

# Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer

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Received 20 February 2003; accepted 7 July 2003

## Abstract

During trials of aluminium adsorbed diphtheria–tetanus/acellular pertussis vaccines from a single producer, persistent itching nodules at the vaccination site were observed in an unexpectedly high frequency. The afflicted children were followed in a longitudinal observational study, and the presence of aluminium sensitization was investigated in the children with itching nodules and their symptomless siblings by patch tests. Itching nodules were found in 645 children out of about 76,000 vaccinees (0.8%) after both subcutaneous (s.c.) and intramuscular (i.m.) injection. The itching was intense and long-lasting. So far, 75% still have symptoms after a median duration of 4 years. Contact hypersensitivity to aluminium was demonstrated in 77% of the children with itching nodules and in 8% of the symptomless siblings who had received the same vaccines ( $P < 0.001$ ). Children with persistent itching nodules and/or aluminium sensitization should be warned about aluminium containing products (e.g. vaccines and antiperspirants). The reason for the high incidence of itching nodules after SSI vaccines is unknown and should be further investigated.

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**Keywords:** Adsorbed vaccines; Itching nodules; Aluminium sensitization

## 1. Introduction

Persistent itching nodules or granulomas at the injection site after vaccination with aluminium adsorbed vaccines have been described since 1960 [1], but are considered to be rare [2–5]. The reaction is reported after tetanus, diphtheria–tetanus (DT), DT–whole cell pertussis (DTwP), DT–polio, diphtheria–tetanus/acellular pertussis (DTaP)–polio, hepatitis B and influenza vaccines [2,5–21] and after injection with aluminium precipitated antigen extracts used for hyposensitization in allergic diseases [10,22–26]. Contact allergy to aluminium in individuals with persistent itching nodules has been reported since 1980 [4,9–13,16,17, 22–25,27].

During trials of an acellular pertussis vaccine performed in western Sweden, an unexpectedly high frequency of itching nodules was observed after vaccination with aluminium hydroxide adsorbed DT, DTaP and aP. The aim of the present

study is to describe the incidence, clinical course and prognosis of vaccine-induced itching nodules and the presence of aluminium sensitization in children with itching nodules and in a control group without this symptom.

## 2. Patients and methods

### 2.1. Patients

The children with itching nodules described here were either participants in the vaccine studies described below or received the DTaP in clinical routine. The vaccination schedules and numbers of participants and vaccine doses given are shown in Table 1.

### 2.2. The pertussis vaccine trials and the post-study period

The *Efficacy Study* (1991–1994) was a double-blind trial of an aP [28]. Infants were randomized to vaccination with DTaP or DT at 3, 5 and 12 months of age. The recipients of

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Table 1

Numbers of participants and vaccine doses given in the trials and during routine vaccination, mode of injection, numbers of doses of aluminium-containing vaccines received before entering the trial, total numbers of cases of itching nodules, incidence rates (numbers of cases/numbers of first doses given) and numbers after intramuscular injection

Vaccine, schedule and mode of injection	Numbers of doses of vaccine from SSI given			Doses of aluminium-adsorbed vaccine before the trial	Total number of cases of itching nodules (April 30, 2002)	Incidence (%)	Number of itching nodule cases who received all doses i.m.
	Dose 1	Dose 2	Dose 3				
<i>Efficacy Study</i>							
DTaP × 3 (s.c.)	1724	1708	1692	0	6	0.35	
DT × 3 (s.c.)	1726	1717	1687	0	6	0.35	
<i>Booster Study<sup>a</sup></i>							
DTaP(-IPV) × 1 (i.m.)	618			3	1	Not calculated <sup>f</sup>	
<i>Control Children Study<sup>b</sup></i>							
aP × 3 (s.c.)	1128	1086	1034	3	5	0.44	
<i>Mass Vaccination Project</i>							
DTaP × 3 (s.c./i.m.) <sup>c,d</sup>	29993	29440	27504	0	161	0.54	9
DTaP + aP + aP (s.c.)	7243	6419	5058	2	120	1.66	
aP × 3 (s.c./i.m.) <sup>c</sup>	28202	26710	25503	3	335	1.19	2
<i>Combination Vaccine Study</i>							
DTaP-IPV(-Hib) × 3 (i.m.)	407	405	400	0	1	Not calculated <sup>f</sup>	1
<i>Routine vaccination</i>							
DTaP × 3 (i.m.) <sup>e</sup>	~7000	~5500	~1700	0	10	Not calculated <sup>f</sup>	10

<sup>a</sup> These children had previously participated in the DTaP group of the *Efficacy Study*.

<sup>b</sup> These children had previously participated in the DT group of the *Efficacy Study*.

<sup>c</sup> The mode of injection was changed from subcutaneous to intramuscular in October 1998.

<sup>d</sup> Two of these children received Pentavac<sup>®</sup> in their third vaccination.

<sup>e</sup> Six of these children received Pentavac<sup>®</sup> in their third vaccination.

<sup>f</sup> Not calculated because the denominator is small.

DTaP were offered a booster dose of DTaP with or without an inactivated polio vaccine (IPV) at 6 years of age (“*Booster Study*”, unpublished). The recipients of DT who at the age of 3–4 years had not experienced pertussis were offered three doses of aP with intervals of 2 and 6 months (“*Control Children Study*”, unpublished).

The *Mass Vaccination Project* (June 1995–February 1999) had the aim to study if herd immunity could be achieved by mass vaccination of infants and children [29]. Three different vaccination schedules were used depending on previous DT vaccinations: (1) unvaccinated infants received three doses of DTaP at 3, 5 and 12 months of age; (2) children aged 12 months who had previously received two doses of the routinely used Swedish aluminium phosphate adsorbed DT were given one dose of DTaP followed by two doses of aP with intervals of 2 and 6 months; (3) children older than 12 months who had previously received three doses of the Swedish DT received three doses of aP with the same intervals.

In the *Combination Vaccine Study* (1997), infants received either DTaP-IPV mixed with a *Haemophilus influenzae* type b-tetanus toxoid conjugate vaccine (Hib) or DTaP-IPV alone at 3, 5 and 12 months of age [30].

Between March 1, 1999, and February 28, 2000, the DTaP was routinely used at Child Health Centers in 8 of the 11 communities (with 85% of the birth cohort) which were included in the *Mass Vaccination Project*. Infants vaccinated

during this period were not participating in any trial, but cases of itching nodules were reported to us. In the remaining three communities, a pentavalent DTaP-IPV-Hib vaccine (Pentavac<sup>®</sup>, Aventis-Pasteur) was introduced. From March, 2000, this vaccine was used for routine infant vaccination in the whole former study area.

### 2.3. Vaccines, aluminium content, mode and site of administration

The pertussis toxoid (pertussis toxin inactivated with H<sub>2</sub>O<sub>2</sub>) was produced by North American Vaccine Inc., MD, USA (now acquired by Baxter Vaccine AG, Austria). The diphtheria and tetanus toxoids and the IPV were produced by Statens Serum Institut (SSI), Denmark. SSI also performed the final formulation of all vaccines, including the adsorption to an aluminium hydroxide gel (Alhydrogel<sup>®</sup>, Superfos (now Brenntag Biosector), Denmark). The aluminium adsorption was performed by mixing the aluminium hydroxide and the vaccine antigen(s). The adsorption is close 100%, checked by Rocket immunoelectrophoresis (for the DT toxoids) and by enzyme link immunosorbent assay (for the aP and polio components) (personal communication, Kaare Hasløv, Quality Control Department, SSI, Copenhagen, Denmark). The aluminium content in the vaccines corresponds to 0.5 mg aluminium per dose except in the DTaP-IPV, where the amount is 1 mg per dose.

The vaccines were injected subcutaneously (s.c.) in the *Efficacy Study*, *Control Children Study* and in the *Mass Vaccination Project* through September 1998. In the *Booster Study*, *Combination Vaccine Study*, *Mass Vaccination Project* from October 1998 and during routine vaccination after the studies, the vaccines were injected intramuscularly (i.m.) (Table 1). All infants were vaccinated in the left thigh, and children older than 12 months in the left upper arm. If an itching nodule was observed after the first or second dose, the following dose was given in the opposite limb unless the vaccination series was interrupted.

#### 2.4. Finding and following children with itching nodules

In the *Mass Vaccination Project*, the parents were asked to report suspected vaccine reactions either when the child came for its next vaccination or directly to the staff of the Vaccine Study. In the other studies, structured interviews were performed 1 week after each vaccination. During 1997, a structured follow-up of known cases of itching nodules was initiated with regular telephone interviews and a yearly questionnaire. From 2000, all Child Health Centers, school nurses, pediatricians and dermatologists in the area were informed regularly about itching nodules and their relation to the vaccination, with a request that all suspected cases should be referred to the Vaccine Study physicians. The present report includes all cases of itching nodules after vaccination with the study vaccines from SSI which were known by April 30, 2002.

#### 2.5. Testing for delayed (type IV) hypersensitivity to aluminium

From September 2000, all children with itching nodules were offered patch testing with aluminium together with their siblings without symptoms. The children were patch tested on the upper part of the back with aluminium in two forms, aluminiumchloridehexahydrate 2% in petrolatum (Chemotechnique Diagnostics, Sweden) using the manufacturer's plastic IQ Chamber, and metallic aluminium, using an empty Finn Chamber (Epitest, Finland). All applications of the test material were made by two specially trained nurses or one of the authors (EB). The patches were removed after 2 days and the test was read the next day by the authors (AI and/or EB). The results were interpreted according to recommendations of the International Contact Dermatitis Research Group. Positive reactions from + to +++ were regarded as expressions for a type IV hypersensitivity.

#### 2.6. Statistics

Proportions were compared by Fisher's exact test. Incidence rates were tested by comparison of two Poisson distributions. All *P*-values are two-tailed.

#### 2.7. Ethics

All vaccine trials were approved by the Ethics Committee, Göteborg University and by the Medical Products Agency, Uppsala, Sweden. The testing for aluminium hypersensitivity was approved by the Ethics Committee, Göteborg University. All parents gave written approval of the participation of their children in vaccine trials and patch testing.

### 3. Results

#### 3.1. Incidence

Out of about 76,000 vaccinees, 645 (0.8%) children with itching nodules were known by April 30, 2002. The incidence in the different studies is shown in Table 1. Cases occurred in all studies and after all vaccine formulations (DT, DTaP, aP, DTaP-IPV). The incidence in the DTaP and DT groups in the *Efficacy Study* were the same. In the *Mass Vaccination Project*, the incidence in the groups which had received two or three doses of aluminium adsorbed DT before entering the project were significantly higher than among the infants who had not received any vaccines previously ( $P < 0.00001$ ).

#### 3.2. Subcutaneous versus intramuscular injection

Itching nodules were seen after both subcutaneous and intramuscular injection. Altogether, 22 children with itching nodules had received all their vaccinations intramuscularly (Table 1). In the *Mass Vaccination Project*, itching nodules occurred in 9 out of approximately 2800 infants (0.32%) who received all three doses of DTaP intramuscularly from October, 1998 through February, 1999.

#### 3.3. Age, heredity and ethnicity

The 645 children (386 girls and 259 boys) were 3 months–14 years old at the onset of symptoms (median 3 years) and belonged to 594 families. In families with more than one child, totally 471 brothers and sisters to the itching index child also received a vaccine produced by SSI and of those, 51 (11%) developed itching nodules.

The origin of the families was known for 635 of the 645 children. In 134 (21%) of the families, one or both parents were immigrants in the first or second generation from 52 nations in Europe, Africa, Asia and the Americas.

#### 3.4. Clinical course

Itching nodules appeared after the first vaccination in 28 children. Of those, seven were infants who had never received any vaccination before. In 117 children, the itching started after the second vaccination and in 494 after the third. One child had onset after the fourth, and five children

Table 2  
Condition and duration of symptoms for 627 of 645 children with itching nodules as reported at latest follow-up (September 2001–April 2002)

	Nodules	Itching	No. of cases (%)	Median follow-up time (range)
Still itching				
Unchanged symptoms	Unchanged	More or less continuous	55 (9)	42 months (6–68)
Improved	Diminished or appearing intermittently	Intermittent, with free periods for some weeks	236 (37)	52 months (6–111)
Nearly recovered	Appearing intermittently or vanished	Intermittent, with free periods for some months	182 (29)	55 months (22–104)
Recovered	Vanished for $\geq 6$ months	None during $\geq 6$ months	154 (25)	37 months (1–82) <sup>a</sup>

<sup>a</sup> Median duration (range).

Table 3  
Results of patch testing for aluminium hypersensitivity type IV in children with itching nodules and in their siblings without itching nodules

	Median age (years) at time of testing (range)	Numbers positive/numbers tested (%)
Children with itching nodules	6 (1–18)	352/455 (77) a
Siblings without itching nodules who received at least one dose of an SSI vaccine	6 (1–15)	17/211 (8) b
Siblings without itching nodules who were not vaccinated with an SSI vaccine (but received aluminium phosphate adsorbed DT in infancy)	13 (6–29)	0/54 (0) c

a vs. b:  $P < 0.0001$ , b vs. c:  $P = 0.028$ .

after the sixth dose. The median interval between the vaccination which preceded the symptoms and the onset was 3 months (range 2 weeks–5 years).

The clinical course could be followed in 627 of the 645 children until they recovered or until the last interviews, which were performed in September 2001–April 2002. The median follow-up time was 5.5 years (range 1–9 years) (Table 3). In typical cases, the onset of symptoms was noticed when the child scratched on one or a few subcutaneous nodules at the injection site. The nodules were 3–25 mm in size, firm, oblong or rounded and mostly not tender. Periods of intense itching and swelling of the nodules, causing the child to scratch until the skin was bleeding, alternated with periods with milder symptoms. In 251 (39%) of the children a relation between exacerbations of the symptoms and intercurrent upper respiratory tract infections (common cold, otitis, tonsillitis) was noted. Hypertrichosis and/or hyperpigmentation and/or a local eczematous reaction was observed in the itching area in 207 children (32%). Other local skin manifestations like excoriations and lichenification were found in most children. Symptomatic treatment, including topical steroids and/or covering the itching area with a thin hydrocolloid bandage, had only moderate and temporary effect.

In 75 children who received their vaccinations in two limbs, itching nodules appeared at both sites. Four children had itching nodules on three sites.

The prognosis, as it can be evaluated by the latest follow-up, is shown in Table 2. After months or years of itching, the symptoms eventually decrease; the nodules resolve, the itching becomes intermittent and less intense and the skin alterations recede.

So far, 75% of the children still have symptoms after a median duration of 4 years (0.5–9 years).

### 3.5. Aluminium hypersensitivity

Altogether 455 children with itching nodules and 265 of their symptomless siblings were patch tested for delayed hypersensitivity to aluminium (Table 3). Of the siblings, 211 had received at least one dose of an SSI vaccine (in some cases preceded by two to three doses of aluminium phosphate adsorbed DT vaccine; Table 4). The remaining 54 had received the Swedish aluminium phosphate adsorbed DT in infancy, but no SSI vaccine. The children with itching nodules had a significantly higher rate of positive reactions (77%) than their symptomless siblings who were vaccinated with the same vaccines from SSI (8%,  $P < 0.0001$ ). The 54

Table 4  
Age, history of vaccination, and interval between vaccination and patch testing for 17 siblings without local reactions but with type IV hypersensitivity to aluminium after vaccination with aluminium hydroxide adsorbed vaccines from SSI

Vaccination schedule in Mass Vaccination Project	Number of children	Number of doses of aluminium-adsorbed DT received prior to the study	Interval from last vaccination to patch test (years)	Age at patch testing (years)
DTaP $\times$ 3	1	–	3	4
DTaP + aP + aP	5	2	3–4	5–6
aP $\times$ 3	11	3	2–4	6–9

siblings who had only received the Swedish DT, but never an SSI vaccine, were all negative in the test. Fifteen of the 22 intramuscularly injected children were tested, all with positive reactions.

#### 4. Discussion

The incidence of persistent itching nodules after vaccination with aluminium adsorbed vaccines has not been estimated previously. To our knowledge, only about 100 cases have been described during the last 40 years [1,2,5–21], even though several hundred million doses of aluminium adsorbed vaccines have been given since their introduction during the 1940s.

The present study describes an unexpectedly high incidence of persistent itching nodules after vaccination with aluminium hydroxide adsorbed aP, DTaP and DT from a single producer. The true incidence is probably even higher than the documented incidence of 0.8%, because the persistence and severity of this reaction was not obvious during the first years, and parents and medical staff often failed to see the connection between the itching nodules and the vaccination.

It is commonly accepted that itching nodules are induced by the aluminium adjuvant and not the vaccine antigens, since aluminium particles have been demonstrated in the nodules and since they are reported after several different aluminium adsorbed vaccines and hyposensitizing extracts [6,8,15,18,20–22,24–26]. This is confirmed by the present study in which cases occurred after DT, DTaP, aP and DTaP–IPV.

It is apparent that the risk for itching nodules increased with the number of doses of an SSI vaccine and with the number of doses of aluminium phosphate adsorbed DT given before vaccination with the SSI vaccines. There have, however, been no reports of itching nodules after the aluminium phosphate containing Swedish DT alone, though it has been given in four doses to approximately 1,700,000 children in Sweden from 1979 to 1996. Apart from our active search for adverse events in the vaccine trials, we have no explanation for the high incidence of itching nodules and aluminium allergy among the children who received an SSI vaccine.

Persistent itching nodules occurred after intramuscular as well as after subcutaneous administration. The incidence of itching nodules among the intramuscularly injected DTaP recipients in the *Mass Vaccination Project* (9/2800; 0.32%) is comparable to the subcutaneously injected DTaP group in the *Efficacy Study* (6/1724; 0.35%). However, the total number of intramuscular injections given in the trials was so much lower than the number of subcutaneous injections that we refrain from further statistical comparisons. Further, all 10 infants who received DTaP in clinical routine 1999–2000 were injected intramuscularly. Finally, all 15 intramuscularly injected itching infants, who were patch tested for aluminium had positive results.

Probably several individual factors contribute to whether a child will develop itching nodules and aluminium sensitization or not. According to the present study, heredity could be one of these factors. Ethnicity does not seem to be decisive, as children in families originating from the whole world were afflicted in about the same proportions as in the total population in Göteborg.

Contact allergy to aluminium is considered to be extremely uncommon in adults [3,4,11,16,23,24]. Most cases described have occurred after injections with aluminium containing vaccines [4,9–13,16,17,31] and hyposensitizing extracts. The frequency in children has never been investigated. In the present report, a high incidence and a strong association between itching nodules and aluminium sensitization was demonstrated. Contact allergy to aluminium in individuals without any itching reaction after aluminium adsorbed vaccines has, to our knowledge, not been reported before [4,9,13,24], but in the present study 8% of the symptomless children who had received an SSI vaccine had a positive patch test to aluminium. In contrast, the 54 recipients of aluminium adsorbed DT or DTwP vaccines from other manufacturers all had negative tests.

A risk of additional itching nodules and aggravation of the aluminium sensitization after future vaccinations with aluminium adsorbed vaccines (e.g. tetanus, DT, DTP, pertussis, hepatitis A and B, tick born encephalitis) can be anticipated. In agreement with others [9,11,13,14,16,26], we recommend that children with a history of persistent itching nodules and/or delayed hypersensitivity to aluminium should avoid aluminium adsorbed vaccines, if possible, and particularly vaccines manufactured in the same manner as the SSI paediatric vaccines.

It has been suggested that contact allergy to aluminium in children may be transient, since it is almost never observed in clinical routine patch testing with Finn Chambers in adults [11,24]. Kaaber et al. [31] found that two of four patients with positive patch tests were negative at a renewed test 4 years later. Whether this will occur in the children described here is a subject for future studies.

#### 5. Conclusions

Persistent itching nodules and type IV hypersensitivity to aluminium was observed among children who received aluminium hydroxide adsorbed DT, DTaP and aP vaccines from SSI in a higher frequency than has ever been reported. Aluminium sensitization has also, for the first time, been demonstrated in children without any local reaction after vaccination. The intense and prolonged symptoms have caused much anxiety, irritation and frustration in the families, sometimes leading to incomplete vaccination and refusal to vaccinate younger siblings. The benefits of vaccination for the general health of children in the world cannot be questioned, but it is of vital

importance that side effects are studied and reported carefully in a time when fear for vaccine reactions can overwhelm the respect for the diseases themselves [32]. Therefore, the seemingly trivial adverse event described in this report motivates research about the specificities of SSI vaccines regarding their potential to induce itching nodules and trigger aluminium sensitization. In our opinion, alternatives to aluminium adjuvants should be considered.

## Acknowledgements

We thank Professor Cecilia Björkelund, Department of Primary Health Care, Göteborg University and Assistant Professor John Taranger, the Göteborg Primary Health Care, for their support; all nurses, especially Lisbeth Söderström and Tordis Andrén for their devoted work with the children and their families, and Valter Sundh (BSc) for data management and statistical calculations.

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