Epidemiol. Infect. (1999), **122**, 41–49. Printed in the United Kingdom

Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993–6

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(*Accepted 21 August 1998*)

SUMMARY

A surveillance system to assess the impact and changing epidemiology of invasive meningococcal disease in Europe was set up in 1987. Since about 1991, contributors from national reference laboratories, national communicable disease surveillance centres and institutes of public health in 35 European countries provided information on all reported cases of meningococcal disease in their country. We describe some trends observed over the period 1993–6. The main findings were: the overall incidence of meningococcal disease was 1·1 per 100000 population but there was some evidence of a slow increase over time and with northern European countries tending to have a higher incidence (Kendall correlation 0·5772, $P < 0·001$), an increasing predominance of serogroup C, and a shift in the age distribution towards teenagers and away from younger children (χ^2 test for trend 44·56, $P < 0·0001$), although about half of the cases were under 5 years of age. The overall case fatality rate was 8·3% and the most common serosubtypes were B:15:P1.7,16 and C:2a:P1.2,5.

INTRODUCTION

Meningococcal disease is still a public health problem in developed as well as developing countries. The infection remains serious despite the availability of antibiotics and the case-fatality rate is high, particularly in infants and the elderly. The surveillance was set up mainly because of reports of changes in the epidemiology of serogroup B meningococcal disease in Europe, especially in Norway [1] and in England [2], which suggested that European-wide surveillance to monitor and perhaps anticipate further changes was necessary and timely. The prospect of a meningococcal vaccine was another reason for surveillance. Surveillance began with a few countries in 1987. About 33 European countries have participated since 1991. The European Meningococcal Surveillance Group has collaborated with the European Monitoring Group on Meningococci since 1992. In this paper, we report some of the main trends in

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Table 1. *Age specific incidence* (*per 100000*) *and percentage of cases in each age group*

	< 1 m	1–11 m	< 1 y	1–4 y	5–9 y	10–14 y	15–19 y	20–24 y	25–44 y	45–64 y	65 y +	Total
(*a*) Incidence per 100000												
1993§	—	—	14·0	5·0	1·5	1·1	1·7	0·6	0·2	0·2	0·3	0·9
1994‡	5·1	16·6	15·6	5·9	1·7	0·9	2·0	0·7	0·2	0·2	0·3	1·0
1995†	4·8	20·6	19·3	7·1	2·0	1·4	2·5	0·8	0·2	0·2	0·3	1·2
1996*	5·3	19·6	18·4	7·3	2·1	1·4	3·2	1·0	0·3	0·4	0·3	1·3
Overall			16·5	6·2	1·8	1·1	2·3	0·8	0·2	0·03	0·3	1·1
(*b*) Percentage in each age group												
1993§	—	—	18·9	29·2	11·1	7·9	13·5	5·3	5·6	4·6	3·8	100
1994‡	0·5	18·2	18·7	28·6	11·3	6·1	13·9	5·4	6·3	5·5	4·2	100
1995†	0·4	18·3	18·7	27·9	11·0	7·8	14·7	5·1	6·5	4·7	3·7	100
1996*	0·4	15·5	15·9	26·2	10·4	6·8	16·9	5·9	7·4	6·6	4·0	100
Overall			18·1	27·7	10·8	7·0	15·0	5·4	6·7	5·5	3·8	100

* 28 countries.
† 26 countries.
‡ 20 countries.
§ 25 countries.

meningococcal disease in Europe over the 4 years 1993–6.

METHODS

Contributors from 35 countries provided annual aggregated data until 1995; from 1996 individual cases were reported. This paper summarizes 2 years' aggregated data and two years' individual case reports. For Russia and the Ukraine data covered a limited area (Moscow and Dniepropetrovsk regions respectively). For all other countries national data was provided for all years except for the Republic of Ireland (1995 and 1996 only). The following information on meningococcal disease was requested: age, gender, outcome (died or survived), quarter of the year for aggregated data/date of onset for individual case reports, clinical diagnosis, serogroup, serotype and whether or not isolates were resistant to sulphonamides, penicillin or rifampicin. Some reporters were able to give minimum inhibitory concentration (MIC) values for isolates but others were only able to report if the isolate was sensitive or resistant. For the purposes of the study antibiotic resistance was divided into two categories only. Penicillin resistance was defined as a MIC of 1 μg/ml or greater, sulphonamide resistance as 10 μg/ml or greater and rifampicin resistance as 5 μg/ml or above. The denominator for the case fatality rate was the number of cases in which the outcome was known. Contributors were also invited to report on outbreaks or episodes of special interest, any unusual findings and changes in vaccination and chemoprophylaxis policy.

Most countries had more than one system for collecting information on infectious diseases. Cases were notified on clinical grounds and in addition most countries had reference laboratories which analysed specimens and also reported cases separately. This summary is based on laboratory reports from 20 countries, notifications from 11, combined data from 3 and information from an enhanced surveillance system from 1 (the Czech Republic) for the period 1993–6, when consistency was achieved. Data from 1987 onwards have been used in discussing trends when appropriate. Demographic data provided by contributors were used to calculate age specific incidence rates. Data were analysed using Excel (Microsoft) and SPSS (SPSS Inc.).

The case definition specified any invasive meningococcal infection causing symptoms (ICD-10 codes A39.0 to A39.9). Meningitis and septicaemia were generally considered together because of overlap between these two conditions. However, where there were epidemiological differences in cases reported as meningitis or septicaemia, these have been described. Laboratory diagnosis was by isolation or serology. On average around 5–7% of laboratory cases were confirmed by throat or upper respiratory tract swab alone. The early use of antibiotics may render CSF and blood sterile and throat swabs are now useful in identifying strain types. Notifications were based on clinical features with or without laboratory confirmation. The figures presented here represent the 4-

https://doi.org/10.1017/S0950268898001848 Published online by Cambridge University Press

year annual average unless otherwise stated. Incidence rates are per 100000 population.

RESULTS

Incidence

The annual mean incidence in Europe increased steadily over the 4-year period (Table 1) from 0·9 to 1·3, an increase of 44%. The average for the period was 1·1. Between countries the incidence ranged widely from 0·1 to 8·0, although all except four countries were within the range 0·3–3·6. In 14 countries the incidence was less than 1·0, and 2·0 or more in 12 (Table 2). Northern European countries (defined as countries with more than 50% of their landmass north of the 45° line of latitude) had a higher incidence than those in the south (Kendall correlation coefficient 0·5772, significance $P < 0·001$). Some countries, Greece, Iceland and Russia (Moscow), showed moderate variation in incidence during this time. Incidence increased between 1993 and 1996 in Austria, England and Wales, Finland, Malta and the Slovak Republic and decreased in Israel and Portugal. There was a clear seasonal pattern in Europe (Fig. 1) with most cases in the winter.

Age distribution and case fatality rate (CFR)

The age distribution of cases showed some variation between countries but most followed a similar pattern. The highest incidence was in children under 1 year (Table 1) and about half the cases were under 5 years of age. There was a smaller secondary peak in incidence in teenagers. Over the 4 years there was a marked shift in age distribution away from the under-5s towards the 15–19 years age group (χ^2 test for trend 44·56, $P < 0·0001$). The proportion of cases in the 15–19 years age group increased from 13·5 to 16·9%, whilst those in the under-5s decreased from 48·1 to 42·1%. The overall average CFR was 8·3% with the lowest rate in children aged 5–9 years. The CFR increased almost six-fold with age from 5–9 years to 65+ years (Table 3). This trend was consistent in each year.

Serogroup

Most cases of meningococcal disease in Europe were caused by serogroup B (68%) or C (28%) strains. There was some variation between countries (Table 4). In the Czech Republic serogroup C accounted for nearly half the cases in 1993 and for over two-thirds of cases in 1994, 1995 and 1996; in the Slovak Republic nearly 80% of grouped cases in 1996 were attributed to serogroup C. Almost half of grouped cases in the Moscow Region (population 10 million) were serogroup A and at the beginning of 1996 there was a large outbreak of serogroup A disease in Moscow associated with a Vietnamese community [3]. Serogroup Y accounted for 11% of cases in Israel and 9% of cases in Sweden. Elsewhere serogroups other than B and C were rare. The overall proportion of serogroup C disease increased during this period (Table 5). This increase in serogroup C was consistent in Austria, the Czech Republic, England and Wales, the Republic of Ireland, and Spain. Serogroup C cases also increased in number as reported from Moscow during 1993–5 but declined as a proportion of cases in 1996. In addition, several countries experienced an increase in the proportion of serogroup C disease in 1996 only – Germany, Greece, Iceland, Scotland and the Slovak Republic. A decrease in proportion of serogroup C was seen in Belgium, Finland, France, Israel and the Netherlands over the 4 years (although in Finland there was no decrease in numbers of cases) and in Sweden in 1996.

Serotype/subtype

Most isolates reported by laboratories were serogrouped (80% in 1996 and around 90% in 1995 and 1994). Of these well over half were typed. In 1996, 53% of typed serogroup B were B:4 and 23% B:15; of serogroup C, 60% were C:2a and 33% C:2b. The figures were similar in 1995 except that B:4 accounted for 43% cases. In previous years countries were only asked to indicate which were the major serotypes and these were generally the same as in subsequent years.

The five most common serosubtypes were B:15:P1.7,16, B:4:P1.4, C:2a:P1.5, C:2a:P1.2 and C:2b:P1.2,5 (Table 6). During this period the dominant serotype/subtype remained unchanged in each country (although the number of cases may have changed) except in England and Wales, Scotland and Spain. In 1993 the main serogroup B serotype in England and Wales and in Scotland was B:2b. In 1995 this changed to B:4 in England and Wales, and in Scotland to B:15 in 1995 and B:4 in 1996. There was also a change in the serogroup C subtype in Scotland from C:2b to C:2a. The major serotype in

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Table 2. *Meningococcal disease in Europe 1993–6 (crude average incidence per 100000)*

Low (incidence < 1)		Average (incidence 1 < 2)		High (incidence ⩾ 2)	
Bulgaria	0·1	Europe	1·1	Portugal (N)	2·0
Hungary (N)	0·3	Finland	1·1	Russia (Moscow)	2·0
Italy (N)	0·3	Israel	1·1	Scotland	2·3
Poland* (N)	0·4	Switzerland	1·2	England & Wales	2·4
France	0·6	Malta	1·3	Ukraine/	
Slovenia	0·7	Estonia	1·5	Dniepropetrovsk Region	2·4
Romania (N)	0·8	Belgium	1·7	Northern Ireland	2·7
Slovak Republic (N)	0·8	Latvia (C)	1·8	Norway (N)	3·1
Spain	0·8	Czech Republic (E)	1·9	Netherlands	3·5
Austria	0·9			Albania (N)	3·6
Croatia	0·9			Denmark	4·0
Germany (N)	0·9			Rep. of Ireland	5·4
Greece (N)	0·9			Iceland	8·0
Sweden (C)	0·9				

* Meningococcal meningitis only.
(C) combined system, (E) enhanced surveillance, (N) notifications; all others are laboratory reports.

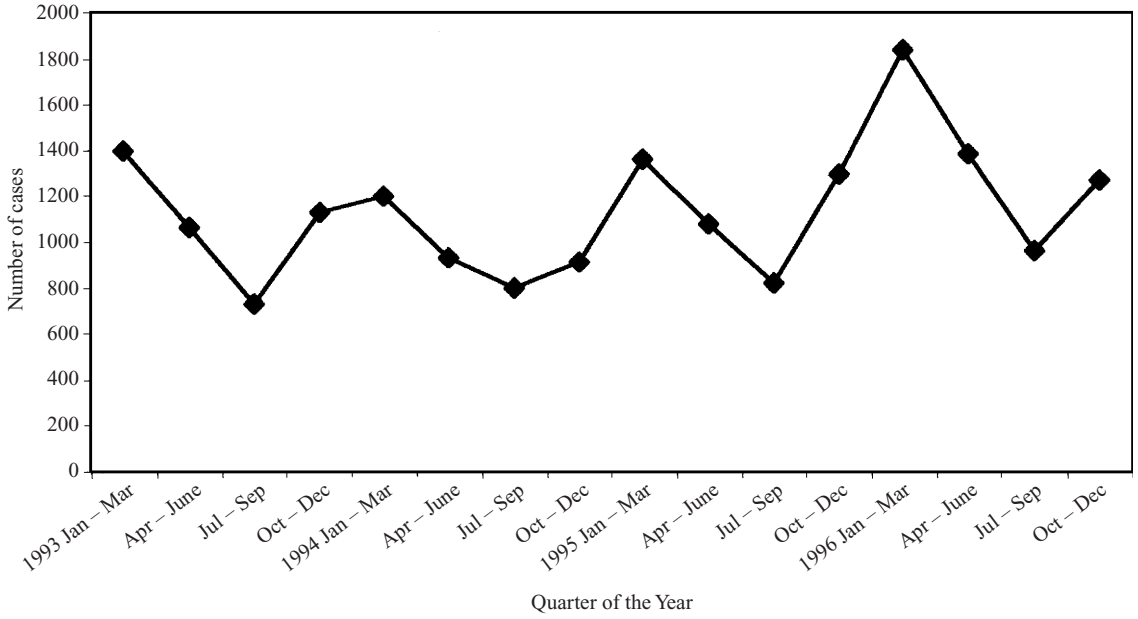

Fig. 1. Seasonal distribution of cases of meningococcal disease by quarter, Europe 1993–6 (based on reports from laboratories in 23 countries).

Spain changed from C:2b:P1.1 to C:2b:P1.2,5. There was evidence from our data that some serotypes and serosubtypes had different age and mortality patterns and this will be reported elsewhere.

Increase in serogroup C and other serotype changes

During this period the number of cases of serogroup C in Europe increased by 35%; as there was also an increase in the number of cases of serogroup B this represented an increase in the proportion of serogroup C of 23% (from 26 to 32%). Overall in 1995, C:2a strains more than doubled in number compared with 1994, whereas C:2b strains increased by 27%. The increase persisted in 1996 and young adults as well as children were affected. Nine countries reported an increase in the number of cases (range 5–220%) and in the proportion of serogroup C (range 11–133%). One country, Iceland, reported an increase in the proportion of serogroup C but not an increase in cases

https://doi.org/10.1017/S0950268898001848 Published online by Cambridge University Press

Table 3. *Annual case fatality rate (CFR) by age group, Europe 1993–6*

	Age group											
	< 1 m	1–11 m	1–4 y	5–9 y	10–14 y	15–19 y	20–24 y	25–44 y	45–64 y	65 y +	Age unknown	Annual CFR
1993§	0·0	4·4	4·7	3·5	4·3	6·4	5·4	10·9	10·7	14·3		5·8
1994‡	0·0	6·4	6·3	4·3	8·6	5·7	7·2	14·1	12·1	26·0		7·6
1995†	50·0‖	8·1	7·6	2·6	9·3	13·0	5·3	7·8	15·9	17·8		9·1
1996*	0·0	11·0	8·5	4·2	5·9	7·2	12·0	9·3	12·1	23·1		7·5
Overall	4·0	7·5	7·5	4·1	7·6	8·5	9·2	10·7	11·5	21·1	6·3	8·3

* Total based on laboratory reports from 25 countries (no. deaths 221).
† Total based on laboratory reports from 13 countries (no. deaths 112).
‡ Total based on laboratory reports from 16 countries (no. deaths 151).
§ Total based on laboratory reports from 18 countries (no. deaths 107).
‖ Few cases.

Table 4. *Distribution of serogroup by country, Europe 1993–6 (percentage in each group). Arranged in descending order for serogroup B, except for Russia (Moscow) where serogroup A was important*

Country	A	B	C	Y	W135	Other	Number of strains serogrouped
Czech Republic	0·8	30·7	67·3	1·0	0·2		590
Slovak Republic	0·8	33·9	64·5			0·8	124
Greece*	0·8	41·7	47·5	0·8	3·3	2·5	120
Malta		50·0	16·7		16·7	16·7	6
Spain	0·1	54·3	44·8	0·6		0·3	1251
Republic of Ireland	0·2	57·5	41·6	0·5	0·2		562
Northern Ireland*		58·7	35·7	0·8	2·4	2·4	126
Israel	0·4	60·5	24·7	11·1	2·9	0·4	243
England & Wales	0·1	65·3	30·8	1·7	1·6	0·5	5349
Scotland		65·9	32·0	0·7	0·7	0·7	419
Sweden		67·9	18·8	9·2	3·5	0·5	261
France	0·5	68·5	24·7	4·3	1·1	0·9	1487
Europe	1·1	67·5	28·0	1·8	1·1	0·4	16901
Denmark	0·1	70·8	26·7	1·0	0·8	0·5	763
Norway		70·9	26·1	2·4	0·6		495
Finland		71·1	25·8	2·2		0·9	225
Iceland		71·1	28·9				76
Switzerland*	0·5	72·6	21·0	3·7	2·3		219
Italy*	2·5	74·5	15·2	2·5	2·9	0·5	204
Germany	0·4	75·8	19·6	2·3	1·4	0·1	811
Romania	17·4	76·1	2·2	4·3			46
Austria	0·4	82·1	13·5	1·6	1·6	0·8	252
Belgium	0·3	85·5	11·9	0·8	1·3	0·2	622
Netherlands		85·5	12·1	1·0	0·8	0·4	2304
Slovenia		88·9	8·9	2·2			45
Russia (Moscow)	47·3	40·3	11·7	0·4	0·4		273

* 3 years.

overall and the Republic of Ireland an increase in cases (by 87%) but a slight decrease in proportion of serogroup C. The Czech Republic experienced outbreaks of infection caused by C:2a:P1.2 which affected particularly those aged 15–19 years [4]. Austria reported a more localized increase in serogroup C disease on the border with the Czech Republic in 1995, which was caused by the same serosubtype, and this became more widespread in 1996. Greece also reported an increase in C:2a:P1.2

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Table 5. *Distribution of serogroup by year* (*percentage of cases*)

	1993		1994		1995		1996		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Serogroup										
A	14	< 1	33	< 1	26	< 1	118	2	191	1·1
B	2817	71	2522	70	2912	69	3114	62	11365	67·9
C	1025	26	940	26	1123	27	1583	32	4671	27·9
W135	31	2	40	2	88	2	73	2	232	1·4
Y	72	2	71	2	48	2	84	2	275	1·6
Total	3959		3606		4197		4972		16734	

Table 6. *Major sero/subtype in each country*

Major sero/subtype (Serogroup B)						
B:15:P1.7,16	B:15	B:14:P1.7,16	B:4:P1.15	B:4:P1.4	B:4	B:2b
Austria Denmark France Germany Iceland Norway Scotland	Finland Italy Sweden	Israel	Spain	Belgium Netherlands Spain Scotland	England & Wales Italy	Greece

Major sero/subtype (Serogroup C)				
C:2a:P1.5,2	C:2a:P1.2	C:2a	C:2b:P1.2,5	C:2b
Czech Republic Norway	France Germany Israel Republic of Ireland	Belgium Denmark Eire England & Wales Finland Israel Netherlands Scotland	Spain	Republic of Ireland

in 1996. At the end of 1995 and beginning of 1996 England and Wales experienced an increase in clusters of meningococcal disease, mainly due to serogroup C:2a and 2b which increased in number by 61% compared with 1994 [5–7]. Clusters of serogroup C were also observed in other countries [8]. In Galicia, north western Spain, there was a sharp increase in serogroup C meningococcal disease which began in 1993/4. This largely affected children, although incidence in all ages increased. The serosubtype responsible was C:2b:P1.2,5 which accounted for more than 70% of serogroup C isolates. During 1995 Finland had an increase in both serogroup B and serogroup C disease. Some of the increase was due to C:2a:P1.2. The other countries that reported an increase were Germany in 1996, the Slovak Republic in 1995 and Scotland where there was a small increase which began in 1995.

Though there was little change in overall incidence of meningococcal disease in Moscow until 1996 the percentage of cases due to serogroup C increased from 11% in 1993 to 21% in 1995. In 1996 the percentage of serogroup C cases decreased and in January, Moscow experienced a large outbreak of serogroup A disease which mainly affected a Vietnamese community. The epidemic of serogroup B:15 continued to decline in Norway during this period.

Meningitis and septicaemia

Although there was probably some overlap between these two diagnoses, analysis of the reports showed

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Table 7. *Percentage by age group of meningococcal disease cases diagnosed as meningitis and septicaemia*

	< 1 m	1–11 m	1–4 y	5–9 y	10–14 y	15–19 y	20–24 y	25–44 y	45–64 y	65 y +	Age unknown	*n*
Meningitis	0·2	22·1	30·1	11·1	7·2	12·5	4·4	5·5	4·8	2·0	736	9318
Septicaemia*	0·4	16·2	34·3	12·3	7·1	11·6	3·7	5·1	4·8	4·5	237	5577

* Includes cases of meningitis and septicaemia.

that the reported case fatality rate for septicaemia was 12·2% and for meningitis 5·1%. There were also some differences in the age distribution which were consistent over this 4-year period, of an excess of cases of septicaemia in the 1–4 years age group and in the elderly (Table 7).

DISCUSSION

Quality of surveillance data

Comparisons of disease incidence between countries need to be made with caution. Velimirovic [9] attempted to assess the accuracy and comparability of European reports to the World Health Organisation Regional Office for a number of infectious diseases. The design, extent and timeliness of surveillance systems varied considerably. In our surveillance of this one disease, in which most countries collected data from two sources (notifications and microbiological diagnoses) notifications of meningococcal disease were either optional or compulsory and were based on clinical diagnosis. Laboratory surveillance tended to be voluntary with data collected by one, usually specialist, microbiologist, who also did typing and subtyping for other laboratories. In all countries, except Denmark, Latvia and Norway (and Scotland in 1996) which had fully integrated systems, the laboratory reporting and notification systems were run separately.

In some countries disease surveillance centres have been set up (Czech Republic, England and Wales, Norway and Scotland), in others (Sweden) the systems are laboratory-based. Under-reporting by countries was common and variable in extent, but the similar age profile of cases in each system suggested that the data were nevertheless representative. To ascertain the extent of under-reporting of meningococcal disease, a questionnaire was sent to participating countries. The response suggested that completeness of reporting ranged widely from 25 to 100% and some were unable to assess completeness. In England and Wales the reporting rate for meningococcal disease was found in one study to be about 65% [10].

CFRs were also difficult to assess accurately, but trends were consistent. Several countries considered that under-reporting of mortality occurred, as outcome was not always communicated to the laboratory afterwards.

The need for completeness of reporting can be exaggerated. Effective surveillance requires a balance of attributes – representatives, timeliness, simplicity, acceptability and cost are important too. Detection of disease trends by time, place and person is possible with incomplete data [11] and striving for completeness may waste resources. As a general rule any surveillance system improves when feedback is prompt and is accompanied by comment and analysis and not just seen as bureaucratic [9]. Contributing to a Europe-wide surveillance stimulated a number of countries to improve the quality of their data. Following the increase in serogroup C disease in 1993 the Czech Republic set up an enhanced surveillance system which actively sought cases and this resulted in fuller reporting.

Epidemiology in Europe

The overall European picture is of a fairly stable endemic situation with small localized epidemics (like bubbles breaking the surface of a simmering liquid) and some more protracted outbreaks. There is also evidence of a slow increase in incidence. Over 95% of disease was attributed to serogroups B and C with serogroup B dominant; only in the Czech Republic did serogroup C consistently overtake serogroup B in all years. In addition, serogroup C was dominant in Greece, the Slovak Republic and Spain in 1996. Norway appears to be at the tail end of a long serogroup B:15:P1.7,16 epidemic which began in 1975 and peaked in 1981 [12–14] and the Czech Republic serogroup C epidemic probably peaked in

https://doi.org/10.1017/S0950268898001848 Published online by Cambridge University Press

early 1996 (Dr P. Kriz, personal communication). The Republic of Ireland has unified and improved its surveillance system for meningococcal disease but the large increase in incidence in 1995 was real and not due to enhanced case ascertainment [15]. In England and Wales however the merging of data from the Meningococcal Reference Unit and the Communicable Disease Surveillance Centre in 1995 may have had the effect of accentuating the increase. Given the small population in Iceland (266 978) small changes in the number of cases caused marked swings in incidence; nevertheless Iceland consistently had the highest incidence of meningococcal disease each year during this period, which was unlikely to be due entirely to completeness of reporting. The increased incidence of serogroup C disease in 1995 in England and Wales, Finland, Greece and Spain, coupled with the reports of outbreaks, may have been a warning of the change which persisted into 1996 with serogroup C becoming increasingly important in other countries too. Another indication of change was the shift in age distribution towards teenagers which also continued into 1996. The age distribution of meningococcal disease is known to change during epidemics with an increased proportion of cases among teenagers and adults. The reason for this is unknown but may be associated with the type of strains involved [16, 17].

The north–south gradient in incidence is one of the most consistent findings of this data set. It is possible that this is mainly attributable to more complete reporting in northern countries, but it seems unlikely that this is the sole explanation. It may relate to the seasonality of meningococcal disease and environmental factors. Most countries followed the known seasonal pattern for meningococcal disease in Europe with cases generally being commoner in the winter months than in summer. The seasonality of meningococcal disease implies that environmental factors are important in its aetiology. Spain and Portugal had an accentuated seasonal pattern. The Czech Republic, Norway and Finland showed a flatter seasonal distribution of cases. In the Czech Republic the serogroup C outbreak peaked in 1996 and the seasonal pattern may have been lost within the rising incidence. Similarly in Norway seasonal effects may have been overshadowed by a declining incidence. Another feature of the disease in Europe in 1993–6 was that the dominant sero/subtypes seemed to change slowly within individual countries. There is some evidence in our dataset (not presented here) that different serotypes may have different age distributions. The CFR varied considerably and increased with age. Indeed adults over 65 years were five times more likely to die from meningococcal disease than children aged 5–9 years and this trend was consistent for several years. This age differential may be important if the proportion of disease continues to increase in the older age groups. Case fatality was higher in those reported as septicaemia, although it may be that patients who died were more likely to be given this diagnostic label.

Europe-wide surveillance of meningococcal disease began in 1987, and in spite of the varying quality of the data reported, some clear trends can be detected. Surveillance was based on both notifications and laboratory data. Notifications were more complete but were less detailed. Laboratory data included microbiological typing results and other information such as clinical outcome.

The main findings for the years 1993–6 were:

(*a*) a stable endemic situation with some evidence of a small but steady increase in incidence from 1 to 1·3/100000 per annum between 1993 and 1996;
(*b*) occasional outbreaks of disease against this background;
(*c*) a predominantly serogroup B (70%)/group C (26%) background, with other serogroups rare (except for serogroup A in Romania and Russia (Moscow), and serogroup Y in Israel and Sweden);
(*d*) some evidence of a greater proportional increase in serogroup C disease;
(*e*) some evidence of an increase in teenage disease;
(*f*) increasing case-fatality with age from 5–9 years onwards.

Contributing to a Europe-wide surveillance of meningococcal disease has helped to improve the quality of surveillance for this disease in a number of countries and continuing surveillance should help to improve quality further. In addition, the production of more timely surveillance reports, made possible by the electronic transfer of information, may help in the control and management of this disease continent wide.

ACKNOWLEDGEMENTS

We thank Nicky Smith and Alex Garland who helped to develop the surveillance project initially, Dr Norman Begg, Dr Richard Hooper and Dr Tove Ronne for support and advice and the European

Monitoring Group for Meningococci. Financial support was provided by Wyeth-Lederle and the National Meningitis Trust.

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