

Safety of influenza vaccination in children with allergic diseases

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Global guidelines strongly recommend annual influenza vaccination in people age 6 months and older, particularly in asthmatic children. There is no doubt about the benefit of influenza vaccination in asthmatic children. However, some of the vaccine's components may elicit an IgE mediated hypersensitivity or disease exacerbation, including life-threatening events, in children with allergic diseases. As a result, concerns regarding the safety of the vaccine still continue today. The influenza vaccine is grown on hens' eggs and contains a trace of egg protein. Consequently, it can provoke an allergic reaction or anaphylaxis in children with an egg allergy or exacerbation in those with asthma. Therefore, we need to know the risks and benefits of the influenza vaccine and the best strategy for safe vaccination. Although most guidelines have consistently reported the safety of influenza vaccination in children with allergic disease, and have recommended annual administration, safety concerns impede guideline-based performance in practice. The safety and efficacy of influenza vaccination for allergic children are summarized in the present review.

Keywords: Asthma, Egg hypersensitivity, Child, Influenza, Vaccines

Introduction

Asthma is the most common chronic respiratory illness in childhood, and it causes a serious socioeconomic burden [1]. At present, there are no overall signs of a declining trend in asthma prevalence; rather, asthma continues to increase in many parts of the world [2,3].

Food allergy (FA) is a common allergic disease in childhood, with 3%-4% prevalence, and egg allergy is the most common FA, with approximately 0.5%-2.5% prevalence in preschool children [4]. In Korean children, the overall prevalence of the immediate type of FA is 7%, and egg allergy is a leading cause of FA [5,6].

Influenza occurs globally with an annual attack rate estimated at 5%-10% in adults and 20%-30% in children [7], resulting in more than 20,000 hospitalizations and 100 deaths each year in the United States in children [8]. Hospitalization rates as high as 34.2% were observed in the H1N1 pandemic season in Korean children with underlying cardiopulmonary diseases [9]. Influenza infection is a potential cause of asthma exacerbation and hospitalization in asthmatic children, in the winter season [10,11]. Moreover, asthmatic children are at an approximately 31%-91% increased risk of influenza related complications [12].

Influenza vaccines are classified as inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV) based on the active components. Most of the available IIVs, and LAIVs as well, are cultured on embryonated hens' eggs and consequently contain trace amounts of egg protein (ovalbumin). Trace ovalbumin can provoke allergic reactions or anaphylaxis in children with egg allergy [13,14]. For this reason, influenza vaccination in children with egg allergy has raised serious concerns about anaphylaxis or severe allergic reactions [15]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in the United States have strongly recommended an annual influenza vaccination in people age 6 months and older [7,16], particularly in those with a chronic underlying disease such as asthma. Children with asthma or egg allergy mostly do not receive the vaccination because of concerns about either asthma exacerbation or an allergic reaction to the residual ovalbumin [8].

Unquestionably, annual influenza vaccination is the most effective preventive measure to reduce influenza-related burdens.

The aims of the present study are to review the publications on the safety and efficacy of influenza vaccines and to provide the best vaccination strategies for children with asthma or egg allergy.

Global Recommendation of Influenza Vaccination in Children

The WHO strongly recommends influenza vaccination for all children older than 6 months, particularly in high-risk priority groups, such as pregnant women, children aged 6-59 months, the elderly, individuals with specific chronic medical conditions (e.g., human immunodeficiency virus/acquired immune deficiency syndrome, asthma, and chronic heart or lung diseases), and health care workers [7]. The Advisory Committee on Immunization Practices (ACIP) updated its recommendations for influenza vaccination on August 15, 2014 [17]. The general recommendations for healthy children are as follows: routine annual influenza vaccination is recommended for all persons aged ≥ 6 months who do not have contraindications; vaccination optimally should occur before onset of influenza activity in the community; vaccination should be offered as long as influenza viruses are circulating; and children aged 6 months through 8 years who require 2 doses should receive their first dose as soon as possible after the vaccine becomes

available and the second dose ≥ 4 weeks later [18].

The American Academy of Pediatrics (AAP) and the US CDC also recommend annual seasonal influenza vaccination for all people 6 months and older with rare exceptions [16,19].

The Korean Committee on Infectious Disease and the CDC guidelines include recommendations that are similar to those of the WHO, the AAP, and the US CDC [20].

One meta-analysis that reviewed 10 randomized controlled trials concluded that LAIV had the highest efficacy in young children [21]. A more recent meta-analysis of 9 randomized controlled clinical trials that encompassed 26,000 children aged 6 months to 17 years showed LAIV's greater efficacy compared with IIV; LAIV led to approximately 45% fewer cases of influenza illness [22]. A meta-analysis that included all previously published randomized clinical trials of LAIV in children aged 24-71 months showed greater relative efficacy of LAIV compared with IIV, 52.2% for moderate/severe influenza and 45.0% for mild influenza [23]. Recently, growing evidence has consistently reported the superior efficacy of LAIV in children. A randomized controlled trial conducted among 7,852 children aged 6-59 months demonstrated a 54.9% reduction in culture-confirmed influenza among children who received LAIV compared with those who received IIV [24]. One randomized, open-label trial conducted among 2,229 asthmatic children aged 6 to 17 years reported that LAIV showed 32% increased protection against culture-confirmed influenza [25]. Based on recent clinical trials, the Canadian Pediatric Society (CPS) and the ACIP have changed their vaccine recommendations to a preference for LAIV over IIV for healthy children 2 to 6 years of age [26] and 2 through 8 years [24,25]. LAIV is not indicated for children under 2 years of age because of increased risk of wheezing [24,27]. Currently, the ACIP is planning to recommend either LAIV or IIV as an appropriate option without preference based on the non-superiority vaccine effectiveness (VE) of LAIV; higher VE in the A/H3N2 and B strains in 2010-2014, but lower VE in the A/California H1N1pdm09 strain in 2010-2011 and 2013-2014, in the United States [28].

Growing Evidence: Safety of Influenza Vaccination in Children with Egg Allergy

Until 2010, influenza vaccination in children with egg allergy was contraindicated because the residual ovalbumin could cause anaphylaxis or a severe allergic reaction in sensitive children [29].

Recently, most vaccine manufacturers began reporting the residual amounts of ovalbumin in their influenza vaccines annually, and the residual amount in the reported vaccines is less than $\leq 1 \mu\text{g/mL}$, which is safe for use in patients with egg allergy [30,31]. The residual amounts that were in the vaccines that were on the Korean market in 2004-2006 were also $\leq 0.1 \mu\text{g/mL}$ [32].

Recently, numerous observational studies and guidelines have consistently reported the safety of IIV in children with egg allergy, even in those with a previous history of anaphylaxis from egg [8,33-35]. Des Roches et al. [33] reported no occurrences of anaphylaxis in a review of 26 studies of 4,172 patients (513 were patients with a history of severe reactions), suggesting that severe allergic reaction or anaphylaxis appears sufficiently low that patients with egg allergy can be vaccinated the same as all other individuals without requiring administration by an allergist. More recently, a total of 28 studies comprising 4,315 subjects with egg allergy, including 656 subjects with a previous history of anaphylaxis following egg ingestion, showed no serious reaction after influenza vaccination [8]. Recent clinical trials have also reported the safety of LAIV in children with egg allergy. A phase IV open-labeled trial in the United Kingdom reported that LAIV appears to be safe for use in children with egg allergy. A total of 433 doses of LAIV were administered to 282 children with egg allergy aged 2 to 17, including 41% who had had previous anaphylaxis with egg, and the children showed no systemic reactions [36]. Another study of 69 children with egg allergy and 55 controls reported no allergic reaction after LAIV vaccination. This study proposed that the quantity of ovalbumin in LAIV is insufficient to cause an allergic reaction and that the systemic absorption of ovalbumin via intranasal vaccination is likely much lower than that through intramuscular administration. This study concluded that LAIV in children with egg allergy had many potential benefits including superior efficacy over IIV and better coverage because of its less-invasive route of administration [37]. In Korea, Shin et al. [35] reported on the safety of IIV in Korean children with egg allergy, even in those who had had previous anaphylaxis with egg.

One recent study has suggested that one reason for the safety of LAIV that was found in the previous studies above is the use of batches with low ovalbumin contents $< 0.3 \mu\text{g/mL}$. This study reported mild symptoms of rhinitis at $10\text{-}100 \mu\text{g/mL}$ of intranasal egg protein in children with positive skin prick tests for egg white. Nasal symptoms were not observed at a dose of $1 \mu\text{g/mL}$ or in controls without egg sensitivities [38]. Although

rhinorrhea and nasal congestion are known as the most common adverse events with LAIV [24], the amount of ovalbumin in LAIV is approximately 10 times lower than the amount of egg protein that has been found to trigger local rhinitis symptoms. Therefore, the study above suggested that LAIV is unlikely to provoke an IgE-mediated response when administered into the nasal airway of egg-allergic children [36]. However, there is no study that has investigated LAIV's safety and efficacy in children with allergic rhinitis. There is a strong probability that LAIV can be used safely in those with allergic rhinitis, but the subject requires further research.

Similar to the studies discussed above, growing evidence has demonstrated the safety of influenza vaccination in children with egg allergy, even in those with previous anaphylaxis with egg [8,33-37]. Based on these results, the vaccine practice parameter developed by the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI), announced the safety of IIV in children with egg allergy in 2012 [13]. Based on this recommendation, there has been a significant shift in influenza vaccination practices; however, 4.8% of allergists reported not administering IIV to children with egg allergy, and 17% only administered it to children with mild cases [39].

Global Recommendations for Influenza Vaccination in Children with Egg Allergy

The evidence based on the numerous clinical trials discussed above changed the ACIP's policy to permit influenza vaccination in subjects with mild egg allergy in 2011 [40]. The ACIP also suggests the safe use of IIV in children with egg allergy and no longer recommend skin tests or divided doses [19]. The ACIP updated its recommendations for influenza vaccination on August 15, 2014 [17]. That revision maintains one previous recommendation: additional measures (e.g., two-step approaches, skin tests) are no longer needed before IIV can be administered in egg-allergic children [18]. The update repeatedly highlights that IIV can be safely administered in children with egg allergy and that the use of LAIV is contraindicated in any persons with egg allergy. However, the ACIP recommends that with patients with previous severe reactions to egg, the precaution should be taken of having the vaccine administered by a physician with experience in recognizing and managing severe allergic conditions.

The JTFPP's vaccination practice parameters also recommend that patients with egg allergy receive annual influenza vaccinations because the risks of vaccinating are outweighed by the risks of not vaccinating. It has stated that IIV rather than LAIV is recommended in children with egg allergy and that neither skin testing nor dividing doses is required because all influenza vaccines contain insufficient amounts of ovalbumin to provoke anaphylaxis [13]. The JTFPP concluded that patients with egg allergy can receive influenza vaccinations under observation for 30 minutes in a primary care setting and that only those with a previous severe reaction to egg ingestion should receive their influenza vaccinations in an allergist's office. Encouragingly, there has not been an increase in reports of IIV-related allergic reactions since 2012 [41]. Based on the absence of influenza-related allergic reactions, the JTFPP has repeatedly encouraged routine influenza vaccination for these patients without testing or special accommodation [42].

Recently, two non-egg-based IIVs have been developed. Unfortunately, they are not approved for children aged <18 years [17]. A recent editorial in the *Journal of Allergy and Clinical Immunology: in Practice* proposes that "no longer seeking out a particular brand of influenza vaccine with a particularly low amount egg protein is necessary" [43].

Conclusively, most guidelines recommend the use of IIV rather than LAIV in children with egg allergy and find that skin tests and divided doses are unnecessary [13,17,26].

Although the ACIP and the CPS officially do not recommend the use of LAIV in children with egg allergy or asthma because LAIV contains trace amounts of ovalbumin and because of the lack of data concerning its safety to date, growing evidence has shown its superior efficacy and safety to those of IIV even in patients with egg allergy and asthma.

Growing Evidence: Safety of Influenza Vaccination in Children with Asthma

A number of studies have demonstrated the safety of LAIV in children with asthma. One randomized, open-label trial conducted among 2,229 asthmatic children aged 6 to 17 years reported that LAIV showed 32% increased protection against culture-confirmed influenza without worsening asthma symptoms or peak expiratory flow rates [25]. Two cross-over trials involving 712 children (over 3 years old) with asthma compared IIV with a placebo injection and demonstrated no significant asthma exacerbations in the 2 weeks following the

influenza vaccination [44]. Ambrose et al. [45] reported the safety and efficacy of LAIV using secondary analysis from 2 randomized, multinational trials of LAIV in children aged 2-5 years with asthma or prior wheezing.

A phase IV open-labeled trial in the United Kingdom, discussed above, reported that LAIV appears to be safe for use in children with a diagnosis of asthma or recurrent wheezing. Among 282 children, 67% had physician-diagnosed asthma. Although 13 parent-reported self-limited wheezing incidents were reported, no asthma exacerbations that needed medical care were observed. In this study, 69 (25%) patients were using high-dose inhaled corticosteroids [36]. The study found an important clinical indication: no asthma exacerbation in moderate persistent asthma. Another study of 69 children with egg allergy and 55 controls reported no allergic reaction after vaccination. Among the 69 study participants, 40 (59%) had mild asthma. Interestingly, no asthma exacerbation after LAIV vaccination was reported. This study proposed that LAIV in children with asthma may be safe even in asthma that is not mild [37]. The two studies above are the only two published studies on the use of LAIV in children with asthma and egg allergy; both studies showed consistent results, with neither allergic reactions nor asthma exacerbation.

Global Recommendations for Influenza Vaccination in Children with Asthma

Annual influenza vaccination is strongly recommended as a preventative measure for all children with asthma [46]. The Global Initiative for Asthma (GINA) also recommends influenza vaccination for children with allergic diseases, particularly asthma, to prevent asthma exacerbations [47]. However, concerns about asthma exacerbation and poor immune response in patients with maintenance inhaled-corticosteroid (ICS) therapy [46] impede guideline-based performance in practice. Despite their potential for increased morbidity, 75% to 90% of asthmatic children do not receive an influenza vaccination [10]. The immune response to the influenza vaccine is not affected by ICS therapy, but high-dose ICS therapy may diminish the response to the vaccine's B antigen. Further research will be needed to develop a best protective strategy in children with severe asthma [46].

The ACIP still does not recommend LAIV with children aged 2 through 4 years with asthma or recent wheezing because the available data are insufficient to determine the asthma severity level for which administration of LAIV would be

inadvisable [17]. They also recommended caution in using LAIV with asthmatic children aged ≥ 5 years.

The CDC guidelines state that people with severe, life-threatening allergies to the influenza vaccine or any ingredient in the vaccine, children 2 years through 4 years who have asthma, and children who have a history of wheezing in the past 12 months are contraindicated for an influenza vaccination. In addition, the CDC defines people with asthma as a special population who should talk to their doctors before receiving LAIV [16]. The CPS recommends that IIV may be used in individuals with egg allergy; however, they determined that LAIV has not yet been evaluated in this population, and they do not recommend it at this time [26]. The Korean guideline recommends consistent consideration of the ACIP's recommendations for children with asthma [20].

Concerns regarding the causes of wheezing after influenza vaccination consequently impede guideline-based performance in practice. Unfortunately, many guidelines have still not changed their policy that LAIV is contraindicated in asthmatic children.

Summary of Global Influenza Vaccine Recommendations for Children with Allergic Disease

The overall recommendations for influenza vaccination in children with asthma and egg allergy are as follows:

- Influenza vaccination is strongly recommended in children with asthma.
- IIV is recommended as a first choice in children with asthma. However, the efficacy of IIV is likely to be less than that of LAIV.
- IIV is not contraindicated in children with egg allergy. A single dose with 30 minute-observation without skin test is recommended in the usual manner.
- IIV is not contraindicated in children with egg anaphylaxis. A single dose with 30-minute observation without skin test is recommended under the care of appropriate personnel and emergency equipment. If emergency equipment is not available, refer to an allergist.
- Re-vaccination is contraindicated in children with anaphylaxis from a previous influenza vaccination. Evaluation for trace components other than egg protein is necessary.
- LAIV is currently not recommended in children with asthma; there are few data on its safety. However, the growing evidence supports the safety and efficacy of LAIV in chil-

dren with asthma.

- LAIV is not recommended in children with egg allergy. There are few data on its safety. However the growing evidence supports the safety and efficacy of LAIV in children with egg allergy.
- Further evaluation is needed regarding the influenza vaccine for children with special considerations, including IIV with severe asthma with egg anaphylaxis and LAIV with severe allergic rhinitis. There are few data on safety, risks, and benefits.
- Neither vaccination nor asthma guidelines provide a proper vaccination strategy for children with severe asthma or asthma concurrent with egg anaphylaxis. Further research will be needed.

Special Consideration

Children with FA are 2-4 times more likely to have concurrent asthma [48], and in patients with asthma, concurrent FA is known as a risk factor for severe asthma exacerbations and future anaphylaxis [42,49-51]. Although anaphylaxis is rare after influenza vaccination, the vaccine should be administered in a setting in which anaphylaxis can be recognized and treated [13]. Therefore, patients with concomitant asthma and FA should be advised regarding these risks, and all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available.

Taken together, concerns about residual ovalbumin and lack of safety data do not allow for the use of LAIV in children with egg allergy or asthma, despite growing evidence [17,19,20,26].

Conclusion

Although most influenza vaccines contain trace ovalbumin, it is less likely to provoke allergic reactions in children with egg allergy because the ovalbumin content is insufficient to provoke a reaction. The vaccine can be safely administered in children with egg allergy, even in those with anaphylaxis from egg. As the guidelines recommend, physicians can administer IIV in children with asthma or egg allergy with minimal precautions.

Conclusively, IIV is recommended as the first choice in children with asthma or egg allergy. However, the growing evidence for the better efficacy and safety of LAIV may change this rec-

ommendation in the near future. Finally, further research is needed on special considerations for children with severe asthma and with concurrent asthma and egg anaphylaxis.

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