The Role and Safety of Aluminum Adjuvants in Childhood Vaccines

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Aluminum salts have been used as adjuvants in vaccines for nearly a century, enhancing the immune response to purified antigens and ensuring durable protection against serious infectious diseases. Despite their longstanding record of safety and effectiveness, aluminum adjuvants have become a focus of public concern, with claims linking them to developmental, neurologic, allergic, and autoimmune diseases. This review summarizes the immunologic rationale for aluminum adjuvants and evaluates the evidence for proposed safety risks. Aluminum salts have consistently been demonstrated over nearly a century of use to enhance the immune responses elicited by vaccines while also being well tolerated by nearly all who take them. Pharmacokinetic studies show that aluminum released from intramuscular vaccines is slowly absorbed and efficiently cleared by the kidneys, contributing minimally to systemic levels. Large-scale clinical and epidemiologic studies consistently demonstrate no association between aluminum-adjuvanted vaccines and autism spectrum disorder, neurotoxicity, allergic disease, or autoimmune disease. Clinically, vaccines adjuvanted solely with aluminum salts generally do not result in systemic reactogenicity, although local reactions are common. Collectively, the evidence strongly supports the safety of aluminum adjuvants and their necessity in certain vaccines. Clinicians can reassure caregivers that aluminum-containing vaccines provide clear benefits, with risks largely limited to transient local reactions and no systemic toxicity signal in large clinical and epidemiologic studies.

INTRODUCTION

Vaccination is among medicine's most successful interventions, preventing millions of child deaths annually.[1–4] Central to this success in saving lives, averting illness, and reducing health care costs is the role of vaccine adjuvants. Adjuvants are components of vaccines combined with antigen(s) to enhance the magnitude and duration of protection[5–7] and enable dose sparing (fewer doses and lower antigen content)[5–7] and may steer responses away from harmful immunopathology (eg, vaccine-associated enhanced respiratory disease).[8,9] Aluminum salt–based adjuvants ("alum") have been incorporated into vaccines for nearly a century and remain the most widely used adjuvants in pediatric immunization. The first published use of adjuvants for improving favorable responses to vaccination was by Gaston Ramon in 1925.[10] Ramon's work led Glenny et al to experiment with alum, finding that alum enhanced antibody responses to diphtheria toxoid in guinea pigs.[11] Alum's balance of immunogenicity and tolerability was central to its widespread adoption.[12,13] By 1932, alum-adjuvanted diphtheria vaccines were administered to children (the first use of an adjuvant in human vaccination).[14] Until 1994, alum was the only vaccine adjuvant licensed for human use, reflecting its enduring record of safety and effectiveness.[15,16]

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Despite this history, alum has become a basis for vaccine hesitancy.[17,18] Concerns have arisen that aluminum in vaccines could contribute to autism spectrum disorder (ASD), neurodegeneration, allergy, and autoimmune disease.[17,18] Although unsubstantiated by high-quality clinical and epidemiologic studies, these claims persist in the public discourse and present challenges during vaccine counseling.

For clinicians, understanding the immunologic rationale for aluminum adjuvants, their pharmacokinetics, and the supporting clinical and epidemiologic evidence is critical for effective, evidence-based, patient-centered vaccine counseling. This review summarizes the immunologic basis for use of alum, contextualizes vaccine-derived aluminum exposure (Table 1) relative to other common exposures, and examines the evidence regarding proposed risks to provide a clear framework for counseling caregivers.

TABLE 1. Aluminum Content of Currently Licensed, Alum-Containing Pediatric Vaccines in the United States

Vaccine Name	Aluminum per Dose
Engerix-B (Hepatitis B recombinant)	0.25 mg[408]
Recombivax HB (Hepatitis B recombinant)	0.25 mg[409]
PedVaxHIB (*Haemophilus influenzae* type B/ hepatitis B recombinant)	0.23 mg[410]
DAPTACEL (Diphtheria/tetanus/acellular pertussis)	0.33 mg[411]
Infanrix (Diphtheria/tetanus/acellular pertussis)	0.50 mg[412]
Kinrix (Diphtheria/tetanus/acellular pertussis/inactivated poliovirus)	≤0.50 mg[413]
Quadracel (Diphtheria/tetanus/acellular pertussis/ inactivated poliovirus)	0.33 mg[414]
Pediarix (Diphtheria/tetanus/acellular pertussis/ inactivated poliovirus/hepatitis B recombinant)	≤0.70 mg[415]
Pentacel (Diphtheria/tetanus/acellular pertussis/ inactivated poliovirus/*Haemophilus influenzae* type B)	0.33 mg[416]
VAXELIS (Diphtheria/tetanus/acellular pertussis/ inactivated poliovirus/*Haemophilus influenzae* type B/ hepatitis B recombinant)	0.32 mg[417]
Vaxneuvance (Pneumococcal conjugate vaccine 15-valent)	0.13 mg[418]
Prevnar 20 (Pneumococcal conjugate vaccine 20-valent)	0.13 mg[419]
Havrix (Hepatitis A inactivated)	0.23 mg[421]
Vaqta (Hepatitis A inactivated)	0.45 mg[422]
Gardasil 9 (HPV 9-valent recombinant)	0.50 mg[423]
Penbraya (Meningococcal capsule groups A, B, C, W, Y)	0.25 mg[424]
Penmenvy (Meningococcal capsule groups A, B, C, W, Y)	0.50 mg[425]
Bexsero (Meningococcal capsule group B)	0.52 mg[426]
Trumenba (Meningococcal capsule group B)	0.25 mg[427]
Adacel (Tetanus/reduced diphtheria toxoid/acellular pertussis)	0.33 mg[428]
Boostrix (Tetanus/reduced diphtheria toxoid/acellular pertussis)	0.30 mg[429]

Aluminum content rounded to 2 decimal places.

IMMUNOLOGY OF ALUMINUM ADJUVANTS

The necessity of adjuvants is most clearly illustrated in the immune response elicited by subunit vaccines. Subunit vaccines are nonreplicating preparations of purified pathogen components (peptides, proteins, polysaccharides, or protein-polysaccharide conjugates).[19] Subunit vaccines are favored for their ability to focus immune responses on defined protective antigens or epitopes that can be difficult to target with whole-pathogen approaches[20,21]; safety for patients who are immunocompromised, pregnant, or lactating[22–24]; ease of production[25]; and convenient storage at 2–8 °C.[26] Adjuvants are needed because purified subunits lack microbial nucleic acids or cell-wall components that engage innate immunity (present in other vaccine designs), often failing to induce durable protection.[19,27–33]

Effective activation of the immune response requires innate immune signals that mark an encounter as potentially dangerous.[30–33] Signals of cellular stress or injury (ie, alarmins)[34–36] and the activation of pattern recognition receptors by microbial or endogenous ligands together provide the context that induces adaptive immunity but are generally absent from subunit vaccines administered without adjuvants.[7,30,31,33,36–44] Adjuvants enable soluble subunit antigens to elicit durable, high-titer, functional antibody and T-cell responses.[38,45–58] Some vaccines are self-adjuvanting: live-attenuated viruses produce and contain viral RNA, activating innate receptors[37,59–64]; mRNA-lipid nanoparticle vaccines use ionizable lipids to activate innate pathways[65–67]; and virus-like particles stimulate B cells directly through crosslinking of B-cell receptors.[68–76]

Alum's adjuvant activity arises through parallel, redundant mechanisms that are incompletely characterized.[7,77–79] Alum's enhancement of type 2 immunity (responses against macroparasites, allergens, venoms, and some other antigens)[80–86] is conserved across species,[87] but in humans, limited data suggest that alum can also augment type 1 immunity (responses against intracellular infections[85,88–90]).[91–93] Upon intramuscular injection, alum and antigen are taken up by dendritic cells and macrophages,[94–96] wherein alum particles disrupt the endolysosomal membrane, causing leakage of cathepsins and other proteases into the cytosol.[97,98] These proteases then activate the NLRP3 inflammasome, which triggers the liberation of alarmins[97–108] and activation of antigen-presenting cells.[38] The immune response becomes type 2 polarized through complex, incompletely characterized mechanisms that depend on IL-33, IL-4, and IL-10.[109–111] Through these mechanisms, alum-adjuvanted vaccines elicit superior antibody responses and seroconversion rates in clinical trials than nonadjuvanted formulations.[112–116]

Adjuvants are especially important during infancy, when developmental factors constrain vaccine immunogenicity.[117–126] Due to adaptations required to avoid fetal alloreactivity to the mother,[127,128] the fetal and infant immune systems generally suppress type 1 immune responses[117,118,124,129–134] and have a high propensity for type 2 immune responses[117,118,124,135–141] and tolerance.[127,129,130,135,142–151] Maternal antibodies can also blunt infant vaccine responses.[152–156] The infant immune system is still capable of diverse immune responses (including type 1) but may require stimulation through adjuvantation to produce them.[157–160]

ALUMINUM EXPOSURE, SAFETY, AND PHARMACOKINETICS

Defining a "toxic level" of aluminum is inherently context dependent, varying with route of exposure, renal function, and physiologic state.[161] Although we describe the entity known as "dialysis dementia" below, a review of aluminum toxicity is beyond scope and has been detailed previously.[161] In dialysis patients with chronic parenteral exposure via dialysate fluid, treatment is typically initiated at a serum aluminum level of greater than 60 μg/L.[162] Such thresholds are not translatable to infants receiving intramuscular vaccination, for whom the absorbed dose of aluminum is undetectable.[163] Despite billions of alum-adjuvanted vaccine doses administered and extensive pharmacovigilance networks to study safety, we are unaware of any reports consistent with aluminum toxicity being credibly triggered by vaccination.[161] The cumulative exposure to aluminum contributed by the entire current American Academy of Pediatrics (AAP) childhood immunization schedule (through age 18 years; hereafter, "the AAP schedule") ranges from 4.14 to 7.47 mg (Table 2).

For clinicians, 2 questions are paramount: (1) how vaccine-derived aluminum exposure (Table 1) compares with everyday exposures and (2) how the infants clear aluminum.

Aluminum is the third-most abundant element on Earth and is ubiquitous[161]: it is measurable at birth (in serum),[164,165] acquired via diet (including via both breastmilk and formula),[161,166] and a component of several medications (notably antacids and parenteral nutrition).[161,166,167] Relative to these exposures, the amount of aluminum contributed by vaccines over the AAP schedule is small (Table 2).

Weisser et al developed a pharmacokinetic model for aluminum exposure validated by both clinical[168,169] and preclinical data[170,171] to examine the risk of aluminum toxicity from subcutaneous immunotherapy (SCIT), which uses alum adjuvants (mainly in Europe[172]) to treat allergies.[173] They note that SCIT performed for 1 year could contribute as much as 15 mg of aluminum exposure (up to 1.25 mg per dose), a value twice the maximal exposure of the childhood immunization schedule to age 18 (7.47 mg aluminum; Table 2).[173] Their model, which factors in dietary and other exposures, shows that even if SCIT were performed for 40 years continuously (in someone with normal renal function), up to 95% of people would not achieve aluminum levels associated with toxicity.[173] Moreover, in more typical SCIT durations of 5 years (up to 75 mg aluminum cumulatively), toxic levels could not be attained under any background exposure scenario.[173] This provides reassuring evidence that alum exposure via the AAP schedule cannot plausibly produce toxic aluminum levels.

However, the model by Weisser et al has not been validated for preterm infants and SCIT modeling did not begin before age 5, whereas the AAP schedule front-loads alum-adjuvanted vaccines because many vaccine-preventable diseases pose their greatest risk in early life.[174] This limitation, however, is addressed in a comprehensive analysis by Mitkus et al, which examined the first year of the AAP schedule's aluminum content, finding that any realistic scenario of aluminum uptake from vaccines could not attain even the highly conservative minimal risk levels (MRLs) established by the Agency for Toxic Substances and Diseases Registry (ATSDR).[161,175] Although the ATSDR does not define MRLs for aluminum via intramuscular routes, Mitkus et al used the oral MRL and used 0.78%[176] as the oral bioavailability to benchmark intramuscular exposures at various percentiles of infant body weight, factoring in the kinetics of aluminum release from alum.[175] Furthermore, the modeled level of aluminum exposure contributed by vaccines in Mitkus et al actually exceeds the exposure from the AAP schedule (Mitkus: 4.23 mg aluminum in first 12 months; current schedule: 1.96–3.38 mg in first 12 months; Table 2).[175]

One major source of aluminum exposure is antacids.[167] Previously, the use of aluminum-containing antacids at high doses (700 mmol/1.73 m^2/d), for gastroesophageal reflux disease, was recommended in infants as young as 2 months.[177] As an illustration, an average 2-month-old infant weighing 5 kg and 57 cm tall[178] would receive ~1.54 g of elemental aluminum per day under this dosing, resulting in a bioavailable dose (0.78%[175]) of ~12.01 mg per day.[179] Such a single-day dose would exceed the cumulative aluminum exposure from the entire AAP schedule up to age 18 (Table 2). Once aluminum-containing pediatric antacids were associated with potentially toxic levels of aluminum in serum, medical societies recommended alternative agents.[177] Despite these high exposures, several cohorts of infants receiving aluminum-containing antacids had serum aluminum concentrations exceeding levels considered toxic, yet none demonstrated clinical evidence of toxicity (although tissue biopsies were not performed).[177,180–182] Furthermore, serum aluminum primarily reflects recent exposure rather than tissue accumulation,[161] suggesting that transient elevations in

TABLE 2. American Academy of Pediatrics Childhood Immunization Schedule[430] and Associated Cumulative Aluminum Load for a Child at Standard Risk

Time	Vaccine	Minimal (Top) and Maximal (Bottom) Contribution to Aluminum Load	Cumulative Aluminum Load From Vaccination (Range)
Birth	• HepB dose 1 • RSV (monoclonal antibody)	• Engerix-B or Recombivax HB: 0.25 mg	0.25 mg
2 mos	• HepB dose 2 (if not done at 1 mo) • PCV15 or PCV20 dose 1 Hib dose 1 • IPV dose 1 • DTaP dose 1 • Rotavirus dose 1	• Vaxelis (DTaP/IPV/Hib/HepB): 0.319 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg • Infanrix (DTaP): 0.5 mg Al • PedvaxHib (Hib): 0.225 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg	0.69–1.10 mg
4 mos	• PCV15 or PCV20 dose 2 Hib dose 2 • IPV dose 2 • DTaP dose 2 • Rotavirus dose 2 (Dose 3 of HepB may be given if part of combination vaccine)	• Vaxelis (DTaP/IPV/Hib/HepB): 0.319 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al • Infanrix (DTaP): 0.5 mg Al • PedvaxHib (Hib): 0.225 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al	1.14–1.95 mg
6 mos	• Hepatitis B dose 3 or 4 • Rotavirus dose 3 (if 3-dose series) • Hib dose 3 (depending on vaccine used) • IPV dose 3 • DTaP dose 3 • PCV15 or PCV20 dose 3 • Influenza dose 1 • COVID-19 dose 1	• Vaxelis (DTaP/IPV/Hib/HepB): 0.319 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al • Infanrix (DTaP): 0.5 mg Al • PedvaxHib (Hib): 0.225 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al	1.58–2.80 mg
7 mos	• Influenza dose 2 (repeat annually) • COVID-19 dose 2	N/A	1.58–2.80 mg
12–15 mos	• MMR dose 1 • Varicella dose 1 • Hib dose 3 or 4 • Hepatitis A dose 1 • PCV15 or PCV20 dose 4	• Havrix or Vaqta (HepA): 0.25 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al • PedVaxHIB (Hib): 0.225 mg Al • Vaqta or Havrix (HepA): 0.225 mg Al • Prevnar20 (PCV20) or Vaxneuvance (PCV15): 0.125 mg Al	1.93–3.38 mg
15–18 mos	• DTaP dose 4	• DAPTACEL (DTaP): 0.33 mg Al • Infanrix (DTaP): 0.5 mg Al	2.29–3.88 mg
18–21 mos	• Hepatitis A dose 2	• Havrix or Vaqta (HepA): 0.225 mg Al	2.51–4.10 mg
4–6 y	• MMR dose 2 • Varicella dose 2 • DTaP dose 5	• DAPTACEL (DTaP): 0.33 mg Al • Infanrix (DTaP): 0.5 mg Al	2.84–4.60 mg
9 y	• HPV dose 1	• Gardasil-9 (HPV):0.5 mg Al	3.34–5.10 mg
9.5–11 y	• HPV dose 2	• Gardasil-9 (HPV):0.5 mg Al	3.84–5.60 mg
11–12 y	• MenACWY dose 1 • Tdap dose 1	• Boostrix (Tdap): 0.3 mg • Adacel (Tdap): 0.33 mg • Penmenvy (MenABCWY): 0.50 mg	4.14–6.43 mg
16 y	• MenB dose 1 (shared clinical decision-making) • MenACWY dose 2	• None (if no MenB vaccination under shared clinical decision-making) • Bexsero (MenB): 0.519 mg	4.14–6.95 mg
16.5–18 y	• MenB dose 2 (shared clinical decision-making)	• None (if no MenB vaccination under shared clinical decision-making) • Bexsero (MenB): 0.519 mg	4.14–7.47 mg

Abbreviations: DTaP, diphtheria/tetanus/acellular pertussis; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; IPV, inactivated polio vaccine; MMR, measles/mumps/rubella.
Aluminum content rounded to 2 decimal places.

serum aluminum do not uniformly correspond to clinically meaningful toxicity.

Beyond modeling, real-world evidence from high-risk populations provides additional reassurance that the small amount of alum in vaccines does not pose a toxicity risk. For example, patients with chronic kidney disease experience immune dysfunction, often requiring additional doses of alum-containing vaccines (pneumococcal, hepatitis B).[183–189] Despite impaired aluminum clearance due to renal failure and increased vaccine exposure, no reports of aluminum toxicity from vaccination have been observed across safety studies of vaccines in this population.[186,190–199]

Alum's safety record reflects its unique pharmacokinetics.[200–204] Alum forms a depot at the injection site and dissolves slowly over several months.[200,204] These kinetics prevent significant spikes in serum aluminum levels that would hypothetically allow the ion to disseminate throughout the body to cause target-organ toxicity.[166,200,204] Consistent with this, blood or hair aluminum levels cannot predict vaccination history,[205] and even in a cohort of 15 preterm infants, no rise in serum aluminum levels could be detected 24 hours following vaccination.[163]

These parallel, independent lines of evidence suggest that a toxicological risk from alum exposure via the AAP schedule is untenable.

PUTATIVE HEALTH OUTCOMES ATTRIBUTED TO ALUMINUM ADJUVANTS

Caregiver concerns about aluminum in vaccines most often center on developmental outcomes, neurologic disease, allergic disease, and autoimmune disease.

Autism Spectrum Disorder

ASD diagnoses have increased in recent decades, although whether this reflects a true rise remains contested.[206,207] Various factors have been proposed as potential causes of increased ASD incidence,[208–213] but large-scale studies show that the major drivers for this increase include the broadening of diagnostic criteria, diagnostic substitution, and changes to screening practices.[214–216] ASD has high heritability, ranging from 64% to 91% across studies,[217,218] indicating that environmental contributors to its causation are likely minor. Because converging evidence suggests ASD originates in utero,[219–221] postnatal exposures are unlikely causes; consistent with this, extensive epidemiologic studies show no association with postnatal vaccination.[222–231] Although this would not rule out a role for prenatal vaccination as a contributor, Vaccine Safety Datalink studies of maternal Tdap vaccination (an alum-adjuvanted vaccine) and influenza vaccination also show no observed increase in the risk of ASD.[232,233] Taken together, these data indicate that neither vaccine-derived nor other postnatal aluminum exposures increase ASD risk.

Most recently, Andersson et al analyzed more than 1.2 million children in Denmark born from 1997 to 2018 to assess the risk of multiple conditions in association with cumulative aluminum exposure via the childhood immunization schedule, finding no link between ASD or other neurodevelopmental outcomes and aluminum exposure, and no dose response.[230]

Alzheimer Disease and Neurotoxicity

It has long been hypothesized that aluminum accumulation in the brain may cause Alzheimer disease (AD).[234,235] While not conclusive, there are key lines of evidence suggesting this hypothesis is erroneous, although the possibility of aluminum aggravating or accelerating clinical decline in dementia remains under investigation. The aluminum-AD hypothesis emerged after a study in rabbits, where it was observed that intracerebral injection of aluminum resulted in neurofibrillary tangles and plaques that appeared similar to those that occur in AD.[234] Although initially suggestive, it was subsequently shown that the aluminum-associated plaques lacked apple-green birefringence under Congo red staining (indicating they were not composed of amyloid, as they would be in AD),[236] the localization of the plaques was principally at the cell body of neurons rather than diffusely as seen in AD,[237] and the neurofibrillary tangles were composed of neurofilament rather than tau as is the case in AD.[236] Autopsied brain specimens from patients with AD are inconsistent in demonstrating increased aluminum burden, may reflect contamination, and, most critically, cannot be used to retrospectively establish a direction of causality.[238–240]

Clinical experience with dialysis encephalopathy and preterm infants given high-aluminum total parenteral nutrition establishes that aluminum exhibits neurotoxicity under conditions of sustained, high systemic (often intravenous) exposure, and impaired clearance — conditions that are not comparable to intramuscular exposure via vaccines.[241,242] Superficially, this would appear to support a potential association between aluminum and AD, but the presence of seizures in dialysis encephalopathy as a cardinal pathologic manifestation is not consistent with AD.[243] AD is also associated with blood-brain barrier dysfunction, potentially enhancing aluminum deposition to the central nervous system (CNS), suggesting deposition may be an effect, rather than a cause, of AD.[244] Finally, a meta-analysis of 7 studies (n = 6310) examining the risk of AD in the context of aluminum-containing antacid use found no evidence for a link.[245]

A separate hypothesis posits that alum-laden macrophages may traffic from the injection site to the CNS, a concept largely derived from a single experimental study.[246] The study's most critical flaw is that the investigators actively induced CCL2-dependent translocation of alum into the CNS by directly supplying the chemokine into the brain

via catheter.[246] This model is artificial, forcing blood-brain barrier disruption and thus failing to represent human physiology after intramuscular vaccination or a clinically relevant mechanism of alum neurotoxicity.[247–249]

Finally, it is notable that the literature consistently finds vaccination with alum-adjuvanted vaccines is associated with reduced risk of dementia.[250–256] The available data do not support a long-term neurologic hazard from vaccine alum.

Allergic Disease and Asthma

Alum promotes the production of antigen-specific immunoglobulin E (IgE) antibodies, the critical effector for type 1 hypersensitivity reactions.[257,258] However, alum's induction of IgE is antigen specific, and vaccination is not shown to sensitize to common allergens.[259] Nonetheless, because of alum's propensity to elicit IgE, some have raised concerns that alum might contribute to allergy risk.[260] Hypersensitivity reactions to alum are well documented: subcutaneous nodules, which are self-limited delayed-type hypersensitivity reactions, rarely occur following exposure to alum (especially if administered subcutaneously rather than intramuscularly), and children usually lose this reactivity over time.[261–265] Moreover, the suggestion that alum contributes to allergic disease encounters challenges on both mechanistic and epidemiological grounds.

To treat certain severe allergies, alum is incorporated with allergens as part of SCIT,[266–268] which promotes production of blocking IgG1 and IgG4 antibodies.[269–272] These antibodies function to prevent allergic reactions by outcompeting mast cell–bound IgE for epitopes and suppressing the IgE-mediated signaling that enables mast cell degranulation.[269–273] Although alum is used in experimental models of asthma, it is neither necessary nor sufficient to induce airway hyperreactivity and cannot produce it on its own.[274–276] Furthermore, alum induces IL-10, which promotes the induction of regulatory T cells that are protective in allergic disease.[110,277–280]

A single US observational study reported an association between modeled cumulative aluminum exposure from vaccines before age 24 months and persistent asthma diagnosed at ages 24 to 59 months, with small effect sizes (adjusted hazard ratio per 1-mg increase: 1.26 in children with eczema vs 1.19 in children without eczema).[281] Because eczema is a strong marker of atopic predisposition and asthma risk, a causal pathway through immune dysregulation would be expected to produce a markedly greater increase in asthma risk among children with eczema.[282] Instead, the study identified only a minimal incremental difference, which weakens the plausibility of a true biologic effect. Furthermore, the association weakened when children were compared in more closely matched groups.[281] Notably, the models could not adjust for breastfeeding status, environmental exposures, or family history of atopy—all factors linked to asthma risk.[282–285] Taken together, the evidence indicates that the observed association between vaccine alum and asthma more likely reflects residual differences between groups, such as environmental exposures or baseline health not captured by the models (ie, unmeasured confounding), rather than a true effect of vaccine alum.

Two large, population-based cohorts provide critical context. A nationwide Danish cohort of more than 1.2 million children that modeled cumulative aluminum from vaccine exposures found no increased risk of asthma or allergic disease between vaccinated and unvaccinated children.[230] In addition, a large, nationally representative cohort study of more than 15 000 German children that compared vaccinated with unvaccinated participants found no increased risk of atopic disease among vaccinated children and noted a decrease in allergic rhinitis diagnoses associated with vaccination.[286,287] The sum of the available, high-quality evidence does not support a relationship between exposure to vaccine alum and allergic diseases.[230,286,287]

Autoimmune Disease

Several autoimmune conditions can be triggered by vaccination, but these events are generally rare, are self-limited, or occur more frequently after natural infection than after immunization (Table 3).[288–301] Although many autoimmune diseases have been reported to occur sporadically in association with various vaccines,[302] epidemiologic evidence is consistent in finding associations with immune thrombocytopenia,[288,289,303] Guillain-Barré syndrome,[290–292,298–300,304,305] and the recently described vaccine-induced immune thrombosis with thrombocytopenia[295,296,301]; none of these are associated with alum-adjuvanted vaccines.

A proposed clinical entity, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), posits that vaccine adjuvants trigger systemic autoimmunity.[306] To date, this construct has not been substantiated by high-quality human evidence, particularly for alum-adjuvanted pediatric vaccines, and is not a recognized diagnosis by professional allergy and immunology societies.[307–309] Given that escalating inflammatory intensity heightens the risk for autoimmunity,[310–318] several features argue against a causal role for alum in the development of autoimmune disease.[110,319–333] First, alum is a less potent stimulator of the immune system than other licensed vaccine adjuvants,[329,332–334] which are in turn less potent than pathogen-associated molecular patterns from natural infections (ie, endotoxin, viral RNA, etc).[335–340] Second, alum demonstrates excellent tolerability: systemic reactions (eg, fever) are uncommon and transient,[12,77] with the notable exception of rare NLRP3 gain-of-function syndromes,[341–345] arguing against a propensity to drive chronic, deleterious inflammation. Third, alum's induction

TABLE 3. Autoimmune Diseases Associated With Vaccination and Their Incidence Following Vaccination vs Infection (None Associated With Alum-Adjuvanted Vaccines)

Autoimmune Disease	Incidence From Vaccination	Incidence From Infection	Comments
Immune thrombocytopenia	~1 in 30 000 doses of MMR[288]	At least 1 in 3000 rubella cases, manifesting with purpura[289]	Generally self-limiting in children[303] and generally does not recur with second doses of MMR.[431]
Guillain-Barré syndrome	1–2 per million doses of influenza vaccine[290]	17.2 per 1 million medically attended influenza infections[290]	Evidence of a link between seasonal influenza vaccination and excess cases of Guillain-Barré is firmly established only for the 1976 vaccine; in other seasonal vaccine data, the risk increase is not consistently observed.[292]
	3 per million doses of recombinant zoster vaccine[294]	Rare from zoster; rate not well defined[432]	
	6.5–9 attributable cases per million doses of protein RSV vaccine[433]	Rare from RSV; rate not well defined[434]	
	Approximately 3–6 cases per million doses of adenovirus vectored COVID-19 vaccine[291,298]	14.5 cases per million positive SARS-CoV-2 tests[300]	
Immune thrombosis with thrombocytopenia syndrome	3–15 per million initial vaccinations with adenovirus vectored vaccines[295,296,301]	Recognized as a rare consequence of adenovirus infections but rate not defined[297]	Identified through robust pharmacovigilance. For Janssen, the signal was investigated after 6 cases were identified in >6.8 million doses.[435] Demonstrates the sensitivity of vaccine pharmacovigilance.

Abbreviations: MMR, measles/mumps/rubella; RSV, respiratory syncytial virus.
Note that none of the above vaccines are adjuvanted with alum.

of IL-4[329,332–334,346,347] leads to upregulation of the inhibitory receptor FcγRIIB on macrophages, which generally protects against autoimmune disease and exerts anti-inflammatory effects.[348–352] Lastly, alum is a poor activator of CD8 T cells, which are critical to the pathogenesis of certain autoimmune diseases (such as vitiligo and type 1 diabetes).[353–356]

Within the proposed ASIA construct, macrophagic myofasciitis (MMF) warrants discussion.[357,358] MMF is an expected histologic reaction to alum, characterized by infiltration of alum-laden macrophages in skeletal muscle at prior aluminum-adjuvanted injection sites.[200,358–360] MMF is also proposed to be associated with diffuse arthralgias, myalgias, fatigue, and myalgic encephalomyelitis/chronic fatigue syndrome, among other symptoms.[357,361] However, available evidence does not support an association between these symptom complexes and alum-adjuvanted vaccination because MMF lesions are present in healthy individuals as well as those reporting symptoms.[358–360] Additionally, in nonhuman primates, similar lesions develop after vaccination without accompanying evidence of disease through 12 months of follow-up.[200] Although a theoretical contribution of genetic susceptibility or other modifying factors cannot be excluded, no evidence to date supports such interactions or demonstrates any link between MMF lesions and systemic symptoms. Collectively, the evidence supports MMF as a marker of vaccination rather than a pathologic entity.

Beyond biological implausibility, human epidemiologic data are reassuring. Following vaccination, direct evaluations have found rates of autoimmune outcomes in vaccinees comparable to background incidence.[293,304,362–376] Further, in a large cohort of more than 18 000 patients with allergic disease receiving SCIT with alum-adjuvanted allergens, subsequent autoimmune diagnoses were less frequent than in more than 400 000 matched patients treated with intranasal steroids and antihistamines.[377] These SCIT patients received far greater cumulative aluminum exposure than that received through the AAP schedule and were found to have a lower risk of autoimmune disease compared with the conventional therapy group.[377] Overall, extensive epidemiologic data fail to substantiate a link between exposure to alum and autoimmune disease.

COMMUNICATING ABOUT ALUMINUM-CONTAINING ADJUVANTS

Questions about aluminum adjuvants may arise in pediatric practice.[378,379] Caregivers want to understand why aluminum is present in vaccines, how much their children are exposed to (Tables 1 and 2), and whether this exposure is harmful. For clinicians, these conversations require a balance of evidence, clarity, and empathy.[380–384] Communication that validates concerns while providing accurate information is most effective in reducing caregiver anxiety and maintaining vaccine confidence and uptake[380,381,384–392]; merely sharing facts about vaccines is generally ineffective in increasing intent to vaccinate.[393] Clinician trust remains critical,[384,391,394] and health care clinicians with longstanding rapport are consistently rated among the most trustworthy sources of medical information for patients.[395,396]

Caregivers may ask: *Why is aluminum present in vaccines?*

The answer is straightforward: aluminum salts are included as adjuvants that improve immune response and reduce side effects compared with alternative vaccine

designs.[5,6,79,329,332–334] This allows the vaccine to provide robust, long-lasting protection against infectious diseases that cannot be generated without adjuvants.[38,45–58]

Another concern is: *How much aluminum do children receive?* (Tables 1 and 2).

Aluminum is the third-most abundant element on Earth and is ubiquitous.[161] Individual aluminum exposure will vary but will range from 4.14 to 7.47 mg of aluminum via the AAP schedule through age 18 (Tables 1 and 2), a level at which there is no credible evidence of toxicological risk.[168,170,171,173,175] The fact that individual antacid doses can contain markedly more aluminum than the entire AAP schedule and can occasionally be absorbed sufficiently to produce an aluminum toxicity, but no such reports following vaccination with aluminum-adjuvanted vaccines exist, is reassuring.[182,397,398] Moreover, alum forms depots that release aluminum slowly, such that it is easily cleared by the kidneys.[176,200,204] Consistent with this, no change in blood aluminum levels after vaccination can be detected in preterm infants.[163] Finally, SCIT involves much greater levels of exposure to aluminum than the AAP schedule yet is tolerated without issue.[173,377] These pharmacokinetic distinctions can reassure caregivers that vaccination does not result in meaningful systemic accumulation.

Caregivers may ask: *Has aluminum in vaccines been linked to specific diseases: ASD, autoimmune conditions, or asthma?*

The strongest available studies, drawing on hundreds of thousands to more than a million children, consistently find no association.[222–233,292,304,305,363,364,366,368,373,375,377,399–404] Small signals occasionally reported in observational studies[281] have not been replicated in larger independent cohorts,[230] underscoring the importance of scale and replication in interpreting such findings. For clinicians, acknowledging the existence of these studies while emphasizing the weight of the overall evidence can be an effective strategy for maintaining credibility.

Finally, the *framing of relative risk* can be powerful.

Clinicians can remind families that alum adjuvants represent one of the most studied components of vaccines, with a safety record extending nearly a century and across billions of doses.[11,14,230,405–407] The risks posed by the vaccine-preventable diseases themselves (Table 4) are concrete and serious, whereas the risks attributed to alum are speculative and unsupported by high-quality evidence. Positioning vaccination as the far safer option aligns with both scientific evidence and clinical experience (Table 5).

CONCLUSION

Alum remains an essential component of many pediatric vaccines, enhancing immunogenicity, allowing dose sparing, and contributing to durable protection. Over nearly a century, alum-adjuvanted vaccines have demonstrated an exceptional safety record supported by convergent

TABLE 4. Infectious Diseases Preventable With Alum-Adjuvanted Vaccines

Pathogen	Major Outcomes of Concern
Hepatitis B virus (HBV)	• Cirrhosis[436] • Death[436] • Fulminant hepatitis[436] • Hepatitis D infection[437] • Hepatocellular carcinoma[436] • Membranous nephropathy[438] • Polyarteritis nodosa[439]
Streptococcus pneumoniae (Pneumococcus)	• Death[440] • Empyema[441] • Endocarditis[442] • Hearing loss[443] • Invasive pneumococcal disease[444] • Mastoiditis[445] • Meningitis[446] • Otitis Media[447] • Pericarditis[448] • Pneumonia[449] • Peritonitis[450] • Sinusitis[451] • Septic arthritis[452] • Waterhouse-Friedrichsen syndrome[453]
Haemophilus influenzae type b (Hib)	• Bacteremia[454] • Death[455] • Epiglottitis[456] • Meningitis[457] • Pericarditis[458] • Pneumonia[459] • Septic arthritis[460] • Waterhouse-Friedrichsen syndrome[461]
Corynebacterium diphtheriae (Diphtheria)	• Death[462] • Laryngeal diphtheria[462] • Myocarditis[462] • Nephritis[463] • Pharyngeal and tonsillar diphtheria[462] • Polyneuritis[464]
Clostridium tetani (Tetanus)	• Cephalic tetanus[465] • Death[465] • Dysautonomia[465] • Generalized tetanus[465] • Local tetanus[465] • Neonatal tetanus[465]
Bordetella pertussis (Pertussis)	• Apnea[466] • Death[467] • Encephalopathy[468] • Pneumonia[466] • Rib fracture[469] • Seizures[466]
Hepatitis A virus (HAV)	• Death[470] • Fulminant hepatitis[470]
Neisseria meningitidis (Meningococcus)	• Death[471] • Hearing loss[471] • Limb amputation[471] • Meningitis[471] • Meningococcemia[471]

(Continued on next page)

TABLE 4. Infectious Diseases Preventable With Alum-Adjuvanted Vaccines (Continued)	
Pathogen	**Major Outcomes of Concern**
	• Myocarditis[471] • Pericarditis[471] • Pneumonia[471] • Purpura fulminans[471] • Waterhouse-Friedrichsen syndrome[471]

TABLE 5. Clinician Talking Points for Aluminum Adjuvant Conversations
1. **Aluminum is present by design.** It serves as an adjuvant to make vaccines more effective and durable, not as a preservative or filler.
2. **Human data outweigh preclinical signals.** Laboratory and animal studies may identify potential risks, but vaccination counseling should be grounded in rigorous and high-quality human data. To date, human studies have not substantiated harm from aluminum-adjuvanted vaccines.
3. **No credible evidence links aluminum to chronic disease.** Large, well-designed studies show no association with autism spectrum disorder, asthma, or autoimmune outcomes.
4. **Empathy precedes evidence discussion.** Listening to caregivers' concerns and validating their questions builds trust; evidence is then more likely to be heard and accepted.
5. **Strong recommendation matters.** A clear, confident clinician recommendation remains the most powerful predictor of vaccine acceptance.

evidence from pharmacokinetic data, prospective clinical trials, and large population-based cohorts.

Local reactions such as transient injection-site pain or nodules are the most common adverse effects and are generally mild. Systemic safety concerns (ASD, neurotoxicity, allergic disease, and autoimmune disease) have been rigorously studied, with large and well-conducted analyses finding no causal association.

Contextualized against other sources of aluminum exposure, including diet and medical therapies, vaccines represent a small and transient contribution. Theoretical risks remain far outweighed by the demonstrated benefits of preventing severe, potentially fatal infectious diseases.

For clinicians, this evidence base allows for confident reassurance of patients, parents, and caregivers (Table 5). Clear, empathetic communication that contextualizes exposure, emphasizes high-quality evidence, and reinforces the benefits of immunization can address concerns and maintain trust in vaccination.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AD: Alzheimer disease
ASD: autism spectrum disorder
ASIA: autoimmune/inflammatory syndrome induced by adjuvants
ATSDR: Agency for Toxic Substances and Disease Registry
CNS: central nervous system
DTaP: diphtheria/tetanus/acellular pertussis
HAV: hepatitis A virus
HBV: hepatitis B virus
Hib: *Haemophilus influenzae* type B
HPV: human papillomavirus
IgE: immunoglobulin E
IgG1: immunoglobulin G1
IgG4: immunoglobulin G4
IL: interleukin
IPV: inactivated polio vaccine
MenABCWY: meningococcal (*Neisseria meningitidis*) capsule groups A, B, C, W, and Y
MenACWY: meningococcal (*Neisseria meningitidis*) capsule groups A, C, W, and Y
MenB: meningococcal (*Neisseria meningitidis*) capsule group B
MMF: macrophagic myofasciitis
MMR: measles/mumps/rubella
MRL: minimal risk level
RSV: respiratory syncytial virus
SCIT: subcutaneous immunotherapy
Tdap: tetanus/reduced dose diphtheria toxoid/acellular pertussis

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