

Efficacy and safety of influenza vaccination in children with asthma

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The mean global prevalence of asthma among children is approximately 12%, making it the most common chronic disease in children. Influenza infection has been associated with complications such as exacerbations of wheezing and asthma, increased airway hyper-reactivity and hospitalization. Although influenza vaccination is recommended for asthmatic patients by all health authorities, vaccination coverage remains significantly lower than expected and is lowest of all in children. Compliance is affected by the uncertainty of parents and physicians concerning the clinical risk of influenza in asthmatic subjects, the benefits of influenza vaccination in preventing asthma exacerbations and the safety of immunization. The aim of this review is to analyze the rationale for using influenza vaccine, discuss the relationship between influenza and the severity of asthmatic episodes and document the efficacy and safety of influenza vaccination in the pediatric asthmatic population.

KEYWORDS: asthma • asthmatic patients • children • influenza • influenza prevention • influenza vaccine • live-attenuated influenza vaccine • pediatrics • trivalent influenza vaccine • wheezing

The mean global prevalence of asthma among children is approximately 12% [1]. It is mainly episodic in childhood, and acute respiratory viral infections are a major trigger of wheezing in infants and asthma exacerbations in older children [2–6]. The use of molecular diagnostic techniques such as real-time PCR has increased the number of respiratory viruses that can be detected, and viral infections are now recognized in up to 85% of wheezing episodes [7,8].

Influenza is a common disease that affects 10–30% of the pediatric population every year [9,10], and it is a significant cause of respiratory morbidity in children and adults. In an 11-year study of children younger than 7 years attending an emergency room (ER) because of acute respiratory disease, Bourgeois *et al.* documented an influenza virus (IV) infection in 9.2% of cases [9], and an Italian study of 2060 otherwise healthy children younger than 15 years, admitted to the ER during the 2003–2004 winter season because of acute disease, documented IV in 30% of cases [11]. IV infection plays a confirmed role in wheezing and asthma exacerbation, although the relationship between IV infection and asthma seems to be less close than that of other viruses, such as rhinovirus (RV) or respiratory syncytial virus [11].

In addition, it is known that children with chronic, severe underlying diseases are at higher risk of complications when infected by IV, and all of the guidelines support the opinion that children with asthma should be vaccinated against influenza [12–14]. However, influenza vaccination rates in the asthmatic population remain significantly lower than expected (usually <30%) and are lowest of all in children [15,16]. Compliance to the vaccine is affected by the uncertainty of parents and physicians regarding the clinical risk of IV infection in asthmatic subjects, the benefits of influenza vaccination in preventing asthma exacerbations and the safety of immunization.

This review will analyze the rationale for using influenza vaccine, discuss the relationship between influenza and the severity of asthmatic episodes and examine the efficacy and safety of influenza vaccination in the pediatric asthmatic population. The most relevant articles published in PubMed in the past 10 years on influenza or influenza vaccination in asthmatic patients have been considered. All those that regarded children were included in the references and those related to adults were included when pediatric studies were not available.

Role of seasonal IV in asthma exacerbations

Influenza can cause asthma exacerbations or influenza-related complications in asthmatic patients. The pathogenic mechanisms that may increase susceptibility to IV in patients with asthma include the slightly impaired immunologic response to influenza B antigens caused by high-dose inhaled corticosteroid therapy [17]. In a study of 147 consecutive hospitalized adults with influenza, Lee *et al.* found slower viral clearance in those with asthma [18]. Finally, in atopic children, respiratory viral infections (including IV) may initiate an atopy-dependent cascade that amplifies the airway inflammation initiated by innate antiviral immunity by means of underlying atopy-associated mechanisms [19].

The clinical importance of influenza as a cause of acute wheezing and asthma has been documented. Miller *et al.* prospectively studied children aged 6–59 months who were hospitalized because of acute respiratory illnesses or fever between 2000 and 2004, and children who attended outpatient clinics or ERs during two influenza seasons (2002–2004) [20]. Outpatient surveillance identified asthma in 15% of the patients with confirmed influenza and a higher rate of visits in the 2003–2004 season among children with asthma than among healthy children aged 6–23 months (316 vs 152 cases per 1000 children) and 24–59 months (188 vs 102 cases per 1000 children) [20]. Moreover, 23% of the hospitalized children had asthma, and the average annual influenza-attributable hospitalization rate was significantly higher among children with asthma than among healthy children aged 6–23 months (2.8 vs 0.6 cases per 1000 children) [20]. A 10-year retrospective population-based study found a marked increase in primary care visits due to respiratory diseases in young children during the winters, with respiratory syncytial virus and IV significantly influencing asthma symptoms ($p = 0.0060$) [21]. In another 19-year retrospective study of the Medicaid database of children younger than 15 years with asthma, the annual rate of outpatient visits attributable to IV was 12–20% [22].

Although these studies demonstrated the substantial morbidity associated with influenza in asthmatic patients, other studies of children have failed to identify influenza as a cause of asthma exacerbation. An observational 1-year case–control study of 142 asthmatic children aged 2–17 years compared viral detection in those with acute exacerbations and those with well-controlled asthma. RV was by far the most prevalent virus and the only one significantly associated with exacerbations, whereas IV was not detected in either group during the year [23]. In another study of 128 children aged 2–16 years attending an ER because of acute asthma exacerbations, the only child with influenza (0.8%) was coinfecting by RV and metapneumovirus [24]. In an Italian study primarily aimed at evaluating the infectious agents associated with the first episode of severe acute wheezing in 85 otherwise healthy infants younger than 12 months, IV was detected in 7.5% of patients, all of whom were younger than 3 months [25]. Finally, in a letter to the editor, it was reported that none of the 40 patients younger than 11 years who were hospitalized with acute asthma exacerbations and enrolled in

a 2-year study had influenza A, and only 8% had influenza B infection [26].

However, the studies that have not found any role of IV in children with asthma have some limitations. Influenza is a seasonal disease characterized by winter epidemics, whereas viruses such as RV are present throughout the year. Studies over short or excessively long periods may underestimate the real importance of IV. The severity of influenza seasons and the degree to which the circulating strains of IV and the vaccine match vary annually, which is a particular concern for 1-year studies. Furthermore, pediatric asthmatic patients who do not require hospitalization are not always included in studies of influenza-attributable exacerbations, which are therefore not a good indicator of morbidity. In a study by Mandelcwajg *et al.*, 339 children younger than 18 months who had been previously diagnosed as having asthma were referred to an ER because of acute wheezing between November and March of four successive winters, and influenza A virus was detected in 2.6% of the hospitalized cases and in 14.1% of those who were not hospitalized [27].

Nevertheless, studies of children with chronic underlying diseases, including asthma, have found that IV is the second most common respiratory virus after respiratory syncytial virus causing hospitalization and serious clinical complications. Neuzil *et al.* found that the rates of influenza-attributable hospitalizations of low-income children in Tennessee (TN, USA) with high-risk conditions, including asthma, were two- to four-times higher than those of healthy children [22]. The annual rates for the high-risk children in the <1-, 1–3- and 3–15-year age groups were, respectively, 19, eight and two per 1000 [22]. Glezen *et al.* studied children with an underlying condition (mainly asthma) who were hospitalized because of an acute respiratory illness, and found proven influenza infection in 10% of those aged younger than 5 years and 21% of those aged 5–17 years [28]. Moreover, Coffin *et al.* found that the incidence of influenza-related complications in 745 children hospitalized because of community-acquired laboratory-confirmed influenza during a 4-year study period was higher among those with a pre-existing high-risk condition (mainly asthma) than among the previously healthy children (29 vs 21%) [29]. Children with high-risk medical conditions were also more likely to require intensive care (odds ratio 1.6) or develop respiratory failure (odds ratio 2.8) [29]. Similar findings have been described by Dawood *et al.*, who found that 32% of the children aged 2–17 years who were hospitalized because of seasonal influenza during the 2003–2009 influenza seasons were asthmatic: 40% of these were diagnosed as having pneumonia, 14% required admission to an intensive care unit and 3% developed respiratory failure [30]. Finally, a population-based surveillance study by the same authors found that asthmatics who were younger than 18 years were significantly more likely to have pneumonia when hospitalized because of influenza than previously healthy children (odds ratio 1.4) [31].

Pandemic 2009 H1N1 influenza A

The pandemic 2009 H1N1 influenza A virus infection emerged in Mexico in February 2009, and then spread rapidly throughout

the world [32]. The majority of infected patients were children and young adults, and their mortality rate was no higher than that of patients infected by seasonal IV [33], although there have been reports of severe disease and deaths in children [34]. This virus was more likely to cause severe lung injury, especially in patients with risk factors for severe disease (including asthma): epidemiologic studies have found that asthma was a pre-existing clinical condition in 6–50% of the patients infected with pandemic 2009 H1N1 influenza A [35–38]. O’Riordan *et al.* found that children admitted with pandemic 2009 H1N1 influenza A were significantly more likely to have asthma than those with seasonal IV (22 vs 6%) [36]. Hasegawa *et al.* found that the virus increased the risk of lower respiratory tract complications such as asthma, pneumonia and atelectasis in comparison with seasonal IV, and that 32% of the children with an asthma attack caused by the virus required admission to an intensive care unit [39].

Furthermore, in comparison with asthmatic children with seasonal IV, more asthmatic children infected by the pandemic virus required intensive care (22 vs 16%; $p = 0.01$) and were diagnosed as having pneumonia (46 vs 40%; $p = 0.04$) [30]. An association was also found between an asthma diagnosis and markers of the severity of pandemic 2009 H1N1 influenza A, such as mechanical ventilation and mortality [40]. Because healthy children can shed pandemic 2009/H1N1 influenza A virus for up to 2 weeks after the onset of illness [41], these data underline the importance of vigilance in distributing influenza vaccine to asthmatic patients.

Types of influenza vaccines

All health authorities recommend routine influenza immunization for asthmatic children with the aim of reducing complications and mortality in this high-risk category of patients [12–14].

Most of the data concerning vaccinations in asthmatic children relate to injected trivalent inactivated IV (TIV) vaccine and inhaled live-attenuated IV (LAIV) vaccine. There are few data concerning virosomal-adjuvanted TIV vaccine, and none concerning MF-59-adjuvanted TIV or intradermal TIV vaccines. All of the vaccines have the same antigenic composition, which is updated yearly as recommended by WHO on the basis of antigenic changes in the circulating viruses in 94 countries. In some years the antigenic composition may differ for the Southern and Northern Hemisphere [101].

The marketed TIV vaccines are approved for children aged 6 months or older and include split or subunit vaccines [42]. All of the currently available influenza vaccines are prepared by inoculating virus into chicken eggs and contain 15 µg of antigen from each of the three selected strains: two influenza A strains (H1N1 and H3N2) and one influenza B strain [101]. Split vaccines contain virus particles disrupted using detergents, whereas subunit vaccines consist of purified hemagglutinin and neuraminidase proteins, with the other viral components removed. The immune response to the TIV vaccines is mainly based on neutralizing serum antibodies against surface hemagglutinin and neuraminidase viral proteins, which are strain specific [43], whereas the induction of T-cell-mediated immune responses is almost negligible [44]. More recently, adjuvants have been included in some

TIV vaccines in an attempt to improve immunogenicity without increasing serious side effects [45,46].

LAIV vaccine is a cold-adapted, temperature-sensitive trivalent influenza vaccine that can replicate in the cold temperature of the upper airways, but not in the warmer lower airways. It is approved in the USA for intranasal use in healthy children younger than 2 years [47] and has recently been registered but not yet marketed in Europe [102]. It was originally derived from the cold adaptation of an influenza type A strain by means of serial passages in chick kidney cells at progressively lower temperatures, during which multiple highly attenuated and equally immunogenic gene mutants were selected. Each dose of vaccine contains 10^7 viral particles of one type B and two type A (A/H1N1 and A/H3N2) virus strains, and no preservatives are added to the vaccine produced from the vaccine seed strain [47]. LAIV vaccine evokes a more physiologic response than TIV vaccines because, by replicating in the respiratory epithelium of the nasal mucosa, it elicits both mucosal IgA antibody responses and strong cell-mediated immune responses [48]. Moreover, it can induce immune memory, which can modulate the immune response to a more heterosubtypical challenge by affecting both innate and adaptive responses [48].

Trivalent inactivated vaccines for asthmatic children

The major barriers to influenza vaccination in the medical community are the lack of convincing evidence concerning its efficacy in preventing asthma exacerbations, its potentially severe complications and concerns that it may increase airway resistance and induce asthma exacerbations [15,16]. Most of the data concerning the efficacy of TIV vaccine in preventing asthma exacerbations are old, come from methodologically different retrospective studies and are still a matter of debate. In a recent study of 80 asthmatic children aged 3–18 years, current influenza vaccination status was associated with a significant reduction in oral steroid use in the 12 months before the survey and nonsignificantly fewer ER or unscheduled clinic visits in the same period [49].

A retrospective uncontrolled cohort study based on medical and vaccination records during three consecutive influenza seasons found that asthmatic children aged 1–6 years who had received TIV vaccine were protected against exacerbations after controlling for the severity of the underlying disease. The unadjusted rates of asthma exacerbations were higher in the vaccinated group, but after adjusting for asthma severity, the results favored vaccination and showed reductions ranging from 22 to 45% [50]. In another two-season retrospective study of 349 asthmatic children aged 0–12 years, TIV vaccine was associated with a 27% reduction in the occurrence of acute respiratory diseases and was significantly more protective in children younger than 6 years (55%; 95% CI: 20–75%; $p = 0.01$) than in older children (-5%; 95% CI: -81 to 39%; $p = 0.85$) [51].

In a previous Japanese, nonrandomized observational study, the efficacy of split TIV vaccine was documented in 137 children aged 2–14 years with moderate-to-severe asthma during the 1992–1993 epidemics [52]. The children aged 7 years or older showed significant protection against both influenza A/H3N2 and

B infections, but those younger than 7 years were not protected against influenza B [52].

However, other studies have failed to show any benefit against asthma exacerbations. In one randomized, double-blind, placebo-controlled trial, asthmatic children aged 6–18 years received inactivated influenza vaccine (n = 349) or placebo (n = 347) and were followed-up throughout the influenza season. The presence of respiratory virus infections at the time of asthma exacerbations was investigated by means of cultures. There was no difference between the intervention and control groups as 24 of the 47 culture-positive influenza-associated exacerbations occurred in the vaccine group and 18 in the placebo group (although their duration was shorter in the vaccine group) [53]. In a retrospective study, Christy *et al.* selected 400 asthmatic children aged 1–19 years who received influenza vaccine for the 1996–1997 season, and 400 who did not [54]. They found that the vaccinated children were more likely to have clinic visits for asthma and pneumonia (odds ratio 2.9; 95% CI: 2.0–4.1).

Nevertheless, the absence of any clear efficacy of the vaccine in some clinical trials may be due to methodological reasons, including the use of a placebo or not, the size of the population of asthmatic children and the heterogeneous enrolment of asthma cases without adjusting for asthma severity. Finally, the concomitant administration of inhaled steroids may affect antibody responses to vaccine. Using a virosomal-adjuvanted TIV vaccine in a study of 106 asthmatic children aged 3–9 years, the seroprotection rate was high and persistent, ranging from 87–90% after 1 month to 74–77% after 6 months, regardless of steroid therapy [55]. Long *et al.* also found optimal humoral and cell-mediated immune responses to a monovalent pandemic 2009 H1N1 influenza A TIV vaccine in asthmatic children at the time of vaccination and 46 ± 15 days later [56]. However, in a large study, Hanania *et al.* compared the immune responses of 294 subjects aged 3–64 years who were receiving no or low-dose inhaled corticosteroids (<336 γ /day for children) with those of subjects receiving medium- or high-dose inhaled corticosteroids (>336 γ /day) or oral corticosteroids [17]. The immune response to the influenza A antigens was similar in all of the groups, but high-dose inhaled corticosteroids may have reduced the response to influenza B antigens [17]. Similarly, Busse *et al.* found that an unadjuvanted pandemic 2009 H1N1 influenza A TIV vaccine provided equal seroprotection at doses of 15 μ g (90.6%) and 30 μ g (95%) in patients with mild-to-moderate asthma; however, in the patients with severe asthma (defined as a need for 880 μ g/day or more of inhaled fluticasone, systemic corticosteroids or both), seroprotection was slightly lower in the 15- μ g dose group (77.9%), but remained the same in the 30- μ g dose group (94.1%) [57]. Differently, Park *et al.* showed that influenza vaccination can be given safely and effectively to asthmatic children regardless of asthma symptoms or concurrent prednisone therapy when necessary [58]. They also highlighted that vaccination of all moderate-to-severe asthmatic patients visiting clinics or emergency departments would improve the overall vaccination rate significantly [58]. Similarly, Fairchok *et al.* observed that prednisone bursts did not diminish the response of asthmatic

children to the 1996 IV vaccine compared with controls. They concluded that children can be effectively vaccinated against IV while they are receiving prednisone therapy bursts for asthmatic exacerbations [59].

There is more extensive evidence showing that TIV vaccine is safe and well tolerated in asthmatic children. A multicenter, randomized, double-blind, placebo-controlled crossover trial involving 2032 asthmatic children and adults aged 3–64 years found a similarly high frequency of asthma exacerbations during the 2 weeks after vaccination and after a placebo injection (28.8 vs 27.7%) [60]. The results of subgroup analyses based on the severity of asthma, age and other demographic characteristics were similar [60]. In asthmatic adults, Nicholson *et al.* showed that abnormalities in pulmonary function may occur as a complication of influenza vaccination, but the risk of pulmonary complications is small and outweighed by the benefits of vaccination [61]. In a recent Cochrane report, the authors concluded that the pooled results did not show any significant increase in asthma exacerbations in the 2 weeks after TIV vaccination [62].

In addition, virosomal-adjuvanted TIV vaccine can be safely administered to children with even severe egg allergy because it contains less ovalbumin than the amount allowed by the European Pharmacopeia in other influenza vaccines (1 ng vs 1 μ g) [63]. However, a safe maximum threshold of ovalbumin, below which no anaphylactic reactions would be expected, is not known. Moreover, ovalbumin concentration can vary from season to season and from lot to lot for a given vaccine. In general, many studies over the past year have demonstrated that the TIV vaccine is safe in subjects with egg allergy, although significant differences in the ovalbumin content of different vaccines and batches have been described [64–68]. Nevertheless, in subjects with a proven history of egg anaphylaxis, a two-step graded challenge is preferable [65]. In the USA, the current CDC recommendation for influenza vaccine administration varies by the severity of egg allergy [103].

LAIV vaccinations for asthmatic children

Although the data collected in many studies indicate the superiority of LAIV vaccine over TIV vaccine, especially in protecting younger children [46], it is still recommended that asthmatic children are vaccinated with TIV because of concerns that the LAIV vaccine is associated with an increased risk of asthma. In a major randomized, double-blind study by Belshe *et al.*, nearly 8000 children aged 6–59 months without a recent history of wheezing or asthma received LAIV or TIV [69]. There were 54.9% fewer cases of culture-confirmed influenza in the LAIV group (153 vs 338 cases; $p < 0.001$), but within 42 days of the first dose in previously unvaccinated children, there were more wheezing episodes in the LAIV group, especially in children younger than 12 months (3.8 vs 2.1%; $p = 0.08$) [69]. However, because most of the episodes occurred between 2 and 4 weeks after vaccination, and the children were not tested for other respiratory viruses that may have produced an intercurrent illness, it certainly cannot be excluded that wheezing may have been caused by something other than IV. Another large study of children aged 1–17 years also found an increased risk of asthma in those aged 18–35 months

during the 42 days after LAIV administration; however, when only the asthmatic children were analyzed, no association was found between the vaccine and reactive airway disease in the same 42 days [70].

Other studies have shown that LAIV vaccine is more efficacious than TIV vaccine, without any evidence of a significant increase in adverse pulmonary outcomes even in asthmatic children. Redding *et al.* studied 48 children aged 9 years or older with moderate-to-severe asthma who were randomly assigned to receive LAIV vaccine or placebo and found no difference in spirometric values between the treatment and control groups and no difference in the percentage of subjects showing a $\geq 15\%$ reduction in forced expiratory volume in 1 s after vaccination (8% in the treated group vs 4% in the control group; $p = 1.0$) [71].

In a larger randomized, open-label study involving 2229 European asthmatic children aged 6–17 years, the incidence of culture-confirmed influenza was lower in the LAIV than in the TIV group (4.1 vs 6.2%), indicating the 35% greater efficacy of the former (95% CI: 3.9–56%) [72]. Less than 3% of the subjects in both groups reported asthma symptoms in the 15 days after vaccination (2.8% in the LAIV group and 2.7% in the TIV group), and the incidence of asthma during the 42 post-vaccination days was also comparable, with an estimated difference of -0.1% (95% CI: -2.8 to 2.6%). Furthermore, there were no significant between-group differences in mean peak expiratory flow or asthma symptom or night awakening scores.

In another large study, Ashkenazi *et al.* randomized 2187 children aged 6–71 months with recurrent respiratory tract infections to two doses of LAIV or TIV vaccine separated by an interval of 35 ± 7 days [73]. The results showed 52.7% fewer cases of influenza caused by antigenically similar virus strains in the LAIV group (95% CI: 21.6–72.2%), and there were no significant between-group differences in terms of the occurrence of wheezing symptoms associated with influenza-like illness (7.3% in the LAIV group and 6.9% in the TIV group). LAIV vaccine also significantly reduced the number of healthcare provider visits for respiratory tract infections. More recently, Gaglani *et al.* have confirmed that LAIV vaccine is safe in children aged 1.5–18 years with intermittent wheezing: over a 4-year period, there was no increase in wheezing illness or any medically attended acute respiratory illness during the 14 days after LAIV vaccination [74].

Finally, a recent postmarketing study of children younger than 60 months who received LAIV or TIV in two influenza seasons [75] found no evidence of an increase in ER visits or hospitalization

for any diagnosis within 42 days of vaccination in the LAIV group. Thirty-one of the 3045 LAIV-vaccinated children with asthma or wheezing (0.01%) visited the ER or were hospitalized because of a lower respiratory condition within 42 days, and the rates were similar to or lower than those observed in the TIV-vaccinated children with asthma or wheezing.

Expert commentary & five-year view

There has been a disparity in the outcome of studies on whether or not influenza infection increases asthma morbidity and whether or not influenza vaccination helps in preventing asthma exacerbations. Further studies are needed to clarify which patient subgroups are susceptible to potential complications such as asthma exacerbation, increased airway hyper-reactivity and hospitalization, their prevalence and whether they are more frequent in patients with persistent symptoms that require prolonged steroid therapy.

However, vaccination against seasonal influenza remains the most efficient method of prevention in the general pediatric population and in asthmatic patients. Further efforts are needed to increase influenza vaccination coverage among asthmatic children and their families and pediatricians, who often do not receive influenza vaccine because of a lack of awareness of the role of IV in respiratory complications and concerns about the potential clinical risks related to the vaccination.

Evidence from many large studies suggests that influenza vaccinations are unlikely to cause short-term exacerbations of asthma or severe respiratory complications in general and, therefore, they can also be considered safe in asthmatic children. Further studies are needed to evaluate the efficacy, immunogenicity and safety of adjuvanted influenza vaccines, which seem more effective than traditional TIV vaccines and may reduce influenza-related complications in asthmatic patients in the first years of life. Moreover, given the superiority of LAIV vaccine over TIV vaccines in asthmatic children, and its substantially comparable safety, the recommendations for using it in children older than 2 years with intermittent wheezing or asthma should be reassessed.

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Key issues

- There has been a disparity in the outcome of studies on whether or not influenza infection increases asthma morbidity.
- Vaccination remains the most efficient method of preventing seasonal influenza in the general pediatric population and asthmatic patients.
- Evidence from many large-scale studies suggests that influenza vaccination is also safe in asthmatic children.
- Trivalent inactivated influenza vaccines (TIVs) seem to be immunogenic and effective in asthmatic children.
- Further studies are needed to evaluate the efficacy, immunogenicity and safety of adjuvanted influenza vaccines, which seem to be more effective than traditional TIV vaccines and may reduce influenza-related complications in young asthmatic patients.
- Given the superiority of live-attenuated influenza vaccine over TIVs, and its substantially comparable safety, the recommendations for using it in children older than 2 years with intermittent wheezing or asthma should be reassessed.

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