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Does Influenza Vaccination Exacerbate Asthma?

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Abstract

A few anecdotal reports have described serious asthma exacerbations following influenza vaccination. However, a causal relationship has not been clearly established since the vaccine is administered at the time of year when the background incidence of asthma exacerbation is high. Some reports describing minor pulmonary function changes or increased bronchial reactivity in patients with asthma receiving influenza vaccination did not include placebo controls and the results as they are reported are difficult to interpret. Results from several placebo-controlled studies, open trials, and US and European postmarketing surveillance data have shown no evidence of asthma exacerbation related to killed influenza vaccination, although 1 recent placebo-controlled study demonstrated a decrease in peak flow in a small number of first-time vaccinees without clinical exacerbation of asthma. A recent report demonstrated that a group of children with acute asthma exacerbation tolerated influenza vaccination to the same degree as patients with stable asthma. Thus, a plethora of evidence indicates that killed-subunit influenza vaccination is well tolerated and does not exacerbate asthma to a clinically significant degree. Limited experience with live influenza vaccine also suggests that it may be safely given to patients with asthma. Although vaccine efficacy has not been unequivocally demonstrated in patients with asthma, the potential benefits from prevention of morbidity associated with influenza infection in these patients outweighs the theoretical concerns over the safety of influenza vaccination.

Influenza increases morbidity and mortality during epidemic periods among patients with chronic lung diseases such as asthma.[1-4] Influenza vaccination is recommended each autumn for all individuals with persistent asthma,[5-7] although the efficacy of vaccination in this group is difficult to assess.[1,8] Efficacy in the general population is 60 to 80%.[9-11] Gross et al.[9] reported a 59% reduction in influenza-associated mortality among elderly populations. Barker and Mullooly[10] reported an 87% reduction in influenza-associated mortality and a 72% reduction in hospitalisations and mortality among elderly populations. Vaccine efficacy was higher in children aged at least 7 years old (78% for influenza type A, 60% for type B) than in children younger than 7 years old (53% for type A and 22% for type B). Sugiura et al.[11] reported that vaccine efficacy was 80% for type A and 43% for type B among high school students, and Meiklejohn et al.[12] reported vaccine efficacy of

80% in military school. Sugaya et al.[13] reported 67.5% protection against type A and 43.7% against type B in children with moderate to severe asthma.

Unfortunately the overall vaccination rate for patients with asthma is low, less than 10 to 15%.[8,14,15] This may be partly attributed to poor patient motivation but may also be because of healthcare providers' concerns about the safety of influenza vaccination in patients with asthma. Adverse effects of influenza vaccinations usually manifest within 24 hours after vaccination as local and/or systemic reactions. Local reactions are mainly pain at the site of injection; the systemic reactions are usually headaches, sometimes with fever. The adverse reactions are seen less frequently in young children than in older children or adults.[5,15,16] In a randomised, placebo-controlled, crossover study in the general elderly population, there was no significant difference between a split-antigen influenza vaccine and placebo with respect to the proportion of patients reporting respiratory or other systemic symptoms.[17]

Viral respiratory illnesses often provoke airway hyperresponsiveness and exacerbation of asthma.[18] The precise way viral respiratory illnesses alter airway function is not known. The virus may induce epithelial damage in the respiratory tract and stimulate vagally enervated irritant receptors located in the epithelium,[19] it may stimulate production of virus-specific immunoglobulin (Ig) E antibodies,[20] enhance histamine release from human basophils,[21] and prime leucocytes to generate increased amounts of superoxide which, in turn, may cause airway epithelial injury.[22] Can vaccination cause such changes and induce asthma exacerbation? Since influenza vaccine is given in autumn during the peak season for colds and asthma exacerbation, a vaccinee may experience asthma symptoms or a decrease in pulmonary function because of a concurrent cold or because of weather change rather than the vaccination.

The vaccines currently in use include inactivated 'whole-virus' vaccines prepared from intact, purified virus particles, 'split-virus' (subvirion or subunit) vaccines prepared by the additional step of disrupting the virus and purified surface-antigen vaccines. All are generally well tolerated, but the whole-virus vaccines are associated with higher rates of adverse effects in young children.[5] Split-product vaccines are much less reactogenic. Live influenza virus vaccines are not yet available but have been in clinical trials for a number of years.

1. Anecdotal Reports of Severe Asthma

A few anecdotal reports have described serious asthma exacerbations with vaccination.[23,24] However, a causal relationship has not been clearly established since the vaccine is administered at the time of year when the background incidence of asthma exacerbation is high. Only well designed placebo-controlled, prospective studies will be able to provide accurate estimates of such severe asthma exacerbations, but few placebo-controlled studies have been performed, partly for ethical reasons. However, a crossover design should avoid ethical problems.[25] In addition, it is difficult to conduct such trials because of the large number of patients required, especially when the difference of incidence between the 2 groups is small. For example, if the true difference in severe asthma exacerbations in 2 groups were 5%, 750 patients would be required; if the difference were 2%, about 2220 patients would be required to achieve a statistical power of 80% at a significance level of 0.05.

2. Open Trials in Stable Patients with Asthma

Several investigators described mild adverse effects ranging from decreased peak flow (PK), increased medication requirements or increased airway irritability measured by histamine or methacholine challenge within 48 hours after vaccination.

Ouellette and Reed[26] reported increased bronchial reactivity to methacholine in 9 out of 10 asthmatic adults for 3 days following polyvalent influenza vaccine. They measured the change in forced expiratory volume (FEV_1) after a standard dose methacholine challenge. There was a 24.7% decrease before vaccination and 42.2% decrease 1

day after vaccination in patients with asthma *vs* 3.2% and 2.7%, respectively in normal controls. However, baseline FEV_1 and peak expiratory flow (PEF) were unchanged before and after vaccinating both groups.

Bell et al.[27] administered killed-virus vaccine to 79 children with chronic asthma who required long term residential rehabilitation. Half of the patients were immunised 2 weeks before the rest, and those not yet immunised acted as controls over the 2 week interval. They observed a significant rise in the need for bronchodilating drugs, 0.35 more treatments per day ($p < 0.01$) in vaccinees versus controls at 48 hours after vaccination. They also recorded a transient decrease in morning PEF rate [equivalent to a mean PF decrease of 12% ($p < 0.05$)], in vaccinees compared to controls, 48 hours after vaccination. These modest changes, although statistically significant, could certainly lie within the range of daily variation seen in an open trial, especially in moderate to severe asthma populations during the autumn. Two-thirds of the patients were receiving long term corticosteroid therapy. A similar proportion of patients experiencing an adverse reaction (i.e. a decrease in PF of 20% or more) and patients not experiencing an adverse reaction (i.e. no change or increased PF), were receiving long term prednisone therapy (79% and 68% respectively). This result implies that there is no significant correlation between pulmonary function changes and long term prednisone therapy after influenza vaccination. They also found that there was no correlation between the magnitude of antibody response and corticosteroid therapy status.

Banks et al.[28] observed no change in overall mean PEF, diurnal variation in PEF, symptom scores or bronchodilator requirements, in a group of 19 patients with asthma after they received an injection of killed influenza virus vaccine. However, they did record an increase in bronchial reactivity to histamine in 47% of patients with asthma following influenza vaccination as measured by the histamine dose that induced a 20% fall in specific airway conductance from baseline (D_{20}) [3.27 ± 3.54 before and 1.47 ± 2.13 after vaccination]. This increase in bronchial reactivity was noted only among those patients who experienced an increase in antibody titre soon after vaccination.

Other investigators reported no significant adverse effects on asthma symptoms following influenza vaccination. Albazzaz et al.[29] administered subunit influenza vaccine to 14 adults with moderately severe asthma. None of the patients reported local or systemic adverse effects and there were no significant changes in the symptoms of asthma, use of bronchodilator drugs or PF. Pulmonary function test (PFT) and histamine challenge test results obtained during the week before, 2 days and 2 weeks after vaccination showed no significant changes.

DeJongste et al.[30] administered inactivated vaccine to 9 patients with asthma and 7 control patients. They reported that pulmonary function, bronchial responsiveness to histamine and leucocyte histamine release were not different between patients with asthma and controls following vaccination. However, they did notice increased bronchial responsiveness to histamine in children with asthma after live influenza vaccination.

Ghirga et al.[31] reported no systemic adverse effects following the administration of 150 doses of a highly purified surface-antigen (subunit) influenza vaccine ('Agrippal') to children aged between 7 months and 12 years with moderate to severe asthma. No patients reported worsening of asthma in the following 2 months.

It is important to note that none of the studies described here included placebo-injected patients with asthma.

3. Placebo-Controlled Trials in Stable Patients with Asthma

Kava et al.[32] conducted a placebo-controlled study in adult patients with mild to moderate asthma. Sixteen patients received polyvalent split-virus vaccine and 11 received saline. PFT and bronchial reactivity to histamines were measured immediately before and 2, 3 and 21 days after injection. The need for bronchodilating drugs was not increased in any of the patients. There were no

significant alterations in mean airway resistance, intrathoracic gas volume and specific airway conductance after vaccination. The median dose of histamine inducing a 40% decrease in specific airway conductance (PD_{40}) also remained unchanged. An increased sensitivity to histamine, as indicated by a decrease of PD_{40} of more than 50%, was noted in 33% of vaccine recipients and 45% of saline-injected patients. There was no correlation between airway reactivity and the intensity of the serological response or the symptoms induced by the vaccination.

Stenius-Aarniala et al.[33] conducted a randomised, multicentre, double-blind, placebo-controlled study involving 318 adult patients with moderate to severe chronic asthma with a daily need for anti-asthma medication. 161 patients received vaccine and 157 patient received saline injection. There was no significant difference in mean PF rate, clinical symptoms of bronchial obstruction or need for inhaled bronchodilator medication between vaccinees and controls during the week after immunisation. All vaccinees showed good antibody response as documented by more than 4-fold increase in antibody titre after vaccination.

Recently Nicholson et al.[25] reported a randomised, placebo-controlled crossover trial on the effects of inactivated influenza vaccine on pulmonary function in asthma. Among 255 adults with stable asthma, 11 (4.3%) reported a fall in PEF of more than 20% after receiving the vaccine and 3 (1.2%) after receiving placebo ($p = 0.06$); however, when participants with colds were excluded, there was no significant difference between vaccine and placebo ($p = 0.51$). PEF decreases of more than 30% approached significance (binomial test, $p = 0.06$) only among the first-time vaccinees. The use of β-agonist therapy was not different before and after vaccine or placebo injection in either group. Nicholson et al.[25] concluded that pulmonary-function abnormalities may occur after influenza vaccination but that the risk of pulmonary complications was very small and was outweighed by the benefits of vaccination.

4. Surveillance of Adverse Events

Data from the US,[34] after vaccination of 48 million persons with influenza vaccine against the influenza strain A/NewJersey/76 in 1976 to 1977, revealed an association between vaccination and Guillain-Barre syndrome, yet did not show any evidence of increased occurrence of asthma exacerbation. However, since this vaccine was monovalent it may have been associated with fewer complications than the polyvalent vaccines that are currently being used. Between 1963 and 1991, the UK Committee on Safety of Medicines received reports on 990 adverse reactions to influenza vaccines; of these, only 26 were cases of asthma or bronchospasm.[35] Palache et al.[36] reported that out of 40 million vaccinations with subunit vaccine ('Influvac') since 1981, only 89 serious adverse events were reported to the manufacturer; of those, 5 cases were asthma exacerbations.

5. Influenza Vaccination in Patients with Asthma During Acute Exacerbation

At our institution, we have investigated the safety and immunogenicity of influenza vaccination during acute asthma exacerbation in patients receiving concomitant prednisone therapy.[37] 109 children with a known diagnosis of asthma, aged 6 months to 18 years old, were recruited from a paediatric allergy/pulmonology clinic and paediatric emergency room in inner city Chicago, Illinois, US. 59 patients without asthma symptoms who were not receiving prednisone formed the control group and 50 patients with acute asthma exacerbation requiring prednisone burst therapy formed the prednisone group. All patients from both groups were vaccinated with a trivalent subvirion influenza vaccine. Serum antibody titres to A/H1, A/H3 and B were measured before and 2 weeks after vaccination. Adverse effects noted within 48 hours after the vaccine dose were ascertained during the follow-up visit.

Antibody responses to A/H1 and A/H3 in the prednisone and control groups were the same. Significantly better response to B antigen was seen in

the prednisone group. Only 3 patients (2.7%), 1 in the control and 2 in the prednisone group, reported asthma exacerbations; none required visits to clinics or hospitals. These results suggest that influenza vaccination is not associated with clinically significant asthma exacerbation or worsening of asthma symptoms in patients with acute exacerbation or in patients with stable asthma.

6. Live Influenza Vaccines

Live attenuated vaccines are known to produce more adverse effects including upper respiratory tract infection symptoms.[38] Therefore, there has been even greater concern over the possibility of these vaccines causing asthma exacerbation when administered to patients with asthma. Earlier studies of live attenuated vaccines in adults and children with stable asthma showed increased bronchial reactivity to histamine following vaccination.[30] However, more recent open tolerance studies showed no evidence of increased bronchial reactivity or exacerbations of asthma in patients with asthma vaccinated with live attenuated vaccines. Atmar et al.[39] administered intranasal live influenza vaccine or placebo to 17 adults with asthma and 74 healthy adults; there were no significant changes in PFT, forced vital capacity (FVC), FEV_1 or forced expired flow at 25 to 70% of FVC, in the week after immunisation. Tanaka et al.[40] immunised institutionalised children with asthma and psychomotor retardation with live trivalent influenza vaccine. In this trial, 20 children with asthma received vaccine and 25 placebo. Major complaints were fever and rhinorrhoea but no children reported wheezing. However, it would not be prudent to use this type of vaccine for patients taking long term systemic corticosteroids until extensive safety data in this population are available.

7. Conclusion

Extensive experience with killed subunit influenza vaccine has shown no evidence that vaccination exacerbates asthma or is harmful to patients with asthma. Limited experience with live influenza vaccine also suggests that it may be safely given to patients with asthma. Earlier reports describing minor pulmonary function changes or increased bronchial reactivity did not include placebo controls and the results as reported are difficult to interpret. A recent study using a placebo-controlled crossover design showed that pulmonary function abnormalities may occur after influenza vaccination in some patients without exacerbation of the clinical symptoms of asthma.[25] Although vaccine efficacy has not been unequivocally demonstrated in patients with asthma, the potential benefits from prevention of morbidity associated with influenza infection in these individuals outweighs the theoretical concerns over the efficacy and safety of influenza vaccination.

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