Effects of Influenza Vaccine in Children with Moderate to Severe Allergic Rhinitis

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Background: *Wheezy episodes in moderate to severe allergic rhinitis patients may be associated with influenza infection. Children with allergic airway diseases are a priority group for influenza vaccinations. To date, our study is the first to evaluate the outcome of the influenza vaccine in moderate to severe allergic rhinitis children.*

Objective: *To analyze the effects of inactivated influenza vaccine in children with moderate to severe allergic rhinitis on influenza-like illness (ILI) and wheezy episode after ILI.*

Material and Method: *A cross sectional non-randomized patient preference study was performed on 314 children with moderate to severe allergic rhinitis who attended the Pediatric Allergy clinic between June 2015 and July 2016 in Chiang Rai Hospital. One hundred sixty two patients were immunized with an influenza vaccine (quadrivalent influenza vaccine). ILIs and wheezy episodes were compared between the immunized and the un-immunized groups. The present study compared between the age groups of younger children (younger than 7 years) and older children (7 to 15 years).*

Results: *The two study groups had similar demographic and clinical characteristics in younger and older children except with regards to co-morbid asthma, snoring child, positive skin prick test to American cockroach in younger children, and family incomes, co-morbid asthma, rhino-sinusitis in older children including allergic rhinitis controllers usage and skin prick testing results. One year after the vaccine was administered, the immunized group had significantly reduced ILIs, wheezy episodes, and severity of asthmatic events in children with co-morbid mild persistent asthma (ER visits, medical usages for wheezy episode, hospitalizations, and their duration) in both younger and older children ($p<0.05$).*

Conclusion: *Immunization of inactivated influenza vaccine is beneficial in children with moderate to severe allergic rhinitis, it can reduce ILIs, wheezy episodes, and severity of asthmatic events in children with co-morbid mild persistent asthma.*

Keywords: *Quadrivalent influenza vaccine, Wheezy episodes, Moderate to severe allergic rhinitis, Children, Thailand*

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Allergic rhinitis is the most common allergic disease in children, it impacts the quality of life and finances[1,2]. The prevalence has increased dramatically from 17.9% according to the survey[3] in 1990 to 44.2% according to the International Study of Asthma and Allergies in Childhood (ISAAC) phase I study in 2002[4]. Typical symptoms include sneezing, rhinorrhea, postnasal drip, nasal obstruction, and itching[5]. The diagnosis was confirmed by clinical signs and symptoms with positive skin prick test/positive specific IgE for aeroallergen[5]. It classified the type as "intermittent" and "persistent" symptoms according to the Allergic Rhinitis and its Impact on Asthma guideline (ARIA)[1,6,7]. The severity was divided into mild and moderate to severe, and symptoms included one or more of these symptoms such as sleep and or activity disturbance, bothersome, and complications[1,7]. The complications included of uncontrolled asthma[8,9], rhino-sinusitis[10,11], allergic conjunctivitis, snoring, and otitis media[12]. Most of the Thai children had moderate to severe allergic rhinitis[13,14].

Allergic rhinitis is a chronic inflammation of nasal mucosa[15] that may cause inflammation of bronchiole and hyper-responsive airway disease as systemic inflammation in the process of "one airway, one disease"[16-18]. Ten to 40% of co-morbid asthma[19] and allergic rhinitis children who have no asthma symptom have three to five times more chances to become adult asthma than healthy children[20]. Wheezy episodes after acute viral infection in respiratory system[21-24] such as respiratory syncytial virus (RSV, <2 years), rhinovirus (<3 years), influenza (all age), para-influenza (all age) may occur in allergic rhinitis patients, especially moderate to severe allergic rhinitis. The severe respiratory tract infections were RSV in children under three years and influenza virus in all age groups.

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Influenza virus is an orthomyxoviruses exhibiting three antigenic types (A, B, and C). Influenza epidemic episodes are usually caused by types A and B. These infections affect all age groups and children with chronic underlying conditions such as asthma, are among the most susceptible. The children with allergic airway disease are vulnerable not only to the influenza-like illness (ILI) caused by influenza, but to complications, such as influenza-related pneumonia or bronchiolitis[25,26], and severe exacerbation of asthma in young children. Approximately 80% of exacerbation of asthma was precipitated by influenza A infections[26]. Griffin et al[27] found that the admission rate for acute respiratory illness/fever in children younger than five years of age in the surveillance areas was 180 per 10,000. In Thailand, influenza virus is the etiologic agent of 30% of acute respiratory tract infections[23] and influenza-related pneumonia was responsible for 300 fatalities in 2009[25].

Influenza infection may result in ILI, the symptoms were comprised of fever and sore throat and wheezy episode as bronchitis may occur in all age groups, it will have more severity and prolonged duration of illness in allergic airway disease than in non-allergic children, especially in children with moderate to severe allergic rhinitis.

Annual influenza vaccine is recommended for children six months of age and older with one or more specific risk factors, such as asthma, chronic pulmonary diseases, cardiac diseases, immuno-suppressive therapy, chronic renal dysfunction, chronic metabolic diseases, pregnancy, and obesity[28]. This influenza vaccine is recommended for children with allergic airway disease to prevent infection and decrease the severity of disease in these vulnerable groups[8,28,29]. Up to date, there has been no study to assess the efficacy of influenza vaccination in children with allergic rhinitis. Our study was undertaken to analyze the effects of influenza vaccine administration in children with moderate to severe allergic rhinitis in relation to ILI and wheezy episode.

Material and Method

A cross sectional non-randomized prospective cohort study was performed in children with moderate to severe persistent allergic rhinitis between the age of 2 and 15 years who met all the following criteria[1,5,6]: had repetitive nasal symptom as sneezing, rhinorrhea, nasal congestion more than four days per week and more than four weeks, positive skin prick test for aeroallergen, one or more of sleep or activity disturbance/bothersome/complication of diseases, controlled with oral antihistamine and intranasal steroid or oral montelukast. All of them were with or without comorbid asthma; in case with asthma, it should be mild persistent asthmatics who had at least four episodes of wheezing during the previous year, positive modified Asthma Predictive Index (API)[8,9], using low-dose inhaled budesonide (100 to 200 mg per day in patient aged <5 years, 200 to 400 mg per day in patient aged >5 years) or oral montelukast 5 mg per day.

The immunized group comprised children who received two doses of influenza vaccine (quadrivalent influenza vaccine) intramuscularly at one-month intervals in children two to nine years old, and one dose of influenza vaccine in children aged older than 9 to 15 years old[30]. The unimmunized group comprised of allergic rhinitis children whose parents denied influenza vaccination after having been advised by physicians.

The outcome parameters used to assess the effectiveness of the vaccine at reducing ILI and wheezy episodic events included the rate of wheezy episodes, emergency room visits for wheezy episode, hospitalizations, length of stay for hospitalization, bronchodilator usage, and systemic steroid. The wheezy episode was symptom of partial obstruction in bronchiole associated with bronchiolitis, bronchitis, pneumonia, asthmatic exacerbation, which includes the following symptoms, audible wheeze, tachypnea, dyspnea, and retraction[8,31]. Jaiwong et al study showed that influenza vaccination decreased respiratory illnesses and asthma-related events in children with mild persistent asthma[34]. Based on that study, the estimated sample size for two-sample comparison were 93 in our study. All data were recorded in OPD cards and case record forms on each visit. Both groups were followed up every two months at the outpatient allergy clinic, Department of Pediatric, Chiang Rai Hospital. All patients or guardians gave informed consent before enrollment. The present study was approved by the Ethical Committee of the Faculty of Medicine, university International Coordination Committee of National Human Rights Institutions.

Statistical analysis

Statistical analysis was performed using STATA version 11.0. Descriptive statistics were used to account for the characteristics of the subjects in the study. Categorical variables were described as frequency and percentage, while continuous variables were described as means and standard deviation (SD).

Exact tests and Independent t-tests were used to compare the characteristic between immunized and unimmunized group. The outcome data were described as means and SD. Exact tests and Independent t-tests were used to compare the outcome between immunized and unimmunized groups and a propensity score was used to adjust differentiations among study groups due to nonrandomized study. A *p*-value of less than 0.05 was considered statistically significant.

Results

Of the 314 allergic rhinitis children, 162 children were immunized with influenza vaccine, 152 children were not. The rates of immunization were 50.0% (58 immunized/58 unimmunized) and 52.5% (104 immunized/94 unimmunized) in children younger than 7 years and 7 to 15 years of age, respectively. The two study groups did not differ in their demographic characteristics ($p>0.05$) except with regards to co-morbid asthma, snoring, positive skin prick test for American cockroach in younger children and family income, co-morbid asthma, rhino-sinusitis in older children. Clinical characteristics such as tobacco smoke exposure, co-morbid/complications, asthma, allergic conjunctivitis, rhino-sinusitis, snoring, otitis media, allergic rhinitis controller usage (intranasal steroid, oral antihistamine, oral montelukast), results of skin prick test for house dust mite (HDM) [*Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f)], American cockroach, cat, dog, and Bermuda and Johnson grass were similar between groups (Table 1).

During the 1-year follow-up period, all outcome parameters in immunized groups had decreased significantly, compared to the unimmunized groups, in both younger and older children (Table 2). After subgroup analysis, we found that all outcome parameters in immunized groups had decreased significantly compared to the unimmunized groups, in both younger and older in children with co-morbid mild persistent asthma (Table 3). Furthermore, it can reduce the rate of ILI, wheezy episode after influenza-liked illness and bronchodilator usage in children without co-morbid mild persistent asthma (Table 4).

Table 1. Demographic data of the children with moderate to severe persistent allergic rhinitis (n = 314)

Characteristics	<7 years			7 to 15 years		
	Immunized children (n = 58) n (%)	Unimmunized children (n = 58) n (%)	*p*-value	Immunized children (n = 104) n (%)	Unimmunized children (n = 94) n (%)	*p*-value
Gender: male	36 (69.2)	39 (69.6)	1.000	65 (62.5)	60 (63.8)	0.883
Age (years), mean ± SD	4.6±1.2	4.3±1.1	0.064	10.5±2.1	10.7±2.2	0.626
Family income >10,000 THB/month	48 (92.3)	45 (80.4)	0.096	29 (27.9)	5 (5.3)	<0.001
Tobacco-smoke exposure	1 (1.9)	4 (7.1)	0.365	4 (3.9)	5 (5.3)	0.738
Asthma	32 (55.2)	19 (32.8)	0.019	31 (29.8)	14 (14.9)	0.017
Allergic conjunctivitis	0 (0.0)	2 (3.6)	0.496	1 (1.0)	4 (4.3)	0.193
Rhinosinusitis	20 (38.5)	28 (50.0)	0.250	35 (33.7)	49 (52.1)	0.010
Snoring child	26 (50.0)	39 (69.6)	0.049	74 (71.2)	62 (66.0)	0.447
Otitis media	0 (0.0)	2 (3.6)	0.496	0 (0.0)	3 (3.2)	0.105
Oral antihistamine	58 (100.0)	58 (100.0)	1.000	104 (100.0)	94 (100.0)	1.000
Oral montelukast	17 (32.7)	17 (30.4)	0.838	12 (11.5)	10 (10.6)	1.000
Intranasal corticosteroid	41 (78.9)	46 (82.1)	0.808	96 (92.3)	91 (96.8)	0.220
Eosinophils ≥4%	18 (34.6)	16 (28.6)	0.539	47 (45.2)	36 (38.3)	0.387
Positive skin prick test						
Mite Der p	51 (98.1)	54 (96.4)	1.000	104 (100.0)	92 (97.9)	0.224
Mite Der f	50 (96.2)	55 (98.2)	0.608	104 (100.0)	93 (98.9)	0.475
American cockroach	34 (65.4)	24 (42.9)	0.022	70 (67.3)	57 (60.6)	0.374
Cat	15 (28.9)	17 (30.4)	1.000	33 (31.7)	38 (40.4)	0.236
Dog	8 (15.4)	14 (25.0)	0.241	26 (25.0)	26 (27.7)	0.747
Bermuda grass	11 (21.2)	21 (37.5)	0.091	26 (25.0)	27 (28.7)	0.630
Johnson grass	9 (17.3)	20 (35.7)	0.050	28 (26.9)	27 (28.7)	0.874
Propensity score for vaccination	0.51±0.07	0.48±0.10	0.056	0.58±0.10	0.46±0.21	<0.001

THB = Thai Baht; Der p = *Dermatophagoides pteronyssinus*; Der f = *Dermatophagoides farinae*

Discussion

Influenza infections may cause life threatening illnesses to a greater extent in young children as influenza-related pneumonia and bronchiolitis[23]. There are associations with asthmatic exacerbration and re-admission of patients co-morbid with asthma[32]. Visitsunthorn et al[32] studied the risk factors associated with re-admission 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 re-admission was a history of influenza vaccination (OR 0.24, 95% CI 0.16 to 0.36).

Despite effective controller usage in moderate to severe allergic rhinitis, wheezy episodes may occur after respiratory tract infection such as RSV, influenza, parainfluenza, rhinovirus, and bacterial sinusitis. Patients without asthma are vulnerable to ILI and wheezy episodes after influenza infection[15-19]. Our study showed that children with moderate to severe allergic rhinitis who had influenza vaccinations

Table 2. The outcome parameters at 1 year in children with moderate to severe persistent allergic rhinitis (n = 314)

Outcome	<7 years			7 to 15 years		
	Immunized children (n = 58) mean (SD)	Unimmunized children (n = 58) mean (SD)	p-value	Immunized children (n = 104) mean (SD)	Unimmunized children (n = 94) mean (SD)	p-value
Number of influenza-like illnesses	2.2 (1.5)	7.9 (2.3)	<0.001	1.5 (1.1)	6.8 (1.6)	<0.001
Number of wheezing episodes	1.1 (1.3)	7.6 (1.9)	<0.001	0.5 (7.0)	6.7 (1.5)	<0.001
Number of emergency-room visits	0.1 (0.3)	0.8 (1.6)	0.007	0.0 (0.1)	0.3 (0.9)	<0.001
Number of hospitalizations	0.0 (0.1)	0.3 (0.6)	<0.001	0.0 (0.1)	0.2 (0.5)	0.018
Number of steroids administrations	0.0 (0.2)	0.6 (1.4)	<0.001	0.0 (0.10	0.3 (0.7)	<0.001
Number of bronchodilator administrations	1.1 (1.3)	7.6 (1.9)	<0.001	0.6 (0.7)	6.7 (1.5)	<0.001
Average days for hospitalization	0.0 (0.1)	0.8 (1.5)	<0.001	0.0 (0.2)	0.3 (0.9)	0.017

Table 3. The outcome parameters at 1 year in children with moderate to severe persistent allergic rhinitis with co-morbid mild persistent asthma (n = 96)

Outcome	<7 years			7 to 15 years		
	Immunized children (n = 32) mean (SD)	Unimmunized children (n = 19) mean (SD)	*p*-value	Immunized children (n = 31) mean (SD)	Unimmunized children (n = 14) mean (SD)	*p*-value
Number of influenza-like illnesses	2.2 (1.5)	8.5 (2.9)	<0.001	1.4 (1.1)	7.7 (1.6)	<0.001
Number of wheezing episodes	1.3 (1.1)	8.1 (2.3)	<0.001	0.5 (0.7)	7.6 (1.6)	<0.001
Number of emergency-room visits	0.1 (0.4)	1.5 (2.0)	<0.001	0.1 (0.2)	1.2 (1.3)	<0.001
Number of hospitalizations	0.0 (0.2)	0.6 (0.8)	<0.001	0.0 (0.2)	0.4 (0.8)	0.016
Number of steroids administrations	0.1 (0.2)	1.1 (1.8)	0.003	0.1 (0.2)	1.1 (1.0)	<0.001
Number of bronchodilator administrations	1.3 (1.1)	8.1 (2.3)	<0.001	0.5 (0.7)	7.6 (1.6)	<0.001
Average days for hospitalization	0.0 (0.2)	1.5 (1.7)	<0.001	0.1 (0.4)	0.8 (1.5)	0.006

Table 4. The outcome parameters at 1 year in children with moderate to severe persistent allergic rhinitis without co-morbid mild persistent asthma (n = 218)

Outcome	<7 years			7 to 15 years		
	Immunized children (n = 32) mean (SD)	Unimmunized children (n = 33) mean (SD)	*p*-value	Immunized children (n = 73) mean (SD)	Unimmunized children (n = 80) mean (SD)	*p*-value
Number of influenza-like illnesses	2.1 (1.6)	7.6 (1.9)	<0.001	1.5 (1.1)	6.4 (1.3)	<0.001
Number of wheezing episodes	1.0 (1.4)	7.3 (1.6)	<0.001	0.5 (0.7)	6.2 (1.2)	<0.001
Number of emergency-room visits	0.0 (0.2)	0.4 (1.1)	0.099	0.0 (0.0)	0.3 (0.9)	<0.066
Number of hospitalizations	0.0 (0.0)	0.1 (0.3)	0.059	0.0 (0.0)	0.2 (0.5)	0.067
Number of steroids administrations	0.0 (0.0)	0.3 (1.0)	0.076	0.0 (0.0)	0.2 (0.7)	0.053
Number of bronchodilator administrations	1.0 (1.4)	7.3 (1.6)	<0.001	0.6 (0.8)	6.3 (1.2)	<0.001
Average days for hospitalization	0.0 (0.0)	0.4 (1.2)	0.081	0.0 (0.0)	0.3 (0.9)	0.066

(quadrivalent influenza vaccine) had better outcome, in both younger and older children than unimmunized groups. It was effective in reducing ILI, wheezy episodes, and severity of asthmatic events in children with co-morbid mild persistent asthma (ER visits, hospitalizations, average days for hospitalization, and medical usages for wheezy episode), and reduced ILI, wheezy episode after influenza-liked illness, and bronchodilator usage in children without co-morbid of mild persistent asthma.

The present study showed that the prevalence of co-morbid asthma is high in younger children (77.6%) compared to the report from Shah and Pawankar (80.0%)[19]. Prevalence of complications such as snoring and rhino-sinusitis are high in older children (70.0% and 40%, respectively), which is similar to the report from Dykewicz[10]. High prevalence of positive skin prick testing for aeroallergen, such as Der p, Der f, American cockroach were found in the present study, but low prevalence for cat and dog dander, Bermuda and Johnson grass, which was similar to the report by Kongpanichkul et al[33]. Current evidence demonstrated that intranasal steroids are the most effective treatment for allergic rhinitis[1,5,6]. The medication to control allergic rhinitis in our study were oral antihistamine 100%, intranasal steroid 87.3%, and oral montelukast 17.8%.

To date, no study has investigated the effects of inactivated influenza vaccine on allergic rhinitis. Our study is the first to evaluate the effects of influenza vaccination (quadrivalent influenza vaccine) in moderate to severe allergic rhinitis. Most published researches focus on the outcome of influenza vaccine in asthma[34,35]. Noteworthy, we report that almost half of the their parents of the allergic rhinitis patients included in our study refused influenza immunization even after having been advised by the physicians.

Limitation

Our study was a non-randomized due to limited budget to support a free influenza vaccine. Another limitation was the lack of information related to other confounding factors in allergic rhinitis as other organisms of acute respiratory tract infection, compliance, and controller usage, pollution, and how they could affect patients.

Conclusion

Our study shows that complete influenza vaccine immunization is beneficial for children with moderate to severe allergic rhinitis. It can reduce ILI, wheezy episodes, and the severity of asthmatic events in children with co-morbid mild persistent asthma. An annual, well-organized, computerized, multi-component strategy should be implemented for optimizing influenza immunization in the high-risk population including allergic rhinitis patients, especially those with moderate to severe symptom.

What is already known on this topic?

Despite effective controller usage in children with moderate to severe allergic rhinitis, ILI, and wheezy episodes may occur after respiratory tract infection, especially influenza infection.

What this study adds?

Influenza vaccine immunization is beneficial for children with moderate to severe allergic rhinitis. It can reduce ILI, wheezy episodes, and the severity of asthmatic events in children with co-morbid mild persistent asthma, this will improve quality of life in these children.

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Potential conflicts of interest

None.

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ประสิทธิภาพของวัคซีนป้องกันโรคไข้หวัดใหญ่ในผู้ป่วยเด็กโรคจมูกอักเสบจากภูมิแพ้เรื้อรังขั้นปานกลางถึงมาก

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ภูมิหลัง: *ผู้ป่วยเด็กโรคจมูกอักเสบจากภูมิแพ้เรื้อรังขั้นปานกลางถึงมาก มีโอกาสจับหืดเมื่อป่วยไข้หวัดใหญ่ วัคซีนป้องกันไข้หวัดใหญ่ถูกแนะนำให้ใช้ในผู้ป่วยภูมิแพ้ทางเดินหายใจ แต่ยังไม่มีการศึกษาผลทางคลินิกในผู้ป่วยเด็กโรคจมูกอักเสบเรื้อรังขั้นปานกลางถึงมาก*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของวัคซีนป้องกันไข้หวัดใหญ่ในผู้ป่วยเด็กโรคจมูกอักเสบจากภูมิแพ้เรื้อรังขั้นปานกลางถึงมากในการป้องกันป่วยไข้หวัดใหญ่ และภาวะจับหืดเมื่อป่วยไข้หวัดใหญ่*

วัสดุและวิธีการ: *ทำการศึกษาแบบไปข้างหน้าในผู้ป่วยเด็กโรคจมูกอักเสบจากภูมิแพ้เรื้อรังขั้นปานกลางถึงมาก ที่เข้ารับการรักษาคลินิกภูมิแพ้ กลุ่มงานกุมารเวชกรรม โรงพยาบาลเชียงรายประชานุเคราะห์ โดยเปรียบเทียบกลุ่มที่ได้รับวัคซีนป้องกันไข้หวัดใหญ่กับกลุ่มไม่ได้รับวัคซีนถึงผลของการป่วยไข้หวัดใหญ่ และภาวะจับหืดเมื่อป่วยไข้หวัดใหญ่ โดยแบ่งผู้เข้ารับการศึกษาเป็นช่วงอายุเด็กเล็ก และเด็กโต*

ผลการศึกษา: *ผู้ป่วยเด็กทั้งหมด 314 ราย แบ่งเป็นผู้ป่วยที่ได้รับวัคซีน 162 ราย และไม่ได้รับวัคซีน 152 ราย หลังปรับข้อมูลพื้นฐานโดยใช้ propensity score แล้ว ทั้งสองกลุ่มมีข้อมูลพื้นฐานใกล้เคียงกัน คือ เพศ อายุ รายได้ผู้ปกครอง ประวัติการสัมผัสคนในครอบครัวสูบบุหรี่ โรคร่วมหรือภาวะแทรกซ้อน การใช้ยารักษาโรคภูมิแพ้จมูกอักเสบเรื้อรัง และผลการทดสอบทางผิวหนัง ผลลัพธ์หลังติดตามการศึกษา 1 ปี พบว่ากลุ่มที่ได้รับวัคซีนป้องกันไข้หวัดใหญ่ อัตราการป่วยไข้หวัดใหญ่ และภาวะจับหืดเมื่อป่วยไข้หวัดใหญ่ลดลงในผู้ป่วยที่ไม่มีโรคร่วมหอบหืด ส่วนผู้ป่วยที่มีโรคร่วมหอบหืดเรื้อรังขั้นเล็กน้อยอัตราการป่วยไข้หวัดใหญ่ อัตราหอบหืดกำเริบและความรุนแรงของหอบหืดกำเริบลดลงเช่นกัน เมื่อเปรียบเทียบกับกลุ่มที่ไม่ได้รับวัคซีนอย่างมีนัยสำคัญในทางสถิติ*

สรุป: *การให้วัคซีนป้องกันไข้หวัดใหญ่มีประโยชน์ในผู้ป่วยเด็กโรคจมูกอักเสบจากภูมิแพ้เรื้อรังขั้นปานกลางถึงมาก ทั้งกลุ่มที่มีโรคร่วมหอบหืดเรื้อรังขั้นเล็กน้อย และกลุ่มที่ไม่มีโรคร่วมหอบหืด*