Review

Vaccination and autoimmune disease: what is the evidence?

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As many as one in 20 people in Europe and North America have some form of autoimmune disease. These diseases arise in genetically predisposed individuals but require an environmental trigger. Of the many potential environmental factors, infections are the most likely cause. Microbial antigens can induce cross-reactive immune responses against self-antigens, whereas infections can non-specifically enhance their presentation to the immune system. The immune system uses fail-safe mechanisms to suppress infection-associated tissue damage and thus limits autoimmune responses. The association between infection and autoimmune disease has, however, stimulated a debate as to whether such diseases might also be triggered by vaccines. Indeed there are numerous claims and counter claims relating to such a risk. Here we review the mechanisms involved in the induction of autoimmunity and assess the implications for vaccination in human beings.

Autoimmune diseases affect about 5% of individuals in developed countries.[1] Although the prevalence of most autoimmune diseases is quite low, their individual incidence has greatly increased over the past few years, as documented for type 1 diabetes[2,3] and multiple sclerosis.[4] Several autoimmune disorders arise in individuals in age-groups that are often selected as targets for vaccination programmes. Therefore, in the context of an increasing number of vaccination episodes, coincidence of events should be expected. The potential interactions between vaccines and autoimmune diseases have become a common topic of claims and counter claims, and questions are often raised with respect to the potential risk of autoimmune diseases after vaccination. Some of these questions have been selected by the WHO Vaccine Safety Advisory Committee for further research (panels 1, 2, and 3).[5] Our aim is to provide a rational approach to answer these frequent queries.

Autoimmunity is generally assumed to result from complex interactions between genetic traits and environmental factors.[6] Most often, autoimmune responses are not followed by any clinical manifestations unless additional events favour disease expression—eg, a localised inflammatory process at tissue level. An understanding of the mechanisms by which autoimmune responses are generated and of how they might or might not lead to autoimmune diseases is of paramount importance in defining the real risk of vaccine-associated autoimmunity. Infections are usually considered as key elements in the control of immune responses, and there is evidence that they might either precipitate or prevent autoimmune disorders.[7] Here we analyse our understanding of how infections can lead to autoimmune disease and thus assess the relative risk of autoimmune disease arising as a consequence of vaccination.

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Autoimmune disease and infection

Human beings have a highly complex immune system that evolved from the fairly simple system found in invertebrates. The so-called innate invertebrate immune system responds non-specifically to infection, does not involve lymphocytes, and hence does not display memory. The adaptive immune system, shared by vertebrates, displays both specificity and memory, and is designed to provide protection against almost all infections. Furthermore, polymorphisms in genes that control the immune system ensure that the species as a whole can generate sufficient immunological diversity to survive any new infectious onslaught.

The drawback to such a broadly responsive defence mechanism is the possibility that, in responding to infection, the immune system of a few individuals will turn against their own tissues, thus causing autoimmunity. One could argue that the immune system should have evolved mechanisms that would allow it to respond only to infectious agents and not self-antigens. Indeed there are mechanisms by which many self-reactive lymphocytes are removed from the immune repertoire of the adaptive immune system. Thus, self-reactive B cells are deleted in the bone marrow, and self-reactive T cells are deleted in the thymus during ontogeny.[8] However, it is noteworthy that an immune system from which all self-reactive lymphocytes are deleted would not provide a sufficiently broad repertoire to combat infection.

An infection can induce or trigger autoimmune disease via two mechanisms—antigen-specific or antigen non-specific—which can operate either independently or together. An autoimmune disease will only arise, however, if the individual is genetically predisposed to that particular condition.

Search strategy

We did a computer-aided search of PubMed and ISI Web of Science, using the search terms: vaccine and autoimmune disease, and vaccination and autoimmune disease. This search provided a list of published work up to August, 2002, which we used to supplement our existing knowledge of the primary published work on the subject. We did not limit our search to articles published in English.

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Molecular mimicry

A popular explanation for how infectious agents stimulate autoimmunity in an antigen-specific way is via molecular mimicry.[9] Antigenic determinants of micro-organisms can thus be recognised by the host immune system as being similar to antigenic determinants of the host itself (figure 1). Molecular mimicry among sugar structures is common and leads to numerous manifestations of infection-associated and antibody-mediated neuropathies.[10,11] For example, about a third of all cases of Guillain-Barré syndrome are preceded by *Campylobacter jejuni* infection.[12] This bacterium expresses a lipopolysaccharide molecule that mimics various gangliosides present in high concentrations in peripheral nerves. Numerous viruses also collect gangliosides as they incorporate plasma membrane from the host cell. As a result, viral infections are often associated with Guillain-Barré syndrome, and both bacterial and viral vaccines have been linked with induction of the condition.[13]

The situation is more complex for molecular mimicry that involves T lymphocytes. These cells recognise their antigen as short fragments (peptides) bound to MHC molecules. To serve as a molecular mimic for an autoreactive T cell, a microbial antigen must, therefore, copy the shape of a self-antigenic epitope bound to an appropriate MHC molecule. Molecular mimicry for T cells was first demonstrated in an experimental model of multiple sclerosis, in which a hepatitis B virus polymerase peptide was shown to cause histological signs of autoimmune encephalomyelitis in rabbits.[14] Results of experiments with viral vectors have provided further evidence for molecular mimicry in vivo.[15,16] Cantor and colleagues[17] provided compelling evidence, for instance, that herpes simplex keratitis is an autoimmune disease induced by CD4 T cells elicited by herpes simplex virus 1 infection. The group showed that T cells specific for a peptide derived from this virus provoked keratitis in immunodeficient animals.

Panel 1: **Frequently asked questions about autoimmunity and autoimmune diseases***

What is autoimmunity?
A situation characterised by the development of one or several abnormal immune responses, directed against antigenic components of the host. Autoimmunity can lead to autoantibodies (antibodies against host antigens) or to autoreactive T cells (lymphocytes). Autoimmunity is not a rare event, particularly later in life. Autoimmunity does not always result in autoimmune disease

What is an autoimmune disease?
A disease that results from autoimmunity, when pathogenic autoantibodies or autoreactive T cells (cell-mediated autoimmune disease) can reach corresponding targets (epitopes) with the appropriate configuration or presentation in host tissues

What diseases have been proven to have an autoimmune basis?
Examples of diseases proven to be of an autoimmune nature are: systemic lupus erythematosus, type 1 diabetes (insulin-dependent diabetes), multiple sclerosis, Graves disease and Hashimoto's thyroiditis, rheumatoid arthritis, autoimmune thrombocytopenia and haemolytic anaemia, and myasthenia gravis. Other diseases probably have an autoimmune basis—eg, Reiter's syndrome, Addison's disease, dermatomyositis, Sjögren's syndrome

Are autoimmune diseases always clinically apparent?
No. Clinical expression will be present only when tissue destruction is sufficient to have a visible clinical effect. For example, the autoimmune process that leads to the destruction of pancreatic islets in type 1 diabetes can take months or years before the appearance of clinical signs of diabetes

Does the presence of autoantibodies or autoreactive T cells always indicate that disease is present or will occur in future? What is required to produce autoimmune disease?
Disease will not always occur. To be pathogenic, autoantibodies must be able to reach the corresponding antigen in a target organ, often at the cell surface—eg, erythrocytes—or to form pathogenic immune complexes with antigens released from host cells—eg, DNA. The pathological expression of cell-mediated autoimmunity also requires favouring factors—eg, coexisting inflammation in the target organ

How does atopy differ from autoimmunity?
Atopy is a totally distinct immunological process associated with IgE antibody responses against foreign antigens (allergens) and not directed against host antigens

*These questions were formulated by the WHO Advisory Committee on Vaccine Safety. Responses to these questions were prepared by us.

Panel 2: **Frequently asked questions about possible causes of and factors in favour of autoimmune diseases***

What are known causes of autoimmunity?
Autoimmune responses usually result from the combined effects of antigen-specific stimuli on the immune system and of antigen-non-specific activation of antigen-presenting cells. Regulatory mechanisms limit the development of autoimmune processes

How can infections induce autoimmune responses?
First, there is a potential role of antigenic similarity between microbial molecules and host antigens (antigenic mimicry). Second, infection-related signals that trigger innate immunity seem to play an essential part in enhancing the immunogenicity of host antigens or of host-mimicking epitopes, and in possibly overcoming regulatory mechanisms that limit autoimmune responses

Are all people equally susceptible to autoimmune diseases?
There is a clear genetic predisposition for some autoimmune diseases, but environmental factors also play a crucial part

At what age is autoimmune disease most likely to be seen?
Specific age patterns are seen for most autoimmune diseases. For example, juvenile idiopathic arthritis or type 1 diabetes have an early onset (age 1–16 years), whereas systemic lupus erythematosus and multiple sclerosis predominate in adolescents or young adults, and thyroid autoimmune diseases generally affect elderly individuals

What is meant by the term trigger?
Some events do not cause autoimmunity but can lead to the exacerbation (triggering) of an underlying silent autoimmune process, and thus to the clinical expression of an autoimmune disease. For example, acute respiratory infections by influenza frequently trigger relapses in patients with the relapsing form of multiple sclerosis. In this context, the agent is not causal but triggers an event that would otherwise have likely happened some time later

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Panel 3: **Frequently asked questions about vaccination and autoimmunity***

Which autoimmune diseases, if any, have been proven to be due to vaccines?
A form of rabies vaccine produced from infected rabbit CNS tissue induced an acute disseminated encephalomyelitis in 0·1% of vaccinees.[5] In 1976, cases of Guillain-Barré neuritis arose after vaccination with swine influenza virus, albeit still a rare event. Autoimmune thrombocytopenia has been described after measles vaccination, but with a much lower frequency than that seen after wild measles virus infection (one in 30 000 *vs* one in 5000)

How can one demonstrate or exclude that a vaccine caused an autoimmune disease?
Only epidemiological studies or clinical trials with an extremely large sample size can allow for a consistent assessment of the relative risk of vaccine-related increased incidence. Studies with such large sample sizes are complex, difficult to do, and costly, which limit their availability

Does immunisation with a killed or a live vaccine make someone with a proven previously diagnosed autoimmune disease worse?
As a general rule, patients with an autoimmune disease are not at risk of exacerbation after administration of any of the available vaccines. Conversely, several vaccine-preventable infections are known to negatively affect the course of defined autoimmune diseases

Can minimum criteria be established for diagnosing vaccine-related autoimmune disease?
There exist no general criteria, and this question has to be analysed on a case-by-case basis

Can the prototypes for drug (non-vaccine)-related autoimmune disease serve as any indication of what might characterise a vaccine-related illness?
Several drugs are occasionally associated with the occurrence of autoimmune syndromes. A prototype example of drug-related autoimmune syndrome is drug-induced lupus. Criteria that have been identified to help the recognition of a causal association include: duration of exposure, common presenting clinical symptoms, laboratory profile, and improvement of symptoms within days or weeks after discontinuation of the suspected drug. This last point is of particular import, but would hardly be applicable to the assessment of vaccine-related adverse effects in view of the persistence of most vaccines

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In theory, one could propose that any microbe expressing an epitope that could serve as a molecular mimic for an autoantigen would be able to induce disease. The prospect for such cross-reactive activation of autoreactive T cells becomes even more plausible when we consider the nature of T-cell-receptor recognition of peptide epitopes. Findings of experiments have shown that a single T-cell receptor can recognise a broad range of epitopes, including peptides with totally different sequences.[18,19] Mason[20] calculated that each individual T cell should be able to recognise more than 1 million distinct peptide epitopes.[19] Only a few of these epitopes would be sufficiently potent to activate a naive T cell, though many would be able to stimulate positive selection in the thymus or survival of the T cell in the periphery. The theoretical prospect that a particular bacterial or viral T-cell epitope might mimic a self-antigenic T-cell epitope is high. In fact, the likelihood of T-cell cross-reactivity is theoretically so high that one wonders why all infection do not induce life-threatening autoimmune disease.

Infection-induced autoimmunity

Another mechanism whereby micro-organisms might induce autoimmune disease involves bystander activation, which is an antigen non-specific mechanism. In this instance, microbial infection causes the release of previously sequestered self-antigens or stimulates the innate immune response, resulting in activation of self-antigen-expressing antigen presenting cells (figure 2). Evidence for this non-specific effect of infection has arisen from studies in transgenic mice containing high numbers of autoreactive T cells;[17,20,21] simple administration of inflammatory mediators, or even physical insult to the target tissue, was sufficient to induce disease.

Autoimmune disease is most likely to be induced in the infected organ. For example, infection of the CNS by Theiler's virus in mice leads to activation of T cells responsive to myelin antigens in the same animal, presumably as a result of the release and processing of myelin antigens in association with the viral infection.[22] Likewise, mice that harbour high numbers of islet antigen-specific T cells developed diabetes only when infected with an islet-cell tropic virus (Coxsackie B4).[23] Furthermore, the effect of this virus has been reproduced by an islet-damaging drug but not by a drug that causes non-specific T-cell activation.[24] These findings imply that viruses can precipitate disease by damaging tissue, thus causing the release and presentation of the sequestered self-antigen.

T lymphocytes respond to antigens presented by antigen presenting cells. These cells display an innate response to infection by up-regulating the antigen processing machinery required for activation of naive T cells. Indeed, microbial products engage Toll-like receptors on dendritic and other antigen presenting cells, resulting in up-regulation of the membrane expression of MHC and co-stimulatory molecules, and secretion of cytokines, promoting T-cell activation.[25] Furthermore, naive T cells are inherently more cross-reactive to antigen presented by antigen presenting cells activated in response to such infectious stimuli than resting antigen presenting cell.[26] The innate immune response to infection, therefore, produces a heightened degree of awareness in the immune system, which can result in the activation of otherwise dormant autoreactive T cells.

Fail-safe mechanisms

Analysis of the mechanisms by which micro-organisms can initiate autoimmune disease indicates that there is a high probability that microbial antigens can cross-react with self-antigens. Furthermore, there is increasing evidence that autoimmune disease could be provoked by the innate immune response to micro-organisms. The challenge is, therefore, to ascertain why autoimmune disease is not more frequently induced by infection. We believe that the immune system has evolved to protect the host from infection. However, fail-safe mechanisms have also evolved to prevent the immune response to infection causing excessive tissue damage and thereby triggering autoimmune disease.

The immune system is controlled by homoeostatic mechanisms.[27] Lymphocytes, for example, must compete with one another for antigen and growth factors. Furthermore, T-cell responses to antigen are limited by

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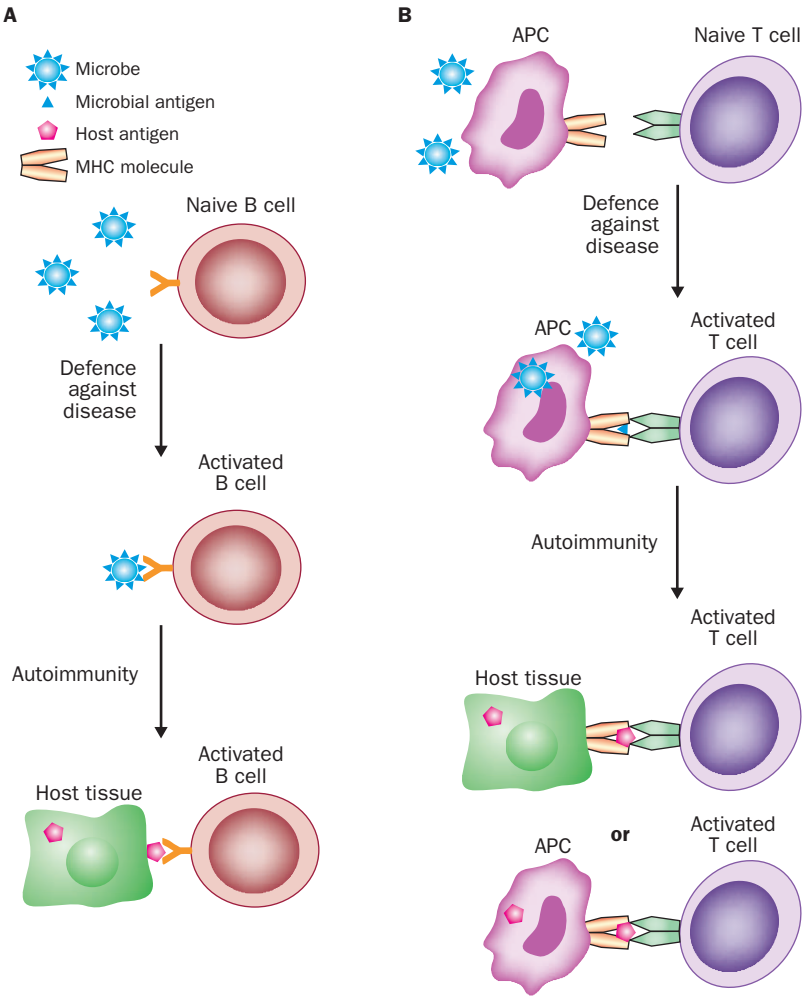


Figure 1: **Mechanisms of molecular mimicry**

APC=antigen presenting cell. A: Microbe-reactive B lymphocytes are activated by direct recognition of microbial antigen. Activated B cells then cross-react with antigens expressed by host tissues, leading to autoimmunity. B: Microbe-reactive T lymphocytes are activated by recognition of broken down microbial antigens presented by MHC molecules on APCs. These cells cross-react with self-antigens expressed by host tissue or presented by APCs, leading to autoimmunity.

the process of activation-induced cell death.[28] These mechanisms are designed to keep the lymphocyte pool at an optimum predetermined level. There is overwhelming evidence that the process of homoeostatic control limits the expansion of self-reactive lymphocytes.[27] In a lymphopenic setting, self-reactive lymphocytes undergo homoeostatic proliferation, are released from peripheral tolerance, and can thus cause autoimmune disease.[29–34]

The immune system is equipped with a wide range of lymphocytes, bearing receptors with varying affinity for antigen. However, the immune response to a given antigen selects only a strictly limited set of these cells. This selection depends on several mechanisms, including: (a) the role of antigen processing and MHC-peptide complex formation; (b) selective binding of antigenic epitopes to specific MHC molecules (determinant capture); and (c) selective depletion of specific lymphocytes by overstimulation (clonal exhaustion or deletion).[35] Furthermore, the fact that the threshold for activation of T cells is close to the threshold for activation-induced cell death results in the immune system responding in a highly focused way to antigen.[36,37] These mechanisms limit the response of the immune system to a specific antigen and prevent activation of cells bearing high-affinity receptors. Since cells with high-affinity receptors are more likely to be cross-reactive for self-antigens, we believe that this affinity-tuning mechanism has evolved to prevent collateral tissue damage, which arises during the immune response to infection, and to limit the likelihood of self-reactive lymphocyte activation during infection.

There is increasing evidence that the immune response to antigen is also controlled by regulatory T cells. Probably the best characterised subset of regulatory T cell is the CD4+CD25+ cell.[38,39] These CD4 cells arise in the thymus, where they are positively selected by recognition of self-antigen.[40] All T cells are positively selected, but most then emigrate the thymus as naive lymphocytes. CD25+ cells, however, emigrate the thymus, but do not proliferate in response to antigen and are capable of suppressing the response to self-antigens. Sakaguchi and colleagues[41] first described these cells and noted that thymectomy of young mice prevented their generation, resulting in widespread autoimmune disease in adult animals. Furthermore, transgenic mice that bear only T-cell receptors specific for self-antigens develop spontaneous autoimmune disease unless they are reconstituted with such cells.[42]

There are further examples of regulatory cells that can be induced from naive lymphocytes in peripheral lymphoid tissues. These include T-helper-3 cells, arising through antigen encounter at mucosal surfaces,[43] and interleukin-10 secreting cells, resulting from repeated peptide[44] or superantigen recognition.[45] This latter group of cells are similar to T-regulatory type 1 cells, which arise after repeated antigen recognition in vitro.[46] The physiological role of T-regulatory type 1 cells is probably to moderate the immune response to infection and thereby limit the collateral damage that results from the immune response to an infectious agent.[47]

The combined homoeostatic and regulatory mechanisms described above have evolved to ensure that the immune response to infection is both focused and controlled. These fail-safe mechanisms prevent the individual from developing autoimmune disease during the course of infection. Thus, autoimmune disease is remarkably infrequent despite the high, hypothetical risk of molecular mimicry and the bystander activation that can take place during infection.

These fail-safe mechanisms apply equally to the host response to vaccination. Autoimmune responses should always, however, be considered in the design of new vaccines. Based on first principles, one could argue that a killed vaccine would be less likely than a live-attenuated vaccine to activate the innate immune response or cause tissue disruption. For these reasons, one might predict that a killed vaccine would be inherently less likely to induce autoimmunity than a live-attenuated one. Nevertheless, the degree of activation achieved by an attenuated organism will be much lower than that induced by the corresponding wild-type pathogenic strain. Every

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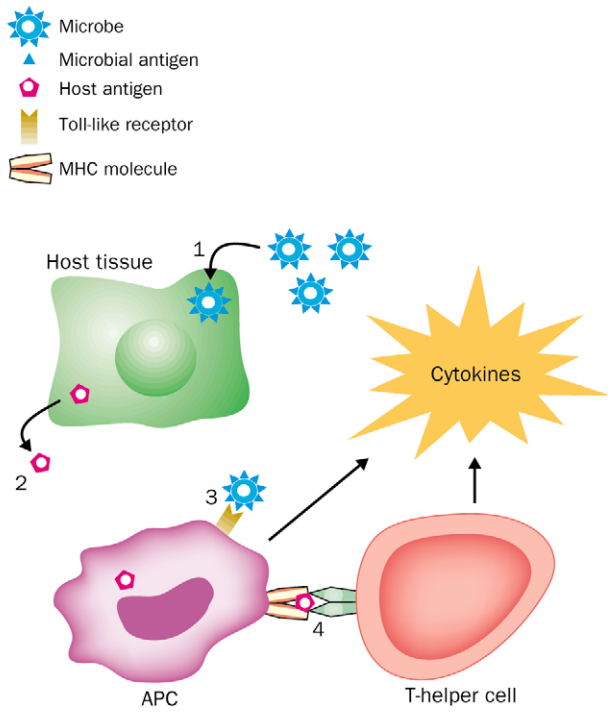


Figure 2: **Mechanisms of infection-induced autoimmunity**
APC=antigen presenting cell. Microbial infection of host tissue leads to tissue damage (1) and release of self-antigen (2). Microbial molecules engage Toll-like receptors on APCs, resulting in up-regulation of MHC and co-stimulatory molecule expression and secretion of cytokines (3). Up-regulation of self-antigen expression by APCs activates autoreactive T cells, leading to a burst of cytokine secretion, local inflammation, and recruitment of additional autoreactive lymphocytes (4).

new vaccine should, therefore, be assessed on a case-by-case basis, giving due consideration to the potential benefit offered by live-attenuated vaccines in terms of public-health provision. An effective vaccine should generate protective immunity while keeping to a minimum molecular mimicry and bystander activation.

Vaccination and autoimmune disease

The medical literature is full of claims and counter claims with respect to the risk of autoimmune disease as a consequence of vaccination. Only in a few rare cases, however, has autoimmune pathology been firmly associated with particular vaccines. For example, a form of Guillain-Barré syndrome (polyradiculoneuritis) was associated with the 1976–77 vaccination campaign against swine influenza, using the A/New Jersey/8/76 swine-flu vaccine.[48] The estimated attributable risk of vaccine-related Guillain-Barré syndrome in the adult population was just less than one case per 100 000 vaccinations, and the period of increased risk in swine-flu vaccinated versus non-vaccinated individuals was concentrated primarily within the 5 weeks after vaccination (relative risk 7·60).[48] With subsequent influenza vaccines, no significant increase in the development of Guillain-Barré syndrome was noted,[49] and the risk of developing the Guillain-Barré syndrome after vaccination (one additional case per 1 million people vaccinated) is now judged substantially lower than the risk for severe influenza and influenza-related complications.[50] Another example of confirmed autoimmune adverse effects after vaccination is idiopathic thrombocytopenia, which might arise after administration of the measles-mumps-rubella vaccination.[51–55] The reported frequency of clinically apparent idiopathic thrombocytopenia after this vaccine is around one in 30 000 vaccinated children. However, it is noteworthy that the risk of thrombocytopenia after natural rubella (one in 3000) or measles (one in 6000) infections is much greater than after vaccination.[50] Patients with a history of immune thrombocytopenic purpura are prone to this complication, and in these individuals the risk of vaccination should be weighed against that of being exposed to the corresponding viral disease.[56]

The advent of new vaccines and the increasing number of highly publicised reports that claim a link between certain immunisations and autoimmune disease have led to public concern over the risk of inducing autoimmune disease by immunisation.

Hepatitis B and multiple sclerosis

The possibility of an association between the hepatitis B vaccination and development of multiple sclerosis was first raised in France, after a report of 35 cases of primary demyelinating events occurring at a hospital in Paris between 1991 and 1997, within 8 weeks of recombinant hepatitis B vaccine injection.[57,58] The neurological manifestations were similar to those observed in multiple sclerosis. There were inflammatory changes in the cerebrospinal fluid and lesions were noted in the cerebral white matter on T2-weighted MR images. Clinically definite multiple sclerosis was diagnosed in half of the patients, after a mean follow-up of 3 years. These neurological manifestations arose in individuals judged at high risk of multiple sclerosis—eg, a preponderance of women, mean age around 30 years, over-representation of the HLA-DR2 antigen, and a positive family history of the disease. The French pharmacovigilance system responded rapidly to these observations, and from 1993 to 1999, several hundred cases with similar demographic and clinical characteristics were identified. It is essential to note that this episode occurred in a very special context. In France, nearly 25 million people (40% of the population of the country) received the hepatitis B vaccine during this period, of whom 18 million were adults. Since the initial reports, at least ten studies aimed at defining the significance of such observations have been completed; there was no significant association between hepatitis B vaccination and the occurrence of demyelinating events or multiple sclerosis in any of these studies. However, the studies were weakened by insufficient statistical power.

Nevertheless, findings of two large-scale studies have shown no significant association between hepatitis B vaccination and the occurrence of multiple sclerosis.[59,60] Confavreux and colleagues[59] undertook a case-crossover study in patients included in the European Database for Multiple Sclerosis who had a relapse between 1993 and 1997. The index relapse was the first relapse confirmed by a visit to a neurologist and was preceded by a relapse-free period of at least 12 months. Exposure to vaccination in the 2-month risk period immediately preceding the relapse was compared with that in the four previous 2-month control periods for the calculation of relative risk. Of 643 patients who had a relapse, 2·3% had been vaccinated during the preceding 2-month risk period by comparison with 2·8–4·0% who were vaccinated during one or more of the four control periods. The relative risk of relapse associated with exposure to any vaccination during the previous 2 months was 0·71 (95% CI 0·40–1·26). There was no increase in the specific short-term risk of relapse associated with the hepatitis B vaccine.

The second study also excluded a possible link between hepatitis B vaccine and multiple sclerosis.[60] The researchers did a nested case-control study in two large cohorts of nurses in the USA—ie, those enrolled in the

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Nurses' Health Study (which has followed up 121 700 women since 1976) and those who took part in the Nurses' Health Study II (which has followed up 116 671 women since 1989). For each woman with multiple sclerosis, five healthy women and one woman with breast cancer were selected as controls. The analyses included 192 women with multiple sclerosis and 645 matched controls. The multivariate relative risk of multiple sclerosis associated with exposure to the hepatitis B vaccine at any time before the onset of the disease was 0·9 (95% CI 0·5–1·6). The relative risk associated with hepatitis B vaccination within 2 years before the onset of the disease was 0·7 (95% CI 0·3–1·8). These results were similar to those of analyses restricted to women with multiple sclerosis that began after the introduction of the recombinant hepatitis B vaccine.[60]

These reassuring data are consistent with the fact that, since the introduction of the hepatitis B vaccine into national childhood immunisation schedules in more than 125 countries, it has been used in more than 500 million people and has proved to be among the safest vaccines yet developed.

Diabetes

Over the past few decades, there has been a regular increase in the incidence of type 1 diabetes in most countries of the world. That childhood vaccines have been identified as a potential trigger event for this disease is, therefore, not surprising.

This possibility has been assessed in a few epidemiological studies. Results of a case-control study done in Sweden in the mid-1980s did not indicate any great effect of vaccination against tuberculosis, smallpox, tetanus, pertussis, or rubella on risk of diabetes.[61] However, one group has suggested that the timing of vaccination could be of importance, and that certain vaccines—eg, *Haemophilus influenzae* type b (Hib)—might increase the risk of type 1 diabetes if given at age 2 months or older.[62,63] This theory was not confirmed by a 10-year follow-up study of more than 100 000 Finnish children involved in a clinical trial of the Hib vaccine.[64] In this study, there was no increased risk of diabetes when children who had received four doses of vaccine at age 3, 4, 6, and 14–18 months were compared with those who received only one dose at age 2 years. Furthermore, the risk of diabetes did not differ between children in the latter two cohorts and those in a non-concurrent unvaccinated group.

Additionally, findings of a study undertaken in four large health-maintenance organisations in the USA did not suggest an association between administration of routine childhood vaccines and increased risk of type 1 diabetes, irrespective of the timing of Hib or hepatitis B vaccination.[65] Therefore, at this time, there are no serious indications of any great effect of childhood vaccines on the occurrence of type 1 diabetes.

How can a doctor assess a potential link?

There exist no general criteria for diagnosing vaccine-related autoimmune disease, which has to be assessed on a case-by-case basis. Appropriate epidemiological studies should be done before a particular autoimmune clinical condition is associated with a given vaccination. Such investigation can then be followed by the identification of known biological markers of the identified autoimmune disease in other vaccinees. However, the degree of vaccine-related risk should always be compared with that associated with the corresponding natural infection, either for the whole population or for a specific subgroup.

Criteria underpinning the assessment of adverse events of vaccines have been established by the WHO,[66] and the four basic principles that apply to autoimmune diseases are the consistency, strength, and specificity of the association between the administration of a vaccine and an adverse event, and the temporal relation.

Consistency and strength

The association of a purported autoimmune event with the administration of a vaccine should be consistent. Therefore, the findings should be the same if the vaccine is given to a different group of people, by different investigators not unduly influencing one another, and irrespective of the method of investigation. The association should be strong in an epidemiological sense.

Specificity

The association should be distinctive and the adverse event linked uniquely or specifically to the vaccine concerned. The association should, for instance, not arise frequently, spontaneously, or commonly in association with other external stimuli or conditions. An adverse event could be caused by a vaccine adjuvant or additive, rather than by its active component, hence spuriously affecting the specificity of the association between vaccine and adverse event.

Temporal relation

There should be a clear temporal relation between the vaccine and the adverse event, in that receipt of the vaccine should precede the earliest manifestation of the event or should occur a few weeks before a clear exacerbation of a continuing condition. Therefore, an association between vaccine administration and an autoimmune adverse event is most likely to be considered strong when the evidence is based on:

- the results of carefully undertaken clinical trials for which a study design was ascertained a priori specifically for testing the hypothesis of such an association. Such studies will normally be one of the following, in descending order of probability of achieving the objective of the study: a randomised controlled clinical trial, cohort study, case control study, or controlled case-series analysis. Case reports can form the basis on which a hypothesis can be formulated. However, even numerous case reports cannot be used to adequately test a hypothesis. When autoimmune events seem to be attributable to a vaccine, investigators should then ascertain whether they are studying a predisposed set of individuals (by age, population, or genetic, immunological, environmental, ethnic, sociological, or underlying disease conditions). Such predisposition is most likely to be identified in case-controlled studies.
- the results of more than one clinical trial being consistent. The studies should all be carefully undertaken, by different investigators, in different populations, but have consistent results, despite the use of different study designs.
- a non-random temporal association between administration of vaccine and adverse event. There should be a strict definition of the autoimmune adverse event in clinical, pathological, and biochemical terms, as far as is achievable. To be considered associated with the vaccine, the frequency of the adverse event in the immunised population should be substantially different from that in the non-immunised population.

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New-generation vaccines

Although available epidemiological data are reassuring we must remain vigilant, particularly with respect to some of the new-generation vaccines. Special attention should be paid to new vaccine adjuvants, especially when they produce strong, innate responses.[67] Additionally, cancer vaccines based on dendritic cells pulsed with tumour antigens carry a substantial risk of autoimmunity.[68]

During the course of vaccine development, only a comprehensive and multidisciplinary strategy can help to reduce the risk that a new vaccine will induce autoimmune manifestations.

First, one should question whether clinical manifestations of an autoimmune nature are known to be associated with the infectious disease that will be the target of the new vaccine. If such events have been reported—eg, for group A streptococcal diseases—attention should be given to avoid reproducing the natural pathogenic process; this process might include the identification and exclusion of naturally pathogenic epitopes.

Second, potential molecular and immunological mimicry between vaccine antigens and host components should be extensively analysed through a combination of bioinformatics and immunological studies. One should bear in mind that, by itself, an identified mimicry is of little pathogenic importance. Information should be gathered on the relative ability of such epitopes to bind to MHC molecules, to be processed by antigen-presenting cells, and to be recognised by autoreactive T cells. Molecular mimicry in itself is not sufficient to trigger autoimmune pathology, and 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 β2 integrin family.[69] Although this homology raised concern about the safety of this vaccine, there was no evidence for an increased frequency of arthritis in individuals who received the Lyme vaccine.[50]

Third, indicative information can be obtained through the use of ad hoc experimental models of autoimmune diseases. Different vaccine formulations and adjuvants can be compared with respect to their potential capacity to induce or enhance the expression of pathology in relevant models.

Fourth, appropriate immunological investigations—eg, autoimmune serology—can be systematically included in phase I–III clinical trials.

Finally, clinical surveillance of potential autoimmune adverse effects and appropriate laboratory tests should be considered for inclusion in the monitoring protocol. Such surveillance should be extended through the post-marketing stage if specific rare events have to be ruled out.

Concluding remarks

A clear distinction should be made between autoimmunity and autoimmune disease. Autoimmunity is a feature of the normal healthy immune system. There is little doubt that laboratory measurable signs of autoimmunity can associate with infection and might occasionally appear after vaccination. It is comforting to appreciate that the immune system has evolved sufficient fail-safe mechanisms to ensure that these signs rarely develop into clinical disease.

Contributors

D C Wraith, M Goldman, and P-H Lambert designed, researched, and wrote this review conjointly.

Conflict of interest statement

M Goldman has served as a consultant for Aventis-Pasteur, BruCells, Glaxo SmithKline, and OM-Pharma. P-H Lambert has served as a consultant for Aventis-Pasteur, Chiron, Glaxo SmithKline, and OM-Pharma. D Wraith is a director of Apitope Technology (Bristol), and has served as consultant for Glaxo SmithKline, Peptide Therapeutics, and Teva Pharmaceutical Industries.

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