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Review

Prospects for pneumococcal vaccination in African children

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Abstract

Streptococcus pneumoniae (pneumococcus) remains a major cause of morbidity and mortality in both developed and undeveloped countries. Accurate disease burden estimates for developing countries and Africa in particular, where diagnostic facilities are less adequate and a disease surveillance system virtually non-existent, is difficult. However, from conservative estimates, the pneumococcus is probably responsible for at least 1 million of the 4 million deaths that occur from acute lower respiratory infections in children aged less than 5 years. The global burden of disease has been accentuated by the rising menace of multi-drug resistant strains, which defy geographic and racial borders. Thus, now more than ever before, there is an urgent need to identify and implement preventive measures to avert this problem. The currently licensed pneumococcal polysaccharide vaccine, comprises 23 capsular polysaccharides of the pneumococcus, many of which are poorly immunogenic in the very vulnerable age group of under-fives. A possible solution to the problem of poor immunogenicity is to use a protein/polysaccharide conjugate vaccine similar to that recently introduced successfully for *Haemophilus influenzae* type b (Hib) and using this approach, several workers have reported promising results from safety and immunogenicity studies. However, unlike Hib, the development of conjugate vaccine against pneumococcal disease is complicated by the existence of more serotypes than can be feasibly incorporated in a single conjugate vaccine formulation. Whilst this challenge has been taken on by some vaccine manufacturers, novel approaches such as the identification or construction of protective protein antigen, common to all clinically important strains are being explored. Novel application of the pneumococcal polysaccharide vaccines in pregnancy for protection of disease in early infancy is an approach that has not been evaluated. For maximum impact, the ultimate vaccine formulation should be affordable and available to resource poor countries where the burden of disease is highest. Establishing disease surveillance systems in such countries now will greatly facilitate the introduction of the vaccines.

Keywords: *Haemophilus influenzae*; Meningitis; B-cells

1. Introduction

Acute lower respiratory tract infections (ALRI) are a major cause of mortality and morbidity in

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children throughout the developing world. It is estimated that at least 4 million children die from pneumonia and related conditions each year, nearly all in developing countries (Leoswki, 1986; Shann and Steinhoff, 1999). The importance of bacteria as a cause of pneumonia was recently demonstrated during a *Haemophilus influezae* type b vaccine trial in which there was a 21% reduction in radiologically proven pneumonia. The potential impact of a vaccine against the pneumococcus is highlighted by the fact that it is a more important respiratory pathogen than *H. influenzae*. In the Gambia more than two-thirds of bacterial isolates in children with pneumonia are *Streptococcus pneumoniae*. In developing countries where diagnostic facilities are suboptimal and disease surveillance systems are virtually non-existent, the burden of disease is more difficult to quantify. However, it is estimated that in developing countries, the pneumococcus is the leading cause of death in children less than 2 years of age with an estimated 1.2 million deaths, causing 9% of all deaths and surpassing diarrheal deaths. It is estimated that with the advent of an effective pneumococcal vaccine for children less than 2 years of age, deaths from invasive pneumococcal disease could be decreased by 400 000–580 000 (CVI Forum, 1996).

Over the past two decades the rapid emergence of antibiotic resistant pneumococci and the increasing number of immunocompromised individuals pose a formidable threat to health in developed and developing countries alike. The emergence of multi-drug resistant strains has rekindled the search for a vaccine, which is efficacious not only in a healthy adult population, but also in vulnerable groups including those at the extremes of life, and the immunocompromised.

Acute bacterial meningitis is another important but a relatively neglected cause of mortality and morbidity among children in developing countries, which accounts for 100–500 000 deaths a year among young children (Greenwood, 1987). In addition, many children who survive an episode of meningitis are left with severe neurological damage. Incidence estimates of invasive pneumococcal disease in children in Africa and developing countries have been based largely on few etiology studies conducted in hospitals where facilities for bacterial culture are available. Thus it is unlikely that these figures are true estimates and may at best only represent minimal estimates of invasive pneumococcal disease. One such study was conducted in the Gambia. Evaluation of the cause of death was undertaken by verbal autopsy technique to ascertain the principal causes of death in childhood. During the period 1988–1994, all deaths in children younger than 5 years of age were recorded in The Upper River Division, The Gambia, and the cause of death was investigated by post-mortem questionnaire technique (De Francisco et al., 1993). Over a five year period 3755 deaths were recorded of which 645 (17%) were considered to be caused by acute lower respiratory tract infection (Jaffar et al., 1997). In the same region, during the period 1988 through 1990, blood cultures were obtained from 1222 children, who attended health centres in the Upper River Division, and who had an illness that satisfied the WHO criteria for pneumonia (O'Demsey et al., 1996a). These yielded 96 positive cultures, of which 44 (46%) were positive for pneumococcus. Thus estimates of invasive pneumococcal disease, based on the catchment population is about 500/100 000 in children younger than 1 year of age and 250/100 000 in those younger than 5 years of age (O'Demsey et al., 1996b). These conservative estimates are already over ten-times the incidence of invasive pneumococcal disease in the United States and in Europe (Leoswki, 1986; Breiman et al., 1990; Meyer and Fich, 1992).

It is generally known that blood culture alone tends to underestimate the etiology of pneumococcal pneumonia, with a positive isolation rate of less than 30%. The yield can be considerably increased by the use of lung aspirates in the diagnosis of acute lower respiratory infections. In 1986, Shann reviewed 11 studies of the etiology of pneumonia in children in the developing world, undertaken since 1974, which had used lung aspiration (Shann, 1986). Three hundred and fourteen organisms were isolated from 744 patients (42%). Pneumococcus comprised 43%. Subsequent studies in the Gambia (Wall et al., 1986; Forgie et al., 1991; Adegbola et al., 1994; Usen et al., 1998), Papua New Guinea (Barker et al., 1989) and Zimbabwe (Ikeogu, 1988) that have employed

lung aspiration and/or blood culture have confirmed the dominance of the pneumococcus as a cause of pneumonia in children in these countries.

Determination of the etiology of acute bacterial meningitis is relatively easier than that of pneumonia as microscopy and culture of cerebrospinal fluid yield a positive result in 70–80% of cases. Antigen detection assays such as the latex test which can be carried out on stored samples provide an important means of obtaining information on the pattern of acute bacterial meningitis in areas where there are no facilities for bacterial culture or there is high incidence of non-prescription antibiotic use.

A critical obstacle to the assessment of disease burden and consequently the need for pneumococcal vaccines is the lack of adequate diagnostic facilities in most developing countries, particularly in Africa. Most physicians are compelled to offer an antibiotic prescription for presumed bacterial pneumonia or acute bacterial meningitis when the cerebrospinal fluid is cloudy on visual inspection. While this approach is pragmatic in most settings, it does not allow for etiologic diagnosis of these conditions, estimation of disease burden attributable to potential vaccine preventable pathogens and also makes it impossible to determine the trend in antimicrobial resistance.

Table 1
Risk factors associated with pneumococcal infection

Physiological
Very young (<2 years of age)
Elderly (> 65 years of age)
Non-immunological defects
Skull fracture
Disruption of bronchial epithelium (e.g. influenza, noxious chemicals, smoking)
Obstruction of eustachian tube
Decreased vascular perfusion (sickle cell disease, congestive cardiac failure, nephrotic syndrome)
Immunological defects
Primary antibody deficiencie
Hypogammaglobulinaemia, IgG subclass deficiencies, specific antibody deficiency, B-cell malignancies)
Phagocyte abnormalities (neutropenia, hyposplenia, cirrhosis of the liver)
Complement deficiencies (C2, C3, sickle cell)
Secondary antibody defects
Human immunodeficiency virus infection (HIV)
Lymphorecticular malignancies, post-cancer chemotherapy

2. Risk factors

Clearance of pneumococci following invasion requires adequate opsonisation and phagocytosis by macrophages and neutrophils. Clinical conditions associated with impaired production of opsonins, including serotype specific anti-pneumococcal polysaccharide antibodies and defects in polymorphonuclear cell function, commonly predispose to invasive pneumococcal disease. Individual factors that contribute to the development of invasive pneumococcal disease include immune (both specific and innate), genetic, and environmental elements. Specific defects in host responses may involve age, deficiencies in levels of antibodies and complement factors, and splenic dysfunction. Combinations of these immune defects contribute to the increased rates of invasive pneumococcal disease in patients with sickle cell disease, chronic cardiopulmonary disease, nephrotic syndrome, neoplasms, and underlying medical conditions such as diabetes and alcoholic liver disease. The number of risk factors are greatest and the rates of invasive disease are highest in patients with HIV-1 infection, which has emerged as a major risk factor for serious *S. pneumoniae* infection worldwide (see Table 1). While most of the currently recognised risk factors for invasive pneumococcal disease are derived mainly from studies done in developed countries, a study of risk factors in rural West Africa suggests that poor weight gain, history of serious illness in previous 6 months, exposure to cigarette smoke or being carried on mother's back while cooking were risk factors (O'Demsey et al., 1996a). There are other risk factors that deserve particular mention for Africa.

2.1. Age

The epidemiology of invasive pneumococcal disease in young children in developing countries differs from that in developed countries. Children with pneumococcal meningitis have been noted to

have a younger mean age than that from studies outside Africa (Eskola et al., 1992; Davidson et al., 1993; Zangwill et al., 1996; Usen et al., 1998). A similar shift in age distribution towards younger cases was observed when invasive pneumococcal disease in Alaskan natives was compared with that in non-native American (Davidson et al., 1993). In developing countries, neonatal infections are a frequent cause of neonatal death. Until recently, the pneumococcus was not considered to be a significant cause of serious neonatal infections. In a recent WHO coordinated study conducted in five developing countries including the Gambia, the pneumococcus was responsible for 20% of 167 serious bacterial infection diagnosed in 4552 children during the first 3 months of life (WHO Young Infants Study Group, 1999). The pneumococcus was the most important cause of meningitis in children in this age group.

2.2. Underlying illness

In industrialized countries, high proportions of children who develop invasive disease have a serious underlying illness or a major congenital abnormality. There is a suggestion that in developing countries invasive pneumococcal disease is more likely to affect a child who had been previously well but this has not been established definitely.

2.2.1. HIV

In developed countries, infection with human immunodeficiency virus (HIV) is a strong risk factor for invasive pneumococcal disease, even during the early phase of the infection. In Kenya, Gilks and his colleagues (Gilks, 1998) have shown that the incidence of invasive pneumococcal disease is increased 20-fold in HIV positive prostitutes and that recurrent pneumococcal infection is common in these women.

The incidence of pneumococcal disease among HIV-infected children is estimated to be 11 114/100 000/year based on 1996 data (Jones et al., 1998). It was also shown that more than 90% of bacteremias occur in children younger than 2 years and that 51% of children with pneumococcal bacteremia are HIV-infected. It is likely that the true incidence of pneumococcal disease is much higher as these studies only described isolates from blood and not other sterile body fluids. Given that the detection rate of bacteremia by blood culture is only about 20–30%, the true rates may be about 5-fold higher.

The incidence of penicillin resistant infections has also been notably higher in HIV-infected children (Crewe-Brown et al., 1997). In Zimbabwe, pneumococci constituted a higher proportion of bacterial isolates obtained from HIV positive than from HIV negative children with pneumonia (Nathoo et al., 1993) and in South Africa and Malawi pneumococcal infection is common in HIV infected children (Crewe-Brown et al., 1997). As increasing numbers of African children are born with HIV infection the incidence of invasive pneumococcal disease in African children will rise.

2.2.2. Antecedent viral infection

Influenza virus infection predisposes to invasive pneumococcal disease in adults and it has been suggested that respiratory syncytial virus (RSV) plays a similar role in children. However, there is only limited evidence to support this view. Only nine of 255 of Gambian children (3.5%) with severe RSV infection had a positive blood culture for the pneumococcus (Weber et al., 1998).

2.2.3. Malnutrition

Prospective longitudinal studies in malnourished children have shown that they are more at risk of death from pneumonia, some of which could presumable be caused by the pneumococcus. Malnourished children in Asaro, Papua New Guinea, were four times more likely to be admitted to hospital with acute lower respiratory tract infection and once admitted were four times more likely to die (Lehmann, 1992). Although malnutrition is a recognised risk factor for etiologic agents of lower respiratory infection such as Mycobacterium tuberculosis and opportunistic organisms, recovery of *S. pneumoniae* from lung aspirates in malnourished children is not more frequent than in normal children (Mimica et al., 1971; Diallo et al., 1979; Adegbola et al., 1994).

2.2.4. Malaria

There is considerable clinical overlap in the clinical diagnosis of malaria and ALRI, particularly in areas where diagnostic facilities are limited, as is the case in most developing, malaria endemic countries. Several clinical studies have alluded to this clinical observation. A study in Kenya estimated that up to 45% of children admitted with respiratory signs indicative of ALRI probably had malaria (English et al., 1996). Whilst the clinical distinction remains a problem, it has been suggested that malaria infection causes impairment of the host defence as a result of damage to the immune system by the parasite (Weistein and Swartz, 1974). Transient loss of B-cell control and a reduction in T-cell polpulation has been reported following acute malaria (Whittle et al., 1989). Furthermore endemic malaria affects the spleen and recticuloendothelial system such that it is conceivable that this could affect the clearance of pneumococci from the circulation and may also affect immune response to the pneumococcal polysaccharide. Thus malaria may be an important factor to consider as a possible risk factor contributing to the risk of invasive pneumococcal disease. This interaction deserves further evaluation.

2.2.5. Genetic factors

There have been observations that the incidence of invasive pneumococcal disease is higher in American blacks than in white Americans, even after correction for socioeconomic inequalities (Hennerberger et al., 1983). This observation suggests that genetic risk factors for invasive pneumococcal disease may be associated with racial groups. However, characterisation of such predisposing genetic factors is not complete. Homozygosity for the sickle cell gene is one such characteristic. Patients with sickle cell disease are at high risk of invasive disease and must be protected by vaccination and/or chemoprophylaxis. There is also some evidence to suggest that polymorphisms in genes influencing mannose-binding lectins and macrophage Fcγ receptors may predispose to recurrent or severe invasive pneumococcal disease (Van de Winkel and Capel, 1993).

2.3. Socioeconomic factors

Poor socioeconomic conditions have been traditionally associated with increased risk of respiratory infections. Although the study by O'Demsey and colleagues (1996) was not primarily designed to evaluate socioeconomic factors, there was increased risk of pneumococcal disease associated with mothers who did not have a personal income. Exposure to smoke in outside kitchens, parental cigarette smoking and a history of a recent illness were identified as risk factors.

3. History of pnuemococcal vaccines

The first generation of pneumococcal vaccines began with a whole bacterial vaccine that was used clinically in 1911 to prevent pneumonia among South African gold miners. The efficacy of this vaccine in preventing pneumonia prompted researchers to identify the diverse pneumococcal serotypes, in order to formulate a polyvalent vaccine. Such a vaccine was initially formulated containing six killed pneumococcal types in place of the whole bacterium and was successfully developed and brought into clinical use in the early 1930s. Vaccines of this kind were soon improved and upon the discovery of the immunogenicity of pneumococcal polysaccharides in man, they were replaced with vaccines containing purified capsular material. Throughout the 1940s, various formulations of pneumococcal polysaccharides were developed and proved beneficial; however, their use declined as treatment with penicillin gained favour. As this trend continued in the early 1950s, the first generation of polysaccharide vaccines was removed from the market (reviewed by Bruyn and Van Furth, 1991; Watson et al., 1993). This unfortunate event was based on the assumption that pneumococcal disease would either be eliminated through the use of antibiotics, or at least readily amenable to treatment (Fedson and Musher, 1994). The observation by Austrian and colleagues (Austrian et al., 1976) that pneumococcal morbidity remained considerably high despite the availability of penicillin triggered resumption of interest in pneumococcal vaccination and mortality.

3.1. Efficacy

Clinical trials in South Africa demonstrated the efficacy of the 6-, 12-, and 14-valent vaccines in reducing the incidence of pneumonia, additionally, the 14-valent vaccine was shown to reduce the incidence of bacteraemia caused by vaccine-related pneumococci (Austrian et al., 1976). The 14-valent vaccine was evaluated in Papua New Guinea, where pneumonia is endemic and it was shown to reduce both bacteraemia and mortality (Riley et al., 1986). In the late 1970s, a 14-valent vaccine was licensed in the USA. Since that time, the 14-valent vaccine has been evaluated in many high-risk groups. Although shown to be useful in the prevention of pneumococcal disease, use of the 14-valent vaccine remains limited because the original selection of its 14 components was based upon limited epidemiologic and immunochemical information (Lee et al., 1991). Since the time that this selection was made, more complete information has become available on the distribution of capsular types that cause bacteraemia and meningitis (Bruyn and Van Furth, 1991). Additionally, more is known now about the biochemical and immunological relations among the several cross-reacting serotypes (Robins et al., 1983). Developed on the basis of this new information, the 23-valent vaccine is composed of the serotypes responsible for approx. 90% of invasive pneumococcal infections.

3.2. Polysaccharide vaccine studies in African children

There have been very limited immunogenicity and no efficacy studies of the pneumococcal polysaccharide vaccine in African children, despite promising results in Papua New Guinea. In 1991, an immunogenicity study of a 23-valent pneumococcal polysaccharide vaccine was undertaken in groups of Gambian infants aged 2, 4, 5 or 9 months or 5–10 years of age. Modest IgG responses to types 1, 3, and 5 polysaccharides were seen in children of all ages but only the older children in any group responded to 6A polysaccharide (Temple et al., 1991). The antibody levels following vaccination would have been unlikely to produce significant protection against infection by pneumococci of the less immunogenic serotypes. Consequently, this approach was not evaluated in a large-scale efficacy trial. In contrast however, Studies in Papua New Guinea of the polysaccharide vaccine have suggested that it reduces morbidity (Lehmann et al., 1991) and mortality (Riley et al., 1986) from pneumonia in children. Even among children younger than 2 years of age, the vaccine reduced total mortality by 25% (95% CI −6 to 47%) and mortality from pneumonia by 29% (95% CI −25 to 60%) (Riley et al., 1986). Subsequent to this study, there has been no other trial of the pneumococcal polysaccharide vaccine in children. The findings from this study have been the subject of debate. It is possible that the effect seen during the study was as a result of an outbreak of pneumococcal pneumonia caused by one of the immunogenic serotypes in children. Another controlled trial with the pneumococcal polysaccharide vaccine in children has been advocated (Shann, 1998).

4. Development of pneumococcal conjugate vaccines

The reason for the limitations with carbohydrate based vaccine is the profound difference in the immunological properties of carbohydrates as compared with proteins. T-cells help B-cells to produce antibodies to protein antigens. Such help is not required by B cells in their response to carbohydrates and thus define their inability to respond to the later as T-independent. When B cells respond to protein antigens their response is characterised by a number of immunological phenomena, which result in memory to the specific antigen being generated.

Since the pioneering work of Goebel and Avery (1929), it has become clear that the immunogenicity of polysaccharides can be greatly improved by chemical coupling to protein carriers. This principle has been applied to a number of pneumococcal polysaccharide serotypes and the first so-called conjugate vaccines have now been produced. Carbohydrates are traditionally viewed as T-independent antigens with a number of unique and

Table 2
Major characteristics of TD, TI and PS-protein antigens

	TD antigens	TI	PS-protein conjugates
T-cells required	Yes	No	Yes
Memory induction	Yes	No	Yes
Response in infants	Yes	No	Yes
Affinity maturation	Yes	No	Yes
Maturation of response	Early	Late	Early
IgG isotype restriction	No	Yes	No

important immmunological characteristics that are not encountered when immune response is induced by a protein antigen. These include no overt requirement for T-cells to induce immune response, dominance of IgM, lack of immunological memory following re-immunisation and poor immunogenicity in infants, the elderly and the immunocompromised (see Table 2). These properties of carbohydrates have precluded the use of pure carbohydrate vaccines in high-risk groups. Conjugate vaccine technology, where a carbohydrate antigen is chemically coupled to a protein carrier, renders the carbohydrate component of such vaccines immunogenic, even in the very young. Following conjugation to a protein, carbohydrate antigens are able to induce antibody response in a thymus-dependent manner. Thus a protein conjugate-polysaccharide antigen will induce production of antibodies with T-cell help and generate immunological memory (Paul et al., 1971; Alonso de Velasco et al., 1993) (see Table 2). It has become clear that the immunogenicity of a given conjugate is determined by several variables, such as the size of the saccharide, immunogenicity of the carrier protein, method of coupling including the use of spacer molecules, saccharide to protein ratio, and the conformation of the conjugate (reviewed by Dick and Beurret, 1989; Peeters et al., 1991).

During the last decade, considerable progress has been made with the development of different pneumococcal protein conjugate vaccines. Different protein carrier molecules such as tetanus toxoid, cross reactive material from diphtheria toxoid (CRM) and outer membrane protein of *Neisseria meningitidis* have been used (Fattom et al., 1990; Vella et al., 1992; Steinhoff et al., 1994). Attempts have also been made to combine different pneumococcal polysaccharide types in a polyvalent preparation. Phase II studies have progressed through 4, 5, 7, 9 and more recently 11-valent preparations. Although none of these preparations has been licensed as yet, it is likely that the 7-valent CRM (cross reactive mutant of diphtheria toxoid) conjugate will be licensed soon following the completion of the efficacy trial in Northern Carlifornia.

4.1. Current status of conjugate pneumococcal vaccine field trials in Africa

Safety and immunogenicity studies with the 9-valent CRM conjugate has been completed in the Gambia and South Africa. In South Africa an efficacy trial which evaluates the impact of the vaccine on all-cause severe pneumonia is near completion. In the Gambia a trial with the same vaccine will evaluate the impact on all-cause mortality in young children. The final vaccine to be selected for widespread use will have a strong attraction if it is compatible with the current EPI schedule, as this will minimise cost and clinic visits.

4.2. Future of pneumococcal conjugate vaccine application in Africa

Results of completed phase II trials in The Gambia, South Africa and elsewhere outside the continent of Africa have been encouraging. The vaccines elicit antibodies against the pneumococcal serotypes included in the vaccines, although not quite to the levels seen with the Hib vaccine but certainly higher than that seen with the standard polysaccharide vaccine. Furthermore these antibodies have been shown to be functionally active and able to effectively opsonize the pneumococcus in in -vitro assays. In addition studies from The Gambia have shown that the conjugate vaccine is able to prime the immune system of

young infants for response to the pneumcoccocal polysaccharide later in childhood (Obaro et al., 1997). In practical terms this implies that following the primary series of vaccination, the immune system is able to recognize and respond rapidly to the pneumococcal polysaccharide when encountered either as a bacterium or in a vaccine. This phenomenon is critical to the prevention of the onset of disease and perhaps more important than the absolute concentration of serotype specific antibody levels after vaccination. In addition to these properties, limited carriage studies from The Gambia, (Obaro et al., 1996), South Africa (Mbelle et al., 1997) and Israel (Dagan et al., 1998) suggest that the vaccine is able to protect against nasopharyngeal carriage of pneumococci of vaccine serotypes.

Thus the capacity to induce production of functionally active antibodies, immunological memory and protection against carriage has raised great optimism that this vaccine will have a significant impact on protection from invasive pneumococcal disease. However, there are still some unresolved questions about the potential of these vaccines.

4.3. Timing of immunisation

A significant burden of invasive pneumococcal disease in African children occurs in early infancy. A report from the WHO young infant etiology study revealed that $\sim 30\%$ of pneumococcal meningitis in infants occur before the age of 2 months. Thus the application of protein conjugate vaccine in the scheme of the current EPI vaccination schedule of 6, 10 and 14 weeks or 2, 3 and 4 months would not offer protection to these group of infants. An approach, which offers immune protection prior to this period, either through maternal or neonatal immunization will be preferable.

4.3.1. Maternal immunization

Immunization of women with pneumococcal polysaccharide during the third trimester could offer protection to the young infant through:

- Transplacental transfer of antibody
- Provision of secretory IgA and other immune factors in breast milk

Critical to this approach is the establishment of safety of the vaccine when administered during pregnancy and also to ensure that exposure of the infant in utero to the pneumococcal polysaccharide antigen does not induce immunological tolerance in the infant. This approach has been evaluated on a very limited scale in The Gambia, Philippines, Papua New Guinea, Bangladesh, Burkina Faso and the United States. Results from these studies were reviewed at a WHO Vaccine Research and Development meeting in Geneva in 1998 (WHO, 1998). The meeting concluded that data available was not conclusive, either way, to recommend the strategy of maternal immunisation and more studies with larger sample size were to be conducted to evaluate safety and efficacy. Some studies are currently planned to evaluate these parameters concurrently.

4.3.2. Neonatal immunization

Another approach would be to vaccinate during the first few weeks of life. There has been very limited experience with the use of protein conjugate vaccines in the neonatal period. Experience with the conjugate Hib vaccine suggests that anticapsular antibody production after one dose is generally low but comparable to levels obtained in older infants following completion of three doses. Furthermore, this approach is also able to induce immunologic memory (Kurikka et al., 1996).

A critical consideration is whether immunologic tolerance is induced when the conjugate pneumococcal vaccine is administered in early infancy as has been reported with pneumococcal polysaccharide (Mosier et al., 1987). Results from published studies are contradictory. A preliminary report from one study (Ward et al., 1992) suggested that immunologic tolerance may be induced but this finding was not confirmed in two other studies (Lieberman et al., 1995; Kurikka et al., 1996). There are studies planned in South Africa to evaluate the safety and immunogenicity of protein conjugate pneumococcal vaccines during the neonatal period.

5. Unresolved questions about the widespread use of pneumococcal conjugate vaccines

The progress with the development and testing of pneumococcal conjugate vaccines has so far, been very exciting and promising. However, in making projections into the future there are certain questions which are as yet unresolved, but have significant implications for the success of its application in the effective control of invasive pneumococcal disease in Africa in particular and globally.

5.1. Will the vaccine induce herd immunity?

For the vaccine to have a very strong impact on protection, it should offer protection against carriage and transmission and consequently offer protection to unvaccinated individuals, as was the case with Hib vaccine. Studies that have evaluated carriage following vaccination with the protein conjugate vaccines demonstrate protection against carriage of vaccine serotypes and it seem likely that there would be herd immunity. However, some of these studies have also reported an increase in carriage of non-vaccine serotypes (Obaro et al., 1996; Mbelle et al., 1997). Although it is not clear at this stage what the implication of this observations are, some of these non-vaccine serotypes are potentially pathogenic and it is possible that the wide spread use of these vaccines may alter the epidemiology of invasive pneumococcal disease.

5.2. What degree of protection will it confer against different disease conditions?

5.2.1. Vaccine formulation

Estimates of protection of a multi-valent pneumococcal vaccine formulation vary by geographical area and the prevalent serotypes. Seven-to-11-valent conjugate vaccines are currently at different stages of clinical evaluation. The 7-valent conjugate vaccine includes serotypes 4, 6B, 9V, 14 18C, 19F and 23F. These cover $\sim 52-81\%$ of pneumococci causing invasive disease in children (Sniadack et al., 1995) and about 58% of those causing acute otitis media (Karma et al., 1985). In the 9-valent formulation, serotypes 1 and 5 are added to the 7-valent formulation. If efficacious the proposed nine-valent protein conjugate pneumococcal vaccine will offer protection against 80% of invasive pneumococcal serotypes in children. The 11-valent preparation incorporates serotypes 3 and 7V and this increases the coverage to 73–92% of invasive infections (Fedson et al., 1999). Furthermore, strains, which are known to acquire mutliple antimicrobial resistance most frequently, are also included in this vaccine formulation. Thus there is a strong potential for reducing the incidence of multi-resistant infections.

5.2.2. Host immune response

There are still unfilled gaps in the understanding of the pathogenesis of invasive pneumococcal disease. The minimal protective antibody concentration, which has been clearly defined for Hib disease, has remained elusive for the pneumococcus. Protective antibody concentration may well differ for different disease conditions such as otitis media, bacteremia and meningitis and vary with constitutional host factors such as Fcγ receptor phenotype and immunoglobulin allotype (Obaro et al., 1995). It is also likely that there will be variation between serotypes, as the spectrum of immunogenicity between serotypes is very broad. There would even be more questions to address in hosts with deranged immune system as in acquired immunodeficiency disease, hypogammaglobulinaemia, or post cancer therapy.

5.3. Cost and availability to developing countries

An issue critical to the global control of pneumococcal disease is the availability of effective control measures in areas where the disease is highly prevalent which unfortunately, in the case of pneumococcal disease, are also areas that are least able to afford them. Although the unit cost of the protein conjugate pneumococcal vaccine has not been determined it is likely to be expensive and not readily affordable by resource-poor countries. Therefore were the vaccine to be very efficacious in on-going field trials, availability of the vaccines to resource poor countries will re-

quire extensive negotiations with donor agencies, vaccine manufacturers and health policy makers.

6. Pneumococcal protein antigen vaccines

A major limitation with protein conjugation of pneumococcal polysaccharide is the number of serotypes that can be included in a vaccine preparation because of manufacturing considerations and cost of production. One approach under consideration is the use of immunogenic pneumococcal species-common proteins as vaccine candidates. These proteins would be immunogenic in young children, offer protection against a greater number of serotypes and induce immunologic memory, resulting in a possibly more efficacious and economical vaccine. The most attractive features of a protein pneumococcal vaccine are the potential for a non-serotype dependent immune protection and high volume production at low cost, an invaluable attribute relevant to their application in resource-poor countries.

Of the reported pneumococcal proteins, only pneumococcal surface protein A (PspA) and pneumolysin have been extensively studied for their suitability as vaccine candidates. Pneumococcal surface protein A (PspA) is a choline binding protein on the pneumococcal cell surface that has been found to be immunogenic in animal models. Although serolgically variable, it is sufficiently cross-reactive that immunisation with a single PspA type can elicit protection against pneumococci of diverse PspA and capsular types (Briles et al., 1996).

Pneumolysin is one of the family of toxins produced by four genera of Gram-positive bacteria (Streptococcus, Clostridium, Listeria, Bacillus). It has a membrane damaging property and is irreversibly inhibited by cholesterol and, in crude preparations, being inactivated by oxidation and activated by thiol-reducing agents. The specific sequences of the pneumolysin protein responsible for several activities of the toxin have been identified and several animal protection studies have been done. On the basis of these protection studies pneumolysin molecules containing several amino acid substitutions are being evaluated as protective immunogens for use in humans.

Another immunogenic 37-kDa species-common protein from *S. pneumoniae* was recently identified and designated pneumococcal surface adhesin A (PsaA) (Russell et al., 1990). It is a surface-exposed protein that has significant gene sequence homology with fimbrial adhesion proteins and has been shown by immunoblot analysis to be common to all 90 pneumococcal serotypes (Russell et al., 1990; Sampson et al., 1997). Furthermore, in vivo protection studies showed that antibodies to the 37-kDa protein protect mice from lethal challenge (Tharpe and Russell, 1996). Thus this protein has attracted much attention as a potential vaccine candidate.

7. Conclusion

An effective pneumococcal vaccine in developing countries has an enormous potential for decreasing morbidity and mortality. In these countries the disease burden caused by pneumococcal infections may be underestimated due to inadequate diagnostic facilities and it is possible that the true burden of disease may exceed that due to hepatitis B, malaria and typhoid fever (Leoswki, 1986; Fedson, 1988). The true burden of pneumococcal disease may only become obvious after the introduction and widespread use of an effective pneumococcal vaccine. Incorporating such a vaccine into the World Health Organisation's Expanded Program of Immunisation would significantly reduce the global scourge. The development of such a vaccine warrants urgent attention and field trials of such vaccines in developing countries to evaluate their efficacy against all cause mortality and ALRI-specific mortality will be invaluable in convincing health policy makers of the need for preventing pneumococcal disease.

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