Allergy / Early View

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Experience with polyethylene glycol allergy-guided risk management for COVID-19 vaccine anaphylaxis

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Abstract

Background

Polyethylene glycol (PEG) may elicit anaphylaxis to COVID-19 mRNA vaccines, and guidance for patients at risk is needed.

Methods

In retrospective patients with PEG allergy collected from 2006 till 2019, clinical, skin, and basophil activation test (BAT) characteristics discriminative for PEG allergy were analyzed and compared with the literature. In 421 prospective real-life patients asking for allergy workup for COVID-19 vaccine hypersensitivity in 2020/2021, risk assessment was performed and tolerance of the recommended vaccination approach was assessed.

Results

Ten patients with PEG allergy were found in the retrospective cohort. Patients reacted with immediate anaphylaxis (100%) not only to PEG-based laxatives/bowel preparations or injections, but also to cold medication, antiseptics, analgetics, or antibiotics. Skin tests ± BAT with PEG ± elicitors were positive in 10/10. Provocation tests were positive in 7/9 patients. From the prospective cohort, 370/421 patients self-reporting increased risk for vaccine allergy lacked criteria necessitating allergy workup and were recommended for routine vaccination. A total of 51/421 patients were tested, and three (6%) with PEG

allergy were identified, whereas 48 patients remained negative in skin tests. Vaccination was recommended in all those patients. No hypersensitivity reactions were reported to vaccination including six PEG-allergic patients tolerating COVID-19 vaccination.

Conclusions

Taking a detailed history excluded PEG allergy in most referred patients and enabled direct safe vaccination. Immediate urticaria/anaphylaxis to typical elicitors identified patients requiring PEG allergy workup. Skin tests ± BAT identified PEG allergy and helped to select the vaccine and the vaccination approach. Even PEG-allergic patients can tolerate COVID-19 vaccines.

Abbreviations

BAT
: basophil activation test

COVID-19
: Coronavirus disease 2019

IDT
: intradermal test

IgE
: Immunoglobulin E

MW
: molecular weight

OPT
: oral provocation test

PEG
: polyethylene glycol

SARS-CoV-2
: severe acute respiratory syndrome coronavirus type 2

SPT
: skin prick test

1 INTRODUCTION

Polyethylene glycols (PEGs, synonym macrogols) comprise a family of hydrophilic polymers produced by polymerization of ethylene oxide.[1] PEGs are ubiquitously used in medicine such as in laxatives and intestinal cleaning solutions (molecular weight (MW) 3350–4000), in injection solutions or liquid cosmetics (MW<800), emulsions (varying MW), as auxiliary materials in tablets (MW ≥ 6000) and for chemical, biological, industrial, cosmetic, and recreational uses.[1] Anaphylaxis to PEG has been described.[2-5] PEG 2000 is also a component in the artificial lipid layer in SARS-CoV-2 mRNA vaccines of Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162B24, Comirnaty®), whereas the DNA vaccines of AstraZeneca (Vaxzevria®) and Johnson & Johnson (Janssen®) are vector-based vaccines containing polysorbate 80

(PS80) and trometamol.[2, 6] PEG is the only excipient in COVID-19 mRNA vaccines that clearly demonstrated to cause delayed-type and immediate-type allergic reactions, while the role of trometamol and PS80 as relevant allergens in DNA vaccines remain more questionable.[2-4, 7] Cases with anaphylaxis to mRNA vaccines for COVID-19 have been reported with an incidence of 4.7 cases/10^6 doses for the Comirnaty® and 2.5/10^6 doses for Moderna vaccinations, about 2–4 times higher than that expected for other vaccinations.[8-11] Such reports fueled public concern about the allergenic potential of PEG.[3, 12-15] Several individuals report alleged hypersensitivity reactions to the first dose of COVID-19 vaccination. Additionally, those with previous severe allergic reactions and anaphylaxis to a variety of elicitors including medications seek allergy testing before vaccination.[16, 17] Recommendations on how to manage patients at risk for PEG allergy have been published but have not been evaluated for their safety in real-life patients.[18-22]

The objective of this study is to (a) identify clinical criteria in our patients with PEG allergy and compare these with criteria reported in the literature, (b) to apply these criteria to 421 prospective real-life patients who were asking for allergy workup for COVID-19 vaccine hypersensitivity, and (c) to report the outcome of the recommendations for patient management according to individual risk assessment.

2 METHODS

2.1 Identification of criteria indicating PEG allergy in retrospective patients

Patients with immediate-type allergic reactions to PEG between 2006 and 2019 were retrospectively retrieved from the medical charts of two large allergy units in southern Germany (Table 1). Clinical data including history, skin prick (SPT), intradermal (IDT) and oral provocation test (OPT) results were extracted from the patient charts. Main clinical criteria were identified and compared with those published in the literature.[18-20]

TABLE 1. Immediate-type hypersensitivity reactions to polyethylene glycol observed in two allergy units in South Germany between 2006 and 2019

Age	Sex	Exposure	Immediate-type reaction	PEG test results	Oral challenge test (OCT)	Further obse
77	M	(1) Colon cleansing solution (Klean-Prep®, is PEG 3350) (2) Accidentally exposed to colon	Generalized urticaria, bronchial obstruction, unconsciousness	SPT: Pos. to Klean-Prep®, PEG 1500, 3350, 4000 Neg. to PEG 400, PEG 600	OCT with Klean-Prep®: generalized urticaria, shortness of breath 40 min	PEG as excipie found in patier term medicatic —Blopress® (P 8000), Gallobe 4000), and

Age	Sex	Exposure	Immediate-type reaction	PEG test results	Oral challenge test (OCT)	Further obse
		cleansing solution of PEG 4000 in hospital setting	Generalized urticaria, bronchial obstruction		after drinking 10 mL of the solution (cumulative dose ~590 mg)	calcium/vitami tablet. The pat advised to con intake
35	F	(1) Colon cleansing solution (Endofalk Classic®, is PEG 3350) (2) Disinfectant	Generalized urticaria, angioedema, vomiting 10 min after drinking	SPT: Pos. to Endofalk Classic®, Paroex® solution, PVP-Jod-ratiopharm®, and	OCT with magnesium capsules containing PEG 4000	As permanent medication. an contraceptive (30®, active ingr levonorgestrel,

Abbreviations: BAT, basophil activation test; IDT, intradermal test; mi, minutes; Neg, negative; OCT, oral challenge test, SCT, subcutaneous challenge test; PEG, polyethylene glycol; Pos, positive; PS80, polysorbate 80; SPT, skin prick test.

2.2 Management of patients asking for allergy workup for COVID-19 vaccine hypersensitivity

Patients referred to the allergy unit from April 2020 until April 2021 because of self-reported adverse reactions after the first dose of a mRNA (Comirnaty® or Moderna vaccine), or DNA (Vaxzevria® or Janssen®) COVID-19 vaccine, or reporting possible allergy against a vaccine ingredient were assessed and managed prospectively as outlined in Figure 1. Testing was carried out with vaccines, PEG, PS80, and trometamol, the latter only if relevant in the patient history (reaction to Moderna® or other preparation containing trometamol). Patients without clinical criteria for PEG allergy (Table 3) were referred for direct vaccination without allergy tests,[1, 6, 18] as recommended by the algorithm of the German Federal Institute for Vaccines and Biomedicine (Paul Ehrlich Institute) and German allergy associations (Figure S1),[21, 22] which mirrors other published recommendations.[18-20] Mastocytosis without criteria for vaccine excipient allergy was no indication for testing.[23] Unclear cases were handled by shared decision-making discussing the case between the allergy resident, allergy supervisors, and the department director. Patients with suspicion for possible allergy to vaccine ingredient(s) were skin tested, and in patients with PEG allergy, the basophil activation test (BAT) was added as described and outlined in Table S1 and in Supplementary Methods.



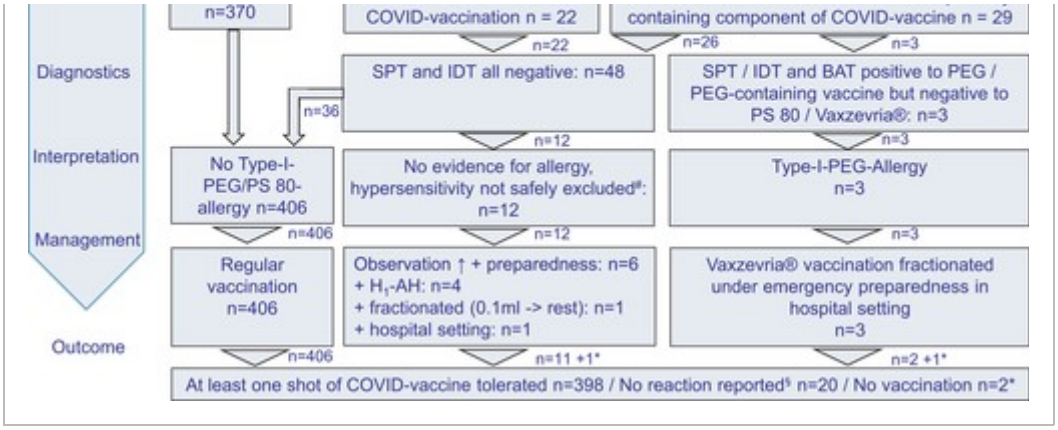


FIGURE 1

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Flow chart of patients evaluated requesting allergy diagnostics regarding vaccination against COVID-19 and tolerating vaccination. # Patients with immediate urticaria or anaphylaxis-like reaction as a precaution for safety in case of non-allergic hypersensitivity; *patients who did not want to be vaccinated; §patients not reporting despite call to report any hypersensitivity reaction

2.3 Outcome of vaccination

Outcome of vaccinations with regard to hypersensitivity reactions was recorded by patient interview asking for events occurring within 1 hour and by telephone interview of those 51 patients in whom we performed allergy tests. We asked the patients without need of allergy workup to report to us, if such reactions occur.

3 RESULTS

3.1 Retrospective patient series with PEG allergy

Ten patients with confirmed IgE-mediated allergic reactions to PEG were identified in our two allergy units within the last 14 years (Table 1). This report includes the highest number of allergy-tested PEG-allergic patients in the literature. Nevertheless, our study spanning a 14-year period shows that PEG allergies are rare. In the medical history of PEG-allergic patients, reports of repeated reactions were frequent (40%), but not in the majority of patients. The common clinical manifestation was anaphylaxis according to the NIAID/FAAN criteria for anaphylaxis by Sampson et al (10/10; 100%),[24] and with generalized skin reaction (urticaria in 9/10 and generalized erythema in 1/10) in all patients (Table 1). Two patients developed unconsciousness (patients 77 m, 35 f). The onset of the allergic reactions was rapid, within few minutes in case of injections and within 60 minutes following oral uptake of the allergen. A common feature was that the systemic allergic reactions occurred after exposure to PEG 3350 or PEG 4000 in the dissolved form in most cases. The medications containing PEG were intestinal cleansing preparations, laxatives, lozenges, effervescent tablets, and solutions for injection. PEG uptake was oral, via the intestinal or genital mucosa or via subcutaneous tissue following injections. SPT with the suspected drugs and/or PEG

solutions (PEG 3350 or PEG 4000) were positive in 8/10 cases. Skin test reactivity was negative in 2/2 patients to PEGs of lower MW, as has been reported in the literature.[1] Mild systemic symptoms (tingling of the tongue or palate, sneezing/rhinorrhea, and dizziness), similar to those observed during OPT, were observed in 2/10 (19 f, 12 m) individuals following skin tests. Whereas in two patients, OPT was stopped because of safety concerns after having received a knife tip (~10 mg) or 30 mg of PEG 4000, respectively, before a reaction developed, in 7/9 patients (77 m, 35 f, 19 f, 46 m, 47 f, 21 f, and 24 f), the allergic reaction could be reproduced by OPT using the appropriate PEG preparation; two patients developed bronchial obstruction or shortness of breath (77 m and 46 m). The criteria we found for PEG allergy in the history in these 10 patients were in accordance with and confirmed those published in reviews and recommendations (Tables 2 and 3).[2, 6, 12, 18, 19]

TABLE 2. Parameters indicative of PEG allergy in patients in our study and comparison to a review and a large case series in the literature

Parameter	PEG allergy in this study	Wenande et al.[1]	Bruusgaard et al.[6]
Gender (f/m)	7/3	14/23	6/4
Age (y: median, range)	38.5 (12–77)	24–86	35 (18–64)
Time interval[a] (min)	18.5 (4–30)	"Rapid in onset within minutes"	<10 min
Elicitors[b] (n)	Laxatives/bowel preparations (3) Analgetic tablets (2) Injectable contraceptive (2) Antibiotic tablets/sirup (2) Calcium or vitamin effervescent tablet (2) Cold medicine	Laxatives/bowel preparations 20/37 (54%), corticosteroids, vitamins/minerals, throat lozenges, ultrasound gels, disinfectants, antiepileptics, antiemetics, anticoagulants, antidepressants, analgesics, antibiotics, anti-inflammatory drugs, reflux medication toothpaste, dental floss, creams, shampoos, paint, wound dressings, tissue sealants, hydrogels	Oral medication (analgesics, antacids, antibiotic tablets) Injections Laxatives Cough medicine Cream/ointment, shaving products, hand soap, toothpaste, mouth wash, dental floss, hair products (shampoo, coloring), make-up, make-up remover, vaseline, epoxy, cleaning

Abbreviation: ns, not specified.

[a] Time interval from exposure to reaction.

[b] Individual episodes counted separately.

[c] Severe anaphylaxis according to Ring and Messmer grades III and IV.

TABLE 3. Patients for which polyethylene glycol allergy testing is required before vaccination

Clinical suspicion of PEG allergy:
Patients with severe systemic allergic reactions or anaphylaxis within 1–2 h to
- PEG-based laxatives/bowel preparations or PEG-containing drug injections
- PEG-containing cough medication, lozenges or vaginal suppositories
- PEG-containing products after sensitization to active ingredients have been excluded or only certain brand names of the same drug containing PEG
Individually consider clinical possibility of PEG allergy:
Patients with severe doctor-confirmed or doctor-treated allergic reactions anaphylaxis to structurally different drugs

3.2 Patients self-reporting a history of COVID-19 vaccine hypersensitivity

In total, 421 e-mails and telephone calls were received from patients or referring doctors self-reporting a history of COVID-19 vaccine hypersensitivity or alleged increased allergy risk for vaccination against COVID-19 (Figure 1). Cases were assessed for signs indicative of PEG allergy or for immediate-type hypersensitivity to vaccination against COVID-19 (see section 2). Most patients reported unspecific and/or delayed reactions not indicating immediate-type allergy, such as swellings at the reaction site, delayed urticaria, flu-like symptoms,[25] or a history of other drug, insect venom, or food allergies not qualifying for further allergy workup for PEG allergy. Thus, exclusion of criteria indicative of PEG allergy (Table 3) and published recommendations (Figure S1) were helpful to recommend direct vaccination without allergy test or additional precaution in 370 patients (88%). Hence, the vast majority of patients suspecting allergic reactions could be encouraged to proceed to vaccination without allergy tests by history alone (Figure S1, Table 3).

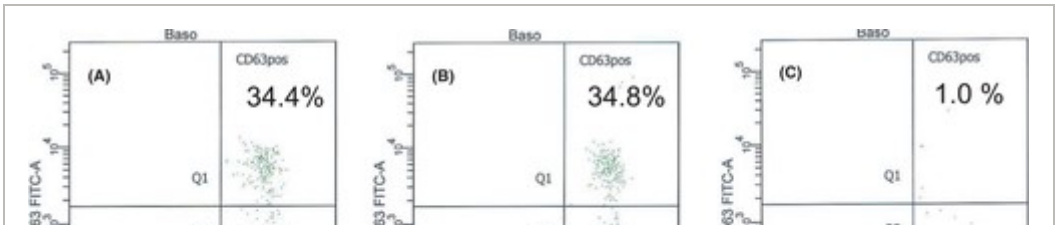
Other 51 patients (12%) were invited for allergy skin testing, when it was felt that an allergy to a vaccine ingredient could not be safely excluded by history alone. In three patients (6%), PEG allergy was diagnosed: In two patients, PEG allergy was newly diagnosed by us and in one patient externally 8 years ago. They were identified by their typical history and by positive SPT and IDT results (Table 4). BAT was positive in 3/3 PEG-allergic patients but not in

controls (Figure 2, Table 4, Tables S2 and S3). One patient showed pronounced reactions (max. %CD63-positive basophils) to Comirnaty®, Moderna vaccine, PEG 4000, and PEG 6000 (34%, 35%, 16%, and 36%), one patient to Moderna® (16.1%), and one patient to both mRNA vaccines (37% and 42%).

TABLE 4. Characteristics and vaccination management of new patients with confirmed PEG allergy

Age	Sex	Elicitor	Reaction	Skin test results	Interpretation	Manageme
73	M	Colon cleansing solution (=PEG 3350)	30 min after third or fourth cup of PEG-preparation palmar erythema, generalized itch, dizziness	SPT: Pos. to PEG 3350, 4000 Neg. to: PEG 2000, PEG 6000, PS 80 IDT: Pos. to PEG 3350, 4000, 6000. After IDT generalized itch and palmar erythema Neg. to PEG 2000 and PS 80 BAT: Pos. to	No OCT was performed because of systemic reaction after skin test High risk for reaction to mRNA-containing COVID-19 vaccines. Low risk for reaction to Vaxzevria® because of negative skin tests and BAT and thus unlikely cross-reactivity to	mRNA vaccination avoidance DNA vaccination against COVID-19 indicated. Tolerated fir shot of fractionated Vaxzevria® (0.1 mL; 0.4 mL) under inpatient emergency preparedne without premedicati

Abbreviations: BAT, basophil activation test; IDT, intradermal test; mi, minutes; Neg, negative; OCT, oral challenge test; PEG, polyethylene glycol; Pos, positive; PS80, polysorbate 80; SPT, skin prick test.



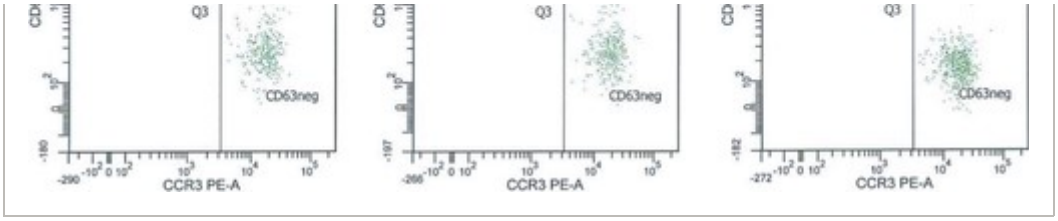


FIGURE 2

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Skin test and basophil test results (A: Comirnaty® diluted 1:5, B: Moderna diluted 1:5, C: Vaxzevria® diluted 1%) in a patient with skin test-confirmed PEG allergy who was successfully vaccinated with Vaxzevria®

In 48/51 patients (94%), no hint for PEG allergy could be identified by skin tests. Depending on the history of the reaction and backed up by lacking skin test reactivity, a risk assessment for future COVID-19 vaccine reactions was performed by shared decision-making. Vaccination was recommended in all patients; however, different management measures were selected for vaccination according to the risk assessment (Figure 1).

3.3 Management and outcome of COVID-vaccination

In the retrospective cohort of 10 patients, one elderly patient died of cancer unrelated to allergy, three could not be contacted, two were not yet vaccinated, and four patients tolerated vaccination against COVID-19: Two patients were vaccinated with Vaxzevria®, but without our consultation also one patient tolerated two shots of Comirnaty® with prophylactic antihistamine and one a Vaxzevria®-Comirnaty® cross-over vaccination.

In the 3/51 prospective skin test-identified PEG-allergic patients, skin tests and BAT with Vaxzevria® were negative and Vaxzevria® vaccination was tolerated in the first two patients, first vaccination under inpatient conditions in the absence of premedication with fractionated doses (0.1 mL; 0.4 mL; separated by 2 hours) and the third received the full second dose under emergency preparedness at a vaccination center (Table 4). Thus, PEG-allergic patients could be vaccinated using a COVID-19 vaccine that does not contain PEG, such as a DNA vaccine.

A total of 36 of the 48/51 skin test-negative patients received routine vaccination without allergy-specific precautions and in the remaining 12 patients, non-allergic hypersensitivity reactions/skin-test negative allergic reactions could not be excluded. Therefore, depending on the history, the risk for COVID-19 vaccine anaphylaxis was assessed by shared decision-making and different individual vaccination approaches were proposed (Figure 1). Vaccinations were tolerated in 48/48 patients without immediate hypersensitivity reaction.

Of note, the 370 patients who were not allergy tested reported no event of immediate allergic reactions. Two patients reported delayed reactions (urticaria, nausea, stiffness, and palsy). This indicates that shared decision-making for vaccination management based on medical history and supported by skin tests is a helpful and safe approach.

4 DISCUSSION

PEG allergy has been widely discussed as cause of anaphylaxis to mRNA vaccines for COVID-19 protection.[4, 26] Consequently, in patients with PEG allergy, withholding vaccination with PEG-containing vaccines is recommended, but, in real life, many more miss to be vaccinated based on pure suspicion.[12, 18, 19, 21] Based on our data, we propose a more personalized approach showing that (a) most patients can be vaccinated without allergy tests just based on detailed history taking, that (b) allergy testing identifies patients with PEG allergy and may help in selecting the right approach for vaccination, and that (c) patients with PEG allergy can be vaccinated against COVID-19.

An analysis of criteria indicating PEG allergy in our patients confirmed previously published clinical signs (Tables 2 and 3).[2, 3, 5, 6, 27] Position papers on how to handle vaccinations against COVID-19 in patients at risk for allergic reactions are important guidelines.[12, 21, 22] In contrast, collections on real-life data on patients asking for allergy workup concerning COVID-19 vaccine allergy are just in the process of being published and future recommendations need to include these and adjust the guidelines, if applicable.[28, 29] There is consensus on the following: (a) Testing of "all" is not feasible nor necessary, (b) procedures should aim at allowing vaccinations to be carried out over avoiding vaccination, and (c) selected patients should be tested prior to vaccination.[12, 22] In addition, a delay from COVID-19 protection due to allergy tests that are actually not needed may cause harm to individual patients.

To this end, we analyzed how many patients are eligible for vaccination just based on detailed history taking and found that 370/421 patients with concerns in regard to vaccine hypersensitivity could be referred to vaccination without further allergy workup (Figure S1, Table 3). In another 48/51 patients with negative skin tests, an allergy was largely excluded, which aided to select a less controlled vaccination approach. Of note, PEG hypersensitivity despite negative skin tests has been described and was seen also in one of our patients.[30] As we could not safely exclude non-allergic hypersensitivity (e.g., chronic or stress-associated urticaria and non-IgE-mediated hypersensitivity reactions) in 10 patients with immediate allergy-like and in 2 with anaphylaxis-like reactions despite negative skin test, we individually recommended prolonged observation, increased emergency preparedness and antihistamine premedication (for those with prominent urticaria), and/or fractionated vaccination ± inpatient setting for those with anaphylaxis-like reactions (Figure 1). As none of our patients reported adverse reactions after taking the recommended shot, we conclude that the combined test regimen has a tolerable sensitivity.[25] A study from the United States reported good tolerance of the second vaccination against COVID-19 in 80% of 159 patients with allergy-like reaction to the first dose, however, after excluding patients with PEG allergy and those with severe symptoms, which indicates that that a decision-making according to personalized history can augment the amount of patients receiving vaccinations.[29]

Our allergy tests identified three new patients with PEG allergy, which is similar to data from

the literature.[12, 16, 28, 31] Confirming suspected IgE-mediated PEG allergy with skin tests needs application of special variants of PEGs, since PEGs of lower molecular weight (MW) tend to be unresponsive.[2, 4] Of note, PEG 2000 is declared to be part of the mRNA vaccines (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (Comirnaty®) or PEG 2000 dimyristoyl glycerol (Moderna vaccine)); however, using PEG with MW of 4000 also produced positive skin test results in our patients.[2, 4, 12] Although false-positive skin test results to PEG 4000 cannot be ultimately excluded, our results are in agreement with those of other groups describing positive responses only in patients with PEG allergy.[1, 4] Similar results were obtained with BAT also showing positive reactions to both mRNA vaccines and negative results with Vaxzevria® (Figure 2, Table S2). Also, Troelnikov et al. presented patients positive in BAT to Comirnaty® and PEGylated liposomal doxorubicin but negative to Vaxzevria®.[32] Therefore, it can be assumed that only the special PEG arrangement on the surface of these lipid nanoparticles leads to a sufficient cross-linking of IgE on basophils in some PEG-allergic patients.[32] However, future provocation tests with PEG and mRNA vaccines would be necessary to confirm the clinical relevance of these findings.

Despite the ongoing discussion about the safety of IDT and OPTs in PEG allergy, we used these procedures to confirm a suspicion of PEG allergy and found that they can be performed with caution.[1, 12, 18, 20] Indeed, systemic reactions may occur to SPT as described in the literature and as seen in our patients.[1, 5] Therefore, it is recommended to start skin tests and OPT with low concentrations and doses, respectively, and under emergency preparedness. Skin tests to vaccines still remain unsatisfyingly validated, with sensitivity and specificity not yet being determined and vaccines, in general, may elicit test reactions of uncertain significance, for example, based on previous immunity or vaccine adjuvants.[11] OPT is the gold standard in drug allergy and PEG-hypersensitive patients with negative SPT have been described.[30] Thus, IDT and OPT should be considered in SPT-negative patients with clinical suspicion of PEG allergy.[1, 5, 33] IDT with PEG-containing vaccines should be considered in patients with reactions after vaccination with such vaccines, as it has been suggested that PEGylation itself might have an effect on test response to PEG products.[32] In OPT, doses between 500 mg-1.5 g PEG 3350 and 10–60 mg PEG 4000 elicited reactions and confirmed PEG allergy, demonstrating reactivity to lower amounts of PEG compared to the available data in the literature (55 g PEG 3350 and 7.1 g PEG 4000).[1]

Allergy to PEG is a contraindication for applying PEG-containing vaccines.[2, 3, 5, 8, 12, 18, 19, 21] However, unexpectedly two of our historical patients with PEG allergy were ignorant of the risk despite allergy pass and tolerated Comirnaty® vaccination. In a Danish study, a further patient with isolated delayed skin reaction to Comirnaty® and positive skin test to PEG tolerated revaccination.[28] The reasons for tolerance remain unclear. Their PEG allergy may have been lost over the years, the amount of PEG in mRNA vaccines was too small, the MW was too low (MW 2000), or it may be a combination of different factors. Until further clarification, PEG-responsive patients may receive DNA vaccines containing PS80 under emergency preparedness, as did four of our patients, who tolerated Vaxzevria®. This

vaccination was given under close observation and emergency preparedness but without premedication for better monitoring of symptoms, and not all patients received fractionated dosing, indicating that these additional safety measures may not be needed in skin test-negative patients in this setting. Although skin test cross-reactivity between PEG and PS80 has been reported, the relevance of this observation remains unknown and was not confirmed in our patients.[1, 20] Likewise, negative BAT to PS80 in our four PEG-allergic patients argues against cross-reactivity.[34]

In conclusion, in this largest allergy-tested series of patients with PEG allergy, we confirmed clinical criteria indicating PEG allergy (Table 3), attested the practicability of existing recommendations (Figure S1) [21, 35], demonstrated the value of allergy tests for detecting PEG allergy, and safely vaccinated all patients, including those with PEG allergy with a DNA vaccine, by giving specific individual recommendations for the vaccination approach according to risk analysis and with shared decision-making.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Supporting Information

Filename	Description
all15183-sup-0001-Supinfo.docx Word 2007 document , 31.8 KB	Supporting information
all15183-sup-0002-FigS1.pdf PDF document, 592.2 KB	Fig S1
all15183-sup-0003-TableS1.docx Word 2007 document , 21.1 KB	Table S1
all15183-sup-0004-TableS2.docx Word 2007 document , 22.3 KB	Table S2
all15183-sup-0005-TableS3.docx Word 2007 document , 94.2 KB	Table S3

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Supplementary Materials

Detailed methods and results of the basophil activation test

Patients and controls

In the three new PEG allergic patients, in one of the PEG patients from the cohort of 2006 – 2019 (73 years, male; 59 years, female; 28 years, female; 76 years, female) and in three tolerant controls vaccinated with Comirnaty® (52, 56 and 62 years old, females), the basophil activation test was performed as described below. Additionally, in one 59 year-old female patient with suspected hypersensitivity to compounds of the vaccines and negative skin test to them, the BAT was performed with negative results (data not shown).

Reagents for BATs

BAT was performed using different dilutions in reconstitution (undiluted, 1:5, 1:25, 1:125 diluted) of two mRNA COVID 19 vaccines (Cormirnaty®, BioNTech Europe GmbH, Mainz, Germany; Moderna COVID-19 Vaccine®, Moderna, Cambridge, Massachusetts, USA) and a vector COVID 19 vaccine (Vaxzevria®, AstraZeneca, Oxford, United Kingdom). In two patients and one control also the COVID 19 vaccine Janssen® (Johnson & Johnson, New Brunswick, New Jersey, USA) was tested. Furthermore the following different types of polyethylene glycol (PEG) were used: PEG 2000 (Rotipuran®, Carl Roth GmbH, Karlsruhe, Germany; concentrations: 15 mg/ml, 3 mg/ml. 0.6 mg/ml), PEG 2000 (BAG2-CPEG2, BÜHLMANN Laboratories AG, Schönenbuch, Switzerland; concentrations: 0.91 mg/ml, 0.182 mg/ml, 0.036 mg/ml), DMG PEG 2000 (BAG2-CPEG3, BÜHLMANN Laboratories AG, Schönenbuch, Switzerland; concentrations: 0.00182 mg/ml, 0.00036 mg/ml, 0.0000728 mg/ml); PEG 3350 (Movicol®, Norgine B.V., Amsterdam, The Netherlands; concentrations: 15 mg/ml, 3 mg/ml. 0.6 mg/ml), PEG 4000 (Macrogol 4000, hospital pharmacy Klinikum rechts der Isar, Munich, Germany; purchase via Dow Chemicals, Midland, USA; concentrations: 15 mg/ml, 3 mg/ml. 0.6 mg/ml), PEG 4000 (BAG2-CPEG, BÜHLMANN Laboratories AG, Schönenbuch, Switzerland; concentrations: 0.91 mg/ml, 0.182 mg/ml, 0.036 mg/ml; available since June 2021), PEG 6000 (Rotipuran®, Carl Roth GmbH, Karlsruhe, Germany; concentrations: 15 mg/ml, 3 mg/ml. 0.6 mg/ml). The concentrations were chosen according to the manufacturer or adjusted according to previous publications (1,2,3,4). Polysorbat 80 (Tween® 80, Carl Roth GmbH, Karlsruhe, Germany) was used at concentrations of 22.7 mg/ml (0.23%) and 2.3 mg/ml (0.023%).

BATs

The Flow CAST (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) was used for quantitative measurement of in vitro basophil activation, as previously described (1). Venous blood was collected in 10-mL EDTA tubes from each subject. For each subject and allergen, polystyrene tubes were prepared with 50 µL of allergen at the defined concentration and diluted in 100 µL of stimulation buffer (containing heparin, Ca^{2+}, and IL-3 [2 ng/mL]). An anti-FcεRI mAb and anti–N-formyl-methionyl-leucyl-phenylalanine were used as positive controls. Background values were assessed with 50 µL of stimulation buffer. We added and gently homogenized 50 µL of each subject's whole blood (with EDTA), added 20 µL of staining reagent (anti-CD63–fluorescein isothiocyanate and anti-CCR3–phycoerythrin mAbs), and mixed and incubated the solution at 37°C for 25 minutes in an incubator. Two milliliters of lysing buffer stopped the stimulation within 5 minutes of incubation in the dark at room temperature, followed by centrifugation of the solution for 5 minutes at 460g. The supernatant was decanted, and stained cells were washed with 300 µL of washing buffer. Cells were resuspended by means of gentle vortexing and analyzed by using LSR Fortessa

flow cytometers (Becton Dickinson Immunocytometry System; Becton Dickinson, Heidelberg, Germany) with BD FACSDiva software. Basophils were gated as low side scatter $CCR3^{+}$/side $scatter^{low}$. Anti-CCR3 was used as a selection marker to separate basophils from other leukocytes. Upregulation of the basophil activation marker CD63 was calculated based on the percentage of $CD63^{+}$ cells compared with the total number of identified basophils. In each assay a minimum of 300 events (ie, basophils) were recorded. A cutoff of 15% $CD63^{+}$ cells for all compounds was used according to a previous study (1) and because it is the highest cutoff recommended by the manufacturer. Due to the small number of patients or the negative results ROC curves were not performed.

Results

The 73-year old patient showed a positive basophil activation with the Pfizer/BioNTech COVID-19 vaccine (undiluted: 20.0%, 1:5 diluted: 34.4%, 1:25 diluted: 18.4% CD63 expression), with the Moderna COVID-19 vaccine (1:5 diluted: 34.8%, 1:25 diluted: 30.6% CD63 expression), with PEG 4000 (15 mg/ml: 16.2% CD63 expression) and with PEG 6000 (15 mg/ml: 35.9% CD63 expression). No activation (values < 10% CD63 expression) was found with other concentrations of the above mentioned substances, with AstraZeneca COVID-19 vaccine, COVID-19 vaccine Janssen®, the other types of PEGs and polysorbate 80. Positive control (anti-FcεRI): 90.0%, negative control (buffer): 1.6%.

The 59-year old patient showed a positive basophil activation with the Moderna COVID-19 vaccine (undiluted: 16.1% CD63 expsression). No activation (values < 10% CD63 expression) was found with other concentrations of Moderna COVID-19 vaccine, with Pfizer/BioNTech COVID-19 vaccine, with AstraZeneca COVID-19 vaccine, COVID-19 vaccine Janssen®, the other types of PEGs and polysorbate 80. Positive control (anti-FcεRI): 16.0%, negative control (buffer): 3.2%.

The 28-year old patient showed a positive basophil activation with the Pfizer/BioNTech COVID-19 vaccine (undiluted: 17.4%, 1:5 diluted: 37.2% CD63 expression) and with the Moderna COVID-19 vaccine (undiluted: 13.4%, 1:5 diluted 41.8%, 1:25 diluted: 21.8%). No activation (values < 10% CD63 expression) was found with other concentrations of the above mentioned substances, with AstraZeneca COVID-19 vaccine, the other types of PEGs and polysorbate 80. Positive control (anti-FcεRI): 90.2%, negative control (buffer): 0.2%.

The 76-year old patient showed a positive basophil activation with the Pfizer/BioNTech COVID-19 vaccine (1:5 diluted: 16.9%, 1:25 diluted: 21.3% CD63 expression) and with the Moderna COVID-19 vaccine (1:5 diluted: 19.1%, 1:25 diluted: 20.5% CD63 expression). No activation (values < 10% CD63 expression) was found with other concentrations of the above mentioned substances, with AstraZeneca COVID-19 vaccine, the other types of PEGs and polysorbate 80. Positive control (anti-FcεRI): 90.4%, negative control (buffer): 4.5%.

All substances were negative in controls.

Details are found in Table S2 and Table S3.

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Table S2: Results of the basophil activation test (% CD63 basophils) in PEG patients

Compound	**Concentration**	**Pat. 1** (73 y, male)	**Pat. 2** (59 y, female	**Pat. 3** (28 y, female)	**Pat. 4** (76 y, female)
Negative control	-------	1.6	3.2	0.2	4.5
Positive control 1 (anti-FcεRI)	-------	90.0	16.0	90.2	90.4
Positive control 2 (fMLP)	-------	23.2	14.4	43.7	29,2
Cormirnaty®, Pfizer/BioNTech	Undiluted*	**20.0**	5.6	**17.4**	9.4
	1:5 diluted*	**34.4**	7.8	**37.2**	**16.9**
	1:25 diluted*	**18.4**	7.4	6.6	**21.3**
	1:125 diluted*	2.2	3.6	2.0	n.d.
Moderna COVID-19 vaccine®, Moderna	Undiluted*	6.6	**16.1**	**13.4**	6.2
	1:5 diluted*	**34.8**	9.6	**41.8**	**19.1**
	1:25 diluted*	**30.6**	6.2	**21.8**	**20.5**
	1:125 diluted*	9.8	2.5	5.2	n.d.
Vaxzevria®, AstraZeneca	Undiluted*	0.4	1.0	1.0	5.1
	1:5 diluted*	1.0	0.3	0.7	3.9
	1:25 diluted*	1.6	0.3	0.0	5.2
	1:125 diluted*	1.2	0.6	0.7	n.d.
COVID-19 vaccine Janssen®, Johnson&Johnson	Undiluted*	2.0	4.6	n.d.	n.d.
	1:5 diluted*	1.3	3.3	n.d.	n.d.
	1:25 diluted*	5.0	0.7	n.d.	n.d.
	1:125 diluted*	6.3	1.3	n.d.	n.d.
PEG 2000, Rotipuran®, Carl Roth GmbH	15 mg/ml	1.0	0.3	0.3	2.6
	3 mg/ml	2.4	1.3	0.6	3.0
	0.6 mg/ml	1.0	1.3	0.6	3.0
PEG 2000, BAG2-CPEG2, Bühlmann	0.91 mg/ml	2.1	0.3	1.0	3.6
	0.182 mg/ml	4.6	1.0	0.7	4.0
	0.036 mg/ml	5.3	2.0	2.6	3.3
DMG PEG 2000^{+}, BAG2-CPEG3, Bühlmann	0.00182 mg/ml	3.0	2.4	1.7	3.6
	0.00036 mg/ml	1.3	0.6	5.3	3.9

	0.0000728 mg/ml	n.d.	1.6	4.7	3.3
PEG 3350, Movicol®, Norgine B.V.	15 mg/ml	2.3	3.0	2.0	2.3
	3 mg/ml	2.7	1.3	1.3	1.7
	0.6 mg/ml	3.0	0.7	0.3	2.6
PEG 4000, Macrogol 4000, DOW Chemicals	15 mg/ml	**16.2**	2.9	0.3	8.3
	3 mg/ml	8.8	0.7	1.0	8.0
	0.6 mg/ml	7.0	0.6	0.0	9.0
PEG 4000, BAG2-CPEG, Bühlmann	0.91 mg/ml	4.3	n.d.	2.6	n.d.
	0.182 mg/ml	5.0	n.d.	1.3	n.d.
	0.036 mg/ml	7.3	n.d.	0.3	n.d.
PEG 6000, Rotipuran®, Carl Roth GmbH	15 mg/ml	**35.8**	4.7	0.7	4.9
	3 mg/ml	5.4	1.6	0.3	8.3
	0.6 mg/ml	1.7	2.0	1.3	4.6
Polysorbat 80, Tween® 80, Carl Roth GmbH	22.7 mg/ml (0.23%)	1.3	0.3	1.0	7.3
	2.3 mg/ml (0.023%)	1.0	0.0	0.3	5.6

***** For concentrations in stimulation values have to be divided by 4.4.
[+] DMG = 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
n.d.= not done

Table S3: Results of the basophil activation test (% CD63 basophils) in controls

Compound	**Concentration**	**Control 1** (62 y, female)	**Control 2** (56 y, female)	**Control 3** (52 y, female)
Negative control	-------	2.2	1.0	1.0
Positive control 1 (anti-FcεRI)	-------	90.8	82.2	86.3
Positive control 2 (fMLP)	-------	4.5	11.8	2.2
Cormirnaty®, Pfizer/BioNTech Coronavirus-Impfstoff BioNTech+	Undiluted*	2.0	0.6	0.8
	1:5 diluted*	1.6	1.0	3.5
	1:25 diluted*	0.3	1.3	2.6
	1:125 diluted*	n.d.	3.2	4.1
Moderna COVID-19 vaccine®, Moderna	Undiluted*	1.0	0.3	2.0
	1:5 diluted*	1.5	0.0	0.6
	1:25 diluted*	0.3	0.0	2.0
	1:125 diluted*	n.d.	0.6	2.2
Vaxzevria®, AstraZeneca	Undiluted*	1.0	0.6	2.2
	1:5 diluted*	0.6	2.3	1.6
	1:25 diluted*	0.7	0.3	0.8
	1:125 diluted*	n.d.	1.0	1.9
COVID-19 vaccine Janssen®, Johnson&Johnson	Undiluted*	n.d	n.d.	2.0
	1:5 diluted*	n.d.	n.d.	2.0
	1:25 diluted*	n.d.	n.d.	0.6
	1:125 diluted*	n.d.	n.d.	1.6
PEG 2000, Rotipuran®, Carl Roth GmbH	15 mg/ml	1.7	0.7	0.4

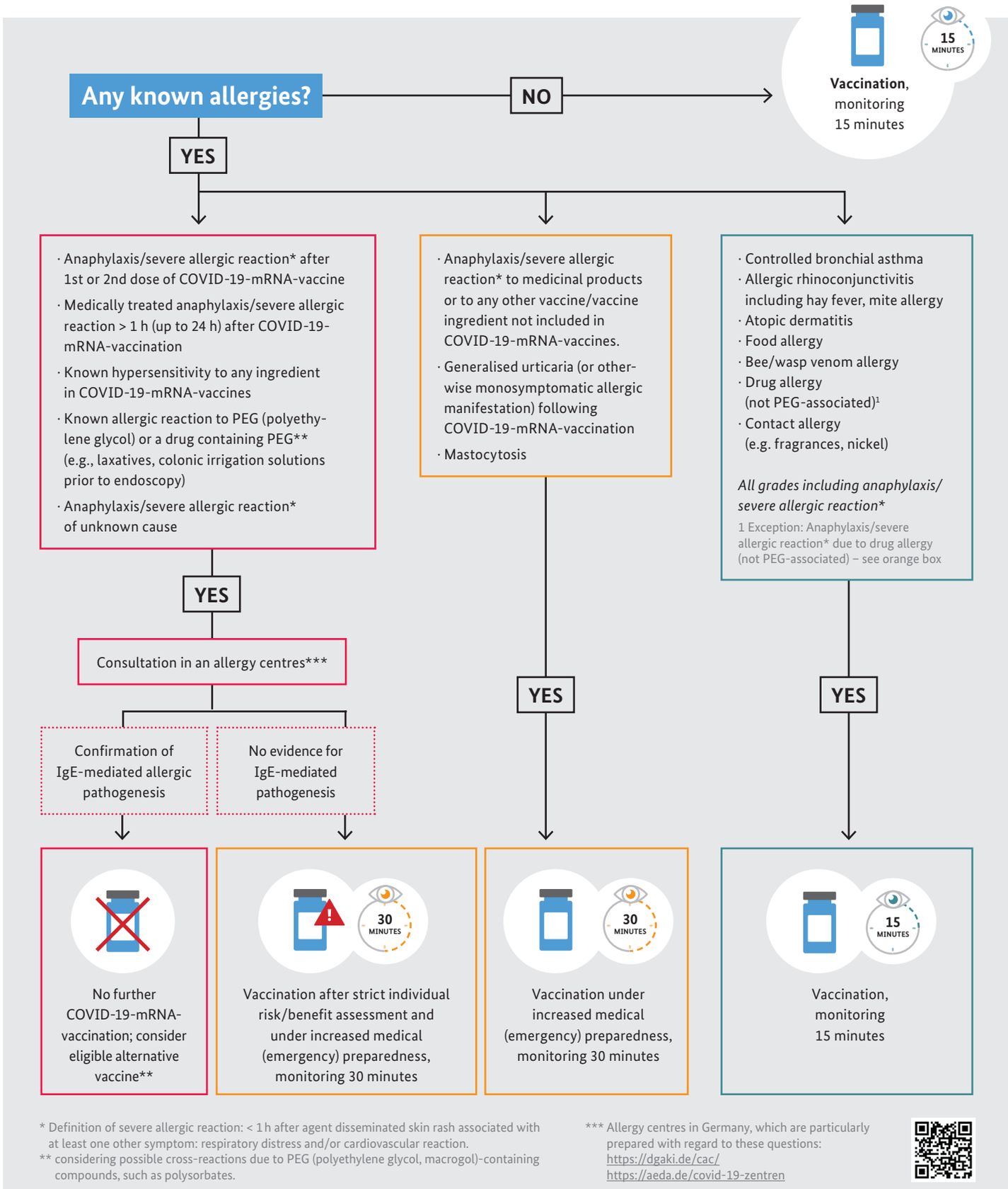
	3 mg/ml	2.0	2.2	0.3
	0.6 mg/ml	2.0	1.0	0.6
PEG 2000, BAG2-CPEG2, Bühlmann	0.91 mg/ml	2.0	2.4	1.4
	0.182 mg/ml	0.7	1.9	3.2
	0.036 mg/ml	1.9	2.3	3.3
DMG[+] PEG 2000, BAG2-CPEG3, Bühlmann	0.0182 mg/ml	1.0	1.6	2.8
	0.0036 mg/ml	1.3	1.2	2.6
	0.000728 mg/ml	1.0	n.d.	2.3.
PEG 3350, Movicol®, Norgine B.V.	15 mg/ml	3.3	3.0	1.5
	3 mg/ml	1.0	0.9	0.9
	0.6 mg/ml	1.9	2.9	1.9
PEG 4000, Macrogol 4000, DOW Chemicals	15 mg/ml	1.0	1.8	1.4
	3 mg/ml	0.3	2.3	0.3
	0.6 mg/ml	1.9	1.6	1.0
PEG 4000, BAG2-CPEG, Bühlmann	15 mg/ml	n.d	n.d.	0
	3 mg/ml	n.d.	n.d.	1.9
	0.6 mg/ml	n.d.	n.d.	1.6
PEG 6000, Rotipuran®, Carl Roth GmbH	15 mg/ml	2.3	1.8	0.6
	3 mg/ml	1.3	2.3	0.3
	0.6 mg/ml	1.3	1.6	0.6
Polysorbat 80, Tween® 80, Carl Roth GmbH	22.7 mg/ml (0.23%)	7.0	0.6	0
	2.3 mg/ml (0.023%)	0.3	1.6	0.3

***** For concentrations in stimulation values have to be divided by 4.4.

[+] DMG = 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000

n.d.= not done

How to proceed in case of positive allergy history prior to COVID-19 mRNA vaccination?



* Definition of severe allergic reaction: < 1 h after agent disseminated skin rash associated with at least one other symptom: respiratory distress and/or cardiovascular reaction.
** considering possible cross-reactions due to PEG (polyethylene glycol, macrogol)-containing compounds, such as polysorbates.

*** Allergy centres in Germany, which are particularly prepared with regard to these questions:
https://dgaki.de/cac/
https://aeda.de/covid-19-zentren

General considerations
- After other immediate reactions (e.g. vaso-vagal reactions or panic attacks), vaccination may be given under increased emergency preparedness and monitoring for 30 minutes.
- Vaccination centres or mobile vaccination teams must be equipped with emergency equipment to treat any anaphylactic reactions that may occur.

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Version 1 (as of 25.03.2021)

Zusammen gegen Corona · Paul-Ehrlich-Institut · Robert Koch Institut · AEDA Ärzteverband Deutscher Allergologen e.V. · DGAKI · NORA · Deutsche Dermatologische Gesellschaft DDG

Table S1. Allergy test procedure to exclude PEG or polysorbate allergy in this study (modified by German Comprehensive Allergy Centers from [21, 35])

SPT	with PEG 2000, 3350, 4000, 6000, PS 80, trometamol 1/100 → 1/10 with vaccines* 1/10 → undiluted and/or injectable PEG-containing preparations 1/10 → undiluted and suspected preparations 1/10 → undiluted
IDT	with PEG 2000, 4000, 6000, PS80, trometamol* 1/10000 → 1/1000 with vaccines** 1/100 → 1/10 and/or injectable PEG-containing preparations, if available and suspected preparations
sIgE	consider sIgE to ethyleneoxide, chlorhexidine, latex
Tryptase	to exclude mastocytosis and hereditary alpha-tryptasemia
BAT* **	PEG 2000, 3350, 4000, 8000, PS 80, Pfizer/BioNTech, Moderna, AstraZeneca COVID-19, COVID 19 Johnson&Johnson vaccines (for details see Supplementary Materials)

Diluted with saline; higher concentrations only tested in negative skin tests; PEG 2000, 3350, 4000, 6000 (Rotipuran®) and Polysorbat 80 (Tween 80®) from Carl Roth GmbH, Karlsruhe, Germany; trometamol from hospital pharmacy; *Only in patients with history for trometamol hypersensitivity; **Allergy testing with Comirnaty®, Vaxzevria® and Moderna vaccine was performed with residuals from emptied vials;***Only done in patients with positive skin tests; PEG, polyethylene glycol; PS80, = polysorbate 80.

Table S2: Results of the basophil activation test (% CD63 basophils) in PEG patients

Compound	**Concentration**	**Pat. 1** (73 y, male)	**Pat. 2** (59 y, female)	**Pat. 3** (28 y, female)	**Pat. 4** (76 y, female)
Negative control	-------	1.6	3.2	0.2	4.5
Positive control 1 (anti-FcεRI)	-------	90.0	16.0	90.2	90.4
Positive control 2 (fMLP)	-------	23.2	14.4	43.7	29,2
Cormirnaty®, Pfizer/BioNTech	Undiluted*	**20.0**	5.6	**17.4**	9.4
	1:5 diluted*	**34.4**	7.8	**37.2**	**16.9**
	1:25 diluted*	**18.4**	7.4	6.6	**21.3**
	1:125 diluted*	2.2	3.6	2.0	n.d.
Moderna COVID-19 vaccine®, Moderna	Undiluted*	6.6	**16.1**	**13.4**	6.2
	1:5 diluted*	**34.8**	9.6	**41.8**	**19.1**
	1:25 diluted*	**30.6**	6.2	**21.8**	**20.5**
	1:125 diluted*	9.8	2.5	5.2	n.d.
Vaxzevria®, AstraZeneca	Undiluted*	0.4	1.0	1.0	5.1
	1:5 diluted*	1.0	0.3	0.7	3.9
	1:25 diluted*	1.6	0.3	0.0	5.2
	1:125 diluted*	1.2	0.6	0.7	n.d.
COVID-19 vaccine Janssen®, Johnson&Johnson	Undiluted*	2.0	4.6	n.d.	n.d.
	1:5 diluted*	1.3	3.3	n.d.	n.d.
	1:25 diluted*	5.0	0.7	n.d.	n.d.
	1:125 diluted*	6.3	1.3	n.d.	n.d.
PEG 2000, Rotipuran®, Carl Roth GmbH	15 mg/ml	1.0	0.3	0.3	2.6
	3 mg/ml	2.4	1.3	0.6	3.0
	0.6 mg/ml	1.0	1.3	0.6	3.0
PEG 2000, BAG2-CPEG2, Bühlmann	0.91 mg/ml	2.1	0.3	1.0	3.6
	0.182 mg/ml	4.6	1.0	0.7	4.0
	0.036 mg/ml	5.3	2.0	2.6	3.3
DMG PEG 2000^{+}, BAG2-CPEG3, Bühlmann	0.00182 mg/ml	3.0	2.4	1.7	3.6
	0.00036 mg/ml	1.3	0.6	5.3	3.9
	0.0000728 mg/ml	n.d.	1.6	4.7	3.3
PEG 3350, Movicol®, Norgine B.V.	15 mg/ml	2.3	3.0	2.0	2.3
	3 mg/ml	2.7	1.3	1.3	1.7
	0.6 mg/ml	3.0	0.7	0.3	2.6
PEG 4000, Macrogol 4000, DOW Chemicals	15 mg/ml	**16.2**	2.9	0.3	8.3
	3 mg/ml	8.8	0.7	1.0	8.0
	0.6 mg/ml	7.0	0.6	0.0	9.0
PEG 4000, BAG2-CPEG, Bühlmann	0.91 mg/ml	4.3	n.d.	2.6	n.d.

	0.182 mg/ml	5.0	n.d.	1.3	n.d.
	0.036 mg/ml	7.3	n.d.	0.3	n.d.
PEG 6000, Rotipuran®, Carl Roth GmbH	15 mg/ml	**35.8**	4.7	0.7	4.9
	3 mg/ml	5.4	1.6	0.3	8.3
	0.6 mg/ml	1.7	2.0	1.3	4.6
Polysorbat 80, Tween® 80, Carl Roth GmbH	22.7 mg/ml (0.23%)	1.3	0.3	1.0	7.3
	2.3 mg/ml (0.023%)	1.0	0.0	0.3	5.6

***** For concentrations in stimulation values have to be divided by 4.4.
[+] DMG = 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
n.d.= not done

Table S3: Results of the basophil activation test (% CD63 basophils) in controls

Compound	**Concentration**	**Control 1** (62 y, female)	**Control 2** (56 y, female)	**Control 3** (52 y, female)
Negative control	-------	2.2	1.0	1.0
Positive control 1 (anti-FcεRI)	-------	90.8	82.2	86.3
Positive control 2 (fMLP)	-------	4.5	11.8	2.2
Cormirnaty®, Pfizer/BioNTech Coronavirus-Impfstoff BioNTech+	Undiluted*	2.0	0.6	0.8
	1:5 diluted*	1.6	1.0	3.5
	1:25 diluted*	0.3	1.3	2.6
	1:125 diluted*	n.d.	3.2	4.1
Moderna COVID-19 vaccine®, Moderna	Undiluted*	1.0	0.3	2.0
	1:5 diluted*	1.5	0.0	0.6
	1:25 diluted*	0.3	0.0	2.0
	1:125 diluted*	n.d.	0.6	2.2
Vaxzevria®, AstraZeneca	Undiluted*	1.0	0.6	2.2
	1:5 diluted*	0.6	2.3	1.6
	1:25 diluted*	0.7	0.3	0.8
	1:125 diluted*	n.d.	1.0	1.9
COVID-19 vaccine Janssen®, Johnson&Johnson	Undiluted*	n.d	n.d.	2.0
	1:5 diluted*	n.d.	n.d.	2.0
	1:25 diluted*	n.d.	n.d.	0.6
	1:125 diluted*	n.d.	n.d.	1.6
PEG 2000, Rotipuran®, Carl Roth GmbH	15 mg/ml	1.7	0.7	0.4
	3 mg/ml	2.0	2.2	0.3
	0.6 mg/ml	2.0	1.0	0.6
PEG 2000, BAG2-CPEG2, Bühlmann	0.91 mg/ml	2.0	2.4	1.4
	0.182 mg/ml	0.7	1.9	3.2
	0.036 mg/ml	1.9	2.3	3.3
DMG PEG 2000^{+}, BAG2-CPEG3, Bühlmann	0.00182 mg/ml	1.0	1.6	2.8
	0.00036 mg/ml	1.3	1.2	2.6
	0.0000728 mg/ml	1.0	n.d.	2.3.
PEG 3350, Movicol®, Norgine B.V.	15 mg/ml	3.3	3.0	1.5
	3 mg/ml	1.0	0.9	0.9
	0.6 mg/ml	1.9	2.9	1.9
PEG 4000, Macrogol 4000, DOW Chemicals	15 mg/ml	1.0	1.8	1.4
	3 mg/ml	0.3	2.3	0.3

	0.6 mg/ml	1.9	1.6	1.0
PEG 4000, BAG2-CPEG, Bühlmann	0.91 mg/ml	n.d	n.d.	0
	0.182 mg/ml	n.d.	n.d.	1.9
	0.036 mg/ml	n.d.	n.d.	1.6
PEG 6000, Rotipuran®, Carl Roth GmbH	15 mg/ml	2.3	1.8	0.6
	3 mg/ml	1.3	2.3	0.3
	0.6 mg/ml	1.3	1.6	0.6
Polysorbat 80, Tween® 80, Carl Roth GmbH	22.7 mg/ml (0.23%)	7.0	0.6	0
	2.3 mg/ml (0.023%)	0.3	1.6	0.3

***** For concentrations in stimulation values have to be divided by 4.4.
[+] DMG = 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
n.d.= not done