

CURRENT TOPIC

New pneumococcal vaccines for children

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Streptococcus pneumoniae remains a major cause of childhood morbidity and mortality. At least 1 million children die of pneumococcal infections each year, mostly in developing countries.¹ In addition, pneumococcal resistance to antibiotics such as penicillin is an increasing problem worldwide. The polysaccharide capsule is the main virulence factor of the pneumococcus; 90 different capsular polysaccharide serotypes have been described.² The prevalence of individual serotypes varies among different age groups and different geographical areas, and changes over time. In this review, we discuss the current epidemiology of paediatric pneumococcal disease in Europe and the potential role of new pneumococcal conjugate vaccines.

Pneumococcal epidemiology

S pneumoniae causes a variety of clinical syndromes, including invasive infections such as bacteraemia and meningitis, as well as pneumonia, and otitis media, with children under 2 years at greatest risk.

INVASIVE DISEASE

The incidence of invasive pneumococcal disease (IPD) per 100 000 children in England and Wales is 39.7 under 1 year of age, 14.5 under 5 years of age, and 6.6 under 15 years of age, based on laboratory reports to the Public Health Laboratory Service.^{3,4} These rates are comparable to paediatric IPD rates observed in enhanced surveillance studies in the Oxford area⁵ and South and West England,⁵ and rates reported from Denmark,⁶ Switzerland,⁷ and Finland.⁸ The proportion of reported IPD isolates in England and Wales showing intermediate or full penicillin resistance increased from 0.3% in 1989 to 2.9% in 1995.⁹ In other European countries, current rates of penicillin resistance for IPD isolates range from less than 2% in Denmark⁶ and Germany,¹⁰ to more than 30% in Spain¹¹ and Hungary.¹²

In a meta-analysis of bacterial meningitis outcomes in developed countries,¹³ *S pneumoniae* caused more deaths and neurological sequelae than either *Haemophilus influenzae* or *Neisseria meningitidis*. Of the children with pneumococcal meningitis reviewed in the meta-analysis, 17% developed mental retardation, 14% a seizure disorder, 28% deafness (16% profound or severe), and 12% spasticity or paresis. The case fatality rate was 15%. There is little information about outcomes of

paediatric IPD in the UK. Hospital admission rates in England for pneumococcal meningitis and septicaemia, based on ICD 10 codes, were 1.9 and 1.2 respectively per 100 000 children under 15 years in 1997, with a mean duration of stay of 14 days in the former and seven days in the latter group.³ In 1996–98, 16% of paediatric meningitis cases and 9% of other paediatric IPD cases in England and Wales were reported to have died of their infection.³ Unfortunately outcome was only reported in 28% of the IPD cases, potentially biasing the case fatality. Indeed, in a recent retrospective case note review of children under 5 years, identified by enhanced surveillance of IPD in the Oxford region, mortality was only 1%.¹⁴ There was, however, significant morbidity: 7% of children developed persisting neurological disability and the mean duration of hospital stay was eight days.

PNEUMONIA

Accurate epidemiological data about childhood pneumonia are difficult to obtain as a result of difficulties with diagnosis and empirical antibiotic treatment. Djuretic *et al* studied hospital admissions in England in 1994–95 in children aged less than 5 years diagnosed with pneumonia.¹⁵ Admission rates for “lobar pneumonia”, “bronchopneumonia”, and “pneumonia, unspecified”, based on ICD 9 codes, were 104, 36, and 85 per 100 000 respectively (225 per 100 000 for all three codes); mean duration of stay was four days for each diagnosis.

A retrospective case note review was also performed. There were lobar/focal changes on chest x ray (CXR) in 79% of cases, although only 46% were coded as “lobar pneumonia”. Only half the cases that met the authors’ definitions of “definite” pneumococcal pneumonia (pneumococcus in blood culture) or “likely” pneumococcal pneumonia (lobar/focal consolidation on CXR and white cell count of at least $15 \times 10^9/l$, with more than 60% neutrophils, or C reactive protein of at least 8 mg/l) were coded as “lobar pneumonia”. Half the cases coded as “lobar pneumonia” met the authors’ definitions of “definite” or “likely” pneumococcal pneumonia. *S pneumoniae* was isolated from blood culture in only 1% of cases. Thus ICD codes are probably poor indicators of the true incidence of hospital treated paediatric pneumonia.

The incidence of pneumonia in children in the community is not known for the UK. In

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1981–82, a large population based study of community acquired pneumonia was conducted in Finland.¹⁶ Pneumonia was defined as “typical radiologic pneumonia” (CXR was available in 97% of cases), “clinical suspicion of pneumonia and uncertain radiologic pneumonia”, or “pneumonia found at autopsy”. The incidence of community acquired pneumonia was 36 per 1000 children aged under 5 years, and approximately half these children required hospital admission. The case fatality rate was 0.1% for children under 15 years of age.

Describing the epidemiology of childhood pneumonia caused by the pneumococcus is more problematic. Recent studies in Finland^{17–20} and France²¹ have attempted to determine the microbial aetiology of pneumonia in children using various serological methods in addition to standard culture methods. The studies suggest that 13–38% of community acquired pneumonia in children is caused by *S. pneumoniae*. These data, and recent results from a controlled efficacy trial of a pneumococcal conjugate vaccine (discussed later),²² suggest that pneumococcal pneumonia is a major disease burden in children.

OTITIS MEDIA

There is a paucity of published data on the epidemiology of acute otitis media (AOM) in the UK. An estimated 31 per 100 children aged under 5 years are seen annually by general practitioners in England for this condition, based on general practices reporting to the Royal College of General Practitioners sentinel surveillance scheme.³ In 1994–95, the incidence of AOM in children under 10 years of age was investigated in a community based study in Finland.²³ A diagnosis of AOM was made if there were acute symptoms of otitis media and suggestive otoscopic signs. The incidence was 32 AOM attacks per 100 children years; 32% of children who had an episode of AOM had at least one recurrent attack and 13% had at least two recurrent attacks.

Little is known about the microbiology of AOM in UK children as myringotomy is rarely performed. In recent Finnish^{24–25} and multicentre studies,^{26–27} *S. pneumoniae* was cultured from middle ear fluid in 18–30% of children with AOM, suggesting that pneumococcal AOM is a common paediatric illness.

Pneumococcal vaccines

Pneumococcal polysaccharide vaccines were first licensed in the USA in 1946, but soon withdrawn from the market when penicillin and sulphonamides became available.² The vaccines were reintroduced in the USA in 1977, and the current 23-valent pneumococcal polysaccharide vaccine, 23vPS (containing 25 µg of each of 23 pneumococcal capsular polysaccharides), was licensed in 1983. In the UK, this vaccine is recommended for use in children aged 2 years and above with asplenia or severe splenic dysfunction, chronic renal disease or nephrotic syndrome, immunodeficiency or immunosuppression, chronic heart disease, chronic lung disease, chronic liver disease, and diabetes mellitus.²⁸

Polysaccharide antigens are poor immunogens in infants and do not induce immunological memory. The technique of conjugation, the covalent coupling of capsular polysaccharide (or oligosaccharide) with protein carrier, was used to develop vaccines against *Haemophilus influenzae* type b (Hib) disease. Protein antigens, unlike polysaccharide antigens, can be processed by antigen presenting cells and presented to T cells. The T cells then “help” B cells produce antibodies, and some of the B cells remain as memory B cells. Thus Hib polysaccharide–protein conjugate vaccines are thought to elicit T cell “help”, resulting in an enhanced antibody response to the Hib polysaccharide antigen in young children and the induction of immunological memory. Conjugate technology was subsequently applied to meningococcal and pneumococcal conjugate vaccines.

PNEUMOCOCCAL CONJUGATE VACCINES

The candidate pneumococcal conjugate vaccines consist of seven, nine, or 11 capsular saccharides individually conjugated to either CRM₁₉₇ (a non-toxic variant of diphtheria toxin), tetanus and diphtheria toxoids, or an outer membrane protein of non-typable *H. influenzae* (table 1). The 7-valent vaccine contains types 4, 6B, 9V, 14, 18C, 19F, and 23F saccharides; the 9-valent vaccine contains two additional saccharides, types 1 and 5; and the 11-valent vaccines contain another two saccharides, types 3 and 7F. The serotypes included in the 7-valent vaccine are responsible for 69–79% of reported IPD cases in children aged less than 5 years in England and Wales, and the 9-valent and 11-valent vaccines cover 77–87%

Table 1 Pneumococcal conjugate vaccines in recent randomised controlled phase II and phase III immunogenicity studies

Study vaccine	Saccharides	Protein carrier(s)	Manufacturer	Published studies	Number immunised with study vaccine
7vCRM (Prenar)	2 µg of types 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of 6B	CRM ₁₉₇	Wyeth Lederle	Rennels <i>et al</i> , 1998 ³² Shinefield <i>et al</i> , 1999 ³³ Black <i>et al</i> , 2000 ³⁴ Choo <i>et al</i> , 2000 ³⁵	106 183 18 927 (efficacy trial) 248
9vCRM	Above and 2 µg of types 1 and 5	CRM ₁₉₇	Wyeth Lederle	Mbelle <i>et al</i> , 1999 ³⁶ Obaro <i>et al</i> , 2000 ³⁷	250 103
11vTD	1 µg of types 1, 4, 5, 7F, 9V, 19F, and 23F; 3 µg of types 3, 14, and 18C, and 10 µg of 6B	Tetanus toxoid Diphtheria toxoid	Aventis Pasteur	Phase II trials in progress	
11vOMP	5–10 µg of types 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	Non-typable <i>H. influenzae</i> outer membrane protein	SmithKline Beecham	Phase II trials starting	

and 82–91% respectively.^{3–4} In other European countries,^{6–8, 10–11, 29–30} 60–80% of paediatric IPD cases are caused by serotypes included in the 7-valent vaccine.

Little is known about the specific pneumococcal serotypes that cause pneumonia and AOM in UK children. A study of pneumococcal bacteraemia in Finnish children aged 0–15 years in 1985–89 showed that 69% of the serotypes associated with pneumonia were included in the 7-valent pneumococcal conjugate vaccine, compared with 86% for bacteraemia without focus.⁸ With respect to AOM, a US multicentre study of blood, CSF, and middle ear fluid isolates in 1978–94 found that serotypes included in the 7-valent vaccine accounted for 80% of IPD in children under 6 years of age, but only 65% of pneumococcal AOM.³¹ These data suggest that a 7-valent vaccine directed at IPD serotypes may not be optimal for the prevention of pneumonia and AOM. Therefore higher valent vaccines (for example, 9-valent and 11-valent vaccines) would be preferable for broader coverage of both invasive and non-invasive pneumococcal disease.

IMMUNOGENICITY

One pneumococcal conjugate vaccine, 7vCRM (a 7-valent vaccine containing CRM₁₉₇), was recently licensed in the USA. It is currently under review by the European Medicines Evaluation Agency, and European licensing approval is expected in 2001. 7vCRM has been shown to be immunogenic in randomised controlled studies conducted in the USA^{32–34} and UK³⁵ (table 1). In the US trials, the vaccine was given at 2, 4, and 6 months of age, as a separate injection, concomitantly with routine infant vaccines (diphtheria–tetanus–whole cell pertussis vaccine (DTwP) or diphtheria–tetanus–acellular pertussis vaccine (DTaP), Hib vaccine containing CRM₁₉₇ (HbOC), oral polio vaccine (OPV) or inactivated polio vaccine (IPV), with or without Hepatitis B vaccine (HepB)). A 7vCRM booster was given at 12–15 months. In the UK study, 7vCRM was administered with routine vaccines (DTwP, HbOC, OPV) at 2, 3, and 4 months of age, either as a separate injection or as a combined 7vCRM/HbOC injection, and a 23vPS booster was given at 13–16 months. In these immunogenicity studies,^{32–33, 35} pneumococcal anticapsular antibody concentrations in 7vCRM recipients after primary immunisation were significantly higher than in control infants for all seven vaccine serotypes. After booster immunisation, more than fivefold and tenfold rises in anticapsular antibody titres were observed in the US and UK studies respectively, suggesting immunological memory.

There have been two randomised controlled studies of the 9-valent pneumococcal conjugate vaccine, 9vCRM, conducted in South Africa³⁶ and The Gambia³⁷ (table 1). 9vCRM was given concomitantly with routine infant vaccines (DTwP, OPV, HepB, with or without HbOC) as a separate injection at, or close to, 2, 3, and 4 months of age. Infants who received 9vCRM achieved significantly higher pneumococcal anticapsular antibody concentrations

after primary immunisation than control infants for all the 9vCRM serotypes.^{36–37}

Hib and diphtheria responses are enhanced in 7vCRM and 9vCRM recipients compared with control infants who receive routine vaccines only.^{35–36} No significant interference with any of the primary schedule vaccine antigens has been observed following concomitant immunisation with 7vCRM or 9vCRM in studies to date. Infants immunised with a 7vCRM/HbOC combination had significantly lower pneumococcal anticapsular antibody concentrations after primary immunisation for five of the seven vaccine serotypes compared with infants given 7vCRM and HbOC at separate sites.³⁵ However, these 7vCRM/HbOC recipients responded well to the 23vPS booster (a vaccine that is poorly immunogenic in unprimed infants), consistent with a memory response.

Phase II trials have recently commenced on 11vTD, an 11-valent pneumococcal conjugate vaccine (table 1). Preliminary data suggest that the vaccine is safe and immunogenic when administered concomitantly with routine infant vaccines to Israeli, Finnish, Icelandic, and Filipino infants,^{38–41} and furthermore it primes for memory.⁴²

THE HIGH RISK CHILD

There is great potential for the use of pneumococcal conjugate vaccines in children at high risk of IPD and children with recurrent non-invasive pneumococcal infections. A 5-valent pneumococcal conjugate vaccine has been shown to be immunogenic in HIV infected infants and children.^{43–45} Children aged 2 years or above with sickle cell disease, who have been primed with 7vCRM and boosted with 23vPS, achieve significantly higher pneumococcal anticapsular antibody titres than those immunised with 23vPS alone.⁴⁶ 7vCRM is also immunogenic in children with recurrent infection who are non-responders to 23vPS,^{47–48} and induces significantly higher anticapsular antibody concentrations than 23vPS in otitis prone children.⁴⁹

Further studies are needed to assess pneumococcal conjugate vaccines in other high risk groups such as asplenic children. Priming with a high valent pneumococcal conjugate vaccine and boosting with 23vPS would provide children at high risk of IPD and children with recurrent non-invasive pneumococcal infection with optimal serotype coverage. In the USA, immunisation schedules involving 7vCRM priming and 23vPS boosting have been recommended by the American Academy of Pediatrics for children at high risk of IPD.⁵⁰

SAFETY

Studies of 7vCRM and 9vCRM suggest that the vaccines are well tolerated and safe.^{32–37, 51} With respect to local reactions, these vaccines are significantly less reactogenic than DTwP or DTwP/HbOC,^{32–33, 35–37} but significantly more reactogenic than DTaP, MenC (serogroup C meningococcal conjugate vaccine containing CRM 197), or IPV.^{34–37} Systemic reaction rates in 7vCRM and 9vCRM recipients are comparable with control infants receiving routine

vaccines,^{35–37} although fever is significantly more common in 7vCRM recipients than in controls who receive MenC.^{32–34} No serious adverse events have been attributed to 7vCRM or 9vCRM in studies to date.

EFFECT ON CARRIAGE

The success of Hib conjugate vaccines has been partly a result of their capacity to reduce nasopharyngeal carriage of Hib, thereby decreasing person to person transmission and inducing herd immunity.^{52–54} Primary vaccination with 9vCRM reduces nasopharyngeal carriage of vaccine type pneumococci, although carriage of non-vaccine type pneumococci may increase.^{36–55–56} However, it is thought that the vaccine serotypes are more likely to cause disease than the non-vaccine serotypes. Moreover, vaccine serotypes are more likely to be antibiotic resistant than non-vaccine serotypes, and 9vCRM recipients have been shown to have significantly lower rates of carriage of penicillin resistant pneumococci than control infants, regardless of serotype.^{36–56}

7vCRM induces serotype specific anticapsular IgA and IgG antibody responses in saliva in infants,^{57–58} and primes for memory responses in saliva.⁵⁷ These mucosal antibodies may play an important role in the eradication of vaccine type pneumococci from the mucosal surfaces of the upper respiratory tract.

EFFICACY

Two double blind randomised controlled trials evaluating the efficacy of 7vCRM have been completed (table 2). The US trial involved 37 868 infants who received 7vCRM or MenC (control vaccine) at 2, 4, 6, and 12–15 months of age.³⁴ There were 40 IPD cases caused by vaccine serotypes, one case in the 7vCRM group and 39 in the control group. Efficacy was 97% for vaccine type IPD and 89% for all IPD, and there was no evidence of any increase of non-vaccine type IPD. For pneumonia, efficacy was 11% for any pneumonia visit (clinical diagnosis), 35% if the CXR had any abnormality, and 63% if there was consolidation of at least 2.5 cm on the CXR as agreed by a radiologist and a paediatrician.²² The vaccine was 7%, 9%, and 20% effective in preventing AOM episodes (clinical diagnosis), recurrent AOM (three episodes in six months or four in one year), and ventilatory tube (grommet) placement respectively.³⁴

In the Finnish trial, 1662 infants were randomised to receive 7vCRM or HepB (control vaccine) at 2, 4, 6, and 12 months of age.⁵¹

There were 107 clinically diagnosed AOM episodes caused by vaccine type pneumococci in the 7vCRM group and 250 in the control group. Efficacy was 57% for culture confirmed vaccine type AOM, 34% for culture confirmed pneumococcal AOM, and 6% for all clinically diagnosed AOM episodes. However, there was a 34% increase in AOM episodes caused by non-vaccine serotypes in 7vCRM recipients compared with control infants.⁵⁹

Another AOM efficacy trial has recently been completed in Finland (table 2).⁶⁰ The study vaccine was 7vOMPm, one of the first pneumococcal conjugate vaccines to be developed.^{61–63} This 7-valent vaccine contains the same pneumococcal serotypes as 7vCRM, conjugated to the outer membrane protein complex of serogroup B *N meningitidis*. In this efficacy trial, 1666 infants were randomised to receive 7vOMPm or HepB at 2, 4, and 6 months of age, and at 12 months, the children received 7vOMPm or 23vPS. There were 110 clinically diagnosed culture confirmed AOM episodes attributed to the seven vaccine serotypes in the 7vOMPm group and 250 in the HepB group. 7vOMPm efficacy was 56% for vaccine type pneumococcal AOM and 25% for all pneumococcal AOM; the number of all clinically diagnosed AOM episodes was similar in both groups. Thus the efficacy of 7vOMPm for vaccine type pneumococcal AOM was similar to that of 7vCRM, an interesting finding in view of the fact that 7vOMPm, when administered to US infants at 2, 4, 6, and 15 months of age,⁶⁴ appears to be less immunogenic than 7vCRM.^{32–34}

THE CASE FOR ROUTINE IMMUNISATION

Results from the immunogenicity studies and efficacy trials are very encouraging. Pneumococcal conjugate vaccines are safe and immunogenic in infants and induce immunological memory. They induce mucosal immune responses and reduce carriage, and their widespread use should result in herd immunity. Most importantly, these vaccines have the potential to save lives and reduce morbidity in children by preventing the vast majority of IPD, most cases of clinically diagnosed, radiologically confirmed lobar pneumonia, and 6–7% of clinically diagnosed AOM.

CURRENT LIMITATIONS AND CONCERNS

There is very little epidemiological data available about non-invasive pneumococcal infections in UK children. Active surveillance of childhood pneumonia based on clinical and

Table 2 Efficacy studies of pneumococcal conjugate vaccines

Country	Vaccine	Schedule	Study design	Primary end point	Status
US (northern California)	7vCRM (Wyeth)	2/4/6 and 12–15 months	Double blind, randomised, controlled (MenC)	Culture confirmed invasive disease	Completed (Black <i>et al</i> , 2000 ³⁴)
Finland	7vCRM (Wyeth)	2/4/6 and 12 months	Double blind, randomised, controlled (HepB)	Culture confirmed otitis media	Completed
Finland	7vOMPm (Merck)	2/4/6 months and 7vOMPm or 23vPS at 12 months	Double blind, randomised, controlled (HepB)	Culture confirmed otitis media	Completed
US (Navajo and Apache Indians)	7vCRM (Wyeth)	2/4/6 and 12–15 months	Double blind, randomised, controlled (MenC)	Culture confirmed invasive disease	In progress
South Africa	9vCRM (Wyeth)	6/10/14 weeks	Double blind, randomised, controlled (placebo)	Culture confirmed invasive disease and severe pneumonia	In progress

Men C, group C meningococcal conjugate vaccine containing CRM₁₉₇ protein carrier; Hep B, hepatitis B vaccine.

radiological criteria (such as the criteria used in the US efficacy trial) should commence, as should active surveillance of AOM based on clinical criteria (for example, acute symptoms and otoscopic signs). Enhanced laboratory surveillance of paediatric IPD is needed, which should include data collection of clinical syndromes (for example, pneumonia in bacteraemic patients) and outcomes, in addition to centralised serotyping of all clinical isolates. Changes in capsular type can arise in *S. pneumoniae* by recombinational exchanges within capsular biosynthetic genes.⁶⁵ The possibility that the use of pneumococcal conjugate vaccines may lead to an increase in disease caused by non-vaccine serotypes is a potential concern. Thus, surveillance of clinical isolates should continue after the introduction of these vaccines, which in the future may require reformulation.

More studies are needed to assess pneumococcal conjugate vaccines in different immunisation schedules and in different populations. As new vaccines are added to our primary schedules, there is an increasing need for safe and immunogenic combination vaccines. The immunogenicity of combinations containing pneumococcal conjugate vaccines (for example, combinations with Hib and group C meningococcal conjugate vaccines in the UK schedule and combinations with DTaP and IPV vaccines in many European schedules) should be studied carefully, as interference between vaccine antigens may occur. Studies to investigate the duration of protection of these vaccines are also needed to establish if and when boosters will be required. There will be two options for boosting: a pneumococcal conjugate vaccine³²⁻³⁴ (which would prime new B cells), or 23vPS³⁵ (which would be cheaper and could provide greater and broader protection).

Pneumococcal conjugate vaccines are likely to cost more than any of the vaccines currently available in our primary immunisation schedules. A US cost effectiveness study estimated that 7vCRM would need to cost less than US\$46 per dose to result in net "savings" in the USA.⁶⁶ It is possible that the vaccine will be more expensive than this. However, important psychological factors such as child distress and parental anxiety cannot be quantified in cost effectiveness studies. We may therefore decide to include pneumococcal conjugate vaccines in our primary schedules for the benefit of our children, despite the net "costs" to society.

THE FUTURE

As pneumococcal conjugate vaccines cover only a limited number of serotypes, pneumococcal proteins such as pneumolysin, pneumococcal surface protein A (PspA), pneumococcal surface adhesin A, and choline binding protein A have been proposed as vaccine candidates.⁶⁷ These proteins are common to virtually all pneumococci and could provide protection against almost all of the 90 serotypes. As protein antigens, they are likely to be immunogenic in infants and to induce immunological memory. In a recent phase I trial,^{68,69} a recombinant PspA vaccine was

shown to be safe and immunogenic in healthy adults, inducing broadly cross reactive serum antibodies. Further human studies of protein based pneumococcal vaccines are awaited.

In this era of increasing antibiotic resistance, safe and effective pneumococcal vaccines for children should be a priority. We look forward to the licensing of pneumococcal conjugate vaccines in Europe and the future introduction of these vaccines into primary immunisation schedules in the UK and other European countries.

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