Immunization and atopy: Possible implications of ethnicity

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The possible effects of immunization on subsequent development of asthma and atopy remains a matter of controversy. Although some studies have suggested that immunization might increase the risk for atopic disease, a number of studies have found no association or have even reported a protective effect for immunization against atopy. Recent studies have provided evidence that ethnicity might affect the susceptibility to the immunomodulatory effects of vaccination. In this review the association between immunization and atopy and the effect of ethnicity on this association are briefly outlined. The focus will be particularly on BCG vaccination. (J Allergy Clin Immunol 2004;113:401-6.)

Key words: *Allergy, asthma, atopy, immunization, immigrants, vaccines*

Considerable controversy exists as to whether vaccination has any effect on the subsequent development of asthma and atopy and, if so, whether the effect is protective or inciting in nature. Irrespective of a number of large epidemiologic studies, as well as data from animal models, the matter remains inconclusive. The question is of great relevance because any adverse event, either short term or long term, associated with immunization raises serious public concern and might diminish the current high coverage rates of vaccinations.[1] The question is also of relevance when testing the hygiene hypothesis in epidemiologic settings: Is immunization a major confounding factor for the interaction of infections and atopy? Which vaccines might have an effect? Is the cumulative dose rather than any single dose operative here?

This article critically reviews current literature on the association between immunization and atopy and the possible effect of ethnicity on this association. The emphasis is on pertussis, measles, and particularly BCG vaccines, all of which have immunomodulatory potential[2-4] and have been, in many countries, part of routine vaccination programs for decades. Data were identified by MEDLINE searches and references from relevant articles. Search terms were "allergy," "asthma," "atopy," "immunization," and "vaccination." Articles in the English language were reviewed. Available human data comprising over 20 population studies with more than 600,000 subjects are summarized in Table I.[5-23] Although there exists some discrepancy in regard to the long-term effects of immunization, the short-term adverse effects of certain vaccine components are well known (eg, allergic reactions to egg-derived components, vaccine adjuvants, gelatin, and antibiotics [neomycin]). This issue of short-term adverse effects has been thoroughly reviewed recently and is beyond the scope of this review.[24]

Comprehensive vaccination programs in Western societies have been proposed as one of the major contributory factors in the substantial increase in asthma and atopy prevalence during the last 40 years.[25,26] Two possibilities exist for the mechanisms involved: vaccination raises risk for subsequent development of asthma and atopy directly or does so indirectly by reducing exposure to invasive childhood infections thought to strengthen the T_H1 response and memory immunity and thus favor normal maturation of the immune system.[1] Concern that immunization might lead to increased risk for asthma and atopy has largely arisen from 3 epidemiologic studies that showed a positive association between pertussis vaccine and atopic disease.[5-7]

PERTUSSIS VACCINATION AND ATOPY

Odent and Kimmel[5] reported in 1994 that among 243 pertussis-vaccinated children at a mean age of 7.8 years, 10.7% were given a diagnosis of asthma compared with 1.97% of the 203 children who had not been immunized (relative risk, 5.4; 95% CI, 1.9-15.3; $P = .0005$). Similar differences between vaccinated and unvaccinated children were, however, not evident for other atopic diseases. Kemp et al[6] found, among a birth cohort of 1265 children, that at the age of 10 years, among those 23 children who had not received the pertussis component of the triple (diphtheria-pertussis-tetanus) vaccine, none had asthma or other allergic diseases, whereas among children receiving diphtheria-pertussis-tetanus vaccine, 23% had asthma and 30% had consultations for other allergic diseases. The very small number of unvaccinated children in that study, however, weakens the data and might include selection bias. A large British 1975 through 1984 birth cohort study at a family physician's practice comprising 1934 subjects (of whom 517 had not received the pertussis component of the triple vaccine) found that vaccination with whole-cell pertussis vaccine in infancy predicted significantly subsequent atopic disease (asthma, hay fever, and eczema; odds ratio, 1.76; 95% CI, 1.39-2.23; $P < .0001$).[7] As noted by the authors and others,[8] this positive association must be interpreted with caution because of several possible confounding factors associated with the study methodology.

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TABLE I. Summary of studies of the association between immunization and the subsequent development of asthma and atopy

Reference	Type of study	No. of subjects	Vaccination	Comment
Positive association				
Odent and Kimmel, 1994[5]	Cross-sectional	446	Pertussis	
Kemp et al, 1997[6]	Retrospective	1265	Pertussis	Limited no. of control subjects
Farooqi and Hopkin, 1998[7]	Retrospective	1934	Pertussis	
Negative association				
Lewis and Britton, 1998[12]	Retrospective	6350	Measles	In children with older sib.
Strannegård et al, 1998[14]	Cross-sectional	185	BCG	In immigrants
Aaby et al, 2000[21]	Cross-sectional	400	BCG	
Grüber et al, 2002[16]	Cross-sectional	6102	BCG	In immigrants
Marks et al, 2003[22]	Retrospective	44	BCG	In genetically predisposed subjects
Grüber et al, 2003[23]	Prospective	943	Cumulative dose	
No association				
Nilsson et al, 1998[9]	Prospective	669	Pertussis	
Henderson et al, 1999[10]	Prospective	9444	Pertussis	
DeStefano et al, 2002[11]	Prospective	167,240	Pertussis, measles	
Strachan, 2000[8]	Prospective	>13,000	Measles	
Alm et al, 1997[13]	Retrospective	574	BCG	
Strannegård et al, 1998[14]	Cross-sectional	6312	BCG	In native subjects
Grüber et al, 2001[15]	Prospective	774	BCG	
Grüber et al, 2002[16]	Cross-sectional	38,808	BCG	*
Anderson et al, 2001[20]	Ecological (ISAAC)	>400,000	BCG	†
Omenaas et al, 2000[18]	Cross-sectional	574	BCG (at the age of 14 y)	
Jentoft et al, 2002[19]	Cross-sectional	588	BCG (at the age of 14 y)	
Krause et al, 2003[17]	Cross-sectional	1575	BCG	
Marks et al, 2003[22]	Retrospective	751	BCG	

ISAAC, International Study of Asthma and Allergies in Childhood.
*There was no association for hay fever or atopic eczema and a weak negative association for asthma.
†For pertussis and measles vaccines, discrepant results were obtained depending on whether the immunization data were derived from national or local registers.

Pertussis vaccine could theoretically have allergy-promoting potential. Pertussis toxin (a cell-wall component of the bacterium *Bordetella pertussis*) has been shown to stimulate the production of specific IgE antibodies both in animal[2,27] and human[28,29] models. However, it has been shown later that a transient increase of pertussis-specific IgE after immunization is common, particularly with acellular pertussis vaccine and in atopic subjects, but this specific IgE itself has no association with increased risk for atopic conditions.[30]

In short, 3 studies have reported a positive association between whole-cell pertussis vaccination in infancy and subsequent development of atopic disease. The study populations involved have been mostly confined to a single clinic or to general practice and thus were susceptible to selection bias. The absence of vaccination might be a sign of a general attitude of ignoring disease[5] or be a surrogate marker of different lifestyle in families not accepting routine vaccinations. Moreover, several more recent, well-controlled studies failed to confirm any (positive) association between pertussis vaccination and atopic diseases.[9-11] The association between immunization, particularly from the perspective of possible long-term adverse effects, and atopy has been thoroughly reviewed recently.[1,31]

MEASLES VACCINATION AND ATOPY

Natural measles infection elicits a biphasic response; the early phase is characterized by a T_H1-type response with increased levels of IL-12.[3] In the later phase, a prolonged T_H2-type response predominates, with increased levels of IL-4 and IgE, which in turn could favor the development of atopic conditions. However, little convincing evidence exists that measles immunization has any allergy-promoting capacity in human subjects. A British birth cohort study of 6350 children examined at the age of 16 years suggested that measles vaccination in early life might slightly increase the risk for hay fever among children with no siblings but might, in contrast, confer protection among those with older siblings. The occurrence of hay fever was found to be lowest among children who had older siblings and had been both vaccinated against and contracted the natural measles infection.[12] This analysis was, however, restricted to a subpopulation in which male subjects and children from the lowest social classes were underrepresented, thus limiting the generalizability of the findings.[12] Moreover, no major differences in the prevalence of hay fever or eczema between measles-vaccinated and unvaccinated

children appeared in the same birth cohort when the children were examined at the age of 5 years (n > 13,000).[8] Nor could further analysis of another British birth cohort confirm any specific effect of older siblings on the association between measles vaccination and atopy.[8] Similarly, a large prospective American study of more than 160,000 children followed from birth to the median age of 28 months could provide no evidence that measles vaccination in infancy is related, positively or negatively, to asthma.[11]

Overall, the finding of a protective effect for measles vaccination against atopy could not be confirmed in other larger studies, which found no association between measles immunization in infancy and atopy in later life.

BCG VACCINATION AND ATOPY

Most studies examining the relationship between immunization and atopy have focused on BCG. This is expected because mycobacteria are among the most potent bacterial immunomodulators.[4,32,33] A natural *Mycobacterium tuberculosis* infection has been found to confer protection against development of subsequent atopic conditions,[34,35] although this interaction might be complex and differ between the sexes. In one matched-pair study a protective effect of tuberculosis against asthma and atopic conditions in later life was found only among women.[35] BCG vaccination was widely given to infants until the early 1990s, but this practice has been halted in many countries because of the low prevalence of tuberculosis and continued only in selected risk groups.[1]

A number of animal studies have shown that in sensitized mice mycobacteria are able to prevent or downregulate the development of allergic reaction, airway hyperreactivity, airway inflammation, eosinophilia, and vascular cell adhesion molecule 1 expression,[36-41] even after an established allergic response.[37,41] The route of administration appears to be of crucial importance because the nasal route in murine models has been shown to be superior to the intradermal or intraperitoneal routes.[36,39,42]

The few intervention studies have demonstrated that mycobacteria might have immunomodulatory potential also in human subjects, and the bacteria need not be alive to exert their beneficial effects. These preliminary studies have used BCG[43,44] or heat-killed *Mycobacterium vaccae*[45,46] as the therapeutic agent in atopic subjects. Two recent, randomized, placebo-controlled trials with adult asthmatic patients receiving BCG or *M vaccae* have, however, shown contradictory results.[47,48] Optimal treatment regimens are still unknown, and in particular, the route of administration needs careful clarification.

In their hallmark study in 1997, Shirakawa et al[49] showed an inverse association among Japanese schoolchildren between exposure to mycobacteria and subsequent development of atopy and were among the first to provide epidemiologic evidence in favor of the hygiene hypothesis. These results have later been debated; to what extent the results are explained by exposure to mycobacteria, BCG vaccination, or by host factors is unknown.[50,51] Tuberculin reactivity has been found to be unreliable as a marker of exposure to *Mycobacterium tuberculosis* because considerable genetic variations have been recognized in tuberculin reactivity.[52]

Several large studies from Western countries, both prospective and cross-sectional, have failed to show the inverse association reported by Shirakawa et al.[49] Alm et al[13] compared, in a retrospective cohort study, 216 native Swedish children who had received BCG vaccination during their first months of life with 358 age-matched control subjects who had not been vaccinated. No significant differences appeared between the groups of children aged 3 to 7 years in the occurrence of atopy, as defined by skin prick tests and specific IgE measurements, and atopic disease. These results were replicated in a cross-sectional study among 6312 Swedish-born preschool and school-age children.[14] Furthermore, 2 large German studies have similarly failed to show any protective effect for BCG vaccination against occurrence of atopy in later life. The other work was a prospective study of 774 children (of whom 92 were BCG vaccinated in early life) followed from birth until age 7 years. BCG vaccination showed no association with decreased risk for atopy or allergic conditions, nor was tuberculin skin test reactivity found to be impaired among the atopic subjects.[15] The other study with more than 38,000 preschool children from Berlin further showed no major differences in the prevalence of allergic conditions between BCG-vaccinated and unvaccinated children.[16] A Danish cross-sectional study among 1575 schoolchildren in Greenland confirmed further that BCG-vaccinated children had the same risk for atopy (determined by specific IgE measurements) as unvaccinated children.[17] Two Norwegian studies have examined the effect of BCG vaccination, when administered at the age of 14 years, on subsequent occurrence of atopy,[18] as well as of asthma and bronchial hyperreactivity,[19] among a cohort of more than 500 young adults. These studies did not show any protective effect for BCG vaccination.

Although studies among Scandinavians and Germans, as well as data from the International Study of Asthma and Allergies in Childhood,[20] are consistent in showing that BCG vaccination and subsequent development of atopy are not inversely related, this might not necessarily be true for all ethnic groups.

Evidence exists that BCG vaccination might confer protection against atopy among individuals originating from nontemperate regions. A cross-sectional study with 400 children from Guinea-Bissau, Africa, aged 3 to 14 years showed that occurrence of atopy, as demonstrated by skin prick tests, was lower among BCG-vaccinated than unvaccinated children (21% vs 40%; adjusted odds ratio, 0.19; 95% CI, 0.06-0.59). The largest reduction in atopy was found in children vaccinated during the first week of life.[21] Strannegård et al[14] reported that among immigrants (n = 185) originating mainly from Asian and South American countries, a higher prevalence of allergic conditions (eczema, rhinoconjunctivitis, and asthma) occurred among unvaccinated (28%) than among BCG-

vaccinated (13%) children. Furthermore, the large study among preschool children in Berlin referred to above[16] revealed that, in line with the Swedish study, among immigrants (n = 6102), BCG vaccination in infancy conferred strong protection against atopic diseases, eczema, asthma, and hay fever.

BCG vaccination might provide protection not only in immigrants but also in other individuals with high genetic risk for atopic disease. An Australian retrospective cohort study among 751 schoolchildren revealed that in a subgroup of subjects with a family history of rhinitis or eczema (n = 44), BCG vaccination in infancy was associated with a lower prevalence of current asthma, defined as current wheezing and airway hyperresponsiveness.[22] Swedish children with atopic heredity had shown no such effect,[13] but as noted by the authors, children in the Swedish study were younger, and more importantly, there might exist some still-unidentified factors associated with the very high prevalence of atopy in the Australian population that might increase their susceptibility to the protective effect of BCG vaccination.[22]

As to the question of the effect of cumulative dose versus single dose on development of atopy, interesting data have recently come from Grüber et al,[23] who found in a prospective study of 943 German children followed from birth to age 5 years that cumulative vaccine dose, rather than any single vaccination, was inversely related to occurrence of atopic diseases (eczema and asthma). Whether this effect was transient or more long-lasting is not clear on the basis of that study.

ETHNICITY AND DEVELOPMENT OF ATOPY

Results from immigrant and African children raise the possibility that BCG vaccination prevents atopy only in certain ethnic groups, as proposed earlier.[21] Some evidence shows that the number and relative importance of asthma-susceptibility genes varies between ethnic groups.[53] Data from a rodent model have also shown that the degree and pathway of the immunomodulatory effect of BCG immunization is dependent on the genetic predisposition of the animals to have a T_H2-type response.[54] An intriguing hypothesis has been recently put forward proposing that evolutionary adaptations have provided differences in disease susceptibility. Over hundreds of generations, the population's genetic profile of immune responses might have become less T_H2 inflammatory as a result of the changing exposure profile of infective organisms, along with the movement of human beings from tropical to more temperate regions.[55] This hypothesis is based on data on the epidemiology of tropical disease, the relative prevalence of T_H2 inflammatory alleles in different populations, and disease patterns in those individuals who have migrated from tropical to temperate regions. For several genes, the allele associated with an increase in T_H2 inflammatory disease has been found to be more common in populations originating from tropical regions than those from temperate regions. These include the genes encoding Clara cell protein, the high-affinity IgE receptor, the β_2-adrenoreceptor, the IL-4 promoter and IL-4 receptor, and RANTES and eotaxin. Individuals from the tropics with a high prevalence of T_H2 inflammatory alleles, when immigrating to Western countries, might exhibit a vigorous response to harmless environmental agents, resulting in a high incidence of atopic disease in the new environment.[55]

Indeed, compelling data on African American subjects suggest that asthma and atopic disease are markedly more common in these subjects than in white American subjects.[55] Increasing income has not been found to affect asthma prevalence, suggesting that rather than socioeconomic factors, ethnicity might largely explain the difference.[56] Furthermore, Leung[57] reported that among subjects who had immigrated from southeast Asian countries to Australia, prevalence of asthma and atopic conditions increased with their duration of residence in the new country; after 10 years in Australia, up to 60% of the immigrants had hay fever, and 15% had symptoms of asthma. Similarly, Rosenberg et al[58] found, in a case-control study of 906 adult Ethiopian immigrants residing in Israel, that after 7 to 14 years, their asthma prevalence was 3 times as high as that of the general population in the same Israeli area. A recent Italian study among 234 immigrants attending an allergy clinic revealed that most of the immigrants, originating mainly from Central and South America, North Africa, and Asia, were symptom free before leaving their native countries approximately a decade previously. Among these immigrants, the overrepresentation of Central and South American subjects indicates a very high genetic risk for asthma and atopy, especially in this population.[59]

The increased asthma-atopy susceptibility of immigrants moving from tropical areas to Western societies thus appears to be associated with their genetic composition,[55] one appropriate in their original hostile environment but harmful when living in a clean environment offering minimal, if any, exposure to, for example, parasitic infections. At the molecular level, recent research on the effects of the HLA-DRB1 locus associated with IgE production on asthma prevalence in aboriginal people in Australia support the view that genetic predisposition to atopic disease might be driven by adaptation to helminth infections.[60]

To summarize, there is little evidence to suggest that BCG vaccination in infancy is associated, positively or negatively, with development of atopic disease. An exception, however, appears to be immigrants from tropical regions, among whom a negative association has been found.

IMMUNOMODULATORY CAPACITY OF BCG VACCINE

How could BCG vaccine confer protection against atopic disease, specifically among certain genetically highly susceptible individuals, such as immigrants from the tropics living in Western societies? This question remains unanswered, although recent discoveries in immunology have shed some light on this issue.

Although BCG vaccination is able to induce a potent T_H1 response at a systemic level to mycobacterial antigens even in infants,[61] the T_H1/T_H2 paradigm alone is unable to explain the mechanisms that underlie this BCG vaccine–mediated immunomodulation. Recently, a novel subset of $CD4^+$ T cells, called regulatory T (T_R, T_H3) cells,[62,63] have been recognized as playing a crucial role in ameliorating inflammation and preventing tissue pathology at mucosa sites by secreting IL-10 and TGF-β.[63,64] Attenuated *Mycobacterium bovis* (BCG) might, in addition to T_H1 cytokines, stimulate the production of IL-10 by T_R cells, as shown in other mycobacterial and helminth infections.[33,65] This IL-10 might be one critical factor during the window period, the time of T_H1/T_H2 bifurcation able to prevent development of atopic disease in these highly susceptible individuals. By contrast, individuals originating from nonhostile environments in temperate climates who do not commonly have T_H2 inflammatory alleles[55] appear not to benefit from BCG vaccination in this respect.

CONCLUSION

Most of the evidence available to date suggests no association between measles and pertussis vaccination and subsequent development of asthma and atopy.[1,31] This appears to hold true also for BCG vaccination among subjects originating from Western countries. However, immigrants from the tropics living in a clean environment might be genetically susceptible to the protective effect of BCG vaccination against atopic disease. Whether a certain cumulative vaccine dose is needed to confer protection against atopy among children from Western countries and whether this effect is persistent remains to be verified.

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