycin	Antibiotic	Anaphylaxis	DTaP Hepatitis A Influenza MMR Polio Rabies Smallpox Varicella Zoster

Table 1 (continued)

Component	Function	Reaction	Vaccine
Natural latex	Present in vial stopper or syringe plunger within the conditioning material	Delayed local reaction Urticaria Anaphylaxis	Anthrax DTaP/Tdap/Td Hepatitis A/B Influenza Meningococcal Rotavirus YF
Egg proteins	Residual medium Stabilizer	Anaphylaxis	Influenza MMR Rabies YF
Yeast	Residual medium Medium nutrient	Anaphylaxis	DTaP Hepatitis A/B Meningococcal Pheumococcal Typhoid HPV
Milk proteins	Residual medium Medium nutrient	Anaphylaxis	DTaP/Tdap Hib Influenza Meningococcal
Polyethylene glycol	Surfactant of mRNA	Anaphylaxis	COVID-19
Trometamol	Stabilizer	Anaphylaxis	COVID-19 DTaP-IPV-HB-Hib Hib-N. Meningitidis Meningococcal
Polysorbate-80	Surfactant	Non-immunological anaphylaxis Local	COVID-19 DTaP Hepatitis A/B Influenza Meningococcal Pneumococcal Rotavirus HPV Zoster

Modified from Sampath V et al. [16]

with thiomersal does not contraindicate administration of a vaccine [24]. This preservative has been used less frequently in recent years to prevent toxicity in children.

Beta-propiolactone and formaldehyde

Both beta-propiolactone and formaldehyde are used to inactivate viruses and toxins. Six percent of people who receive booster doses of the human diploid cell rabies vaccine develop a response induced by immune-complexes at 2–21 days. This response was associated with altered beta-propiolactone in human albumin in the vaccine [25, 26]. The Sinopharm/Sinovac vaccines have recently been using beta-propiolactone to inactivate SARS-CoV-2 [27, 28••]. Formaldehyde is found in small amounts in vaccines. Systemic contact dermatitis caused by formaldehyde in the influenza vaccine has been reported [29].

Antibiotics

Neomycin, kanamycin, streptomycin, and/or polymixin B are added as preservatives to prevent contamination and may be present in trace amounts. Allergic reactions are very rare, and an IgE-mediated mechanism has been demonstrated in only a few cases. Some neomycin-allergic patients may experience mild local reactions 48–96 h after injection, but does not contraindicate future vaccination [30]. Vaccines containing antibiotics are contraindicated in patients with history of anaphylaxis after administration of the specific antibiotic [31].

Latex

Component of the cap of the vial of some vaccines or the seal of the plunger in syringes. Reactions to latex after vaccination are very rare. The VAERS reported that 0.01% of persons with a history of latex allergy who received a latex-containing vaccine experienced allergic reactions [32]. Vaccines in preloaded vials or syringes containing latex are contraindicated in patients with history of latex-induced anaphylaxis [33].

Proteins

Reactions to residual proteins include those caused by yeast and milk and egg proteins, with the latter being the most frequent.

The egg protein content depends on the manufacturing process and is very low if the vaccine is prepared using chicken embryo fibroblasts (measles, mumps, rabies, and MMR) (0.2–42 µg/mL) and somewhat higher if embryonated chicken eggs are used (influenza [0.02–1.0 µg/dose], and YF). Final product contains trace amounts of protein, 100,000 times lower than the threshold that would cause a reaction in a challenge test. Highest concentration of proteins is found in the YF [34]. Children with egg allergy tolerate

not only the MMR and influenza vaccines [35, 36], but also the YF, even in those with history of anaphylaxis to egg [37, 38•]. The CDCs and the Advisory Committee on Immunization Practices recommend a 30-min observation period in children with moderate egg allergy after influenza vaccination; in those with severe allergy, the vaccine should be administered at a center where severe reactions can be managed [39, 40].

Allergic reactions to the DTaP, Tdap, oral polio, and MMR in children with milk allergy are rare. These vaccines may contain nanograms of residual casein, and most allergic patients tolerate them [41]. EAACI position paper recommends standard vaccination in children with milk allergy [13].

Yeasts are found in the HBV and HPV, manufactured using cell cultures of *Saccharomyces cerevisiae*. Residual protein content is minimum, and allergic reactions are extremely rare. However, if yeast allergy is suspected, sIgE should be determined and skin tests performed before their administration [42]. Yeast is also used in the production of the carrier protein CRM197; therefore, its proteins may be found in vaccines such as pneumococcal conjugate vaccine 13, meningococcal, and oral typhoid vaccines [43].

COVID-19 vaccine components

The potential allergenic excipients in currently available COVID-19 vaccines are polyethylene glycol (PEG), trometamol, and P80.

Polyethylene glycol (macrogol)

While unusual, allergy to PEG has been increasingly reported in recent years [44]. Patients diagnosed with allergy to this excipient generally experience recurrent systemic reactions with several types of drugs. This observation, together with the fact that the presence of the excipient may vary between formulations (oral, parenteral, and commercial brand) has led to consider PEG as a hidden allergen in drugs.

Moreover, allergy workup for PEG is complex, since skin testing carries a risk of anaphylaxis, to the extent that they are considered as risky as exposure to a drug [45]. Intradermal test should be systematically avoided or performed with caution, especially in patients with comorbid conditions or history of severe reaction.

Cross-reactivity exists between PEG of different molecular weights, whereas others state that only high-molecular-weight PEG (>3500 Da) and that contained in parenteral drugs induce allergic responses.

Trometamol

Excipient in various contrast agents, including gadolinium and iodated agents, it is widely used in buffer solutions in topical products, cosmetic industry, and medications (fosfomycin, ketorolac, and some vaccines). One case of anaphylaxis induced by gadolinium has been reported [46].

Polysorbate-80

Also known as propylene glycol, Tween 80, and E433, polysorbate-80 (P80) is increasingly found in foods and drugs, ranging from biologic to oncologic products. There is some controversy over its cross-reactivity with PEG [44].

Drugs to which is has been thought to induce allergic reactions include vitamins, parenteral corticosteroids, etoposide, erythropoietin, darbepoetin, acyclovir, factor VIII, and monoclonal antibodies used in autoimmune diseases and cancer.

Prevalence of allergy to polysorbate-80 is very low, although it is expected to increase, since more than 70% of biologic drugs contain polysorbate 20 or 80. Some studies show that it only induces allergy when administered parenterally [47].

Adverse reactions to specific vaccines

Diphtheria, tetanus, and pertussis

Reaction may be due to a vaccine antigen or a preservative (thiomersal), adjuvants (aluminum salts), stabilizers (gelatin in the pertussis component), culture medium (casein), and other causes (latex).

Systemic reactions are uncommon and usually mild (fever, joint pain, and general malaise). There have been reports of cases of urticarial/angioedema with positive allergy workup for diphtheria and tetanus toxoid and of systemic allergic reactions (0.2%), some of which were associated with gelatin [19]. Anaphylaxis has also been reported after booster dose of diphtheria-tetanus, with positive results for both toxoids [48].

Successful desensitization has been reported in patients with allergy to vaccine toxoids [49]. Nevertheless, children who react to the diphtheria-tetanus vaccines may lose hypersensitivity over time. Therefore, future use of this vaccine should be evaluated [50].

Measles-mumps-rubella

Reactions may be caused by virus contained in the vaccine or components used during manufacture (gelatin, egg, dextran, neomycin, latex). Reactions to virus are mainly mild and transient.

Most allergic reactions are caused by gelatin. sIgE to gelatin has been reported in 92% of children who experienced a systemic reaction to the measles vaccine, and in up to 27% of those who experienced a reaction to the MMR [51]. Some patients who reacted to the MMR became sensitized owing to the gelatin in the DTaP vaccine [52].

Dextran, present in some MMR, can lead to severe immediate reactions; therefore, vaccines containing dextran have been withdrawn.

Influenza

Trivalent/quadrivalent inactivated influenza vaccines are generally harmless, although injection site reactions are common (> 1%). Fever, general malaise, and myalgia are also relatively frequent, especially in small children who have not been previously exposed to vaccine antigens [19].

Adverse reactions occur mainly to thiomersal, gelatin, and latex. Gelatin is found at concentrations of 250 µg/0.5 to 2000 µg/0.2 mL, although this is an uncommon cause of anaphylaxis.

Some studies have shown that the trivalent/quadrivalent inactivated vaccines, which have a low ovalbumin content, can be safely administered in patients with egg allergy [53, 54].

Yellow fever

Anaphylaxis to YF may be due to egg proteins and gelatin. While American reports show good tolerance to single dose in children with severe egg allergy, EAACI recommends an allergy study before administration [13].

Haemophilus influenzae type B

Reports of anaphylaxis after vaccination against Hib were not confirmed by allergy workup. In anaphylaxis after conjugate Hib vaccine administration, causative agent was the nontoxic conjugate protein of diphtheria toxin, CRM197. This finding highlights the value of allergy study, since it may be contained in other vaccines [55].

Hepatitis B virus

HBV may contain small amounts of yeast proteins (around 25 mg/dose) [16]. Allergic reactions are extremely rare. A review of more than 180,000 allergic reactions registered in the VAERS revealed that 15 could be attributed to yeast proteins, although sensitization was not confirmed [42]. An anaphylaxis has been reported after administration of the HBV, with the causative allergen being latex in the cap [56].

Poliomyelitis

It contains alfa-lactalbumin, rarely responsible for reactions in milk-allergic children [57]. Both injected and oral poliomyelitis vaccines contain traces of neomycin, streptomycin, and polymyxin b.

Varicella

It contains gelatin, responsible for anaphylaxis [52].

Human papillomavirus

In most cases, anaphylaxis appears after the first dose and are less frequent after the second one. Allergy is biologically possible owing to the viral particles (highly immunogenic when injected), residual yeast, and polysorbate-80, included in the quadrivalent vaccine as a stabilizer. However, no positive results have been recorded for any of the three components in cases of anaphylaxis. HPV is associated with syncope in adolescents [58].

Pneumococcus

There has been one report of anaphylaxis with pneumococcal conjugate vaccine 13, attributed to the nontoxic conjugate protein of diphtheria, CRM197 [15].

COVID-19 vaccines

Most frequently reported events are general disorders (fever and pain at the injection site), nervous system complaints (headache and dizziness), and musculoskeletal disorders (myalgia and arthralgia). However, other more severe effects have been reported, including anaphylaxis (Table 2) [59••].

A meta-analysis of adverse reactions to COVID-19 vaccines (Pfizer/Moderna) in adults confirmed a female predominance, for both anaphylactic and nonanaphylactic reactions [60••]. Reactions induced by a lipid derivative bound to PEG are more frequent in women. They are thought to be due to use of cosmetics or effect of hormones [61].

Local skin reactions are frequently reported with mRNA vaccines and include late local reaction ("COVID arm"), urticaria/angioedema, and self-limiting morbilliform rash. Other reported skin reactions include erythema multiforme, pernio (chilblains), herpes simplex reactivation reactions, and pityriasis rosea-like reactions, which mainly affect high-risk patients [62••, 63].

Table 2 Adverse reactions to COVID vaccines: most common vaccine type, incidence and possible pathogenetic mechanisms involved

Reaction	Associated vaccines	Incidence (× 100.000)	Origin	Mechanism involved	Clinical symptoms
Anaphylaxis	Pfizer Moderna Vector adenoviral AstraZeneca Janssen	1.1	PEG and Trometamol Polysorbate-80	Type I hypersensitivity IgE mediated Activation of MRGPRX2 receptor	Urticaria/angioedema Airway and/or breathing and/or cardiovascular compromise
Thrombosis/thrombocytopenia	Adenoviral vector vaccines: AstraZeneca Janssen	0.73 More common in women < 60 years of age, Norway	Immune response to viral stimulus	Activation of the platelets by the anti-PF4 antibodies that cause arterial/venous thrombosis and platelet consumption	Cerebral/abdominal thrombosis, low platelet count, D-dimer (> 4 times normal values) Abs anti PF4
Myocarditis Pericarditis	Pfizer Moderna	1.2 More common in young men 16–24 years	Spike protein generated	Cross-reaction of myocardial proteins with spike protein Non-immunological inflammatory response	Retrosternal chest pain, respiratory distress Troponin elevation C-reactive protein elevation EKG changes
Guillain Barré syndrome	Adenoviral vector vaccines: AstraZeneca Janssen	AstraZeneca 5.14 Janssen 0.78	Immune response to viral stimulus	Acute peripheral nerve neurological disease Abs antigangliosides Complement activation	Ascending weakness in legs and cranial nerves Flaccid paralysis Distal paraesthesia or quadriparesis with facial diplegia Cerebrospinal proteins increased with normal cellularity
Acute transverse myelitis	Adenoviral vector vaccine: AstraZeneca	Sporadic or unknown	Immune response to viral stimulus	Immune-mediated neurological disease	Quadriplegia or paraplegia
Acute disseminated encephalomyelitis	All	Sporadic or unknown	Immune response to viral stimulus or spike protein generated	Molecular mimicry that generates autoimmune response	Acute disseminated encephalomyelitis
Bell's palsy	Pfizer Moderna	Sporadic or unknown	Immune response to viral stimulus or spike protein generated	Molecular mimicry that generates autoimmune response	Unilateral facial paresis or paralysis

Table 2 (continued)

Reaction	Associated vaccines	Incidence (× 100.000)	Origin	Mechanism involved	Clinical symptoms
Rhabdomyolysis	All	Sporadic or unknown	PEG Trometamol Polysorbate-80	Exaggerated response to adjuvants	Myalgia, dark urine, high plasma creatine kinase, and urine myoglobin

Other reactions include persistent enlarged lymph nodes (both axillary and supraclavicular). This reaction hampered screening for and diagnosis of breast cancer, as it interfered with the mammogram and lymph node assessment [64]. COVID-19 vaccine should also be considered in follow-up of other malignant neoplasms with the potential to cause adenopathy at this level (head and neck cancer, lymphoma, and melanoma).

Severe allergic reactions have been reported, especially with the two mRNA vaccines (Pfizer/Moderna); reactions to viral vectors are less frequent [65–67]. For patients who have experienced anaphylaxis, Medicines Agencies and Scientific Societies recommend an allergy study before additional doses [68•, 69, 70]. Recently reported data indicate a frequency of three moderate-severe reactions per 100,000 vaccines administered. Women and subjects with history of adverse drug reactions seem to be at greater risk of moderate-severe adverse reactions to mRNA vaccines. Within the vaccines used, the most severe and common reactions reported were with Moderna, even though 5 times more Pfizer was administered in the study population (Audicana MT, personal communication, SEAIC, Zaragoza, Spain, October 20, 2021). The results are consistent with others that point to a non-allergic mechanism associated with the mRNA vaccines [71•]. Structures other than PEG may play a role in the allergenicity of these vaccines. This hypothesis would explain why patients previously diagnosed with allergy to PEG-asparaginase tolerated Pfizer vaccine [72]. Several authors suggest pathophysiological mechanisms other than IgE in these adverse reactions.

1. Complement activation-related pseudoallergy. This mechanism is based on the presence of pre-existing PEG IgG/IgM. Once the vaccine has been administered, they activate complement, thus generating anaphylatoxins (C3a, C4a, and C5a), which in turn degranulate mastocytes [73]. In a report on 22 patients, possible IgE-mediated anaphylaxis and complement activation-related pseudoallergy (CARPA) were evaluated after vaccination with mRNA vaccines. Authors concluded that reactions were probably due to the CARPA mechanism owing to anti-PEG IgG [71•]. However, further studies are necessary.
2. Phenomena associated with ACE-2 receptor stimulation. The S1 subunit of the spike protein, detected in the bloodstream up to 2 weeks after vaccination [74], can trigger thrombosis and other adverse inflammatory reactions, including activation of the kallikrein-bradykinin system [75]. This mechanism could explain episodes of urticaria/angioedema induced by COVID-19 and by vaccination, in much the same way as the mechanism involved in episodes caused by angiotensin-converting enzyme inhibitors.
3. Antibody-dependent enhancement and/or cytokine storm. Cytokine storm has three basic characteristics: high cytokine levels, acute systemic inflammatory symptoms, and organ failure. Antibody-dependent enhancement (ADE) has been associated with vaccines (syncytial respiratory virus, and dengue). Increased levels of biomarkers such as D-dimer, ferritin, and C-reactive protein are associated with a poor prognosis for COVID-19, and the spike protein S1 subunit can induce pro-inflammatory responses [76]. This syndrome has been recognized as vaccine-induced immune thrombotic thrombocytopenia, as confirmed first for the AstraZeneca vaccine [77] and later few cases have been reported with other vaccines [59••]. In the case of reactions with the first dose of the Pfizer vaccine, some authors propose a 2-step vaccination protocol with 0.05 mL, followed by 0.25 mL with a 30-min interval between the steps. However, the immune response induced should be tested [78].
4. Finally, the involvement of the activation of MRGPRX2 receptor as inducer of non-IgE-mediated anaphylaxis via pharmacologic agents cannot be excluded [79].

Diagnosis of hypersensitivity reactions to anti-infective vaccines

First, it is essential to grade the allergic reaction after vaccination, especially to determine anaphylaxis [80]. Serum tryptase assay in the 2 h following reaction and basal determination, 48 h after the reaction, can help to guide diagnosis. Significant increase in serum levels after reaction is a marker of mastocyte-mediated response [81].

Approach to suspected anaphylaxis

In patients with a history of allergic reaction to vaccines or vaccine components, every effort should be made to investigate the composition of the vaccine. Manufacturer's summary of product characteristics should be reviewed to identify causative agent. In reactions occurring after the first dose of the vaccine, possibility that the vaccine antigen is responsible decreases [82]. In this case, it is relevant to analyze a history of allergy and vaccine components other than vaccine antigen.

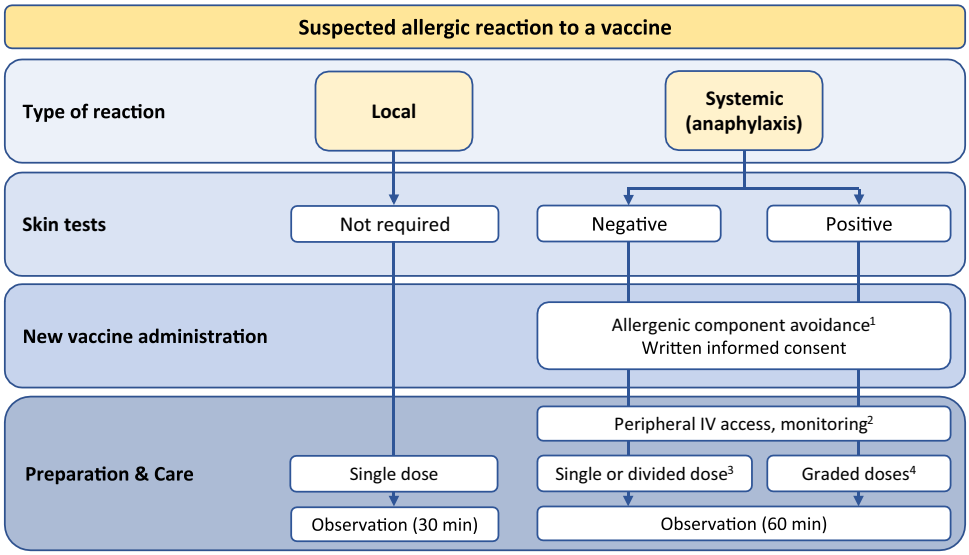
Need for subsequent doses

Patients who have experienced a severe reaction are considered at risk for a subsequent dose. However, without a diagnosis, allergy is only a presumption, and subsequent doses may be delayed without justification [83]. The need for future doses with the same vaccine or a vaccine containing similar components should be evaluated by the clinician. In serially administered vaccines, it should evaluate whether the severity of the reaction is reason enough for cancelling new doses.

Skin tests with vaccines and vaccine components

When a severe reaction to a vaccine is suspected and patient needs to be vaccinated in the future, it should be performed skin tests with vaccine or its components (Fig. 1) [84]. These tests should only be done by allergists trained.

First step should involve prick test using undiluted vaccine (1:1), unless the reaction that led to the workup was anaphylactic shock, in which case the vaccine must be diluted [19]. If the result is negative, intradermal testing (0.02 mL) should be performed with the vaccine diluted 1:100 in 0.9% saline solution. The 1:10 dilution could prove to be irritant and yield false positives, especially with the influenza, MMR, and varicella vaccines. The same is true of the 1:1,000 dilution for the DT, DTaP, and influenza vaccines [85].



[1] Use, if possible, an alternative vaccine without the allergenic component.
[2] Monitoring: pulse oximetry, blood pressure, ECG.
[3] Example of divided dose (two-dose split protocol): 10% and 90% of the dose at 30 minute-interval (Schuler JE, et al[84]).
[4] If subsequent doses are necessary, alternative vaccines are not available, and skin test result is positive, stepped administration of a new dose under observation can be evaluated after agreeing with the patient. Vaccine administration via graded doses protocol. Example for a vaccine of 0.5 mL volume: 0.05 mL dilution 1:10 (sterile water), 0.05, 0.1, 0.15 and 0.2 mL undiluted at 15 minute-intervals (Kelso, et al[19]; Mustafa SS, et al[94]).

Fig. 1 Proposed algorithm for diagnosis and management of patients with suspected allergic reaction to a vaccine

In the case of COVID-19 vaccines, it is sufficient to perform skin tests with remains of a vaccine that was constituted in the previous 6 h. These should be prick tests with the undiluted vaccine and intradermal tests with vaccine diluted 1:100. Skin tests with Pfizer vaccine have proven to be nonirritant [86]. Interpretation of intradermal tests with this vaccine may be limited, since patients who have received 1–2 doses may experience delayed reactions with induration [87]. These reactions are not relevant for diagnosis. In case of immediate positive result, skin testing with PEG can be considered. However, its clinical usefulness is limited [82].

Non-immediate local reactions can be assessed using patch tests. However, this approach is not essential when deciding on future vaccinations.

It is not necessary to perform a systematic preventive allergy workup for a vaccine before in persons who have experienced severe allergic reactions to drugs and/or foods [68•], except for patients with confirmed allergy after ingestion of gelatin. In this case, it would be appropriate to perform skin test with the gelatin-containing vaccine [51].

Serum = specific IgE to microbial and vaccine components

sIgE to microbial components is not useful in the diagnosis of allergic reactions to vaccines; in any case, testing is not available for all components [13]. When tests can be performed for some components (e.g., tetanus toxin, ethylene oxide, milk, egg, gelatin, yeast, and latex), its value for predicting an allergic reaction is low, because the patients with a positive result who experience reactions to a vaccine containing these components are scarce [53].

Administration of vaccines

Immediate reactions

Patients should be classified by the reaction severity [70].

Patients with mild reactions (erythema, self-limiting acute urticaria, and subjective mild spontaneously resolving airway symptoms) do not generally have to be evaluated. Most can tolerate a second dose [82, 88, 89]. In these patients, the vaccine should be administered in a controlled environment, and patient should be kept under observation for 30 min.

Patients with moderate or severe reactions should be assessed by an allergist. In the case of the mRNA-COVID-19 vaccines, a second dose is not recommended, and a non-mRNA vaccine should be considered [90, 91]. Some studies report that administering 2 different vaccines confers immunity. However, a greater frequency of adverse events has been observed (fever, myalgia, asthenia, and headache) [92, 93]. Skin tests can be performed to evaluate the administration of subsequent doses in serial vaccines. If the result is negative, new doses can be administered as a single dose or as a split dose in a center prepared to treat anaphylaxis with a 30-min observation period. If the result is positive, stepped administration of a new dose under observation can be evaluated after agreeing with the patient [91, 94]. If the vaccine is essential, such as tetanus, and more recently the COVID-19 vaccine, desensitization can be considered [49, 95]. An alternative is periodic evaluation of the presence of IgG as evidence of immune reactivity to a previous dose [96]. However, in persons vaccinated with fewer doses than recommended, protective antibodies may not be maintained over such a long period.

Delayed reactions

Urticaria/angioedema appearing hours or days after administration of a vaccine is unlikely allergy related [97]. If necessary, a new dose can be recommended following the usual procedure, with a 30-min observation period.

Patients with delayed local reactions can receive a second dose as in usual practice, preferably in the other arm [98]. When local reactions are

type IV, vaccine can be administered via deep intramuscular injection [24].

Facial edema has been reported with Moderna vaccine, as has the association with previous cosmetic soft tissue fillers, although data are limited. Nevertheless, vaccination should not be avoided in patients previously treated with soft tissue fillers [99]. Some authors propose a 4-–8-weeks interval between injection of filler and vaccination [100].

Conclusions

Vaccines play a key role in individual and public health by reducing the expansion, morbidity, and mortality of infectious diseases. Low incidence of adverse reactions to vaccines observed, even with COVID-19 vaccines, is another reason for not delaying or canceling subsequent doses. An allergy workup is only necessary in people with a specific allergy history or who have reacted to vaccines in the past. Analysis of vaccine components and clinical studies, including skin and in vitro tests, could help to identify the allergens involved and individuals at risk. All these approaches could help to eliminate barriers to vaccination and to plan the safe administration of vaccines.

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Declarations

Conflict of interest
Carmelo Escudero declares that he has no conflict of interest. Patricia Prieto-Montaño declares that she has no conflict of interest. Mª Teresa Audicana received financial support from ROXALL group in the preparation of an online presentation entitled "Updates on PEG-induced allergic reactions."

Human and animal rights and informed consent
This article does not contain any studies with human or subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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