New techniques in medicine

Pneumococcal vaccine

Keith L Hattotuwa, Charles RK Hind

Summary

Streptococcus pneumoniae is a frequent cause of pneumonia and meningitis. This article looks at the pneumococcal vaccine, its uses, efficacy, and adverse effects and how vaccination may be improved. We also look at the role of the new conjugate vaccines.

Keywords: *Streptococcus pneumoniae*, vaccination, pneumonia, meningitis, conjugate vaccines

Infections caused by *S pneumoniae*

- meningitis
- pneumonia
- otitis media
- peritonitis
- acute endocarditis
- bacteraemia
- suppurative sinusitis
- suppurative arthritis
- purulent conjunctivitis

Box 1

Figure Left upper-lobe pneumonia

The London Chest Hospital,
London E2 9JX, UK
KL Hattotuwa

Royal Liverpool University Hospital,
Liverpool L7 8XP, UK
CRK Hind

Accepted 17 April 1996

Streptococcus pneumoniae is the most common aetiological agent in community-acquired pneumonia, accounting for over two-thirds of cases. Pneumococcal pneumonia affects 1/1000 adults per annum, with a mortality of 10–20%. In addition, 20% of cases of bacterial meningitis are pneumococcal in origin in the UK.¹ *Streptococcus* is also the commonest cause of bacterial meningitis in the US below five years of age with a 6% mortality. With the advent of Hib conjugate vaccine, *Haemophilus influenzae* invasive disease has almost disappeared in developed countries, thus making the pneumococcus the most important organism causing bacterial meningitis in children.

The vaccine - historical aspects

A 23 polyvalent vaccine for prevention of pneumococcal infection has been available since 1983 (a 14 polyvalent vaccine had been available since 1978). It is supplied as a 0.5 ml single-dose vial for intramuscular or subcutaneous injection and is available as Pneumovax II (Merck Sharp & Dohme) and Pnu-Immune 23 (Lederle-Praxis). The vaccine against 23 major serotypes contains 25 µg of purified capsular polysaccharide from each serotype. These 23 serotypes account for about 90% of infections in adults and about 85% in children.^{1,2} Predominant serotypes vary world-wide and have the potential to change, but serotypes 1, 6, 14 and 19 are the commonest serotypes causing disease.

The take-up rate of this vaccine has only been a fraction of the influenza vaccine. It has been estimated that only 10% of persons for whom the vaccine has been recommended have received it.^{2–4}

Effectivity of vaccination

Many studies have failed to draw firm conclusions regarding the efficacy of pneumococcal vaccination. Hirschman and Lipsky in their review conclude that the only prospective, randomised, placebo-controlled trials of pneumococcal vaccination conducted in the US since the mid-1940s failed to show any benefit from vaccination.³ However this statement has been disputed, as several well-conducted retrospective studies have shown its importance in various clinical groups. Thus, Butler *et al* showed an overall efficacy of 57%² while other studies have shown an overall efficacy of 60–70%.⁵ In their indirect cohort analysis, Butler *et al* have shown efficacy among patients with diabetes mellitus to be 84%, patients with coronary vascular disease to be 73%, chronic pulmonary disease 65% and anatomical asplenia 77%. Efficacy was not shown in patients with chronic liver disease, alcoholism, chronic renal failure, leukaemia, lymphoma, multiple myeloma or sickle cell disease, although the sample sizes in these groups were too small to draw firm conclusions.

Those in favour of vaccination argue that it may prevent invasive pneumococcal disease, and that previous studies had flaws in methodology as regards diagnosis. To avoid uncertainties in diagnosis, studies using positive blood cultures or isolation from sterile sites such as cerebrospinal fluid have shown Pneumovax to be clinically effective.² With the growing presence of drug-resistant pneumococci (currently not a problem in the UK) vaccination may play a greater role in prophylaxis.

Pneumovax has not convincingly been shown to be effective in severely immunocompromised individuals.⁶ Colonisation rates are much higher in HIV-positive patients, where there is a 100–300-fold increased risk of bacteraemia due to decreased local mucosal IgA.¹ In this group continuous antibiotic prophylaxis may be better. However, in the immunocompetent elderly (over 65 years of age) it has been shown to be clinically effective. Since the morbidity and mortality in this age group is higher they may benefit from vaccination.

Revaccination does not seem to provide additional protection as the polysaccharide antigens do not seem to stimulate B cell memory. However, due to the high risk of fatal pneumococcal sepsis in asplenic and nephrotic

patients and generally lower antibody titres, revaccination is recommended (see below).

The cost of Pneumovax II is approximately £10 per vial. This cost is considered small compared to the cost of treatment of a case of invasive pneumococcal infection.

Vaccination

The deltoid muscle or lateral aspect of the thigh are the preferred sites for intramuscular injection. Intradermal injection is not recommended and the vaccine should not be given intravenously. Immunity develops approximately three weeks following inoculation. Immunogenic studies have shown that antibody levels decline after five to ten years. Pneumococcal vaccination can be offered all year around. It is, however, most conveniently given as a one-off dose in the other arm during influenza vaccination. This can be done both at general practitioner surgeries as well as on discharge from hospital. Patients should be issued a card with details of vaccination.

Vaccination should be given at least 10 days prior to splenectomy or immunosuppressive treatment.

Target groups

Patients with chronic diseases, hyposplenism and immunodeficiency states are the main target groups for vaccinations (box 2). The recommendations in the US are broader than those in the UK. High-risk patients (eg, asplenic patients) who have received the 14 polyvalent vaccine should be offered the 23 polyvalent vaccine. Revaccination should be done after five years in asplenic and nephrotic patients.⁷

Uptake of vaccination will be improved by increasing awareness of its usefulness in high-risk patients. The role of the general practitioner is central in increasing uptake; displaying posters in surgeries is most effective, especially when influenza vaccine is being advertised.

Routine enquiry into vaccination status in the listed high-risk groups should be part of history taking and those not vaccinated should be identified. Hospital discharge summaries and clinic referral letters may also be used to indicate high-risk status and thus alert general practitioners to the need for vaccination.⁸

Drug interactions, contraindications and adverse effects

No drug interactions have been shown to date for pneumococcal vaccine. Adverse effects are generally mild and serious reactions are rare. However, care must be taken in patients who are severely compromised cardiovascularly or with respiratory impairment where systemic adverse reactions may be dangerous. Revaccination is not recommended due to the increased incidence of adverse effects, except in the special cases mentioned above. Children below two years of age do not show a satisfactory immune response and therefore vaccination in this age group is not recommended.

Future developments

New conjugate vaccines covering seven serotypes are under study. With the Hib conjugate vaccine there appears to be a virtual disappearance of invasive *Haemophilus influenzae* infections. Conjugate vaccine are more immunogenic as they confer T-cell-dependent immunity, which is not dependent on polysaccharide antigen detection. Polysaccharide antigens have only a short-term effect in adults, however, and are not effective in children under two years of age. They elicit a poor response in the immunocompromised.

Preliminary studies have shown that, with the conjugate vaccines, immunity has been conferred to infants, recipients of bone marrow transplants where the donor was immunised, and newborn babies whose mothers were immunised. Preliminary results have also shown it to decrease the newborn's response to measles, pertussis, tetanus and Hib vaccines. Therefore, further controlled studies are required prior to advocating this practice.

Conjugate vaccines also have been shown to prime for a booster vaccine with polysaccharide vaccines. Type 6B, which is poorly immunogenic and causes invasive disease, requires at least three doses to achieve significant immunity.

The Lederle 7-valent conjugate vaccine covers 62.9% of disease in Europe and 93.6% in the USA. This is due to variation in serotypes world-wide and the fact that the predominant serotypes may change. It has been suggested that a 9-valent global vaccine should be made.

Pneumococcal vaccination: indications

UK

- chronic cardiac disease
- chronic pulmonary disease
- chronic liver disease (including cirrhosis)
- chronic renal disease (including nephrotic syndrome)
- diabetes mellitus
- hyposplenism (including homozygous sickle cell disease)
- immunodeficiency states (including HIV infection)

US (additional indications)

- age ≥65 years
- cerebrospinal fluid leakage
- Hodgkin's disease
- multiple myeloma
- alcoholism

Box 2

Pneumococcal vaccination: contraindications

- pregnancy
- breast feeding
- age <2 years
- acute infection
- pneumococcal vaccination in last three years

Box 3

Pneumococcal vaccination: adverse effects

- erythema, induration and pain (50%)
- low-grade pyrexia (1%)
- anaphylaxis (rare)

Box 4

Conclusions

Pneumococcal vaccination appears to be a safe, cheap, effective vaccination to protect certain high-risk groups against invasive pneumococcal disease. It is under-utilised in the UK and an increased awareness programme among healthcare workers and patients is required.

The UK guidelines, like the US guidelines, should include all patients above 65 years of age.⁹ Further evaluation of vaccination is needed in the severely immunocompromised.⁶

The new conjugate vaccines which preliminary studies have shown to be safe, efficacious, and more immunogenic, and which can be offered to children under two years, are eagerly awaited for general use.

- 1 Department of Health. *Immunisation against infectious disease*. London: HMSO, 1996; pp 167–72.
- 2 Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993; 270: 1826–31.
- 3 Hirschman JV, Lipsky BA. The pneumococcal vaccine after 15 years of use. *Arch Intern Med* 1994; 154: 373–7.
- 4 Fiebach N, Beckett W. Prevention of respiratory infection in adults. Influenza and pneumococcal vaccines. *Arch Intern Med* 1994; 154: 2545–57.
- 5 Fedson DS, Shapiro ED, Laforce FM, *et al*. Pneumococcal vaccine after 15 years of use. Another view. *Arch Intern Med* 1994; 154: 2531–5.
- 6 Jain A, Jain S, Gant V. Should patients positive for HIV infection receive pneumococcal vaccine? *BMJ* 1995; 310: 1060–2.
- 7 Working party of the British Committee for Standards in Haematology, Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996 312: 430–4.
- 8 Morgan R, King D, Turnbull C. Influenza vaccination: do the aged reap the benefit? *Postgrad Med J*, 1995; 71: 22–3.
- 9 Mayon-White D. Pneumococcal pneumonia: why vaccinate elderly people? *Care of the Elderly* 1994; 355.

Medical Anniversary

WILLIAM H WELCH, 8 APRIL 1850

William Henry Welch (1850–1934) was born in Norfolk, Connecticut, USA, son of a large medical family (his father, grandfather and four uncles were doctors). He studied at Yale before joining the College of Physicians and Surgeons, Columbia University, New York, for his medical degree (1875). A medical school prize of a microscope, an uncommon instrument for those days, surely helped to shape his future as a pathologist and bacteriologist. He was Professor of Pathology at Bellevue Hospital (1879–84), until he was invited to take the Chair of Pathology at the Johns Hopkins Hospital; and in 1893 became first Dean of the medical school. His name is attached to *Bacillus* or *Clostridium welchii*, isolated from a syphilitic bricklayer with subcutaneous ‘emphysema’, which was, of course, gas gangrene.

He was known affectionately as Popsy and as the Dean of all American medicine. He was a short and portly bachelor with a white moustache, Van Dyck beard, twinkling eyes; a lover of cigars and good wine, he was a supporter of both opera and of the Baltimore Orioles baseball team.

— DG James

Commemorative window from the ‘Human Endeavor’ series in Grace Cathedral, San Francisco, USA