

The role of aluminum adjuvants in vaccines raises issues that deserve independent, rigorous and honest science

Guillemette Crépeaux, François-Jérôme Authier, Christopher Exley, Lluís Luján, Romain K. Gherardi

▶ **To cite this version:**

Guillemette Crépeaux, François-Jérôme Authier, Christopher Exley, Lluís Luján, Romain K. Gherardi. The role of aluminum adjuvants in vaccines raises issues that deserve independent, rigorous and honest science. Journal of Trace Elements in Medicine and Biology, 2020, 62, pp.126632 -. 10.1016/j.jtemb.2020.126632 . hal-03492551

HAL Id: hal-03492551
https://hal.science/hal-03492551

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Version of Record: https://www.sciencedirect.com/science/article/pii/S0946672X20301978
Manuscript_7909ebb79c6634033c3eb8290f6cdc62

The role of aluminum adjuvants in vaccines raises issues that deserve independent, rigorous and honest science

Guillemette Crépeaux[1,2]*, François-Jérôme Authier[1], Christopher Exley[3], Lluís Luján[4,5], Romain K Gherardi[1]

[1] Université Paris Est-Créteil, Faculté de Médecine, INSERM U955 E10, Biologie du système neuromusculaire, 94010 Créteil, France
[2] Ecole Nationale Vétérinaire d'Alfort, 7 Avenue du général de Gaulle, 9400 Maisons-Alfort, France
[3] The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, ST5 5BG, United Kingdom
[4] Department of Animal Pathology, University of Zaragoza, Spain
[5] Instituto Universitario de Investigación Mixto Agroalimentario de Aragón (IA2), University of Zaragoza, Spain.

* Correspondence: guillemette.crepeaux@vet-alfort.fr
+33 143967001

Comments on the review « Aluminum and vaccines: Current state of knowledge, Aluminium et vaccins, ce que l'on sait aujourd'hui » by J.-P. Goullé & L. Grangeot-Keros, Médecine et maladies infectieuses, 2019.

In their recent review on aluminum and vaccines [1], JP Goullé & L Grangeot-Keros described general knowledge on aluminum (Al) exposure, kinetics and toxicity but made very little effort to delineate the scientific questions specifically related to Al adjuvants in vaccines. Instead of representing the bulk of their review, the subject of Al adjuvants covered no more than one third of the 3 page-text. Numerous important papers on the topic were omitted, *i.e.* 20 years of scientific publications in clinical, post-mortem, *in vitro* and *in vivo* experimental studies published by independent research teams, worldwide experts in this topic were simply omitted.

For instance, in 2018, a critical analysis of reference studies on Al adjuvant toxicokinetics revealed their extreme paucity, several major methodological weaknesses, and profound misconception of the fate of injected Al adjuvants [2]. The Goullé and Grangeot-Keros review suffers from the same fundamental misunderstanding of the question. Specialized Al toxicologists have now recognized that comparing toxicological properties of different forms of Al (soluble *vs* particulate) administered by different routes (oral *vs* intramuscular (im) or intravenous) is incorrect [3]. In the case of Al adjuvants such comparisons are misleading and therefore inadmissible [2]. Goullé and Grangeot-Keros stated that, similarly to lead for instance, "only biologically measurable excessive levels of aluminium in the organism can be potentially toxic". Such a sweeping statement of classical toxicology may be in line with the "dose makes the poison" paradigm but does not correspond to the true situation when, for example, i) particulate forms of metals are considered; ii) specific intracellular capture is involved. Moreover Al in vaccines do not represent low doses, especially for babies [4,5]. Let us ironically state that a man shot dead by a lead bullet does not die from saturnism (lead

© 2020 published by Elsevier. This manuscript is made available under the CC BY NC user license
https://creativecommons.org/licenses/by-nc/4.0/

toxicity!). In contrast to soluble dietary Al reaching the blood across the intestinal barrier and excreted in urine, Al hydroxide adjuvant particles are nearly insoluble at pH 7.35 [2]. They are rapidly phagocytosed after injection, and selectively concentrate with very long residence time in immune cells which represent a very small but highly reactogenic cell compartment (for review see [6]). Isotopic ^{26}Al hydroxide adjuvant studies indicate that a single vaccine dose administered through im injections to an adult rabbit will induce a small increase of 0.8% in plasma concentration, masked by the Al background, with cumulative Al excretion becoming quasi-flat a few days after injection [7]. This is due to the insolubility of Al hydroxide and explains why increased Al is not found in blood and hair of vaccine recipients [8]. This represents a legitimate reason of concern since instead of being efficiently eliminated the insoluble crystalline particulate adjuvant persists intra-cellularly. In contrast to the opposite contention made by Goullé and Grangeot-Keros, it has been repeatedly shown, in both mouse and sheep, that Al particles exit the injection site to reach the draining lymph nodes and spleen and more distant organs like the central nervous system [9-14]. There is no reason to believe that the adjuvant particles translocated beyond the vaccine injection site lose their immunogenic properties and are non-toxic.

Goullé and Grangeot-Keros focused on the lack of detectable increase of Al plasma levels following Al adjuvant injections and so apparently ignored that increased Al tissue levels have been indeed repeatedly reported following Al adjuvant or adjuvanted vaccines injections, in rabbit brains [7], in mouse brains [11], in rat bones and brains [15], and in sheep draining lymph nodes and spinal cord [13,14]. This was observed despite a marked dilution effect linked to the selective distribution of Al particles to a limited microglial cell compartment.

Other “reassuring” claims of Goullé and Grangeot-Keros were related to clinical studies. They dismissed the fact that Al-containing vaccines may be associated with myalgia, chronic fatigue syndrome and cognitive impairment typically observed in patients with Al hydroxide induced macrophagic myofasciitis [16,17], on the grounds of an ANSM study on HPV-vaccine that excluded these symptoms from the survey [18]. Moreover, they ignored that these symptoms have been significantly and uniquely associated with immunization in US military personnel undeployed during the Gulf War II [19], and an array of cognitive and behavioral changes have been naturally observed and experimentally reproduced in sheep repetitively inoculated with Al-containing vaccines [20,21]. Furthermore, growing evidence offers clues as a putative role of Al early exposure in the marked increase of neurodevelopmental disorders in humans [22-30].

In the light of these elements, we thus agree with the conclusion of Goullé and Grangeot-Keros that health authorities should design specific multidisciplinary experimental protocols to clarify Al adjuvants toxicokinetics and hazards, instead of accept the use of Al-adjuvants as placebos in clinical trials [31]. It will be of particular importance to map the fate and effect of particles of Al adjuvant beyond the vaccine injection site. A similar effort by relevant health agencies should be made epidemiologically, considering the complete lack of population-based studies specifically evaluating associations between clinical outcomes and Al adjuvants. According to the CDC, though feasible, such studies have not been conducted until now [32].

Finally, in this inherently incomplete review on Al adjuvants, several dozens of papers from the first signal of alert concerning Al adjuvants biopersistency and toxicity are purely and simply excluded! Altogether, these rigorous and complementary available published studies show biopersistence and toxic effects of Al salts, both in human and in various animal models, and allow a better understanding of the behavior of these molecules after injection due to *in vitro* approaches. Such scientific data should be used by public health policies to assess the risk of Al-adjuvants, instead of relying on this widespread misinformation about the presumed safety of these molecules.

Furthermore, on the Goullé & Grangeot-Keros paper, apparent refusal to debate on this issue citing rationales such as "irrational polemics" and "one cannot question the safety of Al salts contained in vaccines" is not acceptable from scientists. Scientific debate should always be encouraged, especially in a topic where long-term safety studies are notoriously lacking in both adults and children. We believe that an issue as crucial to public health as the safety of vaccines, on which optimal vaccine coverage depends, deserves more than a subjective publication of badly documented personal opinion and should be addressed in the light of all available scientific studies, in an honest, rigorous and objective manner.

While reaffirming our position in favor of vaccination, we claim that the safety of aluminum-based vaccine adjuvants, like that of any environmental factor presenting a risk of neurotoxicity and to which the young child is exposed, must be seriously evaluated without further delay, particularly at a time when the CDC is announcing a still increasing prevalence of autism spectrum disorders, of 1 child in 54 in the USA (2020 figure for 2016) [33].

Authors contribution

RKG & GC wrote the first draft of the letter. FJA, CE & LL corrected and improved the letter.

References

[1] J.O. Goullé, L. Grangeot-Keros, Aluminum and vaccines: Current state of knowledge. Med Mal Infect (2019) https://doi.org/10.1016/j.medmal.2019.09.012.
[2] J.D. Masson, G. Crépeaux, F.J. Authier, C. Exley, R.K. Gherardi, Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants. J Inorg Biochem (2018) 181:87–95.
[3] C. Exley, The toxicity of aluminium in humans. Morphologie (2016) Jun;100(329):51-5. doi: 10.1016/j.morpho.2015.12.003.
[4] C. Exley, An aluminium adjuvant in a vaccine is an acute exposure to aluminium. J Trace Elem Med Biol. (2020) Jan;57:57-59. doi: 10.1016/j.jtemb.2019.09.010.
[5] Lyons-Weiler J, Ricketson R. Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum. J Trace Elem Med Biol. 2018;48:67-73. doi:10.1016/j.jtemb.2018.02.025
[6] Shardlow, E., Mold, M. & Exley, C. Unraveling the enigma: elucidating the relationship between the physicochemical properties of aluminium-based adjuvants and their immunological mechanisms of action. Allergy Asthma Clin Immunol 14, 80 (2018). https://doi.org/10.1186/s13223-018-0305-2.
[7] R.E. Flarend, S.L. Hem, J.L. White, D. Elmore, M.A. Suckow, A.C. Rudy, et al. In vivoabsorption of aluminium containing vaccine adjuvants using 26Al. Vaccine (1997) 15:1314–8.
[8] Bohrer D, Schmidt M, Marques RC, Dórea JG. Distribution of aluminum in hair of Brazilian infants and correlation to aluminum-adjuvanted vaccine exposure. Clin Chim Acta. 2014;428:9-13. doi:10.1016/j.cca.2013.10.020.
[9] Z. Khan, C. Combadiere, F.J. Authier, V. Itier, F. Lux, C. Exley, et al. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. BMC Med (2013) 11:99.
[10] G. Crépeaux, H. Eidi, M.O. David, E. Tzavara, B. Giros, C. Exley, P.A. Curmi, C.A. Shaw, R.K. Gherardi, J. Cadusseau. Highly delayed systemic translocation of aluminum-based adjuvant in CD1

mice following intramuscular injections. J Inorg Biochem (2015) Nov;152:199-205. doi: 10.1016/j.jinorgbio.2015.07.004.
[11] G. Crépeaux, H. Eidi, M.O. David, Y. Baba-Amer, E. Tzavara, B. Giros, et al. Non-linear dose-response of aluminium hydroxide adjuvant particles: selective low dose neurotoxicity. Toxicology (2017) 375:48-57.
[12] H. Eidi, M.O. David, G. Crépeaux, L. Henry, V. Joshi, M.H. Berger, M. Sennour, J. Cadusseau, R.K. Gherardi, P.A. Curmi. Fluorescent nanodiamonds as a relevant tag for the assessment of alum adjuvant particle biodisposition. BMC Med. (2015) Jun 17;13:144. doi: 10.1186/s12916-015-0388-2.
[13] J. Asín, J. Molín, M. Pérez, P. Pinczowski, M. Gimeno, N. Navascués, A. Muniesa, I. de Blas, D. Lacasta, A. Fernández, L. de Pablo, M. Mold, C. Exley, D. de Andrés, R. Reina, L. Luján, Granulomas following subcutaneous injection with aluminum adjuvant-containing products in sheep. Veterinary Pathology (2019) 56:418-428. doi: 10.1177/0300985818809142
[14] A. de Miguel, J. Asín, A. Rodríguez-Largo, J. Molín, I. Echeverría, D. de Andrés, M. Pérez, I. de Blas, M. Mold, R. Reina, L. Luján, Detection of Aluminum in Lumbar Spinal Cord of Sheep Subcutaneously Inoculated with Aluminum-Hydroxide Containing Products. Journal of Inorganic Biochemistry (2019) Mar;204:110871. doi: 10.1016/j.jinorgbio.2019.110871.
[15] K. Weisser, T. Göen, J.D. Oduro, G. Wangorsch, K.O. Hanschmann, B. Keller-Stanislawski, Aluminium in plasma and tissues after intramuscular injection of adjuvanted human vaccines in rats. Arch Toxicol. (2019) Oct;93(10):2787-2796. doi: 10.1007/s00204-019-02561-z.
[16] M. Rigolet, J. Aouizerate, M. Couette, N. Ragunathan-Thangarajah, M. Aoun-Sebaiti, R.K. Gherardi, J. Cadusseau, F.J. Authier, Clinical features in patients with long-lasting macrophagic myofasciitis. Front Neurol. (2014) Nov 28;5:230. doi: 10.3389/fneur.2014.00230. eCollection 2014. Review.
[17] R.K. Gherardi, G. Crépeaux, F.J. Authier, Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system, Autoimmunity Reviews. 18 (2019) 691–705. https://doi.org/10.1016/j.autrev.2019.05.006.
[18] ANSM et CNAMTS. Vaccins anti-HPV et risque de maladies autoimmunes: étude pharmacoépidémiologique. Rapport final; 2015. p. 92.
http://ansm.sante.fr/var/ansmsite/storage/original/application/ea5e12b9c18ae41c2b8163ae5d7cb6f3.pdf [accessed on January, 2020].
[19] L. Steele, Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. Am J Epidemiol. 2000 Nov 15;152(10):992-1002.
[20] L. Luján, M. Pérez, E. Salazar, N. Álvarez, M. Gimeno, P. Pinczowski, S. Irusta, J. Santamaría, N. Insausti, Y. Cortés, L. Figueras, I. Cuartielles, M. Vila, E. Fantova, J.L. Gracia Chapullé, Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep. Immunologic Research (2013) 56:317-324. (doi: 10.1007/s12026-013-8404-0)
[21] J. Asín, M. Pascual-Alonso, P. Pinczowski, M. Gimeno, M. Pérez, A. Muniesa, L. de Pablo, I. de Blas, D. Lacasta, A. Fernández, D. de Andrés, R. Reina, L. Luján, Cognition and behavior in sheep repetitively inoculated with aluminum adjuvant-containing vaccines or aluminum adjuvant only. Journal of Inorganic Biochemistry (2019) 2020 Feb;203:110934 doi: 10.1016/j.jinorgbio.2019.110934.
[22] Gallagher CM and Goodman MS. Hepatitis B vaccination of male neonates and autism diagnosis, NHIS 1997-2002. J Toxicol Environ Health A, 2010. 73(24):1665-77.
[23] Tomljenovic L, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? J Inorg Biochem. 2011;105(11):1489-99.
[24] Seneff S, Davidson RM, Liu J. Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure. Entropy 2012, 14, 2227-2253.
[25] Shaw CA, Li Y, Tomljenovic L. Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes. J Inorg Biochem. 2013 Nov;128:237-44.
[26] Shaw CA, Tomljenovic L. Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. Immunol Res. 2013;56(2-3):304-316. doi:10.1007/s12026-013-8403-1.

[27] Mold M, Umar D, King A, Exley C. Aluminium in brain tissue in autism. J Trace Elem Med Biol. 2018 Mar;46:76-82.
[28] Sheth SKS, Li Y, Shaw CA. Is exposure to aluminium adjuvants associated with social impairments in mice? A pilot study. J Inorg Biochem. 2018 Apr;181:96-103.
[29] Wang X, Yang J, Xing Z, Zhang H, Wen Y, Qi F, Zuo Z, Xu J, Yao Z. IL-4 mediates the delayed neurobehavioral impairments induced by neonatal hepatitis B vaccination that involves the down-regulation of the IL-4 receptor in the hippocampus. Cytokine, 2018. 110: 137-149.
[30] Bruce M, Streifel KM, Boosalis CA, et al. Acute peripheral immune activation alters cytokine expression and glial activation in the early postnatal rat brain. J Neuroinflammation. 2019;16(1):200. Published 2019 Oct 31. doi:10.1186/s12974-019-1569-2.
[31] Exley C. Aluminium-based adjuvants should not be used as placebos in clinical trials. Vaccine. 2011;29(50):9289. doi:10.1016/j.vaccine.2011.08.062.
[32] J.M. Glanz, S.R. Newcomer, M.F. Daley, D.L. McClure, R.P. Baxter, M.L. Jackson et al. Cumulative and episodic vaccine aluminum exposure in a population-based cohort of young children. Vaccine 2015;33(48):6736-44.
[33] Maenner MJ, Shaw KA, Baio J, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ 2020;69(No. SS-4):1–12.