

Review Article

Do early childhood immunizations influence the development of atopy and do they cause allergic reactions?

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Concerns about allergic side-effects of vaccines and about a possible promotion of allergic diseases contribute to incomplete vaccination rates in childhood. This article reviews the current understanding of these issues. There is evidence that pertussis and diphtheria/tetanus antigens elicit immunoglobulin E (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. In contrast, bacille Calmette–Guérin (BCG) and measles vaccination have been proposed as suppressors of allergy because of their T helper 1 (Th1)-fostering properties. In the murine system, BCG inhibits allergic sensitization and airway hyper-reactivity. Some epidemiological 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. Other vaccine components such as egg proteins, gelatin, and antibiotics are a potential hazard to children with severe clinical reactions to these allergens. These rare children should be vaccinated under special precautions. 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 for allergy.

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The prevalence of atopic diseases in children has increased, during recent decades, in many countries. The reasons for this epidemiological trend are not fully understood; however, it is obvious that this increase is the result of environmental factors and not a shift in genetic disposition. Environmental factors investigated to date, such as differences in indoor climate or outdoor pollution, seem to account for only some of the epidemiological trends (1).

Recently, changes in exposure to common respiratory or childhood infections have been

highlighted as potential modifiers of the course of allergic disease. Several studies suggest an association between the declining incidence of infections and the rising prevalence of allergic disease (2–4). From these observations, the hypothesis was derived that recognition of microbial constituents such as lipopolysaccharides (LPS) results in predominant production of T helper 1 (Th1)-type cytokines and thus would help to overcome the impairment of Th1-type cytokine production that is observed in atopic individuals (5). In contrast, other microbial

products such as pertussis toxin are known for their capacity to foster secretion of T helper 2 (Th2)-type cytokines and thus might promote allergic disease.

Routine vaccinations expose infants and children early in life to antigens of infectious agents (Table 1). Immunization in infancy may be more prone to induce a Th2-dominated vaccine specific response than immunization later in life (6,7). Concerns have therefore been raised that vaccinations early in life may induce allergy. These concerns were supported by data from some animal experiments (8,9) and clinical observations (4,10,11).

Theoretically, protection from allergy may result from withholding potentially pro-allergic vaccines acting either indirectly by preventing infections which otherwise would stimulate Th1-type immunity or directly by stimulating a Th2-type cytokine pattern. Some retrospective studies have indicated a lower prevalence of atopy among children with a low vaccination coverage level (4,10,11). Protection might also be possible by administration of Th1-polarizing immunizations that inhibit immunoglobulin E (IgE)-mediated allergic disease (12). Vaccines commonly also contain adjuvants (such as aluminum) and stabilizers (i.e. gelatin), which conceivably enhance allergenicity (13,14).

Hypersensitivity reactions to vaccines, particularly local painful erythema (type IV cell-mediated hypersensitivity and type III immune complex-mediated hypersensitivity) do occur, while IgE-mediated anaphylactic (type I hypersensitivity) reactions are very rare but may be potentially life-threatening.

The impact of childhood vaccinations on IgE antibody formation and on the development of atopic disease has not yet been fully elucidated. This review summarizes animal and human studies related to the effect of childhood vaccinations on atopy and its clinical manifestations in general. Furthermore, the evidence for specific allergic reactions to vaccines is summarized.

Vaccines

Pertussis vaccines

All pertussis vaccines contain chemically detoxified pertussis toxin (pertussis toxoid). Whole-cell pertussis vaccines also contain some active pertussis toxin. Pertussis toxin has been used for many years as an adjuvant to enhance IgE formation against simultaneously administered antigens in animal models (8,9,15,16).

Evidence for an association between whooping cough and atopy or its clinical manifestations is conflicting. Peripheral blood mononuclear cells (PBMC) obtained from patients after a pertussis infection and then stimulated *in vitro* with pertussis antigens respond with a Th1-type cytokine pattern, as indicated by secretion of high levels of interferon- γ (IFN- γ) and low levels of interleukin (IL)-5 (17,18). In most children with culture-confirmed pertussis infection, IgE to pertussis toxin and common allergens can be detected as well as increased serum levels of total IgE (19–23). An early Th1-type cytokine response is necessary for bacterial clearance in the murine system (24), although it is later balanced by secretion of Th2-type cytokines (25). Disseminating respiratory infection with *Bordetella pertussis* has been reported in B-cell-deficient mice (26).

In animals, *B. pertussis* induces a β -adrenergic blockade that persists for several weeks (27). Similarly, prolonged wheezing is common in children after whooping cough (28–30). A causal relationship between whooping cough and wheezing has not been established. It is therefore possible that whooping cough worsens symptoms in subjects predisposed to wheeze. This notion is supported by a small prospective trial which found that whooping cough in infancy did not predispose to subsequent asthma (31).

Different pertussis vaccines elicit different cytokine secretion patterns. PBMC from recipients of a whole-cell vaccine respond with a Th1 secretion pattern, as indicated by production of high levels of IFN- γ and IL-2 but low levels of IL-4 and IL-5 (32,33). This is in line with the studies in pertussis-infected children. In contrast, PBMC from recipients of an acellular vaccine show a mixed Th1/Th2-type cytokine profile, as indicated by the production of IFN- γ , IL-4, and IL-5 (32,33). A Th2-polarized response is particularly obvious after booster vaccination with an acellular vaccine, as indicated by increased secretion of IL-5 and reduced production of IFN- γ (33,34).

Transiently elevated serum levels of IgE to pertussis toxin are commonly detected after primary immunization with whole-cell and acellular vaccines (13,19,35–37). Acellular vaccines seem to be associated with even higher levels of IgE to pertussis toxin (38). Booster immunization results in a higher and longer-lasting IgE response in children primarily immunized with an acellular vaccine (19,38,39) than in those primarily immunized with a whole-cell vaccine (36,38,39). In a murine

study, simultaneous administration of pertussis toxin and diphtheria or tetanus toxoid increased the primary IgE and IgG₁ response to the latter toxoids (40). In children, whole-cell pertussis vaccine, co-vaccinated with diphtheria and tetanus toxoids, was found to suppress IgE and IgG₄ formation against these toxoids (C. Grüber et al., unpublished).

It is possible that the more distinct Th1-type cytokine pattern and down-regulated IgE formation in response to whole-cell pertussis vaccines are related to cell wall components, such as LPS, which are known to stimulate IL-12 synthesis and thus to enhance Th1 responses (41). A murine study indicated that LPS stimulated B cells to differentiate into IgG-producing plasma cells only if LPS was given before the immunoglobulin-isotype switch had occurred (42). If given after the switch, then LPS stimulated only those B cells which had already been primed to produce IgE (42). In humans, whole-cell pertussis vaccine has the potential to suppress the Th2-associated branch of the humoral immune response to simultaneously administered antigens (C. Grüber et al., unpublished). Sensitization to unrelated nutritive or inhalant allergens, however, does not seem to be enhanced after pertussis vaccination (34,38,43,44).

The appearance of a specific IgG response to pertussis antigens, jointly with a specific IgE response, indicates that transient levels of IgE antibodies are a part of the regular response (45). In fact, a balanced profile of both Th1- and Th2-type cytokines seems to be a prerequisite for successful protection from pertussis (24,26,46). Production of IgE against pertussis toxin is exaggerated in atopic children with clinical manifestations (38) and in children with a family history of atopy (38). Elevated pertussis toxin IgE levels are associated with local adverse effects (45), although these are not more frequent among children predisposed for atopy (47).

A five-fold increased risk for asthma in pertussis-vaccinated children has been reported in a retrospective comparison of vaccinated and non-vaccinated children (48). In another study, comparing children with and without diphtheria (whole cell) and polio vaccination, 23% of 1,265 vaccinated children and none of the 23 control children had asthma episodes (10). In another retrospective study, an odds ratio of 1.8 for atopic manifestations was reported for whole-cell pertussis-vaccinated children in comparison with non-vaccinated children (3). In contrast, a large Swedish prospective trial of pertussis vaccines revealed no significant differences at 30 months of age between subjects who received

whole-cell vaccine, two- or five-component acellular vaccines, or placebo. This was true for symptoms suggestive of atopic dermatitis, asthma or hay fever (47,49). Moreover, the prevalence of atopic diseases in the four groups was similar at 7 years of age, except for an increased proportion of sensitized children in one of the two acellular groups. In another study, the incidence of asthma was similar among pertussis-immunized and non-immunized children at 42 months of age (50).

In summary, although data from animal experiments and circumstantial clinical reports suggest that pertussis vaccination can promote atopy and allergic diseases, well-controlled clinical trials do not support this hypothesis.

Diphtheria and tetanus vaccines

Billions of diphtheria and tetanus vaccinations have been administered to infants and young children. Transient erythema and painful induration at the injection site are not rare, but allergic reactions to the toxoids are quite uncommon in primary vaccination. Allergic reactions may occur to accessory antigens (such as bacterial cell fractions) present in the vaccines (51,52). The introduction of highly purified toxoids without reactogenicity has added to the safety of these vaccines.

Immediate-type allergic reactions following booster vaccination with diphtheria or tetanus toxoids occur occasionally (51,53), but life-threatening anaphylactic reactions are extremely rare (54). However, IgE antibodies against tetanus and diphtheria toxoids were detected after booster immunization with an aluminum-adsorbed vaccine (55,56), and were related to the occurrence of local side-effects (57,58). As the adjuvant effect of aluminum on IgE production is well known, there has been controversy regarding the extent to which the local reactions are caused by the toxoids themselves (59–61). Non-significant, higher prevalences of atopic manifestations have been found in children immunized with aluminum-adsorbed vaccines as compared to recipients of non-adsorbed ones (37). Furthermore, IgE antibodies against tetanus and diphtheria toxoids are detectable after booster doses of non-adsorbed vaccines (57). The IgE response peaks between 7 and 14 days after booster immunization and often lasts for longer than 12 months (62,63).

The levels of IgG₄ and IgE antibodies against the toxoids correlate well, indicative of Th2-subset activation (63). Interestingly, there

is a poor correlation of specific IgG and IgE levels in serum (57,64). Thus, a high IgE antibody level does not seem to be a prerequisite for a protective IgG level (57,65). Atopic subjects are particularly likely to produce IgE against the toxoids (62–64,66), but the formation of specific IgE is not restricted to subjects with early markers of atopic disease (62). A transient delay of the specific Th1-type response after vaccination with diphtheria, tetanus, and acellular pertussis (DTaP) in the first year of life has been observed in 55 healthy children and was overcome by 6 years of age (7,67). Under a regular vaccination regimen, no differences in the level of vaccine-specific immunity against pertactin and tetanus toxoid at 6 years of age were seen between atopic and non-atopic individuals (67). In conclusion, IgE formation against the vaccine antigens seems to be part of a regular Th2-mediated immune response to immunization and not to be associated with atopic disease.

Bacille Calmette–Guérin (BCG) vaccine

In the past, BCG vaccinations were routinely given in the neonatal period, but this practice has been abandoned in many countries with a low prevalence of tuberculosis and replaced by vaccination of selected risk groups (Table 1).

Exposure to mycobacteria results in the preferential secretion of Th1 cytokines and subsequent activation of macrophages (68). Although the fetal and neonatal immune system is Th2-skewed, BCG vaccination given at birth induces a memory Th1-type response of similar magnitude as when vaccinated later in life (69). Balancing the release of Th2 cytokines has also been observed later during the course of mycobacterial infection (70) but seems to play a less important role in the host defense than the Th1-type response (71,72). Hence, a decreased risk of atopic disease could be the consequence of BCG-induced skewing of the cytokine micro-environment towards preferential selection of Th1 cytokines. This hypothesis is supported by data from experimental studies in which BCG-infected mice were demonstrated to express a cytokine shift towards a Th1-like pattern and inhibited formation of IgE and airway allergy when sensitized (12,73).

Several epidemiological studies investigated the relationship between tuberculosis and atopy in humans. An inverse correlation between purified protein derivative (PPD) skin test reactivity and total IgE or atopic disease in Japanese BCG-vaccinated school children was

taken as evidence that infected children are better protected from atopic disease (74). A Finnish retrospective study reported lower prevalences of asthma and allergic disease in adult females who were tuberculosis-infected before reaching 17 years of age (75). In an ecological analysis, a weak, but significant, inverse association between lifetime prevalence of wheeze and asthma, as recorded in the International Study of Asthma and Allergy in Childhood (ISAAC), and global tuberculosis notification rates was reported (76). No individual vaccination data were available in this study.

The relationship between BCG vaccination and development of atopy has been specifically addressed in several recent observational studies. A cross-sectional study in Swedish pre-school children revealed similar prevalences of atopic sensitization or atopic disease between BCG-vaccinated and non-vaccinated individuals (77). In another Swedish cross-sectional study, the prevalence of allergy was similar in BCG-vaccinated and non-vaccinated Swedish children, although there was a non-significant tendency in favor of fewer allergies among BCG-vaccinated children who were born abroad (78). Furthermore, there was no correlation between tuberculin reactivity and atopy among Norwegian adults who had been BCG vaccinated at 14 years of age (79) and among German BCG-vaccinated and non-vaccinated children who had been vaccinated as infants (80). In the latter study of a prospectively followed-up German birth cohort, only a transient and weak inhibitory effect of BCG vaccination was seen on the prevalence of atopic diseases and allergic sensitization early in life (80). The strongest evidence comes from a study in Guinea-Bissau where BCG-vaccinated children were less reactive to local indoor aeroallergens, as measured by skin-prick tests, and this was particularly true for those children who were vaccinated during their first week of life (81).

There are several explanations for what could be regarded as conflicting evidence. The Japanese study (74) included exclusively BCG-vaccinated children and was based on the observation that a positive tuberculin response was associated with a lower incidence of atopic disorders. A considerable proportion of the tuberculin skin test results were strongly positive. Thus, this study addressed infection and not vaccination. It is possible that decreased tuberculin skin reactions in atopics, as documented in the Japanese study, represent

a marker of atopy rather than pointing towards BCG as a cause of being non-atopic. The genetic aspect of PPD reactivity is highlighted by an epidemiological study of tuberculosis household contacts in which PPD reactivity correlated between siblings but not between unrelated children living under the same roof (82). In fact, several Scandinavian studies have demonstrated that PPD skin test reactions and indurations in response to pertussis vaccination are smaller among allergic children (38,78,83,84). In a German study, however, no such difference was seen (80). Shirakawa et al. claimed that a fixed determination of atopy and diminished tuberculin responses by genetic factors is unlikely because of intra-individually changed tuberculin responses over time from positive to negative, and *vice versa* (74). In addition, the immunological stimulus given by mycobacteria differs in various ways between Japanese and European children. The Japanese children received a 10-fold higher dose of a BCG strain which differs biochemically from the strain used in the European populations (85,86). Finally, it may be hypothesized that environmental mycobacterial infections co-influenced tuberculin responses and development of atopy by continuously stimulating Th1-like clones.

In summary, the currently available retrospective studies provide little evidence for an allergy-preventing effect of early BCG vaccination.

Measles vaccine

In many countries, measles vaccine is given together with vaccines against mumps and rubella (Table 1). Measles vaccination has been discussed as a potential hazard for egg-allergic children, as virus used in the vaccine is grown on chick embryo fibroblasts. A recent critical review of patients with allergic reactions to measles, mumps, and rubella vaccines showed that the majority of reported allergic reactions are probably caused by gelatin, which is frequently added as a stabilizer for these vaccines (87).

Natural measles infection is characterized by a mixed Th1/Th2-type immunologic response. During the early phase, Th1 cells are activated with increased production of IL-2 (88). In the convalescent phase, the immune system is suppressed, as indicated by depressed skin test responses to recall antigens (89,90) and impaired *in vitro* lymphoproliferative responses (91). The production of Th1-type cytokines – IL-2 and IFN- γ – becomes inadequate (91). In contrast,

production of the Th2-type cytokine, IL-4, is predominant (88) and IgE antibody formation is promoted (92). Augmentation of Th2-type cytokines is also observed following measles vaccination (93). Binding of measles virus particles to CD46 on monocytes, which inhibits IL-12 production and subsequently down-regulates IFN- γ production, has been suggested as a mechanism for skewing towards Th2 and the induction of IgE class switching (94–97).

A recent epidemiological study analyzed young adults from Guinea-Bissau who survived a measles epidemic (98). Children who had not been infected were vaccinated against measles. Infected individuals had a two-fold odds ratio for anergy to recall antigens. This is in line with an inhibited IL-12 production. Interestingly, subjects who had a history of measles had a lower odds ratio for sensitivity to common aeroallergens than vaccinated subjects (99). In a British study, a weak protective effect against hay fever was seen in measles-infected children and measles-vaccinated children in comparison with non-infected and non-vaccinated children (100). There was also some protective effect of measles against asthma in children who were infected when >3 years old (2). The incidence of adult-onset asthma was lower among infected individuals if measles was acquired before 3 years of age (101). In two large European epidemiological studies, however, this type of association between measles infection and atopic diseases was not evident (3,102). In fact, in one of the studies, clinical manifestations of atopy tended to be more prevalent among measles-infected subjects (102). Furthermore, a later study in Guinea-Bissau did not reveal a negative association between measles infection (or vaccination) with atopy (81).

In summary, measles vaccination is not a risk factor for allergy. Well-controlled prospective trials are needed to possibly confirm an allergy-preventing effect of measles vaccination that was seen in some retrospective studies.

Hepatitis B vaccine

Genetically produced recombinant hepatitis B vaccines have replaced the plasma-derived surface antigen that was used in earlier vaccines. Recombinant human hepatitis B vaccines are commonly produced in yeast cells. Therefore, sensitization to yeast contaminants could theoretically account for allergic reactions that rarely occur after hepatitis B vaccination. Production of detectable IgE or IgG levels to yeast does not seem to be elicited by vaccination (103–105). In

Early childhood immunizations: Influence on development of atopy and allergic reactions

Table 1. Immunization schedules used in selected countries*

	Age (months)														
	0	1	2	3	4	5	6	7	10	12	14	15	16	18	
Argentina	Hep B	HepB	DTP		DTP		DTP HiB OPV Hep B DTPa			MMR				DTP	
	BCG		HiB OPV DTPa		HiB OPV DTPa HiB Hep B								MMR	HiB OPV DTPa	
Australia	BCG† Hep B†		HiB OPV	DTP	DTP HiB HepB OPV DTP HiB	DTP	OPV OPV				MMR	HiB Hep B	DTP		
Austria	BCG† Hep B†		DTP HiB IPV HepB	HiB HepB DTP HiB IPV HepB	HepB OPV DTP HiB IPV HepB	HiB HepB				MMR	HiB		OPV HepB	IPV	
France	BCG† Hep B†		HepB	HepB DTaP	HepB DTaP	DTaP				HiB DTaP HiB IPV HepB MMR					
Germany	BCG†		HiB IPV HepB DTaP OPV	HepB DTaP OPV Hep B†	HiB	HiB IPV HepB			OPV Hep B*						
Italy	Hep B†		DTaP OPV DTaP HiB IPV	Hep B† DTaP OPV DTaP HiB IPV	Hep B† DTaP OPV DTaP HiB IPV	DTaP DTaP OPV DTaP HiB IPV		DTaP				MMR			
Japan			DTaP OPV DTaP HiB IPV	DTaP OPV DTaP HiB IPV	DTaP OPV DTaP HiB IPV	DTaP OPV DTaP HiB IPV				MR DTaP HiB IPV					
Sweden	Hep B† Hep B†		DTP HiB OPV	DTP HiB OPV	DTP HiB OPV						MMR			MMR	
UK	BCG†		DTaP HiB IPV	DTaP HiB IPV	DTaP HiB IPV		DTaP HiB IPV Hep B			HiB MMR Var					
USA	Hep B	HepB	IPV		IPV								DTaP		

*Adapted from Salisbury & Dittmann (179) and Orenstein et al. (180).

†In high-risk groups only.

BCG, bacille Calmette–Guérin; DTaP, diphtheria, tetanus, acellular pertussis; DTP, diphtheria, tetanus, whole-cell pertussis; HiB, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; OPV, oral polio vaccine; MMR, measles, mumps, rubella.

contrast, other vaccine additives such as thiomersal, aluminum, formaldehyde, and possibly hepatitis B surface antigen itself, have been identified as causes for allergic reactions in recombinant or plasma-derived hepatitis B vaccines (106–109).

Vaccine adjuvants

Adjuvants are used to reduce the antigen doses needed for a sufficient vaccination efficacy and thereby to reduce side-effects. Prolonged contact of the antigen with the macrophages, as a result of greater surface and inflammatory reactions, correlate with the adjuvancy of so-called repository adjuvants (110). Aluminum salts – Al_3PO_4 and the more potent $\text{Al}(\text{OH})_3$ – are widely used (Table 2). $\text{Al}(\text{OH})_3$ directly stimulates human

antigen-presenting cells to secrete IL-4 and thereby increases the cell-surface expression of major histocompatibility complex (MHC) class II antigen (111). Enhanced antigen presentation could be an important mechanism of the adjuvancy of $\text{Al}(\text{OH})_3$. In animal models, $\text{Al}(\text{OH})_3$ is known to be an effective Th2 adjuvant, enhancing the production of IgG and also IgE antibodies (55,56,112). It also enhances bronchial hyper-reactivity (113). Furthermore, aluminum salts can cause occupational asthma (114).

The safety record of aluminum adjuvants in vaccines is excellent, although long-term pruriginous nodules containing aluminum crystals are occasionally found at the injection site (108,115,116). The occurrence of local side-effects is related to antigen-specific IgE formation (57),

Table 2. Common childhood vaccines and typical constituents

Vaccine	Aluminum compounds	Mercury compounds	Antibiotics	Human gelatin	Yeast formaldehyde	Egg albumin	Derived	Derived
Diphtheria	+	(+)	–	–	+	–	–	–
Tetanus	+	(+)	–	–	+	–	–	–
Pertussis	+	(+)	(+)	–	+	–	–	–
Polio (IPV)	–	–	+	–	–	–	–	–
Polio (Sabin)	–	–	+	+	–	–	–	–
Measles	–	–	+	+	–	+	–	+
Mumps	–	–	+	+	–	+	–	(+)
Rubella	–	–	+	(+)	–	+	–	–
Hib	(+)	(+)	–	–	–	–	–	–
Hepatitis B	+	(+)	–	–	(+)	–	+	–
Hepatitis A	+	–	+	–	+	–	–	–
Influenza	–	+	+	–	+	–	–	(+)
Tick-borne disease	–	–	+	(+)	+	(+)	–	(+)
BCG	–	–	–	+	–	–	–	–
Pneumococci	–	(+)	(+)	–	–	–	–	–
Meningococci	–	(+)	–	–	–	–	–	–
Varicella	–	–	(+)	–	–	+	–	–
Yellow fever	–	–	–	+	–	–	–	+

+, common; (+), some; –, uncommon.

BCG, bacille Calmette–Guérin; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine.

but in a small study it was found not to be related to atopy in general (116). Anaphylaxis caused by aluminum adjuvants has not been reported.

Calcium phosphate has been proposed as an alternative to aluminum salts because it is highly immunogenic in allergy vaccination therapy (117) and does not stimulate IgE antibody formation in animal models (118). In clinical trials of diphtheria and tetanus vaccines, calcium phosphate-adjuvanted vaccines were effective, but they caused a rise in IgE levels and did not add to the safety of aluminium hydroxide (119). Other experimental vaccine adjuvants are currently being evaluated for use in humans (120).

Vaccine contaminants

Egg

Traces of residual egg-related proteins are found in vaccines that are produced in chick embryo fibroblast cell cultures (measles and mumps vaccines, tick-borne encephalitis vaccines, rabies vaccines) (121,122). Higher (but still low) amounts of egg protein may be present in influenza vaccines that are produced in embryonated eggs. The highest amounts of egg protein are to be expected in yellow fever vaccines, which are grown in chick embryos (123).

Systemic allergic reactions to measles vaccine occur in fewer than one dose per million (124), but can be life-threatening (122,125–129). They had previously been thought to be related to egg allergy. Theoretically, patients highly allergic to

egg could be at risk for an anaphylactic reaction to these vaccines. However, in most instances allergic reactions to the combined measles, mumps, and rubella (MMR) vaccine were not caused by egg allergy but by other components of the vaccine, such as neomycin or gelatin (122,126,130,131). The predictive value of skin testing with the vaccine prior to vaccination is low (122,130,132). Most egg-allergic children tolerate the vaccine well and egg allergy is not predictive of reactions to MMR vaccination (122,130,133,134).

De-sensitization has been proposed in order to increase immunization rates in egg-allergic children (131). However, it may cause systemic hypersensitivity reactions (131,135) and therefore this approach is no longer recommended. In Europe, a measles vaccine with the Edmoston-Zagreb strain grown in human diploid cell culture (Triviraten Berna Vaccine; Swiss Serum and Vaccine Institute, Berne, Switzerland) has been developed and recommended for children who are highly egg allergic. However, as a result of weak immunogenicity, concerns have been raised regarding the efficacy of this strain (136).

Influenza vaccines may be associated with a higher risk than measles vaccination in egg-allergic individuals. Two anaphylactic shock reactions have been reported among 76,000 military recruits who were vaccinated against influenza (123). In one study, skin testing with the vaccine was a more reliable predictor of vaccine sensitivity than a history of sensitivity to eggs (137). Influenza vaccines are safe in egg-allergic

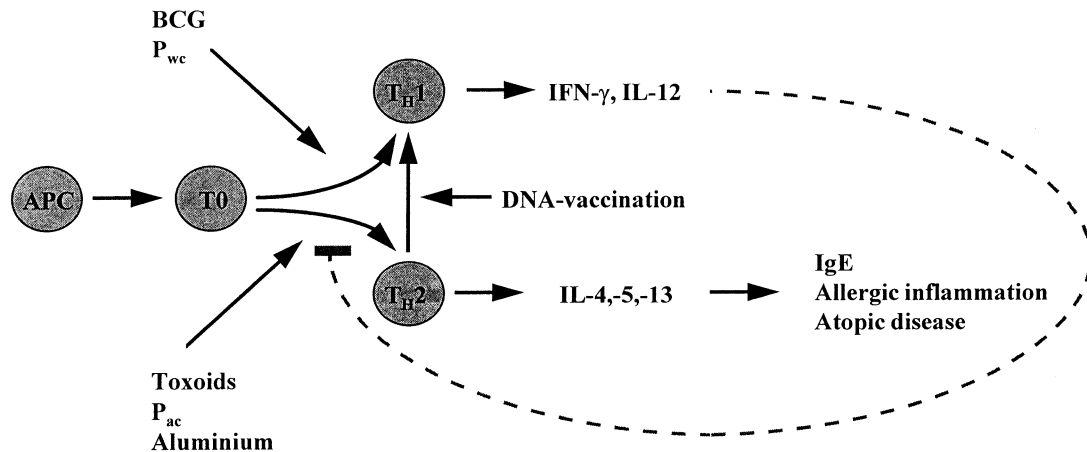


Fig. 1. Potential interference of vaccines with the natural course of atopic disease. P_{wc}, pertussis whole-cell vaccine; P_{ac}, pertussis acellular vaccine; arrow and solid line, promoting effect; block and broken line, inhibitory effect.

children, even if the vaccines contain up to 1.2 µg/ml of egg protein (138). In large groups of children with confirmed egg allergy, egg-derived influenza vaccination was tolerated without any significant allergic reactions (134,138). As the risk for severe asthma exacerbations is increased by influenza infection, vaccination is recommended. Alternative cell lines for growth of influenza virus are currently being evaluated (139,140).

Yellow fever vaccines may contain substantial amounts of egg protein. Among more than 5 million doses, there are 40 reports compatible with anaphylaxis following yellow fever vaccination. The vaccines contained gelatin (141). To date, however, no findings suggest the induction of asthma or other allergic manifestations (142).

In conclusion, sensitization to hen's egg is no contra-indication for vaccines grown on egg-derived media. Those rare individuals with severe clinical manifestations to egg might benefit from special precautions, although the predictive value of egg allergy for allergic reactions to the vaccines is low. Individuals who are highly egg-sensitive should be immunized in a safe setting where appropriate medication and the ability to treat systemic allergic reactions are directly on hand. A sufficient observation interval after vaccination (30 min) is also important.

Gelatin

In 1991, a severe immediate-type anaphylactic reaction was reported in a patient receiving the MMR vaccine. The symptoms were similar to reactions she experienced when eating gelatin. An allergologic work-up revealed that gelatin was the only vaccine component to which IgE antibodies were detectable in her serum (143). Gelatin used as a vaccine stabilizer is mostly of porcine origin, whereas ingested food gelatin is mostly from a

bovine source. Thus, absence of food allergy to gelatin does not necessarily rule out the possibility of a gelatin-mediated reaction to vaccines.

Studies from Japan confirmed the relevance of gelatin in anaphylactic reactions following immunization with vaccines containing gelatin, whereas no allergic sensitization was found in the sera of patients with delayed adverse reactions (87,144–146). The lymphocyte proliferation assay and antigen-specific IL-2 responsiveness have established the presence of immune responses to gelatin (146). Immediate-type reactions are associated with a mixed Th1/Th2-like response, as indicated by the production of mRNA for IFN-γ/IL-2 and IL-4/IL-13, whereas no Th2-like response was detected in patients with a delayed-type reaction and no cytokine response was observed in control subjects (147).

Sensitization to gelatin among subjects with an anaphylactic reaction to an MMR vaccine containing gelatin has been reported in relation to preceding vaccination with a DTaP vaccine containing gelatin. In Japan, no anaphylactic reactions to MMR vaccination were recorded when children were first vaccinated with a trivalent MMR vaccine containing gelatin and later with a DTaP vaccine brand with or without gelatin (87). When the sequence was switched, i.e. DTaP vaccination was given before administration of monovalent MMR vaccines, numerous anaphylactic reactions occurred, suggesting a causal relationship in the development of gelatin allergy (87). Allergic reactions have also been observed in gelatin-containing vaccines other than the MMR vaccine (148,149).

Investigations are underway to test whether the Japanese experiences are reproducible in other populations (14). In view of the high distribution of vaccines containing gelatin, immediate-type

anaphylactic reactions following administration of these vaccines are rare. More extensively hydrolyzed gelatin preparations may add to the safety of vaccinations (150). However, replacement of gelatin by a less hazardous stabilizer would be the first choice. In the meantime, caution should be exercised when gelatin-containing vaccines are administered to children who have previously shown an anaphylactic reaction to gelatin-containing products.

Latex

Latex rubber stoppers are commonly used for vials containing vaccines. Given the high number of patients receiving vaccines from latex rubber-stopper sealed vials, there is scarce, if any, evidence for a causative role of these stoppers in allergy following vaccination (151).

Other additives

Thimerosal is very effective in killing bacteria and therefore it is used to prevent bacterial contamination. The presence of mercury compounds in vaccines has raised concerns of possible neurodevelopmental toxicity in infants (152). Although the compounds can cause contact dermatitis and may result in a transient deterioration in atopic eczema in thimerosal-sensitized infants, they are not associated with an increased risk of severe reactions to vaccines (153–155). Thimerosal-free vaccines are about to be launched.

Formaldehyde is used as a preservative in vaccines and in the manufacturing process of diphtheria and tetanus vaccines (52). It is known for its potential to elicit production of IgE antibodies against formaldehyde (156) and possibly against other antigens (157). There is little evidence that formaldehyde in vaccines is of any significance with regard to clinical allergy, as only one case report of exacerbation of atopic dermatitis (by a hepatitis B vaccine containing formalin) has been reported in a formaldehyde-allergic patient (106).

Antibiotics (mostly neomycin) are commonly added in trace amounts to vaccines. Neomycin is known to cause both local and systemic allergic reactions. Neomycin has been suspected to be responsible for a rare, immediate-type allergic reaction to MMR vaccine in neomycin-allergic individuals (158). Patients with a history of contact dermatitis to neomycin do not seem to be at increased risk of anaphylactic reactions to neomycin in vaccines (159). However, it has been recommended that persons who have experienced anaphylactic reactions to neomycin should not receive neomycin-containing vaccines (124).

General discussion

Recently, some epidemiological studies have suggested that general vaccination could be one of the reasons for the increasing prevalence of allergies in many countries. Severe, allergic reactions to vaccines – although very rare – do occur. Parents and physicians who administer vaccines are concerned because of the risk to children who are predisposed for allergy. This concern contributes to incomplete vaccination rates. On the other hand, other studies suggest that some vaccines may in fact protect against the development of allergy. There are two mutually exclusive mechanisms by which vaccination could affect the development of allergy. The first mechanism would be to skew the cytokine microenvironment towards preferential secretion of Th2-type cytokines and thus possibly facilitate IgE formation and subsequent allergy; the second mechanism would be to inhibit the development of allergy in early childhood by administering a vaccine that induces a predominant Th1-type cytokine pattern and thus possibly skew the immunological balance away from Th2-dependent allergic disease (Fig. 1).

Candidates for the induction of a predominant Th2 response include vaccines to pertussis, diphtheria, tetanus, and – indirectly by preventing infection – measles. Transient formation of specific IgE to the immunizing agent seems to be that part of the regular immune response to many childhood vaccines, including pertussis, diphtheria, tetanus, and measles. However, this transient response does not seem to be associated with an increased responsiveness to unrelated allergens and does not seem to increase the risk for clinical manifestations of atopy (Table 3). The few studies which investigate the impact of measles vaccination on the development of clinical manifestations of atopy show no increased risk for respiratory allergies or atopic dermatitis.

Candidate vaccines for induction of a Th1 shift include BCG and measles. The evidence for a protective effect of measles vaccination is scarce (100). BCG does prevent atopy and airway hyper-reactivity effectively in mice. In infants, however, data from most cross-sectional studies (77,78) and a longitudinal study (80), showed little, if any, protective effect.

Allergic reactions to vaccines occur, but they are mostly transient and confined to the injection site. Potentially life-threatening anaphylactic reactions are rare and they have limited the vaccination rates among children believed to be predisposed for such events. In particular,

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Table 3. Vaccines and evidence for effects on specific or unrelated immunoglobulin E (IgE) formation and atopic disease in children

Vaccine	Specific IgE	Unrelated IgE	Atopic disease	References
BCG	Unknown	No effect	No effect	(77,78,80)
Diphtheria, Tetanus	Elicited	—	—	(37,55–57,59,62–64,66)
Measles	Elicited	—	Probably no effect	(2,3,81,99,100,102)
	Elicited			
Pertussis, whole cell	co-vaccinated	Suppressed if	Probably no effect	(3,13,19,35,36,38,39,43,47,48,50)
Pertussis, acellular	Enhanced	No effect	No effect	(19,36,38,44,47)

BCG, bacille Calmette–Guérin.

residual egg protein in MMR vaccines, but also in influenza and yellow fever vaccines, have been a concern with regard to egg-allergic children. The children who will react cannot be identified, as most egg-allergic children tolerate the vaccines well. Gelatin added as a stabilizer to MMR vaccines has been identified as a major cause of allergic reactions to the vaccine. Generally, MMR and influenza vaccines can be administered to egg-allergic children. However, children who have previously shown a serious reaction to vaccine constituents such as egg, gelatin or neomycin, should be vaccinated in a setting that provides competence to treat systemic allergic reactions.

Future directions

Vaccines should elicit a protective immune response; however, a high IgE-inducing capacity is not desired. Studies in diphtheria/tetanus-vaccinated children suggest that an IgE response to the vaccine occurs frequently, but it is not a prerequisite for a good IgG response (57,65). The additives or residuals that are associated with allergic reactions to vaccines, such as gelatin, egg proteins, or antibiotics, can be avoided. Where not avoidable, they can be reduced or replaced by additives that are better tolerated (160).

Could Th1-inducing vaccines such as BCG be used to prevent allergy? Most current studies do not show a protective effect of BCG vaccination on allergy in humans. Theoretically, an improved mycobacterial vaccine given to susceptible infants might be effective in inducing a long-lived cytokine pattern that is less Th2-biased and thus contribute to lower prevalences of allergy (Fig. 1). The allergy-preventing effect of non-pathogenic immunogenic mycobacteria (*Mycobacterium vaccae* or derivatives) is currently under investigation in prospective trials. Pilot studies results indicate a possible beneficial effect (161). As immune responses to mycobacteria seem to be compartmentalized (162), local administration onto the respiratory mucosa might be an attractive alternative for the preven-

tion of Th2-mediated respiratory allergies. This approach has been shown to work in the murine system (73). Other approaches include improvements and new adjuvants for the BCG vaccines currently available (163,164).

Recently, an immune-stimulatory effect of prokaryotic DNA fragments ('CpG motifs') has been described (165). In murine models, CpG is a more potent vaccine adjuvant and produces fewer local side-effects than alum (166). Intra-peritoneal injection of a synthetic oligodeoxynucleotide containing CpG motifs prevents Th2-dependent airway inflammation upon sensitization with ovalbumin (167–169). These findings are paralleled by *in vitro* studies of human immune cell responses to CpG motifs (170) and by *in vivo* studies in non-human primates (171). My-1, a DNA fraction purified from BCG which is not toxic in humans, inhibits IgE production of human PBMC *in vitro* (172). CpG DNA is a promising immunotherapeutic agent, and clinical trials employing CpG DNA for treatment of existing allergic disease are expected to start soon.

However, there are also limitations on pushing the Th1 arm of the immune system by vaccination against its Th2 arm. Findings from animal studies support the view that successful recovery from infection requires a delicate balance of these two arms and that an unbalanced Th1-driven inflammation may actually be harmful to the organism. Unbalanced production of Th1-type cytokines may actually promote allergic airway inflammation and autoimmune diseases such as diabetes (173). Aside allergic diseases, Th1-associated autoimmune diseases such as insulin-dependent (type I) diabetes mellitus and multiple sclerosis seem to rise with 'Westernization' of lifestyle (174). These findings suggest that the dysregulation occurs on a level above cell-secreting Th1- and Th2-type cytokines. Evidence emerges for a third T-cell population (Th2-like regulatory T cells) that functions as a down-regulator of Th1-driven responses (175,176). In this context it is noteworthy that there are indications that BCG is beneficial in the treatment of type I diabetes mellitus and multiple sclerosis (177,178).

Concluding remarks

The suspicion that childhood immunizations could have immunostimulatory effects on atopy and could elicit anaphylactic reactions makes it necessary to balance two risks when vaccinating infants. First, there is a known serious risk of disease and death caused by failure to immunize infants against preventable infectious diseases; second, there is a very small risk of anaphylaxis by exposure to immunizing agents. Evidence for an association of vaccination with allergy is weak and is limited to cross-sectional and retrospective studies. None of the prospective trials has confirmed this association. Thus, the risk of not vaccinating far outweighs the much smaller risk of vaccinating. Therefore, childhood vaccinations should not be withheld because of a suspicion that the propensity towards allergy may be increased.

Future design of vaccines should include careful consideration of the doses and the type of microbial components and the additives that are required for the optimal protection of our infants. Vaccines may also provide an attractive opportunity to skew the immune system away from atopy very early in life. If engineering succeeds in preparing vaccines that direct the immune system specific or non-specific away from atopy, without losing control of the Th1-branch of the immune system, this could result in a significant contribution to the large-scale prevention of allergy.

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