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Toxicology

Acute exposure and chronic retention of aluminum in three vaccine schedules and effects of genetic and environmental variation

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ABSTRACT

Like the mechanisms of action as adjuvants, the pharmacodynamics of injected forms of aluminum commonly used in vaccines are not well-characterized, particularly with respect to how differences in schedules impact accumulation and how factors such as genetics and environmental influences on detoxification influence clearance. Previous modeling efforts are based on very little empirical data, with the model by Priest based on whole-body clearance rates estimated from a study involving a single human subject. In this analysis, we explore the expected acute exposures and longer-term whole-body accumulation/clearance across three vaccination schedules: the current US Centers for Disease Control and Prevention (CDC) schedule, the current CDC schedule using low aluminum or no aluminum vaccines, and Dr. Paul Thomas' "Vaccine Friendly Plan" schedule. We then study the effects of an implicit assumption of the Priest model on whether clearance dynamics from successive doses are influenced by the current level of aluminum or modeled by the assumption that a new dose has its own whole-body dynamics "reset" on the day of injection. We model two additional factors: variation (deficiency) in aluminum detoxification, and a factor added to the Priest equation to model the potential impact of aluminum itself on cellular and whole-body detoxification. These explorations are compared to a previously estimated pediatric dose limit (PDL) of whole-body aluminum exposure and provide a new statistic: *%alumTox*, the (expected) percentage of days (or weeks) an infant is in aluminum toxicity, reflecting chronic toxicity. We show that among three schedules, the CDC schedule results in the highest *%alumTox* regardless of model assumptions, and the Vaccine Friendly Plan schedule, which avoids >1 ACV per office visit results in the lowest (expected) *%alumTox*. These results are conservative, as the MSL is derived from data used by FDA to estimate safety of aluminum in adult humans. These results demonstrate high potential utility of modeling variation in patient responses to aluminum. More empirical data from individuals who are suspected of being intolerant of aluminum from vaccines, evidenced by high aluminum retention, neurodevelopmental disorders and/or a myriad of chronic illnesses would help answer questions on whether the model predictions can be used to estimate parameter values tied to genetic factors including genomic sequence variation and family history of chronic illnesses tied to aluminum exposure.

1. Introduction

Aluminum compounds used in some vaccines include aluminum oxyhydroxide and aluminum hydroxyphosphate. Aluminum compounds are added specifically to provoke an immune response and therefore improve the ability of the vaccine to stimulate immunity. The precise mechanisms of aluminum as an adjuvant are not well characterized, but they induce a myriad localized cellular and systemic immunologic effects ([1]; 25,932,368) including Th2-skewed short-term response ([51], 20,132; 23,335,921) as opposed to a balanced Th1/Th2 long-term reaction ([2]; 9,627,130). Presented possibilities of mechanisms include cellular effects and molecular-level effects. Cellular effects include humoral antigen targeting ([1]; 25,932,368), cell death leading to cytokine release ([3]; 19,734,227) and macrophage activation ([4]; 27,139,352). Molecular pathway effects include activation of both the Complement System and the Alternative Pathway

Abbreviations: ACVs, Aluminum-containing vaccines; CDC, US Centers for Disease Control; CFR, Code of Federal Regulations (US); ER-stress, Endoplasmic reticulum stress; FDA, US Food and Drug Administration; PDL, Pediatric Dose Limit; MSL, Minimum Safe Level; *%alumTox*, A measure of the chronic toxicity of aluminum (whole body)

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including generation of anaphylatoxins ([5]; 24,040,248). At the tissue level, non-specific necrosis, apoptosis and a depot effect at the site of injection can occur ([57]; 23183095, [6]10837642, [7]; 17114826). A more recently proposed mechanism is that alterations of antigen and non-antigen protein shape in aluminum-intoxicated cells is associated with ER stress and the unfolded protein response(Lyons-Weiler, 2018 doi: 10.4172/2165–7890.1000224).

While aluminum content in some vaccinations may be necessary to enable these vaccinations to trigger immunity, total exposure to injected aluminum is also an important health consideration. Aluminum oxyhydroxide is currently allowed to be used in vaccines with per-dose limits that are body-weight independent. It may be used up to 25 μg/L in large-volume parenteral drug products (FDA; 21 CFR 201.323), and up to 1250 μg/single dose, depending on calculation method (FDA; Table 6; 21 CFR 610.15), "provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research" (FDA; 21 CFR 610.15). This regulation apparently does not, but perhaps should, apply to individual vaccine office visits to consider cumulative doses from multiple vaccines received at one time. The inexact regulatory *modus operandi* of employing per-dose aluminum limits that are independent of body weight are problematic, because the CDC schedule permits many vaccines per office visit (and thus per day).

Aluminum in the body has been cited as a likely contributing factor to both autoimmune conditions and other chronic illnesses ([8,9], 31,059,838; [10], 29,307,441; [11]; 27,908,630, [12]; 25,506,338). Person-to-person variation in whole body clearance rates due to genetics and environmental factors has been under-studied. Studies of human plasma or blood clearance rates ([13];15,152,306) offer little useful information to toxicology, for the known mechanisms of toxicity of aluminum are intracellular and are thus intra-tissue. Thus, rapid serum or blood clearance rates can be misleadingly reassuring when considering chronic or even acute toxicity of aluminum injected with vaccines. Aluminum in many forms has been long suspected of playing a role in Alzheimer's disease ([14]; 26,494,454) and is supported by studies showing disease symptom reduction from ingestion of silicon-rich mineral waters ([15]; 22,976,072). "Tagging" of aluminum released by detoxification with compounds in chlorella and spirulina ([16]; 7,687,764; [17]s; 23,986,974) may be essential to allow removal by the liver, and to prevent "detox-retox" that occurs when aluminum is freed from cell death, redistributed and deposited via resequestration within and among tissues in the body.

Medically, proper organ, cellular and body aluminum detoxification appears to be of ever-increasing importance: Aluminum has been found in the brains of patients with Parkinson's Disease ([18]; 29,189,118; [19]), Alzheimer's disease (Mizra et al., 2017; 28,159,219), epilepsy ([20]; 31,208,130), and autism ([21]; 29,413,113). Evidence is growing that a host of chronic illnesses of unknown cause that are difficult to diagnose such as PANDAS/PANS([22]; 25,150,567; [23], 29,309,797), chronic fatigue syndrome ([24]; 31,394,725) may at least in part be due to vaccine aluminum intolerance ([10]; [9], 31,059,838; Crepeaux et al., 2018; 29525002, Crepeux et al., 2017; 27,908,630; [12]; 25,506,338).

Aluminum compounds occur naturally in the environment and in food, but very little ingested aluminum is absorbed through the intestines. Total aluminum exposure is affected by the aluminum amount in individual vaccines and the timing of repeated vaccinations in the first two years of life. Dórea and Marques [25] (2009;20,010,978) compared the expected levels of aluminum uptake into the body from intravenous and oral intake and concluded that human infants have higher exposure to aluminum from vaccination than from food, water, and formula. Our calculations (Appendix) confirm that for the CDC schedule, infants up to six months of life receive most of their metabolically available aluminum from vaccines. It should be expected that most aluminum retained in the body of infants comes from vaccinations combined with the levels of exposure from other exposures to manifest health risks from total exposure, making the timing and total aluminum content of different vaccine schedules an important consideration. In this study, we explore the effects of different dose schedules, reflecting three different vaccination schedules, on aluminum retained fractions. We also study the effects of an important model construction assumption reflecting the effects of previous aluminum exposures on first-day clearance, genetic variation in clearance rates, and the potential impact of aluminum impairment on its own detoxification on the expected retained fraction in the body over time. We represent the results as the number of days a child can be expected to experience aluminum body burdens (i.e., the entire amount of aluminum present in the body) that exceed proposed safe levels of exposure in the first two years of life and emphasize the expected chronic toxicity in the first seven months of life.

2. Methods

This study considers three schedules: (A) the CDC schedule for 2019, (B) a CDC that we modified schedule specifically choosing low dose aluminum for DTaP and no aluminum for Hib vaccines, and (C) the schedule from Dr. Paul Thomas' "Vaccine-Friendly Plan" (VFP; [26]). The Vaccine Friendly Plan also chooses low dose aluminum for DTaP and no aluminum for Hib vaccinations as the modified CDC schedule, but delays HepB and HepA vaccinations. No aluminum Hib is given at the same time as either low dose aluminum DTaP or PVC13. Only one aluminum containing vaccine is given at a time with the Vaccine Friendly Plan schedule. The dosage and timing of all three schedules are summarized in Table 1.

Minimum safe levels (MSLs) for aluminum (in the form of aluminum oxyhydroxide, aluminum phosphate, or aluminum potassium sulfate) are equivalent to the Pediatric Dose Limit estimated by Lyons-Weiler and Ricketson (29,773,196), based on the FDA's limit of 850 μg of aluminum per dose for adults. Assuming an average adult weight of 60 kg and using Clark's rule (cited in Lyons-Weiler and Ricketson) leads to a target "safe" limit of 14.2 μg of aluminum per kg of body weight as a way of calculating a body weight-adjusted Pediatric Dose Limit (PDL: Lyons-Weiler and Ricketson, 29,773,196); Fig. 1. This curve, derived by Lyons-Weiler and Ricketson, is the only available dose limit for human infants that considers body weight. As a limit, it attends to the cumulative dosage and body burden from any source if the values are known. This target limit per body weight was used along with weight distributions across the population to estimate a minimum safe level (MSL) of aluminum exposure as a function of a child's age and weight percentile. All of the methods, data sources computations used to derive Fig. 1 are available in Lyons-Weiler and Ricketson [27].

None of the individual vaccines violates the guidance of a maximum of 850 μg of aluminum for an adult (Table 1). However, because of multiple vaccines typically given together at 2, 4, and 6 months, the CDC schedule violates this limit even assuming an adult weight ([27]; 29,773,196). Adjusting the safe dose limit based on a child's weight at these ages therefore results in doses that far exceed the estimated safe limit of acute toxicity (Lyons-Weiler and Ricketson, 29,773,196).

A limitation of the previous study ([27]; 29,773,196) was that it did not consider chronic toxicity due to accumulation. The Priest study of 2004 (15,152,306) made repeated measurements of retained aluminum over a 12-year period of a single adult volunteer after a single injection with citrate solution containing ^{26}Al and a small study of a further six adult male subjects over a shorter period of time ([28]; 7,576,820). The resulting model may be limited because citrate solutions are not used in vaccination and the studies involved adults rather than infants. This could be especially important for infants, especially neonatal infants, because a high percentage of them have underdeveloped renal function. With these caveats, Priest suggested that the fraction of injected aluminum retained in the body a given number of days after a dose can be

Table 1
Aluminum Microgram Doses in the 2019 CDC Schedule, a Modified CDC Schedule, and the Vaccine Friendly Plan schedule.

Age (Months)	CDC 2019 Schedule		Modified CDC Schedule		Vaccine Friendly Plan	
	Vaccine (Al μg)	Total Dose (μg)	Vaccine (Al μg)	Total Dose (μg)	Vaccine (Al μg)	Total Dose (μg)
Birth	HepB (250)	250	Hep B(250)	250	None	0
2	HepB (250) DTaP (625) Hib (225) PVC13 (125)	1225	Hep B(250) Low Al DTaP (330) ActHib (0) PVC13 (125)	705	Low aluminum DTap(330) ActHib (0)	330
3	None	0	None	0	PVC13 (125)	125
4	DTaP (625) Hib (225) PVC13 (125)	975	LowAl DTaP (330) ActHib (0) PVC13 (125)	455	Low aluminum DTap(330) ActHib (0)	330
5	None	0	None	0	PVC13 (125)	125
6	HepB (250) DTaP (625) PVC13 (125)	1000	HepB(250) LowAl DTaP(330) PVC13 (125)	705	Low aluminum DTap(330) ActHib (0)	330
7	None	0	None	0	PVC13 (125)	125
12	Hib (225) PVC13 (125) HepA (250)	600	ActHib (0) PVC13 (125) HepA(250)	375	ActHib(0) PVC13 (125)	125
18	DTaP (625) HepA (250)	875	LowAl DTaP (330) HepA (250)	580	LowAl DTaP(330)	330
	Total(μg)	4925	**Total**	3070	**Total**	1820

modeled as:

$$\% \text{ Retained Al} = (1\text{-}E)/\text{Days}^{n} \quad (1)$$

where E = % of aluminum eliminated in first day after dose (E = 65 % in Priest fit), and n = time constant (n = 0.32 in Priest fit).

The Priest model only considered excretion from urine, leaving out the percentage of excretion from feces, sweat, hair and nails. They also used a form of aluminum citrate, not used in vaccines [54]. Nevertheless, with these fitting parameters, the Priest equation estimates the retained fraction of a dose over two years showing significant retention over time (Table 2).

As shown in Table 2, this model estimates that three days after an injected dose of aluminum oxyhydroxide the body will still retain 25 % of the original injected aluminum.

Andress et al. [48] (3,807,961) showed that ¼ of aluminum introduced via dialysis was present at two weeks. Priest et al. (7,779,460)

Table 2
Aluminum retention modeled by Priest's equation.

Days from Dose	% Aluminum Retained
0	100%
1	35 %
2	28 %
3	25 %
7	19 %
1 Months	12 %
3 Months	8 %
6 Months	7 %
1 Year	5 %
2 Years	4 %

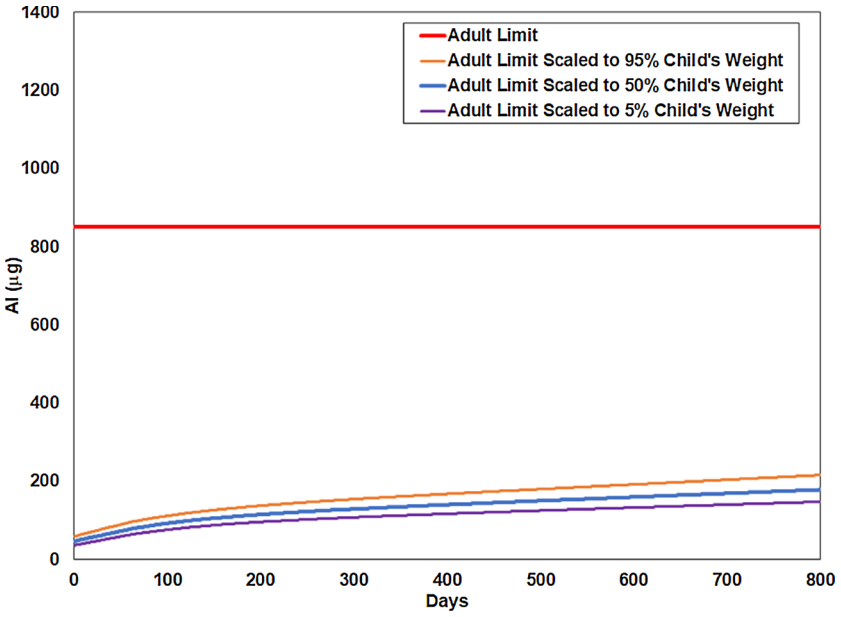

Fig. 1. FDA Adult aluminum per dose limit scaled to child's weight (Clark's Rule) following Lyons-Weiler and Ricketson [27].

Table 3
Short Retention Model Exposure for the three schedules.

Short Retention Model Exposure	CDC Schedule	Modified CDC Schedule	Vaccine Friendly Plan
Max Exposure vs Scaled Limit	x15.9	x9.3	x4.2
% Days Over Limit Birth to 7 months	70 %	26 %	5 %
% Days Over Limit Birth to 2 years	24 %	8 %	2 %

showed the half-life of that aluminum present at 2 weeks was 7 years, concluded that aluminum had a biological half-life of 7 years, and that accumulation (i.e., a "progressively increasing internal deposit") must be expected. Thus, in a schedule dense with aluminum-containing vaccines (ACVs), accumulation can be expected, leading to the possibility of chronic illness and impaired neurodevelopment due to chronic toxicity. There are no good data available on how the retention of subsequent doses of aluminum is impacted by aluminum already in the body. One possibility is that the body's clearing of aluminum is impacted only by the total aluminum after a new dose, in which case the Priest equation can be applied to the total aluminum with each new dose resetting the rate at which aluminum is being cleared. Another possibility is that there is a slowing of the rate of aluminum clearing over time. Aluminum remaining in the body months after an injected dose is aluminum that has settled in tissue, and the body clears aluminum from those deposits very slowly, especially from the brain. Under this assumption, the immediate rate that aluminum is cleared from the body shortly after exposure is therefore likely only mildly affected by the addition of new aluminum from a subsequent dose. This analysis presents both short- and long-retention results that model aluminum clearing rates reset with each new dose or the clearing of each dose being independent of all the others Table 3.

We know little about whether aluminum doses impact their own whole-body (not serum) clearance, however it is known that aluminum induces ER stress and the unfolded protein response, and this has been identified as plausible mechanisms of Al-induced autoimmunity and detoxification deficiency (doi Lyons-Weiler, 10.4172/2165–7890.1000224). There appears to be variation in the ability of humans to detoxify environmental toxins related to neurodegenerative disorders [29] Table 4.

We further explore factors such as genetic deficiency in aluminum clearance, which may be expected in some families, and discuss how to model the possibility that, for some individuals, aluminum body burden itself may contribute to detoxification deficiency.

3. Results

3.1. Model 1 – short retention

Applying Priest's equation to the different schedules allows us to estimate the total aluminum in the body at different ages compared to the body-weight scaled safe limit (Fig. 2).

Table 4
Short Retention Model Exposure comparing body weight.

Short Retention Model Exposure	Weight Percentile	CDC Schedule	Modified CDC Schedule	Vaccine Friendly Plan
Max Exposure vs Scaled Limit	95 %	x13.0	x7.6	x3.4
	50 %	x15.9	x9.3	x4.2
	5 %	x19.6	x11.4	x5.2
% days of first 2 years over safe limit	95 %	18 %	5 %	1 %
	50 %	24 %	8 %	2 %
	5 %	31 %	13 %	2 %

The CDC schedule crosses the recommended limit of aluminum for an adult by recommending multiple vaccinations containing aluminum being delivered together. Note that on all days of injection the safe limit for a child is exceeded for all three schedules; this points to acute toxicity Fig. 2.

All of these schedules greatly exceed the weight-adjusted limit for aluminum from Lyons-Weiler and Ricketson (29773196). The CDC schedule has the largest violation at 15.9 times the recommended safe level. This occurs at 2 months, when four recommended vaccinations containing aluminum are simultaneously administered. In addition, modeling the time to clear aluminum from the body using Priest's equation estimates that for this schedule a child will be over the safe level of aluminum in the body for 149 days from birth to 7 months, constituting about 70 % of days in this period (Fig. 3). This points to chronic toxicity. Over the first two years of life, days over the estimated limit are estimated as 176 days or 24 % of the days in this period. The modified CDC schedule assumes the same vaccinations at the same times as the CDC schedule, but like the Vaccine Friendly Plan it assumes a lower dose aluminum DTap vaccine, and also combines the ActHib (containing no Al) with low aluminum DTap or PVC13 so that the aluminum adjuvant in the aluminum containing vaccine (ACV) activates an immune response for the ActHib vaccine. This drops the maximum level of exposure to about 60 % of the original CDC plan with (from 15.9 to 9.3) and drops days above the estimated safe limit in the first 7 months from 70 % of days to 26 % and in the first 2 years from 24 % of days to 8 %. The Vaccine Friendly Plan schedule skips some vaccinations in the first two years (like HepB) and avoids giving more than two vaccinations containing aluminum together. The VFP thus further limits maximum exposure to approximately 25 % of the original CDC schedule (from 15.9 to 4.2) and drops days above the estimate limit in the first seven months from 70 % of days to 5 % and in the first two years from 24 % of days to 2 %.

These results can be made illustrative by calculating "time spent in toxicity" (*%alumTox*); i.e., the percentage of days of each week an infant spends with a body burden that exceeds the minimum safe level (MSL, aka, pediatric dose limit) curve proposed by Lyons-Weiler and Ricketson [27]. These three expected results (Fig. 4) demonstrate that the CDC schedule results in the highest percentage of time over the MSL (3A); the CDC schedule using lower dose aluminum vaccines follows with a significant reduction in time spent in toxicity (3B); and the Vaccine Friendly Plan schedule results in even further reduction of time spent in toxicity (3C).

Using the different estimated safe limits based on what percentile of the population an infant's weight falls into can show how the same three schedules might have different impacts on different children merely because they were above or below median weight (Table 7).

3.2. Model 2 – long retention

Another factor to consider is how the Priest equation is best applied to multiple doses. The results in Model 1 assume a "short retention" behavior; i.e., that each new dose resets the rate at which aluminum is cleared from body for the entire current aluminum body burden. If the clearing of aluminum is mainly driven by the total amount in the body, this is a reasonable model. However, if aluminum is more difficult to clear from some tissues in the body relative to others, then the decreasing rate at which aluminum clears from the body is not solely due to decreasing concentration over time. Instead it is also impacted by where the aluminum remaining from each dose is currently stored. In adults, a new influx of aluminum from the next vaccination-level dose might not have much immediate impact on aluminum already stored in the brain or bones. In the extreme, each dose of aluminum would clear at the same rate over the same time regardless of what aluminum doses came previously or thereafter. Model 2, the "long retention" model, makes this assumption by modeling each aluminum dose independently of all the others. This changes significantly what total aluminum

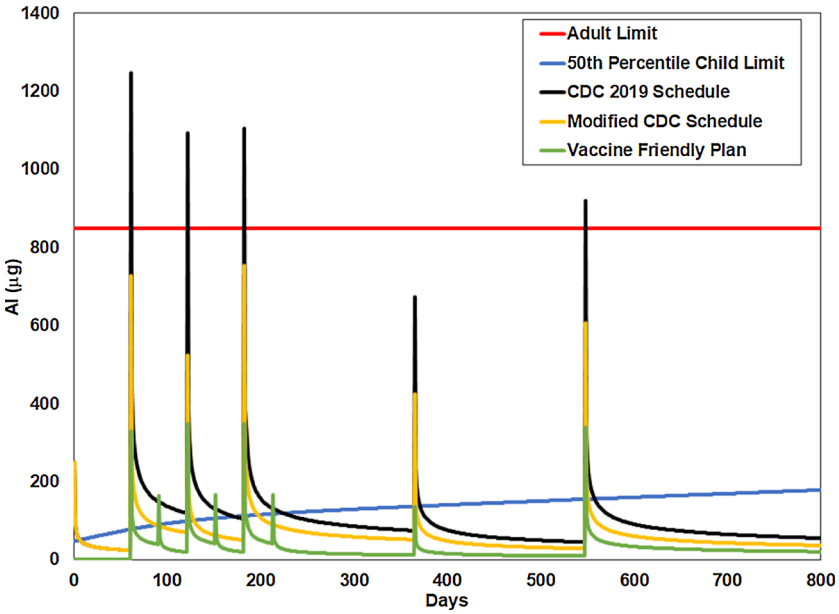

Fig. 2. Aluminum Content in Body over First Two Years for Three Vaccine Schedules.

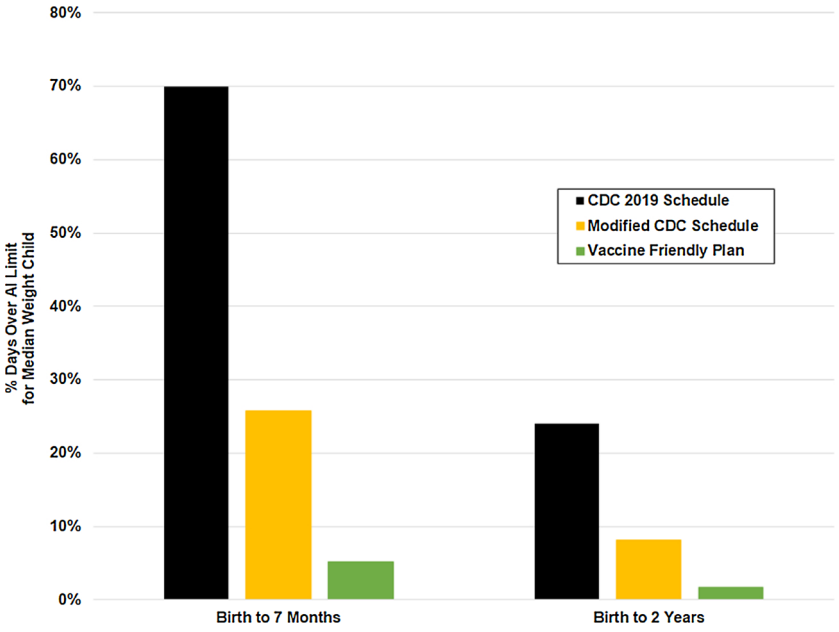

Fig. 3. Percent Days Over aluminum Limit (*%alumTox*) Birth to 7 Months and 2 Years.

accumulation is expected over time from multiple doses (Fig. 5). Given Priest's model, higher concentrations of aluminum in the body should in general drive faster clearing rates, but aluminum retained from previous doses will tend to be stored in harder-to clear-tissues, including the brain.

The CDC Pediatric schedule, however, is applied to infants, children and teens. Both Model 1 and Model are expected to overly optimistic compared to reality due to body weight differences between adults and infants. In fact, Priest's clearance levels may not have approached toxic levels in the adults studied, which is why they imply rapid clearance rates at high initial doses. This may cause one to expect that at even higher doses per body weight in infants, that the fastest clearance rates would occur at high doses. However, with increasing body burden at low body weight, the toxicity of aluminum in all tissues would increase. At the intracellular level, this means impairment of mitochondria, ER stress, impairment of Golgi apparati, leading to reduced clearance rates of aluminum with cellular and organ damage expected to be in proportion to per-organ dose (µg/kg) and duration of exposure per organ or tissue. Our modification of Priest's model in Model 1 and Model 2 does not specifically address this aspect of per-body weight increased toxicity, and thus our treatment is optimistic (biased toward underestimating accumulation).

In Fig. 5, the dotted lines show the expected aluminum in the body from the dose in the CDC schedule and the Vaccine Friendly Plan, assuming the short retention model, as was for previous Figures and tables. The solid lines show the additive effects to both schedules assuming the long retention model. This shows how old aluminum is accumulating faster than the body can clear and the baseline level of aluminum in the body before each new dose is steadily increasing over the first two years. Whether this is a more accurate representation of aluminum in the body or not is not clear since the data collected for Priest's original paper did not measure the effects of multiple doses

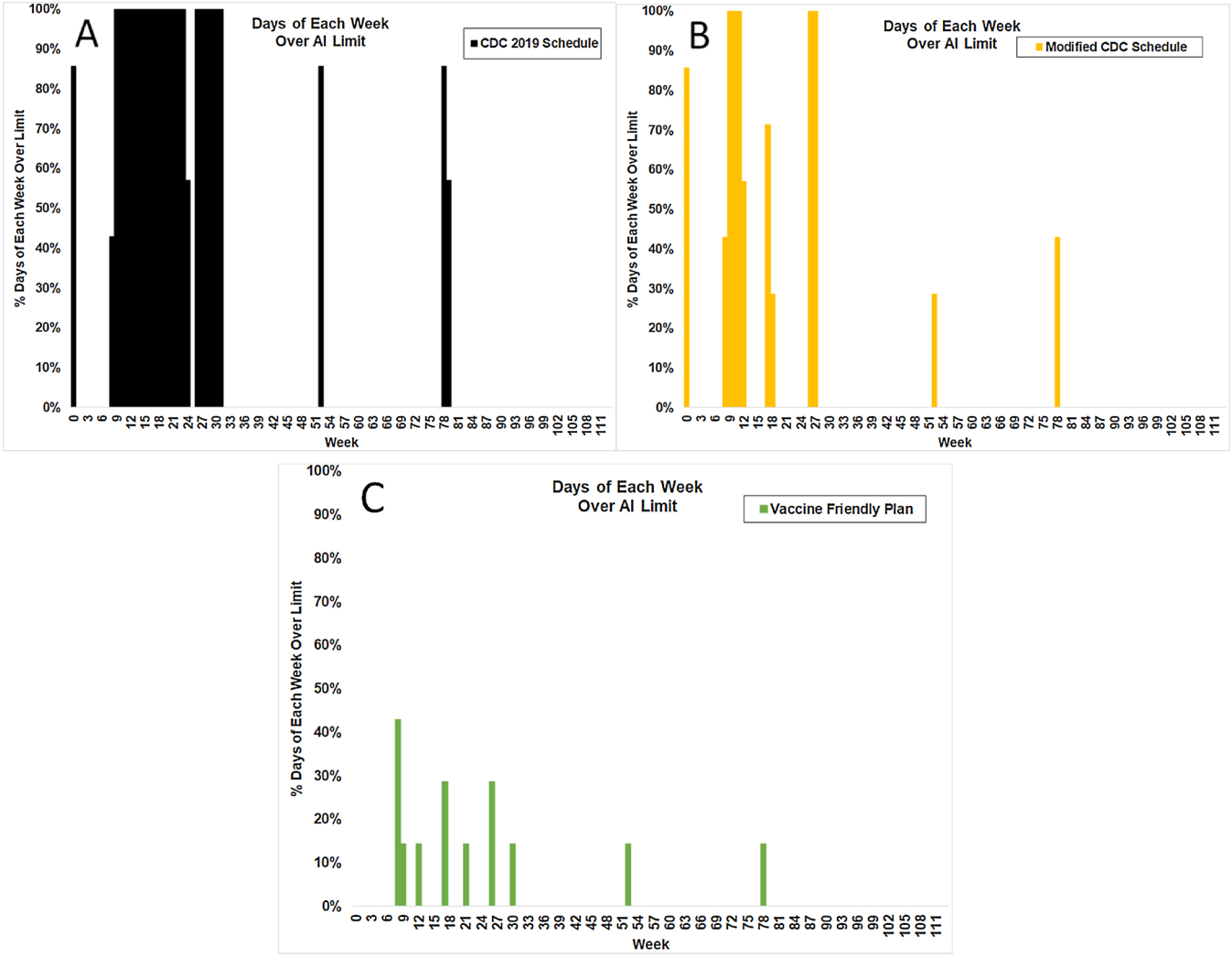

Fig. 4. Comparison of *%alumTox* (days spent over the PDL) for the three schedules for a median body weight male infant. In the first six months of life, the total expected % of days in each week spent in toxicity were CDC: 24 %, Modified CDC: 8 %, Vaccine Friendly Plan: 2 %. The differences among these results reflect differences in chronic toxicity per schedule.

Table 5
Schedule Comparison vs for Short and Long Retention Models.

%alumTox Over First Two Years Short vs Long Retention Exposure	Weight %	Al Retention Assumption	CDC Schedule	Modified CDC Schedule	Vaccine Friendly Plan
	95 %	Short	18 %	5 %	1 %
		Long	92 %	30 %	3 %
	50 %	Short	24 %	8 %	2 %
		Long	93 %	63 %	9 %
	5 %	Short	31 %	13 %	2 %
		Long	93 %	93 %	19 %

Table 6
Schedule Comparison vs aluminum Limit for Typical and "Slow" Al.

%alumTox Over First Two Years Typical vs Slow Elimination	Weight %	Al Clearing Assumption	CDC Schedule	Modified CDC Schedule	Vaccine Friendly Plan
	95 %	Typical	18 %	5 %	1 %
		Slow	57 %	30 %	6 %
	50 %	Typical	24 %	8 %	2 %
		Slow	66 %	42 %	10 %
	5 %	Typical	31 %	13 %	2 %
		Slow	81 %	56 %	15 %

spaced in time. If it is, current understanding of accumulation of aluminum due to the CDC schedule is incorrect. Comparing days of exposure for the short and long retention models shows this behavior reveals a critical assumption (Table 5).

3.3. Model 3 – impact of genetic variance in aluminum clearance

In Priest's original analysis, the study followed a single adult volunteer over 12 years to estimate how aluminum is retained in the body. If we assume this volunteer was typical in his ability to clear aluminum from the body, it is reasonable to wonder if some children because of genetic factors might clear aluminum at a slower rate than average. Mathematically, this simply means that different individuals may be best modeled by using different values for the E (excretion) parameter in Priest equation. We can modify the fitting parameters used in Priest's equation to try and model how a vaccine schedule might impact children with a reduced ability to clear aluminum by assuming some of the population might clear aluminum at only half the typical rate which

Table 7
Expected *%alumTox*, First Two Years of Life, Across Three Schedules With and Without Slowdown.

%alumTox Over First Two Years Modeled with and without elimination slowdown	Weight%	Al impact on clearing rate	CDC Schedule	Modified CDC Schedule	Vaccine Friendly Plan
	95 %	No slowdown	18 %	5 %	1 %
		With slowdown	45 %	15 %	2 %
	50 %	No slowdown	24 %	8 %	2 %
		With slowdown	52 %	23 %	2 %
	5 %	No slowdown	31 %	13 %	2 %
		With slowdown	59 %	35 %	4 %

would correspond to an E parameter of 30 %. Reproducing the method 1 result (assuming short retention) while assuming a rate of clearing aluminum at one half of typical demonstrates expected variation among schedules (Fig. 6).

The typical vaccination schedule puts doses close enough together in time that children with significantly reduced ability to clear aluminum would in fact see meaningfully higher levels during much of their first two years of life as a result (Fig. 6). Comparing the typical exposure and the exposure of this subpopulation shows variation among the schedules (Table 7).

Because the aluminum dosage is the same regardless of how well aluminum is cleared from the body, the maximum exposure vs the recommended limit does not change significantly based on different assumptions about aluminum retention. However, days over the scaled limit do change dramatically. For a median weight child, the CDC schedule changes from 24 % of days in the first two years over the recommended limit for a typical child to 66 % if aluminum is cleared at only half the normal rate. The Modified CDC Schedule and Vaccine Friendly Plan likewise see large increases in days over the estimated limit although remaining significantly below the total days of the CDC schedule. How large a subpopulation that would clear aluminum in this fashion is not known, but these simple equations imply variation across the population in aluminum detoxification ability could easily lead some children to high aluminum exposure over many more days than a typical child.

3.4. Model 4 – impact of aluminum-induced detoxification deficiency

In addition to likely variation in the value of E that would best model different children, it has been speculated that for at least some individuals the body's ability to clear aluminum might be slowed by previous exposure to aluminum. This would be modeled by making the E parameter a function of the level of aluminum currently in the body. Model 3 estimated the impact on individuals for whom genetic factors make the value of E (measuring their ability to eliminate aluminum) lower than typical. In Model 4, we consider how the Priest equation might be modified to show the impact on individuals who have a typical ability to eliminate aluminum without the presence of aluminum already in their body, but who show a reduced elimination ability for subsequent doses because of aluminum induced detoxification deficiency. This can be modeled by modifying the Priest equation to include a slowdown factor (S) as shown in Eq (2):

$$\% \text{ Retained aluminum} = (1\text{-}E/S)/\text{Days}^n \quad (2)$$

A slowdown factor based on the current level of aluminum in the body can be based on a ratio (R) of the level of aluminum at the time of a new dose vs the estimated safe limit of aluminum, and writing the slowdown factor (S) from Eq (2) as:

$$S = 1 + f \times R \quad (3)$$

A value of the fitting parameter f can be chosen to give an expected impact to aluminum retention for a given level of previous exposure. For example, we could assume already being at twice the safe limit (R = 2) when receiving a new dose causes the rate of elimination to be cut in half compared to someone with no exposure. We find that this is true when we assume $f = 0.58$. The impact of this assumption on expected fraction of aluminum retained in the body over time is quite significant (Fig. 7):

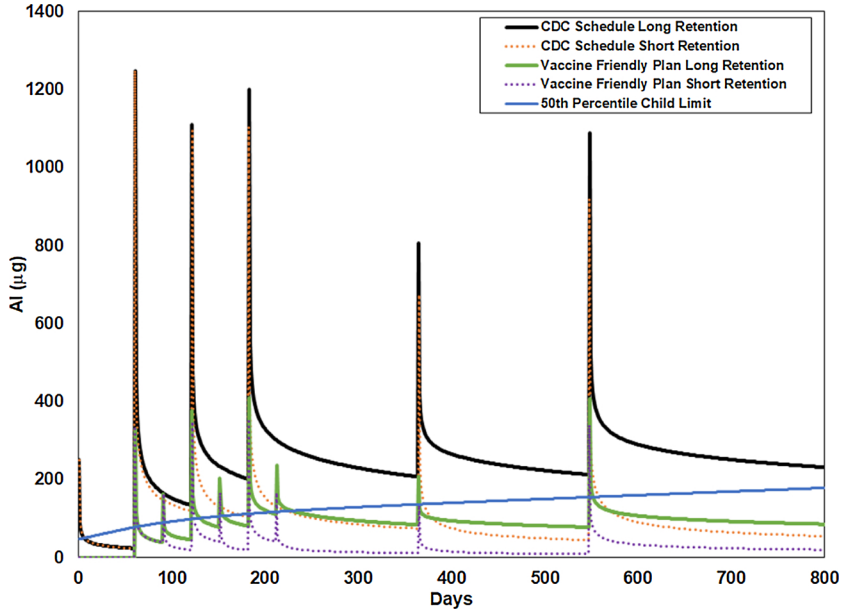

Fig. 5. Long retention vs short retention models accumulation of Al.

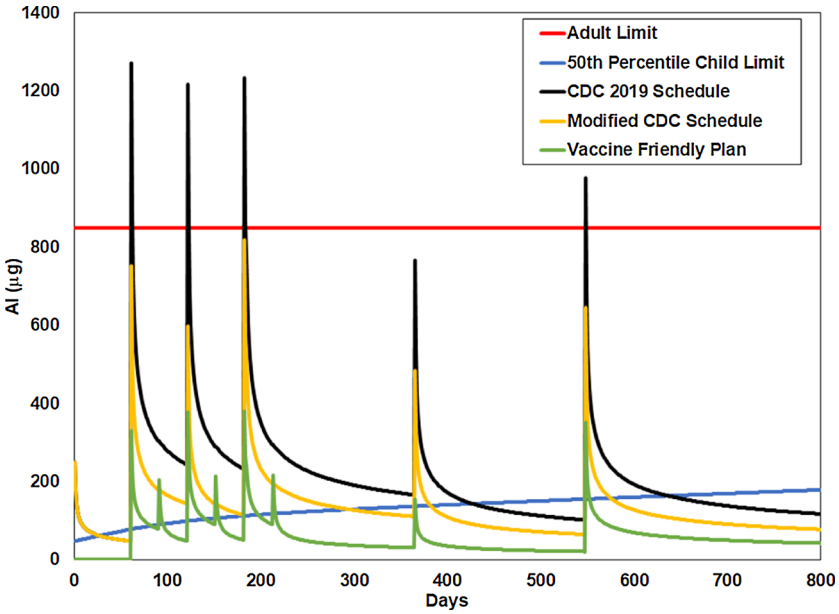

Fig. 6. Aluminum for different schedules with “slow” aluminum clearing.

The impact of this assumed slowdown to the estimated aluminum in the body for the CDC schedule shows increased retention relative to patient model that assumes average aluminum clearance (Fig. 7).

Because the aluminum dosage is the same regardless of how well aluminum is cleared from the body, the maximum exposure vs the recommended limit does not change based on different assumptions about aluminum retention. Biology (genetics) however may place some individuals at a risk of higher chronic toxicity. Days over the scaled limit do change dramatically in response to such assumptions. The CDC schedule changes from 24 % of days in the first two years over the recommended limit for a median weight child to 52 % if aluminum clears at only half the normal rate when a child receiving a new dose is already at double the safe aluminum limit. The Modified CDC schedule and Vaccine Friendly Plan likewise result in large increases in days over the estimated limit although remaining significantly below the total days of the CDC schedule. How quantitatively aluminum in the body impacts the body’s ability to clear aluminum is not known, but these simple equations show that this in an important factor in efforts to assess and understand the relative safety of different schedules Fig. 8

4. Discussion

Under our modeled conditions, the highest expected *%alumTox* would occur in low birth- or bodyweight infants with a genetic or environmental detoxification deficiency, such as those born to low-income mothers or who are malnourished (59 % of days in toxicity, CDC Schedule, 5th percentile bodyweight, with slowdown; Table 7). Factors such as birthweight and gestational age should therefore not be used as confounders in epidemiological studies of the role of vaccines but should, instead, be used as co-risk factors.

An important question these results raise is how to best judge a "safe" level of exposure to aluminum. Estimates of aluminum exposure and retention are not useful without some safe limit to compare against. Links between aluminum and various disorders would make it

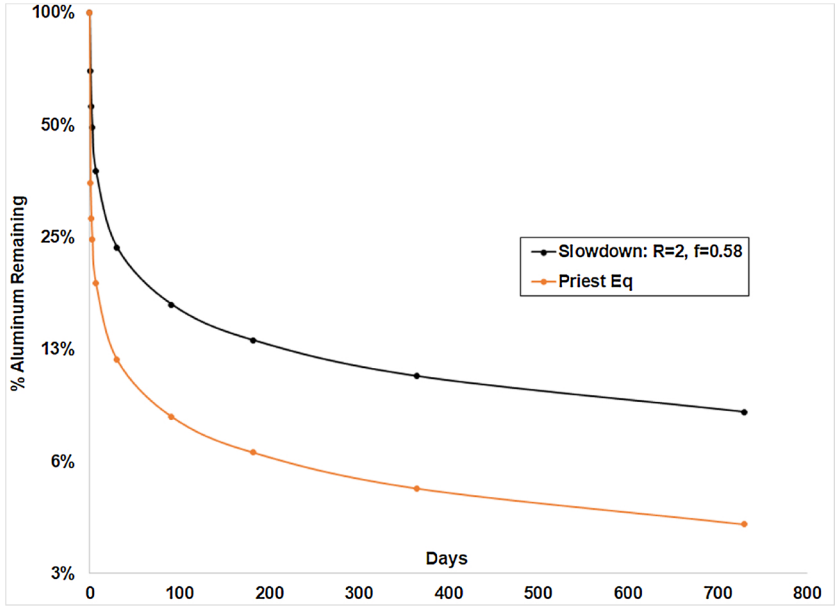

Fig. 7. Expected aluminum retention from a single dose with and without assumed slowdown.

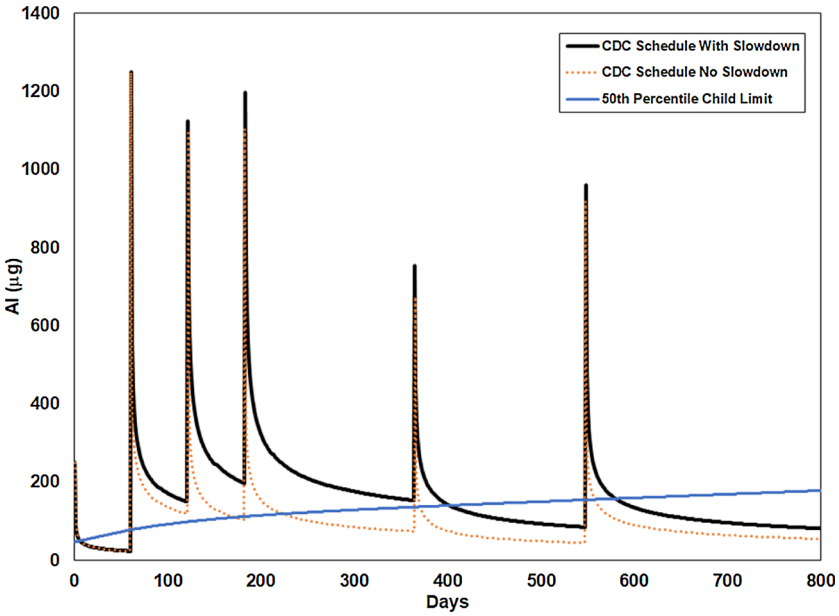

Fig. 8. Slowdown model results in higher retention and increased expected toxicity.

unwarranted to assume that there is a level of aluminum which is universally "safe", and the impact of oral and injected exposure have been demonstrated to vary, with normal absorption of only a tiny percentage of ingested forms of aluminum. The FDA has recommended limiting injected doses for adults to 850 μg. This level reflects the minimum amount considered required to induce an immune response in adults. Standard medical dosing practices and toxicological principles would mandate scaling this limit based on weight to calculate doses for children, assuming that safe dose levels are different for a 60 kg adult compared to a 3 kg newborn. Even if all the individual vaccines in a proposed schedule meet this weight-adjusted limit, administration of multiple aluminum-containing vaccines in a single day could easily exceed a recommended safe limit which considers body weight.

This study has focused on the whole-body retention of aluminum over time in the first two years of life, demonstrating the feasibility of adding model parameters to address biological variation among humans either from genetics or from prior exposures that influence whole-body detoxification rates. Priest's results show that after a single injection approximately 5 % of the original aluminum remains in the body of an adult a year after the dose but examined only aluminum excreted in urine. Even assuming infants clear at the same rate as adults, which is not based on any empirical evidence, it is reasonable to expect that not only the dosage of vaccinations but how closely they are spaced in time will impact the aluminum level for infants in the first two years of life given their low body weight.

Among the three schedules presented here, the CDC schedule exceeds the recommended dose limit for an infant (inferred from FDA adult "safe" levels) as a result of the simultaneous administration of multiple ACVs and insufficient spacing of ACVs. The Vaccine Friendly Plan schedule avoids this by suggesting only giving aluminum containing vaccinations one at a time and by choosing brands of vaccines that are low in aluminum, thereby reducing the number of days an individual's body burden exceeds the PDL-based MSL. Using these same brands in the CDC schedule prevents exceeding the recommended dose limit for an adult. All the schedules exceed a weight-adjusted limit for a median weight child but the percentage of days over the MSL is dramatically impacted by how retention is modeled, showing this to be an important area for future work. Factors considered that could have a large impact on total days over estimated limits include both how subsequent injections affect (if at all) clearing of aluminum already in the body, variation in aluminum clearing rates across the population and whether aluminum itself could impact the body's ability to clear toxins.

Our approach used the weight-adjusted PDL inferred by Lyons-Weiler and Ricketson as an MSL, which is based on the FDA's assumption that 850 μg of aluminum is safe for an adult of 150 kg. This assumption is known to be dubious because it is based on the study of ingested forms of aluminum in adult mice, not injected forms on aluminum in infant mice or humans. The entire provenance of the determination of 850 μg "safety" in adults was reviewed in detail by Lyons-Weiler and Ricketson [27]. Lyons-Weiler and Ricketson also lamented the lack of any safe level data relevant to humans at all beyond the 4–5 mcg/kg/day limit posted by the FDA [30] for individuals with renal dysfunction. Infants in the neonatal unit very often have limited renal function, and yet FDA allows HepB vaccination - with 250 μg of aluminum oxyhydroxide - on day 1 of life if an infant is >2 kg in mass. Lyons-Weiler and Ricketson never used the 4–5 μg/kg/day as a reference point for statistical hypothesis testing, but their analysis suggested that if a bodyweight- adjusted μg/kg/day safe level exists on day 1 of life, it is exceeded by vaccination of even median-weight infants. However, because the FDA determination that 850 μg/kg/day is safe for adults was spurious, the PDL used by Lyons-Weiler and Ricketson itself is only a frame of reference level. Finally, our results represent the 50th percentile body weight in the US population; clearly individuals with lower body weight will have corresponding shifts in chronic toxicity reflected by larger percentage of days in each week spent in whole-body toxic levels of aluminum (*%alumTox*).

Despite these uncertainties, the results of our study suggest that by adjusting the vaccinations given and/or spacing out vaccinations containing aluminum in time, the number of days at high aluminum levels can be significantly impacted, and that chronic aluminum toxicity is a possibility for some individuals, depending on body weight and genetics. The aluminum dose for different vaccines, how they are spaced in time, the weight of the child receiving them, and genetic variants that may limit ability to clear aluminum all appear to be important considerations in determining a safer vaccination schedule. The original Priest et al. (2004; 15,152,306) analysis examined the effects of a single dose but did not consider genetic variation in aluminum clearance rates and appears to have made a "reset" assumption of successive doses. Empirical studies of whole-body clearance in individuals who may reasonably be expected to have high risk of diseases and disorders

thought to be due to genetic intolerance of vaccine types of aluminum, compared to those without any such issue, may be warranted. The effects of successive doses of aluminum on clearance rates would provide data for model and model parameter tuning. Modeling of synergistic toxicity with fluoride ([31]; 30788699, [32], 19,284,184; van der Voet [56]; 10,455,554) and with mercury ([33], 29,938,114; 26,774,584) including thimerosal (29,895,363) could be illuminating and could inform important life choices on the part of consumers of medical and other products.

Aluminum toxicity from vaccines can be expected to be increased from other exposures such as aluminum in food (formula; [34];30,871,123) and aluminum used to buffer drinking water. Individual infants with incompletely closed intestinal barriers, or with autoimmune gastric and intestinal lesions may be experiencing much higher doses of aluminum than a pediatrician may be aware. Aluminum has now been found in the brains of individuals who have died with various diagnoses, including multiple sclerosis, epilepsy, Parkinson's disease, Alzheimer's diseases and autism spectrum disorder ([35]; 31,468,176). Whole-body aluminum toxicity is important because aluminum affects the brain, bones, parathyroid, spleen, kidneys ([36]; 31,008,371), and, of course, the immune system. Of these compartments, brain clearance of aluminum is the slowest; in rats, aluminum half-life was found to be 150 days, but clearance was expedited via deferoxamine (aka desferoxamine; [37]). A study demonstrating that the consumption of silica-rich mineral waters may also enhance the release of aluminum from the brain is of interest ([15]; 22,976,072). Careful supplementation with compounds from *Chlorella* and *Spirulina* are essential to avoid the redistribution and resequestration of an existing aluminum body burden.

All analyses to date, including our own, use aluminum clearance rate data from adults, which likely is an overly optimistic aluminum clearance rate for neonates and infants. Most excretion of aluminum is accomplished by filtration of aluminum from the blood by the glomeruli of the kidney. Renal function in infants is not fully developed: infants' glomerular filtration rate (GFR) is not fully online at birth and increases from 10 to 20 mL/min/1.73 m^2 during the first day of life to 30–40 mL/min/1.73 m^2 by 2 weeks of life (Sulemanji and Vakili [55]; 24,331,094). In neonates, the GFR at birth is even worse (Sulemanji and Vakili [55]; 24,331,094) and increases more slowly compared to infants (3,761,090). While the kidney is structurally mature at 36 weeks, the GFR does not reach adult levels until 2 years of age ([38,49]; 8,006,805). Common emergent conditions in the NICU include respiratory distress syndrome, seizures, and arrhythmias and cardiac arrest. To maximize efficiency, infants in the NICU are often vaccinated simultaneously with crash teams on stand-by. Studies in the 2000's of DTP vaccines showed an incredible 46 % cardiac event rate in infants in the NICU following vaccination ([39]; 17,056,868). Hepatitis B vaccination studies in the 1990s ([40]; 10,591,306) are not relevant to concerns over aluminum-induced adverse events because the HepB vaccine did not contain aluminum oxyhydroxide (although it did contain ethylmercury); however, studies from passive surveillance systems routinely oddly attribute the majority of deaths to coincidence. A Chinese study [58] (30,709,723) found 795 deaths, with >95 % of them occurring following Hepatitis B vaccination in children <5 years old, but the majority were attributed to "coincidence". This is an odd conclusion, given that passive surveillance systems cannot attribute causality. Of the 795 deaths, 594 (74 %) were classified as 'coincidental' events, but SIDS was found to be a main cause of death in infants. SIDS, a condition of otherwise unknown cause, is not considered an expected adverse event. The studies from the 1990s in the US similarly attributed, without independent evidence, the majority of serious adverse events from HepB vaccination to coincidence. Since passive surveillance systems cannot attribute causality, they also cannot rule out causality, and thus attribution to coincidence seems opportunistic at worst and optimistic at best. The authors of the Chinese study lauded the 'sensitivity' of their passive surveillance system after ruling out unexpected deaths as 'coincidence'. In reality, this reflects a serious flaw in the use of passive surveillance systems to monitor vaccine safety, which routinely underreport adverse events by a factor of 100 misses to each report [41].

5. Translational significance

A study of neonatal mice injected with aluminum oxyhydroxide reported diminished social interest and abnormal social novelty compared to saline control mice ([42]; 29,221,615). Given our dosing calculations, and the reality of the differences between human adult, infant and neonatal kidney function, recent and repeated expressed concern over aluminum detoxification deficiency in neonates and infants from both the research and the medical community ([43]; 24801228, [44]; 28,752,219; [45]; 29,721,353; [46]; 29,729,447; Parker et al. [53] 2019; 30,466,934), FDA should have already been acted upon by revisitation of the CDC schedule, and move immediately to recommend use non-ACVs and non-aluminum-containing food and water during these important stages of neurodevelopment. Given the suite of limitations of available estimated clearance rates, our results likely significantly underestimate chronic toxicity, defined by the number of days over a period of time an individual has a body burden of aluminum that exceeds the PDL. We cannot stress how important it is that infants avoid aluminum from all sources, at all doses, due to the realities of cumulative risk from cumulative exposure. Selecting brands of vaccines that contain lower amounts of aluminum and avoiding the combination vaccines that have the greatest amounts of aluminum would be advisable for reducing toxicity. Recalling that aluminum adjuvants induce a Th2-biased immunological state, the use of other adjuvants known to induce both Th1- and Th2- reactions (e.g., [47];17,498,851) may prove to be medically beneficial and economical shift in the focus of developing safer vaccines. Requiring lower doses of adjuvants, longer periods of immunoefficacy, and safer vaccine schedules for vaccine approval by FDA so that neonates and infants have lowered exposures to neurotoxic metals during development may be more acceptable to an increasingly vaccine-risk aware public due to lowered exposures to neurotoxic and immunotoxic metals during development.

The new measure, *%alumTox*, reflects a high degree of chronic toxicity in the first seven months of life under the CDC schedule, which can be avoided by changes to the schedule, including use of non-ACVs. These months are critically important to neurodevelopment and for the development of the immune system. We strongly recommend that the US FDA update their *modus operandi* to consider data from studies from injected forms of aluminum in infant mice, and that the FDA establish age-specific monthly limits of aluminum exposure *in toto* (all sources), including 1 or more ACVs administered in the same month. In the absence of dose escalation studies in infant mice, we suggest they adopt the PDL which considers body weight, and express exposure limits as considering all sources, including 1 or more ACVs per month and considering bodyweight. We are exploring the utility of designing a simple web application via which individuals, parents, and their doctors can estimate the expected aluminum accumulation, including *% alumTox*, under various schedules, so pediatricians and patients can manage infant exposures considering all sources. Given the known synergistic toxicity of mercury and aluminum, our findings may merit formal alerts on intentions for the simultaneous administration of thimerosal-containing vaccines and ACVs.

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Declaration of Competing Interest

JLW is a (sometimes) compensated expert witness in cases in the US National Vaccine Injury Compensation Program involving cases in

which ACVs have been identified as a potential cause of autoimmune disorders. PT receives income in the form of royalties from the sale of his book, and he receives income from the sale and administration of vaccines in his practice. EL and GM have no potential conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jtemb.2019.126444.

References

[1] T.R. Ghimire, The mechanisms of action of vaccines containing aluminum adjuvants: an in vitro vs in vivo paradigm, Springerplus 4 (2015) 181, https://doi.org/10.1186/s40064-015-0972-0 PMID = 25932368.
[2] G.J. Fernando, T.J. Stewart, R.W. Tindle, I.H. Frazer, Vaccine-induced Th1-type responses are dominant over Th2-type responses in the short term whereas pre-existing Th2 responses are dominant in the longer term, Scand. J. Immunol. 47 (5) (1998) 459-65s.
[3] A.S. McKee, M.W. Munks, M.K. MacLeod, et al., Alum induces innate immune responses through macrophage and mast cell sensors, but these sensors are not required for alum to act as an adjuvant for specific immunity, J. Immunol. 183 (7) (2009) 4403–4414, https://doi.org/10.4049/jimmunol.0900164.
[4] A. Gołoś, A. Lutyńska, Aluminium-adjuvanted vaccines–a review of the current state of knowledge, Przegl. Epidemiol. 69 (4) (2015) 731-4, 871-4.
[5] E. Güven, K. Duus, I. Laursen, P. Højrup, G. Houen, Aluminum oxyhydroxide adjuvant differentially activates the three complement pathways with major involvement of the alternative pathway, PLoS One 9 (September (9)) (2013), https://doi.org/10.1371/journal.pone.0074445 e74445. 8.
[6] R.K. Gupta, Aluminum compounds as vaccine adjuvants, Adv. Drug Deliv. Rev. 32 (no.3) (1998) 155–172 PMID = 10837642.
[7] M.S. Petrik, M.C. Wong, R.C. Tabata, R.F. Garry, C.A. Shaw, Aluminum adjuvant linked to Gulf War Illness induces motor neuron death in mice, Neuromolecular Med. 9 (no.1) (2007) 83–100 PMID = 17114826.
[8] G. Crépeaux, R.K. Gherardi, F.J. Authier, Asia, Chronic fatigue syndrome, and selective low dose neurotoxicity of aluminum adjuvants, J. Allergy Clin. Immunol. Pract. 6 (no.2) (2018) 707, https://doi.org/10.1016/j.Jaip.2017.10.039 Mar - Apr 2018. PMID = 29525002.
[9] R.K. Gherardi, G. Crépeaux, F.J. Authier, Myalgia and chronic fatigue syndrome following immunization : macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system, Autoimmun. Rev. 18 (no.7) (2019) 691–705, https://doi.org/10.1016/j.Autrev.2019.05.006 PMID = 31059838.
[10] J.D. Masson, G. Crépeaux, F.J. Authier, C. Exley, R.K. Gherardi, Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants, J. Inorg. Biochem. 181 (04) (2018) 87–95, https://doi.org/10.1016/j.Jinorgbio.2017.12.015 PMID = 29307441.
[11] G. Crépeaux, H. Eidi, M.O. David, Y. Baba-Amer, E. Tzavara, B. Giros, F.J. Authier, et al., Non-linear dose-response of aluminium hydroxide adjuvant particles: selective low dose neurotoxicity, Toxicology 375 (2017) 48–57, https://doi.org/10.1016/j.Tox.2016.11.018 PMID = 27908630.
[12] M. Rigolet, J. Aouizerate, M. Couette, N. Ragunathan-Thangarajah, M. Aoun-Sebaiti, R.K. Gherardi, J. Cadusseau, F.J. Authier, Clinical features in patients with long-lasting macrophagic myofasciitis, Front. Neurol. 5 (2014) 230, https://doi.org/10.3389/fneur.2014.00230 PMID = 25506338..
[13] N.D. Priest, The biological behaviour and bioavailability of aluminium in man, with special reference to studies eEmploying Aluminium-26 as a tracer: review and study update, J. Environ. Monit. 6 (no.5) (2004) 375–403, https://doi.org/10.1039/b314329p PMID = 15152306.
[14] R. Kandimalla, J. Vallamkondu, E.B. Corgiat, K.D. Gill, Understanding aspects of aluminum exposure in alzheimer's disease development, Brain Pathol. 26 (no.2) (2016) 139–154, https://doi.org/10.1111/bpa.12333 PMID = 26494454.
[15] S. Davenward, P. Bentham, J. Wright, P. Crome, D. Job, A. Polwart, C. Exley, Silicon-rich mineral water as a non-invasive test of the' Aluminum hypothesis' in alzheimer's disease, J. Alzheimers Dis. 33 (no.2) (2013) 423–430, https://doi.org/10.3233/JAD-2012-121231 PMID = 22976072.
[16] D.A. Clark, Cytokines, decidua, and early pregnancy, Oxf. Rev. Reprod. Biol. 15 (1993) 83–111 PMID = 7687764.
[17] K.P. Sharma, N. Upreti, S. Sharma, Protective effect of Spirulina and tamarind fruit pulp diet supplement in fish (Gambusia affinis baird & girard exposed to sublethal concentration of fluoride, aluminum and aluminum fluoride, Indian J. Exp. Biol. 50 (no.12) (2012) 897–903 PMID = 23986974.
[18] G. Bjorklund, V. Stejskal, M.A. Urbina, M. Dadar, S. Chirumbolo, J. Mutter, Metals and parkinson's disease: mechanisms and biochemical processes, Curr. Med. Chem. 25 (no.19) (2018) 2198–2214, https://doi.org/10.2174/0929867325666171129124616 PMID = 29189118.
[19] M. Yasui, T. Kihira, K. Ota, M. Mukoyama, L. Adachi, Aluminum deposition in the central nervous system tissues of patients with Parkinson's disease, Rinsho Shinkeigaku 31 (10) (1991) 1095–1098 PMID = 1802464.
[20] M.J. Mold, J. Cottle, C. Exley, Aluminium in brain tissue in epilepsy: a case report from Camelford, Int. J. Environ. Res. Public Health 16 (no.12) (2019), https://doi.org/10.3390/ijerph16122129 PMID = 31208130. 06.
[21] M. Mold, D. Umar, A. King, C. Exley, Aluminium in brain tissue in autism, J. Trace Elem. Med. Biol. 46 (2018) 76–82, https://doi.org/10.1016/j. Jtemb.2017.11.012 PMID = 29413113.
[22] T.K. Murphy, D.M. Gerardi, J.F. Leckman, Pediatric acute-onset neuropsychiatric syndrome, Psychiatr. Clin. North Am. 37 (no.3) (2014) 353–374, https://doi.org/10.1016/j.Psc.2014.06.001 PMID = 25150567.
[23] S. Sigra, E. Hesselmark, S. Bejerot, Treatment of pandas and pans: a systematic review, Neurosci. Biobehav. Rev. 86 (03) (2018) 51–65, https://doi.org/10.1016/j PMID = 29309797.
[24] M. Cortes Rivera, C. Mastronardi, C.T. Silva-Aldana, M. Arcos-Burgos, B.A. Lidbury, Myalgic Encephalomyelitis/Chronic fatigue syndrome: a comprehensive review, Diagnostics Basel (Basel) 9 (no.3) (2019), https://doi.org/10.3390/diagnostics9030091 PMID = 31394725.
[25] J.G. Dórea, R.C. Marques, Infants' exposure to aluminum from vaccines and breast milk during the first 6 months, J. Expo. Sci. Environ. Epidemiol. 20 (no.7) (2010) 598–601, https://doi.org/10.1038/jes.2009.64 PMID = 20010978.
[26] P. Thomas, J. Margulis, The Vaccine-Friendly Plan (Book), Penguin Random House Publishing, New York City, NY, 2016.
[27] J. Lyons-Weiler, R. Ricketson, Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum, J. Trace Elem. Med. Biol. 48 (2018) 67–73, https://doi.org/10.1016/j.Jtemb.2018.02.025 PMID = 29773196.
[28] R.J. Talbot, D. Newton, N.D. Priest, J.G. Austin, J.P. Day, Inter-subject variability in the metabolism of aluminium following intravenous injection as citrate, Hum. Exp. Toxicol. 14 (no.7) (1995) 595–599, https://doi.org/10.1177/096032719501400707 PMID = 7576820.
[29] J.T. Greenamyre, P. Barret, Genetic Factors in Environmentally Induced Disease. Pp 21-43 in: Environmental Factors in Neurodevelopmental and Neurodegenerative Disorders, Academic Press, 2015.
[30] FDA, CFR - Code of Federal Regulations Title 21, (2018) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr = 201.323.
[31] A.A. Kinawy, Synergistic oxidative impact of aluminum chloride and sodium fluoride exposure during early stages of brain development in the rat, Environ. Sci. Pollut. Res. Int. 26 (no.11) (2019) 10951–10960, https://doi.org/10.1007/s11356-019-04491-w PMID = 30788699.
[32] R.L. Blaylock, A possible central mechanism in autism spectrum disorders, Part 3: the role of excitotoxin food additives and the synergistic effects of other environmental toxins, Altern. Ther. Health Med. 15 (no.2) (2009) 56–60 Mar-Apr 2009 PMID = 19284184, .
[33] P.N. Alexandrov, A.I. Pogue, W.J. Lukiw, Synergism in aluminum and mercury neurotoxicity, Integr. Food Nutr. Metab. 5 (no.3) (2018), https://doi.org/10.15761/IFNM.1000214 PMID = 29938114.
[34] J. Redgrove, I. Rodriguez, S. Mahadevan-Bava, C. Exley, Prescription infant formulas are contaminated with aluminium, Int. J. Environ. Res. Public Health 16 (5) (2019), https://doi.org/10.3390/ijerph16050899 pii: E899.
[35] C. Exley, M.J. Mold, Aluminium in human brain tissue: how much is too much? J. Biol. Inorg. Chem. (2019), https://doi.org/10.1007/s00775-019-01710-0 PMID = 31468176.
[36] G.L. Klein, Aluminum toxicity to bone: a multisystem effect? Osteoporos. Sarcopenia 5 (no.1) (2019) 2–5, https://doi.org/10.1016/j.Afos.2019.01.001 PMID = 31008371.
[37] R. Yokel, S.R. Rhineheimer, P. Sharma, et al., Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single 26Al exposure, Science 64 (1) (2001) 77–82.
[38] S.T. Blackburn, S. T. Renal function in the neonate, J. Perinat. Neonatal Nurs. 8 (no.1) (1994) 37–47 PMID = 8006805.
[39] J. Bonhoeffer, C.A. Siegrist, P.T. Heath, Immunisation of premature infants, Arch. Dis. Child. 91 (no.11) (2006) 929–935, https://doi.org/10.1136/adc.2005.086306 PMID = 17056868.
[40] M.T. Niu, M.E. Salive, S.S. Ellenberg, Neonatal deaths after hepatitis B vaccine: the vaccine adverse event reporting system, 1991-1998, Arch. Pediatr. Adolesc. Med. 153 (no.12) (1999) 1279–12782 PMID = 10591306.
[41] R. Lazarus, M. Klompas, Electronic Support for Public Health – Vaccine Adverse Event Reporting System (ESP:VAERS) (Massachusetts) (Final Report). Harvard Pilgrim Health Care, Inc, 2010 https://healthit.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system , Accessed 9/7/2019.
[42] S.K.S. Sheth, Y. Li, C.A. Shaw, Is exposure to aluminium adjuvants associated with social impairments in mice? A pilot study, J. Inorg. Biochem. 181 (2018) 96–103, https://doi.org/10.1016/j.Jinorgbio.2017.11.012 PMID = 29221615.
[43] D.R. Fanni, R. Ambu, C. Gerosa, S. Nemolato, N. Iacovidou, P. Van Eyken, V. Fanos, M. Zaffanello, G. Faa, Aluminum exposure and toxicity in neonates: a practical guide to halt aluminum overload in the prenatal and perinatal periods, World J. Pediatr. 10 (no.2) (2014) 101–107, https://doi.org/10.1007/s12519-014-0477-x PMID = 24801228.
[44] G. Morris, B.K. Puri, R.E. Frye, The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the

evidence and what could Be the mechanisms involved? Metab. Brain Dis. 32 (no.5) (2017) 1335–1355, https://doi.org/10.1007/s11011-017-0077-2 PMID = 28752219.10.

[45] A. Strunecka, R.L. Blaylock, J. Patocka, O. Strunecky, Immunoexcitotoxicity as the central mechanism of etiopathology and treatment of autism spectrum disorders: A possible role of fluoride and aluminum, Surg. Neurol. Int. 9 (2018) 74, https://doi.org/10.4103/sni.Sni_407_17 PMID = 29721353.

[46] R.K. Gherardi, G. Crépeaux, F.J. Authier, L. Lujan, Animal studies are mandatory to investigate the poorly understood fate and effects of aluminum adjuvants administered to billions of humans and animals worldwide, Autoimmun. Rev. 17 (no.7) (2018) 735–737, https://doi.org/10.1016/j PMID = 29729447.

[47] A. Khajuria, A. Gupta, F. Malik, S. Singh, J. Singh, B.D. Gupta, K.A. Suri, et al., A new vaccine adjuvant (Bos 2000 a potent enhancer mixed Th1/Th2 immune responses in mice immunized with hbsag, Vaccine 25 (no.23) (2007) 4586–4594, https://doi.org/10.1016/j PMID17498851.

[48] D.L. Andress, J.B. Kopp, N.A. Maloney, J.W. Coburn, D.J. Sherrard, Early deposition of aluminum in bone in diabetic patients on hemodialysis, N. Engl. J. Med. 316 (no.6) (1987) 292–296, https://doi.org/10.1056/NEJM198702053160602 PMID = 3807961.

[49] L.P. Brion, A.R. Fleischman, C. McCarton, G.J. Schwartz, A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth, J. Pediatr. 109 (no.4) (1986) 698–707, https://doi.org/10.1016/s0022-3476(8680245-1 PMID = 3761090.

[51] H. Hogenesch, Mechanism of immunopotentiation and safety of aluminum adjuvants, Front. Immunol. 3 (2012) 406, https://doi.org/10.3389/fimmu.2012.00406 PMID = 23335921.

[53] A. Parker, Testing new hypotheses of neurological and immunological outcomes with aluminum-containing vaccines is warranted, J. Trace Elem. Med. Biol. 51 (2019) 28–30, https://doi.org/10.1016/j.Jtemb.2018.09.006 PMID = 30466934.

[54] N.D. Priest, D. Newton, J.P. Day, R.J. Talbot, A.J. Warner, Human metabolism of Aluminium-26 and Gallium-67 injected as citrates, Hum. Exp. Toxicol. 14 (no.3) (1995) 287–293, https://doi.org/10.1177/096032719501400309 PMID = 7779460.

[55] M. Sulemanji, K. Vakili, Neonatal renal physiology, Semin. Pediatr. Surg. 22 (2013) 195–198, https://doi.org/10.1053/j.Sempedsurg.2013.10.008 PMID = 24331094 no.4.

[56] G.B. van der Voet, O. Schijns, F.A. De Wolff, Fluoride enhances the effect of aluminium chloride on interconnections between aggregates of hippocampal neurons, Arch. Physiol. Biochem. 107 (no.1) (1999) 15–21, https://doi.org/10.1076/apab.107.1.15.4356 PMID = 10455554.

[57] X.Y. Wang, X. Yao, Y.M. Wan, B. Wang, J.Q. Xu, Y.M. Wen, Responses to multiple injections with alum alone compared to injections with alum adsorbed to proteins in mice, Immunol. Lett. 149 (no.1-2) (2013) 88–92, https://doi.org/10.1016/j.Imlet.2012.11.005 PMID = 23183095.2012.

[58] W. Wu, D. Liu, J.P. Nuorti, K. Li, D. Xu, J. Ye, J. Zheng, L. Cao, H. Wang, Deaths reported to national surveillance for adverse events following immunization in China, 2010-2015, Vaccine 37 (no.9) (2019) 1182–1187, https://doi.org/10.1016/j.Vaccine.2019.01.009 PMID = 30709723.

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Corrigendum

Corrigendum to "Acute exposure and chronic retention of aluminum in three vaccine schedules and effects of genetic and environmental variation". [J. Trace Elem. Med. Biol. 58 (2020) 126444]

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1. Purpose

At the request and recommendation of the Editor-in-Chief, we submit this *Corrigendum* and *Erratum* to our study (McFarland et al. [1]) in which we focused entirely on the question of aluminum toxicity in vaccines, and not vaccination in general. Our study addressed exclusively the aluminum clearance and accumulation from vaccines in three scenarios, including the CDC schedule selecting vaccines with the most aluminum, the CDC schedule selecting vaccines with the lowest aluminum, and the Vaccine Friendly Plan which encourages selecting the vaccine choices with the lowest aluminum content and giving only one aluminum containing vaccine at a time. We compared the expected whole-body accumulation and clearance dynamics of aluminum in the US CDC's recommended schedule to an alternative schedule that minimizes exposure of infants and children to the aluminum from vaccination primarily by spacing out aluminum-containing vaccines over time (with patients receiving no more than one aluminum-containing vaccine per scheduled well-child office visit), and by substituting non-aluminum-containing vaccines for equivalent vaccines whenever possible.

2. Context

The CDC's pediatric vaccination schedule, like their adult vaccination schedule, is a recommended schedule. To encourage vaccine uptake, various states have laws that mandate full adherence or that use punitive measures to coerce adherence by families who might choose to use only some or no vaccines. These coercive measures sometimes include lack of access to public education. However, some states in the US allow personal exemptions. Thus, the public's interest in CDC's recommended schedule, its safety, and possible alternatives is very high. Because no study of fully vaccinated vs. unvaccinated patients has been conducted by CDC, the overall efficacy and safety of the CDC vaccination schedule is unknown.

Our independent evaluation of the schedule was built on our past study (Lyons-Weiler and Ricketson [2]) which showed that children on the CDC schedule could be expected to experience acute aluminum toxicity given our body-weight adjusted estimate of a pediatric dose limit. Similar research has been undertaken by other researchers (e.g, Angrand et al. [3]). Neither the US CDC nor FDA have published a pediatric dose limit, and our earlier study Lyons-Weiler and Ricketson [2] has filled that knowledge gap. In our second study, our purpose was to use the same methodology to study the alternative schedule. The alternative schedule, known as "The Vaccine Friendly Plan" (VFP) fulfills the need to provide parents a way to get protection for the infections addressed by vaccines that are most likely to cause serious illness or be deadly while reducing possible harm from aluminum toxicity and immune activation. Federal Regulations require informed consent for participation in post-market vaccine safety surveillance, which, per vaccine, and for the entire CDC recommended schedule, represent ongoing human subject trials.

3. How the Vaccine Friendly Plan was derived

The Vaccine Friendly plan that we evaluated and compared to the CDC schedule was derived using rational consideration of means to minimize acute exposure to aluminum. At the time of our study, no published data existed for its health effects on patients. Subsequently a study has been completed and published (Lyons-Weiler and Thomas [4]) showing the vaccine-associated disease burden and incidence of various health outcomes under the alternative plan. The study involved an analysis of 561 unvaccinated patients compared to 2763 variably vaccinated patients in a pediatric practice in Oregon, USA. A proper technical description is that every patient in that study is on an alternative schedule since patients may, under Oregon State Law, accept all or only some of the offered CDC recommended vaccines. We do not know how many other practices around the US employ the alternative schedule, or the number that undertake the required rigorous informed

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consent process that inevitably results in variable vaccination.

4. How the VFP is administered

In the administration of informed consent vaccination, during each well child office visit, each family is shown the CDC recommended vaccine schedule. They are informed of the vaccine recommendations for their child and all available information from the CDC, including the Vaccine Information Statements (VISs), are reviewed with each parent. During the process of informed consent, parent's questions are answered, and when requested, the differences and rationale of the VFP are described, with emphasis on the goal of minimizing overall exposure to injected aluminum.

5. Efficacy and comparative safety of VFP is now known

In our study of patients born into the practice over 10.5 years, patients variably vaccinated either according to the VFP or some greater or lesser uptake of vaccines had no cases Diphtheria, Hepatitis A, Hepatitis B, *Haemophilus* influenza type B, Measles, Meningococcus, Mumps, Rotavirus, Pneumococcus, Rubella, or Tetanus. Of the 3324 patients in the study, the incidence of Pertussis diagnosis over 10.5 years was 0.003; the incidence of Rotavirus diagnosis was 0.0006 (compared to national rates of percent positivity of 0.01 to 0.03 per year, with a great deal of regional variation including rates as high as 0.075 in some years in the Midwest; CDC [5]). The within-practice cohort incidence of Varicella was 0.0087; from 2000 to 2014, the national incidence of Varicella in the United States ranged from 0.00004 to 0.00035 (Lopez et al. [6]). Each of the extremely rare cases of newly diagnosed Pertussis, or Varicella of patients born into the practice (i.e., not referred to the practice with the condition) were mild, none required hospitalization. There were unvaccinated twins who were hospitalized for dehydration from rotavirus, who recovered fully. The parents reported they contracted the virus from a vaccinated child in their neighborhood, did not have their children in day care, and continued to refuse all vaccines after informed consent at well child visits given their unique family history putting them at higher risk of vaccine injury. Over 10.5 years there were zero deaths from infectious diseases in the patients born into the practice. Physicians who adopt the VFP approach can relay these statistics to their patients when they provide information required to solicit informed consent.

6. The measles, mumps and rubella vaccine does not contain aluminum

The impetus for this Corrigendum was an anonymous expression of concern to the Editorial Board, which we have been informed included concern over the effects of our study on uptake of the measles vaccine. Our study focused on aluminum clearance and accumulation, and the results are not impacted by the acceptance or refusal of offered measles vaccination, including the Measles, Mumps and Rubella Vaccine since this vaccine does not contain aluminum. While the VFP has variation in the timing of measles vaccination, it does, in fact, include the MMR, albeit at the separate recommended times. Most patients on the plan received as many doses as recommended by the CDC or obtained proof of measles immunity by demonstrating adequate IgG antibody titers against measles as allowed per Oregon State law. While there is difference in timing of the offering of the MMR in the VFP, this is the only difference, and this point is not relevant to the conclusions of the study to which we add this Corrigendum, which again was focused solely on the exposure to aluminum from aluminum-containing vaccinations.

7. Aluminum whole-body burden and intolerance addressed

It is often claimed that aluminum toxicity cannot be a problem because most aluminum is removed quickly from the body by excretion. This claim is falsified by the study by Movsas et al. [7], who found no aluminum in the feces or urine of newborn infants injected with three vaccines with a total of 1200 mg of aluminum within 24 h after vaccination. The study also reported no change in serum aluminum levels within 24 h following vaccination. Without evidence of whole-body excretion and no evidence of increased serum levels of aluminum, the study points to tissue adherence. The finding that 95 % of aluminum had not cleared the body of rabbits by day 28 by Flarend et al. [8] is cause for grave concern.

Aluminum serum pharmacokinetics cannot be addressed by serum clearance rates. Aluminum from vaccines yields Al3+ ions. The Al3+ ions, if slowly released, can be toxic in some people, especially if their slow release from a single dose is followed by successive doses which also are slowly released. Each dose can be thought of as a seeping well, with the cumulative doses all seeping into the corpus, making their way via macrophage uptake of cellular debris from cell death caused by aluminum contributing, along with genetics, to endoplasmic reticulum stress eliciting the unfolded protein response (Mustafa Rizvi et al., [9]). Because the recirculation of aluminum ions from these long-standing depots is not obvious from looking at standard pharmacokinetics (e.g., serum clearance), studies of whole-body toxicity such as our are relevant.

Our study replaces Mitkus et al. [10] an exercise which has been thoroughly excoriated as mere mathematical journey based on the faulty assumption that oral doses of aluminum (of a different form from those found in vaccines) in adult mice could be used to predict the impact of, as if those data can be transformed via math into relevant data for injected forms in human adults and children (Lyons-Weiler and Ricketson, 2018) [2]. Mitkus et al. (2011) [10] has been independently critiqued as fundamentally flawed (Lyons-Weiler and Ricketson, 2018 [2]; Masson et al. (2018) [11]. In short, the Mitkus paper [10] based an assessment of the safety of water-insoluble forms of injected of aluminum in human adults on a single study of dietary water-soluble forms of aluminum in adult mice (Golub et al., 1989) [12]. This study, cherry-picked from among many by ATSDR, was used to claim that the doses of aluminum used on humans are safe. Mitkus et al. (2011) [10] finding no evidence of adverse effects from dietary aluminum has led the medical and scientific community away from what would have been valuable empirical studies of injected aluminum adjuvants such as dose-escalation studies in infant mice. Studies that use oral citrate solution administration of aluminum, such as (Golub 1989) [12] are of no relevance for study of the toxicity of aluminum types from vaccines, as no vaccine contains citrate or is administered with citrate. Animal studies are further limited due to their inability to address the hypothesis of genetic variation aluminum tolerance in humans. The US FDA's involvement in the Mitkus et al. (2011) paper [10] is most unfortunate because it has loaned an air of unwarranted credibility to dosing of aluminum in vaccination based on irrelevant results.

It is sometimes argued that aluminum of the type used in vaccines has never been found in the human brain. This is an argument relying heavily on negative data, which is a function of the lack of science and the lack of the right types of studies done and represents an example of the fallacy of argument from ignorance.

Specific aluminum molecules have been found – in numerous studies - in the brains of individuals (Mold et al., 2018) [13]. Brain amyloid itself is part aluminum, a fact reported in 1985 (Masters, 1985) [14]. Human and animal studies since (e.g., Flarend et al., 1997) [8] suffice as evidence of brain entry of vaccine forms of aluminum (aluminum oxyhydroxide).

While the toxic effects of various forms of aluminum have been reviewed (Willhite et al., 2014 [15]; Igbokew et al. 2019 [16]), insufficient study exists on the specific mechanisms of action of toxicity of vaccine forms of aluminum. Nevertheless, some are well-established, including mitopathy (aluminum lactate; Sharma et al., 2013) [17], persistent gliosis (aluminum trichloride; Belaïd-Nouira et al., 2013) [18], endoplasmic reticulum stress (aluminum maltolate; Savory et al.,

2003) [19], disruption of cytoskeleton dynamics Lemire et al. 2009 [20] and reactive oxygen species generation leading to disruption of iron metabolism and ATP production (Han et al., 2013) [21]. Animal studies routinely use aluminum oxyhydroxide to - reliably and reproducibly - induce autoimmune asthma (Elsakkar et al., 2016) [22], allergic rhinitis (Yasar et al. [23]), systemic lupus erythematosus (Kelly-Scumpia et al. [24]) in doses that overlap or are lower than, per body weight, the CDC pediatric schedule. The evidence from animal studies supportive of causal role of aluminum hydroxide salts in autoimmune conditions in animal models is overwhelming. The recent vaccinated vs. unvaccinated study by Lyons-Weiler and Thomas [4]) study found much higher anemia in vaccinated children than completely unvaccinated children, a result we attribute to the binding of aluminum to transferrin, blocking proper bone deposition of dietary iron [10].

All of these studies show that the impact of injected aluminum on human health is a valid concern, and therefore vaccination schedules that seek to minimize exposure to injected aluminum are worth investigating (Crépeaux et al. [25]). As we showed in McFarland et al. (2020), on the CDC pediatric schedule, children receive more aluminum from vaccines than from any food source or from water, at levels placing them in aluminum toxicity 100% of their days in the first year. These issues can only be addressed by reconsideration of the use of aluminum in pediatric vaccines.

Erratum

In the McFarland et al. study (2020), the sentence “Our approach used the weight-adjusted PDL inferred by Lyons-Weiler and Ricketson [2] as an MSL, which is based on the FDA’s assumption that 850 μg of aluminum is safe for an adult of 150 kg” should end with “150 lbs”.

References

[1] G. McFarland, E. La Joie, P. Thomas, J. Lyons-Weiler, J. Trace Elem. Med. Biol. 58 (2020), 126444.

[2] J. Lyons-Weiler, R. Ricketson, Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum, J. Trace Elem. Med. Biol. 48 (July) (2018) 67–73, https://doi.org/10.1016/j.jtemb.2018.02.025. Epub 2018 Mar 8. PMID: 29773196.

[3] L. Angrand, A.A. Elnar, F.J. Authier, R.K. Gherardi, G. Crépeaux, Exposition à l’aluminium vaccinal en France en 2018 [Aluminium adjuvant exposure through vaccines in France in 2018], Ann. Pharm. Fr. 78 (March (2)) (2020) 111–128, https://doi.org/10.1016/j.pharma.2020.01.002. French Epub 2020 Jan 17. Erratum in: Ann Pharm Fr. 2020 Nov;78(6):544-545. PMID: 32081303.

[4] J. Lyons-Weiler, P. Thomas, Relative incidence of office visits and cumulative rates of billed diagnoses along the axis of vaccination, Int. J. Environ. Res. Public Health 17 (November (22)) (2020) 8674, https://doi.org/10.3390/ijerph17228674. PMID: 33266457; PMCID: PMC7709050.

[5] CDC, Rotavirus Census Regional Trends, 2020. https://www.cdc.gov/surveillance/nrevss/rotavirus/region.html.

[6] A.S. Lopez, J. Zhang, Mona Marin, Epidemiology of varicella during the 2-Dose varicella vaccination program — united States, 2005–2014, MMWR 65 (2016) 902–905. https://www.cdc.gov/mmwr/volumes/65/wr/mm6534a4.htm#F1_down.

[7] T.Z. Movsas, N. Paneth, W. Rumbeiha, J. Zyskowski, I.H. Gewolb, Effect of routine vaccination on aluminum and essential element levels in preterm infants, JAMA Pediatr. 167 (September (9)) (2013) 870–872, https://doi.org/10.1001/jamapediatrics.2013.108. PMID: 23856981.

[8] R.E. Flarend, S.L. Hem, J.L. White, D. Elmore, M.A. Suckow, A.C. Rudy, E. A. Dandashli, In vivo absorption of aluminium-containing vaccine adjuvants using 26Al, Vaccine. 15 (Aug-Sep (12-13)) (1997) 1314–1318, https://doi.org/10.1016/s0264-410x(97)00041-8. PMID: 9302736.

[9] S.H. Mustafa Rizvi, A. Parveen, A.K. Verma, I. Ahmad, M. Arshad, A.A. Mahdi, Aluminium induced endoplasmic reticulum stress mediated cell death in SH-SY5Y neuroblastoma cell line is independent of p53, PLoS One 9 (May (5)) (2014) e98409, https://doi.org/10.1371/journal.pone.0098409. PMID: 24878590; PMCID: PMC4039480.

[10] R.J. Mitkus, D.B. King, M.A. Hess, R.A. Forshee, M.O. Walderhaug, Updated aluminum pharmacokinetics following infant exposures through diet and vaccination, Vaccine. 29 (November (51)) (2011) 9538–9543, https://doi.org/10.1016/j.vaccine.2011.09.124. Epub Oct 11. PMID: 22001122.

[11] J.D. Masson, G. Crépeaux, F.J. Authier, C. Exley, R.K. Gherardi, Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants, J. Inorg. Biochem. 181 (April) (2018) 87–95, https://doi.org/10.1016/j.jinorgbio.2017.12.015. Epub 2017 Dec 28. PMID: 29307441.

[12] M.S. Golub, J.M. Donald, M.E. Gershwin, C.L. Keen, Effects of aluminum ingestion on spontaneous motor activity of mice, Neurotoxicol. Teratol. 11 (May-June (3)) (1989) 231–235, https://doi.org/10.1016/0892-0362(89)90064-0. Erratum in: Neurotoxicol Teratol 1999 May-Jun;21(3):303. PMID: 2755419.

[13] M. Mold, D. Umar, A. King, C. Exley, Aluminium in brain tissue in autism, J. Trace Elem. Med. Biol. 46 (2018) 76–82.

[14] C.L. Masters, G. Multhaup, G. Simms, J. Pottgiesser, R.N. Martins, K. Beyreuther, Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels, EMBO J. 4 (November (11)) (1985) 2757–2763. PMID: 4065091; PMCID: PMC554575.

[15] C.C. Willhite, N.N. Karyakina, R.A. Yokel, N. Yenugadhati, T.M. Wisniewski, I. M. Arnold, F. Momoli, D. Krewski, Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts, Crit. Rev. Toxicol. 44 (October (Suppl 4)) (2014) 1–80, https://doi.org/10.3109/10408444.2014.934439. PMID: 25233067; PMCID: PMC4997813.

[16] I.O. Igbokwe, E. Igwenagu, N.A. Igbokwe, Aluminium toxicosis: a review of toxic actions and effects, Interdiscip. Toxicol. 12 (October (2)) (2019) 45–70, https://doi.org/10.2478/intox-2019-0007. Epub 2020 Feb 20. PMID: 32206026; PMCID: PMC7071840.

[17] D.R. Sharma, A. Sunkaria, W.Y. Wani, R.K. Sharma, R.J. Kandimalla, A. Bal, K. D. Gill, Aluminium induced oxidative stress results in decreased mitochondrial biogenesis via modulation of PGC-1α expression, Toxicol. Appl. Pharmacol. 273 (December (2)) (2013) 365–380, https://doi.org/10.1016/j.taap.2013.09.012. Epub 2013 Sep 29. PMID: 24084166.

[18] Y. Belaïd-Nouira, H. Bakhta, Z. Haouas, I. Flehi-Slim, F. Neffati, M.F. Najjar, H. B. Cheikh, Fenugreek seeds, a hepatoprotector forage crop against chronic AlCl3 toxicity, BMC Vet. Res. 9 (January) (2013) 22, https://doi.org/10.1186/1746-6148-9-22. PMID: 23363543; PMCID: PMC3568417.

[19] J. Savory, M.M. Herman, O. Ghribi, Intracellular mechanisms underlying aluminum-induced apoptosis in rabbit brain, J. Inorg. Biochem. 97 (September (1)) (2003) 151–154, https://doi.org/10.1016/s0162-0134(03)00258-7. PMID: 14507471.

[20] J. Lemire, R. Mailloux, S. Puiseux-Dao, V.D. Appanna, Aluminum-induced defective mitochondrial metabolism perturbs cytoskeletal dynamics in human astrocytoma cells, J. Neurosci. Res. 87 (May (6)) (2009) 1474–1483, https://doi.org/10.1002/jnr.21965. PMID: 19084901.

[21] S. Han, J. Lemire, V.P. Appanna, et al., How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale, Cell Biol. Toxicol. 29 (2013) 75–84, https://doi.org/10.1007/s10565-013-9239-0.

[22] M.G. Elsakkar, O.A. Sharaki, D.M. Abdallah, D.K. Mostafa, F.T. Shekondali, Adalimumab ameliorates OVA-induced airway inflammation in mice: role of CD4(+) CD25(+) FOXP3(+) regulatory T-cells, Eur. J. Pharmacol. 786 (September) (2016) 100–108, https://doi.org/10.1016/j.ejphar.2016.06.002. Epub 2016 Jun 2. PMID: 27262379.

[23] M. Yasar, Y. Savranlar, H. Karaman, et al., Effects of propolis in an experimental rat model of allergic rhinitis, Am. J. Otolaryngol. 37 (2016) 287–293.

[24] K.M. Kelly-Scumpia, D.C. Nacionales, P.O. Scumpia, J.S. Weinstein, S. Narain, L. L. Moldawer, M. Satoh, W.H. Reeves, In vivo adjuvant activity of the RNA component of the Sm/RNP lupus autoantigen, Arthritis Rheum. 56 (October (10)) (2007) 3379–3386, https://doi.org/10.1002/art.22946. PMID: 17907192.

[25] G. Crépeaux, F.J. Authier, C. Exley, L. Luján, R.K. Gherardi, The role of aluminum adjuvants in vaccines raises issues that deserve independent, rigorous and honest science, J. Trace Elem. Med. Biol. 62 (December) (2020) 126632, https://doi.org/10.1016/j.jtemb.2020.126632. Epub 2020 Aug 1. PMID: 32823165.