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Review

Reviewing the association between aluminum adjuvants in the vaccines and autism spectrum disorder

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ABSTRACT

The manuscript reviews the association between aluminum adjuvants (AlAd) in vaccines and autism spectrum disorder (ASD). Aluminum (Al) is neurotoxic. Infants who have received AlAd in vaccines show a higher rate of ASD. The behavior of mice changes with Al injection. Patients suffering from ASD have higher concentrations of Al in their brains. Thus, AlAd is an etiologic factor in ASD. Immune efficacy led to the use of the AlAd in vaccines; however, the safety of those who are vaccinated with such vaccines has not been considered. The mechanisms of action of AlAd and the pharmacodynamics of injected AlAd used in vaccines are not well-characterized. The association between aluminum adjuvants in the vaccines and autism spectrum disorder is suggested by multiple lines of evidence.

1. Introduction

Some vaccines contain different types of aluminum-based adjuvants [1], including amorphous aluminum hydroxyphosphate sulfate, aluminum hydroxide, aluminum phosphate, and potassium aluminum sulfate [2]. Their function is to help boost the body's response to the vaccine. The dramatic increase over the last 40 years in the number of vaccines, administered especially to infants has brought attention to the safety of these adjuvants. Apart from preliminary safety studies, public health surveillance is needed to identify the vaccine adverse events, due to the possibility of accumulation of aluminum from multiple vaccine administrations over the lifetime. Autism spectrum disorder (ASD) is a complex developmental condition that involving challenges in social interaction [3,4]. While ASD is usually diagnosed in childhood, but diagnosis may also be given as an adolescent or adult. ASD is a lifelong condition. The management of children with ASD has become more and more challenging during Covid19 restrictions [5–8].

For those born in the 1950s and 1960s, when the number of vaccines administered to infants was minimal, autism spectrum disorder (ASD) was a rare issue during their childhood. The increase in the number of vaccines administered to infants was followed by an increase in the prevalence of ASD. This simple association and the fact that aluminum (Al) is a neurotoxic substance [9] is not proof that aluminum adjuvants (AlAd) are the cause of ASD. However, associations are a first requirement in the line of evidence in the investigation. Diagnosis of ASD is challenging, and based on the child's developmental history and behavior [10,11].

Figs. 1.a, b present the 2017 incidence of autistic spectrum disorders, and the male vs. female prevalence. Autistic spectrum disorder includes autism and Asperger Syndrome or other autistic spectrum disorders. Figs. 1.b, c present the 2016 incidence of Autism, as well as the male vs. female prevalence of 2016. Autism is considered a sub-category of autistic spectrum disorders. Figs. 1.d, e present the 2017 attention-deficit/hyperactivity disorder (ADHD) incidence and male vs. female prevalence [12]. ASD is more prevalent in countries, such as United Kingdom (UK), Australia, Canada, New Zealand, and Japan. These are the leading countries in the introduction of vaccines over the years, especially in the number of those administered to infants under 12 months of age. The United States (US) follows this group closely. Canada has more than 1.5 % of male citizens affected by ASD. Australia has almost 0.7 % of male citizens affected by autism, and more than 3.5 % of male citizens are affected by ADHD.

The vaccines' history completes the picture. If we look for example at [13], detailing the history of the vaccines in the US, in late 1940 there were 4 recommended vaccines. There were five in the late 1950s and eight in the late 1960s. In the 1970s, one vaccine was eliminated. From 1985 to 1994, there were eight recommended vaccines, which become nine from 1994 to 1995. The recommended vaccines of 2000 were eleven, and the recommended vaccines of 2005 were thirteen. The recommended vaccines of 2010 were fourteen. The 2019 recommended Vaccines list is also made up of fourteen entries.

While it may be argued that the results of Fig. 1 may suffer from the different methods adopted in different countries to detect ASD, this is

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Nomenclature

ADHD	Attention-deficit/hyperactivity disorder
Al	Aluminium
AlAd	Aluminum adjuvants
ASD	Autism spectrum disorders
CAA	Cerebral amyloid angiopathy
CDC	Centers for disease control and prevention
fAD	Familial Alzheimer's disease
MMR	Measles, Mumps, Rubella
NNV	Number needed to vaccinate
VAERS	Vaccine adverse events reporting system

unlikely the general case. While some commentaries have the premise that all countries have the same numbers no matter their policies, this conflicts with the huge differences between countries of similar socio-economic characteristics.

Almost all the nations are converging towards an increased number of recommended immunizations for infants. These recommended immunizations are in many cases compulsory, as children are not accepted without their up-to-date in childcare centers and schools. For example, under the Australian "*No Jab, No Play*" laws, evidence of immunization is necessary for enrolment [14,15].

If AlAd is responsible for ASD, considering the lag time, the present geographical distribution of ASD prevalence rate is correlated to the geographical distribution of the number of vaccines administered in the past, as it seems the case. For example, Italy or Russia have a present reduced prevalence of ASD vs. the UK and reduced past immunization schedules.

The US Centers for Disease Control and Prevention (CDC) admits that ASD affected 1 in 59 children aged 8 years in 2014 (2018 report). This incidence is 15 % higher than the prior report of two years earlier [16]. Since the year 2000, when the CDC began tracking ASD, the incidence has increased dramatically. The 2007 report, stated that ASD was detected in 1 in 150 children. The 2009 report, stated that ASD was detected in 1 in 110 children. The 2012 report, stated that ASD was

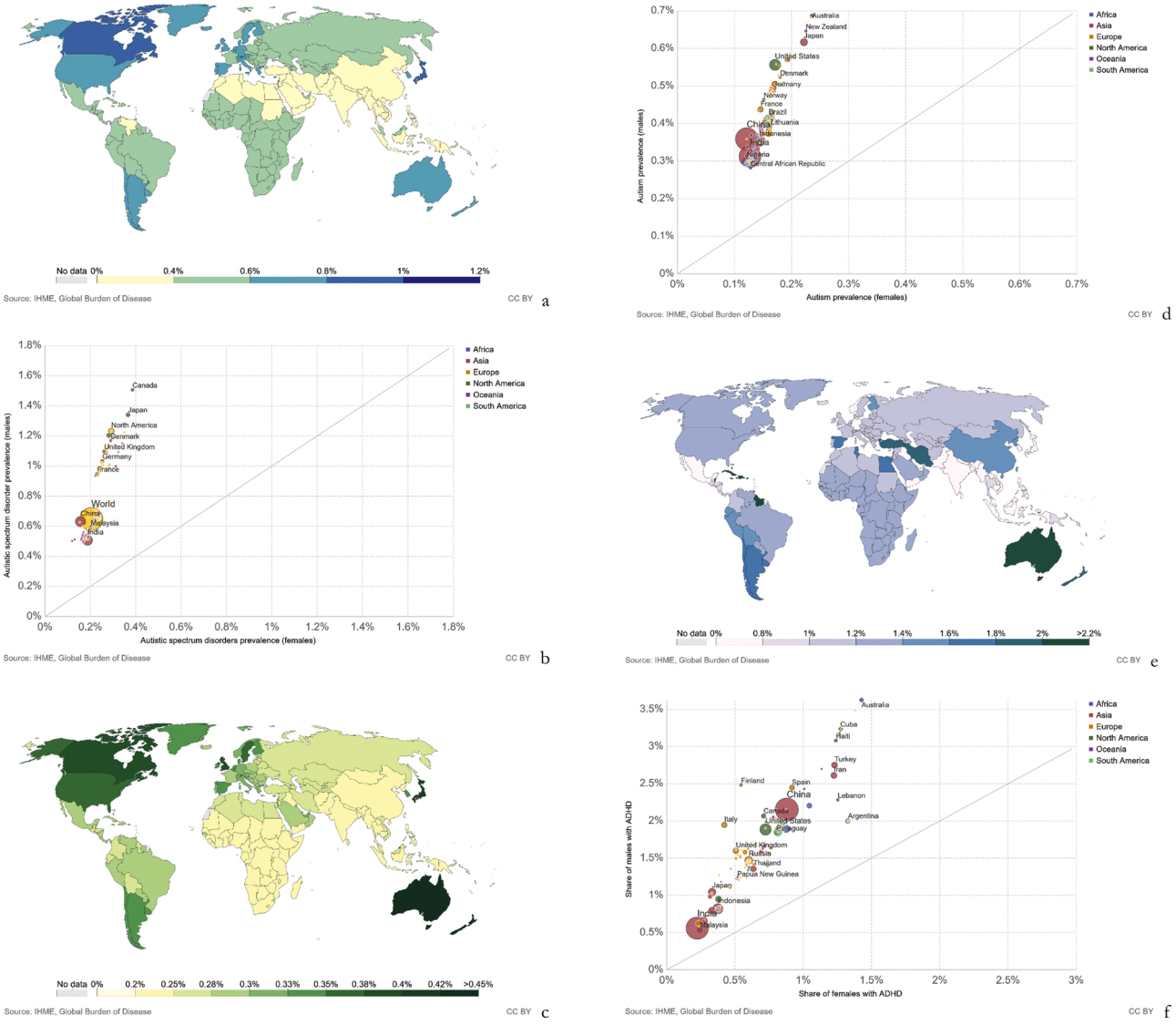

Fig. 1. (a) Share of the population with autistic spectrum disorder for the year 2017. Autistic spectrum disorder includes autism and Asperger Syndrome. (b) Share of males vs. females with autistic spectrum disorder for the year 2017. (c) Share of the population with autism for the year 2016. (d) Share of males vs. females with autism for the year 2016. (e) Share of the population with attention-deficit/hyperactivity disorder (ADHD) for the year 2017. (f) Share of males vs. females with attention-deficit/hyperactivity disorder (ADHD) for the year 2017. Images from [12]. Data from [17]. CC BY.

detected in 1 in 68 children, the same as the 2016 report. The 2018 report, stated that ASD was detected in 1 in 59 children. ASD is four times more likely in boys (1 in 38) than girls (1 in 152). There is a correlation between the prevalence of ASD and the increased number of vaccines. However, there are to mention other factors such as the increased exposure of infants to electromagnetic fields, ultrasounds, and toxins in the foods that also correlate to the increased prevalence of ASD. These correlations do not rule out vaccines, however, as different environmental factors may interact.

While correlation is not proof for causation, this information provides more evidence in support for the hypothesis that the increase in aluminum exposure via vaccines may have a causal role in the increases in ASD prevalence. The following section substantiates the growing body of evidence in the scientific literature supporting this association.

A significant body of literature supports the notion that aluminum is a serious problem. In addition to those references used to support the three lines of evidence, additional lines of evidence on the mechanism are worth considering [18–25]. Al is a neurotoxin. These additional studies offer plausible substantiation that Al may unfavorably influence biological functions and contribute to neurodegenerative and autoimmune disorders.

This review outlines the evidence necessary to conclude that we should raise an alarm on aluminum in vaccines, that current formulations of aluminum-containing vaccines need revision, as AlAd is more likely harmful than safe. AlAd in vaccines may explain the increasing prevalence of ASD. The "Results" section will propose multiple other lines of evidence emerging in the literature that supports the hypothesis that AlAd is likely responsible for the increases in ASD. These lines of evidence include ecological studies, animal models, and measurements of Aluminum (Al) in brain tissues of subjects with ASD. Mechanisms of action are also proposed in this section.

2. Materials and methods

A literature review is performed for the possible link between AlAd in vaccines and ASD. The flow chart of arguments - diagram of evidence supporting the correlation between AlAd and ASD is proposed in Fig. 2.

3. Results

Much published research has concluded that AlAd may be unsafe, with some of them suggesting a clear link between AlAd and ASD. As shown in Fig. 2, in between the works claiming a link between ASD and AlAd, there are three lines of scientific evidence suggesting correlation [26], ecological comparisons associating immunization with AlAd and ASD, experiments in mice connecting AlAd and behavioral disorders, and measurements of much higher concentration of Al in brain cells of subjects with ASD.

Aluminum is used in many pediatric vaccines as an adjuvant [27–29] despite its neurotoxicity. There is concern about the role of AlAd in the rising number of vaccines administered and the rising number of ASD

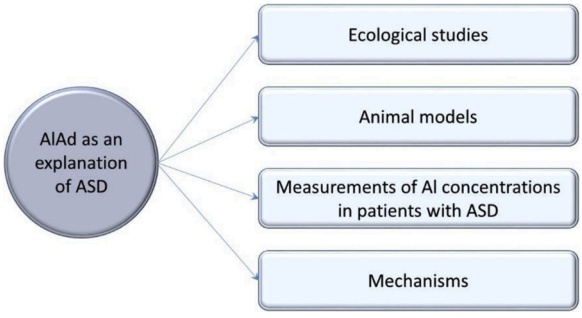

Fig. 2. Flow chart of arguments - diagram of evidence supporting the correlation between AlAd and ASD.

cases. As Al is a neurotoxin and immune stimulator it may induce neuroimmune disorders such as dysfunctional immunity and impaired brain function. AlAd in vaccines are based on immune efficacy but ignore bodyweight for safety [30]. The safety inferences on doses of AlAd in vaccines are theoretical and are derived from dietary studies of different forms of aluminum in adult mice [30]. Doses adjusted per body weight would limit aluminum doses to 15–17 times compared to adults [30,31]. The mechanisms of action of AlAd and the pharmacodynamics of injected AlAd used in vaccines are not well-characterized [31]. Aluminum salts are not solvable in plasma, and therefore serum/plasma level clearance rates are not good measures of whole-body toxicity. How differences in schedules impact accumulation and the influence of genetic and environmental factors on AlAd detoxification are unknown.

As shown in [32], the French vaccination requirements and recommendations of 2018 required the injection of 2545 and 7735 μg of Al3+, with at least 50 % before 12 months of age. The vaccines with higher doses of aluminum are mainly injected at the beginning of life. The ecological study [33] suggested a correlation between the rising ASD and the increased AlAd in vaccines administered during early postnatal life. They found that children from Western countries with the highest ASD frequency have the highest exposure to AlAd in vaccines. The increase in exposure to AlAd correlates well with the increase in ASD especially in the US during the two decades before the study. The amounts of AlAd administered at 3–4 months of age also correlate well with the increase in ASD in seven Western countries. According to [34], AlAd in vaccines carries a risk for autoimmunity, long-term brain inflammation, and associated neurological complications. The risk of potential adverse effects of AlAd is being underestimated. The ecological study [35] suggests a link between AlAd in vaccines and ASD by examining the word frequency patterns in the US CDC Vaccine adverse events reporting system (VAERS) database. ASD in VAERS increased steadily in the late 1990s when mercury was phased out, and the load of AlAd was increased. Signs and symptoms most frequently reported after the start of this century include cellulitis, seizure, depression, fatigue, pain, and death. The authors propose that children with ASD may be vulnerable to Al due to insufficient serum sulfate and glutathione. They also explain the link between ASD and the MMR (Measles, Mumps, Rubella) vaccine via the increased sensitivity to acetaminophen administered to control fever [36].

The evidence for concern over Al and ASD is also proposed in [37, 38]. AlAd injected in the early period of postnatal development, may affect the later social behavior of humans. The persistent claims that vaccines do not contain toxic substances or that they contain them in physiologically negligible amounts are questionable. Al is neurotoxic [39–41]. Transport, distribution, accumulation, and excretion rates of administered aluminum adjuvants are covered in [42–44,34], making plausible the accumulation of Al in brain tissues of patients subjected to multiple vaccinations when infants and young child.

While synergistic toxicity of Al and mercury is known, studies of adverse neurological and immunologic outcomes in children receiving both thimerosal-containing influenza vaccines and Al in the same visit, or the same month, have not been conducted [45]. Countries with higher AlAd exposure – for example, the US – have a much larger ASD than a country with much smaller AlAd exposure – for example, Serbia [46]. According to [46] the 1.09×10^{20} Al ions administered to US children are not a physiologically negligible quantity of toxic Al and they can endanger the health of children.

An animal study [47] found behavioral anomalies in mice injected with AlAd. They injected Al-hydroxide in early post-natal CD-1 mice, both male and female. "High" and "low" AlAd levels correlated to the US or Scandinavian pediatric vaccine schedules. Male and female mice in the "high" AlAd group showed significant weight gains. Male mice in the "high" AlAd group had changes in light-dark box tests and alterations in open-field behavior. "High" and "low" female mice had changes in the light-dark box, but no alterations in open-field behavior. The animal study [48] also investigated the effect of AlAd on the social behavior of

mice. Postnatal exposure to AlAd was associated with behavioral abnormalities. Exposure to AlAd was associated with diminished social interest. Cognitive and behavioral changes were observed in sheep subjected to repetitive inoculation with Al-containing products [49]. Animals in both the "Vaccine" and "Adjuvant-only" groups, both subjected to multiple inoculations with AlAd, exhibited individual and social behavioral changes vs. the "Control" group. Aluminum was detected in the lumbar spinal cord of sheep subcutaneously inoculated with aluminum-hydroxide-containing products [50].

The theoretical study that claimed that doses of Al in pediatric doses were safe [51] was seriously flawed [30]. The presumption of toxicity was derived from different studies by the same research team [52–54]. To be noted, Golub, Donald, Gershwin, and Keen [52] considered both repeated acute and long-term (chronic) toxicity to be an issue; repeated instances of microglia activation can lead to chronic microglial activation, which is seen in children and adults with ASD [55]. Ingested, and not injected, forms of Al, were used in adult, and not infant mice. Ingested and injected forms of Al may have dramatically different consequences [56]. Al injected in infant mice may have dramatically different consequences than Al ingested in adult mice.

If the statistical samples of ecological studies supporting a correlation between AlAd and ASD are often considered small, even smaller statistical samples have been used to support the opposite findings. The study of Al whole-body clearance rates [57] was practically based on repeated measurements of retained aluminum over 12 years for a single adult volunteer after a single injection with citrate solution containing ^{26}Al. A proper safety statistic is certainly missing not only to oppose but also to support the use of AlAd in vaccines, and the issue may only be solved by further unbiased research conducted by applying the scientific method. An in vitro THP-1 cell model was used in [58] to study the cellular uptake of AlAd in vaccines. It is shown that not all AlAds are equal for physical properties, biological reactivity, and potential toxicities. It is argued that high loading of Al oxyhydroxide in the cytoplasm of THP-1 cells may be subjected to subsequent transport to the brain.

Mold, Umar, King, and Exley [59] measured the Al content in the brain tissues of donors with ASD. They used transversely heated graphite furnace atomic absorption spectrometry and an Al-selective fluor to permit fluorescence microscopy. Al content in brain tissue was higher with ASD. Al associated with neuronal cells was present intracellularly in microglia-like cells and other inflammatory non-neuronal cells in the meninges, vasculature, grey, and white matter. Intracellular Al associated with non-neuronal cells was observed in ASD brain tissues.

The above 3 lines of evidence, ecological comparisons correlating immunization with vaccines having AlAd and ASD, an animal study of Al-exposure in mice and behavioral changes, and measurements of Al in ASD brain tissues, make a strong case for AlAd being responsible for ASD. The evidence supporting the claim that AlAd in vaccines causes ASD is incomplete, as a causative link is missing. However, the evidence that AlAd in vaccines does not cause ASD is certainly much less than for the opposite claim.

An explanation of the AlAd neurotoxicity is proposed in [46]. Metabolic cell functions are related to enzymes. Most enzymes are metalloenzymes (biometal incorporated in the enzyme). After a time of active work, an enzyme is degraded, metabolized, and synthesized again. During the resynthesis of an enzyme, if a not-biometal (such as Al) is used instead of a particular biometal, an afunctional enzyme is formed. The afunctional enzyme will then cause a failure of particular metabolic functions.

Ivanovski, Fletcher, Ivanovski, Garavelli, Nikolić, and Ivanovski [46] highlights the similarity between the AlAd neurotoxicity mechanism and the mechanism of the generation of microcytic anemia in chronic lead poisoning [60]. The amount of AlAd in vaccines is not minuscule [61], and it may have a role in ASD. According to [62,63] scientific evidence confirms the presence of Al brain tissue from donors with diagnoses of familial Alzheimer's disease, autism spectrum disorder, multiple sclerosis, and epilepsy. Finally, McFarland, La Joie, Thomas, and Lyons-Weiler [31] highlights how mechanisms of action and pharmacodynamics of injected AlAd in vaccines are not well-characterized, particularly concerning accumulation and clearance.

The possible role of AlAd in ASD following various mechanisms is further stressed in many other recent works. Bjørklund et al. [64] discuss toxic metal pollutants. Arumugham, and Trushin [65] and Swierczynski [66] examine ASD pathogenesis. Bjørklund et al. [67] discusses oxidative stress and ASD. The association of trace elements and minerals and ASD is discussed in [68]. McFarland, La Joie, Thomas, and Lyons-Weiler [31] argue about acute exposure and chronic retention of Al in different vaccines. Dórea [69] discusses the role of multiple low-level exposures in early life. Grochowski et al. [70] discusses methods to detect trace elements in the human brain.

Other pathologies also being related to Al in the brain are stressed in other works such as multiple sclerosis [71], epilepsy [72], cerebral amyloid angiopathy [73], Alzheimer′ s disease [74], or cerebral palsy [75]. Gherardi, Crépeaux, and Authier [76] discuss myalgia and chronic fatigue syndrome following immunization.

Fig. 3 (from [62]) presents the result of measurements of Aluminum in brain tissue from donors diagnosed with (a–c) ASD, (d) cerebral amyloid angiopathy (CAA), (e) epilepsy, and (f) familial Alzheimer's disease (fAD). In healthy subjects, the concentration of Aluminum is practically undetectable. Accumulation of injected aluminum is one explanation. Alternative explanations have not been proposed so far.

Many more studies have demonstrated the presence of Al in brain tissue in subjects with a neurodegenerative and neurodevelopmental disease, for example [77]. This work used microwave-assisted acid digestion and transversely heated graphite furnace atomic absorption spectrometry to measure Al in brain tissues from donors without and with perceptible neurodegenerative disease. About 80 % of tissue samples had Al content below 1.0 μg g of the dry weight of tissue. In the case of sporadic or familial Alzheimer's disease [78,79], ASD [62], and multiple sclerosis [71], Al was significantly increased in the disease groups compared to control [77].

A causative explanation on a molecular level of the role of Al in neurological disorders is given in [80] or [81]. Al negatively impacts the central nervous system in all species that have been studied, including humans.

4. Discussion

The adjuvants are explicitly intended to multiply the immunogenicity of the antigens but they also multiply the incidence of adverse reactions that are associated with the antigen. While adjuvants are essential to vaccines, as they multiply the reactogenicity, they also multiply the toxicity of vaccines: Pre-licensure clinical trials are not powered enough to be significant and are not of long enough duration to detect long-term effects. Studies on the potential synergistic damage from the administration of more than two vaccines when more than two vaccines are injected at the same time are missing [18]. Clinical trials are not designed to determine long-term implications. During Phases I to III, a vaccine is given to thousands of people to test for efficacy and safety [82]. While some vaccines undergo a Phase IV study after the vaccine is approved and licensed, still these studies are not designed to detect neurologic disorders that may develop also many decades after administration of many different vaccines. A better understanding of the work of adjuvants in adverse events is necessary.

What is under discussion is not the general adult body's handling of Al. Studies of adults receiving intravenous nutrition, or total parenteral nutrition, where certainly much larger doses of Al were administered directly into the circulation or in renal disease via dialysis water, do not address the issues of AlAd in vaccines administered to infants. In these cases of adults receiving intravenous nutrition, or total parenteral nutrition the Al load was considerable, but the only patients to develop neurologic findings were those who were uremic. The point in question is the injection in infants of AlAd through their particularly intense

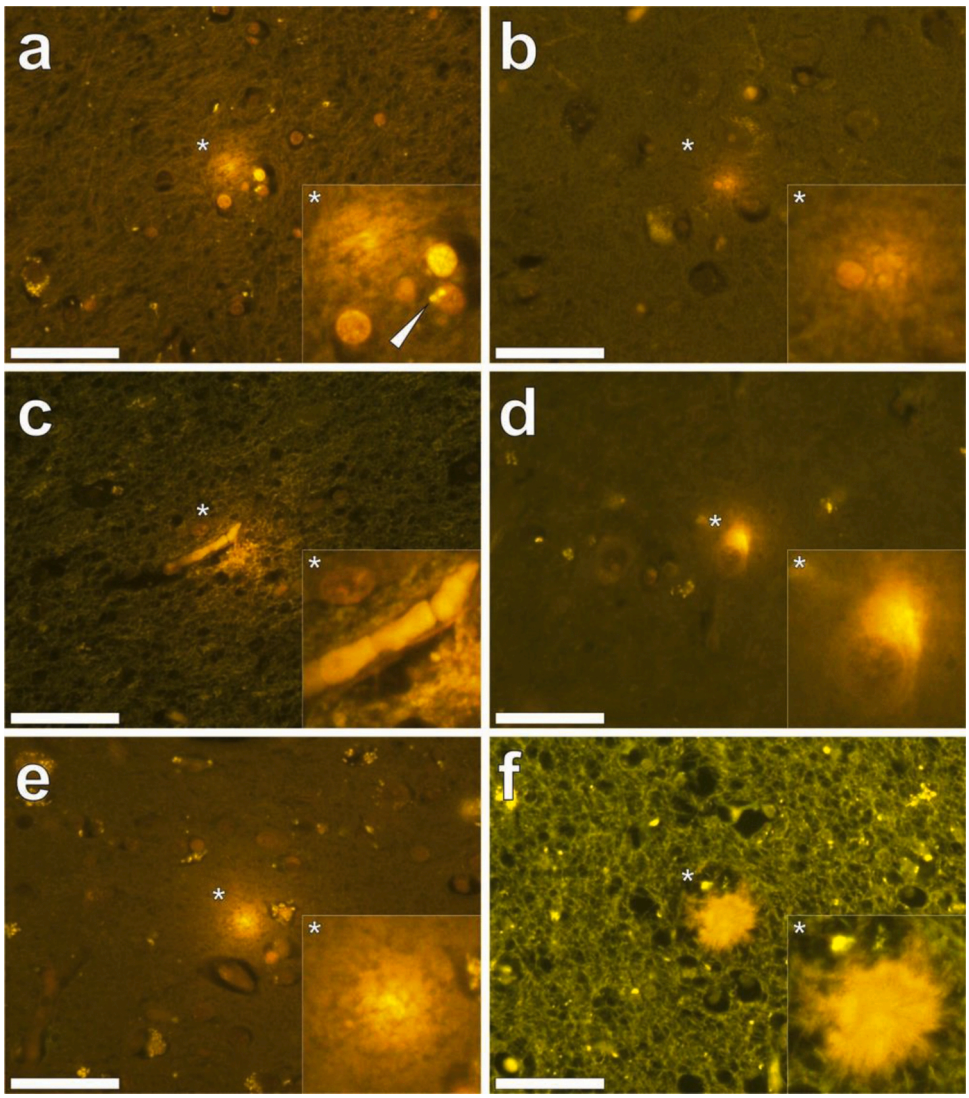

Fig. 3. Measurements of Aluminum in brain tissue from donors diagnosed with (a–c) ASD, (d) cerebral amyloid angiopathy (CAA), (e) epilepsy, and (f) familial Alzheimer's disease (fAD). Image reproduced from [62]. Open-access article distributed under the terms of the Creative Commons CC BY license.

immunization schedules. Not one isolated, but repeated intramuscular injections of AlAd in infants may dramatically contribute to a neurologic disease.

The number needed to vaccinate (NNV), i.e. the number of patients that need to be vaccinated for one patient to benefit [83], is sometimes very large. The larger the number, the worse is the efficacy of the vaccine. According to [84], 1, 852 children have to be vaccinated against influenza to avoid 1 hospitalization [85]. also states that for 1 hospital admission for influenza prevented, vaccination with Fluvax or Fluvax Junior may have caused 2–3 hospital admissions due to febrile convulsions. According to [86] 4, 255 to 6, 897 children 24–59 months of age have to be vaccinated for influenza to prevent 1 hospitalization. Hence, the number of vaccines being administered should be carefully considered.

The safety vs. efficacy of current formulation of vaccines adopting AlAd needs revision. Vaccines that include AlAds that show properties of long-term toxicity should be replaced with alternative formulations [85, 87], or their impact should be otherwise mitigated. Many of the vaccines currently administered may not be essential.

Conflicts of interest prevent a healthy scientific debate on the effect of aluminum adjuvants, [88–92]. The manufacture of consent through mass corporate media [93] defined as "*effective and powerful ideological institutions that carry out a system-supportive propaganda function*" biases a proper debate. The bias of science by mainstream media is a growing concern. As outlined in The Lancet article [94] "Corruption in global health: the open secret" every health professional knows this, but no one addresses it.

5. Conclusion

This work has summarized the three lines of evidence: ecological studies, animal studies, and measurements of Al in brain tissues of subjects with ASD, that together suggest a possible causal relationship between AlAd and the increasing prevalence of ASD. Mechanisms are explaining the Al neurotoxic effects. There is a causative explanation on a molecular level of the role of Al in neurological disorders.

The work has evidenced likely long-term neurotoxicity of AlAd in vaccines. This suggests a reduction of non-essential uses of AlAd: by reducing the number of vaccines being administered to those essential; reducing the amount of adjuvant based on weight; changing the formulation of the adjuvant, or avoiding multiple vaccinations during a single session in infants.

This review of lines of evidence in support of the hypothesis that aluminum adjuvants in vaccines might be a causal factor in neurodevelopmental disorders concludes that this correlation is clear.

Data availability statement

As a review of published information, supporting data when available may be found in the cited references.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

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