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Influenza and pneumococcal vaccination: an update

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ABSTRACT Influenza and *Streptococcus pneumoniae* cause considerable morbidity and mortality. Excess deaths in the UK per year from influenza have been between 2,000 and 4,000 in recent years. There are over 5,000 cases of invasive pneumococcal disease in the UK per annum. Vaccination was introduced to the UK in the eighteenth century. Since then, there have been major advances in the development and administration of vaccines. The use of hens' eggs for viral growth meant that influenza vaccination became more widely available, and the recognition of different serotypes of pneumococcus led to increased effectiveness of immunisation. Recent developments have led to a conjugate pneumococcal vaccine which is effective in children and has had dramatic effects on the incidence of invasive disease in the US. It has recently been introduced into the childhood immunisation programme in the UK. This article gives a background to the development of influenza and pneumococcal vaccination, and an update on recent advances and recommendations.

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INFLUENZA VACCINATION

Background

Influenza has been a major cause of morbidity and mortality for hundreds of years. The Health Protection Agency monitors the activity of influenza each year, and excess deaths attributable to the virus have been estimated at between 2,000 and 4,000 in recent years in the UK.

Influenza viruses are RNA viruses of the orthomyxovirus family. In humans, most major outbreaks are associated with type A or type B viruses. The viruses contain nucleoproteins that determine virus type (A, B, or C). Surface antigens are more variable. They are spike-like structures on the outside of the virus made up of haemagglutinin (H) and neuraminidase (N), the characteristics of which define the sub-type. For example, H2N1 is used to describe a strain of influenza A virus.

The idea of human vaccination was introduced to the UK by Edward Jenner in the eighteenth century. He used cowpox virus to provide protection against the more virulent smallpox virus. The word vaccination is derived from *vacca* (Latin for 'cow') and was later adopted by Louis Pasteur to include immunisation against other diseases. The influenza vaccine has now been available for approximately 60 years. In the 1930s, hens' eggs began to be used for viral growth, and by the 1940s improved techniques meant that the influenza vaccine was more widely available.

The current Department of Health target for uptake of vaccine is to immunise 70% of those recommended for vaccination. In recent years, this target has largely been reached; in the 2005–2006 season, 75·3% of those aged 65 and over were vaccinated in England.

Influenza vaccine is not a single constant vaccine and the composition needs to change on an annual basis, reflecting the fact that influenza viruses themselves are continually undergoing antigenic change. Therefore immunity acquired by being infected with one strain of influenza virus does not protect against further variants of the same subtype. The World Health Organisation issues a recommendation each year for vaccine composition, with the aim that the strains included in the vaccine will match circulating strains of influenza and therefore provide optimum protection. The recommendations are made on the basis of information from the Global Surveillance Network and, for the Northern Hemisphere, currently include two influenza A viruses (H1N1 and H3N2) and one influenza B virus. As the vaccine generally covers three influenza virus strains, the term 'trivalent' vaccine is used.

Influenza vaccines are available as either inactivated or live attenuated influenza vaccine. In most countries, inactivated vaccine is used and is available as either whole virus, split virus, or a sub-unit vaccine.

Live vaccine is still under evaluation and appears promising. The virus is live, but cold-adapted to replicate at 25°C, and so its effects are attenuated when used at body temperature. It therefore acts as a vaccine, rather than causing disease. It is administered as a nasal spray, which is advantageous. Ohmit *et al*[1] have recently published data on the efficacy of both inactivated and live attenuated vaccine. Both appeared to be efficacious, but live nasal vaccine less so (e.g. absolute efficacy of 77% vs 57% when isolating virus in cell culture post-vaccination), potentially because of reduced protection against influenza B viruses. Further studies are awaited.

Owing to the changing nature of the virus, and the need for a different vaccine each year, vaccine cannot be stockpiled. Current global manufacturing capacity is approximately 300 million doses per year, and 90% of this production capability is based in Europe and North America. This would be a concern in the event of pandemic influenza as, even when the pandemic strain is known, production may not be able to meet demand and distribution would be a problem.

How effective is the influenza vaccine?

Large studies of the inactivated influenza vaccine report 70–90% effectiveness in preventing the development of clinical symptoms in children and healthy adults. Ahmed *et al*[2] found that vaccination also reduced hospital admissions by 63% in Leicester during the 1989–1990 epidemic.

However, the vaccine is not as effective in the elderly and in those with immune deficiency when compared to healthy individuals. For instance, Govaert *et al*[3] reported that in 1838 patients over age 65, the vaccination reduced incidence of serological and clinical influenza by only 50%. Effectiveness also depends on the correlation between viral strains chosen for vaccine development and circulating strains. For instance, the vaccine for 2004 was less effective compared with previous years because this correlation was weak.

Who should have the influenza vaccine?

Several studies have suggested that whilst vaccinating the entire healthy adult population is likely to have individual benefits, it is unlikely to be cost-effective. Therefore, target groups based largely on increased susceptibility to infection have been identified for the vaccination. These include: (a) those in institutional care, e.g. nursing homes; (b) those with chronic disease, e.g. heart disease, lung disease, cancer, immune deficiency, renal disease, diabetes, liver disease; and (c) those aged over 65 years.

In addition, vaccination of healthcare workers and those caring for the elderly is recommended in view of the benefits to the elderly under their care. For instance, Hayward *et al*[4] found a significant decrease in mortality (rate difference per 100 residents –5·0), health service use (rate difference –2·0) and influenza-like illness (rate difference –9·0) in residents, following vaccination of care home staff.

Influenza vaccine on discharge from hospital

Many patients over 65 years of age miss influenza (and pneumococcal) vaccinations as a result of hospitalisation. Vaccinating these patients on discharge can have significant benefits in terms of uptake of vaccine. Crouse *et al*[5] demonstrated that implementing a standing order to be considered on hospital discharge improved vaccination rates from 9·6% to 40·3%.

Are there contraindications?

Contraindications to inactivated vaccine include egg allergy and acute febrile illness. There has been some debate over the safety of influenza vaccination during pregnancy. Currently, the Department of Health recommends vaccination of women in high risk groups, whatever their stage of pregnancy.

The live vaccine should not be given in those who are immunosuppressed, have had previous Guillain-Barré syndrome, or those under 18 years who are on aspirin (risk of Reye's syndrome).

PNEUMOCOCCAL VACCINATION

Background

Streptococcus pneumoniae is an encapsulated Gram-positive diplococcus. Variation in the composition of the polysaccharide capsule results in 90 different serotypes. Asymptomatic carriage of *S. pneumoniae* is common, as is self-limiting otitis media in children. The most common forms of invasive disease are pneumonia, meningitis, and bacteraemia. The most susceptible are children, the elderly, and the immunosuppressed. Over 5,000 cases of invasive pneumococcal disease occur in the UK each year leading to considerable morbidity and mortality. Approximately 10% of cases are in children. Antibiotic resistance to pneumococcus is an increasing problem. In 2000, 13% of UK isolates causing invasive disease were resistant to erythromycin and 7% showed intermediate or full resistance to penicillin. Worldwide rates may be higher and rates of more than 30% have been found in Europe, Asia, and the US.

Natural immunity to pneumococcus is low owing to the

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existence of the different serotypes. Immunity tends to increase into adulthood but depends on exposure to these different forms of pneumococcus. Any natural immunity gained tends to decrease in the elderly. The mechanism of immunity to pneumococcus is unclear. Traditionally it has been thought to depend on anti-capsular antibodies. Hence vaccines have been based on the polysaccharide capsule. However, recent studies have highlighted the importance of CD4+ T cells in antibody-independent acquired immunity to pneumococcal colonisation.

POLYVALENT VACCINE

Vaccines against pneumococcus have been available since the early twentieth century, with the earlier forms containing only a small number of antigens. For many years now, polyvalent polysaccharide vaccines have been used. The current polyvalent vaccine contains capsular antigens from 23 of the most common serotypes responsible for invasive disease in Western countries. Although this vaccine is still used in adults, its use in children has been limited by poor antibody response and immunological memory, which led to poor protection rates.

Current Department of Health recommendations for vaccination in adults include the following groups:

- Those over 65 years of age.
- Asplenic patients or those with splenic dysfunction or conditions leading to dysfunction (e.g. coeliac disease).
- Patients with chronic respiratory, heart, renal, or liver conditions.
- Immunosuppressed patients.
- Those with cochlear implants.
- Patients with cerebrospinal fluid leaks.

Clinical effectiveness

There is a marked contrast between clinical effectiveness of the vaccine in healthy young individuals when compared with the other group recommended for vaccination – the elderly. For example, Austrian *et al*[6] conducted large epidemiological studies in a population of healthy young novice gold miners in South Africa in the late 1970s. The population (with previously high rates of invasive disease) showed a 78·5% reduction in invasive pneumococcal illness after vaccination.

In contrast, three randomised controlled trials in the 1990s found the vaccine to have no protective effect against invasive pneumococcal disease or death in the elderly. However, Koivula *et al*[7] did find an efficacy of 59% in the subgroup who were elderly and had other medical factors related to high infection risk. More recently, Vial-Corcoles *et al*[8] found the 23-valent vaccine to have a protective effect against death from pneumonia in those over 65 years.

Cost effectiveness

The cost effectiveness of the vaccination programme in the elderly has also been debated. There have been a number of studies, mainly in the US, that have found vaccination in the elderly to be cost-effective on the grounds of improved health and medical costs of treating those with invasive disease. For example, Sisk *et al*[9] found vaccination to be cost-saving and felt it was greatly underused on both health and economic grounds. As with influenza vaccine, a way of increasing uptake of the vaccination may be to offer immunisation at hospital discharge.

CONJUGATE VACCINE

There have been significant recent advances in the development of pneumococcal vaccine involving the immunisation of children. A new conjugate vaccine made by coupling seven of the most common pneumococcal polysaccharides with a protein carrier (CRM 197) is now available and was licensed in the UK in 2001. As well as being effective in children, surveillance has suggested a decrease in the incidence of penicillin-resistant pneumococcal disease from 15% to 5%. When conjugate vaccine was introduced in the US, the incidence of invasive pneumococcal disease caused by the seven serotypes in the vaccine was reduced by 94% in children under five years and by 62% in children over five years. Whitney *et al*[10] found the vaccine to be effective in 96% of healthy children and in 81% with chronic disease.

A subsequent reduction in invasive pneumococcal disease in adults was seen in the US, which is likely to be related to herd immunity. Since 2006, the conjugate vaccine has been recommended as part of routine childhood immunisation in the UK. Whether corresponding reductions in invasive infection rates in adults will occur remains to be seen.

KEYPOINTS

- Influenza vaccine is a trivalent vaccine based on the circulating strains of influenza with changing recommendations for composition.
- The inactivated influenza vaccine is currently the most commonly available. Live vaccine is still under evaluation and appears promising. It is administered by nasal spray which is potentially advantageous.
- Vaccination of healthcare workers with influenza vaccine is recommended in view of the benefits to the elderly under their care.
- 23-valent pneumococcal vaccine appears to be cost effective in the elderly although debates about clinical effectiveness continue.

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- The new pneumococcal conjugate vaccine became part of routine childhood immunisation in the UK in 2006. When introduced in the US, significant reductions in the incidence of invasive pneumococcal disease in adults were seen.

REFERENCES

1 Ohmit SE, Victor JC, Rotthoff JR *et al.* Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med* 2006; **355(24):**2513–22.

2 Ahmed AH, Nicholson KG, Nguyen-van Tam JS, Pearson JC. Effectiveness of influenza vaccine in reducing hospital admissions during the 1989-90 epidemic. *Epidemiol Infect* 1997; **118(1):**27-33.

3 Hayward AC, Harling R, Wetten S *et al.* Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ* 2006; **333(7581):**1241.

4 Govaert TM, Thijs CT, Masurel N *et al.* The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *BMJ* 2006; **333:**1241. doi:10.1136/bmj.39010.581354.55 (published 1 December 2006)

5 Crouse BJ, Nichol K, Peterson DC, Grimm MB. Hospital-based strategies for improving influenza vaccination rates. *J Fam Pract* 1994; **38(3):**258–61.

6 Austrian R, Douglas RM, Schiffman G *et al.* Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians* 1976; **89:**184–94.

7 Koivula I, Stén M, Leinonen M, Mäkelä PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Eur Respir J* 2005; **26(6):**1086–91.

8 Vila-Córcoles A, Ochoa-Gondar O, Llor C *et al.* Protective effect of pneumococcal vaccine against death by pneumonia in elderly subjects *Lancet* 2006; **368(9546):**1495–502.

9 Sisk JE, Moskowitz AJ, Whang W *et al.* Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997; **278(16):**1333–9.

10 Whitney CG, Pilishvili T, Farley MM *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *JAMA* 1994; **272(21):**1661–5.

FURTHER READING

- Lexau CA, Lynfield R, Danila R *et al.,* Active Bacterial Core Surveillance Team. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* 2005; **294(16):**2043–51.
- Ortqvist A, Hedlund J, Burman LA *et al.* Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. *Lancet* 1998; **351(9100):**399–403.
- Malley R, Trzcinski K, Srivastava A *et al.* CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. *Proc Natl Acad Sci USA* 2005; **102(13):**4848–53.

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