

RESEARCH LETTER

Adverse reactions to BNT162B2 vaccine in health care workers from an Italian Tertiary Care Hospital

To the Editor,

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection has affected over 280 million people worldwide, causing over 5.4 million deaths.¹ The scientific community and pharmaceutical industry have made a great effort to develop effective vaccines to prevent the virus from spreading and prevent infections and deaths. The first SARS-CoV-2 vaccine to be authorized for emergency use by the Food and Drug Administration was m-RNA Pfizer-BioNTech's BNT162B2 vaccine in December 2020.² Within the first days (December 14–23, 2020) of the mass vaccination, the Vaccine Adverse Event Reporting System reported 4393 (0.2%) adverse events (AE) out of 1,893,000 administered first doses, with 21 cases of anaphylaxis (11 cases per 1,000,000 doses administered).³ The reported Adverse Reactions (ARs) elicited public concern and clamour, especially because no cases of anaphylaxis were reported in randomized clinical trials with the vaccine. Afterwards, the anaphylaxis rate of the Pfizer vaccine has dropped to 4.7 cases per 1,000,000 doses with increasing vaccine doses administered (9,943,247 doses between December 14, 2020 and January 2021).⁴

The ARs or AEs to vaccines include any untoward medical occurrence following immunization, although it does not necessarily imply a causal relationship with the administration of the vaccine.⁵ Thus, the ARs can be either true or coincidental events not caused by the vaccine but temporally associated with it.

Although the pathogenic mechanism of allergic reactions to Pfizer-BioNTech's BNT162B2 vaccine has not been clearly elucidated, as well as the culprit trigger, the excipient polyethylene glycol 2000 (PEG-2000) is currently considered as the potential cause of anaphylactic reactions.⁶ Indeed, the nucleoside-modified mRNA encoding for spike protein of SARS-CoV-2 is enclosed in a lipid nanoparticle shell that contains PEG-2000. The scope of PEG-2000 is to stabilize lipids, favouring the entry of the m-RNA into the cell. PEG-2000, or macrogol, belongs to the PEG family, which are widely used in cosmetic, pharmaceutical and food products. Although the PEG family has always been always considered inert and safe, a growing number of cases of immediate hypersensitivity reaction to PEG have been described since 1990. So far, two cases of IgE-mediated allergy to PEG have been described as causing Pfizer-BioNTech's BNT162B2 vaccine reactions.^{6,7}

Extensive data regarding a direct comparison of ARs and hypersensitivity reactions after the Pfizer-BioNTech BNT162B2 vaccination in patients with and without history of allergy are still rare in the literature.

Therefore, the aim of our study was to assess ARs and possible hypersensitivity reactions during the vaccination campaign of 1293 health care workers (HCWs) of Meyer Children's University Hospital in Florence (Italy), carried out with the m-RNA Pfizer vaccine from January 1 to March 2, 2021.

Any ARs declared among the vaccinated HCWs population were recorded both through notifications collected by the hospital Pharmacy after the first and/or second dose of vaccine and face-to-face declarations with medical doctors before the second-dose administration.

ARs include side effects (Type A) or reactions possibly connected to a hypersensitivity reaction (Type B). Among the latter ones, reported reactions were divided by timing into immediate (<1 h), intermediate (1–6 h) and late (>6 h) reactions and singularly described.⁸

A physician collected the allergy history according to the anamnestic charts provided by the Italian National Health System. All patients had to answer the following questions about their allergy status:

- Do you suffer from allergies to latex, foods, drugs or vaccine components?
- Have you ever had a serious reaction after a vaccine administration?

Anaphylaxis is defined as a severe, systemic hypersensitivity reaction characterized by rapid onset with potentially life-threatening airway, breathing or circulatory problems. It is frequently associated with skin and mucosal change.

The population of study described in [Figure 1](#) was divided into two groups: Group I included HCWs claiming an allergic history; all others – with no allergic history declared – belonged to Group II. Different allergies were classified as follows: drugs, latex, other (including inhalants, foods, Hymenoptera, nickel).

Group I accounted for 22.4% of the population of study (290/1293). Women constituted the majority of HCWs analysed in both groups (76.6% of Group I; 72.4% within Group II; $p > .05$).

Within Group I, 44.8% (130/290) declared to be allergic to drugs, 4.1% (12/290) to latex and 64.8% (188/290) to other; history of anaphylaxis was detected, respectively in 10.8% (14/130), 8.3% (1/12) and 2.7% (5/188) of cases.

After the first-dose administration of Pfizer-BioNTech's BNT162B2 vaccine, 85.5% (248/290) of Group I claimed no adverse reactions, 12.8% (37/290) side effects ($p > .05$ vs. Group II) and 1.7% (5/290) clinical manifestations possibly indicating

hypersensitivity reactions ($p = .03$ vs. Group II). Among Group II the frequencies were 89.9% (902/1003), 9.7% (97/1003) and 0.4% (4/1003), respectively.

After the second-dose administration, 92.1% (267/290) of Group I claimed no adverse reactions, 7.2% (21/290) side effects ($p > .05$ vs. Group II) and 0.7% (2/290) reported clinical manifestation possibly indicating hypersensitivity reactions ($p > .05$ vs. Group II). Among Group II the frequencies were 91.3% (916/1003), 8.2% (82/1003) and 0.5% (5/1003), respectively (Table 1).

Considering the completed Pfizer-BioNTech BNT162B2 vaccination cycle, 2.4% of Group I (7/290; $p > .05$ vs Group II) and 0.9% (9/1003) of Group II stated post-vaccination effects possibly connected to a hypersensitivity reaction after the first or the second dose of vaccine.

In Group I, 4/7 hypersensitivity reactions notified after the first or second dose were immediate reactions, whereas 3/7 were late reactions. All 7 declared drug allergy history; 3/7 underwent an allergy evaluation before the first dose (two cases) or after an adverse reaction to the first dose (one case).

In Group II, 2/9 hypersensitivity reactions were immediate and 7/9 were late. No one underwent an allergy evaluation. During the vaccination programme, no anaphylaxis occurred.

The Allergy Unit of Meyer Children's University Hospital carried out 12 examinations to 11 HCWs (one of them was examined twice) on a voluntary basis and/or upon medical request: 58.3% (7/12) before and 41.7% (5/12) after the first-dose administration. Among the HCWs evaluated, 63.6% (7/11) declared a history of anaphylaxis; 81.8% (9/11) reported drug allergy history (Table 2, <https://doi.org/10.5281/zenodo.6428812>).

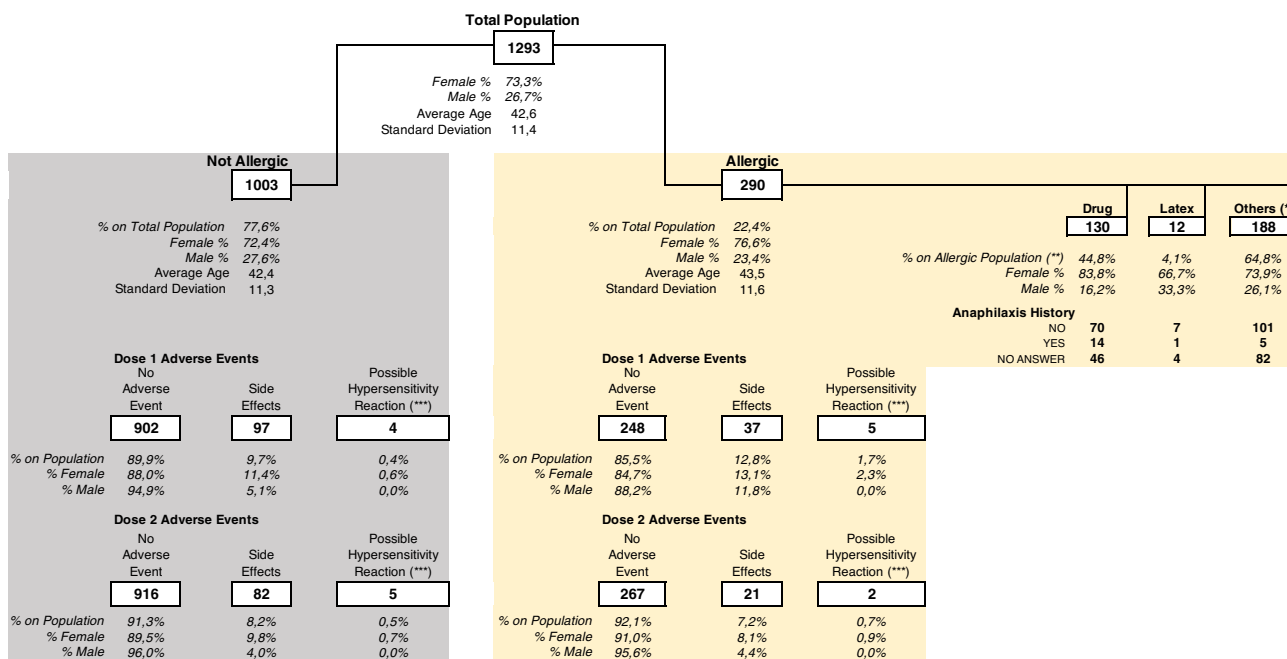
Key messages

- The polyethylene glycol 2000 is the potential cause of allergic reactions to Pfizer-BionTech's BNT162B2.
- No specific allergic history was associated with allergic reaction risk for BNT162B2 vaccine.
- Screening of allergic history/reactions and accurate management from specialized personnel led to safe vaccination.

During the allergy evaluation, in vivo tests consisted of Prick by Prick (PbP) with Macrogol 4000 (polyethylene glycol oral powder without extra excipients) and Pfizer-BioNTech's BNT162B2 vaccine.⁸ The tests were considered positive if the wheal diameter was equal to or >3 mm at 15-min reading. According to current standards, histamine and normal saline were used as positive and negative controls, respectively.

The PbP test with macrogol was performed in all cases with negative response; the PbP test with Pfizer-BioNTech's BNT162B2 vaccine was carried out after the first dose in 4/12 cases (33.3%), with negative results.

Therefore, no contraindications to vaccination emerged during the allergy evaluations. Based on each clinical history, different monitoring and hospital stay times after the injection were recommended. Two cases – who had experienced immediate angioedema reaction (lip oedema) after the first dose – were suggested to adopt



(*) Others include Inhalants, Foods and Others
(**) Percentage do not add up to 100% as there are multiples allergy causes by individual
(***) Details in Table A and B

FIGURE 1 Description of study population: adverse events after first and second dose in allergic and not-allergic population

TABLE 1 Possible hypersensitivity reactions notified after first or second dose of vaccine in allergic population (Group I) and not allergic population (Group II)

	Patient #	Allergy history	Anaphylaxis history	Reaction time ^b	Allergy evaluation	Reaction description
Allergic population (Group I)						
Dose 1	42	Drugs, latex, others ^a	Yes	Immediate	Yes, before Dose 1	Local reaction
	50	Drugs	No	Immediate	No	Loss of consciousness – vasoconstriction – supraclavicular and inguinal chest pain
	106	Drugs	No	Late	No	Asthma attack
	277	Drugs	Yes	Immediate	Yes, after Dose1	Lingual itching and oedema – thoracic constriction
	286	Drugs, others ^a	Yes	Late	Yes, after Dose 1	Lip oedema
Dose 2	174	Drugs	No	Late	No	Local reaction – intestinal disorders – urticarial skin rash
	228	Drugs, others ^a	No	Immediate	No	Dry cough – itching – tachycardia
Not allergic population (Group II)						
Dose 1	915	None	No	Late	No	Eyelid redness – cracking under the eyes
	935	None	No	Late	No	Local reaction
	946	None	No	Late	No	Local reaction
	1158	None	No	Immediate	Yes, after Dose 1	Tachycardia – facial redness
Dose 2	600	None	No	Immediate	No	Local reaction – chills – muscle aches
	671	None	No	Late	No	Fever – pain – nausea – chest pain – dry cough
	915	None	No	Late	No	Eyelid redness and cracking
	935	None	No	Late	No	Local reaction – headache – limb pain – fever with chills – lymphadenopathy
	946	None	No	Late	No	Frontal headache – local reaction

^aOthers include Inhalants, Foods and Others.

^bImmediate: <1 h; Intermediate >1 h <6 h; Late >6 h.

a pre-vaccination medication scheme (steroid plus antihistaminic) before receiving the second dose.

Further research on the mechanism underlying the ARs to Pfizer-BioNTech's BNT162B2 vaccine is crucial to allow a better risk stratification and patient selection for safe vaccine administration, avoiding vaccination hesitancy. Anyway, according to our results, Pfizer-BioNTech's BNT162B2 vaccine seems to be safe. Moreover, even if ARs appear to occur after the first dose more frequently in Group I, this trend seems to disappear after the second dose or when collecting the results of both doses. Thus, we may speculate that patients with allergic history probably are more prone to referring ARs.

The main observation emerging from our study is that no cases of anaphylaxis were recorded, even in the allergic population. Moreover, most of the reactions were mild and did not contraindicate the completion of the vaccine cycle, which was carried out in all HCWs but one who, despite the absence of contraindications, declined the second-dose administration.

Our study confirms that, after carefully screening allergic history/reactions, only a very low number of patients need thorough allergy investigations. In particular, no specific allergic history seems

to expose patients to a higher risk of reaction to Pfizer-BioNTech's BNT162B2 vaccine. Thus, a risk stratification protocol has to focus on identifying only patients with severe reactions to PEG or Polysorbate-80.⁹ In fact, an accurate management, handled by specialized personnel, allows vaccinating a greater number of people more safely.

In conclusion, data from large multicentre international cohorts remain necessary, especially those concerning skin test sensitivity and specificity with vaccines and their components, vaccines graded challenge and/or desensitization protocols. Nonetheless, the pre-evaluation flow charts proposed to define the stratification risk of recipients seem to work well and to be easily applicable on a large scale.

AUTHOR CONTRIBUTIONS

VG, FM, SB, MG and CA have participated in study design, analysis and interpretation of results. VG, FM and SB have prepared the manuscript; VG, FM, GL, SB and MG have contributed to the data acquisition and in vivo tests performance; All authors have critically revised the manuscript and have given final approval of the version to be submitted.

TABLE 2 Allergy evaluations: patients' characteristics, timing, tests and recommendations

Patient #	Allergies		Anaphylaxis history	Timing allergic evaluation	PbP tests		Recommendations
	Latex	Drugs			Macrogol 4000	Pfizer Vaccine	
16	No	Gentamicin sulphate + betamethasone	No	Before Dose 1	0 mm	No	No contraindications to vaccination
19	No	NSIDs, cephalosporin, penicillin	Yes	Before Dose 1	0 mm	No	No contraindications to vaccination; monitoring for 1 h and hospital stay for 2 h
42	Yes	Diclofenac sodium, amoxicillin and clavulanic acid	Yes	Before Dose 1	0 mm	No	No contraindications to vaccination; monitoring for 30 min and hospital stay for 2 h
83	No	Lansoprazole (contains PEG)	No	Before Dose 1	0 mm	No	No contraindications to vaccination; monitoring for 30 min and hospital stay for 2 h
84	No	Cefotaxima, miocamicin, cephaloperazone, oxolamine phosphate, chlorphenamine	Yes	Before Dose 1	0 mm	No	No contraindications to vaccination; vaccination in supine position and monitoring for 30 min
103	No	Ibuprofen	No	After Dose 1	0 mm	0 mm	No contraindications to vaccination; monitoring for 30 min
167	No	Ibuprofen	No	Before Dose 1	0 mm	No	No contraindications to vaccination; monitoring for 30 min
277	No	Cefazoline	Yes	After Dose 1	0 mm	0 mm	No contraindications to vaccination; pre-vaccination medication pattern: cetirizine 10 mg + prednisone 25 mg 12 h before and 2 h before second dose; monitoring for 30 min
286	No	NSIDs	Yes	Before Dose 1	0 mm	No	No contraindications to vaccination; monitoring for 30 min and hospital stay for 2 h
286	No	NSIDs	Yes	After Dose 1	No	No	No contraindications to vaccination; pre-vaccination medication pattern: bilastine 10 mg + prednisone 25 mg, 12 h before and 2 h before second dose
82	No	No	Yes	After Dose 1	0 mm	0 mm	No contraindications to vaccination
1158	No	No	No	After Dose 1	0 mm	0 mm	No contraindications to vaccination

Abbreviation: PbP, Prick by Prick.

KEYWORDS

adverse reactions, allergy, hypersensitivity reactions, Pfizer-BioNTech's BNT162B2 vaccine, polyethylene glycol, skin prick test

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests to disclose in relation to this paper.

ETHICAL APPROVAL

The Ethics Committee of the National Institute for Infectious Disease Lazzaro Spallanzani in Rome reviewed and approved on the study.

INFORMED CONSENT

Our data come from forms filled in by a doctor, following a verbal consent of the employee who voluntarily reported the side effect. Anonymous and aggregate data, used in the study, do not require more detailed consent.

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DATA AVAILABILITY STATEMENT

Aggregate analyses are available on reasonable request to the corresponding author.

Valentina Guarnieri¹
 Simona Barni²
 Mattia Giovannini^{1,2}
 Giulia Liccioli²
 Lucrezia Sarti²
 Silvia Ricci^{1,3}
 Lorenzo Lodi^{1,3}
 Clementina Canessa^{1,3}
 Francesca Lippi^{1,3}
 Maria Moriondo^{1,3}
 Laura Pisano^{1,3}
 Francesco Citera^{1,3}
 Chiara Azzari^{1,3}
 Francesca Mori²

¹Section of Pediatrics, Department of Health Sciences, University of Florence, Florence, Italy

²Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy

³Immunology and Molecular Microbiology Unit, Meyer Children's Hospital, Florence, Italy

Correspondence

Valentina Guarnieri, Section of Pediatrics, Department of Health Sciences, University of Florence, Viale Pieraccini 24, 50139 Firenze, Italy.

Email: valentina.guarnieri@unifi.it

Azzari and Mori contributed equally to this manuscript.

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