

Proportional of wheezing events in asthmatic children post-vaccination of annual flu vaccine

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Abstract

Background: The common childhood chronic disease asthma causes hospitalisation and exacerbations due to respiratory tract viral infections like influenza. Due to uncertainty about the benefits and role of influenza vaccines in preventing asthma exacerbations, many children with asthma do not receive them, despite recommendations from organisations like the Canadian National Advisory Committee on Immunisation. There are two main types of influenza vaccines: intramuscular trivalent inactivated and intranasal cold-adapted, live attenuated. Both vaccines are highly immunogenic and induce an adequate immune response, but their clinical efficacy varies by season and age.

Aim: The aim of this study was to investigate the occurrence of increased wheeze rates in stable asthmatic children who received the annual flu vaccine, compared to a control group of asthmatic children who did not receive the vaccine.

Methods: A retrospective study at the Queen Rania Abdullah for Children Hospital in Amman, Jordan, examined the vaccination status of 200 asthmatic children aged 3-14. The study focused on recurrent wheezing episodes and the minimum 12-month period between the last annual flu vaccination and asthmatic exacerbation. The study excluded uncontrolled or partially controlled patients for the past 12 months. Data was collected from demographic information, vaccination history, and past wheezing episodes. The children were divided into two groups, one without the flu vaccine and the other with the flu vaccine. A comprehensive questionnaire was used to assess sociodemographic and disease-related factors. If children received the vaccination as per the National Vaccination Schedule, their vaccination status was considered complete.

Results: A study of 200 asthmatic children in Jordan found that 35% did not receive a flu vaccine, placing them in Group I. 65% had received a flu vaccine in the previous year. Males had higher distribution rates in both flu-based groups, with a statistically insignificant positive correlation. Age categories showed similar distribution rates, with 21.0% for 3-6 years, 34.0% for 6-9 years, 37.5% for 9-12 years, and 7.5% for 12-15 years. No significant correlation was found between receiving the flu vaccine and wheezing rates in the last seasonal year. Frequent wheezing episodes were higher in experienced groups than in naïve groups.

Keywords: Flu vaccination; Children with asthma; Wheezing episodes; Vaccine experienced; Vaccine naïve; Vaccine adverse outcomes.

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1. Introduction

Childhood asthma is a common chronic illness that can cause hospitalisation and worsening of symptoms when respiratory tract viruses, such as influenza, are present. It has a major socioeconomic impact and is the most prevalent chronic respiratory illness in children. There has been no overall decrease in the prevalence of asthma; instead, it is rising globally. Food allergies (FA) are also prevalent; among preschoolers, egg allergy is the most common type. For instance, one of the main causes of FA in Korea is egg allergy. With an annual attack rate of 5%–10% in adults and 20%–30% in children, influenza is a worldwide illness that causes over 20,000 hospital admissions and 100 fatalities each year. In the winter, influenza infection can exacerbate asthma symptoms in children with asthma and result in hospitalisation. Children with asthma have a 31%–91% higher risk of complications from influenza.

Based on the active ingredients in each vaccine, influenza shots are categorised as either inactivated (IIV) or live-attenuated (LAIV). The majority of IIVs and LAIVs that are currently on the market are cultivated on hen embryos, which have trace levels of the egg protein ovalbumin. When children have an egg allergy, trace ovalbumin can cause allergic reactions or anaphylaxis, which is extremely concerning because it can result in severe allergic reactions or anaphylaxis. There are two primary influenza vaccine types that are available: intranasal trivalent, live attenuated, cold-adapted, and intramuscular trivalent, inactivated. Although both vaccines are very immunogenic and elicit a sufficient immune response, the seasons and age groups they are effective in differing how well they work clinically.

Twenty percent of infants experience wheezing at some point in their early childhood. Th2-dependent inflammation is the hallmark of asthma, and individuals with atopic dermatitis typically exhibit Th-2 polarisation and a diminished Th-1 response, rendering them more vulnerable to infections in comparison to individuals without allergies. Common viral infections are linked to brief early wheezing, which usually goes away by the time a child reaches three years old. Non-atopic wheezing often follows a seasonal pattern and is associated with acute viral infections, particularly respiratory syncytial virus. About 80% of asthma flare-ups were brought on by influenza A infections. Influenza viruses are orthomyxoviruses that have three antigenic types (A, B, and C). Compared to other respiratory tract viruses like RSV, they spread more quickly.

All age groups are susceptible to influenza virus infections, as well as respiratory tract viruses like rhinovirus, parainfluenza, and RSV. Because they are among the most vulnerable to the offending precipitating pathogens, young children with chronic underlying conditions like asthma are particularly vulnerable to influenza virus infection, which can result in life-threatening illness. For instance, in Thailand, influenza virus is the causative agent of 30% of acute respiratory tract infections, and 300 deaths in 2009 were attributed to influenza-related pneumonia. People aged 6 months and older who have one or more specific risk factors, such as asthma, chronic pulmonary diseases, cardiac diseases, immunosuppressive therapy, chronic renal dysfunction, or chronic metabolic diseases, are strongly advised to have an annual influenza vaccination by the World Health Organisation (WHO) and the Centres for Disease Control and Prevention (CDC) in the United States. This recommendation is especially strong for individuals with a chronic underlying disease like asthma. Many children with asthma do not receive influenza vaccinations despite recommendations from groups such as the Canadian National Advisory Committee on Immunisation. This is because they are unsure of the advantages of vaccination and how it prevents asthma exacerbations.

A thorough set of recommendations for influenza vaccination of children with asthma and egg allergies is provided by the Global Influenza Vaccine Recommendations for Children with Asthma and Egg Allergies. To prevent exacerbations, children with allergic diseases, especially asthma, should also receive the influenza vaccination, according to the Global Initiative for Asthma (GINA). Nevertheless, guideline-based performance is hampered in practice by worries about asthma exacerbation and a compromised immune response in patients receiving maintenance inhaled corticosteroid (ICS) therapy. In spite of the possibility of elevated morbidity, between 75 and 90 percent of children with asthma do not receive an influenza vaccination. As a result, due to a lack of information regarding the severity of asthma, the American College of Infectious Diseases (ACIP) does not advise LAIV for children with asthma or recent wheezing who are 2 to 4 years old. Also, they advise exercising caution when utilising LAIV in children with asthma who are older than five.

Research has demonstrated a link between asthma and a higher likelihood of contracting the novel H1N1 influenza (H1N1) infection in children during the 2009 pandemic. The impact of asthma on the severity of H1N1 infections remains unclear. So far, no research has examined the impact of the influenza vaccine on respiratory illnesses and asthma-related incidents in children with asthma, specifically in our Mediterranean region or country. This study could be the initial assessment of the wheezing frequencies associated with the influenza vaccine in controlled asthmatic children in Jordan. The primary objective of this study was to determine if children with stable asthma who were administered the annual flu vaccine had a higher incidence of wheezing compared to a control group of similarly stable

asthmatic children who did not receive the vaccine. In this investigation, we analysed the Pearson correlations between the age and gender of children with asthma who had either received the annual flu shot or had not.

2. Methods

The study was conducted retrospectively at the Queen Rania Abdullah for Children Hospital in Amman, Jordan, and was approved by the Institutional Committee for Ethics in Research under the registration number 50_2/2024. Two hundred controlled asthmatic children between the ages of 3 and 14 were hospitalised in our paediatric clinic for chronic asthma from the beginning of 2022 to the end of 2023 due to recurrent wheezing. Each person with a history of at least four documented wheezing episodes was classified as having frequent wheezing, while those with fewer than four episodes were classified as having occasional wheezing. The study included criteria such as a minimum 12-month period between the last annual flu vaccination and asthmatic exacerbation, as per CDC guidelines.

Asthma exacerbation requiring increased post-exacerbation rescue medication, and the necessity for hospital admission or systemic corticosteroids with or without antibiotics were all considered signs, regardless of the severity of the exacerbation. This study excluded paediatric patients who were deemed uncontrolled or partially controlled for the past 12 months, irrespective of wheezing episodes. Due to the observational and retrospective nature of our study, we did not require informed consent from the parents of the asthmatic and vaccinated children included in the study. To obtain comprehensive data, it is essential to first collect demographic information on the age and sex of the children being tested, as well as the total number of previous wheezing attacks. Children's vaccination status was deemed complete if they had received the vaccination as per the National Vaccination Schedule (NVS).

All children with asthma who were tested will be split into two separate groups for comparison. The first group comprises asthmatic children who did not receive the flu vaccine, and the second group comprises asthmatic children who did receive the flu vaccine. The statistical analysis involved assessing the model's adequacy, calculating the Pearson chi-square statistic, and conducting the Chi Square Test. We calculated the risk estimate ratio and the Pearson correlations for each variable using these methods.

A comprehensive questionnaire was given, covering sociodemographic and disease-related factors like parental education, family income, number of siblings, vaccination history, past wheezing episodes, place of residence, duration of breastfeeding, antibiotic use in infancy, recent antibiotic prescriptions, and frequency of corticosteroid inhalations. If children received the vaccination as per the National Vaccination Schedule (NVS), their vaccination status was deemed complete. A P-value below 0.05 or an odds ratio (OR) with a 95% confidence interval (CI) excluding 1.00 was deemed significant.

3. Results

Out of 200 controlled asthmatic children at a paediatric clinic in Jordan, 35% (70 children) did not receive a flu vaccine and were placed in Group I, while 65% (130 children) had received a flu vaccine in the previous year. 36% of the paediatric patients studied were female (72 out of 200), while 64% were male (128 out of 200).

There were no significant differences in distribution rates between males and females in the naïve flu vaccine group (Group I) and the experienced flu vaccine group (Group II). However, males in the paediatric cohort had higher distribution rates in both flu-based groups: 42 (60.0%) vs 28 (40.0%) and 86 (66.2%) vs 44 (33.8%), respectively.

The Pearson correlation test showed a statistically insignificant positive correlation for males who had experienced flu vaccination compared to those who had not, in contrast to females. The correlation coefficient was $+0.061 \pm 0.071$, with a chi-square value of 0.748 and a p-value of 0.387. The overall risk estimate was 1.303 (95% CI; 0.715-2.376).

When testing the age categories 3 years apart, we found similar distribution rates between the two groups I-II. The overall allocation rates were 21.0% for 3-6 years, 34.0% for 6-9 years, 37.5% for 9-12 years, and 7.5% for 12-15 years. The Pearson correlation coefficient (R) along with its standard error values indicated a statistically insignificant positive relationship [$+0.072 \pm 0.070$, $X^2(3) = 3.31$, 0.387].

There was no significant correlation found between receiving the flu vaccine and wheezing rates in the last seasonal year. The Pearson correlation coefficient was slightly negative at -0.047 ± 0.071 , $X^2(1) = 0.444$, p-value=0.505. The overall risk estimate was insignificant at 0.815 (95% CI; 0.446-1.489). In the experienced flu vaccine group (Group II), the distribution rates of frequent wheezing episodes were 44 (33.8%) and occasional wheezing episodes were 86

(66.2%). In the naïve flu vaccine group (Group I), the distribution rates were 27 (38.6%) for frequent wheezing episodes and 43 (61.4%) for occasional wheezing episodes.

Table 1 Comparatively studied variables across Cohort I-II; Lower co-morbidity burden cohort (Cohort I) versus Higher co-morbidity burden cohort (Cohort II), in the studied patients.

	Naïve Flu (Group I) (70, 35%)	Experienced Flu (Group II) (130, 65%)	Total (200, 100%)	OR	R	χ² (df)	p-Value
Age (Yrs)							
3-6	18 (25.7%)	24 (18.5%)	42 (21.0%)	NA	+0.072±0.070	(3) 3.31	0.346
6-9	21 (30.0%)	47 (36.2%)	68 (34.0%)				
9-12	28 (40.0%)	47 (36.2%)	75 (37.5%)				
12-15	3 (4.3%)	12 (9.2%)	15 (7.5%)				
Gender							
Female	28 (40.0%)	44 (33.8%)	72 (36.0%)	1.303 (95% CI; 0.715-2.376)	+0.061±0.071	(1) 0.748	0.387
Male	42 (60.0%)	86 (66.2%)	128 (64.0%)				
Wheezing episodes							
Occasional	43 (61.4%)	86 (66.2%)	129 (64.5%)	0.815 (95% CI; 0.446-1.489)	-0.047±0.071	(1) 0.444	0.505
Frequent	27 (38.6%)	44 (33.8%)	71 (35.5%)				
<p>Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The strength of associations was also described as odd ratios (OR). The Pearson chi-square statistic (χ²) involves the squared difference between the observed and the expected frequencies. The Goodness of Fit (G-Test of independence) uses the log of the ratio of two likelihoods and tests the goodness of fit of observed frequencies to their expected. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value. The studied patients were dichotomously categorized into 2 comparative cohorts; the cohort whose AACCI was below its explored roundup optimal cutoff point (4) [Cohort I] versus the cohort whose AACCI was ≥ 4 [Cohort II].</p>							
<p>AACCI: Age-adjusted Charlson Comorbidity Index. PD: Protein density. FVC: Fruit and vegetable content.</p>				<p>BMD: Bone mineral density in g per cm². FRAX: Fracture risk assessment tool. LBMD: Lumbar bone mineral density.</p>			

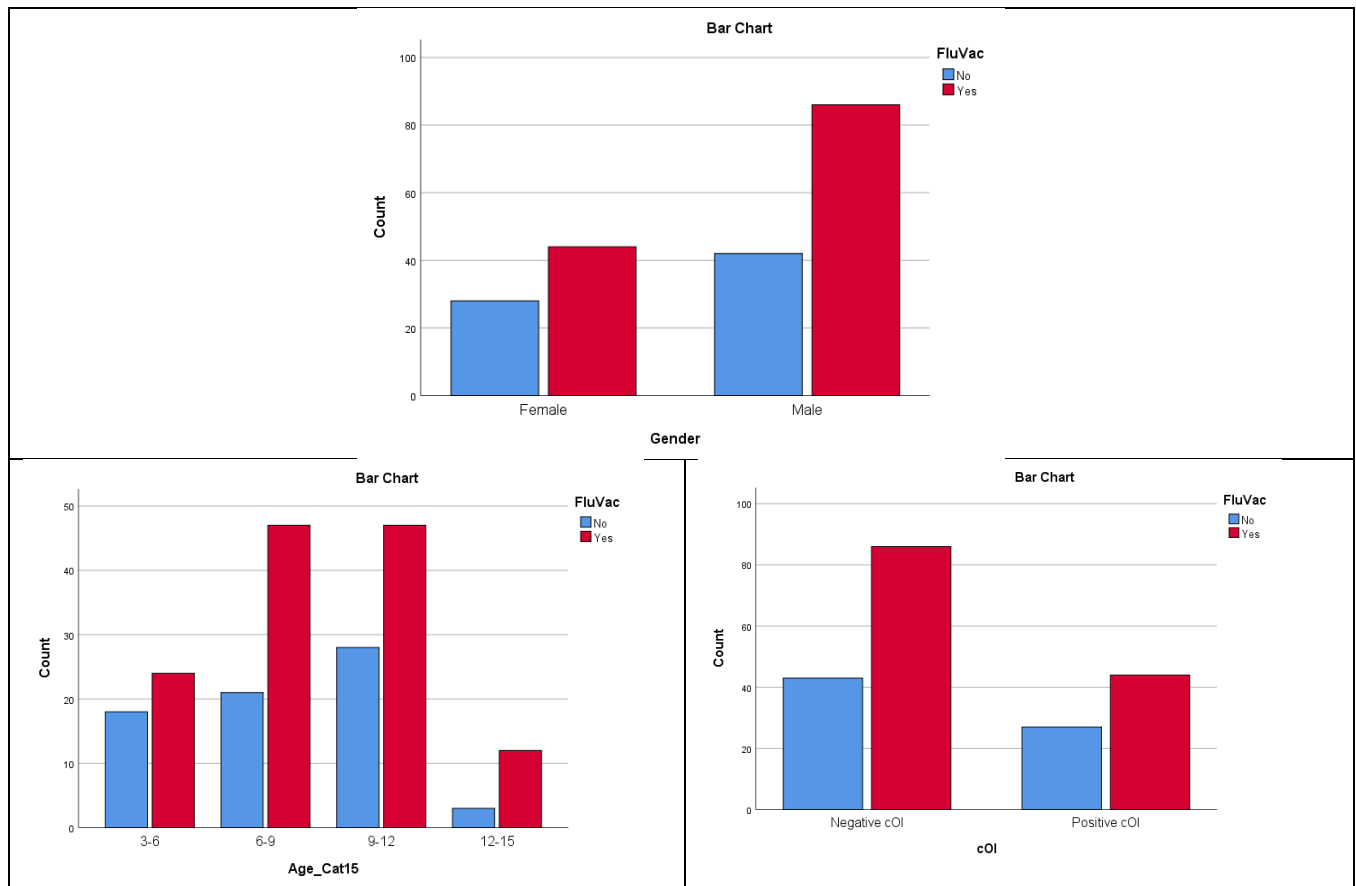


Figure 1 Bar charts' visualization of the studied patients' across groups

4. Discussion

A study was conducted to assess the efficacy of administering influenza vaccine to asthmatic children in relation to respiratory illnesses and asthma-related wheezing episodes. Influenza virus infections impact individuals of all age groups, and various studies have shown the safety of the attenuated, inactivated, and live flu vaccine in children with asthma. An open-label trial found that the live attenuated influenza vaccine (LAIV) provided 32% greater protection against culture-confirmed influenza without exacerbating asthma symptoms or peak expiratory flow rates. A study of 69 children with egg allergy and 55 controls found no allergic reactions after vaccination with LAIV, derived from egg embryos. This suggests that LAIV may be safe for use, even in asthma patients, when recombinant flu vaccines or cell culture-based flu vaccines are not available. These are the only egg-free flu vaccines licenced for use, such as the quadrivalent recombinant flu shot (Flublok Quadrivalent).

Furthermore, multiple related studies indicate that children with chronic stable controlled asthma and recurrent wheezing are frequently not adequately vaccinated with the annual flu vaccine, as most studies demonstrated statistical significance. Typically, these studies indicated that most sociodemographic variables and the age of mothers did not show a significant association with vaccination status. Aside from monthly family income, factors such as parents' low education level, atopic susceptibility, and exposure to infections were found to be statistically significant in their association with recurrent wheezing rates, showing varying degrees of correlation strength ranging from moderate to moderately strong. Allergic children are more susceptible to infections due to mucosal inflammation, leading to increased antibiotic use compared to non-allergic children. The relationship between hypersensitivity syndromes, antibiotic use, and incomplete vaccination status is interconnected.

Previous studies have shown varying results regarding the relationship between flu vaccination coverage and exacerbation of chronic diseases. Some studies found significant negative associations, while others did not find significant correlations, similar to our study. Several studies, including ours, did not find evidence supporting a connection between a child's age, gender, receiving the flu vaccine in the previous season, and an increased likelihood of experiencing frequent wheezing episodes compared to occasional episodes. Our study did not emphasise the

significance of socio-demographic factors, other than age and gender, that impact the vaccination status of children with frequent wheezing episodes. Several limitations were present in this study.

Due to limitations such as a small sample size, single-center retrospective observation, and lack of consideration for potential confounding sociodemographic variables, we did not find a significant association between annual flu vaccination and exacerbation of wheezing. Complete influenza vaccine immunisation is considered beneficial for children with mild persistent asthma as it prevents acute respiratory tract infections, reduces asthma exacerbations, and hospitalisations. This highlights the importance of an annual, well-organized, computerized multi-component strategy for optimising influenza immunisation in high-risk populations, including asthmatic patients.

5. Conclusion

While we found a negative correlation between annual flu vaccination and exacerbation of wheezing in chronically stable asthmatic children, the relationship was not statistically significant. It appears that annual flu vaccination may have an overall positive impact on the quality of life for children, particularly those with persistent wheezing. Pediatricians and healthcare providers should monitor the vaccination status of asthmatic children and offer additional support and encouragement.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

Statement of ethical approval

There is no animal/human subject involvement in this manuscript.

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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