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Review

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects

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ABSTRACT

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post-vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hypothesized to be involved in the onset of adjuvant-induced autoimmunity; a genetic favorable background plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

1. Introduction

Shoenfeld and Agmon-Levin recently coined the term "ASIA–Autoimmune/inflammatory Syndrome Induced by Adjuvants" [1] to describe an "umbrella" for clinical conditions namely siliconosis, Gulf War Syndrome (GWS), Macrophage Myofasciitis Syndrome (MMF), sick building syndrome (SBS) and post-vaccination phenomena which share similar signs or symptoms [2–6]. The most frequently reported symptoms include myalgia, myositis, arthralgia, neurological manifestations, fever, dry mouth and cognitive alterations. Moreover, really common is the presence of chronic fatigue syndrome (CFS) [7], often associated with sleep disturbances or non-restful sleep. These shared symptoms suggested the presence of a common denominator which has been subsequently identified in the adjuvant. The adjuvant is defined as "any substance that acts to accelerate, prolong, or enhance antigen-specific immune response" [8]. It is an agent that may stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect in itself. The abovementioned syndromes, are immune mediated conditions that appear following a chronic stimulation of the immune system by agents with adjuvant characteristics. The prevalence of immune mediated conditions is rising in different geographical areas and these geo-epidemiological changes may be explained by a complex of genetic and environmental factors [9,10]. While specific genetic compositions may predispose to the emergence of an autoimmune or an auto-inflammatory syndrome, the presence of an external or endogenous environmental factor, recently called "exposome" [11], is essential for triggering the immune response itself. The presence of a favorable genetic background as a prerequisite for the development of such conditions explains why they are so rare [12]. It also clarifies why physicians should be aware of the possible complications that may occur post vaccination, in these specific individuals [13]. Silicone, alum, pristane and infectious components are some of the environmental factors that comprise an immune

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adjuvant effect. Also other oil substances, sometimes illegally injected for cosmetic purposes, may have an immune adjuvant effect and are reported as possible inducers of ASIA [14]. These adjuvants seem to be able to induce autoimmunity both in animal models and in humans [15,16]. The mechanisms which have been proposed as instrumental in ASIA, are different (Table 1).

One particular example is that of molecular mimicry, which refers to the concept that an immune response, initially directed at bacterial or viral antigens, can target host molecules that share sequence homology or structural similarities with microbial epitopes [8]. Adjuvants accomplish this task by mimicking specific sets of evolutionarily conserved molecules (liposomes, LPSs, unmethylated CpG dinucleotide-containing DNA, etc.). On the other hand, other possible involved mechanisms which may induce autoimmunity are the polyclonal activation of B cells [17], the bystander activation which enhances cytokine production and further induces the expansion of auto-reactive T cells [18], and finally the epitope spreading by which invading antigens accelerate the local activation of antigen presenting cells and the over processing of antigens [19]. Major and minor criteria have been proposed that may aid in the diagnosis of ASIA syndrome [1] (Table 2).

These criteria were further validated by Zafrir et al. [20]. In this study on ninety-three patients who suffered from a constellation of symptoms, including neuropsychiatric, fatigue, muco-cutaneous, musculoskeletal and gastrointestinal complaints with elevated titers of autoantibodies documented in 80% of sera tested, 86% of the patients fulfilled the proposed criteria of ASIA [20].

Thus, in the following paper, we will detail the protean facets which are part ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to such autoimmune/inflammatory response.

2. ASIA: a deep insight into mechanisms

The pathogenesis of the ASIA syndrome is founded on the hypothesis that an early exposure to an adjuvant may set in motion a chain of biological and immunological events that, in susceptible individuals, may ultimately lead to the development of autoimmune disease. Recent studies advocate that a web of mechanisms underlie this phenomenon, in particular, in relation to aluminum based compounds (Alum) which comprise a major bulk of contemporary adjuvants. Several theories have been suggested for the pathogenesis of the ASIA syndrome in general and for the adjuvanticity of alum in particular (Fig. 1).

Table 1
Suspected mechanism of adjuvant-induced autoimmunity. Several are mimicking the effect of viruses and bacteria in eliciting the immune responses.

Suspected mechanisms of adjuvants-induced autoimmunity
- Alteration of the host's immune system
- Polyclonal activation of B cells
- Effects on cellular immunity
- Effects on immune regulatory cells
- Effects on viral induced antibodies
- Molecular mimicry
- Bystander activation
- Epitope spreading
- Anti-idiotypic network
- Changing the host's antigens
- Expression of HLA* family antigens
- Modification of surface antigens
- Induction of novel antigens
- Interaction with Toll-like receptors (TLRs)
- Antigens translocation
- Release of inflammatory cytokines

*HLA: Human leukocyte antigen.

Table 2
Proposed criteria for the diagnosis of 'ASIA'.

Major criteria:
Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
The appearance of 'typical' clinical manifestations:
• Myalgia, Myositis or muscle weakness
• Arthralgia and/or arthritis
• Chronic fatigue, un-refreshing sleep or sleep disturbances
• Neurological manifestations (especially associated with demyelination)
• Cognitive impairment, memory loss
• Pyrexia, dry mouth
• Removal of inciting agent induces improvement
• Typical biopsy of involved organs
Minor Criteria:
The appearance of autoantibodies or antibodies directed at the suspected Adjuvant
Other clinical manifestations (i.e. irritable bowel syn.)
Specific HLA (i.e. HLA DRB1, HLA DQB1)
Evolvement of an autoimmune disease (i.e. MS, SSc)

3. Alum as an adjuvant

In 1926, Glenny and coll [22] described for the first time that the precipitation of an antigen onto insoluble particles of aluminum potassium sulfate, also known as 'potash alum', before immunization was responsible for better antibody responses than that of soluble antigen alone. Since this discovery and for approximately 60 years, alum was believed to induce a "depot effect": an alum induced consolidation of the desired antigen at the injection site, resulting in slow release of the antigen to antigen presenting cells for an extended period of time. However, that theory was then refuted [23] and interest in aluminum salts has progressively been reignited in the past two decades. In 2002, HogenEsch investigated the mechanisms by which aluminum compounds function as adjuvants. He reported that aluminum salts induce activation of dendritic cells and complement components and increase the level of chemokine secretion in the injection site [24]. These facts were even more substantiated in face of the elaborated research conducted by Flach et al. [25]. From their study, they concluded that aluminum based salts firmly bind to and alter the structure of lipids in the dendritic cells' plasma membrane. The alteration in focal lipid composition results in phagocytosis and delivery of the admixed soluble antigen across the plasma membrane via the endocytic pathway. Therefore, inducing primarily a TH2 immune response which is facilitated by the strong binding of dendritic cells to CD4+ T-cells and subsequent activation of B cells. In addition, it is noteworthy that TLR signaling is not mandatory for the induction of alum associated antibody responses [26]. However, although it is a common belief that alum induces predominantly a TH2 response, recently Tomljenovic and Shaw [27] suggested that aluminum induced TH2 responses can be diverted toward TH1 responses in the presence of TH1 inducing compounds. This may serve to clarify the link between aluminum based adjuvant vaccines and the development of autoimmune diseases characterized by an excessive TH1 immune response in the ASIA spectrum. The NLRP3 inflammasome is a large cytoplasmic complex of proteins that regulates the proteolytic activation of the proinflammatory cytokines IL-1β and IL-18 in response to microbial products and metabolic stress [28]. The role of the NLRP3 inflammasome was thought to be pivotal for the adjuvanticity of alum [29–31]. However, recent evidence suggests that alum adjuvanticity is not compromised in the absence of inflammasomes, as production of cytokines other than IL-1β (e.g. TNF-α) and surface co-stimulatory molecule upregulation (e.g. CD80, CD86, CD40) are not influenced

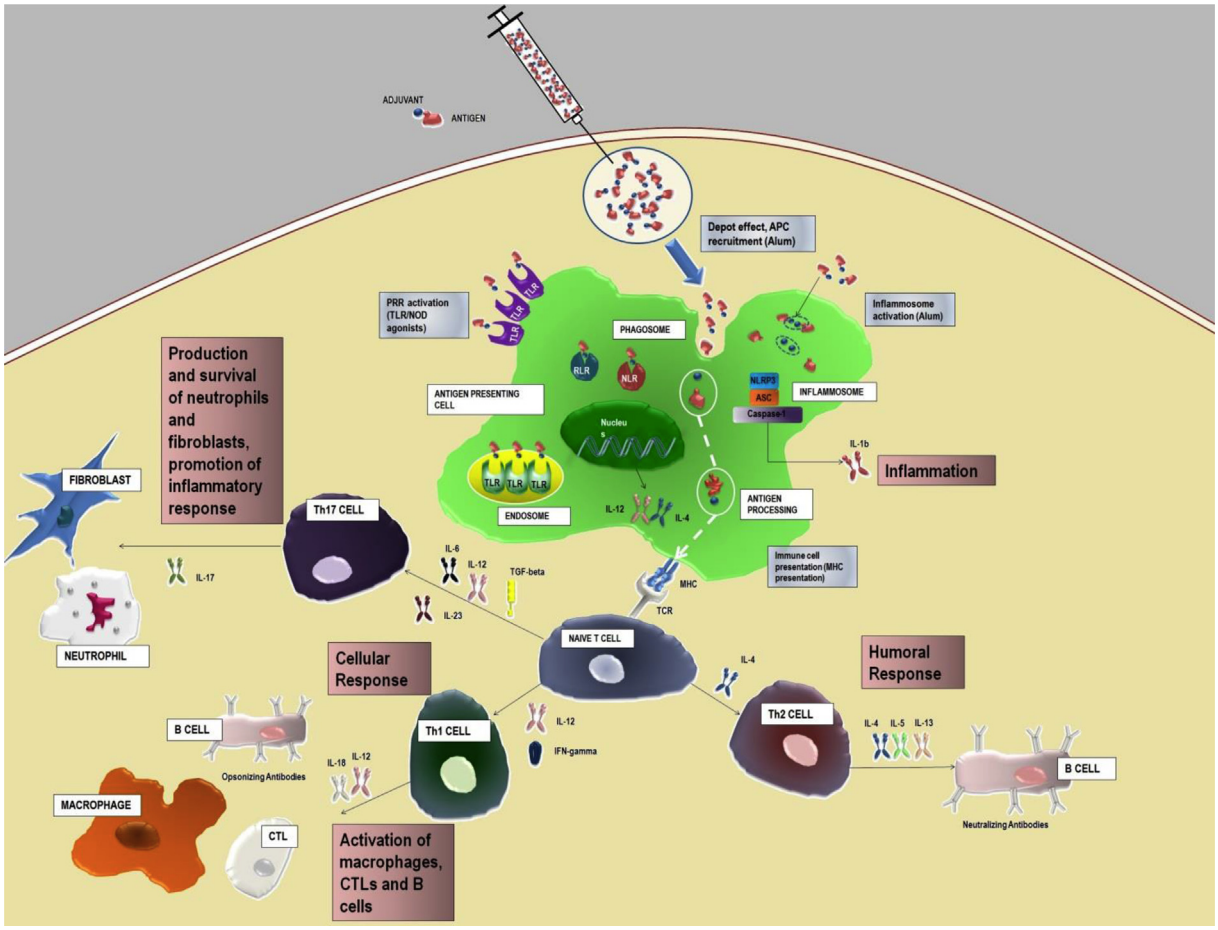

Fig. 1. Mechanisms of adjuvants' effect. 1. Adjuvants (mainly alum) may function as delivery systems by generating depots that trap antigens at the injection site, providing slow release in order to continue the stimulation of the immune system, thus enhancing the antigen persistence at the injection site and increase recruitment and activation of antigen presenting cells (APCs) (depot's effect). 2. Other adjuvants, essentially ligands for pattern recognition receptors (PRR), act by inducing the innate immunity by targeting the APCs via Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs). The downstream signaling pathways leads to the activation of transcription factors such as NF-κB and IRF3. The consequence is the induction of cytokines and chemokines that play a key role in the priming, expansion and polarization of the immune responses. 3. Activation of members of the NLR family, such as NLRP3 and NLRC4, triggers the formation of the inflammasome leading to the production of the pro-inflammatory cytokines IL-1β and IL-18. 4. Adjuvants can direct support antigen presentation by the major histocompatibility complexes (MHC). 5. Adjuvants are essential for enhancing and directing the adaptative immune response to vaccine antigens. This response is mediated by two main types of lymphocytes, B and T cells. Most antigens activate B cells by activated T helper (Th1 and Th2 cells). The Th1 response leads mainly to a cellular response which protects against intracellular pathogens. Indeed, Th1 cells secrete IFN-γ, which activates macrophages and induces the production of opsonizing antibodies by B cells. The cytotoxic T lymphocytes (CTLs) are also induced allowing the killing of infected cells. On the other hand, Th2 cells induce a humoral response crucial in the defense against extracellular pathogens. Th2 cells secrete cytokines, including IL-4, which promote the secretion of neutralizing antibodies by B cells. Th17 cells are essential in the promotion of inflammation through activation of neutrophils and fibroblasts, via IL-17/IL/23 pathway. (modified from Ref. [21]).

by the loss of the inflammasome. This data serves to suggest that membrane proximal events unrelated to the NLRP3 inflammasome are sufficient to mediate dendritic cell activation in response to alum [25]. Another fact related to the adjuvanticity of aluminum compounds refers to their association with uric acid. When crystallized, uric acid is considered a natural endogenous danger signal. Alum is believed to promote an inflammatory response which results in the release of uric acid from necrotic cells. In turn, uric acid is thought to increase the adjuvanticity of alum with an apparent rise in IL-4 levels. Thus, it is not surprising that the inhibition of uric acid formation and the facilitation of uric acid degradation both result in a suppression of alum's adjuvanticity, as evident by a further decrease in IL-4 levels [32,33]. IL-4 itself is related to alum adjuvanticity as up-regulation of monocytic cell surface MHC class II, a crucial component in the development of innate immunity, is dependent on IL-4 levels [34]. Another danger signal hypothesized to enhance the adjuvanticity of alum is host cell DNA which is released from necrotic cells [35]. In susceptible individuals, aluminum based adjuvants can induce autoimmune disease. This phenomenon, though rare, occurs to an unknown extent. Autoimmune/inflammatory diseases correlating with alum based vaccinations encompass conditions such as arthritis, type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, chronic fatigue syndrome, and Gulf War syndrome [27]. Furthermore, aluminum based adjuvants were found to be associated with macrophagic myofasciitis, granuloma formation and allergic reactions due to an increase in IgE levels mediated by alum stimulation [36]. One typical autoimmune disease that may be instigated by the influenza or polio vaccines is Guillain–Barré syndrome. This may be partially due to molecular mimicry, a process in which sequence similarities amongst foreign and self-peptides are sufficient to promote the cross-activation of auto-reactive T cells by viral peptides [37]. Another example of molecular mimicry may be the possible triggering of antiphospholipid syndrome due to tetanus vaccine. This was achieved in an experimental model conducted by Zivkovic et al. [38]. Cross reactivity is defined as the reaction

between an antibody and an antigen which is different from the original immunogen. A possible vaccine related example of immunological cross reactivity, is the autoimmune demyelinating disease multiple sclerosis. This disease may arise due to an antecedent hepatitis B surface antigen vaccine [39]. Experimental autoimmune encephalomyelitis, a model of multiple sclerosis, is known to be enhanced by the administration of *Bordetella pertussis* toxin. Nevertheless, repetitive exposure to the *B. pertussis* toxin was shown to exert protective properties against autoimmune disease on the CNS in mice. This is, presumably, due to the upregulation of anti-inflammatory cytokines and expansion of peripheral T regulatory cells [40]. Yet, another disease thought to be related to aluminum compound exposure is Alzheimer's disease. Growing evidence suggests that the pathogenesis of Alzheimer's disease relates to the accumulation and aggregation of β-amyloid in the grey matter of the brain. In a study conducted by Kawahara et al. [41], it was found that aluminum compounds accelerate the polymerization of β-amyloid and form stable oligomers. Furthermore, they concluded that chronic administration of aluminum compounds caused the accumulation of β-amyloid in several neuronal in vitro models [41]. In addition, aluminum, which was integrated in dialysis solutions, was also known to cause dialysis encephalopathy. Most interestingly, the tau protein – a protein associated with dementia and Alzheimer's disease, was found to accumulate in dialysis patients [42]. Another association between vaccination and autoimmune disease was found by Miller et al., who described an association between the measles vaccine and idiopathic thrombocytopenic purpura [43]. Table 3 summarizes the possible specific mechanisms relating to the adjuvanticity of aluminum compounds.

4. Gulf War syndrome

Gulf War syndrome (GWS) is a clinical condition characterized by the presence of several signs or symptoms: muscle fatigue and tiredness, malaise, myalgia, impaired cognition, ataxia, diarrhea, bladder dysfunction, sweating disturbances, headaches, fever, arthralgia, skin rashes, and gastrointestinal and sleep disturbances [44]. In addition, chemical sensitivity and odor intolerance have been reported. Although the etiology of this syndrome is still not clear, a number of reviews and epidemiological analyses suggest that the exposure to several substances, such as pyridostigmine bromide (PB, used as nerve gas prophylaxis) [45,46], insect repellent, vaccinations, smoke from oil-well fires [47], or depleted uranium from shells [48] could be the cause. Moreover the association with physical and psychological stress has been taken in consideration. Different studies have compared the prevalence of chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), chronic multi-symptom illness (CMI), fibromyalgia, or symptoms of either fatigue or numbness and tingling in Gulf War veterans and non-Gulf veterans [49]. They demonstrated that gulf deployment was most strongly associated with CFS and Gulf War veterans were also approximately three and a half times more likely to report MCS or CMI. The most prevalent symptom in GWS was chronic fatigue [50,51]. Moreover, disabled Gulf veterans were more likely to be overweight, have elevated gammaglutamyltransferase levels, to screen positive for hypertension and, compared with asymptomatic veterans, to experience sleep disordered breathing [52]. Interestingly, among veterans of the Gulf War there was a specific relation between multiple vaccinations given during deployment and later ill health. Multiple vaccinations in themselves do not seem to be harmful but combined with the "stress" of deployment they may be associated with adverse health outcomes [53]. It has been suggested that such mass-vaccination caused a shift in immune response towards a type 2 cytokine pattern (Th2) [54], which was suggested to be accompanied by a CFS-like illness. Moreover, serological abnormalities including hypergammaglobulinemia and abnormal serum proteins have been reported in 45% of GWS patients [55]. Injection of either silicone gel or silicone oil intraperitoneally resulted in high titers of autoantibodies to cholesterol [56]. The silicone component serves as an adjuvant as well as initiates the autoimmune process [57]. This finding points to the pivotal role of the multiple vaccinations given to the veterans in a short period, in the etiology of GWS. In conclusion, regardless of its etiology, GWS fits well with the definition of ASIA and is included as a part of 'Shoenfeld's syndrome'.

Table 3
Specific mechanisms relating to the adjuvanticity of aluminum compounds.

Mechanism
• Depot effect – alum induced consolidation of the desired antigen at the injection site results in slow release of the antigen to antigen presenting cells for an extended period of time.
• Activation of dendritic cells by lipid sorting – aluminum salts induce activation of dendritic cells and complement components and increase the level of chemokine secretion in the injection site. Aluminum based salts firmly bind to and alter the structure of lipids in the dendritic cells' plasma membrane.
• NLRP3 Inflammasome independent dendritic cell activation - membrane proximal events unrelated to the NLRP3 inflammasome are sufficient to mediate dendritic cell activation in response to alum.
• Uric acid augments the effect of alum's adjuvanticity – increase in uric acid mediates upregulation of MHC class II in monocytes via an IL-4 dependent mechanism.
• Host cell DNA – enhances the adjuvanticity of alum
• Alum dependent increase in IgE levels – promotes allergy
• Alum promotes the formation of amyloid plaque – by catalyzing the polymerization of β-amyloid
• Alum may increase the levels of the Tau protein

5. Macrophagic myophasciitis

In 1998 an emerging condition of unknown cause characterized by a pathognomonic lesion at muscle biopsy called macrophagic myofasciitis (MMF) has been described [58]. These lesions, with a maximum size of 1 cm, were mostly present in deltoid muscle and could be differentiated from Whipple's disease and other infectious histiocytoses, and from diffuse dysimmune fasciitis and panniculitis. MMF was detected in middle-aged adult patients with diffuse myalgias and fatigue [59]. Macrophages were the major cell type in the lesion, and enclosed agglomerates of nanocrystals in their cytoplasm contained aluminum were found [60]. Concerning the histopathological findings, typical is the presence of focal infiltration of the epimysium, perimysium and perifascicular endomysium by monocyte and macrophages, usually intermingled with a minor lymphocytic population [58]. Studies have demonstrated that alum particles injected into mouse muscle are taken up by macrophages to form a MMF-like granuloma and an important proportion of particles escape the injected muscle mainly within immune cells. These alum-like particle loaded cells access to the regional lymph nodes and then gain access to distant organs such as spleen, liver and, eventually brain, especially if they produce attracting signals for inflammatory cells or exhibit weak blood brain barrier [61]. The common soil in patients with MMF development was the previous immunization against different vaccines [hepatitis B (HBV), hepatitis A (HAV) or tetanus toxoid (TT)] which contained aluminum oxyhydroxide as adjuvant. MMF is now recognized as a long lasting persistence of alum in the site of muscle injection. Gherardi et al. [62] published in 2003 a review on 457 adults with MMF (70% female; a middle age at biopsy of 45 years) who, in the 10 years before, received 1 to 17 intramuscular administration of alum-containing vaccine (85% of cases HBV

vaccination). The median time elapsed from last vaccine administration was 7 months for initial systemic symptoms and 11 months for first myalgia. Most frequently complained symptoms were: myalgias (89%), disabling chronic fatigue (77%), overt cognitive alterations affecting memory and attention (51%), and dyspnea (50%). Myalgia typically started in the lower limbs and then became generalized. Muscle weakness was rare and an increase in creatine kinase serum level was detected in fewer than half of the patients. In a study performed in 2000 by Cherin et al. on twelve cases of MMF, all patients underwent a gallium scintigraphy of the muscles and demonstrated to have an increased uptake of the contrast-agent in painful areas along the lower limb muscle fasciae and in para-articular tissues [63]. Concerning central nervous system involvement, MMF patients frequently complained of subjective memory impairment, difficulties in sustaining attention, and mood disturbances [64]. In 2003, a case–control study demonstrated that CFS is the most frequent condition complained by MMF patients [65]. Later on, Exley et al. [66] reported the first case of the coincidence of MMF, CFS and aluminum overload in one individual. In addition to CFS, 15–20% of patients with MMF could develop an autoimmune disease or a dysimmune neuromuscular disorder such as: MS-like demyelinating disorders [67], Hashimoto's thyroiditis, dermatomyositis, necrotizing autoimmune myopathy, myasthenia gravis, and inclusion body myositis. Low titers of various autoantibodies, increased inflammatory biomarkers, and abnormal iron status were also commonly detected [59]. In conclusion, MMF lesion is a post vaccination immunogenic granuloma characterized by intracytoplasmic inclusions which correspond to aluminum hydroxide crystals. In addition to generalized myalgia, different other symptoms, in particular neurological complications, may occur.

6. Siliconosis

Silicones are a family of synthetic polymers sharing a silicon-oxygen chain with varying organic side groups. Silicone elastomer (silastic) is one of the three common forms of silicone, the other two being liquid and gel. Silicone, being considered an inert material and thus unable to induce immune reactions [68], was incorporated into a myriad of medical products and devices including artificial heart valves, joint implants, ventriculo-peritoneal shunts, intraocular lenses and more. The most commonly recognized medical use of silicone is as component of breast implants (SBI) which were first introduced in 1960s for reconstructive and cosmetic purposes. The side effects of silicone such as local cutaneous inflammation, regional lymphadenopathy, silicone granuloma, development of sarcoidosis and others have been reported after breast reconstruction with prostheses containing silicone gel. A remission of such clinical conditions following removal of silicone gel breast implants has been described as well [69,70]. Following implantation, a capsule forms around the implant as part of an inflammatory response to a foreign body which is a normal reaction to a non-degradable material too large to be engulfed by macrophages [71]. One of the most common complications (about 50% of cases) in those implants filled with a silicone gel, is the appearance of a capsular contracture [72]. Even in the absence of implant rupture, diffusion of silicone into the surrounding tissues, called 'bleeding' through the silicone elastomer envelope, comprises another possible complication [73]. Bleeding increases with time, thus enhancing the inflammatory response around the capsule. In addition, an allergic reaction to either silicone or platinum, a catalyst used in silicone polymerization, may develop [74]. It has been described how silicone originating from ruptured breast implants, can cause subcutaneous nodules and lead to the development of local reaction known as siliconoma [75]. The appearance of capsular fibrosis around the prothesis is very frequent. However, the mechanism which underlies this phenomenon has not been fully understood yet.

Murine collagen-induced arthritis model and the MRL model of murine lupus showed that silicone was responsible for increased circulating levels of IL-2 in both models, as well as the production of anti-DNA autoantibodies in the MRL model; also, in the collagen-induced arthritis model long term (12 months) silicone implantation resulted in an increased incidence and severity of arthritis [76,77].

Recently it has been proposed that silicone implants trigger a specific antigen-driven local immune response through activated Th1/Th17 cells which suggests that fibrosis is promoted by the production of profibrotic cytokines as a consequence of faltering function of local T regulatory cells [78]. Patients with severe immune-mediated reactions to implanted silicone devices were found to have increased IgG in the surrounding tissue and higher levels of anti-silicone antibodies compared with asymptomatic implanted patients [79]. An adjuvant action, has been hypothesizes to link the breast implants with development of auto-antibodies [80]. In 1999, Zandman-Goddard et al. have shown that the presence of auto-antibodies is increased in symptomatic SBI implanted women compared with asymptomatic women who had undergone the procedure [81].

Alluding to the co-adjuvant effect of this substance, later on the case of a patient with a silicone implant who underwent hepatitis B vaccination and developed a chronic fatigue syndrome with autoimmune features has been reported [82]. All the above data lead to the possible conclusion that silicone particles, disperse throughout body tissues, may lead not only to the production of specific antibodies, but also to the development of a systemic reaction. Although previously considered an inert material, silicone, like other adjuvants, is capable of inducing autoimmune-like phenomena called in the early 1990s "the adjuvant disease" [83]. Case reports and case series of systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, mixed connective tissue disease as well as other connective tissue diseases, developing in women who underwent SBI, appeared in the medical literature soon after their introduction, suggesting a causal relationship between breast implants and the development of these conditions [84–87]. The first case report of a connective tissue disease occurring in a woman who had undergone breast enhancing injections a few years previously was published by a Japanese group in 1964 [88]. Furthermore, different cases of scleroderma following silicone breast implants have been reported [89] and also the presence of antibodies typical of systemic sclerosis such as anti-topoisomerase I have been detected [90]. In 1997, the case of two identical HLA sisters who both received silicone breast implants and developed poly-articular arthritis and neurological symptoms has been described [91]. Several authors have speculated concerning the possible link between silicone implants and activation of the immune system. Karlson et al. [92] concluded that there is just an isolated decrease in C3 and C4 levels in women with breast implants, in the absence of other abnormalities. On the other hand, Teuber et al. [93] found a significant incidence of antibodies to collagen in women with SBI (in 35% of cases). To summarize, most of these reports suggest that silicone implants cause a negligible and nonspecific foreign body reaction, sometimes with autoimmune antibodies, with no clear association with overt autoimmune disease. We have to remind that there might be a genetic predisposition for developing such clinical conditions and on this background silicone might plays the role of an "environmental trigger" [94].

7. Sick building syndrome

As the American Society for Heating, Refrigeration and Air Conditioning Engineering (ASHRAE) has defined, a sick building is a place where at least 20% of occupants report health symptoms and discomfort associated with their staying in the build. No definitive cause of the problem can be identified [95]. The Sick Building Syndrome (SBS) refers to a set of different symptoms and disturbs reported by the occupants of a building. This phenomenon can be observed predominantly in offices, but also in schools, healthcare centers, and residential areas. In SBS the symptoms typically complained by the occupants include: headaches, fatigue, lethargy, eye and throat irritation, nasal congestion, shortness of breath, disturbed ability to concentrate, dry skin, itchy skin and skin rash. Other symptoms such as nausea, dizziness, sneezing, nose bleeds, chest tightness, back and joint pain, tachycardia, sleep disturbances and odor sensitivity have been reported [96]. In 1984, the World Health Organization (WHO) estimated that up to 30% of new buildings might be linked to symptoms of SBS [97]. Women seems to be more affected than man [98] and the most prevalent symptoms are lethargy, mucous membrane irritation, and headache [99]. Nonetheless, variants of building-related disease can be detected because of their different relation with the nature of the pollutants as well as with intensity and duration of exposure [100]. Although a definite causal agent has not been identified yet, a poor indoor air quality (IAQ) often caused by the use of the air conditioning (HVAC), is one of the major causes [101]. These systems may be not only a source of microbial contamination, such as bacteria or spores, but also a factor contributing to dispersion of chemicals in the indoor air. The association of chemical environmental adjuvants, such as toxins or diesel exhaust, with the onset of immune-based inflammatory have been already studied [102]. In 1990, the SBS, together with other conditions (multiple chemical sensitivity, repetition stress injury, the side effects of silicone breast implants, the GWS, the CFS, the irritable bowel syndrome and fibromyalgia), was included in the “functional somatic syndromes” [103]. Nine out of ten symptoms present in these conditions are shared with the main clinical manifestations of ASIA syndrome: myalgia, arthralgias, chronic fatigue, neurological cognitive impairment, fever, gastrointestinal and respiratory symptoms, skin manifestations, and the appearance of autoantibodies [8]. For this reason it has been proposed to include SBS in ASIA syndrome [96]. The exposure to external stimuli, one of the major criteria in ASIA, is observed also in SBS where the pre-exposure is operated by stimuli present in the building environment such as: asbestos, hydrocarbons, organic allergens, molds, mycotoxins, and phthalates. All of these external stimuli may be regarded as environmental adjuvants. Removal of the external stimuli is able to induce remission of SBS [104]. Moreover, as considered in the criteria for ASIA, the presence of antibodies directed to the suspected adjuvants may be detected in SBS. Indeed, in patients with documented exposure to molds elevated titers of antibodies (IgA, IgM, and IgG) to neural-specific antigens have been detected [105]. In addition, the presence of serum IgE specific to fungi was found to be connected with building-related syndrome in individuals working in damp and moldy buildings [106]. One of the minor criteria for ASIA is the eventual evolution of an autoimmune disease. Gray et al. [107], showed that subjects exposed to mixed mold mycotoxins in a water-damaged building had higher risk to develop autoantibodies directed to nuclei, smooth muscle, central or peripheral nervous system myelin and neurofilament. The patients reported a greater frequency and intensity of symptoms, particularly neurological and inflammatory symptoms, when compared with controls.

Table 4
A list of the vaccines more likely to be associated with autoimmune diseases.

Vaccine	Autoimmune disorder
HBV [113,114]	Polyarteritis nodosa, lichen planus, bullous, pemphigoid, Henoch-Schonlein Purpura, Polyneuropathy, Erythema nodosum, ITP, Myasthenia gravis, MS, Uveitis, reactive arthritis, RA, SLE, CNS demyelination, TM, pemphigus, UCTD, CFS
Anthrax [114]	SLE
DTP/Dtap/TT [113]	Optic neuritis, myelitis, GBS, SLE
Influenza [113]	SLE, RA, vasculitis, reactive arthritis, GBS
MMR [113]	ITP
Mumps [113]	T1D
Rabies [113]	Neuritis, GBS
HAV [113]	ITP
Oral polio [114]	GBS
Rubella [114]	Fibromyalgia
Swine flu [113]	MS
BCG [113,114]	Reactive arthritis, polymyositis/dermatomyositis
HiB [114]	T1D
HPV [114]	Vasculitis, cerebral vasculitis, primary ovarian failure

Abbreviations: ITP: idiopathic thrombocytopenic purpura; MS: multiple sclerosis; RA: Rheumatoid arthritis; SLE: systemic lupus erythematosus; CNS: central nervous system; TM: transverse myelitis; CFS: chronic fatigue syndrome; GBS: Guillain–Barré Syndrome; T1D: Type 1 diabetes mellitus, UCTD: undifferentiated connective tissue disease.

8. ASIA and vaccines: the gift with a bug

In the last century science donated humanity the gift of vaccines which have represented a Copernican Revolution by significantly reducing morbidity and virtually eliminating mortality due to infectious diseases [108]. Currently, a child in the United States receives 9–12 different vaccines during the first 6 years of life, while vaccination during adulthood usually involves specific high-risk populations such as immune-compromised individuals, healthcare workers, the elderly or those subjects who travel to potentially threatening areas.

The evidence that vaccines are fundamental for patients with autoimmune diseases has been recently addressed by a committee of experts of the European League Against Rheumatism (EULAR) [109]. These recommendations state that the initial evaluation of a patient with an autoimmune disease should include the assessment of the vaccination status. Other major recommendations include that vaccination should ideally be administered during stable disease, that influenza vaccination and pneumococcal vaccination should be strongly considered, that vaccination can be administered during the use of DMARDs and anti-TNF agents but before starting B cell depleting therapy; and that attenuated vaccines as well as BCG vaccination should be avoided whenever possible especially in immunosuppressed patients [110]. Since infections can trigger autoimmunity and may elicit a flare of an autoimmune disease, their prevention can reduce the incidence of the diseases as well as diseases flare-ups. However, vaccines differ substantially due to the genetic background of the recipient individual. Thus, the vaccination schedule would be better if personalized [111]. Hence, it is imperative that science aims to implement tools such as genomics and proteomics, to allow the prediction of population sets more likely to be non-responsive or develop adverse reactions to vaccines. Thomas et al. have revised this issue gathering a number of examples of genotype/gene polymorphisms mainly in the HLA gene family, related to inter-individual variation to vaccination [112].

Indeed, two kinds of vaccination exist:

1) Active vaccination, i.e. when a live, generally attenuated infectious agent (microbe or virus) is used, or an inactivated

infectious agent (or constituents thereof), or products obtained by genetic recombination, or when the toxoid is injected;
2) Passive vaccination, i.e. the usage of immunoglobulin preparations or antitoxins.

A number of autoimmune disorders have been reported following vaccinations (Table 4). These include limited and organ-specific conditions that can occur after routine vaccination [115] as well as more severe and life-threatening diseases. It is evident that a live attenuated vaccine is more prone than a killed vaccine to activate the immunity response. Perhaps, this is the main reason why live attenuated vaccination is more likely to stimulate the development of an autoimmune disease or autoimmune symptoms [116]. Notwithstanding that molecular mimicry and bystander activation in a genetically predisposed individual have been called to be responsible, the finger should be pointed at the adjuvants. One in particular has raised several distresses: aluminum. Indeed, this has been used as an adjuvant for the past 90 years but it is also an experimentally demonstrated neurotoxin. Experimental research has showed that alum adjuvants have a potential to induce serious immunological disorders in humans. Thus, efforts should be put in clarifying the potential threat of alum-containing vaccines [117]. Another big concern regarding vaccination is that, from time to time, it may go wrong. For instance, this is the case of the initial polio vaccine (Salk). This contained a mixture of three formalin-inactivated polio viral strains that, under the conditions of large-scale production, could escape such inactivation. In 1955, at the Cutter Laboratories the production of not fully secure vaccine led into the induction of acute poliomyelitis in a number of subjects who suffer now of the so-called post-polio syndrome [118]. Still, the available data suggest that the risk to benefit ratio is still overwhelmingly in favor of vaccinations [119]. Nonetheless, further studies are needed to better address this issue.

9. Evidence in animal models

One big demand in the field of vaccines regards of studies performed on large animals, such as dogs and monkeys, in order to identify the development of autoantibodies and/or frank autoimmune diseases. It has been reported the development of anti-laminin, anti-fibronectin and other lupus associated antibodies in immunized dogs [114]. A higher number of studies on mice and rats are available. The development of diabetes has been documented in NOD mice and BB rats after vaccination. Also, studies on salmons have demonstrated that immunization with oil-based vaccines induces the production of autoantibodies [120].

Furthermore, glucan, a polysaccharide from the yeast *Saccharomyces cerevisiae*, was able to increase disease activity and caused early death in NZB/NZW F1 mice [121]. In a study from 1973, *S. cerevisiae* injected in rabbit was able to provoke the onset of acute hematogenou pyelonephritis [122]. A striking article has been recently published by Lujan et al. The authors described a form of ASIA syndrome in commercial sheep. The sheep inoculated repetitively with aluminum-containing adjuvants vaccinations showed an acute neurological episode with low response to external stimuli and acute meningoencephalitis few days after immunization. Later, an excitatory phase, followed by weakness, extreme cachexia, tetraplegia and death appeared. Alum was found in tissues indicating the presence of the adjuvant in the nervous tissue of experimental animals [123]. As mentioned above, an isoprenoid adjuvant, pristane, has been shown to promote lupus-like syndromes and pathologic nephritis in both autoimmune-prone and non-susceptible mouse strains after a single intra-peritoneal administration [124–126]. Furthermore, squalene, a triterpene and Freunds' adjuvants (CFA/IFA) could also provoke lupus-like syndromes in non-autoimmune prone BALB/c mice [127]. To conclude, the increasing number of animal models provide a valid proof of concept for ASIA syndrome [128].

10. Vaccines and autoimmune diseases

Several neurologic demyelinating diseases have been reported following vaccination, the main being Guillain–Barré syndrome (GBS). This is an acute polyradiculoneuropathy, usually manifested by a rapidly evolving symmetric and ascending motor paralysis, with loss of tendon reflexes. It has been shown that the neurological symptoms of GBS are preceded by an acute infection in two thirds of the cases. There is increasing evidence that GBS is an autoimmune disease. Autoantibodies to gangliosides can be found in GBS patients and their T cells can cross-react to nerves heath components. Several vaccines have been related to the appearance of GBS including influenza, tetanus toxoid, BCG, rabies, smallpox, mumps, rubella, oral poliovirus vaccine, hepatitis B vaccines, either plasma-derived or recombinant vaccine and diphtheria vaccine. In 1976, the "swine flu" or New Jersey 76 vaccine caused a marked increase in GBS occurrence occurring during the 6–8 weeks post-vaccination. In a paper published on the New England Journal of Medicine, it was reported that the relative risk of the GBS associated with vaccination, adjusted for age, sex, and vaccine season, was 1.7 [129].

More recently, De Wals et al. [130] found over a total of 3,623,046 person-years of observation, 83 GBS cases identified during the 6 months of follow-up. Of these, 25 had been vaccinated against 2009 influenza A(H1N1) with an adjusted relative risk of 1.80 (95% CI, 1.12–2.87). The number of GBS cases attributable to vaccination was approximately 2 per 1 million doses, concluding that the risk was small and significant but outweighed by the benefits of immunization [130].

However, Baxter et al. did not observe recurrent of GBS that could be considered associated with vaccination. The main limitation was the relatively small size of the study due to the rarity if the disease [131]. Khamaisi et al. described a 52- year-old woman who developed GBS after her second injection of hepatitis B vaccine [132]. This patient was not dissimilar to other 19 cases previously described in the literature. GBS was reported as occurring significantly more often than expected when compared with the Center of Disease Control GBS background rate.

Another demyelinating disease associated with vaccines is the acute disseminated encephalomyelitis (ADEM). This is an inflammatory disease of the central nervous system frequently occurring post-vaccination. Rabies, diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccines have been called to be involved. Huynh et al. focused on the precipitating factor suggesting the presence of mutations in the SCN1A gene, the re-infection theory (the vaccination with an attenuated virus strain may cause problems only if administered in patients previously suffering from an infection) may be responsible but yet not sufficient for the development of the syndrome [133]. The world widespread use of the novel influenza type A virus in 2009, trivalent vaccines against H1N1 (pandemic) 09 and seasonal influenza, gave rise to the description of a number of cases of ADEM, suggesting the existence of a component of the vaccine more likely to trigger this condition [134]. Similar concerns were raised by the usage of the anti-HPV vaccine, specifically Gardasil®, which differently from Cervarix®, contains yeast [135]. Nonetheless, Schäffer et al. reported another case of ADEM following HPV vaccination, but the vaccine used was not specified [136]. The same Gardasil® vaccine was associated with the onset of 5 cases of inflammatory demyelination that fall within the "clinically isolated syndrome/multiple sclerosis" diagnostic

spectrum occurring within 21 days of vaccination. The multifocal and atypical nature of these reports suggested that the vaccine may have influenced the nature and the severity of CNS inflammation [137]. Vaccines can also trigger other rare neurological conditions such as transverse myelitis (TM). In a recent paper, 37 reported cases of TM were associated with different vaccines including anti-HBV, MMR, DTP. The authors found a temporal association between several days and 3 months, although a longer time frame of up to several years was also suggested [138]. Ablin et al. [139] have so addressed the issue of infections and vaccination with the development of another disorder characterized mainly by asthenia and muscle pain: fibromyalgia (FB). The authors pointed the finger towards Rubella and Lyme vaccines, although current data is insufficient in order to establish a causal relationship [139].

Vaccines seem to play a role in another condition of unknown pathogenesis. Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue lasting for more than 6 months associated with physical and mental disturbances such as headache, arthralgia, myalgia, memory impairment, sore throat and tender lymph nodes. Despite the fact that an association between vaccination and CFS is poorly documented, in Canada several reports claimed that CFS was evolved after immunization to HBV. Therefore, a working group was created in order to find any association between anti-HBV vaccination and CFS. Thirty cases of patients with CFS that appeared within 3 months after immunization against HBV were administered. However, the retrospective analysis lead to the conclusion that there is no sufficient evidence to demonstrate an association between CFS and anti-HBV vaccine [140]. It has been showed that rupture and leak of silicone from breast silicone implants can lead to autoimmune diseases, an effect so-called 'adjuvant disease'. It seems that adjuvants which are included in human vaccines may, although rarely, induce autoimmunity. This uncommonness may be explained by complex individual genetic susceptibility [141]. Nonetheless, a bridge case between the abovementioned conditions (FB, CSF and silicone leak from silicone implant) was described by Agmon-Levin et al. [82] indeed, a lady presented with CFS accompanied by FB, demyelination and autoantibodies that developed after the 2nd dose of hepatitis-B vaccine, and aggravated by the 3rd vaccination. Moreover, the silicone breast implants that the patient had implanted 6 years before vaccination with no adverse events, underwent to a local reaction with inflammation after vaccination and a silicone leak was revealed. Whether the hepatitis-B vaccine was a cause or an accelerator of the disease remains unknown, as well as whether the exposure to silicone could have further contributed to the autoimmune process [82].

11. HPV

There are several concerns regarding the human papilloma virus (HPV) vaccine and its ability to prompt an autoimmune response. In the largest post-licensure study there were 51 reports of autoimmune disorders, including 26 unspecified, 1 scleroderma, 1 dermatomyositis, 18 SLE, 13 RA, 1 SS, and 4 reports of MCTD [142]. The authors stressed the idea that data on autoimmune disorders cannot be conclusive given the relatively short time of follow-up and the usage of the VAERS reports. A large proportion of these reports (68%) indeed came from the manufacturer and most of these reports (89%) did not include sufficient identifying information to allow medical review of the individual case. Thus, to better address this issue, an observational safety study of the quadrivalent HPV vaccine in women was conducted by Chao et al. identifying no autoimmune safety concerns [143]. However, the study had several limitations, including the relatively short observation. Indeed, it has been shown that the period of time from vaccination to induction of autoimmunity may necessitate even years [144]. Indeed, the real advantages of HPV vaccination are still a matter of debate since persistently infected women with HPV likely will not develop cancer if they are regularly screened [145]. Finally, it has become tangible that several side effects of the vaccines may have not been recognized so far. The definition of ASIA has changed the idea that a physician should look for the presence of a well-defined autoimmune disease. Rather, vaccinations elicit a corollary of signs and symptoms that can be bounded under the name of ASIA [146]. According with this, Tomljenovic and Shaw recently found evidence of an autoimmune vasculitis potentially triggered by the cross-reactive HPV-16 L1 antibodies binding to the wall of cerebral blood vessels in post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis-like symptoms following vaccination with the HPV vaccine Gardasil®. The abnormalities included increased T-cell signaling and marked activation of the classical antibody-dependent complement pathway in cerebral vascular tissues [147]. In another report, a formerly healthy teenage girl suffered from a sudden unexpected death in sleep 6 months after 3 intramuscular injections of a quadrivalent HPV vaccine, Gardasil®. The postmortem blood and splenic tissue obtained at autopsy were found to contain HPV-16 L1 gene DNA similar to the HPV-16 gene DNA fragments in Gardasil®, suggesting a possible link [148]. Consistent with these is the report from Chang and colleagues who described two patients who presented CNS demyelination in close time relationship with the administration of HPV vaccine. Interesting was the first case, in which causality was noticeable since no medical problems were present prior to the administration of the vaccine and the McDonald's criteria for the diagnosis of MS were met on follow-up MRI scan [149].

It is thus not surprising to find in the literature case reports seeking an association between HPV vaccination and the "mother" of the autoimmune diseases, SLE [150]. Gatto and coll [151]. recently described six cases of SLE and SLE-like disease following HPV immunization; in the reported cases several common features were observed, such as personal or familial susceptibility to autoimmunity, as well as an adverse response to a prior dose of the same vaccine. Not only potentially life-threatening but also severely disabling conditions have been related with HPV vaccination. Premature ovarian failure (POF) in young girls has significant consequences for future health and prospects of motherhood. A lady was diagnosed with POF after she was administered with three quadrivalent HPV recombinant vaccinations. The authors stressed the need for detailed information concerning rat ovarian histology and ongoing fecundity post-HPV vaccination [152]. Furthermore, the cases of three women – including two sisters – who developed secondary amenorrhea following HPV vaccine have been recently described [153]. Interestingly, anti-ovarian and anti-tiroperoxidase (TPO) antibodies were detected in two out of three cases following the vaccine; moreover, as POF developed in two sisters, a genetic susceptibility predisposing to post-vaccination POF has been hypothesized [153].

Finally, HPV vaccine has been related to the *de novo* onset of postural tachycardia orthostatic syndrome (POTS), an autonomic disorder of uncertain origin in which the detection of ganglionic acetylcholine receptor antibodies raised the hypothesis of an autoimmune origin in some cases [154]. The case of 20-year-old woman developing POTS two weeks following HPV immunization - in absence of further risk factors nor events preceding the illness - has been reported by Blitshteyn [155], who suggested for the first time a plausible temporal relationship between POTS and HPV vaccine. Taken altogether, these evidences let to hypothesize that the HPV vaccine may trigger an autoimmune response. This seems to be especially true for Gardasil that yet, was tested in trials against an aluminum containing placebo demonstrating similar safety

profiles [156]. A better look inside the vaccine may give the answer to the manufacturer and, more importantly, to the women who will use it. Then, because the HPV vaccination programme has global coverage, the long-term health of many women may be at risk against still unknown vaccine benefits. Physicians should remain within the rigorous rules of evidence-based medicine, in order to counterbalance the risks towards the benefits of vaccination [157].

12. HBV

The HBV vaccine has been used routinely for almost 20 years. Despite most of the adverse reactions are local and transient, major side events may include protean autoimmune phenomena. Erythema nodosum, lichen planus, vasculitis, glomerulonephritis, Evan's syndrome, thrombocytopenic purpura, rheumatoid and reactive arthritis have been described as post-vaccination singularities. Furthermore, autoimmune demyelinating disorders such as multiple sclerosis, transverse myelitis and GBS, as well as other frank autoimmune diseases including SLE, can occur at variable, though sporadic, frequencies. McMahon et al. claimed that the adverse events caused by the plasma-derived HBV vaccine can be due both to the preservative material thimerosal (a mercurial compound that was found to be neurotoxic but that is not included anymore in the HBV vaccines since 1999) and to alum-hydroxide, used as an adjuvant. Other components of the vaccine, such as yeast, have been also indicted. Yeast, for instance, can reduce the number and function of T regulatory cells, a mechanism that is involved in the generation of autoimmunity. The largest cohort of cases diagnosed with immune-mediated diseases following immunization HBV vaccine has been already mentioned in the introduction [20]. Particular concerns were raised by the evidence of increased CNS inflammatory demyelination following HBV vaccination. Mikaeloff and coworkers [158] found that this appears to be true essentially only for the Engerix B vaccine, while the risk is increased for multiple sclerosis (MS) in the long term. It would be of interest to know the exact compositions of the different HBV vaccines especially in terms of alum and yeast content [158]. Thus, Hernàn and coworkers [159] deeply investigated the potential link between vaccines and the increased risk of MS. They conducted a nested case-control study within the General Practice Research Database in the United Kingdom and their results were consistent with the hypothesis that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS, while there was no evidence of increased risk of MS associated with tetanus and influenza vaccinations [159]. Notably, despite epidemiological association, no causal link was found so far. Nevertheless, Konstantinou et al. [160] described the first case involving the occurrence of 2 episodes of leuko encephalitis in a previously healthy patient after vaccination and re-challenge with hepatitis B vaccine. In this unique case, a direct causal link was suggested by the absence of previous disseminated neurologic disease; the presence of large single lesions with graymatter involvement (an unusual finding in cases of MS), as shown by MRI; the resolution of lesions, as shown by MRI; histopathologic findings; the absence of new neurologic deficits; the lack of detection of new lesions by MRI performed during the 2.5 years of follow-up; and the occurrence of 2 similar but separate clinical and radiological neurologic events soon after administration of the second and third doses of vaccine [160].

Despite the evaluation of a possible association between vaccination and SLE yielded conflicting results, a temporal association was suggested between SLE and different vaccines including the anti-HBV vaccine. A case control study found an odds ratio of 1.4 (0.9–2.21) for post-HBV vaccination autoimmunity. Agmon-Levin et al. [161] first aimed at identifying common and atypical features of SLE diagnosed following HBV vaccination [161]. The authors compared the presentation of the 10 SLE-post vaccination patients showing a similar frequency of certain manifestations (muscles, joints, skin and photosensitivity), but an exceptionally low rates of hematologic involvement as well as the absence of lupus nephritis [161]. Maillefert et al. [162] suggested that SLE can exacerbate after HBV vaccination, partially disagreeing with the results of Battafarano et al. [163] who proposed that immunizations be added to the list of possible triggers for SLE only when symptoms develop within 3 weeks of booster immunization, and integrating the results of Senécal et al. [164] who agreed that pneumococcal vaccination is safe and useful in SLE, but reported a case of exacerbation of SLE following hepatitis B vaccination [162–164].

Another autoimmune disease that can be triggered by vaccinations, specifically HBV, is pemphigus. This is caused by autoantibodies against epithelial intercellular components and there are reports associating the disease with influenza and tetanus with diphtheria vaccination. Nonetheless, the first case of pemphigus following HBV vaccination (Engerix-B) was reported by Berkun et al. [165]. The patients developed pemphigus only three months after the vaccination, suggesting a possible temporal association and that the vaccine per se or its adjuvant may cause a non-specific activation of immune system and unmask already existent but dormant pemphigus [165]. Recently, the association between HBV vaccine and the onset of undefined connective tissue disease (UCTD) has also been described [166]. It has been hypothesized that some components of the HBV vaccine, such as yeast and alum, may contribute to the unbalance of Tregs/Th17 ratio toward a Th17 response, which is found to have a role in the pathogenesis of UCTD [167].

Nonetheless, HBV vaccine can trigger other even rarer autoimmune conditions such as dermatomyositis [168], systemic polyarteritis nodosa [169], and neurological manifestations such as status epilepticus [170]. Thus, it is conceivable that HBV vaccination may have significant effects on the brain through various mechanisms: from demyelination to hyperactivity.

13. Influenza vaccine

Influenza, commonly known as the flu, is an infectious disease caused by RNA viruses of the Orthomyxoviridae family. Following this observation and the ability to grow the virus in embryonated hen eggs, discovered in 1931, the United States military developed the first inactivated influenza vaccine in the 1940s. Current vaccines are considered safe and effective by the medical community, for the general population as well as for patients with autoimmune rheumatic diseases. The link with autoimmune diseases is still a matter of debate. Several case reports show an association between the influenza vaccine and SLE/APS [171]. When considering patients with a previous diagnosis of SLE, Vista et al. [172] were able to demonstrate that influenza vaccination can induce new-onset anti-cardiolipin but not anti-β_2-glycoprotein-I antibodies [172], possibly giving rise to different clinical manifestations, and, possibly, to a more "benign" autoantibody pattern. As abovementioned, influenza vaccine was also associated with the autoimmune neurological disease, GBS, and a link was suspected for patients with ADEM or TM [173]. Another façade of ASIA could be the association between giant cell arteritis and polymyalgia rheumatic (GCA/PMR) developed after the influenza vaccination as described by Soriano et al. [174]. The onset period could encompass over 30 years, thus the authors suggested that rather than the viral specificity of the vaccine, the main role was played by the adjuvants contained, and specifically, by alum [174]. A major strike in Finland was the sudden increase in childhood narcolepsy observed soon after pandemic

influenza epidemic and vaccination with ASO3-adjuvanted Pandemrix. The risk of narcolepsy was 12.7 fold in the vaccinated as compared to the unvaccinated individuals (95% confidence interval 6.1–30.8), with a vaccine-attributable risk of developing narcolepsy of 1:16,000 4 to 19-year-olds vaccinated individuals (95% confidence interval 1:13,000–1:21,000). These data suggested that vaccination contributed to the onset of narcolepsy. Furthermore, the robust linkage of the disease with the HLA DQB1*0602 allele which is twice as common in Northern Europe, reinforces the idea that vaccine/adjuvant mediated immunity develops in genetically predisposed individuals [175].

Finally, during the programme of vaccination against the pandemic influenza A (H1N1) in 2009, pregnant women who were at risk for severe influenza illness were vaccinated and a Norwegian study underlined that if from one side vaccination during pregnancy substantially reduced the risk of an influenza diagnosis, the risk of fetal death in the vaccinated women was increased (adjusted.

OR 1.91; 95% CI, 1.07–3.41). This report raises further worries especially regarding the vaccination during the delicate and precious mechanism of pregnancy [176]. Thus, the cost-effectiveness of influenza vaccination policy requires the consideration of all these adverse events, i.e. the development of autoimmune disorders. At the light of these new acquisitions, it may be time to revise the estimates of the effectiveness and the cost-effectiveness of influenza vaccines [177].

14. BCG and autoimmunity: another two-edged sword

Intra-vescical instillation of BCG has been used successfully since the past 40 years in the treatment of urinary bladder carcinoma. Despite most of the patients tolerate treatment without any serious side-effect, there is the possibility that the BCG by increasing the local immune response, can alter the systemic immune system balance. This may lead into the development of autoimmune reactions.

Shoenfeld et al. first described four patients who developed chronic arthropathies after receiving BCG therapy for bladder carcinoma, one of whom developed Reiter's syndrome [178]. The authors addressed the issue of the 'double-edged sword' of vaccination in patients who receive BCG for urinary bladder carcinoma, suggesting that these patients should be aware that they might experience the development of arthritic and other autoimmune mediated symptoms following BCG therapy. The authors hypothesized a 'Trojan Horse' phenomenon of vaccination, in the meaning that the gift of immunization can generate an attack on the host organism from within. There are several concerns especially regarding some genetically engineered immunizing antigens that by limiting the immune (and autoimmune) reactions, thereby also limiting the potential undesired side effects of the procedure. Moreover, since this events are more relevant in genetically susceptible individuals (such as carriers of HLA-B27 and all patients with previously known autoimmune conditions), treatment should be promptly stopped and HLA screening should be performed in patients who are being considered for BCG immunotherapy [179].

15. Other vaccines and autoimmunity

The onset of autoimmunity after the diphtheria/tetanus/acellular pertussis and polio vaccine (DTap-IPV) is anecdotal, while there are several reports of patients developing neurological complications. Hoffman et al. [180] described a case which exemplifies a bond between these two conditions, reporting a patient who developed anti-NMDA receptor encephalitis, a recently described autoimmune disorder mediated by antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor, 24 h after receiving a booster vaccination against (DTap-IPV). The onset of prodromal viral-like symptoms shortly after the immunization is intriguing and suggests the vaccination as a possible trigger of the autoimmune response [180]. Other relatively safe vaccines may lead to the development of autoimmune conditions. This is the case of Hepatitis A vaccine, which can trigger vasculitides including Henoch-Schönlein purpura (HSP). On the other side, the onset of this condition (alone or together with other autoimmune diseases) has been associated with diverse vaccines including influenza, hepatitis B and pneumococcal vaccinations [181]. Since it was demonstrated that IL-10 production was significantly increased after hepatitis A immunization and that HSP was associated with elevated serum IL-10 levels, it was suggested that hepatitis A antigen–induced production of IL-10 may play a key role in the development of vaccine-induced HSP [182]. One risky business could be the administration of vaccines to subjects living in or leaving to risk areas for specific diseases. Here, the concerns are even increased than routine vaccinations since the vaccines usually do not reach the same efficacy and safety and the vaccination is usually voluntary and dependent on the willingness to stay in that area. Nonetheless, cases of autoimmunity after vaccinations are present in the literature, such as that of a Kawasaki disease developed in a young boy who was vaccinated against yellow fever. Given the unusual age of disease onset, the authors suggested a key contribution of the vaccine in the onset of overt disease [183].

16. The re-challenge, relapse and exacerbation cases

The notion that discontinuing further vaccine boosting in patients who initially develop adverse reactions following first vaccine injection is indeed supported by many clinical observations. Cases of re-challenge, relapse and exacerbations of autoimmune rheumatic diseases have been reported in literature following different types of vaccines, including influenza and hepatitis B vaccines, suggesting cross-reactivity or polyclonal activation mechanism. As abovementioned, Soriano et al. [174] described a case of polymyalgia rheumatica induced by influenza vaccine in an elderly patient who relapsed two years later after a new administration of seasonal influenza vaccine, while the patient was in clinical remission. Konstantinou et al. [160] reported the occurrence of 2 episodes of leuko encephalitis in a previously healthy patient after vaccination and re-challenge with the hepatitis B vaccine. Quiroz-Rothe et al. [184] described a case of post-vaccination polyneuropathy resembling Guillain–Barré syndrome in a Rottweiler dog which suffered two separated episodes of acute polyneuropathy after receiving two different vaccines (both adjuvanted) and where the presence of antibodies against peripheral nerve myelin was demonstrated. There was no other exposure to toxic substances or trauma other than the vaccination with the inactivated rabies vaccine which the dog had received 15 days before clinical signs were first noted. Three months later (after the clinical remission induced by steroids) the dog was presented with the same clinical signs: history revealed that the dog had received 12 days before an inactivated tetravalent adjuvanted vaccine from a different vaccine manufacturer that did not include the rabies virus antigen virus.

Gatto and coll [151]. also described 6 cases of systemic lupus following quadrivalent anti human papilloma virus (HPV) vaccination. In all six cases, several common features were observed, namely, a personal or familial susceptibility to autoimmunity and an adverse response to a prior dose of the vaccine, both of which were associated with a higher risk of post-vaccination full-blown autoimmunity. In one of these cases, a 32-year-old woman was diagnosed as having clinical criteria of systemic lupus

erythematosus after third vaccination with Gardasil®. Her medical history was unremarkable prior to vaccination. However, mild weakness, facial malar rash, and hair loss were observed following the first vaccination (6 months prior to hospitalization); also, local reaction to vaccination, fever, fatigue, mild rash, and arthralgia were documented following the second dose but were misinterpreted as a "common cold". Further cases of re-challenge, relapse and exacerbations are shown in Table 5.

17. Post-vaccination production of autoantibodies

Post-vaccination production of autoantibodies had become one of the safety criteria of vaccines. Abu-Shakra and colleagues evaluated 24 women with SLE who received an influenza vaccine. Antibodies reacting with Sm, Sm/RNP, Ro and La antigens were observed 6–12 weeks following vaccination, and six and three patients developed immunoglobulin G and M anti-cardiolipin antibodies, respectively [192]. Autoantibody production (i.e. antinuclear antibody, aCL and anti-beta-2 glycoprotein 1) was also studied in 92 healthy medical workers after influenza vaccination. Perdan-Pirkmajer et al. [193] found that influenza vaccination caused transient changes in ANA titers, including the development of new ANA and a statistically significant elevation in the titers when women were considered. Antibodies of unknown specificity against rabbit thymus or human spleen extracts after vaccination were found in patients with RA and AS, respectively as the vaccine could induce *de novo* aCL IgG/IgM. Confirming previous studies that showed high titers of anti-Sm, anti-Sm/ribonucleoprotein (RNP), anti-Ro and anti-La in SLE patients 6 weeks after influenza vaccination, in the study by Perdan-Pirkmajer and coworkers the ANA-positive patients also had a tendency to develop more anti-ENA following vaccination [193].

18. Final remarks

Despite the huge amount of money invested in studying vaccines, there are few observational studies and virtually no randomized clinical trials documenting the effect on mortality of any of the existing vaccines. One recent paper found an increased hospitalization rate with the increase of the number of vaccine doses and a mortality rate ratio for 5–8 vaccine doses to 1–4 vaccine doses of 1.5, indicating a statistically significant increase of deaths associated with higher vaccine doses. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive to improve vaccine safety [194].

Moreover, from one side the non-specific beneficial effects of vaccines on survival can be underestimated, on the other side the negative effect of other vaccines may not be captured by current studies [195]. As a matter of fact, in case of vaccine-associated autoimmune phenomena latency periods between the vaccine administration and the appearance of clinical symptoms can be longer (months or years after vaccination) than the time interval commonly established in most vaccine risk assessment studies [196].

Table 5
Re-challenge, relapse and exacerbations cases of autoimmune/rheumatic diseases following vaccinations, including vasculitis. Summary of the most relevant cases detected in literature (Source: PubMed/Medline).

Diagnosis	Age, sex (ys)	Type of vaccine	Time interval	Relevant data	Reference
PMR	F, 67	Inf-V	2–3 wk	**RELAPSE** PMR 7 ys before	Gerth HJ, 1992 [185]
GCA/PMR	F, 64	Inf-V	3 d	**RELAPSE** PMR 2 ys before in clinical remission Hepatitis B vaccination 6 mo before the relapse	Saadoun D et al., 2001 [186]
PMR	F, 68	Tetanus vaccine	Few days later	**RELAPSE** PMR 4 ys before	Saadoun D et al., 2001 [186]
Leuko encephalitis	F, 39	rHBV-V Engerix B ® 3rd dose	11 d	**RE-CHALLENGE** Previous episodes 4 mo before, occurred 4 wk after 2nd dose of HBV-V Engerix B ®	Kostantinou D et al., 2001 [160]
GBS	M, 3.5 ys Rottweiler dog	Inactivated tetravalent vaccine not including rabies virus	15 d	**RE-CHALLENGE** 1st episode 3 mo before following inactivated rabies vaccine	Quiroz-Rothe E et al., 2005 [184]
PMR	F, 71	Inf-V	2 wk	**RE-CHALLENGE** PMR 2 yr before, occurred 2 mo following Inf-V	Soriano A et al., 2012 [174]
HSP	M, 23	Inf-V	21 d	**EXACERBATION** HSP and Residual chronic renal failure	Damjanov I et al., 1980 [187]
PAN	M, 45	rHBV-V Engerix B® 2nd dose	N/A	**EXACERBATION** Myalgia, arthralgia and morning stiffness 2 wk after 1st dose, 1 mo before	De Keyser F et al., 2000 [188]
TD	F, 61	rHBV-V Engerix B® 2nd dose	Over the following month	**EXACERBATION** Myalgia, fatigue and eye pain following 1st V Engerix B® dose	Zaas A et al., 2001 [189]
GPA	M, 20	Inf-V, performed in course of active glomerulonephritis	Not specified,('shortly after')	**EXACERBATION** Fatal relapse	Spaetgens B et al., 2009 [190]
GPA	F, 67	Inf-V	12 d	**EXACERBATION** GPA in remission since 2 yr	Birck R et al., 2009 [191]
SLE	F, 32	q-anti HPV-V Gardasil® 3rd dose	5 d	**EXACERBATION** Mild weaknes, facial malar rash, hair loss since after the 1st Gardasil® dose Family history of autoimmune thyroid disease	Gatto M et al., 2012 [151]

List of abbreviations: d, days; wk, weeks mo, months; ys, years; PMR, polymyalgia rheumatica; GCA, giant cell arteritis; GBS, Guillain–Barré syndrome; HSP, Henoch Schonlein purpura; PAN, polyarteritis nodosa; TD, Takayasu disease; GPA, granulomatosis with polyangiitis (or Wegener's granulomatosis); SLE, systemic lupus erythematosus; rHBV-V, recombinant anti-HBV vaccine; Inf-V, seasonal influenza vaccine; q-anti HPV-V, quadrivalent anti human papilloma virus vaccine; N/A, not available.

The US Supreme Court ruled that vaccines makers are immune from lawsuits charging that the design of vaccine is defective [197]. Thus, there is the need for innovative clinical trial design and the vaccines themselves should be redesigned. Indeed, rather than generating responses through infections, immune stimulation can be achieved by increasingly complex modes of antigen presentation that range from introduction of selected proteins, to gene-delivered immunogens, virus-like particles, structured arrays, or attenuated viruses. In the scenario, the role of adjuvants should be re-evaluated [198]. It is also true that the vaccination rate during child-hood should be improved. But, to accomplish this, clinicians must set an example and comply with vaccine recommendations for themselves and their children. This, in turn, may lower the incidence of unexpected post-vaccination adverse events [199].

To conclude, the accumulation of many reports and the temporal association between the occurrence of autoimmune diseases and vaccination, HBV but also influenza and others, led some authors to hypothesize the presence of a causal link. Such a link does not necessarily means that the vaccine is the actual or single initiator of the autoimmune process, but rather it may serve as a trigger for presentation of an overt disease or exacerbation of a non-symptomatic one, in certain individuals that are probably genetically prone to develop such a devastating adverse event [200]. This and other issues were deeply discussed in a meeting later on summarized by Orbach et al. [201]. The main emerging points were that the vaccine–autoimmunity cause and effect relationship is still debatable. Yet, the adjuvants and preservatives may cause autoimmune phenomena; but the timing of immunization, and — above-all the genetic background of the individual are the utmost importance in determining the onset of autoimmune phenomena. The general opinion in the meeting was that the vaccines are crucial for eradicating infectious diseases with high rate of morbidity and mortality, and should not be therefore withdrawn altogether [201].

Perhaps, in twenty years physicians will be dueling with better characterized particles of autoimmunity, and the vaccines may become fully safe as well as effective. Nonetheless, the recognition of ASIA has initiated the change to put more efforts in identifying the good, the bad and the ugly of vaccines and in particular of adjuvants as triggers of autoimmunity. As we said, the available data suggests that the benefits of vaccination overweigh the risks. However, particular attention should be given in order to develop safer vaccines. Altogether, these evidences brought to light the idea that at least some of autoimmune disease may be triggered by vaccines, a circumstance which physicians should be aware of. Similarly, although silicone implants are safe for the vast majority of subjects, screening for pre-existing autoimmune phenomena and genetic testing have been proposed as useful tools for future risk stratification before the implantation, in order to avoid autoimmune-rheumatic adverse events in predisposed subjects and subsequent explanation surgeries [202]. Finally, it should be emphasized that every patient needs to be individualized if there is to be a rational understanding of individual etiology in the induction of an autoimmune disease, i.e. biologic and medical plausibility is essential. The relationships between genetic susceptibility and environmental factors have gained increased attention and are discussed extensively in recent literature, including discussions of geoepidemiology, epigenetics, infection, animal models, use of twins and gender [203–226].

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