Do Vaccines Have a Role as a Cause of Autoimmune Neurological Syndromes?

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Vaccines are the most important preventive measure against infectious diseases presently available. Although they have led to the eradication or the elimination of some infectious diseases, concerns about safety are among the main reasons for vaccine hesitancy. In some cases, the biological plausibility of a given damage in association with the temporal association between vaccine administration and disease development makes it difficult to define causality and can justify hesitancy. Only well-conducted epidemiological studies with adequate evaluation of results can clarify whether a true association between vaccines and adverse event development truly exists. Autoimmune neurological syndromes that follow vaccine use are among these. In this narrative review, the potential association between vaccines and the development of these syndromes are discussed. Literature analysis showed that most of the associations between vaccines and nervous system autoimmune syndromes that have been reported as severe adverse events following immunization are no longer evidenced when well-conducted epidemiological studies are carried out. Although the rarity of autoimmune diseases makes it difficult to strictly exclude that, albeit exceptionally, some vaccines may induce an autoimmune neurological disease, no definitive demonstration of a potential role of vaccines in causing autoimmune neurological syndromes is presently available. Consequently, the fear of neurological autoimmune disease cannot limit the use of the most important preventive measure presently available against infectious diseases.

Keywords: aluminum, guillain–barré syndrome, mercury, nervous system demyelinating syndrome, vaccine adverse events, vaccine autoimmunity

INTRODUCTION

Vaccines are the most important preventive measure against infectious diseases presently available. They have led to the eradication of smallpox and the elimination of poliomyelitis in most countries. Moreover, their use has significantly reduced the development of several common and frequently severe infections that are associated with relevant morbidity and mortality and high costs for families and national health systems (1–3). Despite these undeniable advantages, vaccines are debated, vaccination coverage remains lower than desired and outbreaks of preventable diseases can occur (4). The recent increase in measles incidence rates in many countries around the world is the best example in this regard (5).
Concerns about safety are among the main reasons for vaccine hesitancy (6). In most cases, particularly when healthy children are considered, concerns about safety have no scientific basis and derive from myths or poor knowledge (7). In some other cases, the biological plausibility of a given damage in association with the temporal association between vaccine administration and disease development makes it difficult to define causality and can justify hesitancy (8). Only well-conducted epidemiological studies with adequate evaluation of results can clarify whether a true association between vaccines and adverse event development truly exists (9). Autoimmune neurological syndromes that follow vaccine use are among these.

In this narrative review, the potential association between vaccines and the development of these syndromes will be discussed. Data for discussion have been derived from studies published in English and reported in PubMed and Scopus from January 1, 1985 to February 29, 2020, using “vaccine hesitancy,” “vaccine adverse events,” “vaccine autoimmune,” “neurologic syndromes,” “Guillain–Barré syndrome,” “aluminum,” and “mercury” as key words.

**VACCINES AND CENTRAL NERVOUS SYSTEM (CNS) DEMYELINATING SYNDROMES**

Central nervous system (CNS) demyelinating syndromes include acute disseminated encephalomyelitis (ADEM), transverse myelitis (TM), neuromyelitis optica (ON), and multiple sclerosis (MS) (10). In general, ADEM is a monophasic disease that occurs mainly in children, whereas MS is a chronic disease of young adults characterized by an alternation of relapses and remissions. However, as ADEM can recur and both TM and ON can be associated with ADEM or MS, distinction between these conditions can be difficult, and a clinical continuum has been supposed. Although typical cases have relevant differences in some clinical manifestations and laboratory test results, all these diseases are thought to be due to an overactive or dysfunctional immune response to self-antigens (11).

Mechanisms that lead to autoimmunity are unknown, although it is supposed that viral and, more rarely, bacterial infections play a fundamental role in triggering abnormal immune responses. Most cases are preceded by an infectious disease, with *Chlamydia pneumoniae*, herpervirus (6), Epstein–Barr virus, and endogenous retroviruses being the most frequently causative agents (12). Molecular mimicry, or the fulminant activation of lymphocytes by microbial superantigens, are the most commonly proposed mechanisms for demyelinating syndrome development (13, 14).

For similarity with what has been shown for infections, it was thought that vaccines could also lead to demyelination. In some cases, a strict temporal relationship between vaccine administration and the development of CNS demyelinating syndromes has been reported, favoring the hypothesis that vaccine administration, despite being able to ensure protection against some infections, could be deleterious and cause clinical problems sometimes even more severe than the prevented disease (15). Most of the reported cases concerned hepatitis B vaccine (HBV) and human papillomavirus vaccine (HPV). The potential role of HBV was first speculated in 1997 in France after the evidence that a large HBV campaign involving neonates, children and young adults at risk had been followed by a sudden and unexpected increase in the number of CNS demyelinating syndromes, including MS, within 8 weeks of HBV administration (16). This resulted in a complete suspension of the national vaccination programme and stimulated the activation of several studies to confirm or refute the association. In most cases, no significant increase in demyelinating syndrome onset within months or years of HBV administration was demonstrated, regardless of the type of vaccine used. Moreover, it was shown that HBV did not cause the exacerbation of previously evidenced demyelinating conditions (17–21). On the other hand, when a potential relationship was found, the application of Hill’s criteria of causation to the data collected with these studies led to the conclusion that the correlation between HBV and MS might be causal (22). Similar results were reported when the impact of HPV on CNS demyelination was evaluated, regardless of the preparation, bivalent, or quadrivalent, used. A systematic review of 5 observational studies, nine reviews, and one randomized clinical trial (RCT) confirmed no significant association between HPV and MS. The risk of MS development following vaccination varied from 1.54 [95% confidence interval [CI], 0.04–8.59] to 1.37 (95% CI, 0.74–3.20). An evaluation of the case-control studies revealed an odds ratio (OR) ranging from 0.3 (95% CI, 0.1–0.9) to 1.60 (95% CI, 0.79–3.25) without significant differences between groups (23). A more recent systematic review and meta-analysis of 11 pharmacoepidemiological studies including a control group with non-significant heterogeneity confirmed that no significant association between HPV and CNS demyelination could be demonstrated (OR 0.96; 95% CI, 0.77–1.20). Similar results were found when MS and ON were considered separately. Sensitivity analyses did not modify conclusions (24). The safety of HPV was further demonstrated in a recent review and meta-analysis of post-licensure observational studies. The OR for MS was 0.96 (95% CI, 0.77–1.21), and for all the other CNS demyelinating syndromes it was 1.02 (95% CI, 0.77–1.33) (25).

An analysis of the impact of other vaccines on MS or other CNS demyelination syndromes is also reassuring, although in many cases available data were collected with studies showing some methodological limitations. Frequently, very few vaccinated subjects were enrolled, time intervals from immunization and symptom onset were not precisely defined, and potentially confounding factors were not correctly considered (26, 27). A good example in this regard is given by a case-centered analysis of the potential association of vaccine administration and TM and ADEM development. This study was carried out with the data collected by the US Vaccine Safety Datalink and regarded the follow-up of 64 million vaccine doses in the 5–28 days after immunization, during which 7 and 8 cases of TM and ADEM, respectively, occurred. TM was not associated with any of the administered vaccines. The same was true for ADEM, except for the Tdap (adolescent and adult tetanus, reduced diphtheria, acellular pertussis) vaccine. However, the
Guillain–Barré syndrome (GBS) is an acute polyradiculoneuropathy that presently is the most common cause of acute flaccid paralysis worldwide. It annually occurs in 0.4–4.0 individuals per 100,000 population, mainly in males older than 75 years of age (32). In most cases, GBS follows an infection due to Campylobacter jejuni or cytomegalovirus and, more rarely, Mycoplasma pneumoniae, influenza virus, Zika virus, and Epstein–Barr virus (33–37). The association of GBS with other pathogens, such as measles virus, varicella-zoster virus and Haemophilus influenzae, is debated (38–40).

Four main subtypes of GBS, which are differentiated by nerve electrophysiological findings, have been identified: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (41). AIDP is the most common. For all the subtypes, an autoimmune pathogenesis has been supposed and, in some cases, clearly evidenced. In AIDP, the evidence of high T cell concentrations in damaged nerves and myelin proteins in the sera of patients supports the hypothesis that lesions can be due to combined cell-mediated and humoral immune reactions (42).

Alternatively, it was suggested that autoantibodies against cell adhesion proteins localized at Ranvier’s nodes were possible targets in AIDP (43). In contrast, in AMAN and AMSAN, where no demyelination occurs and lesions affect only nerve axons, the damage depends on the presence of IgG antibodies against gangliosides. In this case, molecular mimicry seems to be the most important factor for autoimmunity development.

The structure of several gangliosides resembles the structure of bacterial components, as clearly shown by the evidence that the lipopolysaccharides of the outer membrane of Campylobacter jejuni have molecular compositions quite similar to those of GM1 and GD1a gangliosides of nerve axons (44, 45). On the other hand, GBS can be reproduced by immunizing experimental animals with gangliosides (46, 47) or with Campylobacter jejuni lipopolysaccharide from patients with GBS (48).

The role of vaccines in conditioning GBS has been debated for several years, especially when it was found that inactivated nervous tissue anti-rabies vaccine administration could be associated with the development of GBS (49). However, epidemiological studies have excluded any role of polio and diphtheria-tetanus-pertussis vaccines in the determination of GBS. The same seems true for pneumococcal, varicella, hepatitis A and B and Haemophilus influenzae type b vaccines (50). Doubts are still raised for measles and MMR vaccines, HPV, quadrivalent meningococcal vaccine (MCV4), and influenza vaccine. Regarding the measles vaccine and the MMR vaccine, no definitive conclusion can be drawn, although pharmaceutical companies that produce and market these vaccines report this potential risk in the product information leaflets (51).

The results of the studies specifically planned to evaluate the potential association between measles-virus-containing vaccines and GBS development are conflicting. However, most of the data showing an increased occurrence of GBS in subjects immunized with these vaccines have significant methodological limitations that
GBS (95% CI, 1.05–1.99; *p* = 0.04, respectively). Conflicting results were also obtained from studies carried out during the 2009 influenza pandemic. However, in this case, most of the studies revealed a slight but significant increase in the risk of GBS development in immunized subjects, independent of the type of vaccine used and the geographic area where the study was carried out. In the USA, where only non-adjuvanted vaccines were administered, the relative risk of GBS was 2.35 (95% CI, 1.4–4.0), with 1–3 additional cases per million persons vaccinated (85). Similar data were obtained in Canada and Europe (86–90). Moreover, an international study carried out in 15 countries where both adjuvanted and non-adjuvanted pandemic vaccines were used, the calculated RR was 2.42 (95% CI, 1.58–3.72) (76). It was calculated that the influenza vaccine could cause one additional case of GBS every 100,000 doses (77). In the following years, a great number of studies attempted to verify whether this association truly existed (78–84). The results were conflicting. In most of the cases, no relationship was evidenced, but two well-conducted studies carried out in Canada (82) and in the USA (84) showed that in the 6 weeks after immunization, the relative risk of GBS development was significantly increased (relative risk [RR] 1.45; 95% CI, 1.05–1.99; *p* = 0.02 and 1.7; 95% CI, 1.0–2.8; *p* = 0.04, respectively). Conflicting results were obtained from studies carried out during the 2009 influenza pandemic. However, in this case, most of the studies revealed a slight but significant increase in the risk of GBS development in immunized subjects, independent of the type of vaccine used and the geographic area where the study was carried out. In the USA, where only non-adjuvanted vaccines were administered, the relative risk of GBS was 2.35 (95% CI, 1.4–4.0), with 1–3 additional cases per million persons vaccinated (85). Similar data were obtained in Canada and Europe (86–90). Moreover, an international study carried out in 15 countries where both adjuvanted and non-adjuvanted pandemic vaccines were used, the calculated RR was 2.42 (95% CI, 1.58–3.72) (91). However, some of the studies showing that influenza vaccines could be a potential risk for GBS development were strongly criticized because of significant methodological problems, making the results difficult to interpret. Case series were considered inadequate to establish causality. Moreover, in uncontrolled observational studies carried out over time, confounding factors such as changing case definitions or improving case identification could have affected the apparent incidence and prevalence of the adverse outcome. Consequently, the potential relationship between influenza vaccines and GBS remains an unsolved problem. However, if influenza vaccines can cause GBS, the risk is very low and certainly lower than that due to influenza disease. There are data that indicate that the relative risk of GBS in the 6 weeks after an episode of influenza is significantly greater (RR 15.81; 95% CI, 10.28–24.32) than that ascribed to vaccination even in the most pessimistic assessments (92). This seems to indicate that the influenza vaccine remains a fundamental protective measure and should not be feared to cause GBS. However, a means to reduce the
risk of GBS intrinsically related to influenza virus infection must be considered.

ALUMINUM-RELATED NEUROLOGICAL SYNDROMES

Aluminum (Al) is added to several vaccine preparations (tetanus, hepatitis A, hepatitis B, human papillomavirus, Haemophilus influenzae type b, and infections due to Streptococcus pneumoniae and Neisseria meningitidis) to increase the immune response to vaccine antigens and improve the protection evoked by antigens alone (93). It stimulates both the innate and adaptive immune systems through the activation of antigen-presenting cells, complement cascades, and the induction of chemokine secretion. Despite its well-known toxicity, particularly for the central nervous system, Al has been included in many vaccine preparations for many years because it has been calculated that the total amount of Al that children receive when they are given all the vaccine doses included in the national immunization schedules is significantly lower than that associated with neurotoxicity (94). Impaired speech, apraxia, concentration problems, dementia, depression, and fatigue were described in adults who had been exposed for long time to Al because of foundry work or those who were chronically dialyzed with solution containing relevant amounts of Al (95, 96). In pediatric patients, developmental delay has been described in preterm infants maintained for long periods on parenteral nutrition with solutions with high Al content (97). On the other hand, attempts to correlate the development of autism spectrum disorders or Alzheimer’s disease with Al exposure have failed because some studies did not reveal any true association (98, 99), and positive studies in both animals and children (100–102) had several methodological limitations that made it impossible to draw reliable conclusions (103).

Despite a lack of data supporting damage from Al in subjects receiving vaccines containing this adjuvant, the question of whether vaccines containing Al can be dangerous continues to be raised (104). One of the most frequently reported reasons for the elimination of Al from vaccines is the risk that Al could induce the hyperactivation of the immune system, leading to an autoimmune disease. Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) would be the best demonstration of the potentially dangerous role of Al in this regard. With the definition of ASIA, several different clinical entities that are unified by the previous administration of an adjuvant are included. Sick building syndrome, silicosis, Gulf war syndrome and macrophagic myofascitis (MMF) have been described (105, 106). Moreover, it was suggested that lymphoma, Sjogren syndrome, narcolepsy, and phospholipid syndrome can be included in the ASIA group (107–109). Arthralgia, myalgia, and chronic fatigue were the most frequently reported symptoms in most of these conditions (110). However, the real association between Al and ASIA development has not been definitively ascertained. Most of the studies that seem to indicate a relationship between adjuvants and ASIA are burdened by strong methodological limitations. Criteria for the diagnosis of ASIA are extremely coarse and include signs and symptoms that can occur in several non-immunologically based diseases (111, 112). Moreover, some genetic characteristics that are considered specific to ASIA patients can be commonly found in individuals with other autoimmune diseases. Consequently, it seems likely that in many epidemiological evaluations, most of the cases considered ASIA had a different disease, totally independent from autoimmunity, making the results totally unreliable.

However, several other factors make the correlation between Al and ASIA highly unlikely. Association between vaccines with Al and autoimmune diseases is extremely uncommon even when a temporal association between vaccine administration and disease development seems to suggest a linkage (113). The administration of vaccines containing Al does not worsen the clinical course of autoimmune diseases, contrary to what would be expected if Al could evoke autoimmunity (114). Intradermal administration of antigen preparations containing Al for the treatment of allergic diseases is not associated with any autoimmune manifestation despite the long-term exposure to a non-marginal amount of the metal and the administration in a site favoring a strong immune response (115). Finally, some data collected in children with MMF and associated brain damage seem to suggest that Al distribution into the brain and related CNS alterations are strongly influenced by some genetic characteristics (patients in the HLA-DRB1∗01 group or with increased expression of the monocyte chemotactrant protein-1 gene) (116, 117). This indicates the importance of genetics rather than autoimmunity in conditioning Al-related CNS disease development. On the other hand, MMF can also be diagnosed in patients who did not receive an adjuvanted vaccine, which suggests that causes other than vaccines can be associated with ASIA (118).

MERCURY-RELATED NEUROPATHIES

It has been evidenced in both experimental animals and humans that exposure to high mercury levels could be neurotoxic. For many years, mercury has been included in vaccines in the form of thimerosal (ethylmercury bound to thiosalicylate) because of its preservative action. At the end of last century, it was calculated that infants given all the vaccines recommended in the first 6 months of life received an amount of mercury that exceeded the maximum acceptable daily intake according to the Environmental Protection Agency for methylmercury. Although no well-conducted study had shown that fully immunized children were at increased risk of developing any type of neurological disease, including autism and delayed development, this led several scientific societies to recommend that thimerosal was eliminated from all the vaccines (119). This decision was debated by some experts who highlighted that in vaccines, mercury was present as ethylmercury and not methylmercury. As ethylmercury had a significantly more rapid metabolism and excretion than methylmercury (120), it was concluded that the exposure to mercury of immunized children was significantly lower than that calculated and the removal of thimerosal was not truly needed. Despite this, thimerosal was eliminated from all the
vaccines and presently remains only in preparations used in some developing countries and in multidose vial influenza vaccines.

However, to evaluate whether mercury contained in vaccines could cause problems, several studies were performed. Regarding those specifically planned to demonstrate autoimmunity development, it was shown that subjects exposed to mercury through foods or work could have cellular and humoral signs of immune system activation and, in some cases, high levels of serum autoantibodies or anti-nuclear antibodies (121). This was considered evidence of a potential role of mercury in the determination of autoimmunity (122). Moreover, some mercury-related modifications were strictly associated with well-defined genetic characteristics, quite like those found in subjects with autoimmune diseases (123, 124). Despite these findings, no data capable of showing a causative role for mercury in autoimmune diseases are presently available. On the other hand, all the well-conducted epidemiological studies carried out to show whether thimerosal could cause neurological problems did not show any association between this preservative and autism or development delay (125–127). In one case, it has even been highlighted that exposure to mercury can represent an event conducive to better neurological development (127). In particular, it has been highlighted that exposure to mercury during intrauterine life can lead to better language development skills even if it can lead to less attention and less valid executive functions. Exposure to mercury in the period from birth to the end of the 7th month seems to ensure better motor coordination, higher attention and more efficient executive skills. The lack of negative elements and even the possibility of positive data explain why major international scientific institutions such as the WHO, FDA and EMA concluded that a correlation between thimerosal content in vaccines and the development of neurological diseases could be excluded (128–130).

CONCLUSIONS

Most of the associations between vaccines and nervous system autoimmune syndromes that have been reported as severe adverse events following immunization are no longer evidenced when well-conducted epidemiological studies are carried out. Biological plausibility of the autoimmune mechanisms associated with the temporal proximity between vaccine administration and disease development can be misleading. Moreover, bad epidemiological evaluations can worsen the final judgement and lead to conclusions very far from reality. Although the rarity of autoimmune diseases makes it difficult to strictly exclude that, albeit exceptionally, some vaccines may induce an autoimmune neurological disease, no definitive demonstration of a potential role of vaccines in causing autoimmune neurological syndromes is presently available. The fear of neurological autoimmune disease cannot limit the use of the most important preventive measure presently available against infectious diseases.

AUTHOR CONTRIBUTIONS

NP and SE co-wrote the manuscript and critically revised the text with substantial scientific contributions. All authors approved the final version of the manuscript.

REFERENCES

1. Doherty M, Buchy P, Standaert B, Giacunto C, Prado-Cohrs D. Vaccine impact: benefits for human health. Vaccine. (2016) 34:6707–14. doi: 10.1016/j.vaccine.2016.10.025
2. Plotkin SA, Plotkin SL. A short history of vaccination. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed. Philadelphia, PA: WB Saunders (2012). p. 1–13. doi: 10.1016/B978-1-4557-0090-5.00017-3
3. Haj Hussein I, Chams N, Chams S, El Sayegh S, Badran R, Raad M, et al. Vaccines through centuries: major cornerstones of global health. Front Public Health. (2015) 3:269. doi: 10.3389/fpubh.2015.00269
4. Dubé E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. Expert Rev Vaccines. (2015) 14:99–117. doi: 10.1586/14760584.2015.96212
5. World Health Organization. Emergencies Preparedness, Response. Measles-Global Situation. Available online at: https://www.who.int/csr/don/26-november-2019-measles-global-situation/en/ (accessed March 3, 2020).
6. Kennedy J. Vaccine hesitancy: a growing concern. Paediatr Drugs. (2020) 22:105–11. doi: 10.1007/s40272-020-00385-4
7. Principi N, Esposito S. Adverse events following immunization: real causality and myths. Expert Opin Drug Saf. (2016) 15:825–35. doi: 10.1517/14740338.2016.1167869
8. Nguyen XI, Saoudi A, Liblau RS. Vaccine-associated inflammatory diseases of the central nervous system: from signals to causation. Curr Opin Neurol. (2016). 29:362–71. doi: 10.1097/WCO.0000000000000318
9. Committee to Review Adverse Effects of Vaccines. Institute of Medicine. In: Stratton K, Ford A, Rusch E, Clayton EW, editors. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: National Academies Press (2011).
10. Galetta KM, Bhattacharyya S. Multiple sclerosis and autoimmune neurology of the central nervous system. Med Clin North Am. (2019) 103:325–36. doi: 10.1016/j.mcn.2018.10.004
11. Hu W, Lucchinietti CF. The pathological spectrum of CNS inflammatory demyelinating diseases. Semin Immunopathol. (2009) 31:439–53. doi: 10.1007/s00281-009-0178-z
12. Institute of Medicine (US) Forum on Microbial Threats. Knoble SL, O’Connor S, Lemon SM, et al. editors. The Infectious Etiology of Chronic Diseases: Defining the Relationship, Enhancing the Research, and Mitigating the Effects: Workshop Summary. Washington, DC: National Academies Press (2004).
13. Kerr DA, Aytey H. Immunopathogenesis of acute transverse myelitis. Curr Opin Neurol. (2002) 15:339–47. doi: 10.1097/00019052-200206000-00019
14. Yadav SK, Mindur JE, Ito K, Dhib-Jalbut S. Advances in the immunopathogenesis of multiple sclerosis. Curr Opin Neurol. (2015) 28:206–19. doi: 10.1097/WCO.0000000000000205
15. Jakimovski D, Weinstock-Guttman B, Ramanathan M, Dwyer MG, Zivadinov R. Infections, vaccines and autoimmunity: a multiple sclerosis perspective. Vaccines (Basel). (2020) 8:E50. doi: 10.3390/vaccines8010050
16. Marshall E. A shadow falls on hepatitis B vaccination effort. Science. (1998) 281:630–1. doi: 10.1126/science.281.5377.630
17. Ascherio A, Zhang SM, Hernán MA, Olek MJ, Coplan PM, Brodovitz K, et al. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med. (2001) 344:327–32. doi: 10.1056/NEJM200103143440502
18. DeStefano F, Verstraeten T, Chen RT. Hepatitis B vaccine and risk of multiple sclerosis. Expert Rev Vaccines. (2002) 1:461–6. doi: 10.1586/14760584.1.4.461
19. Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. Lancet. (2000) 355:549–50. doi: 10.1016/S0140-6736(00)02991-8
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N Engl J Med. (2016) 373:1218–24. doi: 10.1056/NEJMoa1514318

Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barré syndrome. Vaccine. (2019) 37:5544–50. doi: 10.1016/j.vaccine.2018.05.119

De Stefano F, Bodenstab HM, Offit PA. Principals controversies in vaccine safety in the United States. Clin Infect Dis. (2019) 69:726–31. doi: 10.1093/cid/ciz135

Merck Sharp & Dohme Limited. MMRAVAXPRO. Available online at: https://www.medicines.org.uk/emc/product/6307 (accessed March 3, 2020).

Morii M, Kuwabara S, Miyake M, Noda M, Kurohi K, Hanno H, et al. Haemophilus influenzae infection and Guillain-Barré syndrome. Brain. (2000) 123:2171–8. doi: 10.1093/brain/123.10.2171

Wakerey BR, Uncini A, Yuki N. GBS Classification Group, Guillain-Barré and miller fisher syndromes—an diagnostic classification. Nat Rev Neurol. (2014) 10:537–44. doi: 10.1038/nrneurol.2014.138
61. Miranda S, Chaingnot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: a large cohort study of over 2 million young girls in France. Vaccine. (2017) 35:57461–8. doi: 10.1016/j.vaccine.2017.06.030
62. World Health Organization. Safety of HPV Vaccines. Available online at: http://www.who.int/vaccine_safety/topics/hpv/Dec_2015/en/ (accessed February 28, 2020).
63. Grimaldi-Bensaoud L, Rossignol M, Koné-Paut I, Krivitzky A, Lebrun-Frenay C, Clet J, et al. Risk of autoimmune diseases and human papillomavirus (HPV) vaccines: six years of case-referent surveillance. J Autoimmun. (2017) 79:84–90. doi: 10.1016/j.jaut.2017.01.005
64. Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papillomavirus vaccine: a self-controlled case-series study in England. Vaccine. (2017) 35:1729–32. doi: 10.1016/j.vaccine.2017.01.076
65. Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Vaccine. (2014) 32:466–79. doi: 10.1016/j.vaccine.2014.04.033
66. Gee J, Naleway A, Shui I, Bagg J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the vaccine safety datalink. Vaccine. (2011) 29:8279–84. doi: 10.1016/j.vaccine.2011.08.106
67. Markowitz LE, Dunne EF, Saraiya M, Chesnow HH, Curtis CR, Gee J, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recom Rep. (2014) 63:1–30
68. World Health Organization. Meeting of the global advisory committee on vaccine safety, 7–8 June 2017. Weekly Epidemiol Record. (2017) 92:393–404.
69. Centers for Disease Control and Prevention. Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June–July 2005. MMWR Morb Mortal Wkly Rep. (2005). 54:1023–5.
70. Cho B, Clark TA, Messonnier NE. MCV vaccination in the presence of vaccine associated Guillain–Barré Syndrome risk: a decision analysis approach. Vaccine. (2010) 28:817–22. doi: 10.1016/j.vaccine.2009.10.050
71. Centers for Disease Control and Prevention. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, October 2005–February 2006. MMWR Morb Mortal Wkly Rep. (2006) 55:364–6.
72. Hansen J, Zhang L, Klein NP, Robertson CA, Decker MD, Greenberg DP, et al. Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine. Vaccine. (2017) 35:8879–84. doi: 10.1016/j.vaccine.2017.09.032
73. Velentgas P, Amato AA, Bohn RL, Chan KA, Cochrane T, Funch DP, et al. International collaboration to assess the risk of Guillain-Barré syndrome after seasonal influenza vaccination among recipients of pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. Bmj. (2011) 343:d3908. doi: 10.1136/bmj.d3908
74. Sandhu SK, Hua W, MacCurdy TE, Franks RL, Avagyan A, Kelmam J, et al. Near real-time surveillance for Guillain-Barré syndrome after seasonal influenza vaccination among the medicare population, 2010/11 to 2013/14. Vaccine. (2017) 35:2986–92. doi: 10.1016/j.vaccine.2017.03.087
75. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Kellynside RA, Ziegler DW, Retalialla HF, et al. Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976–1977. Am J Epidemiol. (1979) 110:105–23. doi: 10.1093/oxfordjournals.aje.a112795
76. Vellozzi C, Ishai S, Stewart B, Tokars J, DeStefano F. Cumulative risk of Guillain-Barré syndrome among vaccinated and unvaccinated populations during the 2009 H1N1 influenza pandemic. Am J Public Health. (2014) 104:696–701. doi: 10.2105/AJPH.2013.301651
77. Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, et al. International collaboration to assess the risk of Guillain-Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. Vaccine. (2013) 31:4448–58. doi: 10.1016/j.vaccine.2013.06.032
78. Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza-health care encounters: a self-controlled study. Lancet Infect Dis. (2013) 13:769–76. doi: 10.1016/S1473-3099(13)70104-X
79. Eickhoff TC, Myers M. Workshop summary Aluminium in vaccines. Proc Nutr Soc. (2012) 81:1191–210. doi: 10.1017/S0029665111004988
80. Kielmann E, Schaper M, Burchardt C, Schaller KH, Rosbach B, Scherhag A, et al. Longitudinal study on potential neurotoxic effects of aluminium: I. assessment of exposure and neurobehavioral performance of Al welders in the train and truck construction industry over 4 years. Int Arch Occup Environ Health. (2007) 81:41–67. doi: 10.1007/s00420-007-0191-2
81. Kielmann E, Schaper M, Burchardt C, Schaller KH, Rosbach B, Kraus T, et al. Longitudinal study on potential neurotoxic effects of aluminium: II. assessment of exposure and neurobehavioral performance of Al welders in the automobile industry over 4 years. Int Arch Occup Environ Health. (2009) 82:1191–210. doi: 10.1007/s00420-009-0414-9
82. Fewtrell MS, Edmonds JC, Isaacs E, Bishop NJ, Lucas A. Aluminium exposure from parenteral nutrition in preterm infants and later health outcomes during childhood and adolescence. Proc Nutr Soc. (2011) 70:299–304. doi: 10.1017/S0029665111004988
105. Shoenfeld Y, Agmon-Levin N. ‘ASIA’—autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. (2011) 36:4–8. doi: 10.1016/j.jaut.2010.07.003

108. Arango MT, Kivity S, Shoenfeld Y. Is narcolepsy a classical autoimmune disease? Clin Immunol. (2013) 60:366–75. doi: 10.1016/j.clim.2010.01.005

109. Butnaru D, Shoenfeld Y. Adjuvants and lymphoma risk as part of the ASIA spectrum. Immunol. Res. (2015) 61:79–89. doi: 10.1007/s12026-014-8622-0

110. Wadat A, Quaresma M, Brown S, Cohen Tervaert JW, Rodriguez-Pint I, Cervera R, et al. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld’s syndrome)—an update. Lupus. (2017) 26:675–81. doi: 10.1177/0961203316686406

113. Colafrancesco S, Perricone C, Priori R, Valesini G, Shoenfeld Y. Sjögren’s syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). J Autoimmun. (2014) 51:10–6. doi: 10.1016/j.jaut.2013.04.003

115. Deshmule SL, Kremlev S, Amini S, Sawaya BE. Monocytic chemotractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res. (2009) 29:313–26. doi: 10.1089/jir.2008.0027

116. Deshmule SL, Kremlev S, Amini S, Sawaya BE. Monocytic chemotractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res. (2009) 29:313–26. doi: 10.1089/jir.2008.0027

117. Park JH, Na KS, Park YW, Paik SS, Yoo DH. Macrophagic myofasciitis unrelated to vaccination. Scand J Rheumatol. (2005) 34:65–7. doi: 10.1080/0300745051007913

118. Park JH, Na KS, Park YW, Paik SS, Yoo DH. Macrophagic myofasciitis unrelated to vaccination. Scand J Rheumatol. (2005) 34:65–7. doi: 10.1080/0300745051007913

119. Pint I, Cervera R, et al. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld’s syndrome)—an update. Immunol Res. (2014) 51:10–6. doi: 10.1007/s12026-014-8586-9

120. Martínez-Naya B, Cervera R, et al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): implications in the study of autoimmune diseases. Immunopathol. (2010) 37:483–93. doi: 10.1016/j.sypim.2010.06.002

121. Pollard KM, Cauvi DM, Toomey CB, Hultman P, Kono DH. Mercury-induced inflammation and autoimmunity. Biochim Biophys Acta Gen Subj. (2019) 1863:129299. doi: 10.1016/j.bbagen.2019.02.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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