PREVENTING PNEUMOCOCCAL DISEASE IN THE UNITED KINGDOM WITH PNEUMOCOCCAL VACCINES

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INTRODUCTION

Disease caused by *Streptococcus pneumoniae* (the pneumococcus) is an important cause of avoidable morbidity and mortality in the UK.[1] It particularly affects very young children, the elderly and individuals with chronic systemic illnesses, including heart, lung and kidney disease, diabetes, immunosuppression, asplenia and alcoholism. These groups are predisposed to serious infections, including pneumonia, bacteraemia and meningitis. A recent paper has identified cigarette smoking as the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, non-elderly adults.[2] The risk of invasive pneumococcal disease is particularly high in human immunodeficiency virus (HIV) infected persons, and is estimated to be 100- to 300-fold greater.[3] The A 23-valent polysaccharide vaccine is licensed for use in the UK, and a new 7-valent conjugate vaccine has recently obtained a licence in the US. This paper reviews the epidemiology of *S.pneumoniae* and the scope for disease prevention using polysaccharide or conjugate vaccines.

THE EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE

Pneumococcal disease is a major single cause of potentially vaccine preventable bacterial disease in the UK and other countries. Since it is not reportable, its precise incidence is unknown. Evidence suggests that 36-50% of community-acquired pneumonias are due to *S. pneumoniae*.[4, 5] The estimated annual incidences of pneumococcal pneumonia, bacteraemia and meningitis are 100 per 100,000, seven per 100,000 and 0.4 per 100,000 respectively in the UK,[4, 6] with corresponding case fatality rates of 5%, 20% and 30%.[7] Pneumococcal otitis media is also common in children under the age of five, among whom it has an estimated annual incidence of 40,000 per 100,000.[8, 9] The prevalence of penicillin and erythromycin resistant pneumococcal isolates has increased from <1% to 3.6–7.4% and from 5% to11% respectively during 1990/91 to 1997/98.[10] The increasing incidence of pneumococcal disease – largely due to the rise in numbers of elderly people, the global HIV pandemic, and multidrug resistant epidemic underscores the importance of pneumococcal infection as a significant public health problem.

Since *S. pneumoniae* was first isolated in 1880, this capsulated Gram-positive bacterium has been found to have at least 90 serotypes. The mucosal epithelium of the nasopharynx is the primary site of colonisation with risk of carriage depending on age, overcrowding and daycare centre attendance, breast feeding, season, smoking and prior antibiotic therapy.[11] The reported carriage rate is up to 60% in pre-school children, 25–35% in high school students, 18–29% in adults with children in household and 6% in adults without children in household.[12] The carriage rates in children in developing countries are two- or three-fold higher than in children in developed countries.[13] Nasopharyngeal colonisation is achieved by interaction between pneumococcal surface proteins and human epithelial cell receptors.[14] It occurs at some point in the first two years of life in most children.[15] The development of disease and spread of the pathogen are associated with nasopharyngeal colonisation.[16, 17]

The pneumococcus has three main surface layers; cell membrane, cell wall and capsule.[18] The polysaccharide capsule protects this bacterium from phagocytosis.[19] The level of pneumococcal virulence is based on the chemical composition of the capsule and varies considerably among the 90 known serotypes.[20, 21] Immunity to pneumococci depends on the production of serotype-specific protective antibody in response to capsular polysaccharide.[22, 23] Colonisation and development of antibody to relevant polysaccharide have been observed in military personnel and family members of persons with pneumonia.[24, 25]

Pneumococcal serotypes vary with age, source of specimens, geographic locations and time.[26-29] Between five and eight serogroups are responsible for at least 75% of invasive pneumococcal disease in children, and around ten or 11 in older children and adults in both developed and less developed countries.[30] Serogroups 4, 6, 9, 14, 18, 19 and 23 in young children, and 4, 6, 9, 12, 14, 19 and 23 in older children/adults, are more often associated with invasive disease in developed countries.[30] Types 1 and 5 are the most common causes of invasive pneumococcal disease in less developed countries.[28] In Scotland the most prevalent 11 serotypes and serogroups were, in numerical order, 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, and these accounted for 84% of the total.[31] In addition, the prevalent serotypes causing mucosal and invasive infections are different. The data from the US showed that types 3, 19A and 23F, types 4, 9V, 14 and 18C, and type 6B were more frequently isolated from middle ear fluid, blood and cerebrospinal fluid (CSF) respectively.[27] Since the effectiveness of immunisation depends on the distribution of vaccine serotypes in the population being immunised,[28] a knowledge of the distribution of serogroups and serotypes is vital for vaccine policy in the prevention of invasive pneumococcal disease.

In 1967 the first isolate resistant to penicillin was reported from Australia, and the first multidrug-resistant pneumococci (resistant to three or more antimicrobial agents) from South Africa in 1977.[32, 33] Studies using molecular techniques have shown that the spread of only a few resistant clones account for the vast majority of resistant pathogens.[34] Evidence indicates that modern transport and the movement of people are responsible for the worldwide distribution of resistant mutants.[35] Pneumococcal serogroups 6, 9, 19 and 23 are the major causes of drug resistance world-wide, accounting for 80% of all pneumococcal resistant isolates.[36, 37] Nasopharyngeal colonisation with these strains is common in children and may play a major role in their spread.[17, 38, 39] Prior antibiotic

use and daycare attendance correlate with increased antibiotic resistance in children under the age of five.[40, 41] Geographic variation in the prevalence of drug resistance has been observed in Europe, North America, Asia and South Africa.[42] The highest penicillin resistance rates were reported from Hungary (58%)[43] and some countries in Asia (>70%).[44]

The high level penicillin resistance (minimal inhibitory concentration, MIC ≥2 mg/ml) in Scotland was very low, with only two serotype 14 (0.02%) blood isolates tested possessing this.[31] Penicillin intermediate resistance (MIC between 0.12 and 1.0mg/ml) accounted for 8% of isolates, most of which were serotype 14. In the US and other European countries, the most prevalent penicillin resistant serotypes are 23F, followed by 6, 14, and 19.[45] Studies from the US showed that a large proportion of penicillin resistant strains were also resistant to other antibiotics.[46, 47] The molecular epidemiology of penicillin resistant pneumococci in 15 countries found that the 23F and 9V clones are responsible for global spread of drug resistant pneumococcal isolates.[48]

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Although a 14-valent pneumococcal polysaccharide vaccine was first licensed in the UK in 1979 and the 23-valent vaccine in 1989, the UK's Joint Committee on Vaccination and Immunisation (JCVI) did not recommend its use in vulnerable groups until 1992. The current 23-valent vaccine includes serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F and accounts for over 95% of invasive disease in the UK[49] and 88% in the US.[50] The current 23-valent polysaccharide covers above 95% of invasive disease in Scotland.[31]

The polysaccharide vaccine is effective in preventing 70–80% of invasive pneumococcal disease.[51, 52] Based on this effectiveness, economic analysis from the US and Europe (including the UK) has suggested that pneumococcal vaccination would be a cost effective strategy for preventing invasive disease in the elderly.[53, 54] In addition, the most frequently encountered global drug resistant isolates (6B, 9V, 14, 19A, 19F, 23F) of invasive pneumococcal disease are included in this vaccine.[42] Therefore, the increased use of polysaccharide vaccine may reduce the incidence of antibiotic susceptible and non-susceptible invasive pneumococcal disease. A single dose of the vaccine is currently recommended for those aged two years or older in whom pneumococcal infection is likely to be more common or more serious, including those with chronic cardiac disease, chronic pulmonary disease, chronic liver disease, chronic renal disease, diabetes mellitus, splenic dysfunction and immunodeficiency states.[55] The uptake of vaccine was estimated to be 5% in 1995 and 15% in 1998 among recommended groups in the UK.[56, 57] Re-immunisation should be considered for persons at highest risk of pneumococcal disease, including those with asplenia, splenic dysfunction or the nephrotic syndrome. These individuals may need booster doses after five or ten years because of declining antibody levels.

Unfortunately, the current polysaccharide vaccine is poorly immunogenic in children under the age of two, the age group with the highest incidence of invasive and mucosal disease, and as a consequence it is not recommended for them. Moreover, the vaccine does not reduce carriage, and antibody levels fall over time.[58] Since polysaccharide antigens are T-cell independent, the vaccine is unable to induce immunological memory and protection is relatively short-lived.[59]

Four systematic reviews or meta-analyses of randomised controlled trials evaluating the effectiveness of immunisation with pneumococcal polysaccharide vaccine have been

TABLE 1
Conclusions of four systematic reviews or meta-analyses on the efficacy of pneumococcal polysaccharide vaccine.

Reference	Type of review	Conclusion
Fine MJ *et al*.[60]	Meta-analysis of nine trials published up to 1991	Pneumococcal vaccination appears efficacious in reducing bacteraemic pneumococcal pneumonia in low risk adults. However, evidence from randomised controlled trials fails to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of subjects currently labelled as high risk.
Watson L[61]	Systematic review and meta-analysis of 16 trials published up to March 1999	For studies carried out in the West, there was no protective effect found on mortality, all pneumonia or pneumococcal pneumonia, although there was a protective trend for pneumococcal bacteraemia, a surrogate outcome. In Third World studies, a significant protective effect was found for the three clinical outcomes.
Hutchison BG *et al*.[52]	Meta-analysis of 13 trials published up to November 1996	Vaccination with pneumococcal polysaccharide vaccine can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%. The vaccine was not less efficacious for the elderly, institutionalised people, or those with chronic disease.
Bandolier [62]	Systematic review of nine trials published up to 1999	Polysaccharide pneumococcal vaccines have yet to be shown to work in the types of people given them in industrialised countries. The only real evidence that they do comes from two improperly randomised studies from the 1940s.

carried out (Table 1).[52, 60, 62] Unfortunately, these papers reached differing conclusions, highlighting problems with meta-analysis which have been the subject of debate in journals.[63] Trials included had insufficient power to detect a number of different endpoints of relatively low incidence using vaccines of different composition. Due to study design problems in the published trials, expert reviewers have considered evidence from other case control and indirect cohort studies, and the current international consensus is that the vaccine can be considered to be 50–80% effective against invasive pneumococcal disease.[51, 64, 65] Although data from case control and indirect cohort studies have lower validity than those from randomised trials, it has been suggested that they offer logistical, ethical and statistical advantages in estimating the vaccine's effectiveness in patients with various high risk conditions.[66, 67] Tables 2 and 3 present the summaries of randomised trials, case control and indirect cohort studies conducted in the high risk groups. The current consensus of opinion from expert reviewers supports the recommendations of the JCVI to promote the uptake of pneumococcal polysaccharide vaccine for the prevention of invasive disease in at risk groups until the new conjugate vaccines become available in the UK.

CONJUGATE VACCINE

To address the inherent problems of polysaccharide vaccines, pneumococcal conjugate vaccines have been developed by coupling the capsular polysaccharides of the epidemiologically important serotypes to carrier proteins. The latter include tetanus toxoid, diphtheria toxoid, CRM_{197} (a non-toxic mutant of diphtheria toxin), pneumolysin or meningococcal outer membrane protein complex.[68] This has the effect of rendering the antigen T-cell dependent, leading to an anamnestic response to future infection.[69] Although the threshold antibody level which confers protection is unknown at present, pneumococcal conjugate vaccines elicit higher antibody responses than pneumococcal polysaccharide vaccines, induce mucosal antibody and immunologic memory and are likely to have a higher efficacy in preventing both invasive and non-invasive disease.[70] The conjugate pneumococcal vaccine contains 7 to 11 serotypes that cause the majority of pneumococcal disease in young children.[71] The 7-valent conjugate vaccine includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. In the 9-valent and 11-valent vaccines, serotypes 1 and 5 and serotypes 1,5, 3, and 7F are added respectively. In the US, the 7-valent vaccine would cover above 80% of invasive and 65% of non-invasive pneumococcal disease in children under six years of age.[27] The coverage of 9- to 11-valent vaccines covers serotypes causing 76–93% of invasive disease in children in the US and Europe.[72] A substantially lower coverage, 65–68%, of invasive isolates with 11-valent vaccine was observed in adults in developed countries.[30] In Scotland, the 7-, 9- and 11-valent conjugate vaccines would cover 61%, 68% and 80% of invasive pneumococcal isolates in all ages.[31]

Antibody responses to pneumococcal conjugate vaccines vary with serotypes and vaccine formulations.[71] Studies in developed and developing countries have reported that the pneumococcal conjugate vaccines are immunogenic in infants aged six to eight weeks.[70, 73] Antibody levels at seven months of age after a series of three doses range from 0.5 to 4.29 mg/ml for the poor immunogenic serotypes to 1.13 to 14.09 mg/ml for the most immunogenic serotypes.[70] It has been suggested that antibody levels of 0.3 mg/ml may afford protection against invasive disease caused by serotypes 3, 4, 6A, 8, 14, 19F and 23F in children.[74] Studies in patients with immuno-compromised disorders[75, 78] (HIV, Hodgkin's and sickle cell diseases) and recurrent respiratory infections[79, 80] have shown that pneumococcal conjugate vaccines are capable of inducing higher antibody responses than the polysaccharide vaccine.

The first available data from a large scale double blind randomised controlled clinical trial in children have been reported from the three year Northern California Kaiser Permanente study among 37,000 children using Wyeth-Lederle's 7-valent pneumococcal CRM_{197} conjugate vaccine,[81] and the results of the Finnish efficacy trial for the prevention of pneumococcal otitis media are expected soon. Table 4 shows the vaccine efficacy in preventing various types of pneumococcal disease after immunisation at two, four, six and 12 to 15 months of age in the American study. The vaccine also appears to be safe and immunogenic. The adverse reactions to conjugate pneumococcal vaccines are minimal and comparable to the 23-valent polysaccharide vaccine and other routine paediatric vaccines.[71, 82-84]

The vaccine currently licensed in the US contains serotypes which are associated with multidrug resistant invasive strains.[42] Studies in other countries have shown a significant reduction in nasopharyngeal carriage in vaccinated infants and children.[85-87] Data from South Africa showed a reduction of 50% in nasopharyngeal carriage in vaccine serotypes in infants immunised at six, ten and 14 weeks.[87] This suggests that universal childhood vaccination with pneumococcal conjugate vaccine has the potential to produce herd immunity and decrease the spread of antibiotic resistant pneumococcal disease in children. Nevertheless, studies in South Africa and the Gambia found that colonisation with non-vaccine serotypes were increased in vaccines compared to controls.[85, 87] Therefore, continued surveillance data are essential to monitor the long-term colonisation effects of widespread use of conjugate vaccines in future.

Health economic studies in the US have concluded that infant immunisation with pneumococcal conjugate vaccine has the potential to be cost effective.[88, 89] If the vaccine costs were less than the manufacturer's list price of $58 for each dose, vaccination could even be cost saving.[88] The experience following the introduction of Hib vaccine in 1992 could therefore be repeated with pneumococcal conjugate vaccine (Figure 1).

The results of the US trial raise questions about the use of conjugate vaccine in adults. Unfortunately, the results are not directly applicable to older age groups for a number of reasons and the effectiveness of pneumococcal conjugate vaccines in preventing pneumonia and other respiratory infections, as well as their role in the elderly and high risk adults, require further examination. One problem is the more limited coverage of invasive disease serotypes in adults than in children, as noted above. Eight clinical studies of conjugate vaccines in adults have been reported.[58] Of these, six studies in younger adults showed that the conjugate vaccine produced higher antibody responses than the polysaccharide vaccine.[68, 78, 83, 90-92] In contrast to these findings, two other studies in persons

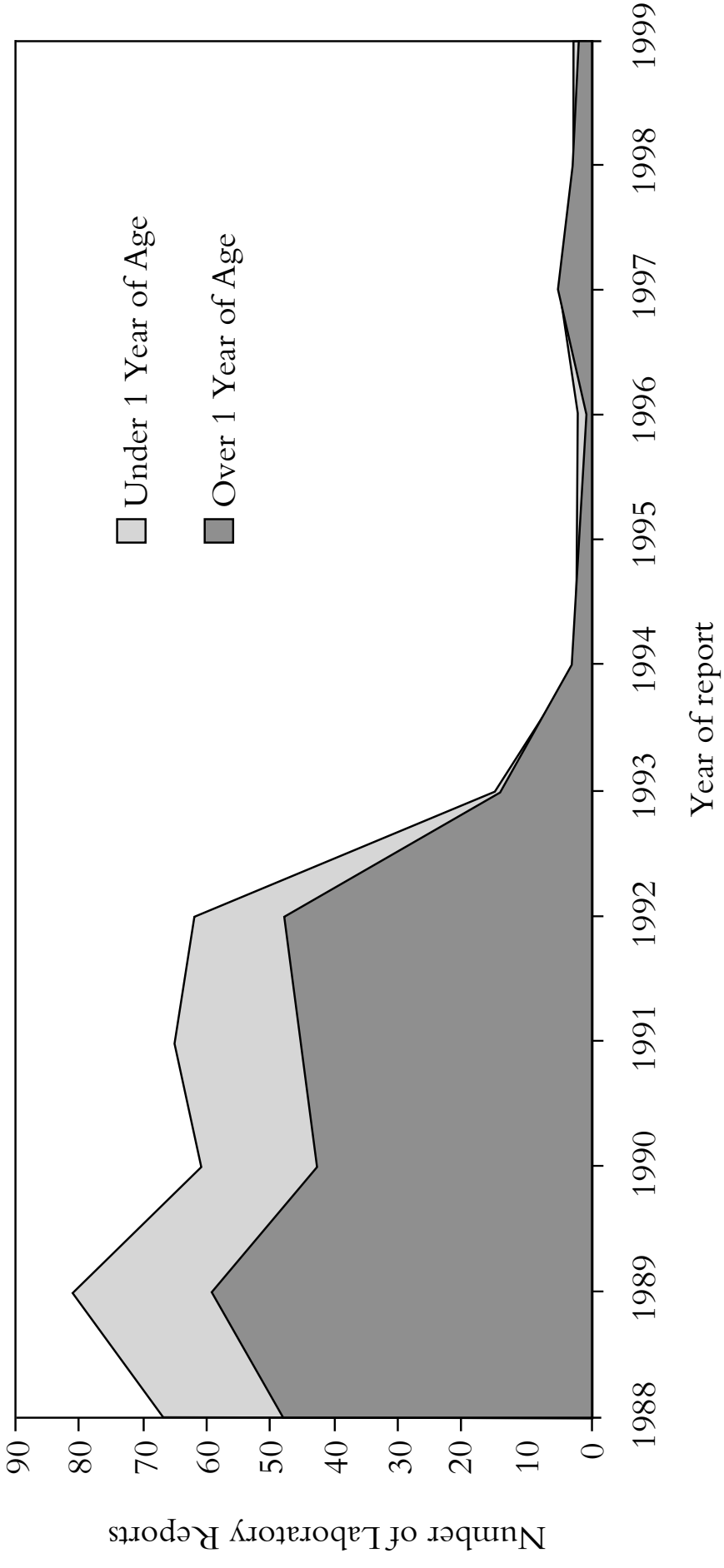

FIGURE 1
Laboratory reports of *Haemophilis influenzae* type B, Scotland 1988–99.

TABLE 2
Summary of randomised controlled trials conducted in high risk groups.

References	Trial site	Trial type	Characteristics of subjects	Outcome measure	Vaccine type	% efficacy (95% CI)	No. of subjects
Kaufman *et al.*[93]	US	Single blind	Institutionalised elderly	• Pneumonia	4-valent	92 (72,98)	11,000
				• Bacteraemia	4-valent	93 (45,100)	
Austrian *et al.* (unpublished)	US	Single blind	Mentally ill elderly	• Pneumonia	12-valent	15 (<0,52)	1,300
Gaillet *et al.*[94]	France	Open	Nursing home residents	• Pneumococcal pneumonia	14-valent	77 (51,89)	1,686
Simberkoff *et al.*[95]	US	Double blind	Elderly	• Pneumonia	14-valent	<0 (<0,45)	2,295
				• Bronchitis	14-valent		
Koivula *et al.*[96]	Finland	Double blind	Elderly	• Pneumococcal pneumonia	14-valent	59 (6, 82)	2,837
Ortqvist *et al.*[97]	Sweden	Double blind	Elderly	• Pneumonia	23-valent	-28(-150,34)	691
				• Pneumococcal pneumonia	23-valent		
Macleod *et al.*[98]	US	Single blind	Military recruits	• Pneumonia	4-valent	85 (79,100)	17,035
Austrian *et al.*[99]	South Africa	Single blind	Gold miners	• Pneumonia	13-valent	79 (65,88)	2,973
				• Bacteraemia	13-valent	82 (66,92)	
Smit *et al.*[100]	South Africa	Double blind	Gold miners	• Pneumonia	6-valent	76 (52,89)	3,019
				• Pneumonia	12-valent	92 (49,100)	
Riley *et al.*[101]	Papua New Guinea	Double blind	Persons with age >10 years	• Bacteraemia	14-valent	86 (<0, 99)	11,958

TABLE 3
Summary of case-control and indirect cohort studies of pneumococcal vaccine effectiveness in high risk groups.

References	Outcome measure	% effectiveness (95%CI)	Location	No. of subjects
[2]Broome *et al.*[102]	Invasive infection	36*all ages (≥2 years) 60†(>10 years old) <0‡	US CDC (isolates from 46 hospitals in 26 States)	427/427
[1]Shapiro *et al.*[103]	Invasive infection	67† (13,87) (≥18 years) <0%‡	New Haven, US	90/90
[2]Bolan *et al.*[104]	Invasive infection	61* (1,85) (≥2years) 64† (47,76)	US CDC (isolates from 37 hospitals in 22 States)	1,887/1,887
[1, 2]Forrester *et al.*[105]	Bacteraemia	<0* (<0,35) elderly	Denver, US	89/89
[1]Sims *et al.*[106]	Invasive infection	70† (37,86) elderly	Philadelphia, US	122/244
[1,2]Shapiro *et al.*[107]	Invasive infection	56 (42, 75)* (≥18 years) 61 (47, 72)† 21 (<0, 60)‡ 71 (30,88) elderly	Connecticut, US	983/983
[2]Butler *et al.*[50]	Invasive infection	57 (45,66)* (≥5 years) 49 (23,65)† 49 (22,64)‡ 75 (57,85) elderly	CDC (isolates from 54 hospitals in 26 States)	2,837/2,837
[1]Farr *et al.*[108]	Bacteraemia	81 (34,94)* (≥2 years)	Charlottesville, US	85/152
[2]Davidson *et al.*[109]	Invasive infection	79 (49,92)† adults	Alaska, US	87/87

[1] case control study
[2] indirect cohort study
* all conditions
† with underlying medical conditions (chronic lung, heart, liver, renal, diabetes mellitus and alcoholism)
‡ immunocompromised conditions (splenic disorders, sickle cell disease, haematological malignancies, organ transplant and systematic lupus erythematosus)

TABLE 4
Protective efficacy of 7-valent protein conjugate pneumococcal vaccine against invasive disease and otitis media.[81]

Analysis	Per protocol % (95% confidence interval)	Intention to treat % (95% confidence interval)
For serotypes contained in the vaccine, fully vaccinated, invasive disease	97·4 (82·7–99·9)	93·9 (79·6–98·5)
For all cases regardless of serotypes contained in the vaccine, invasive disease	–	89·1 (73·7–95·8)
Otitis media visits	8·9 (5·8–11·8)	7·8 (5·2–10·5)
Otitis media episodes	7·0 (4·1–9·7)	6·4 (3·9–8·7)
Frequent otitis (five episodes in six months/six in a year)	22·8 (6·7–36·2)	12·3 (0–23·2)
Ventilatory tube placement	20·1 (1·5–35·2)	20·3 (3·6–34·1)

aged 50 years and older did not show significant advantages in antibody responses over polysaccharide vaccine with the conjugate vaccine.[68, 83] Further studies are planned using different formulations and different schedules to assess the implications of conjugate vaccine for the prevention of pneumococcal disease in adults.

AREAS FOR FURTHER RESEARCH

Many questions which remain unanswered on pneumococcal immunisation need to be addressed. At this stage we do not know whether to recommend the polysaccharide or the conjugate vaccine for children over the age of two, nor under what circumstances or criteria. Will a course of conjugate vaccine require periodic boosting with conjugate or polysaccharide vaccine? Does the vaccine impair the immunological response to other childhood vaccines when given in the UK's accelerated immunisation schedule? Even more importantly, what effect would mass infant immunisation have on carriage among children and adults? Could this result in serotype displacement and the emergence of invasive or mucosal disease caused by serotypes not commonly associated with infection? Would the potential elimination of carriage result in ecological niches being filled with these other virulent strains of pneumococci or other organisms? Post-vaccine carriage studies of the kind currently being undertaken in relation to meningococcal C conjugate vaccine will be necessary to resolve this. Some of these questions are already the subject of current studies.

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