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Received: 13 September 2021 | Revised: 17 December 2021 | Accepted: 3 January 2022

DOI: 10.1111/all.15241

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

POSITION PAPER

Allergies and COVID-19 vaccines: An ENDA/EAACI Position paper

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Abstract

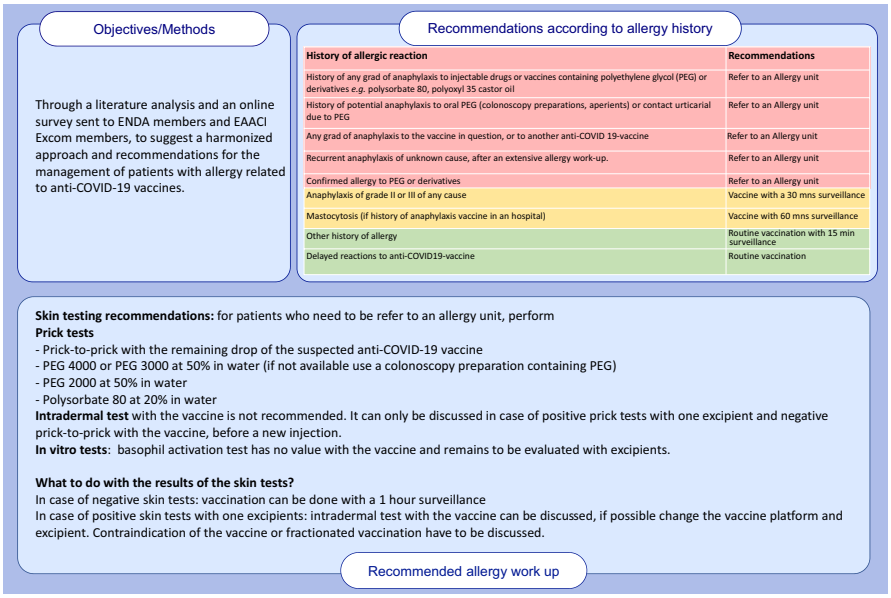
Background: Anaphylaxis, which is rare, has been reported after COVID-19 vaccination, but its management is not standardized.

Method: Members of the European Network for Drug Allergy and the European Academy of Allergy and Clinical Immunology interested in drug allergy participated in an online questionnaire on pre-vaccination screening and management of allergic reactions to COVID-19 vaccines, and literature was analysed.

Results: No death due to anaphylaxis to COVID-19 vaccines has been confirmed in scientific literature. Potential allergens, polyethylene glycol (PEG), polysorbate and tromethamine are excipients. The authors propose allergy evaluation of persons with the following histories: 1—anaphylaxis to injectable drug or vaccine containing PEG or derivatives; 2—anaphylaxis to oral/topical PEG containing products; 3—recurrent anaphylaxis of unknown cause; 4—suspected or confirmed allergy to any mRNA vaccine; and 5—confirmed allergy to PEG or derivatives. We recommend a prick-to-prick skin test with the left-over solution in the suspected vaccine vial to avoid waste. Prick test panel should include PEG 4000 or 3500, PEG 2000 and polysorbate 80. The value of in vitro test is arguable.

Conclusions: These recommendations will lead to a better knowledge of the management and mechanisms involved in anaphylaxis to COVID-19 vaccines and enable more people with history of allergy to be vaccinated.

KEYWORDS
allergy test, anaphylaxis, COVID-19 vaccine, mRNA vaccines, risk assessment



GRAPHICAL ABSTRACT
Through a literature analysis and an online survey sent to ENDA members and EAACI Excom members, to suggest a harmonized approach and recommendations for the management of patients with allergy related to anti-COVID-19 vaccines.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human coronavirus, has caused the global COVID-19 pandemic and public health crisis. COVID-19 vaccination is a major global preventive measure in the fight against SARS-Cov-2, and since December 2020, many million doses of various vaccines have been administered globally. Several vaccines have been developed, all in less than one year, and some of them use a technology not previously used in vaccine manufacturing. This means that experience about short-and long-term adverse effects, including the risk of allergic reactions, is limited.

The COVID-19 vaccines used are based on different vaccine platforms[1-11] (Table 1). The different platforms are based on nucleic acids, artificial vectors or recombinant viruses, virus protein subunits or disabled (live attenuated or inactivated) viruses.

The innovative platform based on messenger ribonucleic acid (mRNA) encoding spike protein that is encapsulated in lipid nanoparticles containing lipids and polyethylene glycol (PEG) is used in the production of the Pfizer-BioNtech (with PEG 2000), Moderna (with PEG 2000) and Curevac CvnCoV vaccines.[1,3,4] Recombinant viruses with coronavirus DNA coding for spike protein on an adenovirus backbone are non-replicating adenovirus vectors. The adenovirus can be from a strain that infects humans, as in Gam-COVID-Vac (Sputnik V) from Russia[5] or one that infects other species, such as the chimpanzee adenovirus used in Vaxzevria® manufactured by Astra Zeneca and the University of Oxford.[6] The Janssen Johnson & Johnson COVID-19 vaccine uses an adenovirus 26 vector.[7,8] Protein subunit vaccines based on virus-like particles of protein subunits like for a spike pre-fusion protein as in the adjuvanted recombinant protein nanoparticles used in the Novavax vaccine (Medicago).[9]

CoronaVac® (Sinovac) is a based on virus production from Vero cells, then inactivated and absorbed on aluminium hydroxide.[10]

Using PEG in vaccines is novel and PEG with a molecular weight of 2,000 (PEG 2000) serves as a stabilizer to prevent premature degradation of the nanoparticles in the Pfizer-BioNtech and Moderna vaccines.[2]

Other excipients of allergologic interest include tromethamine in the Moderna vaccine, aluminium hydroxide in the CoronaVac vaccine, disodium EDTA in the AstraZeneca vaccine, polysorbate 80 (PS80) in the AstraZeneca, Janssen and Novavax vaccines and polysorbate 20 in the Sanofi Pasteur/GSK vaccine.[1,2] The Novavax vaccine contains an adjuvant called Matrix M™ that consists of two 40-nm-sized particles, the Matrix-A and Matrix-C particles formed by formulating purified saponin from the tree Quillaja saponaria Molina with cholesterol and phospholipid.[9]

TABLE 1 Components and excipients of anti-SARS-CoV-2 vaccines[1-10]

Vaccine platform	Type of vaccine	PEG	Polysorbate 80	Polysorbate 20	Tromethamine	EDTA	Other components
BioNTech-Pfizer BNT162b2 *(Comirnaty)*	mRNA encoding spike protein	2-[(**polyethylene glycol)−2000**]-N,N-ditetradecylacetamide (ALC−0159)	−	−	−	−	((4-hydroxybutyl)azanediyl) bis (hexane−6,1- diyl)bis(2-hexyldecanoate) (ALC−0315) − 1,2-Distearoyl-sn-glycero−3-phosphocholine (DSPC) − Cholesterol − Potassium chloride − Potassium dihydrogen phosphate − Sodium chloride − Disodium phosphate dihydrate − Sucrose − Water for injections
Moderna mRNA−1273 *(Moderna COVID−19 vaccine)*	mRNA encoding spike protein	SM−102, 1,2-dimyristoylrac-glycero−3-**methoxypolyethylene glycol−2000 [PEG2000**-DMG]	−	−	+	−	Cholesterol − 1,2-distearoyl-sn-glycero−3-phosphocholine (DSPC)− Acetic acid − Sodium acetate − Sucrose
CureVac, CVnCoV	mRNA	PEGylated lipid	?	?	?	?	cholesterol, 1,2-distearoyl-sn-glycero−3-phosphocholine (DSPC), and a cationic lipid
Astra Zeneca AZD1222 *(COVID−19 vaccine Astra Zeneca, Vaxzevria)*	ChAdOx1-SnCov−19 Non replicating chimpanzee adenovirus expressing spike protein	−	+	−	−	+	Histidine − L-Histidine hydrochloride monohydrate − Magnesium chloride hexahydrate −**Ethanol** − Sucrose − Sodium chloride − Water for injections
Janssen Ad26.COV2.S vaccine *(Johnson and Johnson COVID−19 Vaccine)*	Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full length and stabilized SARS-CoV−2 spike (S) protein	−	+	−	−	−	citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), sodium chloride, water for injection.
Gamaleya Research Institute of Epidemiology and Microbiology Gam-COVID-Vac *(Sputnik V)*	Recombinant replication-deficient adenovirus (rAd)-based vaccine	−	+	−	−	+	Tris-(hydroxylmethyl)-aminomethane Sodium chloride Sucrose Magnesium chloride hexahydrate **Ethanol** 95% Water

(Continues)

TABLE 1 (Continued)

Vaccine platform	Type of vaccine	PEG	Polysorbate 80	Polysorbate 20	Tromethamine	EDTA	Other components
Medicago Novavax NVX-CoV2373	Protein based vaccine, recombinant nanoparticles with antigens derived from the full length spike protein	-	+	-	-	-	**Saponin-based Matrix M 1** adjuvant
Sanofi Pasteur and GSK, protein Spike subunit	Protein based vaccine	-	-	+	-	-	Sodium phosphate monobasic monohydrate, sodium phosphate dibasic, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride
Sinovac CoronaVac	Inactivated vaccine prepared on Vero cells	-	-	-	-	-	**Aluminium hydroxide**, phosphate buffered saline, water solution

Severe allergic reactions to vaccines are very rare and can be caused by the vaccine itself or its excipients.[11-14] In December 2020, the first cases of anaphylaxis were reported after the Pfizer-BioNTech COVID-19 mRNA vaccination, but no deaths as a result of anaphylaxis have been reported so far in the scientific literature.[15,16] The incidence of anaphylaxis following Pfizer-BioNTech COVID-19 vaccination has been reported to be 11.1 per million doses administered, about 10-fold higher than for other vaccines.[15,16] The incidence of COVID-19 vaccine anaphylaxis was estimated at 7·91 cases per million doses.[17]

The mechanisms behind these reactions are unclear unknown, but the excipients have been suggested as a potential cause, in particular PEG-2000.[18-21] A Center for Disease Control (CDC) report on the Moderna vaccine suggests an incidence of anaphylaxis of 2.5 per million cases.[22] For reactions to both mRNA vaccines, there was a very strong female predominance possibly reflecting that initial vaccination schemes primarily included healthcare workers. Symptom onset was within 10–15 min in the majority of cases and commonly manifest as diffuse or generalized rashes, periorbital oedema, tongue swelling and feeling of throat closure.[15,16] The Paul Ehrlich Institute (PEI) in January 2021 received reports of 17 patients in Germany with anaphylactic reactions to mRNA vaccines, and all survived the reactions without harm.[2] In the majority of reported reactions to the mRNA vaccines, there was a history of unspecified allergy to either food, drugs, insects, other vaccines, etc., but the clinical significance of this anamnestic data is uncertain. In March 2021, in France there were 159 cases of anaphylaxis (grades I or II) after 6 282 094 injected doses of the Pfizer-BioNTech vaccine, *that is* an incidence of 2.53/100 000.[23] In the UK, 246 severe anaphylaxis reactions were reported in March 2021 after 13.6 million of Pfizer-BioNTech doses (1.89 reports/100 000 doses).[24]

With the Astra Zeneca vaccine, in March 2021, in Australia, 5 cases of anaphylaxis occurred after more than 20 000 doses administered,[25] in France, the incidence was 0.6 /100 000 after 1 430 790 doses,[23] and in the UK, 390 cases were reported among 15.8 million doses administered (incidence 2.47 /100 000).[24]

It is important to consider that adverse reactions to the vaccines including suspected allergic reactions are scored using the Brighton collaboration case definition, developed specifically for adverse reactions to vaccines.[26] This system has not traditionally been used to classify anaphylaxis to other causes and may overestimate the incidence of anaphylaxis compared to other scoring systems traditionally used for anaphylaxis.[26]

Allergists all over the world are confronted with referrals of patients with suspected allergic reactions to the vaccines, and with pre-vaccination concerns about the risk of allergic reactions to COVID-19 vaccination, both from patients and healthcare workers. It is essential that we share our knowledge across borders so that we can utilize the experience of others and ensure that as many people as possible can receive the vaccine. There is an urgent need for recommendations to specify clearly, which patients require precautions for COVID-19 vaccination. The EAACI Research and Outreach

Committee has recently published a statement on the diagnosis, management, acute treatment and prevention of severe allergic reactions to COVID-19 vaccines[27] stating that unless the patient has a history of an allergic reaction to any of the vaccine components, there is no contraindication to administer the currently approved COVID-19 vaccines. There is a need for recommendations for allergological work-up to determine the mechanisms behind reactions. In order to reach a consensus as large as possible, an online questionnaire was prepared and sent by email to European experts in the field of drug allergy concerning the management of patients with history of severe allergy and patients with a suspicion of hypersensitivity to any COVID-19 vaccine. Through the synthesis of data from the rapidly expanding literature[1,2,27-29] and the analysis of the survey, the objective was to provide harmonized practical recommendations for the management of patients suffering from allergy or having a suspicion of hypersensitivity to COVID-19 vaccines.

The objectives of this paper are to suggest a harmonized approach and recommendations for the management of patients with allergy related to COVID-19 vaccination. These recommendations are based on data from the rapidly expanding literature,[1,2,27-29] the experience of the authors of the paper and a survey sent to members of the European Network of Drug Allergies (ENDA), the board of the EAACI Drug Allergy Interest Group (DAIG) and EAACI Executive Committee.

2 | METHODS

A Pubmed search has been done with the name of each vaccine likely to be available for use in Europe and the following terms #COVID-19 vaccine allergy, #COVID vaccine hypersensitivity, #COVID-19 vaccine hypersensitivity, #COVID-19 vaccine adverse effects, # polyethyleneglycol hypersensitivity and # polysorbate hypersensitivity. All papers concerning anaphylaxis reactions or hypersensitivity reactions to COVID-19 vaccines have been analysed. The literature analysis was stopped in April and then completed in July following the EAACI executive committee advice and recommendations.

An online survey was conducted. An online questionnaire was prepared by the members of the board of the EAACI Drug Allergy Interest Group (DAIG), then sent by email to all members of the European Network of Drug Allergies (ENDA), members of the EAACI Executive Committee in February 2021. The questionnaire included 32 questions relating to the available vaccines, how administered, in which location (dedicated clinic or department, vaccination centre), the existence of national recommendations for vaccination of allergic patients, the profile of the patients for whom allergy consultation was requested before vaccination, the management and allergy work-up in the event of an allergic reaction after a first injection of a COVID-19 vaccine (On line-depository).

From the results of the survey and analysis of the literature, we have proposed updated and detailed recommendations for vaccination of patients with history of allergy. In addition, we have suggested allergology work-up for patients with a suspicion of sensitization to vaccine excipients (primarily PEGs or PS) or with a hypersensitivity to a COVID vaccine. Following the analysis of the results of the allergy work-up, an algorithm with practical recommendations for continuing the vaccination procedure was written, updated finally endorsed by all participants in April 2021, who are the co-authors. These recommendations were updated and corrected after a review and advice of the EAACI Excom in July 2021.

3 | RESULTS

3.1 | Literature analysis: characteristics of excipients in COVID-19 vaccines and their allergenic potential

3.1.1 | Polyethylene glycols

PEG, also called PEG or macrogols (E1521), are manufactured by polymerization of ethylene oxide with water. They are amphiphilic linear polymers, consisting of a repeating unit of ethyleneoxide (-O-CH2 -CH2). In drug formulation, the term macrogol or 'PEG' is used in combination with a numerical value, indicating their mean molecular weight (MW).[30] PEGs with a mean MW up to 400 are liquids, PEGs with 1000 to 2000 MW are viscous and above 3000 MW, PEGs are in solid form. All PEGs are soluble in water.

In cosmetics, a different nomenclature is used and the number of a PEG refers to the average number of ethylene oxide units (MW = 44). Thus, the same PEG may be called PEG 3350 (approximately 75 × 44) in a drug or PEG 75 in cosmetics.[30] PEG-2000 in drugs is called PEG-40 in cosmetic nomenclature. PEG derivatives are also widely used, and cross-sensitization has been suggested between PEGs, polysorbates (PS) and poloxamers.[30] They include PEG ethers, PEG fatty acid esters, PEG amine ethers, PEG castor oil, PEG-propylene glycol copolymers, PEG sorbitans (PS) and PEG soy sterols.

PEG ranges in molecular weight from 200 to 35 000[30] PEGs under 400 MW are absorbed through intact gastrointestinal mucosa, but less than 10% of PEG 3300 MW are absorbed. Only PEGs under 3350 MW are absorbed through intact skin. There are reports of contact dermatitis due to PEG derivatives such as PEG-22/dodecyl glycol copolymer.[31-33]

There is no evidence of cross-reactivity with propyleneglycol or polypropyleneglycol.[34]

PEG hypersensitivity may be provoked via multiple exposure routes including oral, intramuscular, intra-articular and intravenous. Patients may also report immediate skin symptoms on exposure to skin care products especially if applied on broken skin such as during shaving.[30]

Anaphylaxis to PEG contained in laxatives/colonic preparations, aperients, depot steroid injections, tablets or linked to other therapeutic enzymes or proteins such as PEGylated asparaginase have recently been reported.[30,35-39]

Contact dermatitis induced by PEG seems to be rare. Even in a population with a high risk of contact dermatitis, as patients with chronic leg ulcers, PEG seldom induce sensitization. Among 309 patients with chronic leg ulcers, only two (0.6%) had a positive patch test, and in another series, patch test to PEG glycol 6 and 32 was positive in 3/423 cases (0.7%).[40,41]

The immunological mechanisms involved in PEG and PS anaphylaxis are poorly understood.[16,30,42-44] An IgE-mediated mechanism has been suggested.[16,30,45-48] Anti-PEG immunoglobulin G (IgG-PEG) have been detected in patients receiving PEG-conjugated therapeutic proteins,[36] but have not been studied in cases of unconjugated PEG anaphylaxis.[46] Anti-PEG IgE and IgG have recently been reported in patients with severe reactions to PEG contained in injectable drugs, using a sensitive technique based on flow cytometry.[47] These anaphylactic mechanisms may be related to direct activation of the classical complement pathway by IgM or IgG-PEG resulting from mast cell activation via the C3a and C5a complement fractions (complement activation-related pseudoallergy, CARPA).[46,48,49] Recently, CARPA has been demonstrated for PEGylated nanodrugs.[44,50] PEGylated nanodrugs can activate the complement pathway,C3a and C5a binding to anaphylatoxin receptors can induce mast cell degranulation. Moreover, PEGylated nanoparticles through their direct link to pattern recognition receptors may have a synergistic effect for mast cell degranulation.[44,50]

3.1.2 | Polysorbates

PS 80 is commonly used in food, cosmetics and drug formulations as a solubilizer, stabilizer or emulsifier.[51] PS 80 is a non-ionic, hydrophilic polyethoxylated surfactant, also called PS 80, E433, Tween 80, polyoxyethylene sorbitan monooleate. It is a fatty acid ester of polyoxyethylenesorbitan. PS 20 and 60 (Tween 20 and 60) are also included in this family of surfactants.

Cremophor-EL (CrEL =polyoxyethylated castor oil in 50% ethanol) activate the complement system in vitro, in normal human serum and plasma. CrEL and PS 80 activate the complement system to a similar extent. Therapeutic side effects, such as acute hypersensitivity and systemic immunostimulation, caused by intravenous medicines containing polyethoxylated detergents, can be attributed to complement activation-derived inflammatory mediators.[52] IgE-mediated reactions with positive intradermal tests (IDT) with PS 80 at 0.004 mg/mL in two patients sensitized to PS 80 containing injectable corticosteroids have also been reported.[42] Cross-sensitization in the skin tests between PS 80 and PEG with positive prick tests to PS 80 and PEG have been reported,[18,45] this was the case in a teenager who developed anaphylaxis after the first injection of omalizumab which contains PS 20.[53]

Polyoxyl castor oil (polyethoxylated castor oil, Kolliphor EL, CrEL) is prepared by reacting ethylene oxide with castor oil in a ratio of 35:1; thus, it is a PEG. It is used as a pharmaceutical solvent for many drugs, such as ciclosporin, and also co-administered with anticancer drugs, such as paclitaxel.

Serious forms of hypersensitivity reactions have been reported in a number of medicines containing non-ionic polyethoxylated surfactants, including paclitaxel with CrEL, docetaxel, erythropoietin, human papillomavirus vaccine with PS80[42,54,55] and intravenous fosaprepitant.[51]

3.1.3 | Disodium EDTA

Disodium EDTA, a polyamino carboxylic acid, is contained in Astra Zeneca vaccine. EDTA salts have applications in foods, manufacturing, cosmetics, and pharmaceuticals as preservatives and stabilizers. Contact dermatitis to EDTA has been reported with cosmetics and contact lens solution.[56] Anaphylaxis to EDTA seems rare but has been reported. Basophil activation tests (BAT) were positive to EDTA in a patient with anaphylaxis to radiocontrast media and local anaesthetics all containing EDTA as excipient.[54] The IDT with EDTA at 0.3 mg/mL was positive.[56]

3.1.4 | Trometamol, tromethamine

Trometamol or tri-(hydroxymethyl) aminomethane is used to prevent the formation of uric acid and cystine stones, and it is also used as excipient in drugs (NSAIDs, contrast media for CT and MRI scans). It is contained in Moderna mRNA vaccine. Ketorolac tromethamine can induce anaphylaxis; one case tested positive in IDT from 0.01 to 1 mg/mL (3 negative controls).[57] No IDT with pure trometamol has been done.[57,58] In our experience, trometamol can be a skin irritant. Prick test with trometamol at 16.5 mg/mL induces false-positive results but seems specific at 1.65 mg/mL (10 negative controls).

3.2 | Results of the online survey

The survey concluded at the end of February 2021, and we received 64 answers from 19 countries: Austria (1), Czech Republic (2), Denmark (1), Germany (4), France (5), Italy (10), Kuwait (1), Lithuania (1), Turkey (6), Netherlands (2), Poland (4), Portugal (5), Romania (2), Serbia (1), Slovenia (2), Spain (8), Switzerland (3), Sweden (2) and UK (4).

A summary of the main findings at the end of February 2021 is listed below. Detailed results can be found in the online deposit.

Analysis of 62 returns, most centres and countries have available the Pfizer BioNTech (92.2%), Moderna (84.4%) and AstraZeneca (84.4%) vaccines. Only few countries had other adenovirus vector Janssen (6;3%) or Sputnik V (1.6%, 1 centre in Serbia) or protein subunit vaccine Sinovac (9% of the centres, only in Turkey and Serbia).

In most countries, vaccination can be done in a vaccination centre (VC) outside of a hospital (55, 85.9%). Vaccination in a hospital setting is possible in 71.9% of the centres (46/62) and for healthcare workers only in 4 more centres. Vaccination in a hospital setting for any patients is possible only for a limited number of centres (18, 28.1%). Vaccination in an allergy clinic setting is possible only for

19 centres (29.7%). Vaccination can also be done in nursing homes, primary care centres, senior residences and family care physician's office.

Vaccinating people with a history of allergies or to manage hypersensitivity reactions to COVID-19 vaccine, out of the 64 returns, 54.7% replied that national recommendations were available, but only a limited number of countries had published recommendations, such as in Germany[2] or UK.[59]

In patients with a history of only skin symptoms to a non-COVID vaccine, 36/62 (58.1%) participants consider that vaccination can be done in a vaccination centre, but the majority advised extending the observation time to 30–60 min, 27.4% suggested that vaccination should be performed in an allergy clinic setting and 14.5% suggested immunization in a hospital VC.

In patients who develop grade II or higher anaphylactic reactions, after a non- COVID vaccine 46/62 (74.2%) returns recommended to vaccinate in a hospital VC, preferably in an allergy department for 43.5% of the participants and only 25.8% suggested vaccination in a vaccination centre.

In a patient with a history of anaphylaxis after administration of an injectable drug, where PEG, or PS as ingredients cannot be excluded (e.g. drug not known sufficiently to get drug leaflet), 53/59 (89.8%) of the centres recommended a vaccination in a hospital VC, in an allergy department in 71.2%.

In a patient with a history of anaphylaxis after administration of an injectable drug that does not contain PEG, PS or tromethamine, 32/62 (51.6%) recommended vaccination in any vaccination centre.

In a patient with a history of anaphylaxis after administration of a non-COVID vaccine or due to an injectable drug, in case of vaccination in an Allergy Unit 83.9% of the 56 participants recommended to test vaccine excipients before vaccination, in patients who have anaphylaxis to an injectable drug containing PEG, PS or tromethamine.

In a patient with a history of anaphylaxis after administration of a non-COVID vaccine or due to an injectable drug (potentially) containing PEG or PS, in case of negative skin tests with vaccine excipients and vaccination in an Allergy Unit, 22/60 responders (36.7%) would vaccinate with the full dose and 33/60 (55%) suggested vaccinating with fractionated doses. The majority suggested observation time of 1–2 h.

In a patient with history of anaphylaxis with (additional) extracutaneous involvement of unknown cause (idiopathic anaphylaxis), 37.7% of the 61 answering centres suggested to perform skin tests with excipients, 45.9% recommended a vaccination in a hospital VC, in an allergy unit for 19.7%.

In a patient with history of grade II or III anaphylaxis with (additional) extracutaneous involvement of unknown cause (idiopathic anaphylaxis), the breakdown from 59 answers to the question whether COVID-19 vaccination can be done in an allergy unit, 29 (49.2%) participants would vaccinate with the full dose with an observation time of 1 h, 22 (37.3%) suggested fractionated doses. Some colleagues emphasized that all allergy centres that provide COVID-19 vaccination are able to manage any anaphylactic reaction; thus, fractionated doses could be avoided.

In case of anaphylaxis with (additional) extracutaneous involvement (grade II or III) induced by a drug taken orally (but not a laxative or a bowel preparation), containing PEG or PS as excipients in its formulation, without any skin test with excipients, 37/62 participants (59.7%) recommended performing drug skin tests, 17.7% directly contraindicate mRNA vaccines, while 29 (46.8%) would vaccinate with the full dose with at least 30 min observation, and 15 (24.2%) answers recommending vaccinating in an Allergy Unit.

In a patient with a high risk for COVID-19 infection, who has a history of urticaria or systemic skin reaction after administration of an injectable drug containing PEG or PS and who has positive skin tests for PEG or PS, the majority of the participants (57.6%) would not vaccinate the patient. Among 59 centres, 42.4% of the participants would vaccinate with fractionated doses.

In a patient with systemic mastocytosis and no history of anaphylaxis due to injectable drugs or vaccine, 39.3% of the 61 participants considered that mastocytosis patients with no history of anaphylaxis can have injection in any vaccination centre, 28 (45.9%) would prefer a vaccination in a hospital VC and in an allergy unit in 21.3% of the answers.

In a patient with an uncontrolled asthma and no history of anaphylaxis due to injectable drugs or vaccine, 38.7% of the participants would vaccinate in a VC as for non-asthmatic patients, 28/62 (45.1%) preferred to vaccinate in a hospital VC and 18 (16.1%) in an allergy department.

Among 64 participants, 62.5% would consider vaccination in fractionated doses, but twenty-two participants contraindicated a fractionated vaccination, with the following reasons:

fractionation reduced volume of the vaccine solution (dead volume in the needle) (4/18.2%); concerned about the efficacy of the vaccine while waiting after thawing it up (5/22.7%); strictly adhere to vaccination protocol, an allergy team knows how to manage an anaphylactic reaction, (11/50%). The other answers all detailed in the *online deposit* took into account an improper use of vaccine; its loss of efficacy, the absence of official recommendation or too little data for doing fractionated injection or the small volume of available vaccine solution to fractionate it.

Among 44 participants who considered fractionated vaccination, different fractionated dose protocols were proposed. The results are reported in Table 2. Most of the participants (26, 59%) proposed 1/10 then 9/10 of the vaccine dose (usual full volume for Pfizer vaccine being 0.3 mL and for Moderna 0.5 mL). In case of graded injection, only 5 (11.4%) injected the 2 doses in the same arm. Seven (16%) participants also proposed a desensitization protocol; details are also given in Table 2. Two participants emphasized that 0.3 mL is so small, that it is too inexact to use 1/10 (0.03 mL). Hence, they recommended not to inject less than 1/3 of the usual volume; thus, 0.1ml (1/3) should be the first fraction for Pfizer vaccine.

Considering fractionated doses in specific patients who are skin test positive, 24/28 (85.7%) participants would inject 1/10 of the volume then 9/10 (with a 30 min interval for 50% of the participants) and 4 (14.2%) would inject 1/3 of the volume then 2/3. The proposals are summarized in Table 2.

Fractionated doses	Interval between each dose (min)	Percentage in the survey (44 answers)
Fractionated doses proposed in the survey		
Injection of 1/10 of the volume and 9/10 *	30	16 (36.4%)
Injection of 1/10 of the volume and 9/10 *	60	10 (22.7%)
Injection of 1/3 of the volume and 2/3	30	7 (15.9%)
Injection of 1/3 of the volume and 2/3	60	4 (9.1%)
Propositions given by participants for desensitization procedures (in open text)		
injections in an at least 6–12 steps with 30 min intervals with a strict surveillance	(no detail given)	
Placebo, then 10% (0.03 mL), 30% (0.09 mL) and 60% (0.18 mL)	30	
1/10 (0.03 mL)+ 2/10 (0.06 mL)+3/10 (0.09 mL) +4/10 (0.12 mL)	30	
Performed, adapted from the publication of Kelso et al.[13] in 5 steps, taking into account the total ml of the vaccine (*e.g* 0.3 mL of Pfizer BioNntech and 0.5 mL of Moderna require different adjustment).	15 (followed by an observation period of 60 min after the last injection)	
For Pfizer 0.05 ml+0.1ml +0.15 ml For Moderna 0.05 mL;0.1 mL; 0.15 mL; 0.2 mL	15	

TABLE 2 Methods proposed by participants for fractionated (graded) vaccine doses, Kelso et al.[13] recommend for any vaccine solution to inject graded doses as follows. If the full vaccine dose is normally a volume of 0.5 mL, the patient is first given 0.05 mL of a 1:10 dilution and then given full-strength vaccine (at 15-min intervals) at doses of 0.05, 0.1, 0.15 and finally 0.2 mL, for a cumulative dose of 0.5 mL.* Some participants point out that it is impossible to be precise for a volume to 1 / 10th. One third of participants contraindicate to fraction

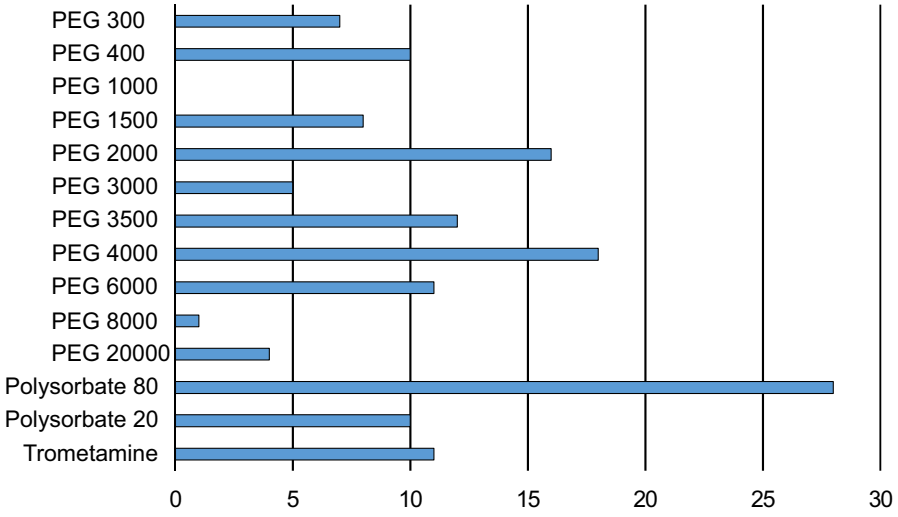


FIGURE 1 Availability of pure excipients for skin testing in 42 participating centres (Survey results). PEG: polyethyleneglycol

Skin tests to ascertain whether vaccination is possible from 64 returns showed that in 51.6% of the centres, 38 (59%) would test with the vaccine and 81.6% perform prick to prick with the residua in the vaccine vial. 65.2%[30] of the 46 returns did not perform IDT using the same vial of vaccine.

Considering the availability of PEG or PS for skin tests in their centres, 62.5% of the 64 participants were able to tests with the pure excipients of the vaccines. The list and percentage of the excipients tested by 42 participants are summarized in Figure 1. The main excipients tested were PEG 4000 (42.9%), PEG 2000 (38.1%) and PS 80 (66.7%).

Concerning the possibility for testing excipients of COVID-19 vaccines, among 64 answers, 51.6% of the participants tested with drugs containing the same excipients as the vaccines, but among 48 responders, 54.2% did not test with long-acting corticosteroids and 74.5% of 51 did not use other vaccines containing excipients of interest for IDT.

In the case of delayed urticaria occurring more than 4 h after injection, among the 60 answers there were various approaches. In 32 centres, no skin tests were done but they vaccinate in a hospital centre (in allergy unit or another department) was proposed in 21/32 cases (65.6%). Tests were done in 25 centres, recommending in case of negative results to inject the following dose under antihistamine treatment in 9/25 cases (36%), with an hospital observation in 14/25 cases (56%) and 3-h duration in 12 cases.

In some centres, it was possible to perform skin tests, if negative, to inject on same day the full vaccine dose with a 30 min hospital observation. Among 43 answers, in case of negative skin tests with

vaccine and excipients, 30 centres (70%) proposed to inject the vaccine 30 or 60 min after the reading of the skin tests.

In case of delayed exanthema, 44 of the 64 participants (68.8%) would not do patch tests with the vaccine, 48/64 (75%) would inject the full dose, after prescribing topical corticosteroids for 39 of them (60.9%), but 13 (20.3%) preferred to switch to another vaccine of a different vaccine platform.

Considering in vitro tests, only 37.5% of the 64 participants are able to perform in vitro tests, mainly BAT in 37 centres. Among 48 answers, 37 participants considered BAT (77.1%), 15 (31.3%) specific IgE against PEG and 11 (22.9%) specific IgE against PS 80 or PS20. Only 5 (10.4%) considered basophil histamine release test, but 6 centres (12.5%) answered that *in vitro* tests were not relevant.

4 | DISCUSSION AND PROPOSALS

There are many open questions relating to the administration of COVID-19 vaccines in patients with history of allergy. Also, there is no global consensus on the optimal allergological investigation and management of patients with prior reactions to COVID-19 vaccines. In the present survey, the main area of disagreement is on whether doses should be fractionated when vaccinating patients with a perceived increased risk of reactions to the vaccines. However, we consider that consensus can be reached and recommendations developed. Concerning the delay of occurrence of anaphylaxis, we have followed the EAACI anaphylaxis guidelines,[60] emphasizing that severe anaphylaxis occurs within the 2 h after exposure to the allergen.

According to the International Consensus on allergic reactions to vaccines,[61] immediate allergic reactions will be those occurring less than 4 h post-vaccination and delayed reactions those appearing more than 4 h after administration of the vaccine. With the COVID-19 vaccines, we consider that immediate reactions occur within the 2 h following the injection.

4.1 | How to vaccinate allergic patients with COVID-19 mRNA vaccines?

Concerning mRNA vaccines, according to the CDC recommendation,[15] Banerjee et al,[28] EAACI statements,[27] German recommendations,[2] UK recommendations[59] and our survey, we have proposed the recommendations, which are summarized in Table 3. There are no recommended restrictions on first vaccination of allergic patients with non-mRNA vaccines. However, the recommendation for what to do in patients who had having previously reacted to PS 80 contained in many non-mRNA vaccines remains debatable. In such cases, on the same principle that applies to other vaccines containing PS 80, mRNA COVID-19 vaccines are contraindicated.

We consider that the risk needs to be centred in identifying or ruling out an undiagnosed allergy to PEG or PS. An allergy work-up is recomme

nded in case of (1) history of an immediate (<2 h) or severe allergic reaction (anaphylaxis) to injectable drugs (e.g. Depot-steroids) or vaccines containing PEG, PS 80 or 20, polyoxyl 35 castor oil (e.g. paclitaxel), (2) history of immediate or severe allergic reactions due to PEG or PS especially if due to several different drugs, mainly drugs with PEG as active ingredient (laxatives, colic preparation), (3) history of prior severe allergic reaction (anaphylaxis) to the vaccine in question, or to another COVID-19 vaccine with the same platform, (4) history of anaphylaxis of unknown cause, after an extensive allergy work-up, which might be caused by PEG, PS or polyoxyl.

If a patient takes daily medications containing PEG, allergy to PEG is quite unlikely. Also, patients may have a distant history of an allergic reaction to a vaccine, but if they have since tolerated injectable drugs such as biologicals or even the same or other vaccines containing PS 80 a significant allergy to PS is less likely.

In 131 patients with a history of severe allergies, wider contraindications to a vaccination than usual were evaluated by questionnaire followed by prick tests to vaccines and excipients (PEG 3350 and trometamol).[62] SPTs with the mRNA vaccine and trometamol were negative in all cases. Two patients had positive PEG 3350 prick tests and were not vaccinated,24/25 and 104/104 were, respectively, vaccinated with Pfizer vaccine or Moderna with a good tolerance. The more stringent selection proposed herein should be assessed in the same way.

The management of patients according to the results of allergy work-up is reported in Figure 2.

4.2 | How to test patients who had developed reaction after injection of a COVID-19 vaccine?

The first step of evaluation is a detailed clinical history including allergy history, any previous allergic reactions to drugs and detailed description of the reaction to the COVID-19 vaccine.

In case of a **local reaction** to COVID-19 vaccine, the recommendation is to administer the full dose as a normal vaccination with 15 min observation. A topical corticosteroid could be prescribed, and the patient should be told to present to an outpatient clinic in case of renewed symptoms.

In case of a **generalized immediate reactions (< 2h)**, skin testing is the most important method for diagnosis, although sensitivity and specificity remain undetermined. Skin prick tests and IDT are carried out according to ENDA guidelines.[63]

We recommend a prick-to-prick test with the suspected vaccine and prick tests with a range of excipients (see Table 4). There is no latex in the vaccine vial, but if latex material has been used during the injection, prick test with latex material or specific IgE to latex may be considered. If chlorhexidine or other disinfectant was applied at the injection site, a prick test and if possible, IDT and/or specific IgE to chlorhexidine may be considered.[64] If the left-over vaccine in used vials is accessible, a prick test can be performed with the vaccine solution (recommended by 81% of the participants). As there is a global shortage of vaccine, we do not recommend using a

TABLE 3 Recommendations for vaccination with mRNA vaccines of allergic patients according to their allergy history. In accordance with the German recommendations[2] mainly in accordance with Banerji et al. recommendations[28] and UK recommendations.[59] Anaphylaxis is classified as recommended by EAACI.[60] RV: routine vaccination in any vaccination centre, with 15 min surveillance, Q: question and answer of the survey (detailed found in on line depository)

History of allergic reaction	*Procedures for vaccination*	*Specific support and comments*
History of an immediate (<2 h) or severe allergic reaction (any grade of anaphylaxis) to injectable or vaccine containing: - polyethylene glycol (PEG), - polysorbate 80 - polyoxyl 35 castor oil (e.g. paclitaxel)	Do not vaccinate	Refer to an Allergy Unit[28] for skin tests with mRNA vaccine and excipients (Survey)
History of potential anaphylaxis to oral PEG (colonoscopy preparations, aperients).	Do not vaccinate	Refer to an Allergy Unit[28] Perform skin tests excipients *(Q 12)*
History of suspected hypersensitivity reaction (anaphylaxis) to the vaccine in question, or to another mRNA vaccine Non severe (grade I) Severe (Grades II and III)	Do not vaccinate	Refer to an Allergy Unit[28] skin tests with mRNA vaccine and excipients (Survey) Skin tests with excipients (37.7% of the participants) or direct vaccination under hospital surveillance Skin tests and vaccination in an allergy unit with 1 or 2 h surveillance and/or pay attention to fractionated doses with 1 or 2 h surveillance (has to be evaluated).
History of recurrent anaphylaxis of unknown cause, after an extensive allergy work-up, which might be caused by PEG, polysorbate or polyoxyl	Do not vaccinate	Refer to an Allergy Unit Perform skin tests excipients or vaccination in an hospital VC *(Q10)*
Confirmed allergy to any mRNA vaccine	Do not vaccinate	Refer to an Allergy Unit Ineligible for mRNA vaccine[28]
Confirmed allergy to PEG, polysorbate 80, to polyoxyl 35 castor oil	Do not vaccinate	Refer to an Allergy Unit[28] Ineligible for mRNA vaccine (57.6% of the answers) or pay attention to fractionated doses. *(Q13)*. Pay also attention to adenovirus vector or protein vaccines in the event of a polysorbate 80 allergy
History of severe allergic reaction to an **injectable medication** (intravenous, intramuscular or subcutaneous) containing PEG or polysorbate as ingredients	Routine vaccination contra indicated	Vaccine in an hospital VC (89.8%) and in an allergy centre (71% of the answers) (Q6)
History of severe allergic reaction to an **injectable medication** (intravenous, intramuscular or subcutaneous) without PEG or polysorbate	RV[28] with 30 min surveillance Also, for 51% of the answers (Q7)	48% recommend vaccination in an hospital VC (Q7)
Prior delayed reaction>4 h to an COVID vaccine	Surveillance at hospital, duration undetermined, some recommend 3 h (20%)	Skin tests can be discussed Vaccine in an hospital VC (65.5% of the answers) Pre-treatment with antihistamine can be discussed (41.6% of the answers) Q27
Non severe prior reaction to a COVID−19 vaccine, inflammatory reaction at the injection site, muscle aches, fever, delayed rashes	RV[28]	For localized reactions and rash, prescribe topical corticosteroids. For flu-like syndrome prescribed symptomatic treatment (e.g. paracetamol)[2]
History of an immediate (<2 h) or severe allergic reaction (anaphylaxis) to **another vaccine** (non-COVID−19 vaccine) that does not contain PEG or polysorbate		
Grade II or III anaphylaxis	RV with 30 min surveillance	Vaccination in an hospital VC (74% of answers) and in Allergy department if possible (43.5%) (Q5)

TABLE 3 (Continued)

History of allergic reaction	*Procedures for vaccination*	*Specific support and comments*
Urticaria, angio-oedema, Inflammatory reaction at the injection site, muscle aches, fever, delayed rashes	RV RV	
Any prior reaction to vaccines except anaphylaxis (exanthema, vasculitis)	RV	
Allergy to an **oral drug**		
Anaphylaxis Grade II, III If containing PEG or PS	RV with 30 min surveillance[28] Do not vaccinate in a routine way	Refer to an Allergy Unit Skin tests recommended (59.7% of the survey answers) (Q12)
Urticaria, angio-oedema	RV	
Mastocytosis (with prior anaphylactic reactions with triggers or without known triggers (idiopathic anaphylaxis), but not to PEG)	RV with 60 min surveillance[68]	
Mastocytosis (Patients with previous anaphylaxis to vaccination, unstable patients with mastocytosis and severe uncontrolled MCAS symptoms)	Vaccination in hospital setting With 60 min surveillance[68]	
Mastocytosis (without previous history of anaphylaxis)	RV with 30 min surveillance	Some add antihistamines, other prefer a vaccination in a hospital VC (45.9%) (Q14)
Delayed reactions to drugs even in case of severe cutaneous drug reactions (DRESS, Lyell's syndrome or Stevens Johnson's syndrome)	RV	
Familial allergy history (including anaphylaxis)	RV	
Rhinitis, conjunctivitis, allergic asthma due to aeroallergens	RV	
Contact dermatitis	RV	
Chronic urticaria or histamine angio-oedema	RV	Suggest to ensure usual antihistamine treatment is continued on day of vaccine or started 3 days before if not on regular antihistamines
Bradykinin-induced angio-oedema	RV	
Latex allergy		
Urticaria, angio-oedema, eczema	RV	
Anaphylaxis	RV with 30 min surveillance	
Hymenoptera venom allergy Urticaria, reaction at the injection site Anaphylaxis	RV RV with 30 min surveillance	
Food allergy		
Non severe: oral allergic syndrome, urticaria, eczema	RV	
Anaphylaxis	RV with 30 min surveillance	

new vaccine vial to perform IDT. A case for performing IDT, starting with very low concentrations, is in the case of positive prick tests to PEG and PS 80 but negative prick-to-prick to mRNA vaccines. IDT with mRNA vaccine have been observed to induce unspecific delayed reactions in patients and controls *(Mihaela Zidarn personal communication)*. Immediate reading could be specific. It has been reported that IDT with the pure Pfizer vaccine solution were negative on immediate reading in 53/54 controls (96%).[65] The solution was obtained after extracting 5 doses from the Pfizer vaccine vial,the injected volume was not specified. We emphasize that the updated recommendations for this vaccine are to use special syringes capable of extracting 7 doses per vial and not 5 doses. It will not be possible to perform IDT with the residua in the vial.

As 62.5% of the 64 participants of the survey were able to test with the pure excipients of the COVID-19 vaccine, we recommend prick tests with the excipients in pure form (Question 22). As the excipients in pure form are not in sterile form, they cannot be used for IDT. We have no recommendation for their use for patch tests in

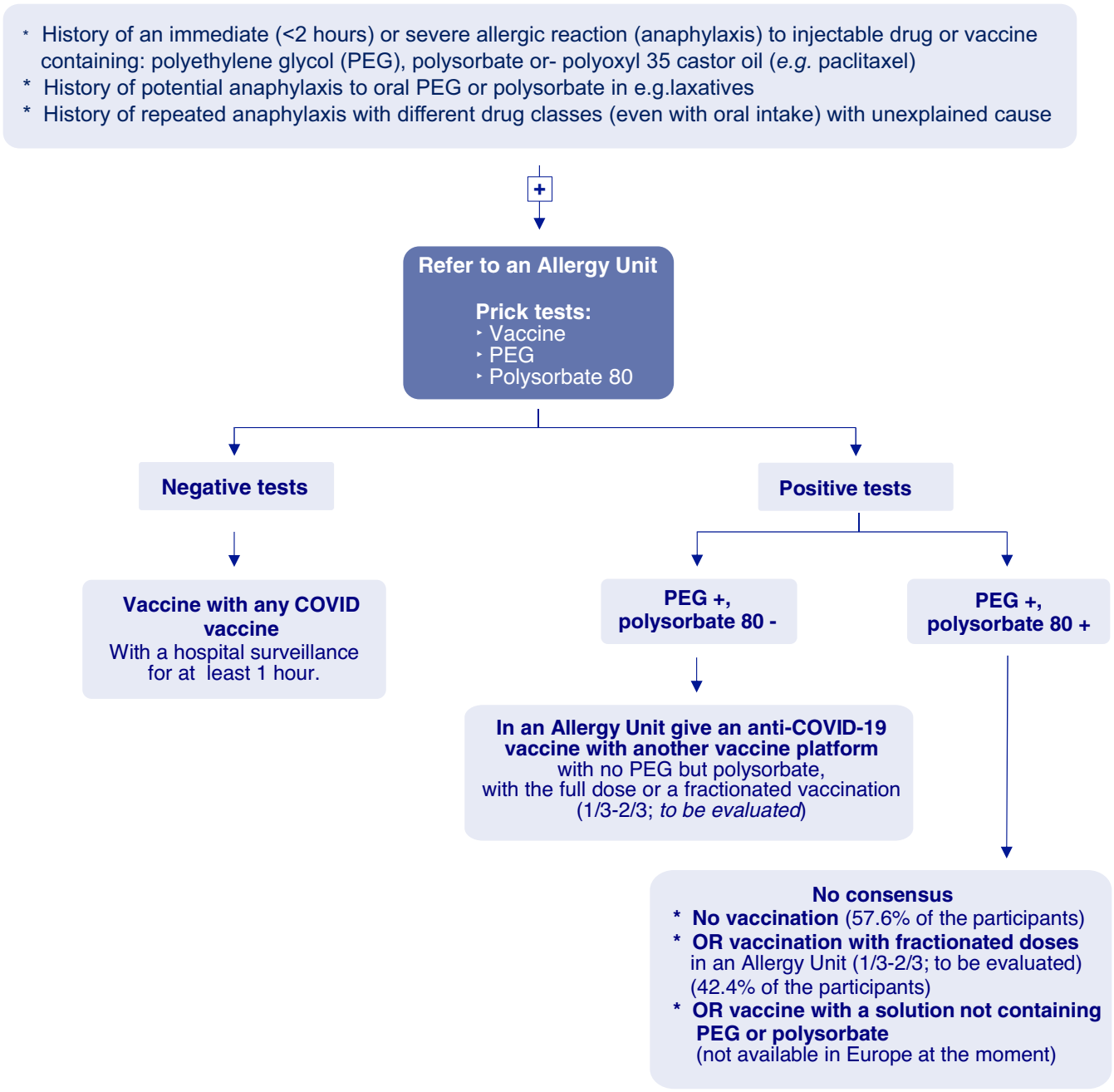


FIGURE 2 Algorithm for the management of patients at risk of anaphylactic reactions to COVID-19 vaccines before immunization. We do not know if there is any case with positive skin tests with polysorbate but negative with PEG; therefore, we have not considered this situation

delayed reactions (question 30). Some have published the results of IDT with PS 80,[43] but, as PS 80 in pure form is not sterile and available for human use, we do not recommend IDT done with pure excipients.

In 37.5% of the centres, pure excipients were not available (Question 22), and in some countries, skin tests are allowed only with commercialized drugs; thus, an alternative method can be proposed in using injectable drug containing the excipients of interest.[21] Even if many participants do not agree (Question 25), injectable drugs, corticosteroids (methylprednisolone acetate containing PEG 3350, triamcinolone acetonide containing PS80) or single-use sterile eye drops containing polysorbate 80 may be used for SPT and IDT,[28] but 74.5% of the participants do not recommend performing IDT with vaccines containing PS (Question 26). In literature, there is only one case with a positive IDT done with EDTA diluted at 0.3 mg/mL.[56]

Trometamol can be tested in using injectable drugs containing it such as radiocontrast media. In one case of sensitization to gadolinium-based contrast agents, IDT with trometamol at 1:1000 was positive (10 negative controls with IDT at 1:10), but unfortunately, the trometamol initial concentration was not given.[66]

TABLE 4 Recommendations for methods for skin tests based on literature and experiences from participating centres

	Drug		SPT		IDT		Patch test
	Name of the tested products	**Concentrationin the original preparation[1]**	**Dilution**	**Maximum concentration[a] (mg/ml)**	**Dilution**	**Maximum concentration[a] (mg/ml)**	**Concentration (w/w%)**
COVID–19 vaccines	Comirnaty ® (Pfizer Biontech)	0,03 mg/0,3 ml	1:1	0,1 mg/ml	Not recommended		
	COVID–19 Vaccine Moderna	0,1 mg/0,5 ml	1:1	0,2 mg/ml			
	Vaxzevria ® AstraZeneca COVID–19 Vaccine	2,5x10^8 Inf.U. /0,5 ml	1:1	2,5x10^8 Inf.U. /0,5 ml			
	COVID–19 Vaccine Janssen/Johnson & Johnson	not less than 8.92 log10 Inf.U. /0,5 ml	1:1	not less than 8.92 log10 Inf.U. /0,5 ml			
PEG -pure substances	PEG 300 (liquid)[b]		1:1				
	PEG 400 (liquid)		1:1				100% PEG in petrolatum (commercialized)
	PEG 1500 (waxy solid)[c]		50% in water	500 mg/ml			
	PEG 2000 (powder)[c]		1% in water 10% in water 50% in water	10 mg/ml 100 mg/ml **500 mg/ml**			
	PEG 3000 (waxy solid)[b]		50% in water	500 mg/ml			
	PEG 4000 (waxy solid)[c]		50% in water	500 mg/ml			
	PEG 6000 (waxy solid)[b]		50% in water	500 mg/ml			
PEG – containing medications	Methylprednisolone acetate Depo-Medrol®	40 mg/ml	1:1	40 mg/ml	1:100 1:10	0,4 mg/ml **4 mg/ml**	
	Colic enema (e.g. Miralax, Moviprep powder)	100 mg/ml –170 mg/ml	1:100 1:10 1:1	1,7 mg/ml 17 mg/ml **170 mg/ml**			
	Poloxamer 407 (viscous liquid)[b]		10% in water	100 mg/ml			
	Polysorbate 80 (Tween® 80)[b]		1% in water 10% in water 20% in water[b]	10 mg/ml 100 mg/ml **200 mg/ml**[b]	0,1% in saline 1% in saline 10% in saline[6]	1 mg/ml 10 mg/ml **100 mg/ml**	5% polysorbate in petrolatum (commercialized)
Polysorbate 80 – containing medications	Refresh® eye drops, Optive Plus® eye drops or similar		1:1		1:10		
	Picloxydine eye drops (e.g. Vitabact® 0,05%)[c]	0,2 mg/0,4 ml	1:1	0,5 mg/ml	1:10	0,05 mg/ml	

(Continues)

TABLE 4 (Continued)

Drug		SPT		IDT		Patch test
Name of the tested products	Concentrationin the original preparation[1]	Dilution	Maximum concentration[a] (mg/ml)	Dilution	Maximum concentration[a] (mg/ml)	Concentration (w/w%)
Trometamol citrate[d]		1:10	1,65 mg/ml	ND	ND	ND
Disodium EDTA dihidrate[e]			0,3 mg/ml		0,3 mg/ml	
Chlorhexidine digluconat 20% (aqueous solution)	200 mg/ml	1:40	5 mg/ml	1:100000	0,002 mg/ml	
Latex material		1:1				

Abbreviations: SPT, skin prick test; IDT, intradermal test; PEG, polyethylene glycol; inf. U., infectious units; ND, no data.

[a]denotes concentration of active ingredient in the original preparation as commonly used, PEG at 50% weight / weight (1g PEG +1g of water (= 1mL)),

[b]data on more than 350 controls,

[c]data on 15 controls,

[d]data on 15 controls,

[e]data only in one patient and 3 controls, [6]—data on 10 controls.

According to limited data on the specificity of these tests, some recommendations can be given. They are summarized in Table 4. As far as possible, we recommend testing pure excipients by prick tests. As PEG are in powder or crystalized form, they have to be diluted after being heated in a water bath.[67]

As only 62.5% of the centres could use pure excipients for skin testing, taking into account the US,[28] German[2] and UK[59] recommendations and the online returns, a minimal common protocol has been proposed and is summarized in Table 5.

In case of **delayed reaction**, **occurring after 4 h**,[61] skin tests are debatable and not recommended in 68.8% of the answers to the survey (questions 27, 29, 30). The further injection is recommended as usual in prescribing topical corticosteroids in case of relapse of the exanthema, for 61% of them. Switching to a non-mRNA vaccine has been proposed by 20.3% of the participants. Patch tests have a poor value in investigating delayed reactions to other vaccines. If one decides to do patch tests, they could be done with commercialized patch test material for PEG 400 1:1, PS 80 at 5% in petrolatum, ethylenediamine tetraacetic acid disodium salt dehydrate (EDTA) at 1% in petrolatum.

The Moderna vaccine is responsible for very frequent local reactions called 'COVID arm' that start 3–7 days after vaccination and last for several days, consisting of reddish swellings at the injection site sometimes a bit painful or itchy and responding well to NSAIDs.[68] Some suggest applying topical clobetasol.[68] The second vaccination can proceed without any precautions,the other arm is recommended *(K Scherer Hofmeier personal communication)*. The major delayed reactions are delayed urticarial and/or angio-oedema, morbilliform, papulovesicular or pseudo-vesicular, pityriasis rosea-like or purpuric rashes.[69,70] Delayed inflammatory reaction to facial dermal hyaluronic acid filler rapidly following vaccination for COVID-19 should not to be confused with angio-oedema. It can be treated by lisinopril.[71]

4.3 | According to the results of skin tests how can we propose to continue the vaccination?

Figure 3 shows the algorithm summarizing what to do after an anaphylaxis with mRNA vaccines, taking into account clinical features and skin test results. Positive results on prick tests with PEG or PS 80 present a problem because most of the non-mRNA vaccines contain PS 80 except for the Sanofi vaccine that contains PS 20. However, sensitizations to PS or PEG in patients tested referred for assessment of allergy risk related to COVID-19 vaccination are exceptional at least in Germany and Denmark *(Knut Brockow, Lene Heise Garvey personal communication)*.

Cross-reactivity between PEG and PS 20 is poorly elucidated. Among 15 PEG allergy patients in one centre in Denmark, 7 have been tested with PS 20 and all tested negative. In these cases, Sanofi vaccine might be an option. The clinical relevance of cross-sensitization with PS 80 is uncertain. The AstraZeneca vaccine contains very low amount of PS 80 but requires two doses. The Johnson and Johnson vaccine has a slightly higher amount of PS 80, but is

TABLE 5 Skin tests for a minimal common protocol. In bold letters the recommended tests. If pure excipients are not available, commercialized drugs listed can be used in replacement

	Prick tests	Intradermal tests
Responsible vaccine	**Prick-to-prick with the remaining drop**	NO
PEG 4000 If not available PEG 3000 or 3500	**50% in water** 50% in water	
PEG 2000	**50% in water**	
If PEG 2000 not available, use *Methyl prednisolone acetate 40 mg/mL- Depo-Medrol (PEG 3350)*[28]	*Pure (40 mg/mL)*	*0.4 mg/mL, 4 mg/mL* *If positive control with methyl prednisolone sodium succinate (Solumedrol), without PEG*[28]
polysorbate 80	**20% in water** ***(50% could be irritant)***	
If polysorbate 80 is not available, use *Refresh-sterile eye drops (polysorbate 80)*[28] **Picloxydine eyedrops (polysorbate 80)**	**1:1**	**1:10** (irritant in pure form)

a single-dose vaccine *(Lene Heise Garvey, personal communication)*. CoronaVac (Sinovac) does not contain PEG or PS but it is not available in most of the European countries.[10]

4.4 | Limitations of management due to the specific characteristic of COVID-19 vaccines

As there is a huge shortage of vaccine doses all over the world, ethically, it is not possible to propose to use a vaccine for an allergological work-up or fractionated re-administration. Therefore, for drug skin tests, it is only possible to suggest to perform prick-to-prick with the vaccine solution and not IDT. As used for food allergy, you dip the lancet in the vaccine solution then immediately prick the skin.

Obviously, hypersensitivity to the active substance or to any of the excipients is a formal contraindication for drug administration (according to summary of product characteristics), but some advocate that fractionated doses could be given after risk-benefit assessment and obtaining the informed consent of the patient. A third of participants would not fractionate vaccine to immunize.

The method to inject fractioned doses is debatable. 62.5% of the 62 participants disapproved to consider fractioned doses with COVID-19 vaccines. With non-COVID-19 vaccines, Kelso et al.[13] have recommended to inject graded doses with a 5 step-protocol. If the full vaccine dose is normally a volume of 0.5 mL, the patient is first given 0.05 mL of a 1:10 dilution and then given full-strength vaccine (at 15-min intervals) at doses of 0.05, 0.1, 0.15 and finally 0.2 mL, for a cumulative dose of 0.5 mL. When reconstituted for use, the mRNA BioNtech-Pfizer has a 0.3 mL volume and the Moderna 0.5 mL. Therefore, with a unique dose, it will be necessary to prepare 0.03 mL of the solution diluted at 1:10, then with the usual concentration to inject every 15 min 0.03 mL, 0.06 mL, 0.09 mL and then 0.12 mL. Technically, in using only one dose of 0.3 mL, this seems impossible to do. Some participants have emphasized that 0.3 mL is so small, that it is too inexact to use 1:10 (0.03 mL). Hence, they recommend not to inject less than 1/3 of the usual volume,thus, 0.1 mL (1/3) should be the first fraction for the Pfizer BioNTech vaccine; and the fractioned doses for mRNA vaccines could be 1/3 then 2/3.

These vaccines have to be injected with specific long needles; this leads a significant dead volume in the needle. Thus, if there are many successive injections in changing the needle, the final volume administered can be lower than recommended. Recently, 1 mL syringes with a peculiar plunger have been recommended for COVID-19 vaccines in order to reduce the dead volume. Thus, these syringes should be used for fractioned doses.

To date, we do not know that in enabling injection of whether it is possible to transfer the vaccine dose into a sterile vial or in another syringe, if pumping successive doses does not run the risk of damaging the lipid nanoparticles, reducing the vaccine load and possibly modifying its immunogenicity.

The risk of destroying the nanoparticles by further diluting the solution to reach the 1:10 concentration is unknown. It should be remembered that the nanoparticles are fragile and that the first dilution must be done without shaking the vial but by gently inverting it 10 times in a row. As we lack information on the stability of the vaccine in a fractionated solution, we cannot recommend it.

In case of necessity to switch from a mRNA vaccine to a vaccine manufactured on a different platform (e.g. adenovirus vector Astra Zeneca), the 2nd injection has to be done, 4 to 6 weeks after the 1st injection.

4.5 | Mastocytosis

According to recent recommendations,[72] there is no evidence for a generally increased risk for vaccination in adults with mastocytosis. In patients without a history of previous anaphylaxis or anaphylaxis to a well-defined trigger (e.g. hymenoptera venom), substances not containing PEG, there is a low risk and routine vaccination in outpatient setting with a prolonged supervision for 30 min after vaccination can be done. The same applies for patients with prior anaphylaxis without known triggers (idiopathic anaphylaxis), but not to PEG and

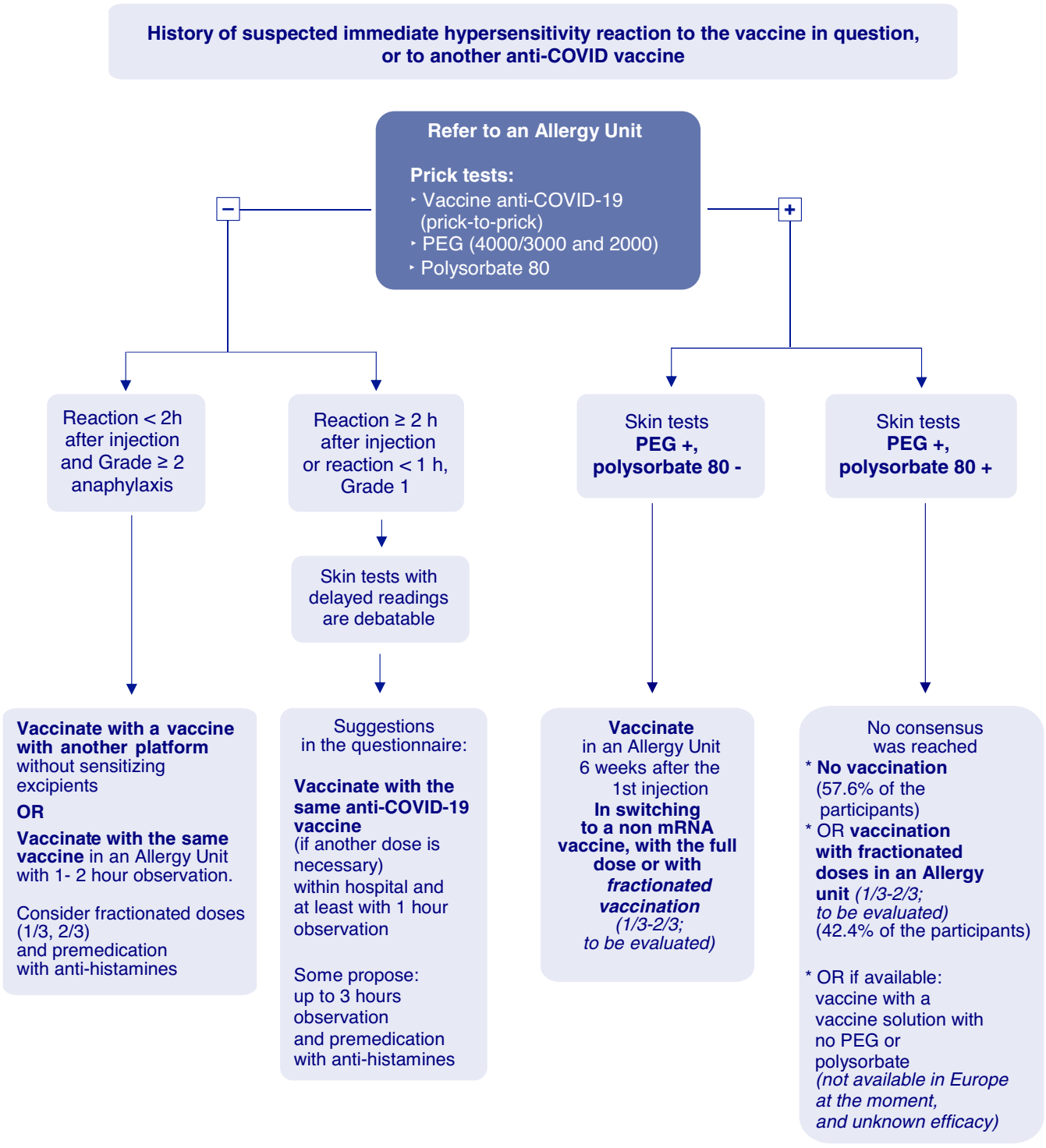


FIGURE 3 Algorithm for the management of patients who have had immediate reactions after an injection of an anti-COVID vaccine

in those with previous non-anaphylactic reactions (e.g. local redness, fever, generalized malaise) to other vaccines, in whom routine vaccination with 30–60 min supervision can be done and premedication with a sedating or non-sedating H1 antihistamine should be considered. For mastocytosis, patients at high risk of anaphylaxis to the first dose of COVID-19 vaccine are those with known or suspected allergy to PEG or PS 80/20, patients with previous anaphylaxis to vaccination, unstable patients with mastocytosis and severe uncontrolled MCAS symptoms. These patients require allergy evaluation to decide whether vaccination can be attempted at all, avoiding vaccines and ingredients (e.g. PEG) with positive skin tests, in a hospital setting with resuscitation capabilities, emergency awareness. All adult mastocytosis patients should carry their unexpired adrenaline auto-injectors with them also to the vaccination site.

4.6 | Is there any place for in vitro tests in diagnosis?

After a thorough history, the determination of basal tryptase is necessary. If elevated, a KIT mutation analysis in peripheral blood or bone marrow should be done to exclude mastocytosis.

According to the history, specific IgE against latex, chlorhexidine, ethylene oxide, α-Gal or gelatine could be tested.[2]

Some participants in the survey think that *in vitro* tests are not relevant. Participants in the survey who have the opportunities to perform in vitro tests recommend BAT over specific IgE against PEG or PS. According to German recommendations, as IgE antibodies against PEG 2000 (or IgM antibodies), which are thought to play a role in triggering complement-mediated hypersensitivity reactions to PEG, are currently not available, a BAT can be considered, but no certified and validated test systems are currently available.[2] Calogiuri et al.[48] emphasized that BAT has to be performed with the original PEG-formulation inducing the adverse reaction. Since February 2021, PEG 2000 used in mRNA vaccines has been commercialized, thus is available for *in vitro* tests. From literature, there are six cases of positive BAT with PEG in patients with drug-induced anaphylaxis due to PEG who also had positive prick tests with the same PEG.[30,73,74] One patient with positive prick test to PEG 3350 and a second one with positive IDT to Pfizer vaccine had positive BAT with pegylated liposomal particles. BAT were negative with PEG with molecular weights from 200 to 6000 MW.[75] From a limited number of patients sensitized to the COVID-19 vaccines, BAT has been shown not to be helpful to determine an allergy to the vaccine, as a positive result in BAT probably indicates a past SARS-COV-2 infection rather than vaccine sensitization. BAT could be useful for detecting a sensitization to the excipients.[76]

ELISA for PEG has not been standardized.[48]

Histamine release tests with PEG give disappointing results, because they may be positive shortly after diagnosis, but become negative over time.[77] In 10 cases with positive prick tests to PEG or PEG derivatives, only 2 patients had positive histamine release tests.[67]

5 | LIMITATIONS OF THIS STUDY

As the recommendations have been done early in 2021, when all participants had a limited experience in the management of patients with history of severe allergy or after allergy to a COVID-19 vaccine, the usefulness of the recommended skin tests, mainly prick tests, will remain to be evaluated in prospective studies. Prick tests with any drugs have a lower sensitivity than IDT, but at the moment, as vaccines are in short supply, we cannot recommend using COVID-19 vaccine for doing IDT.

6 | CONCLUSION

This questionnaire, the analysis of the literature and experiences after a few months of vaccination practice in Europe make it possible to refine the recommendations for vaccinating allergic patients. Vaccination is the best way to control the pandemic. Allergists, in harmonizing their practices, will limit contraindications to vaccination and help to vaccinate people supposed to be at risk of allergic reactions. These recommendations will help, through in vivo and in vitro tests, to better understand the mechanisms of anaphylactic reactions to these vaccines, which fortunately remain very rare. The algorithm to vaccinate patients after a previous anaphylaxis due to a COVID-19 vaccine will need to be evaluated.

AUTHOR CONTRIBUTION STATEMENT

BA, GLH, AA, BK, MF, MC, BP, A-MM, ML and TMJ involved in preparation of the questionnaire. BA, GLH and AA involved in preparation and analysis of the online questionnaire. AA involved in sending of the online questionnaire. BA, GLH, AA, BK, BP, GJ and TMJ served as main writers. All co-authors involved in answering to the questionnaire or correcting the manuscript and endorsement of the manuscript.

CONFLICT OF INTEREST

Stefan Wöhrl: ThermoFisherScientific (Lecture fees, Consulting), Siemens Healthineers (Lecture fees). Other co-authors have no COI.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Barbaud A, Garvey LH, Arcolaci A, et al. Allergies and COVID-19 vaccines: An ENDA/EAACI Position paper. *Allergy*. 2022;00:1–22. doi:10.1111/all.15241