Effectiveness and safety of seasonal influenza vaccination in children with underlying respiratory diseases and allergy

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Influenza causes acute respiratory infections and various complications. Children in the high-risk group have higher complication and hospitalization rates than high-risk elderly individuals. Influenza prevention in children is important, as they can be a source of infection spread in their communities. Influenza vaccination is strongly recommended for high-risk children with chronic underlying circulatory and respiratory disease, immature infants, and children receiving long-term immunosuppressant treatment or aspirin. However, vaccination rates in these children are low because of concerns regarding the exacerbation of underlying diseases and vaccine efficacy. To address these concerns, many clinical studies on children with underlying respiratory diseases have been conducted since the 1970s. Most of these reported no differences in immunogenicity or adverse reactions between healthy children and those with underlying respiratory diseases and no adverse effects of the influenza vaccine on the disease course. Further to these studies, the inactivated split-virus influenza vaccine is recommended for children with underlying respiratory disease, in many countries. However, the live-attenuated influenza vaccine (LAIV) is not recommended for children younger than 5 years with asthma or recurrent wheezing. Influenza vaccination is contraindicated in patients with severe allergies to egg, chicken, or feathers, because egg-cultivated influenza vaccines may contain ovalbumin. There has been no recent report of serious adverse events after influenza vaccination in children with egg allergy. However, many experts recommend the trivalent influenza vaccine for patients with severe egg allergy, with close observation for 30 minutes after vaccination. LAIV is still not recommended for patients with asthma or egg allergy.

Key words: Influenza, Vaccination, Allergy, Respiratory disease

Characteristics and effects of influenza infection in children

Influenza frequently results in the development of acute respiratory infection in children younger than 2 years, with a higher admission rate than that caused by respiratory syncytial virus infection\(^1\). During an influenza epidemic, influenza-related morbidity increases significantly in children younger than 1 year, with the ratio of emergency department visits increasing to 237/100,000\(^2\) and an influenza-associated hospitalization rate of 120/100,000\(^3\). High admission rates have been reported for children younger than 1 year with underlying circulatory or respiratory disease. During an influenza epidemic, the influenza infection attack rate is approximately 40% and 30% in preschool children and school children, respectively, implying high infectivity\(^4\)\(^5\).

Clinically, influenza causes acute respiratory infections such as croup, bronchitis, and primary and viral pneumonitis. Consequently, it may lead to complications such as...
secondary bacterial otitis media, pneumonia, myositis, encephalitis, myocarditis, Guillain–Barre syndrome, and Reye’s syndrome, and multiorgan failure may develop. These serious complications are not rare. The rates of complication development and admission can be higher in children in the high-risk group than in the high-risk elderly population. In addition, infected children can be a source of infection spread in their family. Therefore, preventing influenza infection in children is very important.

**The importance of vaccination in the control of influenza infection**

Prevention of influenza by vaccination is the most effective means of decreasing the socioeconomic burden of influenza. Trivalent inactivated influenza vaccines containing two influenza A and one influenza B subtype are usually employed. The antigen type to be included in the vaccine is reviewed by the World Health Organization (WHO) annually, and this varies to match the strains most prevalent in the hemisphere. In general, available influenza vaccines limit disease severity and reduce serious complications associated with influenza infections. Clinically, the protective value of influenza vaccines is related to their immunogenicity. Additionally, there is a clear link between immunogenicity and vaccine effectiveness; however, it is difficult to accurately quantify this link due to several factors that cannot be accurately quantified. These factors include herd immunity due to high vaccination rates and mismatched types in circulation or resistance to recurring strains after considerable periods. Furthermore, the efficacy of influenza vaccines may be influenced by various factors including age, prior vaccination, prevaccination antibody titers, immune status of the vaccinee, and the concurrent use of drugs such as steroids or immunosuppressive agents. However, influenza vaccination decreases influenza morbidity and mortality and reduces societal costs. Cost-effectiveness has also been confirmed in various studies on high-risk infants and children. Vaccination is useful in preventing influenza in approximately 31%–91% of healthy children and children with asthma. In particular, vaccination significantly prevents hospitalization due to influenza-related complications.

**General recommendations for the use of influenza vaccines in children**

As described, children with influenza can be a source of disease spread in the community. Therefore, influenza vaccination is very important; if the vaccine is in short supply, children should be given priority. When vaccination was conducted proactively for children, influenza infection and death rates decreased in adults in particular, intensive vaccination of school children and infants aged 6–23 months is essential.

The modern influenza split vaccine was developed by the Pasteur Company in 1969, and the use of split or subunit influenza vaccines was widespread in the 1970s. Since 1981, each 0.5 mL of influenza vaccine is mixed with 15 µg of hemagglutinin antigen for use as the trivalent inactivated split vaccine (two types of A antigens and one type of B antigen). For infants aged 6–35 months, a 0.25-mL dose of influenza vaccine should be administered. Children aged 6 months to 8 years, who are receiving the influenza vaccine for the first time require two doses, administered at an interval of more than 4 weeks; only a single dose is needed from the second year of vaccination. The prefilled influenza vaccine was introduced in 1995, and the live-attenuated influenza vaccine (LAIV) was developed for use in healthy children aged 2 years or older. However, the recombinant influenza vaccine and cell culture-based vaccine, which were developed later, have not yet been used in children.

The WHO strongly recommends influenza vaccination for young children, and since 2011, vaccination has been recommended for all individuals older than 6 months. In 2012, the B antigen was mixed with one type of Victoria lineage antigen and one type of Yamagata lineage antigen as a quadrivalent influenza vaccine; this new formula has been used since 2013. Because of the 2–4 times higher risk of influenza infection, hospital admission, and the development of complications compared with healthy children, vaccination is strongly recommended for high-risk children with cancer, chronic circulatory or respiratory disease, or human immunodeficiency virus infection; immature infants; and children receiving long-term treatment with immunosuppressive agents or aspirin. As a cocooning strategy, vaccination is recommended not only for these high-risk children but also for individuals who cannot avoid physical contact. To reduce the risk of infection, vaccination is strongly recommended for mothers of infants younger than 6 months. Vaccination is also recommended for children in other high-risk groups, including children younger than 2 years, children in daycare centers, and children aged 5–17 with chronic diseases. In South Korea, elderly people aged 65 years or older are vaccinated as part of the national immunization program. This vaccine is also strongly recommended for children aged 6 months or older. Nevertheless, no detailed recommendations for children in the high-risk group with underlying diseases have been proposed yet, particularly in the case of children with underlying respiratory diseases or allergies such as bronchopulmonary dysplasia (BPD), asthma, or egg allergy. Currently, five types of influenza vaccines are used in children (Table 1) in Korea.
observed within 24 hours. Forty-eight hours after vaccination,
compared to healthy children, and no adverse reactions were
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against the B antigen
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antigens, asthma patients had slightly lower immunogenicity than
healthy children. Nevertheless, the actual vaccination rate is low because of
concerns that the influenza vaccination exacerbates asthma and questions regarding its efficacy in patients receiving steroid treat-
ment. To help resolve these problems, many clinical studies have been conducted since the 1970s (Table 2).
In 1978, Bell et al. conducted the first study of the bivalent
split influenza vaccine in 6- to 16-year-old children with chronic
asthma. The authors found no differences in immunogenicity
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observed within 24 hours. Forty-eight hours after vaccination,
several children showed a temporary decrease in the peak expir-
atory flow rate and required the use of a bronchodilator. Accord-
ing to a study on 31 unprimed children and young adults with
cystic fibrosis conducted by Gross et al. in 1980, a direct response
was observed in a group of children who received the influenza
vaccine, and there was no difference in adverse events compared to
the placebo group. In another study on two types of the trivalent
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the trivalent subunit influenza vaccine, which included 95 infants
and children with moderate to severe asthma and reported that
subjects showed no deterioration in asthma after vaccination,
although three subjects experienced a temporary limitation in
limb movements, without systemic reactions. In 1991, Grothuis
et al. reported that, in 113 children with BPD or congenital
heart disease aged 3–18 months, mild adverse reactions were
reported in 6%–14% of cases, and two-dose vaccination was
required in order to achieve four-fold seroconversion. In a 1998
clinical report, Brydak et al. reported that six infants with BPD
aged 8–21 months who received two doses of 0.25 mL of the
trivalent split influenza vaccine showed a high-fold increase in
geometric mean titers. Since 1990, numerous studies on split
or subunit influenza vaccines for children with asthma showed
no difference in immunogenicity against A antigens between
asthma patients and healthy children, whereas in the case of B
antigens, asthma patients had slightly lower immunogenicity than
healthy children. In addition, some studies reported a temporary
deterioration in asthma; however, most studies reported no adverse
effect of the influenza vaccine on the course of asthma and no
significant difference in adverse reactions between children with
asthma and healthy children. Considering these results, although short-term corticosteroid or alternative therapies affect
antibody formation to a small extent, these treatments may not
interfere with the influenza vaccine. However, in the case of high-
dose administration at 2 mg/kg or 20 mg/day, a delay in vaccina-
tion is recommended. However, vaccination guidelines for
patients with persistent asthma who use inhaled corticosteroids
(ICSs) on a long-term basis have not yet been clearly established.
According to a study of children and adults with persistent asthma
conducted by Hanania et al. in 2004, antibody reactions against
A antigens (H1N1, H3N2) were not affected in chronic ICS users;
however, reactions against B antigens may be sluggish in high-dose
ICS users. This outcome corresponded with those of previous
studies. In association with directly linked B-cell function, the
influenza vaccine usually shows antibody reactions; however,
with decreased function of T helper cells, antibody reactions also
declined. Accordingly, these outcomes provide chronic ICS users

**Studies of the safety and efficacy of inactivated influenza vaccines in children with underlying respiratory diseases**

Severe influenza infection is observed in all children; however,
vaccination is essential for children with chronic respiratory dis-
 ease, heart disease, and cancer, and for children receiving long-
term immunosuppressant therapy. This is because of the risk for
serious complications. More specifically, children with chronic
respiratory diseases, including BPD and asthma, can experience
deterioration of pulmonary function or have other complications
after influenza infection, increasing the admission rate. Therefore,
vaccination is strongly recommended for these children as well.
Nevertheless, the actual vaccination rate is low because of
concerns that the influenza vaccination exacerbates asthma and
questions regarding its efficacy in patients receiving steroid treat-
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### Table 1. Available seasonal influenza vaccines for children in Korea

| Trade name   | Manufacturer             | Presentation                      | Type of vaccine | Mercury content (μg Hg/dose) | Ovalbumin content (μg/0.5 mL) | Age indication | Route |
|--------------|--------------------------|----------------------------------|----------------|----------------------------|-------------------------------|----------------|-------|
| GC Flu       | Green Cross Corporation  | 0.5-mL Single dose prefilled syringe | SV trivalent    | 0                          | ≤0.05                         | ≥3 yr          | IM    |
| Fluarix      | GlaxoSmithKline          | 0.5-mL Single dose prefilled syringe | SV trivalent    | 0                          | ≤0.05                         | ≥3 yr          | IM    |
| Vaxigrip     | Sanofi Pasteur           | 0.5-mL Single dose prefilled syringe | SV trivalent    | 0                          | ≤0.05                         | ≥3 yr          | IM    |
| Agriflu      | Novartis Vaccine         | 0.5-mL Single dose prefilled syringe | SV trivalent    | 0                          | ≤0.2                          | ≥3 yr          | IM    |
| Flumist      | MedImmune                | 0.2-mL Single dose prefilled intranasal sprayer | CAIV-T*        | 0                           | <0.24                         | 2–49 yr        | IN    |

SV, split vaccine; IM, intramuscular; CAIV-T, cold-adapted live attenuated influenza vaccine, trivalent; IN, intranasal.

*Indication for healthy children, adults, and nonpregnant women.
Table 2. Characteristics and end results of clinical studies involving children with asthma and underlying respiratory diseases that evaluated efficacy and safety of seasonal influenza vaccines (inactivated or live attenuated)

| Reference no. | Type of vaccine | Route of administration | Age | No. of subjects | Population | End results | Adverse events (AE) |
|---------------|-----------------|--------------------------|-----|----------------|------------|-------------|---------------------|
| 31            | SV bivalent     | According to insert      | 6–16 yr | 79          | Children with chronic asthma | Transient decrease in peak expiratory flow rate at 48 hr. Good serologic response | No acute ill AE at 24 hr |
| 32            | SV monovalent   | IM                       | 7–25 yr | 31          | Children and adults with CF | A direct dose response observed | Similar to placebo group |
| 33            | SV trivalent    | IM                       | 2–25 yr | 76          | Infants, children & adults with asthma or CF | Among the unprimed individuals, after 1 dose of vaccine, the geometric mean responses to both strains of influenza A were 100, whereas the same responses to the B component were 32. | No febrile reactions within 24 hr, 6 to 7 recipients from each vaccine group had local arm tenderness |
| 34            | SU trivalent    | IM                       | 7 mo–12 yr | 95  | Infants & children with asthma | No child had asthma worsening | Limited motion of limb for 8–12 hr after vaccination |
| 35            | SV trivalent    | IM                       | 3–8 mo | 113         | Infants with BPD or CHD | Seroconversion (i.e., a 4-fold increase in titer) required 2 doses of vaccine | More frequent solicited AE in young infants |
| 36            | CRIV IN         | 11.2 yr                  | 68   | 68          | Children with asthma, 19; severe SPR pts., 52 | CRIV demonstrated significant protective effects against natural exposure to the A H1N1 virus | Well tolerated and safe when given to patients with bronchial asthma and severe psychomotor retardation |
| 37            | SU trivalent    | IM                       | 2–14 yr | 137         | Children with asthma | Total vaccine efficacy, 42.1%; 61.7% in children with over 7 yr of age, but 16.1% in young children | No differences in the severity or frequency of asthmatic attack between both groups |
| 38            | SV trivalent    | IM                       | 6 mo–18 yr | 109 | Control, 59; children with asthma, 50 | Influenza vaccination can be given to asthmatic children regardless of asthma Sxs | AEs were not different in the two groups |
| 40            | SV trivalent    | IM                       | 3–64 yr | 2,032       | Children & adults with asthma | The frequency of exacerbations of asthma was similar in the two weeks after the influenza vaccination | No fever or pain at the vaccine site |
| 41            | CAIV-T IN       | 9–17 yr                  | 48   | 48          | Children with asthma, 349 placebo, 347 study group | No result in important reductions in pulmonary function, and not worsen clinical features & symptom scores | Body aches were more frequent after the vaccine injection |
| 42            | CAIV-T IN       | 6–17 yr                  | 696  | 696         | Children with asthma: 349 placebo, 347 study group | Influenza-related asthma exacerbations was 3 days shorter in the vaccine group (not statistically significant) | Local and systemic AE significantly more often in the vaccine group |
| 43            | CAIV-T IN       | 6–17 yr                  | 2,229 | 2,229       | Children with asthma: CAIV-T, 1114; SV-trivalent, 1115 | Chronic ICS therapy did not affect the humoral immune response to influenza A antigens. But, high dose ICS therapy may affect to immune response to the B antigen | No serious adverse events in either group |
| 44            | CAIV-T IN       | 6–35 mo                  | 130  | 130         | Healthy infants, 68; recurrent wheezing infants, 62 | The nasal Sxs was higher for CAIV-T (66.2%) recipients. | NA |

AE, adverse event; SV, split vaccine; NS, not significant; CF, cystic fibrosis; IM, intramuscular; SU, subunit vaccine; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CRIV, cold-adapted reassortant influenza vaccine; SPR pts., severe psychomotor retardation patients; Sxs, symptoms; GMT, geometric mean titer; HA, hemagglutinin; NA, neuraminidase; CAIV-T, cold-adapted live attenuated influenza vaccine, trivalent; IN, intranasal; ICS, inhaled corticosteroid; TIV, trivalent inactivated vaccine.
with a basis for the recommendation of influenza vaccination. According to a recent study by Bae et al., infants with recurrent wheezing, even those who received steroids for a short period of time, developed immunogenicity against A and B antigens after influenza vaccination. In studies since the mid-1990s on cold-adapted live attenuated influenza vaccine targeting asthma patients aged 5 years or older, immunogenicity was achieved without difficulty, and the level was even higher than that achieved with the inactivated split influenza vaccine, without adverse reactions other than nasal symptoms. Considering these outcomes, inactivated split-virus influenza vaccination is recommended for children with underlying respiratory diseases, including asthma, in many countries. However, LAIV is still not recommended for children younger than 5 years of age with asthma and recurrent wheezing.

Guidelines for the use of influenza vaccines in children with egg allergy

Influenza vaccination is contraindicated in patients severely allergic to egg, chicken, or feathers, because ovalbumin may remain in egg-cultivated influenza vaccines. In previous studies, direct skin tests with the influenza vaccine or whole eggs were suggested for determining the feasibility of vaccination. According to a study on 142 allergic children conducted by Berman et al., an intradermal skin test using a 1:100 mixture of the influenza vaccine and normal saline was more objective in determining the feasibility of influenza vaccination than a history of egg allergy.

In recent studies on trivalent influenza vaccination in children with a history of egg allergy, no serious adverse reactions such as respiratory distress, hypotension, or shock were reported; however, minor adverse reactions such as hives and mild wheezing were reported, indicating that development of serious systemic adverse reactions is rare with trivalent influenza vaccination. Even in patients with severe allergic responses to egg ingestion, no serious adverse reactions were observed, and there were no differences in adverse reactions between patients with positive and negative skin test results. Accordingly, these skin tests were reported to be unnecessary for patients with egg allergy. In addition, a study comparing a divided dose and single dose found no difference in adverse reactions. The amount of ovalbumin present is usually less than 1 μg per 0.5 mL-dose, and the products currently in use have a lower amount of ovalbumin; thus, a severe adverse reaction may not occur, even in patients with serious egg allergy. A small amount of ovalbumin is present in LAIV; however, the use of LAIV in patients with egg allergy has not been studied. Therefore, LAIV administration is not recommended for patients with egg allergy. The Advisory Committee on Immunization Practices (ACIP) in America recommends the trivalent influenza vaccine for patients with serious egg allergies, with close observation for 30 minutes after vaccination; however, the use of LAIV in patients with asthma or egg allergy is contraindicated. In addition, the ACIP recommends that patients with circulatory symptoms such as hypotension and shock; respiratory symptoms such as wheezing, or digestive symptoms such as severe nausea and vomiting and patients requiring epinephrine or emergency medical attention after ingesting eggs or egg foods consult with professionals prior to receiving vaccination.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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