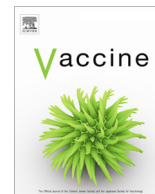




Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Efficacy of a rational algorithm to assess allergy risk in patients receiving the BNT162b2 vaccine

Mona-Rita Yacoub^{a,b,*}, Valentina Cucca^{a,1}, Chiara Asperti^b, Giuseppe A. Ramirez^{a,b}, Emanuel Della-Torre^{a,b}, Matteo Moro^c, Camilla Zandalasini^c, Davide Di Napoli^c, Alberto Ambrosio^c, Carlo Signorelli^d, Sergio Colombo^{b,e}, Luigi Beretta^{b,e}, Fabio Ciceri^{b,f}, Alberto Zangrillo^{b,e}, Lorenzo Dagna^{a,b}

^a Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy^b Vita-Salute San Raffaele University, Milan, Italy^c Medical Affairs Department, IRCCS Ospedale San Raffaele, Milan, Italy^d School of Hygiene and Public Health, Vita-Salute San Raffaele University, Milan, Italy^e Anaesthesiology and Intensive Care Unit, IRCCS Ospedale San Raffaele, Milan, Italy^f Haematology and Bone Marrow Transplantation Unit, IRCCS Ospedale San Raffaele, Milan, Italy

ARTICLE INFO

Article history:

Received 18 June 2021

Received in revised form 17 September 2021

Accepted 19 September 2021

Available online xxxx

Keywords:

Anaphylaxis

COVID vaccine

Drug allergy

Mast cell disorders

Safety

Trypsinase

ABSTRACT

Among 6146 hospital employees, 118 subjects with severe allergic background were identified through a screening questionnaire and stratified into 3 groups (Low-risk (LR), Intermediate (IR) and High-risk (HR) group), based on their allergic anamnesis.

Data reports on hypersensitivity reactions (HypR) have been collected in both allergic and non-allergic subjects. Seventeen patients (14%) in the allergic population had a HypR after the first, the second or both doses. Skin manifestations were the most frequent ones. Allergic events were more frequent in HR (35%) than IR (10%; $p = 0.005$) or LR (0%; $p = 0.074$) subjects. No patient had anaphylaxis. All patients completed the vaccination schedule.

13 HypR occurred in patients without severe allergic background (13/6028, 0.2%) including one (1/6148, 0.016% of total population) WAO grade-4 anaphylaxis.

Our data suggest that BNT162b2 mRNA Covid-19 vaccine is relatively safe also in patients with severe allergic background; however, some precautions are required for high-risk patients.

© 2021 Elsevier Ltd. All rights reserved.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated disease (COVID-19) is a systemic infectious disease associated with high morbidity and mortality. Vaccines based on liposomal mRNA are most effective at lowering the risk of severe COVID-19. Immune-mediated adverse events including anaphylaxis (reportedly occurring with a rate of 12–19 cases/million vaccine doses [1,2]) have however been reported [3–6] in association with mRNA vaccines and have a major role in vaccine hesitancy among patients with known immunological disorders, including allergy [7–9]. Little is known about the pathophysiological mechanisms and potential risk factors favouring the development of

hypersensitivity reactions (HypR) to mRNA-based vaccines. Excipients such as high molecular weight-polyethylene glycole (PEG), polysorbate-80 (a detergent with chemical similarity to PEG) or trometamol have been hypothesised as targets of allergic sensitisation and triggers of HypR to mRNA vaccines, being *hidden allergens* of difficult identification in patients with multi-drug allergy [10]. Other authors have questioned the role of excipient allergy and proposed alternative mechanisms to explain the occurrence of vaccine-related systemic reactions [11,12]. Early recommendations from drug regulatory agencies emphasised the role of reaction severity in stratifying patients based on their allergy history, restricting indications to skin tests and graded dose challenges to patients with a highly suggestive history of allergic sensitisation to PEG or with anaphylaxis after the first dose of mRNA vaccines [13]. Eventually, real-life series confirmed the limited utility of pre-emptive skin tests in the setting of adequate clinical screening [14,15].

To assess the efficacy of a rational algorithm to screen and manage patients at high-allergy risk according to their expected

* Corresponding author at: Immunology, Rheumatology, Allergy and Rare Diseases Unit, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Via Olgettina 60 – 20132, Milan, Italy.

E-mail address: yacoub.monarita@hsr.it (M.-R. Yacoub).

¹ These authors equally contributed.

individual risk of allergy to mRNA-based vaccines based on clinical history, we set up a prospective observational study in a large cohort of health professionals candidate to vaccination with the BNT162b2 vaccine.

2. Methods

2.1. General screening

From January 4th, 2021 to March 19th, 2021, all employees of the San Raffaele Hospital, Milan, Italy were invited to complete a simplified screening questionnaire (Suppl. Table 1), assessing the presence and self-reported severity of an allergic history. Red flags for a severe allergic history encompassed 1) past severe reactions to vaccines, drugs, hymenopter venom, foods, latex; 2) multiple drug HypR; 3) a known or suspected allergy to PEG/polisorbates; 4) mast cell disorders (mastocytosis or mast cell activation syndrome [MCAS] [16,17]; 6) uncontrolled asthma and/or chronic spontaneous urticaria (CSU).

2.2. Patient stratification

Patients with one or more red flags at the screening questionnaire were further screened with direct clinical interviews (including assessment of previous clinical records when available) by an expert allergist and, upon informed consent, enrolled in a wider observational protocol approved by the Institutional Review Board (Panimmuno research protocol, reference code 22/INT/2018). Baseline tryptase levels were measured in patients with clinical history of anaphylaxis, systemic mastocytosis and MCAS. The allergy evaluation encompassed 1) “de-labeling” unconfirmed allergy diagnoses; 2) treatment adjustment for patients with uncontrolled asthma and/or CSU; 3) indication to premedication before vaccination in cases of CSU, unexplained severe hypersensitivity or mast-cell diseases or elevated tryptase levels (i.e. tryptase $\geq 10 \mu\text{g/l}$); 4) assessment of PEG-allergy risk. Patients who could not recall having tolerated PEG-containing drugs, were referred to skin tests with PEG, as previously described [8]. Patients with confirmed allergy risk were classified into three risk categories: *Low-risk (LR) group*, *Intermediate-risk (IR) group* *High-risk (HR) group* (Table 1). Each category was assigned a distinct indication for post-vaccinal observation according to national and international guidelines available at time of evaluation and to the expected timing of severe immediate-type allergic reactions to vaccines and drugs [13,18–20].

All “at-risk” patients were followed up through telehealth for two weeks after each dose to assess the occurrence of allergic and non-allergic adverse reactions. Health professionals with HypR after vaccination, but without red flags at the screening questionnaire served as controls and were enrolled in the study protocol. Adverse events were classified by timing of onset as immediate

or delayed, when they occurred within vs after 4 h from vaccine administration [12]. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 was used to grade non-anaphylactic event severity, while the modified WAO grading system was used for anaphylaxis [21,22].

2.3. Statistical analysis

Categorical variables were compared among groups using chi-square test with Fisher's exact correction. Non-normally distributed continuous variables were compared among groups by using the Mann-Whitney's *U* test or the Kruskal-Wallis' test for two or more groups respectively. Normally distributed variables were compared among two or more groups by employing the Student's *t*-test or ANOVA respectively. Statacorp STATA® version 15 was used for statistical analysis. Data are expressed as median (interquartile range, IQR) unless otherwise specified.

3. Results

3.1. Patients with low to high allergy risk

Two-hundred-twenty of 6146 hospital employees receiving the BNT162b2 vaccine reported a history of clinically relevant allergy risk at the screening questionnaire and 118 subjects were considered at risk after expert evaluation (Suppl. Fig. 1). This at-risk group encompassed 103 women (87%) and 15 men (13%) with a median age of 48 (39–53) years. Among the 118 patients at-risk, nine were classified as LR, 83 as IR and 26 as HR for severe HypR (Table 2). Patients in the LR group were significantly younger [32 (30–45) years old] than patients at intermediate [48 (40–54) years old; $p = 0.006$] and high risk [50 (43–54) years old; $p = 0.002$]. None of those patients was referred to PEG skin test, since no one had severe reaction to injective PEG/polisorbates containing drug and all did tolerate at least one oral drug containing high molecular weight PEG.

One hundred patients at-risk for HypR (85%) experienced at least one adverse event (Table 3). None of them was severe. Seventeen patients (14%) had HypR after the first (14/118, 12%), the second (11/118, 9%) or both doses (8/118, 7%; Table 3). Most HypR manifested with skin signs. Patients who developed at least one HypR were older than patients who did not [51 (48–55) vs 46 (37–53) years; $p = 0.009$]. HypR were more frequent in HR (35%) than IR (10%; $p = 0.005$) or LR (0%; $p = 0.074$) patients. Skin manifestations after the first dose were more frequent in patients in the HR group (27%), than in the IR (4%; $p = 0.002$) or LR groups (0%; $p = 0.153$). No other demographic or clinical factor correlated with allergy after the first dose. There was also no significant difference in terms of frequency of allergic reactions after the second dose when stratifying for demographics or clinical history. However, patients with allergy after the second dose had higher baseline

Table 1
patient stratification based on allergy history.

	Classification criteria	Setting of vaccination and timing of observation after vaccination
Low-risk (LR) group	-mild [^] HypRs to drugs [*] and/or-controlled asthma/urticaria ^{**}	standard setting; 30-minute medical observation
Intermediate-risk (IR) group	-single previous anaphylaxis and normal tryptase levels ($<10 \mu\text{g/l}$)and/or-multiple drug HypR [*] and/or-severe but controlled asthma and/or CSU ^{**}	standard setting; 60-minute medical observation
High-risk (HR) group	- history of at least two previous anaphylaxes induced by different agentsand/or- of one or more severe anaphylaxes (involving loss of consciousness/ cardiac arrest)and/or- mast cell disorders (tryptase level $> 10 \mu\text{g/l}$).	two hours of medical observation;dedicated setting with trained personnel, a senior allergist and an anaesthesiologist

^{*} after PEG allergy exclusion

^{**} patients with uncontrolled asthma and/or urticaria were treated until clinical stability and eventually vaccinated.

[^] Mild HypRs: according to grade 1 of WAO criteria

Table 2
general demographics and allergy history of the at-risk population.

	All patients (n = 118)	High risk (n = 26)	Intermediate risk (n = 83)	Low risk (n = 9)
Females: n(%)	103 (87)	21 (81)	74 (89)	8 (89)
Age (years): median (IQR)	48 (39–53)	50 (43–54)	48 (40–54)	32 (30–45) [^]
Allergy history: n(%)				
Drug allergy	89 (75)	21 (81)	63 (76)	5 (56)
Allergy to > 2 drugs	58 (49)	17 (65)	39 (47)	2 (22)
Drug classes				
NSAIDs	39 (33)	11 (42)	27 (33)	1 (11)
Penicillins	35 (30)	7 (27)	26 (31)	2 (22)
Other antibiotics	14 (12)	7 (27) [*]	6 (7)	1 (11)
Vaccines	13 (11)	2 (8)	11 (13)	0 (0)
Contrast media	11 (9)	2 (8)	8 (10)	1 (11)
Opioids	2 (2)	1 (4)	1 (1)	0 (0)
Other drugs	25 (21)	11 (42)	12 (14)	2 (22)
Food allergy	27 (23)	9 (35)	17 (20)	1 (11)
Respiratory allergy	38 (32)	6 (23)	28 (34)	4 (44)
Hymenopter venom allergy	2 (2)	2 (8)	0 (0)	0 (0)
Anaphylaxis	20 (17)	4 (15)	15 (18)	1 (11)
Comorbidities				
Asthma	42 (36)	4 (15) [*]	35 (42)	3 (33)
Urticaria	12 (10)	1 (4)	9 (11)	2 (22)
Mastocyte diseases	7 (6)	7 (27) ^{***}	0 (0)	0 (0)
Basal tryptase (μg/dl): median (IQR)	5.2 (4.2–7.8)	6.2 (4.1–11)	5.15 (4.4–6.9)	

Abbreviations

[^]: p < 0.05 vs both intermediate- and high-risk patients

^{*}: p < 0.05; ^{**}: p < 0.010; ^{***}: p < 0.001 between high- vs intermediate-risk patients

[§]: p < 0.05 when comparing low- vs intermediate-risk patients

tryptase levels compared to patients with no allergy [8.8 (5.5–11.8) μg/dl, n = 6 vs 4.8 (4.0–7.4) μg/dl, n = 45; p = 0.021]. Regarding HypR severity, seven patients (41%) had mild (CTCAE grade-2; n = 4) to moderate (CTCAE grade-3n = 3) reactions. Five of them (71%), including all three patients with at least one CTCAE grade-3 reaction belonged to the HR group. Therefore, no patient was reclassified to HR from the LR or IR groups. Fifteen CTCAE grade-1–2 reactions (60%), but no grade-3 reaction, were delayed. Nonetheless, 1/3 grade-3 reactions occurred after 1 h of observation. No patient had anaphylaxis.

Non-allergic adverse events were experienced by 98 (83%) patients after the first (73/118, 62%), the second (96/118, 81%) or both doses (71/118, 60%; **Suppl.Table2**). Constitutional symptoms (including fever, chills, lymphadenopathy, arthromyalgia and/or fatigue) showed up at least once in 76/118 (64%) patients and accounted for the most frequent non-allergic manifestations. Constitutional symptoms were more frequent after the second (59%) than after the first dose (33%; p < 0.001). Patients in the HR group reported a higher frequency of post-vaccinal fatigue after the first dose (31%) than patients in the intermediate-risk group (12%; p = 0.035). Local pain after the second dose was less frequent in HR (15%) than among IR patients (39%; p = 0.033). Baseline tryptase levels were higher in patients who had fever after the first dose [8.6 (6.4–11.8) μg/dl, n = 5 vs 4.7 (4.0–7.5) μg/dl, n = 46 among patients with no fever; p = 0.021].

3.2. Control subjects

Among 6028 vaccinated healthcare workers with negative screening, 13 (0.2%) control subjects (CS), all women, had HypR after the first (n = 11) and/or the second (n = 4) BNT162b2 vaccine dose (**Table3**). One subject (0.02% of the vaccinee population) had WAO grade-4 anaphylaxis. Four patients with HypR after the first dose did not receive the second dose. Compared to at-risk patients who had HypR, CS were slightly younger [age 48 (38–50) vs 51 (48–55) years; p = 0.031], but did not differ in terms of non-allergic comorbidities (**Suppl.Table3**). Nine CS (70%) had a history of allergy not meeting the criteria for the LR group. Drug allergy

was less frequent in CS (n = 4/13 vs 15/17; p = 0.004), while atopy was similarly represented (n = 6/13 vs 7/17, p = NS) compared to at-risk patients. There were no differences in the frequency of patients with at least one CTCAE grade-2 or grade-3 reaction, although patients with grade-1 reactions only were less frequent among CS (1/13 vs 10/17; p = 0.007).

4. Discussion

In this study, we prospectively followed up 118 patients with allergy history receiving the BNT162b2 vaccine and assessed the efficacy of a screening strategy based on clinical interview and drug history to stratify patients according to their individual risk and optimise vaccine safety and adherence. HypR occurred in 14% of patients at allergic risk compared to only 0.2% of vaccinees who were not included in the screening programme. Nonetheless, CTCAE grade-1 manifestations might have been underreported by CS due to their limited clinical relevance. Allergic reactions were more frequent and severe in the HR group suggesting that previous reactions severity is a valid parameter to predict the likelihood of eventual allergic reactions. Notably, our data suggest that some moderately severe HypR can occur after 1 h from vaccine administration, indicating the potential need for prolonged observation at least in selected patient categories. Interestingly, non-allergic adverse reactions were relatively frequent in our cohort, especially in the HR group, suggesting the potential existence of shared mechanisms of immune dysregulation leading to multiple distinct systemic inflammatory manifestations [11,23,24]. Only one case of anaphylaxis was observed in the control group. This evidence confirms that allergy to mRNA-based vaccines has a relatively low prevalence [15] and suggests that a screening protocol based on clinical history might be sufficient to rule out PEG allergy and enable a safe vaccination of most patients at risk. Furthermore, our results suggest that tailored non-steroidal premedication in patients with mast-cell diseases and CSU might be sufficient to prevent systemic reactions, with no additional costs in terms of vaccine efficacy [25]. On the other hand, the occurrence of *de novo* severe reactions in patients with no clear risk factors highlights the

Table 3
hypersensitivity reactions in patients and controls.

Patient #	Age	Sex	HypR after d1	HypR after d1 (description)	Timing of onset of HypR after d1	Resolution of HypR after d1 within 24 h	Prophylaxis before d1	Treatment of HypR after d1	Received d2	HypR after d2	HypR after d2 (description)	Timing of onset of HypR after d2	Prophylaxis before d2	Treatment of HypR after d2	Resolution of HypR after d2 within 24 h	CTCAE
Patients at risk (n = 17/118 subjects at low to high risk based on clinical history)																
1	66	f	yes	itching	delayed	yes	Oral antiH1 (chronic)	none	yes	no	none	-	Oral antiH1 (chronic)	-	-	1
2	51	f	yes	itching	immediate	yes	-	Oral antiH1	yes	no	none	-	-	-	-	2
3	53	f	no	-	-	-	-	Intravenous anti H1	yes	yes	skin rash	delayed	-	-	-	2
4	55	f	yes	disphonia, cough	immediate	yes	-	Intravenous anti H1	yes	yes	disphonia, cough	immediate	-	Intravenous anti H1	yes	3
5	42	f	yes	-	-	-	-	-	yes	yes	urticaria	delayed	-	Oral antiH1,	yes	2
6	48	f	yes	itching, urticaria	delayed	yes	-	-	yes	no	none	-	-	-	-	1
7	43	f	yes	pharyngeal discomfort	delayed	yes	-	-	yes	yes	cough	delayed	-	-	-	1
8	43	f	yes	rash	delayed	yes	-	Intravenous anti H1	yes	yes	itching, rash	immediate	Oral antiH1	Intravenous anti H1	yes	3
9	53	f	yes	pharyngeal discomfort	delayed	yes	-	-	yes	yes	cough	delayed	-	-	-	1
10	58	f	no	-	-	-	-	-	yes	yes	itching	delayed	-	-	-	1
11	50	m	yes	itching	delayed	yes	-	-	yes	yes	itching	delayed	-	-	-	1
12	51	f	yes	itching	delayed	yes	-	-	yes	no	none	-	-	-	-	1
13	45	m	yes	lingual angioedema	immediate	no	-	Oral antiH1, proton pump inhibitor	yes	no	none	-	-	-	-	3
14	61	f	yes	itching	delayed	yes	-	-	yes	no	none	-	-	-	-	1
15	60	f	no	flushing	immediate	yes	-	-	yes	yes	confusion-itching	immediate	-	-	yes	1
16	51	f	yes	itching, rash	immediate	yes	-	antiH1 os, local glucocorticoid	yes	yes	itching, rash	-	Oral antiH1, antil.	-	-	2
17	51	f	yes	itching	immediate	yes	-	-	yes	yes	itching	delayed	Oral antiH1, antil.	-	-	1
Control subjects (n = 13/6028 vaccinees)																
A	49	F	yes	local erythema, itching, labial angioedema	immediate	no	-	-	no	NA	-	-	-	-	-	2
B	38	F	yes	rash	delayed	no	-	Oral antiH1	yes	no	-	-	anti H1, antil.	-	-	2
C	34	F	yes	sensation of throat discolor, tachycardia	immediate	yes	-	Intravenous anti H1 and glucocorticoids	no^	NA	-	-	-	-	-	3
D	60	F	no	-	-	-	-	-	yes	yes	rash, thoracic pain, tremor	immediate	-	Intravenous anti H1 and glucocorticoids	no	3
E	25	F	no	maculopapular rash	delay ed	no	-	-	yes	no	-	-	anti H1, antil.	-	-	2
F	38	F	yes	sensation of throat discolor, mouth itching	immediate	yes	-	-	yes	no	-	-	anti H1, antil.	-	-	2
G	50	F	yes	itching	delayed	no	-	-	yes	no	-	-	-	-	-	1
H	49	F	no	-	-	-	-	-	yes	yes	vasculitic rash	delayed	-	-	no	2
I	43	F	yes	mild urticaria	delayed	yes	-	-	yes	yes	urticaria, angioedema, flushing	immediate	-	Oral antiH1, local glucocorticoids	no	2
J	52	F	yes	anaphylaxis	immediate	yes	-	Intravenous anti H1	no	NA	-	-	-	-	-	4
K	27	F	yes	urticaria, thoracic pain	immediate	yes	-	Intravenous glucocorticoids	no	NA	-	-	-	-	-	3
L	55	F	no	-	-	-	-	-	yes	yes	diffuse rash, angioedema	delayed	-	Oral antiH1, local glucocorticoids	yes	2
M	48	F	yes	urticaria, Labial angioedema . rash	immediate	no	-	Intravenous anti H1 and glucocorticoids	yes	no	-	-	anti H1, antil.	-	-	3

Group comparison		HypR frequency: n (%)	Anaphylaxis frequency: n (%)	Skin reaction frequency: n (%)	Respiratory manifestation frequency: n (%)	Gastrointestinal manifestations frequency: n (%)	Immediate onset: n (%)	Delayed resolution (>24 h): n (%)	Complete vaccination: n (%)	HypR treatment with glucocorticoids: n (%)
Patients (n = 17)										
D1		14 (82)	0 (0)	10 (71)	1 (7)	2 (14)	6 (43)	1 (7)	14 (100)	0 (0)
D2		11 (65)	0 (0)	7 (64)	3 (27)	0 (0)	4 (36)	0 (0)	11 (100)	0 (0)
D1 + D2		17 (100)	0 (0)	12 (71)	3 (18)	2 (12)	8 (47)	1 (6)	17 (100)	0 (0)
Controls (n = 13)										
D1		11 (85)	1 (9)	8 (70)	2 (20)	1 (10)	5 (45)	5 (45)	7 (64)	3 (27)
D2		4 (31)	0 (0)	3 (75)	0 (0)	0 (0)	2 (50)	3 (75)	4 (100)	1 (25)
D1 + D2		13 (100)	1 (8)	9 (70)	2 (15)	1 (8)	8 (62)	8 (62)**	9 (70)	4 (31)

**<0.01 when comparing patients and controls
 ^ due to superimposed COVID-19
 Abbreviations
 HypR = Hypersensitivity reactions
 antil = anti-leukotrienes
 antiH1 = H1 antihistamines
 GI = gastrointestinal
 d1 = dose 1 d2 = dose 2

need for further research to identify additional clinical and/or laboratory predictors of vaccine-related HypR, also in the prospect of further boost doses at least in fragile populations.

Our study has the strength of providing real-life data from a relatively large cohort of patients who might have been excluded from or might have refused vaccination due to their high-risk allergic profile at the beginning of the Italian vaccination campaign [7–9]. In addition, our population included a wide age range of patients, representative of the general population. However, it also has some limitations, including the lack of data regarding vaccine efficacy.

Notwithstanding these limitations, our data suggest that BNT162b2 mRNA Covid-19 vaccine is relatively safe also in patients with a severe allergic background, including those with history of anaphylaxis and mast cell disorders. Managing such patients in dedicated clinics with trained personnel and with longer post-vaccinal observation might ensure a timely and effective treatment of adverse events and minimise vaccine hesitancy. Specifically, our data do not support the need for corticosteroid premedication, which might rather hamper effective immunization [12,26] nor a widespread use of skin tests to assess excipient sensitisation, which can be efficiently ruled out based on clinical history in the majority of cases. More studies are needed to define additional potential risk factors for severe HypR to the BNT162b2 mRNA Covid-19 vaccine.

Contributorship

MRY, VC, CA, GAR, EDT and LD designed the study. MRY, VC, CA, MM, CZ, DDN, AA, collected clinical and administrative data. GAR and CA performed statistical analysis. MRY, VC, CA and GAR drafted the paper. All authors contributed in revising the draft and in providing important intellectual content. All authors approved the final version of the article and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work will appropriately be investigated and resolved.

Ethical Statement

Patients were enrolled upon informed consent within the Pan-Immuno research protocol (conforming to the declaration of Helsinki and approved by the IRCCS Ospedale San Raffaele ethics committee with reference code 22/INT/2018).

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding Statement

The authors did not receive any funding to support this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful to Patrizia Maxenti, Simona Carente, Giuseppina Robustella, Raquel Moreno Calderon, Anna Vigna and Carmine Farias for the nursing assistance and to the residents of

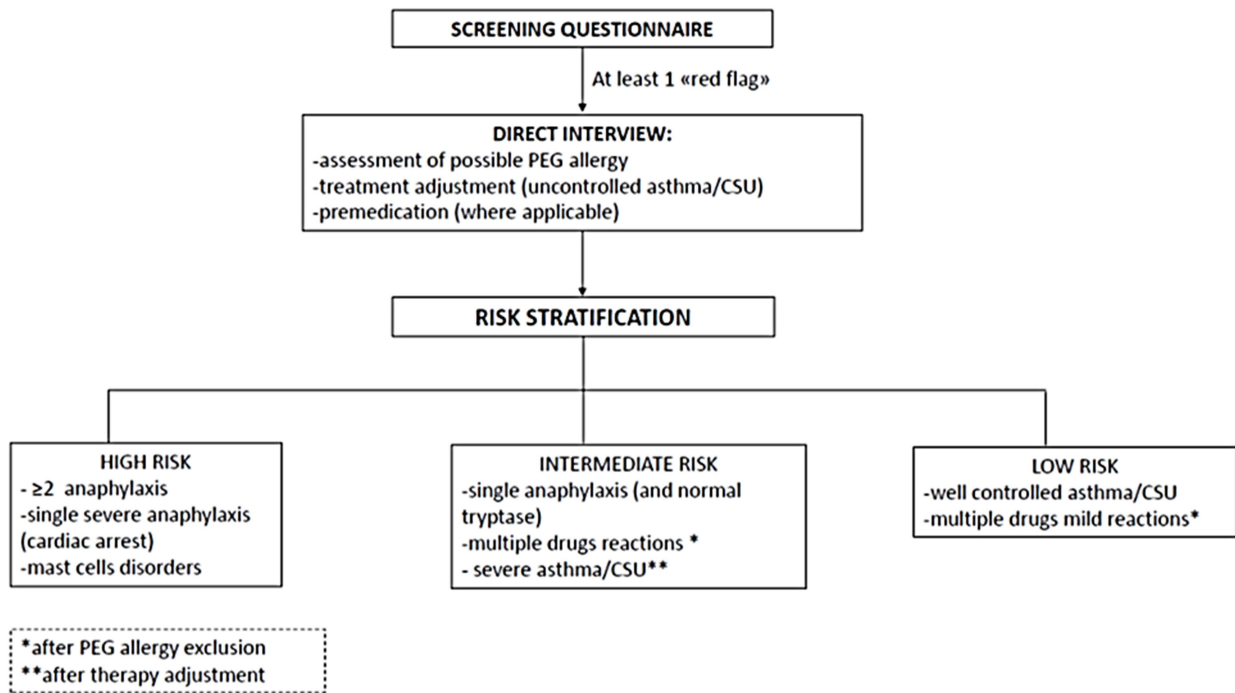
Anaesthesiology and Intensive Care Unit Raffaele Cuffaro, Ottavia Pallanch, Gaia Recca, Federica Morselli and Giulia Fenu for their medical support during the protected vaccination sessions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2021.09.048>.

References

- [1] European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker: Doses By Product. 2021 [cited 2021-09-10]; Available from: <https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab>
- [2] European Medicines Agency. EudraVigilance: European Database of suspected adverse drug reaction reports. 2021 [cited 2021-09-10]; Available from: <https://www.adrreports.eu/>
- [3] Nittner-Marszalska M, Rosiek-Biegus M, Kopec A, Pawlowicz R, Kosinska M, Lata A, et al. Pfizer-BioNTech COVID-19 Vaccine Tolerance in Allergic versus Non-Allergic Individuals. *Vaccines (Basel)*. 2021 May 25; 9(6).
- [4] Larson KF, Ammirati E, Adler ED, Cooper LT, Hong KN, Saponara G, et al. Myocarditis After BNT162b2 and mRNA-1273 Vaccination. *Circulation* 2021;144(6):506–8.
- [5] Tan CK, Wong YJ, Wang LM, Ang TL, Kumar R. Autoimmune hepatitis following COVID-19 Vaccination: true causality or mere association? *J Hepatol*. 2021 Jun;18.
- [6] CDC Covid-Response Team Food and Drug Administration. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14–23, 2020. *Morb Mortal Wkly Rep*. 2021 Jan 15;70(2):46–51.
- [7] Turner PJ, Larson H, Dubé E, Fisher AJTJoA, Practice CII. Vaccine Hesitancy: Drivers and how the Allergy Community can help. 2021.
- [8] Ramirez GA, Argolini LM, Bellocchi C, Moroni L, Della-Torre E, Farina N, et al. Impact of the COVID-19 pandemic in patients with systemic lupus erythematosus throughout one year *Clinical Immunology*. 2021; Epub ahead of print.
- [9] Caminati M, Guarnieri G, Batani V, Scarpieri E, Finocchiaro A, Chieco-Bianchi F, et al. COVID-19 Vaccination in Patients with Severe Asthma on Biologic Treatment: Safety, Tolerability, and Impact on Disease Control. *Vaccines (Basel)*. 2021 Aug 4; 9(8).
- [10] Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907–22.
- [11] Moghimi SM. Allergic Reactions and Anaphylaxis to LNP-Based COVID-19 Vaccines. *Mol Ther*. 2021;29(3):898–900.
- [12] Longo DL, Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med*. 2021;384(7):643–9.
- [13] Banerji A, Wickner PG, Saff R, Stone CA, Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J Allergy Clin Immunol Pract*. 2021;9(4):1423–37.
- [14] Rojas-Perez-Ezquerria P, Crespo Quiros J, Tornero Molina P, Ochoa B, de Ocariz ML, Zubeldia Ortuno JM. Safety of New mRNA Vaccines Against COVID-19 in Severely Allergic Patients. *J Investig Allergol Clin Immunol*. 2021 Apr 20;31(2):180–1.
- [15] Paoletti G, Racca F, Piona A, Melone G, Merigo M, Puggioni F, et al. Successful SARS-CoV-2 vaccine allergy risk-management: The experience of a large Italian University Hospital. *World Allergy Organ J*. 2021;14(5):100541. <https://doi.org/10.1016/j.waojou.2021.100541>.
- [16] Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood* 2017 Mar 16;129(11):1420–7.
- [17] Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126(6):1099–1104.e4.
- [18] Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990–2016. *J Allergy Clin Immunol*. 2019;143(4):1465–73.
- [19] Nilsson L, Brockow K, Alm J, Cardona V, Caubet J-C, Gomes E, et al. Vaccination and allergy: EAACI position paper, practical aspects. *Pediatr Allergy Immunol*. 2017;28(7):628–40.
- [20] Agenzia Italiana del Farmaco (Italian Medicine Agency). Domande e Risposte sui vaccini COVID-19 2021 [cited 28/04/2021]; Available from:
- [21] Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. *The World Allergy Organization journal*. 2020;13(10):100472. <https://doi.org/10.1016/j.waojou.2020.100472>.
- [22] Health UDO, Services H. Common Terminology Criteria for Adverse Events. Version 5.0. Published November 27, 2017. 2020.
- [23] Ramirez GA, Della-Torre E, Moroni L, Yacoub MR, Dagna L, group O-Cs. Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'. *Ann Rheum Dis*. 2021 May 24; In Press.
- [24] Stone CA, Rukasin CRF, Beachkofsky TM, Phillips EJ. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol*. 2019;85(12):2694–706.
- [25] Rama TA, Moreira A, Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. *J Allergy Clin Immunol*. 2021;147(3):877–8.
- [26] Vormehr M, Lehar S, Kranz LM, Tahtinen S, Oei Y, Javinal V, et al. Dexamethasone premedication suppresses vaccine-induced immune responses against cancer. *Oncoimmunology*. 2020;9(1). <https://doi.org/10.1080/2162402X.2020.1758004>.



Supplementary figure 1

This flow chart depicts the algorithm used to screen patients with self-reported allergy history according to their expected risk of hypersensitivity reaction to the BNT162b2 vaccine. Risk stratification was based on severity of previous hypersensitivity reactions, active comorbidities including asthma and chronic spontaneous urticarial (CSU), and mast cell activation according to serum tryptase levels. Potential allergy to excipients including polyethylene glycol (PEG) was ruled out based on drug history. Skin tests were performed only when drug history was not sufficient to rule out PEG sensitization.

Supplementary 1: simplified screening questionnaire for patient enrolment

It is recommended that you undergo a pre-vaccination allergy evaluation if you answer “yes” to any of the following questions

- 1- Have you ever had anaphylaxis to drugs, vaccine, latex or hymenopter venom?
YES ☐ NO ☐
- 2- Are you allergic to more than one type of drug?
YES ☐ NO ☐
- 3- Do you have a history of food anaphylaxis and have been prescribed an epinephrine autoinjector?
YES ☐ NO ☐
- 4- Are you allergic to PEG (macrogol)/polisorbates?
YES ☐ NO ☐ I DON'T KNOW ☐
- 5- Do you have systemic mastocytosis or mast cell activation syndrome?
YES ☐ NO ☐
- 6- Is your asthma and/or chronic spontaneous urticaria under poor control?
YES ☐ NO ☐

Supplementary Table 2: adverse post-vaccinal events

	All patients (n=118)	HR (n=26)	IR (n=83)	LR (n=9)
Any adverse event: n(%)	100 (85)	23 (88)	71 (86)	6 (67)
Any allergic adverse event: n (%)	17 (14)	9 (35)**	8 (10)	0 (0)
Any non-allergic adverse event: n (%)	98 (83)	22 (85)	70 (84)	6 (67)
Adverse events after the 1st dose: n(%)	75 (64)	18 (69)	53 (64)	4 (44)
Allergic events	14 (12)	8 (31)**	6 (7)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)
Skin manifestations	10 (8)	7 (27)**	3 (4)	0 (0)
Itching sensation	8 (7)	5 (19)*	3 (4)	0 (0)
Urticaria/angioedema	2 (2)	1 (4)	1 (1)	0 (0)
Diffuse erythematous rash	2 (2)	1 (4)	1 (1)	0 (0)
Respiratory symptoms	1 (1)	1 (4)	0 (0)	0 (0)
Gastrointestinal symptoms	2 (2)	1 (4)	1 (1)	0 (0)
Other	1 (1)	0 (0)	1 (1)	0 (0)
Non-allergic events	73 (62)	17 (65)	52 (63)	4 (44)
Local pain	36 (31)	7 (27)	28 (34)	1 (11)
Constitutional symptoms	39 (33)	11 (42)	26 (31)	2 (22)
Fever	11 (9)	3 (12)	8 (10)	0 (0)
Chills	10 (8)	3 (12)	6 (7)	1 (11)
Arthralgia/myalgia	18 (15)	5 (19)	13 (16)	0 (0)
Fatigue	20 (17)	8 (31)*	10 (12)	2 (22)
Lymphadenopathy	3 (3)	2 (8)	1 (1)	0 (0)
Headache	14 (12)	3 (12)	10 (12)	1 (11)
Gastrointestinal symptoms	1 (1)	1 (4)	0 (0)	0 (0)
Other	16 (14)	1 (4)	14 (17)	1 (11)
Adverse events after the 2nd dose: n(%)	97 (82)	21 (81)	70 (84)	6 (67)
Allergic events	11 (9)	4 (15)	7 (8)	0 (0)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)
Skin manifestations	7 (6)	3 (12)	4 (5)	0 (0)
Itching sensation	6 (5)	2 (8)	4 (5)	0 (0)
Urticaria/angioedema	1 (1)	0 (0)	1 (1)	0 (0)
Diffuse erythematous rash	3 (3)	2 (8)	1 (1)	0 (0)
Respiratory symptoms	3 (3)	1 (4)	2 (2)	0 (0)
Gastrointestinal symptoms	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (1)	0 (0)	1 (1)	0 (0)
Non-allergic events	96 (81)	21 (81)	69 (83)	6 (67)
Local pain	36 (31)	4 (15)*	32 (39)	0 (0)*
Constitutional symptoms	70 (59)	17 (65)	49 (59)	4 (44)
Fever	47 (40)	9 (35)	36 (43)	2 (22)
Chills	13 (11)	5 (19)	7 (8)	1 (11)
Arthralgia/myalgia	38 (32)	9 (35)	28 (34)	1 (11)
Fatigue	46 (39)	12 (46)	31 (37)	3 (33)
Lymphadenopathy	4 (3)	1 (4)	3 (4)	0 (0)
Headache	21 (18)	5 (19)	13 (16)	3 (33)
Gastrointestinal symptoms	8 (7)	4 (15)	4 (5)	0 (0)
Other	16 (14)	4 (15)	11 (13)	1 (11)
Adverse events after both doses: n(%)	72 (61)	16 (62)	52 (63)	4 (44)
Allergic events	8 (7)	3 (12)	5 (6)	0 (0)
Non-allergic events	71 (60)	16 (62)	51 (61)	4 (44)

Abbreviations

HR: high risk IR: intermediate risk LR: low risk

*:p<0.05; **:p<0.010; ***: p<0.001 between high- vs intermediate-risk patients

*:p<0.05 when comparing low- vs intermediate-risk patients

Supplementary Table 3: non-allergic comorbidities

Patient #	Comorbidities
Patients at risk (n=17/118 subjects at low to high risk based on clinical history)	
1	CAD, hypertension
2	-
3	malignancy
4	CAD, hypertension
5	migraine
6	-
7	-
8	-
9	spondyloarthritis
10	type 2 diabetes
11	-
12	CAD
13	GERD
14	mitral valve regurgitation , hypertension, trigeminal neuralgia
15	-
16	-
17	endometriosis, gastritis
Control subjects (n=13/6028 vaccinees)	
A	mitral valve regurgitation
B	-
C	-
D	thyroid nodule
E	hyperhomocysteinemia
F	rheumatoid arthritis
G	-
H	-
I	rheumatoid arthritis, tachycardia, autoimmune gastritis
J	Brugada syndrome
K	-
L	autoimmune gastritis, pituitary adenoma
M	GERD, hypertension

Abbreviations

CAD: Coronary artery disease

GERD: gastroesophageal reflux diseases