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Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

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ABSTRACT

FDA regulations require safety testing of constituent ingredients in drugs (21 CFR 610.15). With the exception of extraneous proteins, no component safety testing is required for vaccines or vaccine schedules. The dosing of aluminum in vaccines is based on the production of antibody titers, not safety science. Here we estimate a Pediatric Dose Limit that considers body weight. We identify several serious historical missteps in past analyses of provisional safe levels of aluminum in vaccines, and provide updates relevant to infant aluminum exposure in the pediatric schedule considering pediatric body weight. When aluminum doses are estimated from Federal Regulatory Code given body weight, exposure from the current vaccine schedule are found to exceed our estimate of a weight-corrected Pediatric Dose Limit. Our calculations show that the levels of aluminum suggested by the currently used limits place infants at risk of acute, repeated, and possibly chronic exposures of toxic levels of aluminum in modern vaccine schedules. Individual adult exposures are on par with Provisional Tolerable Weekly Intake "limits", but some individuals may be aluminum intolerant due to genetics or previous exposures. Vaccination in neonates and low birth-weight infants must be re-assessed; other implications for the use of aluminum-containing vaccines, and additional limitations in our understanding of neurotoxicity and safety levels of aluminum in biologics are discussed.

1. Introduction

Aluminum is used as an adjuvant in vaccines licensed by the US Food and Drug Administration [1–7] to enhance the immunogenicity of the vaccine in various forms (e.g., aluminum oxyhydroxide and aluminum hydroxyphosphate) [9,10] (Fig. 1). The Center for Biologics Evaluation and Research (CBER) sets the amount of aluminum per dose in biological products, including vaccines, to 850 μg aluminum if measured by assay. Two additional levels are specified by the regulations (1140 and 1250 μg respectively), depending on how the level is measured [8].

The 850 μg of aluminum per vaccine FDA amount was derived from data that demonstrated that this amount of aluminum per dose enhanced the antigenicity and effectiveness of the vaccine [9,10], but does not include safety considerations. Current amounts of aluminum are not adjusted to body weight of an infant. To avoid toxicity associated with variation in body weight between adults and children related to aluminum in vaccines, standard of care dose levels convert mg to mg/kg for the weight range being considered [28,39]. At the current time, there are no known or published studies specifically defining levels of Al in any vaccine product based on safety studies of Al.

Safety for aluminum from all sources is based on the No Observed Adverse Effect Level (NOAEL), Minimal Risk Level (MRL), and the Lowest Observed Affect Level (LOAEL) [15–20]. The Joint Expert Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) for aluminum to be 7000 μg/kg body weight per week in 1989, which applies to all aluminum compounds in food, including additives. That level remained in effect until 2011 when the PTWI was revised to 2000 μg Al/kg per week [12,13]. The Agency for Toxic Substances and Disease Registry (ATSDR) had used an MRL of 1000 μg Al/kg per day (7000 μg/kg per week) [24–27].

We found two important errors in the provenance and derivation of provisional aluminum intake levels from World Health Organization (WHO; Supplementary Material) which, unfortunately, led to overestimation of safe exposure levels.

Here we consider adjusted child equivalent aluminum doses (CED) in vaccines by body weight, to determine putative pediatric dose limits

Abbreviations: NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level; MRL, minimal risk level; JECFA, joint expert committee on food additives; ATSDR, agency for toxic substances and disease registry; PTWI, provisional tolerable weekly intake; PDL, pediatric dose limit; CED, child equivalent dose; HED, Human Equivalent Dose

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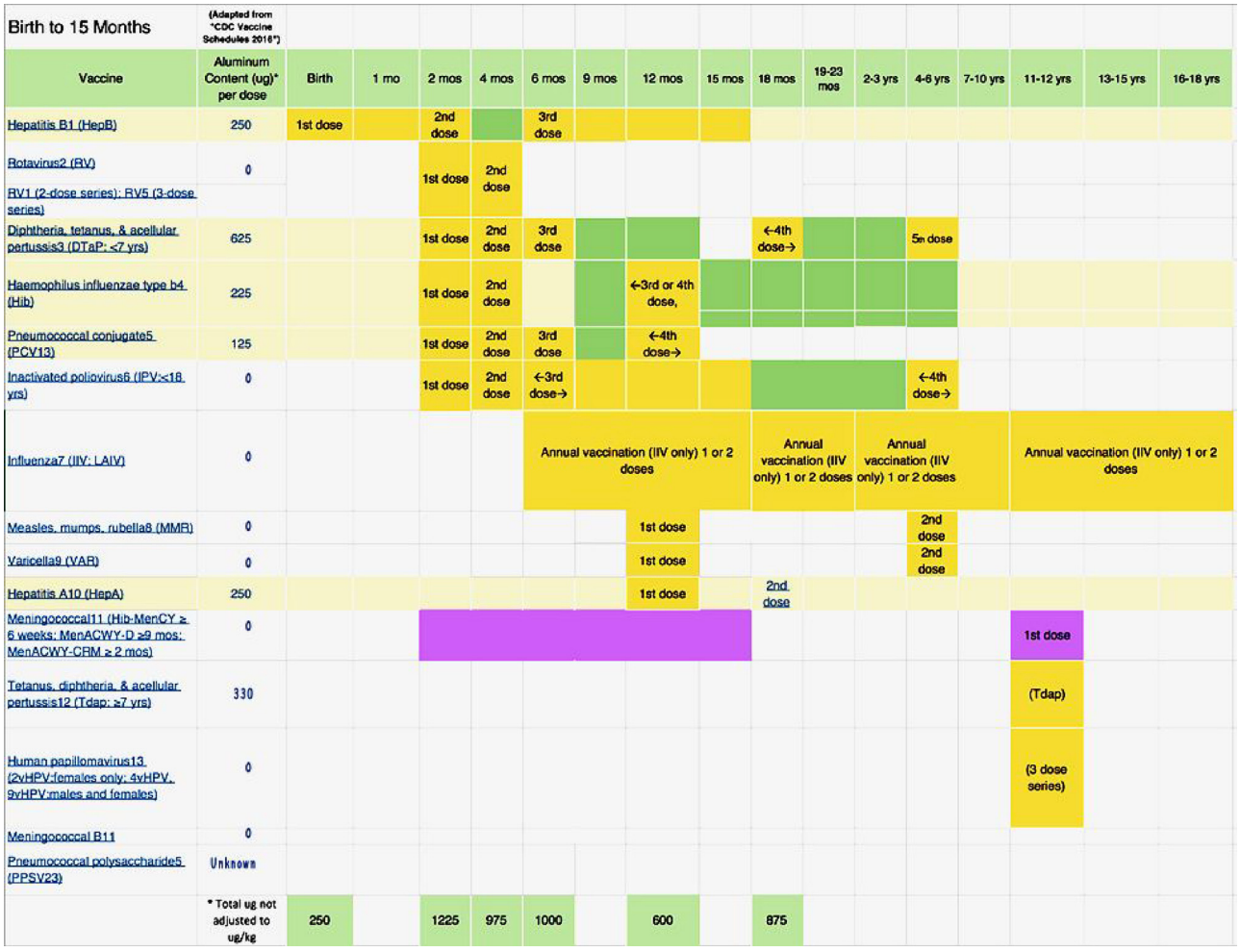

Fig. 1. Pediatric Vaccine Schedule 2016–2017.
The CDC schedule reflects the expected timing of administration of vaccines containing aluminum (shaded light yellow) as adjuvant at birth, 2, 4, 6, 12, and 18 months. The total amount of aluminum per vaccine visit (green shaded box below each scheduled interval) is reported from birth through 24 months.

(PDLs) of aluminum estimated by Clark's Rule for the pediatric population, to investigate further the effect those discrepancies that exist between the JECFA and ATSDR may have regarding the MRL of aluminum in biologics, and to compare relative dosing from dietary and injected sources in the pediatric population.

2. Materials and methods

2.1. FDA dose amounts of aluminum adjusted by body weight in infants and adults

FDA regulations require that proteins in vaccines be tested for safety. Aluminum is a known neurotoxin and it is unfortunate that additives in vaccines are not required to be subjected to animal safety studies prior to use on human subjects. Several known methods exist for pediatric dosing by weight. In Clark's Rule [28–39] of pediatric dose calculations, for example, the adult body weight reference is usually (as published) considered to be 150 bs. (68 kg) with the calculated dose being converted to mg/kg.

Aluminum toxicity studies use 60 kg as the reference adult body weight to calculate the MRL and LOAEL [16–18]. For that reason, we used 60 kg as the adult body weight reference rather than the more commonly used 68 kg adult body weight reference in Clark's Rule of pediatric calculations. Our calculations are thus consistent with past aluminum toxicity studies [16–18], and more comparable to the toxicities at the No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effects Level (LOAEL).

Each of the established FDA-approved doses of 850 μg, 1140 μg, and 1250 μg were converted to the equivalent dose expressed in mg/kg using Clark's Rule [28,39]:

$$Child's\ Dose\ (\mathrm{mg}) = Adult\ Dose\ (\mathrm{mg}) \times \frac{BW\,(Child)lbs}{BW\,(Adult)lbs}$$

The body weights for infants from birth through 24 months used in the Clark's Rule calculation were obtained using calculated monthly growth velocities obtained from Weight for Age standards in males and females from the 5th to the 95th percentile [40,41]. The resulting pediatric doses were compared to the same doses in an adult also adjusted by the body weight of 60 kg.

2.2. Minimal risk level of aluminum in children

Minimal Risk Levels (MRLs) are usually derived for hazardous substances using the NOAEL/uncertainty factor approach [16,17] to avoid toxicities [21]. The resulting exposures using the adjusted body weight calculations are presented by plotting the calculated MRL in children against the FDA doses of 850 μg adjusted by body weight at the 50th percentile in children birth through 24 months.

We estimated the human equivalent dose (HED) [11,20,21] in a child first obtaining the adult HED using the equation

HED = Animal dose NOAEL (mg/kg) × [Animal weight (kg)/Human