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Invited review

# Vaccines, adjuvants and autoimmunity

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ABSTRACT

Vaccines and autoimmunity are linked fields. Vaccine efficacy is based on whether host immune response against an antigen can elicit a memory T-cell response over time. Although the described side effects thus far have been mostly transient and acute, vaccines are able to elicit the immune system towards an autoimmune reaction. The diagnosis of a definite autoimmune disease and the occurrence of fatal outcome post-vaccination have been less frequently reported. Since vaccines are given to previously healthy hosts, who may have never developed the disease had they not been immunized, adverse events should be carefully accessed and evaluated even if they represent a limited number of occurrences.

In this review of the literature, there is evidence of vaccine-induced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients. Adjuvants and infectious agents may exert their immune-enhancing effects through various functional activities, encompassed by the adjuvant effect. These mechanisms are shared by different conditions triggered by adjuvants leading to the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome).

In conclusion, there are several case reports of autoimmune diseases following vaccines, however, due to the limited number of cases, the different classifications of symptoms and the long latency period of the diseases, every attempt for an epidemiological study has so far failed to deliver a connection. Despite this, efforts to unveil the connection between the triggering of the immune system by adjuvants and the development of autoimmune conditions should be undertaken. Vaccinomics is a field that may bring to light novel customized, personalized treatment approaches in the future.



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## 1. Introduction

Vaccines have been a preventive treatment option available for over 200 years. They have been proven to be effective in preventing infections that previously had high morbidity and mortality. An example of this is the eradication of small pox, which was mainly attributed to successful vaccination programs. Preventing a high burden disease has since proven to be a cost effective measure and, as such, vaccines have become a part of multiple national health programs. These promising results led to the development of more and more vaccines and to the study of its applicability in other fields such as cancer prevention and treatment.

Vaccines are drugs administered to healthy individuals, and much like other drugs, vaccines are associated with adverse events. Usually the described adverse events are transient and acute, but may rarely present with hypersensitivity and induction of autoimmunity that may be severe and fatal. These adverse events play an important role in the life of the vaccinated patients.

Immune mediated diseases arise from various different sources; these include environmental, genetic, hormonal and immune defects. The combination of these defects can be described as the mosaic of autoimmunity [1]. Patient background can be used as a clue to determine the response that may be elicited following drug administration.

It has been proven that infectious agents may elicit an autoimmune disease in a prone subject through various mechanisms, including, but not limited to, molecular mimicry, epitope spreading and polyclonal activation [2].

Scientific findings suggest that autoimmunity may be triggered by vaccine adjuvants, of which aluminum compounds (aluminum hydroxide and phosphate) have been the most studied and the most widely used. Adjuvants are molecules, which, in combination with antigens, enhance immunological response. This enables an easier and more effective recognition of "non self", which in turn permits the triggering of adaptive and innate immune responses [3].

Recently a new syndrome was described: "Autoimmune/inflammatory syndrome induced by adjuvants" (ASIA). This embodies a spectrum of reactions, which are usually mild but may also be severe. These reactions are attributed to adjuvant stimulation, which can include chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum, infectious components and other adjuvants. All of these environmental factors have been found to induce autoimmunity and inflammatory manifestations by themselves both in animal models and in humans. The mechanisms of this disease will be described in further detail [4].

This review will focus on general mechanism of vaccines, adjuvant-induced autoimmunity, and on vaccines and the specific autoimmune diseases that they may trigger.

## 2. General mechanisms of vaccines and adjuvant induced autoimmunity

### 2.1. Adjuvants role in infections and autoimmunity

Adjuvants approved to date for human vaccines are: aluminum, MF59 in some viral vaccines, MPL, AS04, AS01B and AS02A against viral and parasitic infections, virosomes for hepatitis B virus (HBV), human papilloma virus (HPV), hepatitis A virus (HAV), and cholera toxin for cholera.

Adjuvants may be composed of several different compounds. Currently, oil based adjuvants, virosomes, toll-like receptors (TLRs) related adjuvants, MPL, adjuvants made of unmethylated CpG dinucleotides and tuftsin have all been described.

**Table 1**
Types of adjuvants in development or use.

| Type of Adjuvants | Name of compound | Vaccines in test or use |
|---|---|---|
| Related to Toll like receptors (TLRs) | Aluminum hydroxide and phosphate | PCV7, PCV13, MenC, HPV, HAV, Hib; tetanus vaccine |
| | IC31 | Influenza [14] |
| | ASO4 (MPL + QS-21), ASO2A (MPL + Alum), CPG 7907, and GM-CSF RD-529, ISS, Flagellin TLR agonists | Papilloma virus, hepatitis B, malaria [15] |
| Oil based emulsions | CFA, IFA, MF59™ montanide, adjuvant 65, lipovant, QS-21 [16] | Influenza |
| | ISCOMs, ADVAX™, algammulin | |
| Xenobiotic adjuvants | Unmethylated CpG dinucleotides [17] | Hepatitis B, allergens, tumor cells |
| Tuftsin auto adjuvant | Tuftsin | Influenza, malaria, autoimmune encephalomyelitis, restoration of innate immune system (HIV patients), SLE [18–21] |

CFA: complete freund adjuvant; IFA: incomplete freund adjuvant; PCV: pneumococcal conjugated vaccine; MenC: meningitis C; HPV: human papiloma Virus; HAV: hepatitis A virus; Hib: haemophilus influenza type b.

It is of great interest the understanding of the mechanisms related to the adjuvant effect, as well as to aluminum salts. Aluminum acts through multiple pathways, which do not depend solely on TLRs signaling. Each of these pathways leads to an enhanced host immune response [5].

There are many oil based adjuvants. One is incomplete Freund adjuvant (IFA), which contains water in oil emulsion. Another is complete Freund adjuvant (CFA), which is the same as IFA, except that it also contains killed Mycobacteria in addition to water in oil emulsion. Usually, CFA is used for primary vaccination and IFA for boosting. Recent oil based adjuvants that have been developed are MF59 (Novartis®), AS03 (GlaxoSmithKline®), Advax™ which are based on inulin compounds (Vaxine™ Pty) and Qs-21/ISCOMs, which are immune stimulating complexes composed of cholesterol and phospholipid with or without antigen (Table 1).

Virosomes are adjuvants that contain a membrane-bound hemagglutinin and neuraminidase obtained from the influenza virus. Both components facilitate the uptake into antigen presenting cells (APC) and mimic the natural immune response [6].

Leucocyte membranes have membrane bound pattern recognition receptors (PRRs) called TLRs, which are responsible for detecting most (although certainly not all) antigen-mediated infections. Their activation leads to adaptive immune responses. For this reason, many adjuvants that are used today are directed to PRRs. These adjuvants are called TLRs related adjuvants [7].

MPL is a series of 4'monophosphoryl lipid A obtained from the purification of a modified lipopolysaccharide (LPS) of Salmonella Minnesota.

Bacterial deoxyribonucleic acid (DNA) is immunostimulatory due to Unmethylated CpG dinucleotides. Vertebrate DNA has relatively low amounts of unmethylated CpG compared to Bacterial DNA. The adjuvant effect of CpG is enhanced when conjugated to protein antigens. This adjuvant is being tested in vaccines directed at infectious agents, allergens and tumor cells [8–10].

Another type of adjuvant is tuftsin. Tuftsin is an auto adjuvant, which is a natural self-immunostimulating tetrapeptide (Thr–Lys–Pro–Arg). This tetrapeptide is a fraction of the IgG heavy chain molecule produced by enzymatic cleavage in the spleen [11]. Its functions include: binding to receptors on neutrophils and macrophages to stimulate their phagocytic activity, increasing tumor necrosis factor alpha (TNFα) release from human Kupffer cells enhancing secretion of IL1 by activating macrophages, activation of macrophages expressing nitric oxide (NO) synthase to produce NO and enhancement of murine natural cell mediated cytotoxicity in vitro [11–13].

In summary, it is an adjuvant with minor side effects with a promising effect in restoring innate immune mediated response.

### 2.1.1. Mechanisms of adjuvanticity

Adjuvants may exert their immune enhancing effects according to five immune functional activities:

1. Translocation of antigens to the lymph nodes where they can be recognized by T cells.
2. Antigen protection enabling longer exposure.
3. Enhanced local reaction at the injection site.
4. Induction of the release of inflammatory cytokines.
5. Interaction with PRRs, specifically TLRs [22].

a Adjuvant effect

The term "adjuvant effect" refers to the co-administration of an antigen with a microbial specific factor to enhance an antigen-specific immune response in vivo. The microbial components of adjuvants activate APCs to produce pro-inflammatory cytokines ("non-specific" signal 2) and to up-regulate molecules essential for antigen presentation. These molecules include major histocompatibility complex (MHC) class II (antigen-specific signal 1) and B7-1/2. These innate immune events allow a more effective presentation to the adaptive immune system, resulting in an augmented activation and clonal expansion of T cells [23].

In accordance to this effect, if self-antigens are used, an autoimmune response can be elicited [24]. It has been shown that auto-reactive T-cells that surpass tolerance mechanisms can be triggered by exogenous adjuvants to become auto-aggressive [25].

Infectious agents are able to naturally generate their adjuvant effect and can induce autoimmunity [26]. An example of this is the causality between viral infection and myocarditis. Half the cases of myocarditis are preceded by an acute viral infection. Infectious myocarditis in humans can be reproduced in experimental murine models of myocarditis [27]. It has also been shown that the autoimmune reaction elicited by an infectious agent can be effective in treating cancer. An example of this is that bladder administration of BCG (*bacille Calmette–Guérin*) has been shown to be effective against superficial bladder cancer development [28]. It can be inferred that the adjuvant effect can be used against specific tumor derived molecules, so that these molecules can be recognized as "non self".

### 2.1.2. Innate immune pattern recognition of pathogens and adjuvants

PRR-PAMP (Pattern Recognition Receptor—Pathogen-Associated Molecular Patterns) interactions activate the APCs to promote antigen-specific lymphocytic responses [29].

The definition of PAMPs has now broadened, in that the recognized structures do not need to be pathogens. Thus the concept of "microbe-associated molecular patterns" (MAMPs) and of "danger/damage-associated molecular patterns" (DAMPs) were defined based on the notion that the endogenous host molecules signal danger or damage to the immune system [30].

### 2.1.3. Innate immune response mediates the adjuvant effect

TLRs are single-transmembrane PRRs localized on cell surface and endosomal membranes. From all the PRRs, these are the most studied. TLRs play a crucial role in innate immune response to "non self" and are biosensors of tissue damage. The interaction between

the four known TLRs adapters: MyD88, TIRAP/Mal, TRAM and TRIF, in TLR signaling, shape the innate immune response.

Besides PRRs the innate immune system also detects proteolytic enzymes generated during infection [31].

Merging the response to different PRRs signaling may be the pathway for developing customized responses to different aggressions [32].

b Experimental models of adjuvants

Many animals have been used in experimental models of adjuvant-related autoimmune conditions [33]. These include primates, salmons, rabbits and swine; however, the most common are murine models.

Murine models include autoimmune prone strains, models of autoimmune disease and autoimmune resistant strains (Table 2).

An interesting model is that described by Lujan et al. The authors described that a commercial sheep, inoculated repetitively with aluminum-containing adjuvants vaccinations, developed an acute neurological episode with low response to external stimuli and acute meningoencephalitis few days after immunization. An excitatory phase, followed by weakness, extreme cachexia, tetraplegia and death appeared. This was suggested to be part of the spectrum of ASIA syndrome. Moreover, the biopsy of the nervous tissue of experimental animals indicated the presence of alum [48].

c Toxicity of aluminum adjuvants

Aluminum nanoparticles have both a unique capacity of surpassing the blood brain barrier (BBB) and of eliciting immune inflammatory responses. These are probably the reasons why Aluminums' most sensitive target is the brain, and also why documented side effects are mostly neurologic or neuropsychiatric [49,50].

Aluminum is present in nature, not only as a vaccine adjuvant, but also in food, water and cosmetics. It has been described as a neurotoxin because even when a relatively small amount of Aluminium reaches the brain [49], is can act as a genotoxin [51], a prooxidant [52], it can be proinflammatory [51], act as an immunotoxin [5] and also as an endocrine disruptor [53]. Aluminum interferes with many essential cellular processes. Memory, concentration, speech deficits, impaired psychomotor control, reduced seizure tolerance and altered behaviour are manifestations of aluminium neurotoxicity. Moreover, Alzheimer's [54], amyotrophic lateral sclerosis, Parkinsonism dementia [55], multiple sclerosis [56], and neurological impairments in children have been linked to aluminum neurotoxicity [57].

Brain susceptibility to aluminum compounds is possibly due to the brain's high metabolic requirement, to the fact that it possesses a large area of biological membranes and to the relatively low concentration of antioxidants [54].

Aluminum adjuvants exert their immunostimulatory effect through many different pathways that activate both the innate and adaptive immune systems. One of the most significant is the activation of the NLRP3 inflammasome pathway [58]. NLPR3 activation has been shown to trigger type 2 diabetes. By using NLPR3 knockout mice it has been demonstrated that the absence of inflammasome components leads to a better maintenance of glucose homeostasis and higher insulin sensitivity [59]. On the other hand, activation of the inflammasome and its downstream components: pro-inflammatory cytokines IL-1β and IL-18 are strongly implicated in the development of several central nervous system (CNS) disorders [60].

The vast majority of people are consuming higher amounts of aluminum through dietary and parenteral intake than what expert authorities consider safe. Upper limits set by US food and drug administrations (FDA) for aluminum in vaccines are set at no more than 850 μg/dose. These values were not based on toxicity studies, but on the minimum amount needed for aluminum to exert its effect as an adjuvant [51]. The quantities of aluminum to which infants, in their first year of age are exposed, have been considered safe by the FDA. However the scientific basis for this recommendation does not take into account aluminum persistence in the body. The concern about aluminum in dietary intake has been reinforced by the Food and Agriculture (FAO) WHO Expert Committee, which lowered the provisional tolerable weekly intake of aluminum from 7 mg/kg/bw (490 mg/week, for an average 70 kg human) to 1 mg/kg/bw (70 mg/week) [61].

The amount of dietary intake of aluminum has risen in urban societies to up to 100 mg/day considering the widespread use of processed convenience foods. However, only about 0.25% of dietary aluminum is absorbed into systemic circulation and most of it is thereafter eliminated through the kidneys [54]. Absorption of aluminum by the skin from ointments and cosmetics containing aluminum has been shown. Moreover, the presence of aluminum in breast tissue was associated with breast cancer [62].

Aluminum compounds persist for up to 8–11 years post vaccination in human body. This fact, combined with repeated exposure, may account for a hyper activation of the immune system and subsequent chronic inflammation [63].

The clinical and experimental evidence collected so far identify at least three main risks associated with aluminum in vaccines:

1. It can persist in the body.
2. It can trigger pathological immunological responses.
3. It can pass through the BBB into the CNS where it can trigger immuno-inflammatory processes, resulting in brain inflammation and long-term neural dysfunction.

### 2.2. Allergy and autoimmunity caused by metals

There is a link between allergies and autoimmunity since both are the result of an abnormal immune response [3,4].

Metals such as mercury, aluminum, nickel and gold are known to induce immunotoxic effects in humans. The immunologic effects of these metals include immunomodulation, allergies and autoimmunity. They may act either as immunosuppressants or as immune adjuvants.

Metals bind firmly to cells and proteins and thus have the ability to modify autologous epitopes (hapetenization). T-cells then recognize the proteins as foreign and trigger an autoimmune response [64].

Hypersensitivity caused by metals may be referred to as Type IV delayed hypersensitivity. The reaction is considered delayed because the first symptoms appear 24–48 h after exposure, because it is mostly T-cell mediated and the gold standard for diagnosis of delayed type hypersensitivity is patch testing [65].

In mercury-sensitized patients, even mercury concentrations within the normal range might provoke neuroallergic reactions in the brain [66].

Identifying metal sensitivity and removal of the sensitizing metals, such as dental amalgam, have been proved successful by showing symptom improvement in patients with previous autoimmune diseases. These diseases included fibromyalgia, autoimmune thyroid diseases and orofacial granulomatosis [67–70] (Table 3).

### 2.3. Genetics and vaccinology

The timeline regarding the field of vaccinology has been divided in two generations, the first regarding the administration of inactivated pathogens in whole or live attenuated forms (e.g., Bacillus Calmette Guerin (BCG), plague, pertussis, polio, rabies, and small-

**Table 2**
Experimental models of adjuvant autoimmunity

| Experimental models | | Strain | Disease model or related signs and symptoms | Adjuvant |
|---|---|---|---|---|
| Murine | Rats | DA (dark agouti) rats | Rheumatoid arthritis | Mineral oil (CFA, pristane, squalene,avridine) [34,35] |
| | | | Arthritis | Collagen [36] |
| | | Sprague Dawley rats | Arthritis | CFA [37] |
| | | | MMF | Aluminum [38] |
| | Mice | BALB/c | Plasmacytomas | Mineral oil, pristane [39] |
| | | | Sclerosing lipogranulomas | SC injection of mineral oil [40] |
| | | | SLE-related autoantibodies | Pristane, CFA, squalene [41] |
| | | C57BL/6 | Antiphospholipid-like syndrome | CFA, IFA [42] |
| | | NZB/NZWF1 | SLE, lupus like GLN | CFA, alum [43] |
| Salmons | | | Impaired growth rate, decreased carcass quality, spinal deformities, uveitis, inflammatory reactions in the abdominal cavity, RF, ANA, ANCA, immune-complex GLN and chronic granulomatous inflammation | Vaccines with adjuvants such as oils [44] |
| Rabbits | | | Inflammation at injection site | Vaccine: CFA, IFA, montanide [45] |
| Swine | | | Granulomatous inflammation<br>Adverse local reactions | Mineral oils [46] |
| Primates | Rhesus macaque | | Potential delayed acquisition of neonatal reflexes | aluminum contained in pre clinical vaccine testing [47] |

C57BL/6 (transgenic factor V Leiden-mutated C57/BL6-back-crossed mice); RF: rheumatoid factor; ANA: antinuclear autoantibodies; ANCA: anti-cytoplasmic autoantibodies; GLN: glumerulonephritis; SLE: systemic lupus erythematous; MMF: macrophagic myofasciitis.

pox) and the second regarding vaccines assembled from purified microbial cell components, also referred as subunit vaccines (e.g., polysaccharides, or protein antigens) [78]. This latter approach relies on recombinant DNA technology and polysaccharide chemistry.

**Table 3**
Metals reported side effects.

| Metal | Derivatives | Main cause of exposure | Side effects |
|---|---|---|---|
| Mercury | Methyl mercury | Skin ointments<br>Dental amalgam fillings | Kidney disease [71]; peripheral neuropathy; multiple sclerosis [72]; ANA positivity [73] |
| | | Polluted fish | |
| | Thimerosal and phenyl mercury | Antiseptics/ preservatives in eye drops vaccines | Flu like symptoms<br>Eyelid eczema and edema |
| Gold | Colloidal gold [74] | Treatment for RA | Nephropathy |
| Nickel [75,76] | | Food<br>Jewelry<br>Tobacco | allergic and autoimmune symptoms; scleroderma-related autoantibodies and cutaneous sclerosis |
| Aluminum [4,77] | | Food<br>Vaccines | Neurotoxic; delayed type hypersensitivity; ASIA syndrome; chronic fatigue syndrome; macrophagic myofasciitis |

RA: rheumatoid arthritis.

There are obstacles to conventional vaccine development methods such as non-cultivable in vitro pathogens (e.g., hepatitis C, papilloma virus types 16 and 18, and Mycobacterium leprae), antigen hypervariability (e.g., serogroup B meningococcus, gonococcus, malaria), opportunistic pathogens (e.g., Staphylococcus aureus) and rapid evolving pathogens such as Human immunodeficiency virus (HIV) [79].

Vaccine research gained a new perspective as the genomics field emerged over the last decades. Bacterial genomes have been sequenced and analyzed making it possible to choose the best candidate vaccine antigens by using the concept of reverse vaccinology [80].

The main known factors influencing the observed heterogeneity for immune responses induced by vaccines are gender, age, ethnicity, co-morbidity, immune system, and genetic background. The interaction between genetic and environmental components will dictate the response to vaccines.

Studying the vaccine and the host will enable the development of customized treatment options.

The combination of genetics, epidemiology and genomics in vaccine design has been denominated “vaccinomics” [81].

The importance of genetic influence is supported by twins and siblings studies, which show familial aggregation. This suggests that genomics is crucial in inter-individual variations in vaccine immune responses [82].

Both Human leukocyte antigen (HLA) and non-HLA gene markers have been identified as markers for immune response to vaccines. Multiple studies have shown connections between HLA gene polymorphisms and non-responsiveness to the HBV vaccine [83].

HLA region is divided in three sub regions: Class I is associated with the induction and maintenance of cell-mediated immune response, class II is associated with presentation of exogenous antigens to helper T CD4+ cells and class III, where immune non HLA related genes are located. Normal human tissue has at least 12HLA

antigens, and although new recombinant haplotypes may occur, it is inherited mostly intact from progenitors [84].

HLA allelic differences are associated with different responses to vaccines, either by hyper or hypo responsiveness. We can infer that a similar response may be associated with different safety in relation to the development of autoimmune reactions to vaccines, particularly in the patients with genetic predisposition to an enhanced response to vaccine inoculation [85]. Furthermore, patients that share the same HLA, for instance siblings, have been diagnosed with ASIA following similar environmental stimuli [86,87].

### 2.4. Autoantibodies induced by vaccines

Autoantibodies help to diagnose certain autoimmune diseases, however, they can also be found in healthy individuals. Thus, autoimmune diseases cannot be diagnosed based solely on antibody detection [88].

Inoculation of vaccines triggers autoimmune responses that result in the development of autoantibodies. Many studies have been carried out in animals, healthy subjects and patients with autoimmune diseases to understand if this development is of clinical significance [89–92]. A difference in eliciting the production of autoantibodies in healthy humans has been observed between adjuvanted and non-adjuvanted influenza vaccines [93]. The annual influenza vaccine has been the most heavily researched vaccine, along with HPV and Pneumococcal vaccines as far as their relationship with patients who have previously been diagnosed with an autoimmune disease [94–96]. Autoantibody induction after HPV vaccination was also shown in adolescent girls with systemic lupus erythematosus (SLE) [97].

Although induction of autoantibodies was proven following vaccine administration, there have been no proven relation with disease diagnosis in either of the specific groups studied so far [92,98].

It has been widely demonstrated that autoantibodies can develop years before the manifestation of a full-blown autoimmune disease [99].

Moreover, the development of a specific autoantibody is also genetically determined, and the link between genetic, autoantibodies and vaccines may become an even more intriguing area of research [100].

### 2.5. Siliconosis and autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)

Silicones are synthetic polymers that can be used as fluids, emulsions, resins and elastomers making them useful in diverse fields. They were thought to be biologically inert substances and were incorporated in a multitude of medical devices such as joint implants, artificial heart valves, catheters, drains and shunts. Of all the silicone-containing products, the most famous are most likely breast implants. Silicon is one of the substances suspected to induce ASIA [5].

It is currently believed that exposure alone is not enough to trigger the disease but that it requires the presence of additional risk factors (e.g., genetic susceptibility, other environmental factors) [4].

Silicone exerts local tissue reactions. Some of these reactions are considered para-physiological, such as capsular tissue formation around an implant. Other reactions are viewed as abnormal, like when capsular contractures and allergic reactions to silicone or platinum (catalyst used in silicone polymerization found in minute concentrations in implants) occur [101]. Cutaneous exposure to silicone with cosmetics or baby bottles could potentially sensitize patients [102].

There is also a systemic component of silicone exposure related to diffusion of silicone through the elastomer envelope, commonly termed "bleeding". It may arouse systemic effects as it degrades and fragments in tissue, it can also spread throughout the body and lead to the development of cancer or autoimmune phenomena [103].

Patients with ruptured implants complain more frequently of pain and chronic fatigue when compared to patients with intact implants [104].

Anti-silicone antibodies were found to be present in human sera more frequently in patients who have undergone silicone breast implants, however, their pathological significance remains uncertain [105]. The same was seen for other antibodies such as autoantibodies directed against dsDNA, ssDNA, SSB/La, silicone and collagen II, which were found to be present in increased levels in patients after exposure to silicone [106].

It has also been shown that the formation of autoantibodies is directly related to implant duration.

Several autoimmune diseases have been linked to silicone exposure including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis, systemic sclerosis (SSc) and fibromyalgia. Although ASIA symptoms may arise 24 years after the onset of exposure to silicone implants [107], most of the follow-up periods are short and concluding evidence is yet to come regarding this causality.

### 2.6. Vaccines and autoimmune diseases

There have been published case reports, epidemiologic and research studies that suggest a connection between several vaccines and certain autoimmune conditions, notwithstanding that, overall the benefits of vaccination outweigh the risks.

## 3. The vaccines

### 3.1. Measles, mumps, rubella (MMR) vaccine

Thrombocytopenia has been reported as the main adverse event following MMR vaccine. After MMR vaccine the onset of immune thrombocytopenic purpura (ITP) usually occurred within 6 weeks at a risk rate of 1:22,000–25,000 MMR vaccine doses, while the incidence of ITP following infections is 1:6000 for measles and 1:3000 for rubella [108]. As the risk of thrombocytopenia is higher in patients who experience natural infection with measles, mumps or rubella than in those receiving the vaccine, vaccination is encouraged. Arthralgia complaints have also been reported and they may present as transient arthralgia, acute arthritis and rarely chronic arthritis [109].

Some risk factors have been found to be associated with the development of arthritis in vaccinated patients such as: female gender, older age, prior seronegativity and specific HLA alleles [110].

### 3.2. Yellow fever (YF) vaccine

YF vaccine is only advisable to people in, or going to endemic areas.

The risk of developing YF vaccine-associated neurologic disease (YEL-AND) is inversely proportional to age [111]. This is why children aged <6 months cannot be vaccinated and <8 months, except during epidemics [112]. Vaccination is not advisable to people >60 years because of possible higher risk of severe adverse effects (SAEs) even though the incidence remains low [113].

### 3.3. Bacillus Calmette-Guérin (BCG) vaccine

Besides being a vaccine for *Mycobacterium tuberculosis* (TB), the BCG has proved effective as immunotherapy for bladder cancer.

Although the mechanism is yet to be fully understood, it is thought that BCG binds to fibronectin forming complexes that enable the recognition as "non-self" by the innate immune response of Th1 cells. Ultimately the pathways result in the apoptosis of tumor cells [114].

Because of its effect in treating non-muscle-invasive urothelial carcinoma, as well as superficial bladder tumors, it was expected that BCG could play a role in treating other types of cancer, despite data having not corroborated this hypothesis so far. Adverse events vary according to the site and method of administration. Intradermal administration of BCG has been reported to elicit arthritis [115], dermatomyositis [116] and Takayasu's arteritis (TA) [117] among others. Intravesical treatment for bladder cancer can cause reactive arthritis (ReA) [118]. The risk relies on a systemic reaction composed of an early infective phase (PCR positive and response to anti-TB treatment) and a late hypersensitivity reaction [119].

### 3.4. Hepatitis B virus vaccine (HBVacc)

HBV is a DNA virus of the *Hepadnaviridae* family, responsible for acute and chronic liver disease.

HBV vaccines are considered the first efficient vaccines against a major human cancer. HBV vaccines have reduced the risk of developing chronic infection and they also have proved to reduce the incidence of liver cancer in children [120].

The vaccine has been associated mainly with autoimmune neuromuscular disorders. They include, but are not limited to: optic neuritis, Guillain-Barre syndrome (GBS), myelitis and multiple sclerosis (MS), systemic lupus erythematosus (SLE), arthritis, vasculitis, antiphospholipid syndrome (APS) and myopathy [121].

HBV vaccine is the most common immunization associated with acute myelitis.

There are studies that indicate that the pathogenicity behind such vaccine and autoimmunity might be based on cross-reactivity between HBV antigen (HBsAg) epitopes, yeast antigens, as well as other adjuvants contained in the vaccine itself [122].

### 3.5. Human papilloma virus (HPV) vaccine

Up to 90% of cervical cancer deaths, occur in developing countries that lack the ability to fully implement the Papanicolau (Pap) screening programs.

HPV poses a special challenge in vaccine safety. HPV is necessary for the development of cervical cancer. However, most women infected with HPV will not develop the disease since 70% of infections will resolve within a year and up to 90% within 2 years without specific treatment. Over the course of decades, cancer may result in a small proportion of the remaining infected women. Death rate from cervical cancer in 9–20 year old girls is zero and long-term benefits are yet to be proven. In this specific case, short term risks to healthy subjects can prove to pose a heavier burden than cervical cancer [123].

There are at least 100 types of HPV strains, 15 of which have been pathologically associated with cancer. Two vaccines, Gardasil™ and Cervarix™, are commercially available against HPV. Both contain the L1 capsid proteins of several HPV strains as antigens. Gardasil™ contains serotypes 16, 18, 6, 11. These antigens are combined with aluminum (Al) hydroxyphosphate sulphate as an adjuvant. Cervarix™ contains a combination of the oil-based adjuvant monophosphoryl lipid A (MPL) and Al hydroxide (ASO4) as adjuvant and is directed at strains 16 and 18 [124].

There have been several reports of post-licensure adverse events, some of which have even been fatal [125]. Compared to other vaccines, an unusually high proportion of adverse drug reactions has been reported associated with HPV vaccines [126].

In 2008, Australia reported an annual ADR rate of 7.3/100,000, the highest since 2003. This increase was almost entirely due to ADRs reported following the commencement of the national HPV vaccination program for females aged 12–26 years in April 2007 (705 out of a total of 1538 ADRs records). The numbers only decreased after the cessation of the catch-up schedule. Although the percentage of convulsions attributable to the HPV vaccine decreased, the overall report remained comparable between 2007 and 2009 (51% and 40% respectively). These reports do not prove the association, but show that there is a higher frequency of ADRs related to HPV vaccines reported worldwide, and that they fit a consistent pattern (i.e., nervous system-related disorders rank the highest in frequency) that deserves further investigation [126–128].

Indeed, several autoimmune diseases have been linked to HPV immunization. Examples include GBS, MS, Acute disseminated encephalomyelitis (ADEM), Transverse Myelitis (TM), postural orthostatic tachycardia syndrome (POTS), SLE, primary ovarian failure (POF), pancreatitis, vasculitis, immune thrombocytopenic purpura (ITP) and Autoimmune hepatitis (AH) [123].

### 3.6. Influenza

Influenza is an acute viral infection that affects the respiratory tract and is caused by influenza type A–C viruses of the Orthomyxoviridae family [129].

H1N1 mortality rates in the 2009 outbreak showed high risk in those aged 70 years and older, presence of chronic diseases and delayed admission. Risk of infection was lower in those who had been vaccinated for seasonal influenza with 2008/9 trivalent inactivated vaccine [130].

Studies have demonstrated that influenza vaccine is safe and immunogenic in patients with SLE or rheumatoid arthritis (RA), diminishing the risk of respiratory infections [129].

It has been shown that adjuvanted vaccine had more local reactions but did not increase systemic adverse reactions [131].

Molecular mimicry has been suggested as a mechanism to explain an autoimmune response following influenza vaccination. However, a causal relationship between influenza vaccines and induction of autoimmune diseases remains unproved [129].

Diseases or symptoms reported after influenza vaccination include mostly neurological syndromes such as GBS [REF]. Nonetheless, influenza vaccines should be recommended for patients with MS, because influenza infection is associated with increased risk of exacerbations.

That being said, influenza vaccinations showed increased risk of autoimmune responses suggestive of ASIA [132], vasculitis [133] and APS [134] among others.

### 3.7. Meningococcal vaccines

Meningococcal disease is caused by *Neisseria meningitidis*. One of the following five serogroups causes almost every invasive disease: A–C, Y, and W-135. Vaccines available so far for its prevention encompass either pure polysaccharide vaccines that use purified bacterial capsular polysaccharides as antigens, or protein/polysaccharide conjugate vaccines, which use the polysaccharide molecule plus diphtheria or tetanus toxoid as T-cell-stimulating antigens.

*N. meningitidis* serogroup B (MenB) MenB glycoconjugate vaccines are not immunogenic and hence, vaccine design has focused on sub-capsular antigens [135].

MenB capsular polysaccharide is composed of a linear homopolymer of $\alpha(2 \rightarrow 8)$ *N*-acetyl-neuroaminic acid (polysialic acid; PSA).

MenB PSA and PSA found on neural cell adhesion molecules are structurally identical. As a result of this, it has been proposed that infection with MenB or vaccination with PSA may be associated with subsequent autoimmune or neurological disease [136].

No evidence of increased autoimmunity was found to be associated with meningococcal serogroup B infection [136]. Regarding vaccination, the inoculation does not cause autoimmune diseases but may unmask autoimmune phenomena in genetically predisposed individuals. Local reactions are more frequent in individuals vaccinated with quadrivalent meningococcal conjugate vaccines compared to plain polysaccharide vaccines. The intramuscular administration of the conjugate vaccine (versus subcutaneous for that of polysaccharide) may, in part, explain the higher reactivity [137].

Diseases previously associated with meningococcal vaccines are GBS [138], Henoch-Schönlein Purpura (HSP) [139] and Bullous pemphigoid (BP) [140].

### 3.8. Pneumococcal vaccine

*Streptococcus pneumoniae* (Pneumococcus) is the main cause of bacterial community-acquired pneumonia and meningitis in western countries, as well as the cause of more than 800,000 children deaths in developing countries [141,142].

There are three anti-pneumococcal vaccines commercially available. Two of these are conjugated to a protein carrier (PCV7 and PCV13) and one is not conjugated (PPV23). PPV23 was licensed in 1983 and consists of the capsular polysaccharides of twenty-three different Streptococcus pneumoniae serotypes (1–5, 6B, 7F, 8, 9N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). It does not elicit immunological memory because the immune response it triggers is T-cell independent. It is usually administered to the elderly (above 65 years), as it is believed to be less effective in children.

PCV7 is composed of the most frequent serotypes 4, 6B, 9 V, 14,18C, 19F, and 23F. PCV13 is directed at serotypes 1, 3–5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F. Contrary to PPV23 both PCV7 and PCV13 have an aluminum adjuvant in their composition that elicits a T-cell mediated response [143].

Ever since vaccines were introduced in the healthcare system, prevalence, fatality and admissions for invasive pneumococcal disease have decreased significantly [144].

Vaccine adverse events vary depending on whether the vaccine is adjuvanted or not. In a non adjuvanted vaccine, local reactions are present in 9% of people vaccinated intra muscularly and in 24% of those immunized sub-cutaneously [145]. In conjugated vaccines, this percentage rises to 50% [146]. Systemic reactions such as fever, irritability, decreased appetite and sleep disturbances occur in 80–85% of recipients of PCV or PPV. Symptoms like arthralgia, arthritis, myalgia, paresthesia and fatigue are more frequent in patients post PPV. This may be related to the fact that the vaccines are administered to different age groups.

Autoimmune risk following PPV vaccine is very low. Only 14 case reports were found after PPV vaccine. Six of these referred to reactivation of a previous autoimmune disorder. Studies directed to access vaccine safety in subjects with autoimmune diseases showed immunization was safe [147,148].

### 3.9. Tetanus vaccine

Tetanus toxoid (TT) is a potent exotoxin produced by the bacteria *Clostridium tetani*. The toxin has a predominant effect on inhibitory neurons, inhibiting release of γ-aminobutiric acid (GABA). When spinal inhibitory interneurons are affected the symptoms appear [149]. The vaccine against *C. tetani* contains deactivated tetanus toxoid plus an adjuvant (usually aluminium hydroxide).

The most studied and prevalent disease associated with TT is antiphospholipid syndrome (APS), but CNS complications have also been reported such as optic neuritis, acute myelitis and encephalomyelitis [150].

In mice, the immune response to TT depends on genetic background and to the specific adjuvant used for immunization. Naive BALB/c mice, immunized with TT, developed antibodies directed to TT, dsDNA and β2GPI and were extremely sick [90].

## 4. The diseases

### 4.1. Anti-phospholipid syndrome (APS)

APS is an autoimmune disease characterized by the occurrence of thrombotic events. Patients suffering from this condition have recurrent fetal loss, thromboembolic phenomena, thrombocytopenia as well as neurological, cardiac and dermatological involvement [151].

The serological marker of APS is the presence of anti-phospholipid antibodies (aPL), which bind negatively charged phospholipids, platelets and endothelial cells mainly through the plasma protein beta-2-glycoprotein-I (b2GPI). The presence of IgG and IgM anti-cardiolipin antibodies (aCL) and lupus anticoagulant is associated with thrombosis in patients with APS [151].

β2GPI was identified as the most important antigen in APS. β2GPI has several properties in vitro which define it as an anticoagulant (e.g., inhibition of prothrombinase activity, adenosine diphosphate-induced platelet aggregation, platelet factor IX production) [152]. Passive transfer of anti-β2GPI antibodies induce experimental APS in naïve mice and thrombus formation in ex vivo model [153].

Evidence suggests that the molecular mimicry mechanism between β2GPI and TT is one of the possible causes for APS.

Besides TT, APS has also been reported following HBV and influenza virus vaccination, although data are scarce [154,155].

### 4.2. Systemic lupus erythematosus (SLE)

SLE is a multisystem autoimmune disease characterized by the production of a variety of autoantibodies. IgG isotype antibodies to double-stranded DNA (dsDNA) are thought to be diagnostic markers and their presence correlates with disease pathogenesis. Several factors including genetic, hormonal, environmental and immune defects are involved in the induction of autoantibodies in this disease [156].

Post vaccination manifestations of SLE or lupus like syndrome have been reported and range from autoantibody induction to full blown clinical disease. Reports have been published associating SLE to HBV, MMR, dTP, HPV, influenza, BCG, pneumococcal and small pox vaccinations [157].

Vaccination in SLE diagnosed patients is associated with disease exacerbation and decreased antibody response, which may be due to the underlying disease and the frequent use of immunosuppressive drugs [158].

A temporal link between SLE and HBV vaccination is the only relation that has been demonstrated [159].

Several studies have demonstrated an increased prevalence of HPV in individuals with lupus compared to the general population, which has increased awareness for the need to vaccinate this high-risk population [160]. To do so, the association between immunization with HPV vaccines and SLE like symptoms, as well as the higher incidence of flares in known Lupus patients must be taken into account.

### 4.3. Vasculitis

Vasculitis is the name given to a group of autoimmune mediated diseases, which involve blood vessels of different types and sizes. They can be categorized according to several disease features indluding: the type of vessel affected, organ distribution, genetic predisposition and clinical manifestation [161].

#### 4.3.1. Large vessels vasculitis

So far, 18 cases of large vessel vasculitis have been detected. This includes 15 cases of giant cell arteritis (GCA) following influenza vaccination, 2 cases of Takayasu disease (TD), and one case of large cell arteritis involving subclavian and renal arteries following HBV vaccines.

Two of these patients had previous received the diagnosis of ankylosing spondylitis and polymyalgia rheumatica (PMR)-like illness [162].

#### 4.3.2. Medium vessels vasculitis

One case of polyarteritis nodosa (PAN) following the administration of Tetanus and BCG vaccine is described. All other cases of PAN in adults follow the administration of HBV vaccine [163–165].

Case reports of medium vessels vasculitis – both polyarteritis nodosa and Kawasaki disease (KD) – have also been published in pediatric patients. KD has been described one day after the second dose of HBV vaccine and following yellow fever vaccine [166,167]. Two cases of pediatric patients with PAN have been reported two months after receiving the HBV vaccine [164,165].

#### 4.3.3. Small vessels vasculitis: ANCA-associated vasculitis

Eosinophilic granulomatosis with polyangiitis (EGPA) after tetanus vaccination [163] and following HBV vaccine [168] have been reported. There are also 3 cases of microscopic polyangiitis (MPA) and 6 cases of granulomatosis with polyangiitis (GPA) following influenza vaccines in the literature [169,170].

#### 4.3.4. Immune complex small vessels vasculitis

Henoch Schönlein purpura (HSP) is the most common vasculitis of childhood. It is generally benign and self-limited. It is mediated by IgA immune complex deposition in various tissues as well as in small-sized blood vessels. Genetic risk factors play an important role in the pathogenesis of the disease: it is associated with HLA-DRB*01, 07 and 11. HSP was associated with seasonal influenza, influenza A (H1N1), pneumococcal and meningococcal disease, hepatitis A virus (HAV), HBV, anti-human papilloma virus (HPV) vaccines, and following multiple combinations of vaccines, such as typhoid, cholera and yellow fever [139,171–173].

Leukocytoclastic vasculitis has been associated with several vaccines, including influenza vaccine [174], HAV vaccine [175], HBV vaccine [176], pneumococcal vaccine [177], varicella [178], rubella, smallpox [179] and the anthrax vaccine [180].

Dermal vasculitis with pan uveitis has also been described following MMR vaccine [181].

### 4.4. Rheumatoid arthritis (RA)

RA is the most prevalent chronic inflammatory arthritis affecting the synovial membrane of multiple diarthrodial joints. Although its etiology has not been completely clarified, deregulation of the immune system is evident with a preponderance of inflammatory cytokines and immune cells within the joints.

RA has an estimated heritability of 60%, leaving a substantial proportion of risk to environmental factors. Immunizations have previously been proposed as potential environmental triggers for RA. In the Norfolk Arthritis Register database, 19 of the first 588 patients reported receiving a tetanus vaccination within 6 weeks prior to the onset of arthritis. Similarly, a transient rise in RF titer was recorded in 10 out of 245 military recruits 2–3 weeks after receiving concomitant immunization against tetanus, typhoid, paratyphoid, mumps, diphtheria, polio and smallpox. However, only 2 showed a persistent elevation in titer and none developed arthritis [182].

Several mechanisms have been proposed to explain the putative association between vaccination and the initiation of RA, the most prominent of which are molecular mimicry and non-specific immune system activation [182].

Vaccines who have been associated with RA include rubella vaccine in which reactive arthritis occurs in 5% of recipients. Controlled studies failed to show persistent arthritis or arthralgia in these patients [110].

Patients following HBV vaccine showed an increase of arthritis in a VAERS study, but this was not seen in a large retrospective epidemiological study [183].

Data so far suggest that vaccines carry an insignificant role in the pathogenesis of RA.

#### 4.4.1. Vaccines in the therapy of RA

Several mechanisms are being studied to produce vaccines mainly targeting inflammatory cytokines as “antigens” such as TNF, aiming to induce high titers of endogenous neutralizing anti-cytokine antibodies with the goal of breaking natural Th tolerance to auto antigens. Other cytokines, namely IL-1 IL-6, MIF, RANTES, IL-18, MCP-1 are also being tested [184].

Another vaccine related therapy uses autologous T cell lines to induce a specific immune response by the host’s T cells directed against the autoimmune (vaccine) T cells [185]. This strategy has been successful in mouse models and has shown encouraging results in a small pilot study of 15 RA patients, where 10 patients showed a clinical response, defined by ACR 50 improvement criteria [186].

### 4.5. Undifferentiated connective tissue disease (UCTD)

UCTD is a clinical condition characterized by signs, symptoms and laboratory tests suggestive of a systemic autoimmune disease but that does not fulfill the criteria for any defined connective tissue disease (CTD).

Such patients with clinical manifestations suggestive of systemic connective tissue disease but not fulfilling any existing criteria are quite frequent: 12-20% of the patients initially asking for a rheumatologic evaluation may at least temporarily be diagnosed as affected by ‘undefined’ or ‘undifferentiated’ connective tissue disease.

Comparing studies on these diseases is unfeasible because of the inexistence of defined criteria for diagnosis [187].

Within 5 years of follow-up, patients usually evolve to defined CTDs, which include SLE, systemic sclerosis (SSc), primary Sjögren’s syndrome (pSS), mixed connective tissue disease (MCTD), systemic vasculitis, poly-dermatomyositis (PM/DM) and RA. Maintaining an undefined profile for 5 years makes evolving into CTDs less probable and the diagnosis of “stable UCTD” reliable [188].

Disease etiology is a concern and it has been associated with Vitamin D deficiency and silicone implants, both of which lead to an imbalance in proinflammatory and anti-inflammatory cytokines [189].

Vaccines have also been associated with this disease, namely the HBV vaccine [190].

Etiopathogenesis of UCTD is unknown and it has been suggested it might fall on ASIA spectrum since symptomatic similarities are striking and UCTD etiopathogenesis has been associated with adjuvants [122].

### 4.6. Alopecia areata (AA)

AA is an autoimmune disease, characterized by one or more well demarcated oval and round non-cicatricial patches of hair loss. The disease may affect any hair bearing part of the body and has a great impact on a patient's self-esteem and quality of life.

Depending on ethnicity and location, AA is the most prevalent skin disease. AA prevalence varies and is estimated to be between 0.1–0.2% in the United States and 3.8% in Singapore [191,192].

As with any other autoimmune disease, the development of AA encompasses genetic and environmental factors. Environmental factors associated with AA development are emotional and/or physical stress, infections and vaccines [193].

Secondary syphilis is one of the most well studied examples, however Epstein Barr Virus [194] and Herpes Zoster [195] infections have also been related to the development of the disease.

As far as vaccines go, HBV vaccine has been associated with AA development. In one study of 60 patients, 48 developed AA after vaccination with HBV vaccine. Of those 48 patients, 16 were re-challenged, and the reappearance of disease was witnessed [196]. In mice this association failed to be established [197]. One case of AA was witnessed following Tetanus Toxoid, as well as two case reports following HPV and MMR vaccine [198–200].

### 4.7. Immune thrombocytopenic purpura (ITP)

ITP is an autoimmune disease defined by a platelet count of less than 105 platelets/μL without overlapping diseases. It can present with or without anti-platelet–antibodies. Thrombocytopenia is relatively common and the overall probability of developing ITP was 6,9% in a cohort of 260 patients. It was also found that 12% of patients developed an overlapping AID other than ITP [201].

The etiology of the disease is yet to be fully understood but it has been detected following infectious diseases, such as Helicobacter pylori, hepatitis C virus (HCV), novel influenza A infection, rotavirus infection and human immunodeficiency virus (HIV) [202].

ITP onset has also been reported, although rarely, as a severe adverse event following vaccine administration. This was more often observed after measles–mumps–rubella (MMR), hepatitis A and B, diphtheria–tetanus–acellular pertussis (DTaP), and varicella vaccinations [203].

Molecular mimicry has been suggested as a possible mechanism for the development of ITP, namely following Helicobacter Pylori infection. Its eradication has been shown to increase platelet count and diminish the levels of anti-CagA antibody in a subset of H. Pylori infected subjects with ITP [204].

These data point towards a beneficial role of H. pylori eradication in chronic ITP.

Two cases of ITP following anti-rabies vaccine have been reported and one after HPV vaccine. Reactivation of ITP was reported two weeks after a tick-borne encephalitis vaccination [202]. The most consistent association with ITP is with the MMR vaccine [205]. However, it should be emphasized that the number of cases are fewer than expected without vaccination.

### 4.8. Type 1 diabetes (T1D)

T1D is due to antigen specific reactions against insulin producing beta cells of the pancreas. Much like other autoimmune diseases, T1D results from a combination of genetic, environmental, hormonal and immunological factors. Environmental factors such as pathogens, diet, toxins, stress and vaccines are believed to be involved in the beginning of the autoimmune process [206].

Although the mechanisms by which viral infections cause autoimmune diabetes have not been fully clarified, there is some evidence to suggest a role for natural infections in the pathogenesis of T1D mellitus in susceptible individuals [207].

It has been hypothesized that vaccination could trigger T1D in susceptible individuals. Although post-vaccination T1D may be biologically plausible, cumulative evidence has not supported an increased risk of T1D following any vaccine [208].

Several experimental data have suggested that, depending on the timing, vaccination might exert a protecting or aggravating effect on the occurrence of diabetes [209].

A study suggests that *Haemophillus influenza* type b vaccine might be a risk factor in the induction of islet cell and anti-GAD antibodies measured at one year of age [210] but there are previous studies that show no association between Hib and T1D [211].

In a cohort of American military officers diagnosed with T1D, there was no association found between vaccination and T1D diagnosis [212].

Available data about a relation between the mumps vaccine and T1D are still incomplete and their interpretation is difficult because of miscellaneous confounding factors associated with the development of T1D [213].

Association between Hemagglutinin 1 Neuraminidase 1 (H1N1) vaccines and T1D is so far unproven [214].

In humans, it has been hypothesized that early-age BCG vaccination is associated with the risk of T1D. The few studies conducted to date provided no consistent evidence of an association. There are, however, studies showing a possible temporary boost of the immune function after vaccination [215]. Studies also show that among BCG-vaccinated children who test positive for islet autoantibodies, there is a higher cumulative risk of T1D [216].

In animal experiments it has been observed that BCG seems to have a protective effect against diabetes, however researchers have yet to translate this benefit to humans [217].

In all, studies results do not support any strong association between vaccination and T1D.

### 4.9. Narcolepsy

Narcolepsy is a sleep disorder described as excessive sleepiness with abnormal sleep pattern characterized by uncontrollable rapid eye movement (REM) events which occur at any time during the day. These event and may or may not be accompanied by a loss of muscle tone (cataplexy) [218].

A plethora of data indicates that narcolepsy is caused by the lack of orexin (also known as hypocretin), an important neurotransmitter, which is involved in the regulation of the sleep cycle. In Narcolepsy patients, a loss of orexin producing neurons in the hypothalamus and low levels of orexin in the cerebrospinal fluid (CSF) has been reported [218].

Narcolepsy has been shown to have an autoimmune background. Antibodies against Tribbles 2 (Trib2) have been found in these patients, which may be related to the pathogenesis of disease. An experimental model of narcolepsy in mice has been made by passive transfer of total IgG from narcolepsy patients into the animal's brains through intra ventricular injection [219].

Environmental factors like Influenza A virus and streptococcal infections have been associated with disease onset. Interestingly, fever by itself without the diagnosis of an infectious etiology was found to be a risk factor for narcolepsy [220].

Several groups have studied and found an increase in the incidence of narcolepsy diagnosis following the introduction of influenza vaccination, specifically, ASO3-adjuvanted Pandemrix™ vaccine. This association was shown in Finland especially in 4–19 year-olds, but also in case reports from other countries [221]. Other studies failed to find an association.

The actual infection with H1N1 has been associated with disease development in China, however no such relationship has been noted in Europe [220].

The above-mentioned associations are specifically related to the ASO3-adjuvanted Pandemrix™ vaccine. The same association has not been reported for other H1N1 adjuvanted or non-adjuvanted vaccines.

The major difference between the ASO3 and the MF59 adjuvants is the presence of the α-tocopherol.

α-tocopherol is unique in that it can achieve the highest and longest antibody response by producing an enhanced antigen-specific adaptive immune response. In vitro it was shown that α-tocopherol could increase the production of orexin as well as increase the proteosome activity. This increased production of orexin fragments may facilitate antigen presentation to MHC class II, thus triggering an autoimmune process [220].

All these data together support the relationship between the H1N1 Pandemrix™ vaccine and the development of narcolepsy.

### 4.10. Celiac disease

Gluten induced enteropathy, gluten sensitive enteropathy, or more commonly called celiac disease (CD) is a life-long autoimmune condition mainly of the gastrointestinal tract, specifically affecting the small intestine.

The abnormal immune response crates autoantigens which are directed towards Tissue transglutaminase (tTG). The two main autoantibodies and the most widespread serological markers to screen for the disease are anti tTG and anti endomysium. Two additional auto-antibodies, namely: anti deaminated gliadin peptide and anti-neoepitope tTG were found recently to be reliable for CD screening as well [222].

CD is an autoimmune disease induced by well-known nutritional environmental factors. The non-dietary ones are less studied and established. Several infectious disease have been linked to its development, the so-called infectome [193].

A clear cause-effect relation is yet to be established for most of the pathogens associated with CD. What has been shown, however, is that in countries with low economic status, inferior hygiene conditions and higher infectious load, CD prevalence is lower [223].

An epidemiologic relationship was established in 2006 between rotavirus infection and CD. Data showed that in genetically predisposed individuals, rotavirus infection was related to childhood CD development [224].

In subsequent research studies, a celiac peptide was recognized and proved to share homology with rotavirus major neutralizing protein VP7 and with the CD autoantigen tTG. The antibodies directed against the viral protein VP7 were shown to predict the onset of CD and induce typical features of CD in the intestinal epithelial cell-line T84 [225].

It has also been suggested that rotavirus vaccine alters B and T behavior, as the percentage of B-cells was higher in the vaccinated infants [226].

Rotavirus vaccine as an inducer of CD is still in discussion and warrants further study.

### 4.11. Polymyalgia rheumatica (PMR)

PMR is an autoimmune inflammatory rheumatic disease characterized by raised inflammatory markers with pain and morning stiffness of shoulders and pelvic girdles and synovitis of proximal joints and extra-articular synovial structures. Its diagnosis is clinical and it is typically a disease of the elderly occurring mainly in subjects above 70. Etiopathogenesis of PMR remains unknown, but genetic and environmental factors play a role [227].

A close temporal relationship has been ascertained concerning epidemics of *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, Parvovirus B19 and peaks of cases of PMR and giant cell arteritis, however this is not clearly proven [228].

Cases of PMR following vaccination have rarely been reported. However, it is believed that post vaccination PMR may be underreported due to its symptomatic similarities with the transient effects of vaccines, namely: arthralgia, myalgia and low-grade fever. This leads to failure in establishing a chronological relationship when the disease is diagnosed.

Most of the reported cases are associated with seasonal influenza vaccine (Inf-V). Often, the time interval between vaccine administration and symptoms onset varies from one day, to three months. Three cases were reported with associated Giant Cell arthritis. A case report of relapsing PMR after four years of remission following tetanus vaccination has also been reported [229,230].

### 4.12. Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system (CNS).

ADEM is usually poly-symptomatic with encephalopathy (i.e., behavioral change or altered level of consciousness). It affects mostly children and young adults and has higher prevalence in males. Its incidence is 0.6–0.8 per 100 000 per year [231].

Although there is no concrete evidence of a clear pathogenic association, ADEM has been associated with immunization or previous viral infection. Post-vaccination ADEM accounts for only 5-10 percent of all cases, while post-infectious ADEM accounts for 66 percent of all cases of ADEM [232].

The hypothesis that better describes these associations is molecular mimicry. T-cells targeting human herpesvirus-6 (HHV-6), coronavirus, influenza virus and Epstein-Barr virus (EBV) have been shown to cross-react with myelin basic protein (MBP) antigens. Anti-MBP T-cells were detected in patients following vaccination with simple rabies vaccine [233–235].

In a post experimental therapy for Alzheimer's disease with a vaccine that contained aggregates of synthetic Aβ42 fragments of amyloid precursor protein, ADEM was shown to develop in mice [236]. The experimental model of MS, EAE mice, may be induced with injection of Aβ42, but only when the latter is administered together with the complete Freund's adjuvant [237]. This observation points to the importance and central role of the adjuvants in induction of ADEM and autoimmunity in general [238].

The overall incidence of post vaccination ADEM is estimated to be 0.1–0.2 per 100 000 and a higher risk has been reported following immunization against measles. Other vaccines accountable for post-vaccination ADEM include vaccines against the varicella zoster, the rubella, the smallpox and the influenza viruses [239]. Surprisingly, certain vaccines such as anti-tetanus vaccine were shown to have a negative correlation with ADEM (statistically significant decreased risk) [240].

HBV immunization has been studied as a possible cause for ADEM but was later associated with clinically isolated syndrome (CIS) (a first time occurring demyelinating episode that may, or not develop to MS) and complete conversion to MS [241].

As far as case reports are concerned, ADEM was associated with vaccination with influenza, hepatitis A and B, MMR, HPV and tetanus [121,242,243].

### 4.13. Bullous dermatoses

Bullous dermatoses are characterized by the presence of blisters and autoantibodies against structural components of the skin: desmosomal proteins (in pemphigus), adhesion molecules of the

dermal-epidermal junction (in pemphigoid diseases), and epidermal/ tissue transglutaminase (in dermatitis herpetiformis).

The most frequent autoimmune bullous diseases are bullous pemphigoid (BP) and pemphigus vulgaris (PV). BP is more frequently observed in the elderly, while the age of onset of PV is between 40 and 60 years. Neither of the diseases have any gender preference [244].

BP and PV etiology is, so far, poorly understood. Both diseases have been associated with various environmental factors, which include emotional and/or physical stress, infections and vaccinations [244].

Genetic predisposition has also been studied with overexpression of certain HLA class II alleles. These include HLA-DQB1*0301, DRB1*04, DRB1*1101, and DQB1*0302. These alleles have been found to be more prevalent in BP patients than in the general population [245]. PV is associated with certain HLA class II loci such as HLA-DR4 and HLADR14 alleles (DRB1*0401 and DRB1*0402, which is prevalent in Ashkenazi Jews, Iranian and Sardinian patients). Other loci include DRB1*1401 (common among Japanese and Italian patients) and two DQB1 alleles (DQB1*0302 and DQB1*0503), which are strongly associated with PV.

BP and PV patients' sera were found to have significantly higher prevalence of antibodies to hepatitis B virus, hepatitis C virus, helicobacter pylori, toxoplasma gondii and cytomegalovirus [244].

As far as vaccination is concerned, BP developed in patients following influenza, diphtheria, tetanus, pertussis, hepatitis B, BCG, polio and herpes zoster vaccines [140,246,247] Furthermore, reactivation of BP following influenza vaccination was reported in one case report [248].

New onset PV was associated with: influenza vaccine, hepatitis B vaccine, anthrax vaccine, typhoid booster and rabies vaccination. In addition, exacerbation of PV after vaccination was also reported following influenza vaccine and tetanus vaccine [121].

### 4.14. Idiopathic inflammatory myopathies (IIM)

IIM compose a group of skeletal muscles diseases in which myositis without a recognized cause occurs. IIM is usually subdivided in 4 entities: dermatomyositis (DM), polymyositis (PM), inclusion body myositis (sIBM) non-specific myositis (NSM) and immune mediated necrotizing myopathy (IAM) [249].

IIM prevalence is around $1.1 \times 10^{-6}$ cases, with a bimodal age of distribution that peaks in childhood and again between 45 and 55 years. DM is the most common inflammatory myopathy while PM is the least frequent.

Despite exhibiting similar clinical symptoms, the subsets of IIM exhibit significant immunopathological variation. DM begins with the activation of the complement and formation of membrane attack complexes (MAC). In PM and sIBM the fundamental process is related to CD8+ T cells mediated cytotoxicity [249].

It is unclear what breaks the tolerance and drives the immune response to induce IIM. So far, DM, PM and sIBM have been linked to vaccination. Several cases have been reported in the literature associating different vaccines with the development of idiopathic inflammatory myopathies. 119 cases of IIM had been reported to VAERS database up to June 2013. Out of these 119 cases, 33 were classified as PM, 85 as DM and an only one as a sIBM. DM has been reported after almost any vaccine, however only a few studies have attempted to clarify the possible relationship between DM and vaccination. PM is a frequent misdiagnosed disorder. Some reports have associated previous immunization, especially hepatitis B vaccine with PM [250]. Despite being recently differentiated from other IIM, sIBM has already been related to HBV vaccine [250]. Some vaccines associated with myositis are MMR vaccine, smallpox vaccine, Poliomyelitis (IPV), diphtheria and tetanus toxoid, influenza, HPV and BCG [250].

### 4.15. Fibromyalgia syndrome (FMS)

FMS is an entity that is related to the inability of the CNS to modulate pain.

The conditioned pain modulation process in the CNS appears to be compromised among many FMS patients, which might explain the enhanced pain sensation experienced by these patients [251].

The etiology of FMS is yet to be unveiled. Genetic predisposition, physical trauma (particularly to the cervical spine), emotional stress (to various stressors) as well as a variety of infections have been linked with FMS.

Vaccines have been associated with the triggering of FMS namely rubella and Lyme disease vaccines [252]. There are several reports of fibromyalgia-like disease after vaccination, specifically HPV (Martinez-Lavin Journal of Clinical rheumatology 2014). The medical community and regulatory agencies should be aware of these possible adverse effects aiming at defining their magnitude.

### 4.16. Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME)/systemic exertion intolerance disease (SEID)

Chronic fatigue syndrome (CFS) is a disease characterized by disabling fatigue, headaches, concentration difficulties and memory deficits (90%). Other symptoms such as sore throat (85%), tender lymph nodes (80%), skeletal muscle pain and feverishness (75%), sleep disruption (70%), psychiatric problems (65%) and rapid pulse (10%) are often observed. It more frequently affects women and has a prevalence of 0.2-2.6% [253].

Although disease etiology is still unknown, there are several pathogens, such as Epstein–Barr virus (EBV), which have been associated with CFS. Patients often have higher titers of IgM to the EBV viral capsid antigen. Cytomegalovirus and human herpes virus 6 antibodies were also detected more often in CFS patients, although other reports failed to replicate these results. Parvovirus B19 infection has also been suggested as a trigger to CFS [253–255].

Vaccine inoculation has also been appointed as a probable cause. Vaccinations against rubella, Q fever and hepatitis B were found to be associated with higher risk of developing CFS while meningococcal vaccine, poliovirus and influenza vaccine were not. Surprisingly, staphylococcus toxoid vaccine appeared to have a protective effect [121,256,257].

### 4.17. ASIA syndrome

Defined in 2011 by Shoenfeld and Agmon-Levin ASIA syndrome is characterized by hyperactive immune response to adjuvants [4].

As previously stated, ASIA incorporates four known medical conditions: Siliconosis, GWS, MMF, and post-vaccination phenomena [4]. Recently, the sick building syndrome (SBS) was proposed as a candidate for the ASIA spectrum [258]. All of these diseases satisfy several criteria for FMS and SEID [252].

a Macrophagic myofasciitis (MMF)

MMF has been described as an emerging condition of unknown cause characterized by a pathognomonic lesion in muscle biopsy mixing large macrophages with submicron to micron-sized agglomerates of nanocrystals in their cytoplasm and lymphocytic infiltrates. These lesions were related to aluminum deposits in muscle following immunization with aluminum containing vaccines [63].

MMF lesion is now universally recognized as indicative of a long-lasting persistence of aluminum adjuvant at the site of prior

intramuscular immunization. The long-lasting MMF lesion should be considered as a biomarker of aluminum bio persistence in a given individual.

Patients with MMF have higher reported myalgia with incidence being up to 90%. Its etiology is not clear but genuine muscle weakness is rare and the diagnosis of fibromyalgia is also rare. Higher prevalence of chronic fatigue syndrome (CFS) in patients with MMF has been reported as well.

Cognitive impairment has been associated with MMF: in one series of 105 MMF patients, up to 97% had attention and memory complaints and neuropsychological tests were abnormal in 89% [259].

b Gulf War syndrome (GWS)

GWS is a clinical entity specifically related to a certain time and place in history. It was described among veterans of the military conflict occurring in 1990–1991 in the Persian Gulf.

The syndrome is characterized by chronic fatigue, musculoskeletal symptoms, malaise and cognitive impairment. It clinically overlaps with Post Traumatic Stress Disorder (PTSD), FMS, CFS and other functional disorders [260].

The unique conditions that have been associated so far with disease development are the exposure to extreme climate in the Persian Gulf, exposure to various chemicals (pesticides, depleted uranium), stress provoked by prolonged waiting without actual combat and the intense exposure to vaccinations of the soldiers for fear of biological weaponry [260].

Comparing Gulf War veterans and veterans of the Bosnian conflict, multiple vaccinations administered to servicemen in the Gulf War was identified as a unique exposure [261].

The mechanism through which vaccination exposure may lead to the development of functional symptoms is not completely understood. The possibility that a shift from Th1 to Th2 type reactions could be of pathogenic significance was raised and is supported by an increased frequency of allergic reactions, low natural killer cell activity and low levels of interferon γ and IL-2 in these patients [262].

One study with GWS patients showed a connection between anti-squalene antibodies and symptoms development. This was refuted by a larger study that found no association between anti-squalene antibodies and chronic multi-symptom illness [263].

c ASIA registry

A registry is a collection of data related to patients with the same specific characteristic. It is often the first approach in the study of an area of inquiry. In rare diseases, registries are often the way to get a sufficiently sized sample of patients which can be used either for epidemiological or research purposes.

ASIA syndrome may be underreported because of unawareness and failure to connect the syndrome with the exposure. This registry was created to fully understand the clinical aspects of disease and compare patients from all over the world in order to have fully validated criteria for disease diagnosis and also to define demographic and environmental history of disease.

The ASIA Syndrome registry website can be found on the following link: https://ontocrf.costisa.com/en/web/asia. Only cases reported by physicians are accepted.

**Table 4**
Most common autoimmune inflammatory rheumatic diseases (AIIRDs) and non-inflammatory autoimmune rheumatic diseases (ARDs).

| AIIRDs | ARDs |
|---|---|
| Rheumatoid arthritis | Degenerative spine diseases |
| Ankylosing spondylitis | Osteoarthritis |
| Reactive arthritis | Osteoporosis |
| Connective tissue diseases | Fibromyalgia |
| Polymyalgia rheumatica | |

## 5. Vaccination in autoimmune diseases.

### 5.1. Autoimmune rheumatic diseases (Table 4)

To make an informed decision in medicine, there is always a need to weigh the pros and cons. ARDs may play an important role in deciding whether vaccination is or is not appropriate to a patient. In these cases, patients are immunosuppressed on account of their diagnosis and even more so if they are under specific immunomodelatory medication [4].

If the efficacy of vaccination is reduced, there is a potential for development of disease flares following vaccination. In the case of live vaccines, its inoculation may even be enough to trigger disease in the host.

For these specific reasons, live vaccines are generally contraindicated in patients receiving immunosuppressant medication. There is a need for screening and treatment of Latent Tuberculosis Infection (LTBI) before starting anti-TNF-alpha therapy. The same is true for vaccination. Preferably, even recommended vaccination (see Table 5) should be administered before the initiation of Disease-Modifying Anti-rheumatic Drugs (DMARDs) because these may reduce vaccine efficacy [264].

### 5.2. Autoimmune inflammatory rheumatic diseases (AIIRD)

Immunosuppression equals high risk of infection and lower vaccine efficacy.

Taking into account safety concerns and efficacy, the EULAR recommendations for immunizations in AIIRD patients are:

- Assess vaccination status in initial investigation.
- Administer vaccines in a stable disease phase.
- Live attenuated vaccines are to be avoided especially if immunosuppressive agents are being administered. BCG is not recommended.
- Administer vaccines ideally before starting DMARDs and anti-TNFα agents.
- Influenza and 23-valent polysaccharide pneumococcal vaccination is recommended.
- Tetanus toxoid vaccination is recommended following recommendations of general population, in case of major and/or contaminated wounds in patients receiving rituximab in the previous 24 weeks Tetanus Ig is indicated.
- HPV and Herpes Zoster should be considered.
- In hyposplenic/asplenic patients, influenza, pneumococcal, Haemophilus Influenza b and Meningococcal C are advisable.
- Hepatitis A and B is recommended in patients at risk.
- Travel patients should be immunized according to general population guidelines except for live attenuated vaccines, which are to be avoided [148].

**Table 5**
Vaccination recommendation in ARDs [265].

| Vaccines | | Recommended | Not recommended | Special 5emarks |
|---|---|---|---|---|
| Live | BCG | | X | |
| | Herpes zoster | Previous contact with varicella (vaccine/infection) | Highly immunosuppressed patients[a] | Single dose >50 y |
| | Yellow fever | Endemic areas [266] | | Routine immunization not recommended |
| | MMR | X | | |
| Non-live | Influenza | X | Allergy to egg or the vaccine itself; GBS up to 6 weeks after vaccination | Annual<br>Rituximab: before starting/6 mts after 1st infusion/4 wks before next dose [148,267] |
| | Pneumococcal | X | | 1 Initial dose + 1 booster (5 y later) |
| | DTaP and DT | X | | DTaP every 10 y<br>Tetanus Igb if exp |
| | Meningococcal | X | | Low data support [268] |
| | Hep A | X | | |
| | Hep B | Neg HBsAg in serum | | |
| | HPV | Adolescents and young women | | Preferably before initiating sexual activity |
| | Hib | X | | |

X – for all ARDs patients; MMR: measles, mumps and rubella; Hib: haemophilus Influenza type B; DTaP: diphteria, tetanus and pertussis; DT: diphteria and tetanus; Hep: hepatitis; Igb: immunoglobulin; y: years; mts: months; wks: weeks; HPV: human papilloma virus; GBS: guillain barré syndrome; exp: exposure; Neg HBsAG: negative hepatitis B antigen.

[a] Highly immunosuppressed patients: high doses of corticosteroids (>20 mg of prednisone per day or equivalent) for 2 weeks or longer, pulse therapy, cytotoxic or alkylating agents, synthetic DMARDs at doses above those recommended, or immunobiological therapy [264].

## 6. Conclusions and future perspectives

Vaccines have many beneficial effects in combating infectious diseases and preventing mortality and morbidity. They have also proved to be effective cancer treatments by immunomodulation, as demonstrated by the intravesical administration of BCG to treat superficial bladder cancer [28].

Vaccines are however, linked to autoimmunity. Beneficial outcomes, like the adjuvant effect are based on immunity triggering and enhanced immunity mechanisms. These same responses account for autoimmunity exertion. Vaccines induce the production of autoantibodies, but their pathologic effect is yet to be unveiled.

Although vaccines are widely considered safe, there are subjects with predispositions to whom vaccines pose a bigger threat. An example is the fact that animal models with autoimmune predispositions develop autoimmune disease following adjuvant exposure.

As many as 1% of recipients of aluminum containing adjuvants may be sensitized to future exposure [269].

Silicon-induced inflammatory fibro proliferative response is irrefutable and well documented. The presence of anti-silicone antibodies and silicone-associated autoimmune phenomena seems very plausible.

ASIA syndrome and aluminum safety studies show that the use of aluminum containing "placebo" in control groups in vaccine safety studies should be carefully evaluated. New studies must be performed using a proper placebo to adequately test vaccine safety. Another evident failure in vaccine safety studies are the short-term periods which are evaluated. Continued immune system activation has been observed to be a potential mechanism of disease. A disease which is poorly understood so far.

Vaccine recommendations should be reassessed frequently in different subsets of the population. This does not invalidate the need for vaccines, however, the lower the possibility of exerting adverse events, the easier it will be for the potential benefits to outweigh the risks.

Vaccinomics represents a major breakthrough in vaccine development and can lead to the development of targeted vaccines to peptides most likely to be immunogenic [81]. A predictable response to vaccine can be achieved by differentiating the host variability. This can be achieved namely in genetics and pathogen variability. Developing a vaccine accordingly will lead to increased specificity in treatment and leave less room for adverse events. By using immunomodulation, vaccinomics can also give rise to novel therapies for autoimmune diseases.

There are several reports of cases of autoimmunity diseases following vaccines but despite in vitro positive results and due to both the limited number of cases and the long latency period of the diseases, every attempt for an epidemiological study has failed to deliver a connection.

Classification as ASIA syndrome, in detriment of classic specific autoimmune diseases, could be the key to finding effective preventative therapeutic strategies. It will enable the study of bigger patient clusters with earlier diagnoses.

Future studies that could help clarify the association between vaccinations, adjuvants and autoimmunity should ideally have a different design, more long-term data and should include autoimmune phenomena as well as large-scale epidemiological studies of autoimmune diseases.

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