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Evaluation of patients with suspected vaccine allergies in Singapore

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Abstract

Background: Hypersensitivity reaction to vaccines has been reported to occur in 5 per 100,000 doses. Although hypersensitivity reactions can occur to either the active vaccine component or other components such as excipients, outcome data from skin testing and provocation remains limited.

Objective: To evaluate the role of skin testing and vaccine provocation in patients with an allergy label to vaccine.

Methods: This is a single centre, prospective study between March 2021 and November 2021 of adults with known allergy to non-COVID vaccine. All participants underwent skin prick testing (SPT) and intradermal testing (IDT) to vaccine and excipients. A subset of patients with negative skin testing underwent graded vaccine provocation.

Results: A total of 264 adults were evaluated. The most common index vaccine reactions were nonspecific rash (47.7%), angioedema (32.2%) and itch (25.0%). All patients had negative SPT to vaccines and excipients. Thirty patients (11.4%) had positive IDT to Hepatitis A, Hepatitis B, Human Papilloma Virus (HPV), Influenza, Measles-Mumps-Rubella (MMR), Pneumococcal, Rabies, Diphteria, Tetanus and Pertussis (DTaP). Out of 234 patients with negative IDT, 32 patients (12.1%) underwent vaccine provocation. Three patients (9.4%) developed reaction to influenza and MMR vaccine. One patient required systemic corticosteroids, one required antihistamine, and another patient did not require any treatment. None required admission or attendance at emergency department.

Conclusion: The majority of allergy labels to vaccine are inaccurate based on low skin test positivity and low reaction rates on vaccine provocation. Vaccine provocation is safe. Excipients are unlikely to be the main cause of hypersensitivity reactions in vaccines.

Key words: vaccine allergy, vaccine hypersensitivity, skin tests, vaccine provocation, excipient

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Abbreviations:

SARS-CoV-2 or COVID-19	severe acute respiratory syndrome coronavirus 2
SPT	skin prick test
IDT	intradermal skin test
DPT	drug provocation test
BCG	Bacillus Calmette-Guerin
MMR	Measles, Mumps and Rubella
DTaP	Diphteria, Tetanus and Pertussis
HPV	Human Papilloma Virus
PEG	polyethylene glycol

Introduction

Confirmed vaccine allergies are rare. The incidence of immediate hypersensitivity reactions following vaccination was estimated to be 5 per 100,000 doses.[1] The rate of anaphylaxis was reported to range between 0.65 and 1.21 cases per million doses in children and adolescents,[2,3]

and 1.31 per million vaccine doses in another study involving children and adults.[4] In the latter study, trivalent influenza vaccine was found to be the most common cause of vaccine-triggered anaphylaxis at 1.35 cases per million vaccine doses of trivalent influenza vaccine given alone.[4] This finding was supported by a later study looking at cases of anaphylaxis reported to Vaccine Adverse Event Reporting System from 1990 to 2016, with influenza vaccine being the most commonly reported vaccine for persons aged 19 years or greater; while MMR, varicella vaccines, and vaccines containing diphtheria toxoids, tetanus toxoids, and/or acellular pertussis were most commonly reported for persons aged less than 19 years.[5] Excipients rather than vaccine antigen were previously thought to be the most frequent cause of reactions to vaccines,[6,7] however more recent studies have shown otherwise.[8]

In a previous study involving 519 subjects with suspected vaccine reactions by Micheletti et al, 80% were effectively vaccinated. Among those who received vaccination, 90% did not show any adverse reactions, and only 10% developed symptoms after vaccination, of which majority were mild allergic reaction. Only one child who received MMR vaccination developed urticaria and bronchospasm with immediate recovery after treatment. In this study, 108 patients with suspected allergic vaccine reactions underwent skin tests and 6 were positive (2 to egg proteins, 1 to porcine gelatin, and 3 to tetanus/diphteria tetanus vaccine).[9] In another recent Brazilian study of 34 patients with history of allergy to a vaccine or vaccine component, 4 out of 27 patients had positive IDT, and 2 patients tolerated alternative vaccine despite positive skin test. More than 90% (32 patients) were successfully vaccinated without serious adverse events.[10] The SARS-CoV-2 pandemic has once again shown that incidence of true immediate hypersensitivity reaction to vaccines was very low. Most subjects who developed reaction after first dose of COVID vaccine eventually tolerated second dose.[11]

Despite the available data to date, systematic evaluation of vaccine hypersensitivity reactions especially to non-COVID vaccine is still limited, and the role of skin testing and vaccine provocation needs to be clarified.

Methods

This is a prospective, cohort, single institution study in an academic medical setting (Allergy Centre, Singapore General Hospital) over the period of March 2021 to November 2021. We recruited 264 adult patients who were referred to Allergy Centre for suspected vaccine allergies. This study was conducted in the midst of COVID-19 pandemic and the rollout of mRNA vaccines. As part of risk mitigation recommendations, an initial national advisory recommendation was issued stating that all patients with a history of any previous documented vaccine allergy would need to be evaluated by an allergist prior to receiving mRNA vaccines. Assessment of prior vaccine allergies included detailed history of previous vaccine reactions, a review of electronic/physical medical notes including drug allergy labels, photo-documentations, investigation results (if available), treatments administered and outcomes. The study was approved by the Institutional Review Board in Singapore (CIRB Reference Number: 2018-2877), and complies with national research guidelines. Written consent was obtained from the patients.

Patients above 18 years old and able to give written consent are included in the study.

Skin tests to evaluate immediate hypersensitivity were performed in two steps. Skin prick tests were performed to culprit vaccine and associated excipients as per protocol.[12] SPT to excipients were performed for each vaccine as follows: Hepatitis A and Hepatitis B vaccines – yeast, influenza – egg and gelatin, MMR – gelatin, rabies – gelatin, DTaP – gelatin and milk, and yellow fever – egg and gelatin.[12] In addition, all patients had skin tests (SPT and IDT) performed to polysorbate and polyethylene glycol (PEG) as a determinant for suitability for mRNA vaccine. SPT was performed by dropping vaccine at neat concentration, and lightly pricking the skin with a lancet, and reading was done after 15 minutes. Positive SPT was interpreted as wheal size of 3 mm or more. If SPT was negative, IDT to the vaccine was performed. IDT comprised of 1:100 dilution of the vaccine injected intradermally into the skin and read 15 minutes later.[12,13] Positive IDT was defined as a wheal 3 mm larger than the baseline, with a flare. If SPT was positive, IDT was not performed. All skin tests were accompanied by positive (histamine) and negative (saline) controls.

Patients with negative skin tests were offered vaccine provocation based on the need for subsequent dose(s). Patients who have completed relevant vaccination according to national immunization schedule were not subjected to vaccine provocation. Graded provocation was performed with 1/10 of the full dose of the vaccine, followed by 30-minute monitoring, and the remaining dose of the vaccine if patient tolerated the first step.

Primary outcome of this study includes response to skin tests to vaccine and excipients, and to vaccine provocation. Secondary outcomes include severity of reaction and treatment required in patients who developed reaction from skin tests or vaccine provocation.

Results

There were a total of 264 patients recruited during the study period. Baseline characteristics of the patients, including demographics, comorbidities, vaccine reactions and onset of reaction were recorded (**Table 1**). There were 69.7% females, and 30.3% males in the cohort. Patients with known atopy (allergic rhinitis, asthma or eczema), and angioedema or urticaria were 25.4% and 6.1% respectively. The most common index vaccine reactions that led to an allergy label were non-specific rash (47.7%), angioedema (32.2%) and itch (25.0%). Onset of reaction was categorized into less than 2 hours (20%), more than 2 hours (47%), and unknown onset (33%).

Table 1. Demographic characteristics.

	n = 264 (%)
Age, mean (SD)	45.0
Gender	
Female	184 (69.7)
Male	80 (30.3)
Co-morbidities	
Angioedema/urticaria	16 (6.1)
Atopic dermatitis	23 (8.7)
Asthma, allergic rhinitis	44 (16.7)
On immunosuppressants	
Yes	7 (2.7)
No	257 (97.3)
Vaccine reaction	
Rash	126 (47.7)
Angioedema	85 (32.2)
Itch	66 (25.0)
Urticaria	55 (20.8)
SOB/wheeze/globus/chest tightness	44 (16.7)
Hypotension	5 (1.9)
Anaphylaxis	4 (1.5)
Other reaction*	64 (24.2)
Unknown	29 (11.0)
Onset of reaction	
Less than 2 hours	53 (20.0)
More than 2 hours	124 (47.0)
Unknown	87 (33.0)

*Other reactions: giddiness, injection site reaction, facial flushing, chest tightness/pain, tachycardia, bradycardia, syncope, choking, fever, palpitations, LOC, face red patches, red eyes, coughing, rhinorrhea, joint swelling, delirium, cyanosis, face skin tightness, arm swelling, sorethroat

Suspected vaccines include influenza (40.6%), tetanus (19.8%), Hepatitis B (8.1%), Tetanus, Diphtheria and Pertussis (7.8%), Measles, Mumps and Rubella (MMR) (3.9%), Human Papilloma Virus (3.5%), Varicella (3.2%), Pneumococcal (2.8%), Rabies (2.5%), Hepatitis A (1.8%), Hepatitis A&B (1.8%), Typhoid (1.8%), Yellow fever (1.1%), Bacillus Calmette-Guerin (BCG) (0.4%), Rubella (0.4%), and Cowpox (0.4%) (**Table 2**).

Table 2. List of suspected vaccines allergy.

Vaccine	Number of suspected allergy (%)
Influenza	115 (40.6)
Tetanus	56 (19.8)
Hepatitis B	23 (8.1)
Diphteria, Tetanus and Pertussis (DTaP)	22 (7.8)
Measles, Mumps and Rubella (MMR)	11 (3.9)
Human Papilloma Virus (HPV)	10 (3.5)
Varicella	9 (3.2)
Pneumococcal	8 (2.8)
Rabies	7 (2.5)
Hepatitis A	5 (1.8)
Hepatitis A&B	5 (1.8)
Typhoid	5 (1.8)
Yellow fever	3 (1.1)
Bacillus Calmette-Guerin (BCG)	1 (0.4)
Cowpox	1 (0.4)
Meningococcal	1 (0.4)
Rubella	1 (0.4)

All patients had negative SPT to the vaccines and the excipients. All patients underwent IDT. Thirty patients (11.4%) had positive IDT, of which 24 (9.1%) had immediate reaction and 6 (2.3%) delayed IDT reaction. The positive IDT reactions were to Hepatitis A (n = 1, 0.4%), Hepatitis B (n = 1, 0.4%), Human Papilloma Virus (HPV) (n = 2, 0.8%), Influenza (n = 20, 7.6%), MMR (n = 1, 0.4%), Pneumococcal (n = 2, 0.8%), Rabies (n = 1, 0.4%), and DTaP (n = 1, 0.4%) (**Table 3**). Categorizing based on vaccine types, 22 patients had positive IDT to inactivated vaccines (8.3%), 5 patients to subunit vaccines (1.9%), 2 patients to live attenuated vaccines (0.8%), and 1 patient to toxoid vaccine (0.4%). Only one patient with positive IDT to influenza vaccine had positive IDT to polysorbate as well. Among the 6 patients with delayed IDT reaction, 4 developed reaction after 4 hours but within 24 hours, and 2 developed reaction after 24 hours.

Out of 234 patients with negative IDT, 32 (13.7%) underwent vaccine provocation and 3 (9.4%) developed a positive reaction (**Figure 1**). Two (6.3%) positive reactions were related to influenza vaccine (inactivated vaccine), and one (3.1%) was related to MMR vaccine (live attenuated vaccine). One patient developed itch, dyspnoea and giddiness one hour after influenza vaccine provocation, one patient developed urticaria 10 hours after influenza vaccine provocation and one patient developed angioedema one day after MMR vaccine provocation (**Table 3**).

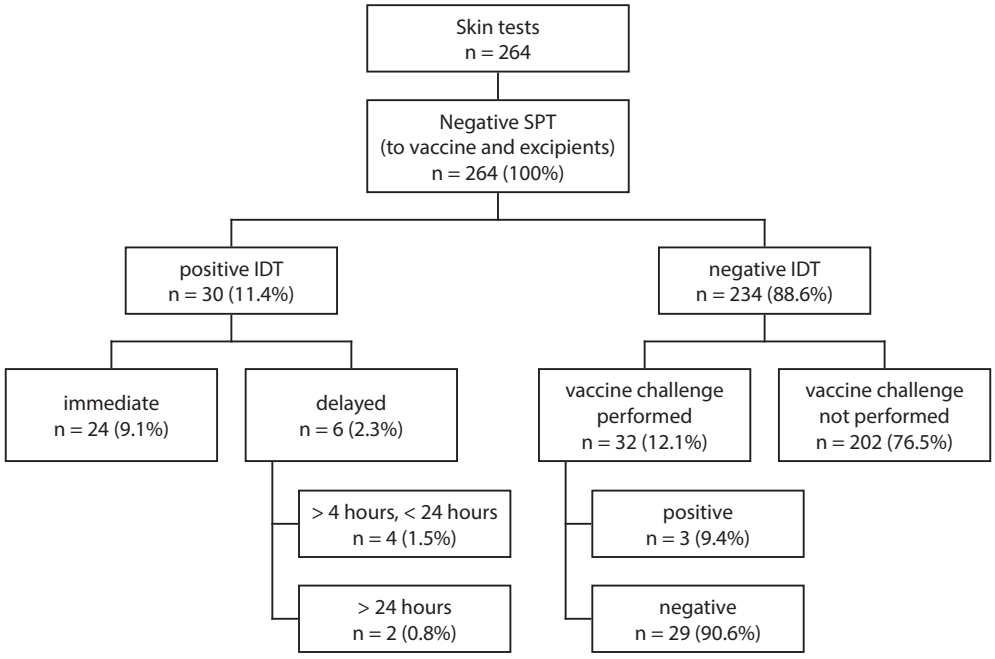

Figure 1. Skin tests and vacine provocation outcome.

Table 3. Skin tests and vaccine provocation outcome.

	n (%)
Vaccine or component tested positive	
Hepatitis A	
Vaccine (IDT)	1 (0.4)
Component (SPT): yeast	0
Hepatitis B	
Vaccine (IDT)	1 (0.4)
Component (SPT): yeast	0
HPV	
Vaccine (IDT)	2 (0.8)
Influenza	
Vaccine (IDT)	20 (7.6)
Component (SPT): egg and gelatin	0
Vaccine provocation (intramuscular)	2 (0.8)
MMR	
Vaccine (IDT)	1 (0.4)
Component (SPT) : gelatin	0
Vaccine provocation (intramuscular)	1 (0.4)
Pneumococcal	
Vaccine (IDT)	2 (0.8)
Rabies	
Vaccine (IDT)	1 (0.4)
Component (SPT) : gelatin	0
DTaP	
Vaccine (IDT)	1 (0.4)
Component (SPT) : gelatin and milk	0

Table 4. Management in positive IDT or vaccine provocation.

	n (%)
Treatment	
No treatment required	29 (87.9)
Antihistamines	3 (9.1)
Systemic corticosteroids	1 (3.0)
Adrenaline	0 (0)
Disposition	
Discharged	33 (100)
Emergency department	0 (0)
Admission	0 (0)

Majority (87.9%) of the patients with positive IDT or provocation did not require treatment, 9.1% required antihistamines, and only 1 patient (3.0%) who developed dyspnoea and itch after influenza vaccine provocation required systemic corticosteroids. No epinephrine was required for this patient as parameters (blood pressure, heart rate and oxygen saturation) remained stable with no objective airway involvement. All the patients were discharged well, and none required hospitalization or attendance at emergency department (**Table 4**).

Table 5. Summary of previous studies on non-COVID vaccine skin tests and provocation outcome.

	Study participants	IDT and vaccine provocation outcome
F. Michelletti, et al. Clinical & Experimental Allergy 2012	519 subjects; 152 skin tests (previous allergic reaction to vaccine, sensitization to components, and allergic disease)	Positive skin tests but provocation outcome not specified - 6/108 with previous allergic reaction to vaccines - 13/29 with sensitization to components - 0/15 with allergic disease
Cheung A. et al. J Allergy Clin Immunol Pract 2019	73 children, with potential IgE-mediated adverse events following immunization; 22 skin tests	4 positive IDT - 2 negative provocation to alternative brand vaccine 18 negative IDT - 2 positive provocation - 14 negative provocation - 2 not re-challenged
Pedro Brandao, et al. J Allergy Clin Immunol Global 2023	34 adults, with history of allergy to vaccine or vaccine components; 44 skin tests	8 positive IDT - 2 negative provocation to alternative vaccine 36 negative IDT - 3 positive provocation - 33 negative provocation

Discussion

Sensitization and true vaccine allergy are uncommon as evidenced by low rate of positive skin tests and vaccine provocation. This study has proved that majority of vaccine allergy labels are inaccurate. In the cohort that underwent provocation, 90% of them tolerated the provocation suggesting that majority of vaccine allergies may be inaccurate. In the remaining 10% who developed reactions, the reactions were mild and self-limiting suggesting that re-administration of vaccine can be a safe approach.

Vaccine hypersensitivity reaction can be due to various vaccine components such as vaccine antigens, adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, residual antibiotics, cell culture materials, and inactivating ingredients.[6,13,14] The more commonly discussed components are egg, gelatin, and surfactants such as PEG and polysorbate. Current recommendations have stated safety on administration of egg-based vaccines to individuals with egg allergy, and no special precautions are required, unless they have had anaphylaxis to egg requiring intensive care support.[15,16] The small amount of egg protein in vaccines is below the threshold required to elicit an allergic reaction. Similarly, allergy to other components such as yeast and milk are exceedingly rare, and the amount present in the vaccines is unlikely to elicit an allergic reaction. In cases of known allergy to gelatin, allergist evaluation is recommended prior to administration of vaccine containing the components.[12,17] In the past, high rate of anaphylaxis from DTaP vaccine was likely due to the use of poorly hydrolyzed bovine gelatin in the vaccine. Since the use of hydrolyzed porcine gelatin, the rate of anaphylaxis has significantly reduced. Although hydrolyzed gelatin is less immunogenic, skin test is still recommended prior to administration of gelatin-containing vaccines in a person with history of anaphylaxis to such a vaccine.

Published studies on skin tests for non-COVID vaccines are limited, as summarized in **table 5**. Therefore, vaccine hypersensitivity reactions and the role of skin testing so far remains limited. Skin testing can help provide additional information about sensitization and narrow down the vaccine or excipient being the culprit. Skin prick test and immediate intradermal skin test would pick up IgE-mediated hypersensitivity reactions, while a delayed intradermal reading would indicate a delayed hypersensitivity reaction. There is a lack of data on the specificity and sensitivity of skin test to vaccines and as with any forms of testing. As there may be false positive or false negative results, the recommendation would still be to administer the vaccine in graded doses under observation if the skin tests are negative In our study of 264 adult patients, in which all of them underwent skin testing (both SPT and IDT), we found that skin tests were positive in 11.4%, and 9.4% had positive reaction to vaccine provocation. All the patients with positive skin tests to vaccine or developed reaction to vaccine provocation had negative skin tests to excipients. This shows that excipients might not be primary cause in true vaccine allergies and should not be a barrier to vaccination.

We performed a systematic evaluation of patients with suspected vaccine allergies. We included only patients with documented vaccine allergy in their national medical records. In addition to review of their medical records, re-validation of allergy history was done in person. This study involves the largest number of skin tests to non-COVID vaccines to date. The limitations of our study include recall bias, as 10.6% of the suspected vaccine reaction occurred more than 10 years ago, and another 6.1% with unknown time elapsed between allergy symptoms and first evaluation in our clinic.

Although only 32 patients (12% of the cohort) underwent vaccine provocation, this is to be expected in view of their vaccination schedule and personal preferences. Patients with positive skin tests in our study did not undergo vaccine provocation. Therefore, we are unable to determine the sensitivity and specificity of skin tests. We were also not able to trace if any of the patients with negative skin tests subsequently received further vaccination in the community setting due to strict Personal Data Protection Act in Singapore. Nonetheless, in our cohort, we have demonstrated that vaccine provocation is safe. Physicians should consider provocation to the vaccine if the vaccine is required again in future.

Although majority of vaccine manufacturers are global producers, there may be alternative manufacturers and processes in other jurisdictions and may potentially limit the generalizability of this study.

Conclusion

Consistent with previous studies, our study shows that true vaccine allergy is infrequent and anaphylaxis due to vaccine is indeed rare. Skin testing can be a useful adjunct, although component testing is unlikely to be useful. Graded vaccine provocation may be a safe approach in patients with suspected vaccine allergy.

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