Received: 29 April 2022 | Revised: 23 July 2022 | Accepted: 2 August 2022

DOI: 10.1111/all.15467

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER

Safety of COVID-19 vaccine challenge in patients with immediate adverse reactions to prior doses: A multi-centre cohort study

To the Editor,

Severe immediate adverse events following immunization (AEFI) with COVID-19 vaccines have been reported in up to 2.5 per 10,000 vaccinations.[1] Differentiating allergic reactions from immunization stress-related responses (ISRR)[2] at the point of vaccination can be difficult, presenting an added burden to allergy clinics. Recent reports suggest that most individuals will tolerate mRNA re-vaccination in a supervised setting.[3,4] More information is needed to help predict those most likely to tolerate future vaccine doses, as excipient skin testing has provided a limited role.[5]

METHODS

This is a retrospective multi-centre cohort study of adults referred to two allergy centres with immediate AEFI to the BNT162b2 or ChAdOx1s vaccines between April and August 2021. Anaphylaxis was defined as per Brighton collaboration criteria.[6] Skin testing and challenge procedures are in the eMethods in Appendix S1. The primary outcome was challenge positivity, stratified into subjective or objective signs or symptoms. To identify predictors of challenge positivity, univariable logistic regression then multivariable analysis via stepwise backward method was performed using variables with $p < 0.2$ on univariable analysis. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

A final cohort of 116 challenge patients were identified after excluding delayed AEFI and those who declined testing (Figure S1). The cohort is described in Table 1. Of these, 58.6% received at least 1 dose of adrenaline. Patients met case definition for anaphylaxis: Level One 11.2%, Level Two 34.5%, Level Three 2.6%. Sixty (51.7%) patients did not meet case definition (Table 1).

Skin testing with PEG and Polysorbate80 panels was performed on 23 patients (19.7%), all were negative (Table S1). Forty-five patients (38.7%) reported a positive challenge, of which 18 (40%) were to ChAdOx1s and 27 (60%) to BNT162b2. Forty (34% of the 116) were mild and subjective versus 5 (4%) with objective signs. Two (1.7%) patients received adrenaline for a combination of rash and throat tightness with normal vital signs. Of the five with objective signs, four did not meet Brighton criteria for their index reaction and one was Level 1.

Univariable analysis of factors that predict positive challenge is in Table S2. Predictors of positive challenge on multivariable analysis included absence of a history of atopy (OR 8.13 [95% CI, 1.66–39.70]), absence of hospitalization (OR 2.89 [95% CI, 0.97–8.66]) and any treatment received for the index reaction (OR 6.06 [95% CI, 1.46–25.16]). Those with a Brighton level 1 (OR 7.27 [95% CI, 1.52–34.66]) or not meeting case definition (OR 3.06 [95% CI, 1.01–9.34]) were more likely to have a positive challenge, compared with a Brighton level 2/3. (Table 2).

DISCUSSION

In this cohort study of patients reporting immediate AEFI post-COVID vaccination, 61.2% of the 116 had negative vaccine challenge with a further 34.4% developing mild, subjective symptoms post-vaccination. Thus, 95.6% of the cohort were able to be re-vaccinated safely with 4.3% developing objective signs of a possible immune AEFI, consistent with international experience.[2–4] Our study is one of the first to report vaccine challenge outcomes in a cohort including the ChAdOx1s vaccine.

Skin testing was not a useful predictor of challenge positivity (Table S1). Atopy and hospitalization were not associated with an increased risk of positive challenge, suggesting those at risk of positive challenge lack classical allergy phenotypes. As the 51.7% of patients who did not meet Brighton criteria had a higher risk of

TABLE 1 Baseline and index reaction characteristics

Factor	Challenged	ChAdOx1s (AstraZeneca)	BNT162b2 (Pfizer)
N	116	50 (43.1%)	66 (56.9%)
Sex			
Female	108 (93.1%)	47 (94%)	61 (92%)
Age at first review, median (IQR)	45.2 (35.75, 56.23)	54.8 (45.7, 62.7)	40.8 (32.8, 46.2)
Ethnicity			
African	0 (0.0%)		
Asian	1 (0.9%)		1 (1.5%)
Caucasian	45 (38.8%)	22 (44%)	23 (34.9%)
Not recorded	70 (60.3%)	28 (56%)	42 (63.6%)
Psychiatric history			
None	54 (46.6%)	29 (58%)	25 (38%)
Unknown	35 (30.1%)	11 (22%)	24 (36%)
Anxiety	16 (13.8%)	6 (12%)	10 (15%)
Bipolar	1 (0.9%)	0 (0%)	1 (2%)
Depression	10 (8.6%)	4 (8%)	6 (9%)
Prior COVID-19 infection			
Yes	2 (1.7%)	0 (0%)	2 (3%)
Mastocytosis	0 (0.0%)	0 (0%)	0 (0%)
Idiopathic anaphylaxis	2 (1.7%)	0 (0%)	2 (3%)
Chronic spontaneous urticaria	10 (8.6%)	4 (8%)	6 (9%)
Prior history of atopy	23 (19.8%)	13 (26%)	10 (15%)
Allergic Rhinitis	11 (9.5%)	6 (12%)	5 (8%)
Atopic Dermatitis	2 (1.7%)	1 (2%)	1 (2%)
Asthma	15 (12.9%)	9 (18%)	6 (9%)
Prior history of PEG or polysorbate allergy, suspected	2 (1.7%)	1 (2%)	1 (2%)
Prior history of immune mediated food allergy history	27 (23.3%)	10 (20%)	17 (26%)
History of food-related anaphylaxis	19 (16.4%)	7 (14%)	12 (18%)
Prior history of immune mediated drug allergy history	33 (28.4%)	16 (32%)	17 (26%)
Penicillin allergy	14 (12.1%)	6 (12%)	8 (12%)
Sulfa allergy	4 (3.4%)	2 (4%)	2 (3%)
Other antibiotic allergy	6 (5.2%)	2 (4%)	4 (6%)
NSAID allergy	3 (2.6%)	1 (2%)	2 (3%)
Flu vaccine allergy	1 (0.9%)	1 (2%)	0 (0%)
Other drug allergy	23 (19.8%)	10 (20%)	13 (20%)
History of drug related anaphylaxis	6 (5.2%)	2 (4%)	4 (6%)
Time since first vaccination (days), median (IQR)	41 (27, 69)	69 (42, 92) ($n = 49$)	30 (22, 42) ($n = 64$)
Vaccine dose 1	115 (99.1%)	50 (100%)	65 (98.5%)
Vaccine dose 2	1 (0.9%)	0 (0%)	1 (1.5%)
Brighton criteria level of certainty			
Level 1	13 (11.2%)	5 (10%)	8 (12.1%)
Level 2	40 (34.5%)	18 (36%)	22 (33.3%)
Level 3	3 (2.6%)	2 (4%)	1 (1.5%)
Did not meet case definition	60 (51.7%)	25 (50%)	35 (53%)
Treatment			
Unknown	1 (0.9%)	1 (2%)	2 (3%)
No	18 (15.5%)	9 (18%)	9 (14%)
Yes	95 (81.9%)	40 (80%)	55 (83%)

TABLE 1 (Continued)

Factor	Challenged	ChAdOx1s (AstraZeneca)	BNT162b2 (Pfizer)
Treatment at vaccination centre	64 (55.2%)	26 (52%)	38 (58%)
Treatment at hospital or medical centre	53 (45.7%)	21 (42%)	32 (48%)
Treatments received			
Prednisolone	16 (13.8%)	6 (12%)	10 (15%)
Antihistamine	45 (38.8%)	19 (38%)	26 (39%)
Adrenaline	68 (58.6%)	24 (48%)	44 (67%)
Unknown/other	11 (9.5%)	6 (12%)	5 (8%)
Adrenaline administration site			
Vaccination centre	45 (38.8%)	15 (30%)	30 (45%)
Community medical centre	6 (5.2%)	5 (10%)	1 (2%)
Ambulance	8 (6.9%)	2 (4%)	6 (9%)
Hospital	20 (17.2%)	8 (16%)	12 (18%)
Adrenaline doses total (IM)			
1	34 (29.3%)	11 (22%)	23 (34.9%)
2	17 (14.7%)	6 (12%)	11 (16.7%)
3	10 (8.6%)	4 (8%)	6 (9.1%)
4	5 (4.3%)	2 (4%)	3 (4.6%)
5	1 (0.9%)	1 (2%)	0 (0%)
Adrenaline infusion	8 (6.9%)	4 (8%)	4 (6.1%)
Hospitalization	41 (35.3%)	18 (36%)	23 (35%)
ICU admission	5 (4.3%)	2 (4%)	3 (5%)

TABLE 2 Predictors of positive challenge

Variable	OR (95% CI)	*p* value
Absence of hospitalization	2.89 (0.97, 8.66)	0.057
Any treatment	6.06 (1.46, 25.16)	0.013
No history of atopy	8.13 (1.66, 39.70)	0.01
Brighton diagnostic certainty		
Level 1	7.27 (1.52, 34.66)	0.049
Level 2/3	Ref	
No level	3.06 (1.01, 9.34)	0.049

positive challenge, it's possible that these reactions are not immune-mediated which may explain why those with severe reactions tolerated challenge. Based on our data, re-vaccination is possible in those with immediate AEFI post-COVID vaccination if selected carefully and challenged in a supervised environment.

ACKNOWLEDGEMENTS

We thank the Infectious Diseases Department of Austin Health, the Victorian Specialist Immunisation Service and the Victorian Department of Health for supporting this program. We also thank the dedicated nursing staff of both participating hospitals.

KEYWORDS

allergy, challenge, COVID-19, SARS-CoV-2, vaccine

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Joseph F. De Luca[1,2]
Andrew Awad[1]
Sara Vogrin[3]
Abby P. Douglas[1]
Antje Lutjen[4]
Sally F. Gordon[5]
Nigel W. Crawford[6,7]
Sara Barnes[4]
Jason A. Trubiano[1,2]

[1]*Centre for Antibiotic Allergy and Research, Department of Infectious Diseases, Austin Health, Heidelberg, Vic., Australia*
[2]*Department of Medicine, University of Melbourne, Melbourne, Vic., Australia*
[3]*Department of Medicine, St Vincent's Hospital, University of Melbourne, Fitzroy, Vic., Australia*
[4]*Department of Allergy, Monash Health, Clayton, Vic., Australia*

[5]*Vaccine Safety and Evaluation, COVID-19 Vaccination Program, Victorian Department of Health, Melbourne, Vic., Australia*
[6]*SAEFVIC, Victorian Vaccine Safety Service, MCRI, Parkville, Vic., Australia*
[7]*Department of Paediatrics, University of Melbourne, Melbourne, Vic., Australia*

Correspondence
Joseph F. De Luca, Centre for Antibiotic Allergy and Research, Department of Infectious Diseases, Austin Health, Heidelberg, Vic., Australia.
Email: joseph.deluca@austin.org.au

ORCID

Joseph F. De Luca https://orcid.org/0000-0001-6541-5512
Andrew Awad https://orcid.org/0000-0003-4604-1062
Jason A. Trubiano https://orcid.org/0000-0002-5111-6367

REFERENCES

1. Blumenthal KG, Robinson LB, Camargo CA, et al. Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA*. 2021;325(15):1562-1565. doi:10.1001/jama.2021.3976
2. World Health Organization. Immunization stress-related responses: a synopsis of the manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. 2019. Accessed July 24, 2022. https://apps.who.int/iris/handle/10665/330276
3. Krantz MS, Kwah JH, Stone CA, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. *JAMA Intern Med*. 2021;181(11):1530-1533. doi:10.1001/jamainternmed.2021.3779
4. Tuong L-AC, Capucilli P, Staicu M, Ramsey A, Walsh EE, Mustafa SS. Graded administration of second dose of Moderna and Pfizer-BioNTech COVID-19 mRNA vaccine in patients with hypersensitivity to first dose. *Open Forum Infect Dis*. 2021;8:ofab507. doi:10.1093/ofid/ofab507
5. Wolfson AR, Robinson LB, Li L, et al. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. *J Allergy Clin Immunol Pract*. 2021;9(9):3308-3320.e3. doi:10.1016/j.jaip.2021.06.010
6. Rüggeberg JU, Gold MS, Bayas J-M, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5675-5684. doi:10.1016/j.vaccine.2007.02.064

SUPPORTING INFORMATION

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