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SHORT REPORT



Potential immediate hypersensitivity reactions following immunization in preschool aged children in Victoria, Australia

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ABSTRACT

Immediate hypersensitivity reactions (IHR) are rare but potentially serious adverse events following immunization (AEFI). Surveillance of Adverse Events following Vaccination in the Community (SAEFVIC) is an enhanced passive surveillance system that collects, analyses and reports information about AEFI in Victoria, Australia. We describe the incidence, timing and type of potential IHR following vaccination in preschool children reported over an 8-year period. A total of 2110 AEFI were reported in 1620 children, of which 23.5% (496) were classified as potential IHR. Of these, 37.1% (184) were suspected to be IgE-mediated, (including anaphylaxis, angioedema and/or urticaria) and 83.5% (414) occurred within 15 minutes of vaccination. The incidence of potential IHR was 5.4 per 100,000 doses, with that of suspected IgE-mediated IHR being 2.0 per 100,000 doses. The incidence of anaphylaxis was extremely low (0.13 per 100,000 doses) and is consistent with other published studies. Potential IHR following immunization should be reported to appropriate local pharmacovigilance systems and patients reviewed by specialists able to evaluate, investigate and manage future vaccinations.

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vaccine hypersensitivity;
vaccine allergy; adverse
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Introduction

In Australia, vaccines on the National Immunization Program are free of charge and are given in local council immunization sessions, primary healthcare provider (general practitioner) clinics and some public hospitals. In 2015, according to the Australian Childhood Immunization Schedule, the definition of “fully immunized” included vaccines for hepatitis B, diphtheria, tetanus, pertussis, *haemophilus influenzae* type b, polio, rotavirus, measles, mumps and rubella, pneumococcal (introduced in 2013), and varicella and meningococcal C (both introduced in 2014).¹ There is also provision of hepatitis A and influenza vaccines for particular at-risk groups e.g. Aboriginal and Torres Strait Islander children. Vaccination is not compulsory but nonetheless a high rate of immunization exists; at the time of the study the percentage of fully vaccinated children aged 12 to 27 months in Victoria was 90–94%.²

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) was established in May 2007 as an enhanced passive surveillance system in the state of Victoria, Australia.³ The SAEFVIC group records all reported adverse events following immunization (AEFI) in Victoria on a database, provides a specialised outpatient service for both children and adults and analyses and reports de-identified information about significant AEFI to the Australian Adverse Drug Reaction Reporting System at The Therapeutic Goods Administration.⁴ As a passive surveillance system, SAEFVIC

relies on voluntary reporting by the vaccination provider (usually a nurse or primary care physician) or parent via website,⁵ fax or immunization hotline. Every report received by SAEFVIC is followed up with telephone calls and clinic visits as required. Each report is diagnostically coded based on the information gathered.

Potential hypersensitivity reactions are coded at SAEFVIC based on criteria determined by the Brighton Collaboration (“anaphylaxis”),^{6,7} the Australian Immunization Handbook⁸ (“generalized allergic reaction” and “non-specific rash”) and SAEFVIC definitions (“angioedema”, “urticaria/hives/allergic rash”).

The main aim of this study was to calculate the incidence of potential Immediate Hypersensitivity Reaction (IHR) occurring following immunization in preschool aged children reported to SAEFVIC. Secondary aims were to describe the timing of the reaction and whether it was likely to be IgE-mediated or not. Based on these results, an algorithm could be created to assist with triage and management decisions.

Method

A request was made to the Australian Childhood Immunization Register (ACIR)⁹ to extract data in order to calculate the number of vaccine doses delivered to Victorian children <5 years of age between 1 July 2007 and 30 June 2015 (8 years), which was used as a denominator to calculate rates.

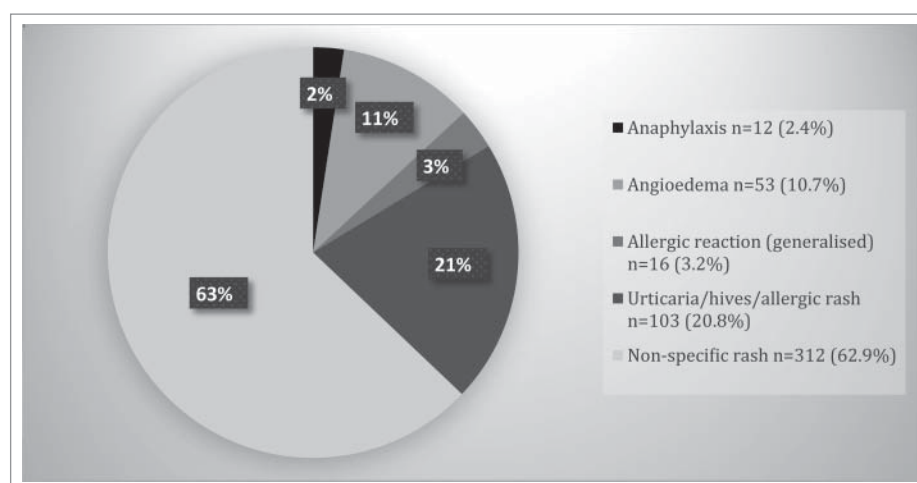


Figure 1. Immediate hypersensitivity reactions by AEFI (n = 496).

Data were extracted from the SAEFVIC database of reports received during the study period involving children <5 years of age and occurring within 60 minutes following any vaccine. Search criteria included reactions suspected to be IgE-mediated i.e. anaphylaxis, allergic reaction (generalized), angioedema, urticaria/hives/allergic rash as well as non-specific rash, which, for this study, was considered not likely to be mediated by IgE.

Reports were examined to determine the time to symptom onset, type (“suspected IgE-mediated” or “not likely to be IgE-mediated”) and the vaccine(s) temporally associated with the IHR.

Data were analyzed with STATA version 13.0 (Statacorp Texas). Descriptive statistics were used to characterize the data. Ethics approval for data collection from the SAEFVIC database was gained from the Royal Children’s Hospital Melbourne Human Research Ethics Committee DA017-2016-08.

An algorithm was created to assist with triage and management decisions, based on SAEFVIC practice.

Results

During the study period, a total of 9,177,244 vaccine doses were given to children under 5 years of age in state of Victoria.¹⁰

In total, 2110 AEFI reactions were reported in 1620 children. Of these reactions, 496 (23.5%) met the criteria for IHR used in

this study, with equal distribution according to gender (51% were in females). The 496 reactions were classified as “Suspected IgE-mediated” 184/496 (37.1%) or “Not likely to be IgE-mediated” 312/496 (62.9%). There were 12 cases of anaphylaxis reported (Figure 1).

The incidence of potential IHR was calculated to be 5.4 per 100,000 doses with that of suspected IgE-mediated IHR occurring at a rate of 2.0 per 100,000 doses. The incidence of anaphylaxis was 0.13 per 100,000 doses.

Of the 496 reactions, 414 (83.5%) were reported to have onset within 15 minutes of vaccination. Importantly, 29/82 (35.0%) of the reactions occurring between 15–60 minutes were also suspected to be IgE-mediated.

Figure 2 illustrates that the majority of reported reactions occurred in infants aged less than 12 months, 59% (293/496), and of these, 67% (196/293) were not likely to be IgE-mediated. The proportion of cases likely to be IgE-mediated increased with age, but remained in the minority until 3.5 years. In children aged 3.5–<5 years, IgE-mediated reactions made up 62% (24/39 reports) of the total reports.

Figure 3 illustrates the cases of anaphylaxis, detailing the vaccines involved and the dose number received. In most cases, more than one vaccine was given prior to the onset of anaphylaxis. A range of dose numbers were recorded and

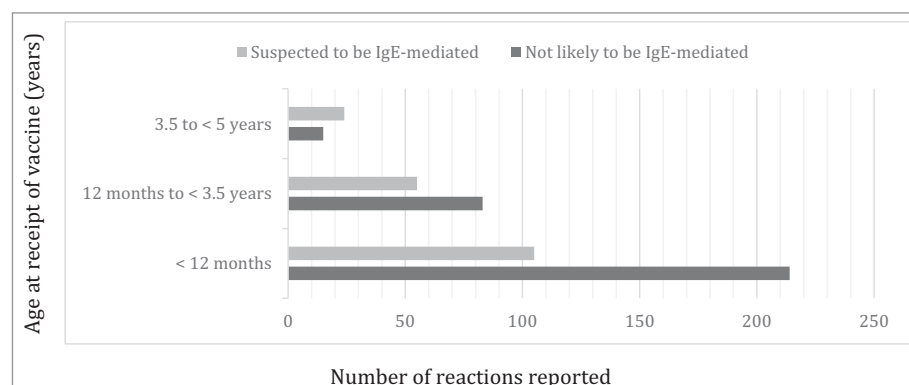


Figure 2. Suspected IgE-mediated and not likely IgE-mediated reactions by age at vaccination.

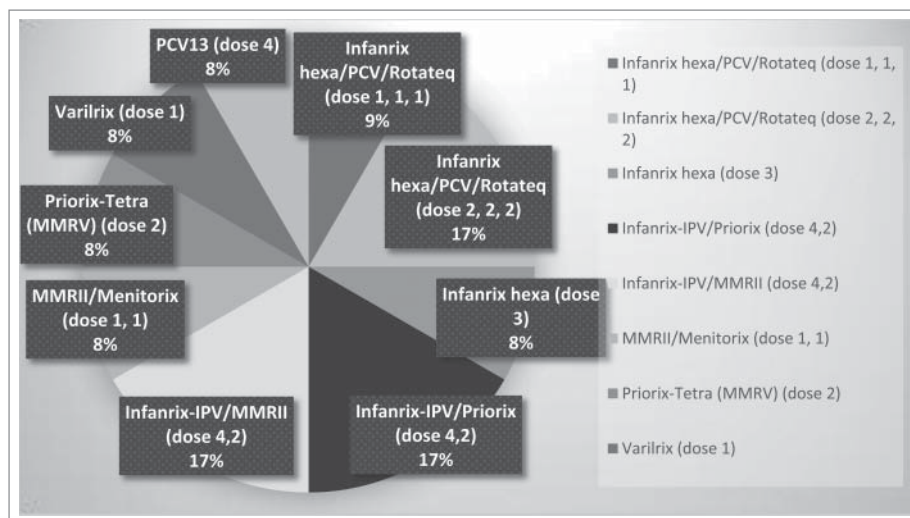


Figure 3. Anaphylactic reactions by vaccine and dose number (n = 12).

3 cases (25%) involved anaphylaxis following the first dose of that particular vaccine. The time interval between vaccine dose and onset of anaphylaxis ranged from 0–40 minutes, with an average of 7.5 minutes and a median of 5 minutes. Ten cases (83%) developed symptoms of anaphylaxis within 5 minutes, while one case was delayed until 20 and another until 40 minutes.

An algorithm suggested for determining management of potential hypersensitivity reactions reported to SAEFVIC, Victoria, Australia is presented in Figure 4.

Discussion

This study analyzed a large comprehensive dataset of AEFI and found that immediate hypersensitivity reactions account for almost one quarter (23.5%) of all AEFI reported in pre-school aged children. Overall, the incidence of potential IHR was very low in pre-school children and occurred at a rate of 5.4 per 100,000 doses with that of suspected IgE-mediated IHR calculated to be 2.0 per 100,000 doses. The incidence of anaphylaxis was extremely low (0.13 per 100,000 doses) and was consistent with published studies, which quote varying rates from 0.01–0.13 cases per 100,000 doses for the same childhood vaccines in international populations.^{11,12,13}

Under the age of 3.5 years, reported IHR were less likely to be IgE-mediated than non-IgE-mediated reactions. This may be because younger children have higher rates of reactive skin conditions e.g. eczema,^{14,15} that may flare following vaccination or because parents of younger children are more likely to report any AEFI including non-specific rashes. Between 3.5–<5 years, suspected IgE-mediated reactions were more prevalent than reactions that are not likely to be IgE-mediated.

As expected, the majority (83%) of all types of IHR reactions occurred within 15 minutes of vaccination, during which time the vaccinated child should have been near the immunization venue for observation and prompt medical treatment if required. However, it is important to note that

approximately a third (35%), of the 17% of reactions that commenced after 15 minutes, were suspected to be IgE-mediated and that anaphylaxis may occur even after several hours.¹⁶ Time elapsed since vaccination should therefore not be used as an absolute criterion when diagnosing a case of suspected anaphylaxis.¹⁷

The main limitations in this study are those inherent with any analysis using a passive surveillance system, namely the retrospective design and the likely under-reporting of cases.¹⁸ However, as the study is limited to reactions within 60 minutes of vaccination and reactions of suspected vaccine allergy or hypersensitivity are a cause of concern for parents, we expect that the number of non-reported cases of IHR is relatively low. It is possible that by restricting the study to such a short time frame that cases of potential IgE-mediated reactions were missed (i.e. if they occurred after 60 minutes), though again this number is likely to be extremely small because delayed anaphylaxis is rare and most delayed instances of skin rash, urticaria, angioedema or maculopapular skin rash are thought to be due to non-specific activation of the immune system and non-specific degranulation of mast cells.^{19,20}

Routine surveillance reports of AEFI often lack the necessary level of clinical detail to definitively establish whether diagnostic criteria are met. However, the robust data collection employed by SAEFVIC minimizes the number of cases likely to have been misdiagnosed by the reporter or misclassified.

In Australia, state-based AEFI reporting e.g. SAEFVIC in Victoria, will soon be combined in a comprehensive National AEFI database. In time, it is hoped this database may be linked with the Australian Immunization Registry. These steps will raise awareness, and facilitate easier and more complete reporting, of AEFI. Further enhancements may include menu options on specific AEFI terms entered which would ensure adequate data are collected to categorize the AEFI according to case definitions from the outset. Future research into the outcome of any investigations (skin testing) following allergy specialist consult (see Figure 4) and provocation testing (challenge) of IHR is urgently needed to identify any possible risks factors for

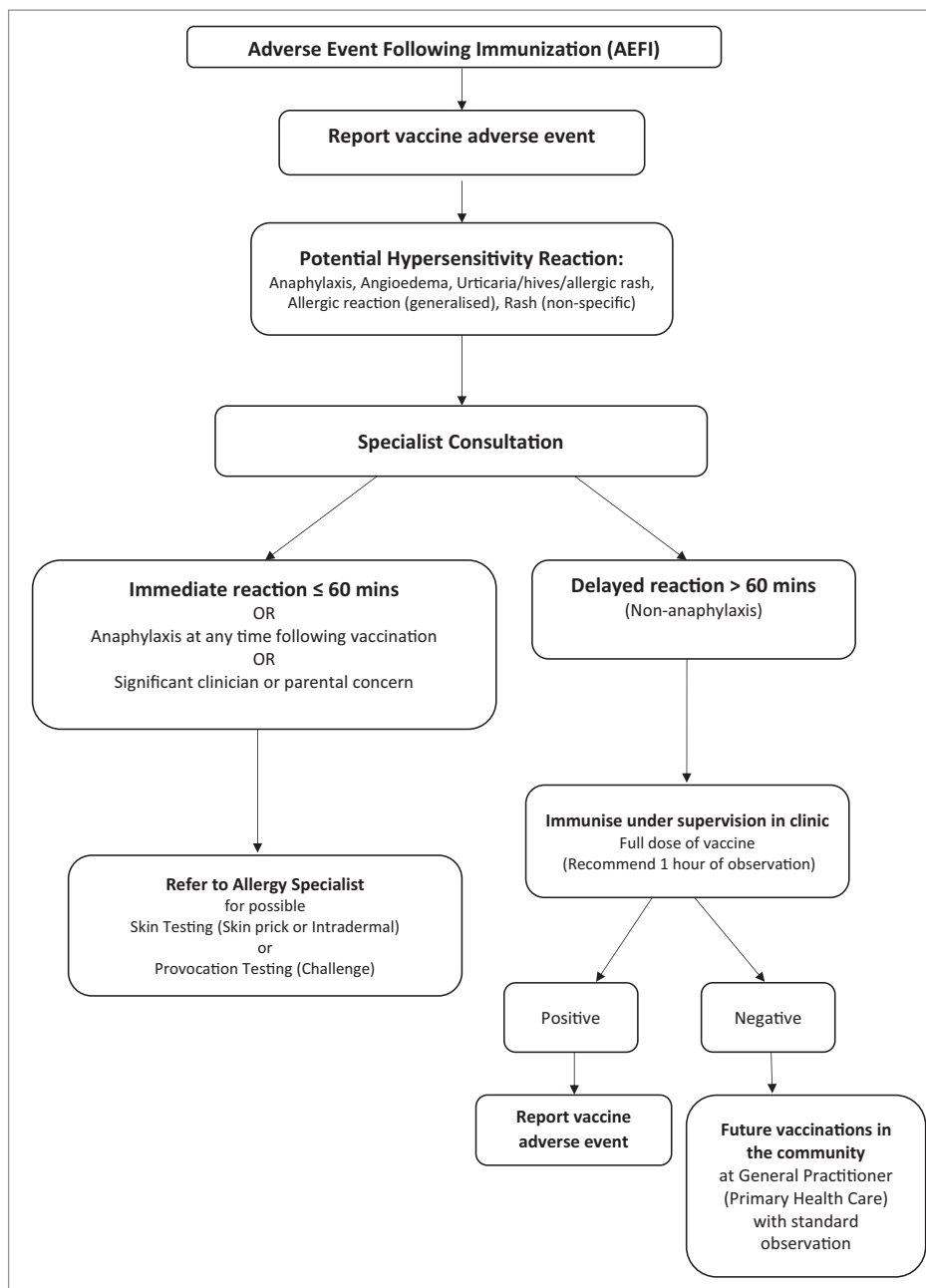


Figure 4. Algorithm for management of potential vaccine hypersensitivity.

recurrence of IHR and rates of true vaccine allergy in children.

Conclusion

Almost a quarter of all AEFI reported to SAEFVIC in pre-school children are due to immediate potential hypersensitivity reactions which occur at a rate of 5.4 per 100,000 doses. Of these, at least 1 in 3 (37%) may be potentially serious allergic manifestations and are suspected to be IgE-mediated. However, most of these reactions are not likely to be IgE-mediated, meaning that subsequent booster doses are usually well tolerated.²¹

All potential hypersensitivity reactions following vaccination should be reported to the local pharmacovigilance services. Clinical review by an expert in immunization and/or allergy is suggested as described in the algorithm. However, further

research is necessary to determine the risk of recurrence following subsequent vaccine exposure, and how to minimize any potential risk so each child may achieve optimal protection against all vaccine preventable diseases.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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