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EXPERT REVIEWS

Asthma prevalence and exacerbations in children: is there an association with childhood vaccination?

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Infections and vaccinations may have a potential role in the normal maturation of the immune system, in the development and balance of regulatory pathways, and in the development and exacerbations of asthma. Asthma exacerbations often result from respiratory viral infections, and, while vaccination towards common viral infections may reduce the occurrence of such exacerbations, there has been concern that vaccinations can increase the risk of asthma. Current studies show that childhood vaccines, including inactivated influenza vaccine, are generally safe. However, there is some concern regarding possible exacerbations in infants or children with frequent wheezing or persistent asthma who are given live-attenuated influenza vaccination. 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, such as egg protein or gelatin. The risks of not vaccinating children far outweigh the risks of allergy and asthma exacerbations. Therefore, childhood vaccination should remain an essential part of child health programs and should not be withheld, even from children with asthma or those predisposed to allergy.

Keywords: asthma exacerbation • asthma in children • atopy • BCG • immunization • influenza • pertussis • vaccination

Vaccines are of major importance in controlling the spread of infectious diseases, but the use of some vaccines has been linked to allergic and autoimmune phenomena in healthy, and often in certain high-risk, populations. Immediate systemic allergic reactions after vaccination with commonly used vaccines are extremely rare, to a degree where it can be argued that there was no association whatsoever between the vaccines and the allergic reactions reported [1,2]. The prevalence of asthma and allergic diseases has increased in recent decades. Most cases of asthma appear in childhood by 6 years of age, and asthma is the most common chronic disease of children and adolescents [3]. Asthma exacerbations often result from respiratory viral infections and account for a large proportion of healthcare encounters in children and approximately a third of school absences [4].

The mechanisms of the interactions between atopy, asthma and viral infections are not clear, but studies suggest that viral infections in atopic individuals can expose them to an increased inflammatory response in the airways [5]. Infections and vaccinations may have a potential role in the normal maturation of the immune system, in the development and balance of the regulatory pathways, and in the development and exacerbations of asthma [6]. Immunologic responses to childhood vaccination in infants and children with asthma are normal, as reflected by the expected increase in antibody levels [7].

It has been feared that vaccinations in infancy and childhood can increase the risk of developing asthma and allergic diseases. This concern has been raised particularly with regard to some of the currently available nonreplicating infant vaccines, which may not mimic a natural infection-mediated immune response that may protect against the development of allergic diseases and asthma. However, there has been no epidemiologic evidence that infant vaccinations with diphtheria, tetanus and pertussis (DTP),

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measles, mumps and rubella (MMR) and bacillus Calmette–Guérin (BCG) vaccines in infancy are associated with the development of allergic diseases [8,9]. The aim of this article is to review whether currently available childhood vaccines have any effect on asthma exacerbations.

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 exacerbations of asthma. Despite recommendations in most countries for giving inactivated influenza vaccine to people with asthma, only a minority currently receive it. One reason for low vaccine coverage has been the concern that vaccination may induce exacerbations of asthma. A major study by The American Lung Association Asthma Clinical Research Centers investigated the safety of the inactivated trivalent split-virus influenza vaccine by a multicenter, randomized, double-blind, placebo-controlled, crossover trial in 2032 adults and children with asthma aged 3–64 years [10]. The frequency of asthma exacerbations was similar in the 2 weeks following the influenza vaccination and after placebo injection. The exacerbation rates were similar in subgroups defined according to age, severity of asthma and other factors. Cross-sectional and controlled clinical trials with inactivated parenteral influenza vaccine in asthmatic patients showed virtually no side effects, and vaccination had no influence on asthma control in the 14-day period after injection [11–14]. Furthermore, a population-based retrospective cohort study with medical and vaccination records in four large health maintenance organizations in the USA during three influenza seasons revealed that, after controlling for asthma severity, influenza vaccination protects against acute asthma exacerbations in children [15].

In similar studies, the safety of influenza vaccination was shown in adults. Investigation of the safety of influenza vaccination in older people with asthma or chronic obstructive pulmonary disease showed that rates of exacerbation were low and there were no statistically significant increases in exacerbation during any risk periods, and there was no increased risk of adverse acute outcomes in the first 2 weeks following vaccination [16]. Episodes of bronchospasm after influenza vaccination do not seem to be 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 [17]. A recently published randomized trial of 291 patients between 18 and 65 years of age showed that inactivated trivalent vaccination did not increase the incidence of asthma exacerbations compared with placebo, and the vaccine was well tolerated in this study [18]. There have been at least five large studies comparing the efficacy and safety of live-attenuated cold-adapted influenza vaccine, trivalent (CAIV-T), with trivalent inactivated influenza virus vaccine (TIV) in children [19–23]. Initially, a *post hoc* analysis of a study of children 1–17 years of age showed an association between live-attenuated influenza vaccine and an increased risk of asthma in children 18–36 months of age [19]. The methodology of this study revealed that the clinical records of events coded as asthma, of which there were 493, were not reviewed to see if the subject had wheezing illness at the time of the visit. When this was done, no difference was found for the incidence of wheezing illness. This was also true if events coded as wheezing and cough were included. In an open-label randomized study in children and adolescents with asthma, the results revealed that CAIV-T was well tolerated [20]. There was no evidence of a significant increase in adverse pulmonary outcomes for CAIV-T compared with TIV. More specifically, there were no significant differences between treatment groups in the incidence of asthma exacerbations, mean peak expiratory flow rate findings, asthma symptom scores or night-time awakening scores. CAIV-T had a significantly greater relative efficacy of 35% compared with TIV in this high-risk population. A very large randomized study of 2187 children aged 6–71 months, which compared the safety of inactivated and live-attenuated influenza vaccinations, showed no difference between the groups in the incidence of wheezing after vaccination [21]. A first episode of wheeze was reported by 12.5% of live-attenuated vaccine recipients and 13.2% of inactivated vaccine recipients during the 42 days following the first vaccine dose, and by 13.8 and 12.3% of vaccine recipients after the second dose, respectively. There was no increased relative risk of asthma in the period of 0–14 days after live-attenuated vaccine administration in any age group. Another very large study of 8352 children aged 6–59 months without a recent episode of wheezing or severe asthma showed that there was a slight excess of wheezing in infants 6–18 months of age who received live-attenuated vaccine (3.8 compared with 2.1%) during the period of 0–42 days after the first dose, only in children aged 6–11 months [22]. Most of these wheezing episodes occurred more than 10 days after vaccination and the causal relationship to the vaccination is questionable. Most of the infants were not tested at the time of wheezing illness, and the few that were tested were likely to have respiratory syncytial virus or rhinovirus infection. In addition, the biologic plausibility of events that occur almost randomly more than 10–14 days after vaccination with no real clustering of these events is not clear [19,22]. A more recently published study confirmed that live-attenuated intranasal vaccine, in children between 18 months and 18 years of age with a history of intermittent wheezing, was safe and was not associated with an increased risk of medically attended acute respiratory illnesses, including acute asthma exacerbation [23]. This was true for the first dose and two to four consecutive annual doses. The first dose of live-attenuated intranasal vaccine was not associated with new-onset asthma in children without a history of wheezing. The live-attenuated influenza vaccine is therefore safe, at least for children older than 18 months of age who do not have a history of asthma or wheezing. These results are in agreement with those of a controlled study of CAIV-T in children and adolescents with moderate-to-severe asthma, which found no change in the percentage of predicted forced expiratory volume in 1 s (FEV_1) [24].

Finally, a Cochrane review based on recently published randomized trials of influenza vaccination in children (over 2 years of age) and adults with asthma showed that there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination). The pooled results

of two trials involving 2306 people with asthma did not demonstrate an increase in asthma exacerbations in the 2 weeks following influenza vaccination. There is concern regarding possible increased wheezing and hospital admissions in infants given live intranasal vaccination [25]. In this regard, intranasal administration of inactivated influenza vaccine to mice reduced allergen sensitization and prevented allergen-induced airway hyperreactivity (AHR). These results revealed the importance of the composition of the influenza vaccine on allergic sensitization and AHR, and suggest that inactivated influenza vaccination may provide a means of preventing atopic asthma [26].

Taken together, these studies present strong evidence that influenza vaccination did not alter bronchial reactivity or lung function, or increase asthma symptoms, exacerbations or use of rescue medications. The inactivated and the more recently introduced live-attenuated influenza vaccine are, therefore, safe to administer to adults and children. Annual influenza vaccination is recommended by the Advisory Committee for Immunization Practices (ACIP) [27], the American Academy of Pediatrics (AAP) [28] and the Expert Panel for the Diagnosis and Management of Asthma to protect asthmatic patients. It is recommended that, in view of the morbidity of influenza, all those with asthma should receive the vaccine annually. Current recommendations of the AAP are that children with asthma should receive the inactivated vaccine and not the live-attenuated vaccine. These recommendations, however, will have to be reassessed in view of the safety of the live-attenuated vaccine in children older than 18 months of age with intermittent wheezing or asthma.

Bacillus Calmette–Guérin vaccine

The association between mycobacterial exposure, vaccination with BCG in early life and atopy remains controversial.

There are conflicting reports on the effect of BCG vaccination on the subsequent development of atopy and asthma in children. One of the problems in attempting to interpret the results is that the studies have not all tested the relationship in the same way; some studies examined tuberculin response, others investigated BCG vaccination, some investigated both and TB infection has also been investigated. The outcomes measured also differed and included asthma, defined in a number of different ways, atopy and manifestations of atopic disease, as well as respiratory symptoms, such as wheeze. When a review of the literature is restricted to BCG vaccination and wheeze, conflicting results are still seen.

The BCG vaccine is thought to be among a group of vaccines capable of manipulating the immune system toward Th1 dominance and, therefore, able to reduce the likelihood of atopic disease. In the murine system, BCG vaccination inhibits allergic sensitization and airway hyperreactivity [29]. Some epidemiological studies in humans suggest an inhibitory effect of TB on allergy [30]. BCG vaccination in children, however, has no or merely a marginal suppressive effect on atopy [31]. 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 [32]. It is unknown if neonatal BCG vaccination affects cytokine responses of lymphocytes that are exposed to allergens *in vitro*. A few studies examined if 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 aged 7–14 years and 442 non-BCG-vaccinated subjects revealed that the rate of allergic sensitization was not lower in BCG-vaccinated subjects compared with nonvaccinated subjects [33]. However, vaccinated subjects with a family history of rhinitis or eczema did have a lower prevalence of asthma. BCG vaccination was also associated with lower levels of allergen-stimulated IL-10 production *in vitro*. Thus, neonatal BCG vaccination had an effect on T-cell allergen responsiveness 7–14 years after vaccination. So far, there are conflicting results regarding whether or not BCG vaccination protects against the development of allergic diseases, particularly when administered just after birth [34]. A cross-sectional study of 1686 school children aged 8–16 years showed that the risk of atopy was the same in BCG-vaccinated children compared with nonvaccinated children, and the risk of atopy in BCG-vaccinated children was not associated with the age at vaccination [35]. The results demonstrated that BCG vaccination administered to infants is not associated with reduced risk of development of atopy. A nested case–control study conducted among 510 Dutch and German children aged 7–8 years participating in a large longitudinal study on respiratory health showed no evidence for an association between BCG vaccination and respiratory symptoms [36]. A Spanish study that used the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to identify prevalence and local BCG vaccination policies to determine vaccination status among children aged 6–7 years showed a statistically significant lower prevalence of asthma (12-month prevalence of wheeze) for BCG-vaccinated children [37]. In a historical cohort study, a parent-completed questionnaire was used to identify the prevalence of wheeze in BCG-vaccinated and nonvaccinated children in Manchester (UK). There were 2414 participants aged between 6 and 11 years. BCG vaccination was associated with a significantly lower prevalence of wheeze. The results demonstrated an association between asthma symptom prevalence and neonatal BCG vaccination, relating to a possible 27% reduction in prevalence [38].

A study of 214 patients with mild-to-moderate asthma accompanied with rhinitis and 220 normal volunteers showed an association between a history of TB infection, tuberculin responses and the development of adult bronchial asthma, allergic rhinitis and atopy. It has been suggested that protection provided by intradermal BCG vaccination in infants to prevent atopic diseases may be limited to early childhood, when the immune system can be more easily modulated [39]. However, a meta-analysis of five of the observational studies with 41,479 patients, comparing vaccinated with unvaccinated children, did not support an association, either provocative or protective, between receipt of BCG vaccination and risk of asthma in childhood and adolescence [40].

Taken together, there is no evidence for asthma exacerbations related to BCG vaccination.

Pertussis vaccine

Pertussis infection has been suspected to be a potential causal factor in the development of atopic disease due to the effect of pertussis immunization on specific IgE antibodies. Pertussis vaccination in infancy has been suggested to increase the risk of developing asthma and allergy. The acellular pertussis vaccine has replaced the whole-cell inactivated vaccine in many countries, but is still widely used outside Europe and North America. There have been conflicting results regarding the possible risk of atopy related to pertussis vaccination. In a randomized controlled trial, vaccination of 669 children using either acellular or whole-cell pertussis vaccination, there was no increase in allergic manifestations after vaccination, regardless of any family history of allergy [41,42]. Other retrospective [36,43] or prospective studies have shown a minimal protective effect or no association of pertussis with atopy and asthma [44–46]. Contrary to a previous retrospective report [38], in a more recent prospective study of 1872 children, there was a positive association between pertussis infection and atopic disorders, including an odds ratio of 2.24 for asthma in the pertussis-vaccinated group [47]. A meta-analysis of seven of the aforementioned studies of pertussis vaccination, although not including the latter (with a total of 186,663 patients), showed no or only a borderline significant provocative effect of whole-cell pertussis vaccination on the incidence rates of asthma during childhood and adolescence [40]. None of the studies reported an acute exacerbation following pertussis vaccination.

Pneumococcal vaccine

Allergic and, especially, anaphylactic reactions to pneumococcal conjugate vaccine (PCV) are very rare. Owing to the presence of specific IgE antibodies and positive skin tests in such cases, it is assumed that these reactions are IgE mediated [48]. Skin test results and specific IgE determination may have good diagnostic value in children reporting severe reactions suggestive of IgE-dependent hypersensitivity to PCV, but this needs confirmation by studies in more children. The safety of PCV was recently analyzed in a systematic review of 42 studies [49]. PCV7 vaccination, which was introduced and licensed in the USA in 2000, may result in more local reactions and fever than certain comparison vaccines. Two of the largest studies of PCVs, one involving PCV7 and the other PCV9, found a statistically significant increased risk of hospitalization for reactive airway diseases, including asthma. The largest trial included 19,922 infants vaccinated with PCV9 at 6, 10 and 14 weeks, and 19,914 infants who received placebo injections [50]. Hyperactive-airway disease and asthma treated with bronchodilatory agents were diagnosed in 59 vaccine recipients and 33 controls (relative risk [RR]: 1.79; p = 0.009), although no temporal relation to vaccination was apparent. The risk remained elevated for multiple episodes of asthma (RR: 1.83; 95% confidence interval [CI]: 0.9–4.1; p = 0.12), as well as when the analysis was restricted to children who were at least 12 months of age (RR: 1.91; 95% CI: 1.1–3.4; p = 0.02). The absolute risk of asthma was 1.66 cases per 1000 among controls and 2.96 cases per 1000 among vaccine recipients. The biologic plausibility of such events beyond 1 month after vaccination with regard to the possible effect of vaccination is certainly questionable. Another large trial of PCV9 did not reveal an increased risk of asthma [45]. There were no major safety problems with PCV7 or any other PCV, with the possible exception of reactive airway disease, which, therefore, requires further follow-up.

Other infant vaccinations

Three other important vaccines are part of the vaccination protocols for infants and children, namely MMR, polio and *Haemophilus influenzae* type b (Hib) vaccination. None of these vaccines increase the risk of atopy or asthma, and none of them have been reported to exacerbate asthma [51,52]. Results from the ISAAC further demonstrated that international variations in childhood atopic diseases are unlikely to be explained by variations in immunization [53].

Reactions to vaccine components

Allergic reactions to different vaccines may result from reactions to the common components of these vaccines. Two main components that have been identified are gelatin and egg protein [1].

The risk of reactions to gelatin was assessed primarily in vaccination with DTP. In one study, serum samples were examined from 87 children who had been vaccinated with diphtheria–tetanus–acellular pertussis (DTaP) vaccine, with and without gelatin, and who had systemic immediate-type reactions (including anaphylaxis) to the vaccines [54]. In total, 91% of these children had antigelatin IgE antibodies. In total, 54 out 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 relationship between gelatin-containing DTaP vaccination, anti-gelatin IgE production and risk of anaphylaxis from immunization with live viral vaccines, which contain a larger amount of gelatin. The mechanism of the reaction remains unknown [55].

Egg allergy is a special challenge in influenza vaccination programs. Influenza vaccines are derived from the extraembryonic fluid of chicken embryos inoculated with specific types of influenza virus. The vaccines typically contain small but measurable quantities of egg-protein allergens, such as ovalbumin. Adverse allergic reactions have been observed in patients with egg allergy injected with inactivated influenza vaccines. The overall prevalence of egg allergy in the general population is estimated to be approximately 0.13%, and reaches 1.6% in young children [56]. The prevalence is higher in allergic children in general (5.6%), and is up to 40% in children with moderate-to-severe atopic dermatitis. The prevalence of egg allergy in asthmatic children is between 2.0 and 3.6%. Even in egg-allergic children, the risk of influenza vaccination is extremely low [56,57]. It is recommended that in all patients, inquiries should be made regarding a possible history of adverse reactions to egg or influenza vaccines before vaccination. Current recommendations by the AAP are that children with any known systemic reactions to egg should not receive influenza vaccines, whether inactivated or live-attenuated, but that less-severe or local reactions should not contraindicate their use [28]. The 2008

recommendations by the ACIP are that individuals who have had hives or swelling of the lips or tongue, those who have experienced acute respiratory distress or who have collapsed after eating eggs should consult a physician for appropriate evaluation to help determine if the vaccine should be administered. Individuals who have documented IgE-mediated hypersensitivity to eggs, including those who have had occupational asthma related to egg exposure or other allergic responses to egg protein, might also be at an increased risk for allergic reactions to influenza vaccine, and consultation with a physician before vaccination should be considered [27]. In the same document, the ACIP recommends that TIV or live-attenuated intranasal vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such individuals [27].

In view of the importance of influenza vaccination, the rarity of life-threatening reactions and the safety of MMR vaccination in egg-allergic children, these recommendations could be challenged so that influenza vaccination is contraindicated only in patients with a severe anaphylactic reaction after egg ingestion. It should be stated, of course, that outgrown egg allergy is not a contraindication for vaccination. The US CDC recommendation, based on an ACIP statement on MMR, is routine vaccination of egg-allergic children without the use of special protocols or desensitization procedures [58]. Substituting tissue-culture substrate with embryonated eggs to grow viruses for vaccine production will eliminate egg allergy as a problem and a cause for vaccine contraindication, and will also allow production of the influenza vaccines in a more timely manner.

Expert commentary

Vaccination has been linked to potential allergic side effects, including exacerbations of asthma in healthy and, often in certain high-risk, populations. Careful examination of the literature shows that such reactions are rare and life-threatening events are extremely uncommon. One should distinguish between two groups of vaccinations: those against general infectious diseases, such as DTP, MMR, polio and Hib, and those against mainly respiratory viral diseases, best represented by influenza vaccination. The latter group of vaccines are of major importance with regard to asthma exacerbations, in terms of either possible prevention of asthma or asthma exacerbation following vaccination. Current studies show that childhood vaccines, including inactivated and live-attenuated influenza vaccines are safe for children with mild-to-intermittent asthma aged 18 months and older. There is concern regarding a possible increase in wheezing and hospital admissions in infants given live-attenuated influenza vaccination through the intranasal route, and further studies are needed. Meanwhile, children with frequent wheezing or more-severe asthma should receive the inactivated influenza vaccine. Although severe allergic adverse events attributable to vaccination are extremely rare, all serious allergic reactions should be assessed further to detect the likely causative vaccine component, such as egg protein or gelatin.

The risks of not vaccinating children far outweigh the risks of allergy and asthma exacerbations. Therefore, childhood vaccination should remain an essential part of child health programs and should not be withheld, even from children with asthma or those predisposed to allergy.

Five-year view

Vaccination in children with asthma can be expected to improve in three major areas: diagnosis, safety and efficacy.

A fundamental problem with attempts to investigate the occurrence and possible exacerbation of asthma following vaccination is the lack of a standardized, universally accepted definition of asthma, especially in infants. Wheeze has been identified as the most important symptom because it can be measured relatively easily, without invasive or expensive tests. It is frequently used as an outcome measure in questionnaire-based epidemiologic studies. The development of better diagnostic markers for asthma-related inflammation, such as nitric oxide measurements, may enable a more accurate diagnosis. Better diagnosis of bronchiolitis and asthma in infancy should be achieved. Similarly, better and faster means to diagnose viral infections using molecular biology techniques, such as PCR, will help us to elucidate whether wheezing following vaccinations is causally associated with the vaccination or is a result of a concurrent illness related to other, nonrelated viral infections.

The experiments with intranasal administration of inactivated whole influenza vaccine to mice, which reduced subsequent allergen sensitization and prevented allergen-induced AHR, suggest that the composition of the influenza vaccine has a major influence on the subsequent development of allergen-induced sensitization and AHR, and suggest that mucosal vaccination may represent a step toward the development of a preventive strategy for atopic asthma. A potential development could be sublingual vaccination, similar to that of sublingual immunotherapy, which is generally safer than subcutaneous immunotherapy. The nasal and potentially sublingual routes of administration may be better accepted by children, easier to administer and may lead to an increase in the vaccination coverage rates in the population. Safety should be balanced against efficacy. Further studies are needed to examine the safety of the live-attenuated influenza vaccine in children with wheezing and asthma.

Finally, improvements in the diagnosis of asthma exacerbations related to vaccinations, and safer and more efficacious vaccines, will lead to better assessment of the cost–effectiveness of various vaccines, especially that of influenza. In this regard, some studies have revealed that influenza vaccination did not result in a significant reduction in the number, severity or duration of asthma exacerbations caused by influenza [59,60]. Additional studies will be needed to justify routine influenza vaccination of children with asthma.

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Key issues

- The prevalence of asthma and allergic diseases has increased in recent decades. Asthma exacerbations often result from respiratory viral infections.
- Vaccines have had a major effect on controlling the spread of infectious diseases but there has been concern that vaccinations in infancy and childhood can increase the risk of developing asthma and allergic diseases in healthy and, often in certain high-risk, populations.
- Vaccination programs do not explain the increasing prevalence of allergic diseases and asthma. Immediate systemic allergic reactions, including asthma exacerbations after vaccination with commonly used vaccines, are very rare. Severe allergic adverse events attributable to vaccination, including asthma exacerbations, are also very rare and life-threatening events are extremely uncommon.
- Serious allergic reactions should be assessed further to detect the likely causative vaccine component, such as egg protein or gelatin.
- Influenza vaccines, both inactivated and live-attenuated, are safe in children with mild-to-intermittent asthma, but there is concern regarding a possible increase in wheezing and hospital admissions in infants administered the live intranasal vaccination.
- Further studies are needed to justify the routine influenza vaccination of children with asthma.
- The risks of not vaccinating children far outweigh the risks of allergy and asthma. Therefore, childhood vaccination should remain an essential part of child health programs and should not be withheld, even from children with asthma or those predisposed to allergy.

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