Hypersensitivity Reactions to Vaccines: Current Evidence and Standards for SARS-CoV-2 Vaccines

Reações de Hipersensibilidade a Vacinas: Evidência Atual e Recomendações para as Vacinas SARS-CoV-2

Jóni Costa CARVALHO✉[1], Francisca CUNHA[1], Iolanda Alen COUTINHO[1], Carlos LOUREIRO[1], Emília FARIA[1], Ana Todo BOM[1]

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ABSTRACT

The first reports of hypersensitivity reactions following the rollout of COVID-19 vaccination programs have raised public concern. Given the recent availability and novel mechanisms of COVID-19 vaccines, there is limited data on possible hypersensitivity reactions. Although it seems rare, the incidence of anaphylaxis for approved COVID-19 vaccines has been suggested as being higher when compared to previous vaccines. Adequate risk assessment, recognition, classification, and management of hypersensitivity reactions is crucial to ensure safe immunization and avoid misinformation and vaccine hesitancy. In this review, we present an overview of the types of hypersensitivity reactions that can potentially occur due to vaccination and the possible allergenic components of COVID-19 vaccines, as well as a suggestion for causality and risk assessment for the BNT162b2, mRNA-1273 and AZD1222 vaccines.

Keywords: Anaphylaxis; COVID-19 Vaccines; Hypersensitivity; SARS-CoV-2

RESUMO

Após o início dos programas de vacinação contra a COVID-19, os primeiros relatos de reações de hipersensibilidade suscitaram alguma preocupação. Dada a recente disponibilidade e os novos mecanismos das vacinas contra a COVID-19, existem poucos dados relativos a possíveis reações de hipersensibilidade. A incidência de anafilaxia às vacinas COVID-19 parece ser mais elevada comparativamente a vacinas anteriores, embora seja igualmente rara. Uma avaliação adequada dos riscos, reconhecimento, classificação e correta abordagem das reações de hipersensibilidade é crucial para garantir uma imunização segura e evitar desinformação e hesitação na vacinação. Nesta revisão, apresentamos uma visão geral das potenciais reações de hipersensibilidade que podem ocorrer após a vacinação com as vacinas BNT162b2, mRNA-1273 e AZD1222, os seus possíveis constituintes alergénicos, bem como uma sugestão de avaliação do risco em doentes alérgicos e causalidade.

Palavras-chave: Anafilaxia; Hipersensibilidade; SARS-CoV-2; Vacinas contra COVID-19

INTRODUCTION

Vaccines are one of the most successful public health interventions.[1] They usually require years of development, but the urgent need for an effective vaccine to suppress the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) motivated its development in record time.[2]

Like any other medication, vaccines may cause adverse events, such as hypersensitivity reactions (HSRs).[1] Given its recent availability and novel mechanism of action, there is limited information on possible HSRs and their incidence. Although seemingly rare,[3] it is expected that many individuals will be affected given the massive vaccination rollout worldwide.[4]

Health care providers need to be made aware of potential HSRs caused by COVID-19 vaccines. After the warning by several drug regulatory agencies regarding the use of vaccines in patients with severe allergies,[3] immunization in these individuals must be approached with caution.[5]

It is essential to assess the risk of HSRs properly before vaccination. Distinguishing the HSRs from other adverse events following immunization (AEFI) is also of paramount importance.[4] An adequate classification of the adverse reactions simplifies pharmacovigilance and decreases misinformation and subsequent vaccine hesitancy.

We present a brief review about the definition and classification of adverse events and HSRs that can potentially occur due to vaccination and the possible allergenic components of COVID-19 vaccines, as well as a suggestion for risk and causality assessment of HRSs for the COVID-19 vaccines licensed in Europe to date [BNT162b2 (Pfizer/BioNTech®), mRNA-1273 (Moderna®), and AZD1222 (Oxford University /AstraZeneca®)].

MATERIAL AND METHODS

We performed a literature search on PubMed for relevant articles until March 2021 regarding hypersensitivity reactions to SARS-CoV-2 vaccines. Combinations of the following MeSH terms were used: 'COVID-19/SARS-CoV-2' and 'Vaccine/Immunization with 'Allergy', 'Anaphylaxis', 'Hypersensitivity, Adverse events' or 'Adverse reactions', resulting in a total of 258 results. After reading through all abstracts, 95 articles were selected. Articles were considered relevant if they provided clear information on hypersensitivity reactions to SARS-CoV-2 vaccines or the classification and management of hypersensitivity reactions to vaccines. Current recommendations from the regulatory agencies of

1. Allergy and Clinical Immunology Unit. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
✉ Autor correspondente: Jóni Costa Carvalho. joniccarvalho@gmail.com

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the European Union, the United States and several allergy societies (European Academy of Allergy and Clinical Immunology; World Allergy Organization; Portuguese, Spanish, German and British Societies) were reviewed.

DEFINITION OF ADVERSE EVENTS FOLLOWING IMMUNIZATION

An adverse event following immunization is any unexpected unpleasant medical event that occurs during or following immunization.[4,6] It can include any undesirable sign or symptom, abnormal laboratory finding or disease.[4,6]

The World Health Organization[6] and Council for International Organizations of Medical Sciences[7] developed the Safety Surveillance Manual and the Causality Assessment of AEFI to monitor and standardize vaccination campaigns. The manuals were recently revised and adapted for the assessment of COVID-19 vaccine-related AEFIs.[4] The adverse events were categorized according to their specific cause and classified as follows:

- Immunization anxiety/stress-related reaction;
- Immunization error-related reaction (inappropriate handling, prescribing or administration);
- Vaccine quality defect-related reaction (defects in the product);
- Vaccine product-related reaction (caused by the inherent properties of the vaccine components);
- Coincidental event (consistent temporal relationship but insufficient evidence for causality).

Immunization anxiety/stress-related reactions are the most frequently reported AEFI after vaccination. They occur typically among young adults but in mass campaigns their incidence increases, affecting all ages.[6,8] Due to the novelty of the SARS-CoV-2 vaccines and media warnings related to possible reactions, an even higher incidence rate is expected, presenting themselves as clusters (group cases of the same AEFIs related in time).[6,8] Clinical manifestations include anxiety and associated signs/symptoms like hyperventilation, vasovagal reactions, and dissociative neurological symptoms (e.g. non-epileptic seizures). They may manifest before, during, or after immunization.[4,6] Vasovagal syncope may simulate an anaphylaxis. It usually happens in the first five minutes, with transient hypotension, bradycardia rather than tachycardia (more typical of anaphylaxis), and resolving spontaneously.[1,8]

Vaccine product-related reactions include those imputed to the antigen activity itself or to other vaccine components (e.g., adjuvant, preservative or stabilizer).[4,6] Most of symptoms are related to reactogenicity (the typical inflammatory immune response to antigen exposure) and are thus expected and labelled. Due to the novelty of the SARS-CoV-2 vaccines, they are based only on pre-licensure studies. Unlabelled or unexpected adverse reactions can occur following implementation of vaccination.[2,4]

Serious adverse events (SAEs) are persistent and life-threatening events requiring hospitalization, or causing a significant disability/incapacity.[4] These events are very rare and determining if there is or not a causal relationship to the vaccine may be only possible once a very large number of individuals have been immunized. For example, during the Moderna® vaccine trials, some of the SAEs reported were myocardial infarction, cholecystitis, and nephrolithiasis.[9] The thromboembolic events reported after the Oxford University/AstraZeneca® vaccine were considered also SAEs.[9,10] A severe adverse reaction is a SAE, but although severe, does not usually result in long-term disabilities and are rarely life-threatening. Some examples are hypersensitivity reactions or seizures.[4,6]

HYPERSENSITIVITY REACTIONS TO IMMUNIZATION

Hypersensitivity reactions to immunization are exaggerated or inappropriate immune responses against the vaccine's antigen or other components. They are considered a subgroup of unpredictable AEFIs and are characterized by reproducible symptoms after exposure to the vaccine.[4,11]

The classification of HSRs to vaccines is based on the timing of the reaction (immediate or delayed), clinical extension (local or systemic) and their mechanisms.[1,11,12] They are summarized in Table 1.[12]

While all allergic reactions are immune-mediated, not all immune-mediated reactions are allergic. HSRs are considered allergic reactions when there is evidence of specific antibodies production or cellular responsiveness triggered by vaccine components to which the affected individual is sensitized.[12,13]

Most immediate HSRs are caused by the presence of immunoglobulin E (IgE) antibodies against a particular vaccine component. Typically, these reactions occur within minutes to four hours after exposure and can be mild to severe.[6] The most common symptoms are urticaria, angioedema, cough, stridor, wheezing, shortness of breath,

Table 1 – Potential immune-mediated reactions to vaccines; (Adapted from Chung E [12])

Mechanism of immune-mediated reaction	Clinical manifestation
IgE mediated	Urticaria, angioedema, rhinoconjunctivitis, bronchospasm, gastrointestinal symptoms (abdominal cramping, vomiting and diarrhea), anaphylaxis
Immune complex (IgG)	Large local reactions, serum sickness, vasculitis, myocarditis
T-cell mediated	Delayed urticaria, maculopapular exanthema, eczema, acute generalised exanthematous pustulosis (AGEP), erythema multiforme
Non-IgE mediated (pseudoallergic)	Urticaria, angioedema, gastrointestinal disorders, anaphylactoid reactions
Autoimmune/inflammatory	Thrombocytopenia, vasculitis, polyradiculoneuritis, macrophagic myofasciitis, rheumatoid arthritis, Reiter's syndrome, sarcoidosis (juvenile), bullous pemphigoid, lichen planus, Guillain-Barré syndrome, polymyalgia

nasal congestion, abdominal pain, vomiting, diarrhoea or hypotension.[11-13] Anaphylaxis is the most severe immediate allergic reaction. It is a rare life-threatening reaction with a rapid onset that involves multiple organs and systems.[5] A delay in treatment causes a higher risk of severe anaphylaxis and poor prognosis.[8]

Most delayed reactions attributed to vaccines are related with complement activation, immune complex deposition and T-cell-activation.[11-13] They usually occur hours to days after immunization, but some can occur up to two to three weeks after exposure. The most common manifestations are large local reactions due to immune complex deposition. Others include arthralgias, polyarthritis, serum sickness, and a variety of hematologic, gastrointestinal or renal manifestations. Delayed urticaria, maculopapular exanthema, erythema multiforme and acute generalized exanthematous pustulosis are examples of T-cell-mediated reactions.[1,11-13]

POSSIBLE ALLERGENIC COMPONENTS OF SARS-CoV-2 VACCINES

Theoretically, any compound of the vaccine may elicit HSRs. These are generally due to adjuvants and other excipients rather than the active component.[13] As SARS-CoV-2 vaccines are novel vaccines, the role of the antigen as a potential trigger cannot be disregarded.[5,14]

The main components of the SARS-CoV-2 vaccines considered potentially allergenic or immunogenic are polyethylene glycol (PEG) 2000, polysorbate 80 (PS80) and aluminium hydroxide.[14,15] The excipients and corresponding vaccines are shown in Table 2.[15-20]

Polyethylene glycol

Polyethylene glycol, also known as macrogol, is a widely used compound in medicinal, cosmetics and household products. It forms part of the composition of pills, suppositories, ointments, lubricants and conductive gels, and injectable solutions.[21,22] PEG is the active ingredient in laxatives and bowel preparations as it is poorly absorbed in the gut and physiologically inert by this route of administration.[21,22]

Their average molecular weight varies from 300 to 10000 Dalton (Da).[23] The Pfizer/BioNTech® and Moderna® vaccines contain PEG 2000, never used before in other vaccines to date. It is bound by PEGylation to a liposomal matrix, shielding the viral mRNA from immune-degradation, thus increasing its distribution and efficiency.[5,14]

There are case reports of immediate and delayed HSRs to PEGs in the literature.[21,22] Most of those are due to high molecular weight PEGs. Data on PEG 2000 associated HSRs are unknown.[22,24] The clinical manifestations are also related with molecular weight: low molecular weight (200 to 700 Da) is associated with immediate-type contact dermatitis and urticaria and high molecular weight (1000 to 7500 Da) is implicated in cases of anaphylaxis.[22,24] Additionally, individuals with HSRs to high molecular weight can tolerate low molecular weight PEGs. Triggering reactions appear to be route and dose-dependent and the amount tolerated

Table 2 – SARS-CoV-2 vaccines (approved in Europe or in late-phase studies, with available data of composition), adapted[15-20]

Developer (Name of Vaccine)	**Mechanism**	**Excipients**
BioNTech/Pfizer® (BNT162b2)	mRNA-based vaccine (encoding spike protein)	Lipids [(4-hydroxybutyl)azanediyl]bis(hexane-6,1-diyl)bis(2-hexyldecanoate); 2[(**polyethylene glycol**)-**2000**] -N,N-ditetradecylacetamide*; 1,2-distearoyl-sn-glycero-3-phosphocholin; cholesterol; monobasic potassium phosphate; dibasic sodium phosphate dihydrate; sucrose.
Moderna® (mRNA-1273)	mRNA-based vaccine (encoding spike protein)	Lipids [1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (**polyethylene glycol 2000**-dimyristoyl glycerol)]*; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine); **tromethamine***; acetic acid; sodium acetate; sucrose.
CureVac® (CVnCoV)	mRNA-based vaccine (encoding spike protein)	Cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine; **PEG-ylated lipid***; cationic lipid.
AstraZeneca/Oxford® (AZD1222)	Adenovirus vector, (containing gene expressing spike protein)	L-histidine; L-histidine hydrochloride monohydrate; magnesium chloride hexahydrate; **polysorbate 80***; ethanol; sucrose; sodium chloride; disodium edetate dihydrate.
Janssen/Johnson & Johnson® (Ad26.COV2.S)	Adenovirus vector (containing gene expressing spike protein)	Citric acid monohydrate; trisodium citrate dihydrate; ethanol; 2-hydroxypropyl-β-cyclodextrin; **polysorbate 80***; sodium chloride; sodium hydroxide; hydrochloric acid.
Sputnik V® (rAd26-S/rAd5-S)	Adenovirus vector (containing gene expressing spike protein)	Tris (hydroxymethyl) aminomethane; sodium chloride; sucrose; magnesium chloride hexahydrate; ethylenediaminetetraacetic acid disodium salt dihydrate; **polysorbate 80***; ethanol.
Novavax® (NVX-CoV2373)	Protein subunit (spike protein)	Matrix M1 adjuvant; **polysorbate 80***; sodium phosphate; sodium chloride.
Sanofi Pasteur and GSK®	Protein subunit (spike protein)	Sodium phosphate monobasic monohydrate; sodium phosphate dibasic; sodium chloride; **polysorbate 20***; disodium hydrogen phosphate; potassium dihydrogen phosphate; potassium chloride.
Sinovac Biotech® (CoronaVac)	Inactivated SARS-CoV-2	**Aluminium hydroxide***; disodium hydrogen phosphate; sodium dihydrogen phosphate; sodium chloride.

* Possible allergenic components; Information was current as of March 1, 2021

varies individually. Conversely, anaphylaxis is described for residual doses of PEG and for most of the types of formulations.[22,24]

The prevalence of HSRs to PEG is estimated to be rare. HSRs might be underreported, in part because of the complexity of this type of HSR and need for a high level of suspicion of the diagnosis.[21,23]

The typical patient with HSRs to PEG has a history of multiple reactions to drugs of different groups, with the same drug being tolerated in a different brand or formulation; or unclarified history of HSRs to medicines prescribed for treating constipation, corticosteroids, antihistamines or biologics; or HSR to multiple drugs without an identified cause after allergological work-up.[14]

The mechanisms of PEG HSRs are unclear, even though most of the described cases appear to be IgE mediated. Patients previously treated with drugs containing PEGs may have IgE or IgG antibodies to PEG.[14,23] *In vitro* PEGs have also been shown to induce complement activation via specific protein-coupled receptors, anti-PEG IgG or IgM, with consequent complement-mediated mast cell activation, and so, theoretically, may result in "complement activation-related pseudo-allergy".[21-25] These mechanisms can explain the non-IgE-mediated anaphylaxis described against PEGylated drugs.[25]

Polysorbates

Polysorbates are also components of many drugs and daily products but also of a high number of vaccines (e.g., hepatitis B, rotavirus, human papillomavirus, pneumococcal conjugate vaccine, influenza vaccines), biologics, monoclonal antibody treatments and chemotherapeutics.[22]

In contrast to PEG, polysorbate 80 and the analogous polysorbate 20 had been previously identified as a rare cause of allergic reactions to vaccines.[14,22,26] Several reports suggested IgE or T-cell-mediated mechanisms, though polysorbates are intrinsically anaphylactogenic, explaining most of the reactions in patients receiving polysorbate-containing medications.[23] Polysorbates are structurally related to PEG, and thereby they can potentially cross-react.[22]

Clinical manifestations range from contact dermatitis to systemic reactions such as urticaria or anaphylaxis. Examples of common involved medications are inhaled budesonide, topical acyclovir, human papillomavirus and influenza vaccines, adalimumab, erythropoietin and omalizumab.[22,26] Influenza vaccines, which contain an equivalent amount of polysorbate 80 as the Oxford University/AstraZeneca® vaccine, are not associated with a higher rate of HSRs when compared with other vaccines without polysorbate.[27]

Aluminium

Aluminium is the most common adjuvant added to vaccines and is used to enhance an immune response.[12] It is also part of many drugs and cosmetics as a colouring agent. Contact allergy, maculopapular rash, itching subcutaneous no-dules or persistent urticaria in the site of injection may occur following vaccines containing aluminium. Most are likely due to a delayed-type hypersensitivity and some due to an irritant reaction.[11-13] These are uncommon and generally begin 48 to 96 hours after vaccination. The subcutaneous nodules and pruritus may persist for months before they gradually disappear.[11-13]

Immediate reactions to aluminium are nearly absent. To our knowledge, there is only one report of anaphylaxis after a tetanus vaccination containing aluminium.[28]

Other vaccine components

The role of other vaccine components and the antigen itself should also be considered as potential triggers for hypersensitivity reactions. For example, tromethamine (in the Moderna® vaccine) was identified as the anaphylaxis trigger after an administration of a gadolinium-based contrast agent containing this excipient.[29]

Other alternative non-IgE pathways for activating mast cells and other inflammatory cells must also be considered. Liposomes can activate the immune system inducing an inflammatory response characterized by the release of pro-inflammatory and monocyte-derived cytokines, activating the complement, which is a known pathway for the liberation of anaphylatoxins.[30,31] It is also possible that the mRNA and the adenovirus vector expressing the SARS-CoV-2 spike protein as immunogenic agents can be themselves triggers to HSRs or hypersensitivity-like reactions.[2,25-29] Exaggerated reactogenicity may give rise to a cascade of immunological events, eventually leading to the aberrant activation of the immune system.[27,32]

ANAPHYLACTIC REACTIONS TO SARS-CoV-2 VACCINES

Anaphylaxis, as a life-threatening reaction, is worthy of particular emphasis.[8] According to the Safety Surveillance Manual and the Causality Assessment of AEFI Manual, anaphylaxis is considered an adverse event of special interest (an event which requires rapid medical intervention, monitoring and mandatory reporting to the regulatory agency).[4,6]

Data from the COVID-19 vaccines approved in the European Union to this date indicate that vaccine safety was overall similar to that of other viral vaccines.[2,33-35] Anaphylaxis has not been reported in the trials[33-35] and has not been reported either in trials of vaccines under review or in advanced stages of development.[16-19] However, it is not surprising given the exclusion of individuals with a history of severe adverse reactions associated with the vaccines or any component of their vaccines.[16-19,33-35]

After the start of the vaccination program rollout, several reports suggested a risk of allergic reactions greater than that of the conventional vaccines.[3,36] Anaphylaxis occurs at a rate of less than one per million doses for most vaccines and for the mentioned COVID-19 vaccines it is estimated at two to 8.5 times higher.[36-38] Based on information since January 18th 2021, the U.S. Food and Drug Administration (US-FDA) reported anaphylaxis/anaphylactoid reactions at a rate of 4.7 cases/million doses administered of the Pfizer-BioNTech®[3,31] and a rate of 2.5 cases/million doses

administered of the Moderna® vaccine.[3,39] On the 30th January 2021, the U.K. Medicines and Healthcare Products Regulatory agency reported a rate between 10 to 20 cases/million doses administered of the Oxford University/AstraZeneca® vaccine.[40] Despite the higher rates, anaphylaxis following vaccination was a rare event. For all vaccines, no anaphylaxis-related deaths were reported.[31,39,40]

The most commonly reported clinical findings of anaphylaxis to the vaccines were generalized urticaria, diffuse erythematous rash, angioedema, respiratory symptoms, airway obstruction symptoms and nausea.[3,31,39,40] In a report concerning 66 patients with anaphylaxis/anaphylactoid reactions after the Pfizer-BioNTech® and Moderna® vaccines, 94% were females, 79% reported a history of allergic reactions and 32% reported a prior episode of anaphylaxis to several exposures. The median time to symptom onset was six minutes (range 1 - 45 minutes) and endotracheal intubation was required in 10% of the anaphylactic events. Facial, tongue or laryngeal angioedema was present in 57% of these patients.[3]

RISK, CAUSALITY ASSESSMENT AND SUGGESTED APPROACH TO HYPERSENSITIVITY REACTIONS TO SARS-CoV-2 VACCINES

Pre-vaccination

Statements by the regulatory agencies from the European Union[41-43] and United States[43] and subsequently, several allergy societies[5,45-48] consistently affirm that vaccination is only contraindicated when there is a known history of allergy to any component of the vaccine or if there was a severe allergic reaction to the first dose.

The first approach to risk assessment is to identify the individuals fulfilling these criteria. Conducting a brief clinical history with questions aimed at identifying possible HSRs to the components of the vaccines is recommended. As mentioned before, an example of a patient with undiagnosed PEG or polysorbate hypersensitivity may have a history of unexplained anaphylaxis to multiple classes of drugs, to corticosteroids, anti-histamines, biologics or chemotherapeutics.[14,15,20-22] Vaccines not containing PEG 2000, such as the approved Oxford University/AstraZeneca®, may be an alternative for patients with HSRs to PEG.[43] There is a possible cross-reactivity between PEG and polysorbates, though rarely reported.[23,43] Previous immunizations with vaccines containing PS80 (e.g., influenza) can be taken as a reference for tolerability.[14,25,27] In case of history of allergy to any component, patients should be referred to an allergist for guidance and further investigation.[14,25,27]

Severity stratification of the assessed reactions is also crucial for risk assessment. Whereas regulatory agencies refer only to “allergy” to any component of the vaccine in safety recommendations, several allergy centres and allergy expert societies consider different approaches according to the severity of the past reaction.[5,45-49] Mild immediate or delayed reactions to vaccines or other injectable medications (suggesting PEGs, polysorbates or aluminium allergy) are considered low-risk and vaccination can proceed followed by a 30-minute observation period. Whereas moderate to severe allergic reactions are considered moderate- to high-risk and vaccination can proceed with precaution, after additional counselling by an allergist and followed by a 30-minute to 1-hour observationperiod.[5,14,45-49]

Vaccination is safe in patients with allergic rhinitis, asthma or eczema. It is also safe in patients with allergy to inhalant allergens, latex, insect venom, food or classic hypersensitivity reactions to drugs (confirmed, for a specific group of drugs, without suggesting excipient allergy).[5,45,47] Routine therapy with antihistamines prior to the first dose is not recommended, as these medicines do not prevent anaphylaxis and could mask symptoms, leading to a delay in treatment.[14,50]

In contrast, data from the first reports after COVID-19 vaccination campaigns raised concerns about the reported anaphylactic reactions. Most patients with confirmed anaphylaxis to mRNA vaccines had a prior allergy history and a third had a prior history of anaphylaxis. Despite the higher rates, it is still a rare event among patients with an allergy history.[3,36] For this reason, the recent consensus of the U.S. FDA and several allergy centres and allergy expert societies was to advise vaccination in centres with full resuscitation facilities and an observation period of at least 30 minutes for patients with a history of anaphylaxis due to any cause.[5,27,45,47] Importantly, as is the case for any medicine, anaphylaxis may occur after vaccination in the absence of a history of allergic disease.[1] For this reason, vaccination should always occur in centres with healthcare personnel trained in the identification and treatment of anaphylactic reactions.[5]

In patients with mast cell diseases or idiopathic anaphylaxis, vaccinations should only proceed under surveillance by allergists or other experts.[5,27,45,47]

Post-first dose vaccination

Risk assessment after a possible HSR to the first dose of COVID-19 vaccine depends on the nature and timing of the reaction. Individuals who develop potentially life-threatening HSRs, in particular anaphylaxis, should receive neither a second dose nor a vaccine with similar excipients.[5,27]

There is no data on the safety of administering the second dose of the vaccine in case of other allergic reactions of any severity. It is worth noting that several allergy societies advise individuals who, for example, just develop a localized urticarial skin reaction could receive the second dose using the same vaccine. In these cases, pretreatment with antihistamines one or two hours prior to the second dose can be considered.[14] Vaccination is recommended in a setting with full resuscitation facilities and an observational period of 30 minutes to one hour.[46,51]

Many immediate adverse events could be misdiagnosed as anaphylaxis due to similar clinical presentations of other AEFIs or to non-specific symptoms not observed by healthcare professionals.[4] At the time of reaction, a blood sample to measure serum tryptase may help in the confirmation of

anaphylaxis. Tryptase is a biomarker of mast cell activation, released following degranulation. The blood sample should be taken 30 minutes to two hours after the reaction, along with a baseline sample (at least 24 hours after resolution of symptoms). A transient elevation and return to the basal level confirm mast cell activation.[27,50] SC5b-9 is a terminal complement complex and has been suggested by the U.S. FDA as a biomarker for reactions mediated by complement activation.[50]

In doubtful cases, allergological work-up is the appropriate procedure to assess the risk of and eligibility for a second dose.[5,27,45,47]

Skin testing is the most used procedure to identify possible allergens. The positive predictive value is generally high although the negative predictive value is low for most drugs. The ideal timing for skin testing after a suspected reaction is after four weeks. Currently, there is no established diagnostic value for skin testing with PEG2000. However, PEGs with other molecular weights, polysorbates and aluminium can be tested.[5,22]

A graded vaccine administration protocol could provide an option for administration in doubtful cases, when the diagnosis of anaphylaxis to the first dose is unlikely, without transient elevation of serum tryptase or in mild immediate hypersensitivity reactions, like urticaria and/or generalized pruritus. Despite occurring with other vaccines, there is still no data to confirm the safety of this approach. It should only be performed by allergists in a hospital setting.[49]

CONCLUSION

SARS-CoV-2 vaccines must be closely monitored. An adequate classification and causality assessment of hypersensitivity reactions is crucial for management and to decrease the misinformation and growing vaccine hesitancy.

The main components indicated as potentially allergenic are polyethylene glycol, polysorbate and aluminium hydroxide. Individuals with a history of severe allergic reactions to these components should avoid vaccination. Most people with allergic diseases, not fulfilling the exclusion criteria, can receive COVID-19 vaccines. They should be monitored for at least 30 minutes after vaccination.

Individuals with mast cell diseases, severe or multiple drug allergy or previous anaphylaxis to other vaccines or unknown cause should be referred to an allergist for guidance and further investigation.

The median time to symptom onset of the reported anaphylaxis to SARS-CoV-2 vaccines was six minutes, ranged between one and 45 minutes. As anaphylaxis may occur in allergic and non-allergic patients, the vaccination setting should have healthcare professionals prepared for the recognition and treatment of anaphylactic reactions.

AUTHORS CONTRIBUTION

JCC: Main author. Literature research, conception and draf of the paper.

FC: Helped with literature research, contributed to drafting and critically revising the paper. Language polishing.

IAC: Supervised the drafting of the paper. Contributed to the critical review. Language polishing.

CL: Supervised the drafting of the paper. Contributed to the critical review.

EF: Contribution to the initial objective of the work and critical review of the paper.

ATB: Contribution to the initial objective of the work and critical review of the paper.

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COMPETING INTERESTS

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