

Epidemiology and prevention of pneumococcal disease

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Abstract

There are comparatively little data on the incidence and morbidity from pneumococcal disease in Australia and elsewhere. Available data suggest that the overall incidence of invasive pneumococcal disease in Australia is comparable with similar populations. Very high rates are reported in Central Australian Aborigines, similar to invasive *Haemophilus influenzae* type b (Hib) disease. Disease incidence is probably greatly underestimated by case ascertainment from sterile site isolates alone. New diagnostic methods, such as serology to detect components of the pneumococcal cell wall, promise to significantly enhance detection of pneumococci as a cause of pneumonia, especially in childhood, but are epidemiologic rather than clinical tools. Resistance to penicillin and other antibiotics is an increasing problem worldwide, promoted by excessive antibiotic use, especially in children. This has focused attention on vaccine prevention. Fortunately, antibiotic-resistant pneumococci appear to belong to a limited range of serotypes, those commonly colonising children, in all areas so far studied. If conjugate pneumococcal vaccines prove to eradicate carriage, in a similar fashion to conjugate Hib vaccines, vaccination may be the major weapon against the spread of antibiotic-resistant pneumococcal infection. Conjugate pneumococcal vaccines are now in large scale efficacy trials, with outcomes of bacteraemia (California) and otitis media (Finland). Results of these trials are eagerly awaited. *Comm Dis Intell* 1997;21:41-46.

Introduction

Streptococcus pneumoniae has been recognised as a major human pathogen since it was described by Pasteur in 1891. Two recent developments have brought preventative strategies for pneumococcal infection into prominence. First, penicillin-resistant and multi-resistant pneumococci have become more prevalent in many parts of the world¹. Second, conjugate

vaccine technology is now being applied to pneumococcal polysaccharides, making vaccines capable of protecting young children a possibility². Recent evidence suggests that conjugate pneumococcal vaccines reduce nasopharyngeal carriage in the same manner as conjugate *Haemophilus influenzae* type b (Hib) vaccines^{3,4}. As paediatric serotypes are over-represented among antibiotic-resistant

strains, immunisation of infants and children may be the best approach to reducing the prevalence of serotypes of pneumococci associated with antibiotic resistance⁵.

Incidence of pneumococcal disease

There are a number of difficulties in case ascertainment and estimation

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Table 1. Incidence of invasive pneumococcal disease in non-indigenous populations

Study	Incidence per 100,000 population	
	Children <5 years	Children <15 years
Sweden ¹³ (1970 to 1980)	25.8 ^a	4.6 ^b
New Zealand ²⁹ (1984 to 1992)	36	13
Finland ¹⁸ (1985 to 1989)	24.2	8.9 ^c
New York ⁴⁴ (1985 to 1989)	90.6	25.2 ^b
Central Australia ¹² (1985 to 1990)	87	15
Alaska ²³ (1986 to 1990)	73	22.2 ^b
South Carolina ⁴⁵ (1986 to 1987)	162 ^d	Not available
Israel ¹⁹ (1988 to 1990)	42	19.9 ^e
Victoria ¹⁴ (1994 to 1995)	63 ^d	Not available
Sydney ^f (1991 to 1996)	32	11

- a. under 1 year of age
- b. under 19 years of age
- c. under 16 years of age
- d. under 2 years of age
- e. under 13 years of age
- f. manuscript in preparation: Liddle J, Davis C and McIntyre P

Table 2. Incidence of invasive pneumococcal disease in indigenous populations

Study	Incidence per 100,000 population	
	Children <5 years	Children <15 years
New Zealand ⁴⁶ (1984 to 1992)	92	39
Central Australia ¹² (1985 to 1990)	935	195
Alaska ²² (1986 to 1990)	327	88 ^a
Apache ⁴⁷ (1983 to 1990)	530	9.9 ^b

- a. under 19 years of age
- b. under 13 years of age

of the incidence of pneumococcal disease.

Sterile site isolates

Unlike invasive *Haemophilus influenzae* disease, which is usually associated with bacteraemia and is predominantly due to one serotype (b), pneumococci have at least 80 different capsular types, and many significant pneumococcal infections, such as pneumonia, are uncommonly associated with bacteraemia⁶. Thus, pneumococcal isolates from sterile sites probably greatly underestimate the incidence of significant pneumococcal infection.

Respiratory isolates

Respiratory specimens are also problematic for case ascertainment because carriage of pneumococci in the respiratory tract is relatively common⁷. The significance of a pneumococcal isolate from sputum therefore depends on the clinical

picture and the adequacy of the specimen. Sputum is not suitable for diagnosis of pneumonia in children below the age of ten years, because adequate sputum specimens are difficult to obtain.

Prior antibiotic therapy

In both adults and children with pneumonia, the apparent incidence of pneumococcal infection is further reduced by preceding antibiotic therapy. In a recent study from Adelaide, adult patients (mean age 60 years) hospitalised with pneumonia had evidence of pneumococcal infection in 44 cases (42%)⁸. Of these 44 cases, blood cultures were positive in 5% of those cases who had preceding antibiotic therapy compared with 19% of others.

Needle aspiration

Needle aspiration of the lung is probably the closest to a gold

standard for bacteriologic diagnosis of pneumonia, but is limited to anatomically accessible sites. Published studies have demonstrated high rates of bacterial and pneumococcal pneumonia in the pre-antibiotic era and in developing countries with a more severe spectrum of disease, but needle aspiration is too invasive for routine use⁹.

Serology

As pneumococcal pneumonia is associated with bacteraemia in 5% or fewer of childhood cases in industrialised countries, groups in Sweden and Finland have developed and promoted serologic diagnosis as a non-invasive method of improving case ascertainment¹⁰. An antibody response to pneumolysin was seen significantly more frequently in children with acute lower respiratory tract infection (12.4% overall and 9.0% below two years) than in controls (2.7% overall and 3.6% below two years). In addition, the significantly higher rate of seropositivity in the presence of radiologic infiltrates (51%) compared with children with normal chest X rays (17%) supports the validity of serologic diagnosis¹¹.

Estimates of the incidence and age distribution of pneumococcal disease

Population-based incidence data from sterile site isolates in children in industrialised countries, including unpublished data from Sydney and Victoria, are summarised in Table 1. Recently, central Australian Aborigines have been reported to have the highest incidence of invasive pneumococcal disease yet described¹². Population-based data from this and other indigenous populations are shown in Table 2. In all populations, the highest incidence of invasive pneumococcal disease is at the extremes of life (the first 12 months of life and over 70 years of age)^{13,14}.

Mortality and morbidity

Data on short- and long-term morbidity from childhood pneumococcal disease in Australia are sparse. In Sydney between 1981 and 1992, 26 children (6.6%) died, with underlying conditions present in 18 (69%)¹⁵. Long-term morbidity was largely limited to meningitis, where 35

of 104 surviving patients (34%) in Sydney had one or more neurologic deficits at discharge. These included hearing loss, which was the only deficit in 12 patients, and a range of other neurologic deficits in the other 23 surviving children. In Victoria between 1994 and 1995, the overall case fatality rate was 10%, with two-thirds of deaths occurring in patients over 60 years of age with pneumonia¹⁴. These findings are in accord with those from other studies, where the case fatality rate was related to extremes of age and the presence of underlying diseases^{13,15}.

Prevalent pneumococcal serotypes

There are now more than 80 serotypes of *Streptococcus pneumoniae* described. Their relative frequency, vitally important for vaccine policy, varies according to site of isolation, age, antibiotic resistance and geography, and over time. Five or six capsular types account for 60-70% of disease in most series from industrialised countries⁶.

Industrialised countries

Among infants and children in four centres in the United States of America between 1957 and 1978, types 6, 18, 19, 23 and 14 were consistently among the five most common invasive isolates¹⁶. More recent data from the United States of America, based on 3,884 isolates, found the three most common serotypes to be 14, 6B and 19F, with little variation by age (less than two years versus two to six years) or geographic area¹⁷. There was variation by site, with serotypes 3, 9A and 23F significantly more frequent from the middle ear. Consequently, 85% of invasive isolate serotypes would be included in a putative heptavalent vaccine, compared with 65% of middle ear isolates. In contrast to the United States of America, population-based studies from Finland¹⁸ and Israel¹⁹ show important differences among prevalent serotypes by age, location and ethnic group. Types 6, 14 and 19 accounted for 53% of 365 strains in Finland but only 33% of 205 strains in Israel, with types 7, 18 and 23 causing 25% of disease in Finland and types 1, 5, 18 and 23 making up 47% of isolates in Israel.

Australia

There are few published Australian data on prevalent pneumococcal serotypes. Among 1,252 isolates in Sydney, including 96 from blood or cerebrospinal fluid (CSF), between 1965 and 1969, types 19, 23, 6, 3 and 9 accounted for 43%²⁰. Other data are unpublished or in abstract form. Hansman has reported the most common serotypes from 588 invasive isolates in adults and children in five States between 1988 and 1993 as 19, 6, 14, 23 and 3²¹. The Australian Group on Antimicrobial Resistance (AGAR) serotyped all invasive or penicillin-resistant isolates received from participating laboratories in 1994 (J Bell, Australian Group on Antimicrobial Resistance, personal communication). Of 282 invasive isolates in children (<15 years), types 14 (40%), 6 (17%), 19 (14%) and 23 (10%) accounted for 81% of serotypes. Of 11 invasive penicillin-resistant isolates, nine were serogroup 6, and one each was type 14 and 23. In Victoria in 1994 to 1995, the most common serotypes among 445 sterile site isolates from patients of all ages were 14 (29%), 6 (12%), 19 (11%), 9 (9%), 23 (8%), 4 (7%) and 18 (6%), with these seven serotypes/groups accounting for 93% of infections in those under two years of age and 80% of infections in those over 60 years of age¹⁴.

Less industrialised countries

The distribution of pneumococcal serotypes is much more diverse on a worldwide scale, making the formulation of a conjugate vaccine with a feasible number of serotypes suitable for use in all areas problematic. Workers from the United States of America Centers for Disease Control and Prevention, with collaborators from all continents, have recently summarised serotype data from sterile site isolates including transtracheal aspirates, pleural fluid and lung aspirates, from a number of developed and less developed countries, with special emphasis on pneumonia²². Serotypes 14, 6 and 19 were consistently important in all geographic areas, while type 18 was important only in developed countries and types 1 and 5 only in developing countries. A formulation containing types 6B, 14, 19F, 23F, 9V, 4 and 18C was thought most appropriate for

developed countries. This covered from 65% (Spain) to more than 85% (Finland and United States of America) of isolates from developed countries, but less than 35% (Rwanda, Egypt and Papua New Guinea) to 59% (Gambia) for a range of developing countries. Their suggested formulation for developing countries substituted types 1 and 5 for 4 and 9V, giving significantly improved coverage (58 - 73%) except for some geographic areas, such as Papua New Guinea (42%) which have very diverse serotypes reported.

Indigenous populations in industrialised countries

In contrast, the serotype distribution among indigenous populations such as Alaskan native Americans²³ and Aborigines in central Australia²⁴ more closely resembles the industrialised countries to which they belong. In Alaska, seven serotypes (4, 6, 9, 14, 18, 19 and 23) which are included in one prototype conjugate vaccine, accounted for 85% of invasive strains from children less than two years old. Among persons older than 19 years, these serotypes accounted for only 40% of invasive strains, although 94% of isolates were covered in the 23-valent polysaccharide vaccine. In central Australia, types 14, 6B, 9V, 4, 18C and 19F accounted for 67% of isolates from children under five years old, while in adults, types 1, 7F, 3, 4, 12F and 8 were most common, accounting for 68% of isolates.

The available data, particularly from developing countries, are limited by lack of control for age and antibiotic and vaccine exposure. Controlled studies of larger size and over a longer time frame are needed from both industrialised and developing countries to judge the most appropriate vaccine formulations.

Epidemiology of antibiotic resistance

Streptococcus pneumoniae remained very sensitive to penicillin, with minimum inhibitory concentrations (MICs) less than 0.02 micrograms per mL, for many years. Although antibiotic resistance was recognised *in vitro* in the 1940s, it was first described as a clinical problem by Hansman and Bullen in 1967²⁵. Initially isolates were only moderately resistant (MIC between 0.1 and 1.0 microgram per mL) but highly

resistant isolates (MIC >2 micrograms per mL) were then reported, first from Spain and South Africa and more recently from Eastern Europe and parts of the United States of America.

Resistance of *Streptococcus pneumoniae* to penicillin and other antibiotics is increasing in all areas of the world²⁶. The pattern of resistance is notable for its uneven distribution both between countries and within countries. South Africa, Spain and Eastern Europe report rates of any (intermediate or high level) penicillin resistance of up to 50%²⁶, compared with less than 10% in most of Western Europe²⁶. In the United States of America, high level penicillin resistance has steadily increased from 0.02% to 1.3% overall, but is concentrated in certain geographic areas²⁷.

In Australia antibiotic resistance is also increasing. In 1989, 31 (1.7%) of 1,822 isolates from major laboratories in all States were penicillin resistant, but no isolates showed high level resistance²⁸. By 1994, of 2,181 pneumococci studied, 127 (5.8%) had intermediate sensitivity to penicillin, 14 (0.6%), including two blood culture isolates, were highly resistant and 8% of all isolates were multi-resistant, defined as resistance to three or more antibiotics²⁹. Resistance to other antimicrobials was also significant, including approximately 10% to erythromycin and tetracycline, 6% to chloramphenicol and 40% to cotrimoxazole. Eight per cent of all isolates were multi-resistant²⁹.

In some Aboriginal communities, levels of antibiotic resistance among pneumococci are much higher. As early as 1981, a surveillance study using nasal swabs among Aboriginal children in central Australia found 27 of 174 (15.5%) of pneumococci isolated to be penicillin resistant³⁰. In 1993 to 1994, a prospective study of antibiotic prophylaxis for otitis media in Aboriginal children in the Northern Territory found that the rate of isolation of multi-resistant pneumococci from the nasopharynx increased from 3/41 (7%) to 14/31 (45%) as the study progressed³¹. There was also evidence of transmission of multi-resistant strains from treated, older infants to untreated, younger infants. A study of children admitted to hospital in Darwin in 1994 to 1995 confirmed

high colonisation rates in rural Aboriginal children, and penicillin-resistant strains in Aboriginal and non-Aboriginal children, with overall rates of penicillin resistance of 30%³². As observed in Israel in 1981⁵ and elsewhere²⁶, a restricted group of serogroups generally associated with carriage in children (6, 9, 14, 19 and 23), were responsible for more than 80% of penicillin-resistant infections.

An important study from Iceland has provided convincing confirmation of the link between antibiotic usage and penicillin resistance in pneumococci³³. Nasopharyngeal swabs for culture of pneumococci were obtained from a cross-sectional sample of children less than seven years of age attending day-care centres in five regions. The overall rate of pneumococcal carriage was 52.7%, with 47 (9.7%) of nasopharyngeal isolates penicillin resistant. Antibiotic usage was strongly associated with carriage of penicillin-resistant pneumococci, after correction for other variables in a multivariate model. Recent exposure was also important, as 1.8% of children who had no courses of antimicrobials in the previous year carried resistant strains, compared with 14% who had any courses and 61% of those who had received antimicrobials in the previous two to seven weeks³³.

Strategies to promote accurate surveillance of penicillin-resistant isolates, appropriate use of pneumococcal vaccination and decreased inappropriate antibiotic use, especially in young children, are crucial to minimising the impact of antibiotic-resistant pneumococcal infections. Recommendations recently made by the Centers for Disease Control and Prevention are likely to be generally applicable in industrialised countries³⁴.

Risk factors for invasive pneumococcal disease in children

Risk factors for childhood pneumococcal disease among populations in industrialised countries have been examined in case-control studies in Finland³⁵ and California³⁶. Day-care attendance was associated with significant risk only in children younger than two years in Finland

(odds ratio (OR) = 36, 95% CI 5.7 - 233) while in California, the OR for children less than five years old was 2.6 (1.6 - 4.3). Recent otitis media was a significant risk factor in both studies (OR 1.6 to 5). Unlike invasive *Haemophilus influenzae* type b (Hib) disease, breast feeding was not found to be protective in either study. In California, an increased incidence of invasive pneumococcal disease was found in Afro-American children (OR 2.8) and, unlike Hib disease, in children of Asian descent (OR 2.5). Both these populations differ substantially from Australian urban populations in a number of demographic features, and similarly to Hib disease, risk factors may not be generalisable.

Pneumococcal vaccines

Polysaccharide vaccine

The currently available pneumococcal vaccine contains purified capsular polysaccharide antigens of 23 serotypes of *S. pneumoniae* (Danish types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F)⁶. Each 0.5ml dose of vaccine contains 25 micrograms of each polysaccharide antigen, compared with 50 micrograms of each in the 14-valent vaccine. Young adults have the strongest responses to pneumococcal polysaccharide vaccine and response is reduced at the extremes of age and in a range of underlying conditions⁶. Almost no response is seen in individuals with leukaemia, lymphoma or Hodgkins disease. Even infants below one year of age will respond to serotypes 3, 4, 8 and 9, but antibody does not persist. Children immunised at six months have similar antibody levels to controls at the age of two years, and demonstrate no boosting response^{6,37}. Unfortunately, children below the age of five years show little response to the prevalent serotypes 6A, 14, 19F and 23F^{6,37}.

The high rates of invasive pneumococcal disease occurring early in life in developing countries, many of which already have maternal tetanus immunisation programs, makes maternal pneumococcal immunisation a potentially important intervention in this setting. A collaborative group of investigators from the United States of America and Bangladesh has studied

pneumococcal antibody in serum and breast milk in 36 maternal-infant pairs following pneumococcal polysaccharide vaccine at 30-34 weeks gestation, with meningococcal polysaccharide vaccine as the control³⁸. Study infants had geometric mean titres (GMTs) two- to three-fold higher than controls. Despite this, rates of nasopharyngeal colonisation with pneumococci were high (50% by three months) and did not differ between study and control infants³⁸. Whether these short-term differences in antibody would translate into disease reduction on a population basis or interfere with subsequent active infant immunisation with a conjugate vaccine is unknown.

Polysaccharide-protein conjugate vaccines

Following the success of protein conjugate vaccines in eliminating *Haemophilus influenzae* type b (Hib) disease in many areas of the world, largely through reduction in nasopharyngeal colonisation, studies of protein conjugate pneumococcal vaccines are of great interest. Each serotype essentially requires a separate vaccine, and probably limits any conjugate formulation to a maximum of 7 to 9 serotypes, although the number of serotypes included has steadily increased with ongoing vaccine development³⁹.

Data on conjugate pneumococcal vaccines are currently limited to immunogenicity studies, pending the results of efficacy trials in Finland and California with endpoints of otitis media and bacteraemia respectively. In contrast to the experience with the comparable Hib conjugates, a vaccine using the outer membrane of *Neisseria meningitidis* type b (OMP) as the conjugating protein gave responses which seem to depend largely on the nature of the pneumococcal polysaccharide⁴⁰. After one dose, responses were seen only to serotypes 14 and 19F, with a response to 6B and 23F, known to be poorer immunogens, requiring two doses irrespective of whether vaccination began at two or four months of age. In a developing country setting, a vaccine using CRM₁₉₇ as the conjugating protein in a 2,3,4 months schedule in Gambia gave significantly higher antibody responses than a control group who received Hib vaccine with the same

protein conjugate. However, the GMT to all serotypes rose substantially in the control group, probably due to high early rates of colonisation with pneumococci in this population⁴¹. The vaccine in the Gambian study, which had a five-fold greater dose of polysaccharide than the Finnish vaccine, was associated with a higher rate of local reactions^{40,41}. This is another possible limiting factor for increasing the number of serotypes in pneumococcal conjugate vaccines, as polysaccharide dose is an important determinant of response⁴⁰. However, like conjugate Hib vaccines, conjugate pneumococcal vaccines provide immunologic priming, so natural boosting may occur⁴². Data suggest that mucosal colonisation with pneumococci may be reduced following conjugate pneumococcal vaccine³ similar to Hib vaccines⁴, but this may be serotype specific, with non-vaccine serotypes filling the ecological niche⁴³. Conclusions must await the results of randomised controlled trials.

Conclusions

Invasive pneumococcal disease remains an important cause of morbidity and mortality in Australia, especially in the very young, the very old and other at-risk populations. The emergence of antibiotic-resistant pneumococci is an important development which will necessitate changes in laboratory and clinical practice. This development should also underline the need for prudent antibiotic use in the community, especially for young children, the great majority of whom have viral rather than bacterial respiratory tract infections. Vaccination with the current 23-valent vaccine (in at-risk adults) and with newly developed conjugate vaccines (in infants) may offer the best chance to control both pneumococcal disease and antibiotic-resistant strains.

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