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Prevalence of moderate penicillin resistant invasive *Neisseria meningitidis* infection in Scotland, 1994–9

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SUMMARY

We examined the serological characteristics of 774 invasive meningococcal isolates collected through an active laboratory-based surveillance system in Scotland from 1994 to 1999. Of these, 72–73% of isolates were tested for susceptibility to several antimicrobial agents. Meningococci with high-level resistance to sulphadiazine had a prevalence of 10% and incidence of 0·22 per 100000 population. High-level resistance to penicillin and other antibiotics was not detected. The prevalence of moderate penicillin resistant meningococci was 8·3%. There was no increase in moderate penicillin resistant meningococcal isolates during the study period, but there were temporal and geographic variations. The estimated incidence of moderate penicillin resistant meningococci was 0·15 per 100000 population. High and low incidence of moderate penicillin resistant meningococci appeared to correlate with the number of doses of penicillin prescribed in some geographic locations. The majority of moderate penicillin resistant isolates belonged to serogroups B (52·2%) and C (39·2%). However, the prevalence of moderate penicillin resistance in serogroup W135 was substantially higher (51·7%) than serogroups B (7·8%) and C (7·6%). Serogroup W135 accounted for a higher proportion of moderate penicillin resistance (8·7%) than disease (1%). There was no predominant penicillin resistant serotype/subtype within any serogroup. Constant surveillance is necessary to monitor the emergence and spread of resistance and to guide appropriate public health interventions in preventing drug resistant meningococci.

INTRODUCTION

Neisseria meningitidis is an important cause of bacterial meningitis and septicaemia in the United Kingdom and worldwide [1, 2]. Despite the availability of effective antimicrobial agents, 10–20% case-fatality and 20% neurological sequelae ratios have been documented [3, 4]. Invasive meningococcal isolates that are resistant to penicillin have been detected in the United Kingdom, Europe and North America [5]. Surveys in the United Kingdom have shown that the prevalence of moderately resistant penicillin meningococcal isolates is increasing: 1–3% in 1986/7, 8% in 1991 [6, 7] and 11% in 1995 [8]. A substantial increase has also been detected in Spain: from 0·4% in 1985 to 46% in 1990 [9], and to 67% in 1996 [10]. In addition, meningococcal strains with high-level resistance to penicillin, through β-lactamase production, have been reported [11–13]. At present, high-level resistant isolates are extremely rare in the United Kingdom and elsewhere.

The failure of standard treatment in a patient with meningococcal disease caused by a penicillin resistant

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strain (minimal inhibitory concentration (MIC) of 0·64 μg/ml) has been reported [14]. Since penicillin is the drug of first choice for the treatment of meningococcal disease, the emergence and spread of penicillin resistant meningococcal strains in the United Kingdom and other countries represents a major challenge. Little is known about the distribution of meningococcal serogroup, type and subtype in relation to penicillin resistance. Here, we examine the prevalence and seroepidemiology of penicillin resistant invasive meningococcal isolates reported to the active population-based surveillance system in Scotland during the period 1994–9.

METHODS

There has been an active population-based surveillance system for meningococcal disease in Scotland since the 1970s. However, the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL) was established in 1993 as the national service for the laboratory confirmation of meningococcal and pneumococcal disease and to monitor the epidemiological characteristics of these diseases, providing serotyping and antimicrobial susceptibility testing. We report on invasive meningococcal isolates submitted to the SMPRL from all diagnostic laboratories in Scotland for serological characterisation and antimicrobial susceptibility testing. Isolates from blood, cerebrospinal fluid (CSF), joint fluid and other sterile sites were regarded as invasive isolates.

Meningococcal isolates with a MIC level of $\leqslant 0{\cdot}06$ μg/ml, 0·1–1 μg/ml, and $\geqslant 2$ μg/ml were regarded as susceptible, moderately and highly resistant to penicillin respectively. Meningococci were considered susceptible, moderately and highly resistant to sulphadiazine when their MICs were $\leqslant 16$ μg/ml, 32–64 μg/ml and $\geqslant 128$ μg/ml respectively. Isolates with MICs of $\leqslant 1$ μg/ml and $\geqslant 2$ μg/ml were indicated as susceptible and resistant to ciprofloxacin, cefotaxime, ceftriaxone and rifampicin respectively. During the study period, the E-test (Cambridge Diagnostics, Cambridge, UK) was used to determine the antimicrobial susceptibility level. The E-test has been proven to be a reliable method for evaluating the antimicrobial susceptibility levels of meningococci [15].

For the purpose of health service administration, Scotland (population 5·1 million) is divided into 15 health boards. The prevalence of antimicrobial resistant meningococci per 100000 population was calculated based on the estimated population of Scotland for the mid point year, 1997 [16]. Information on the number of doses of penicillin prescribed in the whole of Scotland between 1994 and 1999 was obtained from the Information and Statistics Division (ISD) of Common Services Agency, Edinburgh, Scotland. These data were used to calculate the number of penicillin doses prescribed per 100000 population and the number of penicillin resistant isolates in different geographical locations.

Statistical analysis

Data analyses were performed using SPSS version 10 and Stata (Stata Corporation, version 6.0, 1999, College Station, Texas). In comparisons between variables a P-value of $< 0{\cdot}05$ was regarded as statistically significant.

RESULTS

A total of 774 invasive meningococcal isolates were received by SMPRL during the period 1994–9. Of these, antimicrobial susceptibility testing was performed for: 568 (73·4%) isolates for penicillin and sulphadiazine, 567 (73·3%) isolates for rifampicin, 563 (72·7%) isolates for ciprofloxacin and ceftriaxone, and 561 (72·5%) isolates for cefotaxine (Table 1). Of the 774 invasive isolates, serogroup B caused 400 (51·7%) cases of invasive disease, followed by group C with 303 (39·1%) cases, non-typeable group (NG) with 46 (5·9%) cases, W135 with 7 (1%) cases and other serogroups with 18 (2·3%) cases in 1994–9.

Antimicrobial resistant meningococci

The prevalence of antimicrobial resistance in invasive meningococcal infections in Scotland is shown in Table 1. The only drug to which any isolate was highly resistant was sulphadiazine (57 isolates, 10%). Forty-seven isolates (8·3%), 44 isolates (7·7%) and 1 isolate (0·2%) were moderately resistant to penicillin, sulphadiazine or ciprofloxacin respectively.

The estimated incidence of moderately resistant meningococci per 100000 population was 0·15. The rate of sulphadiazine resistance was 0·14 per 100000 population for moderately resistant isolates and 0·22 for highly resistant isolates.

Moderate resistance to penicillin by meningococcal serogroup

All isolates classed as moderately resistant to penicillin belonged to meningococcal serogroups B, C and

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Table 1. *Prevalence of antimicrobial resistant invasive* N. meningitidis *infection in Scotland, 1994–9*

	No. (%) of isolates				Rate per 100000 population		
	Susceptible	Intermediate	Resistant	Total	Intermediate	Resistant	Total
Penicillin*	521 (91·9)	46 (8·1)	0 (0)	567 (100)	0·15	0	0·15
Sulphadiazine†	467 (82·3)	44 (7·7)	57 (10)	568 (100)	0·14	0·22	0·37
Ciprofloxacin‡	562 (99·8)	0 (0)	0 (0)	563†† (100)	0·003	0	0·003
Cefotaxime§	561 (100)	0 (0)	0 (0)	561 (100)	0	0	0
Ceftriaxone¶	563 (100)	0 (0)	0 (0)	563 (100)	0	0	0
Rifampicin**	567 (100)	0 (0)	0 (0)	567 (100)	0	0	0

* MICs: susceptible $\leqslant$ 0·06 μg/ml; intermediate resistant, 0·1–1·0 μg/ml; resistant $\geqslant$ 2 μg/ml.
† MICs: susceptible $\leqslant$ 0·16 μg/ml; intermediate resistant, 32–64 μg/ml; resistant $\geqslant$ 128 μg/ml.
‡ MICs: susceptible $\leqslant$ 1 μg/ml; resistant $\geqslant$ 2 μg/ml.
§ MICs: susceptible $\leqslant$ 1 μg/ml; resistant $\geqslant$ 2 μg/ml.
¶ MICs: susceptible $\leqslant$ 1 μg/ml; resistant $\geqslant$ 2 μg/ml.
** MICs: susceptible $\leqslant$ 1 μg/ml; resistant $\geqslant$ 2 μg/ml.
†† included one isolate with MIC = 1·5 μg/ml.

Table 2. *Prevalence of disease and moderate penicillin resistance in invasive* N. meningitidis *isolates by serogroups, 1994–9*

Year	B	C	W135	Others	Total
1994					
No. total tested	62	27	0	1	90
No. resistant	1	0	0	0	1
Resistant %	1·6	—	—	—	1·1
1995					
No. total tested	36	19	1	1	57
No. resistant	11	4	0	0	15
Resistant %	17·5	21·1	—	—	26·3
1996					
No. total tested	59	38	0	3	100
No. resistant	2	5	0	0	7
Resistant %	3·4	13·2	—	—	7
1997					
No. total tested	46	40	2	3	91
No. resistant	2	3	1	0	6
Resistant %	4·3	7·5	50	—	6·6
1998					
No. total tested	42	60	2	6	110
No. resistant	3	4	2	0	9
Resistant %	7·1	6·7	100	—	8·2
1999					
No. total tested	60	53	2	5	120
No. resistant	5	2	1	0	8
Resistant %	8·3	3·8	50	—	6·7
1994–9					
No. total tested	305	237	7	19	568
No. resistant	24	18	4	0	46
Resistant %	7·8	7·6	57·1	—	8·1

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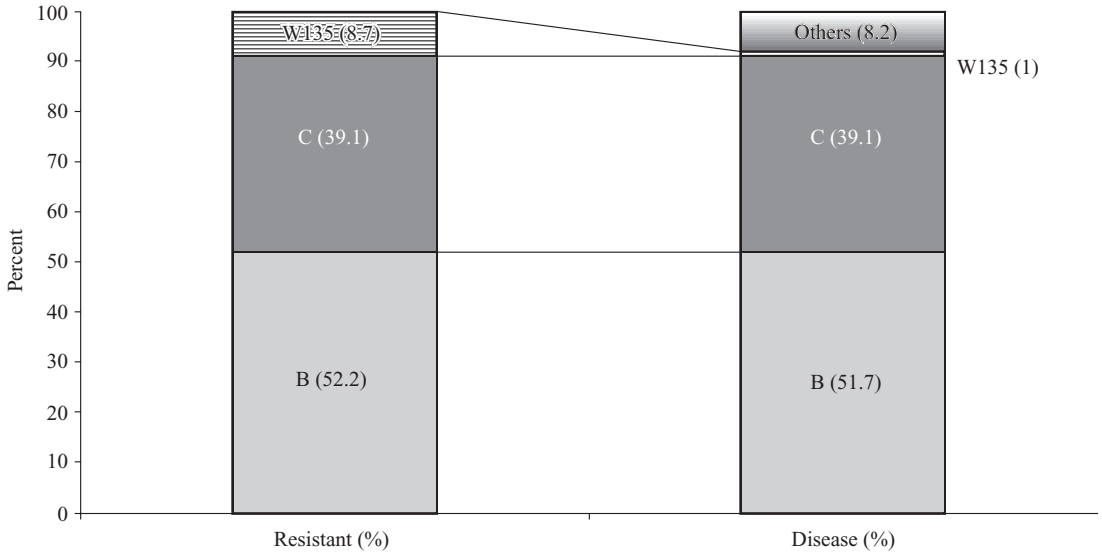

Fig. 1. Distribution of meningococcal serogroups in invasive disease and penicillin resistance, 1994–9.

Table 3. *Temporal and geographic distribution of relatively penicillin resistant invasive* N. meningitidis *isolates and pattern of penicillin prescribing in Scotland, 1994–9*

Laboratory	No (%) of penicillin resistant invasive isolates								No. doses penicillin prescribed	
Location*	1994	1995	1996	1997	1998	1999	Total 1994–9	Incidence rate†, 1994–9	No. of doses prescribed	Rate per 10^5 population
AC	–	2	1	1	2	1	7	0·27	62,770,675	$2·4 \times 10^5$
AA	–	1	2	–	–	1	4	0·18	50,728,780	$2·2 \times 10^5$
BR	–	–	–	–	–	–	–	–	13,329,784	$2·1 \times 10^5$
DG	–	–	–	–	–	1	1	0·11	19,005,257	$2·1 \times 10^5$
FF	–	–	–	–	1	–	1	0·05	49,252,019	$2·3 \times 10^5$
FV	–	1	–	–	1	1	3	0·18	35,266,571	$2·1 \times 10^5$
GR	–	1	–	1	–	–	2	0·06	69,884,948	$2·2 \times 10^5$
GG	1	2	3	1	–	2	9	0·17	151,186,546	$2·8 \times 10^5$
LN	–	3	1	2	3	1	10	0·30	93,133,697	$2·8 \times 10^5$
LO	–	1	–	1	–	1	3	0·06	106,646,135	$2·3 \times 10^5$
OR	–	–	–	–	–	–	–	–	2,277,914	$1·9 \times 10^5$
SH	–	–	–	–	1	–	1	0·72	2,766,403	$2·0 \times 10^5$
TY	–	2	–	–	–	–	2	0·08	55,193,772	$2·3 \times 10^5$
WI	–	–	–	–	–	–	–	–	3,148,540	$1·8 \times 10^5$
HI	–	2	–	–	1	–	3	0·24	26,958,029	$2·1 \times 10^5$
Scotland	1 (2·2)	15 (32·6)	7 (15·2)	6 (13·0)	9 (19·6)	8 (17·4)	46 (100)	0·15	741,549,070	$2·4 \times 10^5$

* AC, Argyll & Clyde; AA, Ayrshire & Arran; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HI, Highland; LN, Lanarkshire; LO, Lothian; OR, Orkney; SH, Shetland; TY, Tayside; WI, Western Isley.

† Incidence rate per 100000 population.

W135 (Table 2). During 1994–9, as a whole, serogroup B was the predominant cause of invasive disease (51·7%) and of moderate resistance to penicillin (52·2%) (Fig. 1). This was followed by serogroup C, which accounted for 39·1% of invasive disease and of isolates with moderate resistance to penicillin. The proportion of isolates moderately resistant to penicillin and belonging to serogroup W135 (8·7%) was marked higher than the proportion of invasive disease due to serogroup W135 (1%) (Fig. 1). Indeed, the prevalence of moderate penicillin resistance in serogroup W135 was substantially higher (51·7%) than in serogroups B (7·8%) ($p = 0·0001$) and C (7·6%) ($P = 0·0001$) (Table 2). Although an increasing trend for

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Table 4. *Distribution of moderately penicillin resistant invasive meningococcal isolates by serogroup, type and subtype*

Serogroup B				Serogroup C				Serogroup W135			
Type/Subtype	Total no.	(rate*)	No. resistant	(rate*)	Type/subtype	Total no.	(rate*)	No. resistant	(rate*)	Type/subtype	Total no.	(rate*)	No. resistant	(rate*)
4:P1.4	44	(0·14)	5	(0·02)	2a:P1.2	27	(0·09)	4	(0·01)	NT:P1.3, 6	1	—	1	—
NT:P1.9	20	(0·07)	4	(0·01)	2a:P1.5	75	(0·24)	3	(0·01)	NT:P1.3, P1.6	1	—	1	—
NT:P1.16	9	(0·03)	3	(0·01)	2b:P1.16	7	(0·02)	3	(0·01)	NT:P1.6, P1.3	2	—	2	—
4:P1.15	9	(0·03)	2	—	2a:P1.2, 1·5	1	—	1	—					
1:P1.9	1	—	1	—	2a:P1.2, 5	15	(0·05)	1	—					
1:P1.14	13	(0·04)	1	—	2a:P1.10	2	—	1	—					
1:P1.16	1	—	1	—	2a:P1.2, P1.5	10	(0·03)	1	—					
15:P1.16	2	—	1	—	2b:P1.2	1	—	1	—					
15:P1.7, 16	13	(0·04)	1	—	2b:P1.2, 5	8	(0·03)	1	—					
21:P1.3, 1.6	1	—	1	—	NT:P1.12	1	—	1	—					
2b:NT	5	(0·02)	1	—	NT:NT	12	(0·04)	1	—					
NT:P1.4	10	(0·03)	1	—										
NT:NT	55	(0·18)	1	—										
NT:P1.15	11	(0·04)	1	—										

* Incidence per 100 000 population.

moderate penicillin resistance caused by serogroup B was not consistent during the period 1994–9, a clear increase was noted from 3·4% in 1996 to 8·5–9·5% in 1998/9 (Table. 2). In contrast, the proportion of group C isolates which were moderately penicillin resistant decreased from 21·1% in 1995 to 3·8% in 1999. On the other hand, invasive meningococcal disease caused by serogroup C increased from 28·9% in 1994 to 52·6% in 1998 and to 46·5% in 1999. There was no increase in group B invasive meningococcal disease in the study period. No apparent change in the incidence of group W135 meningococcal disease or moderate penicillin resistance was noted between 1994 and 1999.

Temporal and geographic distribution of moderately penicillin resistant meningococci and the pattern of penicillin prescribing

Table 3 shows the temporal and geographic distribution of moderately penicillin resistant meningococci and pattern of penicillin prescribing in Scotland. There was no association between moderately penicillin resistant isolates and penicillin prescription rate across all health boards (Pearson correlation, $r = 0{\cdot}129$, $p = 0{\cdot}646$).

Serotype and subtype distribution of isolates in relation to moderately penicillin resistant invasive isolates

The serotype and subtype of invasive isolates moderately resistant to penicillin were diverse (Table 4). Twenty-four serotypes/subtypes in group B, 18 serotypes/subtypes in group C and 4 serotypes/subtypes in group W135 were found to have moderate resistance to penicillin. A higher proportion of isolates moderately resistant to penicillin had the serotype/subtype 4:P1.4, NT:P1.16, NT:P1.9 or 4:P1.15 in group B, and 2a:P1.2, 2a:P1.5 or 2b:P1.16 in group C. Three serogroup W135 isolates moderately resistant to penicillin were serotypes/subtypes NT:P1.3,6, NT:P1.3, P1.6, and NT:P1.6, P1.3. The incidence of disease or resistance was higher in type and subtype 4:P.14, NT:P1.9 and NT:P1.16 of group B and type and subtype 2a:P1.2 and 2a:P1.5 of group C.

DISCUSSION

Our study shows a low prevalence of invasive meningococcal isolates resistant to penicillin and other third generation antibiotics in Scotland between 1994

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and 1999. Ten percent of isolates were highly resistant to sulphadiazine but no high level resistance was found to any other antimicrobial agents. High-level resistance to sulphadiazine could be due to the common use of sulphadiazine as chemoprophylaxis in close contacts of index patients during the 1950s to 1970s. However, isolates with resistance to penicillin, ciprofloxacin, ceflotaxime, ceftriaxone and rifampicin are of particular concern because they are generally used to treat patients with meningococcal meningitis and their close contacts. The failure to find any evidence of high level resistance to these antibiotics in the present study suggests that current antimicrobial agents remain effective in treating meningococcal disease. These data on antimicrobial resistance of meningococci are essential to inform guidelines on therapy for patients with meningococcal disease.

The annual incidence of moderately penicillin resistant meningococci was 0·15 per 100000 population. US data reported an incidence of 0·04 per 100000 population for moderate penicillin resistant meningococci in 1991 [17]. The prevalence of meningococci moderately resistant to penicillin was 8·3% and no evidence of an increase in moderate penicillin resistant isolates was observed during the study period. Previous studies have reported that the prevalence of penicillin resistant meningococci was 6% in Belgium in 1998 [18] and $< 2\%$ in the Netherlands [19]. A higher resistance rate was documented in England and Wales [8] and Spain [10]. Similar to our data, the US studies [17, 20] reported no overall increase in penicillin resistant meningococci during 1980s and 1990s. In contrast, a trend of increased resistance to penicillin among meningococci has been documented in England and Wales [6–8] and Spain [10, 21, 22].

The reason for geographic variation in prevalence of meningococcal isolates resistant to penicillin is not clear, but may be due to difference in MIC testing method. Similar to other meningeal bacterial pathogens such as *Streptococcus pneumoniae*, meningococcal disease requires treatment with antimicrobial agents. In addition, the rates of asymptomic carriage of meningococci and pneumococci are also similar in the population. However, the prevalence of penicillin resistance has been shown to increase globally for *Streptococcus pneumoniae* [23], and not for the meningococcus. Further studies are needed to address this issue. In common with evidence from Spain, geographic difference in the incidence of moderately penicillin resistant meningococci has been noted in the present study [22]. Although there was no statistical association, the areas with higher incidences of penicillin resistant meningococci tended to have higher penicillin prescribing rates. One study in Iceland noted that antimicrobial use was significantly related to nasopharyngeal colonisation with penicillin resistant pneumococci in children [24]. However, one survey from England suggested that an association between a high rate of antibiotic prescribing and a high incidence rate of meningococcal disease in some geographic locations might in part, be confounded by increased general practitioner consultation rates for lower respiratory infection [25]. Nevertheless it has been widely accepted that the selective pressure imposed by widespread use of antibiotics is likely to be responsible for the emergence and maintenance of antibiotic resistance [26].

Mechanisms leading to resistance are similar in gonococci and pneumococci [5]. Studies have also shown that the development of penicillin resistance in meningococci is due to altered forms of the penicillin-binding protein (PBP) gene resulting in reduced affinity for the antibiotics [22, 27, 28]. In addition, the emergence of penicillin resistant meningococci has been shown to occur by recruitment of a PBP gene from closely related species such as *Neisseria flavescens* [28]. It appears that antibiotic pressure combined with decreased affinities of penicillin binding proteins has been the primary factors for the development of resistant strains. Therefore, guidelines to limit the excessive usage of antibiotics will be helpful in controlling the emergence of resistance.

In England and Wales, meningococcal serogroups B and C were shown to be responsible for moderate penicillin resistance in 1985–9 [29]. We noted that serogroup B was associated with a higher proportion of penicillin resistance than group C and W135. This is consistent with previous reports in the US [17] and Spain [22]. In the present study, the prevalence of moderate penicillin resistance in meningococcal serogroup W135 was 57·1%. In addition, the proportion of resistant isolates contributed by serogroup W135 (8·7%) was substantially higher than the proportion of invasive disease caused by this serogroup in 1994–9. Recently, meningococcal serogroup W135 cases have been reported among pilgrims who had travelled to the Hajj in Mecca and their close contacts [30, 31]. Our data and this evidence confirm recent UK guidance on the advisability of offering all pilgrims the quadrivalent polysaccharide vaccine before traveling to Mecca.

Although meningococcal disease caused by serogroup C increased during the study period, there was no increase in the prevalence of penicillin resistance

among serogroup C penicillin resistant isolates. One study in Spain also failed to show an associated increase in the prevalence of serogroup C penicillin resistance with an increase in serogroup C disease [32]. Similarly, we did not find any correlation between serogroup C meningococcal disease and penicillin resistant isolates.

In the United Kingdom, widespread use of meningococcal group C conjugate vaccine in November 1999 resulted in a rapid decline of group C disease in age-groups targeted for vaccination, with preliminary data showing a short-term efficacy of 97% for teenagers and 92% for toddlers [33]. In the present study, a higher proportion of meningococcal disease and penicillin moderately resistant isolates was caused by serogroup B. Our data reinforce the additional need for a vaccine against serogroup B meningococcal disease.

Our study shows a wide range of serotypes/subtypes in different serogroups among penicillin resistant isolates. Although group B serotypes/subtypes 4:P1.4 (16·7%) and NT:P1.16 (12·5%), group C serotypes/subtypes 2a:P1.2 (15·8%) and 2a:P1.5 (15·8%) were associated with a high proportion of moderate penicillin resistance, there was no clearly dominant serotype/subtype that was associated with penicillin resistance in a specific serogroup. Studies in Spain have shown conflicting results. One study found that group B serotype/subtype 4:P1.15 was associated with 51·4% of penicillin resistance and group C and non-serogroupable serotype type 2b were associated with 86% and 87% of penicillin resistance respectively [22]. However, an examination of 16 penicillin G-resistant strains in Spain failed to find a serotype specific association for penicillin resistant isolates [34]. We found that serogroups/types/subtypes B:4:P.14, B:NT:P1.9, B:NT:P1.16, C:2a:P1.2 and C:2a:P1.5 were associated with a higher proportion of resistance as well as disease. Due to the limited number of resistant isolates, caution should be taken in the interpretation of these data.

Our results show that at present the prevalence of penicillin resistant meningococci is low in Scotland, with marked geographic and temporal variations. The clinical importance of meningococci moderately resistant to penicillin is not clear, but meningococci with high-level resistance would have serious implications for patients with invasive disease. Since the prevalence of penicillin resistant meningococci could change rapidly, surveillance must be conducted continuously to detect any possible emergence of resistant meningococci. Further understanding of meningococcal seroepidemiology and of the molecular characteristics of disease and penicillin resistance is critical for developing appropriate vaccines to control the disease and antibiotic resistance. Development of group B meningococcal vaccine will be critical in adding to the success of group C conjugate vaccination in the United Kingdom, as vaccination is the most effective method to control the spread of disease and the emergence of resistance.

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