Aluminium adjuvants in vaccines and potential health effects: systematic review

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ABSTRACT

OBJECTIVE

To systematically review and critically appraise human evidence on potential health effects of aluminium adjuvanted vaccines.

DESIGN

Systematic review following PRISMA (preferred reporting items for systematic review and meta-analysis) 2020 guidelines.

DATA SOURCES

Six databases and trial registries were searched from inception to 3 March 2023 then updated to 27 November 2025. Reference lists of eligible studies were also screened.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Human studies assessing health outcomes after aluminium adjuvanted vaccination, including randomised controlled trials, cohort studies, case series, and ecological studies. Investigational vaccines, case reports, and review articles were excluded.

DATA EXTRACTION AND SYNTHESIS

Two reviewers screened studies (with AI assistance for the 2023-25 update), extracted data, and assessed risk of bias (using RoB 2.0, ROBINS-I, or an adapted tool for case series). Certainty of evidence was rated using GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

RESULTS

The review included 59 studies (37 case series, 11 randomised controlled trials, nine cohort studies, two ecological studies). High quality evidence from randomised controlled trials and large cohorts consistently showed no association between aluminium adjuvanted vaccines and serious or long term health outcomes, such as asthma, autism spectrum disorders, or other chronic conditions. Studies on macrophagic myofasciitis were generally small and methodologically limited, and did not provide credible evidence of a causal association (very low certainty). Localised persistent nodules or granulomas were observed infrequently after diphtheria-tetanus-pertussis vaccines, consistent with delayed type hypersensitivity (<1%, self-limited; moderate to low certainty). For common adverse events (eg, headache, myalgia), high certainty randomised controlled trials found no consistent increase in risk with aluminium adjuvanted formulations. When differences were observed, they were small and predominantly mild to moderate in severity. Evidence was dominated by methodologically limited studies, with most case series and ecological studies at serious or critical risk of bias. Conclusions are primarily supported by higher quality randomised controlled trials and cohort evidence.

CONCLUSIONS

Current evidence does not support causal associations between aluminium adjuvanted vaccines and serious or long term health outcomes. The most consistently documented reactions were persistent nodules or granulomas that are uncommon, local, and self-limited hypersensitivity reactions. These findings are broadly consistent with post-licensure surveillance findings. The predominance of methodologically limited studies for some outcomes highlights the need for higher quality research.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42023462831.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Post-licensure surveillance has broadly supported the safety of aluminium adjuvanted vaccines, although concerns about potential long term effects continue to arise in scientific and public settings

The cumulative human evidence addressing these questions has been fragmented and methodologically variable, and has not recently been comprehensively synthesised across outcomes

WHAT THIS STUDY ADDS

Current evidence does not support causal associations between aluminium adjuvanted vaccines and serious or long term health outcomes such as autism spectrum disorder, asthma, and autoimmune conditions

Persistent nodules or granulomas appear to be associated with aluminium adjuvanted vaccines and they are usually uncommon, local, and self-limited

These findings are consistent with the broader post-licensure safety evidence base, which supports continued use of aluminium adjuvanted vaccines in immunisation programmes

Introduction

Since their introduction by Glenny and colleagues in 1926, aluminium salts have become the most widely used vaccine adjuvants worldwide, incorporated into vaccines against diphtheria, tetanus, and pertussis (including combination vaccines), pneumococcus, meningococcus, human papillomavirus, hepatitis A and B.[1] These adjuvants, typically formulated as aluminium hydroxyphosphate sulfate, aluminium phosphate, or aluminium hydroxide, play a critical part in enhancing immune responses and reducing the antigen dose and number of required vaccine administrations needed for protection.[2]

Despite decades of post-licensure surveillance, questions about potential long term effects of aluminium adjuvanted vaccines continue to arise in scientific and public settings, informed by a body of literature including case reports, narrative reviews,

and preclinical research.[3-6] The human evidence addressing these claims has remained fragmented and methodologically variable, and has not recently been comprehensively synthesised.[7-10]

Post-licensure surveillance detects safety signals in real time but does not systematically synthesise cumulative human evidence across outcomes and study designs. To address this gap, a rigorous systematic review was conducted to critically appraise human evidence on health effects and aluminium adjuvanted vaccines, with the objective of supporting evidence based decision making and public health communication.

Methods

Protocol registration

This systematic review followed PRISMA (preferred reporting items for systematic review and meta-analysis) 2020 guidelines and Cochrane guidance.[11] The protocol was registered in PROSPERO (CRD42023462831).[12]

Search strategy

A comprehensive search strategy was developed in Medline (Ovid) by a research librarian and reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist (supplementary table 1).[13] English and French studies were eligible based on reviewers' language proficiency. Animal only studies and editorials were excluded at the search stage to restrict the review to primary human evidence.

The Medline (Ovid) strategy was adapted for Embase (Ovid), Global Health (Ovid), Cochrane Central Register of Controlled Trials (Ovid), ProQuest Public Health, and Scopus (supplementary tables 2-6). We also searched ClinicalTrials.gov, the EU Clinical Trials Register, and the World Health Organization (WHO) International Clinical Trials Registry Platform (supplementary tables 7-9). Searches were first conducted on 3 March 2023 and updated on 27 November 2025. Records were deduplicated using RefWorks (ProQuest LLC, Ann Arbor, MI, USA) and uploaded to DistillerSR (Evidence Partners Inc, Ottawa, Canada) for screening.

Study selection

Screening forms were piloted before use. Two reviewers (PD-P and JC) independently screened titles and abstracts and full text for the 2023 search. Disagreements were resolved by consensus (PD-P and JC) or third reviewer (JZ) adjudication. We used an AI assisted tool, otto-SR, to support screening of records identified in the 2025 updated search (appendix 1).[14] For the 2025 search, all records were flagged as potentially eligible, uncertain, or excluded by otto-SR and then manually reviewed by one reviewer (PD-P), confirmed through independent verification (JZ). We screened reference lists of included studies for additional eligible publications.

Eligibility criteria

Studies were eligible if they reported on health outcomes after exposure to aluminium adjuvants included in vaccines. Comparative studies were included if aluminium adjuvanted vaccines were assessed against a comparator not including aluminium adjuvants (eg, placebo, no intervention, unadjuvanted vaccine, or with a different adjuvant), or with a vaccine containing another aluminium formulation or concentration because they could inform aluminium formulation or dose-response associations. Studies comparing vaccines with similar aluminium formulations were excluded because they cannot appropriately assess the potential effects of aluminium adjuvant. We also excluded investigational vaccines because findings from products not authorised for use cannot be directly applied to existing immunisation programmes, and individual case reports as they cannot distinguish a vaccine related event from a coincidental occurrence. Case series of two or more people were eligible because they allow preliminary assessment of whether a pattern of association exists. We also excluded narrative or systematic reviews, editorials, and opinion pieces. No restrictions were placed on timing, population, or settings.

We identified potential eligible outcomes through an informal preliminary literature search before protocol registration. Eligible studies were not restricted to these outcomes, and any study reporting on health effects of aluminium adjuvanted vaccines and meeting all other inclusion criteria was included. Potential eligible outcomes included but were not limited to persistent nodules or granulomas, headache, myalgia, hypersensitivity reactions, asthma, autoimmune or autoinflammatory syndrome induced by adjuvants, macrophagic myofasciitis (MMF), antiphospholipid syndrome, chronic conditions, autism spectrum disorders (ASD), primary ovarian insufficiency or failure, complex regional pain syndrome, and postural orthostatic tachycardia syndrome.

Data extraction

A standardised extraction form was developed and piloted. One reviewer (JC or PD-P) extracted all data and a second (PD-P or JC) independently verified entries against source studies. Discrepancies were resolved by discussion, and if unresolved, by adjudication with a third reviewer (JZ). Extracted information included study design, population, exposures and comparators, outcome definitions, analytical approaches, effect measures, and limitations. We contacted authors (three attempts) for missing information.

Quality assessment and results synthesis

Two reviewers (PD-P or JC) independently assessed risk of bias using RoB 2.0 for randomised controlled trials,[15] ROBINS-I for non-randomised studies,[16] and a modified ROBINS-I for case series.[17] Certainty of evidence was assessed with GRADE (Grading of Recommendations Assessment, Development, and Evaluation), considering risk of bias, inconsistency,

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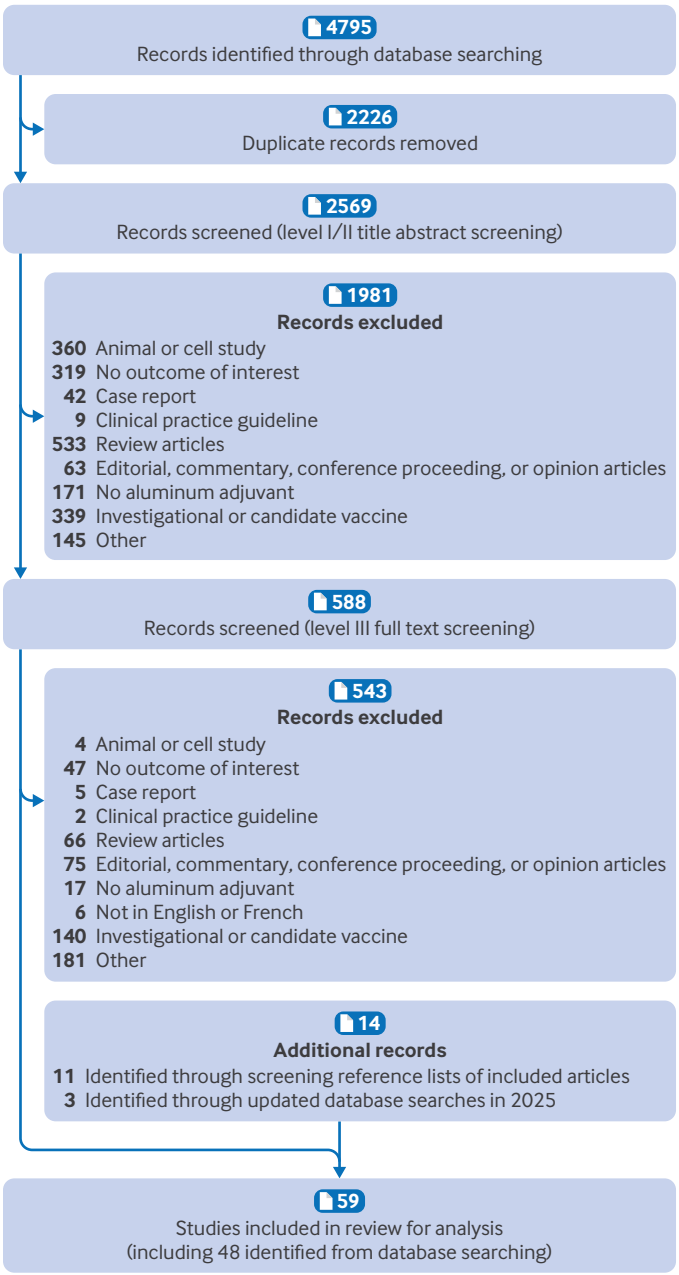

Fig 1 | PRISMA (preferred reporting items for systematic review and meta-analysis) flowchart for new systematic reviews that included searches of databases and registers

indirectness, and publication bias.[18 19] Owing to substantial heterogeneity in study designs, outcome definitions, comparator types, and target populations across included studies, meta-analysis was not feasible and results are presented as a narrative synthesis structured by outcome.

Patient and public involvement

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this systematic review. All health outcomes with eligible studies were included; potential outcomes identified in a preliminary review were used to inform the search strategy, not studies' inclusion or exclusion.

Results

Study selection

Initially, 45 articles met the inclusion criteria,[20-64] 11 more were identified from reference lists,[41 65-74] and three additional studies were identified from the 2025 updated literature search (supplementary figure 1),[75-77] yielding a total of 59 included studies (fig 1).

Study characteristics

Included studies (1971-2025) comprised 37 case series, 11 randomised controlled trials, nine cohort studies (including one single arm cohort), and two ecological studies (table 1, table 2, table 3). Most studies (n=33) enrolled children or adolescents.

Investigated outcomes included ASD,[40 46 75] asthma,[64 75] other chronic conditions,[45 51 59 75 76] MMF,[26 28-31 34 37 38 43 48 49 57 71] headache,[24 36 39 44 50 51 52 62 63 70 77] myalgia,[47 50-52 62 77] and hypersensitivity reactions (ie, Wells syndrome, persistent nodules, granulomas).[21 23 25 32 33 41 42 53 55 56 58 61 65 66 68 73 74 78] No eligible evidence was identified for autoinflammatory syndrome induced by adjuvants, antiphospholipid syndrome, primary ovarian insufficiency or failure, complex regional pain syndrome, or postural orthostatic tachycardia syndrome. Twenty four studies contributed data on more than one outcome.

Risk of bias

Using ROBINS-I, 11 observational studies were assessed: six at critical risk and five at moderate risk mostly owing to confounding (supplementary figure 2). Of the 11 randomised controlled trials assessed with RoB 2.0, eight were at low risk, two had some concerns, and one was at high risk, with issues mostly related to outcome measurement (supplementary figure 3). Most case series were at serious (n=18) or critical (n=13) risk of bias, while six were at moderate risk, with concerns primarily related to participant selection, intervention classification, and selective reporting (supplementary figure 4).

Results of individual studies

Autism spectrum disorders

Three studies reported data on ASD[40 46 75] (table 2, table 3). Two ecological studies examined correlations between aluminium in paediatric vaccine schedules at the time (ie, vaccine administered from birth to 18 months or <6 years) and ASD prevalence in the United States (1991-2010), and other high income countries.[40 46] Both reported positive correlations[40 46]; however, neither measured ASD incidence or severity. Aluminium exposure was estimated from vaccine schedule content, representing a feasible proxy available for population level analyses; however, ecological designs cannot adjust for individual level confounders such as diagnostic changes, increased clinical and public awareness of ASD, genetic factors, or environmental exposures, limiting their ability to support causal inference. Both studies were judged at

Table 1 | Characteristics of studies performed from 1971 to 2003

Author, year	Country	Study design	Study period	Population	Intervention	Control	Outcome	Risk of bias
Erdohazi, 1971[20]	England	Case series	1969-70	Children with lump or nodule (n=2)	Aluminium hydroxide vaccine (DTP and TT)	NA	Granulomas	Critical*
Pembroke, 1979[21]	UK	Case series	NR	Children with itching nodules at site of previous injections (n=3)	Aluminium hydroxide adsorbed vaccines (DT and DTP)	NA	Persistent nodules, contact allergy	Critical*
Slater, 1982[22]	NR	Case series	NR	Children with subcutaneous nodules (n=3)	Aluminium hydroxide adsorbed vaccine (DTP)	NA	Granulomas	Critical*
Fawcett, 1984[69]	UK	Case series	NR	Patients with single or multiple nodules at the site of previous injections (n=3; 2 children and 1 adult)	Aluminium adsorbed vaccines (DTP, DT, and TT)	NA	Granulomas	Critical*
Veien, 1986[66]	Denmark	Case series	1 January 1982 to 30 June 1986	Patients with itchy lesions at sites of childhood immunisation (n=4; children)	Aluminium hydroxide vaccine (Di-Te-Pol vaccine)	NA	Persistent nodules, contact allergy	Serious*
Cox, 1988[65]	NR	Case series	NR	Children with persistent symptoms at vaccination sites (n=3)	Aluminium adsorbed DTP vaccine	NA	Persistent nodules, contact allergy	Serious*
Cosnes, 1990[68]	NR	Case series	NR	Women with itchy nodules at previous injection sites (n=2)	HBV (Hevac B, Pasteur)	NA	Persistent nodules, contact allergy	Critical*
Kaaber, 1992[23]	NR	Case series	NR	Children who had had granulomas for more than 1 year (n=23)	Aluminium hydroxide vaccine (Di-Te-Pol vaccine)	NA	Granulomas Contact allergy	Serious*
Cominos, 199367	Australia	Case series	NR	Woman with itchy lump (n=2; 1 adolescent and 1 adult)	Aluminium phosphate adjuvant adsorbed tetanus toxoid vaccination	NA	Granulomas	Critical*
Miliauskas, 1993[72]	NR	Case series	NR	Patients with single subcutaneous nodule at site of previous injection (n=4; 3 children and 1 adolescent)	Aluminium adsorbed vaccines (DTP and TT)	NA	Granulomas	Serious*
Blennow, 1994[24]	Sweden	Cohort study	January to June 1990	10 year old children (n=517)	Booster dose of DT vaccine adsorbed to aluminium phosphate	NA	Headache	Critical†
Skowron, 1998[25]	NR	Case series	NR	Adults with persistent nodule at injection site (n=4)	HBV (Genhevac B Pasteur, n=3 and Engerix B, n=1)	NA	Persistent nodules, contact allergy	Critical*
Authier, 2001[26]	France	Case series	NR	Seven patients with MMF with symptomatic demyelinating central nervous system disorder (all adults)	Aluminium containing vaccines (HBV, and tetanus)	NA	MMF	Serious*
Bordet, 2001[27]	NR	Case series	NR	Children with subcutaneous nodules at previous injection site (n=3)	Aluminium adsorbed D TwP-IPV (Tetracoq vaccine)	NA	Granulomas	Serious*
Chérin, 2001[71]	France	Case series	1978-99	Three patients with inclusion body myositis and associated MMF (all adults)	Aluminium containing vaccines (HBV, HAV, and tetanus)	NA	MMF	Serious*
Gherardi, 2001[28]	France	Case series	1993 to 31 August 1999	All patients with MMF detected during study period (2 children and 48 adults)	Aluminium hydroxide containing vaccines (HBV, HAV, and tetanus)	NA	MMF	Moderate*
Guis, 2002[29]	France	Case series	1993-97	Two 64 year old identical twins with MMF	HBV (Engerix B containing aluminic hydroxide)	NA	MMF	Serious*
Lacson, 2002[30]	North America	Case series	NR	Two children with MMF	Age appropriate immunisation	NA	MMF	Critical*
Authier, 2003[31]	France	Case series	NR	Consecutive patients with MMF (n=30, adolescents and adults)	Aluminium containing vaccine before onset of symptoms	NA	MMF	Critical*
Bergfors, 2003[78]	Sweden	Case series (based on participants from multiple studies or trials)	1991-2002	Infants and children with itching nodules who participated in vaccine studies (n=645)	Aluminium hydroxide adsorbed DT, DTaP, and aP vaccines	NA	Persistent nodules, contact allergy	Moderate*

aP=acellular pertussis; DT=diphtheria-tetanus; DTaP=diphtheria-tetanus-acellular pertussis; DTwP-IPV=diphtheria-tetanus-whole cell pertussis inactivated poliovirus vaccine; DTP=diphtheria-tetanus-pertussis; HAV=hepatitis A vaccine; HBV=hepatitis B vaccine; HPV=human papillomavirus; MMF=macrophagic myofasciitis; NA=not applicable; NR=not reported; TT=tetanus toxoid.
*Risk of bias assessed using modified Cochrane Risk of Bias in Non-randomised Studies in Interventions (ROBINS-I) tool.
†Risk of bias assessed using Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.[16]
‡Risk of bias assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[15]

critical risk of bias and the certainty of evidence rated very low (table 4 and supplementary table 10).

A large nationwide Danish cohort study (1997-2020, n=1 224 176) assessed cumulative aluminium exposure from vaccines received in the first two years of life and found no increased risk of neurodevelopmental disorders overall (adjusted hazard ratio 0.93, 95% confidence interval (CI) 0.90 to 0.97) or ASD specifically (0.93, 0.89 to 0.97; incidence 141 per 100 000 person years), with no dose-response association.[75] Risk of bias and certainty were rated moderate (table 4 and supplementary table 10).

Table 2 | Characteristics of studies performed from 2005 to 2015

Author, year	Country	Study design	Study period	Population	Intervention	Control	Outcome	Risk of bias
Bergfors, 2005[32]	Norway, Sweden	Case series	May 1999 to April 2005	Children with pruritic nodules (n=19)	DTaP-IPV-Hib (Infanrix, Pentavac)	NA	Persistent nodules, contact allergy	Moderate*
Bovier, 2005[70]	Switzerland	RCT, crossover trial	NR	Healthy adults (n=118)	Aluminium adsorbed HAV (Havrix 1440)	Virosomal HAV (Epaxal)	Headache	Low‡
Maubec, 2005[33]	NR	Case series	1993-2003	Patients with persistent cutaneous lesions at site of previous injection (n=9; adolescent and adults)	Aluminium hydroxide adsorbed HBV and HAV vaccines (Havrix, Engerix B and GenHevac B)	NA	Persistent lumps or nodules, contact allergy	Serious*
Rivas, 2005[34]	Spain	Case series	January 1998 to December 2003	Seven children with MMF	HBV at 0, 2, and 6 months and TT vaccine at 2, 4, 6, and 18 months	NA	MMF	Moderate*
Chong, 2006[35]	NR	Case series	NR	Patients with persistent deep dermal and subcutaneous swellings (n=14; children, adolescents, and adults)	Aluminium hydroxide vaccines (HBV, TT, DT)	NA	Granulomas	Critical*
Clarke, 2006[36]	UK	RCT phase 4	19 August 2003 to 31 August 2004	Healthy people aged 2 years and older (n=540; children, adolescents, and adults)	Aluminium adsorbed HAV (Havrix Monodose for adults and Havrix Junior in children <16 years)	Aluminium free virosomal HAV (Epaxal)	Headache	High‡
Kalil, 2007[37]	Brazil	Case series	NR	Three children with MMF	Age appropriate immunisation (including HBV)	NA	MMF	Critical*
Lach, 2008[38]	NR	Case series	NR	Eight children with MMF	DTP, MMR, hepatitis B, *Haemophilus influenzae* vaccination	NA	MMF	Serious*
Surquin, 2010[39]	Belgium, Hungary, Czech Republic	RCT phase 3	23 February 2006 to 14 July 2006	Patients ≥15 years with renal insufficiency (n=300; adolescents and adults, likely mostly adults)	Aluminium adjuvanted HBV (FENDrix, HB-AS04)	Non-aluminium adjuvanted HBV (HB-AS02)	Headache	Low‡
Tomljenovic, 2011[40]	United States, UK, Australia, Canada, Sweden, Finland, Iceland	Ecological study	1991-2008	Children and adolescents aged 6-21 years	Aluminium exposure (µg) from paediatric vaccines (given <6 years old) and number of aluminium adjuvanted vaccines in yearly vaccination schedule	NA	ASD	Critical†
Bergfors, 2013[41]	Sweden	Case series	1999-2011	Patients with persistent itching nodules after DTP vaccination (Infanrix and Pentavac) between 1999 and 2011 (n=64; children)	Aluminium hydroxide vaccines (DTaP-IPV and DTaP/IPV-Hib vaccines)	NA	Persistent nodules, contact allergy	Moderate*
Lidholm, 2013[42]	Sweden	Case series	October 2007 to May 2008	Children with itching nodules after vaccination and showing aluminium allergy 5-9 years before (n=241)	Aluminium hydroxide adsorbed DT, DTaP, and aP vaccines	NA	Persistent nodules, contact allergy	Serious*
Ragunathan-Thangarajah, 2013[43]	France	Retrospective single arm cohort study	NR	Consecutive patients with arthro-myalgia previously immunised with aluminium containing vaccines (n=130; adolescents and adults)	Aluminium containing vaccine (ie, HBV, HAV, TT, Revaxis, Infanrix vaccines)	NA	MMF	Critical†
Basavaraj, 2014[44]	India	RCTs phase 1	Phase 1: January-February 2010	Healthy adults aged 18-65 years (n=160)	Aluminium adjuvanted monovalent MDCK based H1N1 pandemic influenza vaccine	Unadjuvanted monovalent MDCK based H1N1 pandemic influenza vaccine; adjuvanted placebo; unadjuvanted placebo	Headache	Low‡
Bergfors, 2014[73]	Sweden	Cohort	2009 to January 2014	Children in Östergötland County, Sweden born in 2008 (n=4758)	DTP-polio-Hib (Infanrix, Pentavac, Prevenar)	NA	Granulomas, contact allergy	Critical†
Konno, 2014[45]	Japan	RCT phase 3	June 2009 to February 2011	Women aged 20-25 years	HPV-16/18 AS04-adjuvanted vaccine (Cervarix, GSK vaccines)	Aluminium free hepatitis A vaccine (Aimmungen, Kaketsuken)	Chronic conditions	Some concerns‡
Nevison, 2014[46]	United States	Ecological study	1991-2010	Children aged 6-17 years	Cumulative amount of aluminium adjuvants administered postnatally by 18 months	NA	ASD	Critical†

(Continued)

Table 2 | Continued

Author, year	Country	Study design	Study period	Population	Intervention	Control	Outcome	Risk of bias
Meulen, 2015[47]	Finland, United States	RCT phase 1	September 2009 to March 2010	Healthy, afebrile children aged 12-15 months who previously completed a 3 dose series of PCV7 (n=90)	Aluminium adjuvanted PCV15, aluminium adjuvanted PCV7	Unadjuvanted PCV15	Myalgia	Low‡
Santiago, 2015[48]	Portugal	Case series	January 2003 to July 2013	Patients with MMF (n=16; adults)	Aluminium containing vaccines	NA	MMF	Serious*
Van Der Gucht, 2015[49]	France	Case series	NR	Patients with MMF and cognitive symptoms (n=76; adults)	Aluminium containing vaccines	NA	MMF	Serious*

aP=acellular pertussis; ASD=autism spectrum disorders; DT=diphtheria-tetanus; DTaP=diphtheria-tetanus-acellular pertussis; DTaP-IPV-Hib=diphtheria-tetanus-acellular pertussis inactivated poliovirus-*Haemophilus influenzae* type b; DTP=diphtheria-tetanus-pertussis; HAV=hepatitis A vaccine; HBV=hepatitis B vaccine; HPV=human papillomavirus; MDCK=Madin-Darby canine kidney; MMF=macrophagic myofasciitis; MMR=measle mumps rubella; NA=not applicable; NR=not reported; PCV=pneumococcal conjugate vaccine (general); PCV7=7-valent pneumococcal conjugate vaccine; PCV15=15-valent pneumococcal conjugate vaccine; RCT=randomised controlled trial; TT=tetanus toxoid.
*Risk of bias assessed using modified Cochrane Risk of Bias in Non-randomised Studies in Interventions (ROBINS-I) tool.
†Risk of bias assessed using Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.[16]
‡Risk of bias assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[15]

Overall, evidence from two methodologically limited ecological studies and one large well controlled cohort does not support a causal association between aluminium adjuvanted vaccines and ASD.

Asthma

Two cohort studies reported data on asthma[64 75] (table 3). A large US retrospective cohort study (Vaccine Safety Datalink, 2008-14, n=326 991) evaluated cumulative aluminium exposure before 24 months and persistent asthma incidence between 24 and 59 months.[64] Adjusted analyses showed modest associations in children with eczema (adjusted hazard ratio 1.26, 95% CI 1.07 to 1.49) and without eczema (1.19, 1.14 to 1.25).[64] However, the statistical significance was not consistently maintained when restricting the analysis to fully vaccinated infants or those who were breastfed. Asthma severity (eg, hospital admission or exacerbation) was not assessed. The study authors attributed the associations in part to unmeasured confounding and exposure misclassifications, and encouraged additional investigations. A recent Danish nationwide cohort study (1997-2020; n=1 224 176) also assessed aluminium exposure from vaccines in the first two years of life and subsequent asthma risk.[75] In adjusted models, cumulative aluminium exposure was not associated with increased asthma incidence (adjusted hazard ratio 0.96, 95% CI 0.94 to 0.98; incidence 1395 per 100 000 person years).[75] Risk of bias was moderate for the two cohort studies and certainty of evidence was rated moderate (table 4 and supplementary table 10).

Overall, available evidence does not support a causal association between aluminium adjuvanted vaccines and asthma; a modest and inconsistent association observed in one US cohort was not replicated in a larger Danish population based cohort.

Other chronic conditions

One randomised controlled trial,[45] three cohort studies,[59 75 76] and one case series[51] examined potential associations between aluminium adjuvanted vaccines and chronic conditions (table 2, table 3). A Japanese randomised controlled trial (n=1040) followed women for four years after human papillomavirus (HPV)-16/18 AS04 adjuvanted versus aluminium-free hepatitis A (HAV) vaccination finding similar rates of new chronic conditions (1.2%, n=6/519 *v* 1.5%, n=8/521), indicating no association with aluminium exposure.[45] The trial was well conducted, with some concern for bias and moderate certainty (table 4 and supplementary table 10).

A large US cohort study (n=584 171) examined type 1 diabetes mellitus in children aged 2-14 years and found no increased risk with cumulative aluminium exposure (adjusted hazard ratio 0.77, 95% CI 0.60 to 0.99).[59] Another large US cohort study (n=69 625) found no increased risk of new onset immune mediated conditions over 13 months of follow-up in adults receiving aluminium adjuvanted compared with non-aluminium adjuvanted hepatitis B (HBV) vaccine.[76] More recently, a Danish nationwide cohort study (n=1 224 176) found no increased risk of chronic conditions with cumulative aluminium exposure from vaccines during the first two years of life, including autoimmune conditions (adjusted hazard ratio 0.98, 95% CI 0.94 to 1.02; incidence 0.8-50.5 per 100 000 person years), and atopic or allergic conditions (0.99, 0.98 to 1.01; incidence 1.0-849.9 per 100 000 person years).[75] Risk of bias was moderate (n=3) and certainty of evidence was moderate with concerns for confounding bias (table 4 and supplementary table 10).

A small case series of 16 girls who developed somatoform and neurocognitive symptoms after HPV vaccination found no aluminium specific lymphocyte response at testing approximately two years after vaccination; the authors concluded that cell mediated immune activation to aluminium is an unlikely mechanism for the observed neurofunctional symptoms.[51] Certainty was low owing to design and sample size limitations, with serious concerns for risk of bias (table 4 and supplementary table 10).

Overall, no evidence supports an association between aluminium containing vaccines and chronic conditions. Evidence is limited by the low incidence in some outcomes, methodological heterogeneity, and low-to-moderate certainty of evidence.

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Table 3 | Characteristics of studies performed from 2016 to 2025

Author, year	Country	Study design	Study period	Population	Intervention	Control	Outcome	Risk of bias
Leroux-Roels, 2016[50]	Belgium, Germany	RCT phase 2	December 2008 to July 2011	Healthy adults 18-45 years (n=710)	HBsAg-Aluminium (2 doses: day 0 and 30)	HBsAg-AS01$_B$, HBsAg-AS01$_E$, HBsAg-AS03$_A$, or HBsAg-AS04 (2 doses: day 0 and 30)	Headache, myalgia	Some concerns‡
Salik, 2016[74]	Denmark	Case series	January 2003 to October 2013	Children aged ≤10 years with persistent skin reactions after vaccination (n=47)	DTaP-IPV/Hib, PCV, MMR, and BCG vaccination	NA	Persistent nodules, contact allergy	Serious*
Poddighe, 2017[51]	Italy	Case series	2015	Young girls 12-24 years with somatoform, neurological, and vasomotor symptoms (n=18; adolescents and adults)	4vHPV (Gardasil), 2vHPV (Cervarix)	NA	Headache, myalgia, somatoform and neurocognitive symptoms	Serious*
Burny, 2019[52]	Belgium	RCT phase 2	January 2013 to September 2016	Healthy adults 18-45 years (n=149)	HBsAg-Aluminium (Engerix B, 3 doses: day 0, 30 and 180)	HBsAg-AS01$_B$ (2 doses: day 0 and 30)	Headache, myalgia	Low‡
Sechi, 2019[53]	Italy	Case series	NR	Children with vaccination granuloma (n=3)	Second booster dose of aluminium hydroxide DTaP-HB-IPV-Hib (Infanrix-Hexa) or aluminium phosphate PCV13 (Prevenar 13)	NA	Granulomas, contact allergy	Critical*
Fournier, 2020[54]	NR	Case series	NR	Children presenting with pruriginous annular plaques (n=2)	Aluminium hydroxide vaccines: HBV (Recombivax HB) and HPV (Cervarix and Gardasil 9)	NA	Hypersensitivity	Critical*
Hoffmann, 2020[55]	Denmark	Cohort study	1 January 2010 to 1 September 2018	Children aged ≤15 years with suspected contact allergy (n=238)	Aluminium adjuvanted vaccine (DiTeKiPol/Hib)	Vaccine not containing aluminium (MMR vaccine)	Granulomas, contact allergy	Critical†
Kelly, 2020[56]	Ireland	Case series	2010-18	Children with suspected vaccination granulomas (n=13)	Aluminium salts adjuvanted vaccine (DTaP-IPV/HiB)	NA	Granulomas contact allergy	Serious*
Kim, 2020[57]	Korea	Case series	2015-19	Seven children with MMF	HBV, HAV, and TT vaccines	NA	MMF	Moderate*
Zanoni, 2020[58]	Italy	Case series	2016-19	Children with localised reactions owing to suspected allergy to vaccine components (n=8)	Children 5-8: aluminium adjuvanted MenB and hexavalent vaccine	NA	Persistent nodules, contact allergy	Serious*
Glanz, 2021[59]	United States	Retrospective cohort study	1 January 2004 to 31 December 2019	Children born from 1 January 2004 to 31 December 2014 identified from VSD databases	Cumulative aluminium exposure (mg) from vaccines up to 23 months of age	NA	Type 1 diabetes mellitus	Moderate†
Hoffmann, 2022[60]	Denmark	Cohort study	1 January 2009 to 31 December 2020	Children born in Denmark between 1 January 2009 and 31 December 2018 (n=553 932)	DTaP-IPV-HiB and PCV	NA	Granulomas	Moderate†
Lidholm, 2022[61]	Sweden	Case series	1997-19	People who participated in Gothenburg trial with itching nodules at aP vaccination site (n=745; children)	Aluminium hydroxide vaccines (aP or DTaP and DT booster)	NA	Persistent nodules, contact allergy	Serious*
Walsh, 2022[62]	United States	RCT phase 1/2	April 2018 to November 2019	Healthy adults 18-49 years (n=618)	Aluminium hydroxide RSVpreF vaccine (120 µg)	Non-adjuvanted RSVpreF vaccine (120 µg)	Headache, myalgia	Low‡
NCT04032093, 2022[63]	United States, Argentina, Chile, New Zealand, South Africa	RCT phase 2b	7 August 2019 to 30 September 2021	Pregnant women at 24-36 weeks' gestation (n=587; adults)	Aluminium hydroxide RSVpreF vaccine (120 µg)	Non-adjuvanted RSVpreF vaccine (120 µg)	Headache	Low‡
Daley, 2023[64]	United States	Retrospective cohort study	1 January 2008 to 31 December 2017	Children born from 1 January 2008 to 31 December 2014 receiving care at a VSD site (n=326 991)	Cumulative aluminium exposure (mg) from vaccines before 24 months of age	NA	Persistent asthma at 24-59 months of age	Moderate†
Ackerson, 2023[76]	United States	Prospective cohort study	7 August 2017 to 30 November 2020	KPSC members ≥18 years vaccinated with HBV between 7 August 2017 and 31 October 2019 (n=69 625)	Aluminium hydroxide HBV (Engerix-B)	Non-aluminium adjuvanted HBV (Heplisav-B)	New onset immune mediated conditions	Moderate†

(Continued)

Table 3 | Continued

Author, year	Country	Study design	Study period	Population	Intervention	Control	Outcome	Risk of bias
Marks, 2025[77]	United States, South Africa, Botswana, Kenya, Malawi, Uganda, Thailand, Vietnam, Philippines, Brazil	RCT phase 3	1 December 2020 to 4 September 2023	Adults ≥18 years with HIV and previous vaccine non-response (n=561)	Aluminium hydroxide HBV (Engerix-B)	Non-aluminium adjuvanted HBV (Heplisav-B)	Headache, myalgia	Low‡
Andersson, 2025[75]	Denmark	Retrospective cohort study	1 January 1997 to 31 December 2020	Children born from 1 January 1997 to 31 December 2018 who were alive and residing in the country at 2 years of age (n=1 224 176)	Cumulative aluminium exposure (mg) from childhood vaccines received by 2 years of age	NA	Autoimmune disorders, atopic or allergic outcomes (including asthma and allergy), neuro-developmental disorders (including ASD)	Moderate†

2vHPV=bivalent human papillomavirus vaccine; 4vHPV=quadrivalent human papillomavirus vaccine; aP=acellular pertussis; ASD=autism spectrum disorders; BCG=Baccile Calmette-Guérin vaccine; DT=diphtheria-tetanus; DTaP=diphtheria-tetanus-acellular pertussis; DTaP-HB-IPV-Hib=diphtheria-tetanus-acellular pertussis-hepatitis b inactivated poliovirus-*Haemophilus influenzae* type b; DTaP-IPV-Hib=diphtheria-tetanus-acellular pertussis inactivated poliovirus-*Haemophilus influenzae* type b; HAV=hepatitis A vaccine; HBV=hepatitis B vaccine; HBsAg=hepatitis B surface antigen (antigen only, no adjuvant); HBsAg-AS01$_B$=hepatitis B surface antigen adjuvanted with AS01$_B$; HBsAg-AS01$_E$=hepatitis B surface antigen adjuvanted with AS01$_E$; HBsAg-AS03$_A$=hepatitis B surface antigen adjuvanted with AS03$_A$; HBsAg-AS0$_4$=hepatitis B surface antigen adjuvanted with AS0$_4$; HPV=human papillomavirus; KPSC=Kaiser Permanente Southern California; MenB=serogroup B meningococcal vaccine; MMF=macrophagic myofasciitis; MMR=measle mumps rubella; NA=not applicable; NR=not reported; PCV=pneumococcal conjugate vaccine (general); PCV13=13-valent pneumococcal conjugate vaccine; RCT=randomised controlled trial; RSVpreF=respiratory syncytial virus prefusion F protein vaccine; TT=tetanus toxoid; VSD=Vaccine Safety Datalink.
*Risk of bias assessed using modified Cochrane Risk of Bias in Non-randomised Studies in Interventions (ROBINS-I) tool.
†Risk of bias assessed using Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool.[16]
‡Risk of bias assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[15]

Macrophagic myofasciitis

Thirteen studies (12 case series and one cohort study)[26 28-31 34 37 38 43 48 49 57 71] reported on MMF, with about half conducted in France[26 28 29 31 43 49 71] (table 1, table 2, table 3). Across 12 case series,[26 28-31 34 37 38 43 48 49 57 71] 210 reports were described, including 28 children, with three large French series accounting for 74% (n=156/210) of reports.[28 31 49]

All reports of MMF were identified through deltoid muscle biopsy, with 97.6% (n=205/210) investigated for diffuse myalgias, arthralgias, or muscle weakness. Histology consistently showed periodic-acid-Schiff positive macrophage infiltrates, with aluminium inclusions in 39.0% (n=82/210),[28 30 34 37 38 48 57] concurrent focal chronic inflammatory reaction in 9.0% (n=19/210),[34 48 57 71] and concurrent autoimmune conditions in 23.8% (n=50/210).[26 28 29 37 48 57 71] Most people (93.3%, n=196/210) had previous aluminium containing vaccination before biopsy; the interval between vaccination and symptom onset and duration of symptoms varied considerably across studies, with some studies reporting onset and persistence ranging from months to years.[31 48]

In a French cohort of 130 patients with chronic musculoskeletal pain of at least six months who had received an aluminium adjuvanted vaccine within the preceding 10 years, MMF lesions were detected in 32.3% (n=42/130) at deltoid muscle biopsy. The number of aluminium containing vaccine injections was similar in those with and without lesions (3.2±1.5 *v* 2.7±1.2), indicating that MMF lesions were absent in most people (67.7%, n=88/130) with similar exposure and comparable symptoms.[43]

All studies lacked control groups and were limited by selective biopsy referral, incomplete exposure characterisation, and heterogeneous histological reporting. Risk of bias was moderate to critical, and certainty of evidence was very low (table 1, table 2, table 3, table 4, and supplementary table 10). MMF lesions can be detected histologically in some people biopsied in the deltoid of the vaccinated arm; however, current evidence does not support a causal association between MMF lesions and systemic clinical symptoms.

Headache

Eleven studies evaluated headache, typically within one month of aluminium adjuvanted vaccination: nine randomised controlled trials,[36 39 44 50 52 62 63 70 77] one single arm cohort,[24] and one case series[51] (table 1, table 2, table 3). Across four HBV randomised controlled trials, headache frequencies were similar between aluminium adjuvanted and non-aluminium formulations.[39 50 52 77] Two HAV randomised controlled trials found no significant differences between aluminium adsorbed and virosomal formulations in headache frequency, though one reported slightly higher frequency with the aluminium formulation (2.7%, n=2/75 *v* 0.9%, n=3/338; P=0.49).[36 70] Two RSVpreF (respiratory syncytial virus prefusion F protein vaccine) randomised controlled trials reported slightly higher headache rates with the adjuvanted formulation (16.5% (n=19/115) to 33.3% (n=4/12) *v* 8.3% (n=1/12) to 18.4% (n=21/114)), with events predominantly mild or moderate.[62 63] A H1N1 influenza randomised controlled trial found no increase in headache with the aluminium formulation.[44] Seven randomised controlled trials were at low risk of bias, one had some concerns, and one was at high risk owing to missing data and outcome measurement[36] (table 1,

Table 4 | Summary of evidence

Outcome	Type of evidence	Incidence	Severity*	Methodological limitations	Direction of association	Certainty of evidence	Causal association (conclusion)
Autism spectrum disorder	1 large cohort, 2 ecological studies	Rare	Serious	Confounding, ecological fallacy	No association (cohort); positive correlation (ecological studies)	Moderate, very low (ecological studies)	Not in favour of a causal association
Asthma	2 large cohorts	Common	Serious	Residual confounding	No consistent association	Moderate	Not in favour of a causal association
Chronic conditions†	1 RCT, 3 cohorts, 1 case series	Rare	Serious	Confounding, imprecision	No association (RCT, cohorts, case series); inverse association (type 1 diabetes mellitus cohort)	Moderate, low (neurofunctional symptoms)	Not in favour of a causal association
Macrophagic myofasciitis	12 case series, 1 cohort	Not quantifiable (about 210 reports)	Serious	Selective reporting, selection bias, recall bias	Reported association	Very low	Not in favour of a causal association
Headache	9 RCTs, 1 single arm cohort, 1 case series	Common	Mostly mild or moderate	Confounding and recall bias in non-RCTs	No increased risk except for RSVpreF	High	Not in favour of a causal association for most studies (risk may vary by vaccine)
Myalgia	5 RCTs, 1 case series	Common	Mostly mild or moderate	Selective reporting and recall bias (case series)	Slight increased risk with RSVpreF, PCV15; otherwise no difference	High	Not in favour of a causal association
Wells syndrome	1 case series	2 children	Moderate or severe	Selection bias	Positive association	Low	Insufficient evidence
Persistent nodules	12 case series, 1 cohort	Uncommon (<1%)	Mild	Selection and misclassification biases, selective reporting	Consistent association	Low	Consistent with a causal association
Granulomas	10 case series, 3 cohorts	Uncommon (<1%)	Mild or moderate	Selection and misclassification biases, selective reporting	Consistent association	Moderate	Consistent with a causal association

PCV15=15 valent pneumococcal conjugate vaccine; RCT=randomised controlled trial; RSVpreF=respiratory syncytial virus prefusion F protein vaccine.
*Severity rated based on expected impact as mild (minor impact on daily activities), moderate (interfered with but did not prevent daily activities), severe (prevented daily activities), serious (life threatening, results in hospital admission, prolongs existing hospital stay, or causes persistent disability).
†New onset, type 1 diabetes mellitus, neurofunctional symptoms, autoimmune disorders.

table 2, table 3, table 4). Overall, certainty of evidence was high (supplementary table 10).

A single arm cohort found no difference in headache risk between recipients of diphtheria-tetanus vaccine regardless of whether their primary series included aluminium phosphate or non-adjuvanted diphtheria-tetanus-pertussis (DTP).[24] A small HPV case series reported headache in only two of 16 people.[51] Both were at serious to critical risk of bias, providing moderate certainty of evidence (table 4 and supplementary table 10).

Overall, high certainty randomised controlled trial evidence indicates no consistent increase in headache risk with aluminium adjuvanted vaccines. When differences were observed, they were small, inconsistent across studies, and predominantly mild to moderate in severity.

Myalgia

Six studies (five randomised controlled trials[47 50 52 62 77] and one case series[51]) evaluated myalgia within one month of vaccination (table 2, table 3). Across three randomised controlled trials comparing aluminium adjuvanted with non-aluminium adjuvanted HBV vaccines, two reported fewer myalgia events in aluminium adjuvanted groups and one found similar frequencies.[50 52 77] Two randomised controlled trials reported slightly higher myalgia frequencies with aluminium adjuvanted formulations: RSVpreF (50.0%, n=6/12 *v* 33.3% n=4/12, predominantly mild to moderate) and 15-valent pneumococcal conjugate vaccine (30.3%, n=10/33 *v* 28.6%, n=8/28, severity not reported).[47 62] Four randomised controlled trials had low risk of bias[47 52 62 77] and one had some concerns[50]; certainty was high (table 4 and supplementary table 10). A small HPV case series reported myalgia as a primary symptom in four of 16 people and was rated at serious risk of bias with low certainty of evidence[51] (table 4 and supplementary table 10).

Overall, randomised controlled trial evidence does not show a consistent association between aluminium adjuvants and myalgia. When higher frequencies were observed, differences were small and severity was predominantly mild to moderate, while some studies found lower rates with aluminium formulations.

Hypersensitivity reaction: generalised hypersensitivity reactions to aluminium

Wells syndrome—A single case series described two paediatric patients with Wells syndrome occurring 12-14 days after HBV or HPV vaccination, or both[54] (table 3). Both patients developed pruritic erythematous or violaceous annular plaques with vesicles; patch testing showed aluminium sensitisation (one patient to aluminium hydroxide and one to aluminium chloride hexahydrate). Symptoms resolved in both patients with a short course of corticosteroids over 2-6 weeks. The study had critical risk of bias owing to selection bias and certainty of evidence was low (table 4 and supplementary table 10). These

findings are insufficient to establish causality between aluminium adjuvants and Wells syndrome.

Hypersensitivity reaction: localised delayed-type hypersensitivity to aluminium

Persistent nodules and granulomas are presented separately to reflect the terminology and classification used in the primary studies, noting that granulomas are often considered a possible histopathological subcategory of persistent nodules requiring confirmatory histopathology for diagnosis.

Persistent nodules—Thirteen case series reported 885 non-overlapping events of persistent nodules after aluminium adjuvanted vaccination, several representing longitudinal follow-up of previously described events[21 25 32 33 41 42 58 61 65 66 68 74 78] (table 1, table 2, table 3). Most were conducted in Scandinavia (Sweden, n=5[32 41 42 61 78]; Denmark, n=2[66 74]), with others in Italy (n=1)[58] and the UK (n=1).[21]

Among reports with available data (86.6%; n=766/885), nodules developed almost exclusively after DTP or related combination vaccines (98.0%, n=751/766) and after the third dose (75.8%, n=581/766); less often after the second (17.9%, n=137/766) or first (5.0%, n=38/766) dose.[25 33 41 58 65 68 74 78] Onset ranged from days to several years after vaccination, with a median of about three months in larger series.[33 41 78] Symptoms varied in duration, typically persisting for months to years. Pruritus was common, sometimes severe, and symptoms often (33.0%, n=292/885) worsened during intercurrent infections such as upper respiratory tract infections or gastroenteritis.[41 74 78]

Across 582 patch tests performed, 80.6% (n=469/582) were positive for aluminium, supporting delayed type hypersensitivity as an underlying mechanism. A large Swedish study (about 76 000 children) found a 0.98% (n=745/76 000) incidence,[61 78] with most occurring after the third dose. Symptoms often persisted for years (median four years), with 75.4% (n=473/627) of children still symptomatic at follow-up.[78] Exacerbations during intercurrent infections were reported in 38.9%. Aluminium sensitisation occurred in 77.4% (n=352/455) of children with symptoms versus 8.1% (n=17/211) of siblings without symptoms who had received the same vaccines (P<0.0001).[78] Long term follow-up showed declining sensitisation: 77.2% (n=186/241) were no longer sensitised after 5-9 years[42] and 85.5% (n=637/745) had full symptom resolution after a median of 6.6 years, with low recurrence after boosters.[61] Findings were consistent across Scandinavian series, showing similar onset, duration, and hypersensitivity patterns.[32 41]

Most studies were at serious (n=7) or critical (n=3) risk of bias, and only three at moderate risk (table 1, table 2, table 3). Common issues included selective referral, intervention misclassification, and selective outcome reporting. About one third of the case series (n=5) originated from the same research group; total number of reports was derived accordingly, though residual overlap cannot be excluded. Certainty of evidence was rated low (table 4 and supplementary table 10).

Overall, evidence suggests a reproducible association between aluminium adjuvanted vaccines and persistent nodules, likely mediated by delayed hypersensitivity. Available follow-up data indicate these reactions are local and non-progressive, with declining sensitisation and low recurrence after boosters.

Granulomas—Thirteen studies (10 case series, three cohort studies) reported granulomas, mostly from Europe (n=7) and Australia (n=1), published between 1971 and 2022[20 22 23 27 35 53 55 56 60 67 69 72 73] (table 1, table 2, table 3).

Among 59 reports of granulomas across 10 case series, most (91.5%, n=54/59) occurred after DTP combination vaccines, with a few after HBV[35] or other unspecified aluminium adjuvanted vaccines.[35 56] Histology (n=25/59, 42.4% confirmed) showed granulomatous inflammation, often necrotising or fibrotic, with mixed infiltrates of lymphocytes, histiocytes, and eosinophils.[20 22 27 35 56 67 69 72] Aluminium was detected in 60.0% (n=15/25) with histological confirmation.[20 22 27 67 69 72] Most granulomas appeared after the third dose (88.9% with dose data, n=32/36), consistent with sensitisation; nearly all patch tests were positive (n=32/33). Onset ranged from weeks to years, and lesions typically persisted for two to more than five years.

Cohort incidence estimates ranged from 0.34% (n=1901/553 932)[60] to 0.83% (n=38/4558).[73] Granulomas were often pruritic, with symptoms exacerbated by intercurrent infections or aluminium exposures (eg, sunscreen, canned food).[55 73] Reported risk factors included higher aluminium dose (>1.0 mg), aluminium hydroxide adjuvant, revaccination, and female sex.[60] Having an affected sibling was the strongest predictor (rate ratio 46.15, 95% CI 33.67 to 63.26). Combination adjuvants (hydroxide plus phosphate), prematurity, and younger maternal age (<20 years) were associated with lower risk. Most granulomas occurred before age 2, peaking after the third dose.[60]

Risk of bias was high across case series (serious, n=4; critical, n=6) and mixed in cohorts (one moderate, two critical; table 1, table 2, table 3). Limitations included confounding, selection and misclassification biases, and selective reporting, as well as lack of standardised histopathology and incomplete follow-up (table 4). Certainty of evidence was judged moderate (supplementary table 10).

Granulomas are uncommon but consistently reported after aluminium adjuvanted DTP vaccination, typically after the third dose and associated with aluminium hypersensitivity. Cohort data provide incidence estimates and identify potential risk factors including a possible dose-response association, though methodological limitations preclude definitive causal inference.

Discussion

Principal findings

This systematic review finds that human evidence does not support causal associations between aluminium adjuvanted vaccines and serious or long term health outcomes. High quality evidence from randomised controlled trials and large cohort studies consistently showed no association between aluminium adjuvants in vaccines and systemic conditions, including ASD, type 1 diabetes mellitus, asthma, headache, myalgia, and other chronic conditions. Although histological MMF deposits were identified in a subset of people who had biopsies for musculoskeletal symptoms after vaccination, available evidence does not establish how, if at all, these local aluminium inclusions relate to systemic symptoms. For Wells syndrome, a single small case series raised only the possibility of a rare hypersensitivity response without sufficient evidence for causal inference. The only consistently observed events were uncommon, local hypersensitivity reactions (ie, persistent nodules and granulomas) supported by convergent clinical, histological, and patch test evidence suggesting a delayed type hypersensitivity mechanism, which though self-limited may cause prolonged discomfort.

The strength of conclusions varies across outcomes and reflects a clear gradient in study quality. Randomised controlled trials at low risk of bias provide the most reliable evidence, with null findings for chronic conditions and increase in risk of headache and myalgia observed in some studies. Large cohort studies at moderate risk of bias similarly found no association with serious systemic outcomes such as asthma, type 1 diabetes mellitus, and ASD. By contrast, most case series and both ecological studies are structurally limited in their ability to support causal inference, therefore findings pertaining to MMF and ASD derived from these studies should be considered hypothesis generating. The evidence base was dominated by methodologically limited studies and conclusions should be interpreted accordingly. Taken together, the convergent findings of higher quality studies provide a meaningful evidence base to inform public health decision making on aluminium adjuvanted vaccines.

Comparisons with other studies

These findings align with previous systematic reviews and post-licensure surveillance evaluations finding no increased risks of chronic diseases attributable to aluminium adjuvanted vaccines, and align with conclusions reached by the WHO Global Advisory Committee on Vaccine Safety for ASD, MMF, and other serious outcomes.[5-10 79] The positive correlations reported in the two ecological studies are limited by their inability to control for confounding and absence of individual level exposure data, contrasting with the large Danish cohort included in this review and several large epidemiological studies finding no association between vaccination and ASD.[75 80-82] For MMF, a French cohort study found a similar number of previous aluminium containing vaccine injections in those with and without MMF lesions, providing no evidence of dose-response association.[43] Further contextual support comes from patients receiving allergen immunotherapy, who accumulate substantially higher cumulative aluminium doses without increased risk of autoimmune disease, and from pharmacokinetic modelling, suggesting the total aluminium contained within recommended childhood vaccine schedules falls well below established reference values.[83 84] The geographical concentration of nodule and granuloma evidence in Scandinavia and MMF evidence in France raises questions about whether these patterns reflect local scientific interest and reporting practices, population level phenomena, regional formulation differences, or local referral practices, a consideration not addressed in previous reviews.

Interpretation of these findings should consider differences in scope and eligibility criteria between this review and previous systematic reviews on aluminium adjuvants.[10 85] This review excluded investigational or candidate vaccines and was restricted to studies including a vaccine authorised for use. Studies with similar aluminium formulations and dosage between the intervention and comparator were also excluded because they do not allow isolation of the potential effects of aluminium adjuvants. While these eligibility criteria resulted in fewer included studies, they ensure that findings specifically reflect the evidence on vaccines used in immunisation programmes, which is most directly relevant to clinical and public health decision making.

Strengths and limitations of this study

Strengths of this review include its comprehensive search strategy, application of validated risk-of-bias tools, GRADE certainty assessment, and incorporation of evidence to November 2025. Important limitations remain. Evidence on specific vaccine components is sparse compared with whole vaccine research, with a high proportion of methodologically weak studies, predominantly from high income countries. Randomised controlled trials comparing identical formulations with and without aluminium adjuvants remain logistically and ethically challenging for rare or delayed outcomes requiring large sample sizes and extended follow-up. Most studies were uncontrolled case series from a small number of investigators. Despite efforts to exclude overlapping populations, residual overlap cannot be excluded, and true incidence estimates may be conservative or inflated. Very rare reactions may be underrepresented given the exclusion of individual case reports. The search strategy could not be fully updated in ProQuest owing to platform limitations. The absence of patient and public involvement is acknowledged as a limitation, particularly for outcomes such as ASD and MMF when community perspectives are relevant.

Further research should examine individual susceptibility factors including sex, ethnicity, family history, adjuvant type, and aluminium dose, while accounting for total exposure from non-vaccine sources

such as diet, antacids, breast milk and formula.[86] Sex and gender disaggregated data were rarely reported in primary studies, limiting the evaluation of potential differences in health risks. Although granulomas are considered a histopathological subcategory of persistent nodules, the clinical and biological boundary between the two reactions in the absence of confirmatory histology remains unclear, and whether aluminium induced delayed type hypersensitivity manifests as a spectrum of severity rather than discrete entities warrants further investigation. Several outcomes including Alzheimer's disease, bone disease, primary ovarian insufficiency, complex regional pain syndrome, and postural orthostatic tachycardia syndrome lacked eligible human studies, underscoring the need for further study. Animal, in vitro, and mechanistic studies were beyond the scope of this review, which focused on direct human evidence. Although preclinical data can inform understanding of biological mechanisms, findings from animal and laboratory studies cannot be directly applied to human health outcomes.

Conclusion

Current evidence does not support causal associations between aluminium adjuvanted vaccines and serious or long term health outcomes, including ASD, type 1 diabetes mellitus, asthma, and other chronic conditions. Local hypersensitivity reactions, such as persistent nodules and granulomas, represent the only consistently observed reactions and carry a favourable long term prognosis. These findings are consistent with the broader post-licensure safety evidence base, which supports continued use of aluminium adjuvanted vaccines in immunisation programmes. Ongoing investment in higher quality primary research remains important given the predominance of uncontrolled case series, the limited number of long term population based studies, and persistent evidence gaps for rare or delayed outcomes. Clear, evidence based communication remains essential to address concerns and support informed decision making.

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Contributors: PD-P, EMA, RP, and JZ designed the study. PD-P, JC, and JZ assessed study eligibility. PD-P and JC conducted data extraction, critical appraisal and analysis. PD-P, JC, and JZ drafted the manuscript. EMA and RP provided clinical and methodological expertise. PD-P, JC, EMA, RP, KY, MT, and JZ reviewed and approved the final version. PD-P acts as the guarantor. AI assisted tool was used in one aspect of this systematic review. Otto-SR (version 2025), a large language model based screening tool, was used to facilitate title/abstract and full text screening of records identified in the 2025 updated search. All records flagged as potentially eligible by otto-SR were manually reviewed and verified by human reviewers. All final inclusions and exclusions were made by human reviewers. The corresponding author (JZ) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required. This systematic review involved no primary data collection from human participants.

Data sharing: All data underlying this systematic review were extracted from studies that are already publicly available. The data extraction form, risk of bias assessments, and GRADE certainty assessments are provided in the supplementary materials. Reconciled extracted data are available upon request.

Transparency: The lead author (PD-P) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects have been omitted; and that any deviations from the registered protocol (PROSPERO CRD42023462831) have been disclosed and explained.

Dissemination to participants and related patient and public communities: Because this systematic review did not involve recruitment of participants, there are no individual study participants to whom results can be directly disseminated. Findings will be disseminated through scientific publication, research networks relevant to vaccine safety and public health, and relevant professional and public health organisations.

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Web appendix: Supplementary materials