



ORIGINAL ARTICLE

COVID vaccination can be performed in patients with a history of allergic reactions to the vaccines or their components: experience from a specialist clinic in South Australia

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Key words

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Abstract

Background: The development of vaccines against SARS-CoV2 has been a key public health response to the COVID-19 pandemic. However, since their introduction, there have been reports of anaphylactic reactions to vaccines in individuals with history of allergic reactions to other vaccines, excipients or to COVID vaccines.

Aim: A dedicated adult COVID vaccine allergy clinic with a standardised allergy testing protocol was set up to investigate safety and suitability of available COVID vaccines in Australia.

Methods: Patients referred to a state-wide COVID-19 vaccine allergy clinic between March and August 2021 with a history of allergy underwent skin-prick testing and intradermal testing to both available vaccine formulations (BNT162b2 and ChAdOx1-S), excipients (polyethylene glycol and polysorbate 80), excipient-containing medications and controls. Basophil activation testing was conducted in few subjects with convincing history of immediate type reactions.

Results: Fifty-three patients underwent testing for possible excipient allergy ($n = 19$), previous non-COVID vaccine reaction ($n = 13$) or previous reaction to dose 1 of COVID-19 vaccine ($n = 21$). Patients were predominantly female ($n = 43$, 81%), aged 18–83 (median 54) years. Forty-four patients tested negative and 42 of these received at least their first dose of a COVID-19 vaccine. Nine patients tested positive to excipients or excipient-containing medication only ($n = 3$), or vaccines ($n = 6$). Five patients were positive to just BNT162b2, 3/5 have been vaccinated with ChAdOx1-S. One who was skin test positive to both vaccines, but negative BAT to ChAdOx1-S was successfully vaccinated with ChAdOx1-S.

Conclusion: Even in a high-risk population, most patients can be vaccinated with available COVID-19 vaccines. This paper reports local experiences using a combined allergy testing protocol with skin testing and BAT during the pandemic.

Introduction

The rapid development and introduction of vaccines against severe acute respiratory syndrome coronavirus (SARS-CoV2) have been a key public health measure against the coronavirus disease 2019 (COVID-19)

pandemic. However, early after their introduction, reports emerged of cases of anaphylaxis.¹ This caused considerable community concern and resulted in the international allergy community to formulate guidelines outlining specific precautions and/or contraindications for COVID-19 vaccination which were primarily based on expert allergy opinion.^{2–4} Further evidence is required to inform COVID-19 vaccination in individuals with a history of excipient allergy, with a history of allergy to a non-COVID-19 vaccine, and those who have

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been reported to have experienced anaphylaxis to their first COVID-19 vaccine dose.

In the case of COVID-19 vaccines, the proposed mechanisms of allergy related to the excipients of available vaccine formulations – polyethylene glycol (PEG) for messenger RNA (mRNA) vaccines and polysorbate 80 (PS80) and disodium edetate (EDTA) for adenoviral vector vaccines.⁵ A history of documented anaphylaxis to PEG and/or PS80 is regarded as a contraindication to vaccination with the BNT162b2 or ChAdOx1-S vaccines respectively. However, it remains unclear whether excipients are allergens in COVID-19 vaccines and whether these individuals can tolerate a COVID-19 vaccine containing one of these excipients. The ChAdOx1-S COVID-19 vaccine and several non-COVID-19 vaccines contain polysorbate as an excipient. History of anaphylaxis to a non-COVID-19 vaccine is regarded by some as a precaution to vaccination because of this possible shared excipient.

Anaphylaxis is a clinical syndrome that can be difficult to define when reported as an adverse event following immunisation (AEFI). In the context of AEFI surveillance, the Brighton Collaboration case definition is often used.⁶ However, some symptoms of anaphylaxis may be difficult to differentiate from an immunisation stress-related response, triggered by anxiety or needle phobia.⁷ As the vaccine rollout has continued worldwide, reports of allergic reactions have decreased in frequency.⁸ Reports have also emerged of patients with reactions to dose 1 tolerating subsequent challenge with the same vaccine.⁹ It is therefore important that patients who are suspected of having COVID-19 vaccine anaphylaxis are referred for appropriate evaluation.

In March 2021, South Australia established an adult tertiary care COVID-19 specialist immunisation service to investigate vaccine allergy and other AEFI. We developed an allergy testing protocol for COVID-19 vaccines consisting of combined skin-prick testing (SPT), intradermal testing (IDT) and basophil activation testing (BAT) to vaccine as well as excipients and other excipient-containing medications to guide vaccination choices in referred patients. We report our experience with 53 patients evaluated between March 2021 and August 2021.

Methods

The current study had local institutional ethics board approval, followed standardised reporting guidelines for case series, and patients provided written informed consent.^{10,11}

Our centre is the dedicated statewide adult allergy service for COVID-19 vaccines, servicing a population of 1.77 million people. Patients undergoing allergy testing

between 10 March 2021 and 11 August 2021 were included for analysis. Patients considered for allergy testing were those referred with a history of excipient (PEG and/or PS80) or vaccine allergy, including those who had a history of possible allergic reaction to the first dose of a COVID-19 vaccine. In those referred for concern of excipient allergy, a thorough clinical history for suggestive reactions was obtained. Those referred for first-dose reactions were categorised according to the Brighton Collaboration case definitions for anaphylaxis.⁶ Patients underwent allergy testing if they met the case definition for anaphylaxis or had signs and symptoms suggestive of allergy but did not meet the criteria for anaphylaxis including urticaria, erythematous rash, angioedema, wheeze, dyspnoea and cough.

A standardised protocol of SPT and IDT was developed, summarised in Table 1.¹² In brief, depending on clinical history, patients received SPT using the single-lancet technique to both vial remnants of available vaccine formulations (ChAdOx1-S and BNT162b2), as well as implicated excipients (for ChAdOx1-S – PS80 optive eye drops and cellufresh control, EDTA; for BNT162b2 – methylprednisolone acetate and methylprednisolone succinate control, PEG molecular weight 3350). Histamine (1 mg/mL) and normal saline were used as positive and negative controls respectively. During the study period, SPT protocols were altered to include multiple molecular weights of PEG and higher concentrations of PS80, as described by Bruusgaard-Mouritsen *et al.*¹³ Measurements were conducted at 15 min for SPT and 20 min for IDT by trained allergy nursing staff.

Patients with negative SPT proceeded to IDT at 1:100 concentrations for the same agents, although only PEG3350 was tested intradermally because of increased risk of systemic reaction with IDT.¹³ Patients with negative results were also tested at 1:10 concentrations.

Select patients with highly suggestive histories of anaphylaxis to either the first dose of vaccine or excipients additionally underwent BAT to both vaccines where available. BAT was performed using an established in-house assay, as previously described.^{14,15} Interleukin 3 primed heparinized whole blood was stimulated for 20 min at 37°C with BNT162b2 or ChAdOx1 vaccine diluted 1:10, 1:20, 1:200 and 1:2000 in phosphate-buffered saline (PBS). Polyclonal goat anti-human IgE (Sigma-Aldrich, St Louis, MO, USA) and PBS were used as controls. After incubation, basophil degranulation was stopped by chilling blood on ice; cells were stained with CD45-APC-H7, CD123-PE-CY5, HLA-DR-PE-CY7 and CD63-PE (BD Biosciences, San Jose, CA, USA). Erythrocytes were lysed. Basophils were gated as SSCloCD45 + CD123 + HLA-DR-, and basophil activation was measured as percentage of basophils that upregulate CD63

Table 1 Initial skin-prick testing and intradermal testing protocol (final testing agents in bold)

Skin-prick testing	Intradermal testing 1:100	Intradermal testing 1:10
Optive Advanced Eye Drop (Polysorbate 80 5 mg/mL)	1:100 Optive Advanced Eye Drop (Polysorbate 80 0.05 mg/mL)	1:10 Optive Advanced Eye Drop (Polysorbate 80 0.5 mg/mL)
Cellufresh Eye Drop (Carboxymethyl cellulose 5 mg/mL 0.5%)	1:100 Methylprednisolone acetate (Depo-Medrol 0.4 mg/mL)	1:10 Methylprednisolone acetate (Depo-Medrol 4 mg/mL)
Polyethylene glycol (PEG)/Macrogol 3350 500 mg/mL (Movicol/Macrovic)	1:100 Methylprednisolone succinate (Solu-Medrol 0.4 mg/mL)	1:10 Methylprednisolone succinate (Solu-Medrol 4 mg/mL)
Methylprednisolone acetate (Depo-Medrol 40 mg/mL)	1:100 Disodium Edetate (EDTA 0.03 mg/mL)	1:10 Disodium Edetate (EDTA 0.3 mg/mL)
Methylprednisolone succinate (Solu-Medrol 40 mg/mL)	1:100 Pfizer Comirnaty COVID-19 vaccine (1 µg/mL)	1:10 Pfizer Comirnaty COVID-19 vaccine (10 µg/mL)
Triamcinolone	1:100 Astra Zeneca ChAdOx1-S COVID-19 vaccine	1:10 Astra Zeneca ChAdOx1-S COVID-19 vaccine
Disodium Edetate (EDTA 3 mg/mL)		
Pfizer Comirnaty COVID19 vaccine 100 µg/mL (30 µg/0.3 mL)		
Astra Zeneca ChAdOx1-S COVID-19 vaccine		
PEG 2001000 mg/mL 100%		
PEG 4001000 mg/mL 100%		
PEG 6001000 mg/mL 100%		
PEG 2000 500 mg/mL 50%		
PEG 6000 500 mg/mL 50%		
Histamine 10 mg/mL		
Normal saline 0.9%		

expression. Acquisition and analysis were performed with FACSCanto II with FACSDiva software (BD Biosciences, San Jose, CA, USA).

Clinical recommendations for first or second doses following testing depended on the findings of allergy testing, and the national COVID-19 recommendations regarding vaccine choice. During the early study period, national guidelines on vaccine administration recommended preferential BNT162b2 vaccination for patients younger than 60 years and ChAdOx1-S vaccination for patients older than 60 years (older than 50 from 17 June 2021).¹⁶

Demographic and clinical information was retrieved from the electronic health records of patients and is presented as median with range or percentage as appropriate. The detailed testing results of three early patients have been previously described.¹⁴

Results

During the period from March 2021 to August 2021, 53 patients underwent allergy testing. Patient age ranged from 18 to 83 years (median, 54 years) and the population of patients were predominantly women ($n = 44$, 78.5%).

Reasons for referral were concern for excipient allergy ($n = 19$), a previous non-COVID-19 vaccine-suspected

allergic reaction ($n = 13$), and previous COVID-19 vaccine-suspected allergic reaction ($n = 21$). Patients testing negative were recommended to receive a vaccine based on national guideline age criteria. Following allergy testing, 49/53 patients have undergone vaccination. A summary flow diagram is presented in Figure 1, while individual patient characteristics can be found in Table S1.

History of excipient allergy

Relevant excipients to which patients had a possible history of allergy included combined PEG/PS80 ($n = 5$), PEG ($n = 13$) and PS80 ($n = 1$). The most commonly reported sentinel drug reaction was to PEG-based bowel preparations (six of 19, 32%).

Of these patients, 11/19 had negative skin testing and 10/11 have since received at least one dose of a COVID-19 vaccine regimen (BNT162b2 $n = 6$, ChAdOx1-S $n = 4$). Two patients had minor reactions to vaccination that resolved without medical intervention (Table S1 nos. 50, 51).

Of the 19 patients with histories of excipient allergy, eight were ultimately positive on skin testing. Two were positive on SPT (Table S1 nos. 40, 46). The first was positive to PEG3350 on SPT and triamcinolone (PS80-containing) on IDT, but following this IDT 1:10 was abandoned because of

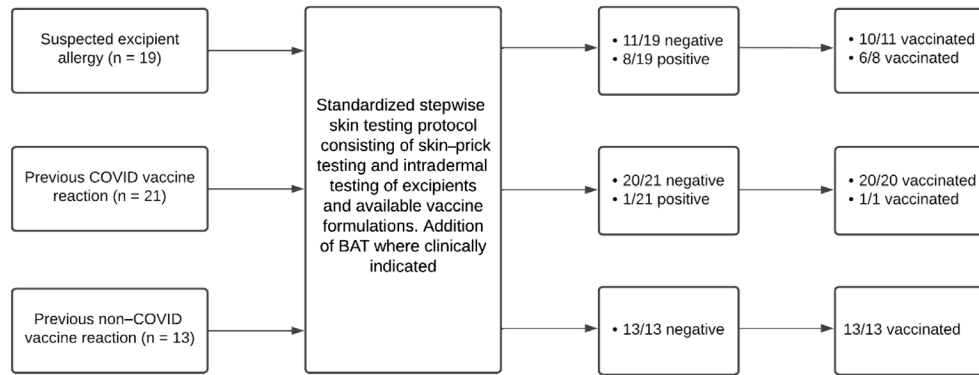


Figure 1 Flow diagram of patient assessments, testing results and vaccinations following allergy testing.

the development of generalised urticaria. BAT was only positive for BNT162b2. The second was positive to PEG3350, methylprednisolone acetate and PS80 on SPT, and both vaccines on IDT. BAT was similarly only positive for BNT162b2. Both patients were successfully challenged with ChAdOx1-S using a three-step protocol of 1:100, 1:10 and neat vaccine without systemic reaction.

One of 19 patient was positive on IDT 1:100 concentration to methylprednisolone acetate, but not vaccine. This patient received BNT162b2 without reaction (Supplementary Table S1 no. 53).

Five of 19 patients were positive to BNT162b2 vaccine. Four were positive on IDT 1:100 concentration to BNT162b2 (Table S1 nos. 43–46), while another one was positive on IDT 1:10 concentration to BNT162b2 (Table S1 no. 41). All five of these patients were referred for suspected PEG allergies, all with index reactions to PEG-based bowel preparations. None of these patients tested positive to either PEG or other PEG-containing medications. Four of five were BAT positive for BNT162b2, and three of five were additionally tested and BAT positive against PEGylated liposomal doxorubicin. No patients were BAT positive for ChAdOx1-S. All five of these patients were recommended to proceed with preferential ChAdOx1-S vaccination, and three of five have undergone vaccination with at least one dose without systemic reaction.

Previous non-COVID-19 vaccine-suspected allergic reactions

Of the 13 patients with previous suspected allergic reactions to non-COVID-19 vaccines, seven had reacted to other PS80-containing vaccines (Table S1 nos. 22–28) and six to non-PEG- and non-PS80-containing vaccines (Table S1 nos. 29–34).

All patients were negative on SPT and IDT to COVID vaccines and PS80, and the six who underwent BAT were

either non-responders ($n = 1$) or negative ($n = 5$). All 13 have subsequently been vaccinated with either ChAdOx1-S or BNT162b2. One patient with a significant history of allergies and brittle asthma on mepolizumab and omalizumab therapy did develop a delayed wheal response to BNT162b2 IDT 9 h later. This patient developed a delayed exacerbation of asthma 12 h following BNT162b2 vaccination requiring intensive care unit (ICU) admission.

Previous COVID-19 vaccine-suspected allergic reactions

Twenty-one patients were referred for suspected allergic reactions to the first dose of a COVID-19 vaccine regimen, either BNT162b2 ($n = 13$) or ChAdOx1-S ($n = 8$). Four of 13 patients with reactions to BNT162b2 met Brighton criteria for anaphylaxis (level 1 $n = 3$, level 2 $n = 1$). Two of eight patients with reactions to ChAdOx1-S met Brighton criteria for anaphylaxis (level 2 $n = 1$, level 3 $n = 1$).

No patients had histories of reactions to excipients contained in the implicated vaccine, and only one of 21 patients had positive testing (Table S1 no. 13). This patient had Brighton level 1 anaphylaxis to BNT162b2 dose 1 and developed an early systemic reaction during SPT characterised by a widespread erythematous and pruritic rash, dyspnoea, cough and periorbital swelling meeting criteria for Brighton level 2 anaphylaxis requiring intramuscular adrenaline administration and hospital admission. SPT was positive to PEG6000, but IDT was abandoned because of the systemic reaction, and BAT responses were equivocal. Event tryptase was not elevated. The patient underwent vaccination with ChAdOx1-S with a mild reaction of chest flushing.

Twenty of 21 patients were negative on SPT and IDT, and have since undergone a second dose of the same vaccine. Five of 20 patients developed symptoms after vaccination as follows: two developed symptoms

suggestive of an immunisation stress-related response, two developed minor and transient skin changes and in one vaccination triggered an exacerbation of brittle asthma requiring ICU admission.

Of two patients with a stress-related response, one patient's index reaction was classified as Brighton level 3 anaphylaxis to dose 1 of ChAdOx1-S. She developed a similar systemic reaction during testing with a feeling of throat thickness managed with a saline nebuliser. The patient had a background of vocal cord dysfunction. Testing was negative and the patient underwent a second dose of ChAdOx1-S with similar symptoms that recovered fully. The other patient with immunisation stress-related response developed palpitations 3 h after vaccination that resolved.

The remaining 15 patients were vaccinated without symptoms. Thus, of the 21 patients referred for suspected vaccine allergy, only one is likely to have experienced anaphylaxis to BNT162b2. Four patients declined offers of vaccination or desensitisation.

Discussion

Since the early reports of anaphylaxis following administration of COVID-19 vaccines, there has been significant debate regarding the potential underlying mechanisms.⁵ PEG allergy is rare, and cross-reactive or specific PS80 allergies are even rarer, although they may be under-recognised.^{17,18} This is, in part, attributable to the insensitivity of PEG in skin testing, compared with PEGylated lipid nanoparticles such as the BNT162b2 vaccine.¹⁴ Symptoms and signs reported following COVID-19 vaccination suggestive of vaccine allergy may be caused by mast cell degranulation, which can be IgE-mediated or non-IgE-mediated.^{19,20} Complement activation-related pseudoallergy to PEG has been suggested as a potential additional mechanism,²¹ and there is some evidence that patients with first-dose reactions have increased circulating PEG-specific IgG that may have complement-fixing activity.²² Symptoms and signs following vaccination may also not be caused by mast cell degranulation, and these likely reflect a spectrum of immunisation stress-related responses.

There have already been reports of patients who have had immediate or delayed hypersensitivity-type reactions to the first dose of an mRNA vaccine who tolerate a second dose.²³ In our cohort of high-risk patients referred for COVID vaccine allergy assessment either prospectively or following reaction to a first dose, we used a combined allergy testing protocol to identify patients potentially at risk of a mast cell degranulation-related reaction and arranged appropriate vaccination strategies.

Of the patients referred, 21/53 had a reaction to their first vaccine dose. Only one of these patients tested positive by skin testing. This suggests that the causes of reported cases of anaphylaxis to the COVID-19 vaccines are heterogeneous, and it is possible that cases of classical hypersensitivity are underrepresented because of successful screening.

Of 32 patients with a history of excipient allergy, eight of 32 (25%) had positive skin testing. Only one patient was positive for both excipients and vaccines (Table S1 no. 46). Three patients were positive for excipients but not vaccines. However, one of three of these patients was positive to methylprednisolone acetate but still tolerated BNT162b2 (Table S1 no. 53), and in the remaining two of three, IDT had to be abandoned because of anaphylaxis and generalised urticaria respectively (Table S1 nos. 13, 36). Conversely, five patients were positive for vaccines only, but not excipients. Skin tests with these excipients are known to have variable results, even in the same patient over time,^{13,24} and our results have demonstrated that they are not reliable indicators of reaction to the vaccines themselves.

Importantly, the one patient who was positive on skin testing to both available vaccines was negative on BAT to ChAdOx1-S and could be successfully challenged with this vaccine. Previous reports of other vaccine allergy testing have had variable results, with reports of allergic reactions on vaccine challenge following negative skin testing,²⁵ and vice versa.²⁶ BAT may increase confidence in cases of positive skin testing given the true positive and negative predictive values of vaccine skin testing remain unknown.

Given the variable performance of excipients and excipient-containing medications in vaccine allergy testing, an extensive testing protocol as we initially developed is not required. We now utilise a streamlined allergy testing protocol utilising only vaccines in a step-wise fashion, with SPT to neat vaccine, and IDT to 1:100 and then 1:10 concentrations (Fig. 1). In patients who have negative skin testing to vaccine, local experience has been that it is safe to proceed with immunisation. In patients who test positive, performing BAT is useful, as a negative BAT can still provide reassurance that it is safe to proceed with immunisation. No patients with negative skin testing were BAT positive. However, we would not recommend the use of BAT alone for screening as it is less representative of the *in vivo* environment. The exception to this may be the use of BAT with PEGylated doxorubicin in situations where BNT162b2 is not available for testing, as doxorubicin is cytotoxic and should not be used for skin testing.¹⁵

Testing is generally safe, with two systemic reactions in our case series. Testing should be undertaken

in the hospital setting to reduce risk. Some patients noted small macules at vaccine IDT sites within 1 week of testing and lasting up to 1 month. There were no severe dermatological reactions to testing, although localised blistering has been reported elsewhere in one case.²⁷

In the 49 patients undergoing vaccination following allergy testing, two severe adverse events occurred with two patients developing severe asthma exacerbations following BNT162b2 vaccination. Both patients had histories of multiple allergies and severe brittle asthma, each with multiple exacerbations requiring ICU admission within the preceding 3 months. Vaccination in this cohort should be performed under observation in a high-risk hospital environment rather than in community centres.

This study has limitations attributable to its uncontrolled case series design. The reproducibility of *in vivo* testing was not determined in this study, as this was a clinical cohort and the goal of the allergy evaluation was to find a safe COVID vaccine for each individual patient. However, randomised trials are difficult to perform in allergy testing, and specificity is difficult to estimate as patients with positive testing results were not

challenged with the vaccine. Further study will be needed to elucidate the underlying mechanisms of vaccine reactions.

Conclusion

Vaccination efforts against COVID-19 need not be slowed by allergy concerns. IgE-mediated allergic responses are rare. Not all excipient allergies correlate with vaccine allergy, and excipient allergy testing has poor sensitivity for detection of vaccine reactions. In practice, there is little crossover between PEG and PS80 allergies, and ultimately almost all patients can be successfully vaccinated against COVID-19.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Characteristics of patients undergoing allergy testing during the study period March 2021 to August 2021.