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

Jefferson T, Rudin M, Di Pietrantonj C

CRD summary
The evidence of adverse effects following immunisation with aluminium-containing diphtheria, tetanus and pertussis (DTP) vaccines was reviewed. The authors concluded that no evidence of any serious or long-lasting effects was found. The authors' conclusions seem reasonable, but the limited quantity and poor quality of the evidence on which they are based should be kept in mind.

Authors' objectives
To review the evidence of adverse effects following immunisation with aluminium-containing diphtheria, tetanus and pertussis (DTP) vaccines, alone or in combination, compared with identical vaccines that did not contain aluminium salts or that contained them in different concentrations.

Searching
Several sources were searched without language restrictions, up to May 2003, including MEDLINE, EMBASE, the Cochrane Library, the Cochrane Vaccines Field Register, DARE, Biological Abstracts, Science Citation Index, and the Vaccine Adverse Event Reporting System website. Search terms were reported. Reference lists of relevant papers and reviews were also searched.

Study selection
Studies that compared aluminium containing diphtheria, tetanus and pertussis (DTP) vaccines, alone or in combination, with identical vaccines that did not contain aluminium or contained the salts in different concentrations were eligible for inclusion. Randomised controlled trials (RCTs), controlled clinical trials (CCTs) and comparative cohort studies were included provided they reported the aluminium concentration used, the vaccine composition and safety outcomes.

The included studies were mainly of children under 18 months old; there were single studies of 10 year old children, 15 to 16 year old children, and adults. Most of the studies compared aluminium hydroxide or aluminium phosphate containing DTP or DT vaccine to the same vaccine with no adjuvant. Where reported, the mode of administration was intramuscular or subcutaneous.

More than one reviewer independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality using criteria from the Cochrane Reviewers Handbook (Version 4.1.4) for RCTs and the Newcastle-Ottawa Scale for cohort studies.

Data extraction
Two reviewers independently extracted data. The adverse event rates were extracted based on the number of observations.

Methods of synthesis
Pooled odds ratio (OR) and 95% confidence interval (CI) were obtained using fixed-effect model (with random-effects model for sensitivity analysis), grouped by type of comparison: studies comparing aluminium hydroxide to no adjuvant in children up to 18 months old; and studies comparing any type of aluminium to no adjuvant in children 10 to 16 years old.

Results of the review
Eight studies were included in the review: three RCTs (508 participants); four CCTs (2,074 participants); and one cohort study (10,028 participants). The overall study quality was described as low, reporting was poor, and there was
limited information on how specific adverse events were defined or variability in definition. Three studies (one RCT, one CCT and the cohort study) were excluded from the synthesis; two did not use an adjuvant comparator; the cohort study was described as having inconsistencies. Length of follow-up in the studies ranged from 24 hours after each immunisation to six weeks.

**Aluminium hydroxide versus no adjuvant in children up to 18 months old:** There was significantly more erythema and induration up to seven days after vaccination containing aluminium hydroxide compared to no adjuvant (OR 1.87, 95% CI 1.57 to 2.24; 2,231 observations), and significantly fewer reactions of all types up to 24 hours after vaccination (OR 0.21, 95% CI 0.15 to 0.28; 975 observations). There were no statistically significant between group differences for the other adverse events.

**Aluminium of any type versus no adjuvants in children from 10 to 16 years old:** There was significantly more local pain up to 14 days after vaccination containing aluminium compared with no adjuvant (OR 2.95, 95% CI 1.25 to 3.38; 395 observations); this was not statistically significant in the random-effects sensitivity analysis. There were no statistically significant between group differences for the other adverse events.

**Authors’ conclusions**
No evidence was found that aluminium salts in vaccines cause any serious or long-lasting effects.

**CRD commentary**
The review had clearly stated inclusion criteria and a number of relevant sources were searched for studies. There were no restrictions on publication status or language, reducing the risk of relevant studies being missed. Appropriate methods were used to reduce error and bias in the review processes.

The quality of studies was assessed and the findings of the review were discussed in the context of the poor quality evidence available. The analysis seemed appropriate, albeit restricted by the small number of studies included.

The authors’ conclusions seem reasonable, but the limited quantity and poor quality of the evidence on which they are based should be kept in mind.

**Implications of the review for practice and research**
**Practice:** The authors stated that they doubt whether there is sufficient evidence to support the replacement of aluminium salts in vaccines.

**Research:** The authors stated that, despite the lack of good quality evidence, they do not recommend that any further research on this topic is undertaken due to the findings of the review, the ethical issues related to exposing control groups to vaccines with no adjuvant, and the known effects of aluminium-containing vaccines in every-day use.

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