ORIGINAL ARTICLE

Twenty year surveillance of invasive pneumococcal disease in Nottingham: serogroups responsible and implications for immunisation

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Aims: To evaluate the incidence, spectrum of clinical manifestations, and outcome of invasive pneumococcal disease (IPD) in children. To determine the major serogroups of *Streptococcus pneumoniae* responsible for invasive disease and the potential coverage by the new pneumococcal conjugate vaccines.

Methods: Analysis of prospectively recorded information of all children admitted to two teaching hospitals in Nottingham with IPD between January 1980 and December 1999.

Results: A total of 266 episodes of IPD in children were identified; 103 (39%) were aged <1 year and 160 (60%) <2 years. Major clinical presentations were meningitis in 86 (32%), pneumonia in 82 (31%), and bacteraemia without an obvious focus in 80 (30%). The age specific mean annual incidence rates of IPD overall among children aged <1, <2, and <5 years were 47.1, 37.8, and 20 per 100 000 population, respectively. Mortality rates for children with meningitis and non-meningitic infection were 20% and 7%, respectively. Neurological sequelae following meningitis were documented in 16 (26%) of the 61 survivors assessed. The potential coverage rates in children between the ages of 6 months and 5 years are 84% by the 7-valent, 91% by the 9-valent, and 95% by the 11-valent conjugate vaccines.

Conclusion: This study indicates that inclusion of a pneumococcal conjugate vaccine in the primary immunisation programme in the UK would have a considerable effect on the mortality and morbidity associated with IPD.

The most common organism responsible for invasive bacterial infection in young children is *Streptococcus pneumoniae*.¹⁻⁴ Bacteraemia alone (without an obvious focus of infection) accounts for over 50% of all cases of invasive pneumococcal disease (IPD), followed by pneumonia and meningitis.¹⁻³ In the USA, *S pneumoniae* is the leading cause of bacterial meningitis in young children;⁵ in England and Wales, it is second only to *Neisseria meningitidis*.⁶ Mortality in children with pneumococcal meningitis is at least twice as high as meningococcal meningitis⁷⁻⁸ and the survivors have the highest incidence of sequelae of all meningitides.⁷⁻¹⁰ In developing countries, *S pneumoniae* is one of the most important causes of serious infections and death in young infants.¹¹ Furthermore, the worldwide emergence of antibiotic resistance among *S pneumoniae* isolates in the past decade,¹²⁻¹⁴ has complicated the antimicrobial therapy of IPD.¹⁵

The dramatic reduction of the incidence of *Haemophilus influenzae* type b (Hib) disease in infants and young children since the introduction of Hib conjugate vaccine,¹⁶⁻¹⁷ has prompted renewed efforts to develop an effective vaccine against pneumococcal disease. The currently available 23-valent pneumococcal polysaccharide vaccine is not recommended for children under 2 years of age, in whom most IPD occurs.^{1-3, 4, 18} Currently, three main formulations of a pneumococcal conjugate vaccine (PCV) are being evaluated in different parts of the world.¹⁹ A large clinical trial in healthy infants of heptavalent PCV, in the USA, has shown that it is highly effective in preventing invasive disease in children.²⁰

The pneumococcal serotypes included in the conjugate vaccines were selected to cover those strains that caused most IPD in children throughout the world.²¹⁻²² The frequency with which the major serotypes cause IPD varies according to age, source of isolation, geographic region, and time.^{4, 18, 21-23} In the USA, the 7-valent vaccine, PCV7, which includes serotypes 4,

6B, 9V, 14, 18C, 19F, and 23F,¹⁹ has already been incorporated into the primary immunisation programme.²⁴ In the UK, however, use of PCV7 is confined to selected high risk groups of children.²⁵ In the 9-valent vaccine, PCV9 serotypes 1 and 5 are added, and the 11-valent vaccine, PCV11 also includes serotypes 3 and 7V.¹⁹

Epidemiological data on IPD and knowledge of the major serogroups of *S pneumoniae* which cause disease in infants and children is important in deciding whether to introduce a PCV into the primary immunisation programme and in assessing its impact. We therefore report our experience of children with IPD in Nottingham and estimate the vaccine coverage against the pneumococcal serogroups identified.

PATIENTS AND METHODS

All children with IPD who presented to the University Hospital Nottingham (UHN) or the Nottingham City Hospital between January 1980 and December 1999 were included. The two hospitals provide an in-patient service for all the children in the Nottingham conurbation. It covers a population of about three quarters of a million and is served by a single Microbiology and Public Health Laboratory. IPD in a child aged 0-16 years was defined by the isolation of *S pneumoniae* from blood, cerebrospinal fluid (CSF), or from other normally sterile body sites. Only one isolate per disease episode was analysed. A second episode separated by an interval of at least four weeks from the first was considered as a separate case of IPD.

A diagnosis of meningitis in the vast majority of cases was based on a compatible clinical picture and the isolation of *S pneumoniae* from the CSF, subdural collection or meningeal

Abbreviations: CSF, cerebrospinal fluid; Hib, *Haemophilus influenzae* type b; IPD, invasive pneumococcal disease; MIC, minimal inhibitory concentration; PCV, pneumococcal conjugate vaccine

swabs, with or without a positive blood culture. In four children non-cultural techniques established the diagnosis of pneumococcal meningitis—Gram positive diplococci seen on Gram staining of the CSF with pleocytosis ($n = 2$), and the presence of pneumococcal antigen in subdural collection using counterimmune electrophoresis. Pneumococcal pneumonia was defined in children with a compatible clinical picture and/or chest x ray findings together with a positive blood culture. Over two decades, brief prospective records of all patients with bacteraemia²⁶ and most other serious infections²⁷ have been maintained in our department. Case notes were retrieved for additional information. Antimicrobial susceptibility testing of *S pneumoniae* was performed by the Stokes version of the disc diffusion technique including a 1 µg oxacillin disc.²⁸ Isolates of *S pneumoniae* showing a reduced inhibitory zone to penicillin, ampicillin, or oxacillin were submitted to the Central Public Health Laboratory of the Public Health Laboratory Service (PHLS), Colindale, London, to determine the minimal inhibitory concentrations (MICs) of penicillin and other agents against the isolate. Serogrouping of *S pneumoniae* isolates was carried out by the Reference Laboratory of the PHLS, who until recently did not report the serotype results within relevant serogroups of *S pneumoniae*.^{4, 13} We cannot therefore comment on the distribution of subtypes within the serogroups.

RESULTS

Epidemiological and clinical data

There were 266 children (168 males, 98 females) with IPD in the 20 years. A total of 106 (40%) of 266 children presented in the first decade of this study (1980–89), and 160 (60%) in the second decade (1990–99). The total number of children with IPD annually in the first decade, ranged from 2 in 1980 to 21 in 1989. In the second decade, it ranged from 12 in 1997 to 18 in 1991, 1992, 1995, and 1996. No sharp increase was seen in any particular month of the year, but IPD was more common in January to May (135 cases, 51%) and October to December (79 cases, 30%) than in June to September (52 cases, 19%). Meningitis, with or without bacteraemia was present in 86 (32%), pneumonia in 82 (31%), bacteraemia without an obvious focus in 80 (30%), septic arthritis in 7 (3%), periorbital cellulitis in 7 (3%), and cellulitis in 4 (1%).

Of the 86 children with meningitis, 63 were admitted from home to one of the two hospitals in Nottingham; 12 were in hospital for other reasons prior to developing meningitis; and the remaining 11 were initially admitted to other hospitals with meningitis or other conditions, but were transferred to UHN for further management. Blood and CSF cultures were positive in 84% and 90%, respectively, and CSF Gram stains revealed Gram positive diplococci in 86%. With the exception of four children with non-bacteraemic septic arthritis, the remaining 176 children with non-meningitic IPD were bacteraemic.

Figure 1 shows the age distribution of 86 children with meningitis and 180 with other IPD and the associated mortality. Overall, 103 (39%) were less than 1 year and 160 (60%) were less than 2 years of age. Meningitis was commoner in younger children. Seventeen of the 19 infants below 2 months of age were less than 30 days old (neonates). Symptoms of infection appeared within 72 hours in 14 neonates, seven of whom died. Infection was acquired while in hospital in 16 (19%) of 86 children with pneumococcal meningitis and in 27 (15%) of 180 children with other IPD.

The mean annual incidence rates of IPD overall and meningitis only were calculated using the mid-decade (1985 and 1995) population estimates for the Nottingham conurbation. Eighteen children who were not living within this area were excluded in the calculation of incidence, but

included in the remaining analysis. Table 1 shows the age specific incidence rates. The incidence of IPD overall and meningitis was highest among children under 1 year of age. A modest increase in the incidence of IPD was noted in the second decade in each age category, but the incidence of meningitis in the two decades remained relatively stable.

At least one underlying condition was documented in 33 (38%) of 86 children with pneumococcal meningitis and in 69 (38%) of 180 children with other IPD. These were the presence of CSF shunts ($n = 7$), neurological deficits prior to meningitis ($n = 8$), recent neurosurgery ($n = 5$), previous episode of meningitis ($n = 4$), head injury ($n = 4$), congenital anomaly/syndrome ($n = 4$), acute otitis media ($n = 4$), and others ($n = 4$) in children with meningitis. Underlying conditions in those with other IPD included congenital anomaly or syndrome ($n = 13$), congenital heart disease ($n = 6$), haematological malignancy ($n = 14$), other malignancy ($n = 10$), preterm newborn ($n = 7$), asthma ($n = 7$), chronic kidney or lung disease ($n = 2$), recent proven viral infection ($n = 2$), and the presence of CSF shunts ($n = 2$).

Initial therapy of children with suspected pneumococcal meningitis pending culture results often consisted of a combination of antibiotics. This was usually benzylpenicillin plus chloramphenicol in the first decade of the study and penicillin plus cefotaxime in the second. Monotherapy used either as initial or subsequent therapy, changed from benzylpenicillin in the first decade to cefotaxime in the second. Forty seven (55%) of 86 children with meningitis were managed in the paediatric or neonatal intensive care units in the initial stages of infection, 26 (55%) of whom required mechanical ventilation.

Outcome

Thirty (11%) of 266 children with IPD died. There were 17 (20%) deaths among 86 children with meningitis; mortality rates for 63 children admitted directly from home, 12 already in hospital, and 11 referred from other hospitals were 11%, 50%, and 36%, respectively. Thirteen (7%) deaths occurred among 180 children with other IPD. Mortality was 42% among infants less than 2 months of age and 9% beyond this age (fig 1). It was higher in those with a pre-existing underlying condition (23%) than in those without (4.3%). Mortality with hospital acquired IPD was 42% compared with 5.4% for community acquired IPD. The mean length of hospital stay among the 69 survivors of pneumococcal meningitis and 150 survivors of community acquired non-meningitic infection was 18.7 and 5.4 days, respectively.

Analysis of neurological sequelae among survivors of meningitis is based on the number of children rather than the number of episodes. Of the 83 children with meningitis, 17 died and 66 survived. Excluded from the analysis were survivors whose neurological deficits were transient or those who had pre-existing neurological deficits. Sixteen (26%) of 61 survivors had at least one neurological sequela. These included cerebral palsy in six children, global developmental delay in eight, epilepsy in seven, and sensorineural hearing impairment in seven (14%) of 51 children who had auditory assessment. Eight children had multiple neurological deficits.

Serogroups

A total of 226 (85%) of the 266 isolates of *S pneumoniae* were serogrouped. Serogroups of isolates from children with meningitis and other IPD and the overall cumulative coverage rates of the serogroups included in the three conjugate vaccines are summarised in table 2. Serogroup 14 was commonest, accounting for 22% of those grouped. Serogroup 1, uncommon among isolates from children with meningitis, was the second most frequent isolate from children with other forms of IPD and accounted for 20

Figure 1 A total of 266 episodes of invasive pneumococcal disease by age.

(13%) of 150 isolates. Serogroups included in PCV7, PCV9, and PCV11 accounted for 71%, 82%, and 90%, respectively of all isolates grouped from children with IPD. An additional 12 serogroups, not included in the three PCVs (non-vaccine serogroups) were identified among 23 isolates. The non-vaccine serogroups were recovered more frequently from children with meningitis (17%), than from those with other IPD (7%).

Distribution of serogroups included in the three formulations of PCVs and found among the isolates from children with IPD in each of the two decades is summarised in table 3. Apart from an increase in serogroups 14 and 6 and a decrease in serogroup 7 noted in the second decade, the serogroups remained stable during the study period. Serogroup 14, the leading serogroup, accounted for 43 (28%) of 155 isolates from children under 3 years of age, but for only 7 (10%) of 71 isolates from older children. Serogroup 1 accounted for 17 (24%) of 71 isolates from older children but for only 5 (3%) of 155 isolates from younger children. Non-vaccine serogroups accounted for 10 (23%) of 44 isolates from infants less than 6 months of age, and for 13 (7%) of the remaining 182 isolates. Primary immunisation starts at 2 months of age and is completed by 4 months in the UK.²⁵ If PCV were to be included in this country, our findings suggest that 50 (19%) children below 6 months (including six children whose isolates were not serogrouped) would remain unprotected. Figure 2 presents the potential coverage rates by the 7-, 9-, and 11-valent pneumococcal conjugate vaccines against IPD in children of different age groups.

Antimicrobial susceptibility

Between 1993 and 1998, three strains of *S pneumoniae* from children with meningitis (two serogroup 14 and one serogroup 9), showed intermediate susceptibility to penicillin

(MIC 0.1–1.0 µg/ml). The two serogroup 14 isolates were also resistant to erythromycin. In 1995, a penicillin resistant strain (MIC 2.0 µg/ml), belonging to serogroup 23, was isolated from a child with a non-meningitic episode of IPD. Isolated erythromycin resistant strains, first seen in children with IPD in 1986, accounted for 22 (8%) of 266 isolates. Sixteen of these isolates belonged to serogroup 14.

DISCUSSION

In the UK, epidemiological data on IPD in children is mainly obtained from surveillance studies by the PHLS in England and Wales^{4 23 29–31} and by the Scottish Centre for Infection and Environmental Health in Scotland.³² The first UK based report of the outcome of IPD recently described 106 children admitted to hospitals in the Oxford region in 1991–96.³³ We therefore believe that ours is the largest and longest study of IPD in children from one institution in the UK, in which the incidence, clinical manifestations, underlying conditions, place of acquisition of infection, major serogroups responsible, and outcome have been described.

Like others, we found that most children with IPD were less than 2 years of age and that meningitis occurred more frequently in younger children than non-meningitic infections.^{1 3 4 18 34–36} Underlying disease or predisposing factors were present in 38%, comparable to the 27–37% reported by others.^{3 35 36}

The age specific incidence rates of IPD in children in different countries were summarised recently.³¹ They not only vary between countries but also between ethnic groups in the same country.^{31 37} Geographical, ethnic, and over time variation in the incidences may be due to differences in hospital admission rates, number of blood cultures performed, methods of data collection, changes in the immunity in the population, or socioeconomic factors.^{4 18 31 36–38} Our age

Table 1 Incidence of any invasive pneumococcal disease and meningitis alone among children in Nottingham

Age	Clinical manifestation	Incidence per 100 000 children per year		
		1980–99	1980–89	1990–99
<1 year	Any IPD	47.1	38.0	55.2
	Meningitis only	21.8	20.0	23.4
<2 years	Any IPD	37.8	32.8	42.1
	Meningitis only	14.8	14.5	15.0
<5 years	Any IPD	20.0	17.1	22.5
	Meningitis only	6.6	6.1	6.9
<15 years	Any IPD	7.9	6.5	9.3
	Meningitis only	2.4	2.1	2.6

Table 2 Serogroup distribution of *S pneumoniae* among 226 isolates from children with IPD and the percentage of invasive disease isolates covered by the three pneumococcal conjugate vaccines

Serogroups included in the pneumococcal conjugate vaccines	Total number of isolates (n = 226)	Cumulative percentage	Number of isolates from:	
			Meningitis (n = 76)	Other IPD (n = 150)
7-valent pneumococcal conjugate vaccine, PCV7				
14	50	22	12	38
6	29	35	12	17
19	28	47	13	15
23	19	56	6	13
18	16	63	5	11
4	11	68	2	9
9	7	71	4	3
Subtotal	160	71	54	106
9-valent vaccine, PCV9 = PCV7 + the following serogroups				
1	22	81	2	20
5	3	82	1	2
Subtotal	25	82	3	22
11-valent vaccine, PCV11 = PCV9 + the following serogroups				
3	8	85	3	5
7	10	90	3	7
Subtotal	18	90	6	12
Non-vaccine serogroups	23	100	13	10

specific incidence rates of IPD are comparable to those reported by others from the UK^{4 31 32} and elsewhere in Europe,^{1 18} but much lower than the figures from the USA² or Israel.^{34 37}

Mortality rates of children with pneumococcal meningitis in recent studies have ranged from 7.7% to 19%.^{4 7-10 36} The outcome in secondarily referred children⁹ and in the newborn³⁹ is known to be poor. The inclusion of these groups may have contributed to a higher rate in this study. Nevertheless, our mortality rates of 11% with any IPD and 20% for meningitis are remarkably similar to 10.5% and 16%, respectively, reported from the UK⁴ and to the 13% and 19%, respectively, reported from Sweden.³⁶ Mortality rates vary according to age, disease manifestation, underlying conditions, or place of acquisition of infection^{3 4 35 36 39} as was noted in this study.

The incidence of neurological sequelae among survivors of pneumococcal meningitis has ranged between 28% and 36%,^{7 9 10} but in one study it was as high as 57%.⁸ In some studies,^{9 10} evaluation was based on the neurological deficits noted at discharge from hospital. However, the immediate

neurological sequelae of bacterial meningitis may improve with time and can resolve completely.⁴⁰ The 26% incidence in this report is comparable with the findings of others.^{7 9 10} Sensorineural hearing impairment is lower (14%) than the reported incidence of 19–43%.⁷⁻¹⁰

Ninety per cent of all isolates were of the serogroups that are included in the PCV11 (table 2). Knowledge of the distribution of the pneumococcal serogroups/serotypes within a defined population is important in developing a policy for the use of pneumococcal conjugate vaccines to prevent IPD. Serogroups 14, 6, 19, 23, 18, and 9, which commonly cause IPD in children in the USA, Canada, and Europe,^{1 3 4 9 10 21 23} accounted for two thirds of all isolates in our study. Serogroups of isolates from children with meningitis and non-meningitic infection have been known

Figure 2 Coverage rates by pneumococcal conjugate vaccines (PCV) against invasive pneumococcal disease in children of different age groups.**Table 3** Serogroup distribution of *S pneumoniae* among isolates from children with IPD in each decade, according to the serogroups present in the pneumococcal conjugate vaccines

Serogroups included in the pneumococcal conjugate vaccines	Number of isolates (%)	
	1980-89 (n = 91)	1990-99 (n = 135)
7-valent pneumococcal conjugate vaccine, PCV7		
14	16 (18)	34 (25)
6	7 (8)	22 (16)
19	13 (14)	15 (11)
23	9 (10)	10 (8)
18	7 (8)	9 (7)
4	4 (4)	7 (5)
9	3 (3)	4 (3)
Subtotal	59 (65)	101 (75)
9-valent vaccine, PCV9 = PCV7 + the following serogroups		
1	9 (10)	13 (10)
5	1 (1)	2 (1)
Subtotal	10 (11)	15 (11)
11-valent vaccine, PCV11 = PCV9 + the following serogroups		
3	4 (4)	4 (3)
7	9 (10)	1 (1)
Subtotal:	13 (14)	5 (4)
Non-vaccine serogroups	9 (10)	14 (10)
Total	91 (100)	135 (100)

to differ.^{1 3 4 18 22 23} Serogroup 14, the most common isolate in children with IPD, declines with age.^{3 4 18 23}

Serogroup 1, which is not included in the PCV7, is an uncommon isolate from children in the USA and Canada²¹ and it accounted for only 2.1% of all isolates from children with IPD in a recent report.³ In two recent studies from England,⁴ and Denmark,¹⁸ however, serogroup 1 accounted for 7.2% and 8.3%, respectively, of all isolates from children with IPD, similar to our 9.7%. Serogroup 1 was recovered from only one neonate (out of 14 grouped) in our study, although others^{18 31} have noted it to be the most common isolate. On the other hand, serogroup 1, which is a rare cause of meningitis in Europe and America^{3 18 22 23} is the most frequent cause of meningitis in Africa and India.²² Vaccine choice must therefore be made on the basis of local knowledge.

Infants who receive their first dose of PCV7 at 2 months of age would complete the primary course of three doses by 4 months in the UK,²⁵ and would then be considered as fully immunised. In a prospective double blind study of pneumococcal conjugate vaccine in healthy infants and toddlers in the USA, PCV7 was 97.4% and 93.9% effective against vaccine serotypes causing invasive disease in fully or partially vaccinated children, respectively.²⁰ Furthermore, even when non-vaccine or cross-reactive serotypes were included in the analysis, the efficacy of PCV7 was 89.1%.²⁰

The duration of protection after vaccination with PCV7 is unknown, but immunological memory does occur.²⁴ It can therefore be assumed that in children who have received a booster dose of the vaccine,^{24 25} protection would last at least until 5 years of age. Theoretically, 50 (19%) children under 6 months of age in this study would be outside the protection limit of the conjugate vaccines. The potential coverage rates of 84% by the 7-valent, 91% by the 9-valent, and 95% by the 11-valent pneumococcal conjugate vaccines against IPD in children between the ages of 6 months and 5 years noted here are similar to an earlier report from the UK⁴ and Denmark.¹⁸

In a study of pneumococcal bacteraemia and meningitis in England and Wales, the proportion of isolates of *S pneumoniae* resistant to penicillin and erythromycin rose between 1989 and 1995 from 0.3% to 2.9% and 3.3% to 10.9%, respectively.³⁰ Nevertheless, penicillin resistant rates of *S pneumoniae* in England and Wales are lower^{4 30} than those in other European countries, the USA, and other parts of the world.¹⁴

PCV7 is the only PCV licensed in the UK and its use is confined to selected high risk groups of children.²⁵ Epidemiological data on IPD presented here and elsewhere^{4 23 30-32} will aid in planning a wider use of pneumococcal conjugate vaccines in children. Other factors likely to guide this policy decision include results of vaccine trials in the UK, assessment of the cost effectiveness of routine immunisation programme,⁴ and the USA experience of mass use of PCV7 in recent years.²⁴ Finally, although PCVs reduce nasopharyngeal carriage of vaccine-type serotypes, in some studies, non-vaccine serotype carriage was found to be higher in vaccinated children.⁴¹ Ongoing surveillance of IPD in children is therefore essential to identify the incidence of IPD by non-vaccine serotypes with the introduction of these new conjugate vaccines.

We hope the data in this study is useful and timely. It provides baseline information on the incidence, spectrum of clinical manifestations, serogroups responsible, and outcome of IPD in children over a 20 year period and should serve as a benchmark for IPD in children prior to a wider use of pneumococcal conjugate vaccines in the UK. Despite the use of powerful antibiotics and aggressive supportive therapy, *S pneumoniae* meningitis remains the most serious manifestation of IPD. One in five children died and one in

four survivors have some degree of neurological damage. It is unlikely that further improvements in therapy will alter the outcome, so efforts should be directed towards prevention.

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"ANOTHER SHOT?! JUST WHEN I THOUGHT
I WAS IN THE CLEAR!"