Vaccines and Aluminum Adjuvants

Considerations and Query for the Advisory Committee for Immunization Practices

Presented by Dr. Evelyn Griffin, MD, FACOG, IFMCP
Child/Adolescent Immunization Schedule Work Group
Vaccinations during Pregnancy Work Group
HPV Work Group

Background

Child/Adolescent Immunization Schedule Work Group Discussion

Objectives

ACIP Charter: provide “advice and guidance to the Director of the CDC regarding the use of vaccines and related agents”

- Consideration of an ACIP Adjuvant Work Group
- Educational forum

Vaccine Overview

Some categories of vaccines:

- live attenuated (ie MMR), killed/subunit/recombinant, gene therapy-based

Many ingredients in vaccine products:

- Antigens
- Adjuvants
- Preservatives
- Stabilizers
- Surfactants
- Residuals
- Diluents
- (Adulterants in rare cases)

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Each vaccine is unique, and each component may contribute to risk, safety, efficacy, and effectiveness of a vaccine final drug product.

What is an Adjuvant?

- An adjuvant is any substance or compound added to a vaccine to enhance the body's immune response to the antigen (portion that mimics the pathogen).
- It stimulates the innate and adaptive immune responses to augment vaccine efficacy and longterm effectiveness.

Vaccine Overview: Adjuvants

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Does the FDA approve adjuvants?

- FDA approves final drug products, it does not approve adjuvants.
- There are no “FDA approved” adjuvants.

Are there Different Types of Adjuvants?

- Some adjuvants and adjuvant categories:
  - Aluminum salts
  - Oil-in-water emulsions
  - Liposome-based
  - Toll-Like Receptor (TLR) agonists
  - Saponin (plant) -based

- Most killed/subunit/recombinant vaccines rely on aluminum salt-based adjuvants (ABA). Since the 1920s, these have been the most widely used adjuvants in FDA-licensed human vaccines.
- Examples of ABA: aluminum oxyhydroxide (Alhydrogel®) and aluminum hydroxyphosphate (Adju-Phos®)

Aluminum and Aluminum Salt Adjuvants

- Aluminum is the most abundant metal in the Earth's crust.
- Aluminum is never found as a free metal in nature because it is "a very reactive element".
- Environmental aluminum is NOT the same as aluminum salts used in vaccine adjuvants
- The vaccine adjuvant activity of aluminum salts was discovered largely by accident by British immunologist Alexander Glenny in the 1920s.
- Aluminum salts trigger local inflammation and recruit antigen-presenting cells (dendritic cells, macrophages).
- Aluminum salt adjuvants predominantly drive an antibody response (Th2) rather than a cellular immune response (Th1).

Biodistribution and Pharmacokinetics

Movsas et al. 2013

The only published/peer-reviewed study of aluminum blood levels observed in infants after aluminum-adjuvant containing vaccine administration.

- Sample size (n= 15), serum aluminum levels measured before and 24 hours after vaccination
- No significant detectable mean increase at 24h relative to pre-vax levels
- No long-term data, or organ distribution data

Current US Aluminum Exposure Limits

US Agency for Toxic Substances and Disease Registry (ATSDR) determined a Minimum Risk Level (MRL) for orally ingested aluminum:

- Oral MRL ≈ 1 mg (1,000 mcg) Al/kg/day based on animal data
- Assumes ~0.1% oral absorption
- Converted to an injected-equivalent threshold,

this approximates 1 mcg/kg/day

Current US Aluminum Exposure Limits

The U.S. Code of Federal Regulations (21 CFR 610.15(a)) limits aluminum in vaccines to ≤0.85 mg (850mcg) per dose, regardless of age group.

- Flarend et al., 1997: Doses up to 850 mcg total IM aluminum (including aluminium hydroxide and aluminium phosphate adjuvants) in rabbits resulted in transient blood level increases that resolved quickly, with no acute or chronic adverse effects observed.
- This is still the current FDA-accepted benchmark for human vaccine adjuvant dosing.
- Masson et al., 2018 examined the limitations of using the Flarend study as a basis for regulatory threshold setting.

Why Focus on Aluminum Dose in Vaccines?

- Infants receive multiple aluminum-containing vaccines in a single visit under the current schedule.
- Dose per kilogram body weight is far higher in early infancy than in adults.
- Neonatal kidneys, blood–brain barrier, and detoxification systems are immature.

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*There are similar considerations for children and fetuses through pregnancy vaccination.

Aluminum Content in Different Vaccines

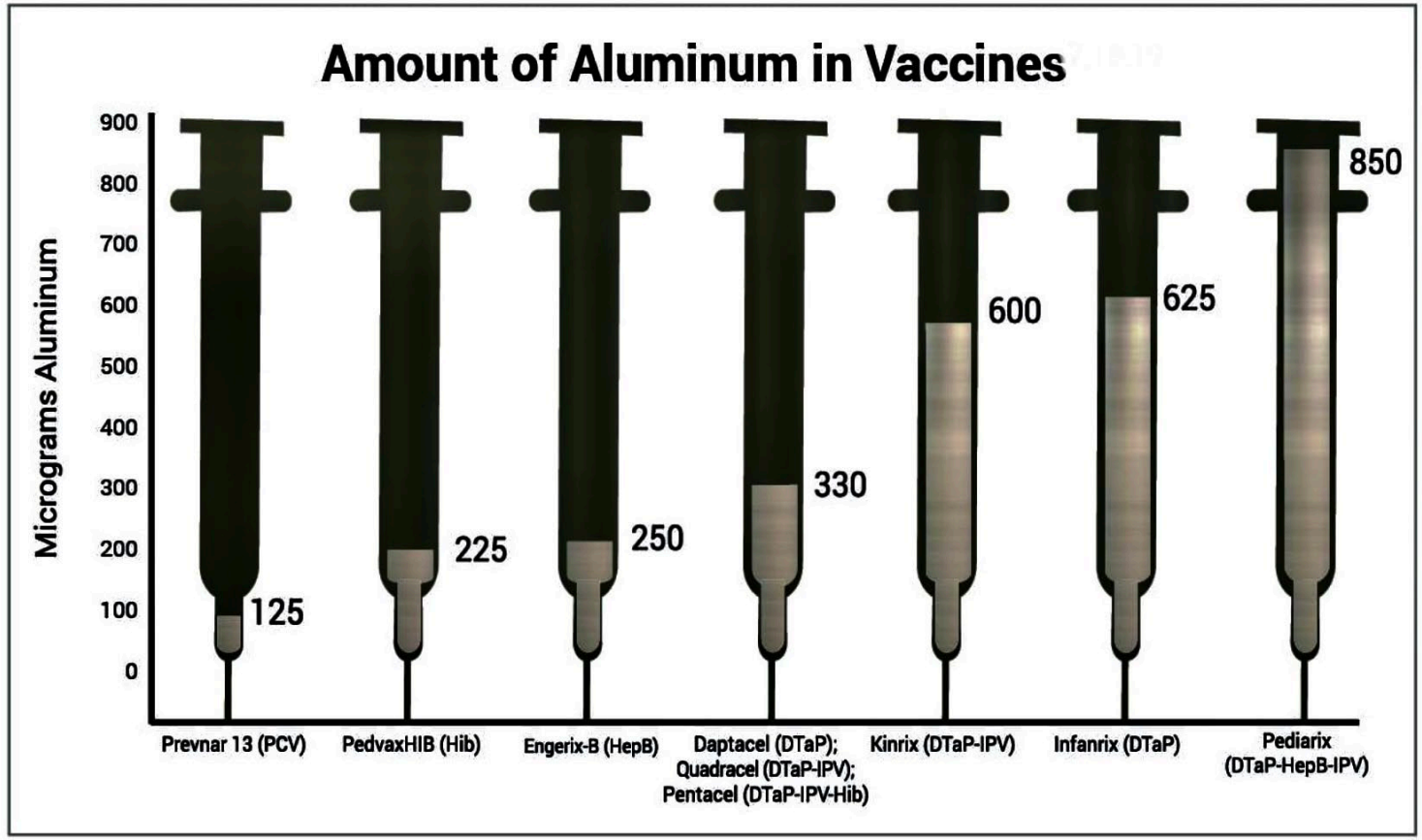
Vaccine	Amount	HepB	DTaP	Hib	Polio
PedvaxHIB	0.225 mg			X	
Recombivax-HB	0.250 mg	X			
Vaxelis	0.319 mg	X	X	X	X
Pentacel	0.330 mg		X	X	X
Daptacel	0.330 mg		X		
Quadracel	0.330 mg		X		X
ActHIB	0 mg			X	
Engerix-B	0.250 mg	X			
Pediarix	0.850 mg	X	X		X
Infanrix	0.625 mg		X		
Kinrix	0.500 mg		X		X
Hiberix	0 mg			X	
Ipol	0 mg				X

Aluminum Content in Different Vaccines

Vaccine	Amount	Pneumococcal	HepA	HPV
Prevnar20	0.125 mg	X		
Vaxneuvance	0.125 mg	X		
Vaqta	0.225 mg		X	
Havrix	0.250 mg		X	
Gardasil 4	0.225 mg			X
Gardasil 9	0.500 mg			X
Cervarix (2)	0.500 mg			X

* MMR, varicella, rotavirus, meningococcal A and influenza vaccines are aluminum free

Multiple Aluminum Adjuvanted Vaccine Doses Results in Cumulative Aluminum Exposure



The administration of one dose each of Prevnar 20, PedvaxHIB, Engerix-B, and Infanrix at one visit delivers **1,225 mcg** of aluminum.

PCV, Hib, HepB, and DTaP vaccines are administered multiple times by 6mo of age.

The rate at which aluminum from vaccines migrates from human muscle to the bloodstream is not known.

Vaccine Selection Can Double Aluminum Exposure on the Same Schedule

Birth	Recombivax-HB	0.250 mg	Engerix-B	0.250 mg
2 m	Vaxelis	0.319 mg	Pediarix+Hiberix	0.850 mg
4 m	Pentacel	0.330 mg	Infanrix+Hiberix+Ipol	0.625 mg
6 m	Vaxelis	0.319 mg	Pediarix+Hiberix	0.850 mg
12 m	ACTHIB	0.000 mg	Hiberix	0.000 mg
Total Aluminum		1.218 mg		2.575 mg

* **Children in Denmark are exposed to 3-4 fold lower amounts of aluminum during the first 12 months of life**

US FDA Child Health Concerns, June 2003

"Term infants with normal renal function may also be at risk because of their rapidly growing and immature brain and skeleton, and an immature blood-brain barrier. Until they are 1 to 2 years old, infants have lower glomerular filtration rates than adults, which affects their kidney function. The agency is concerned that young children and children with immature renal function are at a higher risk resulting from any exposure to aluminum.”

Cited in the Federal Register

Aluminum Biodistribution

Experimental and clinical data suggest intramuscular injected aluminum and aluminum salts can persist at the injection site, then migrate via immune cells to liver, spleen, and other organs including the brain.

ELSEVIER

PII: S0264-410X(97)00041-8

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In vivo absorption of aluminium-containing vaccine adjuvants using ^{26}Al

Richard E. Flarend*, Stanley L. Hem†‖, Joe L. White‡, David Elmore*, Mark A. Suckow§, Anita C. Rudy¶ and Euphemie A. Dandashli†

Aluminium hydroxide (AH) and aluminium phosphate (AP) adjuvants, labelled with ^{26}Al, were injected intramuscularly (i.m.) in New Zealand White rabbits. Blood and urine samples were collected for 28 days and analysed for ^{26}Al using accelerator mass spectrometry to determine the absorption and elimination of AH and AP adjuvants. ^{26}Al was present in the first blood sample (1 h) for both adjuvants. The area under the blood level curve for 28 days indicates that three times more aluminium was absorbed from AP adjuvant than AH adjuvant. The distribution profile of aluminium to tissues was the same for both adjuvants (kidney > spleen > liver > heart > lymph node > brain). This study has demonstrated that in vivo *mechanisms are available to eliminate aluminium-containing adjuvants after i.m. administration. In addition, the pharmacokinetic profiles of AH and AP adjuvants are different. © 1997 Elsevier Science Ltd.*

Keywords: adjuvant absorption, antigen desorption, ^{26}Al

"The distribution profile of aluminium to tissues was the same for both adjuvants (AH and AP) kidney > spleen > liver > heart > lymph node > brain."

Persistence and Macrophagic Myofasciitis

Gherardi RK et al

Macrophagic myofasciitis (MMF)

- Muscle biopsies show aluminum-containing macrophages in granulomas at prior IM vaccination injection sites (MMF lesions).
- Symptoms in many MMF patients: chronic myalgias, fatigue, and cognitive difficulties.
- Causal link between injected aluminum or aluminum salts (aluminum oxyhydroxide) to systemic symptoms is not universally accepted.
- Demonstrates long-term persistence of aluminum in human tissue.

Aluminum Based Adjuvants: Biocompatible and Always Well Tolerated?

- Exley and Mold, 2019: Aluminum in postmortem brain tissue of neurological patients, reflecting cumulative environmental exposure
- Shoenfeld and Agmon-Levin, 2011: Auto Immune/Inflammatory Syndrome Induced by Adjuvants
- Shaw and Tomljenovic, 2014: aluminum neurotoxicity
- Daley et al., 2023: Association between aluminum exposure from vaccines before age 24 months and persistent asthma at age 24 to 59 Months
- Emerging research in mechanisms of aluminum oxidative stress: mitochondrial dysfunction, and impaired energy metabolism, pro-inflammatory effects and microglial activation, promotion of amyloidogenesis and disruption of metal homeostasis (i.e. iron)

Aluminum Adjuvant Toxicology: Data Gaps and Ambiguity

- Currently available infant safety assessments rely on a small number of toxicokinetic studies and modeled assumptions.
- No long-term human studies tracking vaccine-derived aluminum kinetics in infants or children have been published.
- Critical reviews challenge absorption factors and clearance assumptions in influential models (e.g., Mitkus 2011)
- No large, prospective, well-controlled studies comparing neurodevelopmental or autoimmune outcomes by cumulative aluminum dose have been performed or published.
- No established safe dose of injected aluminum for fetuses, neonates and preterm infants has been established.
- Existing toxicology and pharmacokinetic data are too sparse and model-dependent to support definitive conclusions of safety at current cumulative doses.

Query for ACIP

How should ACIP continue to assess effectiveness and safety of adjuvants in currently authorized vaccines on the schedule (childhood/adolescent, adult, and vaccines during pregnancy), and related implications of the entire schedule?

Additional discussion

- Should multiple aluminum-containing vaccines be administered on the same day in early infancy?
- Should lower-aluminum formulations and spacing strategies be preferred when possible?
- What research is needed to define a genuinely evidence-based safety margin for injected aluminum?
- What prudent policy would reduce peak and cumulative aluminum exposure in the most vulnerable while urgent research gaps are addressed?

Acknowledgement & Invitation For Collaboration