The Role of Influenza Vaccination in Asthmatic Children

Herman J. Bueving and Johannes C. van der Wouden

Introduction

Asthma is the most occurring chronic disease in children. Asthma related genes and environmental factors play a role in the etiology. Nowadays, asthma is regarded as a chronic inflammatory disease of the airways instead of solely a reversible airway obstruction. Asthma is often diagnosed on specific symptoms such as chest tightness, wheezing, dyspnea, and coughing. It is likely that, rather than a single disease entity, asthma consists of related, partially overlapping syndromes. The first symptoms often are experienced before the age of 5. Children with the highest risk have a family history of atopy and/or asthma. Viral infections with symptoms of wheezing acquired in the first year of life may be associated with the risk of developing asthma later on [1]. However, making the diagnosis with a reasonable certainty that is supported by spirometry is only possible from the age of 6 onward. More than 50% of children with a period of wheezing earlier on in life are not diagnosed as having asthma at the age of 6 [2].

The use of rescue and anti-inflammatory medication has largely altered the prospects of asthma patients and has improved their quality of life. Thus, nowadays, most asthma patients lead a normal life without restrictions. Disease control achieved by the asthmatics is an important predictor of the likelihood of complications of the disease [3]. However, asthma exacerbations neither respond to inhaled steroids nor can they substantially be prevented in this way [4, 5]. Only the use of oral corticosteroids seems to be unmistakably effective in case of exacerbations [6, 7].

Children with asthma are believed to be prone to more severe respiratory illness than healthy children when infected with airway pathogens.

Influenza is the only (lower) respiratory tract infection in humans for which a vaccine has existed for decades. The guidelines of most Western and developing countries advise to vaccinate patients with asthma, including children [8].

H.J. Bueving (✉) and J.C. van der Wouden
Department of General Practice, Erasmus MC, University Medical Center Rotterdam,
Burg. s'Jacobsplein 51 3015 CA Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
e-mail: h.bueving@erasmusmc.nl

R. Pawankar et al. (eds.), *Allergy Frontiers: Therapy and Prevention*,
DOI 10.1007/978-4-431-99362-9_37, © Springer 2010

So, administering influenza vaccination to children may prevent the development of asthma and when having asthma may prevent subsequent morbidity, health use, and complications.

In this contribution, we will address the current state of affairs regarding the effect of influenza infection in children and the effectiveness of influenza vaccination in children with asthma.

Influenza: Incidence and Clinical Impact

Viral infections, including influenza, have long been associated with asthma exacerbations.

The influenza viruses are classified in three genera, labeled A, B, and C. Only types A and B cause considerable epidemics. Every year influenza viruses change their genome partially, which is called antigenic drift. Because of different subtypes and antigenic drift, formerly built-up natural immunity or vaccine-initiated immunity will not provide protection throughout subsequent seasons. Three types of influenza A viruses are known to infect humans and transmit from human to human: H1N1, H2N2, and H3N2.

Estimates for the seasonal incidence of influenza vary, depending on the methods used. To reliably assess influenza, the presence of influenza virus should coincide with symptomatic disease. However, in reports on the impact of influenza outbreaks, proxy measures are often used, such as isolated serologic incidence rates, rates of influenza like illness, and complications. Seasonal incidence measured in that way varies from 0–48% [9]. But for discussing the overall impact of influenza and protective measures such as vaccination, one should obviously use an average incidence. The best estimates for an average incidence come from two prospective long-term open population studies. Reported incidences are 4.6% (children aged 0–19 years) respectively 9.5% (children aged 0–5 years) [9–11]. The overall picture is that in healthy children in the majority of cases influenza can be characterized as a self-limiting disease.

The mechanism by which influenza causes asthma exacerbations is not yet known precisely. Postulations vary from direct infection to indirect induction of inflammatory responses [12]. Influenza primarily infects the lower respiratory tract, but also causes systemic symptoms (fever and malaise) and upper respiratory tract (URT) symptoms. Studies in asthmatic children report varying incidences, suggesting that between 30 and 80% of exacerbations are due to a virus [13–15]. Viruses found are rhinovirus, coronavirus, respiratory syncytial virus (RSV), influenza virus, and an assortment of other viruses. Rhinovirus is most frequently associated with exacerbations of asthma.

We found three studies that assessed the incidence of influenza-related respiratory illness in asthmatic children while confirming the presence of influenza by culture. This “hard” incidence was found to be 11.5% for both influenza A and B in 48 unvaccinated children (aged 2–14 years) under the surveillance of an asthma

clinic in Japan [16]. Three children (6%) were hospitalized for pneumonia. In another, community-based, study 18% of schoolchildren (aged 9–11 years) had influenza-related asthma exacerbations but no serious complications occurred [14]. Asthma exacerbations as well as episodes of URT symptoms lasted for about 7 days and did not differ between viruses detected. In the placebo arm of a trial in asthmatic children over two seasons, the incidence of laboratory-confirmed influenza-related asthma exacerbations was found to be 5%, again no serious complications occurred [17]. Influenza-related URT episodes lasted 8 days whereas influenza-related asthma exacerbations lasted 11 days. Incidences in children with asthma as reported here are between 5 and 18%. Although the one small study, with children under the surveillance of an asthma clinic, found a hospitalization rate of 6%, no complications were found in the above mentioned community-based study on asthmatic children not in the placebo arm of the study that recruited patients in general practice.

Of all viral induced exacerbations, influenza accounted for 3.6% respectively 2% of lower respiratory tract (asthma) episodes [14, 15]. In conclusion, the incidence of influenza-related asthma exacerbations in children and its complications have not been extensively investigated.

However, an observational study in children of 1–14 years over several seasons did not find excess morbidity diagnosed as asthma exacerbations [18].

The consequences of influenza infection in asthmatic children can be a rise in morbidity (e.g., exacerbations), more physician visits, the use of medication and hospitalizations or death. As some of these consequences are rare, data are only available from large observational studies [19]. Furthermore, quality of life may also be affected [15]. Because influenza can cause all kinds of illness in children, whether healthy or not, only part of the consequences of infection will be associated with asthma.

Availability and Immunogenicity of Vaccines

Two main types of influenza vaccine are available for the prevention of influenza: the trivalent inactivated vaccine (TIV) for parenteral use and the trivalent cold adapted live attenuated vaccine (CAIV) for intranasal administration. Both vaccines are highly immunogenic and induce adequate immune response with a high level of seroprotection. Inactivated vaccine has been licensed for children with asthma, while cold adapted vaccine has not yet been licensed for asthmatic patients.

Unlike vaccination, natural infections with influenza provide an immune response on several levels, i.e., secretory antibodies (IgA) present at the mucosal surface, serum antibodies (IgG) and stimulate T-cells directed at the influenza virus. Immune resistance is a lifelong one against the specific strain and provides partial protection against antigenic drifts. Inactivated vaccine only produces serum protection while live attenuated vaccine mimics natural infection better by also providing mucosal antibodies. There is limited evidence that live attenuated vaccines also give some protection against antigenic drifts of the influenza virus [20].

Although efforts are being made to develop an influenza vaccine with a broader spectrum and long-lasting immune response, research has only recently started, and success is not guaranteed [21].

Adverse Effects of Influenza Vaccination

Safety and tolerability of inactivated vaccine in children with asthma, especially regarding exacerbations of asthma, are nowadays well established [22–24]. Cold adapted live attenuated vaccine also is generally well tolerated in children and adolescents with asthma [25, 26]; nevertheless, an increased risk of asthma/reactive airway disease in children younger than 36 months of age is of potential concern [27]. Even egg allergy should no longer be an absolute contraindication for influenza vaccination [28].

Effectiveness

The effect of inactivated influenza vaccination in preventing clinical symptoms is a much-debated item [29]. Over the past years, live attenuated vaccines have been developed, tested, and used for intranasal administration. The less invasive route, of course, is a benefit in administering the vaccine. Besides, there is hope that the induced mucosal IgA immune response will provide a better protection against infection. In a large multicenter trial, a direct comparison between intramuscular inactivated and intranasal live attenuated vaccine in children with asthma [26] was made in which the live attenuated vaccine was 53% more efficacious in preventing influenza infection. However, as the authors correctly state, because there was no placebo group, the absolute efficacy cannot be calculated. A systematic review indicates that vaccines can have an efficacy of 65% for TIV and 79% for CAIV in reducing serologically confirmed cases of influenza in healthy children, i.e., by comparing pre and postseason antibody titers. However, when using symptom-based outcomes, i.e., influenza-related disease, the vaccines showed an efficacy of only 28% for inactivated and 38% for live attenuated vaccine [30]. Moreover, in case of a mismatch between the vaccine composition and the natural virus, efficacy probably will be much lower or absent.

In asthmatics, few studies shed light on the clinical effect of inactivated influenza vaccine (Table 1). Observational studies report varying and sometimes even contradictory outcomes. In a retrospective cohort study, effectiveness was only reached for severe asthmatics in a separate analysis, whereas analysis of the whole group revealed an increase of asthma exacerbations [31]. In another study, effectiveness on physician diagnosed acute respiratory disease episodes including otitis media was only significant in asthmatic children under 6 years of age and no effectiveness was found on any children [32]. A third retrospective cohort study showed

Table 1 Clinical effectiveness of inactivated influenza vaccine in asthmatic children

Article	Age in years	Study type	Main outcome	Season(s) and key results vaccine/ placebo	Peculiarities
[16]	2–14	Non-randomized clinical trial	Febrile episodes,influenza confirmed by culture	Vaccine effectiveness 1992–1993 0.49	No differences in the severity or frequency of asthma attacks found, three hospitalizations in control and two in vaccine group
[30]	1–6	Retrospective cohort	Asthma exacerbations evaluated in emergency department or hospital	Adjusted incidence rate ratio results severe asthmatics only 1993–1994 0.78 (NS)[a] 1994–1995 0.59 1995–1996 0.65	Results total vaccine group significant increase in exacerbations in all seasons
[31]	1–12	Retrospective cohort	Combined endpoint: influenza like illness, pneumonia, bronchitis, bronchiolitis, asthma exacerbations, otitis media	Subgroup analysis 1–6 years 1995–1996 1996–1997 OR 0.45	Results all children showed no significant effect
[32]	0–12	Retrospective cohort	Clinic visits, emergency department (ED) visits, hospitalizations for asthma	1996–1997 OR clinic visits 2.9 OR ED visits 2.0 OR hospitalizations 1.9 (NS)[a]	
[17, 23]	6–18	Randomized controlled trial	Children with asthma exacerbations,influenza confirmed by culture or PCR	1999–2000 2000–2001 OR 1.24 (NS)[a]	
[15]	6–18	Randomized controlled trial	Minimal important difference in quality of life compared with baseline in influenza positive weeks,influenza confirmed by culture or PCR	1999–2000 2000–2001 OR 0.43 (NS)[a]	Some distinct effects on the quality of life

[a]*NS* = Not Significant

that children in the vaccine group unexpectedly had a significantly increased risk of asthma related clinic visits and ED visits [33].

Although in one small prospective non-randomized study in a tertiary asthma clinic center a positive effect was found on febrile episodes, clinical efficacy for asthmatics has not been established yet at the highest level of evidence [23]. For asthmatic children in a prospective randomized controlled study, no positive clinical effect of vaccination on asthma exacerbations was found [17]. However, a distinct effect on the quality of life in influenza-related episodes in asthmatic children was reported [15].

In conclusion, of the few studies in this area, most show a suboptimal design, and uncertainty remains about the degree of protection vaccination offers against influenza-related symptoms such as asthma exacerbations.

Vaccine Uptake in Children with Asthma

According to most national and international guidelines, people with moderate or severe asthma should be vaccinated [8]. However, definitions of asthma vary because of differences in the standardization of severity subcategories and because of differences in the views of physicians and patients on the severity of the disease. Besides, asthma in individual patients varies in degree of severity over the years, so when asthma patients have been vaccinated once, it does not mean that they will always need to be vaccinated. Asthma is a disease with an increasing incidence and is, both in absolute and relative numbers, one of the major disease categories to receive influenza vaccination, especially in children [34]. Despite the proven absence of serious side effects, vaccination uptake in asthmatic children, though differing worldwide, is far from optimal [35, 36]. Fear that vaccination causes illness and doubts about the benefits and effectiveness of influenza vaccination, are still, despite of vast opposite evidence, important reasons for patients and physicians to refrain from vaccination [37].

Cost Effectiveness of Influenza Vaccination

When determining cost effectiveness of influenza vaccination, several seasons should be considered and included in the analysis of cost-effectiveness. However, an overall incidence of influenza-related illness between 4.6 and 9.5% in children [9–11] as found before or 5% [17] or even 18% [14] as found in asthmatic children is a difficult starting point. Using these figures, disregarding clinical relevance and assuming protective effectiveness of vaccination to be 100%, 22 children (0–19 years), 11 children (0–5 years),or 20 children (6–18 years) respectively six children (9–11 years) with asthma would have to be vaccinated in order to prevent influenza-related illness in one child. Because the effectiveness of influenza vaccination is of

course lower than 100% and clinical relevance has to be taken into account, the numbers needed to treat will be higher than calculated here. For instance, in healthy subjects, a clinical effectiveness of the vaccine of just 28% for TIV and 38% for CAIV was found [30]. When extrapolating, this fact alone at least triples the above mentioned numbers needed to treat.

In asthmatics, there is no evidence about the degree of protection vaccination provides against influenza-related asthma exacerbations [23]. When assuming a 5% incidence and taking into account the upper boundary of the confidence interval in this study, a maximum protection rate of 34% can be derived [17]. Thus, vaccinating 59 children with asthma could prevent only one influenza-related asthma exacerbation.

Conclusion

Although intuitively the best option for preventing influenza and subsequent clinical deterioration in children with asthma seems to be vaccination, no unequivocal evidence for its effectiveness is present. CAIV could prove to be a better alternative than the current TIV, when it is released for asthmatic children.

Although from a pathophysiological point of view influenza is believed to be a threat for asthmatic children, very few data are available about this subject. Future research should first of all focus on a long-term observational research, spanning multiple seasons, to determine the real impact of influenza in children with (and without) asthma. Regarding vaccination, CAIV seems to be an improvement, although it still has to be delivered yearly, a huge logistic operation. Future research into influenza vaccination will understandably be focussed on broad-spectrum and long-lasting vaccines. If this goal is ever reached, it will make preventing influenza infections much easier.

References

1. Kiley J, Smith R, Noel P (2007) Asthma phenotypes. Curr Opin Pulm Med. 13:19–23
2. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ (1995) Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 332:133–138
3. Johnston NW, Sears MR (2006). Asthma exacerbations. 1: epidemiology. Thorax 61:722–728
4. McKean M, Ducharme F (2000) Inhaled steroids for episodic viral wheeze of childhood. Cochrane Database Syst Rev. CD001107
5. Edmonds ML, Camargo CA, Jr., Pollack CV, Jr., Rowe BH (2003) Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev. CD002308
6. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW (2001) Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev. CD002178

7. Weinberger M (2003) Treatment strategies for viral respiratory infection-induced asthma. J Pediatr. 142:S34–S38
8. van Essen GA, Palache AM, Forleo E, Fedson DS (2003) Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. Vaccine 21:1780–1785
9. Bueving HJ, van der Wouden JC, Berger MY, Thomas S (2005) Incidence of influenza and associated illness in children aged 0–19 years: a systematic review. Rev Med Virol. 15:383–391
10. Monto AS, Koopman JS, Longini IM, Jr. (1985) Tecumseh study of illness. XIII. Influenza infection and disease, 1976–1981. Am J Epidemiol. 121:811–822
11. Neuzil KM, Zhu Y, Griffin MR, Edwards KM, Thompson JM, Tollefson SJ, Wright PF (2002). Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis. 185:147–152
12. Tan WC (2005). Viruses in asthma exacerbations. Curr Opin Pulm Med. 11:21–26
13. Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE (1974) Viruses as precipitants of asthmatic attacks in children. JAMA 227:292–298
14. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, et al. (1995) Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 310:1225–1229
15. Bueving HJ, van der Wouden JC, Raat H, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Osterhaus AD, Rimmelzwaan GF, Molken MR, Thomas S (2004) Influenza vaccination in asthmatic children: effects on quality of life and symptoms. Eur Respir J. 24:925–931
16. Sugaya N, Nerome K, Ishida M, Matsumoto M, Mitamura K, Nirasawa M (1994) Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. JAMA 272:1122–1126
17. Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, Rutten-van Molken MP, Thomas S, van der Wouden JC (2004) Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. Am J Respir Crit Care Med. 169:488–493
18. Fleming DM, Pannell RS, Elliot AJ, Cross KW (2005) Respiratory illness associated with influenza and respiratory syncytial virus infection. Arch Dis Child. 90:741–746
19. Belshe R, Lee MS, Walker RE, Stoddard J, Mendelman PM (2004) Safety, immunogenicity and efficacy of intranasal, live attenuated influenza vaccine. Expert Rev Vaccines. 3:643–654
20. Hampson AW, Osterhaus AD, Pervikov Y, Kieny MP (2006) Report of the second meeting on the development of influenza vaccines that induce broad-spectrum and long-lasting immune responses, World Health Organization, Geneva, Switzerland, 6–7 December 2005. Vaccine 24:4897–4900
21. The American Lung Association Asthma Clinical Centers (2001) The safety of inactivated influenza vaccine in adults and children with asthma. N Engl J Med. 345:1529–1536
22. Cates CJ, Jefferson TO, Bara AI, Rowe BH (2004) Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev. CD000364
23. Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, Rutten-van Molken MP, Thomas S, van der Wouden JC (2004) Does influenza vaccination exacerbate asthma in children? Vaccine 23:91–96
24. Redding G, Walker RE, Hessel C, Virant FS, Ayars GH, Bensch G, Cordova J, Holmes SJ, Mendelman PM (2002) Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 21:44–48
25. Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, Oymar K, Garcia ML, Krygier A, Costa H, Heininger U, Pregaldien JL, Cheng SM, Skinner J, Razmpour A, Saville M, Gruber WC, Forrest B (2006) Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 25:860–869

26. Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, Walker R, Hessel C, Cordova J, Mendelman PM (2004) Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J. 23:138–144
27. Zeiger RS (2002) Current issues with influenza vaccination in egg allergy. J Allergy Clin Immunol. 110:834–840
28. Jefferson T (2006) Influenza vaccination: policy versus evidence. BMJ 333:912–915
29. Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C (2005) Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. Lancet 365:773–780
30. Kramarz P, Destefano F, Gargiullo PM, Chen RT, Lieu TA, Davis RL, Mullooly JP, Black SB, Shinefield HR, Bohlke K, Ward JI, Marcy SM (2001) Does influenza vaccination prevent asthma exacerbations in children? J Pediatr. 138:306–310
31. Smits AJ, Hak E, Stalman WA, van Essen GA, Hoes AW, Verheij TJ (2002) Clinical effectiveness of conventional influenza vaccination in asthmatic children. Epidemiol Infect. 128:205–211
32. Christy C, Aligne CA, Auinger P, Pulcino T, Weitzman M (2004) Effectiveness of influenza vaccine for the prevention of asthma exacerbations. Arch Dis Child. 89:734–735
33. Erhart LM, Rangel MC, Lu PJ, Singleton JA (2004) Prevalence and characteristics of children at increased risk for complications from influenza, United States, 2000. J Pediatr. 144:191–195
34. Daley MF, Beaty BL, Barrow J, Pearson K, Crane LA, Berman S, Kempe A (2005) Missed opportunities for influenza vaccination in children with chronic medical conditions. Arch Pediatr Adolesc Med. 159:986–991
35. Gnanasekaran SK, Finkelstein JA, Hohman K, O'Brien M, Kruskal B, Lieu T (2006) Parental perspectives on influenza vaccination among children with asthma. Public Health Rep. 121:181–188
36. Lin CJ, Nowalk MP, Zimmerman RK, Ko FS, Zoffel L, Hoberman A, Kearney DH (2006) Beliefs and attitudes about influenza immunization among parents of children with chronic medical conditions over a two-year period. J Urban Health. 83:874–883
37. Neuzil KM, Wright PF, Mitchel EF, Jr., Griffin MR (2000) The burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr. 137:856–864