Epidemiol. Infect. (2000), **125**, 561–572. Printed in the United Kingdom

Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implications for vaccine strategies

M. H. KYAW[1,3]*, S. CLARKE[2], G. F. S. EDWARDS[2], I. G. JONES[3] AND H. CAMPBELL[1]

[1] *University of Edinburgh, Public Health Sciences, Edinburgh*
[2] *Scottish Meningococcus and Pneumococcus Reference Laboratory, Glasgow*
[3] *Scottish Centre for Infection and Environmental Health, Glasgow*

(*Accepted 24 July 2000*)

SUMMARY

Based on the invasive pneumococcal isolates referred to reference laboratories in Scotland in 1988–99, we identified the distribution of serotypes/groups and their antimicrobial resistance patterns in order to evaluate the coverage of polysaccharide and the new pneumococcal conjugate vaccines. A total of 5659 invasive isolates were included. Of these, 5124 (90·5%) were blood isolates, 308 (5·5%) were CSF isolates, 143 (2·5%) were blood and CSF and 84 (1·5%) were other normally sterile isolates. The most prevalent 11 serotypes/groups were 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, in numerical order. These accounted for 84% of total serotypes/groups.

The serotypes/groups included in the 23 and 14-valent polysaccharide vaccines accounted for 96% and 88% of all isolates. Both vaccines accounted for 98% of penicillin non-susceptible and 100% of erythromycin non-susceptible isolates. The 7, 9, and 11-valent conjugate vaccines covered 61, 68 and 80% of invasive isolates respectively. The coverage of these vaccines was substantially higher in youngest age group with 84, 86 and 93% of invasive isolates in children < 2 years included in the 7, 9 and 11-valent conjugate vaccines compared with 58, 64 and 77% in adults $\geqslant 65$ years of age.

The serotype/group distribution of invasive isolates in Scotland varied from year to year over the period 1993–9. The coverage of the 23-valent vaccine remained above 95% in each year but the coverage of the 7, 9 and 11-valent conjugate vaccines showed more marked fluctuation with coverage as low as 53, 60 and 75% in some years. Continued surveillance of invasive pneumococcal isolates is required to inform the development of appropriate vaccine strategies to prevent pneumococcal disease in Scotland.

INTRODUCTION

Despite the availability of effective antibiotics, invasive pneumococcal disease remains a serious public health problem worldwide. *Streptococcus pneumoniae* is a leading cause of bacteraemia and meningitis [1, 2] particularly among the very young and elderly and those with chronic medical conditions [3]. The current 23-valent polysaccharide pneumococcal vaccine covers at least 90 and 88% of serotypes/groups causing invasive pneumococcal disease in the UK [4] and US [5, 6] respectively. However, this vaccine is poorly immunogenic in children < 2 years old, the age group with the highest burden of invasive pneumococcal disease [7]. Therefore, new 7 to 11-valent conjugate pneumococcal vaccines are now

* Author for correspondence: Clifton House, Clifton Place, Glasgow, G3 7LN.

being developed and evaluated [8]. In addition, conjugate pneumococcal vaccines may have a future role in protecting the elderly and adults with conditions placing them at increased risk of pneumococcal disease.

The effectiveness of polysaccharide and conjugate vaccines is dependent on the distribution of vaccine serotypes in the population being immunized [9]. Therefore, knowledge of the distribution of pneumococcal serotypes/groups within a defined population is important in developing rational vaccine policy for the future use of conjugate pneumococcal vaccines in the prevention of invasive pneumococcal disease. This paper reviews population based data on *Streptococcus pneumoniae* isolates identified from sterile body site specimens in Scotland during the period 1988–99 and examines the seroepidemiological characteristics of invasive pneumococcal disease.

METHODS AND MATERIALS

Background

The data for this study were obtained from Scottish Centre for Infection and Environmental Health (SCIEH) and Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). SCIEH serves as a national surveillance centre for monitoring infectious diseases and environmental hazards. Reports from laboratories throughout Scotland are received by SCIEH on a weekly basis. SMPRL is the national reference laboratory for pneumococcal disease. It has been established to enhance national surveillance for these diseases and has excellent links with microbiology laboratories throughout Scotland. It acts as a national centre for serotyping and antibiotic sensitivity testing of pneumococcal isolates. Laboratory records of *Streptococcus pneumoniae* reported to SCIEH (1988–1998/9) and the pneumococcal isolates received routinely by SMPRL (1993–1998/9) from all diagnostic laboratories in Scotland have been combined in a single database.

Study data

Only invasive isolates (blood, cerebrospinal fluid (CSF) and other normally sterile sites) were included in this study. Duplicate records in SCIEH and SMPRL datasets were excluded. The Danish system of nomenclature was used for reporting pneumococcal serotypes/groups in both data bases. Isolates that had values of minimal inhibitory concentration (MIC) $\leqslant 0{\cdot}06\ \mu$g/ml, between 0·12 and 1·0 μg/ml and 2·0 μg/ml or higher were defined as sensitive, intermediate, and high level penicillin resistance respectively. Isolates with MICs of intermediate and resistant levels were described as non-susceptible. Pneumococcal isolates that had erythromycin level of $< 1\ \mu$g/ml and $> 1\ \mu$g/ml were recorded as sensitive and resistant respectively. The MICs were determined on the receipt of organism with the use of standard agar dilution MIC method in 1992–3 and the E-test method (Cambridge Diagnostics, Cambridge UK) since 1994.

Statistical analysis

Data analysis of pneumococcal isolates, serotypes/groups, specimen type, vaccine serotypes/groups and antimicrobial resistance were performed on the combined study dataset using SPSS version 8. 95% confidence intervals were calculated for the coverage of vaccines in different age groups during 1993–9.

RESULTS

A total of 17628 *Streptococcus pneumoniae* cases were recorded in the SCIEH and SMPRL databases over the study period. After removal of duplicate records, 10150 cases remained. Of these, only 5659 cases were from blood, CSF and other sterile site specimens and were included in the study. Of the 5659 invasive isolates, 5124 (90·5%) were blood isolates, 308 (5·5%) were CSF isolates, 143 (2·5%) were isolated from both blood and CSF, and 84 (1·5%) were other sterile site isolates (Table 1). A high proportion, 2499 (44·2%) were from elderly $\geqslant 65$ years old and only 661 (11·7%) were from children $\leqslant 5$ years old. 2601 (46%) were from females, 2886 (51%) from males and 172 (3%) sex unknown were included. The median and mean age of patients was 63 and 54 years old respectively. Information on serotypes/groups was available for 1531 isolates. Of these, only 105 (6·9%) isolates had their serotype/group reported during 1988–92. However, a high proportion, 1426 (93·1%) isolates had their serotype/group recorded in 1993–99 due to the establishment of SMPRL in 1992/3. The distribution among the 15 Health Boards in Scotland of isolates whose serotypes/groups were determined was as follows: Greater Glasgow, 428; Lothian, 400; Lanarkshire, 235; Grampian, 120; Ayrshire and Arran, 88; Argyll and Clyde, 60; Forth

Table 1. *Number of pneumococcal isolates from sterile sites*

	No. of isolates (%)				
Year	Total	Blood	CSF*	Blood +CSF	Others†
1988	296	248	23	23	2
1989	350	305	25	20	0
1990	343	300	28	14	1
1991	390	358	17	15	0
1992	441	403	27	10	1
1993	536	482	27	19	8
1994	622	560	38	14	10
1995	599	551	27	13	8
1996	617	563	34	7	13
1997	615	586	19	2	8
1998	646	590	32	5	19
1999‡	204	178	11	1	14
Total	5659 (100)	5124 (90·5)	308 (5·5)	143 (2·5)	84 (1·5)

* CSF, cerebrospinal fluid.
† Bone marrow, pleural aspirate, lung aspirate, pericardial fluid, bronchial aspirate.
‡ Data only available up to Aug. 1999.

Valley, 53; Tayside, 51; Highland, 44; Borders, 20; Fife, 13; Dumfries and Galloway, 12; Western Isles, 4; Orkney and Shetland, 0; and unknown area, 3.

Serotypes/groups distribution 1988/9

Most prevalent 11 serotypes/groups

The leading 11 serotypes/groups were identified among different age groups (Table 2). In all age groups, these serotypes/groups accounted for over 80% of all invasive pneumococcal isolates.

Overall, type 14 was the most prevalent serotype, accounting for about 10–32% of invasive isolates. Serotype 1 was the most prevalent in the age group 5–64 years accounting for 13% of invasive pneumococcal isolates.

Annual pattern of most prevalent serotypes/groups

The prevalence of individual serotypes/groups fluctuated from year to year of the period 1993–9 (Table 3). This shows an increase in serotype 14 and a decline in serotype 3 in recent years.

Prevalence of vaccine-related serotypes/groups

Coverage by 23-valent and 14-valent polysaccharide vaccines

The current 23-valent and previous 14-valent vaccines covered 96 and 88% of reported pneumococcal serotypes/groups isolated in all age groups in the study period. The reported coverage in individual age groups is shown in Table 4.

Coverage by 7, 9 and 11-valent conjugate pneumococcal vaccines

The 7-valent conjugate vaccine includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F [8]. Serotypes 1 and 5 are added in the 9-valent vaccine and 1, 3, 5, 7F in the 11-valent vaccine [10]. These 7, 9 and 11-valent conjugate vaccines covered 61, 68 and 80% of reported pneumococcal serotypes/groups isolated in all groups respectively. Coverage was substantially higher in the < 2 years than in older age groups (Table 4).

Coverage of invasive serotypes/groups with 23-valent polysaccharide and the 7-, 9- and 11-valent conjugate vaccines: annual fluctuation over the period 1993–9

The 23-valent polysaccharide vaccine covered $> 90\%$ of invasive isolates in all ages. However, the annual coverage of the 7, 9 and 11-valent conjugate vaccine showed substantial annual variation. Coverage was 59–97, 64–97 and 77–100% for 7, 9 and 11-valent conjugate vaccine in < 2 years age group, 42–69, 47–75 and 57–88% for 7, 9 and 11-valent conjugate vaccine in $\geqslant 65$ years age group and 53–73, 60–76 and 75–82% for 7, 9 and 11-valent conjugate vaccine for all ages (Table 5).

Table 2. *Most prevalent (11) pneumococcal serotypes/groups in different age groups*

Serotypes/ groups	No. of isolates (%)	Serotypes/ groups	No. of isolates (%)
< 2 years		⩾ 65 years	
14	69 (31·8)	14	83 (14·5)
6	38 (17·5)	19	61 (10·6)
19	22 (10·1)	3	56 (9·8)
23	22 (10·1)	9	53 (9·2)
9	14 (6·5)	23	47 (8·2)
18	10 (4·6)	4	41 (7·2)
7	8 (3·7)	6	41 (7·2)
4	7 (3·2)	1	35 (6·1)
3	6 (2·8)	8	26 (4·5)
1	5 (2·3)	22	19 (3·3)
8	2 (0·9)	7	18 (3·1)
Total*	203 (93·5)	Total*	480 (83·8)
Total†	217 (100)	Total†	573 (100)
⩽ 5 years		All ages	
14	72 (29·3)	14	254 (16·6)
6	40 (16·3)	9	144 (9·4)
23	24 (9·8)	19	140 (9·4)
19	23 (9·3)	6	133 (8·7)
18	18 (7·3)	23	126 (8·2)
9	16 (6·5)	1	114 (7·4)
7	10 (4·1)	3	104 (6·8)
1	9 (3·7)	4	94 (6·1)
4	8 (3·3)	7	70 (4·6)
3	6 (2·4)	8	64 (4·2)
8	2 (0·8)	18	40 (2·6)
Total*	228 (92·7)	Total*	1283 (83·8)
Total†	246 (100)	Total†	1531 (100)
5–64 years			
1	66 (13·2)		
9	55 (11·0)		
14	52 (10·4)		
7	36 (7·2)		
4	36 (7·2)		
23	31 (6·2)		
3	30 (6·0)		
8	29 (5·8)		
6	29 (5·8)		
19	28 (5·6)		
22	18 (3·6)		
Total*	410 (82)		
Total†	500 (100)		

* Total for top 11 serotypes/groups.
† Overall total.

Most prevalent serotypes/groups not included in the new 11-valent conjugate vaccine

Serotypes/group 8, 11, 12 and 22 were the most common nor-vaccine serotypes/groups, accounting for 178 (12%) of invasive isolates in all ages (Table 6). A higher proportion of them was recorded in those ⩾ 5 years of age.

Penicillin/erythromycin susceptibility

The distribution of serotypes/groups that were penicillin and erythromycin susceptible and non-susceptible is shown in Table 7. The prevalence of high level penicillin resistance is very low. Only two blood isolates were shown to have penicillin resistance. Both were serotype 14.

Table 3. *Most prevalent (11) serotypes/groups: annual variation (1993–9)*

Serotypes/ groups	No. of isolates							
	1993	1994	1995	1996	1997	1998	1999	Total
1	15	22	16	23	11	11	7	105
3	11	16	15	14	20	9	6	91
4	13	9	20	12	10	10	11	85
6	22	17	17	24	13	18	17	128
7	8	12	14	4	13	9	3	63
8	10	12	6	6	11	7	8	60
9	19	11	19	21	12	30	24	136
14	21	31	26	35	29	52	50	244
18	4	10	5	3	3	8	1	34
19	21	20	18	15	15	23	20	132
23	14	23	13	17	14	13	26	120
Others	30	46	32	32	30	27	31	228
Total*	158	183	169	174	151	190	173	1198
Total†	188	229	201	206	181	217	204	1426

* A total of top 11 serotypes/groups in each year.
† All total serotypes/groups in each year.

Table 4. *Vaccine coverage of pneumococcal serotypes/groups in different age groups*

Vaccines	No. of vaccine related isolates (%)				
	< 2 years	⩽ 5 years	5–64 years	⩾65 years	All ages
23-valent	NA†	244 (99·2)	475 (95)	550 (96)	1476 (96·4)
14-valent	NA	232 (94·3)	427 (85·4)	481 (83·9)	1354 (88·4)
11-valent*	201 (92·6)	226 (91·9)	379 (75·8)	440 (76·8)	1221 (79·8)
9-valent*	187 (86·2)	210 (85·4)	313 (62·6)	366 (63·9)	1047 (68·4)
7-valent*	182 (83·9)	201 (81·7)	247 (49·4)	331 (57·8)	931 (60·8)
Total	217 (100)	246 (100)	500 (100)	573 (100)	1531 (100)

* Pneumococcal conjugate vaccine.
† NA, not applicable.

Erythromycin resistant serotypes included types 4, 6, 9, 14, 19 and 23. Of these, serotype 14 accounted for 81/108 (75%) of isolates. The most prevalent serotypes associated with penicillin intermediate resistance were types 6, 9, 14, 19 and 23, accounting for 97/105 (92%) of isolates.

Vaccine coverage of antibiotic susceptible and non-susceptible invasive pneumococcal isolates

The 23- and 14-valent polysaccharide vaccine provided 97–100% and 86–98% coverage of all penicillin susceptible and non-susceptible isolates respectively. The conjugate pneumococcal vaccines covered 58–79% and 94–100% of susceptible and non-susceptible isolates (Table 8). A similar pattern was noted for erythromycin sensitive and resistant isolates (Table 8).

DISCUSSION

There are very few contemporary data on the distribution of invasive pneumococcal serotypes/groups in the UK. This study reports seroepidemiological characteristics of invasive pneumococcal isolates referred to reference laboratories in Scotland over the period 1988–99. The 7, 9 and 11-valent conjugate vaccines are now undergoing clinical trials in both developed and developing countries [8].

Earlier data on safety and immunogenicity of conjugate vaccines are encouraging among infants, and young children, [11–16] adults, [17, 18] and those

Table 5. *Yearly coverage of pneumococcal vaccines for* < 2 *years old,* $\leqslant 5$ *years old,* $\geqslant 65$ *years old and all ages 1993–9*

	< 2 years				⩽ 5 years				⩾ 65 years				All ages			
	No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)			
Year	23	11*	9*	7*	23	11*	9*	7*	23	11*	9*	7*	23	11*	9*	7*
1993	26 (100)	24 (92·3)	23 (88·5)	22 (84·6)	27 (100)	25 (92·6)	25 (92·6)	24 (88·9)	47 (90·4)	42 (80·8)	39 (75)	35 (67·3)	180 (95·7)	148 (78·7)	129 (68·6)	114 (60·0)
95 % CI	(87, 100)	(75, 99)	(70, 98)	(65, 96)	(87, 100)	(76, 99)	(76, 99)	(71, 98)	(79, 97)	(67, 90)	(61, 86)	(53, 80)	(92, 98)	(72, 84)	(61, 75)	(53, 68)
1994	35 (97·2)	34 (94·4)	32 (88·9)	29 (80·6)	42 (97·7)	41 (95·4)	38 (88·4)	33 (76·7)	73 (94·8)	44 (57·1)	36 (46·8)	32 (41·6)	220 (96·1)	171 (74·7)	143 (62·4)	121 (52·8)
95 % CI	(85, 100)	(81, 89)	(74, 97)	(64, 92)	(88, 100)	(84, 99)	(75, 96)	(61, 88)	(87, 99)	(45, 68)	(35, 58)	(30, 53)	(93, 96)	(69, 80)	(56, 69)	(46, 60)
1995	22 (100)	17 (77·3)	14 (63·6)	13 (59·1)	26 (100)	21 (80·8)	18 (69·2)	17 (65·4)	77 (96·3)	70 (87·5)	55 (68·7)	48 (60)	193 (96·0)	163 (81·1)	134 (66·7)	118 (58·7)
95 % CI	(85, 100)	(55, 92)	(41, 83)	(36, 79)	(87, 100)	(61, 93)	(48, 86)	(44, 83)	(89, 99)	(78, 94)	(57, 79)	(48, 71)	(92, 98)	(75, 86)	(60, 73)	(52, 66)
1996	29 (100)	29 (100)	28 (96·6)	28 (96·6)	33 (100)	31 (93·9)	30 (90·9)	30 (90·9)	80 (95·2)	68 (80·9)	58 (69)	48 (57·1)	199 (96·6)	168 (81·6)	150 (72·8)	127 (61·6)
95 % CI	(88, 100)	(88, 100)	(82, 100)	(82, 100)	(89, 100)	(80, 99)	(76, 98)	(76, 98)	(88, 99)	(71, 89)	(58, 79)	(46, 68)	(93, 99)	(76, 87)	(66, 79)	(55, 68)
1997	23 (100)	23 (100)	22 (95·7)	22 (95·7)	29 (100)	27 (93·1)	27 (93·1)	25 (86·2)	84 (98·8)	66 (77·7)	46 (54·1)	44 (51·8)	175 (96·7)	142 (78·5)	109 (60·2)	96 (53·0)
95 % CI	(85, 100)	(78, 100)	(78, 100)	(78, 100)	(88, 100)	(77, 99)	(77, 99)	(68, 96)	(94, 100)	(67, 86)	(43, 65)	(41, 63)	(93, 99)	(72, 84)	(53, 67)	(45, 60)
1998	38 (97·4)	36 (92·3)	35 (89·7)	35 (89·7)	41 (97·6)	39 (92·9)	38 (90·5)	38 (90·5)	74 (97·4)	62 (81·6)	55 (72·4)	51 (67·1)	209 (96·3)	179 (82·5)	165 (76·0)	154 (70·9)
95 % CI	(87, 100)	(79, 98)	(76, 97)	(76, 97)	(87, 100)	(81, 99)	(77, 97)	(77, 97)	(91, 100)	(71, 90)	(61, 82)	(55, 77)	(93, 98)	(77, 87)	(70, 82)	(65, 77)
1999	29 (100)	26 (89·7)	23 (79·3)	23 (79·3)	31 (100)	27 (87·1)	23 (74·2)	23 (74·2)	73 (97·3)	56 (74·7)	53 (70·7)	52 (69·3)	201 (98·5)	165 (80·9)	156 (76·5)	149 (73·0)
95 % CI	(88, 100)	(73, 98)	(60, 92)	(60, 92)	(89, 100)	(70, 96)	(55, 88)	(55, 88)	(91, 100)	(63, 84)	(59, 81)	(58, 79)	(96, 100)	(75, 86)	(70, 82)	(65, 79)

* Pneumococcal conjugate vaccines; CI, confidence interval.

with medical conditions which compromise immune function [19–24]. The result of the first large-scale clinical trial from Southern California showed that the 7-valent conjugate vaccines had 100 % efficacy in prevention of invasive pneumococcal infections in infants and children caused by the vaccine serotypes/groups [25]. This suggests that the 7-valent conjugate vaccine may soon be licensed for use in infants and children in developed countries. It has been proposed that pneumococcal conjugate vaccines may also have an important role in preventing pneumococcal disease in the elderly [26].

Therefore, an understanding of the serotype distribution of pneumococcal isolates will be crucial in developing appropriate immunization policy for different age groups in Scotland. This study reports on the coverage of serotypes/groups in the current polysaccharide and the new conjugate pneumococcal vaccines in Scotland.

Serotypes/groups distributions

We found that the most prevalent serotypes (14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18) accounted for over 82–94 % of total serotypes/groups in all age groups. Inclusion of these serotypes/groups in the new 11-valent conjugate vaccine will therefore cover > 80 % of invasive pneumococcal serotypes/groups in children, adults and the elderly. This is similar to previous findings from the US [27, 28], Europe [29–31], New Zealand [32] and Australia [33]. In contrast, data from Africa and Asia showed that serotypes 1 and 5 were the predominant invasive isolates [9, 34].

The major serotypes/groups in different age groups included serotypes/groups 14, 6, 19, 23 and 9 in < 2 years, 14, 6, 23, 19 and 18 in $\leqslant 5$ years, 1, 9, 14, 7 and 4 in 5–64 years old and 14, 19, 3, 9 and 23 in $\geqslant$ 65 years old. In common with some other studies, our data indicate that type 14 was the most common infectious serotype in all age groups [9, 35].

Among the age group 5–64 years, serotype 1 was the main cause of invasive disease, accounting for about 13 % of cases. Earlier reports from US have observed that serogroup 12 is the most frequent cause of bacteraemia in patients with pneumonia [36] and associated with outbreaks in both children [37] and adults [38]. In addition, surveillance data from the US and Europe indicate that a shift of serotypes distribution can occur over time [39]. Types 1–3 were the most prevalent isolates in bacteraemic cases at the beginning of the century, accounting for c. 70 % of

Table 6. *Common prevalent serotypes/groups in Scotland not included in the new 11-valent conjugate vaccine*

Serotypes/ groups	< 2 years	⩽ 5 years	5–64 years	⩾ 65 years	All ages
8	2	2	29	26	64
11	0	1	13	14	33
12	3	3	18	12	35
22	3	6	18	19	46
Total*	8 (3·7)	12 (4·9)	78 (15·6)	71 (12·4)	178 (11·6)
Total†	217 (100)	246 (100)	500 (100)	573 (100)	1531 (100)

* Total, percentages given in parentheses for nonvaccine serotypes in the 11-valent vaccine.
† Overall total, percentages given in parentheses.

invasive isolates [40, 41]. However, since 1979, these isolates have been very much less common (< 5%) [42], and serotypes 6, 14, 18 and 23 are more frequently isolated in the US [43] and Europe [30, 31, 44].

This suggests that continued surveillance systems are essential to monitor the stability of pneumococcal serotypes/groups distribution in Scotland. Review of serotype data from sterile site specimens from 16 countries showed that serotypes/groups 14, 6 and 19 were consistently found in all geographic locations [9]. However, the important invasive serotypes in children < 5 years of age varied, with serotype 18 most prevalent in developed countries, type 23 in Europe and serotypes 1 and 5 in developing countries. These differences in serotypes/groups distribution impose a challenge for designing a conjugate vaccine with appropriate serotypes distribution for all locations.

The 23- and 14-valent pneumococcal polysaccharide vaccines

The increase in antibiotic resistant pneumococcal [45] and the high burden of invasive pneumococcal disease among high-risk groups has been documented consistently [10]. Pneumococcal polysaccharide vaccines have been estimated by case-control and indirect cohort studies, to be 50–80% effective in reducing invasive pneumococcal disease in the elderly and in adults with chronic medical conditions [46]. We have found that the 23-valent and (previous) 14-valent polysaccharide vaccines covered 97% and > 83% respectively of invasive isolates. This is similar to published data from other parts of UK, Europe and North America; 91–97% in England and Wales, and Scotland [35, 47, 48], 89–97% in Sweden [49], > 85% in the US [5, 27], > 90% in Canada [50], 95% in Finland [31] and 92% in Denmark [30] for older children and adults.

Limited data are available on serotypes/groups distribution in Asia and Africa where mortality rates from pneumococcal disease are high. The available data from Asian countries show a large variation in the proportion of invasive pneumococcal isolates covered by the 23-valent vaccine: 75% in Bangladesh, 70·5% in Korea [51] and 62·9% in Taiwan [52].

Conjugate vaccines

Conjugate pneumococcal vaccines are undergoing phase I, II, and III clinical trials in the US, South Africa, Israel, Gambia, Finland and Philippines [8, 53]. Based on serological data, pneumococcal conjugate vaccines appear to produce a more immunogenic response in infants, the elderly, and immunocompromised individuals than pneumococcal polysaccharide vaccines [26]. In addition, findings from South Africa [54] Gambia [55] and Israel [56] reveal that conjugate vaccines reduce nasopharyngeal carriage of vaccine serotypes. Therefore, it may be possible to achieve herd immunity by widespread use of conjugate vaccines in the future. Data from the US suggest that the serotypes included in the current 7-valent conjugate vaccine could prevent 86% and 83% of pneumococcal bacteraemia and meningitis in children < 6 years old [43]. A previous survey in England and Wales [4, 48] noted that about 73% of isolates found in children ⩽ 2 years old were included in the 9-valent conjugate vaccines. We found a higher coverage of > 90% with the 11-valent conjugate vaccine and > 80% with the 7–9 valent conjugate vaccines for children < 2 years of age. The 11-valent vaccine also covers serogroups

Table 7. *Penicillin and erythromycin susceptible and non-susceptible invasive pneumococcal serotypes/groups*

Penicillin susceptibility						Erythromycin susceptibility					
		No. of isolates from sterile sites						No. of isolates from sterile sites			
MIC	Serotypes/ groups	CSF	Blood	Others	Total	MIC	Serotypes/ groups	CSF	Blood	Others	Total
	1	3	90	4	97		1	2	74	5	81
	2	—	6	—	6		2	—	6	—	6
	3	7	67	6	80		3	8	56	5	69
	4	7	69	3	79		4	6	53	3	62
	5	—	1	—	1		5	—	2	—	2
	6	17	66	3	86		6	13	63	4	80
	7	5	51	1	57		7	5	43	1	49
	8	8	45	1	54		8	7	38	1	46
S*	9	8	83	1	92	S	9	7	88	81	176
	10	—	9	1	10		10	—	8	—	8
	11	3	23	1	27		11	2	20	—	22
	12	5	24	—	29		12	4	21	—	25
	13	—	2	—	2		13	—	1	—	1
	14	25	151	9	185		14	5	83	8	96
	15	1	14	1	16		15	1	12	—	13
	16	1	5	—	6		16	1	4	—	5
	17	1	3	—	4		17	1	3	—	4
	18	10	23	—	33		18	7	18	—	25
	19	11	89	3	103		19	9	79	5	93
	20	—	15	—	15		20	—	14	—	14
	21	—	1	—	1		21	—	1	—	1
	22	5	28	—	33		22	5	22	—	27
	23	14	65	5	84		23	10	62	6	78
	24	2	3	—	5		24	1	3	—	4
	27	—	—	1	1		27	—	—	1	1
	29	—	4	—	4		29	—	4	—	4
	31	1	6	—	7		31	1	5	—	6
	38	1	9	—	10		38	1	6	—	7
	34	—	3	1	4		34	—	3	1	4
	35	—	3	—	3		35	—	2	—	2
	38	—	5	—	5		38	—	4	—	4
	41	—	1	—	1		41	—	1	—	1
	42	—	1	—	1		42	—	1	—	1
Total		135	965	41	1141			96	800	121	1017
	1	—	—	1	1		1	—	—	—	—
	3	1	1	1	3		3	—	—	—	—
	4	—	—	—	—		4	—	1	—	1
	5	—	1	—	1		5	—	—	—	—
	6	—	19	3	22		6	—	10	2	12
I*	8	—	1	—	1	R	8	—	—	—	—
	9	1	23	9	33		9	—	3	2	5
	14	—	18	2	20		14	16	63	2	81
	15	—	1	—	1		15	—	—	—	—
	19	—	8	2	10		19	1	4	—	5
	23	—	9	3	12		23	—	3	1	4
	29	—	1	—	1		29	—	—	—	—
Total		2	82	21	105			17	84	7	108
R*	14		2		2						
Total		—	2	—	2						

* S, sensitive isolates; I, intermediate isolates; R, resistant isolates.

Table 8. *Penicillin and erythromycin susceptible and non-susceptible pneumococcal serotypes/groups covered by the vaccines. No. (%) of vaccine-related isolates*

	Penicillin*				Erythromycin		
Vaccines	S	I	R	Total	S	R	Total
23	1100 (97·3)	104 (99·0)	2 (100)	1206 (96·6)	910 (96·3)	108 (100)	1018 (96·7)
14	985 (86·3)	103 (98·1)	2 (100)	1090 (87·3)	813 (86·0)	108 (100)	921 (87·5)
11†	897 (78·6)	102 (97·1)	2 (100)	1001 (80·2)	738 (78·1)	108 (100)	846 (80·3)
9†	760 (66·6)	99 (94·3)	2 (100)	861 (69)	620 (65·6)	108 (100)	728 (69·1)
7†	662 (58·0)	97 (97·4)	2 (100)	761 (61)	537 (56·8)	108 (100)	645 (61·3)

* S, sensitive isolates; I, intermediate isolates; R, resistant isolates (non-susceptible isolates = intermediate and resistant isolates).
† Pneumococcal conjugate vaccine.

3, 19 and 23 that were mainly responsible for otitis media in US, Canadian and European children [57].

Therefore, it is unlikely that pneumococcal conjugate vaccines for children need to include >11 serotypes. However, a substantially lower coverage was observed, (about 50–57% with 7-valent, 62–63% with 9-valent and 75–76% with 11-valent conjugate vaccines) in those above 5 years (including elderly $\geqslant 65$ years). In addition coverage in this age group fluctuated from year to year, over the period 1993–9.

Serotypes/groups 8, 11, 12 and 22 were the most common invasive isolates not present in the 11-valent vaccine, accounting for 15·6 and 12·4% of isolates in 5–64 years old and $\geqslant 65$ years old respectively. Including these serotypes/groups in the 11-valent could increase the vaccine coverage to >80% of invasive isolates in these age groups. However, a larger number of serotypes attached to a carrier protein could lead to poorer immunogenicity and possibly promote serious local reactions [58]. Further research is required on this issue. Furthermore, concerns about the replacement of vaccine serotypes by serotypes not in the vaccine have been expressed [55] and are now under investigation [54].

Drug susceptible pneumococcal isolates

Pneumococcal isolates that are resistant to penicillin and other antimicrobial drugs have been detected on all continents [59, 60]. Serogroups 6, 19 and 23 have been most associated with drug resistance [59, 61].

In the present study, serotypes/groups 6, 14, 19 and 23 were the most commonly associated with intermediate resistance and serotype 14 with penicillin and erythromycin resistant isolates. A previous survey from England and Wales identified similar serotypes/groups (23F, 6B, 19A, 19C, 19F and 23F) associated with intermediate or high penicillin resistance. Resistance to erythromycin was associated with serotypes/groups (3, 5, 9, 14, 19 and 22) in 1990 and with serotypes/groups (3, 6, 14, 15, 19 and 23) in 1995 [48]. Other UK studies also indicated that type 23, 9 and 6 were most commonly associated with penicillin resistance [62–64].

The commonest serotypes/groups associated with penicillin resistance in other countries included 9, 23 in Canada [50, 65], 6, 14, 19 and 23 in South Africa, Spain and Hungary [45] and 6B, 9V, 14, 19F and 23F in the US [66]. In general, these data suggest that the main serotypes patterns associated with lack of susceptibility to penicillin and erythromycin are similar in most geographical areas. However, recently, type 15 in Spain and type 10 [67] and 16 and 13 in Kenya [68, 69] have been found to be associated with penicillin resistance.

Our data show that the 23-valent vaccine covers $\geqslant 99$% of invasive isolates which were found to be non-susceptible to penicillin or resistant to erythromycin. The 11-valent conjugate vaccine covered >78%, and 7- and 9-valent covered >56% of non-susceptible and resistant invasive isolates for both drugs. Therefore, a greater use of 23-valent or the new 11-valent conjugate vaccine could possibly reduce the majority of penicillin non-susceptible and erythromycin resistant invasive pneumococcal isolates.

The data presented in this study should be helpful in predicting the potential impact of pneumococcal vaccines on invasive pneumococcal disease. There is a need for complementary data on isolates associated with important non-invasive pneumococcal disease such as otitis media in order to inform future policies on the prevention of pneumococcal disease in Scotland.

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr Claire Bramley, John Mooney, Lynn Young and Mary Locking for their advice and assistance for statistical analysis.

REFERENCES

1. George G. Epidemiology of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. Royal Society of Medicine International Congress and Symposium series, **210**. London: Royal Society of Medicine, 1995: 1–5.
2. Schuchat A, Robinson K, Wenger J, et al. Bacterial meningitis in the United States in 1995. NEJM 1997; **337**: 970–6.
3. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; **46**: 1–24.
4. Johnson AP, Speller DCE, George RC, et al. Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. BMJ 1996; **312**: 1454–6.
5. Robbins J, Austrian R, Lee CJ, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis 1983; **148**: 1136–59.
6. Breiman R, Butler J, Tenover FC, et al. Emergence of drug resistant pneumococcal infections in the United States. JAMA 1994; **271**: 1831–5.
7. Gray B, Dillion HJ. Clinical and epidemiologic studies of pneumococcal infection in children. Pediatr Infect Dis J 1986; **5**: 201–7.
8. Eskola J, Anttila M. Pneumococcal conjugate vaccines. Pediatr Infect Dis J 1999; **18**: 543–51.
9. Sniadack DH, Schwartz B, Lipman H, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children – implications for vaccine strategies. Pediatr Infect Dis J 1995; **14**: 503–10.
10. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: W.B. Saunder Company, 1999: 553–607.
11. Steinhoff M, Edwards K, Keyserling H, et al. A randomized comparison of three bivalent *Streptococcus pneumoniae* glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. Pediatr Infect Dis J 1994; **13**: 368–72.
12. Kayhty H, Ahman H, Ronnberg P-R, et al. Pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine is immunogenic in infants. J Infect Dis 1995; **172**: 1273–8.
13. O'Brien K, Steinhoff M, Edwards K, et al. Immunologic priming of young children by pneumococcal glycoprotein conjugate, but not polysaccharide, vaccines. Pediatr Infect Dis J 1996; **15**: 425–30.
14. Leach A, Ceesay SJ, Banya WAS, et al. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J 1996; **15**: 333–9.
15. Anderson E, Kennedy DJ, Geldmacher KM, et al. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatrics 1997; **128**: 649–53.
16. Ahman H, Kayhty H, Lehtonen H, et al. *Streptococcus pneumoniae* capsular polysaccharide-diphtheria toxoid conjugate vaccine is immunogenic in early infancy and able to induce immunologic memory. Pediatr Infect Dis J 1998; **17**: 211–6.
17. Fattom A, Lue C, Szu SC, et al. Serum antibody response in adult volunteers elicited by injection of *Streptococcus pneumoniae* type 12F polysaccharide alone or conjugated to diphtheria toxoid. Infect Immun 1990; **58**: 2309–12.
18. Schneerson R, Robbins JB, Parke JC, et al. Quantitative and qualitative analyses of serum antibodies elicited in adults by *Haemophilus influenzae* type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates. Infect Immun 1986; **52**: 519–28.
19. Chan C, Morline D, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. J Infect Dis 1996; **173**: 256–8.
20. King JJ, Vink P, Farley JJ, et al. Comparison of the safety and immunogenecity of a pneumococcal conjugate vaccine with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus infected children. Pediatr Infect Dis J 1996; **15**: 192–6.
21. King JJ, Vink P, Farley JJ, et al. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics 1997; **99**: 575–80.
22. King JC, Vink PE, Chang IH, et al. Antibody titers eight months after three doses of a five-valent pneumococcal conjugate vaccine in HIV and non-HIV-infected children less than two years of age. Vaccine 1998; **16**: 361–5.
23. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. J Pediatr 1998; **133**: 275–8.
24. Sarnaik S, Kaplan J, Schiffman G, et al. Studies on pneumococcus vaccine alone or mixed with DTP and a pneumococcus type 6B and *Haemophilus influenzae* type b capsular polysaccharide tetanus toxoid conjugates in two- to five-year-old children with sickle cell anaemia. Pediatr Infect Dis J 1990; **9**: 181–6.
25. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; **19**: 187–95.

26. Klein DL, Ellis RW. Conjugate vaccines against *Streptococcus pneumoniae*. In: Levine MM, Woodrow GC, Kaper JB, Cobon GS, eds. New generation vaccines, 2nd edn. New York: Marcel Dekker Inc, 1997: 503–25.
27. Butler J, Breiman R, Campbell J, Lipman H, Broome C, Facklam R. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 1993; **270**: 1826–31.
28. Zangwill K, Vadheim C, Vannier AM, et al. Epidemiology of invasive pneumococcal disease in Southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. J Infect Dis 1996; **174**: 752–9.
29. Fenoll A, Bourgon C, Munoz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. Rev Infect Dis 1991; **13**: 56–60.
30. Nielsen S, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989–1994. Epidemiol Infect 1996; **117**: 411–6.
31. Sankilampi U, Herva E, Haikala R, et al. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. Epidemiol Infect 1997; **118**: 7–15.
32. Mansoor O. Pneumococcal infections in New Zealand. Vaccine 1999; **17**: S122–3.
33. Hogg G, Strachan J. Pneumococcal infections in Victoria, Australia. Vaccine 1999; **17**: S119–21.
34. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. Clin Infect Dis 2000; **30**: 100–21.
35. Smith M, Stuart J, Andrews NJ, et al. Invasive pneumococcal infection in South and West England. Epidemiol Infect 1998; **120**: 117–23.
36. Austrian R. Some observation on the pneumococcus and on the current status of pneumococcal disease and its prevention. Rev Infect Dis 1981; **3**: S1–17.
37. Cherian T, Stenhoff M, Harrison L, Rohn D, Dougal L, Dick J. A cluster of invasive pneumococcal disease in children in child care. JAMA 1994; **271**: 695–8.
38. MMWR. Outbreak of invasive pneumococcal disease in a jail – Texas 1989. MMWR 1989 ; **38**: 733–4.
39. Kalin M. Pneumococcal serotypes and their clinical relevance. Thorax 1998; **53**: 159–62.
40. Finland M, Barnes M. Changes in occurrence of capsular serotypes of *Streptococcus pneumoniae* at Boston City hospital during selected years between 1935 and 1974. J Clin Microbiol 1977; **5**: 154–66.
41. Watson D, Musher D, Verhoef J. Pneumococcal virulence factors and host immune responses to them. Eur J Clin Microbiol Infect Dis 1995; **14**: 479–90.
42. Barry M, Craven D, Finland M. Serotypes of *Streptococcus pneumoniae* isolated from blood cultures at Boston City Hospital between 1979 and 1982. J Infect Dis 1984; **149**: 449–52.
43. Butler J, Breiman R, Lipman H, Hofmann J, Facklam R. Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. J Infect Dis 1995; **171**: 885–9.
44. Colman G, Cooke E, Cookson B, Cooper P, Efstratiou A, George R. Pneumococci causing invasive disease in Britain 1982–1990. J Med Microbiol 1998; **47**: 17–27.
45. Appelbaum P. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin Infect Dis 1992; **15**: 77–83.
46. Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. Vaccine 1999; **17**: S85–90.
47. Smart L, Dougall A, Girdwood R. New 23-valent pneumococcal vaccine in relation to pneumococcal serotypes in systemic and non-systemic. J Infect 1987; **14**: 209–15.
48. Johnson A, Speller D. Antibiotic resistance. Epidemiology of antibiotic resistance: blood and cerebrospinal fluid (CSF). J Med Microbiol 1997; **46**: 445–7.
49. Hedlund J, Stevenson S, Kalin M, et al. Incidence, capsular types, and antibiotic susceptibility of invasive *Streptococcus pneumoniae* in Sweden. Clin Infect Dis 1995; **21**: 948–53.
50. Lovgren M, Spika JS, Talbot JA. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992–1995. Can Med Assoc J 1998; **158**: 327–31.
51. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. Vaccine 1999; **17**: S75–8.
52. Lee C. Bacterial capsular polysaccharide – biochemistry, immunity and vaccine. Mol Immunol 1987; **24**: 1005.
53. Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. Phil Trans R Soc Lond B 1999; **354**: 777–85.
54. Mbelle N, Huebner RE, Wasas AD, et al. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; **180**: 1171–6.
55. Obaro S, Adegbola R, Banya W, Greenwood B. Carriage of pneumococci after pneumococcal vaccine. Lancet 1996; **348**: 271–2.
56. Dagan R, Melamed R, Muallem M, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996; **174**: 1271–8.
57. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000; **30**: 122–40.
58. Klein D. Pneumococcal conjugate vaccines: review and update. Microb Drug Resist 1995; **1**: 49–58.
59. Klugman K. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 1990; **3**: 171–96.
60. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. Clin Infect Dis 1997; **24** (Suppl): S85–8.
61. Klugman K, Koornhof H. Drug resistance patterns and

serogroups or serotypes of pneumococcal isolates from cerebrospinal fluid or blood, 1979–1986. J Infect Dis 1988; **158**: 956–64.
62. Ridgway E, Allen K, Galloway A, Rigby A, Donoghue O. Penicillin-resistance pneumococci in a Merseyside hospital. J Hosp Infect 1991; **17**: 15–23.
63. George R, Ball L, Cooper P. Antimicrobial-resistant pneumococci in the United Kingdom. CDR 1992; **2**: R37–43.
64. Boswell T, Frodsham D, Nye K, Smith E. Antibiotic resistance and serotypes of *Streptococcus pneumoniae* at Birmingham Public Health Laboratory, 1989–1994. J Infect 1996; **33**: 17–22.
65. Jette L, Ringuette L, Dascal A, Lapointe J. Pneumococcal resistance to antimicrobial agents in the province of Quebec, Canada. J Clin Microbiol 1994; **32**: 2572–5.
66. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. NEJM 1995; **333**: 481–6.
67. Coffey T, Berron S, Daniels M, et al. Multiply-antibiotic-resistant *Streptococcus pneumoniae* recovered from Spanish hospitals (1988–1994): novel major clones of serotypes 14, 19F and 15F. Microbiol 1996; **142**: 2747–57.
68. Paul J, Kimari J, Gilks C. Serotypes and antibiotics susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. J Infect Dis 1996; **32**: 139–42.
69. Scott J, Hall A, Hannington A, et al. Serotype distribution and prevalence of resistance to benzyl-penicillin in three representative populations of *Streptococcus pneumoniae* isolates from the coast of Kenya. J Infect Dis 1998; **27**: 1442–50.