

# Vaccine Allergy? Skin Testing and Challenge at a Tertiary Pediatric Hospital in Melbourne, Australia



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**What is already known about this topic?** There is limited data on rates of true vaccine allergy; however, established investigation protocols often suggest invasive skin testing in the majority of patients.

**What does this article add to our knowledge?** Our data show that the vast majority of children presenting with a potential IgE-mediated vaccine allergy are able to tolerate the suspect vaccine at challenge.

**How does this study impact current management guidelines?** We identified that risk factors for true vaccine allergy were reaction onset within 15 minutes of immunization or anaphylaxis. We present an investigation protocol for potential IgE-mediated vaccine reactions, recommending skin testing only in children with a history of anaphylaxis.

**BACKGROUND:** The rate of true vaccine allergy is unknown. Children with potential IgE-mediated adverse events following immunization (AEFI) should undergo allergy investigation that may include skin testing or challenge. Previous protocols tend to be highly conservative and often suggest invasive testing for all, a practice not evidence based, technically difficult, and unpleasant in children. It has more recently been suggested that skin testing may be restricted to those with allergic-like events within the first hour and those with a history of anaphylaxis.

**OBJECTIVE:** We aimed to describe the outcome of vaccine skin testing and challenge in children referred to a tertiary pediatric hospital with a potential IgE-mediated AEFI. The secondary aim was to identify any significant risk factors for vaccine allergy.

**METHODS:** A retrospective review of all children (<18 years) who underwent vaccine skin testing (skin prick testing or intradermal testing [IDT]) or challenge over a 5-year period (May 1, 2011, to April 30, 2016) at the Royal Children's Hospital Melbourne is presented.

**RESULTS:** There were 95 admissions in 73 children. Eight percent (6 of 73) of children had confirmed vaccine allergy (positive skin testing or challenge to the index vaccination). Two had positive IDT to a suspect vaccine but challenge negative to an alternative brand vaccine. Two had negative IDT but subsequent positive challenge and two had immediate urticaria on challenge without prior skin testing. All children in the positive group either had index reaction within 15 minutes of vaccination or had history consistent with anaphylaxis.

**CONCLUSIONS:** The vast majority of children (92%) presenting with a potential IgE-mediated AEFI are able to tolerate challenge to a suspect vaccine without reaction. We present our investigation protocol recommending skin testing in all children with anaphylaxis and challenge with a suspect vaccine if negative testing or previous nonanaphylactic potential IgE-mediated AEFI. Crown Copyright © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1541-9)

**Key words:** Vaccine; Immunization; Allergy; Hypersensitivity; Adverse event

Although the rate of reported possible hypersensitivity adverse events following immunization (AEFI) is high, many of these are unlikely to represent true vaccine allergy but rather coincidental symptoms that may mimic an allergic reaction. The rate of anaphylaxis after vaccination is estimated to be 0.36 to 1.25 per 100,000 vaccine doses<sup>1</sup> in the Australian population. Anaphylaxis can obviously present as a life-threatening medical emergency and caution must be taken in investigation and revaccination.

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**Abbreviations used**

AEFI- Adverse events following immunization

HPV- Human papillomavirus

IDT- Intradermal testing

IH- *Infanrix hexa (contains diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis virus, and Haemophilus influenzae type b)*

IM- Intramuscular

NIC- Nonirritating concentration

SPT- Skin prick testing

Published review papers on vaccine allergy have various protocols for investigation and challenge.<sup>2,3</sup> However, these have previously tended to be highly conservative with skin testing recommended for all children with possible hypersensitivity reaction. In clinical practice, particularly in the pediatric population, this can be difficult logistically. Skin testing is an invasive procedure, and in our experience, many parents are reluctant to have it performed, particularly in young infants—a population where hypersensitivity reactions are reported more commonly. It was recently proposed that skin testing and graded dose reimmunization should be restricted to those with a suspected IgE-mediated AEFI within the first hour after vaccination or those with presentation consistent with anaphylaxis (irrespective of the timeframe).<sup>4</sup> We present our clinical experience and investigation protocol.

## METHODS

A retrospective review of all children, under the age of 18 years, who underwent in-hospital vaccine skin testing and/or challenge over a 5-year period (from May 1, 2011, to April 30, 2016) is presented. The Royal Children's Hospital is a major tertiary care referral allergy center located in Melbourne, Australia. The study was approved by the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne, Australia (DA013-2017-16).

### Study population

Children were identified through a search of the RCH Allergy Department database (DB013—Medipath) of skin testing/challenges who were in the defined age group and admitted with an admission procedure code that included "vaccine." Vaccine antigens and brand names were also searched. Notes were reviewed by a single, trained data abstractor.

Decision and referral for vaccine skin testing and/or challenge was at the discretion of the child's primary allergy specialist, depending on the history of clinical reaction, the child's coexisting comorbidities, and requirement for further vaccines. Within the timeframe of analysis, there were only 2 clinicians operating within this context.

Children were included if they were <18 years of age and had undergone either skin testing and/or challenge to either a suspect vaccine or a vaccine with a suspect antigen. Children were excluded if they were given a vaccine that did not include a suspect antigen.

### Skin testing

Skin prick testing (SPT) and/or intradermal testing (IDT) were performed in the allergy challenge unit on the same day. SPT was performed using a quintip with neat (undiluted) concentration of the vaccine and positive (histamine) and negative (normal saline) controls. SPT was measured after 15 minutes and considered positive when the weal size was 3 mm or greater in diameter than the

negative control, as per the recommendations of the Australasian Society of Clinical Immunology and Allergy SPT manual.<sup>5</sup>

IDT was performed with nonirritating concentrations (NICs) of vaccine as previously reported<sup>6,7</sup> and positive (histamine) and negative (normal saline) controls. Vaccine dose of 0.02 mL was injected intradermally into the skin with measurement at 20 minutes. IDT was considered positive when the vaccine weal size was 3 mm or greater in diameter than the negative control.<sup>8</sup> All children with skin testing had both SPT and IDT. There were no children with isolated SPT or IDT. Testing to excipient was not performed in any children; however, an alternative vaccine was tested where the positive skin test was found in the first instance. Excipient testing may be an option if no alternative vaccine was found but was not required in our children.

### Challenge protocol

The challenge protocol was determined by the referring allergy specialist. Children were either challenged with split dosing (10% of vaccine dose followed by 90% of vaccine dose 30 minutes to 1 hour later) or single full vaccine dose. Challenge observation time period was determined by the referring specialist with a minimum of 1 hour after the final dose.

## RESULTS

### Study population and vaccines challenged

There were a total of 95 allergy testing episodes in 73 children. Eighteen children had both SPT and IDT. There were 59 children with 73 separate vaccine challenges (without preceding skin testing). Children with IDT to 1 vaccine were also included in the challenge group if they underwent challenge to a separate vaccine without preceding IDT. These results are shown in Figure 1.

The number of each vaccine challenged is demonstrated in Table I. The ages of children included in this study range from 3 months to 18 years, with female predominance (54%). The highest number of hypersensitivity reactions prompting skin testing or vaccine challenge occurred in 2 population groups—infants with their immunizations in the first 6 months of life ( $n = 34$ ) and adolescents with their human papillomavirus (HPV) vaccination ( $n = 17$ ).

### Index reactions

Reactions were classified into the following categories: anaphylaxis, anaphylactoid, angioedema, urticaria/allergic rash, allergic reaction (generalized), and nonspecific rash. The classification of anaphylaxis was based on the Brighton Collaboration. The level of anaphylaxis is representative of likelihood of true anaphylaxis rather than severity of reaction, with level 1 representing the highest level of diagnostic certainty and level 3 of the lowest. An anaphylactoid reaction included those with respiratory or cardiovascular symptoms, which did not fulfill that of the Brighton Collaboration for anaphylaxis.<sup>9</sup> A generalized allergic reaction included those with symptoms other than cutaneous, which did not fall into the respiratory or cardiovascular systems—for example, those with gastrointestinal features. The number of types of reactions referred to our service is described in Table II.

The majority of reactions in our cohort were within the first 15 minutes after vaccination ( $n = 51$ , 69%). The majority of presentations consisted of cutaneous changes—either rash (nonurticarial), urticaria, or angioedema in each time group.

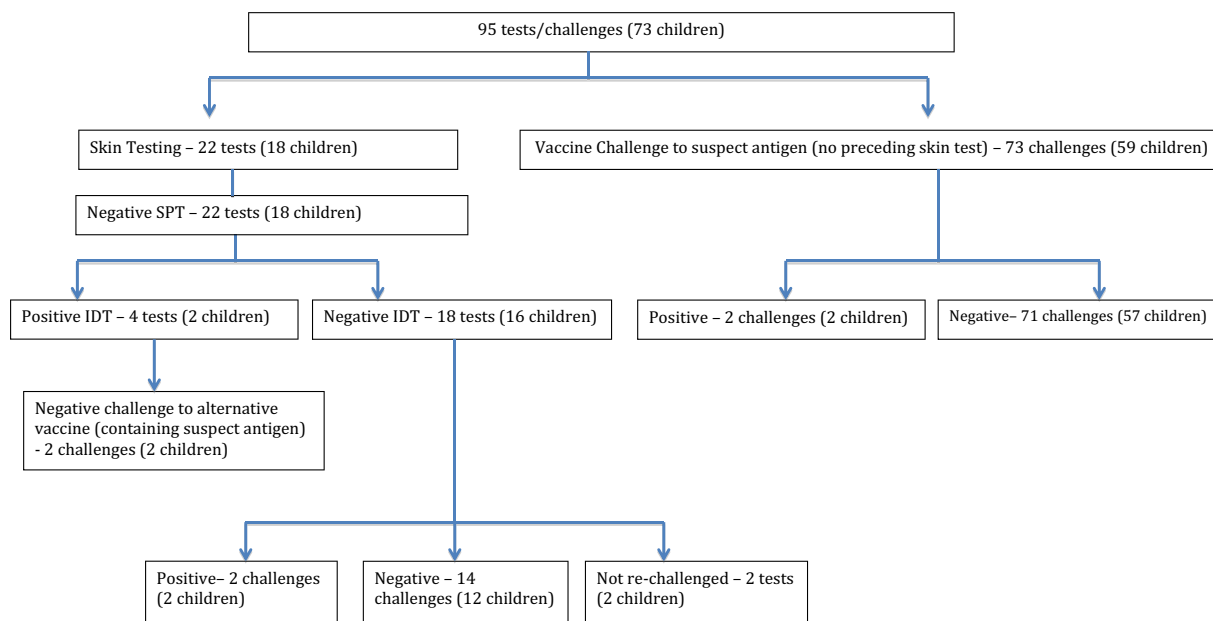


**FIGURE 1.** Study population. *SPT*, Skin prick testing; *IDT*, intradermal testing.

### Skin testing

Skin testing was performed in 18 children, all of whom either had prior reaction fulfilling Brighton criteria for anaphylaxis or reaction occurring within 1 hour of vaccination. This included both SPT and IDT. No child had isolated SPT without IDT or vice versa. Eight children presented with anaphylaxis (4 with level 1, 1 with level 2, and 3 with level 3). Three children presented with anaphylactoid reactions and 1 with generalized allergic reaction. Six children had a history of urticaria but all within 15 minutes of index vaccination. All children but one had their index reactions within the first hour after vaccination with 15 of these occurring within 15 minutes. The last child had his reaction at 18 hours after vaccination but was referred for skin testing because of a history consistent with level 1 anaphylaxis. This child is discussed in the positive allergy testing group below.

Twelve children in our referral group were referred with anaphylaxis (inclusive of all levels). However, only 8 of these children were referred for IDT. Of the children without IDT, 2 were challenged with an alternative vaccine that contained an antigen in the suspect vaccine. Both of these children had level 2 anaphylaxis with a history of urticaria, angioedema, and only subjective respiratory symptoms. The third child did not require further doses of his suspect vaccine and so was given an alternative vaccine with separate antigens. The fourth child had a history of reported facial angioedema and loss of consciousness with tachycardia after HPV vaccination. It was felt that this previous reaction was more likely a vasovagal, and thus decision for cautious challenge was made that was tolerated. Although vasovagal reaction in the adolescent group is commonly reported, only 3 of the children with HPV as a suspect vaccine were thought to have had a vasovagal reaction in our cohort, although up to 5 were retrospectively thought to have an acute stress reaction to the vaccine.

### Positive allergy testing

Children with positive IDT or positive vaccine challenge were considered together as having “true vaccine allergy.” There were a

total of 6 children with either positive skin testing or challenge, making up a total of 8.1% of a total cohort. No skin prick tests were positive. These children are outlined in Table III.

All children except one had an index reaction within 15 minutes of vaccination. Three of 6 children presented with level 1 anaphylaxis. The other 3 presented with urticaria/angioedema. Of these, 2 developed urticaria on challenge with a suspect vaccine (both of whom proceeded directly for challenge without skin testing prior). Of those who reacted at challenge, 2 of 3 reacted at full dose.

Child 1 had an index reaction to his 4-month vaccines (Infanrix hexa [IH] and Prevenar-13) with onset of generalized erythema within 15 minutes and then developed increased work of breathing and oxygen desaturation 4 hours later. He had negative IDT to IH (1:100 dilution) and underwent a split-dose challenge. Forty-five minutes after full dose, he developed urticaria and wheeze. Of significant concern, he required 4 doses of intramuscular (IM) epinephrine with admission to the intensive care unit for observation. This child had a history of prematurity and chronic lung disease, and it is likely that this had significant contribution to the severity of his reaction.

Child 2 presented with a history of urticaria and angioedema after the first dose of HPV vaccine (Gardasil). IDT to both Gardasil and alternate HPV brand (Cervarix) was negative. Cervarix was chosen to be challenged and was tolerated. His third dose of HPV (Cervarix) was administered under observation. With this dose, he developed level 3 anaphylaxis.

Child 3 developed level 1 anaphylaxis after multiple vaccinations were given, one of which included Fluvax that was tested positive on IDT. An additional alternative brand influenza vaccination (Fluarix Tetra) was negative at IDT and tolerated at challenge.

Child 4 had his index reaction 18 hours after vaccination; however, his reaction was consistent with level 1 anaphylaxis. Of note, he was unwell with a viral illness for the days surrounding his vaccination and regular over-the-counter medication was being administered (this preparation included the antihistamine,

TABLE I. Vaccine challenges

| Antigen challenged              | Brand names                           | Skin testing performed | Positive skin testing | Total number of challenges performed | Positive challenge |
|---------------------------------|---------------------------------------|------------------------|-----------------------|--------------------------------------|--------------------|
| dTpa/Tdap                       | Adacel (Sanofi Aventis)               | 4                      | 3 (1 child)           | 3                                    | 0                  |
|                                 | ADT (CSL Limited)                     |                        |                       |                                      |                    |
|                                 | Boostrix (GlaxoSmithKline)            |                        |                       |                                      |                    |
| DTPa-hepB-IPV-HiB               | Infanrix Hexa (GlaxoSmithKline)       | 3                      | 0                     | 29                                   | 1                  |
| DTPa-IPV                        | Infanrix IPV (GlaxoSmithKline)        | 1                      | 0                     | 3                                    | 0                  |
|                                 | Quadracel (Sanofi Aventis)            |                        |                       |                                      |                    |
| HPV                             | Cervarix (GlaxoSmithKline)            | 11                     | 0                     | 18                                   | 1                  |
|                                 | Gardasil (bioCSL/Merck Sharp & Dohme) |                        |                       |                                      |                    |
| Hepatitis A                     | Havrix (GlaxoSmithKline)              | 1                      | 0                     | 2                                    | 0                  |
|                                 | Havrix Jnr (GlaxoSmithKline)          |                        |                       |                                      |                    |
| Hepatitis A-typhoid             | Vivaxim (Sanofi-Aventis)              | 1                      | 0                     | 1                                    | 0                  |
| Hib                             | Hiberix (GlaxoSmithKline)             | 0                      | —                     | 1                                    | 0                  |
| Influenza                       | Fluarix (GlaxoSmithKline)             | 1                      | 1                     | 7                                    | 1                  |
|                                 | Fluarix Tetra (GlaxoSmithKline)       |                        |                       |                                      |                    |
|                                 | Fluvax (CSL)                          |                        |                       |                                      |                    |
|                                 | Vaxigrip (Sanofi Pasteur)             |                        |                       |                                      |                    |
|                                 | Vaxigrip Jnr (Sanofi Pasteur)         |                        |                       |                                      |                    |
| Meningococcal C                 | NeisVacC (Baxter Healthcare)          | 0                      | —                     | 1                                    | 0                  |
| Meningococcal C-Hib             | Menitorix (GlaxoSmithKline)           | 0                      | —                     | 1                                    | 0                  |
| Measles-mumps-rubella           | Priorix (GlaxoSmithKline)             | 1                      | 0                     | 1                                    | 0                  |
| Measles-mumps-rubella-varicella | Priorix-tetra (GlaxoSmithKline)       | 0                      | —                     | 3                                    | 0                  |
| Pneumococcal                    | Prevenar-13 (Pfizer)                  | 2                      | 0                     | 27                                   | 1                  |
| Rotavirus                       | Rotarix (GlaxoSmithKline)             | 0                      | —                     | 11                                   | 0                  |
|                                 | Rotateq (CSL)                         |                        |                       |                                      |                    |
| Typhoid                         | Typhim VI (Sanofi Aventis)            | 1                      | 0                     | 1                                    | 0                  |
| Varicella                       | Varilrix (GlaxoSmithKline)            | 0                      | —                     | 3                                    | 0                  |
|                                 | Varivax (bioCSL)                      |                        |                       |                                      |                    |
| Total                           |                                       | 26                     | 4                     | 112                                  | 4                  |

dTpa/Tdap, Diphtheria, tetanus and acellular pertussis; hepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliomyelitis virus.

chlorpheniramine). The last dose was approximately 24 hours before the vaccine was administered. IDT over a number of sessions was positive to multiple different brands with the same vaccine antigens (Infanrix-IPV, Boostrix, Adacel, ADT). He was eventually tested to a monovalent tetanus vaccine (Tetanol) that was tolerated. He is therefore presumed to have an IgE-mediated allergy to a diphtheria antigen.

Children 5 and 6 both had immediate urticaria on index reaction with the development of urticaria on challenge to a suspect vaccine. Child 5 developed a localized hive to 0.05 mL (1/10th dose). Because of this reaction, 0.15 mL was given as a second dose with generalized urticaria within 10 minutes of this dose. Therefore, the challenge was considered positive and no further doses were given; however, the rash resolved spontaneously without treatment.

Child 6 developed urticaria within 15 minutes of full dose of the suspect vaccine at challenge that responded to oral antihistamine.

All children in the positive group either had index reaction within 15 minutes of vaccination or had history consistent with anaphylaxis. Of those patients with anaphylaxis, 3 of 4 patients with level 1 anaphylaxis were confirmed to have true vaccine allergy (the fourth patient in this group had an alternative unrelated vaccine and did not undergo IDT). No patients presenting with level 2 or 3 anaphylaxis had reaction to a suspect vaccine.

Children in the positive group had higher rates of asthma (33% vs 17%) and eczema (67% vs 50%). There were no other significant differences in age range or rates of allergic rhinitis between the 2 groups. There were only 2 children who were reported to have chronic idiopathic urticaria, who were both in the negative group. The presence of dermatographism was not reported for all children. Any child included in the positive group was entirely excluded from the negative group for this analysis. There were 2 children with negative skin testing who did not proceed with challenge for nonmedical reasons and were also excluded from this analysis.

### Nonspecific rashes

There were 11 children who developed nonurticarial rash, consisting of erythematous macular rash. Nine of 11 children (82%) were <18 months of age at challenge. Three of 11 children (27%) developed recurrent nonspecific rash in response to more than 1 vaccine challenged, and of these, 2 were also included in the positive challenge group. None of these children required treatment for their rash.

These children are documented in Table IV. Note that administered vaccines that did not include a suspect antigen were excluded from our analysis but were included in this table demonstrating that many of these rashes are not related to an underlying IgE-mediated mechanism. Child 1 and child 6

**TABLE II.** Classification of index reaction

| Timing of potential vaccine hypersensitivity reaction after immunization | N (%)<br>(N = 73) | Type of reaction                 |
|--------------------------------------------------------------------------|-------------------|----------------------------------|
| <15 min                                                                  | 51 (69%)          | Level 1 anaphylaxis: 2           |
|                                                                          |                   | Level 2 anaphylaxis: 3           |
|                                                                          |                   | Level 3 anaphylaxis: 2           |
|                                                                          |                   | Anaphylactoid: 5                 |
|                                                                          |                   | Generalized allergic reaction: 1 |
|                                                                          |                   | Urticaria/angioedema: 19         |
| 15-60 min                                                                | 10 (15%)          | Angioedema: 3                    |
|                                                                          |                   | Rash (nonurticarial): 16         |
|                                                                          |                   | Level 1 anaphylaxis: 1           |
|                                                                          |                   | Level 3 anaphylaxis: 1           |
|                                                                          |                   | Anaphylactoid: 2                 |
|                                                                          |                   | Urticaria/angioedema: 3          |
| 1-4 h                                                                    | 7 (9%)            | Rash (nonurticarial): 3          |
|                                                                          |                   | Level 2 anaphylaxis: 1           |
|                                                                          |                   | Anaphylactoid: 1                 |
|                                                                          |                   | Urticaria/angioedema: 2          |
| >4 h                                                                     | 5 (7%)            | Rash (nonurticarial): 3          |
|                                                                          |                   | Level 1 anaphylaxis: 1           |
|                                                                          |                   | Urticaria: 1                     |
|                                                                          |                   | Rash (nonurticarial): 3          |

documented in Table IV correlate with child 1 and 6 in Table III, respectively.

## DISCUSSION

Potential hypersensitivity AEFI are commonly reported, but the incidence of true vaccine allergy is likely to be much lower, with the rate of anaphylaxis reported to be 0.65 cases per million vaccine doses in children and adolescents<sup>10</sup> and vaccine-specific anaphylaxis rates ranging from 0 to 5.14 per million vaccine doses.<sup>11</sup> We found a rate of 8% of true vaccine allergy in our cohort; however, it must be noted that this is in patients already deemed suspicious of a previous IgE-mediated vaccine reaction, and would not be representative of rates seen in the normal population. Reassuringly, we found that the vast majority of children (92%) presenting with a potential IgE-mediated AEFI in our cohort were able to tolerate challenge to a suspect vaccine or a vaccine with an index antigen without reaction, with only 5 of 62 children (8%) with index reaction less than 1 hour having reaction on revaccination. It is important to note that there were 2 children who were not challenged to the suspect vaccine due to nonmedical reasons, and so vaccine allergy status was not determined in these children, although both had negative skin testing.

Zafack et al<sup>4</sup> report 16% of patients with a history of immediate reaction (<4 hours) recurring on reimmunization, with all these occurring within the first hour. However, we do note that this study included adults as well as children with only 1 reaction in a preadolescent and no reactions in preschool children.

The reported potential hypersensitivity AEFI were most commonly reported in infants and adolescents. This is likely reflective of the fact that the highest number of vaccines are provided during the infancy period.<sup>12</sup> Anxiety can also be high in

the adolescent group, and it is suspected that many of these reported reactions may in fact be secondary to coexisting factors other than true allergy. For example, postvaccination syncope is well documented and most common in the adolescent and female population.<sup>13,14</sup> In the Australian population, syncope has been reported in as high as 10% of adolescents in association with HPV vaccination.<sup>15</sup> However, clinically, it can sometimes be difficult to discriminate between anxiety, syncope, and vaccine allergy, particularly if symptoms include shortness of breath or nonspecific rash. Where there is uncertainty in diagnosis, it is important that these AEFI should still be considered as potential allergy and investigated appropriately.

The majority of children in our cohort (69%) had reactions within the first 15 minutes after vaccination. This is likely affected by preselection bias as in our center most referrals are screened by the Surveillance of Adverse Events Following Immunization in the Community—an enhanced passive surveillance unit in Victoria—before allergy consultation. Therefore, vaccine allergy referrals generally consist only of children with a higher likelihood of true allergy. Rash was the most common clinical presentation, which is reflective of the current literature with rash being the third most common AEFI reported (after fever and local reactions).<sup>16</sup>

Our skin testing cohort consisted largely of children with either anaphylaxis or anaphylactoid reactions, although 6 children only had cutaneous reaction. The reasons for referral for these children included time from vaccination or parental concerns of challenge without initial testing. All of these 6 children had negative testing, with negative challenge in 5 of them. The last child in this cohort initially tolerated alternate brand dose at challenge but had subsequent anaphylaxis on the third dose. It is important to highlight that the risk of anaphylaxis per each dose is independent and IDT is only useful in identifying risk at the time of testing but is unable to guarantee ongoing tolerance. This child did not undergo repeat testing after reaction given that he had completed the course and would not need further HPV-containing vaccines.

In 2 of our children, IDT was used to identify a suitable alternative to the suspect vaccine, with both tolerating alternative vaccine at challenge. We recommend that IDT to the suspect vaccine be performed in the first instance, but where testing is positive, an alternative vaccine should be identified through further skin testing. If an alternative is not able to be found, excipient testing should then be considered.

One child with negative IDT had positive challenge to a suspect vaccine. IDT was performed using 1:100 dilution, which has been previously reported to produce a little irritant effect.<sup>5</sup> However, we have used 1:10 dilution clinically with previous nonirritant results, and it is possible that a higher concentration may have elicited a positive IDT result in this patient. There is limited literature and consensus on NICs for vaccines and further research in this area is needed.

This child had a severe reaction requiring multiple doses of IM epinephrine and observation in the intensive care unit. The child also had a significant past medical history of ex-prematurity and associated chronic lung disease. Asthma is known as a significant risk factor for fatal anaphylaxis in food allergy,<sup>17</sup> and it is likely that this pre-existing lung disease had major contribution to the severity of his reaction. It is, however, also important to note that he had nonurticarial rashes with 2 other unrelated vaccinations on other occasions, as well as intermittent wheeze without other

TABLE III. Positive allergy testing (skin and challenge testing)

| Patient no. | Age at the time of challenge, sex | Index vaccine                                                                                    | Previous reaction                                                      | Time of previous reaction | Skin testing (dilution)                                                                                                       | Challenge vaccine             | Challenge outcome                                                                                                                                         |
|-------------|-----------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1           | 7 mo, M                           | 4-month vaccinations: Infanrix hexa (DTPa-hepB-IPV-Hib) and Prevenar-13 (pneumococcal conjugate) | Rash, delayed SOB (level 1 anaphylaxis)                                | <15 min                   | Infanrix hexa negative intradermal test (tested 1:100)                                                                        | Infanrix hexa                 | Positive<br>Full dose: urticaria, wheeze after 45 min. Treatment with antihistamine, salbutamol, 4× IM epinephrine                                        |
| 2           | 14 y, M                           | Gardasil (HPV) (1st injection)                                                                   | Urticaria, erythema and facial angioedema                              | <15 min                   | Gardasil and Cervarix intradermal test negative (tested both 1:100 and 1:10)                                                  | Cervarix (HPV)                | Negative (2nd dose)<br>3rd dose Cervarix given with positive reaction: immediate itch then cough and drowsiness after 90 min. Treated with IM epinephrine |
| 3           | 8 y, F                            | Fluvax (influenza)<br>Havrix Jnr (hepatitis A)<br>Typhim VI (typhoid)                            | Itch, lip and facial urticaria, wheeze and cough (level 1 anaphylaxis) | 15 min                    | Typhim (1:10), Fluarix Tetra (1:100), Havrix Jnr (1:10) intradermal test negative<br>Fluvax intradermal test positive (1:100) | Fluarix Tetra (influenza)     | Negative                                                                                                                                                  |
| 4           | 12 y, M                           | Priorix (MMR)<br>Infanrix (DTPa-IPV)                                                             | Rash, facial swelling, pallor, SOB (level 1 anaphylaxis)               | >4 h                      | Boostrix positive IDT (1:100)                                                                                                 | Did not proceed               |                                                                                                                                                           |
|             |                                   |                                                                                                  |                                                                        |                           | Adacel (dTpa) positive (1:100)<br>Priorix negative                                                                            | Priorix                       | Negative                                                                                                                                                  |
|             |                                   |                                                                                                  |                                                                        |                           | ADT (dTpa) positive IDT (1:100)<br>Vivaxim negative (1:10)                                                                    | Vivaxim (hepatitis A-typhoid) | Negative                                                                                                                                                  |
| 5           | 5 y, M                            | Vaxigrip (influenza)                                                                             | Localized urticaria                                                    | <15 min                   | Not performed                                                                                                                 | Vaxigrip                      | Positive—urticaria at 10 min (no treatment required)                                                                                                      |
| 6           | 9 mo, M                           | 4-month vaccinations: Infanrix hexa Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus)    | Generalized urticaria                                                  | <15 min                   | Not performed                                                                                                                 | Prevenar-13                   | Positive—urticaria at 15 min. Treated with antihistamine                                                                                                  |

hepB, Hepatitis B; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IM, intramuscular; IPV, inactivated poliomyelitis virus; SOB, shortness of breath.

**TABLE IV.** Patients with nonurticarial rash at challenge

| Patient no. | Age at the time of challenge | Sex | Index vaccine                                                                                | Previous reaction          | Challenge vaccine                               | Onset (min after vaccine) | Duration (min) |
|-------------|------------------------------|-----|----------------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------|---------------------------|----------------|
| 1           | 8 mo                         | M   | Infanrix-hexa (DTPa-hepB-IPV-Hib)                                                            | Level 1 anaphylaxis        | Prevenar-13 (pneumococcal conjugate)            | <15                       | 40             |
|             | 13 mo                        |     |                                                                                              |                            | NeisVacC (Meningococcal C)                      | <15                       | 40             |
| 2           | 12 y                         | F   | Gardasil (HPV)                                                                               | Urticaria                  | Gardasil (IDT negative)                         | 60                        | 30             |
| 3           | 7 mo                         | F   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Level 2 anaphylaxis        | Prevenar-13                                     | <15                       | 25             |
| 4           | 18 mo                        | M   | Priorix (measles-mumps-rubella)                                                              | Rash (nonurticarial) 1-4 h | Priorix-tetra (measles-mumps-rubella-varicella) | 50                        | 15             |
| 5           | 8 mo                         | M   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Urticaria                  | Infanrix hexa                                   | 60                        | 30             |
| 6           | 5 mo                         | M   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Rash (nonurticarial)       | Infanrix hexa                                   | <15                       | 30             |
|             | 6 mo                         |     |                                                                                              |                            | Infanrix hexa                                   | <15                       | 180            |
|             | 9 mo                         |     |                                                                                              |                            | Prevenar-13, Infanrix                           | <15                       | 240            |
|             | 12 mo                        |     |                                                                                              |                            | Priorix                                         | <15                       | 240            |
|             | 18 mo                        |     |                                                                                              |                            | Varicella                                       | <15                       | 110            |
| 7           | 4 mo                         | F   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Urticaria                  | Prevenar-13                                     | <15                       | 90             |
| 8           | 5 mo                         | F   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Rash (nonurticarial)       | Infanrix hexa                                   | <15                       | 30             |
|             | 6 mo                         |     |                                                                                              |                            | Prevenar-13                                     | <15                       | 55             |
|             | 6 mo                         |     |                                                                                              |                            | Rotateq                                         | <15                       | 10             |
| 9           | 15 y                         | M   | H-B Vax II (hepatitis-B)/Gardasil (HPV)/Cervarix (HPV)                                       | Level 2 anaphylaxis        | Boostrix (dTpa)                                 | <15                       | 50             |
| 10          | 11 mo                        | M   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Urticaria                  | Prevenar-13                                     | <15                       | 60             |
| 11          | 7 mo                         | M   | Infanrix hexa (DTPa-hepB-IPV-Hib), Prevenar-13 (pneumococcal conjugate), Rotateq (Rotavirus) | Urticaria                  | Infanrix hexa                                   | <15                       | 5              |

hepB, Hepatitis B; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IDT, intradermal testing; IPV, inactivated poliomyelitis virus.

symptoms noted sporadically. In retrospect, it is difficult to know if this was a true allergic reaction or a combination of his pre-existing conditions and propensity for rash development, particularly given his failure to adequately respond to epinephrine. However, he has not had repeat IDT or repeat challenge given the severity of his previous reaction.

We also noted in our cohort, a clear proportion of children with nonurticarial rash after vaccination. There were no associated symptoms, and no treatment was required for any of these children, although 2 of these children also had a positive challenge. Our positive challenge rate was low, and as such, we are unable to comment whether developing a nonspecific rash is a risk factor for an allergic reaction.

One limitation of our study is that there is considerable preselection bias given that we included only those children who had been referred to the allergy service. Therefore, some children who may have had potential IgE-mediated symptoms but were deemed low risk may have been vaccinated with full dose in the immunization clinic instead of referral. However, if any of these children had an immediate or severe potential IgE-mediated reaction on revaccination, they would have subsequently been referred to our unit. This preselection bias is also likely to overestimate rates of true vaccine allergy rather than the reverse.

Our database also included only those children who had undergone skin testing or challenge. This may have missed children who were referred with vaccine reaction but in whom investigation

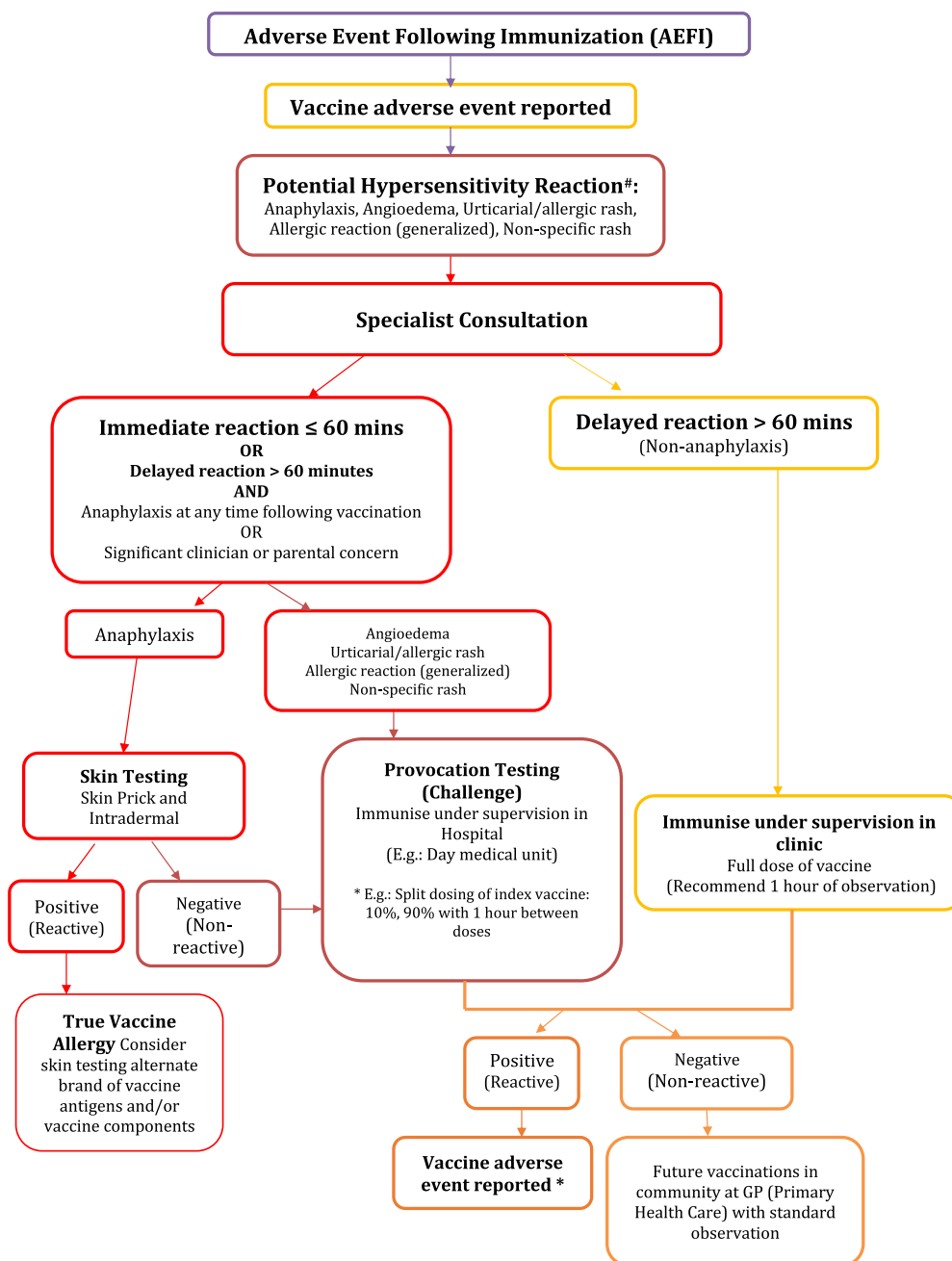


**FIGURE 2.** Suggested algorithm of suspected hypersensitivity reactions to vaccine. #May include any of the major and minor criteria used in the Brighton Collaboration case definition of anaphylaxis.<sup>9</sup> \*If suspected IgE-mediated reaction at 10% dose, seek specialist guidance before proceeding with further doses.

or vaccination was not performed. However, it is likely that this would be the minority of patients in our care.

Zafack et al<sup>4</sup> proposed that skin testing and graded dose reimmunization should be restricted to patients with reaction onset within an hour from immunization or those meeting criteria for anaphylaxis irrespective of timing.

On the basis of the findings and experience in our center, we provide our investigation and management protocol for potential hypersensitivity AEFI in Figure 2. We would also consider previous

nonanaphylactic delayed reactions (>1 hour after vaccination) as low risk and recommend that these children be immunized in a clinical setting with full dose of the suspect vaccine and 1-hour observation. In this study, no children with nonimmediate or nonanaphylactic reactions had reaction at challenge.

In comparison with the protocol proposed by Zafack et al,<sup>4</sup> we recommend that children with immediate (<1 hour) but non-anaphylactic reaction should undergo challenge in a day medical unit setting (which may be performed without prior skin testing).

From our experience, we recommend split dosing with 10% and 90%, given 30 to 60 minutes apart depending on the timing of index reaction. It is presumed that the smaller dose is less likely to cause severe reaction with this approach recommended in previously published investigation protocols.<sup>18</sup> Of the few children in this group who reacted on challenge to a suspect vaccine, we found that their reaction was nonsevere and usually (if anything) similar to the index reaction. This disparity in observation of outcomes may be explained by the difference in adult and pediatric populations.

For all children with anaphylaxis, SPT and IDT may be useful before challenge. Given our experience, this should always be performed regardless of the timing of the index reaction. If skin testing is negative, a challenge to a suspect vaccine should be performed with the split dosing protocol. If skin testing is positive, the suspect vaccine should be avoided (child is deemed allergic to that vaccine) and skin testing for alternate brands of vaccine antigens and/or vaccine components may be performed. Rarely, other factors in the clinical setting may indicate that skin testing should be performed before challenge, including if there is significant clinician or parental concern.

If a child reacts at challenge, then an alternative vaccine should be sought. If no alternative is found, excipient testing and/or desensitization should be considered. If a child reacts to the 10% dose, decision to give a further dose of the vaccine should be made depending on the severity of the reaction.

For any child with a previous hypersensitivity reaction who has tolerated challenge to the suspect vaccine may have further doses as a single full dose. It is important to note that even after a negative challenge, a child may still be at risk of reaction in the future and future vaccinations should be given in a setting where observation and emergency management is available.

## CONCLUSIONS

In conclusion, we find that the vast majority of children presenting with a possible IgE-mediated adverse event after vaccination are tolerant to a suspect vaccine or antigen on rechallenge. We identified that all children with positive testing either had index reaction within the first 15 minutes after vaccination or history consistent with anaphylaxis.

Given our findings, we present our investigation protocol. We hope that this proposed protocol will assist in the appropriate investigation (without unnecessary invasive testing) and management of potential hypersensitivity after immunization and ensure that all children may be optimally protected against all vaccine-preventable diseases.

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