

How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study

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Abstract The frequency of long-lasting, intensely itching subcutaneous nodules at the injection site for aluminium (Al)-adsorbed vaccines (vaccination granulomas) was investigated in a prospective cohort study comprising 4,758 children who received either a diphtheria-tetanus-pertussis-polio-*Haemophilus influenzae* type b vaccine (Infanrix[®], Pentavac[®]) alone or concomitant with a pneumococcal conjugate (Prevenar). Both vaccines were adsorbed to an Al

adjuvant. Altogether 38 children (0.83 %) with itching granulomas were identified, epicutaneously tested for Al sensitisation and followed yearly. Contact allergy to Al was verified in 85 %. The median duration of symptoms was 22 months in those hitherto recovered. The frequency of granulomas induced by Infanrix[®] was ≥ 0.66 % and by Prevenar ≥ 0.35 %. The risk for granulomas increased from 0.63 to 1.18 % when a second Al-adsorbed vaccine was added to the schedule. **Conclusion:** Long-lasting itching vaccination granulomas are poorly understood but more frequent than previously known after infant vaccination with commonly used diphtheria-tetanus-pertussis-polio-*Haemophilus influenzae* type b and pneumococcal conjugate vaccines. The risk increases with the number of vaccines given. Most children with itching granulomas become contact allergic to aluminium. Itching vaccination granulomas are benign but may be troublesome and should be recognised early in primary health care to avoid unnecessary investigations, anxiety and mistrust.

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Abbreviations

Al	Aluminium
CHC	Child health care (center)
DTaP	Diphtheria-tetanus-acellular pertussis (vaccine)
DTaP comb	Combination vaccine including DTaP, polio, Hib, (hepatitis B)
E.B.	Elisabet Bergfors (project leader of the study)
Hib	<i>Haemophilus influenzae</i> type b (vaccine)
HPV	Human papilloma virus (vaccine)
i.m.	Intramuscular (injection)
MMR	Measles-mumps-rubella (vaccine)
TBE	Tick-borne encephalitis (vaccine)

Introduction

Vaccines adsorbed to aluminium (Al)-based adjuvants can induce long-lasting, intensely itching subcutaneous nodules at the injection site and also contact allergy to Al [16, 18, 19, 24–27, 34]. Histopathological examination of the nodules shows granuloma formations in which Al crystals can be demonstrated by staining or atomic absorption spectrometry (vaccination granulomas, aluminium granulomas) [11, 16, 17, 25, 35]. Both adverse events were considered uncommon and only described as case reports [2, 12, 13, 35, 38] until 2003 when persistent itching nodules were reported in 745 of 76,000 children (0.98 %) in clinical trials of Danish diphtheria-tetanus-acellular pertussis (DTaP) vaccines [7, 22] and later on also after vaccination with commercial DTaP-polio-*Haemophilus influenzae* type b (Hib) combination vaccines (Infanrix® and Pentavac®) in clinical routine in Sweden [4, 6]. Contact allergy to Al was verified in 77–95 % of children with vaccination granulomas. Other typical findings were a remarkably long delay between vaccination and onset of symptoms (median 3 months), intense itching at the vaccination site causing local eczema, hypertrichosis (Fig. 1) and discoloration, exacerbation of symptoms during intercurrent infections and a very prolonged course (median 3–4 years). The risk for itching granulomas increased with the number of Al-containing vaccine doses. The onset of symptoms could be preceded by another vaccination, mostly measles-mumps-rubella (MMR), which does not contain Al but seems to act as a triggering factor [6].

Al adjuvants (mostly Al hydroxide) are used in all vaccines against diphtheria, tetanus, pertussis, hepatitis B, human papilloma virus (HPV) and tick-borne encephalitis (TBE), in pneumococcal and meningococcal conjugate vaccines and in some

vaccines against hepatitis A. Itching granulomas are described after all these vaccines except, so far, those against pneumococcal and meningococcal infections and TBE [6, 7, 9, 26, 27, 31, 34, 35]. The Swedish child vaccination programme presently includes two Al-adsorbed vaccines (Table 1). Most countries in Europe and the Americas have included up to six Al-containing vaccines in their programmes during the last decades (acellular pertussis, hepatitis B, pneumococcal and meningococcal infections, HPV and hepatitis A), but to our knowledge, the frequency of itching granulomas and Al allergy induced by these vaccines has not been investigated or reported previously.

Itching vaccination granulomas are poorly known and often unrecognised in health care [3, 5–7, 20]. In several cases, the nodules have been mistaken for tumours leading to unnecessary anxiety, investigations and even surgery [1, 5, 6, 30]. The pruritus is difficult to treat and can affect the child for a long time [4, 6, 7, 16, 18, 32, 38]. Al allergy can lead to contact dermatitis after exposure to Al-containing antiperspirants [12, 21] (Fig. 2) and other skin care products [29] and cause problems in individuals tattooed with Al-containing pigments [28, 33]. Further vaccination of the afflicted children with Al-adsorbed vaccines has been questioned by many authors [8, 15, 19, 31] and declined or postponed by parents in fear for new problems [6].

Thus, itching granulomas can cause significant trouble, but the width of the problem cannot be estimated because the frequency of granuloma reactions after vaccination in clinical practice is unknown. The aim of the present study was to investigate the risk to develop long-lasting itching vaccination granulomas and contact allergy to Al in children after primary vaccination with frequently used DTaP combination vaccines (Infanrix®, Pentavac®) and a pneumococcal vaccine (Prevenar).

Materials and methods

The study was a prospective cohort study including all children in Östergötland County, Sweden, born in 2008. The county has about 427,000 inhabitants and a yearly birth cohort of about 4,700. About 20 % of the children are of non-Swedish ethnicity. The child health care is performed at 42 regional Child Health Centers (CHC) to which 96.7 % of children ≤6 years of age attend (2008) [37]. The study was performed from 2009 through January 2014. None of the cases described in this study have been reported previously.

Sample size

A sample of 3,000 children (64 % of a birth cohort) was estimated to be sufficient to conclude that the risk for itching vaccination granulomas would be ≥ 0.6 % (80 % statistical



Fig. 1 Locally increased hair growth on the left thigh at the injection site for two doses of Infanrix®. A 6-year-old girl with itching vaccination granulomas persisting since the age of 13 months

Table 1 The present Swedish child vaccination programme, available vaccines and their content of aluminium (Al) adjuvant

Vaccine against	Age at primary vaccination (months)	Age at booster vaccination (years)	Available vaccines (producer) Adjuvant (Al content)
Diphtheria, tetanus and pertussis (DTP)	3, 5 and 12	5–6 and 14–16	“DTaP + polio:”
Polio	3, 5 and 12	5–6	Infanrix® Polio (GlaxoSmithKline, Rixensart, Belgium)
Haemophilus influenzae type b (Hib)	3, 5 and 12	–	Al hydroxide (0.5 mg Al/dose)
Hepatitis B (offered to ethnic risk groups)	3, 5 and 12	–	“DTP + polio + Hib:” Infanrix®-Polio + Hib (GlaxoSmithKline) Al hydroxide (0.5 mg Al/dose) Pentavac® (Sanofi, Lyon, France) Al hydroxide (0.3 mg Al/dose) “DTP + polio + Hib + HepB:” Infanrix® hexa (GlaxoSmithKline) Al hydroxide (0.5 mg Al/dose)
Invasive pneumococcal disease (introduced in autumn, 2008)	3, 5 and 12	–	Prevenar (Pfizer, Kent, UK) Prevenar 13 (Pfizer) Al phosphate (0.125 mg Al/dose) Synflorix (GlaxoSmithKline) Al phosphate (0.5 mg Al/dose)
Measles, mumps and rubella (MMR)	18	6–8	MMRVAXPRO Priorix® No content of Al

power) according to the hypothesis that between 0.1 and 1.0 % of the vaccinated children would be afflicted; more than 0 because granulomas induced by Infanrix® and Pentavac® had been spontaneously reported earlier in Sweden [6] but lower than 1 % because 0.98 % was reported through active surveillance in the clinical trials in Gothenburg [7].

Step 1. Inventory of itching vaccination granulomas

Children with itching vaccination granulomas were identified by a population-based enquiry and/or by individual reports by CHC nurses in the county. The enquiry comprised all children born in 2008 and living in Östergötland at 20 months of age ($n=4,758$). This age was chosen in order to include children who had received the third Al-adsorbed vaccinations at the age of 12 months but whose onset of symptoms was delayed until the MMR vaccination was given at 18 months. Parents who did not answer the questionnaire received a reminding letter 2–3 months after the initial one. Parents were asked whether their child had been itching on an induration on the front or lateral side of a thigh for some time or not. Parents who answered “Yes” were interviewed by telephone by the project leader (E.B.) for further details in order to distinguish between “true” itching vaccination granulomas and pruritus for other reasons. In cases which were difficult to evaluate by telephone, the child was examined at a personal meeting. To ensure that the location of an itching nodule corresponded with the injection site for an Al-adsorbed vaccine, medical records including data on vaccines given and date and site of injection were requested from the CHCs.

CHC nurses were informed about the study at regional meetings and asked to refer a child with itching nodules at any age. Parents were then interviewed in the same way as described above.

Step 2. Clinical study

All children with itching vaccination granulomas, as judged by the telephone interview or at a personal visit, were invited



Fig. 2 Contact dermatitis in left axilla after the use of an aluminium containing deodorant. A 15-year-old girl sensitised to aluminium after vaccination with a Danish acellular pertussis vaccine. Picture taken after 1 week treatment with strong local steroids

to participate in a clinical study including examination of the child, an epicutaneous (patch) test with Al and an annual follow-up until 12 months after the booster dose of DTaP-polio vaccine (scheduled at 5–6 years) was given. The parents of all participating children gave informed consent before taking part in the clinical study.

All examinations (general inspection of the skin and inspection and palpation of the itching areas on the thighs) were performed by E.B. The onset and duration of the symptoms and the impact on the child were noted. Children with the following criteria were judged to have long-lasting itching vaccination granulomas:

1. One or more subcutaneous nodules or indurations on the front or lateral part of one or both thighs at the site of vaccination with Infanrix-polio + Hib[®], Infanrix[®] hexa, Pentavac[®] or Prevenar
2. Local itching at the site of the nodule for ≥ 6 months

Local skin alterations in the itching area (excoriations and scars, increased hair growth, hyperpigmentation, bluish discoloration and eczema), a history of worsened symptoms during intercurrent infections and a long interval between the vaccination and the onset of symptoms (weeks or months) contributed to the diagnosis but were not mandatory. Children with palpable nodules/infiltrations but having a short period of itching (2–5 months) and children with local itching on a thigh but uncertain history of nodules were classified as observational cases. They were patch-tested if the parents asked for it, but not included in the study.

The patch tests, metallic Al (an empty Finn Chamber[®]; SmartPractice, Phoenix, AZ, USA) and Al chloride hexahydrate 2 % in petrolatum in a plastic chamber (Chemotechnique Diagnostics, Vellinge, Sweden) were applied by E.B. or a specially trained nurse, removed by the parents 48 h later and read 72 h after application by a dermatologist (L.F.) or allergologist (U.N.K.). The test results were interpreted according to the recommendations of the International Contact Dermatitis Research Group [39]. Positive reactions from + to +++ were regarded as expressions for delayed (type IV) hypersensitivity.

The annual follow-up was performed by a written questionnaire in which parents were asked to categorise the child's on-going symptoms in one of four stages:

1. *Unchanged symptoms*: Nodules distinctly palpable. Daily or almost daily more or less intense itching. Fresh, sometimes bleeding excoriations in the itching area.
2. *Improved*: Nodules diminished or present intermittently. Periods of itching alternating with symptom-free intervals for one or some weeks. Excoriations and scars may still be present.
3. *Nearly recovered*: Nodules intermittent or disappeared. Symptom-free periods for some or several months

interrupted by mild itching. Skin mostly normalised, but scars, hypertrichosis and hyperpigmentation may still be present.

4. *Recovered*: No palpable nodules. No itching periods during the past 12 months. No remaining skin alterations.

Vaccination programme, vaccines and aluminium content

The Swedish child vaccination programme at the time of the study is shown in Table 1. DTaP combinations and pneumococcal vaccines were always injected intramuscularly (i.m.) in a thigh. Booster doses were given i.m. in an upper arm.

According to the Swedish Institute for Communicable Disease Control, 4,558 infants in Östergötland County born in 2008 were vaccinated with DTP-polio-Hib vaccines. Most of them received three doses of an Infanrix[®] vaccine but, due to a shift of vaccine deliverers, some children born in the first quarter of 2008 got one, two or three doses of Pentavac[®] during the overlapping period. Pneumococcal vaccination with Prevenar was introduced for all infants born from October, 2008 but was also given earlier this year. In all, 1,693 infants received Prevenar on the same occasions as Infanrix[®]/Pentavac[®] in the contralateral thigh. All infant vaccinations in the county were performed at the CHCs. An overview of the vaccinations given during the study period is shown in Fig. 3.

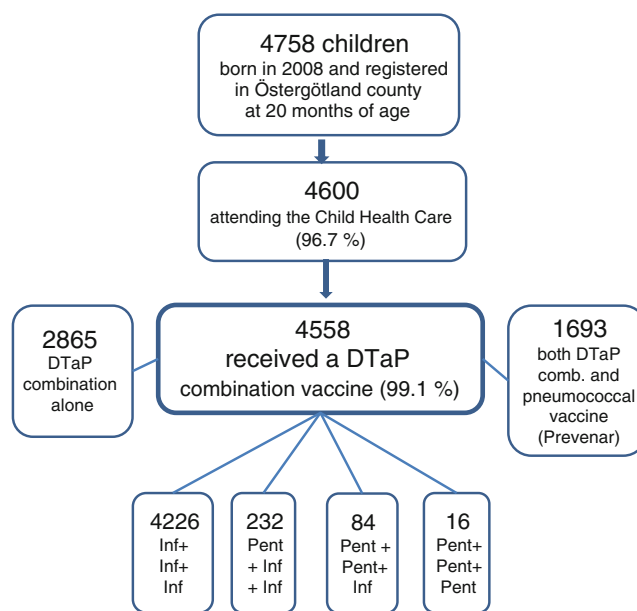


Fig. 3 Primary vaccinations of 4,558 children included in the inventory study. DTaP combination = vaccine against D, T, P, polio and *Hemophilus influenzae* type b (Infanrix[®]-polio + Hib and Pentavac[®]); Inf + Inf + Inf = three doses of Infanrix[®]-polio + Hib or Infanrix[®] hexa; Pent + Inf + Inf = one dose of Pentavac[®] followed by two doses of Infanrix[®]; Pent + Pent + Inf = two doses of Pentavac[®] followed by one dose of Infanrix[®]; Pent + Pent + Pent = three doses of Pentavac[®]

Statistical analysis

Proportions were estimated with 95 % exact confidence interval based on the binomial distribution. The risk ratio was estimated by the odds ratio together with 95 % approximate confidence interval. Statistical tests were two sided and $p < 0.05$ was considered to be statistically significant.

Results

Altogether 38 children fulfilling the criteria for long-lasting itching vaccination granulomas were identified by the enquiry or directly reported by CHC nurses and included in the clinical study (Fig. 4). Their median age at onset of symptoms was 15 months (5–25 months). Eight were of non-Swedish ethnicity (21 %). Fourteen children with short duration of itching or uncertain history of subcutaneous nodule were classified as observational cases.

The symptoms and findings in 63 children to “Yes”-responding parents were not consistent with itching nodules. As judged by interviews and examinations, 40 children had a dermatologic disorder (eczema or local pruritus for other reasons) and 15 common local vaccine reactions (a warm red swelling or an asymptomatic little nodule). The parents of the remaining children had misunderstood the question.

Symptoms and clinical course

The itching nodules appeared 2 weeks–13 months after the preceding vaccination with an Al-adsorbed vaccine (median 2.5 months). Twenty-three children had itching nodules on one thigh and 15 on both. Eight children with prolonged itching had local hyperpigmentation, hypertrichosis, discoloration or eczema on the thigh (Fig. 5). The itching flared and the nodules swelled during intercurrent infections (mostly upper respiratory tract infection) in 28 children. The exacerbation of the granulomas could even precede the common cold with a day or two.

At the recent follow-up, the parents of 37 children could be reached. Twenty-one children (57 %) became free from symptoms after a median duration of 22 months (6–43), 11 were almost recovered and 4 were improved. One boy had still more or less daily symptoms of itching since almost 3 years.

History of vaccination: correlation between vaccine, number of doses and granulomas

Thirty-seven children received an Infanrix® vaccine (32 Infanrix®-polio + Hib and five Infanrix® hexa). One child got two doses of Pentavac® followed by one dose of Infanrix®-polio + Hib. Twenty children received Prevenar in addition to the DTaP combination. The number of Al-containing vaccine doses received prior to the onset of the granulomas varied between two and six (Table 2).

Fig. 4 Identification process of children with itching vaccination granulomas in the inventory study. CHC child health care. “Yes” = parents declared that the child had an itching subcutaneous nodule on a thigh; “No” = parents denied symptoms of itching nodules; Obs case = child with subcutaneous nodule but short duration of itching or local itching but uncertain history of nodule

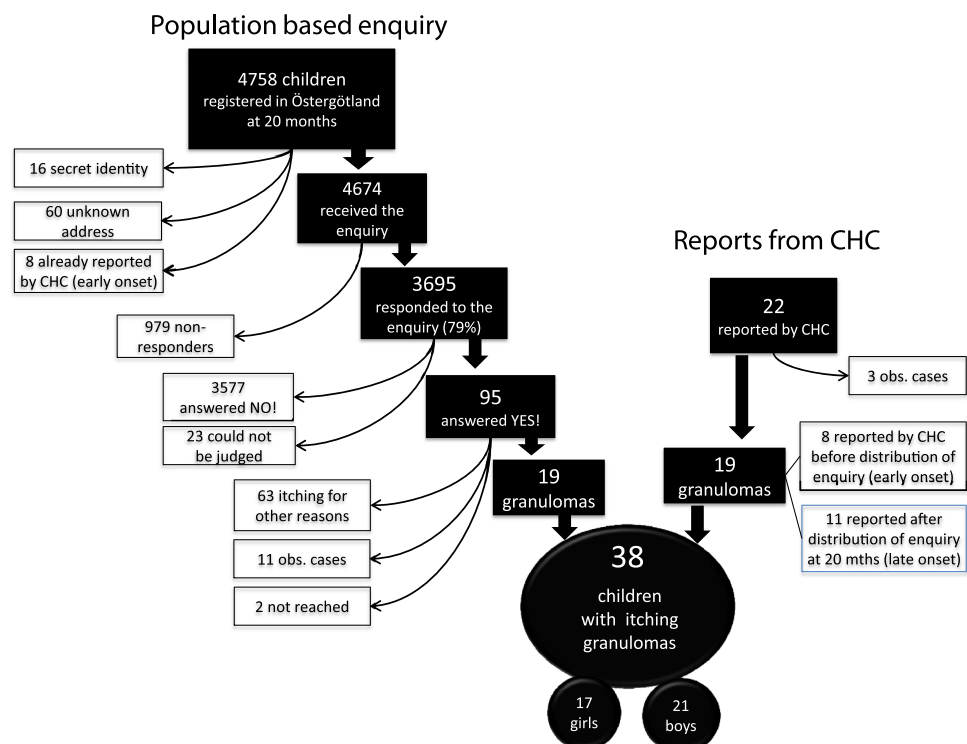




Fig. 5 Excoriations and local eczema overlying an itching granuloma on left thigh at the vaccination site of three doses of Infanrix[®]polio + Hib. A 2.5-year-old girl with 10 months duration of symptoms

The granulomas appeared after the third vaccination in 31 children (82 %) and after the second in seven children. Among those, the third dose was given as planned in three children but postponed for 5–26 months in four. Four children who received both Infanrix[®] and Prevenar had itching nodules at the injection site for both vaccines; the total number of granulomas was thus 42 (Table 3). Twenty-eight granulomas appeared on a site where only Infanrix[®] was injected and six on a site where only Prevenar was injected. Which vaccine induced the remaining eight granulomas could not be determined due to alternating injection sites or lack of documentation.

Frequency of itching granulomas

In all, 0.83 % (38/4,558) of the children injected with one or two Al-adsorbed vaccines in the study fulfilled the criteria for long-lasting itching vaccination granulomas (95 % confidence

interval 0.59 to 1.14 %). The frequency of granulomas obviously induced by Infanrix[®] alone was 0.66 % (28/4,226; 95 % confidence interval 0.44 to 0.96 %) and by Prevenar alone 0.35 % (6/1,693; 95 % confidence interval 0.13 to 0.77 %).

The frequency of granulomas was almost doubled in children who received both Al-adsorbed vaccines (1.18 %) compared to those who received only one (0.63 %) (Table 4). The risk ratio was 1.880 (95 % confidence interval 0.998 to 3.544; $p=0.0509$).

Testing for contact allergy to aluminium

Thirty-four children were epicutaneously tested with Al at a median age of 31 months (16–54 months). Twenty-nine of them (85 %) had a positive reaction to the test (Fig. 6). The reaction to the petrolatum preparation was the strongest in 13 cases and to the metallic Al in one case. In the remaining 15, the reaction was equal at both test sites. All children but three had strong (++ to ++(+)) or very strong (+++) reactions in at least one test area.

Five children had negative patch test results. All had a short duration of their itching granulomas, 6–8 months. Two children in the observational group with itching nodules of very short duration (2–3 months) were epicutaneously tested, both with negative reactions.

Discussion

The demonstration of long-lasting itching vaccination granulomas in 38 of 4,558 children (0.83 %) who received Al-adsorbed vaccines during their first year of life confirmed our hypothesis that 0.10–1.0 % of the children in the study would be afflicted. Neither the frequency of itching granulomas induced by a DTaP combination vaccine in clinical routine (≥ 0.66 % in this study), the occurrence of granulomas induced by a pneumococcal vaccine (≥ 0.35 %) or the increased risk for granulomas when a second Al-adsorbed vaccine was introduced in the vaccination programme has, to our knowledge, been reported previously.

Table 2 Number of aluminium-adsorbed vaccine doses received before onset of symptoms and inclusion in the clinical study (38 children)

Vaccination number preceding onset of granulomas (age at vaccination)	Total number of Al-containing vaccine doses received before onset	Number of children with itching granulomas	Median age at onset of symptoms (min–max)
Second (5 months)	2 doses (DTaP comb ^a)	1	7 months (6–10)
	4 doses (DTaP comb + PCV ^b)	6	
Third (12 months)	3 doses (DTaP comb)	17	18 months (13–25)
	6 doses (DTaP comb + PCV)	14	
Total		38	

^a DTaP comb = combination vaccine against diphtheria, tetanus, pertussis, polio and *Hemophilus influenzae* type b (Infanrix[®] or Pentavac[®] + Infanrix[®])

^b PCV = pneumococcal conjugate vaccine (Prevenar)

Table 3 Long-lasting itching vaccination granulomas induced by Infanrix® and/or Prevenar

Vaccines (no. of children)	Sites of vaccination (no. of children)	Site(s) of itching nodule (no. of children)	Number of granuloma formations induced by		
			Infanrix®	Prevenar®	Either or both vaccines (cannot be judged)
Infanrix® alone (18)	Alternating in both thighs (18)	Both sites (8) One thigh (10)	8 10		
Both Infanrix® and Prevenar (19)	All doses of Infanrix in one thigh and all doses of Prevenar in the opposite (12) Both vaccines alternating in both thighs (7)	Inf thigh ^a (6)	6	2	2
		Prev thigh ^b (2)	4	4	5
		Both thighs (4) Both thighs (2) One thigh (5)			
Pent + Inf ^c and Prevenar (1)	Not documented	One thigh			1
Total 38		38	28 (Total 42)	6	8

^a Inf thigh = the thigh in which all doses of Infanrix® were injected

^b Prev thigh = the thigh in which all doses of Prevenar were injected

^c Pent + Inf = two doses of Pentavac® followed by one dose of Infanrix®

Comparison with previous studies

Occasional cases of long-lasting itching granulomas induced by AI-adsorbed vaccines and antigen extracts have been reported by dermatologists and pathologists since the 1960s [9, 11, 13, 15–19, 24–27, 34, 35], but the course and frequency were first described in the vaccine trials in Gothenburg in the 1990s [7] and in a study of 64 spontaneously reported children in clinical routine [4–6]. A comparison between these studies and the present inventory in Östergötland County is shown in Table 5.

The frequency of itching granulomas demonstrated in the present study, 0.83 %, is consistent with the much larger Gothenburg study (0.98 %) [36] considering that the Danish study vaccines were mainly injected subcutaneously with increased risk for granuloma formation [14], while all children in the Östergötland cohort were injected intramuscularly. The proportion of undetected cases was probably relatively small in both studies due to the active surveillance of adverse events in the clinical trial and the active search for cases in the prospective study.

The clinical symptoms and signs of itching granulomas in the present study are described in numerous case reports and

short series of patients: a long interval between vaccination and onset of symptoms [15, 19, 34, 35]; severely pruriginous subcutaneous nodules [20, 34]; localised hyperpigmentation, hypertrichosis and eczema in the itching area [19, 24, 32]; flaring of symptoms during acute infections [4–7]; and a prolonged course over years [15, 18, 34, 35, 38]. In comparison to the previous study in clinical routine [6], the children in Östergötland County had shorter duration of symptoms and less intense itching as reflected in secondary skin alterations (Table 5). The presence of milder cases in a prospective study with active search for recent cases was expected as well as more severe cases among children who were spontaneously reported due to their long-lasting problems.

The frequency of contact allergy to AI in children with itching vaccination granulomas has not been investigated prior to the Swedish studies. The highest, 95 %, was seen among the spontaneously reported children with the most intense and long-lasting itching and the lowest, 77 %, in the vaccine study in which the children were older at both vaccination and epicutaneous testing (Table 5). This may indicate that young age at onset of granulomas and/or severe symptoms may increase the risk for AI sensitisation.

Table 4 Frequency of itching vaccination granulomas in children who received one or two aluminium-adsorbed vaccines during their first year of life

Vaccines (number of doses of aluminium adjuvant)	Number of vaccinated children	Number of children with itching granulomas	Frequency of itching granulomas
DTaP comb. alone (3 doses)	2,865	18	0.63 % (95 % confidence interval 0.40 to 1.00 %)
Both DTaP comb. and pneumococcal conjugate (6 doses)	1,693	20	1.18 % (95 % confidence interval 0.76 to 1.84 %)
Total	4,558	38	0.83 % (95 % confidence interval 0.59 to 1.14 %)



Fig. 6 Positive epicutaneous test 72 h after application with metallic aluminium (superior) and aluminium chloride hexahydrate 2 % in petrolatum (inferior). A 2-year-old boy with itching granulomas after vaccination with three doses of Prevenar

Possible explanations for findings

Itching vaccination granulomas are often not recognised by nurses or physicians in primary health care because they are uncommon and appear late after vaccination. They are probably highly underreported as indicated in previous studies [6, 7] where the number of reports promptly increased when CHC staff was informed about the condition.

During four decades, from 1960 to 2000, altogether about 125 cases of itching vaccination granulomas were reported in the literature [3], but ever since the number has increased with >800, most of which were reported in Sweden [6–9, 11, 16, 22, 25–27]. This increase is probably a result of the active search for late adverse events in the Gothenburg vaccine trials [7] and a known personal interest leading to spontaneous reports [6]. However, a change in the composition of modern vaccines cannot be ruled out. It is possible that chemophysical or other properties, or the mode of binding or adsorbing the antigen to the adjuvant, can cause a real difference in the tendency to induce itching granulomas [3]. The nature of the Al compound in the adjuvant is another possible but unproven factor. All vaccines (except the pneumococcal conjugate) which were used in this and the two previous Swedish studies were adsorbed to Al hydroxide. On the other hand, a DT vaccine adsorbed to Al phosphate was given to approximately 1,700,000 children in Sweden in the 1980s and 1990s without any reported case of itching nodules [3]. This may indicate that Al phosphate is less reactogenic than the hydroxide.

Children with itching vaccination granulomas are easy to identify in Sweden where all newborns receive a unique ten digit personal number and about 99 % attend the public CHC where all vaccination details including injection site are documented. This was an absolute prerequisite for being able to relate an itching nodule at a vaccination site with the administration of a certain vaccine.

The role of injection technique is controversial. Theoretically, the risk for subcutaneous deposition of a vaccine should be small if it is injected intramuscularly. Injecting children is, however, a delicate art and some amount of vaccine might be deposited more superficially than intended during an intramuscular injection. However, in our opinion, a safe vaccine should endure some leakage during the injection without risking troublesome and long-lasting local reactions and hypersensitivity to any component in the vaccine.

Although there is an obvious and strong association between itching vaccination granulomas and aluminium allergy, the interaction is unclear. Has a sensitisation induced by the first vaccine doses caused the granulomas, or has the aluminium crystals remaining in the granulomas caused the sensitisation?

Another question is why some children get itching vaccination granulomas while others do not. The “granuloma children” seem as healthy as the others. An association between allergies (food, pollen, epithelium) or atopic eczema and itching nodules could be expected but has not yet been studied. Notably, the prevalence of contact allergy to another metal, nickel, was reported to be the same in individuals with or without a history of childhood eczema [23]. Heredity could be a factor according to an accumulation of siblings with itching granulomas in the Gothenburg study [7]. Ethnicity does not seem to be decisive as children originating from foreign countries were afflicted in the same proportions as the total population in both Gothenburg and Östergötland County.

Strengths and limitations of the study

To obtain as reliable data as possible, two additional methods were used to identify children with itching granulomas. Nineteen cases were found through a population-based enquiry, and the equal number was individually reported by CHC nurses. With only one method, the number of identified cases would have been much lower. Another strength was that the history and findings of all children were judged in a uniform way by one person (E.B.) with large experience of itching granulomas. All patch tests were set by her or a specially trained nurse and the reactions were read by either a dermatologist or an allergologist.

The enquiry was responded by 79 % of the recipients after one reminder. The questionnaire was uncomplicated and easy to return but only written in Swedish. Many non-responding parents originated from other countries which may partly explain the drop-out. On the other hand, the proportion of “granuloma children” with non-Swedish origin in the study was the same as in the whole population, 20–21 %. The responders might therefore be acceptably representative for the whole population.

The enquiry was distributed when the children were 20 months, and most granulomas were considered to have

Table 5 Two previous (left and middle columns) and the present study on long-lasting itching vaccination granulomas performed in Sweden: settings and results

Name of study [reference no.] (study period)	“Gothenburg Study” [7, 22] (1991–2000)	“64 Children Study” [6] (1999–2011)	“Östergötland Inventory” (2009–2013)
Way of detecting itching granuloma cases	Active surveillance in a clinical phase 4 vaccine trial	Spontaneous reports by parents and CHC staff in clinical routine	Active search by enquiries and CHC reports in clinical routine
Study area	Gothenburg area in western Sweden	Throughout Sweden	County of Östergötland in eastern Sweden
Type of study	Mainly retrospective	Retrospective	Prospective
Vaccines received by the children with itching granulomas	Study DT, aP and DTaP vaccines manufactured by SSI, Copenhagen, Denmark	Commercial DTaP combinations ^a (Infanrix [®] and Pentavac [®])	Commercial DTaP combination (Infanrix [®]) and pneumococcal vaccine (Prevenar)
Mode of injection	Mainly subcutaneous	Intramuscular	Intramuscular
Number of Al-containing vaccine doses injected before onset of symptoms	1 dose: 28 children (4 %) ^b 2 doses: 117 children (18 %) ^b >3 doses: 500 children (78 %) ^b	1 dose: 6 children (9 %) 2 doses: 8 children (12 %) 3 doses: 50 children (78 %)	1 dose: 0 2 or 4 doses ^c : 8 children (22 %) 3 or 6 doses ^c : 30 children (78 %)
Age at vaccination	3 months–10 years	3–12 months	3–12 months
Gender	60 % girls	59 % girls	44 % girls
Non-Swedish ethnicity	21 %	Cannot be determined	21 %
Number of vaccinated children	About 76,000	Cannot be determined	4,558
Number of children with granulomas	745	64	38
Frequency of granulomas	0.98 %	Cannot be determined	0.83 %
Median delay vaccination—onset of symptoms	3 months	3 months	2.5 months
Median age at onset of symptoms	36 months	16 months	15 months
Median duration of symptoms in children who had recovered	37 months (154 children)	49 months (24 children)	18 months (18 children)
Local skin alterations ^d in the itching areas	32 %	40 %	18 %
Exacerbation of symptoms during infections	39 %	59 %	74 %
Proportion of Al allergy in tested children	77 % (352/455)	95 % (60/63)	85 % (29/34)
Median age at epicutaneous testing (range)	6 years (1–18 years)	3.3 years (1.5–11 years)	2.6 years (1.3–4.5 years)

CHC child health care, DT diphtheria-tetanus, aP acellular pertussis, SSI Statens Serum Institute, Al aluminium

^a DTaP combination = vaccine against D, T, P, polio and *Hemophilus influenzae* type b

^b As registered in the initially reported 645 children

^c Children who received one or two Al-adsorbed vaccines, respectively

^d Hyperpigmentation, hypertrichosis and/or eczema

manifested their first symptoms. However, seven children, whose parents denied symptoms at that time, were later reported from CHCs with typical itching granulomas. We therefore think that 24–26 months would have been a more appropriate age for the enquiry to include those with very late onset of symptoms.

When the study was planned, only one Al-adsorbed vaccine was used in the county, the DTaP combination Pentavac[®]. This allowed us to calculate that one birth cohort (about 4,700 children) would give us data for an appropriate calculation of the frequency of itching granulomas. However, from March 2008, Pentavac[®] was successively replaced by another combination vaccine, Infanrix[®]. Another unexpected change during the study period was the introduction of a

second Al-adsorbed vaccine, the pneumococcal conjugate Prevenar, in autumn, 2008. Instead of one large group of children who received a single vaccine, we now had two smaller groups following different vaccination programmes. This of course impaired the possibility to demonstrate significant data. On the other hand, we now had a chance to compare the frequencies in children who received one or two Al-adsorbed vaccines, respectively, but in all other aspects were treated and identified in the same way. Such a study cannot be repeated as all children now follow the new programme. The destiny of our ambitiously planned study illustrates the difficulty in investigating vaccination outcome and, especially late adverse events, in clinical practice.

According to a former routine, eight children received both Infanrix® and Prevenar alternating in both thighs which made it impossible to determine which vaccine induced the granulomas. If all granulomas could be related to only one vaccine, the frequency would be higher than 0.66 % induced by Infanrix® and/or 0.35 % induced by Prevenar. Since January 2009, all doses of Infanrix® are given exclusively in one thigh and Prevenar in the other in Östergötland county.

Finally, an obvious limitation is that it is next to impossible for parents to estimate a specific time when gradually decreasing symptoms like itching finally ends. We tried to compensate this with yearly follow-up enquiries.

Implications and future directions

Our most important issue is to point out that small children can get long-lasting, often intensely itching subcutaneous nodules (granulomas) at the injection sites for Al-containing vaccines. Most children also get contact allergy to Al. Itching granulomas are easy to recognise once you are aware of them and should be familiar to all staff in health care working with children to avoid anxiety and mistrust in the parents and unnecessary investigations of the child.

Equally important is to point out that although the granulomas may cause great discomfort for a child and his/her family, the condition is benign and self-limiting and, in our opinion, no cause to refrain from vaccination. The discomfort of the granulomas can never be worse than the diseases which the vaccines protect for. We do, however, wish and recommend that Al salts could be replaced by other adjuvants.

In this study, 0.83 % of the children had itching granulomas implying that the incidence could be about 800/year in a country like Sweden with a yearly birth cohort of 100,000 and two Al-adsorbed vaccines in the infant vaccination programme. The yearly incidence of contact allergy to Al would be about 680. Many children would probably have mild symptoms of short duration, as indicated by this study, but they should still be recognised and the adverse events should be reported to the medical products authorities and stated in the product resumés of the vaccines.

Al salts (Al hydroxide and Al phosphate) are used as adjuvants in vaccines against diphtheria, tetanus and pertussis, hepatitis A and B, pneumococcal and meningococcal infections and human papilloma virus. Most of them, or all, are included in the child vaccination programmes in countries all over the world. It is obvious that the risk for itching nodules increases with the number of doses of Al-adsorbed vaccine administered. The almost doubling of cases when a second Al-containing vaccine was introduced in Sweden indicates that countries with five or six Al-adsorbed vaccines in their programmes may have substantially more children with itching vaccination granulomas than hitherto known. We welcome further studies to confirm or reject our apprehensions.

A prerequisite for demonstrating a causal relation between a certain vaccine and an itching granuloma is that all injection sites are registered in the vaccination record. To enable adequate reports of adverse events, we recommend that all doses of one vaccine should be injected in the same limb instead of alternating injection sites.

All children in the Swedish studies were epicutaneously tested with a standard preparation of 2 % aluminium chloride hexahydrate in petrolatum. It has been suggested that this is too weak for detecting all cases of aluminium allergy and that a 10 % preparation should be used [10]. However, all children but three in our study had ++ or +++ reactions to the 2 % preparation already 72 h after application. We therefore recommend that Al chloride hexahydrate preparations in petrolatum used for testing small children shall not be stronger than 2 % to avoid extremely strong reactions.

Children sensitised to Al may get contact dermatitis after exposure to Al-containing sun protectors, lotions, ear drops and antiseptics. However, the greatest problems with Al allergy can be expected when teenagers start to use Al-containing deodorants and get tattooed with Al-containing pigments. Al allergic individuals who undergo allergen immunotherapy against pollen or other allergies later in life should be injected with Al-free extracts to avoid further granuloma formation.

Fortunately, and in contrast to previous belief, contact allergy to Al in children may wane or disappear with time as shown in a recently published study on 241 children from the Gothenburg trials; 77 % of them had negative results when retested 5–7 years after the initial positive epicutaneous test [22]. We therefore plan to offer renewed testing to the Al-allergic children in this study when they are about 7 years old.

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Ethical statements The study was approved by the Ethical Review Board in Linköping, Sweden (Dnr M110-09) and registered in the County Council of Östergötland according to the Personal Data Ordinance. The parents of all children participating in the clinical study gave informed consent before taking part in it.

Conflict of interest The authors declare that they have no financial relationship with the organization that sponsored the research, nor any other conflict of interest.

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