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Review Article

# Induction of Autoimmune Diseases Following Vaccinations: A Review

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## Abstract

Autoimmune reactions to vaccinations have been reported since vaccines were introduced into modern medical technology. Here, we discuss the possible underlying mechanisms of autoimmune reactions following vaccinations and review cases of autoimmune diseases that have been correlated with vaccination. Molecular mimicry and bystander activation are reported as possible mechanisms by which vaccines can cause autoimmune reactions. Idiopathic Thrombocytopenia Purpura, Myopericarditis, Primary Ovarian Failure, Systemic Lupus Erythematosus (SLE) and Acute Disseminated Encephalomyelitis (ADEM) are all autoimmune conditions with reported links to vaccinations. Genetic predisposition was a definite risk factor for people experiencing autoimmune conditions following immunization; thus understanding the genome of patients is vital for both the development of future generations of vaccines and personalized medicine. Further study is encouraged into the direct associations between vaccines and autoimmune conditions, and the biological mechanisms behind them.

## Introduction

Up till date, vaccines and vaccination has the most efficient way of treating and preventing diseases that are mainly infectious as well as neoplasm. Many infectious diseases that were killing people in millions or making them potentially disabled such as Poliomyelitis has been eradicated. Since Edward Jenner's first use of a vaccine against smallpox in 1796, the use of vaccines has become indispensable to the eradication of disease. In the 20th century alone, smallpox claimed an estimated 375 million lives, but since 1978, after the completion of a successful eradication campaign, no death was reported [1]. Today, more than 70 vaccines have been licensed for use against approximately 30 microbes, thus saving countless of lives [2,3]. Diseases including poliomyelitis, measles, mumps, rubella, and others were targeted for vaccination and Polio, for example, was eliminated in the United States by 1979 after widespread vaccination efforts [4]. Five more infectious diseases have been identified as of April 2008 as potentially eradicable with current technology by the Carter Center International Task Force for Disease Eradication i.e. measles, mumps, rubella, lymphatic filariasis and cysticercosis. Limitations on their effectiveness, nevertheless, exist [5].

Many factors can be attributed to the non-effectiveness of vaccinations; mostly chronic diseases that interfere with the immune response to individuals such as diabetes, Human Immunodeficiency Virus (HIV), steroids use for autoimmune diseases or inflammatory diseases, and aging. It could also be due to genetic reasons if the host's immune system includes no strains of B cell lymphocytes that can generate antibodies suited to reacting effectively and binding to the antigens associated with the pathogen which is an important step in fighting the infection and some other condition. Timing in the effectiveness of vaccines is very crucial as slow immunity will lead to a delayed response. Thus, antibodies will not perform their function of making the causative pathogen to be less virulent. Molecular biology and genetic engineering made the creation of many new and improved vaccines possible [6,7]. Twenty percent (20%) of infants are still missed by the six vaccines against diphtheria, pertussis (whooping cough), polio, measles, tetanus and tuberculosis which account for about two million unnecessary deaths each year, especially in the most remote and impoverished parts of the globe [8].

### Brief definition of vaccines and vaccination

Vaccination or immunization is the use of a vaccine to protect, boost and stimulate the immune system of an individual in order to develop adaptive immunity to a specific pathogen. A vaccine is a biological preparation that provides active acquired immunity to a particular disease mainly infectious. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins [9]. These vaccines might be contra indication in some patients or delayed in patients having fever. Based on this principle, the prophylactic effect of this modern medicine can be applied.

Beside the active vaccine itself, the following chemicals are commonly present in vaccine preparations [10]; (1) Aluminum salts or gels Adjuvants are added to promote an earlier, more potent response, and more persistent immune response for the vaccine, (2) Formaldehyde is used to inactivate bacterial products for toxoid vaccines, (3) Monosodium Glutamate (MSG) and 2-phenoxyethanol are used as stabilizers, (4) Thimerosal is a mercury-containing product; thus, it has been removed from most vaccines due to the controversy surrounding it [9-12]. Adjuvants which are compounds added to vaccines for enhancement of immunogenicity has several advantages that include dose sparing as well as induction of a more rapid broader and strong immune response; many have been approved, including aluminum salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04 [13].

Autoimmune reactions to vaccinations have been recorded since vaccines were introduced into modern medical technology. While extremely rare, some vaccines have been linked to an increased chance of an autoimmune reaction, and may be higher in predisposed patients. Here, we discuss the possible underlying mechanisms of autoimmune reactions following vaccinations, and review cases of autoimmune diseases that have been correlated with vaccination.

## Molecular Mimicry and Bystander Activation

Molecular mimicry in itself is not sufficient to trigger autoimmune pathology, other factors intrinsic to infections, such as tissue damage and long-lasting inflammatory reaction, might be required as well. For example, a new Lyme disease vaccine contains an immunodominant epitope of the outer surface protein A of *Borrelia burgdorferi* that displays great homology to human lymphocyte function-associated antigen-1, an adhesion molecule of the 2 integrin family. Although this homology raised concern about the safety of this vaccine, there was no evidence for increased frequency of arthritis in individuals who received the Lyme vaccine [14].

The immune system has a tremendous potential for recognizing "self" cells and initiating an autoimmune condition. However, it has many checks and balances that help prevent autoimmunity; for example, IL-10, and T-regulatory cells. The same checks and balances help limit the cell mimicry and immune cell auto-reactivity following vaccination [14].

Bystander activation represents a second mechanism that has been theorized in an effort to explain autoimmune disease development through vaccination. In bystander activation, microbial infection causes the release of sequestered self-antigens from host tissue. Released antigens from infected tissue activate antigen-presenting cells (APCs) to both secrete cytokines and activate dormant auto-reactive T-helper cells. These auto-reactive T cells, along with macrophages, secrete cytokines, and an additive effect results in local inflammation and the recruitment of additional T-helper cells [14]. This mechanism has primarily gained support through the study of animal models.

One case in point is encephalomyelitis induced in mice by Theiler's murine encephalomyelitis virus [15]. In this study, Miller, *et al.* demonstrated that epitope spreading and molecular mimicry both lead to auto-reactive T cell induction and subsequent inflammation and tissue damage.

One of the bases for autoimmune conditions is cellular mimicry. Similarities between epitopes on pathogens and epitopes on host cells are such that immune cells can share specificity with both pathogens and host cells, and thus have the potential to cause autoimmune conditions. "Molecular mimicry is based on the structural similarity between micro-organisms and host antigens, such as either the epitopes recognized by anti-group A beta-haemolytic *Streptococcus* antibodies cross reacting with heart tissue host antigens in rheumatic fever or the produced monoclonal antibodies to measles and herpes viruses cross reacting with self-proteins" [16]. Autoimmune conditions are complex, and the presence of cellular mimicry does not guarantee the clinical manifestations of autoimmune conditions. "For an autoimmune event to occur, it is necessary to satisfy additional pre-conditions, including the presence of stimulating cytokines in order to activate a critical mass of auto-reactive clones as well as lack of effective regulatory mechanisms" [16].

Many autoimmune conditions have been associated with infectious disease: rheumatic fever, Guillain-Barre syndrome, post-streptococcal glomerulonephritis, multiple sclerosis, post *Neisseria* arthritis and idiopathic thrombocytopenia purpura to name a few. It is interesting to consider that if infectious agents can generate this autoimmune response, vaccines can generate similar autoimmune responses. Vaccines have specific and similar antigenicity to the pathogen being inoculated against, and therefore the immune cells generated by vaccination are similar to the immune cells that would be generated by the natural pathogen. If the natural pathogen stimulates immune cells that are reactive against host cells, then theoretically the immune cells generated by the vaccine for that pathogen will share the same auto-reactivity. Salemi and D'Amelio conducted a literature review from which they concluded several vaccines do have associations with autoimmune conditions: post-1976 swine influenza vaccine and Guillain-Barre syndrome, Measles Mumps Rubella (MMR) vaccine causing idiopathic thrombocytopenia purpura, and smallpox vaccine causing myopericarditis have all been recorded in theliterature [16].

Although they documented associations between certain vaccines and certain autoimmune conditions Salemi and D'Amelio suggested the need for larger epidemiological analysis to determine the significance of these associations [16]. The frequency of autoimmunity associated with vaccine is far lower than the autoimmunity associated with actual natural occurring infection. Salemi and D'Amelio concluded that because the cost effectiveness of vaccines, and the fact that the benefits of vaccines outweigh the chances of causing autoimmunity, it is important to aggressively develop and promote vaccination programs [16].

Adjuvants are not immunogenic themselves but are frequently added to vaccines to initiate the immune response to vaccine, as well as to boost the immune response to the vaccine. Aluminum hydroxide is a common adjuvant. They can act as a depot for the vaccine antigen slowly presenting the antigen to the immune system over a long period of time preventing the immune system from clearing the adjuvant and vaccine rapidly. Also, adjuvants can direct the vaccine towards initiating a specific T-cell response or a B-cell response. Basically, adjuvants help bring about the critical mass of immune cells that are needed to have an autoimmune response.

The immune system has a tremendous potential for recognizing "self" cells and initiating an autoimmune condition. However, it has many checks and balances that help prevent autoimmunity; for example, IL-10, and T-regulatory cells. The same checks and balances help limit the cell mimicry and immune cell auto-reactivity following vaccination [14].

Bystander activation was also displayed with Horwitz and colleagues (1998) on their study of type 1 diabetes induced by Coxsackie B4 virus. Here, Coxsackie virus infection lead to direct inflammation, tissue damage, release of sequestered islet antigens and the stimulation of resting auto-reactive T cells [17].

## Hepatitis B Vaccine and Autoimmunity

Bogdanos and colleagues have demonstrated that there are significant antigenic similarities between the hepatitis B surface antigen (HBsAg) and specific myelin antigens [18]. They have also demonstrated, using ELISA techniques, that antibodies formed on hepatitis B surface antigen, through vaccination, will sometimes cross react with the antigens on myelin which resemble the hepatitis B surface antigen. However, although there is immune cell mimicry, the cross reactivity does not appear to result in long term autoimmune pathogenesis [18]. In fact, it appears that the cross reactivity found between hepatitis surface antigen and myelin antigens actually has some therapeutic benefits as opposed to pathogenesis; people who had autoimmune reactions to their host myelin before vaccination demonstrated a regression in the auto-reactivity to their host myelin post hepatitis B vaccine resulting from a developed tolerance to the self-recognizing immune cells. Such mechanisms could potentially be of benefit in patients with multiple sclerosis in whom Hepatitis B Virus (HBV) vaccination or immunomodulatory treatment with HBsAg mimics as altered peptide ligand might contribute to restoration of tolerance towards myelin antigens [18]. This is most likely due to the viral components of the vaccine and in particular the self-mimicking HBsAg sequences playing a role as altered peptide ligand, i.e. representing sequences unable to induce cross-reactive responses but able to promote tolerance to a given auto-epitope.

## Influenza Vaccine and Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) is a rare autoimmune disorder that targets nerve cells, causing acute flaccid paralysis with bilateral limb paresis and hyporeflexia/areflexia. Most often, GBS occurs days to weeks following gastrointestinal or respiratory infections. The bacterium Campylobacter *jejuni* is linked with approximately 20-30% of all cases of GBS [19]. Influenza, although less common than C. *jejuni,* can also act as a trigger of GBS, with *Haemophilus influenzae* most commonly causing GBS. While respiratory or microbial infection followed by GBS is rare, with a recorded incidence rate of 0.6-4/100,000 person/year worldwide [20]. GBS remains the most common cause of acute flaccid paralysis worldwide. GBS can be devastating, and its outlook differs from patient to patient. Onset may take days to weeks, but recovery can vary in length, anywhere from a few weeks to few years. Thirty percent (30%) of patients affected by GBS have residual weakness three years following onset. While the majority of patients will recover, GBS can be fatal [21]. Recovery rates were adversely affected by increasing age and disease severity [21-24]. Overall mortality rates of GBS vary from study to study, but have been reported as high as 18% [25]. Over the years, GBS has been associated with different vaccines, including rabies, polio, tetanus, Bacillus Calmette-Guerin (BCG), smallpox, mumps, rubella, Hepatitis B, and diphtheria [26]. The most notorious, however, is the association of GBS and the influenza vaccine. In 1976, clusters of reports of GBS following the A/New Jersey influenza vaccinations raised alarms and caused the suspension of the National Influenza Immunization Program, an initiative put forth to vaccinate the entire adult population and at-risk children in the United States. Following 35 million vaccinations, clusters of GBS in influenza vaccine recipients began appearing, prompting active surveillance across all states and territories. Investigations revealed a relative risk ratio of 7.6 for recipients over the age of 18 years when compared with unvaccinated persons [27-29]. A total of 1068 cases of GBS were reported between October 1$^{st}$, 1976 to January 31$^{st}$, 1977, with 532 of these having recently received the A/New Jersey Influenza vaccination and an additional 8 having an unknown vaccination status. From October 3$^{rd}$, 1976 to December 18$^{th}$, 1976, the attributable risk for the population was 9.5 cases per million vaccines, with a peak onset of GBS 2-3 weeks following vaccination [27-29].

Controversy has surrounded the relation of the 1976 swine flu vaccine and GBS, as those carrying out the diagnosis may not have had specific clinical training in the diagnosis of GBS. Physicians may have been biased to diagnose GBS among vaccines, copies of medical records of GBS-diagnosed patients were not obtained (instead, abstract forms were filled out), screening by the Center for Disease Control & Prevention (CDC) to accept or reject abstract forms on patients have been questioned, and other people receiving the swine flu vaccination did not have an increase in GBS reports [30]. Safranek and colleagues readdressed some of these concerns, using a group of clinical neurologists to review in blinded fashion patient records obtained by CDC in 1976 [29]. Their reassessments have suggested that there was an increased risk of developing GBS during the five to six weeks following vaccination [30].

More recently, monitoring GBS risk following influenza A (H1N1) in 2009 was considered a public health priority, with a number of surveillance systems in place [20].

## MMR vaccine and Idiopathic Thrombocytopenia (ITP)

Another confirmed autoimmune adverse effect associated with vaccination is the induction of idiopathic thrombocytopenia (ITP, also known as immune thrombocytopenia) following the Measles-Mumps Rubella (MMR) vaccination [4,15,31-33]. ITP is an autoimmune condition, clinically defined as having a platelet count of less than 100,000 platelets per microliter and the production of immunoglobulin G autoantibodies against platelet surface glycoproteins IIb-IIIa. Often diagnosed by a Complete Blood Count (CBC), ITP exists as two distinct clinical syndromes: acute ITP in

children, often following infection and resolving spontaneously within two months, or chronic ITP in adults, which persists longer than 6 months and has no known cause [34].

ITP risk following the MMR vaccine is seen highest in children ages 12 months-19 months, which is when children would normally be receiving the MMR vaccine as per the immunization schedule recommendations put out by the CDC in 2014. In one study, Rinaldi and colleagues recorded an Incidence Rate Ratio (IRR) of 5.48, (1.61-18.64, $p < 0.006$) [34]. When given with other vaccines at the same time, the incidence increased. A similar study recorded 107 cases of vaccine-related ITP (77 of them linked to the MMR vaccine) between 1992 and 2010, with an overall reported frequency of ITP following MMR vaccine to be approximately 1 in 30,000 children [35].

Other vaccines have also been reported to contain elevated risks of ITP following vaccination [36]. A significantly elevated risk of ITP has been noted following hepatitis A vaccinations in children/adolescents between the ages of 7-17 years [36]. A significantly elevated risk has also been recorded for the varicella vaccine [35], and tetanus-diphtheria- acellular pertussis vaccine for adolescents aged 11-17 years [36].

Variation exists between the pathogenetic process of ITP, with CD8+ and CD4+ T-cell mediated responses both being linked to ITP. One common mechanism is through the release of interleukin (IL)-2 from platelets and subsequent activation of CD4+ T cells against glycoprotein (GP) IIb-IIIa present on activated platelets. Autoantibodies against GPIIb-IIIa, GPIa-IIa and GPIV have also been reported using immunoprecipitation, immunoblotting and antigen-capture techniques [37]. Patients with ITP display antiplatelet antibodies approximately four-eight weeks following infection or immunization.

Some cases that were negative for antiplatelet antibodies are believed to occur through an alternate mechanism. Here, complementary T cell immune-mediated destruction or the reduction in the formation of platelets is suspected [38]. With presentation of glycoprotein antigens to APCs, autoantibody generation is stimulated and ITP can occur [39].While the link between ITP and vaccinations is present in young age group, especially in children ages 12 months-19 months receiving the MMR vaccine, overall, one must keep in mind that infections are much more likely to trigger the onset of ITP. This is a classic case of weighing the risks versus benefits in the current debate surrounding vaccine safety.

## Myopericarditis Following Smallpox Vaccination

Once a devastating disease, smallpox has essentially been eradicated from the western world following the discovery of its vaccine. While numerous changes have been made to the smallpox vaccine, current vaccines utilize the vaccinia virus, a poxvirus belonging to the same subfamily Chordopoxvirinae, genus Orthopoxvirus [40]. Vaccination programs for children ended in 1972 (for military personnel, vaccinations ceased in 1990), after the disease was eradicated [41]. Over the years, growing concern over the use of the Variola virus in a bioterrorism attack has led to the vaccination of military recruits in 2002 against the virus, and has recently been extended to health care and public health workers.

The smallpox-vaccine, while generally safe, has been linked to adverse effects, some of which are fatal. Most notably, the association of myopericarditis following administration of the smallpox vaccine has been recorded throughout the literature, with 7 fatal and 56 non-fatal post-vaccine myocarditis reported cases occurring between the 1950s and 1960s [42,43].

Myopericarditis is the inflammation of both myocardial and pericardial heart muscle. The spectrum of myocardial and pericardial involvement differs from case to case, often presenting clinically as pericarditis with some degree of myocardial involvement. Three mechanisms have been suggested to cause myopericarditis: idiopathic, infectious and immune-mediated [44]. While the exact causes of myopericarditis remain unclear, viral infections are thought to be one of the most common causes [45-48].

In 2011, Sharma presented a case report of two otherwise healthy individuals with vaccine-linked myopericarditis [49]. The first individual, a 27 year old male, presented with sudden sharp chest pain two weeks after receiving the smallpox vaccine. Troponin and creatinine kinase levels were elevated, and a diagnosis of myopericarditis was made [49]. He had no underlying conditions, and his family history for cardiovascular disease was negative. A second male, 41 years old, presented 10 days following smallpox immunization with dull chest pain, reduced exercise tolerance and night sweats. Troponin levels were elevated, and he was diagnosed with myopericarditis. He was determined to have minimal (non-significant) coronary artery disease, but was otherwise healthy. Both individuals were military soldiers.

Overall, the smallpox vaccine initiative that the United States military began in 2002 resulted in 67 cases of acute myopericarditis [50,51]. Smallpox vaccinations were offered to health care and public health workers, resulting in another 7 reported cases of myopericarditis out of 25,645 vaccinated [52]. A study conducted by Eckart and colleague in 2004 discussed 67 cases of myopericarditis occurring 30 days following smallpox vaccine administration of 540,824 individuals [41]. Because post-vaccinial myopericarditis were reported in a number of otherwise healthy individuals, further studies should be undertaken to help address the underlying pathophysiological mechanisms occurring. Further investigations to help define at-risk individuals and increased awareness to physicians and patients are all important steps that should be taken in the future.

## HPV Vaccine and Primary Ovarian Failure

The HPV vaccines were introduced to reduce the incidence of cervical cancer, however, several cases of onset or exacerbations of autoimmune diseases following vaccination have been reported; thus triggering concern on its safety [53].

In 2013, Colafrancesco and colleague reviewed three cases of women that developed primary ovarian failure following HPV vaccine [54]. Two of the three women are sisters, thus bringing the importance of genetics linkage to the forefront. All three women developed secondary amenorrhea, low estradiol, and high Follicle-Stimulating Hormone (FSH) and Luteinizing hormone (LH) following HPV vaccination. Anti-thyroid antibodies were found in one patient and anti-ovarian antibodies were found another patient [54].

Colafrancesco and colleague suggested further that the use of adjuvants in the HPV vaccine is a risk factor for eliciting an autoimmune reaction to the vaccination [54]. They stated that, the

HPV DNA fragments detected in Gardasil vials appeared to be firmly bound to the aluminum adjuvant used in the vaccine formulation thereby protecting against enzymatic degradation by endogenous nucleases; however, HPV DNA fragments were linked with a patient's death following immunization. The HPV DNA fragments were found in 16 different Gardasil vials [54]. Colafrancesco and colleague also note that HPV vaccine has been linked with demyelinating disease processes [54]. Adjuvants have been implicated recently in a new syndrome called "ASIA-Autoimmune / Inflammatory Syndrome Induced by Adjuvants" [13].

## HPV Vaccine and Systemic Lupus Erythematous (SLE)

Since patients affected by SLE are at a high risk for cervical cancer, guidelines required that they are vaccinated during adolescence. However, the concern with the vaccination is the possible reactivation of the disease triggered by viral antigens or adjuvants present in the vaccine [55].

In 2013, Gatto and colleague investigated cases of SLE that emerged in women following HPV vaccination [56]. The onset of SLE occurred during the later doses of the HPV vaccination schedule and all the women had family histories of autoimmune disease. All the patients that developed SLE achieved remission with immunosuppression therapy [56].

Of the observed women a significant number of them had mild adverse effects to the vaccine with the first dose of the HPV vaccine schedule and then developed more serious SLE symptoms with subsequent does. It is important to assess and study the risk factors among high risk populations so that clinicians can make appropriate decisions on a case by case basis when prescribing the vaccine [56]. Another point for consideration was reported in four of the patients described that received booster immunization (second or third vaccination); although mild adverse events were observed following a previous dose of Gardasil. Notably, in most healthy subjects, mild adverse events following immunizations are transient and can be disregarded. In a high-risk population, these mild events may be of significance, and although further studies are required, it seems that assessment following each boost of vaccination may be beneficial.

In regards to the future of the HPV vaccine Gatto and colleague suggested a plausible causal link between HPV vaccination and onset or relapse of SLE is plausible [56]. Thus, although for most patients, the benefits of immunization outweigh its risks, clinicians must be aware of the odds for an autoimmune disease onset or exacerbation following HPV vaccination. A meticulous pre-vaccination risk-benefits assessment, close follow-up during and after each boost of vaccination, as well as assessment of concomitant therapy with immune-modulating agents such as Hydroxychloroquine (HCQ), seems reasonable for patients with an autoimmune disease [56].

In 2013, Macartney and colleague reviewed the literature for adverse events associated with the HPV vaccine and they reported that the predominant adverse reactions were mild reactions such as local injection site swelling or pain and generalized pain [57]. Macartney and colleague reported that there was no significant association between the HPV vaccine and serious adverse reactions, and that there was no chronic disease or autoimmune disease after four years following vaccination [57].

Macartney and colleague added that there are certain weaknesses with regards to the reporting of adverse effects of vaccination that could provide unreliable information regarding adverse effects following vaccination [57]. Passive reporting is the primary source of information regarding vaccine adverse event as opposed to a systematic approach to tracking adverse vaccination events. In addition, short follow up periods that could miss more severe long term adverse reactions and lack of diversity of study groups are limitations of vaccine safety trials. Long term surveillance of vaccines among diverse populations is necessary for accurate safety assessments [57].

Colafrancesco and Tomljenovic with colleagues both suggested some serious study bias with regards to the safety review of the HPV vaccine Gardasil [54,58]. A large study concluded that the HPV vaccine poses no risk for autoimmune reactions, however the study has several potential biases which are that the majority of results reported were based on a women that received only one dose of the vaccine and not the full three-dose recommended course; the review panel for the study had a lack of immunology/autoimmune expertise. The study was driven by scientists that had potential conflicts of interest with MerckCompany, which was the company that produced the vaccine [54,58].

In a study carried out by Pellegrino and colleague to assess whether the number of hospitalizations for lupus in the US increased after introduction of HPV vaccination in 2006 using data from the National Hospital Discharge Survey, National Impatient Sample and the Kids' Impatient Sample, they found no evidence of increase in the emergency department admission as well as in the number of hospitalization [55]. Current review on the Immunogenicity and safety of the HPV vaccine in patients with autoimmune disease by Pellegrino and colleague states that only few data exist on the safety and efficacy of HPV vaccine in patients affected by autoimmune disease unlike in healthy women where the safety and efficacy has been shown in several randomised controlled clinical trials. They stated further that the vaccines are safe and efficacious in most of the patients affected by autoimmune disease; however, their concerns included the effects of concomitant therapies, the risk of disease exacerbation and the cost-effectiveness of the vaccination programs in the population [59]. In another current review on the interaction of vaccine with drug metabolism, Pellegrino and colleagues, put forward a hypothesis based on several cases that had reported changes in drug metabolism after vaccination [60,61]. It was reported that while reduction in the activity of specific Cytochrome P450 (CYPs) following vaccination may occur, perhaps through interferon $\gamma$ overproduction and specific drugs like anticonvulsant and theophyllinethat may have significant clinical importance, clinical interaction between vaccines and drugs that are metabolised by cytochromes uninfluenced by INF$\gamma$ levels like warfarin, are unlikely to occur [60,61].

## Acute Disseminated Encephalomyelitis (ADEM) and Vaccination

Acute Disseminated Encephalomyelitis (ADEM), a rare inflammatory demyelinating disease of the central nervous system is thought to be an autoimmune disorder in which the body's immune system mistakenly attacks its own brain tissue, triggered by an environmental stimulus in genetically susceptible individuals. It is often triggered by a response to an infection or to a vaccination hence it is sometimes referred to as post-infectious or post-immunization

acute disseminated encephalomyelitis. It usually occurs within a month from antigenic challenge and there are other causes as well. Incidence of this disease ranges from $1/10^6$ to $1/10^5$ and is susceptible to change between different vaccine formulations. It is more common in children and adolescents than it is in adults however studies have shown that it may occur at any age when post vaccination. About 5 percent of ADEM cases follow immunization and several vaccines have been implicated. Currently, the measles, mumps, and rubella vaccinations are most commonly associated [62].

## Vaccination and Genetics

Many individuals suffering with autoimmune conditions have specific HLA proteins in common. Certain HLA proteins tend to have a predilection for activating the immune system against "self" cells. It has been suggested that certain HLA proteins also can explain why certain people are more prone to autoimmune conditions that are induced or exacerbated by vaccines. Santoro and colleague analyzed the unique HLA proteins of a woman that developed SLE and nephritic syndrome following vaccination with the hepatitis B vaccine [62]. They mentioned that HLA haplotype influences the antigenic presentation which, in predisposed individuals, leads to an increase in immune response against the self-antigens and that it could explain why only a few individuals are prone to develop autoimmune reactions after vaccinations [63]. Understanding more about the genomics behind specific HLA proteins and autoimmune reactivity could help make vaccination safer in the future. The use of genetic information has played a major role in certain aspects of personalized medicine for the improvement of patient care in the future; such as pharmacogenomics and biomarkers that include targeting of diagnostic or treatment approaches to patients based on their genetic make-up [64]. Personalized medicine is bound to survey and monitor risks by providing patients with a specific treatment considering their peculiar genetic profile as well as their molecular phenotype [65].

The diversity and heterogeneity of the immune response originates from the genetic history of each individual; hence it is believed to be partly related to polymorphisms in immune response genes [65]. Most genes that are important in influencing immune responses to vaccination are still unknown, clearly more work is required. A better understanding of the factors that determine an effective response to vaccination may lead to the identification of specific genes and pathways as targets for the development of novel more uniformly effective vaccines [66]. The collection of genes found on chromosome 6 forming the human leukocyte antigen system provides one of the greatest sources of genetic variation in individuals with respect to their immunological responses, and has been described in recent literature showing significant associations between vaccine response and human leukocyte antigen alleles, which is key to the development of future generations of vaccines [67].

### Future surveillance

The World Health Organization has laid out some guidelines for assessing vaccines with regards to their relationship to causing autoimmune conditions: consistency and strength of association, specificity of association, and temporal association. In addition, there should be clear definitions of the adverse autoimmune event including clinical, pathological and biochemical aspects. To better decipher the possible relationship between vaccinations and autoimmune diseases, future epidemiological research performed on larger groups with well-constructed studies should be undertaken. In addition, the re-visiting of previous case reports (as seen in GBS induced by the 1976 swine flu vaccination) can strengthen or help clarify claims made and help direct future surveillance programs and studies. Genetic scans as well as individual and family history of autoimmune diseases could be a useful method for evaluating new vaccines as well as for translational strategies for the implementation of personalized medicine.

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