

Do vaccines have a role as a cause of autoimmune neurological syndromes?

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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

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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 autoimmunity,” “ nervous system demyelinating syndrome,” “ 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* , herpesvirus ([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 association was based on only 2 exposed cases, leading to an OR of 15.8 (95% CI, 1.2–471.6; $p = 0.04$). The calculated excess risk was 0.385 cases (95% CI, –0.04 to 1.16) per million doses. The authors themselves highlighted that the number of disease cases was too small to draw firm conclusions and that the results could be due to chance alone (28). However, a systematic review of 51 published studies regarding immunization and MS showed that the use of HBV, HPV, seasonal influenza, measles-mumps-rubella (MMR), varicella, tetanus, BCG, polio, and diphtheria vaccines did not cause any appreciable increase in the risk of MS development or relapse (29). Interestingly, in another study, when any type of vaccination was found to be associated with an increased risk of CNS demyelinating syndromes within 30 days after vaccination in subjects <50 years of age, it was evidenced that in some of these subjects, a previous risk factor for demyelinating syndrome development was already present. Starting from this finding and the evidence that in the same study none of the vaccines was associated with any demyelinating syndrome 30 days after vaccination, the authors concluded that vaccines were not the cause of disease. It was assumed that the vaccines could have acted as a

proinflammatory cofactor in subjects with subclinical autoimmunity, showing a condition that would have spontaneously emerged in later times ([30](#)).

However, the need for a meticulous evaluation of epidemiological studies seems clearly shown by the results of a nested case-control study carried out in China with the aim of analyzing the potential relationship between vaccines and ADEM. The cases of patients with this disease hospitalized during the period 2011–2015 after the introduction of the Expanded Program of Immunization in that country were evaluated ([31](#)). A total of 272 patients with ADEM and 1, 096 controls were enrolled. No association with ADEM was demonstrated for HBV, hepatitis A, influenza, live polio, diphtheria, acellular pertussis, tetanus, MMR, varicella, or Japanese encephalitis vaccination within the 180 days after vaccination regardless of the age of the enrolled individuals. However, further analyses revealed that the immunization of children was associated with a statistically significant increase in the risk of ADEM in the 31–60-days exposure interval (OR 4. 04; 95% CI, 1. 07–12. 96), although this risk was not evident for the 0–30 and 61–180-days intervals. The increased risk was not specific to a vaccine and was not evidenced among adults in any of the study subperiods. Moreover, when pediatric and adult data were pooled, the increased risk shown in the 31–60 days after immunization was no longer evincible. Reasons for this finding are not precisely defined. However, as children receiving vaccines were more likely to have had an infectious disease, mainly a respiratory tract infection, in the 6 months before symptom onset ($p < 0. 05$), it could be supposed that infections could have triggered ADEM and that this was already active when vaccines were given.

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In conclusion, no epidemiological study carried out with undisputable methods has clearly shown that vaccines can cause CNS demyelinating syndromes. Fear for the development of these syndromes cannot be considered a reason for the limitation of vaccine use.

Guillain–Barre' Syndrome (GBS)

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

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vaccines have significant methodological limitations that preclude any valid conclusion. For example, in many individuals, the MMR vaccine was given together with other vaccines, making it impossible to state the true importance of the MMR vaccine as a cause of disease ([52](#) - [56](#)). This explains why the US Institute of Medicine stated that available data do not allow us to establish whether there is an association between the MMR vaccine and GBS ([57](#)). On the other hand, if a real risk exists, it must be extremely low, as risk could not be demonstrated in several studies, enrolling a very great number of subjects, that have measured and compared the incidence of GBS in periods with different MMR vaccination coverages. Evaluations carried out in Finland ([58](#)), Iran ([59](#)), and South America ([60](#)) have shown that the incidence of GBS was quite similar in periods with and without MMR vaccine use. Given these findings and the dramatic benefits of the MMR vaccine, the risk of GBS cannot be considered a limitation for MMR vaccine use.

An apparent association between GBS and HPV administration was evidenced in a study carried out in France, in which it was found that the development of this polyradiculoneuropathy within 33 months of vaccination was several times more frequent than in unvaccinated controls (1.4 vs. 0.4 per 100,000 cases) ([61](#)). This finding led the World Health Organization Global Advisory Committee on Vaccine Safety to conclude that, despite being low, the risk was high enough to recommend further studies in adequately sized populations ([62](#)). However, several subsequent retrospective studies carried out on populations that had received millions of HPV doses have yielded completely opposite results ([63](#) , [64](#)). Neither bivalent nor

tetravalent HPV could be associated with an increased risk of GBS development, as no statistically significant difference between vaccinated and control groups in the incidence of GBS could be demonstrated. The lack of any evidence of a causative role of HPV was further confirmed by passive surveillance reports ([65](#)) and active monitoring by both the US Vaccine Safety Datalink ([66](#)) and the US Vaccine Adverse Events Reporting System ([67](#)). All these findings led the World Health Organization Global Advisory Committee on Vaccine Safety to change its statement. It was reported that a true relationship between GBS and HPV could not be demonstrated, and even if existing, statistical calculations allow us to conclude that it could not be > 1 case per million doses ([68](#)). For the MMR vaccine, no limitation in the use of HPV can be derived from the hypothetical risk of GBS development.

The potential association between the tetravalent meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV4) and GBS was supposed when, a few months after the inclusion of this vaccine in the US immunization schedule, five GBS cases were diagnosed among adolescents who had been immunized 2-4 weeks before ([69](#)). Although this finding was not considered a limitation for MCV4 use by the US Advisory Committee of Immunization Practice (ACIP) ([70](#)), the US Food and Drug Administration recommended that this vaccine was not used in subjects with a previous history of GBS and that further adequate studies to evaluate the problem should be performed ([71](#)). In response to these demands, several epidemiological evaluations, in some cases involving millions of MCV4 doses, were conducted ([72](#) - [74](#)). None of them showed any

significant correlation between the vaccine and GBS, as the risk of GBS development after MCV4 administration was not different from that usually reported in unvaccinated subjects. It was highlighted that statistical calculations had shown that, even considering the less favorable circumstances, <1.5 GBS excess cases per million vaccinations could occur after GBS use. These findings were considered fully satisfactory and led the ACIP to remove the limitations to the use of MCV4 and any other tetravalent conjugate meningococcal vaccine regardless of conjugation protein characteristics ([75](#)).

Regarding influenza vaccine, a direct relationship of a strict linkage between this vaccine and GBS development was first supposed in 1976 when the receipt of a swine influenza vaccine in the USA was associated with a significantly greater than expected incidence of GBS ([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 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 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) ([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 AI in subjects receiving vaccines containing this adjuvant, the question of whether vaccines containing AI can be dangerous continues to be raised ([104](#)). One of the most frequently reported reasons for the elimination of AI from vaccines is the risk that AI 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 AI 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 myofasciitis (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 AI 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 AI and ASIA highly unlikely. Association between vaccines with AI 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 AI does not worsen the clinical course of autoimmune diseases, contrary to what would be expected if AI could evoke autoimmunity ([114](#)). Intradermal administration of antigen preparations containing AI 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 AI 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 chemoattractant protein-1 gene) ([116](#) , [117](#)). This indicates the importance of genetics rather than autoimmunity in conditioning AI-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

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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.

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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