

OPINION

Vaccines and autoimmunity

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Abstract | Vaccines have been used for over 200 years and are the most effective way of preventing the morbidity and mortality associated with infections. Like other drugs, vaccines can cause adverse events, but unlike conventional medicines, which are prescribed to people who are ill, vaccines are administered to healthy individuals, thus increasing the concern over adverse reactions. Most side effects attributed to vaccines are mild, acute and transient; however, rare reactions such as hypersensitivity, induction of infection, and autoimmunity do occur and can be severe and even fatal. The rarity and subacute presentation of post-vaccination autoimmune phenomena means that ascertaining causality between these events can be difficult. Moreover, the latency period between vaccination and autoimmunity ranges from days to years. In this article, on the basis of published evidence and our own experience, we discuss the various aspects of the causal and temporal interactions between vaccines and autoimmune phenomena, as well as the possible mechanisms by which different components of vaccines might induce autoimmunity.

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Introduction

In 1798, Edwards Jenner inoculated individuals with ‘fluid from cowpox blisters’, which prevented smallpox disease, thus creating the first vaccine. Thereafter, the concept and use of vaccination spread around the world, eradicating lethal infectious diseases and changing forever the map of world epidemics. Currently, vaccines are one of the most effective methods for the prevention of infectious diseases. For instance, vaccination against hepatitis B virus (HBV) is effective at preventing 95% of infection, and following its use, the incidence of acute hepatitis B declined by 81%.¹ Unfortunately, although vaccines are highly recommended for adults and children, concerns have been raised regarding their safety. Vaccine-associated adverse events, such as fever, rash, flu-like symptoms, lymphadenopathy and swelling at the site of inoculation, are mainly acute and transient; other reactions, such as hypersensitivity, induction of infection and

autoimmune phenomena, are rare. When post-vaccination autoimmunity does occur, it can be subacute and occur quite a long time after the vaccination is given, which leads to difficulties in ascertaining causality between vaccination and autoimmune phenomena. In addition to the question of whether such a cause and effect association exists, other issues that are still debated include the time frame of such an association, whether certain people are prone to develop autoimmunity following vaccination and the influence of the vaccine, vaccine combinations, multiple vaccinations and certain vaccine ingredients on this association. These topics, as well as other aspects of the interplay between vaccination and autoimmune phenomena, will be discussed in this article and are summarized in Box 1.

Vaccines that cause autoimmunity

Numerous studies and case reports have documented the appearance of autoantibodies² and autoimmune phenomena following vaccination; arthritis, vasculitis, encephalitis, neuropathy and demyelination are the most frequently reported adverse events.^{3–8} Establishing a causal relationship

between vaccination and these autoimmune manifestations is difficult as even these ‘frequent’ manifestations are rare. Moreover, the criteria for causality are not well defined, and unlike efficacy, safety cannot be measured directly. Causality can be inferred only indirectly by the relative presence or absence of events, the temporal relationship between two events, the consistency and strength of adverse event reports and the biological plausibility of such a link.^{9–10} Even so, causality between several vaccines and autoimmune phenomena is accepted by the medical community. A causal relationship between influenza vaccine and Guillain–Barré syndrome was noted following an outbreak of the disease after administration of the swine flu vaccine in 1976.⁴ In 1993, the Institute of Medicine of the National Academies used theoretical criteria, clinical history and laboratory results to declare a causal relationship between the oral polio vaccine and transverse myelitis.³ The Advisory Committee of Immunization Practices at the Centers for Disease Control and Prevention concluded 3 years later that a causal relationship exists between arthritis and two vaccination combinations: diphtheria–tetanus–pertussis (DTP) and measles–mumps–rubella (MMR). In addition, a causal relationship between MMR and autoimmune thrombocytopenia has been recognized by the Institute of Medicine. Other associations, such as the clustering of insulin dependent diabetes mellitus following hemophilus influenza type B (HiB) immunization⁵ and Guillain–Barré syndrome after Menactra® (Sanofi Pasteur, Lyon, France) meningococcal vaccination.⁶

Animal studies

Animal models can be useful for studying the cause and effect link between vaccination and autoimmune phenomena. In 1999, Hogenesch *et al.*¹¹ studied autoimmunity following vaccination in young dogs; nine different autoantibodies were produced in immunized dogs including antifibrinectin, antilaminin, antitransferrin and other lupus associated antibodies. Spontaneous development of diabetes has also been documented post-vaccination in NOD mice and BB rats.^{5,12} Classen¹² administered human vaccines to diabetes-prone animals,

Competing interests

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using up to three doses at low concentrations. Immunization before 2 weeks of age prevented the development of diabetes, but administration of the pertussis vaccine starting at 8 weeks of life was associated with an increased incidence of diabetes. Similarly, in 2002, immunization of NOD mice with HiB vaccine increased the risk of developing diabetes.⁵ A study of wild and farm-raised Atlantic salmon demonstrated that intraperitoneal immunization with oil-based vaccines induced the production of autoantibodies (such as antinuclear and anti- β 2 glycoprotein I antibodies) and resulted in autoimmune granulomatous diseases of the liver and peritoneum, thromboembolic disease and immune-mediated glomerulonephritis in some animals.¹³

The temporal association

The interaction between vaccination and autoimmunity is comparable to the more established link between infection and autoimmunity, of which the occurrence of rheumatic fever a few weeks after streptococcal infection is a classic example;¹⁴ however, the temporal relationship changes in relation to the vaccine and the associated phenomena. The appearance of autoantibodies can precede autoimmune disease by many years,^{15–16} and a credible argument exists that exposure to an initial immune insult (that is, infection) can occur years before autoimmunity presents. Toplak *et al.*² reported the production of autoantibodies (such as antinuclear and antiphospholipid antibodies) in 92 healthy medical workers up to 6 months after influenza vaccination. Other studies have demonstrated a latency period of years between HiB vaccination and diabetes mellitus, and between HBV vaccination and demyelinating events;^{5,8} however, some post-vaccination adverse events, including autoimmunity, can appear within days (for example, transverse myelitis).³ Such a short latency period is feasible since many vaccines are given repeatedly and the related infectious agent could have been encountered before vaccination. In these instances, the vaccine provides a second exposure to the same antigen and elicits a quick response by activation of immune memory cells or by unmasking an already existing, but dormant, autoimmune disease.¹⁷ In conclusion, latency periods can range from days to years for post-infection and post-vaccination autoimmunity.

Box 1 | Key points relating to vaccine-associated autoimmunity

Vaccines are an essential part of preventive modern medicine

Vaccines are composed of infectious antigens, adjuvants, preservatives and other ingredients

Vaccines rarely induce autoimmune phenomena

Each component of the vaccine might induce autoimmunity via several mechanisms

A cause and effect interaction between vaccines and autoimmune phenomena is established for certain vaccines, whereas for other vaccines, post-immunization autoimmunity has been indicated by numerous case reports

The latency period between immunization and autoimmunity ranges between days to years. An individual's susceptibility (for example, relating to genetic factors) might have an important role in vaccine–autoimmunity interactions

Post-immunization autoimmune manifestations can be atypical and might not be compatible with a defined autoimmune disease

Many large epidemiological studies failed to demonstrate post-vaccination autoimmunity; possible reasons for this include the 'dilution effect', atypical autoimmune presentations and different follow-up periods

Autoimmune phenomena can be associated with a combination of vaccines or the administration of multiple vaccines ('burden of vaccines')

Vaccine combinations

Children in the USA are immunized with up to 14 different vaccines before they are 2 years of age. Vaccinations can be given either as a single combined inoculation (such as MMR) or as multiple immunizations, which can result in as many as 8 different antigens being given simultaneously. Combined vaccines have the advantage of fewer injections, reduced administration costs and increased compliance; however, practically all combined inoculates have been associated with adverse events. Theoretically, the more complex a vaccine and the more varied its array of antigens, the more it is likely to trigger an immune response that might eventually turn into an autoimmune disease. Moreover, other ingredients contained within vaccines accumulate when multiple vaccines are given, creating what can be termed the 'burden of vaccination'. Currently, the increased complexity of vaccine mixtures leads to difficulties in determining which vaccine or vaccine ingredients are associated with a certain adverse event.

Possible mechanisms

Autoimmune diseases develop in individuals who are genetically susceptible and whose immune systems have been triggered by environmental factors (such as infections or drugs). Infectious agents are considered to be the most common triggers of autoimmunity,¹⁸ and vaccines

that contain antigens from infectious agents might induce autoimmunity by similar mechanisms such as molecular mimicry, epitope spreading, bystander activation and polyclonal activation (Box 2).^{14,18} Other components of vaccines might also induce adverse events (Figure 1). Vaccines include adjuvants, which are used to stimulate the immune system, preferably without having any specific antigenic effect of their own.¹⁹ Although the mechanisms of adjuvancy are not fully elucidated, adjuvants seem to modulate a common set of genes, promote antigen-presenting cell recruitment and mimic specific sets of conserved molecules such as bacteria components, thus increasing the innate and adaptive immune responses to the injected antigen.²⁰

The ability of our immune system to recognize molecules that are shared by pathogens is, in part, due to the presence of Toll-like receptors (TLRs) on cells of the innate immune system. TLR ligands, either in the form of adjuvants or infectious antigens, bind to TLRs and lead to the initiation of an innate immune response, followed by an adaptive immune response. The ability of TLR activation to ultimately induce an adaptive immune response explains why so many adjuvants used in vaccinations today are developed to mimic TLR ligands.^{19,21} Upon activation, TLRs recruit adaptor proteins within the cytosol in order to propagate the antigen-induced signal transduction pathway. These signaling events can lead to cytokine

Box 2 | Mechanisms by which infectious agents induce autoimmunity**Molecular mimicry**

Cross-reactivity between a foreign antigen (such as a microorganism's peptides) and self antigens induces a break of self tolerance and leads to autoimmunity.

Epitope spreading

Broadening or diversification of the initial immune response from the dominant epitope to subdominant (cryptic) epitopes. Thus, the response to a single peptide spreads to several responses directed at different epitopes either within the same antigen (intramolecular spreading) or in other antigens (intermolecular spreading).

Bystander activation

The initial immune response to an antigen might induce tissue damage and the release of sequestered antigens. These newly exposed antigens activate autoreactive lymphocytes (that is, T cells) that were not directly involved in the initial response. In addition, antigen-presenting cells activated by the initial antigen are capable of further activating macrophages, which perturb preprimed autoreactive T cells in a bystander manner.

Polyclonal activation

Prolonged or constant activation of the immune system can lead to polyclonal activation and proliferation of B cells. In some of these cases, a monospecific response can emerge, accompanied by circulating immune complexes and eventually resulting in damage to self tissues.

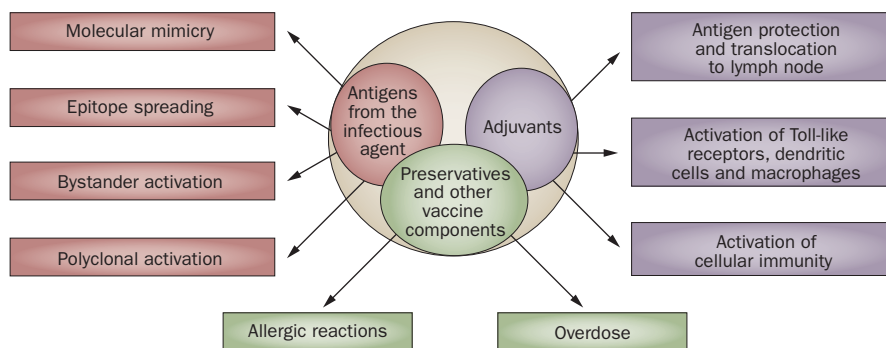


Figure 1 | The mechanisms by which vaccine ingredients might induce autoimmunity. Vaccines are constructed from several components, such as adjuvants and preservatives, in addition to the antigens from the infectious agent. Each component of the vaccine might induce an immune response that can result in the induction or aggravation of autoimmunity. The possible mechanisms activated by each component are shown.

production, cell proliferation and survival, and to enhanced adaptive immunity.¹⁹

In addition to their supportive role, however, adjuvants can lead to an autoimmune-type of illness defined as 'adjuvant disease'.¹⁹ Intraperitoneal immunization of mice and rats with pristane, an oil adjuvant, induced systemic-lupus-erythematosus-like immunity and chronic arthritis;²² immunization of Atlantic salmon with vaccines containing oil adjuvants caused a similar outcome.¹³ A relationship between alum, the most commonly used adjuvant in human vaccines, and human macrophagic myofasciitis syndrome has been suggested.²³ Interestingly, fatigue,

neurological manifestations, neuronal death and other symptoms resembling macrophagic myofasciitis syndrome were seen in veterans from the Gulf War, resulting in this syndrome being named Gulf War syndrome (GWS). According to the US Department of Veterans Affairs, 25% of Gulf War veterans suffer from a chronic multisymptom illness and are twice as likely to be diagnosed with amyotrophic lateral sclerosis than are other veterans of the same era. These veterans were exposed to multiple vaccinations, including a six-shot regimen of anthrax vaccine adjuvanted by aluminum hydroxide and squalene, in addition to

various environmental, physical and emotional stressors (such as smoke, pesticides, pyridostigmine bromide and different biochemical stimuli). To date, no association between these stressors and GWS has been proven. The association between pesticides or pyridostigmine bromide with GWS remains controversial, since similar symptoms were not reported after administration of these chemicals to members of other armed forces. Multiple vaccinations administered over a short period of time has been recognized as a risk factor for GWS;^{19,24} aluminum adjuvant levels comparable to those administered to Gulf War veterans can cause motor neuron death,²⁴ and antibodies to squalene were detected in most (95%) patients with GWS.²⁵

Additionally, other residual components used for the generation of vaccines, such as bovine serum, remnants of yeast, eggs or bacteria, and vaccine stabilizers such as gelatin and formalin might induce an immune-mediated response such as an allergic reaction to egg protein, or an autoimmune reaction to the fibronectin present in bovine serum.

Assessing vaccines safety

Between the years 1991 and 2001, more than 1.9 billion net doses of human vaccines were distributed in the USA, and in the same period about 130,000 adverse events were reported to the Vaccine Adverse Event Reporting System (VAERS). In the past few years, approximately 30,000 reports have been filed with VAERS annually, 10–15% of these being classified as serious. Although VAERS provides useful information on vaccine-related adverse events, these data are limited and cannot confirm causality, nor can the numerous published case reports that might represent coincidental observations.

The clearest and most reliable way of determining whether an adverse event is causally related to vaccination is by randomly comparing rates of events in vaccinated and nonvaccinated individuals.^{9–10} As a result, researchers have turned to large linked databases to study vaccine safety. These databases provide access to the medical records of large cohorts of individuals who have received vaccines and, thus, enable safety assessments of large populations. For example, a retrospective database study evaluated the role of HBV vaccination in 773 patients with autoimmune thyroid diseases and 1,102 controls; this study

concluding that no increased risk of autoimmune thyroid diseases exists following vaccination.²⁶ Limitations to this approach are evident: rare events are difficult to record in such studies; the latency periods of such events are unknown; ill individuals are less likely to be immunized, which might bias the results; and finally, undefined phenomena (for example, demyelination versus multiple sclerosis) are not usually addressed in such studies. For example, an association between the HBV vaccine and confirmed multiple sclerosis has been extensively studied, with conflicting results.⁷ Another study evaluated the first episode of acute central nervous system inflammatory demyelination in 349 children matched with 2,941 healthy controls and demonstrated an increased risk of a demyelinating event 3 years following HBV vaccination (Engerix B®; GlaxoSmithKline Biologicals, Rixensart, Belgium).⁸

Finally, in the process of elucidating or disproving a causal association between vaccination and autoimmunity, the role of risk cofactors, such as other environmental exposures, which could act as a 'second hit' needs to be evaluated. The role of MHC and non-MHC-genes as predisposing traits for autoimmunity is clearly established;²⁷ the assessment of interactions between genetic polymorphisms and post-vaccination autoimmunity might enable genetic susceptibility factors to be identified.

Patients with rheumatic diseases

Patients with autoimmune rheumatic diseases have at least a twofold increased risk of infection compared with healthy individuals, and these infections hold major morbidity and mortality risks. Furthermore, as discussed previously, infections can trigger autoimmunity.¹⁸ Thus, on one hand vaccines prevent infectious diseases and might decrease morbidity and mortality in this population, but on the other hand, vaccines might evoke autoimmunity in a minority of patients. Lately, most studies that have assessed the safety of vaccines in patients with autoimmune rheumatic diseases have not found any strong evidence of exacerbation of an existing autoimmune disease.²⁸ Conti *et al.*²⁹ reviewed the current literature and demonstrated that influenza and pneumococcal vaccines are safe for patients with inactive rheumatoid arthritis or systemic lupus erythematosus. Similarly, vaccination against influenza in 156 patients

with antineutrophil-cytoplasmic-antibody-associated vasculitis did not result in an increased relapse rate.³⁰

Despite these studies, many reports exist of post-vaccination disease flares in almost every autoimmune disease. The risk factors for such disease flares, whether dependant on the vaccine itself, the potency of the individual immune response, the genetic susceptibility of the individual or the stability of the autoimmune disease, are unknown. Studies that evaluate these issues are needed so that risk factors can be determined, which will hopefully lead to improved vaccination compliance. Currently, for most patients with stable autoimmune rheumatic diseases the risk-to-benefit ratio of vaccination seems to be favorable; however, this assumption should be reconsidered in patients with active disease and perhaps in a subgroup of patients with autoimmune rheumatic disease that is yet to be identified.^{28–30}

Conclusions

The association between vaccination and autoimmunity raises many clinical, methodological and ethical questions. Vaccines are clearly essential and safe for most individuals. Nevertheless, our responsibility includes continuing to rigorously assess vaccine safety and attempting to identify possible risk cofactors and at-risk individuals so as to minimize vaccine-associated serious adverse events and improve vaccination compliance. We do believe that the next golden era for vaccinology will be reached by the new science of vaccinomics, similar to the current evolution in drug genomics. Through these approaches and through our increasing understanding of immune responses and the role of genetics in vaccine-related adverse events, the goal of developing more-effective, safe and even personalized vaccines might be achieved.

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