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SURVEILLANCE NETWORK FOR INVASIVE *NEISSERIA MENINGITIDIS* IN EUROPE – 1999 & 2000

Final report

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SUMMARY

Introduction

Decision No. 2119/98/EC for setting up a network for the epidemiological surveillance and control of communicable diseases in the European Community stated that 'bacterial meningitis' was a priority. Invasive disease due to *Neisseria meningitidis* comes within this priority. Building on the surveillance networks already in existence within Europe (the European Monitoring Group on Meningococci (EMGM), and a network for surveillance of bacterial meningitis in Europe), a DG SANCO surveillance network for *N. meningitidis* disease was established in all 15 EU countries and 2 non-EU countries for 2000-2001.

Aims

- To improve the epidemiological information on invasive meningococcal disease within the European Union.
- To improve the laboratory capacity to accurately characterise the isolates of *N. meningitidis*.
- To form a focus for future wider collaboration with non European Union and candidate European Union countries in Europe.

Methods

Agreed usage of a minimum dataset and standard case definitions for *N. meningitidis* has enabled valid comparisons to be made of the disease epidemiology within Europe, and hence assist the monitoring of epidemiological changes. Information collected on the surveillance systems and the vaccination programme(s) in use by each participant country has also aided interpretation of the epidemiological analyses.

Improvements in the laboratory capacity within the EU to accurately characterise *N. meningitidis* have been achieved through gaining information on systems in use by participants, and by undertaking an External Quality Assurance Scheme (EQAS) with the participant reference laboratories. The EQAS helped identify any existing problems in correctly serotyping *N. meningitidis* isolates, and will enable corrections/assistance in laboratory methods to be made, hence improving comparability of data between countries.

Results and Conclusions

This project has demonstrated the successful development of existing networks towards the objective of providing high quality surveillance information on meningococcal infection in the European Union and neighbouring countries. The importance of the reference and diagnostic microbiology under-pinning this data cannot be over-emphasised. The laboratory questionnaire and the quality assurance scheme suggest that standards in reference laboratories in the EU are high.

The data provided on meningococcal disease shows marked variations between countries in overall incidence, with a more than ten-fold variation in the incidence of culture confirmed infection. This is likely to reflect both genuine differences in the epidemiology and in ascertainment. The contribution of each of these is difficult to quantify, but secular trends within countries and between age-groups and serogroups are likely to be valid in most instances. There have been, however, recent changes in clinical and laboratory practice which can have a major effect on ascertainment. For example, reduced used of lumbar puncture for the diagnosis of meningitis, the use of pre-admission antibiotics and the introduction of new laboratory tests. The potential for ascertainment to change because of new technological advances is illustrated by the data provided on PCR diagnosis for those countries where the test is routinely used. In three countries, ascertainment of laboratory confirmed infection has been increased by around 100% and it is likely that similar increases will be achieved in other countries when access to and awareness of PCR diagnosis improves. The ability to confirm and group a larger number of meningococcal infections, however, is clearly

a major advance that will improve the data available and help to better establish the burden of disease with a view to vaccine introduction. We hope that countries without a routine service can learn from other countries in the project about the development and provision of such services.

It is difficult to explain the massive differences in clinical presentation of meningococcal disease between countries. Although the strains causing infection around Europe differ, it seems unlikely that there is a genuine difference in the clinical manifestation of infection. The huge variation in the proportion of cases that present as septicaemia suggests that awareness and labelling of septicaemia as a manifestation of meningococcal infection amongst clinicians in each country may vary. Without further clinical details on cases it is difficult to demonstrate this, but the finding suggests that there is potential for future changes in clinical awareness in participating countries to impact on national ascertainment.

The age-specific incidence and age-distribution of meningococcal disease follows the pattern previously described, with the majority of cases in children under five. Minor differences were noted in the age distribution between countries. Group B is still the commonest cause of infection in Europe, although the proportion of disease due to group C varies quite considerably. The proportion of group C infection did change within countries between years. In some instances this was due to the introduction of a group C vaccine, in others it may reflect changes in epidemiology, such as the introduction of a hyper-virulent strain. Identifying such changes at a European level will be important as such changes might subsequently take place in neighbouring countries. For groups other than B and C, there was also variation in the predominant strains between countries and between years. In 2000, a dramatic increase in cases due to W135 infection was observed in several countries in association with the Hajj. Although cases in pilgrims or their families were reported in several European countries, the increase in W135 infection was noted in other countries – suggesting that this strain may have been more widely distributed than originally thought. In many countries, small numbers of cases prevent valid interpretation of such changes but this phenomenon illustrates the strength of the European project in pooling data from many countries. As well as changes in serogroup, there are differences in major serotypes of group C and group B within Europe. Changes were noted in the predominant group C serotype in two countries and this change may be associated with a future increase in incidence or case-fatality rates, as has been observed in other EU countries in recent years. Group B strain variation is seen across Europe, and phenotypic data displayed in this study, and from previous records, shows marked variation in the prevalent strains across Europe. Observation over more years will allow the early recognition of emerging strains that might be missed within any one country. Consideration needs to be given to the substantial proportion of group B strains that are non-typable for serotype and serosubtype. Differences in the proportions may reflect different methods or reagents in use and should be established via the EQAS scheme. Molecular analysis of meningococcal strains is part of the DGXII funded EU-MENNET project and may shed light on this area in future years.

Analysis of case fatality ratio is prone to difficulties for a variety of reasons. We suspect that the figures presented here are an underestimate of true fatality ratios, as there is likely to be under-ascertainment of outcome in some countries. Comparison between countries is unlikely to be valid as it may be explained by differences in ascertainment, in age distribution or serogroup/serotype distribution between countries. Comparison between serogroups and age-groups however is likely to reflect genuine differences. Analysis indicates that fatality is higher in older individuals. Case fatality ratios for group B infections are low overall, and in most countries lower than that observed for group C or for other serogroups. Case fatality for group Y and W135, however, is high, and the CFR for W135 increased in 2000. This occurred at the same time as the incidence increased in association with the Hajj and is probably due to the strain belonging to a known hyper-virulent lineage.

The impact of vaccination on the epidemiology of meningococcal disease in Europe is small so far. As the UK is one of the largest countries, the impact of conjugate group C vaccine (introduced in late 1999 for those under 17 years) has had a small impact on the overall incidence and a larger impact on the incidence of group C infection. Ireland and Spain have also recently introduced vaccine and other countries are likely to implement vaccination over the next year or so. Demonstration of a change in the epidemiology is likely to encourage neighbouring countries to consider vaccination, particularly if the incidence of group C infection increases or case-fatality becomes higher than previously observed.

1. INTRODUCTION

Decision No. 2119/98/EC for setting up a network for the epidemiological surveillance and control of communicable diseases in the European Community stated that 'bacterial meningitis' was a priority. Invasive disease due to *Neisseria meningitidis* comes within this priority and this project builds on two surveillance networks that already exist within Europe. The European Monitoring Group on Meningococci (EMGM) is a consortium of reference microbiologists and epidemiologists working in Europe to exchange information on meningococcal infection. Secondly, a network for surveillance of bacterial meningitis in Europe was established in 1988 and is supported by commercial funding. This project aims to builds on these networks, avoiding any duplication of activity, and to be in line with the Charter Group's priorities of the EU Communicable Disease Network.

Using the frameworks already established, a DG SANCO surveillance network for *N. meningitidis* disease was established in all 15 EU countries and 2 non-EU countries (2000-2001) to improve epidemiological information and laboratory capacity to characterise isolates of this invasive bacterial infection.

PROJECT AIMS

1. To improve the epidemiological information on invasive meningococcal disease within the European Union.
2. To improve the laboratory capacity to accurately characterise the isolates of *N. meningitidis* using standardised methods.
3. To form a focus for future wider collaboration with non European Union and candidate European Union countries in Europe.

As meningococcal disease is relatively uncommon, this project will allow pooling of such data to increase the power of any epidemiological analysis. European wide analysis should be able to detect changes in serogroup and serotype distribution, which is important in formulation of vaccination strategies. In addition, by pooling data from all countries, the populations under surveillance will be composed of a wider variety of ethnic groups.

This project will set standards for the epidemiological surveillance of infections and for methods used in reference laboratories. Countries will be able to learn from models of good practice in other member states, and these standards can also be applied in other countries, especially Candidate EU and non-European Union countries. In addition, establishment of this network may facilitate the early dissemination of advances in therapy and in public health control measures and lead to the harmonisation of guidance on the control of meningococcal disease. This project will also provide a model and a focus for future research and public health collaborations, for example the evaluation of other new vaccines such as conjugate pneumococcal vaccines.

This project will provide substantial and up-to-date epidemiological information from which meningococcal disease vaccination policy can be developed within individual countries. It may also facilitate the eventual harmonisation of vaccine schedules in the European Union. The project provides an established network for the rapid dissemination of changes in the epidemiology of an infection that may have public health significance. In addition, it facilitates the rapid exchange of information on imported strains of *N. meningitidis* infections.

2. METHODS

Questionnaires on the surveillance system(s) and the laboratory diagnostic methods were sent to all the participating countries. The information gained from both these questionnaires is important in the correct interpretation of the data that was provided by each individual country.

The minimum data set is used by each contributing partner. This data set includes age, sex, date of onset, method of confirmation, site of identification, grouping, typing and subtyping results (as appropriate). (Appendix 2) Analysis of age-specific incidence rates, temporal trends and diversity of *N. meningitidis* infections will be compared. In countries with vaccination programmes, coverage data will also be requested and comparison of rates of infection in both vaccinated and unvaccinated cohorts will be interpreted in conjunction with coverage, schedule and vaccine used, years since implementation and method of introduction.

Standard case definitions developed as part of the previous collaborations are used in this project. Where surveillance is performed using other definitions, datasets are re-coded to provide comparable data for all participating countries.

The descriptive epidemiology will be analysed using standard statistical packages on the minimum data set provided for *N. meningitidis* infection.

An external quality assurance scheme (EQAS) was undertaken using standard micro reagents. A panel of well-characterised strains were freeze-dried and an annual selection was sent to each national or regional reference laboratory. These laboratories characterised the strains according to their routine practice and returned the results to the coordinating laboratory. The results of testing were compared with known identity of the organism and returned to each centre. Aggregate results were anonymised for use in this report and for sharing with the group as a whole. Discussion of problems with identification will occur.

Dissemination of results from the surveillance of invasive *N. meningitidis* disease in the EU occurred through project reports to the network participants of the epidemiological analyses, and presentation of results at meetings and scientific conferences. Monthly reports on the *N. meningitidis* W135 Rapid Reporting Scheme were placed in the Eurosurveillance Weekly. Feedback reports were given to the microbiologist network participants on the External Quality Assurance Scheme (EQAS). With the completion of this report information will be placed on the shared EU MENNET *N. meningitidis* website, and regular updates made.

No funding was available for a meeting of the collaborators within this project period, but a good percentage of the partners were able to meet at the 2001 EMGM meeting in Orebro, Sweden, and gain some benefit from discussions in the limited time available.

3. RESULTS

3.1 Summary of surveillance systems questionnaires

Different methods of case ascertainment were used amongst the participating countries. The forms used were: clinical notification (usually statutory); laboratory reporting; reference laboratory reporting. The notification of meningococcal infection to a government agency is compulsory in all participating countries. Case data reports come from laboratories, clinicians, microbiologists, and local public health doctors. Reconciliation of these sources occurs at national level in some countries. A number of contributing countries were not able to reconcile laboratory reporting with epidemiological case data at a national level, and hence fully reconciled case data is only available for a proportion of the cases on the main database. When more than one data source was supplied from any one country, only one set was used as appropriate to the analysis

The case definitions used within the collaborating countries include laboratory confirmed cases, and clinically diagnosed cases. Culture-confirmed cases make up the major proportion of the laboratory confirmed cases, with the contribution made by PCR-confirmed cases increasing noticeably each year. Small proportions of the main data set are latex-, microscopy- or serology-confirmed cases. In countries accepting a clinical case definition only, the criteria of this definition varies markedly; some countries use meningitis only, others use meningitis and septicaemia, with the remainder accepting all invasive meningococcal infection.

3.1.1 Conjugate Meningococcal C vaccination programmes

Within the surveillance systems questionnaire, countries gave information about conjugate meningococcal group C vaccination programmes. Routine vaccination programmes are now in place in Ireland, Luxembourg, Spain and the United Kingdom, and catch-up programmes of varying structures have been undertaken in each of these countries. (Table 1) The United Kingdom is now extending its catch-up programme to include all those under the age of 25 years. Apart from Luxembourg, all these countries started their programmes in 2000; Luxembourg's began in 2001. The conjugate C vaccine has also been introduced into Belgium and Greece, for administration on a voluntary basis by clinicians, but, in both countries, utilisation is said to be high. The Netherlands and Madeira, an autonomous region of Portugal, are planning to use the vaccine in 2002.

Table 1 : Conjugate meningococcal group C vaccination programmes in the EU, as at January 2002.

Country	Routine	Year	Catch-up	Year	Voluntary	Year
Belgium	No		No		Yes	
Greece	No		No		Yes	Jan 2001
Ireland	Yes	Oct 2000	<23 years	Oct 2000		
Luxembourg	Yes	2001				
Spain	Yes	Oct 2000	< 6 years	Oct 2000		
UK	Yes	Nov 1999	< 18 years 19-25 years	Nov 1999-2000 Dec 2001-2002		

The only mass campaign using polysaccharide vaccine that was reported in the EU occurred in Spain in the period Sept-Nov 1997. Polysaccharide vaccine A+C was administered to the population aged 18 months to 19 years in 16 of the 19 autonomous Spanish regions.

3.2 Summary of Laboratory Diagnostic Methods Questionnaire

Laboratory diagnostic questionnaires were received from fourteen laboratories.

3.2.1 Laboratory Diagnostic Facilities

All countries reported that primary identification of *Neisseria meningitidis* was available in the majority of hospitals and microbiology laboratories, with seven laboratories reporting 100% of hospitals/microbiology laboratories able to perform primary identification, the remaining countries (except Portugal) reporting 80-100% of hospitals/microbiology laboratories. All laboratories attempted isolation from cerebrospinal fluid (CSF), whole blood and from other sterile (joint fluids, pericardial fluid)/non-sterile sites (including several laboratories isolating meningococci from conjunctiva and urogenital sites) where indicated. Only one laboratory indicated pneumonia as a clinical syndrome for isolation of meningococci. The completeness of referring cultures to the Reference Laboratory varied considerably; two countries reported that between 50 and 80% of microbiology laboratories referred isolates whereas the majority reported between 80 and 100%, with three countries reporting 100% referrals. Epidemiological characterisation of meningococci by serotyping and subtyping was virtually exclusive to the National Reference Laboratories.

3.2.2 Laboratory Methods

The source of isolates included CSF and whole blood for all laboratories, nine included isolates from the nasopharynx of suspected cases and the majority included isolates from other sites where indicated. All reference laboratories processed isolates for serogrouping immediately on receipt in the reference laboratory. The majority of laboratories also processed isolates immediately for serotyping and subtyping, but a small number used batching for subtyping. A variety of media were used in the different countries for transport of isolates to the laboratory. Similarly, various media were used for subculture in the laboratory, but Mueller-Hinton with added blood was used most commonly for antibiotic sensitivity testing. The majority of laboratories used oxidase and carbohydrate fermentation test to confirm meningococcal isolates. All the laboratories performed serogrouping, serotyping and serosubtyping for meningococcal isolates, except one which only performed serogrouping. Serogrouping is mostly carried out by slide agglutination using either commercially sourced or in-house polyclonal antisera, with a small number of laboratories using serogroup specific monoclonal antibodies for detection of serogroup, with particular reference to serogroup B. Epidemiological characterisation by serotyping and serosubtyping of meningococcal isolates was performed by whole cell ELISA using monoclonal antibody (mabs) reagents from the National Institute of Standards and Control (NIBSC), UK. However, two laboratories used dot blotting, one using NIBSC reagents and the second laboratory sourced the mabs from their originators, including additional in-house antibodies.

3.2.3 Non-culture confirmation of meningococcal infection

Except for the national reference centres, non-culture confirmation of meningococcal infection is performed by few peripheral laboratories, and would usually be done by latex agglutination and only rarely by PCR. The majority of reference laboratories perform non-culture confirmation by latex agglutination and/or other forms of antigen detection. Serological confirmation of infection was performed by nine reference laboratories, four of which included serum bactericidal antibody detection, and three anti-capsular polysaccharide antibody detection. Several laboratories perform serology for confirmation of immune status only and not for diagnosis. Laboratory confirmation of meningococcal infection by serological testing using outer membrane protein antigens is performed by a number of laboratories . Non-culture confirmation of meningococcal infection by nucleic acid detection (polymerase chain reaction (PCR)) is now carried out by 11 of the 14 reference laboratories. A variety of PCR assays are available in the different laboratories, but serogroup identification by the *sia*D PCR is now available in nine laboratories.

3.2.4 Molecular Subtyping

Half the reference laboratories perform molecular subtyping routinely, with several additional laboratories sending isolates to other centres, as required. Molecular subtyping is done most commonly for outbreak identification and to inform national epidemiology. The molecular methods used include Multilocus enzyme electrophoresis, PCR-based methods, macro-restriction profiling (Pulsed-field gel electrophoresis) and Sequence Typing including MLST.

3.2.5 Antibiotic Sensitivity Testing

All laboratories test for sensitivity of meningococcal isolates to penicillin, and the majority also include rifampicin. The number of antibiotics tested by individual laboratories range from a minimum of three to as many as six. The E-test is the most widely used method of sensitivity testing and three laboratories use agar dilution.

3.2.6 Storage of strain collections

All laboratories permanently store isolates from cases, and the majority store carrier isolates, also. Storage by cryopreservation is the most widely used method and some laboratories include liquid nitrogen and/or freeze-drying. As an increasing number of cases are confirmed by non-culture methods, there are growing collections of CSF, whole blood and serum/plasma specimens.

3.2.7 Annual Reports

All laboratories produce some form of annual report, ranging from annual submission of surveillance data to national epidemiology centres, to full published reports giving full accounts of the reference laboratory activities.

3.3 European External Quality Assurance for *Neisseria meningitidis*

A collection of 15 isolates were distributed to 14 countries. The isolates were selected from the collection of *Neisseria meninigitidis* cultures at the Public Health Laboratory Service Meningococcal Reference Unit (MRU), Manchester Public Health Laboratory, Manchester, England. The isolates were selected to be representative of the hypervirulent lineages recently circulating in Europe. The panel also included isolates which are important in the global epidemiology of meningococcal infection. The isolates were freeze-dried and distributed by the PHLS National Collection of Typed Cultures, Central Public Health Laboratory.

The national meningococcal reference laboratory for each participating country was asked to perform strain characterisation using their standard methods. With the exception of one laboratory (serogrouping only), all laboratories performed serogrouping, serotyping and serosubtyping of the EQA isolate panel. The majority of laboratories performed serogrouping by slide agglutination or coagglutination, using serogroup specific polyclonal antibody reagents occasionally supplemented with serogroup specific monoclonal antibodies. One laboratory performed serogrouping by the dot blot method using monoclonal antibodies. Serotyping and serosubtyping was performed using monoclonal antibody reagents (mabs) prepared by the National Institute of Standards and Control (NIBSC), Potters Bar, England, with the exception of one laboratory which used mabs from various sources including NIBSC. Two laboratories use the dot blot method for serotyping and serosubtyping, and the remainder used the whole cell ELISA technique. The full panel of serogroup reagents was available in all the participating laboratories, as were serotyping and serosubtyping reagents except for a single laboratory

The results were scored against the consensus phenotype obtained from all the laboratory returns for each of the 15 EQA isolates. Isolates were scored for each determinant, giving a maximum isolate total of five in the case of those isolates reacting with the serosubtype P1.6 reagent, whereas the majority of isolates had a maximum score of four. The majority of laboratories achieved maximum scores for serogrouping, and errors were most common for isolates which were non- or poly-agglutinable. The single laboratory which only performed serogrouping achieved the maximum score. The results for serotyping and serosubtyping were more variable with the greatest variation in isolate scores obtained for serotyping versus serosubtyping. The overall scores ranged from a minimum of 45 (one laboratory) to the maximum of 62 (one laboratory). Three laboratories scored less than 50, five laboratories between 50 and 60, and two laboratories 60 and 62.

The EQA clearly demonstrated some problems in use of serotyping for meningococcal strain characterisation. Some of the problems appear to be reagent dependent, however, some laboratories will need to review their operating procedures for meningococcal serotyping. Although the majority of reagents were from common sources, and the same techniques were in widespread use by the participating laboratories, there are a number of steps which could give rise to the variation observed, with the possibility to improve the performance overall.

3.4 Summary of case data received for 1999 and 2000

Eighteen countries have supplied case data to the co-ordinating centre in PHLS CDSC, Colindale, London. Seventeen of these countries have supplied disaggregated case data: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Spain, UK, and Malta and the Czech Republic. Sweden has only provided an aggregated data set and hence Swedish has not been included in data analysis of the central database. No case data has been supplied by Luxembourg for 1999 or 2000. In Portugal an enhanced reference laboratory surveillance system was introduced in mid 1999. In the first year the number of participating laboratories, hospitals and clinicians was smaller than in subsequent years. This is reflected in the case numbers for 1999 and 2000. A noticeable improvement in surveillance and better case ascertainment is seen.

Most countries have provided data on laboratory confirmed cases only (either from laboratory reporting or from reference laboratories). A small number of countries have also provided data on clinical reporting and therefore included unconfirmed cases that were clinically diagnosed. In some countries these cases were reconciled with the laboratory confirmed cases in a single data set, in other instances two sets of data were provided.
Different laboratory confirmation practices are used between and within countries. In addition to culture confirmation, a growing number of countries used PCR, and a few countries used latex, serology, and microscopy for confirmation of cases.

Information on 8,668 cases was obtained from the collaborators for 1999, and information on 8,327 cases for 2000. A small percentage of the cases in each of these years was diagnosed solely on clinical grounds.

Data is fairly complete for age, serogroup, serotype and serosubtype, and method of confirmation. Source(s) of data influence the completeness of case ascertainment, and the completeness of typing information. The differing degree of completeness of data received from the collaborating countries reflects the differences in both the referral of isolates to reference laboratories, and in the reconciliation of data sources/surveillance systems within the countries. For example, Portugal was only able to provide data on cases referred to the reference laboratory. As the referral rate is known t be less than 80% of all culture confirmed cases, the numbers given for Portugal in the following tables will be lower than an expected national total. Similar issues may be relevant to data supplied from other countries, and countries are encouraged to let the centre know of any similar caveats to the data supplied.

3.5 Invasive meningococcal disease case data analyses

3.5.1 Incidence of culture-confirmed cases

The incidence of culture confirmed invasive meningococcal disease varied widely between the participating network countries over 1999 and 2000. (Table 2) In 2000, eight countries exhibited rates of under 1.0 per 100,000 population, two countries were between 1-2/100,000, four between 2-4/100,000, while Iceland, Ireland and Malta were all above 4/100,000 population. All countries exhibited small increases or decreases in the overall rate over the two years.

3.5.2 Incidence of PCR-confirmed cases

PCR-confirmed cases in Greece, Ireland and the UK (England and Wales) accounted for a large proportion of the total number of cases. The incidence of disease, including cases confirmed only by PCR, markedly increases the overall incidence of confirmed infection. (Table 3) In two countries, the number of cases confirmed only by PCR has exceeded the number culture-confirmed, in a third the number confirmed by PCR only is similar to the number confirmed by culture. Increasing use of PCR confirmation of cases in the coming years therefore has potential to increase the number of cases being detected, and hence to inflate the case numbers relative to years when PCR confirmation was not in use. Currently, because only a small number of countries are yet using routine PCR confirmation, most data analyses and comparison will be performed on culture-confirmed cases only.

Table 2: Incidence of culture-confirmed cases of invasive meningococcal disease, by country and year.

	1999			2000		
Country	No. of cases	Population	Incidence	No. of cases	Population	Incidence
Austria	80	7,795,788	1.03	58	7,795,788	0.74
Belgium	297	10,213,752	2.91	267	10,239,085	2.61
Czech Republic	89	10,282,784	0.87	57	10,272,503	0.56
Denmark	151	5,313,577	2.84	121	5,330,020	2.27
England & Wales	1704	51,820,200	3.29	1534	51,820,200	2.96
Finland	57	5,116,826	1.11	48	5,116,826	0.94
France	394	59,146,337	0.67	464	60,254,277	0.77
Germany	402	82,163,475	0.49	452	82,163,475	0.55
Greece	63	10,516,366	0.60	50	10,516,366	0.48
Iceland	21	269,735	7.79	16	269,735	5.93
Ireland	189	3,626,087	5.21	169	3,626,087	4.66
Italy	129	57,679,895	0.28	153	57,844,017	0.27
Malta	13	366,431	3.60	16	366,431	4.37
Netherlands	574	15,760,225	3.64	544	15,863,950	3.43
Norway	73	4,445,329	1.64	74	4,478,497	1.65
Portugal-lab*	21	9,920,760	0.21	59	9,920,760	0.59
Spain	602	39,418,017	1.53	692	39,465,702	1.75
Total	**4859**	**373,855,584**	**1.30**	**4774**	**375343719**	**1.27**

* Portugal's reference laboratory dataset is only a subset of the national meningococcal case data and in 1999 includes only a small number of reporting labs/hospitals

Table 3: Incidence of PCR-only confirmed cases of invasive meningococcal disease, by country and year.

	1999			2000		
Country	No. of cases	Population	Incidence	No. of cases	Population	Incidence
Austria	9	7,795,788	0.12	10	7,795,788	0.13
Czech Republic	1	10,282,784	0.01	0	10,272,503	0.00
England & Wales	1080	51,820,200	2.08	1117	51,820,200	2.16
Greece	60	10,516,366	0.57	110	10,516,366	1.05
Ireland	240	3,626,087	6.62	221	3,626,087	6.09
Norway	3	4,445,329	0.07	9	4,478,497	0.20
Total	**1393**	**88,486,554**	**1.57**	**1467**	**88,509,441**	**1.66**

Table 4: Age distribution of culture -confirmed meningococcal disease in Austria, Belgium, Czech Republic, Denmark, England & Wales, Finland, France, Germany, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Portugal* and Spain: 1999 & 2000

Year	Age group (years)																		
	<1		1-4		5-9		10-14		15-19		20-24		25-44		45-64		65+		Total known
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No
1999	771	16.4	1305	27.7	503	10.7	368	7.8	730	15.5	235	5.0	302	6.4	271	5.8	228	4.8	4713
2000	765	16.6	1225	26.7	457	9.9	304	6.6	580	12.6	265	5.8	397	8.6	345	7.5	258	5.6	4596
Total	**1536**	**16.4**	**2530**	**27.2**	**960**	**10.3**	**672**	**7.2**	**1310**	**14.1**	**500**	**5.4**	**699**	**7.5**	**616**	**6.6**	**486**	**5.2**	**9309**

Table 5: Age specific incidence of culture -confirmed meningococcal disease in the reporting countries (Austria, Belgium, Czech Republic, Denmark, E&W, Finland, France, Germany, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Portugal and Spain): 1999 & 2000

	Age group (years)									
Year	<1	1-4	5-9	10-14	15-19	20-24	25-44	45-64	65+	Not known
1999	771	1305	503	368	730	235	302	271	228	113
2000	765	1225	457	304	580	265	397	345	258	127
Population	4068596	16221278	20938532	21384693	22713060	24530704	109916949	86016761	58304391	
Incidence 1999	18.95	8.04	2.40	1.76	3.21	0.96	0.27	0.32	0.39	
Incidence 2000	18.80	7.55	2.18	1.45	2.55	1.08	0.36	0.40	0.44	
Average annual incidence 99/00	18.88	7.80	2.30	1.60	2.88	1.02	0.32	0.36	0.42	

Table 6 : Age distribution of PCR-only confirmed cases of invasive meningococcal disease in Austria, Czech Republic, England & Wales, Ireland and Norway : 1999 & 2000

Year	Age group																		
	<1 year		1-4 years		5-9 years		10-14 years		15-20 years		20-24 years		25-44 years		45-64 years		65+ years		Total known
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	
1999	227	17	391	30	144	11	108	8	189	14	51	4	103	8	77	6	25	2	1315
2000	235	17	426	31	128	9	95	7	159	12	72	5	125	9	92	7	22	2	1354
Total	**462**	**17**	**817**	**31**	**272**	**10**	**203**	**8**	**348**	**13**	**123**	**5**	**228**	**9**	**169**	**6**	**47**	**2**	**2669**

Table 7 : Age distribution of culture-confirmed and PCR-only confirmed meningococcal disease cases in Austria, Czech Republic, England & Wales, Ireland, and Norway: countries and years (1999 & 2000) combined

Year	Age group																		
	<1 year		1-4 years		5-9 years		10-14 years		15-20 years		20-24 years		25-44 years		45-64 years		65+ years		Total known
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	
Culture	**756**	19	**1098**	27	**386**	10	**250**	6	**514**	13	**210**	5	**306**	8	**268**	7	**211**	5	3999
PCR	**462**	**17**	**817**	**31**	**272**	**10**	**203**	**8**	**348**	**13**	**123**	**5**	**228**	**9**	**169**	**6**	**47**	**2**	**2669**

Table 8: Age specific incidence rate (per 100,000 population) of culture-confirmed meningococcal disease serogroup B in the EU reporting countries: 1999 & 2000

Year	Total	< 1 year		1-4 years		5-9 year		10-14 years		15-19 years		20-24 years		25-44 years		45-64 years		65 years plus	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
1999	3315	568	13.96	950	5.86	415	1.98	258	1.21	468	2.06	155	0.66	193	0.18	173	0.20	135	0.23
2000	3196	679	16.69	893	5.51	322	1.54	189	0.88	381	1.68	157	0.64	227	0.21	217	0.25	131	0.22

Table 9: Age specific incidence rate (per 100,000 population) of culture-confirmed meningococcal disease serogroup C in the EU reporting countries: 1999 & 2000

Year	Total	< 1 year		1-4 years		5-9 year		10-14 years		15-19 years		20-24 years		25-44 years		45-64 years		65 years plus	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
1999	1518	132	3.24	391	2.41	167	0.80	152	0.71	**293**	1.29	106	0.43	97	0.09	99	0.12	80	0.14
2000	1389	107	2.63	363	2.24	156	0.75	110	0.51	200	0.88	102	0.42	149	0.14	108	0.13	94	0.16

3.5.3 Age distribution of culture confirmed cases of invasive meningococcal disease (IMD)

The age distribution of cases of invasive meningococcal disease follows the expected pattern, with the majority of cases being in the children under five years of age.(Table 4) The combined age-specific incidence rates of invasive meningococcal disease in the contributing countries over 1999 & 2000 show the highest rate in infants (19 per 100,000), followed by the 1-4 year age group and the 15-19 year age group. (Table 5) A decrease is, however, seen in all age groups under 20 years of age between 1999 and 2000, while the older age groups exhibit an increase. This pattern is likely to reflect the impact of the UK Group C vaccination programme on overall incidence rates within that country and therefore within this project.

Austria, Czech Republic, England & Wales, Greece, Ireland and Norway confirmed a proportion of their invasive meningococcal disease cases by PCR-only. All except Greece supplied the age of these cases, and the age distribution of the PCR-only confirmed cases shows a very similar pattern to that of the culture-confirmed cases. (Tables 6 & 7) From 2000, Belgium have included PCR confirmed cases in the data-set reported, but this has not been included in the incidence tables below. It is expected that other countries will add PCR data as the methods become more readily available.

3.5.4 Incidence of meningococcal disease serogroups B, by year and agegroup

The incidence of serogroup B meningococcal disease in the European Union was highest in the children under one year of age. (Table 8). A smaller secondary peak in the incidence of serogroup B was seen in the 15-19 year old age group, but remains low in all older age groups. Between 1999 and 2000 an increase was seen in under ones (13.96 to 16.69), while a decrease was observed in 15-19 year olds (2.06 to 1.68).

3.5.5 Incidence of meningococcal disease serogroups C, by year and agegroup

Similar to the incidence of serogroup B, the incidence of serogroup C in the EU is greatest in the infant population, and shows a secondary peak in the 15-19 year olds. (Table 7) However, in both these age groups, and all others up to the age of 20 years a decrease in incidence rate was observed between 1999 to 2000. The largest decreases were shown in the under ones and in the 15-19 year olds: 3.24 to 2.63 and 1.29 to 0.88, respectively. These decreases are likely to be influenced by the impact of MenC conjugate vaccination programme introduction in the UK in late 1999. These two age groups were the first to receive vaccination in the UK.

Table 10: Proportion of meningitis and septicaemia in culture -confirmed cases of meningococcal disease by country, 1999

Country	Meningitis alone	Meningitis or Meningitis & Septicaemia combined		Septicaemia alone		Total
Austria	31	56	74%	20	26%	76
Belgium	107	202	75%	68	25%	270
Czech	42	63	71%	26	29%	89
Denmark	33	112	74%	39	26%	151
E&W	367	560	39%	860	61%	1420
Finland	33	33	66%	17	34%	50
France	270	314	80%	80	20%	394
Germany	167	237	77%	70	23%	307
Iceland	7	14	70%	6	30%	20
Ireland	25	46	24%	143	76%	189
Italy	69	88	68%	41	32%	129
Malta	0	0	0%	12	100%	12
Netherlands	195	341	80%	83	20%	424
Norway	18	42	64%	24	36%	66
Spain-lab*	156	276	63%	162	37%	438
Total	1520	2384	59%	1651	41%	4035

*Spanish reference laboratory data only is used here

Table 11: Proportion of meningitis and septicaemia in culture -confirmed cases of meningococcal disease by country, 2000

Country	Meningitis alone	Meningitis or Meningitis & Septicaemia combined		Septicaemia alone		Total
Austria	27	43	74%	15	26%	58
Belgium	90	167	67%	81	33%	248
Czech	38	46	82%	10	18%	56
Denmark	28	88	73%	33	27%	121
E&W	235	365	38%	608	63%	973
Finland	26	26	65%	14	35%	40
France	300	353	76%	111	24%	464
Germany	197	281	77%	84	23%	365
Iceland	6	10	71%	4	29%	14
Ireland	20	41	24%	128	76%	169
Italy	87	119	78%	34	22%	153
Malta	3	8	50%	8	50%	16
Netherlands	179	332	80%	81	20%	413
Norway	19	46	67%	23	33%	69
Spain-lab*	173	308	63%	181	37%	489
Total	1428	2233	61%	1415	39%	3648

* Spanish reference laboratory data only is used here

3.5.6 Proportion of meningitis to septicaemia in culture-confirmed cases of invasive meningococcal disease, 1999 & 2000

The proportion of culture confirmed cases reported with meningitis varied widely by country and also varied within each country over the two years. The range of proportion of cases with meningitis varied from 0-80% of cases in 1999 to 24-82% in 2000. (Tables 10 & 11) Consistently, England & Wales and Ireland show a predominance of septicaemia (without meningitis) as the clinical diagnosis.(Table 12) Equally consistent are Austria, Czech Republic, Denmark, France, Germany, Iceland and the Netherlands, in that more than 70 % of the cases diagnosed as meningitis or meningitis and septicaemia. In 1999, 100% of Malta's 12 culture-confirmed cases presented with septicaemia, but this reduced to 50% in 2000.

England & Wales and Ireland now both have a large proportion of their meningococcal disease cases being confirmed by PCR. Including cases confirmed only by PCR, increased the proportion of cases with meningitis by only 3-5% in both countries in each of the two years.

Overall, the proportion of culture-confirmed Group B cases presenting with meningitis was 59% and 61% in 1999 and 2000, respectively. (Table 13) All contributing countries, except England and Wales, Iceland, Ireland and Malta exhibited proportions of greater than 60% for meningitis to septicaemia.

The proportion of cases with meningitis in the culture-confirmed Group C cases was lower than for group B, 50% in 1999, and 53% in 2000. (Table 14) Once again, the majority of countries had greater than 60% of their Group C cases presenting with meningitis, whilst England and Wales, Ireland and Malta displayed the opposite pattern.

Table 12: Proportion of meningitis in culture confirmed cases of invasive meningococcal disease, 1999 & 2000

% meningitis	1999	2000
<50%	England & Wales Ireland Malta	England & Wales Ireland
50-70%	Finland Iceland Italy Malta Norway Spain	Belgium Finland Malta Norway Spain
> 70%	Austria Belgium Czech Republic Denmark France Germany Netherlands	Austria Czech Republic Denmark France Germany Italy Netherlands

Table 13 : Proportion of cases presenting with meningitis in the Group B culture confirmed cases, by country: 1999 & 2000

Country	Year	Meningitis alone	Meningitis OR (Meningitis & Septicaemia)		Septicaemia alone	Total	Year	Meningitis alone	Meningitis OR (Meningitis & Septicaemia)		Septicaemia alone	Total
Austria	**1999**	23	42	72%	16	58	**2000**	23	36	77%	11	47
Belgium	**1999**	67	132	75%	44	176	**2000**	54	101	67%	49	150
Czech Republic	**1999**	25	36	75%	12	48	**2000**	26	31	79%	8	39
Denmark	**1999**	28	97	76%	30	127	**2000**	21	75	76%	24	99
E&W	**1999**	249	347	43%	452	799	**2000**	166	252	42%.	353	605
Finland	**1999**	24	24	77%	7	31	**2000**	17	17	71%	7	24
France	**1999**	191	215	79%	55	270	**2000**	200	229	80%	57	286
Germany	**1999**	129	183	81%	42	225	**2000**	143	206	80%	52	258
Iceland	**1999**	2	5	50%	5	10	**2000**	3	4	80%	1	5
Ireland	**1999**	16	34	28%	88	122	**2000**	14	29	29%	70	99
Italy	**1999**	50	68	78%	19	87	**2000**	52	70	85%	12	82
Malta	**1999**	0	0	0%	6	6	**2000**	3	8	53%	7	15
Netherlands	**1999**	173	289	80%	72	361	**2000**	146	265	82%	60	325
Norway	**1999**	14	34	62%	21	55	**2000**	14	35	69%	16	51
Spain-lab*	**1999**	75	154	63%	89	243	**2000**	107	180	64%	102	282
TOTAL	**1999**	**1066**	**1660**	**63%**	**958**	**2618**	**2000**	**989**	**1538**	**65%**	**829**	**2367**

*Spanish reference laboratory data only is used here.

Table 14 : Proportion of cases presenting with meningitis in the Group C culture -confirmed cases, by country: 1999& 2000

Country	Year	Meningitis alone	Meningitis OR (Meningitis & Septicaemia		Septicaemia alone	Total	Year	Meningitis alone	Meningitis OR (Meningitis & Septicaemia)		Septicaemia alone	Total
Austria	**1999**	6	10	767%	3	13	**2000**	4	7	70%	3	10
Belgium	**1999**	31	54	72%	21	75	**2000**	30	53	65%	29	82
Czech Republic	**1999**	15	25	68%	12	37	**2000**	6	9	82%	2	11
Denmark	**1999**	4	13	62%	8	21	**2000**	6	11	61%	7	18
E&W	**1999**	97	183	33%	368	551	**2000**	48	86	29%	209	295
Finland	**1999**	5	5	56%	4	9	**2000**	6	6	60%	4	10
France	**1999**	50	67	80%	17	84	**2000**	56	70	71%	28	98
Germany	**1999**	30	44	65%	24	68	**2000**	42	57	70%	24	81
Iceland	**1999**	5	9	90%	1	10	**2000**	3	6	75%	2	8
Ireland	**1999**	9	12	20%	49	61	**2000**	5	11	18%	51	62
Italy	**1999**	15	17	65%	9	26	**2000**	11	18	55%	15	33
Malta	**1999**	0	0	0%	3	3	**2000**	0	0	0%	1	1
Netherlands	**1999**	18	45	85%	8	53	**2000**	30	61	77%	18	79
Norway	**1999**	4	7	78%	2	9	**2000**	4	10	91%	1	11
Spain-lab*	**1999**	74	111	61%	70	181	**2000**	63	122	62%	76	198
TOTAL	**1999**	**363**	**602**	**50%**	**599**	**1201**	**2000**	**314**	**527**	**53%**	**470**	**997**

*Spanish reference laboratory data only is used here

Table 15: Proportion of invasive meningococcal disease in culture -confirmed cases by serogroup and country – 1999

Country	Group B		Group C		Other		Not known	Total known
	No	%	No	%	No	%	No	
Austria	60	75%	14	18%	5	6%	1	79
Belgium	200	71%	77	27%	4	1%	16	281
Czech Republic	48	54%	37	42%	3	3%	1	88
Denmark	127	84%	21	14%	2	1%	1	150
E & W	960	56%	640	38%	100	6%	4	1700
Finland	35	66%	9	17%	9	17%	4	53
France	270	72%	84	22%	20	5%	20	374
Germany	294	73%	88	22%	19	5%	1	401
Greece	34	54%	22	35%	7	11%	0	63
Iceland	11	52%	10	48%	0	0%	0	21
Ireland	122	65%	61	32%	6	3%	0	189
Italy	87	77%	26	23%	0	0%	47	113
Malta	6	46%	3	23%	3	23%	1	12
Netherlands	470	82%	82	14%	22	4%	0	574
Norway	59	81%	10	14%	4	5%	0	73
Portugal-lab*	5	24%	15	71%	1	5%	0	21
Spain*	346	57%	230	38%	26	4%	0	602
Total	3134	65%	1429	30%	231	5%	96	4794

* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

*Spanish reference laboratory data is used here

Table 16: Proportion of invasive meningococcal disease in culture -confirmed cases by serogroup and country – 2000

Country	Group B		Group C		Other		Not known	Total known
	No	%	No	%	No	%	No	
Austria	47	81%	10	17%	1	2%	0	58
Belgium	165	64%	85	33%	7	3%	10	257
Czech Republic	40	75%	11	21%	2	4%	4	53
Denmark	99	83%	18	15%	2	2%	2	119
E & W	936	61%	451	29%	147	10%	0	1534
Finland	30	64%	11	23%	6	13%	1	47
France	286	66%	98	23%	50	12%	30	434
Germany	321	71%	96	21%	35	8%	0	452
Greece	35	70%	11	22%	4	8%	0	50
Iceland	6	38%	9	56%	1	6%	0	16
Ireland	99	59%	62	37%	8	5%	0	169
Italy	82	71%	33	28%	1	1%	37	116
Malta	15	94%	1	6%	0	0%	0	16
Netherlands	420	77%	106	19%	18	3%	0	544
Norway	53	72%	12	16%	9	12%	0	74
Portugal-lab*	27	46%	29	49%	3	5%	0	59
Spain*	431	62%	235	34%	26	4%	0	692
Total	3092	66%	1278	27%	320	7%	84	4690

*Portugal's reference laboratory data only is used here

*Spanish reference laboratory data is used here

3.5.7 Distribution of serogroups in invasive meningococcal disease, 1999 & 2000

Group B is the major cause of invasive meningococcal disease in Europe, causing the majority of infections in all countries except Iceland. (Tables 15 & 16) The second most common serogroup is group C, but the proportion of cases caused by group C infection is quite variable between countries, ranging from 15% to 56% in 2000. Most countries are fairly consistent across the two years, but it is notable that the proportion of group C infections in England and Wales has declined between 1999 and 2000. This reflects the early impact of conjugate meningococcal group C vaccine. (Table 17).
The serogroup distribution of the PCR-only confirmed cases is difficult to interpret, as the distribution will be affected by the serogroups each particular country is testing for. (Tables 18 & 19) The proportion made up by the cases that were PCR-confirmed but not grouped was notable and again may reflect the algorithm and the methods used in each country.

Table 17: Proportion of cases due to serogroup C by country, 1999-2000

% Group C	1999	2000
<10%	-	Malta
10-19%	Austria Denmark Finland Netherlands Norway	Austria Denmark Netherlands Norway
20-29%	Belgium France Germany Italy Malta	Czech Republic England & Wales Finland France Germany Greece Italy
30-39%	England & Wales Greece Ireland Spain	Belgium Ireland Spain
40+%	Czech Republic Iceland Portugal-lab	Iceland Portugal-lab

Table 18 : Proportion of invasive meningococcal disease in PCR-confirmed cases by serogroup and country – 1999

Country	Group B		Group C		Other		Not grouped		Total known
	No	%	No	%	No	%	No	%	No
Austria	9	100%	0	0%	0	0%	0	0%	9
Czech Republic	1	100%	0	0%	0	0%	0	0%	1
E & W	501	46%	342	32%	0	0%	237	22%	1080
Greece-lab*	34	57%	5	8%	3	5%	18	30%	60
Ireland	156	65%	72	30%	0	0%	12	5%	240
Norway	1	33%	1	33%	0	0%	1	33%	3
Total	702	50%	420	30%	3	0%	268	19%	1393

* Greek reference laboratory data only was used here

Table 19 : Proportion of invasive meningococcal disease in PCR-confirmed cases by serogroup and country – 2000

Country	Group B		Group C		Other		Not grouped		Total known
	No	%	No	%	No	%	No	%	No
Austria	6	60%	4	40%	0	0%	0	0%	10
E & W	704	63%	260	23%	18	2%	135	12%	1117
Greece-lab*	45	41%	9	8%	20	18%	36	33%	110
Ireland	140	63%	76	34%	0	0%	5	2%	221
Norway	7	78%	1	1%	0	0%	1	11%	9
Total	902	61%	350	24%	38	3%	177	12%	1467

* Greek reference laboratory data only was used here

Table 20: No. (Proportion) of invasive meningococcal disease in culture -confirmed cases other than serogroup B and C, by country – 1999

Country	Group W135		Group Y		Group X		Group 29E		Not known of total	Total known
	No	%	No	%	No	%	No	%	No	No
Austria	2	2.5%	3	3.8%	0	0%	0	0%	1	79
Belgium	1	0.4%	2	0.7%	0	0%	0	0%	16	281
Czech Republic	0	0%	2	2.3%	0	0%	0	0%	1	88
Denmark	0	0%	1	0.7%	1	0.7%	0	0%	1	150
E & W	50	2.9%	19	1.1%	5	0.3%	4	0.2%	4	1700
Finland	1	1.9%	8	15.1%	0	0%	0	0%	4	53
France	8	2.1%	9	2.4%	0	0%	0	0%	20	374
Germany	4	1.0%	11	2.7%	1	0.2%	1	0.2%	1	401
Greece	2	3.1%	1	1.6%	0	0%	0	0%	0	63
Iceland	0	0%	0	0%	0	0%	0	0%	0	21
Ireland	4	2.1%	0	0%	0	0%	0	0%	0	189
Italy	0	0%	0	0%	0	0%	0	0%	53	107
Malta	2	17%	0	0%	0	0%	1	8%	1	12
Netherlands	11	1.9%	4	0.7%	1	0.2	0	0%	0	574
Norway	1	1.4%	2	2.7%	1	1.4%	0	0%	0	73
Portugal-lab*	1	4.8%	0	0%	0	0%	0	0%	0	21
Spain*	2	0.3%	3	0.5%	0	0%	2	0.3%	0	602
Total	89	1.9%	65	1.4%	9	0.2%	8	0.2%	101	4789

* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

* Spanish reference laboratory data only is used here

Table 21: No. (Proportion) of invasive meningococcal disease in culture -confirmed cases other than serogroup B and C, by country – 2000

Country	Group W135		Group Y		Group X		Group 29E		Not known of total	Total known
	No	%	No	%	No	%	No	%	No	No
Austria	1	1.7%	0	0%	0	0%	0	0%	0	58
Belgium	4	1.6%	2	0.8%	0	0%	1	0.4%	10	257
Czech Republic	2	3.8%	0	0%	0	0%	0	0%	4	53
Denmark	1	0.8%	0	0%	0	0%	0	0%	2	119
E & W	97	6.3%	25	1.6%	4	0.3%	4	0.3%	0	1534
Finland	3	6.4%	2	4.3%	0	0%	0	0%	1	47
France	38	8.8%	7	1.6%	1	0.2%	0	0%	30	434
Germany	15	3.3%	16	3.5%	0	0%	0	0%	0	452
Greece	3	6.0%	0	0%	0	0%	0	0%	0	50
Iceland	0	0%	1	6.3%	0	0%	0	0%	0	16
Ireland	3	1.8%	4	2.4%	0	0%	0	0%	0	169
Italy	0	0%	1	0.9%	0	0%	0	0%	37	116
Malta	0	0%	0	0%	0	0%	0	0%	0	16
Netherlands	15	2.8%	2	0.4%	1	0.2%	0	0%	0	544
Norway	5	6.8%	3	4.1%	0	0%	0	0%	0	74
Portugal-lab*	2	3%	0	0%	0	0%	0	0%	0	59
Spain*	10	1.4%	8	1.2%	1	0.1%	0	0%	0	692
Total	199	4.2%	71	1.5%	7	0.1%	5	0.1%	84	4690

*** Portugal's reference laboratory data only is used here*** Spanish reference laboratory data only is used here

Other than groups B and C, serogroups W135, Y, and X, 29E were the most common groups identified. Group W135 is the most common of these and the number of such cases increased between 1999 and 2000.(Tables 20 & 21) This probably reflects the increase in W135 associated with the Hajj in 2000. In both years England, Greece, the Netherlands and Portugal all had W135 as the third serogroup for both 1999 and 2000.(Table 22) However, eight countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Norway, and Spain-lab) all had serogroup Y as the third group in 1999, but in 2000 this changed to W135.

Table 22: Major serogroup of invasive meningococcal disease cases other than groups B and C amongst the contributing countries

Major serogroup	1999	2000
W135	England & Wales Greece Ireland Malta Netherlands Portugal-lab	Austria Belgium Czech Republic Denmark England & Wales Finland France Greece-lab Netherlands Norway Portugal-lab Spain-lab
X	Denmark (with Y)	
Y	Austria Belgium Czech Republic Denmark (with X) Finland France Germany Norway Spain-lab	Germany Iceland Ireland Italy
29E	-	-

Table 23: No. of cases (%) of group C serotypes by country : 1999 (cases where serotype known/given)

Country	P2.2a		P2.2b		NT		Other		Total
	No	%	No	%	No	%	No	%	
Austria	1	7%	6	43%	5	36%	2	14%	14
Belgium	29	38%	34	44%	10	13%	4	5%	77
Czech Republic	20	83%	3	13%	1	4%	0	0%	24
Denmark	8	38%	1	5%	2	10%	10	48%	21
E & W	429	67%	65	10%	123	19%	23	4%	640
Finland	1	11%	2	22%	6	67%	0	0%	9
France	31	31%	38	38%	24	24%	7	7%	100
Germany	33	38%	24	27%	20	23%	11	13%	88
Greece	14	78%	0	0%	4	22%	0	0%	18
Ireland	34	81%	4	10%	1	2%	3	7%	42
Italy	15	75%	0	0%	3	15%	2	10%	20
Malta	1	100%	0	0%	0	0%	0	0%	1
Netherlands	61	74%	14	17%	4	5%	3	4%	82
Norway	4	40%	1	10%	1	10%	4	40%	10
Spain	40	17%	175	76%	8	3%	7	3%	230
Total	721	52%	367	27%	212	15%	76	6%	1376

Table 24: No. of cases (%) of group C serotypes by country : 2000 (in cases where serotype known/given)

Country	P2.2a		P2.2b		NT		Other		Total
	No	%	No	%	No	%	No	%	
Austria	6	60%	4	40%	0	0%	0	0%	10
Belgium	40	47%	31	36%	10	12%	4	5%	85
Czech Republic	9	90%	0	0%	1	10%	0	0%	10
Denmark	12	67%	1	6%	1	6%	4	22%	18
E & W	332	74%	31	7%	76	17%	12	3%	451
Finland	3	30%	0	0%	6	60%	1	10%	10
Germany	38	40%	17	18%	35	36%	6	6%	96
Greece	8	80%	1	10%	1	10%	0	0%	10
Ireland	47	92%	3	6%	1	2%	0	0%	51
Italy	12	50%	6	25%	5	21%	1	4%	24
Malta	0	0%	1	100%	0	0%	0	0%	1
Netherlands	71	67%	21	20%	10	9%	4	4%	106
Norway	8	21%	30	77%	0	0%	1	3%	39
Spain	56	24%	147	63%	31	13%	1	0%	235
Total	642	56%	293	26%	177	15%	34	3%	1146

Table 25: No. of cases (%) of selected group B phenotypes by country : 1999 (cases where serotype known/given)

	B:NT:1.9		B:15:1.7,1.16		B:4:1.4		B:2a subtypes		B:NT:P1.5 and/or P1.2		B:NT:NT/P 1.15/NT		B:P3.1:N T/NT/NT		B:NT:NT/ NT/NT		OTHER		TOTAL
	No.	%	No.	%	No.	%	No	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Austria	0	0	11	18.3	0	0	0	0	5	8.3	0	0	0	0	4	6.7	40	66.7	60
Belgium	1	0.5	13	6.6	86	43.4	1	0.5	9	4.5	1	0.5	6	0	9	3.6	72	36.4	198
Czech Rep.	0	0	0	0	0	0	3	8.6	2	5.7	0	0	0	0	4	11.4	26	74.3	35
Denmark	2	1.6	71	57.7	3	2.4	0	0	1	0.8	3	2.4	2	1.6	3	2.4	38	30.9	123
E&W	50	5.2	34	3.6	239	25.0	9	0.9	27	2.8	130	13.6	16	1.7	45	4.7	405	42.4	955
Finland	0	0	1	3.0	2	6.1	3	9.1	1	3.0	0	0	0	0	3	9.1	23	69.7	33
France	7	2.3	24	7.9	23	7.6	0	0	18	6.0	9	3.0	10	3.3	43	14.2	168	55.6	302
Greece	1	3.3	0	0	2	6.7	3	10.0	0	0	1	3.3	0	0	1	3.3	22	73.3	30
Germany	5	1.7	41	13.9	21	7.1	2	0.7	26	8.8	7	2.4	2	0.7	15	5.1	175	59.5	294
Ireland	4	4.7	0	0	27	31.4	0	0	4	4.7	9	10.5	0	0	6	7.0	36	41.9	86
Italy	0	0	2	3.0	3	4.5	0	0	0	0	0	0	0	0	1	1.5	60	90.9	66
Malta	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	100.0	6
Netherlands	5	1.1	11	2.3	148	31.5	0	0	5	1.1	8	1.7	8	4.5	21	4.5	264	56.2	470
Norway	0	0	13	22.8	5	8.8	0	0	0	0	3	5.3	3	5.3	1	1.8	32	56.1	57
Spain	4	1.2	9	2.6	8	2.3	1	0.3	10	2.9	23	6.6	17	4.9	51	14.7	223	64.5	346
TOTAL	79	2.6	230	7.5	567	18.5	22	0.7	108	3.5	194	6.3	64	2.1	207	6.8	1590	51.8	3061

TOTAL = all culture confirmed serotyped/serosubtyped B's incl. B; NT; NT/NT/NT

Table 26: No. of cases (%) of selected group B phenotypes by country : 2000 (cases where serotype known/given)

	B:NT:P1.9		B:15:1.7,1.16		B:4:1.4		B:2a subtypes		B:NT:P1.5 and/or P1.2		B:NT:NT/ P1.15/NT		B:P3.1:NT/ NT/NT		B:NT:NT/NT /NT		OTHER		TOTAL
	No.	%	No.	%	No.	%	No.	%	No	%	No.	%	No.	%	No.	%	No.	%	No.
Austria	2	4.4	11	24.4	2	4.4	0	0	4	8.9	1	2.2	0	0	4	4.4	21	46.7	45
Belgium	0	0	8	4.8	72	43.6	0	0	9	5.5	0	0	2	1.2	1	0.6	73	44.2	165
Czech Rep.	0	0	1	2.9	0	0	3	8.8	1	2.9	1	2.9	0	0	6	17.6	22	64.7	34
Denmark	4	4.1	45	45.9	2	2.0	0	0	2	2.0	2	2.0	0	0	4	4.1	39	39.8	98
E&W	71	7.6	37	4.0	210	22.4	17	1.8	28	3.0	117	12.5	18	1.9	40	4.3	398	42.5	936
Finland	2	6.9	0	0	4	13.8	3	10.3	1	3.4	0	0	0	0	0	0	19	65.5	29
France	N/A		N/A		N/A		N/A		N/A		N/A		N/A		N/A		N/A		N/A
Greece	0	0	0	0	3	9.4	3	9.4	1	3.1	0	0	0	0	1	3.1	24	75.0	32
Germany	6	1.9	43	13.4	21	6.5	1	0.3	27	8.4	6	1.9	2	0.6	25	7.8	190	59.2	321
Ireland	5	6.0	1	1.2	26	31.3	0	0	5	6.0	7	8.4	0	0	1	1.2	38	45.8	83
Italy	1	1.4	7	10.1	6	8.7	0	0	3	4.3	0	0	0	0	1	1.4	51	73.9	69
Malta	0	0	0	0	0	0	0	0	0	0	4	31.0	0	0	0	0	9	69.0	13
Netherlands	8	1.9	8	1.9	136	32.4	0	0	7	1.7	5	1.2	6	1.4	18	4.3	232	55.2	420
Norway	1	2.1	12	25.0	3	6.3	0	0	1	2.1	4	8.3	1	2.1	0	0	26	54.2	48
Spain	10	2.3	5	1.2	8	1.9	2	0.5	10	2.3	22	5.1	28	6.5	81	18.8	265	61.5	431
TOTAL	110	4.0	178	6.5	493	18.1	29	1.1	99	3.6	169	6.2	57	2.1	182	6.7	1407	51.7	2724

TOTAL = all culture confirmed serotyped/serosubtyped B's incl. B; NT; NT/NT/NT

3.5.8 Distribution of serotypes of group C and B meningococcal disease, 1999 & 2000

The leading serotype of group C was type 2a with C2b as the second most common serotype. The proportion of all group Cs of the C2a serotype increased slightly between 1999 and 2000, and this proportion increased in 9 of the 14 countries who supplied data for both years.(Tables 23 & 24) In 1999, serotype 2a was the leading type associated with group C disease in nine of the 15 countries who contributed data. By 2000, serotype 2a had become the most common type in two additional countries. (Table 27).

Table 27: Major serotype of group C invasive meningococcal disease amongst the contributing countries 1999/2000

Major serotype	1999	2000
2a	Czech Republic Denmark England and Wales Germany Greece Italy Ireland Netherlands Norway	Austria Belgium Czech Republic Denmark England and Wales Germany Greece Ireland Italy Netherlands
2b	Austria Belgium France Spain	Norway Spain
NT	Finland	Finland

Group B infections appear to be more diverse, with more than 50% of cases in the "other" category. (Tables 25 & 26) There are considerable differences between countries in strain composition. Of the two major group B sero-subtypes identified (B:15:1.7,1.16 and B:4:1.4), the leading strain in most countries was consistent between years.(Table 28).In both years 7% of the serotyped group B strains were not-typable, and in Czech Republic and Spain this was in the range of 11-19%.

Table 28: Major serotype of group B invasive meningococcal disease amongst the contributing countries 1999/2000

Major serotype	1999	2000
B:15:P1.7, P.16	Austria Denmark France (with B4: P1.4) Germany Norway	Austria Denmark Germany Italy Norway
B:4: P1.4	Belgium England & Wales Finland France (with B:15:P1.7, P.16) Greece Ireland Italy Netherlands	Belgium England & Wales Finland Greece Ireland Netherlands

Table 29: Age specific incidence (per 100,000) of culture -confirmed Group B meningococcal disease by country : 1999

Country	Total cases	<1 yr		1-4yrs		5-9yrs		10-14yrs		15-19yrs		20-24yrs		25-44yrs		45-64yrs		65+yrs		NK
		No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No
Austria	60	11	12.13	13	3.58	8	1.73	9	2.04	7	1.39	2	0.31	4	0.17	6	0.34	0	0.00	0
Belgium	200	17	14.94	68	14.61	26	4.15	18	3.00	40	6.45	14	2.23	7	0.23	6	0.25	4	0.02	0
Czech Republic	48	10	11.15	9	2.41	6	0.98	2	0.31	9	1.26	5	0.56	5	0.17	2	0.08	0	0.00	0
Denmark	127	15	22.66	31	11.13	18	5.39	12	4.14	27	9.39	2	0.57	3	0.19	10	0.74	9	0.11	0
E&W	960	244	37.58	298	10.88	89	2.62	49	1.53	97	3.21	40	1.14	56	0.37	43	0.37	38	0.05	6
Finland	35	4	6.37	8	3.05	3	0.95	0	0.00	9	2.75	2	0.66	5	0.33	2	0.16	2	0.03	0
France	270	45	5.80	78	2.53	31	0.78	20	0.51	38	0.87	15	0.35	26	0.15	11	0.08	6	0.01	0
Germany	294	45	5.83	68	2.14	18	0.42	23	0.49	76	1.64	15	0.33	17	0.07	15	0.07	9	0.01	8
Iceland	11	3	74.66	3	16.85	0	0.00	0	0.00	3	14.1	1	4.74	1	1.24	0	0.00	0	0.00	0
Ireland	122	35	71.64	43	21.34	12	4.24	6	1.84	11	3.24	8	2.73	3	0.30	1	1.42	3	0.07	0
Italy	86	16	2.81	17	0.84	5	0.21	4	0.14	20	0.65	4	0.13	10	0.06	6	0.06	4	0.01	0
Malta	6	0	0.00	0	0.00	1	3.72	2	6.99	0	0.00	0	0.00	1	0.91	2	2.47	0	0.00	0
Netherlands	470	77	38.55	151	19.45	65	6.54	46	4.87	42	4.55	16	1.65	26	0.52	26	0.69	21	0.10	0
Norway	59	8	13.73	23	9.44	8	2.61	4	1.46	7	2.64	0	0.00	1	0.08	5	0.50	3	0.04	0
Portugal-lab*	5	1	0.94	2	0.40	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2
Spain-notifs*	578	37	9.58	138	9.00	125	6.49	63	2.96	82	3.09	31	0.96	28	0.23	38	0.43	36	0.55	0
TOTAL	3331	568	13.96	950	5.86	415	1.98	258	1.21	468	2.06	155	0.66	193	0.18	173	0.20	135	0.23	16

* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

*Spain-notification data is used as it is more representative of the population than the reference laboratory dataset

Table 30: Age specific incidence (per 100,000) of culture -confirmed Group B meningococcal disease by country : 2000

Country	Total cases	<1 yr		1-4yrs		5-9yrs		10-14yrs		15-19yrs		20-24yrs		25-44yrs		45-64yrs		65+yrs		NK
		No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No
Austria	47	7	7.72	18	4.96	4	0.87	1	0.23	3	0.60	0	0.00	3	0.13	6	0.3	5	0.43	0
Belgium	165	27	23.91	45	9.69	25	4.03	11	1.81	26	4.23	8	1.27	10	0.33	9	0.4	4	0.23	0
Czech Republic	40	10	11.12	7	1.93	2	0.34	2	0.31	12	1.74	1	0.11	3	0.14	2	0.1	1	0.07	0
Denmark	99	15	22.62	24	8.75	12	3.51	7	2.34	16	5.69	4	1.18	6	0.38	6	0.4	9	1.14	0
E&W	936	242	37.27	285	10.41	74	2.18	46	1.43	96	3.17	29	0.83	67	0.44	58	0.5	35	0.42	4
Finland	30	7	11.14	3	1.14	1	0.32	2	0.61	3	0.92	3	0.98	2	0.13	7	0.6	2	0.27	0
France	286	69	9.38	54	1.81	17	0.45	19	0.49	41	1.03	33	0.88	24	0.14	21	0.1	8	0.08	0
Germany	321	37	4.80	91	2.86	17	0.40	17	0.36	57	1.23	22	0.49	25	0.10	32	0.2	20	0.15	3
Iceland	6	1	24.89	1	5.62	1	4.48	0	0.00	2	9.38	1	4.74	0	0.00	0	0.0	0	0.00	0
Ireland	99	28	57.31	40	19.85	8	2.83	3	0.92	9	2.65	5	1.70	1	0.10	5	7.1	0	0.00	0
Italy	82	10	1.85	15	0.70	12	0.43	3	0.11	6	0.20	10	0.28	21	0.12	4	0.0	1	0.01	0
Malta	15	1	19.57	5	23.17	3	11.17	3	10.49	1	3.57	0	0.00	1	0.91	1	1.23	0	0.00	0
Netherlands	420	74	36.68	133	17.01	55	5.49	26	2.71	47	5.07	12	1.26	30	0.6	24	0.6	19	0.88	0
Norway	53	5	8.42	18	7.41	5	1.62	1	0.35	7	2.64	9	3.23	1	0.08	6	0.6	1	0.15	0
Portugal-lab*	27	14	13.16	4	0.89	3	0.55	1	0.15	0	0.00	0	0.00	1	0.04	1	0.04	1	0.07	2
Spain-notifs*	579	132	33.70	150	9.75	83	4.28	47	2.28	55	2.17	20	0.64	32	0.26	35	0.39	25	0.38	0
TOTAL	3205	679	16.69	893	5.51	322	1.54	189	0.88	381	1.68	157	0.64	227	0.21	217	0.25	131	0.22	9

*Spain-notification data is used as it is more representative of the population than the reference laboratory dataset

*** Portugal's reference laboratory data only is used here**

Table 31: Age specific incidence (per 100,000) of culture -confirmed Group C meningococcal disease by country : 1999

Country	Total cases	<1 yr		1-4yrs		5-9yrs		10-14yrs		15-19yrs		20-24yrs		25-44yrs		45-64yrs		65+yrs		NK
		No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No
Austria	15	1	1.10	3	0.83	1	0.22	1	0.23	6	1.19	1	0.15	1	0.042	0	0.00	0	0.00	
Belgium	77	3	2.64	23	4.94	8	1.28	13	2.17	15	2.42	3	0.48	2	0.065	3	0.13	7	0.04	
Czech Republic	37	4	4.46	8	2.14	5	0.82	2	0.31	12	1.68	3	0.33	1	0.035	1	0.04	1	0.01	
Denmark	21	1	1.51	2	0.72	0	0.00	2	0.69	7	2.43	3	0.86	1	0.064	3	0.22	2	0.03	
E&W	640	63	9.70	145	5.29	73	2.15	55	1.71	130	4.3	38	1.09	50	0.326	46	0.39	30	0.04	10
Finland	9	0	0.00	3	1.14	0	0.00	1	0.30	0	0	0	0	2	0.132	2	0.16	1	0.01	
France	84	9	1.16	22	0.71	10	0.25	11	0.28	20	0.46	6	0.14	1	0.006	2	0.01	3	0.00	
Germany	88	10	1.30	23	0.72	3	0.07	7	0.15	21	0.45	8	0.18	6	0.024	3	0.01	5	0.00	2
Iceland	10	0	0.00	3	16.85	1	0.00	1	4.92	4	18.8	0	0	0	0	1	0.00	0	0.00	
Ireland	61	12	24.56	17	8.44	8	2.83	6	1.84	10	2.95	3	1.02	2	0.197	2	2.84	1	0.02	
Italy	26	1	0.19	3	0.14	1	0.04	1	0.04	3	0.1	2	0.05	7	0.045	6	0.04	2	0.00	
Malta	3	0	0.00	1	4.63	0	0.00	2	6.99	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0
Netherlands	82	9	4.51	20	2.58	6	0.60	5	0.53	16	1.73	0	0	7	0.139	7	0.18	12	0.06	
Norway	10	1	1.72	0	0.00	3	0.98	0	0.00	4	1.51	0	0	0	0	1	0.10	1	0.01	
Portugal-lab*	15	3	2.82	4	0.89	1	0.18	1	0.15	2	0.26	0	0.00	0	0.00	0	0.00	0	0.00	4
Spain-notifs*	356	15	3.88	114	7.44	47	2.41	44	2.07	43	1.62	39	1.21	17	0.14	22	0.25	15	0.23	
TOTAL	1534	132	3.24	391	2.41	167	0.80	152	0.71	293	1.29	106	0.43	97	0.09	99	0.12	80	0.14	16

* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

*Spain-notification data is used as it is more representative of the population than the reference laboratory dataset

Table 32: Age specific incidence (per 100,000) of culture -confirmed Group C meningococcal disease by country : 2000

Country	Total cases	<1 yr		1-4yrs		5-9yrs		10-14yrs		15-19yrs		20-24yrs		25-44yrs		45-64yrs		65+yrs		NK
		No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No	Incid	No
Austria	10	2	2.21	0	0.00	0	0.00	0	0.00	2	0.40	3	0.46	2	0.08	0	0.00	1	0.09	
Belgium	85	7	6.20	25	5.38	14	2.25	10	1.65	10	1.63	6	0.95	4	0.13	2	0.08	6	0.35	1
Czech Republic	11	1	1.11	2	0.55	2	0.34	1	0.15	3	0.43	0	0	2	0.07	0	0.00	0	0.00	
Denmark	18	1	1.51	5	1.82	3	0.88	2	0.67	1	0.36	1	0.29	2	0.13	0	0.00	3	0.38	
E&W	451	16	2.46	90	3.29	50	1.47	34	1.06	43	1.42	43	1.23	71	0.46	60	0.51	41	0.50	3
Finland	11	1	1.59	2	0.76	2	0.63	2	0.61	0	0.00	1	0.33	1	0.07	0	0.00	2	0.27	
France	98	10	1.36	24	0.81	10	0.26	7	0.18	13	0.33	7	0.19	8	0.05	8	0.06	11	0.12	
Germany	96	1	0.13	25	0.79	3	0.07	7	0.15	30	0.65	5	0.11	10	0.04	9	0.04	2	0.01	4
Iceland	9	0	0.00	4	22.47	0	0.00	0	0.00	3	14.07	1	4.74	1	1.24	0	0.00	0	0.00	
Ireland	62	8	16.38	12	5.95	4	1.41	11	3.37	19	5.60	4	1.36	3	0.3	0	0.00	1	0.24	
Italy	33	1	0.18	5	0.23	2	0.07	2	0.07	10	0.33	5	0.14	7	0.04	1	0.00	0	0.00	
Malta	1	0	0.00	0	0.00	0	0.00	0	0.00	1	3.57	0	0.00	0	0.00	0	0.00	0	0.00	0
Netherlands	106	2	0.99	22	2.81	15	1.50	11	1.15	18	1.94	9	0.94	8	0.16	14	0.36	7	0.33	
Norway	12	0	0.00	3	1.23	3	0.97	1	0.35	2	0.75	1	0.36	0	0	2	0.19	0	0.00	
Portugal-lab*	29	4	3.76	8	1.78	3	0.55	2	0.31	5	0.64	2	0.24	0	0.00	0	0.00	0	0.00	5
Spain-notifs*	370	53	13.53	136	8.84	45	2.32	20	0.97	40	1.58	14	0.45	30	0.24	12	0.14	20	0.30	
TOTAL	1402	107	2.63	363	2.24	156	0.75	110	0.51	200	0.88	102	0.42	149	0.14	108	0.13	94	0.16	13

* Portugal's reference laboratory data only is used here

*Spain-notification data is used as it is more representative of the population than the reference laboratory dataset

3.5.9 Age-specific incidence of group B and C infection by serogroup and country

The incidence of culture-confirmed meningococcal disease serogroups B and C by age group varied widely amongst the participating countries. However, all showed a similar pattern in the age groups with the highest and the lowest incidence rates.

For the incidence of serogroup B, all countries had the highest rate in the under ones year olds, and a second peak in incidence in the 15-19 year olds. This held true for both 1999 and 2000. (Table 29 & 30) The variation in rates between countries was very wide, but this may reflect small numbers in some countries. In the under one year old age group it varied from 0.00 (Malta) to 74.66 (Iceland) in 1999, and from 1.85 (Italy) to 57.31 (Ireland) in 2000.

Once again, the majority of countries in the EU displayed the highest incidence rate of serogroup C disease in the under one year olds, with a secondary increase in incidence in the 15-19 year olds. (Tables 31 & 32) Countries not displaying this were Finland and Iceland in 1999, and the Netherlands and Norway in 2000. These countries had a higher rate in the 1-4 year olds than in the under ones. However, caution must be taken with countries such as Finland and Iceland, as case numbers are very small in comparison to other participant countries. As would be expected, in the countries who had introduced vaccination programmes against group C (UK and Ireland) rates have fallen between 1999 to 2000 in the age groups targeted in the programmes, especially those under one and aged 15 to 19 years.

3.5.10 Overall case fatality rates

The overall case fatality rates (CFR) for all cases of laboratory confirmed meningococcal disease in 1999 and 2000 were 6% and 7%, respectively. (Table 33) Case fatality rates in France, Ireland and Italy showed an increase of 2% or greater, and Norway had a decrease of 4%. Because of differences in method of coding deaths and in order to compare CFR between countries the denominator included all cases, and therefore cases with unknown outcome were assumed to have survived. Using this method, the CFR between countries ranged from 1% - 28% in 1999, and 1% - 14% in 2000, although it is recognised that reporting of outcome was likely to vary in completeness between countries.

There were some minor differences from the above rates seen when case fatality rates for individual countries were calculated taking out PCR-confirmed cases, suggesting that CFR did not vary between cases confirmed by culture and by PCR. The resulting overall CFR for laboratory confirmed cases excluding the PCR-only confirmed cases was 6% in both years

Table 33: Case fatality ratio in laboratory confirmed cases of meningococcal disease, by country: 1999 & 2000

Country	Year	Total cases	Died	CFR	Year	Total cases	Died	CFR
Austria	1999	97	7	7%	2000	83	5	6%
Belgium	1999	297	16	5%	2000	267	13	5%
Czech Republic	1999	93	7	8%	2000	61	5	8%
Denmark	1999	177	14	8%	2000	151	12	8%
E&W	1999	2784	201	7%	2000	2651	199	8%
Finland	1999	57	10	18%	2000	N/A	N/A	N/A
France	1999	411	35	8%	2000	489	59	12%
Germany	1999	402	21	5%	2000	452	28	6%
Greece	1999	108	7	7%	2000	133	9	7%
Iceland	1999	21	2	10%	2000	18	2	11%
Ireland	1999	445	17	4%	2000	410	25	6%
Italy	1999	246	13	5%	2000	217	20	9%
Malta	1999	18	5	28%	2000	21	3	14%
Netherlands	1999	583	23	4%	2000	546	30	5%
Norway	1999	77	9	12%	2000	85	7	8%
Portugal-lab*	1999	N/A	N/A	N/A	2000	N/A	N/A	N/A
Spain-lab*	1999	602	9	1%	2000	692	5	1%
Total	1999	6418	396	6%	2000	6276	424	7%

* Spanish reference laboratory data only is used here

* Portugal's reference laboratory data only is used here, and in 1999 includes a small number of reporting labs/hospitals

Table 34: Case fatality ratio in laboratory confirmed cases (minus PCR) of meningococcal disease, by country: 1999 & 2000

Country	Year	Total cases	Died	CFR	Year	Total cases	Died	CFR
Austria	1999	85	4	5%	2000	68	3	4%
Belgium	1999	297	16	5%	2000	264	13	5%
Czech Republic	1999	92	6	7%	2000	61	4	7%
Denmark	1999	177	14	8%	2000	151	12	8%
E&W	1999	952	59	6%	2000	912	77	8%
Finland	1999	57	10	18%	2000	N/A	N/A	N/A
France	1999	411	35	8%	2000	489	59	12%
Germany	1999	402	21	5%	2000	452	28	6%
Greece	1999	108	7	7%	2000	133	9	7%
Iceland	1999	21	2	10%	2000	18	2	11%
Ireland	1999	205	10	5%	2000	189	8	4%
Italy	1999	246	13	5%	2000	217	20	9%
Malta	1999	18	5	28%	2000	21	3	14%
Netherlands	1999	583	23	4%	2000	546	30	5%
Norway	1999	73	9	12%	2000	76	5	7%
Portugal-lab*	1999	N/A	N/A	N/A	2000	N/A	N/A	N/A
Spain-lab*	1999	602	9	1%	2000	692	5	1%
Total	1999	4329	243	6%	2000	4289	278	6%

*Spanish reference laboratory data only is used here

*** Portugal's reference laboratory data only is used here,** and in 1999 includes a small number of reporting labs/hospitals

Table 36: Case Fatality Ratio in laboratory confirmed cases of invasive meningococcal disease, by serogroup: 1999

Country	A			B			C			W135			Y		
	No	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR
Austria	0	0	0.0%	70	6	8.6%	15	0	0.0%	2	0	0.0%	3	1	33.3%
Belgium	0	0	0.0%	200	14	7.0%	77	2	2.6%	1	0	0.0%	2	0	0.0%
Czech Republic	1	0	0.0%	49	0	0.0%	37	5	13.5%	0	0	0.0%	2	1	50.0%
Denmark	0	0	0.0%	129	12	9.3%	21	2	9.5%	0	0	0.0%	1	0	0.0%
E&W	1	0	0.0%	1461	74	5.1%	982	119	12.1%	50	5	10.0%	19	1	5.3%
Finland	0	0	0.0%	35	6	17.1%	9	2	22.2%	1	0	0.0%	8	1	12.5%
France	3	0	0.0%	277	16	5.8%	92	15	16.3%	8	0	0.0%	9	2	22.2%
Germany	1	0	0.0%	294	14	4.8%	88	7	8.0%	4	0	0.0%	11	0	0.0%
Greece	6	1	16.7%	69	4	5.8%	29	2	6.9%	2	0	0.0%	1	0	0.0%
Iceland	0	0	0.0%	11	1	9.1%	10	1	10.0%	0	0	0.0%	0	0	0.0%
Ireland	0	0	0.0%	292	12	4.1%	135	5	3.7%	4	0	0.0%	2	0	0.0%
Italy	1	0	0.0%	96	6	6.3%	27	4	14.8%	0	0	0.0%	0	0	0.0%
Malta	0	0	0%	8	2	25%	3	2	67%	2	0	0%	0	0	0%
Netherlands	0	0	0.0%	473	19	4.0%	88	3	3.4%	11	1	9.1%	4	0	0.0%
Norway	0	0	0.0%	61	9	14.8%	11	0	0.0%	1	0	0.0%	2	0	0.0%
Portugal-lab*		N/A	N/A		N/A	N/A		N/A	N/A		N/A	N/A		N/A	N/A
Spain-lab*	0	0	0.0%	346	2	0.6%	230	7	3.0%	2	0	0.0%	3	0	0.0%
TOTAL	**13**	**1**	**7.7%**	**3871**	**197**	**5.1%**	**1854**	**176**	**9.5%**	**88**	**6**	**6.8%**	**67**	**6**	**9.0%**

* Spanish reference laboratory data only is used here

* Portugal's reference laboratory data only is used here, and in 1999 includes a small number of reporting labs/hospitals

Table 37: Case Fatality Ratio in laboratory confirmed cases of meningococcal disease, by serogroup: 2000

Country	A			B			C			W135			Y		
	No.	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR	No.	Deaths	CFR
Austria	0	0	0.0%	64	4	6.3%	14	1	7.1%	1	0	0.0%	0	0	0.0%
Belgium	0	0	0.0%	165	6	3.6%	85	7	8.2%	4	0	0.0%	2	0	0.0%
Czech Republic	0	0	0.0%	44	2	4.5%	11	3	27.3%	2	0	0.0%	0	0	0.0%
Denmark	1	0	0.0%	101	9	8.9%	19	3	15.8%	1	0	0.0%	0	0	0.0%
E&W	2	0	0.0%	1640	84	5.1%	711	92	12.9%	111	13	11.7%	29	2	6.9%
Finland	0	0	0.0%	30	0	0.0%	11	0	0.0%	3	0	0.0%	2	0	0.0%
France	5	0	0.0%	297	28	9.4%	104	17	16.3%	38	10	26.3%	7	1	14.3%
Germany	0	0	0.0%	321	15	4.7%	96	9	9.4%	15	2	13.3%	16	2	12.5%
Greece	9	0	0.0%	78	6	7.7%	20	3	15.0%	10	0	0.0%	4	0	0.0%
Iceland	0	0	0.0%	6	1	16.7%	9	0	0.0%	0	0	0.0%	1	1	100.0%
Ireland	0	0	0.0%	258	13	5.0%	139	11	7.9%	3	0	0.0%	4	1	25.0%
Italy	0	0	0.0%	89	8	9.0%	36	7	19.4%	0	0	0.0%	1	1	100.0%
Malta	0	0	0%	15	2	13.3%	1	1	100%	0	0	0%	0	0	0%
Netherlands	0	0	0.0%	421	20	4.8%	107	10	9.3%	15	0	0.0%	2	0	0.0%
Norway	1	0	0.0%	61	7	11.5%	13	6	46.2%	5	1	20.0%	3	0	0.0%
Portugal-lab*		N/A	N/A		N/A	N/A		N/A	N/A		N/A	N/A		N/A	N/A
Spain-lab*	0	0	0.0%	431	2	0.5%	235	3	1.3%	10	0	0.0%	8	0	0.0%
TOTAL	**18**	**0**	**0.0%**	**4021**	**207**	**5.1%**	**1611**	**173**	**10.7%**	**218**	**26**	**11.9%**	**79**	**8**	**10.1%**

*Spanish reference laboratory data only is used here

* Portugal's reference laboratory data only is used here

3.5.11 Case fatality ratio by serogroup

The highest case fatality ratio in the EU countries in 1999 was seen amongst cases with serogroup C infection (9.4%) followed by serogroup Y infection (9.0%). (Table 36) In the year 2000, serogroup W135 infection cases showed the highest CFR overall (11.9%), followed by serogroup C (10.7%), and then serogroup Y (10.1).(Table 37) Greece was the only country with a recorded death due to infection with serogroup A meningococcal disease. Overall, the CFR for serogroup C cases is approximately double that of serogroup B cases in both years. However, in 1999 Austria, Belgium and Norway had the CFR in serogroup B cases was higher than that seen in serogroup C cases.

3.5.12 Case fatality ratio by age for serogroup B and C infections by age

The overall trend for serogroup B infection CFR (Table 38) is for it to decrease from the under one year old age group to 15-19 year age group, where it sees a steady increase to its highest value in the population over 65 years of age. The overall pattern of CFR by age for serogroup C infection is for it to decrease from under ones to 10-14 year olds, from where it steadily increases with age. Variation between countries is present, and care must be taken when making comparisons purely on CFRs, as the case numbers vary greatly within our study partners.

Table 38: Case Fatality Ratio in laboratory confirmed cases of group B and group C meningococcal disease, by age group: 1999 and 2000 (where age group given)

Age group		1999		2000	
		Group B	Group C	Group B	Group C
Under 1	Cases	732	191	799	105
	Deaths	43	11	61	10
	CFR	5.9%	5.8%	7.6%	9.5%
1-4yrs	Cases	1110	479	1133	409
	Deaths	44	30	48	24
	CFR	4.0%	6.3%	4.2%	5.9%
5-9yrs	Cases	419	203	384	178
	Deaths	14	11	9	7
	CFR	3.3%	5.4%	2.3%	3.9%
10-14yrs	Cases	285	167	230	139
	Deaths	2	14	7	15
	CFR	0.7%	8.4%	3.0%	10.8%
15-19yrs	Cases	524	347	483	220
	Deaths	22	44	19	31
	CFR	4.2%	12.7%	3.9%	14.1%
20-24yrs	Cases	167	98	196	124
	Deaths	16	7	15	18
	CFR	9.6%	7.1%	7.7%	14.5%
25-44yrs	Cases	237	123	298	186
	Deaths	12	17	16	25
	CFR	5.1%	13.8%	5.4%	13.5%
45-64 yrs	Cases	193	121	276	118
	Deaths	19	24	19	17
	CFR	9.8%	19.8%	6.9%	14.4%
65+yrs	Cases	178	107	209	114
	Deaths	26	18	25	19
	CFR	14.6%	17.3%	12%	16.7%

3.5.13 Case fatality ratio for meningitis and septicaemia

Overall case fatality rate for culture-confirmed cases of meningococcal disease with septicaemia was higher than the CFR for cases with meningitis in both 1999 and 2000. (Table 39 & 40) Between countries the values varied widely, and case-fatality ratio was not consistentlydifferent amongst countries where septicaemia formed a larger proportion of cases.

Table 39 : Case fatality rate amongst culture -confirmed cases of meningococcal disease presenting with septicaemia, by country: 1999& 2000

Country	Year	Total Septicaemia cases	Died	CFR	Year	Total Septicaemia cases	Died	CFR
Austria	**1999**	20	3	15.00%	**2000**	15	1	6.67%
Belgium	**1999**	68	3	4.41%	**2000**	81	3	3.70%
Czech Republic	**1999**	26	4	15.38%	**2000**	10	2	20.00%
Denmark	**1999**	39	3	7.69%	**2000**	33	3	9.09%
E&W	**1999**	860	86	10.00%	**2000**	608	65	10.69%
Finland	**1999**	17	4	23.53%	**2000**	14	N/A	N/A
France	**1999**	80	10	12.50%	**2000**	111	21	18.92%
Germany	**1999**	70	12	17.14%	**2000**	84	20	23.81%
Iceland	**1999**	6	0	0.00%	**2000**	4	1	25.00%
Ireland	**1999**	143	6	4.20%	**2000**	128	5	3.91%
Italy	**1999**	46	7	15.2	**2000**	34	9	26.47%
Malta	**1999**	12	4	33.3%	**2000**	8	3	37.5%
Netherlands	**1999**	83	8	9.64%	**2000**	81	9	11.11%
Norway	**1999**	24	4	16.67%	**2000**	23	2	8.70%
Portugal-lab*	**1999**	N/A	N/A	N/A	**2000**	N/A	N/A	N/A
Spain-lab*	**1999**	162	3	1.85%	**2000**	181	2	1.10%
TOTAL	**1999**	**1656**	**157**	**9.48%**	**2000**	**1415**	**146**	**10.32%**

* Spanish reference laboratory data only is used here

*Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

Table 40 : Case fatality rate amongst culture -confirmed cases of meningococcal disease presenting with meningitis, by country: 1999& 2000

Country	Year	Total Meningitis cases	Died	CFR	Year	Total Meningitis cases	Died	CFR
Austria	**1999**	56	2	3.57%	**2000**	43	2	4.65%
Belgium	**1999**	202	13	6.44%	**2000**	167	10	5.99%
Czech Republic	**1999**	63	2	3.17%	**2000**	46	3	6.52%
Denmark	**1999**	112	11	9.82%	**2000**	88	8	9.09%
E&W	**1999**	560	34	6.07	**2000**	365	27	7.40%
Finland	**1999**	33	4	12.12%	**2000**	26	N/A	
France	**1999**	314	22	7.01%	**2000**	353	31	8.78%
Germany	**1999**	237	8	3.38%	**2000**	281	7	2.49%
Iceland	**1999**	14	1	7.14%	**2000**	10	1	10.00%
Ireland	**1999**	46	4	8.70%	**2000**	41	2	4.88%
Italy	**1999**	88	5	5.68	**2000**	87	4	4.60%
Malta	**1999**	0	0	0%	**2000**	8	0	0%
Netherlands	**1999**	341	9	2.64%	**2000**	332	16	4.82%
Norway	**1999**	42	5	11.90%	**2000**	46	1	2.17%
Portugal-lab*	**1999**	N/A	N/A	N/A	**2000**	N/A	N/A	N/A
Spain-lab*	**1999**	276	5	1.81%	**2000**	308	2	0.65%
TOTAL	**1999**	**2384**	**125**	**5.24**	**2000**	**2201**	**114**	**5.18**

* Spanish reference laboratory data only is used here

* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

3.5.14 Antibiotics resistance

Twelve countries (Austria, Belgium, Czech Republic, Denmark, England & Wales, Germany, Greece, Iceland, Italy, Malta, Portugal and Spain) contributed antibiotic minimum inhibitory concentration (MIC) data for isolates tested for antibiotic susceptibility. The proportion of such strains in each country varies from 3-100% in 1999 and from 2-100% in 2000. This difference probably reflects differences in methods used. The overall trend seen in the two years is an increase in the percentage of isolates with MICs between 0.06-1.99 for penicillin. (Table 41) However, collection of additional years of data, and further analysis of this data, will be necessary before conclusions can be drawn. As part of the DGXII funded EU-MENNET project, Spain will be leading a work package to look at standardisation of assays of penicillin sensitivity.

Table 41 : Susceptibility of *N. meningitidis* to penicillin, by country: 1999 & 2000

Country	1999			2000		
	MIC <= 0.06	MIC >0.06 and <2.00	Total	MIC <= 0.06	MIC >0.06 and <2.00	Total
Austria	76 (96%)	3 (4%)	79	48 (86%)	8 (14%)	56
Belgium	267 (96%)	12 (4%)	279	237 (94%)	14 (6%)	251
Czech Republic	56 (97%)	2 (3%)	58	46 (98%)	1 (2%)	47
Denmark	95 (65%)	51 (35%)	146	74 (63%)	44 (37%)	118
E&W	517 (31%)	1128 (69%)	1645	418 (28%)	1068 (72%)	1486
Germany	51 (13%)	351 (87%)	402	22 (5%)	430 (95%)	452
Greece-lab*	41 (84%)	8 (16%)	49	38 (86%)	6 (14%)	44
Iceland	20 (95%)	1 (5%)	21	12 (75%)	4 (25%)	16
Italy	80(92%)	7(8%)	87	84(94%)	5(6%)	89
Malta	0(0%)	9(100%)	9	0(0%)	14(100%)	14
Portugal-lab*	5(24%)	16(76%)	21	20(43%)	27(57%)	47
Spain-lab*	381 (63%)	221 (37%)	602	301 (43%)	391 (57%)	692
TOTAL	1589 (47%)	1809 (53%)	3398	1300 (39%)	2012 (61%)	3312

***** Greek and Spanish reference laboratory data was used here as it was the only dataset with antibiotic resistance
* Portugal's reference laboratory data only is used here, and in 1999 includes only a small number of reporting labs/hospitals

4. CONCLUSIONS

This project has demonstrated the successful development of existing networks towards the objective of providing high quality surveillance information on meningococcal infection in the European Union and neighbouring countries. The importance of the reference and diagnostic microbiology under-pinning this data cannot be over-emphasised. The laboratory questionnaire and the quality assurance scheme suggest that standards in reference laboratories in the EU are high. More variable, however, is access to diagnostic services (particularly non-culture diagnosis) in local laboratories and the proportion of cases where isolates or clinical materials are referred to the national reference laboratories. These latter variations have potential to impact on ascertainment at a national level to a large extent and may partly explain some of the differences observed between countries.

The public health importance of meningococcal disease surveillance in each participating country is demonstrated by the finding that the disease is reportable by mandate in all countries. The major sources of data available at a national level, however, vary and therefore the strengths and weaknesses of each system may impact upon the data provided. In some countries, different sources are reconciled at a national level to provide an integrated database containing clinical and laboratory information. This is clearly an ideal scenario but the project recognises the difficulties involved in this process including workload (particularly in the larger countries) and the need for common identifying information (which may be restricted under confidentiality legislation and guidance). However, the importance of this should be recognised within Europe, which may facilitate the development of reconciled data sets in more countries.

Because of the lack of reconciliation in many countries it has been necessary in some instances to use a different data source for different analyses. For example, analysis of serotyping and sero-subtyping information can only be carried out on data that is provided from the reference laboratories. This data, however, may be less complete than data provided from a national reporting system. Therefore, analysis of serotype diversity in some countries may not be truly representative of the national picture. Similarly, clinical and outcome information may be part of a clinical notification system but not reported to laboratories. Analysis of case-fatality ratios and clinical presentation may therefore be affected by the data-set provided to the project.

The data provided on meningococcal disease shows marked variations in overall incidence, with a more than ten-fold variation in the incidence of culture confirmed infection. This is likely to reflect both genuine differences in the epidemiology and in ascertainment. The contribution of each of these is difficult to quantify, but secular trends within countries and between age-groups and serogroups are likely to be valid in most instances. Countries should be aware, however, of the major influence that changes in clinical and laboratory practice can exert on ascertainment. For example, reduced used of lumbar puncture for the diagnosis of meningitis, the use of pre-admission antibiotics and the introduction of new laboratory tests. The potential for ascertainment to change because of new technological advances is illustrated by the data provided on PCR diagnosis for those countries where the test is being used routinely. In three countries, ascertainment of laboratory confirmed infection has been increased by around 100% and it is likely that similar increases will be achieved in other countries when access to and awareness of PCR diagnosis improves. The ability to confirm and group a larger number of meningococcal infections, however, is clearly a major advance that will improve the data available and help to better establish the burden of disease with a view to vaccine introduction. We hope that countries without a routine service can learn from other countries in the project about the development and provision of such services.

It is difficult to explain the massive differences in clinical presentation of meningococcal disease between countries. Although the strains causing infection around Europe differ, it seems unlikely that there is a genuine difference in the clinical manifestation of infection. For example, amongst group C cases, where one major serotype predominates in the majority of countries, the proportion of cases presenting as septicaemia follows the overall pattern for each country. Although two of the countries where PCR confirmation is used extensively have a high proportion of cases presenting as septicaemia this laboratory investigation does not appear to affect the distribution of clinical presentations. Septicaemia is the more severe form of the infection, as evidenced by higher case-fatality ratios, but the observed CFR for septicaemia is substantially lower than that previously reported. Comparison of case fatality between countries shows no evidence that the clinical severity of septicaemia varies in relation to the proportion of infection that it causes. The huge variation in the proportion of cases that present as septicaemia suggests that awareness and labelling of septicaemia as a manifestation of meningococcal infection amongst clinicians in each country may vary. Without further clinical details on cases it is difficult to demonstrate this, but the finding suggests that there is potential for future changes in clinical awareness in participating countries to impact on national ascertainment.

The age-specific incidence and age-distribution of meningococcal disease follows the pattern previously described, with the majority of cases in children under five. Minor differences were noted in the age distribution between countries. Group B is still the commonest cause of infection in Europe, although the proportion of disease due to group C varies quite considerably. The proportion of group C infection did change within countries between years. In some instances this was due to the introduction of a group C vaccine, in others it may reflect changes in epidemiology such as the introduction of a hyper-virulent strain. Identification of such changes at a European level is important, as if may predict changes that will subsequently take place in neighbouring countries. For groups other than B and C, there was also variation in the predominant strains between countries and between years. In 2000, a dramatic increase in cases due to W135 infection was observed in several countries in association with the Hajj. Although cases in pilgrims or their families were reported in several European countries, the increase in W135 infection was noted in other countries – suggesting that this strain may have been more widely distributed than originally thought. In many countries, small numbers of cases prevent valid interpretation of such changes but this phenomenon illustrates the strength of the European project in pooling data from many countries. As well as changes in serogroup, there are differences in major serotypes of group C and group B within Europe. Changes were noted in the predominant group C serotype in two countries and may be associated with a future shift in incidence or case-fatality rates. For example, a suggestion of increasing case-fatality in association with a shift from C2b to C2a in Belgium may become more apparent in future years or in other countries. Group B strain variation is seen across Europe, and phenotypic data displayed in this study, and from previous records, shows marked variation in the prevalent strains across Europe. Observation over more years will allow the early recognition of emerging strains that might be missed within any one country. Consideration needs to be given to the substantial proportion of group B strains that are non-typable for serotype and serosubtype. Differences in the proportions may reflect different methods or reagents in use and should be established via the EQAS scheme. Molecular analysis of meningococcal strains is part of the DGXII funded EU-MENNET project and may shed light on this area in future years.

Analysis of case fatality ratio is prone to difficulties for a variety of reasons. We suspect that the figures presented here are an underestimate of true fatality ratios, as there is likely to be under-ascertainment of outcome in some countries. Comparison between countries is unlikely to be valid as it may be explained by differences in ascertainment, in age distribution or serogroup/serotype distribution between countries. Comparison between serogroups and age-groups however is likely to reflect genuine differences. Analysis indicates that fatality is

higher in older individuals. Case fatality ratios for group B infections are low overall, and in most countries lower than that observed for group C or for other serogroups. Case fatality for group Y and W135, however, is high and the CFR for W135 increased in 2000. This occurred at the same time as the incidence increased in association with the Hajj and is probably due to the strain belonging to a hyper-virulent lineage

The impact of vaccination on the epidemiology of meningococcal disease in Europe is small so far. As the UK is one of the largest countries, the impact of conjugate group C vaccine (introduced in late 1999 for those under 17 years) has had a small impact on the overall incidence and a larger impact on the incidence of group C infection. Ireland and Spain have also recently introduced vaccine and other countries are likely to implement vaccination over the next year or so. In future, therefore, data may need to be presented separately for those countries with vaccination programmes. Demonstration of a change in the epidemiology is likely to encourage neighbouring countries to consider vaccination, particularly if the incidence of group C infection increases or case-fatality becomes higher than previously observed.

Although true penicillin resistance has not been observed, a substantial proportion of strains have MICs in the range of 0.06-1.99. In general, the proportion is fairly constant between years. There were dramatic differences in the proportion of isolates with reduced penicillin sensitivity between countries. This difference probably reflects differences in methods used. In general, the proportion is fairly constant between years. The clinical significance of this finding is not fully established but resistance patterns are being investigated further as part of EU-MENNET.

PROJECT ACHIEVEMENTS

This project has made considerable contributions to:

1. improving epidemiological information on *Neisseria meningitidis*;
2. improving the laboratory capacity of countries within the EU to accurately identify isolates of *N. meningitidis;*
3. forming a focus for wider collaboration with non European Union countries and candidate European Union countries

5.1 Improvements in the epidemiological information on *N. meningitidis* within the EU

A combination of tools have been used to improve the epidemiological information on *N. meningitidis* within the EU. The surveillance system questionnaires from participant countries have allowed greater understanding of the data supplied by each country and have helped to explain any limitations in the data supplied. Use of a minimum dataset and analysis by standard case definitions for meningococcal infection has enabled valid comparisons to be made of the disease epidemiology between member countries, and hence to assist the monitoring of epidemiological changes within Europe. Information collected on the vaccination programme(s) being introduced in various each participant countries has also aided interpretation of the epidemiological analyses. The availability of data on laboratory methods used in identification of *N. meningitidis* and on the characterisation of isolates also contributes significantly to the understanding comparability of the epidemiological information between EU countries.

5.2 Improvements in the laboratory capacity within the EU to accurately identify *N. meningitidis* isolates

These improvements will be achieved through gaining information on systems in use by participant countries, and by feedback of information from the External Quality Assurance Scheme (EQAS) with the participant reference laboratories. Questionnaires completed by network members on the laboratory methods used in the identification of *N. meningitidis* gave information that, and, as with the surveillance system questionnaire results, allowed greater understanding of any limitations that could impact on the data individual countries supplied. The EQAS helped identify any existing problems in correctly serotyping *N. meningitidis* isolates, and enabled corrections/assistance in laboratory methods to be made, hence improving comparability of data between countries. In collaboration with EU-MENNET improvements may also be made in the methods used for assessing and comparing data on penicillin sensitivity.

5.3 Forming a focus for wider collaboration with non European Union countries and candidate European Union countries

Through establishment of this *N. meningitidis* disease surveillance network in the European Union, with standard case definitions, minimum dataset, and laboratory quality assurance scheme, a focus for wider collaboration with non-EU and candidate EU countries is provided. Involvement of the Czech Republic and Malta in this collaboration has increased the population under surveillance. It is hoped that other non-EU countries will join the collaboration later.

5. APPENDICES

Appendix 1: List of collaborators

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Appendix 2. *Neisseria meningitidis* minimum data set

VARIABLE	FIELD TYPE	CODED VALUES
Year	Number	
Country	Text	
IDNo	Text	
Date of birth	DD/MM/YY	
Age year	Number	
Age month	Number	
Age Days	Number	
Date of onset	DD/MM/YY	
Sex	Number	1=male, 2=female, 3=not known
Geographic location	Text	
Imported	Number	1=yes, 2=no, 3=not known
Country of import	Text	
Outcome	Number	1=alive, 2=died, 3= not known
Clinical diagnosis	Number	1=meningitis only, 2=septicaemia only, 3=meningitis & septicaemia combined 4=no disease 5=other 9=not known
Specify other diagnosis	Text	
Case definition	Number	1=clinical case **only**, 2=lab confirmed
Culture	Number	1=yes, 2=no
PCR	Number	1=yes, 2=no
PCR group	Text	
Latex	Number	1=yes, 2=no
Microscopy	Number	1=yes, 2=no
Serology	Number	1=yes, 2=no
Other	Text	
Site of isolate1	Number	1=CSF 2=Blood 3=Throat swab 4=Joint 5=Skin lesion 6=Eye 7=Other (please specify) 8=Not relevant 9=Not known
Specify 1	Text	
Site of isolate2	Number	1=CSF 2=Blood 3=Throat swab 4=Joint 5=Skin lesion 6=Eye 7=Other (please specify) 8=Not relevant 9=Not known
Specify 2	Text	

Serogroup	Text	A B C WI35 X Y Z Z/29E 29E Other (please specify) NGA=Not groupable NK=Not grouped/Not known
Serotype	Text	P2.2a P2.2b P3.1 P3.4 P3.14 P3.15 P3.21 P3.22 NT=Not typable NK=Not known
VR1	Text	P1.5 P1.7 P1.12 NT=Not Typable NK=Not known
VR2	Text	P1.1 P1.2 P1.3 P1.4 P1.9 P1.10 P1.13 P1.14 P1.15 P1.16 NT=Not Typable NK=Not Known
VR3	Text	P1.6: NT=Not Typable: NK=Not Known
Vaccination status	Number	1=yes, 2=no, 3=not known
Resistant to sulphonamide	Number	1=yes, 2=no, 9=not tested
Sulph MIC	Number	
Penicillin G sensitive	Number	1=yes, 2=no, 9=not tested
Pen MIC	Number	
Ceftriaxone/Cefotaxine	Number	1=yes, 2=no, 9=not tested
Cef MIC	Number	
Rifampicin sensitive	Number	1=yes, 2=no, 9=not tested
Rif MIC	Number	
Chloram-phenicol sensitive	Number	1=yes, 2=no, 9=not tested
Chl MIC	Number	
Ciprofloxacin sensitive	Number	1=yes, 2=no, 9=not tested
Cip MIC	Number	

Appendix 3.Surveillance systems questionnaire

Neisseria meningitidis in Europe - Invasive _Neisseria meningitidis_ infections Surveillance systems questionnaire

Country: .....
Name of respondent: .....
Position: .....
Centre: .....
Address: .....
.....
.....

The purpose of this questionnaire is to describe the current surveillance systems for *Neisseria meningitidis* in your country and to provide comparative information for each participating country.

Notes for completion of questionnaire
Please complete Part A **once** for overall *Neisseria meningitidis* surveillance.
Please complete Part B for **each** surveillance system.
Please attach any additional information/reports.

Part A

1 Surveillance methods

1.1 Methods

What methods of surveillance of *Neisseria meningitidis* are used in your country? (please list the methods used and complete Part B of the questionnaire once for each system)

1.2 Data collation

If more than one system: How is the data collated from each system?

☐ Individual case reconciliation*
☐ Comparison of aggregate data only
☐ No collation of systems
☐ Not relevant

* "reconciliation" - cases in one system merged with cases in another system and duplicates removed.
For each method of surveillance please complete one questionnaire Part B.

Part B

1 Surveillance system

1.1 Objectives

What are the objective(s) of this *Neisseria meningitidis* surveillance system method? (please specify if the system aims for sentinel or universal case ascertainment)

1.2 Case definitions

What is the case definition or case category of the health event under surveillance?

- Meningitis ☐
- Septicaemia ☐
- Septicaemia & Meningitis ☐
- Other, please specify .....

1.3 Population

What is the population under surveillance?

Whole country ☐ Region ☐ Please specify which region(s)
.....

Total population ☐
Under 15 years of age ☐
Under 10 years of age ☐
Under 5 years of age ☐
Other (specify) .....

1.3 Type of surveillance system

What type of surveillance system is this?

Type of system		*Characteristics of system*
Active	☐	If yes, is it Stimulated/Not stimulated
Passive	☐	If yes, is it Statutory/Voluntary reporting

Zero-reporting ☐ / No zero reporting ☐

1.4 Start of surveillance system

Which year did this surveillance system start? .....
Years for which data is available .....

Part B

2 Data collection

2.1 Information collected

What information/data is collected?
(please specify the variables routinely collected)

Age ☐
Sex ☐
Date of onset ☐
Geographic location ☐
Clinical condition ☐
Site of isolate(s) ☐
Epidemiological typing of isolate
- Serogroup ☐
- Serotype ☐
- Subtype VR1 ☐
- Subtype VR2 ☐
- Subtype VR3 ☐

Vaccination status ☐
Resistance to sulphonamide ☐
Antibiotic sensitivities ☐

2.2 Reporting sources

Who provides the data? (please specify who reports the data used)
Clinicians ☐
Paediatricians ☐
Microbiologists ☐
Epidemiologists ☐
Scientific staff ☐
Administrative staff ☐
Other, please specify .....

Where is the data received from?
Hospitals ☐
Clinics ☐
Reference laboratory ☐
Local laboratories ☐
Other, please specify .....
.....

2.3 Time period

How frequently is the data reported locally?

Weekly	☐	Monthly	☐	Quarterly	☐
Six-monthly	☐	Annually	☐	Other	

How frequently is the data aggregated nationally?

Weekly	☐	Monthly	☐	Quarterly	☐
Six-monthly	☐	Annually	☐	Other	

2.5 Duplicate reports

Are duplicates routinely detected and eliminated?

Part B

3 Data analysis

3.1 Analysis

Who analyses the data at a national level?

Clinicians		☐	
Paediatricians	☐		
Microbiologists		☐	
Epidemiologists		☐	
Scientific staff	☐		
Administrative staff		☐	

Other, please specify .....
.....

Part B

4 Data dissemination

4.1 Regular reports

4.1a Frequency

How often are reports of the surveillance system produced?
(please state this for all regular reports)

Weekly	☐
Monthly	☐
Quarterly	☐
Six-monthly	☐
Annually	☐

Other .....

4.1b Method of reporting

How are the reports disseminated?
(please state if this is by bulletin, website, newsletter, etc)

4.1c Audience

Who are reports disseminated to?

4.2 Recent publications

Are there any recent or relevant publications demonstrating application(s) of the surveillance system? **And** Are there any recent or relevant publications about evaluation(s) of the system and/or changes in the system?
(please list any recent or relevant publications)

5 Vaccination programmes

Please can you tell us about your current use of vaccines against meningococcal infection :

a. Which meningococcal polysaccharide vaccines are available in your country?

None ☐
AC vaccine ☐
ACYW135 vaccine ☐
Other, please specify ☐

b. How are polysaccharide vaccines used in your country?

Not at all / Rarely ☐
Selective vaccination ☐
If yes, please give key groups:
Travellers ☐
Contacts of cases ☐
Outbreak control ☐
Underlying conditions (eg asplenia) ☐
Other, please specify .....
Mass campaign ☐
If yes, please state the following:
Date of campaign(s).....
Vaccine used .....

Regions .....
Age groups targeted .....

Routine immunisation ☐
If yes, please state vaccine and schedule used

Other , please specify

c. Which conjugate meningococcal conjugate vaccines are available in your country?

None ☐
Group C vaccine ☐
Other, please specify .....

d. How are meningococcal conjugates used in your country?

Not at all / Rarely

Routine immunisation
If yes, please state vaccine and schedule used
.....

Mass campaign (or catch-up)
If yes, please state:
Date of campaign(s) .....
Vaccine used .....
Regions .....
Age groups targeted .....

Other, please specify
.....

e. Please tell us whether policy on meningococcal vaccination is currently being reviewed.

Appendix 4.Laboratory diagnostic methods questionnaire

Invasive *Neissseria meningitidis* infections

LABORATORY DIAGNOSTIC METHODS QUESTIONNAIRE

Country .....

Name of respondent .....

Position .....

Centre .....

Address .....
.....
.....
.....
.....
Tel. .....
Fax. .....
Email .....

The first section of this questionnaire aims to describe the facilities which are available in the hospitals that refer strains to you.

The purpose of the second section is to describe the methods used to identify N. meningitidis by laboratories collaborating in this study.

Please return both sections to :

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UK

Survey of Laboratory Facilities for the Identification of Neisseria meningitidis infection in .....

PART I

I) What proportion of (microbiology laboratories) hospitals in your country/area have the facilities to do the primary identification of meningococcal isolates?

100%	
80-100%	
50-80%	
20-50%	
<20%	

Type of isolating laboratory - Is notification of confirmed meningococcal infections compulsory?

	Yes	No	Compulsory	Voluntary	No. isolates per year
Hospital					
Public Health					
Private laboratory					
Other					

II) For those laboratories which can identify N.meningitidis, what type of cases/specimens would they look for/try to grow the organism from?

All CSFs from suspected bacterial meningitis	
All CSFs from suspected bacterial meningitis in children	
All blood cultures	
All blood cultures in children	
All blood cultures from suspected meningococcal septicaemia	
Throat swabs from cases of suspected meningococcal infection	
Other sites	
Skin lesions	
Other conditions - If yes, specify below	

.....

III) What proportion of laboratories would be able to perform serotyping on isolates of N.meningitidis:-

100%	
80-100%	
50-80%	
20-50%	
<20%	

IV) What proportion of laboratories refer isolates to the national/area reference lab (i.e. your lab)?

100%	
80-100%	
50-80%	
20-50%	
<20%	

PART II : REFERENCE LABORATORY METHODS

1. What is the source of isolates sent to the reference laboratory?

	Yes	No
CSF		
Blood		
Nasopharynx		
Other		

If other, please specify
.....

2. Carriers: How do you detect carriers?

	Yes	No
Culture from throat swabs		
Nucleic acid amplification following extraction from throat swabs		

3. Receipt of strains

		Yes	No
1.11	Are the strains subbed immediately on receipt?		
1.12	Are the strains tested on receipt, or batched?		
1.13	Are the strains stored and tested in batches?		

4. Media

4.1. What media is used to transport strains to the laboratory?
.....
4.2. What media is used to subculture the strains?
.....
4.3. What media is used for susceptibility testing?
.....
4.4. What media is used for long term storage of strains?
.....
4.5. Please state atmosphere of incubation.
.....
4.6. Please state duration of incubation.
.....

5. Identification Methods

5.1. Are the following tests performed? (Please tick the appropriate box)

	Yes	No
Catalase		
Oxidase		
Carbohydrate (sugar) utilisation tests		

5.2.

Are all isolates typed by

	Yes	No
Serogrouping		
Serotyping		
Serosubtyping		
LPS immunotyping		
Antibiotic sensitivity testing		
Other. If yes please specify below		

.....

5.3. Which method is used for serogrouping?

.....

.....

5.4. Where do you obtain reagents for serogrouping meningococci?

.....

.....

5.5. Which method is used for serotyping?

.....

.....

5.6. Where do you obtain reagents for serotyping

.....

.....

5.7. Which method do you use for sero-subtyping meningococci?

.....

.....

5.8. Where do you obtain your reagents for sero-subtyping meningococci?

.....

.....

6. NON-CULTURE CONFIRMATION OF MENINGOCOCCAL INFECTION

6.1. Do microbiology laboratories/hospitals perform non-culture diagnosis of meningococcal infection?

Yes	No

6.2. What proportion of laboratories perform non-culture diagnosis?

100%	
80-100%	
50-80%	
20-50%	
<20%	

6.3. Does the reference laboratory test for non-culture confirmation of meningococcal infection?

Yes	No

6.4. What methods are used by the reference laboratory for non-culture c confirmation?

	Yes	No
Antigen detection		
Latex agglutination		
Serology		
Nucleic acid amplification (PCR)		
Other. (If yes, specify below)		

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6.5. What type of serological assay do you use for confirmation of meningococcal infection

	Yes	No	Number /year
Serum bactericidal assay			
Outer membrane protein ELISA			
Polysaccharide ELISA			
Other (If yes, please specify below)			

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6.6. If you use PCR, which gene do you detect?

	Yes	No
IS1106		
ctrA		
siaD		
porA		
dhps		
pil		
Others (If yes, please specify		

below) ☐ ☐

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6.7. What specimens are tested by PCR?

	Approximate No./Year
CSF	
Whole blood	
Serum	
Plasma	
Other , please specify type below	

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7. MOLECULAR SUBTYPING OF *N.meningitidis*

7.1. Do you carry out molecular subtyping?

Routinely	☐
Occasionally	☐
Never	☐

7.2. Do you refer isolates to another laboratory for molecular subtyping?

If yes, where to? .....

7.3. In what situation is molecular subtyping done?

Outbreak management	☐
National epidemiology	☐
International epidemiology	☐

7.4. How many isolates are examined by molecular subtyping each year?

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7.5. What molecular subtyping methods are used? (Tick all that apply)

MLEE	☐
PCR-RFLP (please state what gene targets)	☐
OMP profiles (SDS-PAGE)	☐
Ribotyping	☐
RAPD	☐
PFGE	☐
Sequence typing	☐
PorA	☐
MLST	☐
AFLP	☐
Other, please specify below	☐

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8. SUSCEPTIBILITY TESTING

8.1 Please list antimicrobial chemotherapeutic agents tested, and concentrations (e.g. disc content, breakpoint values, etc.)

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8.2. If MICs are required, which method is used?

	yes	no
Broth dilution Which antibiotics?	☐	☐
Agar incorporation Which antibiotics?	☐	☐
E-test (AB BIODISK) Which antibiotics?	☐	☐
Other Please specify	☐	☐

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9. STORAGE OF MATERIAL

What material is stored in the reference laboratory?

	Yes	No	How many?	How long?
Isolates from				
(a) Cases				
(b) Carriers				
Serum				
CSF				
Other, please specify, below				

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	yes	no
Agar slopes	☐	☐
Frozen at -80oC	☐	☐
Other (please specify below)	☐	☐

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10. ADDITIONAL INFORMATION

Please give any other information regarding your laboratory methods not covered above. (Please attach additional sheets if necessary, or include your laboratory standard operating procedures)

Does the reference laboratory produce an annual report?

What does the annual report contain?

Epidemiological situation/trends

Other