

The new pneumococcal vaccine

S. K. Obaro

Department of Paediatrics, Imperial College School of Medicine, London, W2 1PG, UK

Pneumococcal disease is now the leading cause of vaccine-preventable bacterial disease in children worldwide. Although a pneumococcal polysaccharide vaccine has been available for over three decades, its use has been limited due to poor immunogenicity in the most vulnerable children, aged less than 2 years. The prevalence of pneumococcal disease worldwide and the alarming global escalation of multiresistant strains of *Streptococcus pneumoniae* (pneumococcus) during the past decade have provided the impetus for the development and application of a new pneumococcal vaccine. The outstanding success of *Haemophilus influenzae* type b (Hib) conjugate vaccine in the control of invasive Hib disease is a reason to be optimistic that the pneumococcal conjugate vaccines will achieve similar results for the control of invasive pneumococcal disease. Remarkable efficacy against invasive pneumococcal disease with a seven-valent pneumococcal conjugate vaccine was demonstrated in infants and toddlers in the USA, and in February 2000 the first pneumococcal conjugate vaccine was licensed. Licensure and widespread use is likely to follow in other countries in which there is a need and the means to afford this live-saving vaccine. Active disease surveillance must be sustained globally, while active research, development of other multivalent conjugate formulations and the search for new candidate protein-based vaccines are in progress.

Keywords *Streptococcus pneumoniae*, pneumococcal diseases, protein conjugate vaccine

Accepted 27 December 2001

Clin Microbiol Infect 2002; 8: 623–633

INTRODUCTION

Streptococcus pneumoniae has provided a remarkable biological model for the understanding of bacterial pathogenesis for over a century, but nevertheless, its conquest has eluded biomedical researchers until very recently [1]. From conservative estimates, the pneumococcus is thought to be responsible for at least 1 million deaths in children aged less than 5 years, worldwide, annually [2,3]. The recent application of *Haemophilus influenzae* type 1 (Hib) conjugate vaccines and the subsequent remarkable decline in the incidence of invasive Hib disease has further highlighted the impact of invasive pneumococcal diseases. The pneumococcus is now arguably the leading cause of bacterial meningitis in children in most settings and

the leading cause of vaccine-preventable bacterial disease in children worldwide.

Treatment of pneumococcal disease has become more expensive and complex during the past decade, as the prevalence of multiresistant strains has increased. The prevalence of penicillin-resistant pneumococcal isolates in the UK increased from 4.2% in 1992 to 12.6% in 1999 [4]. In other countries, the incidence has also been on the rise. The prevalence of penicillin-resistant strains varies from 43% in South Africa, to 49% in the USA, to 53% in France, to 60% in Spain, to 79% in Korea [5]. Although there has been no demonstrable parallel increase in mortality from infection with drug-resistant pneumococcal infections, cure clearly involves expensive antibiotics and longer duration of hospitalization.

Antibiotic use has been consistently associated with carriage of antibiotic-resistant strains of pneumococci and the subsequent development of invasive disease. Suppression of upper respiratory tract organisms by antibiotic treatment

Corresponding author and reprint requests: S. K. Obaro, Department of Paediatrics, Imperial College School of Medicine, St Mary's Campus, Norfolk Place, London W2 1PG, UK
E-mail: s.obaro@ic.ac.uk

removes the competing flora and renders the host susceptible to acquisition of strains that are resistant to the antibiotics [6]. Despite the rapidly evolving technology for the development of new and highly potent antimicrobials, it is now clear that the battle against the pneumococcus can only be won by prevention of infections through the application of potent vaccines.

This update reviews the burden of pneumococcal disease, and the development and application of the new conjugate vaccines in the control of disease, and discusses potential strategies for the control of pneumococcal disease in highly susceptible but resource-deprived populations.

THE PNEUMOCOCCUS

S. pneumoniae (pneumococcus) is an encapsulated Gram-positive bacterium. The capsule consists of polysaccharides, with characteristic chemical structures, which form the basis of serogroups and serotypes. There are currently over 90 recognized serotypes [7]. The polysaccharide capsule constitutes a major virulence factor, and antibodies directed against it facilitate the opsonization of the bacteria for phagocytosis. These antibodies are critical in protection against pneumococcal infections.

The pneumococcus is a common commensal of the respiratory tract, particularly in children, in whom colonization rates may be in excess of 90% in some developing country communities [8–10]. Nasopharyngeal colonization is the initial event from which mucosal and invasive pneumococcal infection develops and is also the nidus of pneumococcal transmission [11].

The different pneumococcal serotypes vary in prevalence and virulence, depending on a multitude of factors, including host, age, region and country. Their distribution is temporal and varies by geographic location, and a few serotypes predominantly cause disease in children [12]. In addition, the immune response is generally serotype specific. Knowledge of the prevalent serotypes and epidemiology of disease in a given population is crucial to the development and implementation of any vaccination program.

DISEASE BURDEN

The pneumococcus is responsible for a broad spectrum of diseases, some of which are invasive

and others non-invasive, affecting only mucosal surfaces. The highest rates of invasive pneumococcal disease (e.g. bacteremia, meningitis or infection of other sterile body sites) occur in young children, aged less than 2 years [13,14].

Invasive disease

In the USA and other developed countries, the most commonly recognized form of invasive disease is bacteremia, which accounts for about 70% of invasive disease. Following the decline of invasive Hib disease, the pneumococcus is now the most common cause of bacterial meningitis. In the USA, prior to the introduction of pneumococcal conjugate vims it accounted for an estimated 3000 cases of meningitis annually [14,15]. Recent data from Scotland have revealed that almost 40% of bacterial meningitis in patients under the age of 5 years is caused by the pneumococcus [16]. Furthermore, complications and long-term sequelae are more frequent with pneumococcal meningitis than with other forms of bacterial meningitis [17]. This observation has been confirmed in other communities where there is a high prevalence of bacterial meningitis [18].

Non-invasive disease syndromes

Otitis media

Otitis media is a source of substantial morbidity in children and perhaps the most common reason for pediatric outpatient consultations. However, since it is caused by a wide variety of organisms, etiologic diagnosis can only be confidently made by tympanostomy and bacteriologic examination of middle ear fluid. Unfortunately, this procedure is not routinely performed, and, consequently, true estimates of the burden of otitis media attributable to the pneumococcus are difficult to obtain. It is estimated that the pneumococcus is responsible for at least 25–50% of all cases of bacterial otitis media [19,20]. In the UK, it is estimated that 14% of children have acute otitis media during the first year of life, 18% in the second and 12% in the third; this implies that *S. pneumoniae* may be responsible for 180 000–350 000 episodes of disease annually in children aged less than 5 years [21].

In the USA, acute otitis media accounts for over 24 million outpatient consultations each year and contributes substantially to the burden of childhood morbidity and parental absence from work [22,23].

From the perspective of pneumococcal disease, in the developed countries otitis media is the least severe but the most prevalent, and consequently incurs the largest component of health-care costs and accounts for the largest morbidity. However, in less developed countries, the burden of otitis media is less well perceived, and more concern is generated by the more 'dramatic' forms of disease, such as meningitis and pneumonia.

Acute lower respiratory infections

Respiratory infections due to this organism are most prevalent in young children and the elderly. However, the true burden of disease attributable to the pneumococcus is difficult to estimate, because lower respiratory tract illnesses in general are managed empirically with antibiotic treatment, with diagnosis often based on clinical signs, sometimes with radiologic confirmation but seldom with bacteriologic confirmation. Most studies that have attempted to quantify the burden of disease have been retrospective. In general, the incidence of respiratory tract infections varies widely, but has been highest in poor, developing countries. In the USA, the pneumococcus was responsible for over 500 000 cases of pneumonia per year [15], until the implementation of routine vaccination. In the UK, a study of hospital admissions in 1994–95 reported estimates for different clinical categories of lower respiratory tract infections such as bronchopneumonia, lobar pneumonia and unspecified pneumonia, as 36, 104 and 85 per 100 000, respectively, in children aged less than 5 years [24]. In Finland, the incidence of community-acquired pneumonia in 1981–82 was estimated as 36 per 1000 children aged less than 5 years [25].

In many developing countries, the etiology of childhood pneumonia is not known and little information is available on the relative importance of bacterial and viral agents of pneumonia in these communities [26]. In the Gambia, an active hospital-based disease surveillance program was undertaken during the efficacy trial of a protein conjugate Hib vaccine study (1994–97). The incidences of pneumococcal disease were 224 per 100 000 child years among children aged 2–11 months, 139 per 100 000 among children aged 12–23 months, and 82 per 100 000 among children aged 24–35 months. Pneumonia was the most common form of invasive pneumococcal disease observed (75.5% of patients) [27].

Studies that have attempted to ascertain the etiologic cause of pneumonia in children have largely utilized serology and bacterial culture and have estimated that 13–38% of cases of community-acquired pneumonia in children are due to *S. pneumoniae* [28–31]. However, studies that have, in addition, utilized bacterial studies of lung aspirates from Africa suggest that this diagnostic technique improves the diagnostic yield for *S. pneumoniae* by an additional 50% [32,33]. The procedure is safe, is less uncomfortable than bronchoscopy, and provides reliable diagnostic information. Technically, it is no more difficult than thoracentesis, and patient acceptance is good. The procedure is not widely used because of the possible risks of pneumothorax or hemoptysis, which are fortunately very rare. The benefits seem to far outweigh the risks [34].

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Once the significance of capsular serotypes was understood, vaccine development was more focused on developing vaccines with the prevalent serotypes. Polyvalent vaccines were manufactured. These contain the individually extracted purified capsular polysaccharides, which are combined into the final product. The first successful clinical trial of a vaccine with four serotypes was demonstrated by MacLeod among military recruits in 1945. This was followed by a trial of a hexavalent pneumococcal polysaccharide vaccine. Unfortunately, interest in further development waned with the advent of penicillin, which was thought to be the 'magic bullet' for the pneumococcus. After nearly a decade, it became clear that the pneumococcus was still a problem, and research into the development of polyvalent pneumococcal polysaccharide vaccines resumed. A 14-valent polysaccharide vaccine was licensed in 1977. This was soon followed by the 23-valent vaccine, which was licensed internationally in 1981 (reviewed in ref. [1]).

The 23-valent capsular polysaccharide vaccine is not effective in children less than 2 years old, the most vulnerable age group for invasive pneumococcal disease. The poor immunologic response to polysaccharide antigens in this age group is due to the lack of T-cell involvement, which is a prerequisite for high-level antibody response and induction of immunologic memory [35,36]. The

immune response can be enhanced by the coupling of the polysaccharide antigen to a protein carrier that can be processed and presented to T-cells bearing specific receptors for the protein complex. The T-cells exposed to the polysaccharide-protein conjugate are able to promote vigorous antigen-specific B-cell proliferation and memory maturation [35,36]. This approach of polysaccharide-protein conjugation was used with great success for the development of the now widely used Hib vaccine.

PNEUMOCOCCAL CONJUGATE VACCINES

Vaccine composition

The development of a protein conjugate vaccine for the pneumococcus has involved the selection of a few prevalent serotypes, and these have been individually coupled to an immunogenic carrier protein. The initial effort for the development of this vaccine has been largely based in the USA, so the vaccine formulations have been based on epidemiologic data from the USA [37].

Different proteins have been selected for conjugation, and these include diphtheria and tetanus toxoids, the meningococcal outer-membrane complex, and diphtheria protein CRM₁₉₇. Several vaccine formulations incorporating between four and 11 pneumococcal capsular polysaccharide types have been subjected to safety and immunogenicity studies. The immune responses to the pneumococcal polysaccharide and the interaction with other vaccines have varied considerably, depending on the carrier protein used.

The seven-valent pneumococcal conjugate vaccine (Prevnar) includes seven purified capsular polysaccharides of *S. pneumoniae*, each coupled to a non-toxic diphtheria protein analog (cross-reactive material, CRM). The vaccine contains approximately 2 µg each of capsular polysaccharide from serotypes 4, 9V, 14, 19F and 23F, and oligosaccharide from 18C, 4 µg of serotype 6B, 20 µg of the carrier protein CRM₁₉₇, and 0.125 mg of aluminum in each 0.5-mL dose as an aluminum phosphate adjuvant.

During the period 1978–94, these serotypes accounted for 86% of bacteremia cases, 83% of meningitis cases and 65% of otitis media cases in children aged less than 6 years of age in the USA [37]. Assuming equivalent efficacy, the coverage conferred by this formulation will vary con-

siderably from one country to another because of the geographic and epidemiologic differences in serotype distribution and disease pattern. For example, serogroups in the seven-valent formulation [4,6,9,14,18,19,23] cause 70–88% of invasive pneumococcal disease in young children in the USA and Canada, Europe, Oceania and Africa. However, this same combination accounts for less than 65% of disease in Latin America and Asia. Serogroups in the nine-valent formulation, which incorporates components of the seven-valent vaccine and in addition serotypes 1 and 5, cause 80–90% of pneumococcal disease in most regions of the world except Asia (66%). Other serotypes not included in the current vaccine formulations tend to cause disease more frequently in older children and adults [12].

Safety

Since the development of protein conjugate vaccines, several studies have evaluated the safety of different formulations, including two-, five-, seven- and nine-valent formulations. Prior to licensure, over 22 000 children received the vaccines, and there have been no reports of severe systemic or life-threatening reactions attributable to the vaccine [38–46]. Currently, there are several pneumococcal polysaccharide-protein conjugate vaccines in various phases of clinical trials with children. In general, these vaccines have demonstrated a good safety profile. The common adverse reactions have been limited to local swelling or redness at the site of injection, and this is self-limiting, resolving within a few days of vaccination. These local reactions are significantly milder than those observed with previously licensed vaccines such as the diphtheria-pertussis-tetanus (DPT) (whole cell) vaccines [45]. Rate, types and severity of the adverse events associated with the seven-valent pneumococcal conjugate vaccine during the Kaiser Permanente studies were acceptable [43,47].

Immunogenicity

Several studies have evaluated immunogenicity in the context of local immunization practices in different populations [44–47]. The majority of children have been offered three doses of the vaccine after the age of 6 weeks or greater at monthly or bi-monthly intervals, and in some instances, a booster

dose at 15–18 months of age. Some of these studies have also demonstrated the induction of immunologic memory with the use of pneumococcal polysaccharide after the primary series [48,49].

Although much work has been done on standardizing the laboratory technique for the determination of antibody concentration in serum, it is still not known what concentration of serotype-specific antibody confers protection. It also remains contentious whether a given concentration will confer protection against the different forms of non-invasive (mucosal) and invasive pneumococcal disease [50]. In general, a cue has been taken from antibody responses to the Hib conjugate vaccine, and this has been applied to the pneumococcus. The importance of antibody quality, and not just quantity, has been recognized in determining protection. In some of these studies, the opsonophagocytic activity of vaccine-induced antibodies has been demonstrated [48,51]. In addition, secretory antibodies in saliva [52,53] and the impact of vaccination on nasopharyngeal carriage have been demonstrated in some studies [44,46, 54]. The vaccine has the capacity to reduce the incidence of nasopharyngeal carriage of serotypes contained in the vaccine.

Vaccine efficacy

These very encouraging reports led to the first large-scale efficacy trial in the USA, and there are now several other studies evaluating the efficacy of the same vaccine or similar formulations against different endpoints in different populations.

Efficacy against invasive disease

The first efficacy trial for a pneumococcal conjugate vaccine commenced in October 1995 and was completed in August 1998; the results led to the licensure of the seven-valent pneumococcal conjugate vaccine in the USA in February 2000. In a randomized, controlled study by the Northern California Kaiser Permanente group, 37 830 infants were assigned to either a seven-valent pneumococcal conjugate vaccine or a control vaccine (meningococcal conjugate vaccine), and all children were monitored for acute illness consistent with invasive pneumococcal disease [47]. Vaccination was administered at ages 2, 4, 6 and 12–15 months, concurrently with routine licensed vaccines. When all cases of invasive disease were

evaluated, there were 40 fully vaccinated cases caused by vaccine serotypes, of which 39 cases occurred in controls, for an efficacy of 97.4% (95% CI = 82.7–99.9, $P < 0.0001$). There were 52 cases in the intent-to-treat analysis in the pneumococcal group, for an effectiveness of 93.9% (95% CI = 79.6–98.5, $P < 0.001$) [47].

Efficacy against pneumonia

The impact of vaccination on pneumonia was evaluated by different categories based on clinical and/or radiologic diagnosis. Vaccine efficacy for clinically diagnosed pneumonia was 11.4% (range 1.3–21%). The efficacy was better when there was a radiologic abnormality suggestive of pneumonia—33% (range 7.5–52%). When efficacy was evaluated for the classic pneumonia with large pulmonary consolidation (> 2.5 cm), efficacy increased to 73% (range 38–88%) [47]. These efficacy results confirm that pneumococci are responsible for many more cases of pneumonia than those associated with the classical lobar consolidation, commonly attributed to the pneumococcus on chest radiographs.

Otitis media

The seven-valent pneumococcal conjugate vaccine in the Kaiser Permanente study had efficacies as follows: against otitis media visits, 8.9%; against acute otitis media episodes, 7%; and against recurrent episodes, 9.3%. It also gave a 20% reduction in ventilatory tube placement [47]. In the USA, acute otitis media is an important cause of clinical consultation, with an annual cost of over \$5 billion, and a small reduction in the incidence of disease could result in substantial annual savings [23].

An etiology-specific study of otitis media from Finland evaluated the efficacy of the same vaccine. In this study, 1662 infants were recruited and offered vaccination at 2, 4, 6 and 12 months of age. Etiologic diagnosis of acute otitis media was made by tympanostomy. There was a 57% (range 44–67%) reduction in the incidence of disease caused by pneumococcal serotypes included in the vaccine. Prevention of otitis media irrespective of etiology was 6% (range 4–16%) [55].

In the Finnish trial, the impact of vaccination on the total number of otitis media episodes, regardless of etiology, was not statistically significant, at 6% (95% CI = 4–16%), whereas in the California study, there was a statistically significant 7% reduction (95% CI = 4–10).

Table 1 Recommended schedule for use of seven-valent pneumococcal conjugate vaccine among previously vaccinated infants and children by age at time of first vaccination

Age at first dose (months)	Primary series (interval in months)	Additional dose
2–6	3 doses (2) ^a	1 dose at 12–15 months
7–11	2 doses (2) ^b	1 dose at 12–15 months
12–23	2 doses (2) ^c	–
24–59		
Healthy children	1 dose	–
Children with sickle cell disease, asplenia, human immunodeficiency virus infection, chronic illness or immunocompromising condition ^d	2 doses (2) apart	

^aFor children vaccinated at age <1 year, minimum interval between doses is 4 weeks.

^bThe additional dose should be administered >8 weeks after the primary series has been completed.

^cMinimum interval between doses is 8 weeks.

^dRecommendations do not include children who have undergone a bone marrow transplantation.

RECOMMENDATIONS FOR USE

The basis of the recommendations for use of the seven-valent pneumococcal vaccine is conferment of protection at the earliest possible opportunity for the young infant. Newborn infants should begin the schedule at 2 months, although the vaccine can be administered as early as 6 weeks [56].

Three doses are offered at 2-month intervals, with a booster between 12 and 15 months of age. All children aged ≤23 months should be vaccinated using the schedule shown in Table 1.

Although formal efficacy data are lacking for clinical conditions that are known to predispose to invasive pneumococcal disease, the use of the vaccine has been recommended. Safety and immunogenicity of some of the pneumococcal conjugate vaccines have been established in sickle cell disease [57] and HIV infection [58,59]. Thus it is recommended that vaccination should be offered to children who have underlying medical conditions or are immunocompromised and at risk of pneumococcal disease. These include children who have sickle cell hemoglobinopathy, functional or anatomic asplenia, chronic pulmonary disease, diabetes mellitus, cerebrospinal fluid leak, HIV infection, lymphomas, or leukemia, and those who have undergone immunosuppressive therapy or solid organ transplantation (Table 2).

In addition to these conditions, The Advisory Committee on Immunization Programs (ACIP) in the USA recommends that all children between 24 and 59 months of age should be considered for

vaccination, with special priority given to the category of children listed in Table 3.

IMPACT OF VACCINATION ON NASOPHARYNGEAL CARRIAGE OF PNEUMOCOCCI

The effect of widespread use of a pneumococcal conjugate vaccine is as yet unknown. Unlike *H. influenzae* type b, *S. pneumoniae* is diverse, and there are concerns that following widespread use of the vaccine in a population, immune pressure may induce capsular transformation or replacement in the nasopharynx by non-vaccine serotypes, with a consequent emergence of disease caused by non-vaccine serotypes [60,61]. There is already evidence that, following vaccination with the conjugate vaccine, there is a reduction in the nasopharyngeal carriage of serotypes included in the vaccine, and an increase in carriage of non-vaccine serotypes has also been reported in some studies [44,54]. It was initially not clear whether this observation would translate into an increase in disease incidence. However, the otitis media studies from Finland reported an increase in incidence of disease caused by non-vaccine serotypes [55]. Thus, there is a need to continuously monitor the epidemiology of disease after introduction of the vaccine into any population. A community randomized study of the seven-valent pneumococcal conjugate vaccine in Native Americans has just been completed [62]. This study will hopefully give insight into the potential impact of

Table 2 Summary of recommendations for the use of seven-valent pneumococcal conjugate vaccine (PCV7) among infants and children**Children for whom PCV7 is recommended**

All children aged ≤ 23 months
 Children aged 24–59 months with the following conditions:
 Sickle cell disease and other sickle cell hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction
 Infection with human immunodeficiency virus
 Immunocompromising conditions including: congenital immunodeficiencies—B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly c1, c2, c3 and c4 deficiency; and phagocytic disorders, excluding chronic granulomatous disease
 Renal failure and nephritic syndrome
 Diseases associated with immunosuppressive therapy or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; or solid organ transplantation
 Chronic illness, including:

1. Chronic cardiac disease, particularly cyanotic congenital heart disease and cardiac failure
2. Chronic pulmonary disease, excluding asthma unless on high-dose corticosteroid therapy
3. Cerebrospinal fluid leaks
4. Diabetes mellitus

Table 3 Children for whom PCV7 should be considered (based on ACIP recommendations in the USA)

All children aged 24–59 months, with priority given to:
 Children aged 24–35 months
 Children of Alaskan Native or Native American descent
 Children of African-American descent
 Children who attend group daycare centers^a

^aDefined as a setting outside the home where a child regularly spends ≥ 4 h/week with ≥ 2 unrelated children under adult supervision.

vaccination of a community on the epidemiology of pneumococcal disease.

IMPACT OF VACCINATION ON ANTIBIOTIC-RESISTANT PNEUMOCOCCI

Pneumococci of serogroups 6, 14, 19 and 23 are often carried in the nasopharynx of children, and these acquire resistance most frequently. Indiscriminate and frequent prescription of antibiotics to children have contributed to the global escalation of antibiotic resistance. Data from Israel [63] suggest that a multivalent pneumococcal conjugate vaccine may reduce the carriage and spread of these pneumococci, particularly in daycare centers. However, this should be monitored closely, as it is possible that, by horizontal gene transfer, antibiotic resistance genes may be transferred to non-vaccine serotypes.

ADDITIONAL EFFICACY STUDIES

The efficacy of this vaccine has been remarkable against invasive and non-invasive disease syndromes. However, additional clinical trials to assess efficacy of the same or similar vaccine formulations in different populations are needed. Limited studies have been conducted in HIV-infected subjects, and these have demonstrated encouraging immunogenicity results [58,59], but efficacy also needs to be determined in populations with a high prevalence of HIV, where the risk of invasive pneumococcal disease is several times higher. It is against this background that the study in South Africa is being conducted, and this is near completion. A further study to evaluate the efficacy of the vaccine is in progress in a rural population in the Gambia, where there is a high prevalence of malaria and high infant mortality.

FUTURE DEVELOPMENTS

The development and licensure of the PCV7 has been a major breakthrough in the control of invasive pneumococcal disease. However, one major limitation with protein conjugation of pneumococcal polysaccharide is the number of serotypes that can be included in a vaccine formulation because of manufacturing considerations and cost of production. For optimal efficacy, vaccine composition will be determined by the prevalent pneumococcal serotypes in a given region, and the target group.

The threat of a change in the epidemiology of pneumococcal disease following the introduction of pneumococcal conjugate vaccine is a reason to continue active surveillance of disease. Furthermore, such surveillance will provide information about trends in antimicrobial resistance, and potential herd immunity, and will allow more comprehensive reports of vaccine-related health events.

Although several high-risk groups for invasive pneumococcal disease are well recognized, formal evaluations of the efficacy of this vaccine in such groups are required so that their use can be optimized.

The current unit cost of a glycoprotein conjugate vaccine may prohibit its use in areas where it is most needed—developing countries. If the ultimate goal is to achieve global control of invasive pneumococcal disease, it is imperative that vaccines are made available at subsidized rates to developing countries.

Control of neonatal and early infant disease

The proposed immunization schedule for the protein conjugate pneumococcal vaccine in developing countries is likely to be a three-dose schedule given at 2, 3 and 4 months or 6, 10 and 14 weeks with DPT. However, because children in developing countries are frequently late in presenting for immunization, it is likely that infants given the conjugate vaccine may not be protected until they reach the age of 4–5 months. In developing countries, by the age of 5 months, as many as 20% of cases of invasive pneumococcal disease in infants would have occurred [27,64]. Although a strong herd effect, resulting from widespread vaccine use, may decrease the incidence of pneumococcal disease in infants too young to be vaccinated, as was observed following the introduction of Hib vaccines, the outcome with these multiserotype bacteria is less predictable. A possible approach to this problem lies in the combination of maternal immunization during pregnancy with active immunization during infancy, an approach that works effectively in the prevention of tetanus. Another alternative approach to control the burden of pneumococcal disease in the first 3 months of life is neonatal immunization with protein conjugate pneumococcal vaccines. Results of neonatal immunization studies with Hib conjugate vaccine based on the protein carriers tetanus toxoid and

CRM₁₉₇ are encouraging, but this approach has not been evaluated for the pneumococcal conjugate vaccines.

Duration of protection

The duration of protection following vaccination is not known. It is assumed that because the vaccine induces immunologic memory, immune protection is likely to last for a long time, possibly for life. However, this is not known for sure. It is, in fact, not clear at this stage if a fourth dose, as recommended by the current schedule in infancy, will be required in all settings.

Correlates of immune protection

Currently, immunogenicity is measured by using ELISA methods to determine serotype-specific antibody concentrations. It is still not known, however, what concentration confers immunity. Functional tests such as opsonophagocytosis and avidity indices are being evaluated, but there is still a need to establish an immune correlate of clinical protection. Such validated immune system correlates will be invaluable in the evaluation of new vaccines against pneumococcal infections.

Combination vaccines

In most developing countries, the immunization schedule during the first year of life already involves about 8–10 injections, and there are concerns that an additional injection may compromise participation in immunization programs. In order to improve delivery and reduce cost, research into combinations of vaccines has been given much attention recently. Thus, vaccine manufacturers have developed different vaccine formulations that combine other already licensed vaccines with new antigens.

The multiplicity of the pneumococcal serotypes has also encouraged the development of newer approaches that would incorporate more serotypes into a vaccine without antigenic interference. There are studies that have evaluated the use of different carrier proteins for different pneumococcal serotypes in the same vaccine, but results of the serotype-specific antibody responses have been lower than those reported with single protein carrier formulations [65]. Since the concentration of serotype-specific antibody that is protective is

not known, it has been difficult to interpret these findings.

CONCLUSION

The availability of the technology to induce immunogenicity in young infants to pneumococcal polysaccharides and to offer protection against disease by the serotypes contained in the vaccine is a giant leap in the progress towards the control of pneumococcal disease worldwide. However, the effort must be sustained, and the current concerns about the limitations of pneumococcal conjugate vaccines should encourage the development of new vaccines using species-common, genetically conserved pneumococcal proteins, either in combination or as a conjugate for the pneumococcal polysaccharide, and there are now several encouraging results, albeit at preliminary stages of development.

Unfortunately, because the diagnostic tools for pneumococcal disease are not very sensitive, the true burden of pneumococcal disease may not be fully appreciated until the vaccines are widely introduced and the incidences of disease syndromes are analyzed before and after the introduction of vaccination—an important issue to be brought to the attention of health planners and policy-makers.

REFERENCES

1. Watson DA, Musher DM, Jacobsen JW, Verhoef J. A brief history of the pneumococcus in biomedical research; a panoply of scientific discovery. *Clin Infect Dis* 1993; 17: 913–24.
2. Denny FW, Loda FA. Acute respiratory infections are the leading cause of death in children in developing countries. *Am J Trop Med Hyg* 1986; 35: 1–2.
3. World Health Organization. *Vaccine research and development: report of the technical review group meeting, June 9–10, 1997*. Geneva: WHO, 1997: 32–6.
4. Reacher MH, Shah A, Livermore DM *et al*. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000; 320: 213–16.
5. Collignon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae*. *Med J Aust* 2000; 173: S58–64.
6. Koomhof HJ, Wasas A, Klugman K. Antimicrobial resistance in *Streptococcus pneumoniae*: a South African perspective. *Clin Infect Dis* 1992; 15: 84–94.
7. Henrichsen J. Typing of *Streptococcus pneumoniae*: past, present, and future. *Am J Med* 1999; 26: 50S–54S.
8. Leach AJ, Boswell JB, Asche V, Nienhuys TG, Mathews JD. Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. *Pediatr Infect Dis J* 1994; 11: 983–9.
9. Lloyd-Evans N, O'Dempsey TJ, Baldeh I *et al*. Nasopharyngeal carriage of pneumococci in Gambian children and in their families. *Pediatr Infect Dis J* 1996; 15: 866–71.
10. Huebner RE, Wasas A, Mushi A, Mazhani L, Klugman K. Nasopharyngeal carriage and antimicrobial resistance in isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children under 5 years of age in Botswana. *Int J Infect Dis* 1998; 3: 18–25.
11. Obaro SK, Adegbola RA. The pneumococcus: vaccines, carriage disease and conjugate vaccines. *J Med Microbiol* 2002; 2: 98–104.
12. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis* 2000; 30: 100–21.
13. Schuchat A, Robinson K, Wenger JD *et al*. Bacterial meningitis in the United States in 1995. *N Engl J Med* 1997; 337: 970–6.
14. Klein JO. The epidemiology of pneumococcal disease in infants and children. *Rev Infect Dis* 1981; 3: 246–53.
15. Centers for Disease Control. Prevention of pneumococcal disease: recommendation of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997; 46(no. RR-8).
16. Scottish Centre for Infection and Environmental Health Surveillance Report: Respiratory Infections. *SCIEH Weekly Report* 2000; 34(4): 30–1.
17. Barraf LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993; 12(5): 389–94.
18. Goetghebuer T, West TE, Wermenbol V *et al*. Outcome of meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in The Gambia. *Trop Med Int Health* 2000; 3: 207–13.
19. Dowell SF, Butler JC, Giebink GS *et al*. Acute otitis media: management and surveillance in an era of pneumococcal resistance: a report from the Drug resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J* 1999; 18: 1–9.
20. Austrian R, Howie VM, Ploussard JH. The bacteriology of pneumococcal otitis media. *John Hopkins Med J* 1977; 141: 104–11.
21. Harrison CJ, Marks MI, Welch DF. Microbiology of recently treated acute otitis media compared with previously untreated acute otitis media. *Pediatr Infect Dis* 1985; 4(6): 641–6.

22. Shappart SM. Office visits for otitis media: United States, 1975–90. *Vital Health Stat* 1992; 214: 1–18.
23. Gates GA. Cost effectiveness considerations in otitis media treatment. *Otolaryngol Head Neck Surg* 1996; 114: 525–30.
24. Djuretic T, Ryan MJ, Miller E, Fairley CK, Goldblatt D. Hospital admissions in children due to pneumococcal pneumonia in England. *J Infect* 1998; 37: 54–8.
25. Jokinen C, Heiskanen L, Juvonen H *et al.* Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993; 137: 977–88.
26. Walsh JA, Warren KS. Selective primary health care, an interim strategy for disease control in developing countries. *N Engl J Med* 1979; 301: 967–74.
27. Usen S, Adegbola R, Mulholland K *et al.* Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia. *Pediatr Infect Dis J* 1998; 17: 23–8.
28. Ruuskanen O, Nohynek H, Ziegler T *et al.* Pneumonia in childhood: etiology and response to antimicrobial therapy. *Eur J Clin Microbiol Infect Dis* 1992; 11: 217–23.
29. Juven T, Mertsola J, Waris M *et al.* Etiology of community-acquired pneumonia in 254 hospitalised children. *Pediatr Infect Dis J* 2000; 19: 293–8.
30. Heiskanen-Kasma T, Korppi M, Jokinen C *et al.* Etiology of childhood pneumonia: serologic results in a prospective, population-based study. *Pediatr Infect Dis J* 1998; 17: 986–99.
31. Korppi M, Heiskanen-Kasma T, Jalonene C *et al.* Aetiology of community-acquired pneumonia in children treated in hospital. *Eur J Pediatr* 1993; 152: 24–30.
32. Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. *Ann Trop Paediatr* 1997; 17: 315–19.
33. Adegbola RA, Obaro SK. Diagnosis of childhood pneumonia in the tropics. *Ann Trop Med Parasitol* 2000; 94: 197–207.
34. Shann F. Bacterial pneumonia: commoner than perceived. *Lancet* 2001; 357(9274): 2070–2.
35. Stein KE. Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J Infect Dis* 1992; 165(suppl 1): S49–52.
36. Siber GR. Pneumococcal disease: prospects for a new generation of vaccines. *Science* 1994; 265: 1385–7.
37. Butler JC, Breiman RF, Lipman HB, Hofmann J, Facklam RR. Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–94: implications for development of a conjugate vaccine. *J Infect Dis* 1995; 171: 885–9.
38. Steinhoff MC, Edwards K, Keyserling H *et al.* A randomised comparison of three bivalent *Streptococcus pneumoniae* glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. *Pediatr Infect Dis J* 1994; 13: 368–72.
39. Kayhty H, Ahman H, Ronnberg P-R, Tillikainen R, Eskola J. Pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine is immunogenic in infants and children. *J Infect Dis* 1995; 172: 1273–8.
40. Leach A, Ceesay SJ, Banya WAS, Greenwood BM. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. *Pediatr Infect Dis J* 1996; 15: 333–9.
41. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatr* 1996; 128: 649–53.
42. Rennels MB, Edwards KM, Keyserling HL *et al.* Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. *Pediatrics* 1998; 101: 604–11.
43. Shinefield HR, Black S, Ray P *et al.* Safety and immunogenicity of heptavalent pneumococcal CRM₁₉₇ conjugate vaccine in infants and toddlers. *Pediatr Infect Dis* 1999; 18: 757–63.
44. Mbelle N, Wasas A, Huebner Kimura A, Chang I, Klugman K. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999; 180: 1171–6.
45. Obaro SK, Adegbola RA, Chang I *et al.* Safety and immunogenicity of a nonavalent pneumococcal conjugate vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants. *Pediatr Infect Dis J* 2000; 19: 463–9.
46. Dagan R, Muallem M, Melamed R, Leroy O, Yagupsky P. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. *Pediatr Infect Dis J* 1997; 16: 1060–4.
47. Black S, Shinefield H, Fireman B *et al.* Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000; 19: 187–95.
48. Obaro SK, Huo Z, Banya WA *et al.* A glycoprotein pneumococcal conjugate vaccine primes for antibody responses to a pneumococcal polysaccharide vaccine in Gambian children. *Pediatr Infect Dis J* 1997; 12: 1135–40.
49. O'Brien KL, Steinhoff MC, Edwards K, Keyserling H, Thoms ML, Madore D. Immunologic priming of young children by pneumococcal glycoprotein

- conjugate, but not polysaccharide, vaccines. *Pediatr Infect Dis J* 1996; 15: 425–30.
50. Obaro SK. Protein conjugate vaccines—how much is enough? *Trends Microbiol* 2001; 9: 364–5.
 51. Vidarsson G, Sigurdardottir ST, Gudnason T *et al.* Isotypes and opsonophagocytosis of pneumococcus type 6B antibodies elicited in infants and adults by an experimental pneumococcus type 6B-tetanus toxoid vaccine. *Infect Immun* 1998; 66: 2866–70.
 52. Neiminen T, Kayhty H, Virolainen A, Eskola J. Circulating antibody secreting cell response to parenteral pneumococcal vaccines as an indicator of salivary IgA antibody response. *Vaccine* 1998; 16: 313–19.
 53. Choo S, Zhang Q, Seymour L *et al.* Primary and booster salivary antibody responses to a 7-valent conjugate vaccine in infants. *J Infect Dis* 2000; 182: 1260–3.
 54. Obaro SK, Adegbola RA, Banya WAS, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. *Lancet* 1996; 348: 271–2.
 55. Eskola J, Kilpi T, Palmu A *et al.* Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001; 344: 403–9.
 56. Advisory committee on immunization practices (ACIP). Preventing pneumococcal disease among infants and young children. *MMWR* 2000; 49 (RR-9): 1–35.
 57. O'Brien KL, Winkelstein JA, Santosham M *et al.* Immunogenicity of a pneumococcal protein conjugate vaccine in infants with sickle cell disease. *Pediatr Res* 1996; 36: 160.
 58. King JC, Vink PE, Farley JJ *et al.* Comparison of the safety and immunogenicity of a pneumococcal conjugate with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1996; 15: 192–6.
 59. King JC, Vink PE, Farley JJ, Smilie M, Park M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. *Pediatrics* 1997; 99: 575–80.
 60. Lipsitch M. Bacterial vaccines and serotype replacement: lessons from *Haemophilus influenzae* and prospects for *Streptococcus pneumoniae*. *Emerg Infect Dis* 1999; 5: 336–45.
 61. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? *Lancet* 2000; 356: 1210–11.
 62. Moulton LH, O'Brien KL, Kohberger R *et al.* Design of a group-randomized *Streptococcus pneumoniae* vaccine trial. *Control Clin Trials* 2001; 22: 438–52.
 63. Dagan R, Melamed R, Muallem M, Piglansky L, Yagupsky P. Nasopharyngeal colonization in southern Israel with antibiotic-resistant pneumococci during the first 2 years of life: relation to serotypes likely to be included in pneumococcal conjugate vaccines. *J Infect Dis* 1996; 174: 1352–5.
 64. Mulholland EK, Ogunlesi OO, Adegbola RA *et al.* Etiology of serious infections in young Gambian infants. *Pediatr Infect Dis J* 1999; 18(10 suppl): S35–41.
 65. Wuorimaa T, Dagan R, Eskola J *et al.* Tolerability and immunogenicity of an eleven-valent pneumococcal conjugate vaccine in healthy toddlers. *Pediatr Infect Dis J* 2001; 20: 272–7.