

## Could Autoimmunity Be Induced by Vaccination?

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*Autoimmune reactions to vaccinations may rarely be induced in predisposed individuals by molecular mimicry or bystander activation mechanisms. Autoimmune reactions reliably considered vaccine-associated, include Guillain-Barré syndrome after 1976 swine influenza vaccine, immune thrombocytopenic purpura after measles/mumps/rubella vaccine, and myopericarditis after smallpox vaccination, whereas the suspected association between hepatitis B vaccine and multiple sclerosis has not been further confirmed, even though it has been recently reconsidered, and the one between childhood immunization and type 1 diabetes seems by now to be definitively gone down. Larger epidemiological studies are needed to obtain more reliable data in most suggested associations.*

**Keywords** vaccinations, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, insulin-dependent diabetes mellitus, vasculitides

## INTRODUCTION

Several publications have reported generally anecdotal cases of autoimmune reactions after preventive anti-infectious vaccinations. Most of the available publications refer to case-reports and observational studies. Mechanisms through which vaccines may induce autoimmune diseases are mainly extrapolated by the known capacity of infectious agents against which vaccines are directed to induce autoimmunity, and by animal models and in vitro studies [1]. In this review, an attempt has

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been made to organize the topic of post-vaccine autoimmunity onset according to the proven or suggested immunological mechanisms, which may be antigen-specific (molecular mimicry) or non specific (bystander activation) [2–4] (Table I).

Molecular mimicry is based on the structural similarity between micro-organisms and host antigens, such as either the epitopes recognized by anti-group A  $\beta$ -haemolytic *Streptococcus* antibodies cross reacting with heart tissue host antigens in rheumatic fever [5] or the produced monoclonal antibodies to measles and herpesviruses cross reacting with self proteins [6]. Molecular mimicry may also be identified at T-cell level, like in the model of experimental autoimmune encephalomyelitis (EAE) induced in rabbits through the injection of a hepatitis B (HB) polymerase peptide mimicking myelin basic protein (MBP) in complete Freund's adjuvant (CFA) [7]. Another example is the herpetic stromal keratitis induced by the herpes simplex virus 1 (HSV-1) [2]. It has, in fact, been demonstrated in mice that T helper (Th)1 clones, elicited by HSV-1, were able to cross recognize an HSV-1 peptide and self antigens, such as a corneal protein and immunoglobulin (Ig) G2a. It should be underlined that the only presence of shared epitopes is not sufficient per se to induce disease, but it is necessary to have mimicry with a peptide that may be presented to autoreactive T-cell clones [4]. It should, however, be remembered that T cell recognition is characterized by a high level of polyspecificity, according to the Mason's calculation on the theoretical possibility for one T cell receptor to recognize more than one million different linear epitopes [8]. Finally, for an autoimmune disease to occur, in addition to the molecular mimicry, the contemporary presence of an infection or at least of a strong adjuvant, such as CFA, is necessary [5].

Bystander activation is mainly inferred from studies of experimental animal models and it is based on the release of sequestered self antigens from the infected host tissue, leading to activation of antigen-presenting cells, able to stimulate preprimed dormant autoreactive T-cell clones [3]. Alternatively, virus-specific T-cells may initiate the process by killing the virus-infected cells after migrating to the affected organ, thus releasing self antigen and contributing, with macrophages, to the local high cytokine levels and consequent inflammation [3]. Examples are the encephalomyelitis induced in mice by Theiler's murine encephalomyelitis virus or type 1 diabetes induced by Coxsackie B4 virus [9, 10] in mice having high levels of islet-antigen specific T-cells.

In addition to the above-reported examples, these mechanisms have been suggested or demonstrated to be involved in several additional infection- or vaccine-induced autoimmune diseases, such as treatment-resistant Lyme arthritis and *Borrelia burgdorferi sensu*

*stricto* [11], multiple sclerosis (MS) and hepatitis B (HB) vaccine [12, 13], Guillain-Barré Syndrome (GBS) and *Campylobacter jejunii* [14], or swine influenza vaccine [15] (Table I). These models represent the scientific basis for also interpreting possible post-vaccine autoimmune reactions and provide data in order to avoid molecular mimicry in the construction of new vaccines. This may be the case for group A  $\beta$ -haemolytic streptococcal vaccine or vaccine against *Neisseria meningitidis* serogroup B. It should be underlined that animal models may hardly be directly transferred to humans. Moreover, the presence of auto-reactive T-cell clones or the identification of auto-antibodies does not mean that an autoimmune disease will automatically develop following infection or vaccination. For such an event to occur, in fact, it is necessary to satisfy additional pre-conditions, including presence of stimulating cytokines in order to activate a critical mass of auto-reactive clones as well as lack of effective regulatory mechanisms [3]. Thus, the actual prevalence of autoimmune reactions to vaccination is remarkably low (much less than 1:10,000 of the hundreds of millions vaccine doses yearly administered in the world [16, 17]), probably as a consequence of the many redundant regulatory mechanisms active in the immune system [3]. Nevertheless, the experimental models may provide a biological plausibility [1] to the hypothesis of a link between vaccine administration and autoimmune disease onset, generally formulated on the basis of single case-reports. Only in a few conditions has such an association been more reliably confirmed on the basis of larger observational studies. However, for the majority of the hypothesized associations, larger, complex, and expensive epidemiological studies should be needed, but they are still lacking for the difficulty to be performed [3]. Moreover, a vaccine-related autoimmune reaction should meet a series of requirements to be actually considered vaccine-induced [18], including consistency, strength, specificity, and temporal relation. In particular, the reaction should occur in different populations and be observed by different physicians, with a strong epidemiological association, only linked to a specific type of vaccine and within a time-period of a few weeks following vaccination [3]. Recently, however, temporal relationship between either infection or vaccination and autoimmunity onset has been challenged, by suggesting a more extensive period involving months/years [19].

Comparing infection- versus vaccine-induced autoimmune reactions, the latter generally show a lower incidence, with the majority of them displaying a milder and self-limiting clinical course [17]. These observations are in agreement with a favorable cost-effectiveness ratio of vaccine use.

**TABLE I Vaccines and Autoimmune Reactions, in Which Mechanisms of Molecular Mimicry or Bystander Activation Have Been Suggested or Demonstrated**

Experimental animal models	Human vaccine	Infection	Immunological mechanism	Clinical syndrome	Mimicking antigen	Recognized autoantigen	References
		Group A $\beta$ -haemolytic <i>Streptococcus</i>	Molecular mimicry	Acute rheumatic fever	Type 5 streptococcal M protein	Cardiac myosin	5
T clones from Hepatitis B polymerase peptide + CFA <sup>a</sup> -immunized rabbits			Molecular mimicry	Experimental autoimmune encephalomyelitis	Hepatitis B virus polymerase	Myelin basic protein	7, 25
CD4 <sup>+</sup> T clones from mice		Herpes simplex virus 1	Molecular mimicry	Herpetic stromal keratitis	Herpes simplex virus 1	Corneal antigen IgG2a	2
Mice		Theiler's murine encephalomyelitis virus	Bystander activation	Encephalomyelitis			9
Mice		Coxsackie B4	Bystander activation	Type 1 diabetes mellitus			10
		<i>Borrelia burgdorferi sensu stricto</i>	Molecular mimicry	Treatment-resistant Lyme arthritis	hLFAI <sup>b</sup>	Ospa <sup>c</sup>	2, 11, 49
	<i>Borrelia burgdorferi sensu stricto</i> + aluminium hydroxide		Molecular mimicry	Arthritis <sup>d</sup>	hLFAI <sup>b</sup>	Ospa <sup>c</sup>	11, 51
	Hepatitis B			Multiple sclerosis <sup>e</sup>			12-13 30-32
		<i>Campylobacter jejunii</i>	Molecular mimicry	Guillain-Barré syndrome	Bacterial lipooligosaccharide	Peripheral nerve gangliosides	14

Influenza	Molecular mimicry	Guillain-Barré syndrome	Swine influenza vaccine	Peripheral nerve Gangliosides	15
<i>Neisseria meningitidis</i> serogroup B	Molecular mimicry		Polysaccharide B	NCAM-1 <sup>f</sup> Many foetal and adult mammalian tissues	57-59
BCG-immunized rats	Bystander activation	Myelin damage			114
T clones from <i>Mycobacterium tuberculosis</i> -immunized rats	Molecular mimicry	Arthritis	Synovial fluid Core protein Chondroitin sulphate	<i>Mycobacterium tuberculosis</i>	73
BCG	Molecular mimicry	Arthritis Uveitis	Mycobacterial antigen	DNA ?	63-75

<sup>a</sup> Complete Freund's adjuvant.

<sup>b</sup> Human leukocytes function associated antigen-1.

<sup>c</sup> Outer surface protein A.

<sup>d</sup> Arthritis after OspA vaccine has been observed but it does not seem to be due to molecular mimicry

<sup>e</sup> Only epidemiological association has been reported, not later confirmed. Recently reconsidered.

<sup>f</sup> Neural Cell Adhesion Molecule -1.

New onset of auto-antibodies not accompanied by any clinical disease after different vaccine administration has been described. Already at the beginning of the 1960s, a transient rise of rheumatoid factor (RF) after immunization of healthy people or rheumatoid arthritis (RA) patients with a variety of vaccines, including tetanus toxoid (TT), typhoid-paratyphoid A and B (TAB), diphtheria, polio, smallpox, and mumps [20, 21] had, in fact, been reported. The inactivated TAB par-enteral vaccine, but not the living oral typhoid vaccine, was able to induce a transient IgM RF positivity 15 and 30 days after vaccination, with return to baseline values by 8 months, not associated with any clinically apparent autoimmune disease [22]. An inactivated vaccine against *Coxiella burnetii*, the etiological agent of Q fever, was able to induce in recipients the onset of anti-Ig antibodies (anti-Fab [40%], anti-IgA [20%], and anti-IgG and IgM [15%]), not accompanied by any clinical sign [23]. Recently, Toplak et al. observed an increase or appearance of auto-antibodies in 15 and 13% of 92 apparently healthy medical workers (with a baseline high rate of auto-antibody positivity), 1 and 6 months after flu vaccination, respectively, suggesting de novo induction of auto-antibodies after influenza vaccination in selected individuals [24].

Clinical syndromes described after vaccination mainly include neurological pictures represented by MS, acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), GBS, and brachial neuritis (BN). Immune thrombocytopenic purpura (ITP), rheumatic syndromes, such as RA, systemic lupus erythematosus (SLE), vasculitis, reactive arthritis, Sjögren's syndrome and inflammatory myopathies (IM), myopericarditis, or finally, insulin-dependent diabetes mellitus (IDDM) have also been described [17].

## **VACCINES AND AUTOIMMUNE REACTIONS IN WHICH MECHANISMS OF MOLECULAR MIMICRY OR BYSTANDER ACTIVATION HAVE BEEN SUGGESTED OR DEMONSTRATED**

In 1985, doubt first arose that HB vaccine could induce MS, based on the observation that 4/11 rabbits, immunized with a peptide belonging to the HB virus polymerase protein identical to a region of rabbit MBP, together with CFA, developed EAE [7]. Against the supposed association of HB vaccine and MS onset mediated by a molecular mimicry process are both the observation that the only protein contained in the HB vaccine is not similar to human MBP [25] and the lack of association between MS and HB infection [26–29]. However, recombinant HB vaccine has been associated with MS onset for the first time in two patients in 1991 [12], then in 35 young women [13]. Subsequent studies

have not been able to confirm such an association [30–32] and the position of the U.S. Committee for the Immunization Safety Review is that for MS there is evidence for refusing the association between MS onset or relapse and HB vaccine, whereas, for ADEM, ON, GBS, and BN, literature data are inadequate to draw any definitive conclusion [32]. More recently, the topic has been re-evaluated through one review [33] and two case-control studies. The first study showed an increased MS risk in patients having received HB vaccine in the three years before MS onset [34]. The second study, instead, reported lack of association between HB vaccine administration and CNS demyelination in childhood, excepting for Engerix B vaccine, which seems to be associated with a higher risk, mainly for confirmed MS, in the long-term (but the authors themselves underline that these results need further confirmation in larger patient populations) [35, 36].

GBS onset has been associated with infections, such as *Campylobacter jejunii* [14] and *Haemophilus influenzae* [37], through a molecular mimicry mechanism between pathogen antigens and peripheral nerve gangliosides. GBS has also been associated with different vaccines, including rabies, polio (no more confirmed as responsible in later studies [38, 39]), TT, Bacillus Calmette-Guérin (BCG), smallpox, mumps, rubella, HB, and diphtheria [40]. However, its strongest association, probably as a consequence of a molecular mimicry process, is with swine influenza (A/New Jersey/76) vaccine in 1976–1977. Then, in the occasion of an outbreak of influenza due to a virus of swine origin in the U.S., general vaccination was recommended. It was performed in over 40 million people, but GBS developed in approximately 1:100,000 vaccinees, a rate five- to tenfold the background rate [41–44], probably due to cross-reacting antibodies against peripheral nerve gangliosides that may develop after vaccination with the influenza virus of swine origin [15]. To our knowledge, no report has been produced, until now, on specific association between GBS and swine influenza vaccination during the 2009 pandemic. This may be due to the evolution from the 1976 to the 2009 viral strain, which only shows a partial identity with the 1976 virus, of 88.6% by nucleotide and 90.8% by amino acid sequence [45]. The Committee for the Immunization Safety Review considered only swine A/New Jersey/76 strain actually associated with a higher risk of developing GBS. Instead, the same Committee considered the literature data to sustain the same interpretation also for influenza vaccination performed after 1976, despite reports of small, but significant, risk for flu vaccines of 1992–1993 and 1993–1994 seasons [46–48] to be inadequate.

Even in the case of *Borrelia burgdorferi sensu stricto*, the etiological agent of Lyme arthritis, a molecular mimicry among outer surface



protein A (OspA) and human alpha myosin heavy chain [11], human leukocyte function associated antigen 1 (hLFA 1) $\alpha$  [49] or neural tissue [50] has been found. In spite of these demonstrations, arthritis arising in vaccine recipients does not seem to be due to a mechanism of molecular mimicry, as recently reported [51]. However, being responsible of the autoimmune manifestations or not [2], such a broad molecular mimicry widely justified the efforts to try to modify existing vaccines in order to avoid any antigenic similarity between vaccine and host [52].

The situation of *Borrelia burgdorferi sensu stricto* with OspA is strictly reminiscent of that of group A  $\beta$ -haemolytic *Streptococcus* M proteins and tropomyosin [53]. OspA and M5 protein, in fact, share antigenic similarity [11], such that in the preparation of a rheumatic fever vaccine [54], the crucial point of molecular mimicry should also very carefully be taken into account.

More recently, *Neisseria meningitidis* serogroup B has been recognized having a capsular polysaccharide identical to the capsular polysaccharide of *Escherichia coli* K1 and *Pasteurella haemolytica* A2 [55] and to the surface component of many fetal and adult mammalian tissues and of the neural cell adhesion molecule (N-CAM) [56–58], thus creating concern that vaccine-induced specific antibodies may be dangerous by exerting autoimmune pathology [59]. The difficult way toward a meningococcus B vaccine, therefore, has considered the possibility of including protein components of the micro-organism instead of the polysaccharide in the composition [60, 61]. For its molecular mimicry with neural mammalian tissues, in fact, this latter may be either scarcely immunogenic or potentially dangerous, even though a formal demonstration of its autoimmune pathogenicity has never been provided [62].

Since the pioneering description of Torisu et al. [63] on the BCG-induced arthritis in 10 out of 159 patients during BCG immunotherapy, additional cases have been reported. Tinazzi et al. in 2005 performed an analytical literature review and could identify at least 57 patients with new onset arthritis after treatment with intravesical BCG for bladder cancer [64]. Since then, five further cases have been reported [65–69]. Also uveitis has been described in patients treated with intravesical BCG for bladder cancer, and it has been interpreted as a consequence of a molecular mimicry process [70, 71]. Since the 1980s, in fact, experimental demonstrations of broad molecular mimicry at cellular and humoral levels have been provided. In 1982, Glynn et al. induced in guinea pigs chronic relapsing EAE by inoculating homologous spinal cord in CFA containing heat-killed *Mycobacteria tuberculosis* and they could demonstrate that the oligoclonal IgG bands found in serum and cerebrospinal fluid (CSF) largely contained anti-mycobacterial and anti-spinal



cord antibodies [72]. In 1985, van Eden and colleagues showed in an animal model that a *M. tuberculosis*-specific T cell clone was also able to recognize antigens belonging to human joint proteins [73]. In the same year, Thorns et al. reported that monoclonal antibodies against mycobacterial antigens were widely cross reactive with host tissue antigens [74], and in 1986, Shoenfeld et al. [75] described that monoclonal antibodies elicited towards either *M. tuberculosis* or anti-DNA could cross recognize mycobacterial cell wall and DNA.

Several infectious agents have been associated with IDDM onset acting through different hypothesized pathogenetic mechanisms, including molecular mimicry, bystander activation, or direct viral  $\beta$ -cell infection [76]. Molecular mimicry with host islet cell antigens has been mainly invoked in relation to enteroviruses [76], rotavirus [77], cytomegalovirus [78], and rubella [79] infections. In particular, it should be taken into account in the construction of a possible enteroviral vaccine, although this mechanism has not been demonstrated being able to induce autoimmunity in the case of polio vaccine [80]. Other pathogenetic mechanisms that have been involved in type 1 diabetes induction are related again to rubella [81–83] and cytomegalovirus [84] and also to mumps [85]. The role of vaccinations as possible IDDM inducers has been largely debated. Moreover, for some vaccines, also a protective effect has been envisaged, such as for mumps [86], measles [87, 88], and BCG [89]. However, a stimulating role of vaccination on IDDM onset has also been described, perhaps linked either to a nonsufficient viral attenuation [90] (one nonsufficiently attenuated mumps vaccine strain has, in fact, been demonstrated, also at molecular level, as being responsible for early post-vaccine mumps-like disease [91]) or to an inadequate and nonprotective specific antibody response to mumps antigen. In fact, Hiltunen et al. observed IDDM development on average 2.5 years after measles/mumps/rubella (MMR) vaccine administration in 364 healthy children. They associated it to a defective post-vaccine mumps-specific antibody response, which may expose to a major risk of pancreatic  $\beta$ -cell damage, induced by natural mumps infection [92]. It should be underlined that also measles vaccination has been reported as protective in a study of 339 Swedish children with recent onset diabetes [88]. In the same study, instead, tuberculosis, smallpox, TT, pertussis, rubella, and mumps vaccines did not seem to influence the diabetes onset. Even nonspecific immune stimulation with BCG has been attempted to prevent IDDM development in clinical and experimental models, with controversial results [93–98]. Moreover, it has been proposed that immunization within the first year of life may be protective for IDDM onset [99], but such hypothesis has not been later confirmed [100]. *Haemophilus influenzae* type b (Hib) vaccine

itself [101] and its timing administration [102] have also been linked to the risk of developing IDDM, but such association has not been found by further studies [103, 104]. In 2001, DeStefano et al. published a large study with the aim of providing a definitive answer to the possible interference of different types and timing of vaccination. The results did not support an association between either any recommended childhood vaccine or timing of administration and an increased risk of IDDM [105]. Later, in 2004, Hviid and colleagues confirmed these observations through a careful study on Danish children born from January 1, 1990 through December 31, 2000, in whom IDDM onset has not been causally associated with childhood vaccinations, including Hib, diphtheria, TT, MMR, inactivated or oral polio virus (OPV), and acellular or whole-cell pertussis [106].

The mechanism of bystander activation should probably be invoked when the vaccine composition contains many pro-inflammatory non specific antigens, including the lipid A fraction of lipopolysaccharides (LPSs) [107], acting as adjuvants, such as the poorly purified vaccines (whole-cell pertussis, TAB), able to strongly stimulate innate immunity through the Toll-like receptors (TLRs). The examples of pertussis or typhoid are paradigmatic: as soon as the whole-cell pertussis vaccine has been replaced by the acellular purified, the adverse reactions at CNS level disappeared [108]. In analogy, after introduction of the living oral vaccine as a substitute for the inactivated and not purified TAB parenteral vaccine, the local and systemic clinical reactions as well as the transient IgM RF positivity have not been observed any more [22]. Bystander activation may also be invoked for the adjuvants, which are substances able to “accelerate, prolong, or enhance antigen-specific immune responses” [107]. The mechanism of action of the until now most used adjuvant in humans, that is the alum (aluminium phosphate or aluminium hydroxide), has been recently elucidated; it may stimulate local inflammation through the release of pro-inflammatory cytokines and activate the intracellular innate immune response system, the Nalp3 inflammasome [109], and dendritic cells, probably through uric acid release [110]. Alum has been implicated as a possible inducer of macrophage myofasciitis, a new autoimmune syndrome [16, 107], clinically characterized by arthromyalgias and fatigue [111] and at a histological level by muscle infiltration of aluminium-engulfed macrophages and lymphocytes [112]. Finally, BCG is a strong inducer of pro-inflammatory cytokine-secreting Th1 lymphocytes [113], thus mimicking the final effects, although through a different immunological mechanism, of the classical adjuvants. BCG is, in fact, composed of attenuated living *Mycobacterium bovis*, thus similar in its composition to the most used adjuvant in animals, CFA,

which is composed of water-in-oil emulsion with killed mycobacteria. An example of BCG-induced damage through a bystander activation mechanism is the Matyszak and Perry observation that intracranial, followed by subcutaneous, BCG injection in rats could induce a bystander myelin damage [114].

### **VACCINES AND AUTOIMMUNE REACTIONS IN WHICH MOLECULAR MIMICRY OR BYSTANDER ACTIVATION MECHANISMS HAVE NOT BEEN SUGGESTED OR DEMONSTRATED**

ITP occurring after MMR vaccine administration has been considered causally linked to vaccine [1] and calculated at a rate of 1:30,000 [115], a risk tenfold lower than that occurring during natural rubella infection [116] and fivefold lower than that reported during measles infection [117] (Table II). The mechanism of autoimmune reaction is unknown, but it may probably be ascribed to the same one invoked in the course of natural disease [118, 119]. In particular, it has been hypothesized as an immune response to infected megakaryocytes or precursors [120]. A recent study on 24 children with post-MMR vaccine ITP occurring within 1 month from vaccination was able to confirm the risk of 1:30,000 vaccinations and could establish that in the majority (74%) of cases the disease disappeared in 1 month, whereas in a minority (10%) it happened in 6 months [121].

Recently, a slight, but statistically significant, association has been found between tetravalent diphtheria toxoid-conjugated meningococcal vaccine and GBS (1.25 of risk per million doses distributed to persons aged 11–19 years) [122].

Encephalopathy or encephalomyelitis occurring after smallpox vaccination, with an incidence of 1:110,000 [123], is among the adverse events that have been more frequently interpreted as due to an autoimmune reaction. More recently, in over 450,000 U.S. immunized military (70.5% first vaccination; 29.5% re-vaccination), 37 cases of acute myopericarditis have been observed, a rate of 8.2:100,000 vaccinees [124]. Among the over 230,000 primary immunized U.S. military, 18 cases of probable myopericarditis have been reported, a rate of 7.8:100,000 [125]. Moreover, a few cases of central or peripheral neuritis have also been described and attributed, like myopericarditis, to vaccine-associated autoimmunity [40].

Recently, Agmon-Levin et al. have analytically reviewed the TM cases arising after vaccination in the period 1970–2009, and they could identify 37 cases occurring between 1971 and 2007 after different vaccine administration, including HB, MMR, diphtheria/pertussis/tetanus

**TABLE II Vaccines and Autoimmune Reactions in Which Molecular Mimicry or Bystander Activation Mechanisms Have Not Been Suggested or Demonstrated**

Autoimmune disease	Vaccine	Rate or number of reported cases	References
ITP	Measles/Mumps/Rubella	1:30,000	115–116
GBS	Menactra®	0.2:100,000 person-months	122
Myopericarditis	Smallpox	8:100,000	123–125
Transverse myelitis	Different vaccines	37 cases in the period 1971–2007	126
Encephalomyelitis-polyneuritis	Semple Rabies vaccine	0.1–0.2:100,000	17, 127
Encephalitis-ADEM-GBS	Yellow Fever	0.4–0.58:100,000	129–130
Vasculitides	Influenza–Hepatitis B–other vaccines	48 cases since 1974	135–154
Inflammatory myopathies	Different vaccines	13 cases	155
SLE	Hepatitis B and other vaccines	25 cases	19, 156–165
RA	Hepatitis B–Tetanus–Anthrax Diphtheria/Tetanus/Polio	16 cases	141, 165–172

ITP: Immune thrombocytopenic purpura; GBS: Guillain-Barré syndrome; ADEM: Acute disseminated encephalo-myelitis; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis.

(DPT), rabies, OPV, influenza, typhoid, pertussis, and Japanese encephalitis. The most frequently reported vaccine was HB, associated with 13 TM cases, followed by MMR in 6 cases, DPT and rabies in 4 cases each, OPV in 3 cases, and influenza in 2 cases. The authors underline that the involvement of different vaccines allows the hypothesis that the cause of TM onset could be ascribed to a common factor, such as a common adjuvant [126].

Major neurological complications of Semple rabies vaccination are encephalomyelitis and polyneuritis accompanied by the presence of serum and CSF high level antibodies towards MBP, cerebroside, and certain gangliosides [127]. Moreover, in subjects immunized with Semple rabies vaccine, the presence of anti-cardiolipin antibodies, directly correlated with the severity of neurological complications, has also been reported [128].

Yellow fever vaccine has been related to neurological complications, including encephalitis, ADEM, and GBS [129]. During a vaccination campaign in Kenya in the first half of the 1990s, the incidence of

post-vaccine encephalitis has been quoted 5.8 per million immunized people [130]. Neurological complications, including encephalitis, ADEM, or GBS, in the U.S. in 2005, have been estimated to be four per million distributed doses [131], a figure not dissimilar from what has been reported from the U.K. [132, 133].

In 2007, a single case of autoimmune hepatitis after HA vaccine had been described [134], although this vaccination had only very rarely been involved in other autoimmune diseases, such as encephalopathy or vasculitis in two subjects and joint disease in another two [17].

Forty-eight cases of vasculitis onset after vaccinations have been described in the literature since 1974, and a causal relationship has been suggested. The most implicated vaccine is influenza, involved in at least 30/48 described cases [135–143], followed by HB in 12 cases [144–153], whereas single cases have been associated to meningitis C (Men C), HA, pneumococcus, BCG, measles [135], and anthrax [154] vaccines. The mechanism of such association is not clear, but it has been postulated to be related to the presence of underlying asymptomatic autoimmune disease, which may be triggered by vaccination in predisposed individuals [143].

Inflammatory myopathies (IM), including polymyositis, dermatomyositis, and juvenile dermatomyositis, have been rarely described after different vaccine administration in anecdotal cases. A recent review by Orbach and Tanay reports 13 IM after DPT (4 cases), HB vaccine (3 cases), BCG (2 cases), smallpox (1 case), influenza (1 case), and inactivated polio (1 case) [155].

SLE onset after vaccination has also been rarely reported. Already in 1948, Ayzavian and Bagder described three fatal SLE cases following TAB parenteral vaccine and scarlet fever *Streptococcus* toxin administration in 750 healthy subjects [156]. After a long silent period, in 1992 SLE onset in a young woman two weeks after the first dose of recombinant HB vaccine has been reported [157]. Moreover, additional cases represented by a girl, two young women, two members of the same family, and another young woman with a family history of autoimmune diseases, developing symptoms of SLE one to a few weeks after HB vaccine administration, have also been described [158–162]. SLE onset has finally been observed in five U.S. soldiers 2–3 weeks after having received several immunizations [163]. In a case-control study on 265 SLE patients and 355 healthy controls, HB vaccination, however, has not been identified as a risk factor for SLE onset [164]. On the contrary, a case-control study on database from the vaccine adverse event reporting system (VAERS) could establish that HB vaccine compared to TT represented a risk factor for different autoimmune diseases, including SLE and RA [165]. Very recently, ten additional SLE

cases have been described in a period ranging from days to up to one year following HB vaccination [19].

Arthritis has also been associated with immunizations, mainly HB vaccine [166–170]. Three cases of arthritis onset after HB vaccination, two of whom with a clinical pattern of reactive arthritis, the third of RA, have, in fact, been reported [166]. Vautier and Carty described another RA appearance in a previously healthy woman within 24 hr from the first HB vaccine administration [167]. RA development in six women in a period ranging from 1–20 days after HB immunization has also been reported [168]. Pope and co-workers reported five firefighters who developed persistent arthritis after recombinant HB vaccine, four of which resembled RA [169]. Moreover, they reported six additional arthritis cases after HB vaccine. HLA DR-4 was frequently present in the above described patients. TT has also been described as a possible RA inducer, and a combined vaccine against diphtheria, poliomyelitis, and TT has been associated with the onset of arthritis [171]. Anthrax vaccine has also been implicated as a possible RA inducer and, in fact, in 2006 the fifth RA case temporally related to anthrax vaccine had been reported [172]. Finally, Pou et al. described one patient who developed RA one month after influenza and TT vaccinations [141].

## CONCLUSIONS

Among the several reports of autoimmune diseases whose onset has been attributed to vaccinations in predisposed individuals, those reliably vaccine-associated may be considered GBS after 1976 swine influenza vaccine, ITP after MMR vaccination [3, 114, 173], and myopericarditis after smallpox vaccination [114], whereas the suspected association between HB vaccine and MS [12, 13] has not been subsequently confirmed [30–32], even though it has been recently reconsidered [32–35], and the one between childhood immunization and IDDM seems, by now, to be definitively reduced [17, 105, 106]. However, the need to perform larger and well-constructed epidemiological studies on vaccine-related autoimmunity onset, in order to obtain more reliable data, should be underlined.

In conclusion, the relationship between vaccinations and autoimmune diseases should be considered in a complex and bidirectional way; vaccinations, in fact, prevent infections, which may in turn trigger autoimmunity, but, on the other hand, vaccinations themselves, by a specific mechanism of molecular mimicry, or a non specific mechanism of bystander activation or finally by yet unknown mechanisms, may trigger autoimmunity [174]. However, although vaccine administration has been associated with autoimmune manifestations in selected

predisposed individuals, who may not be currently identified [3], their very low incidence and mild clinical course, generally lower and milder than those associated with natural infections [17], combined with the general lack of high level of evidence, should not induce to abstain from the immunization practice considering the favorable cost-effectiveness ratio of vaccine use. However, areas of research still include the need to develop autoimmune clinical and serological monitoring during pre-registration studies [3], perform genetic and proteomic systematic studies in order to identify possible predisposed individuals, and finally, further clarify underlying immunological mechanisms exerted by vaccines/adjuvants.

### Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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