EDITORIAL

Pneumococcal vaccine

In the first 13 years, 1979–1991, that pneumococcal vaccines were licensed in Britain, fewer people were vaccinated than died from pneumococcal infection. Pneumococcal vaccines were under-used because they and the burden of pneumococcal disease were unknown to many doctors; amongst the few that knew, vaccine efficacy was thought to be unproved. By 1989, when the current 23-valent pneumococcal vaccine was licensed in Britain, the arguments in favour of using this vaccine were strong, but there was no national policy on the use of pneumococcal vaccine until July 1992. Since then, the use of pneumococcal vaccine in Britain has risen from 10 000 doses a year in 1992 to c. 450 000 doses in 1995 (personal communication, to T. Dick, Pasteur-Mérieux). The British policy is that pneumococcal vaccine should be offered to people over the age of 2 years who have increased risks of invasive pneumococcal disease: people with chronic heart or lung disease, renal failure or nephrotic syndrome, chronic liver disease, asplenia, sickle cell disease, diabetes and people who are immunosuppressed, including those with HIV infection [1]. The campaign to get asplenic people vaccinated may have catalysed this policy into practice, but now the regular Autumn influenza vaccination programme in general practice can reach most of the others with medical indications for pneumococcal vaccine. It is timely to review the basis for this policy, as pressure mounts to extend vaccination to all people over 65 years, as in the USA [2].

The main thrust of the present pneumococcal vaccine policy in the UK is to prevent pneumonia, especially pneumonia with bacteraemia. The incidence of pneumococcal pneumonia is estimated to be 1–4.7/1000 adults each year, and the case fatality rate is 11% [3]. On these estimates, there are at least 40 000 cases and 4000 deaths in the UK each year. The incidence of chest infections seen in general practice patients over the age of 60 years is higher at 66/1000 each year, of which c. 40% are pneumococcal infections [4]. The incidence increases with age, which has an inverse relationship to naturally occurring antibody levels and with the immunological response to pneumococcal vaccination. Immunity to the prevalent types of pneumococci is acquired in childhood, so vaccination in later life can be viewed as boosting pre-existing immunity and filling the gap of types not previously encountered.

Pneumococcal vaccines are purified capsular polysaccharides made from a selection of types of *Streptococcus pneumoniae*. The choice of types was based on the relative frequency of the various types in naturally occurring bacteraemic and meningitic infections, aiming at world-wide coverage of >90% of isolates from invasive infections and to exploit cross-reactions between types [5]. Discussions on the number and selection of types has re-opened with clinical trials of conjugated pneumococcal vaccines for children under 2 years old.

There is no agreement on what is a protective antibody level against pneumococcal disease. A level of 300 ng of antibody nitrogen/ml of serum is the simplest and lowest measure that has been used. A month after vaccination, levels of 400–1000 ng/ml should be expected for each serotype. A rise in antibody levels is another standard, but a 1.4- or 2-fold rise in geometric mean titres is misleading without a statement on the variance of responses. A stricter standard is that 80% of subjects should have a 2-fold rise in antibody to each of the serotypes tested. The subject is further complicated by more difficulties: laboratories have not used standardised methods, and the 23-valent vaccines have been tested by the responses to a partial selection of types (and different investigators have selected different types). In short, there is no way in which the results of different immunological studies can be compared or pooled. Efforts now in progress to standardise antibody assays are to be welcomed.

The efficacy of pneumococcal vaccine has been demonstrated by controlled clinical trials and from retrospective studies. The most outstanding trials were in South African goldminers which established that 6-, 12- and 13-valent vaccines protected against pneumonia [6]. These and other controlled trials have been reviewed recently in a meta-analysis [7], which concluded that the vaccines are efficacious in low-risk adults, but not proven for the mixture of conditions called 'high-risk'. The expression 'high-risk' is confusing, although it is used in national policies. The term includes both the annual 1 in 100 risk of overwhelming sepsis for a young asplenic adult with Hodgkin's disease on chemotherapy and the near-normal 1 in 1000 risk of pneumonia for a middle-aged adult with asthma. Randomised trials on people with

'high-risk' conditions (e.g., American ex-servicemen with chronic diseases [8]) have been unsatisfactory because they were not large enough to prove no benefit. However, case-control and quasi-cohort studies have found that the vaccine is protective for most of those for whom vaccine is recommended [9–11]. These retrospective studies reflect more on the former 14-valent vaccine than on the newer 23-valent vaccine and they may have bias if those who were vaccinated had been fitter than those who were not offered vaccine. Nevertheless, the evidence from these epidemiological studies is consistent with immunogenicity studies, and should encourage us to improve the diagnosis and serotyping of pneumococcal disease so that similar studies can be done in the UK. It is often not realised that the estimated 65% protection from 14-valent pneumococcal vaccine represents an average 97% efficacy for each serotype in the vaccine: a high standard of efficacy.

It is sometimes argued that even if the pneumococcal vaccine is effective, it cannot be afforded. In the USA and in Finland, economic analyses suggest that a public health programme of pneumococcal vaccination for everyone over 60 or 65 years old could save hospital treatment costs [12–14]. Although the present selective policies may not make the best economic and immunological sense, they should be implemented. Microbiologists, as the infection experts in most districts, can recommend vaccination, conferring with other local specialists and general practitioners to ensure that the messages are unanimous and that there is agreement on who does what. If pneumococcal vaccine is seen as a booster for pre-existing but declining immunity in older people, another booster after 10 years would seem logical. To find out if this is necessary, surveillance of pneumococcal disease should be enhanced. This means promoting blood cultures in suspected pneumonic disease, getting pneumococcal isolates serotyped, collecting better information about predisposing factors and previous vaccination, and reporting pneumococcal disease to national databases. Antibiotic resistance must be monitored, because the case for vaccination is strengthened by the increasing prevalence of resistance to penicillin and erythromycin.

The focus of pneumococcal vaccine development is in children. The incidence of pneumococcal pneumonia and bacteraemia in infants is often unappreciated in developed countries. With the successful control of *Haemophilus influenzae* type b meningitis, pneumococci are second only to meningococci as common and damaging causes of meningitis. Parents and general practitioners will value a vaccine that prevents one of the main bacterial causes of otitis media, for

which clinical trials of conjugated vaccines given to infants have started. The conjugated vaccines may also have a role in adults with immunodeficiency and a high risk of invasive pneumococcal disease but who do not get high, long lasting antibody responses from the unconjugated vaccines. In conclusion, the potential of pneumococcal vaccines should be explored and utilised.

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References

1. Joint Committee on Vaccination and Immunization. Immunisation against infectious disease. London HMSO 1992: 100–103.
2. Immunization Practices Advisory Committee. Pneumococcal polysaccharide vaccine. *MMWR* 1989; **38**: 64–75.
3. Macfarlane J. The clinical impact of pneumococcal disease. In: Mayon-White RT (ed) The clinical impact of pneumococcal disease and strategies for its prevention. (International Congress and Symposium Series 210). London, Royal Society of Medicine. 1995: 9–17.
4. Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* 1993; **341**: 511–514.
5. Robbins JB, Austrian R, Lee C-J *et al.* Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983; **148**: 1136–1159.
6. Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977; **238**: 2613–2616.
7. Fine MJ, Smith MA, Carson CA *et al.* Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1994; **154**: 2666–2677.
8. Simberloff MS, Cross AP, Al-Ibrahim M *et al.* Efficacy of pneumococcal vaccine in high risk patients. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **315**: 1318–1327.
9. Sims RV, Steinmann WC, McConville JH, King LR, Zwick WC, Schwartz JS. The clinical effectiveness of pneumococcal vaccine in the elderly. *Ann Intern Med* 1988; **108**: 653–657.
10. Shapiro ED, Berg AT, Austrian R *et al.* The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991; **325**: 1453–1460.
11. Bolan G, Broome CV, Facklam RR, Plikaytis BD, Fraser DW, Schlech WF. Pneumococcal vaccine efficacy in selected populations in the United States. *Ann Intern Med* 1986; **104**: 1–6.
12. Sisk JE, Reigelman RK. Cost effectiveness of vaccination against pneumococcal pneumonia: an update. *Ann Intern Med* 1986; **104**: 79–86.
13. Gable CB, Holzer SS, Engelhart L *et al.* Pneumococcal vaccine. Efficacy and associated cost savings. *JAMA* 1990; **264**: 2910–2915.
14. Mäkelä PH. Cost benefit analysis of pneumococcal vaccination. In: Mayon-White RT (ed) The clinical impact of pneumococcal disease and strategies for its prevention. (International Congress and Symposium Series 210) London, Royal Society of Medicine. 1995: 41–47.