Epidemiol. Infect. (2002), **128**, 139–147. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006586 Printed in the United Kingdom

Incidence of invasive pneumococcal disease in Scotland, 1988–99

M. H. KYAW[1,3]*, S. CLARKE[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 22 October 2001*)

SUMMARY

A review of the epidemiology of invasive pneumococcal disease in Scotland was carried out using data from laboratory-based systems during the period 1988–99. This comprised 5456 (90·8%) isolates of *Streptococcus pneumoniae* from blood, 467 (7·8%) from cerebrospinal fluid (CSF) and 84 (1·4%) from other sterile sites. The mean annual incidence of invasive disease was $9{\cdot}8/10^5$ population ($9{\cdot}0/10^5$ for bacteraemia and $0{\cdot}8/10^5$ for meningitis). Invasive disease was highest in children < 2 years of age and in the elderly $\geqslant 65$ years ($44{\cdot}9/10^5$ and $28{\cdot}4/10^5$ population in these age groups respectively). The highest incidence of pneumococcal meningitis, $11{\cdot}8/10^5$ persons occurred in children < 2 years of age. Males had a higher incidence of pneumococcal bacteraemia and meningitis than females (male:female = 1·2:1 for bacteraemia (RR = 1·17, 95% CI 1·11, 1·24) and 1·5:1 for meningitis (RR = 1·41, 95% CI 1·18, 1·70)). Pneumococcal disease was highest in winter periods and coincided with influenza activity. The proportion of penicillin and erythromycin non-susceptible isolates increased from 4·2% in 1992 to 12·6% in 1999 and from 5·6% in 1994 to 16·3% in 1999 respectively. Our data confirm the substantial and increasing disease burden from pneumococcal disease and rise in prevalence of antibiotic non-susceptibility among pneumococci in Scotland. Continued surveillance of groups at increased risk for pneumococcal disease and the antibiotic susceptibility and serotype distribution of isolates are important to develop appropriate policies for the prevention of pneumococcal disease in Scotland.

INTRODUCTION

Streptococcus pneumoniae is one of the leading causes of bacteraemia and meningitis in the United Kingdom. The incidence of invasive pneumococcal disease is greatest in young children, the elderly and persons with underlying medical conditions which place them at increased risk [1]. Despite the use of appropriate antimicrobial agents, case fatality rates of 12–38% have been documented in high-risk groups [2–4] and the emergence of antimicrobial resistant pneumococci has been noted globally [5]. Although it is not consistently documented [6], there is strong evidence that penicillin resistant invasive pneumococcal strains are associated with increased morbidity and mortality rates [2, 4]. These data clearly highlight the clinical impact and economic burden of pneumococcal disease and the need to prevent it by vaccination.

This paper reports on all invasive pneumococcal isolates referred to reference laboratories in Scotland during the period 1988–99 and examines the epidemio-

* Author for correspondence: Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow, G3 7LN.

logical characteristics of invasive pneumococcal disease. These data should inform future vaccination policy in Scotland.

Background and study data

Analyses were performed on a combined dataset from the Scottish Centre for Infection and Environmental Health (SCIEH) and Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). Detailed background information was given in a previous report [7] which documented the serotypes/groups distribution and coverage of polysaccharide and conjugate vaccines in different age groups. Information on antibiotic prescriptions for penicillin and erythromycin in Scotland between 1992 and 1999 was obtained from the Primary Care Unit, Information and Statistics Division of the NHS in Scotland. Pneumococcal isolates that had minimal inhibitory concentration (MIC) values to penicillin $< 0{\cdot}06\ \mu$g/ml, between 0·12 and 1·0 μg/ml and 2·0 μg/ml or higher were defined as susceptible, intermediate resistant and resistant respectively. The latter two categories were considered non-susceptible to penicillin. For erythromycin a single breakpoint concentration (1 μg/ml) was used to differentiate between susceptible and resistant isolates. MICs were determined by a standard agar dilution method (incorporating the antibiotic into agar) from 1992–3 and by the E-test (Cambridge Diagnostics, Cambridge UK) since 1994. A weekly review of laboratory reports is conducted by SCIEH to ensure the accuracy of records of pneumococcal disease. This showed in 1999 over 90% completeness for both reporting and organism submission for invasive pneumococcal disease. Between 1988 and 1999, the number of laboratories reporting pneumococcal infections to SCIEH and SMPRL increased from 29 to 33 and this increase occurred after 1994. The corresponding denominator population for reporting over this period rose from 5093000 to 5512000 [8]. The mid-point year (1993) population was used to calculate the age specific incidence rate.

Statistical analysis

Pearson correlation coefficients were used to determine associations between variables using SPSS version 8. Relative risk and corresponding 95% confidence intervals and the χ^2 test for trends were calculated using the CIA programme (Gardner SB, Winter PD, Gardner MJ: London, 1991).

RESULTS

A total of 17781 *S. pneumoniae* cases were identified in SCIEH and SMPRL databases. After removal of duplicate records, 10498 cases remained. Of these 6007 were invasive isolates; 5456 (90·8%) were from blood, 467 (7·8%) from CSF and 84 (1·4%) from other sterile sites.

Invasive pneumococcal isolates by age and sex

Of the 6007 invasive isolates, 2675 (44·5%), were from the elderly ($\geqslant$ 65 years of age) and 734 (12·2%) were from children $\leqslant$ 5 years of age, 2186 (36·4%) were from 6–64 age group and for 412 (6·9%) the age was unknown. The age range of patients was 0–99 years (median = 63, mean = 54). There were 2758 (45·9%) isolates from females and 3077 (51·2%) from males. Sex was not recorded in 172 (2·9%) records. Both the frequency and incidence of pneumococcal bacteraemia and meningitis were higher in males than females. The overall incidence in males and females was 9·4 and $8{\cdot}1/10^5$ population (male : female = 1·2 : 1) (RR = 1·17, 95% CI 1·11, 1·24) for bacteraemia and 0·9 and $0{\cdot}6/10^5$ population (male : female = 1·5 : 1) (RR = 1·41, 95% CI 1·18, 1·70) for meningitis.

Annual incidence

The mean annual incidence of invasive pneumococcal disease was $9{\cdot}8/10^5$ population from 1988 to 1999 and a gradual increase was observed over the study period. This was due to an increase in reported bacteraemia from 248 in 1988 to 510 in 1999. No increase in meningitis was noted. Bacteraemia increased in children $\leqslant$ 5 years of age (26 in 1988 to 66 in 1999), and the elderly (114 in 1988 to 245 in 1999). In the last 6 years, the incidence of invasive pneumococcal disease has been relatively stable (Fig. 1). The annual incidences of bacteraemia and meningitis were higher in males than females during the period 1988–99 (except for years 1993 and 1996 for meningitis and 1994 for bacteraemia).

Age specific incidence of disease

Figure 2 shows that the incidence of invasive disease was highest in infants under 2 years of age and the

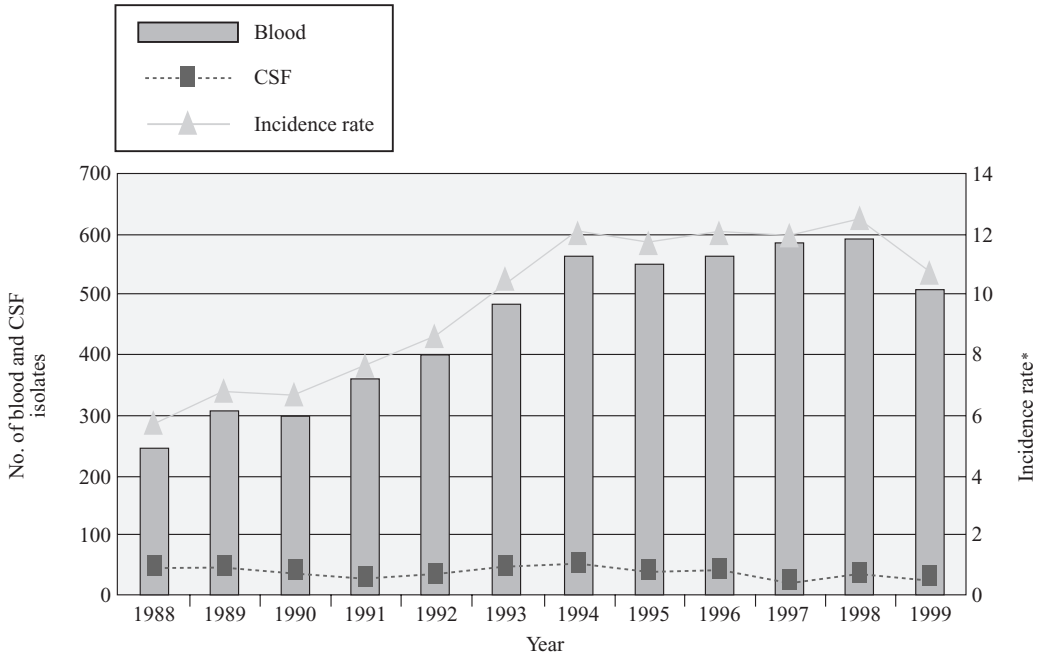

Fig. 1. Incidence of invasive pneumococcal disease (blood and CSF isolates), 1988–99. *Rate per 100000 population.

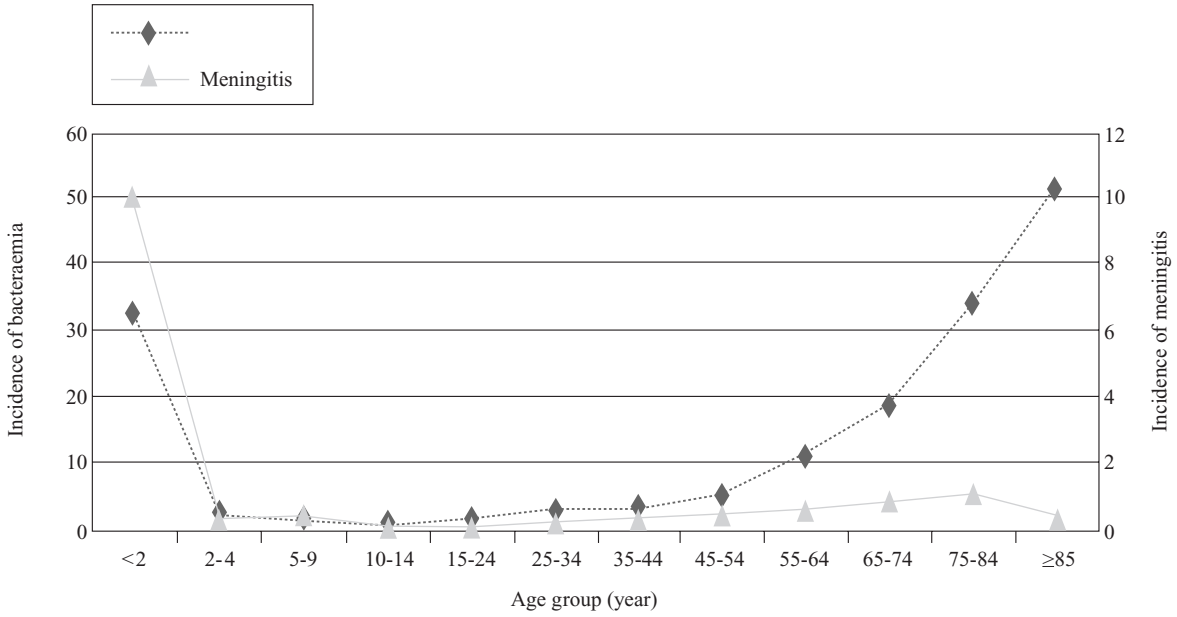

Fig. 2. Incidence of pneumococcal bacteraemia and meningitis per 100000 by age group, 1988–99.

elderly (44·9 and 28·4/10^5 population respectively). The rate for bacteraemia was 9/10^5 population in all ages but reached 33·1/10^5 population in the youngest patients and 27·5/10^5 population in the oldest. The rise in bacteraemia in the study period was particularly marked in infants (16·9 in 1988 to 47·4/10^5 population in 1998) and the elderly (14·5 in 1988 to 31·2/10^5 population in 1999).

The rate of meningitis was 0·8/10^5 population in all ages. The highest incidence (11·8/10^5 population) was in infants but this was significantly lower (0·4/10^5 population) in the 2–4 years age group. There was no increase in pneumococcal meningitis over the study period 1988–99 (Fig. 1).

Seasonal variation

A significant seasonal variation in pneumococcal disease was observed. Data aggregated in 3-month periods over the study period showed that the number

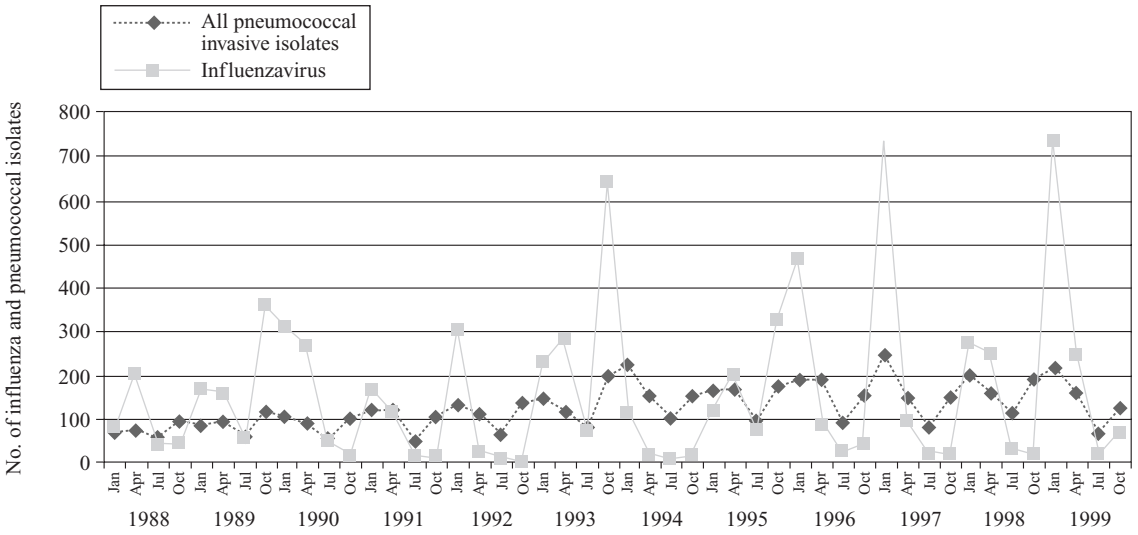

Fig. 3. Seasonal pattern of laboratory reports of influenza and invasive pneumococcal isolates by 3 months-block, Scotland, 1988–99.

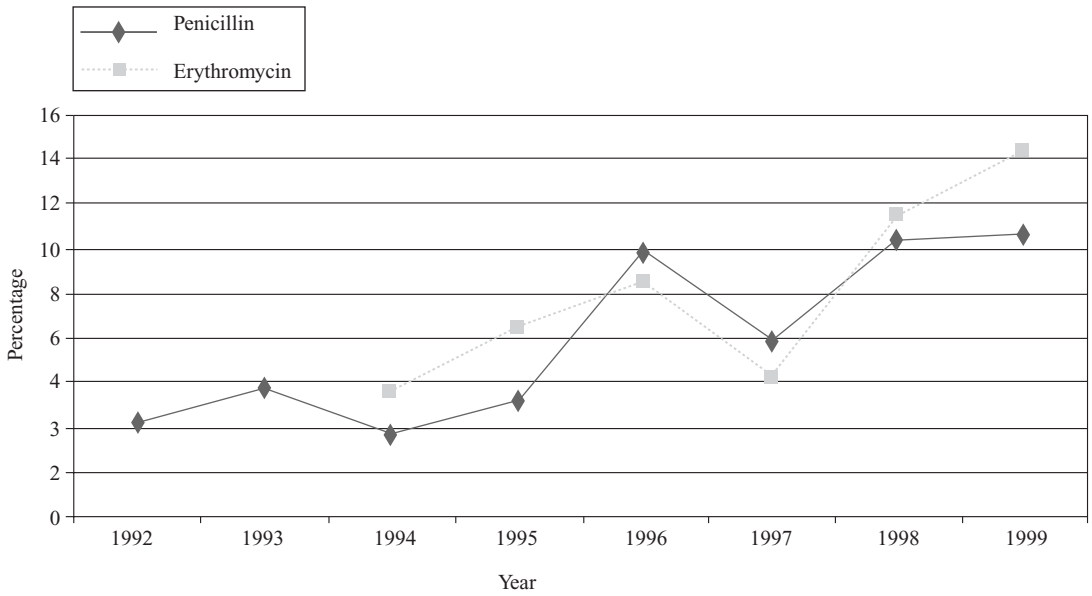

Fig. 4. Penicillin (1992–9) and erythromycin (1994–9) non-susceptible pneumococci in Scotland.

of cases peaked in the first 3 months of the year. This pattern was similar to that for influenza activity reported to SCIEH (Fig. 3).

Antimicrobial susceptibility

Of the 6007 invasive isolates, 1248 and 1053 were tested for penicillin and erythromycin MIC levels respectively and the great majority of them (87% and 95%) were fully susceptible to these antibiotics. Penicillin non-susceptible isolates increased from 1 (4·2%) in 1992 to 21 (12·6%) in 1999 (χ^2 for trend = 11·52, $P = 0{\cdot}0007$) (Fig. 4) and erythromycin resistant isolates from 7 (5·6%) in 1994 to 27 (16·3%) in 1999 ($P = 0{\cdot}0015$). Only 2 cases of penicillin-resistant pneumococci were reported (in 1998).

Antimicrobial susceptibility and antibiotic prescriptions

Scotland is divided geographically into 15 health board areas for administrative purposes. There was some geographical variation in penicillin and erythromycin non-susceptibility patterns of pneumococci (Table 1). A statistically significant correlation was recorded for penicillin prescription rate and the incidence of non-susceptible isolates in each health

Table 1. *Geographic variation in penicillin and erythromycin susceptibility and non-susceptibility of pneumococcal isolates and the patterns of penicillin and erythromycin prescriptions in Scotland.*

Area	Penicillin sensitivity (1992–9):* No. (%)				Rate (per year)		Erythromycin sensitivity (1994–9):‡ No. (%)			Rate (per year)	
	S	I	R	Total	Penicillin non-susceptible isolates†	Penicillin prescription ($\times 10^5$)	S	R	Total	Erythromycin non-susceptible isolates§	Erythromycin prescription ($\times 10^5$)
AC	41 (73·2)	15 (26·8)	0 (0)	56 (100)	0·4	24·6	50 (94·3)	3 (5·7)	53 (100)	0·1	5·9
AA	77 (91·7)	6 (7·1)	1 (1·2)	84 (100)	0·2	22·9	52 (89·7)	6 (10·3)	58 (100)	0·3	5·6
BR	12 (80)	2 (13·3)	1 (6·7)	15 (100)	0·4	21·2	6 (100)	0 (0)	6 (100)	0	5·6
DG	3 (30)	7 (70)	0 (0)	10 (100)	0·6	21·7	6 (75)	2 (25)	8 (100)	0·2	3·7
FF	7 (70)	3 (30)	0 (0)	10 (100)	0·1	23·5	8 (88·9)	1 (11·1)	9 (100)	0·1	6·1
FV	46 (93·9)	3 (6·1)	0 (0)	49 (100)	0·1	21·4	35 (89·7)	4 (10·3)	39 (100)	0·3	5·5
GR	10 (76·9)	3 (23·1)	0 (0)	13 (100)	0·1	22·1	5 (45·5)	6 (54·5)	11 (100)	0·2	6·4
GG	318 (87·1)	47 (12·9)	0 (0)	365 (100)	0·7	28	279 (91·5)	26 (8·5)	305 (100)	0·5	7·6
LN	221 (96·5)	8 (3·5)	0 (0)	229 (100)	0·2	27·6	178 (88·6)	23 (11·4)	201 (100)	0·7	7·3
LO	333 (97·7)	8 (2·3)	0 (0)	341 (100)	0·1	23·4	263 (90·4)	28 (9·6)	291 (100)	0·6	5·9
OR	0 (0)	0 (0)	0 (0)	0 (0)	0	20·7	0 (0)	0 (0)	0 (0)	0	5·4
SH	0 (0)	0 (0)	0 (0)	0 (0)	0	20·9	0 (0)	0 (0)	0 (0)	0	6·3
TY	25 (92·6)	2 (7·4)	0 (0)	27 (100)	0·1	23·8	21 (87·5)	3 (12·5)	24 (100)	0·1	5·7
WI	4 (100)	0 (0)	0 (0)	4 (100)	0	18·6	3 (75)	1 (25)	4 (100)	0·6	5·8
HG	42 (100)	0 (0)	0 (0)	42 (100)	0	21·4	37 (88·1)	5 (11·9)	42 (100)	0·4	5·6
Scotland	1139 (91·5)	104 (8·4)	2 (0·2)	1245 (100)	0·3	24·8	943 (89·7)	108 (10·3)	1051 (100)	0·4	6·3

S, sensitive; I, intermediate; R, resistance; *, 3 patients did not have area locations; †, resistant isolates, non-susceptible (intermediate and resistance); ‡, 2 patients did not have area locations; §, resistant isolates, non-susceptible, Rate = per 10^5 population per year.
AC, Argyll & Clyde; AA, Ayrshire & Arran; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HG, Highland; LN, Lanarkshire; LO, Lothian; OR, Orkney; SH, Shetland; TY, Tayside; WI, Western Isles.

board (Pearson correlation, $r = 0{\cdot}52$, $P = 0{\cdot}047$). No correlation was documented for erythromycin prescription rate and the incidence of erythromycin non-susceptible isolates ($r = 0{\cdot}39$, $P = 0{\cdot}157$).

DISCUSSION

Contemporary population based data on the age and sex specific incidence of pneumococcal bacteraemia and meningitis in the United Kingdom are scarce. This may in part reflect a poor understanding of the public health burden of invasive pneumococcal disease. This study reports on invasive pneumococcal disease throughout Scotland in the years 1988–99 and is based on a large database of high quality data on pneumococcal isolates reported to SCIEH and SMPRL. Because acceptance criteria for the diagnosis of pneumococcal infections differ widely we included only laboratory confirmed cases of *S. pneumoniae* recovered from blood, CSF and other sterile sites.

The reported incidence of invasive pneumococcal disease varies widely between countries. Nevetheless, it is universally recognized that the elderly and young children are most at risk of bacteraemia [9], and those under 2 years, of meningitis [10, 11]. A higher incidence of invasive disease has been reported in native populations in New Zealand [12], Alaska (US) [13], Apache (US) [14], Navajo (US) [15] and Aboriginal (Australia) [16] compared with other population groups in the respective countries. Similarly high rates have been found in young children in Gambia [17, 18], Israel [19] and Chile [20]. Our data show a greater incidence of invasive pneumococcal disease in males (51%) than females (46%). This is consistent with previous studies from the United Kingdom [3], United States [21], Europe [22, 23], and Australian Aboriginals [16].

We found a twofold increase in incidence of invasive disease in Scotland over the period 1988–99 which is similar to that reported in most studies from the United States and Sweden [24, 25] but is different from Finland in the last decade [22]. In contrast to the twofold annual increase in bacteraemia, there was no increase in pneumococcal meningitis during the study period. The increase in bacteraemia may be an artifact due to an increase in the number of blood cultures taken rather than in disease incidence [26, 27] and changing referral practices by diagnostic laboratories may also have had an influence. Furthermore increased clinical awareness and patterns of investigations may also have affected the earlier rise in incidence. However, the participation of an additional four diagnostic laboratories from 1994 onwards is unlikely to explain most of the observed increase in disease incidence since a clear increased trend was established prior to that year.

Our data may still represent an underestimate of invasive disease since most febrile patients are not routinely tested by blood culture. Blood cultures also lack sensitivity for confirmation of pneumococcal disease [28] as only 10–20% of blood cultures are reported positive [29]. Although lung aspirates are more sensitive than blood cultures, the technique is not suitable for routine use [30] and may cause adverse effects [31]. Recently, a PCR method to detect pneumococcal DNA in blood has been shown to improve the diagnosis of bacteraemia [32]. The lack of a reliable diagnostic method may therefore contribute to an underestimate of the burden of pneumococcal disease [30]. Moreover, prior to antibiotic treatment blood culture confounds the diagnosis as a study demonstrated that only 5% of blood cultures were positive in those who had prior antibiotics compared with 19% in those who did not receive them [33].

The prevalence of invasive disease was clearly related to season in the present study with the highest reported cases in January–March each year which coincided with the period of peak influenza activity. Previous studies in the United Kingdom [3, 34], United States [35] and Israel [19] have also shown that pneumococci are isolated more frequently during the winter period. This seasonal increase may be influenced by the coincident circulation of other respiratory viruses as winter is associated with increased respiratory virus activity which has been cited as a risk factor for developing pneumococcal disease [35, 36]. About 50–80% of pneumococcal pneumonia is thought to be associated with prior occurrence of some form of viral respiratory illness [36].

In the present study, the proportion of both penicillin and erythromycin non-susceptible isolates increased by threefold. A gradual increase in the prevalence of drug resistance in *S. pneumoniae* has been documented worldwide [37, 38]. From 1990 to 1998, the PHLS Communicable Disease Surveillance Centre in England and Wales noted an increase from < 1% to 3·6–7·4% for penicillin resistant isolates and of 5% to 11% for erythromycin resistant isolates [39]. In the United States, the level of drug resistant pneumococci increased from 14% in 1993/4 [40] to 25% in 1998 [41]. Increased awareness of invasive disease and improved detection of resistant isolates by

laboratories may also have contributed to this increase.

Penicillin resistance in isolates has serious implications for the management of invasive pneumococcal disease, particularly for meningitis. The clinical failure of third line generation antibiotics (cefotaxime/ceftriaxone or other cephalosporins) effective against penicillin-resistant strains has been documented [42, 43]. Experience in the United States demonstrates that outbreaks of pneumococcal meningitis with multidrug resistant strains (serotype 14) can occur [44] and, indeed, invasive pneumococcal disease with penicillin-resistant strains has been associated with increased mortality rates [4] and longer periods of hospitalization [2].

Seroepidemiology data in the United Kingdom shows that the current 23-valent polysaccharide pneumococcal vaccine includes the majority of serotypes/groups that show resistance to many antibiotics [7, 45]. Thus, the increased use of these vaccines may serve to prevent invasive disease due to antimicrobial resistant strains in high-risk individuals. Seven to 11-valent pneumococcal conjugate vaccines have been reported to reduce nasopharyngeal carriage, particularly associated with drug resistant serotypes, in vaccinated children [46]. Our previous report showed that 7 to 11-valent conjugate vaccines cover $> 94\%$ of penicillin and 100% of erythromycin non-susceptible pneumococcal isolates in Scotland [7]. Therefore, the widespread use of conjugate vaccines has the potential to reduce the transmission of drug-resistant pneumococci. A 7-valent conjugate pneumococcal vaccine has been licensed for use in children in the United States. The decision on use of this new vaccine in the UK is expected soon.

We found variation in antibiotic non-susceptibility in different geographic locations in Scotland. The reasons for this may be complex but mobility of the population probably contributed to these differences [41, 47, 48]. Others have shown that the frequency of antibiotic resistant invasive pneumococcal isolates varies within and between countries [37, 38] with reported rates within the United States of 7–25% to penicillin and 6–15% to erythromycin [2, 49–51]. It has been suggested that variation in antibiotic use influences the prevalence of resistant strains of pneumococci in different locations [52]. Other factors such as differences in populations and different study methods may also play a part. Antibiotic prescription data indicated geographical variation in prescription rates for penicillin and erythromycin and a significant correlation with frequencies of antibiotic resistant strains of pneumococci was recorded for penicillin only, not erythromycin.

In conclusion, our data confirm the substantial and increasing public health burden from pneumococcal disease and the concomitant rise in antibiotic non-susceptibility among pneumococci in Scotland. It is clear that this burden cannot be eliminated by the utilization of antibiotics alone. Polysaccharide or new conjugate pneumococcal vaccines in high-risk individuals remain the most effective preventive measure to reduce disease and control the spread of resistant isolates. Continued surveillance of the incidence of pneumococcal disease, serotypes/groups distribution and antibiotic susceptibility continue to be essential to inform policy and decision making to reduce the burden to the public health.

ACKNOWLEDGEMENTS

We thank the laboratory staff throughout Scotland for reporting cases of pneumococcal infections to the Scottish Centre for Infection and Environmental Health and Scottish Meningococcus and Pneumococcus Reference Laboratory. We are also grateful to Dr Eileen Holmes for statistical advice.

REFERENCES

1. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997: **46**: 1–24.
2. Plouffe JF, Breiman RF, Facklam RR, et al. Bacteremia with *Streptococcus pneumoniae*: implications for therapy and prevention. JAMA 1996; **275**: 194–8.
3. Laurichesse H, Grimaud O, Waight P, Johnson A, George R, Miller E. Pneumococcal bacteraemia and meningitis in England and Wales, 1993 to 1995. Commun Dis Pub Hlth 1998; **1**: 22–7.
4. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance 1995–1997. Am J Pub Hlth 2000; **90**: 223–9.
5. Schreiber J, Jacobs M. Antibiotic-resistant pneumococci. Ped Clin N Am 1995; **42**: 519–37.
6. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteraemic pneumococcal pneumonia in the era of antibiotic resistance. Clin Infect Dis 2001; **33**: 797–805.
7. Kyaw MH, Clarke S, Edwards G, Jones IG, Campbell H. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implication for vaccine strategies. Epidemiol Infect 2000; **125**: 561–72.

8. Office for National Statistics. Monthly digest of statistics. No. 649. 2000 January. London: The Stationary Office, 2000.
9. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: W. B. Saunders Co, 1999: 553–607.
10. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. N Engl J Med 1997; **337**: 970–6.
11. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001; **183**: 239–46.
12. Voss L, Lennon D, Okesene-Gafa K, Ameratunga S, Martin D. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. Pediatr Infect Dis J 1994; **13**: 873–8.
13. Davidson M, Parkinson A, Bulkow L, Fitzgerald M, Peters H, Parks D. The epidemiology of invasive pneumococcal disease in Alaska 1986–1990: ethnic differences and opportunities for prevention. J Infect Dis 1994; **170**: 368–76.
14. Cortese M, Wolff M, Almeido-Hill J, et al. High incidence rate of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med 1992; **152**: 1–6.
15. Overturf GD. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotics prophylaxis. Pediatrics 2000; **106**: 367–76.
16. Torzillo PJ, Hanna JN, Morey F, Gratten M, Dixon J, Erlich J. Invasive pneumococcal disease in central Australia. Med J Aust 1995; **162**: 182–6.
17. O'Dempsey TJ, Mcardle TF, Lloyd-Evans N, et al. Pneumococcal disease among children in a rural area of West Africa. Pediatr Infect Dis J 1996; **15**: 431–7.
18. Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive pneumococcal disease in the Western region, The Gambia. Pediatr Infect Dis J 1998; **17**: 23–8.
19. Dagan R, Englehard D, Piccard E, et al. Epidemiology of invasive childhood pneumococcal infections in Israel. JAMA 1992; **268**: 3328–32.
20. Levine MM, Lagos R, Levine OS, et al. Epidemiology of invasive pneumococcal infections in infants and young children in Metropolitan Santiago, Chile, a newly industrializing country. Pediatr Infect Dis J 1998; **17**: 287–93.
21. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000; **132**: 182–90.
22. Sankilampi U, Herva E, Haikala R, Liimatainen O, Renkonen O-V, Leinonen M. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. Epidemiol Infect 1997; **118**: 7–15.
23. Burman L, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors and prognosis. Rev Infect Dis 1985; **7**: 133–42.
24. Ortqvist A. Pneumococcal disease in Sweden: experiences and current situation. Am J Med 1999; **107** Suppl 1A: S44–S49.
25. Mufson MA, Stanek RJ. Bacteraemic pneumococcal pneumonia in one American city: a 20-year longitudinal study 1978–1997. Am J Med 1999; **107** Suppl 1A: S34–S43.
26. Breiman R, Spika J, Navarro V, Darden PM, Darby CP. Pneumococcal bacteremia in Charleston County, South Carolina a decade later. Arch Intern Med 1990; **150**: 1401–5.
27. 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.
28. Korppi M, Koskela M, Jalonen E, Leinonen M. Serologically indicated pneumococcal respiratory infection in children. Scand J Infect Dis 1992; **24**: 437–43.
29. Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. Phil Trans R Soc Lond B 1999; **354**: 777–85.
30. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis J 1986; **5**: 247–52.
31. Adegbola R, Falade A, Sam B, et al. The aetiology of pneumonia in malnourished and well-nourished Gambian children. Pediatr Infect Dis J 1994; **13**: 975–82.
32. Porath A, Schlaeffer F, Lieberman D. The epidemiology of community-acquired pneumonia among hospitalised adults. J Infect 1997; **34**: 41–8.
33. Lim I, Shaw D, Stanley D, et al. A prospective hospital study of the etiology of community-acquired pneumonia. Med J Aust 1989; **151**: 87–91.
34. Smith M, Stuart J, Andrews N, et al. Invasive pneumococcal infection in South and West England. Epidemiol Infect 1998; **120**: 117–23.
35. Kim PE, Musher DM, Glezen WP, Rodriguez-Barradas M, Nahm W, Wright C. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution and the isolation of respiratory viruses. Clinic Infect Dis 1996; **22**: 100–6.
36. Heffron R Pneumonia with special reference to pneumococcal lobar pneumonia. Cambridge, MA: Harvard University Press, 1979.
37. Forward KR. The epidemiology of penicillin resistance in *Streptococcus pneumoniae*. Semin Resp Infect 1999; **14**: 243–54.
38. Collignon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae*. Med J Aust 2000; **173** Suppl: S58–S64.
39. Reacher MH, Shah A, Livermore DM, et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. BMJ 2000; **320**: 213–6.
40. Butler J, Hofmann J, Cetron M, Elliott J, Facklam R, Breiman R. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centres for Disease Control and

Prevention's Pneumococcal Sentinel System. J Infect Dis 1996; **174**: 986–93.
41. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med 2000; **343**: 1917–24.
42. Bardley J, Connor J. Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to beta-lactam antibiotics. Pediatr Infect Dis J 1991; **10**: 871–3.
43. Sloas M, Barrett F, Chesney P, et al. Cephalosporin treatment failure in penicillin-and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. Pediatr Infect Dis J 1992; **11**: 662–6.
44. Craig AS, Erwin PC, Schaaffner W, et al. Carriage of multi-resistant *Streptococcus pneumoniae* and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. Clin Infect Dis 1999; **29**: 1257–64.
45. 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.
46. Dagan R, Fraser D. Conjugate pneumococcal vaccine and antibiotic resistant *Streptococcus pneumoniae* and reduction of otitis morbidity. Pediatr Infect Dis J 2000; **19** Suppl: S79–S88.
47. Soares S, Kristinsson K, Musser J, Tomasz A. Evidence for the introduction of a multi-resistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. J Infect Dis 1993; **168**: 158–63.
48. Doern GV, Brueggemann AB, Huynh H, Wingert E, Rhomberg P. Antimicrobial resistance with *Streptococcus pneumoniae* in the United States 1997–98. Emerg Infect Dis 1999; **5**: 757–65.
49. Breiman R, Butler J, Tenover F, et al. Emergence of drug resistant pneumococcal infections in the United States. JAMA 1994; **271**: 1831–5.
50. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; **333**: 481–6.
51. Metlay JP, Hofmann J, Cetron MS, et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2000; **30**: 520–528.
52. Arason V, Kristinsson K, Sigurdsson J, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? BMJ 1996; **17**: 387–91.