



Commentary

An aluminium adjuvant in a vaccine is an acute exposure to aluminium

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1. Introduction

Aluminium salts are common adjuvants in vaccines given to children. Their physical, chemical and biological properties have recently been reviewed [1]. However, a debate continues as to whether neonate and infant exposure to aluminium through vaccination is biologically significant with respect to their exposure to aluminium through other routes and especially diet. For example, paediatricians, responsible for administering the vaccine schedule for children, seem in particular, to be uninformed about the properties of aluminium adjuvants and their mode of action in vaccines. This apparent ignorance of the published scientific literature is unexpected in those charged with the wellbeing of neonates and infants and especially in the light of Janeway's description of alum adjuvant as 'the immunologist's dirty little secret' [2]. Paediatricians such as recently (07/04/2019) Andrew Pollard in *The Sunday Times*, have a habit of reverting to pure 'baby talk' when for example; describing how much aluminium is present in an infant vaccine. They use terms such as 'minuscule' and 'teeny-weeny' to tell anyone, who asks, how little aluminium there is in a vaccine. They usually then proceed to compare the amount of aluminium in a vaccine with the amount of aluminium in (an adult's) diet. There are, of course, more accurate, understandable ways to inform parents and other interested parties how much aluminium is present in a vaccine, and I shall endeavour to achieve this herein. An appreciation of how much aluminium is present in a single injection of a vaccine is critical to understanding how aluminium adjuvants are effective in stimulating the immune response.

2. How much aluminium is found in vaccines?

Currently about 20 childhood vaccines include an aluminium adjuvant. Vaccine industry literature (for example; <https://www.medicines.org.uk/emc/product/2586/smpc>) expresses the aluminium content of an individual vaccine as an amount (weight) of aluminium (not aluminium salt) per unit volume of a vaccine (usually 0.5 mL). Industry does this to account for the fact that there are no strict molecular weights for the polymeric aluminium salts that are used as adjuvants in vaccinations. They prepare acid digests of the adjuvants and measure their total aluminium using ICP MS. This is not explained in the literature they provide with vaccines and can cause confusion for

some as the actual weight of hydrated aluminium salt (e.g. aluminium oxyhydroxide, aluminium hydroxyphosphate and aluminium hydroxyphosphatesulphate) in any vaccine preparation is actually approximately ten fold higher. The aluminium salt is the major component of a vaccine (after water) and its high content is why vaccine preparations are invariably cloudy in appearance [1]. As an example, GlaxoSmithKline's *Infanrix Hexa* vaccine is reported by the manufacturer to contain 0.82 mg of aluminium per vaccine (0.5 mL). Thus, the weight of aluminium salt in this vaccine is approximately 8 mg, which is approximately ten times the weight of all of the other components of the vaccine when combined. An aluminium-adjuvanted vaccine is essentially a very high concentration of an aluminium salt (8 mg/0.5 mL or 16 mg/mL or 16 g/L) in which just µg of other vaccine components including antigens and other excipients are occluded.

3. Is the amount of aluminium in a vaccine 'minuscule'?

Generally, in the United Kingdom the first dose of *Infanrix Hexa* vaccine is injected into muscle when an infant is 8 weeks old. All 8 mg of the aluminium salt (or 0.82 mg of aluminium) will immediately be systemic; it is inside the infant's body. The repercussions of this being that the injected aluminium may only leave the body through its excretion in either the infant's urine or sweat. What is the immediate biological response to this exposure to aluminium adjuvant? Aluminium is described as a silent visitor to the human body. What this means is that in the evolution of life on Earth and latterly human evolution, no historic signature is found as evidence for previous exposure to aluminium [3]. By way of comparison with another toxic and non-essential metal, if the adjuvant used in a vaccine was composed of a cadmium salt its injection would immediately initiate a counter-response by the body in an attempt to remove the toxicant. Proteins known to bind and help in the detoxification of cadmium are produced and this is a sure sign that biochemistry had previously encountered non-essential cadmium and selected it out of essential biochemical pathways. Such restorative attempts at detoxification are not triggered for biologically available aluminium and so the 'processing' of aluminium adjuvant at the injection site of a vaccine is completely adventitious and one might suggest, random and chaotic. The latter because the fate of aluminium in the body, unlike essential and other non-essential metals, is not subject to any form of homeostasis. Myriad

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chemical and biological processes will initiate the slow redistribution of the injected aluminium throughout the infant's body. These steps will involve the processes of disaggregation, dissolution, complexation, precipitation, distribution, cellular uptake and translocation. The description of each one of these processes is an essay in itself and we have addressed them all in many complementary publications [1]. An important and vaccination-specific distinction to make at this point and to carry forward to the following discussion is that aluminium injected into muscle as an adjuvant in a vaccine potentially has uninterrupted access to the infant brain. This is because there is no prerequisite for its passage via the liver, the most prominent organ of detoxification in humans.

We asked if 0.82 mg of systemically available aluminium administered as a single dose in a vaccine is, as some paediatricians would suggest, a minuscule amount of aluminium, for example, as compared to aluminium in the diet. Infants receiving Infanrix Hexa vaccine at 8 weeks of age are concurrently either being breast or formula fed. Data show that the former is likely to result in an 8 week old infant ingesting up to 0.1 mg of aluminium each day [4,5]. On the day an infant receives 8 mg of an aluminium salt, or 0.82 mg of aluminium, in a vaccine it will also ingest 0.1 mg of aluminium in breast milk. However, what proportion of this 0.1 mg of dietary aluminium will be absorbed across the infant gut? Previous research has asked a similar question [6]. The reality is that data for the absorption of aluminium across the infant gut do not presently exist and one has to apply gastrointestinal absorption data obtained for adults. The oft-cited value for adults is that less than 0.1% of ingested aluminium in diet is actually absorbed [7]. The infant gut at 8 weeks is incomplete [8] and is likely to be much more permeable to dietary aluminium, perhaps as much as 100 times more permeable. Applying such clearly conditional criteria it can be estimated that 10% of ingested aluminium or 0.01 mg/day of aluminium in breast milk is absorbed across the infant gastrointestinal tract. However, the blood carrying nutrients and toxins that have been absorbed from the gut, to the rest of the body must first pass through the liver, the major detoxification system of the body. Data on the efficiency of the liver in removing aluminium from the blood is, at best, incomplete in adults [9] and completely unknown in infants. If it is estimated that the liver is 75% efficient in this respect for adults then it is probably only 50% efficient in an infant. When these various conditional factors are accounted for it can be estimated that an infant's exposure to systemically available aluminium from breast-feeding is approximately 0.005 mg of aluminium each day. In essence during the first 8 weeks or 56 days of life, breast-feeding ostensibly drip feeds an infant with a combined total of 0.28 mg of systemically available aluminium. On day 56 the infant receives a single dose of 0.82 mg of aluminium in the Infanrix Hexa vaccine, a dose equivalent to 3 times the amount of aluminium the infant received during the entire 55 days of life prior to its vaccination. It is well known, if highly unfortunate, that infant formulas are heavily contaminated with aluminium [10,11] and in a worst-case scenario an infant only being formula-fed from birth might be exposed to 0.030 mg of aluminium each day up to vaccination on day 56. Even in this worst-case scenario, the exposure to systemically available aluminium on vaccination day is 25 times higher through the vaccine than through the diet.

4. Acute versus chronic exposure to aluminium

Breast or formula feeding in an infant is a chronic exposure to aluminium. The infant is exposed to a small but continuous supply of systemically available aluminium, aluminium that has the potential to be stored in the infant's body and excreted from the infant's body in the urine. Perhaps, at no point during continuous chronic (drip feed) exposure in infancy (0–12 months of age) does the concentration of aluminium in any one physiological compartment increase to bring about overt toxicity. How does dietary exposure to aluminium in infants compare to exposure through vaccination, for example, a single Infanrix

Hexa vaccine at 8 weeks of age? The concentration of aluminium (not aluminium salt) in an Infanrix Hexa vaccine upon its injection into muscle is, according to the manufacturer, 0.82 mg/0.5 mL or 1.64 mg/mL or 1.64 g/L or approximately 60 mmol/L. This is the concentration of total systemically available aluminium immediately present at the injection site of the vaccine and available to bring about biological effect. Aluminium adjuvants are not inert depots at the vaccine injection site; they are sources of biologically reactive aluminium [1]. This concentration of total aluminium at the injection site of a vaccine can be put into context by examining the cellular toxicity of aluminium [12] and specifically as identified in recent scientific publications. We can ask the question if we would expect this concentration of aluminium to produce biological effects including cell death at the vaccine injection site. A relevant cell to investigate are lymphocytes and research has demonstrated significant genotoxicity in lymphocytes exposed to only 0.020 mmol/L total aluminium [13]. Similarly, in another study using lymphocytes 0.6 mmol/L total aluminium resulted in significant immunosuppression in both T and B-lymphocytes [14]. Clearly, we would expect profound effects on lymphocytes at the injection site of a vaccine where the total aluminium concentration is 60 mmol/L. Macrophages, a characteristically robust cell, are susceptible to aluminium toxicity demonstrating 50% cell death at a total aluminium concentration of 10 mmol/L [15]. Other more sensitive cell lines would include neuroblastoma where cell viability is reduced by 50% by less than 1 mmol/L total aluminium [16] and similarly for primary hippocampal neurons exposed to only 0.05 mmol/L total aluminium [17]. The concentration of systemically available aluminium immediately present at the injection site of a vaccine is very high in comparison to studies on cell cytotoxicity in the scientific literature. It is an acute exposure to aluminium and it results in significant cytotoxicity including necrotic cell death [1]. The resulting tissue inflammation is the characteristic red mark on the skin at the injection point. This acute toxicity in the immediate vicinity of the injection site underlies the success of aluminium salts as adjuvants in vaccinations [1]. However, while some cells, both present at and infiltrating the injection site, are compromised and especially immediately, other cells act to remedy the situation by taking up aluminium adjuvant into their cytoplasm [18]. This action reduces the concentration of biologically reactive (toxic) aluminium at the injection site and locks away potentially cytotoxic aluminium in intracellular vesicles. Herein may be the real issue linking aluminium adjuvants and severe adverse events following a vaccine. These aluminium-loaded cells remain viable for days, potentially weeks, which means that they can transport their cargo of aluminium anywhere in the body including the infant brain. The recruitment of systemic cells including macrophages to the central nervous system is a widely documented phenomenon [19]. There is now a viable mechanism for the accelerated loading of an infant's brain with aluminium and evidence to support such a mechanism was demonstrated in our recent paper on aluminium in brain tissue in autism [20].

5. Conclusion: is the amount of aluminium in a vaccine 'minuscule'?

Simply by looking at just one dose of a vaccine given at 8 weeks of age it is abundantly clear that science does not support this contention, as espoused regularly by many infant paediatricians. In fact, just a single dose of Infanrix Hexa vaccine represents a severe acute exposure to systemically available aluminium. A single dose of this vaccine is equivalent to the exposure to aluminium that an infant would receive from 150 days breast-feeding. It is equivalent to 25 times the daily dose of aluminium received from the most contaminated of infant formulas. It is pertinent to emphasise that an infant would receive a further two doses of this vaccine during the aforementioned 150 day period. It is also highly relevant that other aluminium adjuvanted vaccines, for example Prevenar 13 (<https://www.medicines.org.uk/emc/product/453/smpc>) and Men B (<https://www.medicines.org.uk/emc/product/>

5168/smpc) are also part of the infant vaccine schedule for this same period. In the United Kingdom it is not uncommon for an infant to receive all three of these aluminium adjuvanted vaccines on the same day. A combined daily exposure of 1.445 mg of aluminium (according to the manufacturer's data), equivalent to 260 days exposure to aluminium through breast feeding. Exposure to aluminium through a vaccine is, in comparison to diet, an acute exposure and an infant's physiology will respond differently to exposure to a high concentration of aluminium over a very short time period. The latter, acute versus chronic exposure, while not yet being taken into account in infant vaccination programmes, must now be considered to help to ensure that future vaccination schedules are safe. Currently the EMA and the FDA limit the aluminium content of a vaccine to 1.25 mg (See for example, https://www.ecfr.gov/cgi-bin/text-idx?SID=832c22988b6c802fe810e16ea34ace1a&mc=true&node=se21.7.610_115&rgn=div8). This limit is based upon the aluminium adjuvant's efficacy in inducing antibody titres. Perhaps now is the time to revise this limit based upon additional factors of vaccine safety.

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