

Vaccination and allergy

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Purpose of review

Vaccines have had a major effect on controlling the spread of infectious diseases, but use of certain vaccines was linked to potential allergic and autoimmune side effects in healthy and often in certain high-risk populations. In this review the authors summarize the current knowledge of such risks.

Recent findings

Immediate systemic allergic reactions after vaccination with commonly used vaccines are extremely rare. Use of certain vaccines was linked to potential allergic side effects in healthy and often in certain high-risk populations. The authors review the data on the risk associated with important vaccines including influenza, smallpox, pneumococcus, Japanese encephalitis, Bacille Calmette–Guerin, pertussis, and measles, mumps, and rubella. Two main components were identified as a source for allergic reactions in vaccines: gelatin and egg protein. There is growing interest in the potential interactions between infant vaccination and risk for development of atopic disease. In addition, there is concern that genetic risk for atopy influences capacity to respond to vaccination during infancy. There is no evidence that vaccines such as Bacille Calmette–Guerin; pertussis; influenza; measles, mumps, and rubella; or smallpox have an effect on the risk of the development of atopy later in life. Immunotherapy provides an efficacious and safe method for the treatment of allergic conditions by immunomodulation of the immune system. The possibility of vaccination triggering or unmasking autoimmunity in genetically susceptible individuals cannot be ruled out, but for the general population the risk-to-benefit ratio is overwhelmingly in favor of vaccinations.

Summary

Childhood vaccination remains an essential part of child health programs and should not be withheld, even from children predisposed to allergy. Vaccinations are safe, but special attention should be taken in high-risk individuals with anaphylactic reactions to foods, and in patients with autoimmune diseases.

Keywords

vaccine, allergy, autoimmunity, viral infection, asthma, immunotherapy

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Abbreviations

BCG	Bacille Calmette–Guerin
DTaP	diphtheria–tetanus–acellular pertussis
DTP	diphtheria–tetanus–pertussis
ISS-ODN	immunostimulatory sequence oligodeoxynucleotide
JE	Japanese encephalitis
MMR	measles, mumps, rubella
Th	T helper

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Introduction

Vaccines have had a major effect on controlling the spread of infectious diseases, but in some individuals they present a risk ranging from local skin allergy to anaphylaxis. Immediate systemic allergic reactions after vaccination with commonly used vaccines are very rare. A data analysis of spontaneously reported suspected adverse drug reactions after the administration of 15 marketed vaccines, from 1994 to 1998, showed an average reporting rate for “allergic” reactions of one case report per 450,000 vaccine doses sold [1]. There was no evidence for an increased risk of allergic reactions for patients with atopy. The risk of anaphylaxis and potentially life-threatening events are after vaccination of children and adolescents is also extremely low [1,2]. Only five cases of potentially vaccine-associated anaphylaxis were identified after administration of 7,644,049 vaccine doses, for a risk of 0.65 cases/million doses. None of the episodes resulted in death.

Allergic reactions resulting from vaccines

Use of certain vaccines was linked to potential allergic side effects in healthy and often in certain high-risk populations. Examination of important vaccines show that such reactions are rare.

Influenza vaccine

Influenza causes substantial morbidity in adults and children, and vaccination can prevent influenza and its complications. However, there is concern that vaccination may cause exacerbation of asthma. A recent study [3] investigated the safety of the inactivated trivalent split-virus influenza vaccine in adults and children with asthma by a multicenter, randomized, double-blind, placebo-controlled crossover trial in 2032 patients with asthma who were 3 to 64 years of age. The frequency of asthma exacerbations was similar in the 2 weeks after the

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influenza vaccination and after placebo injection. The exacerbation rates were similar in subgroups defined according to age, severity of asthma, and other factors. Controlled clinical trials with inactivated parenteral influenza vaccine in asthmatic patients showed virtually no side effects [4]. A Cochrane systematic review of the literature in the year 2000 on the basis of controlled clinical trials through 1998 concluded that the safety of influenza vaccination in patients with asthma remains inconclusive. This uncertainty was driven by a double-blind, placebo-controlled crossover trial that reported a trend toward a higher incidence of patients with a more than 20% decrease in peak expiratory flow 72 hours after influenza vaccination compared with that after placebo injections. This difference, however, disappeared after excluding patients with obvious upper respiratory tract infections. Additionally, no adverse effects were observed for asthma medication use within 72 hours after injection or for hospital admissions, medical consultations, antibiotic use, rescue medication, or oral steroid use during the 7 days after vaccination. A recent double-blind, placebo-controlled crossover study of a large cohort of nearly 2000 children and adults with asthma published after completion of the just-mentioned systematic review convincingly documented the safety of influenza vaccination among asthmatic patients. Taken together, these studies presented strong evidence that influenza vaccination did not alter bronchial reactivity or lung function, asthma symptoms, exacerbations, or increased use of rescue medications. The inactivated influenza vaccine is, therefore, safe to administer to adults and children with asthma, including those with severe asthma. Annual influenza vaccination is recommended by the Advisory Committee for Immunization Practices, the American Academy of Pediatrics, and the Second Expert Panel for the Diagnosis and Management of Asthma to protect asthmatic patients from this increased burden. Given the morbidity of influenza, all those with asthma should receive the vaccine annually.

Smallpox vaccine

As the threat of bioterrorism with pathogenic microbes such as smallpox virus (*Variola major*) increases, the question of widespread voluntary vaccination with smallpox (vaccinia) vaccines is being carefully considered. A major challenge lies in the ability to protect the population from the disease while minimizing the considerable side effects from the vaccine. Individuals with active or quiescent atopic dermatitis are at increased risk for vaccinia complications. Along with its enormous success, the live-virus smallpox vaccine has one of the highest rates of vaccine-associated adverse events, including allergic reactions such as eczema vaccinatum and generalized vaccinia. The greatest challenge facing the smallpox vaccination program will be how to identify those at greatest risk from the vaccine. During a mass vaccination in En-

gland and Wales in 1962, 185 of 6.5 million people vaccinated developed eczema vaccinatum, among whom there were 6% fatalities [5]. The smallpox vaccine complication rate in the United States showed eczema vaccinatum in 123 per million, with 1% fatalities [6]. Eczema vaccinatum and vaccinia were more common as a result of accidental contact than by primary vaccinations. Individuals and especially children with atopic dermatitis are at higher risk for eczema vaccinatum, but no clear and solid guidelines are currently available to determine who should be exempt from vaccination. Studies of the immunologic mechanism involved in reactions to smallpox vaccine suggest cell-mediated immune response might be of greatest importance and that lower immune response in atopic skin could contribute to a lower response to viral replication and spread [7••]. Lower production of interferon- γ and higher levels of interleukin-4 in the skin of atopic patients (namely, lower T helper [Th]1 activity and higher Th2 cytokine-producing lymphocytes) could theoretically promote viral overgrowth. Currently, it is not known how other patients with altered systemic Th2 responses and atopy, such as those with asthma, will respond to vaccinia vaccination. It is also unclear which, if any, other chronic skin disorders might be associated with a risk of eczema vaccinatum. Because of the risk of eczema vaccinatum in patients with atopic dermatitis, immunization with live vaccinia virus is contraindicated unless exposure to smallpox occurs. Development of nonreplicating viral vaccines may lower or eliminate such risk.

A recent report a case of biopsy-proved eosinophilic-lymphocytic myocarditis diagnosed *in vivo* with histologic evidence for eosinophil-mediated cardiac myocyte necrosis shortly after smallpox vaccination follows 26 probable clinical cases of myopericarditis previously reported [8,9]. Lymphocytes and degranulating eosinophils in close proximity to necrotic myocytes strongly suggested an immune-mediated process and presented evidence that the pathogenesis is autoimmune, rather than caused directly by viral damage. Evidence included the patient's dramatic response to steroid therapy, and absence of vaccinia or other viruses in biopsy tissue. These support the current strategy of target smallpox vaccination in response to a bioterrorism incident rather than mass prophylactic smallpox vaccination [10••,11••].

Pneumococcal vaccine

Allergic and especially anaphylactic reactions to pneumococcal vaccine are very rare. The presence of specific IgE antibodies and a positive skin test in such cases shows that the nature of such reactions are IgE mediated. Injections of the 23-valent pneumococcal vaccine are usually well tolerated. Immediate responses in skin tests and specific IgE determination have a good diagnostic value in children reporting severe reactions, suggestive

of IgE-dependent hypersensitivity to the pneumococcal vaccine [12].

Japanese encephalitis vaccine

Japanese encephalitis (JE) vaccine is widely used in Asia for childhood immunizations, but the vaccine is also used for travelers to Asia from other parts of the world. Systemic allergic reactions to JE vaccine, which include urticaria, angioedema, and rash, have been reported. In Denmark more than 400,000 doses have been distributed from 1982 to 2000. In 1989, the first allergic mucocutaneous reactions after JE vaccination were registered in Denmark and, although the number of reactions have decreased since 1992, reactions are still observed. No explanation of these reactions has been found. A case-control study, including 49 travelers with allergic reactions and 148 travelers without similar reactions after JE vaccination was performed to clarify any possible risk factors [13]. Approximately one third of the adverse reactions to the vaccine could be attributed to an allergic predisposition in the vaccines. The main risk factors were young age, female gender, and previous allergic skin reactions or hayfever. Accordingly, information on any history of allergy in young adults should be given before JE vaccination.

Allergic reactions to vaccine components

Although allergic reactions were reported to various vaccines of totally different strains, the etiology of at least some such reactions might be attributable to common components that these vaccines share. Two main components that were identified are gelatin and egg protein.

Gelatin

The number of patients with allergic reactions after administration of gelatin-containing live vaccines is increasing. These allergic reactions appear to be caused by gelatin allergy, although it is still unknown how the patients were sensitized to gelatin. Most events of anaphylaxis to live, attenuated viral vaccines containing gelatin as a stabilizer might be caused by the gelatin. However, the mechanism by which the children were sensitized to gelatin is unclear. In evaluation of 366 patients with adverse reactions after immunization with monovalent measles, mumps, and rubella (MMR) vaccines containing 0.2% gelatin as stabilizer, 34 had anaphylaxis; 76, urticaria; 215, nonurticarial generalized eruption; and 41, local reactions only [14]. In 206 patients from whom serum was available, IgE antibodies to gelatin were detected in 93% with anaphylaxis, 56% with urticaria, and 9% with a generalized eruption. None of a group of 41 patients with only local reactions at the injected site and none of a control group of 29 subjects with no adverse reaction had such antibodies. Of 202 patients for whom prior vaccine information was available, all had received diphtheria-tetanus-acellular pertussis (DTaP) vaccines. Of those for whom the prior DTaP vaccine could be

determined to contain gelatin or be free of gelatin, 98% had received gelatin-containing DTaP vaccines. This rate is higher than would be expected on the basis of the market share of gelatin-containing (*vs* gelatin-free) DTaP vaccines (75%). Furthermore, before 1993, when a trivalent MMR vaccine (with the same 0.2% gelatin content as the monovalent vaccines) was used and administered before DTaP vaccination, no reports of anaphylaxis to the MMR vaccine were received. Taken together, most anaphylactic reactions and some urticarial reactions to gelatin-containing MMR monovalent vaccines are associated with IgE-mediated gelatin allergy. DTaP immunization histories suggest that the gelatin-containing DTaP vaccine may have a causal relation to the development of this gelatin allergy. In a study of DTaP vaccines with and without gelatin serum, samples were examined from 87 children who had systemic immediate-type reactions, including anaphylaxis to the vaccines [15]. Ninety-one percent of these children had antigelatin IgE. Fifty-four of 55 children with such reactions had received gelatin-containing DTaP vaccines and none received gelatin-free DTaP vaccines. These results showed that there was a strong causal relation between gelatin-containing DTaP vaccination, antigelatin IgE production, and risk of anaphylaxis after subsequent immunization with live viral vaccines that contain a larger amount of gelatin. In another study, serum samples were taken from 28 children who showed allergic nonimmediate-type cutaneous reactions to JE vaccine [16]. Serum samples were also taken from 10 children who showed allergic immediate-type reactions with cutaneous signs and/or respiratory symptoms to JE vaccine. Of 10 children who showed immediate-type reactions, all had antigelatin IgE and IgG. Of 28 children who showed systemic nonimmediate-type reactions, one had antigelatin IgE and nine (32%) had antigelatin IgG. The child who had antigelatin IgE showed urticaria 2 hours after JE vaccination. These results suggest that some children who showed allergic nonimmediate-type reactions to JE vaccine were sensitized to gelatin. Gelatin-specific T-cell response was performed to determine whether a series of vaccinations with gelatin-containing diphtheria-tetanus-pertussis (DTP) is a primary sensitization process in gelatin allergy. All subjects inoculated with gelatin-containing DTP vaccine showed positive T-cell responses against gelatin; however, occurrence of adverse reactions did not correlate with T-cell responses [17]. DTP vaccine containing gelatin induced sensitization to gelatin in the recipients, but the mechanism of local reactions remains unknown. Similarly, children with systemic immediate-type reactions to varicella vaccine with gelatin had antigelatin IgE [18]. These children also had systemic nonimmediate-type allergic reactions, which mainly consisted of systemic cutaneous signs appearing several hours or more after the vaccination. In an attempt to investigate the relation between immune responses to gelatin and nonimmediate-type re-

actions to gelatin-containing varicella vaccines, antigelatin IgE and IgG in the sera of the children with these allergic reactions were determined. Of 21 children with nonimmediate-type reactions, two (10%) had antigelatin IgE and six (29%) had antigelatin IgG. In the positive control group, all 33 children with immediate-type reactions had antigelatin IgG as well as IgE. In the negative control group, all 50 children who showed no allergic reaction to varicella vaccines had neither antigelatin IgE nor IgG. These results suggest that the possibility exists that some nonimmediate-type reactions to varicella vaccine are caused by immune reactions to gelatin.

Immunization of egg-allergic children against MMR is often deferred or even denied, although the safety of this vaccination has been clearly shown. The incidence of serious adverse events with possible or indeterminate causal relation with MMR vaccination reported in Finland was 5.3 per 100,000 vaccinees or 3.2 per 100,000 vaccine doses, with allergic reactions accounting for approximately 25% of the reactions [19]. Most severe allergic reactions have occurred in egg-tolerant vaccinees, and gelatin has been suggested as one cause of allergic adverse events. To characterize the actual allergenic vaccine components, serum samples from recipients of MMR vaccine with anaphylaxis, urticaria with or without angioedema, asthmatic symptoms, or Henoch–Schönlein purpura sera were analyzed by the CAP System radioallergosorbent test and immunospot methods to detect the allergenic vaccine component [20]. Of the 36 participants, 10 were demonstrated to be allergic to gelatin. Seven of them had persistent allergic symptoms, possibly attributable to foods containing gelatin or cross-reactive allergens. The results of the immunospot analysis suggested concomitant allergy to gelatin and egg, chicken, and feathers, as well as cow's milk, or they reflected allergen cross-reactivity. These results show that although severe allergic adverse events attributable to MMR vaccination are extremely rare, all serious allergic reactions should be further assessed to detect the likely causative vaccine component, including gelatin.

Egg protein

Egg allergy poses a challenge in influenza vaccination programs. Influenza vaccines are derived from the extra-embryonic fluid of chicken embryos inoculated with specific types of influenza virus. The vaccines typically contain measurable quantities of egg protein allergens, such as ovomucoid–ovalbumin. Adverse allergic reactions have been seen in patients with egg allergy injected with inactivated influenza vaccines. The prevalence of egg allergy in the population is estimated between 0.13% [21••]. The prevalence is higher in young children and reaches 1.6%. The prevalence is higher in allergic children in general (5.6%) and is as much as 40% in children with moderate to severe atopic dermatitis. The prevalence of egg allergy in asthmatic children is between 2.0

to 3.6%. Egg allergy, although present, is extremely uncommon in adults. Regardless of the status of allergy to egg, the risk of influenza vaccination is extremely low. A recent, large-cohort multicenter study extended on these observations in a prospective, controlled clinical trial [22]. This study was conducted in 83 subjects at least 6 months of age and older with egg allergy, nearly all of whom had asthma. All patients had documented IgE reactivity to egg, as determined by means of skin prick test (SPT) or radioallergosorbent test testing, and either positive blinded oral egg challenge results, histories of anaphylaxis, or convincing recent histories of objective reactions to egg on ingestion. The study showed that influenza vaccination could be administered safely, without systemic reactions, to the children in a two-dose injection protocol.

Egg protein (ovomucoid–ovalbumin) levels in influenza vaccines from various manufacturers vary by more than 3 logs and are as low as undetectable to as high as 42 µg/mL. Influenza vaccination in individuals with egg allergy appears to be generally safe when vaccines with no more than 1.2 µg/mL egg protein are used in a two-dose protocol, but no company analyzes or reports the egg content of their influenza vaccines.

A live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine has been shown to be safe, immunogenic, and efficacious in adults and children, and cost-effective against influenza in children. This intranasal influenza vaccine contains egg protein and, until further study, is not recommended in patients with egg allergy.

The American Academy of Pediatrics recommends that reactions to egg less severe than anaphylaxis or local manifestations of allergy to egg or to feathers do not contraindicate influenza vaccination and do not warrant vaccine skin testing [23]. A child with egg allergy, according to the American Academy of Pediatrics, should be skin tested before receiving any egg-containing vaccine. If either an SPT or intradermal skin test reveals a positive result to the vaccine preparation, the influenza vaccine should not be administered in the usual fashion but, if indicated, by means of a graded, multidose protocol.

In all patients one should inquire about a history of adverse reactions to egg or influenza vaccines before vaccination. Egg allergy can be ruled out if an individual currently ingests eggs or egg-containing products in a full portion without any reaction. In those with a history of an adverse reaction to egg who might also benefit from influenza vaccination, referral to an allergist should be recommended. An SPT to egg (1:20) should be performed, with appropriate histamine and saline controls. A negative SPT result to egg with positive histamine control virtually rules out egg allergy and permits influenza vac-

cination in full dose, unless a non-IgE-mediated reaction, such as thimerosal sensitivity, is suspected.

Vaccination and the development of allergy

There is growing interest in the potential interactions between infant vaccination and risk for development of atopic disease. In addition, there is concern that genetic risk for atopy influences capacity to respond to vaccination during infancy. Support for the latter possibility comes from recent studies of the role of developmental factors that determine immune competence during infancy, and attendant risk for inflammatory and infectious diseases [24]. Concerns about allergic side effects of vaccines and about a possible promotion of allergic diseases contribute to incomplete vaccination rates in childhood. A German atopy risk-enhanced birth cohort of 1314 neonates who were born in 1990 in five German cities with 943 children followed to 5 years of age showed that the cumulative vaccine dose was inversely related to atopic dermatitis and asthma. Children with a higher vaccination coverage seemed to be transiently better protected against development of atopy during the first years of life [25•].

Several studies were performed to examine the effect of individual vaccines on the development of atopy or protection against allergies.

Bacille Calmette–Guerin

There are conflicting reports on the effect of Bacille Calmette–Guerin (BCG) vaccination on the subsequent development of atopy and asthma in children. BCG vaccination has been proposed as a suppressor of allergy because of its Th1-fostering properties. In the murine system, BCG inhibits allergic sensitization and airway hyperreactivity. Some epidemiologic studies in humans suggest an inhibitory effect of tuberculosis on allergy. BCG vaccination in children, however, has no or merely a marginal suppressive effect on atopy [26]. BCG vaccination in adult patients with moderate-to-severe asthma improved lung function and reduced medication use. This amelioration was accompanied by a suppressed Th2-type immune response, suggesting that BCG vaccination might be an effective therapeutic modality against asthma [27]. There are no data on the effects of neonatal BCG vaccination on cytokine responses of lymphocytes that are exposed *in vitro* to allergens. It is of interest whether neonatal BCG vaccination or, alternatively, immunologic memory of this vaccination is associated with a reduced prevalence of allergic sensitization, asthma, eczema, and hayfever during childhood. A cohort study of 309 BCG-vaccinated subjects age 7 to 14 years, and 442 non-BCG-vaccinated subjects showed that BCG-vaccinated subjects did not have a lower rate of allergic sensitization than unvaccinated subjects [28]. However, among the subgroup of subjects with a family history of rhinitis or eczema, BCG vaccination was associated with

a lower prevalence of current asthma. BCG vaccination was also associated with lower levels of allergen-stimulated interleukin-10 production *in vitro*. Thus, neonatal BCG vaccination had an effect on T-cell allergen responsiveness 7 to 14 years after vaccination and, among a subgroup of subjects with an inherited predisposition to allergic disease, this was associated with clinically relevant beneficial effects. It has been suggested that BCG vaccination may protect against the development of allergic diseases, particularly when given just after birth, but the results so far are conflicting. BCG vaccination was given routinely to all infants in Greenland until 1990, when it was withdrawn from the vaccination program. Whether stopping vaccination programs for BCG resulted in an increased prevalence of atopy in children is unknown. A cross-sectional study of 1686 schoolchildren age 8 to 16 years showed that the risk of atopy was the same in BCG-vaccinated compared with unvaccinated children, and the risk of atopy in BCG-vaccinated children was not associated with age at vaccination [29]. The results demonstrated that BCG vaccination administered to infants is not associated with reduced risk of development of atopy.

Smallpox

Atopy and allergic diseases have increased after routine smallpox vaccination was stopped in the 1970s. In a study of nearly 2000 women participating in a national birth cohort study to examine whether administration of smallpox vaccination during childhood was associated with a decreased risk of atopy, allergic rhinitis, and asthma, there was no association between having been vaccinated against smallpox during childhood and risk of atopy or allergic rhinitis [30•]. Smallpox vaccination was associated with a slightly decreased risk of asthma. There was no association between age at smallpox vaccination and risk of atopy, allergic rhinitis, or asthma. Adjusting for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood did not change these results. Thus, the results did not suggest that childhood vaccination against smallpox, even if given early in life, influences the development of atopy or allergic rhinitis.

Pertussis

There is evidence that pertussis and diphtheria/tetanus antigens elicit IgE antibody formation as part of the immune response. In murine models, pertussis toxin is an effective adjuvant for IgE formation against simultaneously administered antigens. In children, however, sensitization to unrelated antigens or development of allergic diseases do not seem to be augmented [26]. Exposure of children to pertussis antigens caused by infection or vaccination with whole-cell pertussis vaccine may increase the serum IgE level and predispose to sensitization to the prevalent environmental allergens. Acellular pertussis vaccine, which may be given to adults, may

have a similar effect. A recent study was conducted to determine whether acellular pertussis vaccine causes an increase in environmental sensitization measured by an increase of serum-specific IgE to the allergens to which adults are exposed during the vaccination period [31]. Acellular pertussis vaccine had no significant change in serum-specific IgE levels to cat, dust, *Alternaria species*, or ragweed 1 month after vaccination. Thus, a two-component acellular pertussis vaccine did not predispose to an increase of allergen-specific IgE in an adult population.

Influenza

Influenza virus infection can cause an acute exacerbation of asthma that may result in hospitalization. Annual influenza vaccination is recommended for children with asthma, but fewer than 10% receive it. Influenza virus infection causes substantial morbidity in children with asthma. The effectiveness of influenza vaccine in preventing influenza-related asthma exacerbations, however, is not known. A population-based retrospective cohort study with medical and vaccination records in four large health maintenance organizations in the United States during three influenza seasons revealed that after controlling for asthma severity, influenza vaccination protects against acute asthma exacerbations in children [32].

Concern over the safety of influenza vaccination in individuals with obstructive airway disease has contributed to suboptimal rates of vaccine uptake in this group. Investigation of the safety of influenza vaccine in older adults with asthma or chronic obstructive pulmonary disease showed that asthma or chronic obstructive pulmonary disease diagnoses and oral glucocorticoid prescriptions were increased on the day of vaccination. However, there was no consistent increase in the incidence rate ratios of any of the outcomes on days 1 to 2 or 3 to 14 after vaccination, and most of these incidence rate ratios were close to 1. Rates of exacerbation were low and showed no consistent, statistically significant increase during any risk periods. In conclusion, there was no increased risk of adverse acute outcomes during the first 2 weeks after vaccination. These findings strongly suggest that influenza vaccination is safe in this population [33]. Episodes of bronchospasm after influenza vaccination do not seem related to hypersensitivity to the vaccine, and there were no differences in cytokine production in response to either influenza or egg antigen in association with asthma exacerbations [34].

Summary

The question whether vaccination effects the development of allergy is complicated by the question of the effect of infections and especially viral infections on the development of atopy. A changing pattern of infections may be of importance for the increase in prevalence of

asthma and other allergic diseases in developed countries during recent decades. The clear inverse relation between number of siblings and atopy observed in several studies may be related to a protective role of infections, although specific information is inconclusive. A recent study showed that positive tuberculin responses in schoolchildren correlated with a lower prevalence of atopic disorders, but other studies did not find a relation between BCG vaccination and allergic disease or sensitization [35]. Transient production of IgE antibodies to pertussis toxin has been demonstrated after pertussis immunization; however, randomized clinical trials involving both whole-cell and acellular pertussis vaccines have failed to show any enhancement of atopic manifestations in children. Epidemiologic investigations indicate that viral infections may either promote respiratory syncytial virus (RSV) or inhibit (hepatitis A, measles) atopy, although data are scarce. In conclusion, the evidence is limited regarding a direct role of vaccinations for development of atopic manifestations, but speaks against a major effect of some types of vaccinations. On the other hand, because some infections may offer protection in relation to allergy, vaccination could result in an increased risk. In conclusion, vaccination programs do not explain the increasing prevalence of allergic diseases, but individual children may uncommonly develop an allergic reaction to a vaccine. The risks of not vaccinating children, however, far outweigh the risk for allergy. Therefore, childhood vaccination remains an essential part of child health programs and should not be withheld, even from children predisposed to allergy.

Immunologic response to vaccination in patients with atopy

Recent findings suggest that a hallmark of the atopic phenotype is a reduced capacity to respond to vaccine antigens, as well as to environmental allergens, during infancy. This deficiency, which is most marked for the cytokine interferon- γ , appears transient but can result in a long-lasting imbalance within Th memory responses to allergens. Indirect evidence suggests that parallel effects may occur within immunologic memory responses against vaccine antigens in atopic children. A recent study examined vaccine antigen-specific Th memory responses in atopic and nonatopic children [36]. This was performed by analysis of specific serum IgG and cytokine responses to pertussis and tetanus antigens as well as to mitogen and house dust mite allergen in 25 house dust mite-sensitized atopic and 25 nonatopic 6-year-old children who were vaccinated and boosted with DTP vaccine. The results showed that peripheral blood mononuclear cells from the atopic subjects produced higher levels of Th1 and Th2 cytokines to house dust mite allergen and PHA. Vaccine antibody titers were normal in the atopic subjects. Vaccine-specific Th2 responses were rarely detectable. Yet, Th1 (interferon- γ) responses (in particular against tetanus) were frequent and higher

in the atopic subjects. Corresponding pertactin responses were comparable in both groups. At the completion of the full primer booster DTP vaccination regimen, levels of vaccine-specific immunity in atopic 6-year-old children are at least equivalent to their nonatopic counterparts, indicating that the transient atopy-associated deficiency in Th1 function in childhood can be successfully overcome by appropriate vaccination and boosting regimens.

Vaccination for the treatment of allergy

Allergen-specific immunotherapy is an efficacious treatment of allergic conditions, especially allergic rhinitis and hymenoptera hypersensitivity, as reviewed in detail by Demole *et al.* [37]. The treatment consists of injecting increasing doses of the specific allergen or allergens to which the patient is sensitive over time, until a maintenance dose is reached. The maintenance dose depends on each allergen. The maintenance dose is injected on a monthly basis for 3 to 5 years, which leads to a persistent effect for many years. The immunologic mechanism of immunotherapy is inducing tolerance by immunomodulation of the Th lymphocytes from Th2 to Th1 cells. Recently, two new types of allergen immunotherapy have been developed: namely, allergen gene vaccination and vaccination with allergen-immunostimulatory DNA conjugates [38,39]. In animal models of allergy, both have been shown to induce nonallergic Th1 immune responses to allergens and downregulate preexisting Th2 responses. During initial clinical trials with allergic patients, allergen-immunostimulatory DNA conjugates were well tolerated, induced IgG but not IgE antibodies, and appeared to have great potential as a novel, safe, and efficacious type of allergen-specific immunotherapy. Immunostimulatory sequence oligodeoxynucleotide (ISS-ODN)-based interventions might offer an alternative and potentially a more effective means for extinguishing Th2-biased hypersensitivities. Three basic ISS-ODN-based immunotherapeutic strategies have been studied to date. Immunization with allergen mixed with ISS-ODN, immunization with allergen-ISS-ODN conjugates, and immunomodulation with ISS-ODN alone all have proved efficacy in the attenuation of the allergic phenotype in mice. Preliminary results with allergen-ISS-ODN conjugate vaccines in allergic patients have also been encouraging.

Vaccination and autoimmunity

In recent years it has become increasingly evident that vaccines can be temporarily and/or causally related to the development of diseases thought to involve autoimmunity [40]. A causal relation has been accepted by the Institute of Medicine of the National Academy of Sciences (USA) for several different vaccines and three syndromes: 1) diphtheria and tetanus toxoids, polio and measles vaccines, and Guillain-Barré syndrome; 2) MMR vaccines and thrombocytopenia, which frequently

takes the form of idiopathic thrombocytopenic purpura; and 3) rubella vaccines and acute and chronic arthritis in adult women [41••]. Epidemiologic studies so far have not shown conclusively that there exists a causal relation between any one vaccine and any autoimmune disease. Appropriate epidemiologic studies should be conducted before a particular autoimmune clinical condition is associated with a given vaccination. A possible increased risk for the development of autoimmune conditions has been suggested by findings in several case reports and series, in which familial or genetic risk factors for autoimmune conditions have been found in many of the patients who developed autoimmune disease or phenomena shortly after vaccination [42–44]. It is interesting to note that autoimmune phenomena related to vaccination occur equally in males and females, unlike “regular” autoimmune diseases, which are prevalent mainly in females. The vaccine most often involved with autoimmunity has been the hepatitis B virus (HBV) vaccine, having been connected with systemic lupus erythematosus, rheumatoid arthritis, and nonspecific autoimmune manifestations as well [40,42]. Another very immunogenic agent is mycobacteria. The immunogenicity of mycobacterial components has been demonstrated in several studies [45,46]. The molecular similarity between mycobacterial and host antigens has been determined repeatedly. Numerous autoantibodies have been found in the sera of patients with mycobacterial infection. The presence of autoantibodies in their sera is testimony to the fact that an autoimmune reaction occurs even if it does not manifest clinically. Therefore, the potential for autoimmune illness exists. Because other factors are also required to enable the clinical manifestation of autoimmune illness (genetic, environmental), in their absence there will be no autoimmune disease. The mechanisms suggested to explain the formation of autoantibodies are diverse. Clinical and laboratory evidence suggests that the antitumor activity is concentrated at the site of BCG administration, which reinforces the view that local immune mechanisms are responsible for the therapeutic effect of BCG in bladder carcinoma. Nevertheless, systemic immune responses and autoimmune manifestations have been documented after intravesical instillation of BCG, a fact that confirms that a more generalized stimulation of the immune system occurs as a result of exposure to mycobacterial antigens. It is advisable that, whenever possible, or whenever other risk factors are suspected, genetic screening of the patients for susceptibility to autoimmune disease be performed. In the case of intravesical BCG instillation, a high level of awareness should be maintained for any clinical manifestations of autoimmunity. Based on this knowledge, vaccination of any person with such known risk factors should be carefully considered. 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.

Vaccination of patients with known autoimmune diseases (such as rheumatoid arthritis or systemic lupus erythematosus) has not caused exacerbation of their condition, and of these patients have mounted a good antibody response to the vaccine (even though it is attenuated compared with healthy control subjects). Vaccination of previously diagnosed systemic lupus erythematosus patients with a variety of vaccines (including pneumococcal and influenza vaccines) has proved safe, with vaccine-induced flare-ups of the disease infrequent and mild [47,48]. The safety of hepatitis B vaccination in lupus patients has not yet been determined. However, it is recommended that patients at risk of exposure be immunized. Therefore, because of the increased morbidity and mortality of these patients when they contract infectious diseases (such as pneumonia or influenza), it is recommended that they be immunized.

For the general population, the risk-to-benefit ratio is overwhelmingly in favor of vaccinations. However, the possibility cannot be ruled out that, in genetically susceptible individuals, vaccination can result in the unmasking of an autoimmune disease triggered by the immunization.

Conclusion

Vaccination was linked to potential allergic side effects in healthy and often in certain high-risk populations. Careful examination of the literature shows such reactions are rare, and life-threatening events are extremely uncommon. Although severe allergic adverse events attributable to vaccination are extremely rare, all serious allergic reactions should be further assessed to detect the likely causative vaccine component, including egg protein and gelatin. Vaccination programs do not explain the increasing prevalence of allergic diseases, but individual children may uncommonly develop an allergic reaction to a vaccine. The risks of not vaccinating children, however, far outweigh the risk for allergy. Therefore, childhood vaccination remains an essential part of child health programs and should not be withheld, even from children predisposed for allergy. Immunotherapy provides an efficacious and safe method for treatment of allergic conditions by immunomodulation of the immune system. The possibility of vaccination triggering or unmasking autoimmunity in genetically susceptible individuals cannot be ruled out, but for the general population the risk-to-benefit ratio is overwhelmingly in favor of vaccinations.

References and recommended reading

Papers of particular interest, published within the annual period of review, are highlighted as:

- Of special interest
 - Of outstanding interest
- 1 Zent O, Arras-Reiter C, Broeker M, et al.: Immediate allergic reactions after vaccinations—a post-marketing surveillance review. *Eur J Pediatr* 2002, 161:21–25.
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 - 5 Copeman PWM, Wallace HJ: Eczema vaccinatum. *BMJ* 1964, 2:906–908.
 - 6 Lane JM, Millar JD: Risks of smallpox vaccination complications in the United States. *Am J Epidemiol* 1971, 93:238–240.
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 - As the threat of bioterrorism with pathogenic microbes such as smallpox virus increases, the question of widespread voluntary vaccination with smallpox (vaccinia) vaccines is being carefully considered. A major challenge lies in the ability to protect the population from the disease while minimizing the considerable side effects from the vaccine. Individuals with active or quiescent atopic dermatitis are at increased risk for vaccinia complications. The nature of these complications and other considerations are summarized in this review.
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 - Influenza infection, with its accompanying morbidity and mortality, represents a major public health concern yearly to the elderly and high-risk groups, including asthmatic patients. Active prevention with vaccination consistently falls short of reaching optimal immunization rates in all risk groups. Asthmatic patients and others with concomitant egg allergy might be denied active immunization because of the risk of inducing adverse reactions with a vaccine derived from egg embryo tissue. Evidence supports the relatively safe administration of influenza vaccine to individuals with egg allergy in whom vaccination is indicated when specific protocols are followed under the supervision of experienced physicians. A practical protocol that includes incremental dosing of influenza vaccine is presented to guide clinicians in influenza vaccination in this high-risk group.

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- Vaccinations are invaluable in protecting the population from a wide variety of diseases that can cause substantial morbidity and mortality. Although a rare complication of vaccination, autoimmune disorders represent one of these morbidities. Recently, widespread public concern has arisen from case reports suggesting that (similar to what has been observed after natural viral infections) there might be an association between specific immunizations and autoimmune diseases. Review of the available data suggests that, for the general population, the risk-to-benefit ratio is overwhelmingly in favor of vaccinations. However, the possibility cannot be ruled out that in genetically susceptible individuals, vaccination can result in the unmasking of an autoimmune disease triggered by the immunization.
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