

## ORIGINAL ARTICLE

## Effectiveness of influenza vaccine for the prevention of asthma exacerbations

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**Background:** There is a lack of clinical evidence that annual vaccination against influenza prevents asthma exacerbations in children.

**Methods:** Retrospective cohort study of 800 children with asthma, where one half did, and the other half did not receive the influenza vaccine. The two groups were compared with respect to clinic visits, emergency department (ED) visits, and hospitalisations for asthma. In multivariable analyses, adjustment was made for baseline asthma severity, prior utilisation of health services, receipt of vaccine in the previous year, and demographic variables.

**Results:** After adjusting for other variables, the vaccine group had a significantly increased risk of asthma related clinic visits and ED visits (odds ratios 3.4 and 1.9, respectively).

**Conclusion:** This study failed to provide evidence that the influenza vaccine prevents paediatric asthma exacerbations.

Annual administration of influenza vaccine to children with asthma is recommended in official guidelines, but there is a lack of clinical evidence supporting this recommendation.<sup>1,2</sup> We performed a retrospective cohort study, to determine whether asthmatic children who received the influenza vaccine experienced fewer asthma exacerbations.

## METHODS

We randomly selected, from a total population of 1400 asthmatic children, 400 children 1–19 years old who received the influenza vaccine, and 400 who did not. A total of 800 subjects were required for a power  $(1-\beta)$  of 80% with  $\alpha = 0.05$ , based on the assumption that 30% of children with asthma would experience an asthma event without vaccination, and that vaccination would lead to a 70% risk reduction. Outcome measures included the mean annual number of hospitalisations and visits to the clinic or emergency department (ED) for the diagnoses of asthma and pneumonia. The baseline year was 1995–96 (October to September) and the study year 1996–97. Data were obtained from computerised administrative datasets and verified where possible by chart review. These children were enrolled in two large paediatric teaching practices (46 000 patient visits per year) serving children of low to moderate income in Rochester, New York. Asthma severity was determined by medical record documentation at the time of the influenza vaccine visit or in the autumn of 1996, using the 1991 US guidelines, which categorised asthma as “mild, moderate, or severe”. When severity level was not specified (about 50% of charts), asthma medication use at the time of the vaccine visit (as needed  $\beta$  agonist only versus anti-inflammatory therapy, or mild versus moderate to severe) was used as a proxy of severity. In charts with both measures, medication use agreed with severity in 80% of cases ( $r = 0.57$ ).

Using SPSS 10.0 for Windows (SPSS, Chicago, IL), we performed logistic regression analyses to investigate the association of receipt of the vaccine with asthma related clinical outcomes occurring in the year following vaccination. We adjusted for the following variables: receipt of vaccine in the previous year, asthma severity, race, age, sex, type of health insurance, passive smoking exposure, and health care utilisation; high utilisers were defined as those patients

making more than the median number of visits ( $\geq 4$  visits) for any diagnosis to the outpatient clinic in two years (1995–97). Because asthma is a chronic disease, and the influenza vaccine is given annually, we used the year following vaccination as the time unit of analysis.

## RESULTS

Children in the two study groups were similar with respect to mean age, sex, and rates of exposure to tobacco smoke in their homes. Children in the no-vaccine group were more likely to be black (56% v 42%), less likely to have received the vaccine the previous year (18% v 50%), and less likely to be Hispanic (26% v 34%).

In unadjusted analysis, the group receiving the vaccine had significantly more asthma related clinic visits (2.14 v 0.71), ED visits (0.33 v 0.14), and hospitalisations (0.12 v 0.04) than those not receiving the vaccine.

After adjusting for multiple variables, children who received the influenza vaccine were more likely to have clinic visits for asthma or pneumonia (OR 2.9, 95% CI 2.0 to 4.1) than those who did not receive it (table 1). These children were also more likely to have had asthma related ED visits and hospitalisations (OR 2.0, 95% CI 1.2 to 3.1 and OR 1.9, 95% CI 0.9 to 3.9, respectively). The increased risk was statistically significant for clinic and ED visits, but not for hospitalisations.

## DISCUSSION

Influenza vaccination was associated with an increase in asthma morbidity. Given such surprising findings, one must consider the main limitation of this retrospective study: the possibility that vaccination was somehow merely a marker for bad asthma. If only children with severe asthma received the vaccine, then the vaccine group might do worse for that reason. We also considered that high utilisation may “cause” vaccination, rather than vice versa because children who go to the doctor more often are more likely to receive a vaccine. However, we still failed to find a benefit of the vaccine after controlling for asthma severity, previous receipt of the vaccine, and frequent use of medical services. There was a very good match that year between the viral strains used in the vaccine and those present in the wild virus so poor matching does not explain the findings.

**Table 1** The effect of influenza vaccine on asthma: outcomes adjusted

Independent variables	Odds of a clinic visit		Odds of an ED visit		Odds of hospitalisation	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Study group						
Received vaccine v not	2.9 (2.0 to 4.1)	<0.001	2.0 (1.2 to 3.1)	0.01	1.9 (0.9 to 3.9)	0.10
Asthma severity						
Severe v mild	3.7 (2.5 to 5.5)	<0.001	2.0 (1.3 to 3.1)	0.002	2.5 (1.3 to 4.8)	0.01
Insurance						
Non-private v private	1.6 (1.1 to 2.5)	0.03	0.8 (0.5 to 1.5)	0.52	1.5 (0.6 to 3.8)	0.40
Outpatient clinic utilisation						
High v low	2.5 (1.8 to 3.6)	<0.001	1.1 (0.7 to 1.7)	0.59	2.0 (1.01 to 4.0)	0.047
Race						
Black v white	1.5 (0.9 to 2.4)	0.06	1.6 (0.9 to 2.7)	0.12	1.2 (0.5 to 2.7)	0.63
Hispanic v white	1.4 (0.9 to 2.2)	0.18	1.1 (0.6 to 2.0)	0.82	1.2 (0.5 to 2.9)	0.68
Age						
≤5 years v >5 years	0.7 (0.5 to 0.9)	0.04	1.0 (0.6 to 1.5)	0.93	0.7 (0.4 to 1.4)	0.31
Sex						
Male v female	1.2 (0.9 to 1.7)	0.25	1.3 (0.8 to 2.0)	0.25	1.5 (0.8 to 2.9)	0.19
Smoke-free home						
No v yes	1.0 (0.6 to 1.4)	0.81	1.2 (0.7 to 2.0)	0.50	0.9 (0.4 to 1.9)	0.74
Unknown v yes	0.9 (0.6 to 1.3)	0.55	1.1 (0.7 to 1.9)	0.67	2.0 (0.9 to 4.2)	0.08
Influenza vaccine previous season						
No v yes	0.7 (0.5 to 1.1)	0.06	1.0 (0.6 to 1.6)	0.96	1.1 (0.6 to 2.0)	0.85

All independent variables listed are included in the logistic regression model.

Our results are consistent with the existing body of knowledge regarding influenza vaccine and asthma. Asthmatic children experiencing wheezing episodes are less likely than non-wheezing asthmatic children to have influenza virus isolated from nasopharyngeal swabs.<sup>4</sup> In another study like this one, the adverse effect of vaccination disappeared only after the authors eliminated the unvaccinated group from the analysis, but this is a questionable methodology for assessing vaccine effectiveness.<sup>5,6</sup> Recent systematic reviews have concluded that the available evidence is not sufficient for determining whether the vaccine causes more benefit than harm in patients with asthma.<sup>1</sup> The new intranasal vaccine is specifically contraindicated in patients with asthma, because of the adverse events detected in randomised controlled trials.<sup>3</sup> No such trials have been done for the currently used intramuscular vaccine.

## Conclusion

This study failed to provide clinical evidence in support of the recommendations for annual influenza vaccination of asthmatic children. Even after controlling for several potential confounders, we noted a statistically significant increase in asthma related health care utilisation associated with vaccination. While this disturbing result does not show harm from the influenza vaccine, it is suggestive enough to warrant future study. It appears that a long term, prospective controlled trial may be needed.

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Conflict of interest: The authors have no financial arrangement with any companies that produce influenza vaccine or their competitors

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