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Do aluminum vaccine adjuvants contribute to the rising prevalence of autism?

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ABSTRACT

Autism spectrum disorders (ASD) are serious multisystem developmental disorders and an urgent global public health concern. Dysfunctional immunity and impaired brain function are core deficits in ASD. Aluminum (Al), the most commonly used vaccine adjuvant, is a demonstrated neurotoxin and a strong immune stimulator. Hence, adjuvant Al has the potential to induce neuroimmune disorders. When assessing adjuvant toxicity in children, two key points ought to be considered: (i) children should not be viewed as "small adults" as their unique physiology makes them much more vulnerable to toxic insults; and (ii) if exposure to Al from only few vaccines can lead to cognitive impairment and autoimmunity in adults, is it unreasonable to question whether the current pediatric schedules, often containing 18 Al adjuvanted vaccines, are safe for children? By applying Hill's criteria for establishing causality between exposure and outcome we investigated whether exposure to Al from vaccines could be contributing to the rise in ASD prevalence in the Western world. Our results show that: (i) children from countries with the highest ASD prevalence appear to have the highest exposure to Al from vaccines; (ii) the increase in exposure to Al adjuvants significantly correlates with the increase in ASD prevalence in the United States observed over the last two decades (Pearson $r = 0.92$, $p < 0.0001$); and (iii) a significant correlation exists between the amounts of Al administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3–4 months of age (Pearson $r = 0.89–0.94$, $p = 0.0018–0.0248$). The application of the Hill's criteria to these data indicates that the correlation between Al in vaccines and ASD may be causal. Because children represent a fraction of the population most at risk for complications following exposure to Al, a more rigorous evaluation of Al adjuvant safety seems warranted.

1. Introduction

During prenatal and early postnatal development the brain is extremely vulnerable to neurotoxic insults [1,2]. Not only are these highly sensitive periods of rapid brain development in general [3] but also, the blood brain barrier (BBB) is incomplete and thus more permeable to toxic substances during this time [2,4,5]. Further, immune challenges during early development, including those induced by vaccines, can lead to permanent detrimental alterations of nervous and immune system function [6–9]. Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants, or repeated stimulation of the immune system by the same antigen, can overcome genetic resistance to autoimmunity in animals [10,11]. Moreover, in adult humans, a variety of conditions encompassed by the 'Autoimmune/inflammatory syndrome induced by adjuvants' ('ASIA') have been linked to exposure to aluminum (Al) vaccine adjuvants (Table 1).

In many Western countries, by the time children are 4–6 years old they will have received a total of 23–32 vaccines [12,13], many with Al adjuvants, through routine pediatric vaccine schedules [2,14]. According to the United States Food and Drug Administration (US FDA), safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic [15]. However, if a few vaccines administered to adults can result in adverse outcomes, such as the 'ASIA' syndrome, should we *assume* without experimental evidence that the current pediatric schedules are safe for children?

Analysis of the relevant data shows that the number of vaccinations recommended prior to school entry increased from 10 in the late 1970s to 32 in 2010 (18 of which contain Al adjuvants) [16]. During this same period, the prevalence of autism spectrum disorders (ASD) in the US also increased by as much as 2000% [16]. While such observations have been of interest, the potential role of vaccines in the development of ASD remains controversial. ASD are characterized by marked impairments in social skills, verbal communication, behavior and cognitive dysfunction [17–19]. Although the etiology of 90% of ASD is still largely unknown [20,21], a growing body of scientific literature shows that neuroimmune abnormalities (i.e., abnormal cytokine profiles, neuroinflammation and presence of autoantibodies

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Table 1
Shared aspects between autoimmune/inflammatory diseases (including ASD) and immunostimulatory properties of Al vaccine adjuvants.

Condition			Al adjuvant	
Disease	Th shift	Inflammatory profile	Inflammatory profile	General immunostimulatory effects
Arthritis*,†	Excessive Th1 [129,155]	Increased IL-1, IL-6, IL-12, TNF-α, IFN- γ, MIP-1α and oxidative stress [129,134,155]	Increases cytokines (IL-1α, IL-1β, IL-4, IL-5, IL-6, IL-18, TNF-α), chemokines (IL-8, MCP-1, MIP- 1α, MIP-1β), ROS, and nitric oxide (NO) [34,40,138,155,170,171]	Stimulates recruitment of monocytes, macrophages and granulocytes to the injection site
Autoimmune thyroid disease				Induces differentiation of monocytes to antigen presenting cells (APCs)
Inflammatory bowel disease (IBD)/Crohn s disease (CD)		Increased NLRP3 inflammasome complex signaling and NLRP3-dependent over-production of IL- 1β, IL-6, IL-18, TNF- α and reactive oxygen species (ROS) in MS, EAE, Type 1 diabetes mellitus [164–166] and animal models of IBD [167]		Activates APCs
Type 1 diabetes mellitus*			Activates the NLRP3 inflammasome complex and NLRP3- dependent cytokines [33,34,172]	Promotes antigen uptake and processing by APCs and enhances antigenspecific T-cell responses
Multiple sclerosis (MS)*,† and experimental autoimmune encephalomyelitis (EAE)				Increases the expression of MHC class I and II and associated co-stimulatory molecules on peripheral blood monocytes
Systemic lupus erythematosus (SLE)*	Excessive Th2 [129,156]	Increased IL-10, IL-18, IL-6, IFN- γ, TNF-α [129,156,168,169]		Activates the complement cascade
Macrophagic myofasciitis (MMF) and chronic fatigue syndrome (CFS)*,†	Excessive Th2 [53,157,158]	Increased IL-4, IL-6, B-cell hyperlymphocytosis, infiltration of large periodic acid-schiff (PAS)-positive macrophages, and CD8+ T lymphocytes in the absence of conspicuous muscle fibre damage [53,95,158]		Generally stimulates Th2 responses but can also induce a Th1 shift and activate cytotoxic T lymphocytes (CTLs) in the presence of other Th1 stimulators (i.e., lipopo ysaccharide (LPS), CpG, recombinant influenza protein antigen [138,173–175])
Gulf War Syndrome (GWS)*,†	Mixed Th1/Th2 [159]	Increased IFN-γ, IL-5, IL-6 [159]		Activates astrocytes and microglia [29,97,139]
Autism spectrum disorders (ASD)*	Both Th1 and Th2 shifts have been reported [17,160–163]	Increased IL-1β, IL-4, IL-5, IL-6, TNF-α, IL-8, MCP-1, MIP-1β, MHC class II [17,160,162] Increased astrocyte and microglia reactivity [17,20]		

* Linked to Al-adjuvanted vaccines [32,101,102,176,177].
† Specifically recognized as 'Autoimmune/inflammatory syndrome induced by adjuvants' ('ASIA') [32].

against brain proteins) occur in ASD patients and may contribute to the diversity of ASD phenotypes [17,20,22–26].

Al is an experimentally demonstrated neurotoxin whose ability to impact the human nervous system has been known for decades [16,27–29]. For example, exposure to as little as 20 μg/kg bw of Al for period >10 days is sufficient to cause neurodevelopmental delays in preterm infants [28]. In addition, Al is a potent stimulator of the immune system, indeed this is the very reason why it is used as an adjuvant [14,30–34]. Given this, it remains surprising that in spite of over 80 years of use, the safety of Al adjuvants appears to rest largely on assumptions rather than experimental evidence. For example, nothing is known about the toxicology and pharmacokinetics of Al compounds in infants and children [35]. In addition, the mechanisms by which Al adjuvants interact with the immune system remain far from clear [34,35]. In this regard it is notable that many vaccine trials usually use an Al adjuvant containing "placebo" or another vaccine as the "control" group [36–38], rather than a saline control. This study design has not allowed a direct comparison of the efficacy and safety of the antigen alone versus the Al adjuvant. In spite of these gaps in our knowledge about Al adjuvants, the use of Al in vaccines is widely regarded as safe and effective [35,39,40].

Should it be of concern that so little is known about the potential deleterious impacts of Al adjuvants on the developing central nervous system (CNS) given that worldwide, preschool children are regularly exposed to significant amounts of Al from vaccines [2,14]? To address this question, we investigated pediatric vaccine schedules from various Western countries in order to gain a better understanding of potential Al exposure from vaccines in children. Our results, supported by the Hill's criteria for establishing causality between exposure and outcome [41], suggest that a causal relationship may exist between the amount of Al administered to preschool children at various ages through vaccination and the rising prevalence of ASD.

2. Methods

2.1. Collection of ASD prevalence data

We analyzed the currently available data from the US Department of Education Annual Reports to Congress for ASD prevalence for the period from 1991 to 2008 [42–52] in the 6–21 year-old age cohort and correlated it with the estimated total Al exposure from pediatric vaccines (given to preschool children before the age of 6 years), sourced from the US Centers for Disease Control and Prevention (CDC [12]). In addition, we obtained the most recent available data for ASD prevalence and vaccination schedules from several other countries including the United Kingdom (UK), Australia, Canada, Sweden, Finland and Iceland (see below for source references). Using the latter data, we carried out a correlation analysis to investigate the potential association between ASD prevalence and estimated vaccine-derived Al exposures in preschool children at various ages. We also correlated ASD prevalence with the number of Al-adjuvanted vaccines given to preschool children according to the relevant vaccination schedules from each country.

2.2. Calculations of Al exposure from vaccines

For the purpose of correlating ASD prevalence to Al exposure, for each country studied, we calculated the cumulative amount of Al administered from all vaccines that children receive during the specified age period (i.e., the cumulative exposure to Al at 4 months of age

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includes Al from vaccines given at 2, 3 and 4 months). This rationale for using cumulative amounts of adjuvant Al in our analysis is also supported by the following observation: Al has been shown to persist at the site of injection from several months up to 8–10 years following vaccination in patients suffering from macrophagic myofasciitis, an autoimmune disease linked to Al vaccine adjuvants [53]. The number and types of pediatric vaccines were sourced from the US CDC [12], UK Department of Health [13], Public Health Agency of Canada [54], Australian Government Department of Health and Aging [55], Swedish Institute for Infectious Disease Control [56], KTL (Finish) National Public Health Institute [57] and Iceland's A Surveillance Community Network for Vaccine Preventable Infectious Diseases [58]. The Al content used was derived from an article by Offit and Jew [39] and manufacturer's product monographs (Table 2 [59–62]). Because the Al content varies between different brands of certain vaccines (Table 2), for each vaccination appointment, three possible exposures were calculated: (i) maximum, assuming exposure to vaccines with the highest Al content (i.e., 625 μg Al for DTaP from Infanrix and 225 μg Al for Hib from PedVax), (ii) mean, using the calculated mean Al-content values of different brands of DTaP and Hib (i.e., 375 μg for DTaP = (625 + 330 + 170)/3) and 112.5 μg for Hib = (0 + 225)/2); and (iii) minimum, assuming exposure to vaccines with the lowest Al content (i.e., 170 μg Al for DTaP from Tripedia and 0 μg Al for Hib from Hiberix). All three of these exposures were then correlated with the relevant ASD prevalence data. With regard to vaccine uptake in the US, we acknowledge that there are likely to be variations between individual states due to differences in adopting CDC's recommendations. However, since the ASD prevalence data pertain to the US population as a whole, rather than individual states, we felt that our overall evaluation with regard to US vaccine uptake was the most appropriate measure to use.

2.3. Exclusion/inclusion criteria

Certain vaccines were excluded from our calculations since the addition of these to childhood vaccination schedules occurred after the relevant ASD prevalence study periods. For example, in Australia, pneumococcal vaccine (PCV) was introduced in 2003 [63] and the ASD prevalence study conducted in 2005 provided data for 6–12 year-old children (1993–1999 birth cohort [64]); in Canada PCV and meningococcal serogroup C (MenC) were introduced in 2005 [65] and 2001 [66] respectively, and the ASD prevalence report was for 1987–1998 birth cohort [67]; in Sweden PCV was introduced in 2009 [68], ASD prevalence report was for 1977–1994 birth cohort [69]; in Finland, rotavirus vaccine was introduced in 2009 [70] and the ASD prevalence report was for 1979–1994 birth cohort [71]; in Iceland, meningococcal serogroup C (MenC) was introduced in 2002 [58] with ASD prevalence report for the 1984–1993 birth cohort [72]. ASD prevalence data for the US and UK were from Kogan et al. [73] and Baron-Cohen et al. [74], respectively. We included hepatitis B (HB) vaccine in our calculations for the UK vaccination schedule (at 0, 1 and 2 months [75]) since there was no rationale for excluding high risk groups from our analysis (as these groups have not been specifically excluded from the UK ASD prevalence data [74]). We excluded HB vaccine from our calculations for Sweden and Finland since in these countries HB vaccination for high risk groups was introduced in the mid 1990s [76,77], after the relevant ASD prevalence study periods.

Table 2
Al-adjuvant content in licensed vaccines.

Al adjuvant	Vaccine	Trade name	Manufacturer	Amount (μg) per dose
Al hydroxide	DTaP	Infanrix	GlaxoSmithKline	625 [39]
	DTaP	Daptacel	Aventis Pasteur	330 [39]
	DTaP	Tripedia	Aventis Pasteur	170 [39]
	HA	Havrix	GlaxoSmithKline	250 [39]
	HB*	EngerixB	GlaxoSmithKline	250 [178]
	Hib	PedVax	Merck and Co	225 [39]
	Hib	Hiberix	GlaxoSmithKline	0 [62]
	Anthrax	Biothrax	Bioport Corp	600 [60]
Al phosphate	PCV	Prevnar	Wyeth	125 [39]
	MenC	Meningitec	Wyeth	125 [59]
Al sulfate	HB*	Recombivax	Merck and Co	250 [61]

* Pediatric dose = 250 μg, adult dose = 500 μg.

2.4. Statistical methods

The correlation analysis was carried out using GraphPad Prism statistical software to derive Pearson correlation coefficients (Pearson r; due to normal data distribution) between vaccine-derived Al exposures, Al-containing vaccine number and ASD prevalence. To control for type I errors due to multiple tests, we used permutation resampling-based multiplicity adjustment for p-values according to Westfall and Young [78] to determine whether the correlation between ASD prevalence in seven Western countries and Al exposure at various ages was statistically significant. Unlike the more popular Bonferroni-Holm method, Westfall and Young accounts for correlations between variables (e.g., age of exposure) and was hence a more appropriate choice. The Westfall and Young p-value adjustment was carried out in R software. The correlation was considered statistically significant at $p < 0.05$. In all of the data provided for Al vaccine exposure, Al is expressed either as total, or per kg of body weight. The latter was calculated by dividing total Al exposure with age-specific weight, sourced from Haddad and Krishnan [79].

2.5. Hill's criteria

The Hill's criteria for causation include: (1) the strength of the association (as measured by appropriate statistical tests), (2) the consistency of the observed association (i.e., the association has been repeatedly observed by different persons and/or in different places, circumstances and times), (3) the specificity of the association (established when a single putative cause produces a specific effect), (4) the temporal relationship of the association (exposure precedes the outcomes), (5) the biological gradient or dose–response curve (an increasing amount of exposure increases the risk), (6) biological plausibility (causation is biologically plausible and agrees with a currently accepted understanding of pathological processes of the disease in question), (7) the coherence with the current knowledge (data should be congruent with generally known facts of the natural history and biology of the disease), (8) experimental or semi-experimental evidence and (9) analogy with similar evidence (i.e., different toxins may result in similar disease outcomes because they adversely affect the same underlying processes linked to a specific disease) [41]. In neuropsychiatry, four of Hill's nine criteria are considered critical to assess causality: the strength of the association (criterion 1), the consistency of the observed association (criterion 2), the biologic rationale (criterion 6) and the temporal relationship of the association (criterion 4) [80]. Obviously, if evidence exists for the remaining criteria, conclusions about causality would be further strengthened. Note also that the specificity criterion (3) is not considered necessary in neuropsychiatry [80] given that many neuropsychiatric disorders have multiple causal factors. ASD for example, are partly determined by genetic susceptibility factors and hence fit this category [17,18,20,21].

3. Results

3.1. Al exposure from vaccines in adults and children based on body weight

Table 3 shows the estimated amounts of Al administered through vaccination to preschool children in the US. At 2 months of age, US infants receive the highest amount of Al per body weight from vaccines (172.5 μg/kg bw, mean exposure) compared to other ages. Table 4 shows Al exposure from vaccines per kg of body weight in children from seven Western countries: the UK, US, Canada, Australia, Sweden, Finland and Iceland. Note that children from countries with the highest ASD prevalence (i.e., UK, US, Australia and Canada) appear to have a higher exposure to Al from vaccines than do children from Scandinavian

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Table 3
Al administered from pediatric vaccines to children at different ages under the current US vaccination schedule [12] assuming mean exposure. Ages are expressed in months (mo).

Vaccine	Birth	2 mo	4 mo	6 mo	15 mo	24 mo	72 mo
HB	250	250		250			
DTaP*		375	375	375	375		375
Hib‡		112.5	112.5	112.5	112.5		
PCV		125	125	125	125		
HA					250	250	
Total Al (μg)	250	862.5	612.5	862.5	862.5	250	375
Total Al (μg/kg bw)	73.5	172.5	107.5	113.5	78.4	19.8	19.3

* Mean value from three different brands of DTaP (Infanrix, Daptacel, Tripedia, see Table 2).
‡ Mean value from two different brands of Hib (PedVax and Hiberix, see Table 2).

countries where autism prevalence is lower. Table 5 shows a comparison between vaccine-derived Al exposures in adults and children. Due to their lower body weight, children attain a much higher Al exposure per kg of body weight than adults (73.5–172.5 μg/kg bw versus 7.1 μg/kg bw).

3.2. Correlation between ASD prevalence and vaccine-derived Al exposures in the US

Al exposure from vaccines in the US vaccination schedule from 1991 to 2008 shows a highly significant positive linear correlation with ASD prevalence at all three levels of exposure (Pearson $r = 0.92$, $p < 0.0001$), with 95% CI = 0.79–0.97 (Fig.1; Table 6). In addition, we show in Table 7 that the number of Al-adjuvanted vaccines in the yearly vaccination schedules from 1991 to 2008 also yields a highly significant positive correlation with ASD prevalence (Pearson $r = 0.90$, $p < 0.0001$) with 95% CI = 0.76–0.96.

3.3. Correlation between ASD prevalence in the US, UK, Canada, Australia, Sweden, Finland and Iceland and Al exposure from pediatric vaccines

In Table 8 we show that the estimated cumulative vaccine-derived Al exposure yields a significant positive correlation with the current prevalence of ASD in seven Western countries at all three levels of exposure at 3–4 months of age. (Pearson $r = 0.89–0.94$, $p = 0.0018–0.0248$). ASD prevalence in these countries also significantly correlates with the number of Al-adjuvanted vaccines given at 3–18 months of age (Pearson $r = 0.89–0.94$, $p = 0.0018–0.0368$; Table 8).

Table 4
Estimated total Al exposure from vaccines (μg/kg bw) per vaccination schedule in various Western countries at different ages. Minimum to maximum range of exposure is given where applicable (where DTaP and Hib are scheduled). Age is expressed in months (mo).

	ASD prevalence/10,000	Birth	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
UK	157 [74]	73.5	62.5	109–245	55.7–184	73.7–193	0	0
US	110 [73]	73.5	0	109–245	0	51.8–171.1	0	71.7–161.2
Canada	65 [67]	73.5	0	84–220	0	73.7–193	0	22.4–111.8
Australia	62.5 [64]	73.5	0	84–220	0	73.7–193	0	55.3–144.7
Sweden	53.4 [69]	0	0	0	32.1–160.4	0	25.4–126.9	0
Iceland	12.4 [72]	0	0	0	32.1–160.4	0	25.4–126.9	0
Finland	12.2 [71]	0	0	0	32.1–160.4	0	25.4–126.9	0

Table 5
Comparison of Al exposure from vaccines in children and adults. An infant's vaccine-derived Al exposure of 73.5 μg Al/kg bw is equivalent to that from 10 HB vaccines given in a single day to a 70 kg adult ((73.5 μg Al/kg bw x 70 kg)/(HB dose (500 μg Al)) = 5147/500 = 10.3). The vaccine-derived Al exposure in a 2 month old receiving 172.5 μg Al/kg bw is equivalent to that from 24 HB vaccines given in a single day to a 70 kg adult ((172.5 μg Al/kg bw x 70 kg)/(HB vaccine dose (500 μg Al)) = 12075/500 = 24.2).

	An adult receiving a single HB vaccine (adult dose)	An infant receiving a single HB vaccine at birth (pediatric dose)	A 2 month old receiving the recommended set of injections (mean exposure)
Al (μg)	500	250	862.5
Bw (kg)	70	3.4	5
Total Al μg/kg bw	7.1	73.5	172.5

4. Discussion

4.1. Summary and implications of main findings

To the best of our knowledge, these results are the first to show that Al, a highly neurotoxic metal and the most commonly used vaccine adjuvant, may be a significant contributing factor to the rising prevalence of ASD in the Western world. In particular, we show here that the correlation between ASD prevalence and Al adjuvant exposure appears to be the highest at 3–4 months of age (Pearson $r = 0.89–0.94$, $p = 0.0018–0.0248$; Table 8). We also show that children from countries with the highest ASD prevalence appear to have a much higher exposure to Al from vaccines, particularly at 2 months of age (Table 4). In this respect, we note that several prominent milestones of brain development in humans coincide with these periods. These include the onset of synaptogenesis (birth), maximal growth velocity of the hippocampus (2–3 postnatal months) [3] and the onset of amygdala maturation (8 weeks postnatal age) [81]. In addition, the period between 2 and 4 months is also one of major developmental transition in many biobehavioural systems, including sleep, temperature regulation, respiration and brain wave patterns [82,83], all of which are regulated by the neuroendocrine network [84,85]. Many of these aspects of brain function are known to be impaired in autism (i.e., sleeping and brain wave patterns [86–88]).

According to the FDA, vaccines represent a special category of drugs as they are generally given to healthy individuals [15]. Further according to the FDA, "this places significant emphasis on their [vaccine] safety" [15]. While the FDA does set an upper limit for Al in vaccines at no more than 850 μg/dose [89], it is important to note that this amount was selected empirically from data showing that Al in such amounts enhanced the antigenicity of the vaccine, rather than from existing safety

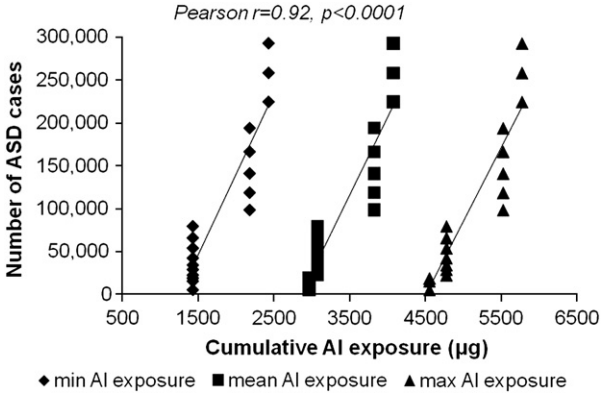

Fig. 1. Correlation between the number of children with ASD (6–21 years of age) and the estimated cumulative Al exposure (μg) from pediatric vaccines in the period from 1991 to 2008 (US data).

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Table 6
Statistical analysis summary. Correlation between the number of children with ASD (6–21 years of age) and the estimated Al exposure (μg) from pediatric vaccines in the period from 1991 to 2008 (US data). Significant change is indicated by the asterisk (*).

	ASD prevalence and estimated yearly cumulative vaccine-derived Al exposures		
	Minimum	Mean	Maximum
Pearson r	0.92	0.92	0.92
95% CI	0.79–0.97	0.80–0.97	0.80 to 0.97
P value (two-tailed)	<0.0001	<0.0001	<0.0001
P value summary	*	*	*
Is the corr. significant? (p<0.05)	Yes	Yes	Yes
R^2	0.84	0.85	0.85

data or from the basis of toxicological considerations [89]. However, in preventative vaccination where a vaccine is administered to healthy individuals, a compromise in efficacy for additional margins of safety should not necessarily be viewed as an unreasonable expectation [30]. It is also of note that the FDA requires limits on Al in parenteral feeding solutions and requires warning labels about potential Al hazards, while setting no safety limits or issuing warnings for Al in vaccines [90].

The lack of an established safety margin for Al in vaccines may be concerning for numerous reasons: (i) Al is highly neurotoxic and can impair prenatal and postnatal brain development in humans and experimental animals [28,91]; (ii) a pilot study showed higher than normal Al levels in the hair, blood and/or urine of autistic children (according to the authors, the correlation between the severity of signs and symptoms and the behavioral pattern found in many patients appeared to be compatible with metabolism disturbances provoked by Al overload [92]); (iii) children are regularly exposed to much higher levels of Al adjuvants than adults (Table 5 [14]); (iv) practically nothing is known about the pharmacokinetics and toxicodynamics of Al adjuvants in children [35] and paradoxically, evaluation of pharmaco- and toxicokinetics is not required for vaccine licensing purposes [93]; (v) in adult humans, Al vaccine adjuvants have been linked to serious neurological impairments, chronic fatigue and autoimmunity (Table 1) [31,32,94–96]; (vi) injection of Al adjuvants at levels comparable to those that are administered to humans have been shown to cause motor neuron death, impairments in motor function and decrements in spatial memory capacity in young mice [29,97]; and (vii) intraperitoneal injection of Al adsorbed vaccines in 4-week old mice was followed by a transient peak in brain Al levels on the second and third days after injection [98]. The latter experiment demonstrated that even a fully developed BBB does not impede Al access to the brain tissue. Altogether, the above observations raise plausible concerns about the overall safety of the use of Al adjuvants in childhood vaccines.

An additional, concern is that for certain Al-adjuvanted vaccines the risks/benefit ratio appears to preclude widespread use. The HB vaccine, the only vaccine recommended to newborn babies, is one such example, since: (i) the HB virus is primarily transmitted through sexual contact with an infected person or by injections with contaminated material and, hence, poses no risk to infants unless the mother is a carrier [99];

Table 7
Statistical analysis summary. Correlation between the number of children with ASD (6–21 years of age) and the number of Al-adjuvanted vaccines in the yearly vaccination schedule in the period from 1991 to 2008 (US data). Significant change is indicated by the asterisk (*).

	ASD prevalence and yearly number of Al-adjuvanted vaccines
Pearson r	0.90
95% CI	0.76–0.96
P value (two-tailed)	<0.0001
P value summary	*
Is the corr. significant? (p<0.05)	Yes
R^2	0.82

Table 8
Pearson correlation summary according to age of vaccine exposure for ASD prevalence data in seven Western countries. Ages are expressed in months (mo). The adjusted p-values were derived using the resampling-based multiplicity adjustment according to Westfall and Young [78]. Note that for each country studied, the Al exposure is from all vaccines that children receive during the specified age period (i.e., the cumulative exposure to Al at 4 months of age includes Al from vaccines given at 2, 3 and 4 months). Significant change is indicated by the asterisk (*).

	ASD prevalence in the US, UK, Canada, Australia, Sweden, Finland and Iceland in correlation with			
Age	Minimum Al exposure	Mean Al exposure	Maximum Al exposure	# Al-adjuvanted vaccines
2 months				
Pearson r	0.89	0.86	0.83	0.86
95% CI	0.40–0.98	0.29–0.98	0.21–0.97	0.30–0.98
p (unadjusted)	0.0077*	0.014*	0.0199*	0.0131*
p (adjusted)	0.0346*	0.0682	0.1283	0.0594
R^2	0.79	0.73	0.69	0.74
3 months				
Pearson r	0.94	0.94	0.92	0.94
95% CI	0.63–0.99	0.62–0.99	0.55–0.99	950.66–0.99
p (unadjusted)	0.0017*	0.0019*	0.0032*	0.0014*
p (adjusted)	0.0018*	0.0018*	0.0038*	0.0018*
R^2	0.88	0.88	0.85	0.89
4 months				
Pearson r	0.89	0.90	0.90	0.93
95% CI	0.43–0.98	0.45–0.99	0.46–0.99	0.60–0.99
p (unadjusted)	0.0067*	0.0059*	0.0055*	0.0022*
p (adjusted)	0.0248*	0.020*	0.0168*	0.0038*
R^2	0.80	0.81	0.81	0.87
6 months				
Pearson r	0.85	0.83	0.82	0.90
95% CI	0.26–0.98	0.21–0.97	0.17–0.9	0.44–0.98
p (unadjusted)	0.0160*	0.0206*	0.0248*	0.0064*
p (adjusted)	0.0895	0.1333	0.157	0.0248*
R^2	0.72	0.69	0.67	0.80
18 months				
Pearson r	0.82	0.80	0.77	0.89
95% CI	0.18–0.97	0.13–0.97	0.05–0.96	0.40–0.98
p (unadjusted)	0.0227*	0.0297*	0.0408*	0.0079*
p (adjusted)	0.1467	0.1871	0.3133	0.0368*
R^2	0.68	0.64	0.60	0.79
72 months				
Pearson r	0.78	0.76	0.74	0.86
95% CI	0.055–0.97	0.03–0.96	−0.02–0.96	0.29–0.98
p (unadjusted)	0.0402*	0.0456*	0.0550	0.0138*
p (adjusted)	0.3087	0.353	0.4128	0.0682
R^2	0.60	0.58	0.55	0.73

(ii) the incidence of the HB infection in Western countries is extremely low (0.9–2.7 per 100,000) and some of these countries indeed only vaccinate high-risk groups [100]; (iii) a striking decline in the incidence of HB virus infections in these countries occurred during the second half of the 1980s, but only a minor part of this decline was due to HB vaccination since rather limited vaccination programs have been introduced in most Western countries at that time [99]; and (iv) epidemiological studies implicate HB vaccination as a risk factor for ASD. For example, in the US, males aged 0–9 years who received a complete triple series of HB vaccine were found to be significantly more susceptible to developmental disabilities [101], while those aged 3–17 years who received HB vaccination during the first month of life had a 3-fold greater risk of ASD than unvaccinated males [102]. Finally, in newborn primates, a single dose of the HB vaccine is sufficient to cause neurodevelopmental delays in acquisition of neonatal reflexes essential for survival [7]. Although the HB vaccines are adjuvanted with Al (Table 2), both the primate and the epidemiological studies mentioned above only draw attention to thimerosal (ethyl mercury vaccine preservative).This point was also noted by Dorea and Marques in their analysis of infant exposure to Al from vaccines and breast milk during the first 6 months of life [2]. These authors also noted that in general, mercury toxicity is well recognized and has been more studied and better understood than Al toxicity

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[2]. Altogether, these observations suggest that, in spite of its well documented neurotoxic effects, Al is not perceived as a potential hazard in vaccines.

4.2. Dietary versus injectable Al: what is the difference?

Given the bioavailability of Al through food sources, a common assertion in relation to Al in vaccines is that children obtain much more Al from diet. From this perspective, Al from vaccination does not represent a toxicological risk factor [39,103]. However, this notion contradicts basic toxicological principles. For instance, it should be obvious that the route of exposure which bypasses the protective barriers of the gastrointestinal tract and/or the skin will likely require a lower dose to produce a toxic outcome [14,16]. In the case of Al, only ~0.25% of dietary Al is absorbed into systemic circulation [104]. In contrast, Al hydroxide (the most common adjuvant form) injected intramuscularly may be absorbed at nearly 100% efficiency over time [105]. In addition, although the half-life of enterally or parenterally absorbed Al from the body is short (approximately 24 h), the same cannot be assumed for adjuvant-Al because the sizes of most antigen-Al complexes (24 to 83 kDa [60,106,107]) are higher than the molecular weight cut-off of the glomerulus of the kidney (~18 kDa [108]) which would preclude efficient excretion of Al adjuvants. In fact, a longer elimination period is one of the major properties of effective vaccine adjuvants, including those using Al salts [2,14]. Additionally, the tightness of bonding between the Al adjuvant and the antigen is considered a desired feature that can be used to predict the immunogenicity of vaccines [109]. Experiments in adult rabbits demonstrate that even in an antigen-free form, Al-hydroxide, the most commonly used Al adjuvant (Table 2) is poorly excreted. The cumulative amount of Al-hydroxide in the urine of adult rabbits as long as 28 days post intramuscular injection was less than 6% as measured by accelerator mass spectrometry [110]. Al-phosphate was more efficiently excreted (22%) [110]. Finally, it is important to recognize that neonates have anatomical and functional differences crucial for toxicokinetics and toxicodynamics of neurotoxic metals (e.g., an immature renal system and an incomplete BBB), which would further compromise their ability to eliminate Al adjuvants [2,4,5].

4.3. Study results in relation to Hill's criteria: is there a causal relationship between Al vaccine adjuvants and the prevalence of ASD?

The positive correlation between Al exposure from vaccines and prevalence of ASD does not necessarily imply causation. However, if the correlation is strong (criterion 1), consistent (criterion 2) and if there is a biologically plausible mechanism by which it can be explained (criterion 6), as well as an appropriate temporal relationship between the proposed cause and the outcome (criterion 4), then the satisfaction of these criteria supports the notion that the two events may indeed be causally related. Our results satisfy not only all four of these criteria applicable for establishing causation in neuropsychiatry [80], but also four others. These additional criteria are: (5) biological gradient, (7) coherence with the current knowledge, (8) experimental or semi-experimental evidence and (9) the analogy with similar evidence (Table 9). These are discussed below as they are extremely relevant for the ways in which Al might induce ASD.

Thus, in total, the results of our study satisfy eight out of nine of Hill's criteria for causation [41]. The only criterion that our current study fails to satisfy is the "specificity" criterion which is actually not applicable to ASD given that the latter is recognized as a multifactorial disease [20,21,111]. Overall, an analysis of our results indicates that the adjuvant effect of Al in vaccines may be a significant etiological factor in the increasing prevalence of ASD in some Western countries.

4.4. Al-adjuvants and the immature brain and immune system

There is a growing body of data that supports a significant role for immune system-related molecules in the etiology of a variety of neurological disorders, including autism [25,111–115]. In addition, some 15 years ago, Cohen and Shoenfeld made the important observation that, "It seems that vaccines have a predilection to affect the nervous system" [116]. With regard to this statement, as well as the ensuing discussion, four key observations ought to be considered. First, there are critical periods in brain development during which even subtle immune challenges (including those induced by vaccinations) can lead to permanent detrimental alterations of brain and immune function [7,9,117,118]. Second, preschool children in developed countries are regularly exposed to significant amounts of Al adjuvants through vaccination programs (250–862.5 μg; Table 3). Such high exposures to adjuvant-Al which are repeated over relatively short intervals during these critical periods of brain development (i.e., first 2 years postnatal) constitute a significant neurotoxicological as well as an immunological challenge to neonates and young children [2,14]. Third, despite a prevalent view that peripheral immune responses do not affect brain function, overwhelming research suggests that neuro-immune cross-talk may be the norm rather than the exception [25,84,119–128]. Indeed, it is now clearly established that this bi-directional neuro-immune cross-talk plays crucial roles in immunoregulation and brain function [84,128–135]. In turn, perturbations of the neuro-immune axis have been demonstrated in many diseases encompassed in the 'ASIA' syndrome (Table 1) and are thought to be driven by a hyperactive/unrestrained immune response [130,135]. Fourth, the very same components of the neuro-immune regulatory system that are known to play key roles in proper brain development and immune function (i.e., interleukin (IL)-1, IL-6, major histocompatibility complex (MHC) class I, complement cascade [25,84,119–129,133,135]), are heavily targeted by Al adjuvants (Table 1). The latter experimental evidence suggests that Al adjuvants have all the necessary biochemical properties needed to induce neurological and immune disorders. In this regard, it is interesting to note that autism is a multisystem disorder characterized by dysfunctional immunity and impaired CNS function [17,20,22].

Although vaccines are credited for decreasing the risk of neurodevelopmental complications arising from natural infections in early childhood, the problem is that in many ways the immune challenge from vaccinations may be much greater in magnitude than that arising from a natural infection. The main reason for this is that early-life immune responses (before 6 months of age) are weaker and of shorter duration than those that are elicited in immunologically mature hosts [136,137]. Hence, in order to provoke and sustain an adequate B-cell immune response in a neonate, strong immune adjuvants and repeated closely spaced booster doses are needed [137]. Furthermore, in the absence of Al, most antigenic compounds fail to launch an adequate immune response [31,40,138], suggesting that a large part of the immunostimulatory effects of vaccines may be driven by the Al-adjuvant itself. While it is generally accepted that potency and toxicity of immune adjuvants must be adequately balanced so that the necessary immune stimulation is achieved with minimal side effects, in practical terms, such a balance is very difficult to achieve. This is because the same adjuvanted-mediated mechanisms which drive the immunostimulatory effects of vaccines have the capacity to provoke a variety of adverse reactions (Table 1). The potential hazards of vaccination with Al adjuvants thus not only arise from the possibility that a single vaccine may change the pre-programmed immune milieu in a neonate and thus compromise neural development, but also that multiple Al-adjuvanted vaccinationes are administered simultaneously. Multiple exposure magnifies the inflammatory response and while this is essential for linking the innate and adaptive immune responses, it may also be responsible for the immunotoxic effects of Al adjuvants (Table 1).

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Table 9
Study results in relation to Hill's criteria applicable for establishing causality between exposure and outcome.

Hill's criterion	Does the current study satisfy the criterion?	Comment
Strength (1)	Yes	The association is highly statistically significant (Tables 6–8).
Consistency (2)	Yes	The positive and statistically significant correlation between vaccine-derived Al exposures (as well as the overall uptake of Al-adjuvanted vaccines), and ASD prevalence is consistently observed in different populations (Table 8). While ours is, to the best of our knowledge, the first study to investigate the possible association between Al vaccine adjuvants and ASD, at least three more studies have found a positive association between the prevalence of autism (and developmental disabilities) and vaccination uptake in early childhood, a result consistent with our findings [101,102,179]. In addition, a recent study showed that autistic children have higher than normal levels of Al in the body (hair, blood and/or urine) [92]. In contrast, neither copper, lead nor mercury were elevated beyond normal levels in these children [92].
Specificity (3)	No	Not applicable to diseases such as ASD with possible multifactorial etiologies [79].
Biological rationale (4)	Yes	Al is a neurotoxin and a strong immune stimulator, hence, Al has the necessary biochemical properties to induce neuroimmune disorders such as ASD. The immunostimulatory properties of Al adjuvants are numerous and affect both innate and adaptive immune responses (see Table 1). Chronic hyperactivation of immune responses by repeated short-interval administration of Al-adjuvants could: (i) disrupt the delicate balance of immune mediators which is crucial for proper brain development and function (i.e., members of the MHC, complement, pro-inflammatory cytokines TNF-α, IL-1β and IL-6 [25,119–127,141,142]); (ii) promote activation of neuroglia and brain inflammation [29,97,139]; and (iii) promote aberrant immune responses [31,32,157], all of which are known pathophysiological features of ASD [17,20,23,111,147].
Temporal relationship (5)	Yes	Up until and during the early 1980s, the prevalence of ASD was relatively low (<5 in 10,000 children [180,181]). Currently, 1 in 91 children in the US is diagnosed with ASD (110 per 10,000 [73]). In the United Kingdom, current reported ASD prevalence is 1 in 64 children (157 per 10,000 [74]). The increase in the number of vaccines given to children precedes the "autism epidemic" (i.e., from 10 in the late 70s to 32 in 2010 (18 of which contain Al adjuvants) [16]. Note also that the dramatic increase in the prevalence of ASD observed over the last three decades in the US and the UK (2000–3000%) cannot be convincingly explained by genetic factors alone nor by changes in diagnostic criteria. Concerning the latter, in many ways such criteria have become more restrictive [182]. Moreover, in a recent analysis comparing the prevalence of autism with that of other disabilities among successive birth cohorts of US school-aged children, Newschaffer et al. [180] clearly show that autism prevalence has been increasing with time, as evidenced by higher prevalences among younger birth cohorts.
Biological gradient (6)	Yes	The higher the Al exposure from vaccines, the higher the prevalence of ASD (Fig. 1; Table 4).
Coherence (7)	Yes	The same pro-inflammatory mediators that are induced by Al adjuvants were shown to be elevated in the blood, cerebrospinal fluid (CSF) and post-mortem brain tissue of ASD patients (see Table 1). Increase in pro-inflammatory mediators in autistic brains was also found concurrent with widespread activation of astro- and microglia and increased immunoreactivity to MHC class II [17], all of which can also be activated by Al-adjuvants (Table 1).
Experimental/semi-experimental evidence (8)	Yes	Al can impair prenatal and postnatal brain development in humans and experimental animals [28,91]. Other well-documented symptoms of Al intoxication in humans that are relevant to ASD include loss of speech skills, cognitive and behavioral impairments, increased incidence of seizures, increased inflammation and microgliosis in the brain, impairment of synaptic plasticity, synaptic loss and myelin sheath damage [16,29,91,94,183–186].
Analogy (9)	Yes	Peripheral stimulation of the immune system during critical periods of brain development can lead to ASD-related outcomes [9,118,187–189].

4.5. Al adjuvants and brain inflammation

Repeated injections of 1 mg/kg of Al nanoparticles to adult Sprague–Dawley rats is sufficient to produce significant inflammatory effects in the rat brain [139]. Comparable amounts of Al are administered to 2, 6 and 15 month old infants according to the US vaccination schedule (Table 3). Moreover, as we have demonstrated previously, only two subcutaneous injections of Al adjuvants (relevant to adult human exposure) in young male mice, spaced two weeks apart, were sufficient to cause dramatic activation of microglia and astrocytes that persisted up to 6 months post-injection. This outcome was accompanied by motor neuron death, impairments in motor function and decrements in spatial memory capacity [29,97]. What then might be the effects of repeated, closely spaced administration of Al adjuvanted vaccines (i.e., every 2–4 months from birth up until 12 months of age) in immature human infants? One possibility is that such treatment would increase the risk of chronic brain inflammation. In this regard, it is worth noting that neuroinflammatory mechanisms appear to play an important role in the pathophysiology of autism [17,20].

It is well established that peripheral immune insults can directly stimulate the synthesis of pro-inflammatory cytokines (i.e., IL-1β, IL-6 and tumor necrosis factor (TNF)-α) within the brain [84,140], acting to promote inflammation even in the absence of a direct CNS infection. Moreover, the same pro-inflammatory mediators that are normally induced by Al adjuvants have been shown to be elevated in the blood, cerebrospinal fluid (CSF) and brain tissues of ASD patients (Table 1). The aberrant neuroinflammatory cytokine profile in autistic brains was found concurrently with widespread microglial and astrocyte activation. In particular, microgliosis in autism coincided with increased immunoreactivity to MHC class II markers [17]. Microglia, astrocytes, as well as members of the MHC and the complement cascade are crucial regulators of synaptic connectivity, function and plasticity and play key roles in establishing and modulating neuronal circuitry in the developing CNS [25,112,119–126,141,142]. Notably, abnormal brain connectivity is well recognized as one of the hallmarks of autism [143,144]. Cerebellar Purkinje cells, which are significantly reduced in autism, are a site of prominent MHC class I expression. One hypothesis currently under investigation is that specifically timed changes in neuronal MHC class I expression could contribute to autism [143].

Given that Al adjuvants activate both MHC class I and II, components of the complement cascade, increase pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, as well as activate microglia and astrocytes in the brain (Table 1), it is possible that they may also interfere with synaptic pruning and developmental activity-dependent synaptic remodeling/plasticity. At present, there is experimental evidence that Al can impair synaptic plasticity *in vivo* [91,145,146], which can be reversed by vasopressin treatment of Al-exposed rats [146].

4.6. Al adjuvants as promoters of autoimmune/inflammatory reactions in the brain

Experimental evidence clearly shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity in animals [10]. While currently there is no

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direct evidence that Al can induce autoimmunity, it is important to recognize that it certainly has a biochemical potential to do so.

Autoimmune manifestations, particularly those affecting the CNS, are prevalent in autistic individuals and do not appear to be limited to only a few nervous system antigens. For example, Vojdani et al. [147] demonstrated elevated levels of immunoglobulins (Ig)G, IgM and IgA against nine different neuron-specific antigens in ASD children. Such widespread manifestation of autoimmunity may have arisen from an alteration in the BBB which would then have enabled access of immunocompetent cells to many different central nervous system antigens [147].

Al is known to disrupt the BBB and can increase its permeability by increasing the rate of trans-membrane diffusion and by selectively altering saturable transport systems [5,148,149]. Even in an adjuvant form, Al can enter the brain [98]. Furthermore, much like mercury, Al may induce autoimmunity through the so-called "bystander" effect [150]. Finally, Al's ability to upregulate chemo-attractants such as monocyte chemoattractant protein (MCP)-1, monocyte inflammatory protein (MIP)-1α and MIP-1β [40], could promote the active recruitment of immunocompetent cells into the brain, leading to inflammation and/or autoimmunity. Consistent with this interpretation, postmortem analysis of six children aged 4–17 months who died within 48 h of exposure to Al-adjuvanted hexavalent vaccines revealed abnormal pathologic findings in the nervous system, including a defective BBB, infiltration of the leptomeninx by macrophages and lymphocytes, perivascular lymphocytic infiltration, diffuse infiltration of the pons, mesencephalon and cortex by T-lymphocytes and increased microglia in the hippocampus and pons [151]. The neuropathological observations made by Zinka et al. [151] are consistent with the well established immunostimulatory and neurotoxicological properties of Al vaccine adjuvants.

5. Conclusions and future directions

By satisfying eight of the Hill's criteria for establishing causality applicable to our study (Table 9), we show that Al-adjuvanted vaccines may be a significant etiological factor in the rising prevalence of ASD in the Western world. We also show that children from countries with the highest ASD prevalence appear to have a much higher exposure to Al from vaccines, particularly at 2 months of age. In addition, the correlation between ASD prevalence and Al adjuvant exposure appears to be the highest at 3–4 months of age. Of note, these periods (i.e., first 4 postnatal months) coincide with several critical stages of human brain development and biobehavioural transitions that are known to be impaired in autism (i.e., onset of synaptogenesis, maximal growth velocity of the hippocampus [3], onset of amygdala maturation [81] and development of brain-wave and sleeping patterns [82,83]).

Clearly, we cannot draw definite conclusions regarding the link between Al adjuvants and autism based on an ecological study such as the present one and hence the validity of our results remains to be confirmed. A case control study with detailed examination of vaccination records and Al body burden measurements (i.e., hair, urine, blood) in autistic and a control group of children would be one step toward this goal. Nonetheless, given that the scientific evidence appears to indicate that vaccine safety is not as firmly established as often believed, it would seem ill advised to exclude pediatric vaccinations as a possible cause of adverse long-term neurodevelopmental outcomes, including those associated with autism.

We have thus provided a hypothesis which we hope will encourage future research into this area in order to resolve the issue of whether or not vaccines might be responsible in some part for the growing prevalence of autism in the developed world. Such future research should consider the following: (i) the postnatal period represents a very sensitive phase in development during which the physiology of the nervous as well as the immune system can be influenced and sometimes permanently changed [8,9,118,119,152–154]; (ii) Al is a neurotoxin and a strong immune adjuvant (Table 1), hence Al has all the necessary biochemical properties to induce neurological and immune disorders; and (iii) autism is a multisystem disorder characterized by dysfunctional immunity and impaired brain function [17,20,22]. Because the current safety data for Al exposure in infants and children is unsatisfactory and because this demographic represents those who may be most at risk for complications following vaccination, a more rigorous evaluation of Al adjuvant safety than what has been provided to date seems warranted.

6. Competing interests

CAS is a founder and shareholder of Neurodyn Corporation, Inc. The company investigates early state adult neurological disease mechanisms and biomarkers. This work and any views expressed within it are solely those of the authors and not of any affiliated bodies or organizations. CAS and LT are in favor of a more rigorous evidence based medicine approach to vaccine safety.

Abbreviations

ASD	autism spectrum disorders
Al	aluminum
APC	antigen presenting cells
BBB	blood brain barrier
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CFS	chronic fatigue syndrome
CTL	cytotoxic T cell
DTaP	Diphtheria, Tetanus, acellular Persussis
EAE	experimental autoimmune encephalomyelitis
FDA	Food and Drug Administration
GFAP	glial fibrillary acidic protein
GWS	Gulf War syndrome
HA	Hepatitis A
HB	Hepatitis B
Hib	Haemophilus influenza type b
IDEA	The Individuals with Disabilities Education Act
Ig	Immunoglobulin
IL	interleukin
LPS	lipopolysaccharide
MCP	monocyte chemoattractant protein
MenC	Meningococcal serogroup C
MHC	major histocompatibility complex
MIP	monocyte inflammatory protein
MMF	Macrophagic myofasciitis
MS	multiple sclerosis
NLRP3	nucleotide-binding domain, leucine-rich, repeat containing family, Pyrin-domain containing 3
NO	nitric oxide
PCV	Pneumococcal
ROS	reactive oxygen species
TNF-α	tumor necrosis factor

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