Received: 16 March 2022 | Revised: 28 April 2022 | Accepted: 3 May 2022

DOI: 10.1111/all.15414

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Autoimmunity and Clinical Immunology

Management of suspected and confirmed COVID-19 (SARS-CoV-2) vaccine hypersensitivity

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Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

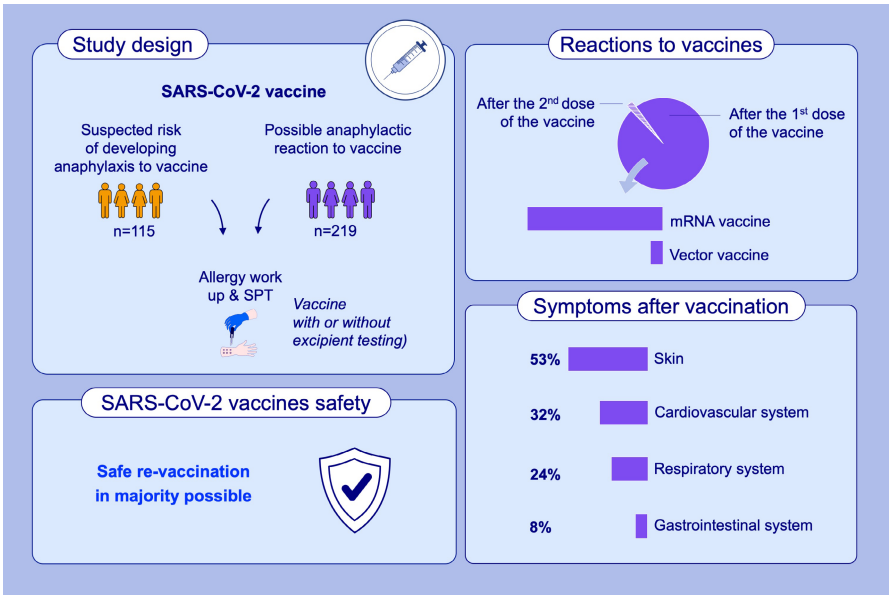
Background: Systemic allergic reactions to vaccines are very rare. In this study we assessed the management and outcome of suspected SARS-CoV-2 vaccine hypersensitivity.

Methods: Totally, 334 individuals underwent an allergy work up regarding SARS-CoV-2 vaccination (group A: 115 individuals suspected to be at increased risk for vaccine-related reactions before vaccination and group B: 219 patients with reactions after COVID vaccination). The large majority of the SPT/IDT with the vaccines were negative; however, we identified in 14.1% ($n = 47$) a possible sensitization to the SARS-CoV-2 vaccine and/or its ingredients defined as one positive skin test. Of the 219 individuals (group B) who experienced symptoms suspicious for a hypersensitivity reaction after vaccination, 214 were reported after the first vaccination with a mRNA vaccine (157 mRNA (Comirnaty®, 38 Spikevax®) and 18 with a vector vaccine (Vaxzevria®), 5 cases were after the second vaccination.

Results: The symptom profile in group B was as follows: skin symptoms occurred in 115 cases ($n = 59$ angioedema, $n = 50$ generalized urticaria and $n = 23$ erythema/flush. Seventy individuals had cardiovascular, 53 respiratory and 17 gastrointestinal symptoms. Of the overall 334 individuals, 78 patients tolerated (re)-vaccination (out of skin test positive/negative 7/19 from group A and 17/35 from group B).

Conclusion: Proven IgE-mediated hypersensitivity to SARS-CoV-2 vaccines is extremely rare and not increased in comparison with reported hypersensitivity to other vaccines. The value of skin tests is unclear and nonspecific reactions, in particular when intradermal testing is applied, should be considered.

KEYWORDS
anaphylaxis, hypersensitivity, polyethylene glycol, SARS-CoV-2, vaccination



GRAPHICAL ABSTRACT

This study assesses the management and outcome of suspected SARS-CoV-2 vaccine hypersensitivity in 334 individuals who underwent an allergy work up. Of the 219 individuals who experienced symptoms suspicious for a hypersensitivity reaction after vaccination, 214 were reported after the first vaccination with a mRNA vaccine and 18 with a vector vaccine. Five cases were reported after the second vaccination. IgE-mediated hypersensitivity to SARS-CoV-2 vaccines is extremely rare and not increased in comparison to the reported hypersensitivity rates for other vaccines.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

In December 2020, vaccination campaigns against the COVID-19 pandemic were initiated on an international level. Soon after authorization, reports of severe allergic reactions and anaphylaxis in the context of SARS-CoV-2 vaccination raised the alertness particularly of patients with a history of previous severe allergic reactions, atopic diseases and other allergic manifestations.[1] Until now four SARS-CoV-2 vaccines have been licensed in Germany: the mRNA vaccines Comirnaty® (BioNTech Manufacturing GmbH) and Spikevax® (MODERNA BIOTECH SPAIN, S.L.) and the vector vaccines Vaxzevria® (AstraZeneca AB) and COVID-19 vaccine Janssen® (Johnson & Johnson).

Vaccine related side effects may be caused by the excipients of the mRNA and vector vaccines, polyethylene glycol (PEG)/polysorbate 80 (PS80).[2,3] Based on previous experience, systemic allergic reactions to vaccines are very rare and range between 1 and 5 cases per 1 one million applications.[4] Regarding the Pfizer/BioNTech BNT162B2 (Comirnaty®) SARS-CoV-2 Vaccine, by January 2021 4.7 cases of allergic reactions occurred per 1 one million applications in the US.[5]

Herewith we established a multicenter protocol for individuals with suspected SARS-CoV-2 vaccination hypersensitivity within the German Comprehensive Allergy Centers (CAC) (Berlin, Giessen, Göttingen, Hannover, Leipzig, Marburg, Dresden, Munich, Aachen, Oldenburg) and other large allergy centers in Germany (Augsburg, Bochum, Kiel, Köln, Freiburg, Hamburg, Leverkusen, Wiesbaden) in order to identify IgE-mediated hypersensitivity against SARS-CoV-2 vaccines as well as their excipients and to evaluate the frequency and characteristics of patients with respective hypersensitivities.

2 | METHODS

2.1 | Patients and procedures

Adult patients were included in this data analysis, if they met at least one of the following inclusion criteria: previous hypersensitivity reactions to vaccines or to medical products containing PEG or PS80, previous idiopathic anaphylaxis, and suspected increased risk of developing anaphylaxis (e.g., because of previous severe anaphylactic reactions to multiple drugs). Patients who had consulted the German Comprehensive Allergy Centers and other large allergy centers between May and September 2021 were included prospectively in this analysis. Patients were seen by an allergist and after taking a detailed medical history, the allergy workup was performed, including skin prick tests (SPT) and in selected cases intradermal tests (IDT), as well as detection of total IgE and serum tryptase. The skin tests were performed in accordance with the medical history. In patients with a documented previous immediate reaction to a COVID-19 vaccine, a SPT with the culprit vaccine was performed, if it was available in the clinic. In inconclusive cases an IDT with the culprit vaccine in a 1:10 dilution was performed in addition. Patients at increased risk of developing anaphylaxis to the COVID-19 vaccine underwent a standardized protocol of skin tests. The COVID-19 vaccines were tested in the skin tests, if availability was given.

Since PEG and PS80 are the most suspected compounds to elicit hypersensitivity reactions, we included based on the literature PEG2000, PEG6000 and PS80 in the test panel (SPT: 1%, 10%; IDT: 0.01%, 0.1%, diluting agent: sterile water for injection).[6] PEG and PS80 were purchased at Carl Roth (Karlsruhe, Germany). The powder of the substances was prepared by the local pharmacies for further testing. In some centers, Trometamol and 1,2-Distearo yl-sn-glycero-3-phosphocholine (DSCP) were applied in the SPT at 1% and 10% (diluting agent: sterile water for injection), these data are not presented in this analysis, due to their limited number. If available, the vaccines were tested undiluted in SPT and at 1% and 10% in IDT (dilution agent: sterile aqua).[7] The skin test (SPT/IDT) was considered positive when the induration (wheal size diameter) was 3 or more millimeters.[8–10] The assessment of the clinical data for research proposes was approved by the ethics committee at the Charité (EA1/049/21) as the initiating center.

3 | RESULTS

3.1 | Study cohort

Between May and September 2021 approximately 2500 individuals (Figure S1) contacted the German Allergy centers and allergy specialized clinics because of a self- and-or clinically suspected immediate-type allergic reactions to SARS-CoV-2 vaccine. In total, 334 were included in this analysis (Figure 1). The median age of this cohort was 49 years (19–91) and 291/334 were female (87.1%). Medical history data covered atopic and other related diseases (Table 1). The history of the patients included in most cases anaphylaxis to previous vaccination or drugs known or suspected to contain PEG or PS80. Few patients reported immediate reactions after the use of cosmetics were sensitized to multiple drugs or had a history of systemic reactions to contrast media (Table 1).

3.2 | Reported cases in allergy centers

We divided the cohort into 2 groups. Group A comprised 115 patients with a suspected increased risk of developing anaphylaxis to a SARS-CoV-2 vaccine, based on the medical history and/or the opinion of the general practitioner. Group B comprised 219 patients with possible hypersensitivity reactions after receiving at least one dose of an available SARS-CoV-2 vaccine (Figure 1). In total, 214 of 219 patients from group B experienced reactions after receiving the first SARS-CoV-2 vaccination and five patients experienced symptoms after receiving the second vaccine dose. Of these, 195 reactions occurred after the first application of an mRNA-based vaccine (157 Comirnaty® and 38 Spikevax®), and eighteen reactions

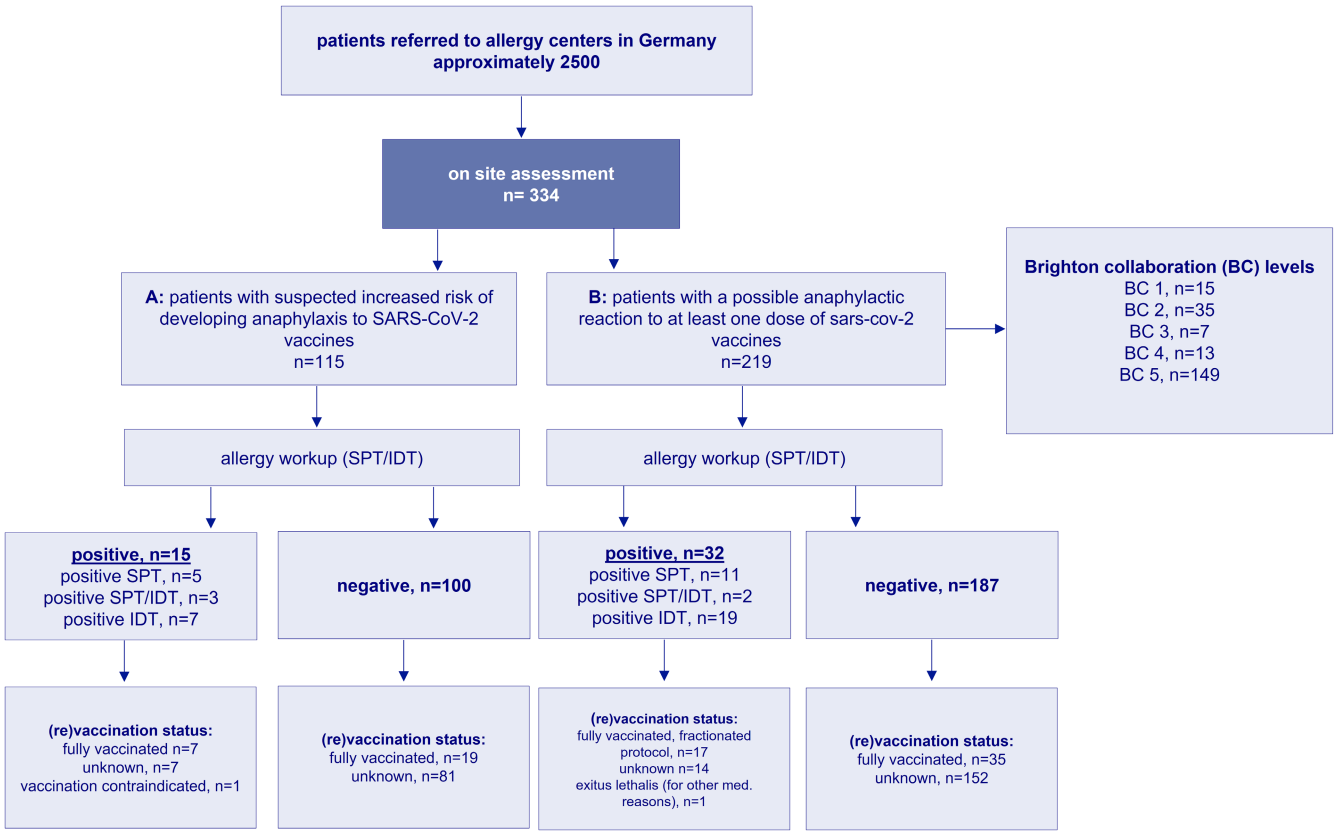


FIGURE 1 Workflow- for analytic purposes, the patients were divided into 2 groups. The first group (group A) comprised of 115 patients with an increased risk of developing anaphylaxis to a SARS-CoV-2 vaccine, based on the medical history. The second group (group B) comprised of 219 patients with possible allergic reactions after receiving at least one dose of an available SARS-CoV-2 vaccine. Patients who fulfilled the inclusion criteria underwent an allergy workup. The available (re)vaccination status of patients with positive results during the allergy workup is presented, as well. SPT, skin-prick-test; BC, Brighton collaboration

were reported from patients after application of a vector vaccine (Vaxzevria®). One patient had a reaction after the first dose of an unknown SARS-CoV-2 vaccine.

3.3 | Symptoms in the context of SARS-CoV-2 vaccination

Totally, 219 patients (group B) experienced any symptom suggestive of an allergic reaction either after receiving the first or second SARS-CoV- 2 vaccine dose. Some patients also showed other adverse reactions or delayed reactions (maculopapular rash $n = 13$, large local reaction at injection site $n = 14$).

Skin symptoms occurred in the majority of the patients ($n = 115$). The most frequent cutaneous symptom was angioedema ($n = 59$), followed by generalized urticaria ($n = 50$) and generalized erythema/flush ($n = 23$). Seventy patients had cardiovascular symptoms; respiratory symptoms were also frequent ($n = 53$), e.g., dyspnea was be reported in 50 patients. Gastrointestinal symptoms were recorded in 17 patients (Table 2). The majority of symptoms occurred within 1 h of vaccination; however, in a few cases, the symptoms appeared within 24 h of vaccination (7 cases with reported symptoms in line with a possible allergic reaction later than 24 h after vaccination and 4 cases with reported symptoms in line with a possible allergic reaction within 6–24 h of vaccination).

According to the Brighton levels for classification of anaphylaxis in the context of vaccination[11] only 57 patients from group B met the criteria of anaphylaxis according to the Brighton criteria (level 1 corresponds to the highest, levels 2 and 3 to lower degrees of diagnostic certainty) (Figure 1).

3.4 | Rate of suspected SARS-CoV-2 vaccine hypersensitivity after allergy work up

The allergy workup in a total of 334 patients revealed a suspected hypersensitivity to the SARS-CoV-vaccine and/or its excipients, defined as one positive skin test (Figure 1), in 47 cases (14.1%). The majority of the SPT and IDT with the vaccines were negative (Table 3). Group A consisted of 15 patients with positive skin tests: 5 had positive SPT, 3 had both positive SPT/IDT and 7 showed positive IDT. Group B consisted of 32 patients with positive skin tests: 11 patients had positive SPT, 2 had positive both SPT/IDT and 19 showed positive IDT (Figure 1). Overall, two patients had a systemic reaction after the IDT (one with Comirnaty® and one with Spikevax®). Baseline tryptase was not elevated in any of the

TABLE 1 Medical history of the patients presenting for risk assessment regarding the SARS-CoV-2 vaccination

Medical history	Group A Patient with suspected increased risk of developing anaphylaxis to SARS-CoV-2 vaccines, $n = 115$	Group B Patients with possible anaphylactic reactions to SARS-CoV-2 vaccine, $n = 219$	Entire cohort
Anaphylaxis (not further specified)	10	2	12
Drug allergy (Type I)/anaphylaxis	50	10	60
Suspected PEG allergy/sensitisation/poor tolerance of products or drugs containing PEG	19	0	19
Suspected Polysorbate allergy/sensitisation/poor tolerance of products or drugs containing Polysorbate	2	0	2
Poor tolerance of vaccination/other reactions or adverse events	9	2	11
Vaccine allergic reactions/anaphylaxis	28	12	40
Contrast medium allergy/anaphylaxis	6	2	8
Food allergy/anaphylaxis	9	6	15
Multiple allergies/multiple type I sensitizations	17	11	28
Atopic dermatitis	1	7	8
Asthma	9	15	24
Type IV sensitisations (diverse)	5	3	8
Type IV sensitisation PEG	1	0	1
Type IV sensitisation Polysorbat	1	0	1
Mast cell disease	2	1	3
Chronic spontaneous urtivaria (CSU)	1	1	2
Hereditary angioedema (confirmed or suspected)	2	3	5

Abbreviation: PEG, polyethylene glycol.

patients except in one who had a known mastocytosis. The median value of baseline tryptase of a total of 113 measured cases was 4.49 µg/ml.

3.5 | Tolerability of re-vaccination

Of the 214 patients showing any symptom in line with a possible allergic reaction after the first vaccination, 71 patients did not show any immediate allergic symptoms after re-vaccination with the identical ($n = 57$) or a nonidentical SARS-CoV-2 vaccine ($n = 13$), for one patient the type of the second vaccine was unknown. Six further patients showed similar tolerability to re-vaccination and one patient had urticaria after the re-vaccination. In some of the above-mentioned cases, the second dose was fractionated ($n = 9$); in other cases, the vaccination was given as a whole dose with extended emergency preparedness and few patients received premedication before vaccination ($n = 3$) (antihistamines and oral corticosteroids).

A re-vaccination with any available SARS-CoV-2 vaccine of patients from group B was contraindicated in one case only, due to SPT strong positivity to several vaccines. 24 Twenty-four of 47 skin test positive patients were successfully re-vaccinated of these 22 with the identical mRNA vaccine and 2 with a different non-mRNA vaccine (Figure 1). Three patients received no further vaccination, in one case re-vaccination was not necessary, due to previous COVID-19 infection, one patient died (due to other medical reasons) and one refused vaccination (Figure 1).

3.6 | Paul-Ehrlich-Institute reported cases

From the beginning of the vaccination campaign in Germany on December 27, 2020, through July 31, 2021, $n = 131,671$ suspected cases of any kind of adverse reaction or vaccination complication have been reported to the Paul-Ehrlich-Institute, thereof $n = 390$ cases of suspected anaphylaxis,[12] in the context of vaccination with the mRNA vaccines Comirnaty® (BioNTech Manufacturing GmbH) and Spikevax® (MODERNA BIOTECH SPAIN, S.L.) as well as the vector vaccines Vaxzevria® (AstraZeneca AB) and COVID-19 vaccine Janssen®. By August 1, 2021, according to data from the Robert Koch Institute 92,376,787 vaccinations had been administered, including 68,962,481 vaccinations with Comirnaty®, 8,506,260 vaccinations with Spikevax®, 12,491,937 vaccinations with Vaxzevria® and 2,416,109 vaccinations with COVID-19 vaccine Janssen®.

Concerning reported allergic reactions, the 390 cases with suspected anaphylactic reactions reported until July 31, 2021, were

TABLE 2 Symptoms and organ system involvement during reactions after SARS-CoV-2 vaccination, Group B, $n = 219$

Reported symptoms	Group B Patients with possible anaphylactic reactions to SARS-CoV-2 vaccine, $n = 219$	%
Skin	115	52.5%
Angioedema	59	26.9%
Urticaria	50	22.8%
(generalised) erythema/flush	23	10.5%
Pruritus	24	11.0%
Respiratory system	53	24.2%
Upper respiratory symptoms/rhinitis/conjunctivitis	3	1.4%
Lower respiratory symptoms/dyspnea/wheezing/plus stridor	50	22.8%
Cardiovascular system	70	32.0%
Cardiovascular reaction not further specified	26	11.9%
Tachycardia	24	11.0%
Hypotension/diziness/syncope	31	14.2%
Hypertension	10	4.6%
Gastrointestinal system	17	7.8%
Nausea/emesis/diarrhea	17	7.8%
Other		
Paresthesia (skin and mucosal)	32	14.6%
Feeling of heat	11	5.0%
Reported anaphylaxis (not further specified)	6	2.7%
Drug eruption (generalised maculo-papular rash)	13	5.9%
Local reaction/edema/erythema on the injection site	14	6.4%

assessed by the Paul-Ehrlich-Institute as Brighton Collaboration (BC) levels 1–4 (level 1 corresponds to the highest, levels 2 and 3 to lower degrees of diagnostic certainty and level 4 are reports of suspected anaphylaxis with incomplete information on clinical symptoms).[4] The number of reported cases of suspected anaphylaxis is specified according to vaccine and applied dose in Table S2.

Based on these data, a suspected allergic reaction to SARS-CoV-2 vaccines occurs in 2.7 cases per 1 one million vaccine applications (considering the Brighton collaboration criteria 1–3). These data are presented as spontaneous reporting and over- or underreporting may be possible.

4 | DISCUSSION

Confirmed anaphylaxis toward an ingredient of a vaccine is extremely rare and may reach an estimated rate of 1–2 cases per million vaccinations in Germany.[13–15] After starting the world-wide vaccination program against COVID-19, an increased reaction rate for SARS-CoV-2 vaccines has been suggested[3] with hypersensitivity to PEG suspected as the cause.[1] However, only in exceptional cases was evidence for PEG as the culprit substantiated.[16] Thus, the association between PEG allergy and anaphylaxis to SARS-CoV-2 vaccines remains uncertain.

So far, drug and/or vaccine-induced hypersensitivity reactions can be IgE-dependent occur via a G-protein signaling pathway (MRG-PX2) or through activation of the complement system.[17] Whether PEGs or further vaccine excipients can induce a hypersensitivity reaction other than through the IgE dependent pathway is currently not known.

In this multicenter data assessment, of 334 individuals with suspected hypersensitivity to SARS-CoV-2 vaccines presenting for an allergy workup, 47 patients (14.1%) were identified with suspected hypersensitivity to the SARS-CoV-vaccine and/or excipients defined as one positive skin test (Figure 1). As reported previously, these patients were mostly female.[18]

The overall analyses of the symptom profiles of these patients revealed less frequent skin symptoms (52.5%) than observed in other drug hypersensitivities,[3] but more similarities with other causes of anaphylaxis like food or venom induced anaphylaxis.[19] Angioedema was more common and even more frequent than urticaria. This finding is an interesting observation as acquired angioedema shows a predominance in female middle-aged patients as well and may indicate a role of sex hormones for the

TABLE 3 Results of skin testing with vaccines (SPT/IDT) and PEG/PS80 as indicated

	Group A		Group B	
	Patient with suspected increased risk of developing anaphylaxis to SARS-CoV-2 vaccines, $n = 115$		Patients with possible anaphylactic reactions to SARS-CoV-2 vaccine, $n = 219$	
Skin tests (SPT + IDT)[a]	Tests performed	Positive tests	Tests performed	Positive tests
SPT Comirnaty ®	58	6	100	4
IDT Comirnaty ® 10%	5	4	22	6
SPT Vaxzervia ®	51	4	50	0
IDT Vaxzervia ® 10%	3	3	8	5
SPT Spikevax ®	21	1	31	0
IDT Spikevax ® 10%	2	2	5	4
SPT PEG 2000 1%	36	1	97	4
SPT PEG 2000 10%	39	1	100	4
IDT PEG 2000 0.01%	26	6	42	9
IDT PEG 2000 0.1%	26	6	42	12
SPT PEG 6000 1%	24	3	74	3
SPT PEG 6000 10%	25	0	81	1
IDT PEG 6000 0.01%	9	9	27	7
IDT PEG 6000 0.1%	7	7	28	10
SPT Polysorbate 80 1%	57	4	73	2
SPT Polysorbate 80 10%	61	2	76	1

Abbreviations: DSPC, Distearoyl-sn-glycero-3-phosphocholine; IDT, intradermal test; PEG, polyethylene glycol; PS80, Polysorbate 80; SPT, Skin prick test.

[a]Multiple mentions in group A and group B are possible, therefore no percentages are given.

development of the observed hypersensitivity reactions. In addition previous studies have shown that females experience allergic symptoms more often, e. g. in food allergies, despite being less frequently sensitized.[20]

Both groups of this analysis are presumed to have theoretically a different pretest probability, expecting that group B has a higher pretest probability. However, considering a strict allergological assessment in group A on one hand and an unknown rate of unspecific clinical reactions in group B after vaccination may affect these assumptions. Considering positive SPT results among the groups comparable rates between group A: $n = 8/115$ (6.9%) and group B: $n = 13/219$ (5.9%) were determined.

The allergy workup in our cohort show a very few positive skin test reactions occurring after IDT (group A $n = 7$, group B $n = 19$) only as the criterion of positive IDT was 3 or more millimeters is quite likely to produce some false-positive results. As nonspecific positive IDT reactions are not uncommon in testing drugs, particularly vaccines, positive results have to be interpreted with great caution.[14] Nevertheless, the negative skin test results in a large proportion of patients ($n = 274$) applying the recommended test concentrations suggest a higher specificity of the test conditions that is probably suitable for allaying concerns of doctors and patients regarding allergy to SARS-CoV-2 vaccines.

Tolerability of the second vaccine dose even after immediate symptoms following the first vaccine, shown by us and by other groups,[6] suggests that re-vaccination is safe in the vast majority of these patients. As some symptoms concerning the respiratory, circulatory or gastrointestinal system are subjective, these may be an expression of anxiety rather than an allergic or other organic adverse reaction or may be triggered via vasovagal activation.

Thus, we propose that patients reporting immediate systemic reactions after SARS-CoV-2 vaccination should be carefully evaluated for the differential diagnoses, including vasovagal, or other psychologically triggered reactions. If possible, patients should be evaluated for an increase in serum tryptase 2–4 h after the reaction to gather further evidence for a mast cell-dependent pathomechanism, and a thorough allergy workup should follow (Figure 2). We propose an SPT with the available vaccines (Table S1A) and – if positive – a SPT with the vaccine excipients PEG and polysorbate 80 (Table S1B), which is in line with the recent ENDA/EAACI Position paper.[21] In cases suggestive for a possible PEG allergy according to the medical history (e.g., previous reactions to laxatives), PEG testing as well as a SPT with PEG should be included primarily in the work up, as hypersensitivity to excipients in COVID-19 vaccines constitutes a risk to patients with allergy to PEG or polysorbates.[22] Recent data from the literature suggest that SPT with PEG 20.000 in careful titration starting at a concentration of 0.01% may be useful in diagnosing PEG allergy when lower molecular weight PEGs test negative. IDT with PEGs are not generally recommended and require confirmation regarding safety and validity.[23] In case of a positive SPT either to

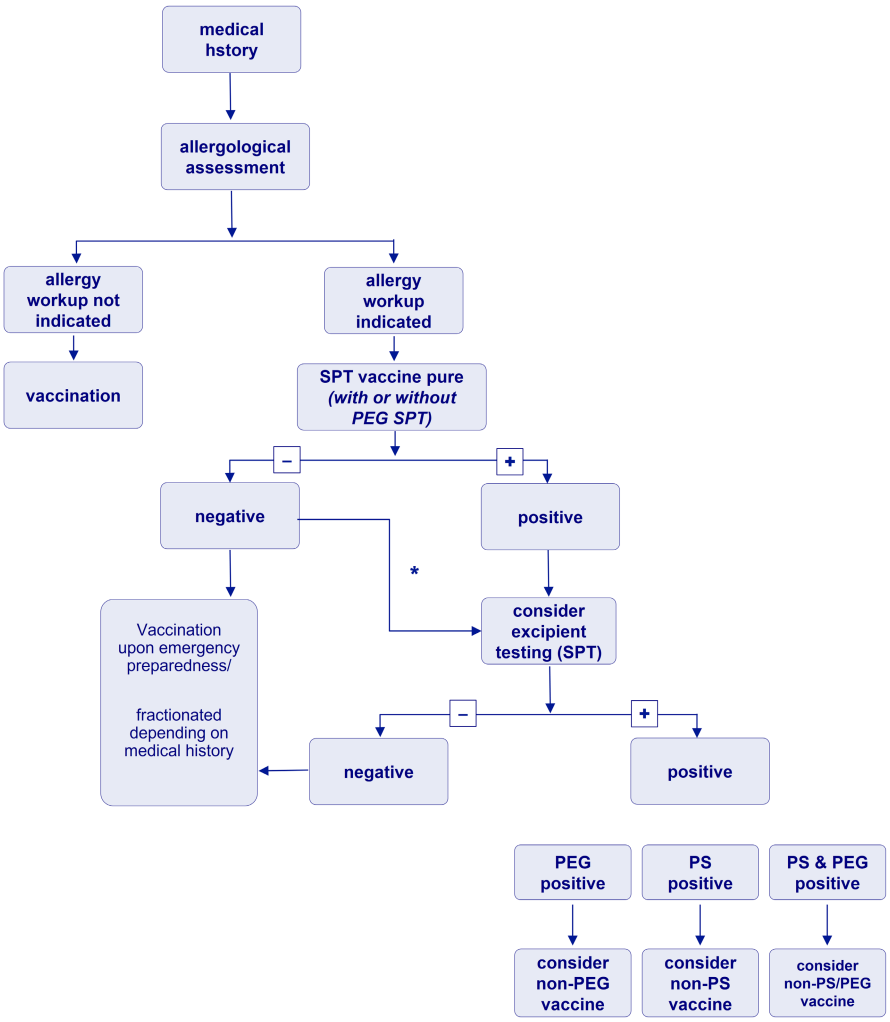


FIGURE 2 Proposed algorithm for individuals presenting for risk assessment regarding SARS-CoV-2 vaccination. *For patients with strong history suggestive for PEG allergy, consider excipient testing even if the SPT with pure vaccine is negative, as hypersensitivity to excipients in COVID-19 vaccines constitutes a risk to patients with allergy to PEG or polysorbates. SPT, Skin prick test; IDT, intradermal test; PEG, polyethylene glycol; PS, polysorbate

the vaccines or excipients, we suggest performing an individual risk assessment and either fractionated vaccination in increased emergency preparedness or to consider vaccinating with another available vaccine, without the culprit excipient (Figure 2).

Overall, IgE-mediated hypersensitivity to SARS-CoV-2 vaccines is extremely rare and not increased in comparison to the reported hypersensitivity rates for other vaccines. However, the tremendous amount of patients seeking allergists advice regarding the tolerability of COVID-19 vaccination points to the need for appropriate information campaigns for the general population in order to facilitate high vaccination rates.

AUTHOR CONTRIBUTION

All authors were involved in patients work-up and care and supported data collection. AA performed literature research, statistical analysis and data interpretation. AA and MW wrote the manuscript. MW conceived the study design, coordinated the manuscript and the data analysis. All authors reviewed and approved the final manuscript.

FUNDING INFORMATION

None.

ACKNOWLEDGEMENTS

We thank all involved colleagues at the allergy centers and private allergy practices for their continued support for this project. We would like also to thank Burkhard Espey (Dermatology department, Ruhr University Bochum) and Sonja Mathes (Dermatology department, Technical University of Munich) for their contribution in this project. We are grateful to Dr. Brigitte Keller-Stanislawski and Prof. Vera Mahler (Paul-Ehrlich-Institute) for the provision of pharmacovigilance data from the spontaneous reporting system and their critical revision of the manuscript. A. Alexiou is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) as part of the clinical research unit (CRU339): Food allergy and tolerance (FOOD@) – project-number 428447634. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Worm M, Alexiou A, Bauer A, et al. Management of suspected and confirmed COVID-19 (SARS-CoV-2) vaccine hypersensitivity. *Allergy*. 2022;77:3426-3434. doi: 10.1111/all.15414