

Outcome of invasive pneumococcal disease: a UK based study

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Abstract

Methods—The records of 106 children aged less than 5 years with invasive disease caused by *Streptococcus pneumoniae* were reviewed.

Results—The clinical manifestations were meningitis (37%), upper respiratory tract infection (24%), pneumonia (19%), and occult bacteraemia (18%). One child died and seven had persisting neurological impairment. Five serotypes caused 83% of disease and 92% of the serotypes are included in the seven valent conjugate vaccines which are undergoing trials.

Conclusions—These data suggest that *S pneumoniae* infection is associated with a low case fatality rate but substantial morbidity in the UK.

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Keywords: *Streptococcus pneumoniae*; morbidity; mortality; outcome

Streptococcus pneumoniae remains an important childhood pathogen worldwide, causing over one million deaths annually in children under the age of 5 years.¹ Following the introduction of *Haemophilus influenzae* type b vaccine in industrialised countries, *S pneumoniae* has become the most common cause of invasive bacterial disease in children under 5 years and the most common cause of bacterial meningitis in children under 2 years in the United States.² Furthermore, the case fatality rates and risk of sequelae following meningitis are reported to be higher for *S pneumoniae* than *Neisseria meningitidis* or *Haemophilus influenzae*.³

Studies have reported a wide spectrum of disease manifestations with case fatality rates varying from less than 1% for occult bacteraemia to more than 30% for meningitis,^{4,5} but outcome for invasive pneumococcal disease in UK children has not been previously reported. The need for UK specific data is emphasised by the preliminary results of a seven valent pneumococcal conjugate vaccine which report protective efficacies of 100% for invasive disease and 57% for otitis media.^{6,7} Local outcome data will be valuable in assessing the potential benefit of childhood immunisation against pneumococcal disease in the UK. We undertook this preliminary study to investigate the impact of microbiologically confirmed invasive pneumococcal disease in the Oxford region in order to provide preliminary data for assessing the usefulness of childhood immunisation. This would also provide valuable background information for the design of a definitive

outcome study of invasive pneumococcal disease in children.

Methods

A retrospective chart review of children under the age of 5 years, identified by the Oxford Pneumococcal Surveillance Group was carried out. This enhanced prospective surveillance of invasive pneumococcal disease is a collaboration between the 10 hospital based microbiology laboratories in the Oxford region which serve a total population of around 190 000 children under the age of 5 years. Cases were defined as children from whom *S pneumoniae* was isolated from a normally sterile site (blood, cerebrospinal fluid (CSF), joint fluid).

A diagnosis of pneumonia was based on a record of clinical signs of lower respiratory tract infection with radiological changes consistent with pneumonia. Cases with upper respiratory tract infection and otitis media were based on the physician diagnosis recorded on admission. In all these cases, *S pneumoniae* was also isolated from blood cultures. Cases of meningitis were defined by: (1) isolation of *S pneumoniae* from CSF; (2) CSF Gram stain showing Gram positive diplococci; or (3) clinical signs of meningitis with *S pneumoniae* isolated from blood cultures. Occult bacteraemia was defined as fever without localising signs.

S pneumoniae was cultured and identified by standard techniques. Serotyping was performed by the Quellung reaction using serotype specific antiserum (Statens SerumInstitut, Copenhagen, Denmark).

Results

Between January 1991 and August 1996, 124 cases of invasive pneumococcal disease were identified and the records for 106 could be traced. The case notes for 18 could not be found. Eighty seven cases (83%; 95% confidence interval 75% to 89%) occurred in children aged less than 2 years. Five cases occurred within 48 hours of birth and four of these cases were born at less than 34 weeks gestation. The serotype results were available for 80 strains (fig 1).

Table 1 shows clinical presentations and underlying illnesses. Meningitis was the most common presentation occurring in 39 cases (37%; 95% CI 28% to 46%). Thirty different underlying medical conditions were recorded in 32 cases presenting after seven days of life. In cases presenting within seven days of birth, prolonged rupture of membranes (>24 hours) occurred in four of six children.

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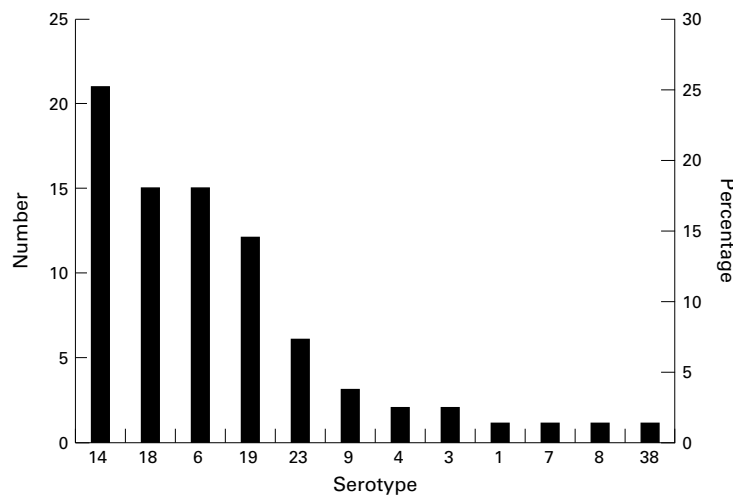


Figure 1 Serotype distribution among 80 of 124 isolates from blood ($n = 45$), cerebrospinal fluid ($n = 34$), or joint fluid ($n = 1$) from children less than 5 years.

Table 1 Clinical features of 106 cases of invasive pneumococcal infection in children aged less than 5 years

	Number of cases
<i>Presenting illness</i>	
Meningitis*	39
Upper respiratory infection/otitis media	25
Pneumonia	20
Occult bacteraemia	19
Other	3
<i>Possible risk factors</i>	
Recurrent otitis media	11
Congenital heart disease	6
Developmental delay	4
Chronic respiratory disease	5
Immunocompromise†	4
Premature delivery or premature rupture of membranes	5

*21 cases of meningitis had seizures and 17 non-meningitis cases had febrile fits.

†HIV, asplenia, leukaemia ($n = 2$).

One neonate born at 30 weeks gestation died. The mean duration of hospital stay for the surviving children was 7.7 days (median 7, range 1–58). Of the 39 cases with meningitis, the results of hearing tests were available in 24 (74%). A sensorineural deficit was detected in five (17%; 95% CI 6% to 36%) and a conductive deficit in seven (24%; 95% CI 10 to 44%) children. Two children had both a sensorineural and conductive deafness detected and two children required auditory aids. Of the cases with meningitis, two required long term anticonvulsant treatment and one other had a persisting hemiparesis.

Discussion

This is the first UK based report of the outcome of pneumococcal disease in children. It has shown that invasive pneumococcal disease has a low case fatality rate, but substantial long term morbidity in the Oxford region. In common with many retrospective studies, the follow up was incomplete, as outcome data could be found in only 106 of the 124 cases identified. However, this case fatality rate of approximately 1% is in line with recent rates of 1% to 7% reported elsewhere in the industrialised world.^{8 9}

An estimate of the full impact of invasive pneumococcal disease requires an assessment of life long sequelae, in addition to mortality.

The observation that 7% of the cases developed permanent neurological disability following pneumococcal meningitis emphasises the importance of including sequelae as a more complete measure of the impact of invasive pneumococcal disease on the community. In children under 5 years, the attack rate of 21 per 100 000 from enhanced surveillance in the Oxford region (K Sleeman, manuscript in preparation) is consistent with the rate of 15.7 per 100 000 found in the national voluntary reporting scheme for England and Wales.¹⁰ Together these measures will provide an estimate of the risk attributable to invasive pneumococcal disease and therefore, the potential benefit of vaccination in this population. However, the potential benefits of immunisation substantially exceed those measured by clinical outcomes alone. For example, the cases reported here needed a mean of 7.7 days of hospital treatment. The cost per day for a hospital bed for a child in the UK is £273.¹¹ Furthermore, results from conjugate vaccine trials suggest that sterile site cultures underestimate the burden of invasive disease.⁶

An important feature of pneumococcal immunisation is the number of capsular polysaccharide antigens (or valency) contained in the vaccine. This study indicates that serotypes 14, 18, 6, 19, and 23, were responsible for 83% of the microbiologically proven invasive disease for which data were available. These five serotypes are found in 71% of invasive childhood isolates in England and Wales,¹² and between 30% and 69% in other European countries.^{8 13–16} Although the serotypes of isolates were available for only 80 of the 124 patients and may have biased our results, the serotype distribution reported here is very similar to those found in children in recent UK based studies.¹² Furthermore, the seven valent conjugate vaccine under trial in California and Finland, would be expected to cover 92% of invasive isolates in the Oxford region.

The confirmation of an excess of identifiable risk factors for invasive disease would help identify risk groups for targeted immunisation. Takala *et al* have identified recurrent otitis media as a risk factor for invasive pneumococcal disease in children,¹⁷ and the large number of cases in this study with potential medical risk factors for invasive disease needs further specific investigation. In addition, information on attack rates, vaccine efficacy, risk factors and outcome will contribute both to understanding the pathogenesis of invasive pneumococcal disease and informing healthcare decisions.

Members of the Oxford Pneumococcal Surveillance Group: L Fitch (Bedford), C Hall (Horton General, Banbury), I Bowler (John Radcliffe, Oxford), R Cox (Kettering), B Das (Milton Keynes), M Severn (Northampton), P Burden, A Stacey (Royal Berkshire, Reading), P Gillette and A O'Driscoll (Stoke Mandeville, Aylesbury), M McIntyre (Wexham Park, Slough), M Lyons, D Waghorn (Wycombe). We are grateful to the paediatric consultants from the above hospitals for their cooperation in this study and Paul Heath for comments.

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Sunscreen and brown naevi

Most parents, you might think, now apply sunscreen to their children when they are to be exposed to bright sunlight. It is perhaps, therefore, surprising that supplying extra sunscreen to parents in Canada (Richard P Gallagher, and colleagues. *Journal of the American Medical Association* 2000;283:2955–60) apparently reduced the number of melanocytic naevi which developed in their children.

A total of 458 Vancouver schoolchildren aged 6–7 or 9–10 years entered the trial and 309 completed it. Parents randomised to the treatment group were supplied with a broad spectrum sunscreen (SPF 30) and advised to apply it to exposed areas whenever the child was to be exposed to sunlight for 30 minutes or more. Parents in the control group were given no sunscreen and no advice (though many of them used sunscreen on their children).

Over three years of follow up the mean number of new melanocytic naevi acquired was 24 in the sunscreen group and 28 in the controls. Protection was greater in freckled children; it was estimated that supplying sunscreen reduced the development of new naevi in freckled children by 30–40%.

The hope, of course, is that use of sunscreen will protect against the later development of malignant melanoma, but that remains to be shown.

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