Influenza Vaccination and Asthma
Current Studies and Recommendations

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Abstract

Influenza is an important epidemic and pandemic illness associated with serious morbidity and mortality in unprotected communities. Patients at increased risk of infection are those with pre-existing cardiopulmonary disease including asthma. The influenza virus has the ability to produce antigenic changes posing problems for vaccine development.

Influenza vaccines have been available for over 50 years. Despite the continuing global threat posed by infection and recommendations in many countries that immunisation should be widely given, uptake rates are variable and often poor. It has been demonstrated that infection with influenza and other respiratory viral pathogens can produce exacerbations of asthma throughout the age groups. Despite this, vaccine uptake rates in asthmatic populations are quite low. Poor uptake rates are attributed to a number of factors and we review the evidence for the widely held view that influenza vaccination produces exacerbations of chronic airflow obstruction including asthma. Observational studies have found conflicting results: some post immunisation changes in bronchial hyperreactivity and increased requirements of bronchodilator therapy have been in some, but not all, studies. Placebo-controlled trials have not demonstrated any clinical deterioration although one study showed a small reduction in peak expiratory flow rate. Intranasal administration of cold-adapted live vaccines and new nucleic acid vaccines are briefly considered. Live adapted vaccines have been shown to be effective in influenza immunoprophylaxis and limited data on their use in patients with asthma suggest that they can be administered safely.

In conclusion, based up on current studies and evidence, it seems likely that influenza infection produces morbidity in patients with asthma but that any potential adverse effects of influenza immunisation are outweighed by the benefits in this population. However, placebo-controlled trials are few and only small numbers of asthmatic patients have been investigated.

Although vaccines have been available for 50 years, influenza remains an important cause of global epidemic and pandemic illness. There have been 4 pandemics in the twentieth century, with over 20 million deaths attributed to the outbreak of 1918-19 alone. The influenza virus has the ability

to change its antigenic characteristics at frequent intervals posing problems with disease prevention by vaccination.

1. Influenza Types A and B

Influenza viruses are enveloped RNA viruses that belong to the family *Orthomyxoviridae*. They were originally classified serologically into 3 distinct types: A, B and C, based on differences between their core proteins. Both influenza A and B possess 2 surface glycoproteins, the haemagglutinin (HA) and neuraminidase (NA) proteins. Influenza A viruses are further divided into subtypes depending on antigenic differences between their surface glycoproteins. Fifteen distinct HAs (H1-H15) and 9 different NAs (N1-N9) are now recognised for influenza A. Influenza A viruses with HAs of the H1, H2, H3 subtypes and NAs of the N1 and N2 subtypes have caused pandemic and epidemic illness in humans this century. Strains of influenza are identified on the basis of type (i.e. influenza A, B or C), host of origin, geographic site of virus isolation, serial number, year of isolation and, for influenza A viruses, subtypes of HA and NA antigens.

Influenza A is usually responsible for pandemics and annual epidemics, while influenza B is more stable and causes outbreaks every 2 to 4 years. Pandemics are the result of 'antigenic shift' which produces a virus with a new HA to which there is little or no background immunity in the population. The pandemics of A/Asian (H2N2) influenza in 1957 and A/Hong Kong (H3N2) influenza in 1968 arose by genetic reassortment between human and avian viruses.

Interpandemic outbreaks are annual and variable depending on the background immunity of the population acquired from previous infections. They are caused by viruses which have undergone minor antigenic changes or 'antigenic drift'. New strains of virus are generated from the accumulation of random point mutations in the RNA genome at points coding for exposed sections of either NA or HA.[1]

2. At Risk Patient Groups

Influenza produces an acute febrile respiratory illness with cough, myalgia and headache lasting for 3 to 4 days. Symptoms can persist for several weeks.[2] Life-threatening complications include viral or secondary bacterial pneumonias and exacerbations of underlying cardiorespiratory disease. Patients at increased risk of mortality and morbidity include those with pre-existing cardiopulmonary disease, asthma, congestive cardiac failure, severe renal impairment, diabetes mellitus, the elderly and long term institutionalised patients.[3,4] Infants and children may develop croup, bronchiolitis and otitis media as a result of infection.[5]

Influenza infection has been associated with exacerbations of asthma in both children[6-8] and adults,[9,10] and it may contribute specifically towards the pathogenesis of asthma.[11] Influenza pneumonitis with secondary bacterial infection is more common in patients with pre-existing cardiopulmonary disease including asthma.[12] The underlying lung disease may limit respiratory reserve increasing the risk of respiratory failure during infection. Hyperreactivity and impaired mucociliary clearance may also contribute to the bronchospasm and mucus plugging associated with infection. During influenza outbreaks, hospital admission rates for respiratory illnesses increase as does mortality from all causes.[13,14]

3. Vaccine Development

The mainstay of prophylaxis against influenza is vaccination. Chemoprophylaxis with amantadine and rimantadine[15] has been available for several decades and, recently, neuraminidase inhibitors have also been successfully developed.[16] Vaccines are usually only effective against viruses with similar antigenic characteristics.[1,17] Although previously formed antibodies to related strains may provide partial protection against viruses produced by antigenic drift, they are not effective against unrelated strains produced by antigenic shift.

The use of killed influenza vaccine was first developed clinically by Stokes in 1936; however, early whole virion formalin-inactivated vaccines were strongly associated with adverse effects. Current vaccines are usually trivalent, containing 2 influenza A subtypes and 1 influenza B strain. Vaccine composition is reviewed annually and the antigenic make-up altered depending on antigenic drift. Split product virus vaccine, containing formalin-disrupted viral particles, and a purified surface antigen vaccine are both widely available.[18]

Serum haemagglutination-inhibition antibody titres of approximately 1:40, a level which represents the 50% protective level, are evident in 90% of normal subjects after vaccination with influenza A antigens.[19] Effective protection against influenza infection can be achieved in 70 to 95% of young healthy adults when there is a good match between the vaccine and circulating strains.[20] Vaccination of elderly patients is associated with significant reductions in infection rates, progression of complications, hospitalisation and mortality rates.[21,22]

4. Vaccination in Patients with Asthma

Influenza vaccination has been shown to reduce exacerbations of asthma prompting recommendations that patients with moderate to severe disease should receive annual immunisation.[23] Many countries in Europe and North America recommend influenza vaccination for those >65 years of age, patients in residential homes and adults and children with chronic cardiopulmonary disease, including asthma.[24] Despite these guidelines, immunisation uptake rates remain variable and are often poor[12,25] with <20% of chronic asthmatics protected in the UK.[26]

Several factors may contribute to this low uptake. Even during influenza outbreaks, less than half of patients with respiratory illnesses actually have laboratory documented influenza.[16,26] Patients become disillusioned as other illnesses may be attributed to influenza and thus vaccine failure or, if infection occurs shortly after vaccination, to the vaccine itself. Some doctors may be reluctant to offer patients influenza vaccination because of the possibility of provoking an exacerbation of asthma.

4.1 Killed and Inactivated Vaccines

4.1.1 Observational Studies
Concern over vaccine safety among asthmatics has been raised because of a small number of adverse case reports.[27,28] However, observational studies looking at pulmonary function and respiratory symptoms have produced conflicting evidence. Postimmunisation decreases in mean peak expiratory flow rates (PEFR), increases in bronchial hyperreactivity, and increases in bronchodilator administration have all been reported,[23,29] but have not been confirmed in other studies.[30-34]

The 1976 US National Influenza Vaccination Program involving over 48 million people (organised in response to an outbreak of swine influenza among military personnel) did not identify any respiratory complications with vaccine administration.[34] Further, a UK Department of Health pilot study in 33 patients did not find any exacerbations of asthma, increased medication use or change in peak flow rates 2 weeks after immunisation.[32] Influenza immunisation of children during acute exacerbations of asthma requiring systemic steroid therapy was not associated with adverse effects, worsening of symptoms or serological vaccine failure.[35]

4.1.2 Placebo-Controlled Studies
Placebo-controlled trials are the best method of studying whether influenza immunisation causes adverse respiratory events. However, large numbers of volunteers would be required to establish the presence of an infrequent complication and, hence, such trials are few. To detect a significant difference ($p < 0.05$) between observed general practitioner consultation rates of 2.8% after placebo and 4.1% after vaccination, a crossover study with 80% power would require 3246 patients.[36]

Separate studies in patients with and without asthma or other chronic respiratory diseases have

reported no significant difference in systemic symptoms or respiratory adverse effects between recipients of vaccine and placebo.[37-40] 1806 elderly Dutch patients involved in a randomised double-blind study did not report any significant systemic adverse effects for 4 weeks after immunisation compared to placebo, although respiratory symptoms were not specifically sought for.[39] A Finnish double-blind placebo-controlled study followed 291 patients with chronic asthma for 8 months postimmunisation with killed influenza vaccine and did not find any reduction in PEFR.[38] However, a small but significant fall in PEFR was reported in an Australian double-blind placebo-controlled crossover trial of only 28 patients, but no additional bronchodilator treatment was required.[40]

Influenza vaccination is undertaken during the autumn when colds and other respiratory viral pathogens commonly exacerbate asthma. A randomised placebo-controlled crossover trial conducted to determine the effects of inactivated influenza vaccine on pulmonary function in patients with asthma was designed to take into account the prevalence of common colds at this time. Using paired data for 255 patients, there was a significant fall in peak expiratory flow of >20% in 11 patients and >30% in 8 patients postvaccination compared with placebo in first-time vaccinees. However, this difference became insignificant when patients with concurrent colds were excluded from the analysis.[36] The authors felt that the benefits of influenza immunisation outweighed any potential respiratory adverse effects.

4.2 Live Vaccines

Intranasal administration, which has been used for live attenuated vaccines, may have improved immunogenicity by evoking local secretory IgA responses and better acceptability, especially in children. Live cold-adapted vaccines in children have been shown to be as effective as killed vaccines in influenza immunoprophylaxis,[41-48] and to reduce complications (such as otitis media) to a greater extent and have similar or better tolerability than killed vaccines.[41-48]

Conflicting results have been obtained with live vaccines in studies of patients with underlying lung disease. Infections with live-attenuated vaccines in normal patients and those with underlying chronic respiratory disease were found to augment airway smooth muscle responses and increase bronchial hyperreactivity.[49-52] Other studies have not reported adverse systemic effects or effects on pulmonary function with live vaccines in patients with[48] or without[50,51] underlying chronic respiratory disease.

4.3 Nucleic Acid Vaccines

Recently, a new approach has been the development of nucleic acid vaccines. DNA sequences encoding the antigenic protein can be integrated into bacterial plasmids, grown, purified, and then inoculated into the host. Expression of the plasmid DNA produces the antigenic protein which, in turn, hopefully leads to an immune response.[53] Experiments in mice have shown that influenza HA-specific IgG and IgA can be induced by both intramuscular and intranasal administration of plasmid-containing HA sequences. Further developments in this field are awaited.[54]

4.4 Pharmacoeconomic Considerations

There has been debate in the US as to the economic benefits of offering influenza vaccination to all healthy adults and children, as well as those at higher risk.[55-59] Influenza and the effectiveness of immunisation are difficult to study for several reasons:

• Annual epidemics vary in incidence and severity and, ideally, studies should continue over several years

• There may be mismatches between vaccine and wildtype strains

• Subclinical influenza and other respiratory viral pathogens make estimates of the incidence of influenza infection during outbreaks imprecise

- Varying endpoints, such as pneumonia, death and hospitalisation rates, should be considered.[59]

The net benefit of vaccination can be estimated from the frequency of vaccine adverse events, the attack rate of influenza and associated complications, and the efficacy of the vaccine. The annual influenza infection rate in young adults aged from 15 to 24 years is around 20 to 25% and 15% for those aged 25 to 59 years based on the Houston family study.[60] Since influenza vaccines prevent about 75% of adult cases and symptomatic influenza causes exacerbations in more than 70% of children and adults with asthma, then vaccination should prevent far more exacerbations than it causes.[36]

5. Conclusions

Whilst early studies found asymptomatic changes in pulmonary function following influenza vaccination, small numbers of studies with inactivated vaccines do not suggest a significant clinical problem with exacerbations of pre-existing asthma or chronic airflow obstruction. However, the number of asthmatic patients in these trials was not large enough to detect unusual effects. Live influenza virus vaccines have been associated with mild pulmonary function abnormalities in patients with underlying lung disease but, again, limited small placebo-controlled trials have failed to reveal significant clinical adverse effects.

In conclusion, the available data indicate that pulmonary function abnormalities may occur as an infrequent complication of influenza vaccination. The risk is considered to be very small and outweighed by the benefits of vaccination. Immunisation of asthmatics is currently recommended in the UK and should be offered by general practitioners to their patients.[59,61]

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