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Vaccination and autoimmunity: influenza vaccination and association with multiple sclerosis

Vakcinacija i autoimunost: vakcina protiv gripa i povezanost sa multiplom sklerozom

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Introduction

Influenza, generally known as the flu, is one of the most common viral respiratory infections with the capacity to disseminate around the world, one could say at lightning speed, in seasonal epidemics, reaching its summit over the course of winter. Influenza is a serious infectious disease caused by RNA viruses which belong to the Orthomyxoviridae family. The first influenza pandemic was documented in 1580 and it has remained a viral disease of global dimension ever since [1]. The four researchers analyzed medical literature reported during the Spanish Flu pandemic from 1918 to 1920. The meta-analysis of these data showed that treatment of new victims of the virus in 1918 with convalescent whole blood, plasma or serum collected from patients who had recovered from Spanish Influenza resulted in reduced case-fatality rate of severely ill patients by 50% [2]. In 1931, Goodpasture was the first who discovered a viral growth in embryonated hen's egg, and in the 1940s, the US military developed the first approved inactivated vaccines for influenza, used during World War II [1]. Unlike other viral vaccines, annual influenza vaccination is recommended due to fast evolution of influenza viruses, evolve one million times faster than mammals, which results in high mutation rates and antigenic variations known as antigenic drift, a minor change such as amino acid substitution in virus surface proteins hemagglutinin (HA) and/or neuraminidase (NA), and antigenic shift, a new combination of different flu genes emerged to infect people [3–5].

Traditional influenza vaccine composition

There are three distinct types of influenza viruses, designated A, B, and C, with types A and B of influenza viruses being the major pathogens in humans. Influenza A can infect humans, birds, pigs and other species [6]. Influenza B and C are primarily human pathogens. Unlike influenza A and B viruses, influenza C virus is of little clinical importance [7]. The core of the A and B viruses is surrounded by a lipid in nature membrane, or 'envelope' derived in part from modified host cell membranes, from which may protrude spikes, glycoprotein complexes, corresponding to the hemoglutinin (HA) trimer ligand and the neuraminidase (NA) tetramer ligand [8]. HA surface protein enables the virus to get attached to sialic acid-containing receptors and viral entry by membrane fusion. NA surface protein is a receptor-destroying enzyme responsible for viral release and cell-to-cell spreading [9]. There are 17 HA subtypes of influenza virus whereas 9 subtypes of NA are known to be present [10]. Nowdays traditional flu vaccines (called "trivalent" vaccines), composed of two types of inactivated influenza viruses: an influenza A (H1N1) subtype virus, an influenza A (H3N2) subtype virus, and an influenza B virus, are used worldwide to protect from influenza and its serious complications [7].

Influenza vaccination: Pros and cons

A vaccine is a preparation of killed or inactivated microbes (parasites, viruses, bacteria), or purified products deri-

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ved from them, used to elicit the immune system to a particular disease [11]. Human vaccines are regarded as one of the safest medical products available, and the most effective method of prophylaxis we have against infectious diseases for the general population. Medical community considers current human vaccines also safe and effective for patients with autoimmune diseases [12, 13], but like any other medical product, there may be risks. In general, all inactivated virus vaccines are considered safe and effective[11].

Even though influenza infection *per se* has seldom been associated with various organ-specific and systemic autoimmune diseases, systemic and neurological autoimmune phenomena have been reported following influenza vaccine that consists of inactivated purified surface fragments and no viral genetic material [14]. In June 2009 the World Health Organization declared the new influenza of swine origin, A (H1N1), which originated in Mexico around March 18, 2009, was pandemic [15]. A concern about pandemic influenza A (H1N1) 2009 vaccine was the possible occurrence of neuroimmunological adverse events, including Guillain-Barré syndrome (GBS). A causal relationship between the vaccine and this autoimmune neurological disease was suggested by the original Centers for Disease Control study during an outbreak of GBS in 1976 that was caused by the swine flu vaccine [16]. A more than seven-fold increment in risk of GBS was observed when the influenza A (H1N1) subtype A/New Jersey/76 (A/NJ/76) vaccine had been applied in the United States in 1976. As a consequence, the vaccination campaign had to be suspended brusquely [17]. In contrast to the A/NJ vaccine, in 1978-1979 introduction of a new HA type of influenza vaccine have failed to show a statistically significant excess risk of acquiring vaccine-related GBS [18]. A retrospective epidemiological study done by Lasky et al. [19] on seasonal influenza vaccines used in 1992–1993 and 1993–1994 showed modest increases in risk of GBS. For the two seasons combined the risk of occurrence of GBS showed 95% confidence interval (1.0, 2.8). The adjusted (age, sex, and vaccine season) relative risk of 1.7 ($p = 0.04$) suggested slightly more than one additional case of GBS within six weeks after vaccination in one million people.

A population-based cohort study in Stockholm, Sweden, investigated over a period of 8–10 months, the risk of neurological and autoimmune disorders of special interest in people vaccinated against pandemic A (H1N1) with monovalent Pandemrix® (GlaxoSmithKline, Middlesex, UK) 2009 vaccine compared with those who remained unvaccinated. The study population comprised 1.98 million people registered in Stockholm county with more than one million people vaccinated and 900,000 unvaccinated. This retrospective cohort study was devised for the purpose of linking individualized data on pandemic vaccinations to an inpatient and specialist database on healthcare utilization in Stockholm county for follow-up during and after the pandemic period. The overall relative risk for GBS, multiple sclerosis (MS), type 1 diabetes, or rheumatoid arthritis among vaccinated compared with unvaccinated people remained unchanged [20].

Three major neurological manifestations of an autoimmune nature have been viewed in conjunction with vaccination: the GBS, MS and autism [21]. Among autoimmune adverse events, GBS remains the most frequently reported influenza vaccine adverse neurological autoimmune event. For that reason, and the issue around GBS in 1976 another prospective multinational case-control study in Europe [22] with an objective to evaluate any association between GBS and adjuvanted pandemic influenza A (H1N1) 2009 vaccine was performed. The main outcome measure was a relative risk estimate for GBS after influenza vaccine. The point estimate showed no association between pandemic influenza vaccination and GBS, although the upper confidence limit was 2.7 meaning a potential increase in risk up to 2.7-fold or three excess cases per one million vaccinated people.

GBS is a transient, often preceded by a respiratory or gastrointestinal illness, acute polyneuropathy, in Europe mostly presents as acute inflammatory demyelinating polyradiculoneuropathy, characterized by areflexic symmetrical motor paresis with mild sensory disturbances [23]. The infections *per se* are usually not enough for triggering autoimmune diseases. There are clearly other factors involved: genetic, immunological and hormonal [24]. This is probably why the role of influenza vaccination as a trigger of GBS remains controversial [22].

Hence, the GBS-vaccine link controversy continuous. Two recent studies from the United Kingdom identified influenza-like illness/upper respiratory tract infection as a strong risk factor. An increased risk of GBS was seen shortly thereafter, consistent with observations that GBS is often preceded by a respiratory illness. It is however difficult to associate GBS with influenza virus infection solely since other respiratory pathogens, that can present as influenza-like illness, are also at their height in the winter. This study found no causal association of GBS with influenza vaccine; instead, it pointed out to increased risk of GBS after influenza-like illness. Furthermore, this study suggests that influenza vaccine should protect against GBS and also finds equally valuable to make an overall risk-benefit assessment - the risk of such events due to pandemic influenza *vs* the degree of vaccine protection [25, 26].

While the substance of epidemiologic evidence, evaluated over the last 30 years, does not support the association between influenza vaccination and GBS, the Committee of the Institute of Medicine (2011) found that an association cannot be ruled out with confidence, particularly because the annual antigenic reformulation of the influenza vaccine varies from year to year and the potential for risk of GBS also varies [27].

Pathophysiological concepts of multiple sclerosis with respect to antigen presenting cells

In general, MS is heterogeneous disorder of the central nervous system. Although the factors that contribute to its heterogeneity are still confounding, at the same time we are quite assured that we talk about a complex genetic trait that is influenced by environmental variables such as exposure to infections, climate etc. There is no doubt that cellular and humoral immune mechanisms are implicated in the pathoge-

nesis of demyelinating autoimmune diseases in the CNS in humans and animal models [28, 29]. Furthermore, pathophysiological studies suggest that MS results from an immunological attack on white matter in the CNS and consequent breakdown of the myelin around axons and the possibility of secondary axonal damage as well. Plaques, the pathological signature of MS, are small round areas of demyelination that may occur anywhere within the white matter. Depending on their stage of development the varying proportions of immune cells and immunoreactive substances can be detected [30].

Antigen presenting cells (APCs) are necessary for the pathogenesis of murine models of MS [31,32]. APCs are involved in multiple stages during MS pathology, thenceforth the growing interest in studying these cells. MS seems primarily to be a disease that involves an immune response to antigens presented by major histocompatibility complex (MHC) class II molecules. Perivascular macrophages are an abundant cell type in the CNS. This location enables them to encounter pathogens and assist in controlling innate and adaptive immune responses in the CNS. They are especially plentiful in actively demyelinating lesions and are characterized by higher levels of MHC class II and CD45 in both rodents and humans compared to microglia [33]. Although microglia are thought to exert a detrimental role on the brain, their precise contribution to brain inflammatory demyelination is largely unknown [34]. In humans MHC class II is expressed in MS lesions [35]. Additionally, human astrocytes express MHC class II *in vitro* upon IFN-γ stimulation [36]. Further, the accumulation of dendritic cells (DCs) within the CNS [37–39] is evident, yet the mechanisms of recruitment of DCs to the CNS continue to be an area of ongoing research. These infiltrating DCs may seem to some of us excessive, given the fact that the CNS has resident APCs (microglia and astrocytes). DCs are of hematopoietic origin, they evolve from lymphoid and myeloid precursors, respectively. There are two main subsets of DCs: conventional DCs (cDCs) and plasmacytoid DCs (pDCs) [40]. DCs, upon activation through either Toll-like receptor (TLR) signaling or encountering with antigen (Ag), travel from resident tissues or sites of inflammation to the lymph nodes (LN). Classically, T cell activation occurs in the LN where DCs migrate after Ag uptake in peripheral tissues. In experimental autoimmune encephalomyelitis (EAE) model, naive T cells are first introduced to myelin antigens in the periphery [41]. Irla et al. [42] proposed that MHCII expression by pDCs confers natural protection against EAE by stimulating the selective expansion of myelin-Ag-specific natural regulatory T cells in secondary lymphoid tissues. In our previous study we suggested that pDCs might be the one to make a connection between mild clinical signs expressed in the myelin oligodendrocyte glycoprotein (MOG) variant of EAE-induced mice and the expression of MHC class II molecules in the secondary lymphoid organs [43]. Activation of DCs leads to their maturation, that is, upgrades the expression of MHC class II as well as co-stimulatory molecules (CD80, CD86, CD40). This way DCs become more efficient at presenting cognate Ag to naive as well as memory T cells, which is essential in the coordination of both the innate and adaptive immune responses [44].

Overly simplified view of the functionally balanced division of CD4(+) T cells into Th1 and Th2 lymphocytes remains useful and remains a model of MS pathogenesis [45, 46]. However, exceptions to Th1-driven MS model may be much more prominent, often plentiful, clonal expansion of CD8+/MHC class I-restricted T lymphocytes, especially in active lesions, whereas the CD4+ phenotype predominates in the perivascular space [47]. Current data suggest that MS is driven by Th1 and Th17 subsets, although they are mechanistically different from each other [38, 48]. Various pathological, experimental, clinical and immunological findings also collectively indicate a pathogenic role of antibodies in MS. Serum autoantibodies that targeted extracellular MOG, the outermost lamellae of the myelin sheath and hence easily accessible to antibody attack, in its native structure were shown to be lytic *in vitro*, supporting a potential pathogenic role of these antibodies in MS [49]. EAE is the most extensively studied mouse model of MS [50] and MOG induced EAE more closely resembles MS than other EAE variants in which inflammation greatly predominates over demyelination [51]. More work is however required to learn the pathogenic details of the demyelinating events observed in the CNS caused by antibodies reactive with myelin constituents in EAE and to determine whether these mechanisms are indicative in MS.

Influenza infection or vaccination as probable trigger of MS

MS is the most common chronic neurological disease in young adults, affecting about 2.5 million people worldwide [52]. It is now generally acknowledged that the etiology of autoimmune diseases, even though still not clear, includes the genetic, immunological, hormonal and environmental factors skewing the immune response towards autoreactivity [53]. Environmental factors, especially infections, are considered to be probable, although usually not sufficient, triggers of autoimmune response and can elicit or exacerbate autoimmune diseases [54, 24]. More recent studies divulge that peripheral B-cell responses are closely involved in the immune pathology of MS through proinflammatory mechanisms, bystander activation, or through regulatory functions [55]. It is proposed that aberrant proinflammatory cytokine responses exhibited by episodically triggered B cells of MS patients mediate bystander activation of disease-related proinflammatory T cells resulting in relapsing disease activity [56]. Since abnormal cell-mediated and humoral immunity play a role in the pathogenesis of disease, a higher susceptibility to infections in MS patients is therefore expected. Although the unbalanced immune system is evident in patients with MS, immune defense against common viral and bacterial infections appears to be preserved. The infection rate of commonly occurring infectious diseases is not increased among MS patients [57, 58]. Additionally, several reports suggested that virus infections could trigger a relapse typically observed in relapse-remitting (RR) form of the MS patients [59]. A possible explanation for disease exacerbation after influenza infection could be loss of down-regulation

within DC clusters and consequent increase of activated cells [60]. Therefore, immunization is considered important for the MS patients not only to prevent an infectious ailment, but also to potentially prevent the MS relapses. The debate about vaccine safety in patients with MS is still wide open [61]. Clinical onset and the MS disease activity after vaccination have been reported [57, 62, 63].

Hepatitis-B vaccine has been of particular concern and most extensively studied in connection with the MS onset. The focus on this vaccine followed case reports, in France and the US, of the CNS demyelization that have been documented days to weeks post-vaccination [64]. A number of epidemiological studies and medical records-based investigations of hepatitis B vaccine and MS followed these case reports and most of these have shown neither increased risk of experiencing a demyelinating episode nor occurrence of MS for vaccinated *vs* unvaccinated individuals [65–67]. Studies that did show the relationship between hepatitis B vaccine and increased risk of MS noted that this vaccine does not represent a widespread risk factor for the disease [68–71]. In 2002, the National Academy of Sciences' Institute of Medicine, after having examined the published, peer-reviewed scientific and medical literature, concluded the lack of association between hepatitis B vaccination and the CNS demyelinating disease [72]. Additionally, studies that have examined the potential effect of hepatitis B vaccination on relapses in people diagnosed with the MS disease could not demonstrate an increased risk of relapse [73, 74].

Other vaccines with potential implications for the MS patients that were studied include influenza, because of its widespread use, tetanus and measles vaccines. There is no definite increase of either occurrence of MS or the risk of triggering the MS bouts following the influenza vaccination that has been reported.

Vaccination has proved effective in neutralizing infectious agents by inducing strain-specific antibodies [14]. Back in 1962 Sibley and Foley [57] observed 24 patients with MS following the administration of influenza vaccine. The quadrivalent inactivated-virus vaccine contained three type A strains and one type B strain. Antibodies to all four viral strains were determined in the MS patients and control patients with other neurological disease. The vaccine was well tolerated in the group of patients with MS with no convincing evidence of adverse reactions to vaccine. Antibody response to influenza vaccination in both groups showed that immunologic responsiveness was similar, with usual rise in titer by an average of twofold to fourfold after vaccination. In a clinical study done by Moriabadi et al. [75] "Influenza vaccination in MS" mean antibody response against influenza A virus was increased in both MS patients and healthy controls after 2 weeks post immunization. He also argues against a general immune stimulation by influenza vaccination since no increase of myelin protein–reactive T-cells was observed after immunization. The overall data presented in this study support the effectiveness and safety of influenza vaccination in the patients with MS. Our group was reported that anti-influenza antibody titers in healthy vaccinated mice and in MOG induced EAE-vaccinated mice, 4 weeks after vaccination with inactivated influenza vaccine (split virion), was significantly higher compared to the unvaccinated control groups, indicating long-lasting antibody response as well as preserved immune response in MOG induced EAE mice [76]. A possible role of several viruses, including influenza A virus, was investigated in a case-control study in 152 children with MS and a significantly higher concentration of antibodies was found in the MS patients comparing with controls. This study pointed out more to a complex infectious background of MS rather than, 'a specific virus causes a specific disease' [77].

Analyzed medical records, which included influenza vaccine among other vaccines found no association between influenza vaccine and increased risk of MS [67, 71]. The studies that analyzed whether influenza vaccination affected the risk of the MS exacerbation or disability progression demonstrated no relation between influenza vaccine and subsequent flare of the disease [78].

Apart from a risk of MS or the MS relapse from vaccination in general, a few studies investigated the issue of vaccine efficacy in the MS patients due to immune system dysfunction in genetically predisposed persons, and found no sufficient evidence to make a determination [79, 80]. The antibody levels following various virus vaccination were present at similar levels in both MS patients and healthy subjects [81]. This suggests that vaccination is likely as effective in the MS patients as in the healthy subjects.

There is a long-lasting concern that a mechanism by which immunization may trigger the MS activity may be shared among other autoimmune diseases such as GBS. In theory, intensified immune response against live attenuated viruses (e.g. measles and varicella), inactive viruses (e.g. seasonal influenza and hepatitis A), or portions of viruses or bacteria [e.g., hepatitis B, human papiloma virus (HPV), and pneumococcus] vaccines, that have been included among the environmental factors, might also induce an aberrant immune response against self-antigens [82]. Many common infections are known to induce a transient rise in autoantibody production. A similar rise in autoantibody production has been observed after various vaccinations. Recently, our group has detected a significant increase of anti-MOG antibodies in sera of MOG induced EAE mice and MOG induced EAE-influenza vaccine vaccinated mice, compared to influenza vaccine vaccinated and intact groups. No difference was found between influenza vaccine vaccinated *vs* intact groups and a positive correlation was found between anti-MOG antibody titer and the development of the EAE clinical signs. The overall data presented in this study indicate that influenza vaccine has no effect on production of autoantibodies and development of clinical signs [76]. A number of cohort studies demonstrated a transient change in autoantibody production, with presumably no clinical significance, after influenza vaccination in apparently healthy participants [83, 84]. These autoantibodies usually resolve within a period of 2 months [85] but can persist in rare cases. Based on several reported studies, the post-vaccination stimulation of autoantibody production became one of the criteria of establishing vaccine safety. Although autoantibodies have the potential of pathogenicity

in several diseases it is often not clear whether they mirror events of certain antigens important in the development of the illness or represent the causal factor [21]. As of now, however, the pathological relevance of antibody-mediated autoimmune encephalomyelitis in MS remains unclear regardless their significant deposits in some demyelinating MS lesions [86]. A recent case report done by Amano et al. [87] supported the view that anti-MOG antibodies were linked to longitudinally extensive transverse myelitis (LETM) established after influenza infection. LETM, defined as a spinal cord lesion that extends over three or more vertebrae, is classically associated with neuromyelitis optica. Spinal cord lesions may, however, arise from a number of autoimmune and inflammatory diseases that involve the CNS such as MS, sarcoidosis or Sjögren syndrome or infectious diseases with the CNS involvement [88]. The clinical significance of anti-MOG antibodies for diagnosis, treatment, and prognosis has yet to be ascertained. Although autoantibodies against MOG are found in the clinical spectrum of MOG associated diseases in humans as well as in different experimental models, the role of anti-MOG antibodies in pathogenesis is still unclear [88].

The mechanism of host response applies equally to an infectious invasion and to vaccination [89]. However, the pathogenic mechanism underlying the association between viruses and MS is still uncertain. Since vaccinations prime the immune system and immune factors are viewed as major players in MS, it is plausible that vaccines might work as the infections do and molecular mimicry, which is immunologic similarity between antigenic determinants of the infectious agent or an antigen in a vaccine and an autoantigen, such as a myelin peptide in MS, remains the most appealing hypothetic mechanism by which infections/vaccines may trigger autoimmune tissue damage [90, 91]. The T cell cross-reactivity is a general property of T cell recognition probably needed to balance the requirement to recognize non-self antigens and to reduce the possibility of loss of self-tolerance. In many cases of autoimmunity, it leaves an open question whether cross-reactivity represents an epiphenomenon or a breakdown in the ability of T-cells to distinguish self from non-self antigens through the mechanism of epitope spreading [92, 93]. It is to be, however, remembered that molecular mimicry usually requires several weeks following first exposure to an antigen, while a second exposure to the same antigen might elicit a response within a shorter period of time [94]. Other possible mechanisms, including pathways of innate immunity that have been offered for explaining vaccine induced autoimmunity are: latent viral infection that could possibly persist in the target tissue and potentially result in demyelination; the potential of induction of autoantibodies production and abnormal cytokine production triggered by vaccination [95].

Influenza vaccine impact on spatial learning and memory in MS

MS affects motor, sensory as well as behavioral and cognitive functions. In the end, it is worthwhile to consider the fact that clinically evident cognitive disorders start early in the MS disease [96]. Cognitive deficits experience approximately up to 65% of the MS patients [97]. The most common cognitive symptoms include deficits in the ability to concentrate, mental processing speed, impairment of short-term and working memory. Among these cognitive deficits, memory dysfunction is especially common [98]. What causes memory dysfunction in MS is currently unknown, but neuroimaging studies show demyelination in the hippocampal (a small region of the brain that forms part of the limbic system) structures suggesting that hippocampal pathology is involved regardless of cognitive status [99]. The number of demyelinating plaques in the *corona radiata* (a pair of white matter tracts adjacent to the body of the lateral ventricle), insula (highly important island of cerebral cortex), and hippocampus is especially correlated with cognitive impairment [100]. A study performed by Sacco et al. [101] indicated that gray matter and hippocampal atrophy occured in the MS patients with and without cognitive deficits [101]. Studies in humans and animal models have provided evidence that hippocampus plays a compelling role in spatial memory; the part of memory with an ability to regulate and encode information about the surroundings and to navigate in space [102, 103]. Nonetheless, the hippocampal involvement in cognitive functions has been poorly examined in the MS patients and the underlying pathophysiology of cognitive symptoms has yet to be unraveled. Further, increasing evidence from EAE model suggests that deficits in hippocampal-dependent learning and memory are in correlation with early microglial activation, synaptic alterations and neurodegeneration. The studies of cognitive deficit in animal model EAE can help understand the early molecular and physiologic events in the MS pathogenesis and they represent a diagnostic tool for an early diagnosis of the disease in individuals with familial susceptibility to MS [104].

Neurological and cognitive effects associated with influenza infection have been reported throughout history but the mechanisms underlying these symptoms remain unclear [105–107]. Most influenza strains, including those responsible for pandemics, are considered non-neurotropic, suggesting that neurological symptoms possibly following an influenza infection are not a result of direct inoculation of virus into the CNS areas relevant to cognitive behavior, instead it may be due to neuroinflammation induced by peripheral viral infection [108–110]. Recent experiments have been designed to investigate whether peripheral infection with influenza virus can impact the brain and behavior and to yield insight for preventing inflammation and neuronal damage associated with peripheral influenza infection. Altered cognitive behaviors accompanied by increased microglial reactivity in the hippocampus of influenza infected mice as well as influenza induced alterations in hippocampal neuron morphology provide the first evidence that neuroinflammation and architectural changes to hippocampal neurons may underlie functional deficits in hippocampal-dependent learning and memory during influenza infection as shown in the doctoral thesis done by Jurgens [111].

There is as yet insufficient data concerning the effects of influenza vaccination on cognitive function. At one point,

the goal of our team was to use a MOG induced EAE model to ascertain the effects of influenza vaccine on memory loss and locomotor dysfunctions in mice using Morris Water Maze (MWM) test. MWM is a test of spatial learning for rodents. The basic procedure for the MWM is that the rodent is supposed to find a platform, either visible (non-spatial version) or invisible (spatial version of the test), to escape the water by using various cues [112, 113]. Cognitive dysfunction in infected mice is related to their inability to efficiently navigate to the relocated platform, which is shown by an increase in time and path length to find a new platform [111]. Our findings mainly confirm that there is no effect of influenza split vaccination on memory impairment in MOG induced EAE mice and no significant influence on hippocampal-dependent spatial learning. Additionally, although clinical signs of EAE are very subtle, the lesions that have been found in the hippocampal region of the brain could be associated with memory dysfunction observed during the course of MWM testing [114]. Even though the initial studies have demonstrated that influenza infection induces deficits in spatial learning and memory loss in adult mice at day 7 post infection, conflicting data exist regarding the connection between MS and other autoimmune illnesses and vaccination [95, 111].

Conclusion

The debate as to whether vaccination brings more risk or benefit continues to be a speculative one and to date neither the advantage of vaccination has been refuted nor the vaccination related autoimmune diseases have been irrevocably proved. Nonetheless, the medical community contemplates current human vaccines, including influenza vaccine, safe and effective for patients with autoimmune diseases, and immunization is considered important for these patients not only to prevent an infectious ailment, but also to potentially prevent relapses. It has become evident that immunization *per se* is not enough for triggering autoimmune diseases, and that genetic, immunological and hormonal factors are equally involved.

A wide work is still ahead of us due to a lack of a well-established pathophysiology of the central demyelinating events and pathogenetic mechanisms underlying the adverse neurological events possibly caused by influenza vaccination.

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Conflict of interest

The authors report no conflicts of interest.

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