THE ROYAL SOCIETY

The epidemiology of pneumococcal infection in children in the developing world

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Pneumonia causes about three million deaths a year in young children, nearly all of which are in developing countries. *Streptococcus pneumoniae* (the pneumococcus) is the most important bacterial cause of pneumonia in young children and so is likely to be responsible for a high proportion of these deaths. The pneumococcus is also responsible for a substantial proportion of the 100 000–500 000 deaths that occur from meningitis in children each year. The incidence of invasive pneumococcal disease in children in the developing world is several times higher than in industrialized countries. This discrepancy may, in part, be due to socio-economic differences but genetic factors may also play a role. Children with sickle cell disease have a substantially increased risk of invasive pneumococcal infection and a search is being made for other possible genetic risk factors. Infection with human immunodeficiency virus (HIV) also predisposes to invasive pneumococcal disease and so the incidence of this disease in young children is expected to rise as increasing numbers of African and Asian children are born with a perinatally acquired HIV infection. Until recently, pneumococcal infections could be treated effectively with penicillin, a cheap and safe antibiotic. However, pneumococci that are resistant to penicillin are becoming prevalent in many countries, necessitating a change to more costly antibiotics which may be beyond the reach of the health services of poor, developing counties. The spread of antibiotic resistance has provided an added stimulus to the development of vaccines that might be able to prevent pneumococcal disease in infants. Recently developed polysaccharide–protein conjugate vaccines show promise and are now undergoing field trials. How deployment of these vaccines will influence the balance between invasive pneumococcal infections and asymptomatic nasopharyngeal carriage of pneumococci is uncertain.

Keywords: *Streptococcus pneumoniae*; pneumococcus; developing countries; children; vaccination

1. INTRODUCTION

Acute lower respiratory tract infections (ALRI) are a major cause of mortality and morbidity in children throughout the developing world. It is estimated that at least three million children die from pneumonia and related conditions each year, nearly all of which are in developing countries (Leowski 1986). In spite of this high death toll, the problem of ALRI in children in the developing world has received little attention from the international research community and research on this topic only attracts sparse funding from the major international donors, currently about $50 million a year. A wide range of bacteria and viruses can cause ALRI in children. However, two bacteria (*Streptococcus pneumoniae* (the pneumococcus) and *Haemophilus influenzae*) and one virus (respiratory syncytial virus (RSV)) account for a high proportion of cases of severe ALRI in young children throughout the world.

Acute bacterial meningitis is another important but relatively neglected cause of mortality and morbidity among children in the developing world which accounts for 100 000–500 000 deaths a year among young children (Greenwood 1987). In addition, many children who survive an episode of acute bacterial meningitis are left with permanent neurological damage. Three bacteria, *S. pneumoniae*, *H. influenzae* type b (Hib) and *Neisseria meningitidis* (the meningococcus) are the most important bacterial causes of meningitis in children.

Thus, the pneumococcus, the primary cause of pneumonia in children and one of the main causes of acute bacterial meningitis, is probably responsible for about a million deaths a year in children, a toll comparable to that attributed to the malaria parasite. In spite of this, the epidemiology of pneumococcal infection in children in the developing world has been little studied. This paper reviews some of the limited information that has been published on this topic.

2. THE PNEUMOCOCCUS AS A CAUSE OF PNEUMONIA AND MENINGITIS

Determining the cause of pneumonia in children is difficult. In the developing world, children with this condition are usually treated at an out-patient clinic or in a peripheral hospital where laboratory resources are few. Even when a child with pneumonia is admitted to a well-equipped hospital, it is difficult to establish a bacterial diagnosis as blood culture, the routine diagnostic test, is positive in only 10–20% of cases. It is possible that new

Table 1. *The role of lung aspiration in the diagnosis of pneumococcal pneumonia in Gambian children*

				positive culture for the pneumococcus		
study	age group	no. of children	no. of lung aspirates done	lung aspirate alone	blood or other sites alone	combined blood or other and lung aspirate
Wall *et al*. 1986	<10 years	51	51	10	10	2
Forgie *et al*. 1991	1–9 years	74	29	7	7	3
Adegbola *et al*. 1994[a]	3–59 months	278	94	36	29	5
O'Dempsey *et al*. 1996	<5 years	1162	16	5	1	0
Usen *et al*. 1998	2–36 months	2256	146	26	32	14
total		4521	336	84	79	24

[a] 159 children were malnourished.

techniques based on the polymerase chain reaction (PCR) will improve the success rate of conventional culture which is limited in part by the amount of blood that can be taken from a sick child. However, many children with pneumonia may not have bacteraemia at the time that they present for treatment and a higher success rate would be anticipated from direct investigation of the lung. This can be done using the lung aspiration technique.

Lung aspiration, which involves the insertion of a fine needle into an area of consolidated lung and the aspiration of a drop of lung fluid for microscopy and culture, was used widely in the investigation of patients with pneumonia in the pre-antibiotic era. Yet, it has been employed less frequently in recent years because occasionally it may cause complications. However, studies which have incorporated lung aspiration have provided vital information on the causes of pneumonia in children in several parts of the developing world and have allowed the antibiotic sensitivities of the causative bacteria to be determined. This information has helped in the formulation of rational treatment guidelines based on local knowledge. In addition, lung aspiration has sometimes provided information of direct benefit to an individual patient, for example the early detection by microscopy of tubercle bacilli in a child for whom this diagnosis would not otherwise have been considered.

During the past 15 years, lung aspiration has been used as a component of several studies of the aetiology of pneumonia undertaken in Gambian children (Wall *et al*. 1986; Forgie *et al*. 1991; Adegbola *et al*. 1994; Usen *et al*. 1998) and during the course of routine clinical care of children with a difficult diagnostic problem. Approximately 400 lung aspirations have been undertaken in The Gambia in recent years without any life-threatening complications, although a few children have had a small haemoptysis or developed subcutaneous emphysema or a small pneumothorax which resolved without intervention (Falade *et al*. 1997). Use of lung aspiration in these Gambian studies has almost doubled the pneumococcal isolation rate given by blood culture (table 1). Experience in The Gambia suggests that provided that lung aspiration is carried out only in patients who have clinical or radiological features of pulmonary consolidation and that the test is only done by investigators trained in the technique, then the risk of complications is small and it is legitimate to use this technique to obtain epidemiological information on the aetiology of pneumonia in children and in the evaluation of intervention studies such as vaccine trials.

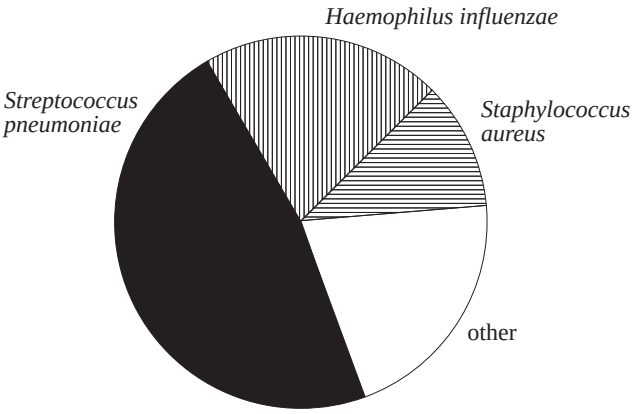

Figure 1. The aetiology of pneumonia in children in developing countries as shown by studies which employed lung aspiration between 1974 and 1986 (Shann 1986).

In 1986, Shann reviewed 11 studies of the aetiology of pneumonia in children in the developing world, undertaken since 1974, which had used lung aspiration. Three hundred and fourteen organisms were isolated from 744 patients (42%). Pneumococci comprised 43% of the positive isolates (figure 1). Subsequent studies undertaken 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.

The studies of the aetiology of pneumonia in children considered above have nearly all been conducted in central hospitals, the only sites where facilities for bacterial culture are usually available. Thus, it can be questioned whether the results of these studies are representative of the pattern of pneumonia in children in the developing world as a whole; most deaths from pneumonia occur among children living in rural or in poor urban areas who may not be able to reach a specialist hospital when they are ill. For this reason, a study was undertaken in 1987–1988 in Upper River Division, The Gambia, the most rural and least developed area of this small West African country, to determine the aetiology of severe or moderately severe ALRI in a group of approximately 500 children under the age of

five years living in a rural community (Forgie *et al*. 1992). The children studied were kept under close surveillance by trained field staff who visited them at home on a regular basis for a period of one year. Whenever a field worker suspected that a child had an ALRI, the child was immediately referred to the Medical Research Council (MRC) field station at Basse where he or she was examined by a paediatrician and a blood culture was obtained. However, only two out of 220 blood cultures were positive, suggesting either that a large majority of these children did not have a bacterial cause for their respiratory infection or that they were investigated too early in the course of their illness for a positive blood culture to be obtained. Therefore, a second study was undertaken in the same area in which children were recruited when they presented, usually a little later in their illness, to a rural health centre (O'Dempsey *et al*. 1994). This time a pathogenic bacterium was isolated from a normally sterile site in 133 (11%) out of the 1162 children investigated. Pneumococci accounted for 44% of all positive cultures. They were obtained from 60% of cases of pneumonia for whom a bacterial diagnosis was made and from 43% of the cases of bacterial meningitis, similar proportions to those seen in hospital patients. Thus, in The Gambia, studies undertaken in a referral hospital do provide a representative view of the causes of pneumonia in children in the country as a whole. Whether this is the case in other developing countries remains to be confirmed.

Determining the aetiology of acute bacterial meningitis is easier than determining the aetiology of pneumonia for microscopy and culture of cerebrospinal fluid (CSF), give positive results 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. Antigen detection assays, and recently developed PCR techniques, may also allow a diagnosis to be made in patients who have received antibiotics before admission to hospital and in whom CSF culture is sterile.

Although the main causes of acute bacterial meningitis in children are similar in developing and in industrialized countries, the incidence of the condition is two to three times higher in developing than in industrialized countries and the mortality rate five to ten times higher (Greenwood 1987). One of the most detailed studies of the pattern of acute bacterial meningitis in the developing world comes from Dakar, Senegal where detailed surveillance of all cases of acute bacterial meningitis admitted to a large general hospital was maintained from 1970–1979 (Cadoz *et al*. 1981). The pneumococcus accounted for 983 out of 3422 (28.7%) of cases. Similar findings have been made more recently in other developing countries (Molyneux *et al*. 1998) and this pattern of acute bacterial meningitis is likely to be widespread except for countries in the African meningitis belt where the meningococcus has a dominant role.

3. THE INCIDENCE OF INVASIVE PNEUMOCOCCAL DISEASE

The approximate size of the population from which children in the rural Gambian study described above were drawn was known and so it was possible to calculate the approximate incidence of invasive pneumococcal disease in children in this community (O'Dempsey *et al*. 1996*a*). This was estimated to be 554 per 100 000 per year in children under the age of one year, 458 per 100 000 per year in those less than two years, and 240 per 100 000 per year in children under the age of five years. However, these are minimum incidence rates as only a proportion of cases of pneumococcal disease are likely to have presented to rural clinics; others are likely to have been treated in their village by village health workers or by traditional healers. A second opportunity for estimating the incidence of invasive pneumococcal disease in Gambian children arose during the course of a trial of a Hib conjugate vaccine conducted in the western half of the country (Mulholland *et al*. 1997). For a period of two and a half years, nearly all infants born in a population of approximately 400 000 were recruited into this trial and active surveillance was maintained at three hospitals for possible episodes of invasive bacterial infection among children in the vaccine cohort. One hundred and ten cases of invasive pneumococcal disease were identified giving a minimum incidence in infants of 185 per 100 000 per year, a rate less than a half of that obtained in the rural area (Usen *et al*. 1998). This may indicate a lower incidence of invasive pneumococcal disease in periurban than in rural areas but could reflect differences in patient ascertainment. In Western Region, (The Gambia) surveillance was maintained only in three hospitals run by the Ministry of Health or by NGOs and not in private clinics or hospitals. The Gambian figures are the only published estimates of the overall incidence of invasive pneumococcal disease in children in a poor developing country based on population data but it is likely that the situation in The Gambia is representative of much of Africa. In Chile, a newly industrialized country, a recent survey showed that the incidence of invasive pneumococcal disease is similar to that seen in established industrialized societies, although the disease in Chile shows some developing country features such as a young age of onset and a high incidence of invasive infections with pneumococci of developing country serotype such as type 1 and type 5 (Levine *et al*. 1998). In The Gambia, the incidence of invasive pneumococcal disease in children is several times higher than that seen in children in industrialized countries and approaches the exceptionally high levels recorded in North American Indians (Cortese *et al*. 1992), Alaskan natives (Davidson *et al*. 1993) and Australian aboriginals (Torzillo *et al*. 1995) (figure 2). Why the incidence of invasive pneumococcal disease is so high in these native populations is not understood. Socioeconomic factors are likely to be important but genetic factors may be involved as well, although these have not been identified.

4. THE PATTERN OF INVASIVE PNEUMOCOCCAL DISEASE

Little information has been collected on the pattern of invasive pneumococcal disease in children in the developing world and much of the following section is based on the results of studies carried out in The Gambia. However, it is likely that the situation found in The

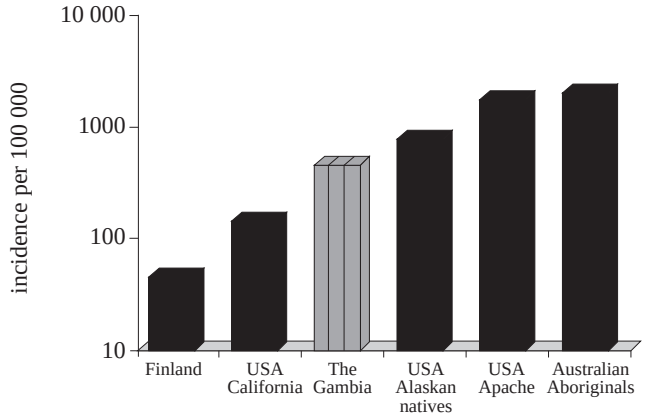

Figure 2. The incidence of invasive pneumococcal disease in children aged less than two years in The Gambia and in various high- or low-risk populations. Data are from Finland (Eskola *et al*. 1992), California (Zangwill *et al*. 1996), The Gambia (O'Dempsey *et al*. 1996*a*), Alaskan natives (Davidson *et al*. 1993), Apache (Cortese *et al*. 1992) and Australian aboriginals (Torzillo *et al*. 1995).

Gambia is representative of that in many other developing countries.

(a) *Risk factors*

(i) *Genetic factors*

The high incidence of invasive pneumococcal disease in Australian and in American native populations and a higher incidence of pneumococcal disease in black than in white Americans, even after corrections have been made for socio-economic inequalities (Hennerberger *et al*. 1983), suggests that there are genetic risk factors for invasive pneumococcal disease that are associated with racial group. Homozygosity for the sickle cell gene is one such characteristic; patients with sickle cell disease are at high risk of invasive pneumococcal disease and must be protected by vaccination and chemoprophylaxis (Wong *et al*. 1992). A search for other genetic risk factors for invasive pneumococcal disease is in progress; possible candidates are polymorphisms in genes influencing mannose-binding protein, macrophage gamma Fc receptors and inflammatory cytokines.

(ii) *Underlying illnesses*

In industrialized countries, a high proportion of children who develop invasive pneumococcal disease have a serious underlying illness such as 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.

(iii) *Antecedent viral infections*

Influenza virus infection predisposes to invasive pneumococcal disease in adults and it has been suggested that RSV plays a similar role in children. However, there is only limited evidence to support this view. Only nine out of 255 Gambian children (3.5%) with severe RSV infection had a positive blood culture (Weber *et al*. 1998), in keeping with the results of previous studies, although a much higher prevalence of co-infections (31%) was recorded in Pakistan (Ghafoor *et al*. 1990).

In the developed world, infection with human immunodeficiency virus (HIV) is a strong risk factor for invasive pneumococcal infections, 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 repeated pneumococcal infections are common in these women. There is surprisingly little information on the importance of HIV as a risk factor for pneumococcal disease in children in the developing world but it would be surprising if it did not act in the same way as in adults. 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; M. Molyneux, personal communication). As increasing numbers of African and Asian children are born with HIV infection the incidence of invasive pneumococcal disease in children in the developing world can be expected to rise.

(iv) *Socio-economic factors*

It would be anticipated that low socio-economic development would be an important risk factor for invasive pneumococcal disease in children. Thus, it was surprising that a formal case control study of risk factors for invasive pneumococcal disease in Gambian children did not find any evidence that crowding, maternal education, paternal education or occupation influenced susceptibility significantly (O'Dempsey *et al*. 1996*b*). Exposure to smoke in outside kitchens, parental cigarette smoking and a history of recent illness were identified as significant risk factors. Atmospheric pollution may be an important risk factor for invasive pneumococcal disease in areas of the developing world where cooking is done in unventilated huts or rooms where young children sleep and play.

(b) *Age*

The age distribution of the 103 Gambian children with invasive pneumococcal disease seen during the community study conducted in Upper River Division is shown in figure 3. The mean age of children with meningitis (13 months) was a little less than the mean age of those with pneumonia (15 months)(O'Dempsey *et al*. 1996*a*). Children with pneumococcal meningitis have been noted to have a younger mean age than children with pneumococcal pneumonia in other studies (Eskola *et al*. 1992; Davidson *et al*. 1994; Zangwill *et al*. 1996; Usen *et al*. 1998). Figure 3 compares the age distribution of Gambian children with invasive pneumococcal disease with that of high- and low-risk populations in the USA. There is a suggestion that cases occur at an earlier age in The Gambia than in the USA. 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 Americans (Davidson *et al*. 1994). Thus, as is the case for invasive *H. influenzae* type b disease, it is possible that among children invasive pneumococcal disease occurs at a younger age in developing than in industrialized countries, but more data are needed to establish whether or not this is the case.

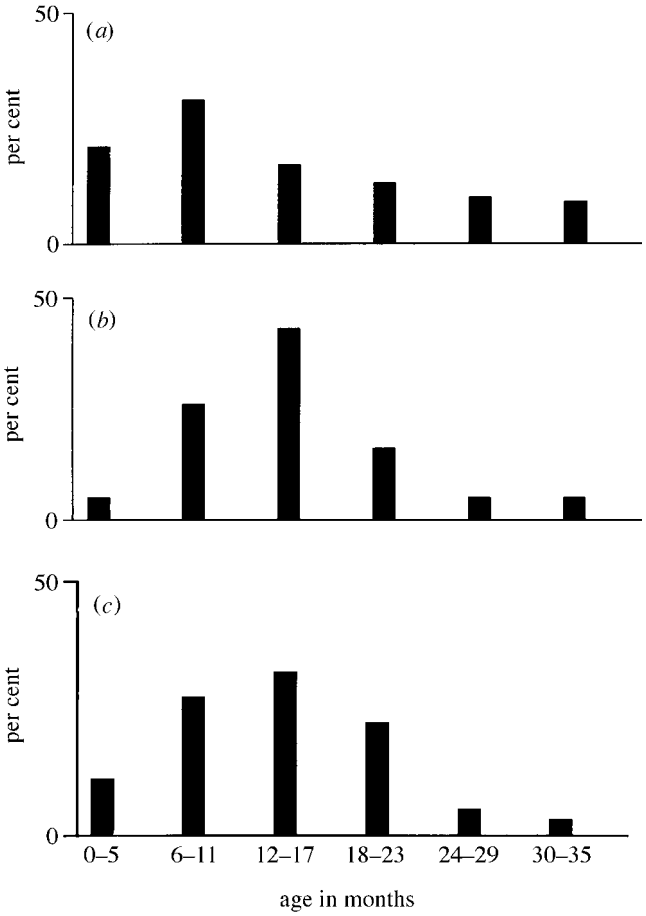

Figure 3. The age distribution of cases of invasive pneumococcal disease in young children. (*a*) The Gambia, West Africa (O'Dempsey *et al*. 1996), (*b*) a high-risk community in the USA (Cortese *et al*. 1992), and (*c*) a low-risk community in the USA (Zangwill *et al*. 1996).

In the developing world, neonatal infections are frequent and they are an important cause of neonatal death. Until recently, the pneumococcus was not considered to be a significant cause of serious neonatal infections. However, a recent WHO-coordinated study conducted in five developing countries showed that, in these communities, the pneumococcus was responsible for 20% of the 167 serious bacterial infections diagnosed in 4552 children during the first three months of life (WHO Young Infants Study Group 1998). The pneumococcus was the major cause of meningitis in children in this young age group. Surprisingly, eight out of 17 CSF isolates belonged to serotype 2, an unusual serotype not represented in current pneumococcal conjugate vaccines.

(c) *Seasonality*

There are few data on the seasonality of invasive pneumococcal disease in the developing world. In poor countries with a temperate climate pneumonia in children occurs most frequently in the winter. In the savannah areas of Africa, pneumococcal meningitis generally occurs more frequently in the dry season than in the rainy season (Diop Mar *et al*. 1979) and this was observed among the Gambian children in the community study, although there was a second peak in incidence of cases in invasive disease at the end of the rainy season when malaria is most prevalent (O'Dempsey *et al*. 1996*a*).

(d) *Clinical features*

No specific clinical features of invasive pneumococcal disease have been identified in children in the developing world, although late complications such as empyema and mastoiditis are probably more prevalent than in industrialized countries. Otitis media attracts less attention in the developing world than in industrialized countries, but it is uncertain whether this is due to differences in incidence or in ascertainment. Provided that treatment with an appropriate antibiotic is given, the prognosis of pneumococcal pneumonia in young children in developing countries is excellent wherever they are treated and much better than that of invasive pneumococcal disease in adults in the industrialized world. Thus, there was only one death among 81 documented cases of pneumococcal pneumonia seen during the Gambian rural community study and two deaths among 83 patients in the urban study (O'Dempsey *et al*. 1996*a*; Usen *et al*. 1998). In contrast, the outlook for children with pneumococcal meningitis is appalling throughout the developing world (Baird *et al*. 1976; Molyneux 1998). This is illustrated by the results of a recent follow-up study of Gambian children with pneumococcal meningitis (Goetghebuer *et al*. 1998). This showed that 48% died during the acute phase of their illness, 23% of the survivors died shortly after their discharge from hospital and that only 35% of the survivors had no serious sequelae. Why the outcome of pneumococcal meningitis is so much worse in developing than in industrialized countries is uncertain for a high mortality is seen even in hospitals with good facilities. A delay in seeking treatment may be one factor but it is possible that genetic factors are also involved.

5. NASOPHARYNGEAL CARRIAGE OF PNEUMOCOCCI

In the highlands of Papua New Guinea, infants are colonized with pneumococci shortly after birth and most young children are carriers (Gratten *et al*. 1986). High pneumococcal carriage rates in children have been recorded in several other developing countries including Zambia (Frederiksen & Hénrichsen 1988), Pakistan (Mastro *et al*. 1993), The Philippines (Lankinen *et al*. 1994) and The Gambia (Lloyd-Evans *et al*. 1996). In Pakistan, high carriage rates were observed in both urban and rural communities. In The Gambia, the carriage rate was highest in children under the age of five years (80%) falling to 20% in adults. This decline in carriage rate associated with increasing age may reflect the gradual acquisition of mucosal immunity to the dominant serotypes present in the community but it could also reflect a reduction in exposure. In the Gambian study, pneumococci of an identical serotype to that responsible for a case of invasive pneumococcal disease in a child were found most frequently among siblings (Lloyd-Evans *et al*. 1996) suggesting that they may have been a frequent source of invasive infections in infants.

The pneumococcal nasopharyngeal carriage rate in children in developing countries is generally two to three times higher than that found in children in industrialized

countries. Crowding, close contacts with a large number of siblings, exposure to smoke and frequent upper respiratory tract infections are likely to be important risk factors for carriage but this has not been demonstrated formally. HIV infection also increases the nasopharyngeal carriage rate of pneumococci (Gilks 1998). High pneumococcal carriage rates in children in the developing world are frequently associated with the carriage of pneumococci of more than one serotype (Gratten *et al*. 1989). In The Gambia, 22% of children carried pneumococci of more than one serotype (Obaro *et al*. 1996) and an even higher rate of multiple carriage was observed in Pakistan (Mastro *et al*. 1993). The frequency with which multiple carriage occurs is of interest because of the potential for pneumococcal conjugate vaccines to disturb the balance between pneumococci of vaccine and of non-vaccine serotype (see below). Routine bacteriological techniques used for detecting nasopharyngeal carriage are poor at detecting a minority population of bacteria and new techniques are being developed to do this more effectively.

6. PNEUMOCOCCAL TYPING

The main pneumococcal typing system is based upon the bacterium's capsular polysaccharide. About 90 antigenically distinct pneumococcal polysaccharides have been described which can induce an antibody response which shows little or no cross-reactivity with other pneumococcal polysaccharides. For this reason, pneumococcal vaccines based on capsular polysaccharides must contain polysaccharides which correspond to the dominant pneumococcal serotypes found in the community where the vaccine is to be used. Thus, many studies have been undertaken of the distribution of pneumococcal serotypes in different parts of the world, including some developing countries. The findings of some of these studies have been summarized recently by Sniadack *et al*. (1995) and Scott *et al*. (1996). Differences in serotype distribution occur between regions and some serotypes, such as types 1 and 5, are more frequent causes of invasive pneumococcal disease in children in developing than in industrialized countries. Serotypes may also change within the same region over time (Lehmann *et al*. 1997). Children may be infected with different serotypes than adults and the serotype distribution of isolates obtained from cases may differ from that of pneumococci obtained from carriers, suggesting that some serotypes have an enhanced propensity to cause invasive disease. Although the relative importance of pneumococci of individual serotype varies from area to area, pneumococci of about ten serotypes account for the majority of cases of invasive pneumococcal disease in both industrialized and developing countries, making it possible to develop vaccines which can be used on a global basis. Most antibiotic resistant pneumococci are found amongst the most prevalent serotypes. However, large areas of the world remain where no typing studies have been done, especially in Asia, and the possibility remains that there are areas in the developing world where unusual serotypes predominate and where existing vaccines would be only partially effective.

Capsular polysaccharide provides the most widely used system for typing pneumococci but several other techniques have been developed and used in epidemiological studies, for example in the tracking of a drug resistant pneumococcus. An alternative typing method is based upon detection of polymorphisms in the surface protein antigen PspA which is polymorphic (Crain *et al*. 1990). Investigation of the prevalence of different polymorphic forms of PspA in children in different parts of the developing world is important because this antigen is being considered as a vaccine candidate.

7. ANTIBIOTIC SENSITIVITY

Until recently, nearly all pneumococci were sensitive to penicillin and to co-trimoxazole (trimethoprim–sulphamethoxazole) so that throughout the developing world it was possible to treat children with this infection with one or other of these drugs, which are both safe and cheap. Unfortunately, this situation is changing rapidly and penicillin-insensitive pneumococci are now prevalent in many areas. Some show only intermediate resistance (MIC 0.1–1.0 $\mu g\,ml^{-1}$) and infections with these bacteria can still be treated effectively with high doses of penicillin. However, others have a higher degree of resistance to penicillin (MIC $>1.0\,\mu g\,ml^{-1}$) and are, in addition, resistant to many other antibiotics including cephalosporins. In the developed world the distribution of penicillin resistant pneumococci is still patchy, although rapidly increasing, with foci of high levels of resistance in parts of southern and eastern Europe. There is only limited information on the distribution of penicillin resistant pneumococci in the developing world but they are likely to be widespread. Early reports of penicillin-resistant pneumococci came from Papua New Guinea (Hansman *et al*. 1971) and South Africa (Appelbaum *et al*. 1977) and penicillin-resistant pneumococci are prevalent in Kenya and other parts of East Africa, especially among HIV-positive patients (Paul 1997; Crewe-Brown *et al*. 1997). A recent study co-ordinated by the Pan American Health Organization revealed high levels of resistance in some South American countries. If highly resistant pneumococci become widespread in poor countries, a medical disaster could follow for health services may be unable to provide the expensive second or third line antibiotics that would then be needed to treat this common childhood infection.

Few laboratories in the developing world monitor antibiotic resistance in a systematic way but steps are being undertaken by international organizations to improve this situation through the establishment of sentinel sites. Obtaining isolates from the blood of patients with invasive pneumococcal disease for antibiotic sensitivity testing is demanding because careful laboratory techniques are required and the isolation rate from blood cultures is low. Thus, it has been suggested that pneumococci obtained from the nasopharynx of patients might be used as a surrogate for sensitivity testing as these are easier to isolate and can be obtained from a high proportion of patients. When this approach was followed in Pakistan (Mastro *et al*. 1993), concordance for capsular serotype between nasopharyngeal isolates and isolates from normally sterile sites was obtained in 99% of cases, suggesting that the same pneumococcus was present at both sites. Concordance was less in Kenya (82%) (Paul 1997), Papua New Guinea (46%) (Lehmann *et al*. 1997)

and The Gambia (77%) (Lloyd-Evans *et al*. 1996), but this technique offers a possible approach to the assessment of the antibiotic sensitivity pattern of pneumococci in areas of the developing world where resources for bacteriological investigations are limited.

8. VACCINATION

The emergence and spread of drug-resistant pneumococci has given an extra impetus to attempts to develop a vaccine that could prevent invasive pneumococcal disease in children. Vaccines prepared from pneumococcal capsular polysaccharides, which have been available for many years, are used to protect adults with an increased risk of pneumococcal infection and the elderly. However, they are little used in children, despite one report of their effectiveness in reducing mortality from ALRI in young children in Papua New Guinea (Riley *et al*. 1986), because they are poorly immunogenic in infants and do not induce T-cell mediated immunological memory. Thus, the recent development of polysaccharide–protein conjugate vaccines which are immunogenic in very young infants and which do induce immunological memory is a major step forward (Klein 1995). Large-scale trials of these vaccines in young children are underway, or in the final stage of planning, in several developing countries including South Africa, The Philippines and The Gambia. The main end-point for these trials will be the incidence of invasive pneumococcal disease caused by pneumococci of vaccine serotype. Secondary end-points will include the overall incidence of pneumonia and, in The Gambia, mortality. These secondary end-points are vital because it will be the effect on these clinical end-points that will determine whether deployment of these vaccines, which are likely to be expensive, will be cost effective. If conjugate vaccines are highly effective at preventing invasive pneumococcal disease, measurement of these clinical end-points will provide an indirect method of determining the importance of the pneumococcus as a cause of different categories of ALRI, something which is difficult to do directly.

Pneumococcal conjugate vaccines, unlike polysaccharide vaccines, are likely to influence nasopharyngeal carriage of pneumococci, perhaps because they induce the formation of antibodies of a different class or affinity. What the consequences of such an effect will be are uncertain. Elimination of a potentially pathogenic pneumococcus from the nasopharynx could be of direct benefit to the vaccine recipient, reducing his or her risk of invasive disease if subsequently exposed to a precipitating factor such as a viral infection. Elimination of nasopharyngeal pneumococci may also reduce the source of new infections and thus, under some circumstances, extend protection to non-vaccinated subjects (herd immunity). Whether pneumococcal conjugate vaccines will induce herd immunity or not will be influenced strongly by the source of infection in young children, a critical feature that is not known. In developing countries, many older children and adults carry pneumococci. If they are a major source of infection in young children, then a vaccination programme restricted to infants is unlikely to exert a herd immune effect for many years.

If pneumococci of vaccine serotype are eliminated from the nasopharynx following immunization it is possible that this 'ecological niche' could be filled by pneumococci with polysaccharides which are not represented in the vaccine. A suggestion that this may be the case has come from pilot vaccine trials of conjugate vaccines carried out in South Africa (Mbelle *et al*. 1997) and in The Gambia (Obaro *et al*. 1996; S. K. Obaro *et al*., unpublished data), although this was not seen in Israel (Dagan *et al*. 1997). Capsulated pneumococci of non-vaccine serotypes are potentially pathogenic so it is possible that, in some circumstances, they could cause invasive disease in children, for example if present in the nasopharynx at the time that a child was infected with a respiratory virus. Considerations of this kind raise the worrying possibility that a pneumococcal conjugate vaccine might be remarkably effective at reducing the incidence of invasive disease caused by pneumococci of vaccine serotype but have little effect on the overall incidence of invasive pneumococcal disease and consequently little effect on morbidity or mortality. This extreme scenario seems unlikely, but it is possible that pneumococcal conjugate vaccines will not be as dramatically effective as the Hib conjugate vaccines with which they are being compared.

The possible effects of a conjugate vaccination on nasopharyngeal carriage of pneumococci have been modelled by Lipsitch and his colleagues (Lipsitch 1997; Lipsitch & Kolczak 1999). They have shown how under some circumstances vaccination could lead to an overall increase in the carriage rate. If pneumococcal conjugate vaccines do cause replacement of pneumococci of vaccine type by those of non-vaccine type, as seems possible, it is uncertain whether this is achieved by allowing the emergence of a pneumococcus that was already present but suppressed or by creating an empty niche that was subsequently invaded. Lipsitch & Kolczak (1999) have shown how, using a mathematical approach, it may be possible to separate these two situations.

Transfer of DNA between bacteria, a well-recognized phenomenon among pneumococci (Coffey *et al*. 1998), provides another possible way in which pneumococci could overcome the protective effects of a pneumococcal conjugate vaccine. If virulence of pneumococci is determined in part by factors other than the nature of their capsular polysaccharide, as seems likely, then in the face of a strong vaccine-induced immune response directed at their capsular polysaccharide, virulent bacteria might be able to escape the effect of the vaccine by picking up the capsular genes of a pneumococcus of non-vaccine serotype with which it is a co-resident in the host. This change is more likely to be found among invasive than carrier isolates. It is, therefore, very important that invasive isolates collected during current vaccine trials are studied in detail using new molecular typing techniques.

9. CONCLUSIONS

Considering its importance as a cause of mortality and morbidity, it is surprising that so little is know about the epidemiology of the pneumococcus in the developing world. In developing countries, nearly all infants are colonized by a potentially invasive pneumococcus shortly

after birth and they continue to carry pneumococci in their nasopharynx throughout childhood. Nevertheless only a few, perhaps 1%, develop the invasive disease. What is special about the latter children? Are genetic or environmental factors primarily to blame for their illness? Little is known about the dynamics of nasopharyngeal carriage of pneumococci in children or about the potential interactions of pneumococci of different serotypes. The nature of such interactions may play a critical role in determining the success or otherwise of the pneumococcal conjugate vaccine trials that are now in progress. These trials provide a unique chance to address some of the outstanding questions concerning the epidemiology of invasive pneumococcal disease in children. This opportunity must not be lost.

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