Effects of inactivated influenza vaccine on respiratory illnesses and asthma-related events in children with mild persistent asthma in Asia

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Summary

Background: **Acute asthmatic exacerbation and readmission may be associated with severe influenza infection and asthmatic children are a priority group for influenza vaccination. To date, our study is the first to evaluate the outcome of the influenza vaccine in asthmatic Asian children.**

Objective: **To analyze the outcomes of inactivated influenza vaccine in children with mild persistent asthma**

Methods: **A cross sectional non-randomized study was performed on 93 mild persistent asthmatic children who attended the Pediatric Allergy clinic between June 2012 in Chiang Rai Hospital and August 2013. Forty eight patients were immunized with 2 doses of inactivated influenza vaccine at one month interval. Respiratory illnesses and asthma-related events were compared between the immunized and the un-immunized groups.**

Results: **The two study groups had similar demographic and clinical characteristic except with regards to eczema, including asthma controllers and skin prick testing results. One year after the vaccine was administered, the immunized group had significantly reduced acute respiratory tract illnesses, asthma exacerbations, ER visits, bronchodilator usage and systemic steroid administrations. Hospitalizations (*p* <0.001) and their duration (*p* <0.034) were also reduced in the immunized group.**

Conclusions: **Immunization of inactivated influenza vaccine in children with mild persistent asthma decreased respiratory illnesses and asthma-related events. *(Asian Pac J Allergy Immunol 2015;33:3-7)***

Keywords: *inactivated influenza vaccine, asthma control, mild persistent asthma, children, Thailand*

Abbreviations
Der f = *Dermatophagoides farinae*
Der p: = *Dermatophagoides pteronyssinus*
HDM: = House dust mite

Introduction

Influenza virus infections affect all ages, and children with chronic underlying conditions such as asthma are among the most susceptible. These children are vulnerable not only to the acute febrile respiratory illness caused by influenza, but also to complications, such as pneumonia, and severe exacerbation of asthma. An association between viral respiratory infections and exacerbation of acute asthma has been noted in several observational studies.[1, 2] Approximately 80% of exacerbation of asthma were precipitated by influenza A infections.[1] Griffin MR, et al.[3] found that the admission rate for acute respiratory illness/fever in children younger than 5 years of age in the surveillance areas was 180 per 10,000 children. In this study, respiratory viruses, among which 30% were respiratory syncytial viruses, were responsible for 61% of the hospitalizations, and one-third of children hospitalized had high risk conditions, primarily asthma (24%). Influenza viruses are orthomyxoviruses exhibiting 3 antigenic types (A, B, and C.). Influenza epidemic episodes are usually caused by types A and B. Influenza virus is spread from person to person by inhalation of small particle aerosols, direct contact or fluids more efficiently than other respiratory tract viruses such as RSV,

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parainfluenza[4-6] and rhino virus.[7] Influenza virus infection may result in life threatening illness, especially in young children. In Thailand, influenza virus is the etiologic agent of 30% of acute respiratory tract infections[6] and influenza-related pneumonia was responsible for 300 fatalities in 2009.[8] Annual influenza vaccine is recommended for children 6 months of age and older with one or more specific risk factors; such as asthma, chronic pulmonary diseases, cardiac diseases, immunosuppressive therapy, chronic renal dysfunction, chronic metabolic diseases and pregnancy.[9]

Asthma is a common chronic underlying condition in children, and the use of anti-inflammatory agents on a regular basis decreases emergency room visits and hospital admissions.[10] Influenza infection in patient with asthma may increase mortality and morbidity and patients with these predispositions were advised to receive influenza A/H1N1 vaccine during the 2009 pandemic.[11] While the influenza A/H1N1 vaccine is reported to be safe and effective,[2,13] its coverage in the population was low worldwide. For instance, in the USA, only 20.3% of population received the vaccine.[14] Nearly one tenth of individuals living in France were immunized against influenza A/H1N1 virus during the pandemic.[15] In England, only 37.1% of the patients in risk groups, including pregnant women, accepted to be vaccinated.[16] Although the WHO has recommended influenza vaccine administration for asthma control,[9] no study assessing the effectiveness of influenza vaccine in controlling asthma in Asian children has been yet conducted. Our study was undertaken to analyze the effectiveness of influenza vaccine administration in asthmatic children in relation to respiratory illnesses and asthma-related events.

Methods

A cross sectional non-randomized prospective cohort study was performed in mild persistent asthmatic children between the age of 1 and 14 years who met all the following criteria: had at least four episodes of wheezing during the previous year, positive modified API[17] (Asthma Predictive Index), using low-dose inhaled budesonide[18,19] (100-200µg per day in patient aged ≤ 5 years, 200-400 µg per day in patient aged > 5years) or oral montelukast 5 mg per day.[18,19] The Immunized group comprised children who received 2 doses of influenza vaccine intramuscularly at 1 month interval. The Unimmunized group comprised asthmatic children whose parents denied influenza vaccination. The outcome parameters used to assess the effectiveness of the vaccine at reducing respiratory illnesses and asthma-related events included the rate of acute respiratory tract illness, asthmatic exacerbations, emergency room visits, hospitalizations, length of stay for hospitalization, bronchodilator usage and systemic steroid. Both groups were followed up every 3 months at the outpatient asthma clinic, Department of Pediatric, Chiang Rai Hospital. All patients or guardians gave informed consent before enrollment. The study was approved by the Ethical Committee of the Faculty of Medicine, International Coordination Committee of National Human Rights Institutions.

Statistical analysis

Descriptive statistical methods (mean±SD, median, and frequency) were applied. Chi-squared tests were performed to analyze frequencies differences among groups for categorical response variables. Levels of variation in continuous response variables were compared with t-tests. Statistical significance was reached when $p < 0.05$. All statistical analyses were performed using STATA version11.

Results

Of 93 asthmatic children, 48 children were immunized with influenza vaccine, 46 children were not. The rate of immunization were 37.5% (18/47) and 62.5% (30/46) in children < 6 years and 6-14 years of age, respectively. The two study groups did not differ in their demographic characteristics ($p > 0.05$) except for eczema rate. ($p = 0.048$). Clinical characteristics such as: exposure from birth, eosinophilia, parental asthma, co-morbid allergic rhinitis, asthma controller (inhaled budesonide, oral montelukast), results of skin prick test for HDM (*Der p and Der f*), American Cockroach, cat and dog danders were similar between groups (Table 1). During the 1-year-follow up period, all outcome parameters in immunized group had improved significantly, compared to the unimmunized group (Table 2).

Discussion

Influenza infections may cause life threatening illnesses to a greater extent in young children as compare to adults. In patients with asthma, despite effective controllers, asthma exacerbations may be triggered by respiratory tract infection such as, RSV, influenza, parainfluenza,[4-6] rhino virus[7] and bacterial sinusitis.[20] The incidence of readmission

Table 1. Demographic and asthma characteristic data of the patients

Characteristics	Immunized Children (N = 48) Number/(%)	Unimmunized Children (N = 45) Number/(%)	*p*-value
Male Sex	34 (70.8)	30 (66.7)	0.823
Tobacco-smoke exposure from birth	12 (25.0)	12 (26.7)	1.000
Eosinophils ≥ 4 %	23 (47.9)	14 (31.1)	0.138
Eczema	4 (8.3)	11 (24.4)	0.048
Allergic Rhinitis	40 (83.3)	36 (80.0)	0.790
Parental asthma	13 (27.1)	14 (31.1)	0.820
Low dose inhaled budesonide	30 (62.5)	28 (62.2)	1.000
Oral montelukast	18 (37.5)	17 (37.8)	1.000
Positive Skin Prick Test for			
Mite Der p	39 (81.3)	37 (84.1)	0.788
Mite Der f	38 (79.2)	34 (77.3)	1.000
American Cockroach	23 (47.9)	19 (43.2)	0.680
Cat	11 (22.9)	5 (11.4)	0.175
Dog	6 (12.5)	5 (11.4)	1.000

Table 2. The outcome parameters at 1 Year

Outcome parameters in the past year	Immunized Children (N = 48) mean (SD)	Unimmunized Children (N = 45) mean (SD)	*p*-value
Number of respiratory tract illness	2.2 (2.1)	6.9 (3.9)	<0.001
Number of wheezing episodes	1.6 (1.6)	6.2 (3.9)	<0.001
Number of emergency room visits for asthma exacerbations	0.4 (0.9)	2.2 (2.6)	< 0.001
Number of hospitalizations	0.2 (0.6)	1.3 (1.5)	< 0.001
Number of prednisolone administrations	0.1 (0.3)	1.1 (1.2)	< 0.001
Number of bronchodilator administrations	1.6 (1.6)	6.2 (3.9)	< 0.001
Average days for hospitalizations	5.3 (2.6)	7.2 (5.0)	0.034

for asthma varies from 15% in France[21] and Rhode Island (USA)[22] up to 40% in Oulu (Finland).[23] Readmission has an impact on children's and parents' quality of life and economy. Cost of hospitalization accounts for 54 % of direct expenditures for medical care for asthmatic children 17 years of age and younger.[24] Forty-three percent of the economic impact of asthma is associated with emergency department visits, hospitalization, and death.[24] Visitsunthorn et al.[25] had studied the risk factors associated with readmission following acute asthmatic attacks in children who were admitted during the 2-year study period and concluded that the factor that decreased the chances of readmission was a history of influenza vaccination (OR 0.24; 95% CI 0.16-0.36). Asthma has been shown to be associated with an increased risk to contract novel H1N1 influenza (H1N1) infection among children during the 2009 pandemic. However, little is known about the role of asthma in severity of H1N1 infections. Salas et al.[26] had conducted a population-based case–control study to determine the association between asthma and other atopic conditions and severity of H1N1 infections. Cases were all Olmsted County residents admitted to the hospital within a week of a positive test for H1N1. Asthma was ascertained using predetermined criteria. They concluded that asthma may be associated with severe H1N1 infection. Individuals with asthma, especially those with poorly controlled asthma, may have more severe H1N1 infection than non-asthmatics. In addition to timely influenza vaccination for asthmatics, consideration for prophylactic treatment for unimmunized asthmatics with significant exposure to influenza and immunized asthmatics with early flu-like symptoms should be given. Associated factors regarding vaccine refusal in the general population have been reported in many studies, however the reasons behind refusals for asthmatic children have not yet been identified. Buyuktiryakia et al.[27] aimed to investigate influenza A/H1N1 virus vaccine acceptance for children with asthma, to determine the attitudes and beliefs of parents concerning

influenza A/H1N1 disease and vaccine and to identify the association of asthma control parameters with vaccination. They concluded that beliefs and attitudes rather than asthma control parameters influenced parental decisions for immunization. Understanding the underlying determinants for refusing the vaccine will help to improve vaccine campaigns in prevision of a future outbreak. To date, no study investigated the effects of inactivated influenza vaccine on respiratory illnesses and asthma-related events in children with asthma in Asia. Most published researches on the outcome of influenza inactivated vaccine were based on data from the Western countries and their results might not be entirely applicable to the Asian population. Our study is the first to evaluate the outcome of inactivated influenza vaccine in asthmatic children in Thailand. Noteworthy, we report that for almost half of the asthmatic patients included in our study, their parents refused immunization even after having been advised by the physicians.

Prevalence of allergic rhinitis, which is a co-morbid of asthma, was high in these study groups.(80-83.3%) which was closed to the report from Shah et al (80%).[28] Prevalence of eczema, another co-morbid of asthma, was low (8.3-24.4%) similar to that was reported by Vichyanond (18.8%).[29] High prevalence of positive skin prick testing for aeroallergen; such as, *Der p, Der f*, American Cockroach but low for cat and dog dander which were similar with the report by Kongpanichkul et al.[30]

Limitations

Our study was a non-randomized one and the sample size was small due to limited budget in support to free influenza vaccine. Another limitation was the lack of information related to other confounding factors in asthmatic exacerbation such as compliance and controller usage, other virus and bacterial infections, pollution, as well as emotional conditions in patient.

Conclusion

Our study showed that complete influenza vaccine immunization is beneficial for children with mild persistent asthma as it can prevent acute respiratory tract infections, decrease asthma exacerbations and hospitalizations. An annual, well-organized, computerized multi-component strategy should be implemented for optimizing influenza immunization in the high-risk population including asthmatic patients.

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Conflict of interest

The authors declare that they have no relevant conflicts of interest.

References

1. Minor TE, Dick EC, Baker JW, Ouellette JJ, Cohen M, Reed Ce. Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis. 1976;113:149-53.
2. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. Association of viral and bacterial respiratory infection with exacerbations of wheezing in young asthmatic children. Chest. 1973(suppl);63:43S.
3. Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD, et al. Epidemiology of Respiratory Infections in Young Children: Insights from the New Vaccine Surveillance Network. Pediatr Infect Dis J.2004; 23:S188–92.
4. Sigurs N, Gustafsson PM, Bjrnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J RespirCrit Care Med.2005;17:137-41.
5. Iwane MK, Edwards KM, Szilagyi PG, Walker FJ, Griffin MR, Weinberg GA, et al. Population- based surveillance for hospitalizations association with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics. 2004;113:1758-64.
6. Clague B, chamany S, Burapat C, Wannachaiwong Y, Simmerman JM, Dowell SF, et al. A household survey to assess the burden of influenza in rural Thailand. Southeast Asian J Trop Med Public Health. 2006;37:488-93.
7. Palmenbefg AC, Rathe JA, Liggett SB. Analysis of the complete Genome sequences of human Rhinovirus. J Allergy Clin Immunol. 2010; 125:1190-9.
8. Simmerman JM, Chittaganpitch M, Levy J, Chantra S, Maloney S, Uyeki T, et al. Incidence, seasonality and mortality associated with influenza pneumonia in Thailand: 2005-2008. PLoS One.2009;11:4.
9. Centers for diseases Control and Prevention(CDC).Prevention and Control of influenza with vaccines recommendations of the Advisory Committee on Immunization Practices. MMWR Recommendations and Rep.2010;59:1-62.
10. Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics, 16th ed. Philadelphia: WB, Saunders;2000.
11. Rank MA, Li JT. Clinical pearls for preventing, diagnosing, and treating seasonal and 2009 H1N1 influenza infection in patients with asthma. J Allergy Clin Immunol. 2009; 124:1123–6.

12. Wu J, Xu F, Lu L, Lu M, Miao L, Gao T, et al. Safety and effectiveness of a 2009H1N1 vaccine in Beijing. N Engl J Med. 2010; 363:2416–23.
13. Busse WW, Peters SP, Fenton MJ, Mitchell H, Bleecker ER, Castro M, et al. Vaccination of patients with mild and severe asthma with a 2009 pandemic H1N1influenza virus vaccine. J Allergy Clin Immunol. 2011;127:130–7.
14. Centers for Disease C. Prevention. Interim results: Influenza A/H1N1 2009monovalent vaccination coverage—United States, October–December 2009.MMWR Morb Mortal Wkly Rep, 59. Centers for Disease C 2010. p.44–8.
15. Bone A, Guthmann JP, Nicolau J, Levy-Bruhl D. Population and risk group uptake of H1N1 influenza vaccine in mainland France 2009–2010: results of a national vaccination campaign. Vaccine. 2010; 28:8157–61.
16. Department of Health. Pandemic H1N1 vaccine uptake figures for England by SHA and PCT[Internet]._2010._[cited 2014March1]._ Available from: www.dh.gov.uk/prod_consum_dh/groups/dh_ digitalssets @en/@ps/documents/digitalasset/dh_114212.pdf
17. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J RespirCrit Care Med.2000; 162:1403-6.
18. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol. 2004; 114:1282-7.
19. Global Initiative for Asthma Executive Committee. Global Strategy for Asthma Diagnosis and Prevention Updated 2010[Internet]. [Place unknown]: Global Initiative for Asthma; c2010 [cited 2011 Oct 7]. Available from: http://www.ginasthma.org/pdf/ GINA_Report 2010.pdf
20. Visitsuntorn N, Balankura K, Keorochana S, Habanananda S, Vichyanond P, Tuchinda M. Sinusitis in Thai asthmatic children. Asian Pac J Allergy Immunol.1992; 10:5-10.
21. Delmas MC, Marguet C, Raherison C, Nicolau J, Fuhrman C. Readmissions for asthma in France in 2002-2005.Rev Mal Respir. 2011; 28:e115-22.
22. Liu SY, Pearlman DN. Hospital readmissions for childhood asthma: the role of individual and neighborhood factors. Public Health Rep. 2009; 124:65-78.
23. Korhonen K, Dunder T, Klaukka T, Reijonen TM, Korppi M. Use of inhaled corticosteroids decreases hospital admissions for asthma in young children. World J Pediatr. 2009; 5:177-81.
24. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. N Engl J Med. 1992; 326:862–6.
25. Visitsunthorn N, Lilitwat W, Jirapongsananuruk O, Vichyanond P. Factors affecting readmission for acute asthmatic attacks in children. Asian Pac J Allergy Immunol. 2013;31:138-41
26. Santillan Salas CF, Mehra S, Pardo Crespo MR, Juhn YJ. Asthma and severity of 2009 novel H1N1 influenza: a population-based case–control study. J Asthma.2013;50:1069–76.
27. Buyuktiryaki B, Soyer OU, Erkocoglu M, Dogan A, Azkur D, Kocabas CN, et al. What a pandemic teaches us about vaccination attitudes of parents Of children with asthma. Vaccine. 2014:32;2275-80.
28. Shah A, Pawankar R. Allergy rhinitis and co-morbid asthma: perspective from India—ARIA Asia-Pacific Work-shop report. Asian Pac J Allergy Immunol. 2009;27:71-7.
29. Vichyanond P, Jirapongsananuruk O, Visitsunthon N, Tuchinda M. Prevalence of asthma, rhinitis and eczema in children from the Bangkok Area using the ISAAC (International Study for Asthma and Allergy in Children) questionnaires. J Med Assoc Thai. 1998;81:84-175.
30. Kongpanichkul A, Vichyanond P, Tuchinda M. Allergy skin test reactivity among asthmatic Thai children. J Med AssocThai. 1997;80:69-75.