

Subcutaneous nodules following immunization in children; in Victoria, Australia from 2007 to 2016



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ABSTRACT

Background: Subcutaneous nodules are a rare adverse event following immunization (AEFI). We aimed to describe nodules at the injection site reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community) using the Brighton Collaboration Case Definition (BCCD), management and recurrence following subsequent immunizations.

Method: We assessed 58 cases (<18 years of age) of 'nodule at injection site' reported to SAEFVIC, Melbourne, Australia, between May 2007 and June 2016. Case details were analyzed from records and phone interview follow-up. The Australian Immunization Registry was reviewed for immunization status. **Results:** 71% (41/58 reported cases) were consistent with the BCCD for subcutaneous nodule, 14% (8 cases) were 'possible subcutaneous nodules', 10% (6 cases) were nodules associated with BCG immunization and 5% (3 cases) were attributable to an alternative diagnosis. The median age at immunization was 12 months, (range 1 month–12 years); 54% male (22/41 cases). 17% (7 cases) had multiple nodules. Nodules were associated with immunizations containing aluminum (74%, 36/49 nodules), no aluminum (8%, 4 nodules) and unknown (18%, 9 nodules). Most cases developed symptoms within 3 days post-immunization (59%, 24 cases) and in the thigh (59%, 29 nodules). Pruritus was associated in 41% (17 cases). Around 1/3 (34%) of nodules resolved 6 months post immunization, 2/3 (68%) by 12 months, however 1/4 (24%) remained persistent for >24 months. 5 cases had prior nodules and 1 case had recurrence with subsequent immunization. 83% (34 cases) were fully immunized for age at follow-up.

Conclusion: Subcutaneous nodules at the injection site may occur following a wide range of vaccines, including vaccines without aluminum. All cases require careful review and where possible, specialist management and to support subsequent immunizations.

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Abbreviations: AEFI, adverse event following immunization; AIR, Australian Immunization Register; BCCD, Brighton Collaboration Case Definition; BCG, Bacillus Calmette-Guerin; DIC, Drop-in Centre; IM, intramuscular; MRI, Magnetic resonance imaging; NIP, National Immunization Program; SAEFVIC, Surveillance of Adverse Events Following Vaccination in the Community; SIC, Specialist Immunization Clinic.

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1. Introduction

Subcutaneous nodules* following immunization are described since the 1960s [1,2] and are considered a rare adverse event following immunization (AEFI) [3]. There are limited estimates of nodule

* We used 'subcutaneous nodule' and 'nodule' as equivalent terms, for consistency we have used the term 'nodule' in the remainder of the paper. When we refer to a diagnosis of nodule, it is implied to be a 'nodule at the injection site'; consistent with the Brighton Collaboration Case Definition used.**References to vaccines with aluminum adjuvant throughout the paper are referring to aluminum salts.

incidence and there is significant variation between these figures. Scandinavian studies have estimated the incidence to be between 3 and 6/10,000 and 83/10,000 in cohorts of children receiving aluminum containing immunizations [4–6]. There are no published incidence rates outside of Scandinavia. Factors associated with nodule development include suboptimal method of delivery; such as incorrect subcutaneous immunization [2,4], shorter needle length which increases the risk of local reactions related to poor intramuscular vaccine delivery [7]. Aluminum has been associated and is often reported as a triggering factor in nodule development [4,8–12]. Aluminum has been used as a vaccine adjuvant since the 1920s – it is incorporated in vaccines as an aluminum salt** (eg. aluminum hydroxide, aluminum phosphate, potassium aluminum sulphate) [13,14]. It is accepted as a safe and effective mechanism to increase immunogenicity [13,14]. Almost all inactivated vaccines contain aluminum. In 2017, 75% (9/12) of all immunizations and 90% (9/10) of inactivated vaccines on the Australian National Immunization Program (NIP) injected in childhood (up to 4 year old) contained aluminum (Supplementary Table 1) [15].

Clinical features vary significantly between cases and may include asymptomatic nodules, localized itch and erythema or chronic changes of pigmentation and hypertrichosis [16–18]. The clinical management of nodules varies widely, from monitoring to surgical excision. The Brighton Collaboration Local Reactions Working Group developed a case definition (Brighton Collaboration Case Definition, BCCD, Table 1) and guidelines for the clinical diagnosis of nodule at injection site in 2004 to facilitate comparability of immunization safety data [19]. They identified a lack of information in the literature regarding onset, duration, and size of nodules. Subsequent reviews have identified the difficulty around case definition of nodules, with low sensitivity and inter-rater reliability of diagnosis [20].

Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is an enhanced passive surveillance system for monitoring AEFI in the state of Victoria, Australia [21,22]. SAEFVIC was established in May 2007 and is within the Murdoch Children's Research Institute, Victoria, Australia. SAEFVIC receives reports of AEFIs from Victoria, Australia. In 2016, Victoria had 81,713 births and a vaccine coverage rate of 93.6% at 5 years of age (with multiple doses per child) [23,24]. SAEFVIC offers a Specialized Immunization Clinic (SIC) for children to follow-up AEFI and support further immunizations. The Immunization Drop-In Centre (DIC) is co-located at the Royal Children's Hospital, Melbourne and children can receive further immunization there. SAEFVIC maintains a database of all reported AEFIs, including contact details of all cases.

The primary aim of this study was to detail the occurrence of nodules, as a 'nodule at injection site' post-immunization in children reported to SAEFVIC between 2007 and 2016, by using the BCCD and symptom onset and duration. The secondary aim was to follow-up cases and collect further information about the duration of symptoms, management, recurrence of nodules following subsequent immunizations and current immunization status for age.

2. Methods

We reviewed all paediatric cases (<18 years at time of reaction) with a 'nodule at injection site' after immunization reported to SAEFVIC between 1st June 2007 and 30th June 2016. We accessed information recorded in the database from the initial report, including demographics, immunization provider, vaccine type and history of AEFI including onset, duration and symptoms. We reviewed the associated medical record for each case, where available; this included details if seen in the SIC and DIC. At the time of

Table 1

Brighton Collaboration Case Definition for nodule at injection site as an adverse event following immunization (Level 1 of diagnostic certainty) [2].

Must be present	Discrete or well demarcated soft tissue mass or lump Firm At the injection site
May be present	May be additional less discrete, soft swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus.
Must be absent	Abscess formation Erythema Warmth

initial report, consent was requested for contact if any future research activities. Where initial consent was given, phone interview was requested and consent obtained. Phone interviews were completed between February–March 2017.

Phone interviews collected information regarding clinical features of nodules including duration, associated features, treatment, recurrence and current immunization status. The current immunization status was reviewed by accessing the Australian Immunization Register (AIR) [25] in January 2017; this was corroborated during the phone interview when available.

All cases were reviewed using the BCCD criteria for nodule at injection site. Cases were independently reviewed by two of RS, KP or NC. Where consensus in case definition was not initially met, the case was reviewed between all three investigators (RS, KP, NC) and consensus reached. Case outcomes were classified as nodules, possible nodules or not nodules, with an alternative diagnosis.

All information collected was securely stored in a RedCap database (Version 6.13.3 - © 2016 Vanderbilt University). Data was extracted to Excel Version 13 Microsoft Office Plus for analysis. The Royal Children's Hospital Human Resources Ethics Committee approved the study (HREC-36314A).

3. Results

SAEFVIC received a total of 7335 AEFI reports in children (<18 years) between 1st June 2007 and 30th June 2016. 58 cases (0.6% total reports) were identified from the SAEFVIC database with a coded diagnosis of 'nodule at injection site' following immunization during this period. Additional information was gathered from phone interviews in 29/58 cases (50%). 46 cases (79%) had consent to follow-up, 29/46 (63%) were contacted and consented to the phone interview (Fig. 1). All 58 cases were then reviewed and outcomes classified (Fig. 1). 41/58 cases (71%) were defined as nodule, 8 cases (14%) possible nodule, 3 cases (5%) other diagnosis and 6 cases (10%) of nodule associated with BCG.

The demographics of the 41 cases are summarized in Table 2. There was a slight male predominance and most cases received immunization in the community, including primary care clinics and local council facilities. The median age at immunization was 12 months, (range 7 weeks–12 years 11 months) and most cases (76%, 31 cases) occurred in those under 24 months (Fig. 2). 83% were up to date with immunizations.

49 nodules were reported within the series of 41 BCCD nodule cases. Most cases had single nodules (83%, 34 cases), 6 cases had 2 nodules and 1 case had 3 nodules. This child had 3 nodules develop after receiving immunizations in different locations (i.e. bilateral thigh and left arm immunizations) on the same day, with a nodule at each location. Most nodules occurred in the thigh (59%, 29 nodules), followed by arm (12 nodules) and the remainder in an unknown site (8 nodules). 5 cases had a previous nodule following

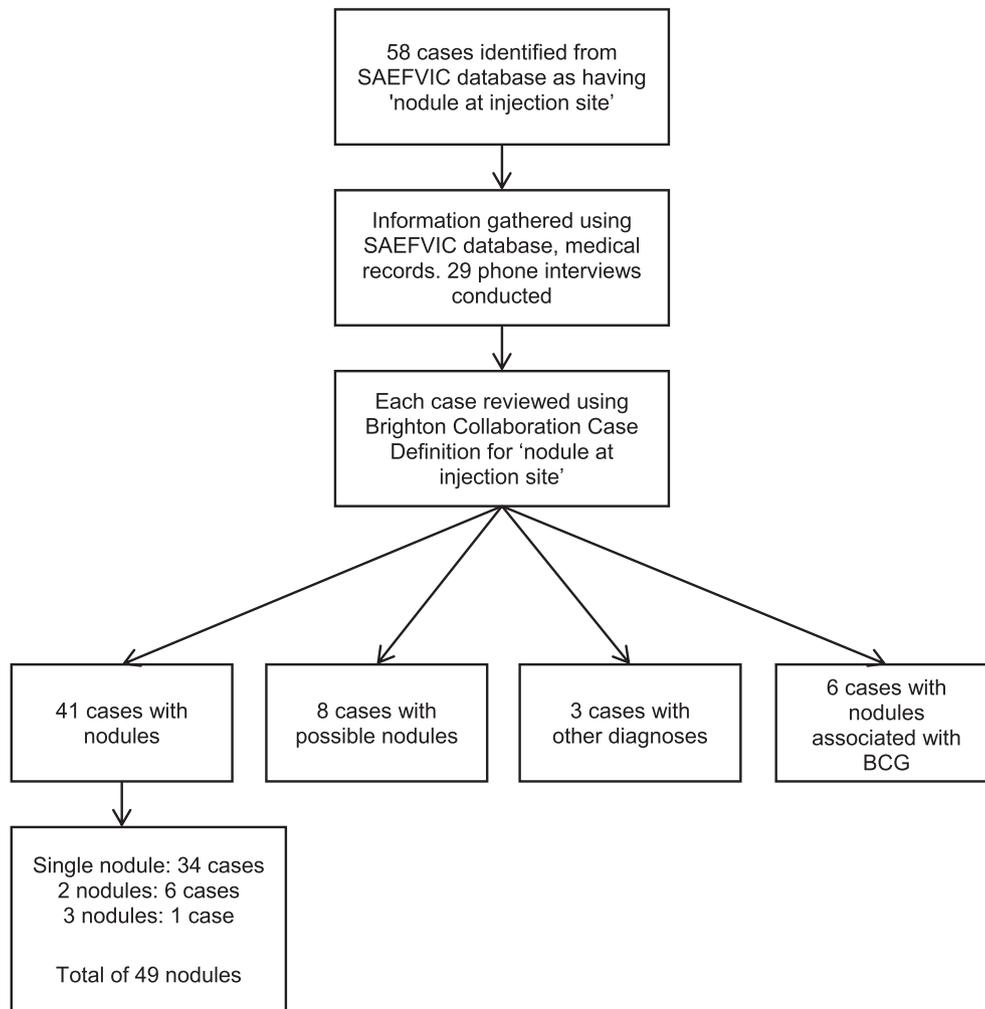


Fig. 1. Summary of case review process.

immunization before the nodule reported to SAEFVIC. 1 case reported nodule development following subsequent immunizations, but this was prior to review in SIC.

Clinical features are outlined in Table 2. The onset of symptoms varied significantly, with 59% (24 cases) reporting symptoms within 3 days of immunization and 12% (5 cases) reporting symptom onset > 4 months after immunization. In cases with symptoms reported < 24 h after immunization, the description was consistent with a local reaction, reporting erythema and swelling. Over subsequent days to weeks, these cases developed a firm nodule at the injection site.

The duration of symptoms also varied widely (Fig. 2 and Fig. 3), with a range from 1 to 2 weeks, up to 5 years (ongoing at data collection) and median range of 6–12 months post immunization. Approximately 1/3 of cases resolved by 6 months (34%), 2/3 (68%) by 12 months, however 1/4 (24%) remained persistent after 24 months.

We found a high proportion of cases at phone interview reported chronic symptoms (Table 3). 79% (23/29 cases) reported symptoms lasting 6 months or greater. Aside from symptoms directly consistent with a nodule, the commonest symptoms included itch, with ongoing itch in 57% (13/23 cases) in the group, along with a variety of skin changes in 44% (10 cases). Within this group, 6 cases had symptoms at phone interview present for between 18 months–5 years.

Many vaccines were associated with nodules (Table 4), with Infanrix Hexa the most common immunization associated with

nodules. In 55% (27/49 nodules) the specific vaccine administered at the site was unknown due to methods of data recording. A small number of cases were not associated with vaccines containing aluminum (Table 4).

Management of nodules varied significantly within the cohort (Table 5). Most cases had no specific treatment; reported treatments included topical steroid cream and moisturizer. Investigations of the lesions were uncommon, but included ultrasound and surgical excision.

Immunization status was examined in all cases (Table 2). 83% (34/41 cases) of children were up to date with scheduled immunization. In 3 cases with incomplete immunization the reason for immunization delay or deferral was discussed during phone interview. Reasons included parental concerns about immunization safety and side effects. In the other 4 cases the information was obtained through AIR alone, so no further details regarding immunization status was available.

4. Discussion

We have described one of the largest cohorts of children with nodules after immunization. This is the first study to define a cohort using the BCCD, to clearly describe nodules associated with and without aluminum adjuvant and to describe nodules in children following immunization from the Australian NIP.

Table 2
Characteristics of 41 nodule cases.

Characteristics	Number of cases (%)
Sex	
Male	22 (54)
Female	19 (46)
Immunization status	
Up to date	34 (83)
Not up to date	7 (17)
Number of nodules per case (related to AEFI reported)	
Single nodule	34 (83)
Multiple nodules	
2 Nodules	6 (15)
3 Nodules	1 (2)
All multiple nodules	7 (17)
Recurrent nodule	
After reported case	1 (2)
Prior to reported case	5 (12)
Age at immunization associated with nodule	
Under 6 months	13 (32)
Between 6 and 12 months	7 (17)
Between 12 and 24 months	11 (27)
Over 24 months	10 (24)
Location of Immunization	
Community (total)	32 (78)
Community Health Centre	9 (22)
Primary Care (General Practice)	22 (54)
School	1 (2)
Hospital	2 (5)
Unknown	7 (17)
Onset of any symptoms (after immunization)	
Under 24 h	12 (29)
Between 1 and 3 days	12 (29)
4–7 days	1 (2)
1–2 weeks	0 (0)
3–4 weeks	1 (2)
1–2 months	2 (5)
3–4 months	0 (0)
Over 4 months	5 (12)
Unknown	8 (20)
Clinical features reported of nodules	
Discrete mass	41 (1 0 0)
Firm	41 (1 0 0)
Tender, painful	5 (12)
Itchy, pruritus	17 (41)
Swelling, raised	9 (22)
Erythema*	6 (15)

* if erythema was reported in clinical features, this was not a lasting feature and a discrete clinical period without erythema recorded (consistent with nodule diagnosis).

4.1. Associated factors

The link between immunization and nodule development is not well understood. Adjuvant aluminum in vaccines is frequently reported as an association and often attributed as a cause of local AEFIs, including nodules [4,6,8–12,26]. Although there is an association between aluminum and AEFIs, causation is not clear. Despite this, many articles implicate aluminum in nodule development [16], including with titles such as ‘aluminum hydroxide granulomas’ [1]. This association is not surprising as most immunizations on childhood schedules contain aluminum, as is true in the Australian NIP. Although most nodules in our cohort were associated with aluminum, a small group (8%, 4 nodules) was reported after immunizations without aluminum. Aluminum has a role as an important adjuvant; we believe it is important to maintain a balanced perspective regarding the risks and benefits. We would argue the current evidence supports the ongoing use of aluminum salt as an adjuvant [27].

Injection method likely contributes to nodule development, with inadvertent subcutaneous injection associated with high rates of nodules [2,4]. The subcutaneous injection is associated with greater local inflammatory reaction, compared to intramuscular

(IM) delivery [9]. This is supported by evidence that longer needle length reduces immunization reactivity, to ensure vaccine delivery to an intramuscular location irrespective of individual delivery technique [7]. The impact of vaccine delivery highlights the importance of quality training for those administering vaccines. We had limited information relating to vaccine delivery, as method of delivery was not recorded for most immunizations. We based assumptions on standard vaccine delivery practice in Australia.

4.2. Symptoms

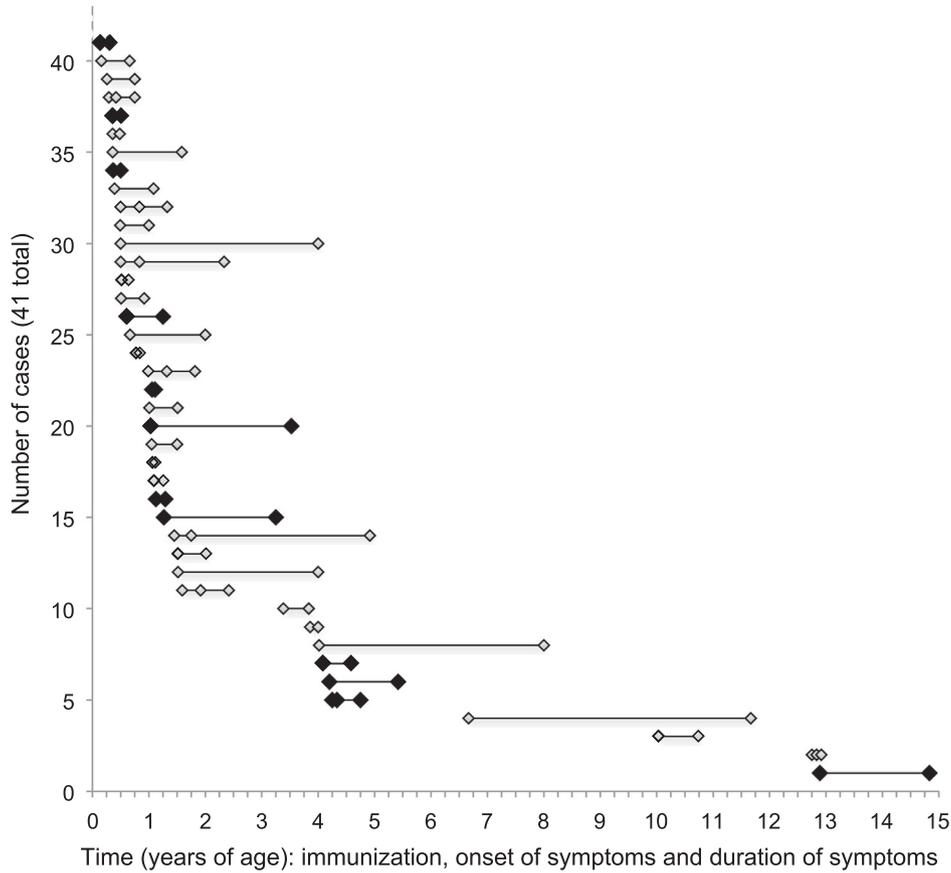
There are many similarities between this cohort and previous reported cases, including the high proportion with pruritic nodules, associated skin changes and proportion of nodules lasting months-years [9,16–18,28–30]. Most cases (59%, 24 cases) reported symptoms within 3 days after immunization, with only 12% (5 cases) reporting symptoms onset after 4 months. This is in contrast to other case series, which typically found delayed symptom onset of months-years [9]. Early onset of symptoms may be due to overlap of symptoms associated with immediate local reactions, with clinical features of erythema and induration in the early days following immunization, with cases later progressing to develop nodules. Symptoms were commonly reported, but especially in those with nodule lasting >6 months. Features such as skin changes, including abnormal hair or pigmentation can cause significant anxiety for the child or parents, particularly for school-aged children. There may be a degree of under-reporting of symptoms, particularly itch and discomfort in the young non-verbal child. Significant morbidity has been attributed to chronic pruritus due to atopic eczema [31] and pruritus associated with nodules may be similar, depending on the severity.

4.3. Management

There is a large variation in reported management of nodules, including routine allergy testing and high rates of surgical excision [6,16,32]. We propose that the management of nodules includes multiple important aspects for the clinician to consider; including the diagnostic approach to a soft tissue lump (particularly if an association with immunization is unclear), symptom management and counseling regarding subsequent immunization (Fig. 4). We would advocate that the approach to treatment of nodules may include topical steroid cream where there are overlying skin changes, along with symptomatic treatments such as paracetamol and cool compresses. Other treatments rarely described in this cohort included intra-lesional steroids and surgical excision. These treatments may have a role in a case-by-case setting but will need to be assessed by the treating physician. Nodules following immunization may be a clinical diagnosis [19], but with a proportion of nodules reported after at least 4 months in our cohort, and up to 4 years in other cases [9], it is prudent to expect the clinician to consider alternative differential diagnoses in the child with soft tissue lump. The differential diagnosis in a small child may include rare pathology such as malignancy or non-malignant pathology eg. vascular malformation (which was seen within our cohort). There was a report from within our cohort, and also in previously published literature [6] where nodules were identified as possible malignant lesions prior to their final diagnosis. These examples illustrate the need for education and early identification of nodules to avoid unnecessary anxiety and investigation.

4.4. Investigations

There is no role for routine investigations in the assessment of possible nodules and a thorough clinical assessment should be



Each horizontal line represents a case.
 All diamonds (◆◊) at left hand side correspond to the time of immunization.
 Where symptom onset was not closely related to time of immunization, this time is demonstrated by a second diamond intersecting the line (either ◆◊).
 At right hand side, an open diamond (◊) corresponds to unknown confirmed resolution of nodule and shaded diamond (◆) corresponds to known time of resolution of symptoms associated with nodule.

Fig. 2. Nodule cases, onset and duration.

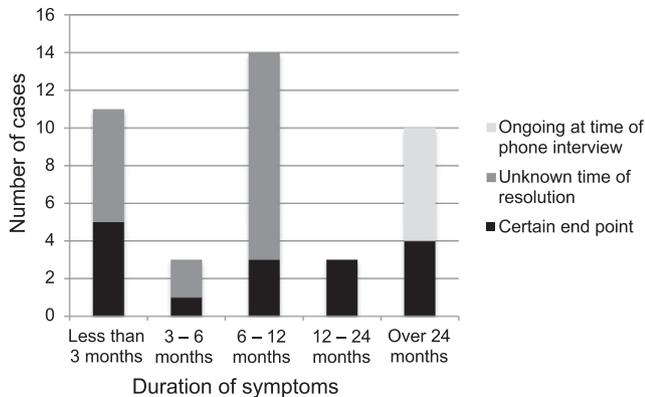


Fig. 3. Reported duration of symptoms, total of 41 cases.

the first priority. Ultrasound may have some utility to further characterize the lump, but was used uncommonly in our case series (one case). Any further investigations should be guided by specific details, with the primary aim to exclude or consider alternative diagnosis rather than to support the diagnosis of nodule. Surgical excision for nodules is common in the published cases [1,16,33],

Table 3
 Summary of clinical features in 23 cases at phone interview with symptoms present for 6 months or greater.

Symptoms	Number of cases (%)
Total reporting itch symptoms	13 (57)
Itch/discomfort daily	8 (35)
Itch/discomfort intermittently	5 (23)
Exacerbation of symptoms with intercurrent illness*	3 (13)
Residual changes at the site	10 (44)
Scar	5 (22)
Hypertrichosis	5 (22)
Hyperpigmentation	7 (30)
Hypopigmentation	2 (9)
Recurrence of nodule	1 (4)

* Exacerbations of symptoms defined as itch, redness or discomfort occurring with intercurrent infections.

although the specific indication is unclear. In some cases, excision may be primarily used to confirm diagnosis, rather than for therapeutic indication. We would advocate minimizing excisions of nodules, to avoid any potentially unnecessary surgical procedures in children.

The role of allergy testing in cases with nodules is unclear. Contact allergy to aluminum has been found in a high proportion of

Table 4
Vaccines associated with nodules and aluminum content, summarizing results of 49 nodules.

		Number of nodules (%)	2017 Australian National Immunisation Program (NIP) Schedule
Vaccine without aluminum	Type of vaccine		
Varilrix	Live attenuated varicella	2 (4)	No
Priorix-Tetra	Live attenuated, measles, mumps, rubella, varicella	1 (2)	Scheduled at 18 months
	Sub-total	3 (6)	
Identified inactivated vaccine, containing aluminum			
Infanrix IPV	Combined diphtheria, tetanus, acellular pertussis (DTPa) and inactivated poliovirus	2 (4)	Scheduled at 4 years
Infanrix Hexa	Combined diphtheria, tetanus, acellular pertussis (DTPa), hepatitis B, inactivated poliovirus and <i>Haemophilus influenzae</i> type b	7 (14)	Scheduled at 2, 4, 6 months
Prevenar 7	Pneumococcal polysaccharide conjugate, 7-valent adsorbed	1 (2)	No
Prevenar 13	Pneumococcal polysaccharide conjugate, 13-valent adsorbed	1 (2)	Scheduled at 2, 4, 6, 12 months
Meningitec	Meningococcal serogroup C conjugate	1 (2)	No
HBVAXII	Hepatitis B	1 (2)	Scheduled at birth
Bexsero	Meningococcal B	2 (4)	No
DTPa (unknown brand)	Diphtheria, tetanus, acellular pertussis	1 (2)	Scheduled at 18 months and 10–15 years
	Sub-total	19 (39)	
Unknown*			
Live vaccine, without aluminum		1 (2)	
Inactivated vaccine, contain aluminum		17 (35)	
Type of vaccine and aluminum content unknown		9 (18)	
	Sub-total	27 (55)	
Summary			
Total vaccines without aluminum		4 (8)	
Total vaccines containing aluminum		36 (74)	
Type of vaccine and aluminum content unknown		9 (18)	

* Vaccine unknown due to inability to associate vaccine with nodule site, most commonly due to multiple vaccine given and records lacking specific documentation of site of vaccine.

Table 5
Clinical management of nodule cases (total of 41 cases).

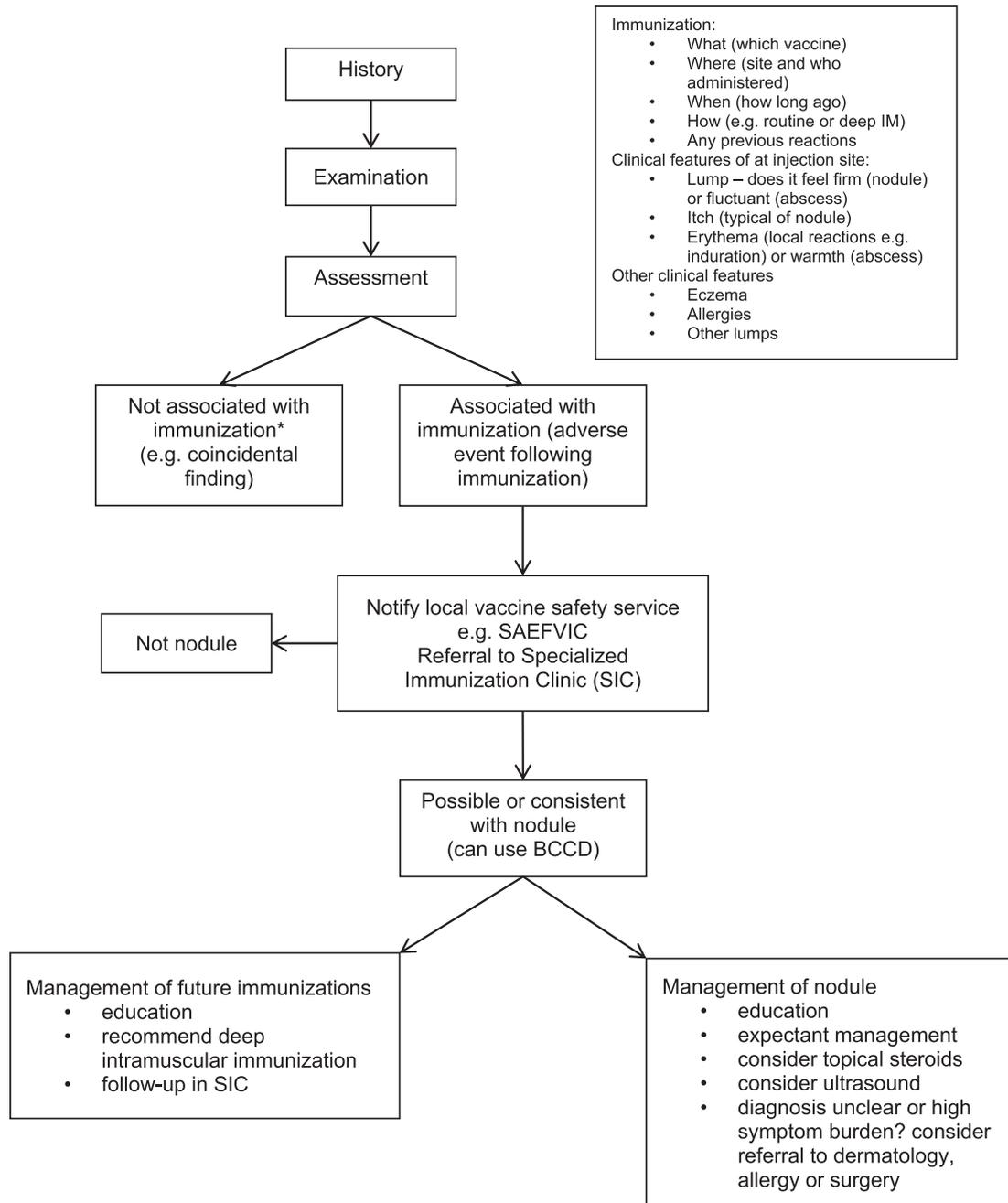
Management	Number of cases (%)
SAEFVIC follow-up	
Review in Specialized Immunisation Centre (SIC)	30 (73)
Attended Drop-in immunization Centre (DIC)	15 (37)
Subsequent immunization administered deep IM injection (at DIC)	8 (20)
Treatment of nodule	
No treatment	28 (68)
Topical treatment	12 (29)
Moisturizer	4 (10)
Topical steroid	12 (29)
Topical anti-fungal	1 (2)
Oral treatment	2 (5)
Oral antibiotics	2 (5)
Oral antihistamines	1 (2)
Other treatment	3 (7)
Intra-lesional steroid injection	1 (2)
Surgical excision	1 (2)
Cool compress topically	1 (2)

children with nodules, in up to 95% cases [6,9]. The rate of aluminum allergy in healthy controls is not well studied. Lidholm et al found that 8% of asymptomatic children had a positive test for aluminum contact allergy [34]. However the same study suggested aluminum allergy in childhood may spontaneously resolve in the majority of cases (77% cases) [34]. Allergy testing is not routinely performed within the SIC service at SAEFVIC, though several cases had referral to the allergy team for opinion. We would strongly recommend that routine allergy testing is not indicated but could be considered in a case-by-case context.

4.5. Future immunizations

Any condition, such as nodule, that has the potential to affect subsequent immunization uptake in the individual, along with community concerns, warrants careful counseling for further immunization. The vast majority of children (83%) with nodules were up to date with their routine immunizations compared to AIR data estimates of 90–94% of Victorian children being fully vaccinated depending on the age timepoint [35]. Vaccine hesitancy is a complex issue, but risks associated with immunization are known to be a major factor in parental concern [36]. Parents' previous experience with immunization is likely to influence their future decisions regarding immunization. Providing balanced information to parents regarding the risks and benefits of further immunization is an important part of nodule management.

In our local context all children in Victoria, Australia with AEFIs reported to SAEFVIC are offered follow-up and subsequent immunizations at the SIC as part of SAEFVIC clinical service. It is generally accepted that nodules are not an indication for withholding subsequent immunizations. Though within the literature, some suggest avoiding or minimizing aluminum exposure in those individuals with evidence of aluminum allergy [37]. The local approach within the cohort with follow-up at the SIC for subsequent immunization is to routinely offer counseling and deep IM injections for subsequent immunizations. Deep IM delivery is used as a method to reduce nodule recurrence, to prevent inadvertent delivery of vaccines to the subcutaneous space. Due to parental request, at least one child also received subsequent vaccines with lower aluminum content (although the difference in total aluminum content between licensed vaccines is negligible). Eight cases were given subsequent deep IM vaccines in the SAEFVIC clinic, none of these cases reported nodule recurrence (Table 5). We believe these



*clinical features of nodule may not be noted up to months-years after immunization

Fig. 4. Suggested approach to nodule at the injection site.

outcomes support ongoing deep IM immunization as a prevention of recurrence.

Looking to the future, novel immunization delivery methods are a focus of technology development; for example nanopatch technology [38]. We are optimistic that with advanced technology, opportunities to modify and reduce the incidence of nodules may evolve.

4.6. Brighton Collaboration Case Definition

The application of the BCCD identified several areas of uncertainty. There was no guidance regarding inclusion or exclusion of BCG local site reactions, nor any minimum duration for a nodule.

And despite the prominence of itch seen within cases of nodules, it remains absent from the diagnostic criteria.

4.7. BCG cases

Local reactions following BCG immunizations are common [39]. Almost all BCG-vaccinees develop mild injection site reactions. Severe local reactions such as abscess rarely occur. We identified 6 cases that were consistent with BCCD nodules following BCG immunization. We excluded these from the main cohort of nodules as they would likely be included within the common BCG reactions.

4.8. Limitations

This study was limited by use of retrospective data, reliant on the quality of recorded data around the time of the AEFI. For example, there was a group of nodules following unknown vaccines and unknown aluminum content. This was largely related to poorly recorded site of immunization and nodule. We were also cognizant that information from phone follow-up was susceptible to recall bias. Case finding through the enhanced passive surveillance may bias the reporting of more severe cases by parents and clinicians. Previous literature identified in a prospective approach, active case finding highlighted a greater proportion of mild cases of nodules [6]. Satisfying the BCCD criteria was limited by the quality of information within the SAEFVIC database, especially if cases were not followed up at phone interview. As mentioned earlier, route of administration information was not routinely recorded within the database, nor was this available from parents. We assumed all vaccines were given in accordance with standard local practices, therefore IM route except for Measles-Mumps-Rubella and Varicella vaccines, which are routinely given subcutaneously [15]. Due to the small size of the cohort, we did not compare the outcomes of different sub-groups e.g. nodules associated with aluminium or different vaccine type, which limited the study findings but is also a reflection of the rarity of nodules.

5. Conclusions

Nodules are a rare but known AEFI that are commonly associated with vaccines containing aluminum, but also likely related to delivery methods. This study describes the natural history of nodules and provides evidence that they can occur following many types of immunizations – including vaccines without aluminum. All children with nodules warrant careful assessment and follow-up, and where possible specialist management, to support future immunizations.

Author contribution statement

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CRedit authorship contribution statement

Rowena Silcock: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Nigel W Crawford:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing, Visualization. **Gowri Selvaraj:** Methodology, Data curation, Writing - review & editing. **Alissa McMinn:** Project administration, Methodology, Data curation, Writing - review & editing. **Margie Danchin:** Writing - review & editing, Visualization. **Teresa Lazzaro:** Writing - review & editing. **Kirsten P Perrett:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.12.066>.

References

- [1] Erdohazi M, Newman RL. Aluminium hydroxide granuloma. *Br Med J.* 1971;3(5775):621–3. <https://doi.org/10.1136/bmj.3.5775.621>.
- [2] Thierry-Carstensen B, Stellfeld M. Itching nodules and hypersensitivity to aluminium after the use of adsorbed vaccines from SSI. *Vaccine.* 2004;22(15–16):1845. <https://doi.org/10.1016/j.vaccine.2003.11.048>.
- [3] Ortvist A, Blennow M, Carlsson RM, et al. Vaccination of children - a systematic review. *Acta Paediatr.* 2010;99(s461):1–192. <https://doi.org/10.1111/j.1651-2227.2010.01823.x>.
- [4] Bergfors E, Trollfors B, Inerot A. Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. *Vaccine.* 2003;22(1):64–9. [https://doi.org/10.1016/s0264-410x\(03\)00531-0](https://doi.org/10.1016/s0264-410x(03)00531-0).
- [5] Netterlid E, Bruze M, Hindsen M, Isaksson M, Olin P. Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium. *Vaccine.* 2004;22(27–28):3698–706. <https://doi.org/10.1016/j.vaccine.2004.03.036>.
- [6] Bergfors E, Hermansson G, Nystrom Kronander U, Falk L, Valter L, Trollfors B. How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study. *Eur J Pediatr.* 2014;173(10):1297–307. <https://doi.org/10.1007/s00431-014-2318-2>.
- [7] Diggle L, Deeks JJ, Pollard AJ. Effect of needle size on immunogenicity and reactogenicity of vaccines in infants: randomised controlled trial. *Br Med J.* 2006;333(7568):571. <https://doi.org/10.1136/bmj.38906.704549.7C>.
- [8] Bergfors E, Bjorkelund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. *Eur J Pediatr.* 2005;164(11):691–7. <https://doi.org/10.1007/s00431-005-1704-1>.
- [9] Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines-prognosis and outcome after booster vaccination. *Eur J Pediatr.* 2013;172(2):171–7. <https://doi.org/10.1007/s00431-012-1841-2>.
- [10] Ben-Zvi G, Burrows N. Two children with persistent, pruritic injection site nodules after receiving vaccinations which contained aluminium. *J Am Acad Dermatol.* 2013;68(4):AB67. <https://doi.org/10.1016/j.jaad.2012.12.278>.
- [11] Leventhal JS, Berger EM, Brauer JA, Cohen DE. Hypersensitivity reactions to vaccine constituents: a case series and review of the literature. *Dermatitis.* 2012;23(3):102–9. <https://doi.org/10.1097/DER.0b013e31825228cf>.
- [12] Bohler-Sommeregger K, Lindemayr H. Contact sensitivity to aluminium. *Contact Dermatitis.* 1986;15(5):278–81. <https://doi.org/10.1111/j.1600-0536.1986.tb01368.x>.
- [13] Baylor NW, Egan W, Richman P. Aluminium salts in vaccines - US perspective. *Vaccine.* 2002;20(S3):S18–23. [https://doi.org/10.1016/s0264-410x\(02\)00166-4](https://doi.org/10.1016/s0264-410x(02)00166-4).
- [14] Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infect Dis.* 2004;4(2):84–90. [https://doi.org/10.1016/S1473-3099\(04\)00927-2](https://doi.org/10.1016/S1473-3099(04)00927-2).
- [15] The Australian Immunisation Handbook 10th Edition: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home>. Accessed 27th March 2018.
- [16] Chong H, Brady K, Metzke D, Calonje E. Persistent nodules at injection sites (aluminium granuloma) - Clinicopathological study of 14 cases with a diverse range of histological reaction patterns. *Histopathology.* 2006;48(2):182–8. <https://doi.org/10.1111/j.1365-2559.2005.02312.x>.
- [17] Skowron F, Grezard P, Berard F, Balme B, Perrot H. Persistent nodules at sites of hepatitis B vaccination due to aluminium sensitization. *Contact Dermatitis.* 1998;39(3):135–6. <https://doi.org/10.1111/j.1600-0536.1998.tb045865.x>.
- [18] Cox NH, Moss C, Forsyth A. Allergy to non-toxic constituents of vaccines and implications for patch testing. *Contact Dermatitis.* 1988;18(3):143–6. <https://doi.org/10.1111/j.1600-0536.1988.tb04500.x>.
- [19] Rothstein E, Kohl KS, Ball L, et al. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine.* 2004;22(5–6):575–85. <https://doi.org/10.1016/j.vaccine.2003.09.005>.
- [20] Kohl KS, Magnus M, Ball R, Halsey N, Shadomy S, Farley TA. Applicability, reliability, sensitivity, and specificity of six Brighton Collaboration standardized case definitions for adverse events following immunization. *Vaccine.* 2008;26(50):6349–60. <https://doi.org/10.1016/j.vaccine.2008.09.002>.
- [21] Clothier HJ, Crawford NW, Kempe A, Buttery JP. Surveillance of adverse events following immunisation: the model of SAEFVIC. *Victoria. Communicable Diseases Intelligence.* 2011;35(4):294–9.

- [22] Clothier HJ, Crawford NW, Russell M, Kelly H, Buttery JP. Evaluation of 'SAEFVIC', A Pharmacovigilance Surveillance Scheme for the Spontaneous Reporting of Adverse Events Following Immunisation in Victoria, Australia. *Drug Safety*. 2017;40(6):483–95. <https://doi.org/10.1007/s40264-017-0520-7>.
- [23] Australian Bureau of Statistics. <https://www.abs.gov.au/ausstats/abs@nsf/Previousproducts/3301.0Main%20Features32016?opendocument&tabname=Summary&prodno=3301.0&issue=2016&num=&view=>. Accessed November 29, 2019.
- [24] Historical data tables for all children. Australian Government, Department of Health. <https://www.health.gov.au/health-topics/immunisation/childhood-immunisation-coverage/historical-coverage-data-tables-for-all-children> Accessed November 29, 2019.
- [25] Australian Immunisation Register. <https://www.humanservices.gov.au/individuals/services/medicare/australian-immunisation-register>. Accessed January 16, 2017.
- [26] Lauren CT, Belsito DV, Morel KD, Case LaRussa P. Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines. *Pediatrics* 2016;138(4). <https://doi.org/10.1542/peds.2014-1690>.
- [27] Schijns VE, Lavelle EC. Trends in vaccine adjuvants. *Expert Review of Vaccines*. 2011;10(4):539–50. <https://doi.org/10.1586/erv.11.21>.
- [28] Miliauskas JR, Mukherjee T, Dixon B. Postimmunization (vaccination) injection-site reactions. A report of four cases and review of the literature. *Am J Surgical Pathol*. 1993;17(5):516–524 doi:10.1097/00000478-199305000-00012.
- [29] Lam M, Patel AN, Leach IH. Nodule on the upper arm. *Clin Exp Dermatol* 2014;39(7):844–6. <https://doi.org/10.1111/ced.12399>.
- [30] Bergfors E, Lundmark K, Kronander UN. A child with a long-standing, intensely itching subcutaneous nodule on a thigh: An uncommon (?) reaction to commonly used vaccines. *BMJ Case Reports*. 2013. <https://doi.org/10.1136/bcr-2012-007779>.
- [31] Jenner N, Campbell J, Marks R. Morbidity and cost of atopic eczema in Australia. *Australas J Dermatol* 2004;45(1):16–22. <https://doi.org/10.1111/j.1440-0960.2004.00046.x>.
- [32] Silcock R, Crawford NW, Perrett KP. Subcutaneous nodules: an important adverse event following immunization. *Expert Review of Vaccines*. 2019;18(4):405–10. <https://doi.org/10.1080/14760584.2019.1586540>.
- [33] Fawcett HA, Smith NP. Injection-site granuloma due to aluminum. *Arch Dermatol* 1984;120(10):1318–22. <https://doi.org/10.1001/archderm.1984.01650460058020>.
- [34] Lidholm AG, Bergfors E, Inerot A, Blomgren U, Gillstedt M, Trollfors B. Unexpected loss of contact allergy to aluminium induced by vaccine. *Contact Dermatitis* 2013;68(5):286–92. <https://doi.org/10.1111/cod.12053>.
- [35] Australian Immunisation Register. 2017; <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/acir-curr-data.htm>. Accessed November 27, 2017.
- [36] Forbes TA, McMiinn A, Crawford N, Leask J, Danchin M. Vaccination uptake by vaccine-hesitant parents attending a specialist immunization clinic in Australia. *Hum Vaccin Immunother*. 2015;11(12):2895–903. <https://doi.org/10.1080/21645515.2015.1070997>.
- [37] Exley C. Aluminium-containing DTP vaccines. *Lancet Infect Dis*. 2004;4(6):324–5. [https://doi.org/10.1016/S1473-3099\(04\)01039-4](https://doi.org/10.1016/S1473-3099(04)01039-4).
- [38] Vaxxas. <http://www.vaxxas.com/about-vaxxas/>. Accessed November 2, 2017
- [39] WHO. Information Sheet: Observed Rate of Vaccine Reactions Bacille Calmette-Guerin (BCG) Vaccine. 2012; http://www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf. Accessed November 30, 2017.