

Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence

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We have reviewed evidence of adverse events after exposure to aluminium-containing vaccines against diphtheria, tetanus, and pertussis (DTP), alone or in combination, compared with identical vaccines, either without aluminium or containing aluminium in different concentrations. The study is a systematic review with meta-analysis. We searched the Cochrane Vaccines Field Register, the Cochrane Library, Medline, Embase, Biological Abstracts, Science Citation Index, and the Vaccine Adverse Event Reporting System website for relevant studies. Reference lists of retrieved articles were scanned for further studies. We included randomised and semi-randomised trials and comparative cohort studies if the report gave sufficient information for us to extract aluminium concentration, vaccine composition, and safety outcomes. Two reviewers extracted data in a standard way from all included studies and assessed the methodological quality of the studies. We identified 35 reports of studies and included three randomised trials, four semi-randomised trials, and one cohort study. We did a meta-analysis of data from five studies around two main comparisons (vaccines containing aluminium hydroxide vs no adjuvant in children aged up to 18 months and vaccines containing different types of aluminium vs no adjuvants in children aged 10–16 years). In young children, vaccines with aluminium hydroxide caused significantly more erythema and induration than plain vaccines (odds ratio 1.87 [95% CI 1.57–2.24]) and significantly fewer reactions of all types (0.21 [0.15–0.28]). The frequencies of local reactions of all types, collapse or convulsions, and persistent crying or screaming did not differ between the two cohorts of the trials. In older children, there was no association between exposure to aluminium-containing vaccines and onset of (local) induration, swelling, or a raised temperature, but there was an association with local pain lasting up to 14 days (2.05 [1.25–3.38]). We found no evidence that aluminium salts in vaccines cause any serious or long-lasting adverse events. Despite a lack of good-quality evidence we do not recommend that any further research on this topic is undertaken.

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Aluminium salts were introduced by Glenn and colleagues in 1926 and have become the standard adjuvant in vaccines such as those against diphtheria, tetanus, and pertussis (DTP), *Haemophilus influenzae* type b, pneumococcus conjugates, and hepatitis A and B.¹ Aluminium salts are added to vaccines in the form of alum (potassium

aluminum sulphate), aluminium sulphate, or aluminium hydroxide; the last seems to be the most immunogenic of the three, especially during primary immunisation.¹ Although they have been used as adjuvants in vaccines for decades, aluminium salts have been blamed for the causation of nodules, granulomas, erythema, and a progressive syndrome characterised by muscle wasting and severe fatigue called macrophagic myofasciitis.^{1–4} Assessment of the safety of aluminium in vaccines is important because replacement of aluminium compounds in currently licensed vaccines would necessitate the introduction of a completely new compound that would have to be investigated before licensing. No obvious candidates to replace aluminium are available, so withdrawal for safety reasons would severely affect the immunogenicity and protective effect of some currently licensed vaccines and threaten immunisation programmes worldwide.^{4,5}

We report a systematic review of evidence of adverse events after exposure to aluminium-containing DTP vaccines, alone or in combination, compared with identical vaccines that either did not contain aluminium salts or contained them in different concentrations.

Methods

Searches

We searched the Cochrane Vaccines Field Register of studies on DTP vaccines (at present including 127 extracted reports of primary and linked studies). Methods of assembling the register have been described elsewhere.⁶ We also searched the Cochrane Library (which includes the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects; and the Cochrane Central Register of Controlled Trials [Central]); Medline (OvidWeb 1966 to April week 4 2003); Embase (1980–2003 week 18); Biological Abstracts (SilverPlatter WinSpirs 1985 to February 2003); and Science Citation Index (Web of Science 1981 to May 4, 2003). The search terms used are reported in table 1. The searches included any language. The search of the Cochrane Controlled Trials Register included trial reports identified in the systematic search by hand of the journal *Vaccine*. To identify other published

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Table 1. Search strategies used in the review

	Cochrane Library	Medline	Embase	Biological Abstracts
1	exp Pertussis vaccine/	exp Pertussis vaccine/	Diphtheria pertussis poliomyelitis tetanus vaccine/	Diphtheria-pertussis-tetanus-vaccine
2	Diphtheria-tetanus vaccine/	Diphtheria-tetanus vaccine/	Diphtheria pertussis poliomyelitis tetanus vaccine/	Diphtheria-tetanus-acellular-pertussis-vaccine
3	Diphtheria toxoid/ or tetanus toxoid/	Diphtheria toxoid/ or tetanus toxoid/	Diphtheria pertussis tetanus <i>Haemophilus influenzae</i> type b vaccine/	Diphtheria-tetanus-whole-cell-pertussis-vaccine
4	DtaP	DtaP	Diphtheria pertussis tetanus vaccine/	Pertussis-vaccine
5	1 or 2 or 3 or 4	1 or 2 or 3 or 4	Diphtheria tetanus vaccine/	Pertussis-toxoid
6	Diphtheria toxin/ or pertussis toxin/	Diphtheria toxin/ or pertussis toxin/	Diphtheria vaccine/	Tetanus-toxoid
7	Tetanus toxin/	Tetanus toxin/	Pertussis vaccine/	Diphtheria-toxoid
8	Whooping cough/	Whooping cough/	Diphtheria tetanus toxoid/ or diphtheria toxoid/ or tetanus toxoid/	DTaP or DTacP or DTwP
9	Free text terms: pertus* or whoop* or tetanus or diphtheria or diphteria or diphteria	Free text terms: pertus\$ or whoop\$ or tetanus or diphtheria or diphteria or diphteria	DtaP	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Vaccines/	exp Vaccines/	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	Pertussis-toxin
11	Vaccination/	Vaccination/	Diphtheria toxin/ or pertussis toxin/ or tetanus toxin/	Diphtheria-toxin
12	Immunization/	Immunization/	Pertussis/	Tetanus-toxin
13	Free text terms: vaccin* or immuni* or inoculat*	Free text terms: vaccin\$ or immuni\$ or inoculat\$	Free text terms: pertus\$ or whoop\$ or tetanus or diphtheria or diphteria or diphteria	Pertussis-
14	(6 or 7 or 8 or 9) and (10 or 11 or 12)	(6 or 7 or 8 or 9) and (10 or 11 or 12)	exp Vaccine/	Whooping-cough
15	5 or 14	5 or 14	exp Vaccination/	Free text terms: pertus* or whoop* or tetanus or diphtheria or diphteria or diphteria
16	exp Aluminium compounds/	exp Aluminium compounds/	exp Immunization/	Vaccine- or immunization- or vaccination-
17	Aluminium/	Aluminium/	Free text terms: vaccin\$ or immuni\$ or inoculat\$	Free text terms: vaccin* or immuni* or inoculat*
18	Free text terms: alum or aluminium or aluminium	Free text terms: alum or aluminium or aluminium	(10 or 11 or 12) and (13 or 14 or 15 or 16)	Combination-vaccines
19	16 or 17 or 18	16 or 17 or 18	9 or 17	(10 or 11 or 12 or 13 or 14 or 15) and (16 or 17 or 18)
20	15 and 20	15 and 20	Aluminum or aluminum derivative/	9 or 19
21			Free text terms: alum or aluminium or aluminium	Free text terms: alum or aluminium or aluminium
22			19 or 20	Aluminium-
23			18 and 21	21 or 22
24				20 and 23

The terms given are those used by the database indexers to describe the subject content of the studies unless free-text terms used by the authors of the studies to describe the subject content of their studies are given. For the Science Citation Index we searched for the free-text terms: (DtaP or DTwP or DtacP) or (diphtheria toxoid or tetanus toxoid or pertussis toxoid) or (diphtheria or diphteria or diphteria or tetanus or pertus* or whoop* or pertussis toxin or tetanus toxin or diphtheria toxin) and (vaccin* or immuni* or inoculat*) and (alum or aluminium or aluminium).

and unpublished studies the Science Citation Index was used to identify articles that cite the relevant studies.

Details of retrieved studies were keyed into PubMed, and the "Related Articles" feature was used. Reference lists of all relevant articles obtained and any published reviews were examined for additional studies. The Vaccine Adverse Event Reporting System website was searched (<http://www.vaers.org>; accessed Dec 10, 2003).

We contacted a vaccine manufacturer and the first author of studies identified that seemed to meet the inclusion criteria but for which the decision was difficult owing to incomplete reporting.

Selection and inclusion criteria

We included randomised controlled trials, semi-randomised controlled clinical trials, and comparative cohort studies on which sufficient information was given for us to identify aluminium concentration, vaccine composition, and safety outcomes. To assess the causal relation between exposure to aluminium and subsequent onset of adverse events, we included only studies reporting comparisons of aluminium-containing DTP vaccines (alone or in combination) with identical vaccines that did not contain aluminium or contained the salts in different concentrations. We applied inclusion criteria independently.

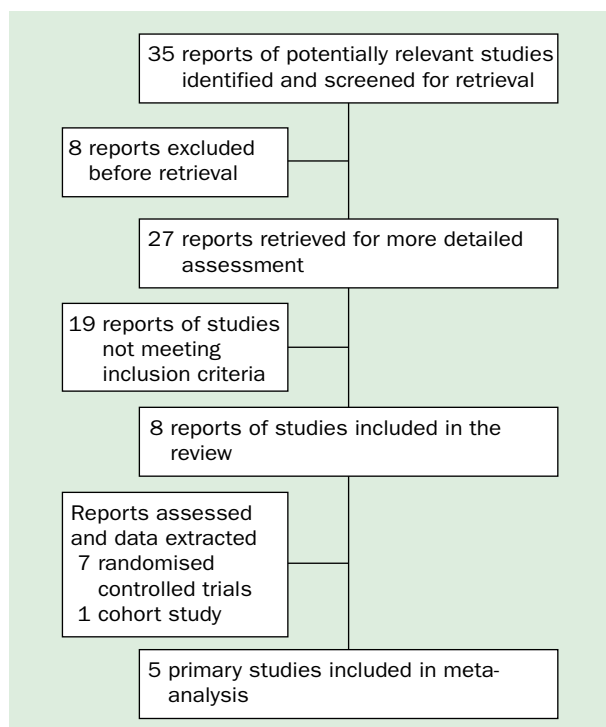


Figure 1. Collection of studies for the review.

Validity assessment, data abstraction, and study characteristics

We used data from available completed extraction sheets within the Cochrane Vaccines Field Register of pertussis vaccines studies and filled new extraction sheets for newly identified studies. We used standard definitions to classify study designs to improve comparability.⁶ Methodological quality was assessed on the basis of the Cochrane Reviewers' Handbook criteria for randomised controlled trials⁷ and the Newcastle-Ottawa Scales for cohort studies.⁸

Quantitative data synthesis

We assessed the possibility of synthesising data by study design, study population, aluminium content or formulation, immunisation route, and outcome by tabulating extracted studies by these variables.

Results

Study flow

We identified 35 reports of studies that possibly met the inclusion criteria. After screening of titles and abstracts, we retrieved 23 reports of studies not included in the Cochrane Vaccines Field Register and four of studies that were listed in the register and had previously been extracted (figure 1). Eight reports that clearly did not meet the inclusion criteria as assessed by title, abstracts, or both, were not retrieved for further assessment (for example, two reported experiments on animals). Two studies in Swedish were translated into English.^{9,10}

We included eight studies in our review: three were classified as randomised controlled trials,^{11–13} four as controlled clinical trials,^{14–17} and one as a cohort study.¹⁸

19 studies were not included. A list of studies with reasons for exclusion is available on *The Lancet Infectious Diseases* website at <http://image.thelancet.com/extras/03ID6016webfr.pdf>.

Study characteristics

Murphy and colleagues¹¹ reported a randomised double-blind trial to test the serological and safety effects of various combinations of DTaP (called extracted pertussis vaccine) and DTwP (whole-cell pertussis) with two different adjuvants (aluminium phosphate or alum) injected intramuscularly. The participants were low-income Hispanic children (n=105) aged 2–3 months at first dose. They were followed up for 24 h after each of the three doses. All vaccine vials were centrally prepared and randomisation was carried out on the basis of a table. Although randomisation and allocation concealment were adequate, poor reporting led to substantial loss of data, which was only partly obviated by statistical manipulation of the confidence intervals around the estimates of effect for one outcome.

Butler and co-workers¹² reported a randomised controlled trial comparing potency and toxicity of three combined DTP vaccines: one was without aluminium hydroxide, and the other two contained aluminium hydroxide, but had differing concentrations of pertussis cells. The vaccines were given by deep subcutaneous injection into the upper arm or thigh to 168 infants. Follow-up was to the day after each vaccination. Randomisation and allocation concealment were not described.

Mark and Granstrom¹³ carried out a randomised double-blind trial in schoolchildren due to have their DT booster vaccine. 235 10-year-old children were assigned either aluminium-phosphate-adsorbed DT or non-adsorbed DT vaccines by deep subcutaneous injection. The follow-up period was 14 days. Randomisation and allocation concealment were not described, though the trial was otherwise well reported.

Aggerbeck and colleagues¹⁴ did a double-blind clinical controlled trial comparing two types of DT vaccines, with different adjuvants (aluminium hydroxide and calcium phosphate) for a booster vaccination in 313 Danish military recruits aged 18–24 years. Vaccines were given by deep subcutaneous injection above the trapezius muscle. Vials were coded and allocation was by alternation. Follow-up for adverse events was 4 weeks after immunisation.

Burland and co-workers¹⁵ reported a semi-randomised controlled trial (no definition of allocation) in 541 children, comparing adsorbed (aluminium hydroxide) DTP vaccine or plain DTP for primary immunisation at 3 months or booster immunisation at 15–18 months. The vaccines were administered by subcutaneous injections. Follow-up was the day after inoculation and day 7. Allocation concealment was not described. Reporting of this study was very poor, with inconsistencies in the reporting of denominators.

Collier and colleagues¹⁶ reported a semi-randomised controlled trial, investigating reactions to two tetanus vaccines: adsorbed tetanus vaccine BP and plain tetanus vaccine BP. Randomisation was based on alternation. The participants were 121 boys and 145 girls aged 15–16 years,

given routine school-leaving tetanus toxoid injections. Follow-up was at days 2 and 7 after injection. Inoculation is likely to have been intramuscular.

Feery and colleagues' double-blind semi-randomised controlled trial¹⁷ compared adverse events after primary immunisation with plain DTwP or adsorbed DTwP (CSL Ltd) 0.5 mL intramuscularly into the upper arm at ages 2 months, 4 months, and 6 months. Follow-up was 2 weeks after each injection. The method of allocation was alternation of children whose parents had given consent. The participants were 542 healthy non-febrile boys and 533 girls aged under 1 year (total 1075 children and 2106 vaccinations).

Pollock and colleagues¹⁸ carried out a cohort study assessing symptoms after primary immunisation with two

DTP preparations (aluminium hydroxide absorbed or plain) or an adsorbed DT preparation in 10 028 infants due their primary course of immunisation; the first dose was due at 3 months, the second 6–8 weeks later, and the third after 4–6 months. No route of administration is stated. The study was badly reported with inconsistencies in denominators and in withdrawals from the groups.

Overall, the methodological quality of included studies was low. Few reports gave details of the randomisation process, allocation concealment, reasons for withdrawals, or strategies to deal with them in analysis. Inconsistencies in reporting, lack of clarity on numerators and denominators, variability of outcome definitions, and lack of outcome definitions led to much loss of data. The important characteristics of included studies are summarised in table 2.

Table 2. Main characteristics of studies included in the review

Ref	Design	Comparison	Population and denominators	Route	Follow-up	Outcomes
11	RCT	DTwP vs DTaP with alum vs DtaP with aluminium phosphate	26 vs 27 vs 28 vs 22 (105) children aged 2–3 months	IM	24 h after each immunisation	Temperature >38.3°C
14	CCT	DT (aluminium hydroxide) vs DT (calcium phosphate)	160 vs 153 (313) recruits (aged 18–24 years)	SC	4 weeks after immunisation	Erythema/induration < 5 cm; severe local reaction; severe systemic reaction
15	CCT	DTP with aluminium hydroxide) vs plain DTP	261 vs 280 (541) children aged up to 18 months	SC	7 days after each immunisation	Local or generalised reactions at 24 h or after inoculation; local reactions at 1 week; cry persistent or of high pitch; collapse or convulsion; bruising or severe local reaction; sterile cyst at site of injection
12	RCT	DTP (aluminium hydroxide) vs DTP plain	47 vs 56 vs 65 (168) children for primary immunisation	SC	24 h after each immunisation	Crying; fretfulness; drowsiness; vomiting; anorexia; rash; erythema; induration; swelling; tenderness; nodule
16	CCT	Tetanus vaccine (aluminium hydroxide) vs tetanus vaccine (plain)	113 vs 120 vs (145) aged 15–16 years	?IM	2 and 7 days after immunisation	Temperature; pain; tenderness; erythema; swelling; lymphadenitis
17	CCT	DTP (aluminium hydroxide) vs DTP plain	350 vs 355 (1075, many lost to follow-up) aged <1 year	IM	2 weeks after each immunisation	Bruising; erythema/induration; irritability or vomiting; fever; persistent crying; persistent screaming; drowsiness; collapse pallor; coldness; convulsions
13	RCT	DT (aluminium phosphate) vs DT (plain)	119 vs 105 (235) children aged 10 years	SC	2 weeks after immunisation	Fever; headache; discomfort; redness; swelling; itching; pain; immediate pain at injection site
18	Cohort	DTP (aluminium hydroxide) vs DTP plain	371 vs 383 312 (10 028) children aged from 3 months	?	Up to 6 weeks after each immunisation	Moderate local reaction (2.8–7.5 cm); large local reaction (>7.5 cm); crying more than usual; crying for >5 h; screaming attacks; feverishness; neurological disorders; myoclonic epilepsy at 1 month after first dose; epilepsy; febrile convulsions 3–6 weeks after vaccination; SIDS within 6 weeks of vaccination; nodule at vaccination site; febrile convulsions at 8 h; respiratory infection at 5 days; convulsions at 5 days; antipyretics or analgesics; GP consultation after immunisation; high-pitched crying/screaming within 48 h; twitching/jerking within 48 h; crying/screaming within 12 h; feverishness within 12 h; upper-respiratory-tract infection between vaccination and first follow-up; vomiting/diarrhoea between vaccination and first follow-up; generalised rash between vaccination and first follow-up

RCT=randomised controlled trial; IM=intramuscular; CCT=controlled clinical trial; SC=subcutaneous; SIDS=sudden infant death syndrome; GP=general practitioner.

Table 3. Summary of meta-analysis by comparison and outcomes with length of follow-up

Symptom and studies	Rates	Odds ratio (95% CI)	
		Fixed-effects model	Random-effects model
Comparison 1: aluminium hydroxide vs no adjuvant in children up to 18 months of age			
Erythema and induration (local) up to 7 days after vaccination ^{15,17}	738/1105 vs 599/1126	1.87 (1.57–2.24)	1.70 (1.07–2.69)
Local reactions up to 7 days after vaccination ^{12,15}	201/486 vs 152/380	1.12 (0.85–1.48)	1.30 (0.52–3.23)
Reactions (all types) up to 24 h after vaccination ^{12,15}	243/616 vs 259/359	0.21 (0.15–0.28)	0.18 (0.08–0.41)
Collapse or convulsions up to 7 days after vaccination (all doses) ^{12,15,17}	1/1626 vs 3/1390	0.34 (0.04–3.27)	0.34 (0.04–3.27)
Screaming, persistent or high-pitched crying up to 7 days after vaccination (first dose) ^{12,17}	11/476 vs 11/397	0.49 (0.42–2.30)	0.99 (0.42–2.30)
Screaming, persistent or high-pitched crying up to 7 days after vaccination (second dose) ^{12,17}	11/455 vs 15/374	0.72 (0.33–1.60)	0.72 (0.33–1.60)
Screaming, persistent or high-pitched crying up to 7 days after vaccination (third dose) ^{12,17}	5/415 vs 5/358	1.09 (0.31–3.79)	1.09 (0.31–3.79)
Screaming, persistent or high-pitched crying up to 7 days after vaccination (fourth dose) ^{12,15,17}	33/1732 vs 41/1390	0.81 (0.51–1.28)	0.50 (0.09–2.70)
Comparison 2: aluminium vs no adjuvants in children aged 10–16 years			
Erythema up to 14 days after vaccination ^{13,16}	96/202 vs 87/191	1.00 (0.52–1.92)	1.01 (0.52–1.93)
Induration/swelling up to 14 days after vaccination ^{13,16}	111/205 vs 92/191	1.29 (0.79–2.09)	1.35 (0.64–2.83)
Pain (local) up to 14 days after vaccination ^{13,16}	69/204 vs 40/191	2.95 (1.25–3.38)*	3.72 (0.44–31.43)
Temperature >37°C up to 14 days after vaccination ^{13,16}	16/205 vs 10/191	1.63 (0.72–3.73)	1.42 (0.42–4.82)

*Significant difference between fixed and random effect model analysis.

Structure of comparisons and quantitative data synthesis

After grouping the main variables (study design, aluminium content, and study population) for possible quantitative pooling of outcome data, we identified two study clusters: the trials comparing the effects of aluminium hydroxide with no adjuvant in children up to 18 months of age^{12,15,17} and those comparing the effects of aluminium adjuvants in older children (aged 10–16 years).^{13,16} Accordingly, we structured our meta-analysis around two main comparisons: vaccines containing aluminium hydroxide versus vaccines containing no adjuvant in children up to 18 months of age and vaccines containing different types of aluminium versus no adjuvants in children aged 10–16 years.

We have tried to present comparisons according to dose whenever the data presentation in the relevant studies allowed. When this was not possible, we have presented all dose data as aggregate. In this case, numerators and denominators in our meta-analysis represent observations rather than individuals (table 3, figure 2).

We carried out two other analyses: by route of injection, and by varying the model of odds ratio analysis, comparing the results of our meta-analysis with fixed-effects and random-effects models to test the possible effects of data heterogeneity. There were insufficient data for analysis by aluminium concentration or the effects of different routes of immunisation.

The results of the meta-analysis and sensitivity analysis are reported in table 3. In younger children, the addition of aluminium hydroxide caused significantly more erythema and induration and significantly fewer reactions of all types than plain vaccines. There was no difference in the rate of

local reactions of all types, collapse or convulsions, or persistent crying or screaming between the two arms of the trials. In older children, there was no association between exposure to aluminium-containing vaccines and onset of (local) induration, swelling, or a high temperature, but there was an association with local pain lasting up to 14 days. This last finding was not significant when analysed by the random-effects model (table 3).

The clinical trials by Aggerbeck and colleagues¹⁴ and Murphy and colleagues¹¹ and the cohort study¹⁸ are one-off comparisons and cannot be readily assimilated into our meta-analysis. The results of the two clinical trials^{11,14} add little information because the range of outcomes and the quality of reporting are so limited that the reported data needed complicated statistical manipulations to aid clarification. The credibility of the results of the large cohort study by Pollock and co-workers¹⁸ is undermined by its inconsistencies.

Discussion

Evidence on the adverse effects of aluminium salts is not plentiful, despite their ubiquitous and long-standing use as adjuvants. We found few comparative studies that assessed the safety of identical vaccines with differing aluminium content. We excluded 19 identified studies because they compared the effects of adjuvants in vaccines of different composition, serological outcomes, or both. Meaningful inference from these studies would not have been possible. Loss of data from the review was further aggravated by the lack of comparability of most of the safety outcomes reported (a known methodological difficulty¹⁹) and near-total absence of outcome definition in the included studies.

Clear definitions could have aided us in our efforts to identify and assemble similar outcomes. We believe we have kept language bias to a minimum by our efforts to locate studies in languages other than English and our success in identifying and translating two Swedish studies^{9,10} (though they were subsequently excluded).

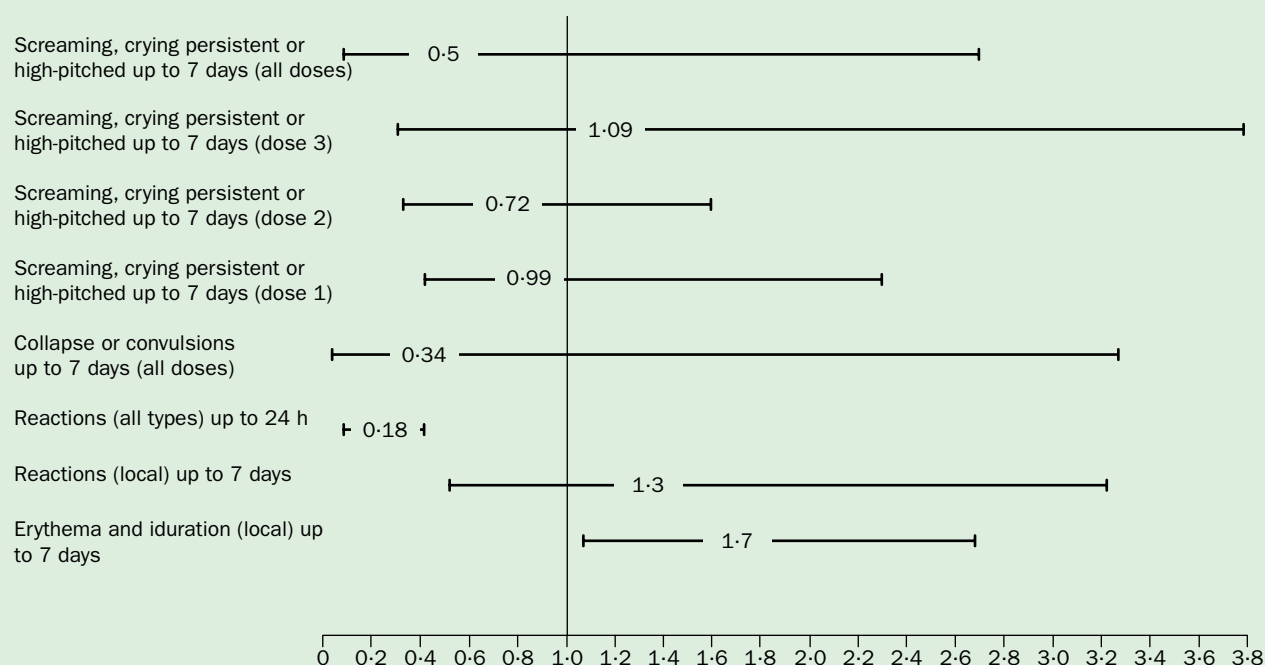
Our meta-analysis of the outcome data has enabled us to reach firm conclusions on the limited amount of comparative data available. Since there was no association with severe adverse events in young children or with induration in older children, we believe any association with chronic outcomes to be unlikely. The results of our review should be interpreted within the limited quantity and quality of available evidence. Within these limits, we found no

evidence that aluminium salts cause any serious or long-lasting adverse events. We found no comparative evidence assessing any possible associations between exposure to aluminium adjuvants and rare and hitherto little known outcomes such as macrophagic myofasciitis.

During the course of the review we became aware of at least two clinical trials that were under way. However, both were testing differing concentrations of aluminium in non-identical vaccines, so the interpretation of any differences is impossible.

The question of further research on the safety of aluminium salts should be judged in the light of the evidence presented in this review, ethical difficulties in exposing controls to non-adjuvanted vaccines, and the known effects

Comparison 1: aluminium hydroxide vs no adjuvant in children up to 18 months of age



Comparison 2: aluminium vs no adjuvants in children aged 10–16 years

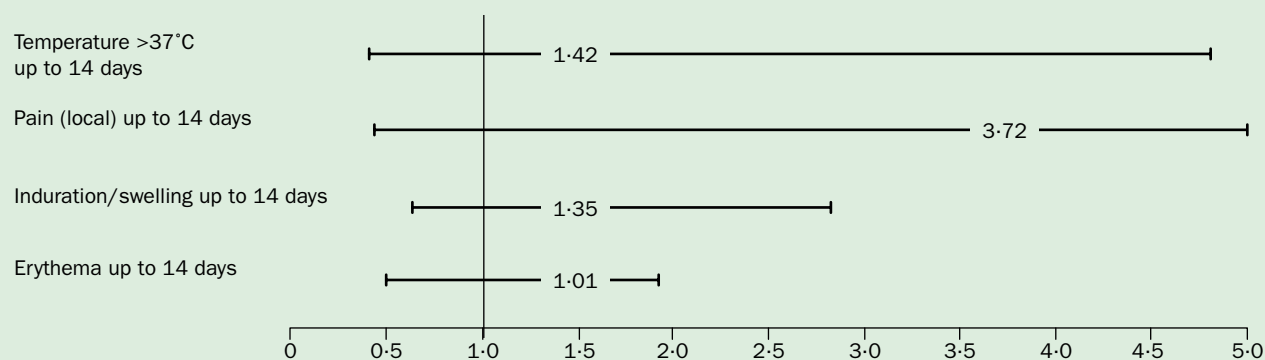


Figure 2. Summary estimates of association between exposure to aluminium-based adjuvants and adverse events expressed as odds ratios and 95% CI (random-effects model).

Search strategy and selection criteria

The search strategy and criteria for selection are described in detail in the Methods section.

of aluminium-containing vaccines in everyday use. Careful assessment of hundreds of thousands of doses of whole-cell and acellular pertussis vaccines and hepatitis B vaccines (most of which contained aluminium adjuvants) derived from large population trials and cohort studies has shown no evidence of serious or long-term effects.^{6,20} We doubt whether there is sufficient evidence to support further

research on the topic or a potentially far-reaching decision such as the replacement of aluminium salts in vaccines.

Acknowledgments

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Conflicts of interest

TJ owns shares in Glaxo SmithKline, manufacturer of some aluminium-containing vaccines. The funding source had no role in the design or conduct of the study; collection, analysis, or interpretation of data; the writing of this report; or the decision to submit it for publication.

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