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INVASIVE *NEISSERIA MENINGITIDIS* IN EUROPE 2003/2004

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SUMMARY

Introduction

EU-IBIS, a surveillance network for invasive meningococcal disease, continues to fulfil its aims to gather and improve epidemiological information about the disease, to integrate and analyse molecular data, and to form the focus for a wider collaboration. The project, having started in 1999, has now collected six years worth of data, including consistent data across those years from 19 of its 27 participants countries. 2004 saw the addition of seven new countries to the network, these being some of the Accession countries which joined the European Union in May 2004.

Methods

Participants have continued to submit epidemiological and molecular data to the network, according to the EU agreed case definitions. There has been an increase in molecular typing data being submitted, and in amount of data that can be used to explore the impact of routine conjugate meningococcal C (MenC) vaccination. The number of cases of invasive meningococcal disease caused by B:P2.2a or B:2.2b strains was carefully monitored in some countries to identify any instances of capsule switching, and the website continued to be developed for easier navigation and usability.

Results

There is an increasing use of non-culture techniques to identify strains of *N meningitidis*, though diagnosis by culture still remains the most common method overall. The incidence of laboratory-diagnosed confirmed and probable cases still varies considerably across Europe, ranging from 0.3 (Poland) to 4.35 (Ireland) per 100,000 population. Generally rates in countries which have introduced routine MenC vaccination have decreased considerably, especially in serogroup C incidence, though decreases have also been seen in some countries whose vaccination policies have not changed. Serogroups B and C remain the major serogroups causing invasive disease in Europe, with B being particularly prevalent in those under 20 years of age. The incidence of both decreases with age, particularly in the 25+ age group. There are distinct serotype distributions for serogroup B and C, with P3.4 and P3.15 associating with the former, and P2.2a and P2.2b with the latter, but no evidence of capsule switching associated with the introduction of MenC vaccine. Serosubtypes tend to cluster with specific serogroup:serotype combinations, but the numbers of isolates bearing these phenotypes do tend to fluctuate with time. Overall case fatality has ranged between 6% and 8% between 1999 and 2004, and remains generally consistent across the different European countries, varying between 5.19% and 11.2%. Disease caused by serogroups C, W135 or Y is most likely to cause death, and death is also most likely to occur in the 65+ age group. Meningitis presents most commonly in the 15-44 age group, and septicaemia and other diagnoses in those 65 years old and above. While disease presentation is not affected by the serogroup

of the causing organism, a case presenting septicaemia is much more likely to result in death than one presenting with meningitis.

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 role of the European Centre for Disease Prevention and Control as it takes over the responsibility of running Dedicated Surveillance Networks such as EU-IBIS is paramount. This will ensure the continuance of the high value to be derived from the network, including integrating available data from different sources and collaborating with other influential organisations such as the European Monitoring Group on Meningococci.

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INTRODUCTION

The network

The bacteria *Neisseria meningitidis* (meningococci) and *Haemophilus influenzae* are important causes of meningitis and other serious invasive disease across Europe and contribute to morbidity and mortality, particularly in young children. The two organisms thus represent a considerable public health problem, and the surveillance of bacterial meningitis has been identified as a priority by the European Commission (European Commission Decision 2119/98/EC, 24/09/1998).

Surveillance of these diseases is vital so that the epidemiology of these infections can be characterised and the impact of any vaccination programmes can be measured. Since these diseases are relatively uncommon (particularly after vaccination has been introduced) pooling data across many European countries increases the power of any epidemiological analysis.

The European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) began in 1999 and is funded by the European Commission DG Sanco. There are two separate, organism-specific, networks, and the countries participating in the *N meningitidis* network are: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Slovak Republic, Slovenia, Sweden, Switzerland, and the UK.

The EU-IBIS *N meningitidis* network built upon established networks including the European Monitoring Group for Meningococci (EMGM) (European Monitoring Group for Meningococci (EMGM), weblink) and the Bacterial Meningitis in Europe surveillance network (Noah and Connolly 1996). EMGM is a consortium of microbiologists and epidemiologists based mainly in reference laboratories in Europe and working to ensure effective and timely exchange of information on meningococcal infections (Taha *et al* 2005). EU-IBIS has collaborated with EMGM to facilitate these aims (Noah and Connolly 1996).

The network originally contained 16 EU and 3 (then) non-EU countries when it was established in 1999, these being Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and the UK, and Czech Republic, Malta and Norway respectively. The number of countries involved has increased over the duration of the project, but particularly in 2004, when 10 Accession countries, including Czech Republic and Malta, joined the EU. The total number of countries involved in the network currently stands at 27; 20 of these countries have contributed comparable data between 1999 to 2004.

Project aims related to meningococcal disease

- To improve the epidemiological information on invasive disease caused by *N meningitidis* within the EU

- To improve the laboratory capacity to accurately characterise the isolates of *N meningitidis* using standardised methods
- To evaluate the impact of immunisation with conjugate vaccines on the epidemiology of *N meningitidis* and to compare the impact of vaccination with conjugate vaccines produced by different manufacturers and according to different schedules
- To form a focus for wider collaboration with non-EU countries and candidate EU countries

Due to the relative rarity of meningococcal disease, particularly following the introduction of routine conjugate meningococcal C vaccine in the pertinent countries, pooling of epidemiological data across countries should increase the power of any analysis undertaken. For example, knowledge of changes in serogroup and/or serotype distribution consistent across Europe could provide valuable input when formulating vaccination strategies. However, care must be taken when interpreting the results of any such analysis to allow for any differences in aspects of national surveillance systems such as diagnosis and ascertainment, and to ensure, as far as is possible, that comparisons are valid.

The project also allows opportunity for the sharing of good practice in both laboratory methods and surveillance strategies. In addition, advances and innovations in treatment and in public health control measures can be disseminated in a timely manner, and guidance on the control of meningococcal disease, such as optimised vaccine schedules and prophylaxis protocols, might become more consistent across Europe.

The disease

In Europe and North America, meningococcal disease is endemic and, while most cases are sporadic, small clusters also occur. There is a clear seasonal variation, with the majority of cases occurring in winter and early spring. Meningococcal disease manifests itself most commonly as meningitis, with or without septicaemia, though a considerable number of cases manifest septicaemia without any other focal features, and it is in this group that death is most likely to occur. Other symptoms can include conjunctivitis, pneumonia, septic arthritis and pericarditis. A significant proportion of meningococcal patients who survive have sequelae, including neurologic disability, limb loss, and hearing loss (ACIP 2000, Harrison 2006, Public Health Laboratory Service 2002, Rosenstein *et al* 2001, Tikhomirov *et al* 1997, WHO Editorial Working Group 1998)

Treatment of meningococcal disease requires the prompt administration of antibiotics (Harrison 2006). Suitable antibiotics include penicillins, 3rd generation celphalosporins (*eg* ceftriaxone, cefotaxime) or chloramphenicol (Public Health Laboratory Service 2002). Prophylaxis of household contacts with antibiotics that eliminate meningococcal nasopharyngeal carriage, such as rifampicin/rifampin, ciprofloxacin and ceftriaxone, has been found to reduce the number of subsequent cases (Fraser *et al* 2005, Public Health Laboratory Service 2002).

The organism and strain identification

N meningitidis is a Gram-negative diplococcus (paired spherical bacterium), normally surrounded by a layer of complex lipids and polysaccharides (the capsule) which protects it against the host immune system and which is thus a potent virulence factor. The organism can be defined by variations in the biochemistry of the capsule, determining its serogroup, and in its outer membrane proteins (OMPs). Class 2 or 3 OMP (Por B gene) determine the serotype and class 1 OMP (Por A gene) determine the sero(subtype). Both PorA and PorB gene products have a number of variable regions which are surface-exposed and thus contribute to antigenic variability between strains; in the case of PorA proteins, the variants for two of the variable regions (VR1 and VR2) are frequently quoted, with a third region (VR3) used less often.

Of the 12 different serogroups identified thus far, the major ones associated with disease are A, B, C, W135, and Y, and to a much lesser extent X and Z/29E. However, some disease strains have been isolated for which the serogroup cannot be identified (designated as NGA, or non-groupable), and are thus assumed to have no capsule. An absence of capsule has been shown to facilitate the adherence of meningococci to the human nasopharyngeal epithelium, this being the major method of transmission of the organism between humans, its only host. Although serogroup A continues to be responsible for most of the major meningococcal epidemics worldwide, its incidence in Europe is relatively low, with serogroups B and C being responsible for most of the invasive meningococcal disease present. Levels of serogroup Y remain relatively low in Europe, but are becoming increasingly important in the US, rising from 2% of cases 1989-1991 to 37% during 1997-2002 (Bilukha and Rosenstein 2005).

It has been shown that meningococcal strains causing disease are much more genetically restricted than those carried in the nasopharynx. As with serogroups, only a few serotypes and serosubtypes are associated with most meningococcal disease, with other types within the same serogroup remaining mostly non-invasive. Thus serotype (PorB) and serosubtype (PorA) identification is important in enabling identification of strains at a more detailed level and so provide epidemiological studies with a greater resolution. Moreover, OMPs are frequently used as components of vaccines in development, and serotype/serosubtype analysis may give an idea of how wide the coverage of a particular vaccine might be in a particular area. Though strain identification has traditionally been made using the appropriate, and commercially available, monoclonal antibodies (Mab), increasingly across Europe and reflected in the data collected by EU-IBIS, PorA (serosubtype) identification is being made using genotyping techniques. This is due to the latter's increased sensitivity over serological analysis for detecting PorA/OMP Class I variability, especially as the panel of serosubtyping Mabs has been shown not to cover the full range of variation present. However, genotypic analysis can not always determine definitively whether or not the PorA gene is actually being expressed and so some phenotypic analysis is still required (Cartwright 2003, Dolan-Livengood *et al* 2003, Frasch *et al* 1985, Harrison 2006, Keith Cartwright 2003, Lindberg 1999, Ramsay *et al* 1997, Russell *et al* 2004, Taha *et al* 2002).

Vaccines

Currently available meningococcal vaccines are serogroup specific, the serogroups which are covered by current vaccines being A, C, W135 and Y. The first vaccines were developed in the 1960's and produced by using purified capsular polysaccharide as antigen. Vaccines protecting against serogroup A and serogroup C were developed first, followed some time later by a tetravalent vaccine covering the A, C, Y and W135 serogroups. An effective vaccine against serogroup B meningococci has yet to be developed, probably due to polysaccharide B having antigenic similarity to a sugar present in mammalian tissue, and thus being poorly immunogenic in humans (Danzig 2004).

It has been shown that the antibody response to capsular polysaccharide vaccine is not long-lived, particularly among children under two years of age, who have the highest incidence of meningococcal disease. Thus, during the 1990s, conjugate vaccines were developed. These involve conjugating the antigenic polysaccharide to a suitable carrier protein, such as tetanus toxoid protein, diphtheria toxoid protein or diphtheria cross-reactive material (CRM), enabling the vaccine to produce a stronger immune response among infants, and also to prime immunologic memory, so eliciting booster responses to subsequent doses. MCC was the first such conjugate vaccine to be developed, licensed in UK in 1999 and protecting against serogroup C meningococci, and in 2005, the quadrivalent MCV4 conjugate vaccine was licensed in US, covering, as before, serogroups A, C, W135 and Y (Bruge *et al* 2004, Danzig 2004, Harrison 2006). A conjugate serogroup A vaccine is currently being developed and trialled for use in Africa (Girard *et al* 2006, Jodar *et al* 2003)

The development of an effective vaccine protecting against meningococcal serogroup B disease continues to prove problematic, leading to investigation of alternative candidates using OMP antigens such as the PorA, PorB and the FetA gene products. Much work must continue to be done in this area (Urwin *et al* 2004).

METHODS

The definitions of the terms used in this report and the glossary are given in Appendix III.

Data submission

Participants are requested to submit data on cases of meningococcal disease at 6 monthly intervals. The agreed minimum dataset comprises information on age, sex, date of onset, method of laboratory confirmation, site of identification, serogroup, serotype and serosubtype. However, not all countries are able to provide this information for all the cases reported to them, especially as some countries which undertake PorA genotyping (=(sero)subtype) do not identify the strain serotype (Por B gene product). Susceptibility of strains to various antibiotics such as penicillin, sulphonamide, the celphosporins and rifampicin are reported by the countries which collect such data. For those countries which have introduced routine serogroup C conjugate vaccination (Belgium, Iceland, Ireland, Netherlands, Spain, UK), information on the vaccine schedule used and vaccine coverage is requested. In addition, these countries report whether or not a case had been vaccinated, if this is known. Case definitions were those adopted by the EC (European Commission Decision 2002/253/EC, 20/03/2002). For most analyses, laboratory-diagnosed probable and confirmed cases were included.

EU case definition to 2006 (European Commission Decision 2002/253/EC, 20/03/2002)

Confirmed case

A clinically compatible case diagnosed by one or more of the following laboratory criteria.

- Isolation of *Neisseria meningitidis* from a normally sterile site
- Detection of *N. meningitidis* nucleic acid from normally sterile site
- Detection of *N. meningitidis* antigen from normally sterile site
- Demonstration of gram-negative diplococci from normally sterile site by microscopy

Probable case

A clinically compatible case that is diagnosed by one or more of the following laboratory criteria.

- *N meningitidis* identification from a non-sterile site
- high levels of meningococcal antibody in convalescent serum

or

Clinical picture compatible with meningococcal disease (*eg* meningitis and/or meningococcemia that may progress rapidly to purpura fulminans, shock and death. Other manifestations are possible.) without any laboratory confirmation.

Note that asymptomatic carriers should not be reported.

Some countries submit more than one dataset (*eg* laboratory reports and clinical notifications) as they regard neither dataset to be complete. Where possible participants are encouraged to reconcile their databases before submission, but if not, then both datasets are accepted, using the most appropriate one for the particular analysis being carried out.

Countries are also asked to indicate publicly available age-specific population denominators, or to submit their own datasets. The data requirements for EU-IBIS are given in Appendix I.

Rapid reporting project

This project was initiated as a result of concern that vaccination with meningococcal serogroup C conjugate (MCC) vaccines would create a selective pressure in favour of serogroup B strains, with serotype strains that had been predominantly associated with serogroup C 'capsule switching' to serogroup B and thus evading vaccine-induced protection (Harrison 2006, Maiden and Spratt 1999, Swartley *et al* 1997). Serotypes P2.2a and P2.2b were chosen as monitoring targets as these were the most common serogroup C serotypes prior to the introduction of vaccination, and in addition P2.2a strains are associated with the hyperinvasive and hypervirulent sequence type 11 (ST-11) clonal complex (Snape and Pollard 2005, Trotter *et al* 2002). Sentinel countries included those which did not have routine MCC vaccination as well as those which did, in order to give a representative picture across Europe, and to provide 'controls' against which to judge B:P2.2a and B:P2.2b trends in countries with routine MCC vaccination. Thus, since September 2003, Austria, Czech Republic, Denmark, England and Wales, France, Germany, Greece, Ireland, Italy, Netherlands and Spain have been submitting on a monthly basis the number of cases reported to them of meningococcal disease due to B:2a and B:2b strains.

Questionnaires

Questionnaires had been sent to all participating countries to ascertain the surveillance systems and the laboratory diagnostic methods in 2000, and the results of these have been presented in previous reports (Handford *et al* 2001). Surveillance and laboratory diagnostic questionnaires were again sent out in 2005, and the results from these will be covered in the 2005 EU-IBIS Annual Report.

Quality assurance

EU-IBIS aims to improve the quality of laboratory surveillance through quality assurance schemes. There have been three in total, in 2001, 2003 and again in 2005. The results of the first two have been reported in earlier Annual Reports (Handford *et al* 2001, Handford *et al* 2003) and the third will be described in full in the 2005 Annual Report.

Website development

Work to upgrade the existing EU-IBIS website (www.euibis.org) has been ongoing since August 2003. This project was carried out initially in partnership with the EU-MenNet project, and the assistance of the Health Protection Agency Bioinformatics Unit was enlisted. The content of the website has been revised to provide more information and the website is now more 'user-friendly' with drop down menus and clear mapping and navigation. Users are able to view the meningococcal disease database online and generate tables and charts. There is also a participant only area, access to which is restricted by a log-in system (username and password required) in which is placed information and applications of use to EU-IBIS participants but which are not currently appropriate for wider

dissemination. Development of the website is an ongoing activity, with a particular focus on facilitating better communication and access to data.

Links with EU-MenNet

EU-IBIS has always maintained close links with the European Monitoring Group on Meningococci (EMGM) (Taha *et al* 2005) and one result of this was the EU-MenNet project, a collaborative multi-disciplinary research project exploring meningococcal population biology (http://neisseria.org/nm/emgm/eumennet). The project established the European Meningococcal MLST centre (EMMC), which collected and sequenced representative disease causing strains from participating countries, and linked this data, as far as was possible, to EU-IBIS surveillance data. However, it was found that some records being submitted to the EMMC had different identification/record numbers to those submitted by the same country to EU-IBIS, and lookup tables were not always provided, hampering or indeed preventing the linking. Some data cleansing and cross-referencing was performed at the Health Protection Agency, and is still in progress, and the full results from this project will be reported in the 2005 Annual Report and in the EU-MenNet report, due for publication in 2006.

Dissemination of results/meetings

A half day EU-IBIS meeting was held the day before the 8th European Monitoring Group for Meningococci (EMGM) conference in Dublin in September 2005, and this will be reported on in the 2005 Annual Report.

RESULTS

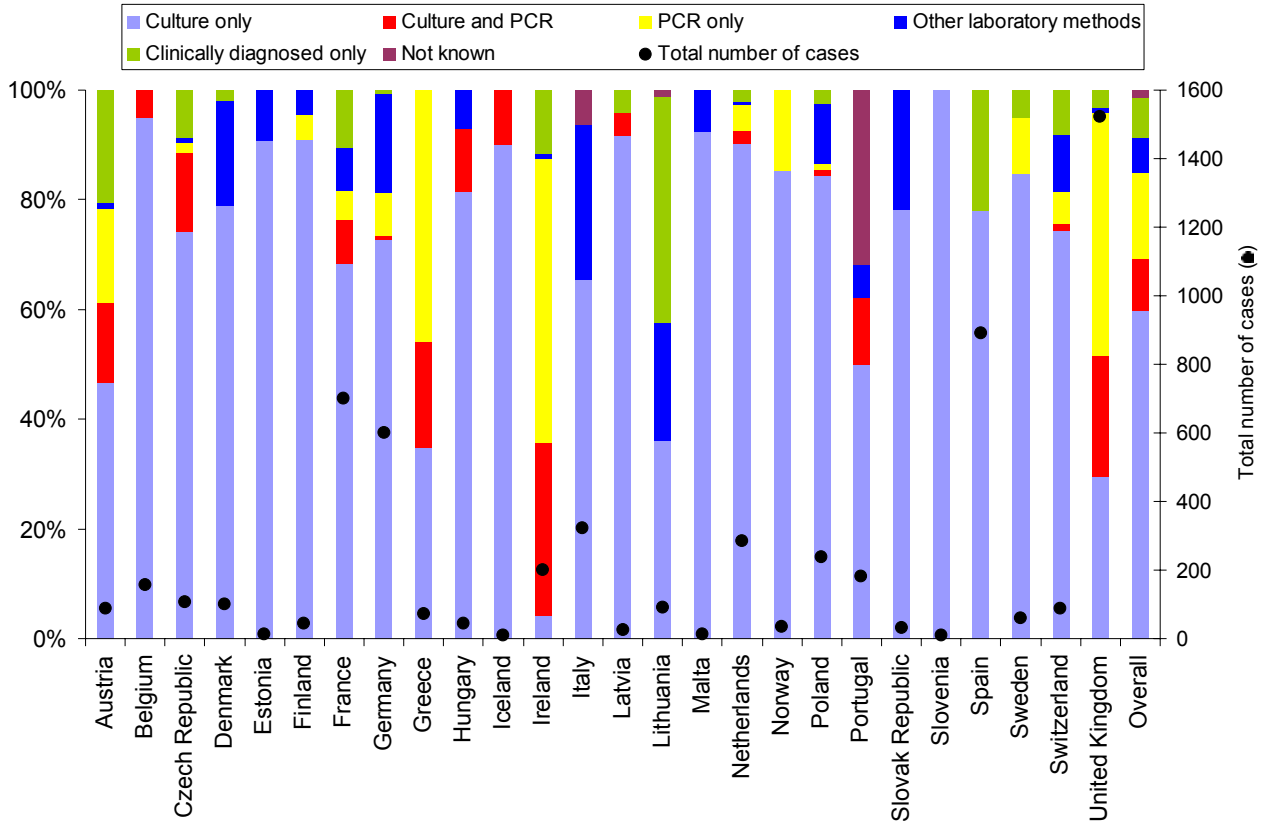
The EU-IBIS database now holds just under 46,500 case reports of meningococcal disease occurring between 1999 and 2004 and submitted by the original participant countries. In addition, just under 1,200 case reports have been received from the EU accession countries between 2003 and 2004, resulting in a total of just under 48,000 cases from 27 countries.

References to table numbers preceded by an 'A' (*eg* Table A3) indicate a table in Appendix IV. Graphs refer to laboratory-diagnosed cases (both confirmed and probable) unless otherwise indicated.

A. Methods of identification

Figure 1 shows the percentage distribution of methods used by different countries to identify all cases of meningococcal disease received in 2004. Also shown in Figure 1 is the total number of cases reported. There is considerable variability in both methods of identification and in the total numbers of reported cases amongst different European countries.

Figure 1 *Percentage distribution of the methods used to identify all reported cases of meningococcal disease for all participating countries 2004*



Determination of an infection by culture still represents the most common method of identification for most countries, but in Greece, Ireland and the UK the primary method is PCR and PCR/culture (See also Table A7). Although its overall numbers are small, Lithuania confirms a considerable proportion of its cases using latex and microscopy, and the proportion of clinically diagnosed only cases peaks at about 20% for Austria and Spain. The total number of cases per country also varies, from about 1500 reported in the UK to 10 and 9 cases being reported in Iceland and Slovenia respectively.

B. Epidemiology

Overall incidence of meningococcal disease

The considerable variability in the overall incidence of meningococcal disease across Europe seen during 1999 - 2002 (Handford *et al* 2003) was also evident in 2003 and 2004, as seen in Figure 2 and Table 1. Table A4 in the Appendix shows the relative incidences of confirmed, and confirmed and probable, meningococcal cases. As can be seen from Table 1, in 2004, the incidence ranged from 0.30 (Poland) and 0.52 (Italy) to 3.42 (Iceland) and 4.35 (Ireland), with the overall European incidence being 1.13 per 100,000 population. The incidence in most countries in 2004 is less or very similar to that of 2003; the rise in incidence in Iceland in 2004 is due to small numbers. Lithuania experienced almost a doubling of incidence rate between 2003 and 2004, though this is probably due more to better reporting than to actual increased incidence (Grazina Mirinaviciute, personal communication).

Figure 2 *Incidence (per 100,000 population) of laboratory-diagnosed confirmed and probable invasive meningococcal disease in all participating countries, 2003-2004*

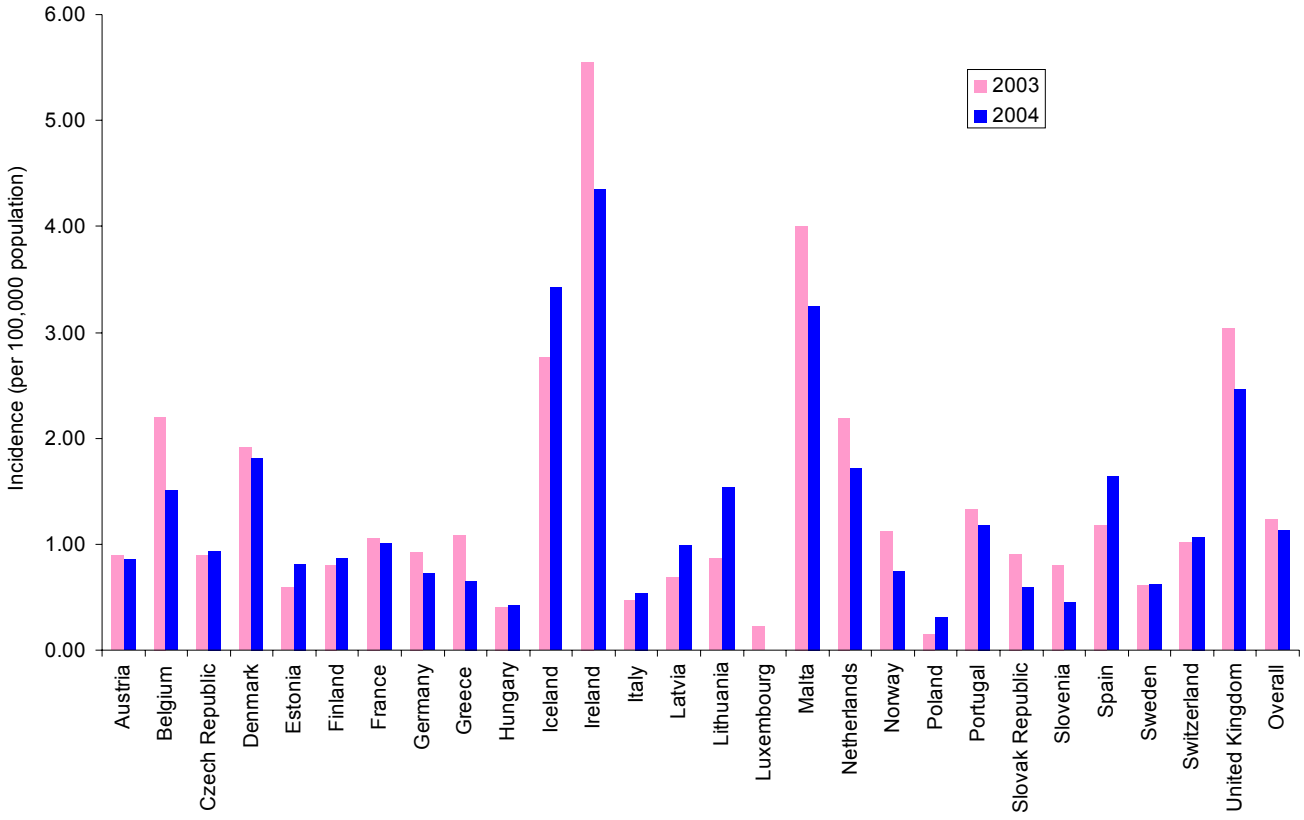


Table 1 Incidence (per 100,000 population) of laboratory-diagnosed confirmed and probable meningococcal disease for all participating countries, 1999-2004

Country	1999	2000	2001	2002	2003	2004
Austria	1.20	1.02	1.30	0.99	0.89	0.86
Belgium	2.90	2.60	3.69	2.54	2.20	1.51
Czech Republic	0.90	0.59	0.91	1.11	0.90	0.94
Denmark	3.33	2.83	3.01	1.82	1.91	1.81
Estonia	0.22	0.66	1.46	0.59	0.59	0.81
Finland	1.11	0.93	0.95	0.94	0.81	0.86
France	0.74	0.81	0.92	1.06	1.06	1.01
Germany	-	-	0.94	0.89	0.93	0.72
Greece	1.19	1.59	1.69	1.78	1.08	0.65
Hungary	-	-	-	-	0.40	0.43
Iceland	7.58	6.40	6.67	5.22	2.77	3.42
Ireland	11.89	10.85	7.72	5.74	5.55	4.35
Italy	0.45	0.43	0.35	0.38	0.47	0.54
Latvia	-	-	-	-	0.69	0.99
Lithuania	-	-	1.00	0.83	0.87	1.54
Luxembourg	4.15	0.23	0.23	0.23	0.22	0.00
Malta	4.34	5.11	3.29	3.52	4.00	3.25
Netherlands	3.65	3.42	4.51	3.82	2.19	1.71
Norway	1.73	1.90	1.71	1.13	1.12	0.74
Poland	0.17	0.11	0.10	0.09	0.15	0.30
Portugal		0.57	1.03	1.78	1.34	1.18
Slovak Republic	-	-	-	-	0.91	0.59
Slovenia	0.30	0.40	0.50	0.40	0.80	0.45
Spain	2.38	2.42	1.59	2.04	1.18	1.64
Sweden	-	-	-	0.51	0.61	0.62
Switzerland	2.09	2.07	2.02	1.24	1.02	1.07
United Kingdom	5.24	5.10	4.37	3.29	3.03	2.46
Overall	1.61	1.58	1.65	1.45	1.24	1.13

The complexity of the epidemiology of meningococcal disease in Europe is further illustrated in Table 2, which shows the percentage change in incidence of meningococcal disease over time, using the 1999 or earliest year in which consistent data was available as the baseline figure. Part of this complexity is due to the introduction in some countries of conjugate vaccine targeted at serogroup C meningococcal disease (MCC) into the routine vaccination schedule, either with or without a catch-up campaign, and this is explored in the next section (Meningococcal serogroup C conjugate (MCC) vaccination). What is evident is that the very high rates of disease experienced by Iceland and Ireland in 1999 (7.58 and 11.89 per 100,000 population respectively) have decreased dramatically by 2004, though these levels are still considerably higher than those of most other European countries. Similar,

though less dramatic, decreases over time can be seen in Belgium, Netherlands and UK, which have introduced MCC, but also in Denmark and Norway, which have not.

Table 2 Percentage change in incidence of laboratory-diagnosed confirmed and probable meningococcal disease over time for all participating countries

Country	Baseline year	+ 1 year	+ 2 years	+ 3 years	+ 4 years	+ 5 years
Austria	1999	-0.15	0.09	-0.17	-0.25	-0.29
Belgium	1999	-0.10	0.27	-0.13	-0.24	-0.48
Czech Republic	1999	-0.34	0.01	0.22	0.00	0.04
Denmark	1999	-0.15	-0.10	-0.45	-0.43	-0.45
Estonia	1999	2.02	5.73	1.70	1.71	2.74
Finland	1999	-0.16	-0.14	-0.15	-0.27	-0.22
France	1999	0.09	0.24	0.42	0.42	0.36
Germany	2001	-0.05	0.00	-0.23		
Greece	1999	0.33	0.41	0.49	-0.10	-0.45
Hungary	2003	0.05				
Iceland	1999	-0.15	-0.12	-0.31	-0.63	-0.55
Ireland	1999	-0.09	-0.35	-0.52	-0.53	-0.63
Italy	1999	-0.04	-0.21	-0.16	0.06	0.22
Latvia	2003	0.45				
Lithuania	2001	-0.17	-0.14	0.53		
Luxembourg	1999	-0.95	-0.95	-0.95	-0.95	-1.00
Malta	1999	0.18	-0.24	-0.19	-0.08	-0.25
Netherlands	1999	-0.07	0.23	0.05	-0.40	-0.53
Norway	1999	0.10	-0.01	-0.35	-0.35	-0.57
Poland	1999	-0.36	-0.45	-0.47	-0.14	0.75
Portugal	2000	0.78	2.09	1.32	1.05	
Slovak Republic	2003	-0.35				
Slovenia	1999	0.33	0.66	0.33	1.65	0.49
Spain	1999	0.02	-0.33	-0.14	-0.50	-0.31
Sweden	2002	0.19	0.21			
Switzerland	1999	-0.01	-0.03	-0.41	-0.51	-0.49
United Kingdom	1999	-0.03	-0.17	-0.37	-0.42	-0.53
Overall	1999	-0.02	0.02	-0.10	-0.23	-0.30

The apparent increasing incidence in countries such as Portugal and Lithuania is likely to be due to improvements in ascertainment over time. The apparent increase in incidence in Portugal from baseline year to +2 years (2000 to 2002) is in fact due to the implementation of a National Programme for Surveillance of Meningococcal disease in 2002, which increased the number of isolates received by the reference laboratory; the decreasing incidence after 2002 probably reflects the impact of MCC vaccination, which was recommended for infants on a national basis in 2002 (personal communication, Laurinda Queirós). Ascertainment varies between countries for a variety of reasons, including under-reporting. The latter has been estimated to be between 40% and 96%, and

completeness of reporting can be improved by reconciliation of data sources (such as laboratory data with notifications) (Trotter *et al* 2005).

In contrast, the trends in many other countries are not due to ascertainment, but may reflect the natural variability in meningococcal disease incidence (Jones 1995). For example, the sharp increase in Estonia's incidence rate in 2000 and 2001, similar to previous periods of high incidence in 1995/1996 (personal communication, Unna Jöks) and the doubling of incidence in Slovenia in 2003, have no clear explanation. Equally, the decrease in incidence of meningococcal disease in Denmark, which occurred in serogroup B and not serogroup C disease, and is reflected in both the surveillance and the reference laboratory datasets, is therefore likely to be a real decrease rather than due to incomplete ascertainment (personal communication, Michael Howitz).

Meningococcal serogroup C conjugate (MCC) vaccination

MCC vaccine schedules

The UK was the first country to introduce MCC vaccines, in November 1999. Between 2000 and 2004 the vaccine has been introduced into the routine vaccination schedules of Ireland, Spain (both 2000), the Netherlands, Belgium and Iceland (all three 2002). The routine vaccine schedules and details of catch-up campaigns in these countries and the use of MCC vaccine in other European countries are summarised in Table 3. The effectiveness of vaccination is clearly illustrated in Figure 3, which compares the change in incidence of laboratory-confirmed serogroup C meningococcal disease in countries with and without routine MCC vaccination (MCC countries and non-MCC countries respectively) between 1999 and 2004.

Vaccine effectiveness

Although the MCC vaccine is clearly efficacious, vaccination schedules in MCC countries can vary quite significantly, from the UK vaccinating at 2, 3 and 4 months to the Netherlands giving one injection at 14 months (Table 3). Recent studies in the UK and Spain have shown that the protection afforded by the vaccine given as a three dose schedule before the age of 1 year decreases over time (Larrauri *et al* 2005). There have been 18 cases of vaccine failure in the 3 year follow-up period more than one year after vaccination in the UK, and in Spain there have been eight vaccine failures in children who had been routinely vaccinated during infancy (Cano *et al* 2004, Trotter *et al* 2004). However, data from the Netherlands, and the UK analysis, suggest that a single dose in the second year of life may provide longer protection. No cases of vaccine failure have been reported in the Netherlands up to summer 2005, and there was a reduction in the number of meningococcal serogroup C cases in <14 months, as well as those vaccinated, probably due to the herd immunity generated both by the introduction of routine vaccination and by the catch-up campaign which targeted 1 year – 18 year olds (de Greeff *et al* 2006, Trotter *et al* 2004).

Table 3 Conjugate meningococcal group C vaccination programmes in European countries, as at September 2005

Countries with routine vaccination

Country		Routine schedule	Year introduced	Catch-up	Year undertaken
Belgium	1. Wallonie	12 months	2002	1 year - 6 years	2002
	2. Flanders	12 months	2002	1 years - 3 years 1 year - 6 years and 14 years - 17 years 10 years - 14 years 7 years - 9 years	2001 2002 2003 2004
Iceland		6 and 8 months	2002	6 months - 19 years	October 2002 – October 2003
Ireland		2, 4 and 6 months	2000	<23 years	October 2000 - March 2002
Netherlands		14 months	2002	1 year - 18 years	June 2002 - November 2002
Spain		2, 4 and 6 months	2000	7 months - 19 years 15 out of 19 Spanish regions	2001 – 2004
UK		2, 3 and 4 months	1999	<18 years 19 years - 25 years	November 1999 – 2000 December 2001 – 2002

Countries with selective or voluntary vaccination

Country	Given to					Year introduced
	Travellers	Contacts of cases	Outbreak control	Underlying conditions	Other	
Czech Republic	Yes	Yes	Yes	Yes	On request	2001
Germany	Yes	No	Yes	Yes		
Greece					Given by private paediatricians, targeted at <14 years	2001
Hungary					Children at request of parents	
Norway	Yes	Of serogroup C cases				
Poland		Yes**	Yes**		Generally recommended**	
*Portugal**					Children, on prescription from paediatrician As above, but now with national recommendation to be included in infant schedule of 3, 5 and 7 months As above, but schedule changed to 3, 5 and 15 months.	2001 2002 2005
Sweden			Yes		Given rarely	
Switzerland	Yes	Yes	Yes	Yes	Military recruits, exposed laboratory workers	2001

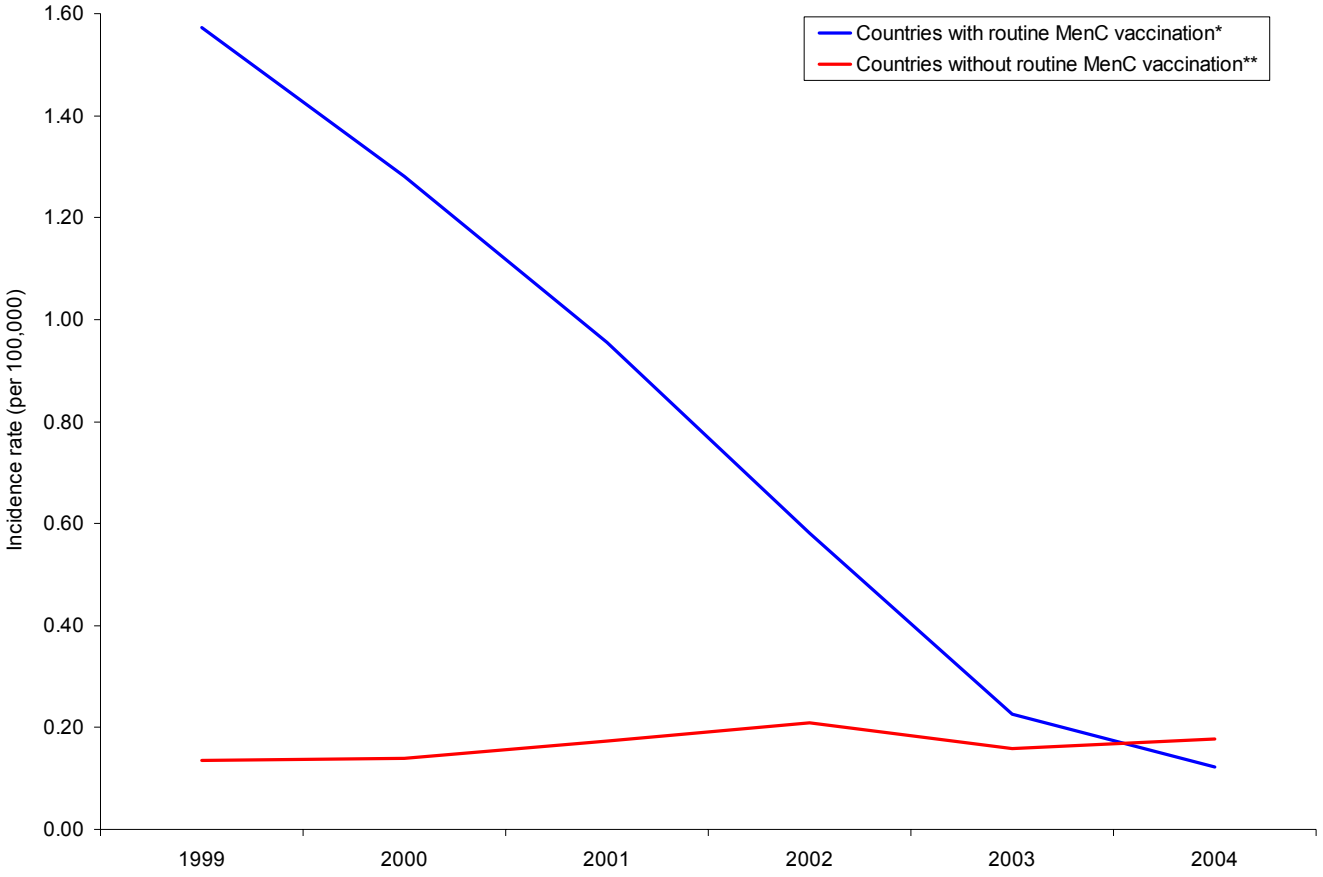
*In January 2006, MenC vaccination will be incorporated into the routine immunisation schedule and so available without cost, and will be accompanied by a catch-up programme targeting the <10's in 2006, and the <19's in 2007

** In practice the vaccine is rarely requested, partly due to the fact that the vaccine is neither free nor partially subsided

Countries with rare or no vaccination

Austria	Estonia	Italy	Malta
Denmark	Finland	Latvia	Slovak Republic

Figure 3 *Incidence of serogroup C laboratory-diagnosed confirmed and probable meningococcal disease in countries which do and do not include MCC vaccine in their routine vaccination schedule, 1999-2004*



** Countries with routine MenC vaccination programmes: Belgium, Iceland, Ireland, Netherlands, United Kingdom

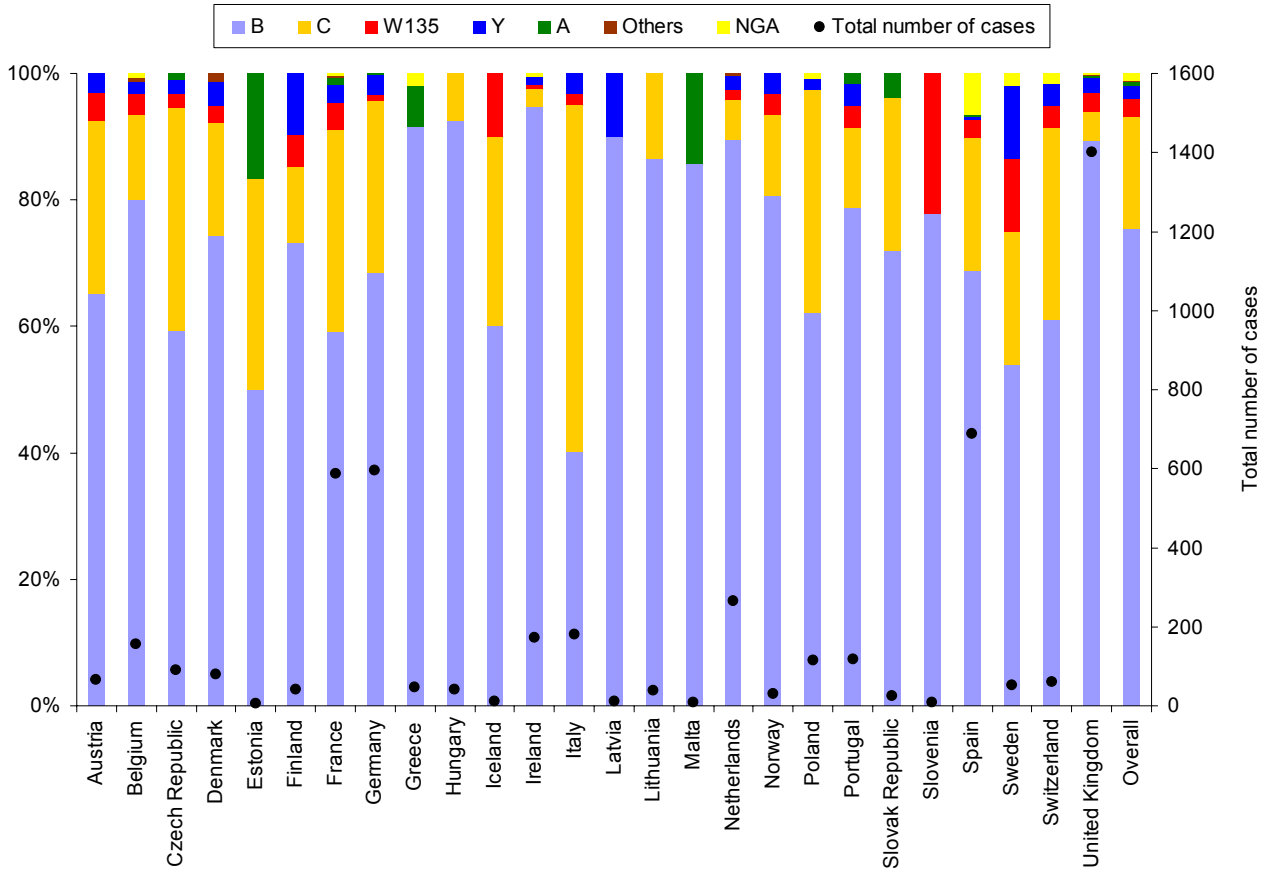
** Countries without routine MenC vaccination programmes: Austria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Luxembourg, Malta, Norway, Poland, Slovenia, Switzerland

Studies have also shown a fall in protective antibody levels after 2 to 4 years after vaccination, though evidence of immunological memory was present and may confer some protection. However, because conjugate MenC vaccination reduces *N meningitidis* carriage, natural immune boosting may not occur as frequently in the general population, and thus may contribute to declining protection over time. This remains to be seen, and ongoing surveillance is essential to determine whether or not this is in fact the case (Snape and Pollard 2005).

Serogroups

The distribution of serogroups in laboratory-diagnosed cases in all participant countries in 2004 is shown in Figure 4 and also in Tables A13 and A14.

Figure 4 Percentage distribution of serogroups causing laboratory-diagnosed confirmed and probable meningococcal disease in all participating countries, 2004

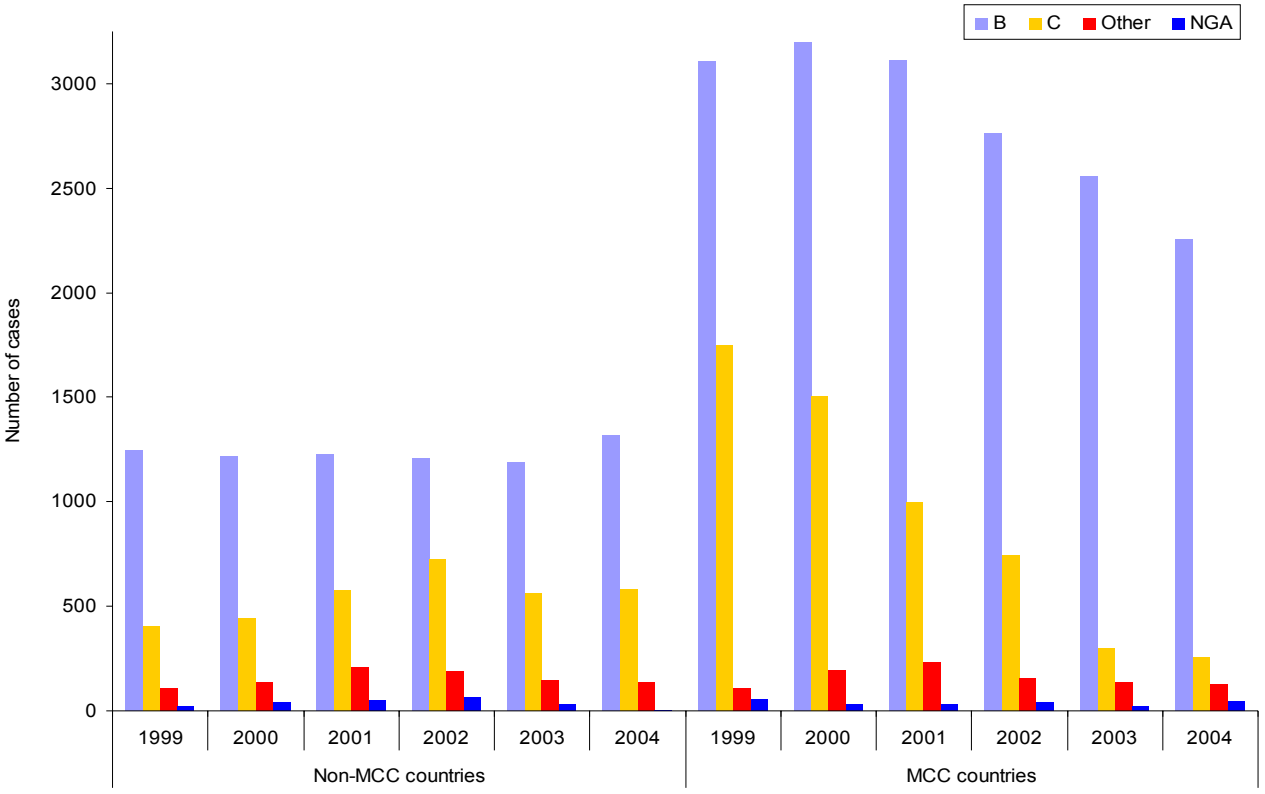


Serogroups B and C comprise the majority of meningococcal isolates recorded, regardless of the total number of cases identified, and together contribute around 90% of cases. An exception to this is Sweden, which has a relatively high proportion of serogroup W135 and Y isolates, although total numbers are fairly small.

The impact of MCC vaccination on serogroup distribution can be seen in Figures 5 and 6. Figure 5 shows the change in number of cases attributable to each serogroup over time, differentiating between MCC and non-MCC countries. Figure 6 shows the percentage distribution of serogroups in MCC countries in the years before and following the introduction of MCC into the routine vaccination schedule.

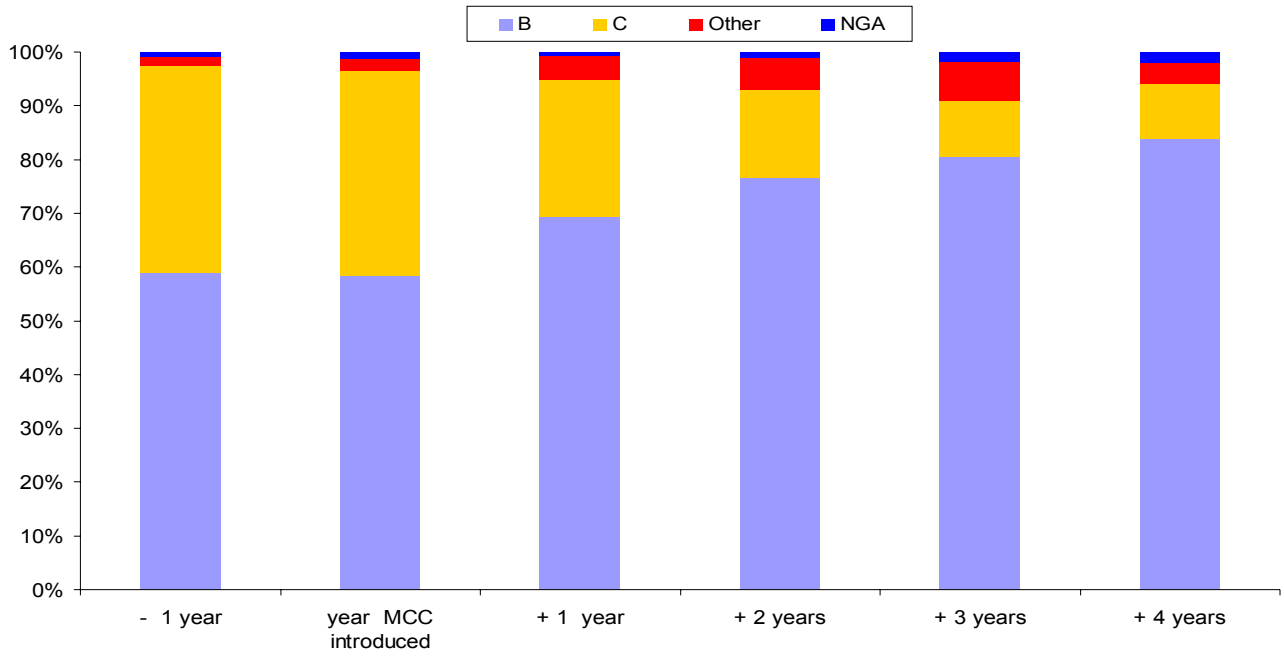
Although there is a decrease in total numbers of cases of both serogroups B and C between 1999 and 2004 in MCC countries, the reduction of serogroup C is much larger, being reduced by over 80% whereas that of serogroup B decreases by less than 30% between 1999 and 2004.

Figure 5 *Serogroup distribution of laboratory-diagnosed confirmed and probable meningococcal disease cases in countries submitting consistent data* with and without routine MCC vaccination, 1999-2004*



* Countries as in Figure 3

Figure 6 *Serogroup distribution of laboratory-diagnosed confirmed and probable meningococcal disease cases in years before, during and after introduction of MCC into routine vaccination schedule**



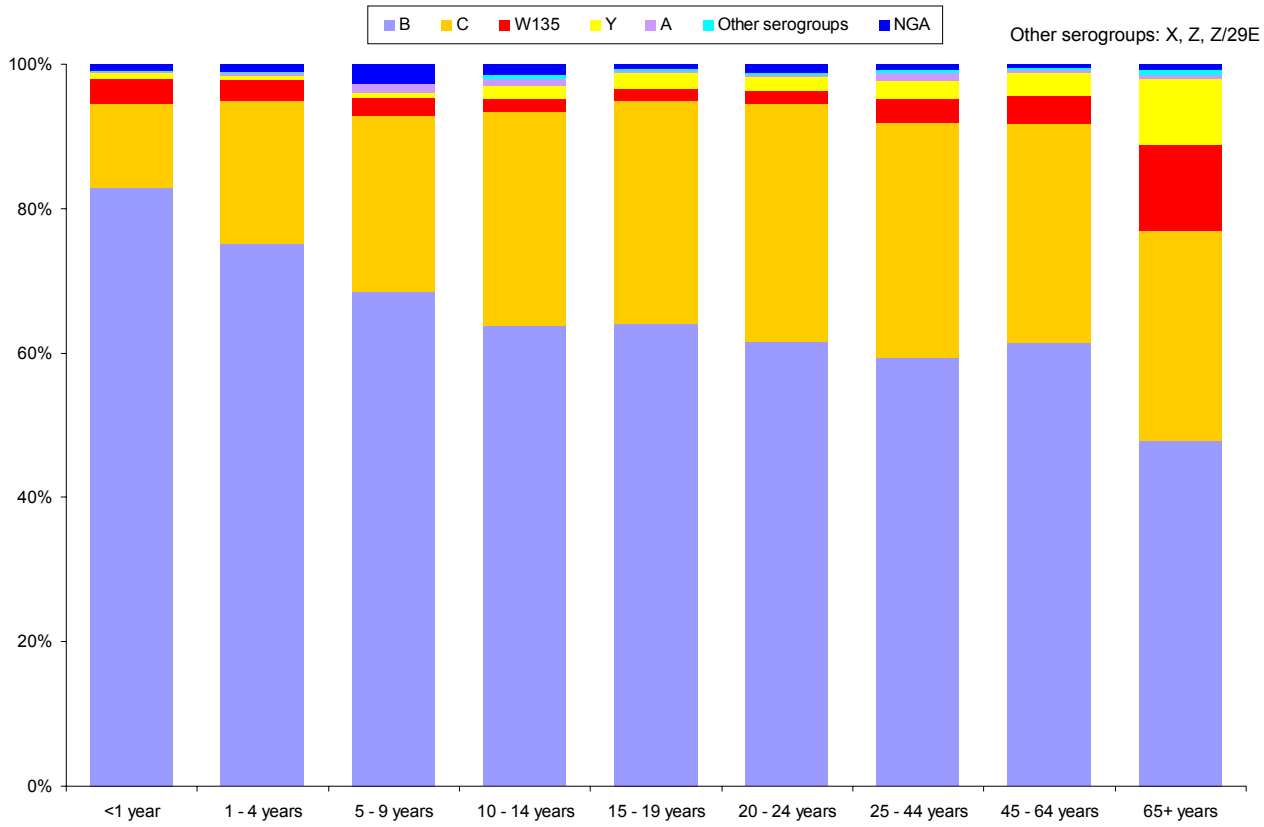
* Data from country (year of MCC introduction) : Belgium (2002), Iceland (2002), Ireland (2000), Netherlands (2002), Spain (2000), UK (1999)

The fairly stable or declining number of cases due to serogroup B appears to indicate that serogroup B strains are not increasing to fill any ecological niches produced by the reduction in serogroup C strains, nor that the latter are undergoing any significant capsule switching events. That the reduction in serogroup C is due to the introduction of MCC is supported both by the fact that there is no similar reduction in serogroup C over the same time period in non-MCC countries (Figure 5), and by the fact that the proportion of cases of meningococcal disease due to serogroup C continues to decrease with the number of years following MCC introduction (Figure 6). Table A17 shows the change in proportion of cases due to serogroup C for all countries which have submitted consistent data between 1999 and 2004.

Age

The association between age group and serogroup is illustrated in Figure 7.

Figure 7 *Percentage serogroup- and age- specific distribution of laboratory-diagnosed confirmed and probable meningococcal disease in countries with consistent data* 1999-2004 combined*

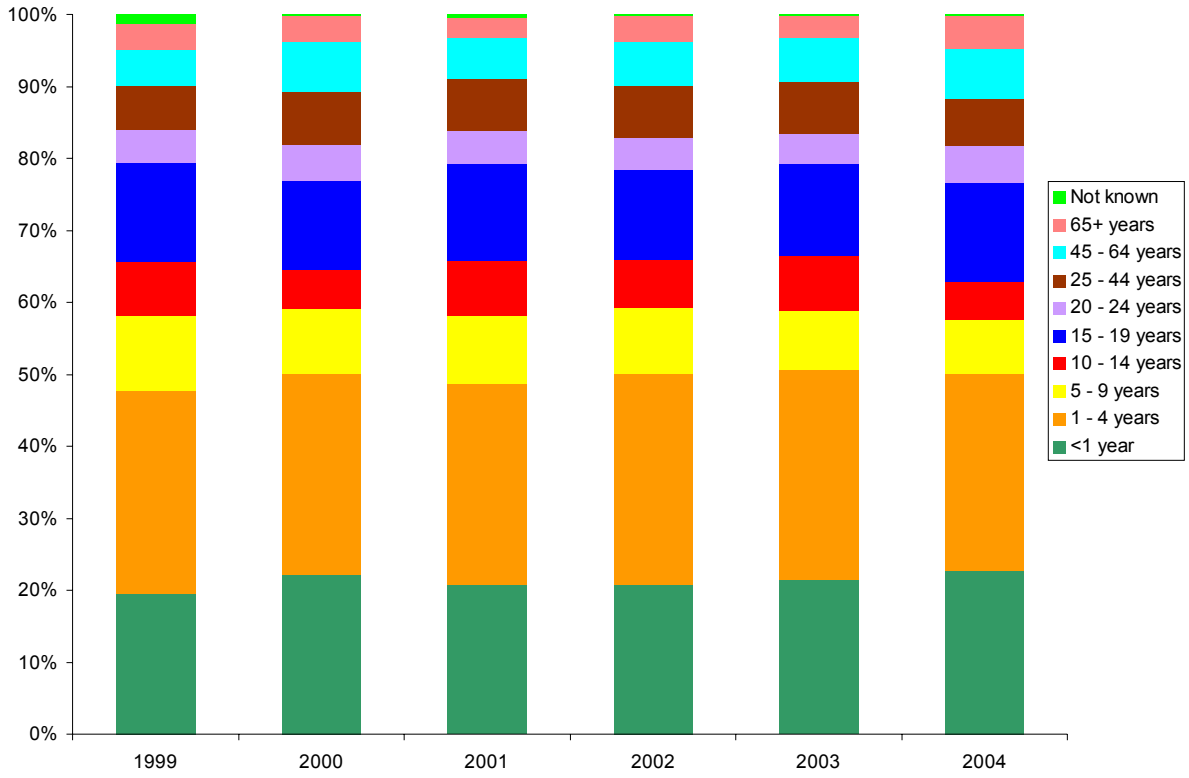


* Data used from: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Slovenia, Switzerland, United Kingdom

There is a clear relationship between serogroup and age, with the highest proportion of serogroup B disease being present in the younger age groups, and by far the highest proportion of non-B, non-C serogroup cases being present in the 65+ age group. The proportion of serogroup C cases generally increases with age.

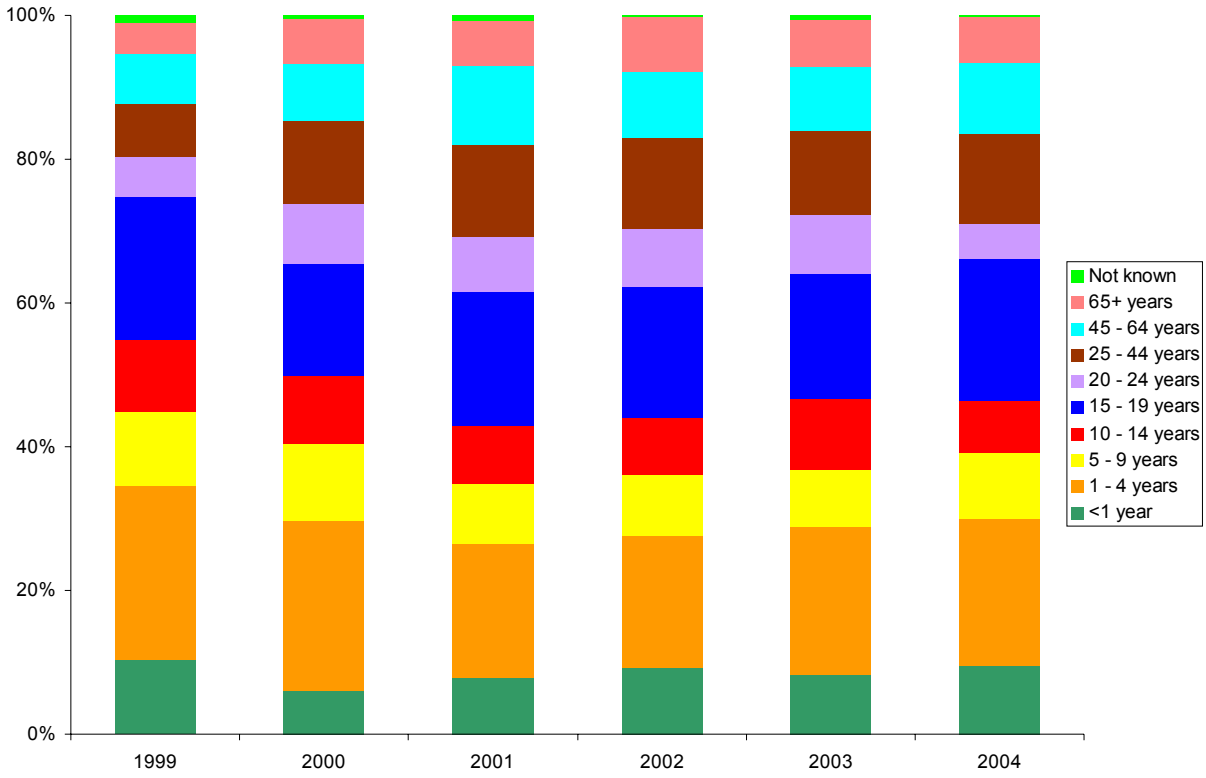
The age distribution of laboratory-confirmed serogroup B and serogroup C meningococcal disease between 1999 and 2004 is illustrated in Figures 8 and 9, and Tables A15 and A16.

Figure 8 Percentage age-specific distribution of laboratory-diagnosed confirmed and probable serogroup B meningococcal disease in countries with consistent data 1999-2004*



* Data used from: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Slovenia, Switzerland, United Kingdom

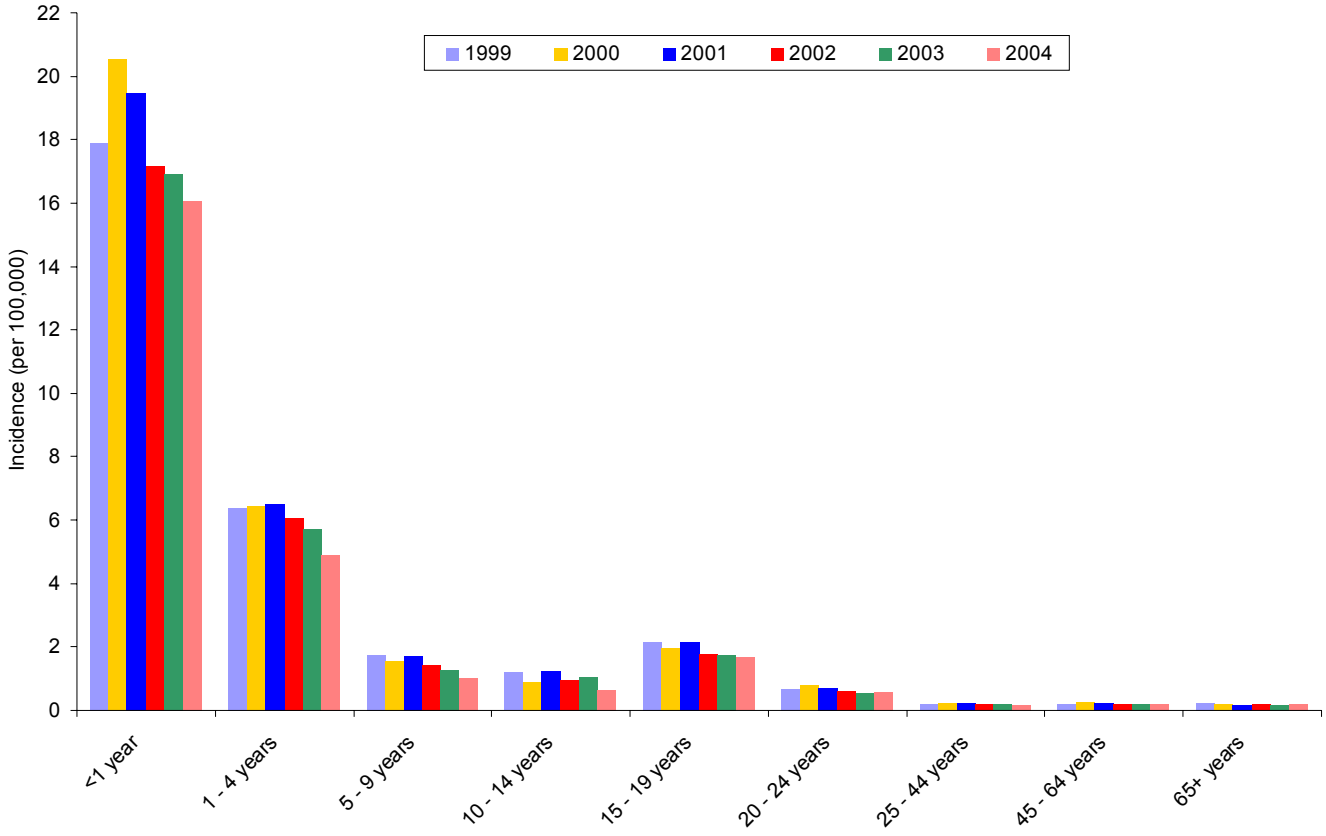
Figure 9 Percentage age-specific distribution of laboratory-diagnosed confirmed and probable serogroup C meningococcal disease in countries with consistent data 1999-2004*



The age distribution of serogroup B meningococcal disease has not changed greatly between 1999 and 2004, with just under 50% of cases occurring in the <5 year olds. The distribution of serogroup C disease is more varied, with an appreciable drop in the proportion of cases occurring in the 1 – 4 year olds between 2000 and 2001, and a corresponding increase occurring in the 25 – 64 year old age group. This probably reflects the decline in serogroup C disease in those countries using MCC vaccine, who have generally targeted children and young adults, though there is a slight increase in those under 25 years old in 2003 and 2004 compared to the two previous years.

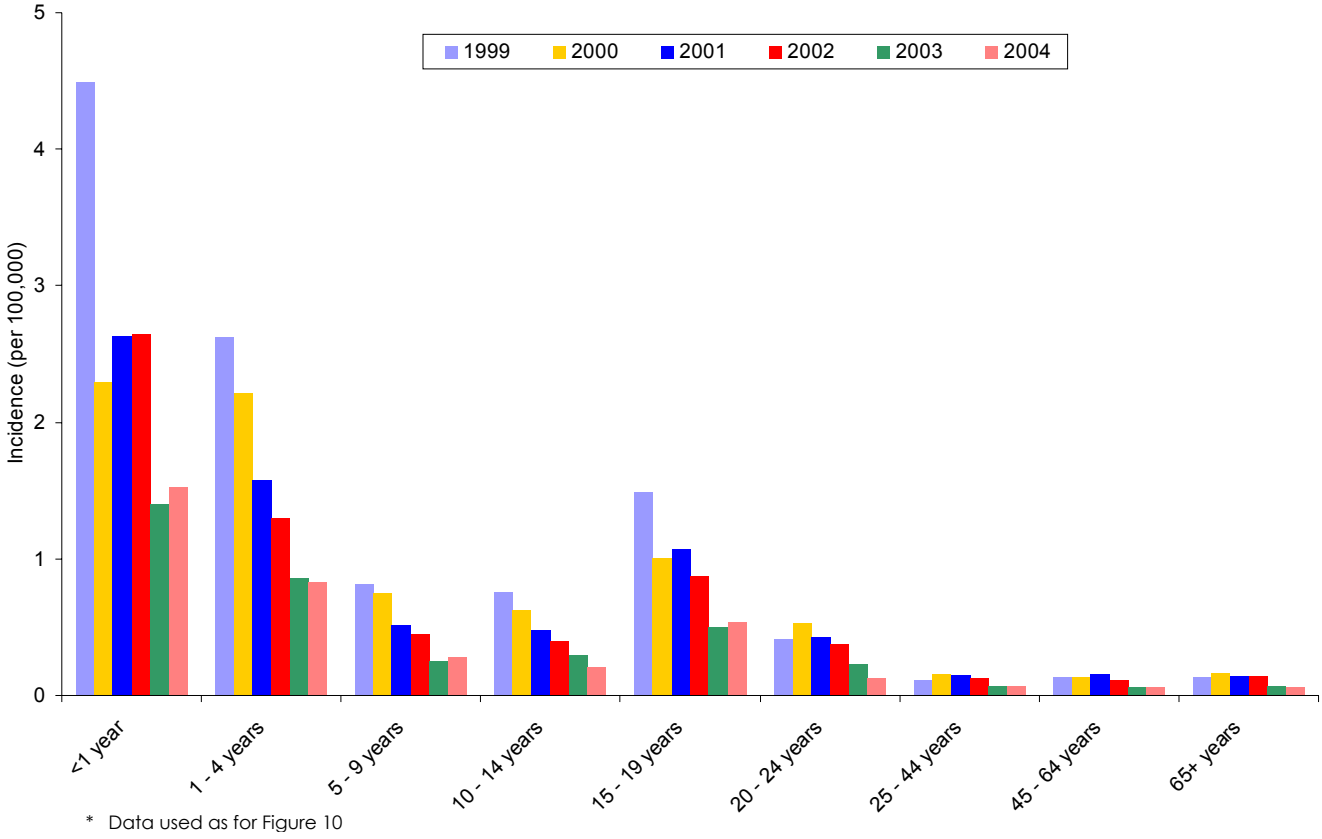
The age-specific incidence of serogroup B and C meningococcal disease from 1999 to 2004 is shown in Figures 10 and 11 respectively.

Figure 10 Age-specific incidence of laboratory-diagnosed confirmed and probable serogroup B meningococcal disease in countries with consistent data 1999-2004*



* Data used from: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Slovenia, Switzerland, United Kingdom

Figure 11 Age-specific incidence of laboratory-diagnosed confirmed and probable serogroup C meningococcal disease in countries with consistent data 1999-2004*



The pattern of incidence across age groups and years is generally similar between serogroups B and C, although the incidence of serogroup B tends to be 4- to 5- fold higher. The highest incidence for both serogroups is found in the <1's, followed by the 1 – 4 year age group, with a small but appreciable peak present in the 15 – 19 year age group. There is a small but consistent decrease between 2000 and 2004 across all age groups in serogroup B incidence; there is a much larger decrease in incidence of serogroup C disease, particularly in the <25 year age group .

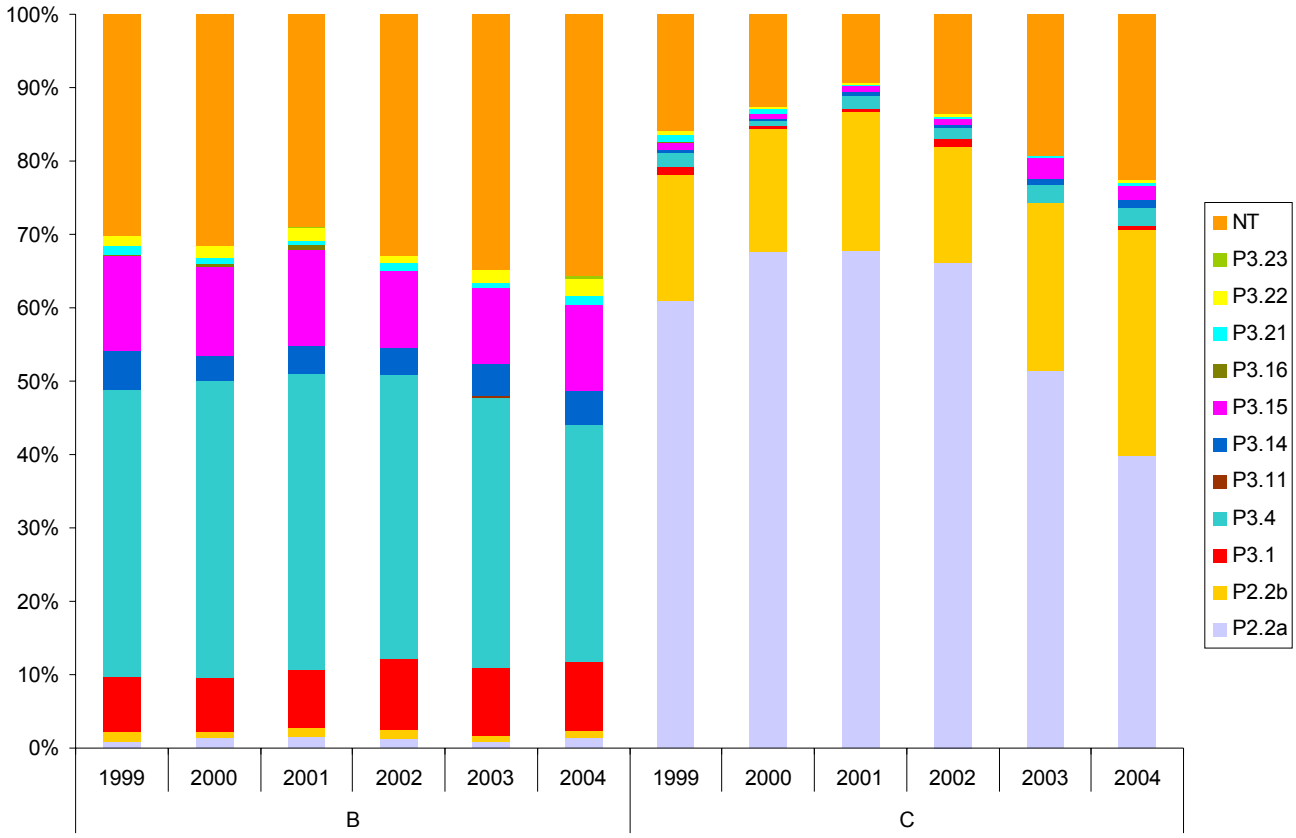
Serotype, serosubtype

Distribution of serotypes

Figure 12 shows the distribution of serotypes associated with serogroups B and C respectively across Europe 1999 - 2004, and Figures 13 and 14, and Tables A18 and A19 show the geographical distribution of these serotypes.

There is a clear difference in the serotypes associated with the two different serogroups; serotypes P2.2a and P2.2b predominate in serogroup C strains, whereas the serotypes most associated with serogroup B are P3.4 and to a lesser extent P3.15.

Figure 12 Distribution of serotypes associated with serogroups B and C respectively, all participating countries, 1999 - 2004*



* Countries with consistent data which type strains: Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Ireland, Italy, Malta, Netherlands, Norway, Poland, Slovenia, Switzerland, United Kingdom

The proportions of the different serotypes associated with serogroup B have generally remained stable between 1999 and 2004, whereas those associated with serogroup C do show a clear trend over time, particularly since 2002, most noticeably in the reduction of P2.2a strains, with corresponding increases in P2.2b and NT strains.

Figure 13 illustrates the regional variability of serogroup B serotype distribution. P3.4 and B3.15 were common in all countries (except Slovenia where only five strains were reported).

Figure 14 illustrates the regional variability in serogroup C serotype distribution in 2004, and Table 4 shows the proportion of serotyped serogroup C strains which are of serotype P2.2a between 1999 and 2004. As indicated in Figure 13, there is a lower level of variability in serotype distribution with serogroup C strains than was seen with serogroup B strains, with P2.2a being the predominant serotype in 9 out of 13 countries.

Figure 13 Distribution of serotypes associated with serogroup B in all participating countries, 2004

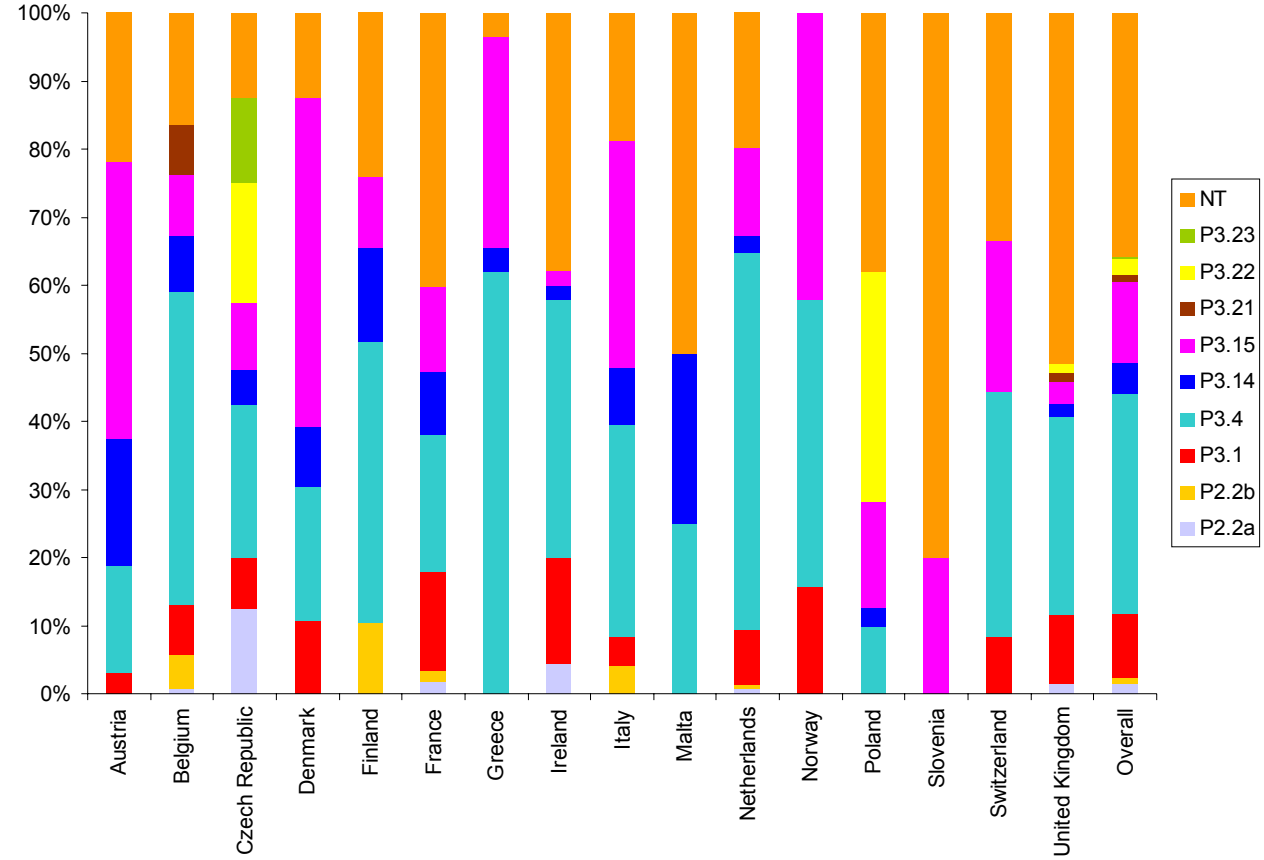
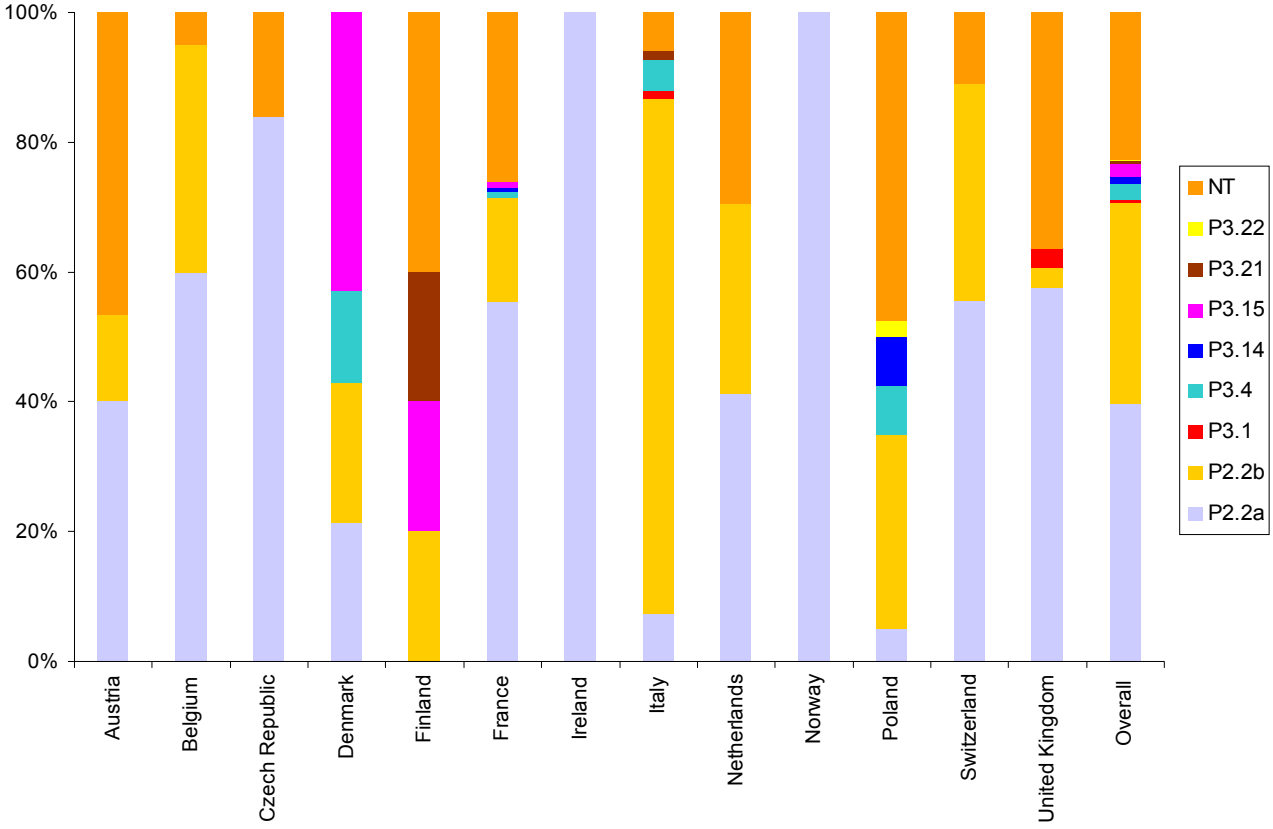


Figure 14 Distribution of serotypes associated with serogroup C in all participating countries, 2004*



Greece, Malta and Slovenia reported no cases of serogroup C meningococcal disease in 2004

Table 4 Proportion (number of all serotyped C cases) of serogroup C cases which are of serotype P2.2a, all participating countries, 1999 - 2004

Country	1999	2000	2001	2002	2003	2004
MCC countries						
Belgium	38% (77)	47% (85)	69% (178)	61% (89)	67% (46)	60% (20)
Ireland	81% (42)	93% (54)	100% (6)	100% (4)	100% (2)	100% (1)
Netherlands	74% (81)	67% (106)	77% (277)	80% (222)	61% (44)	41% (17)
United Kingdom	69% (713)	76% (514)	85% (220)	75% (128)	78% (65)	58% (33)
All MCC countries	68% (913)	73% (759)	78% (681)	75% (443)	71% (157)	55% (71)
Non-MCC countries						
Austria	7% (14)	60% (10)	50% (34)	53% (17)	33% (12)	40% (15)
Czech Republic	77% (26)	90% (10)	57% (23)	71% (28)	78% (23)	84% (25)
Denmark	38% (21)	75% (16)	38% (24)	44% (16)	26% (19)	21% (14)
Finland	11% (9)	30% (10)	33% (9)	67% (6)	0% (5)	0% (5)
France	31% (100)	N/A*	54% (126)	62% (172)	53% (115)	55% (130)
Greece	76% (17)	89% (9)	63% (8)	33% (6)	100% (2)	N/A***
Italy	88% (16)	50% (24)	53% (15)	31% (32)	18% (55)	7% (83)
Malta	100% (1)	0% (1)	0% (1)	N/A**	100% (1)	N/A***
Norway	40% (10)	67% (12)	38% (13)	0% (3)	44% (9)	100% (1)
Poland	13% (8)	14% (7)	0% (4)	18% (11)	10% (21)	5% (40)
Slovenia	N/A***	100% (1)	100% (1)	100% (1)	0% (3)	N/A***
Switzerland	28% (57)	33% (83)	38% (69)	44% (39)	48% (23)	56% (18)
All non-MCC countries	34% (279)	33% (183)	39% (327)	49% (331)	37% (288)	34% (331)
Overall	61% (1192)	65% (942)	65% (1008)	64% (774)	49% (445)	37% (402)

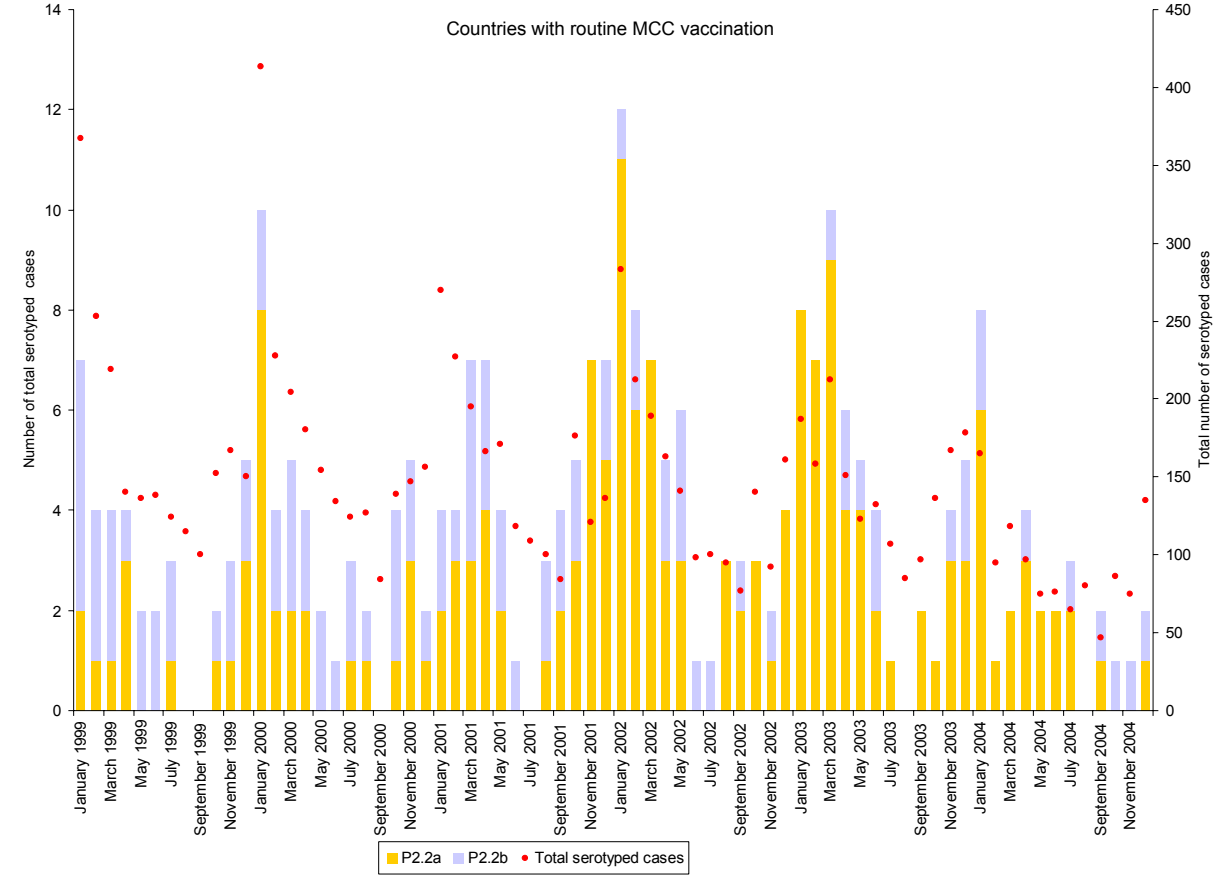
*No data **No serotyped Serogroup C cases *** No serogroup C cases Year MCC introduced

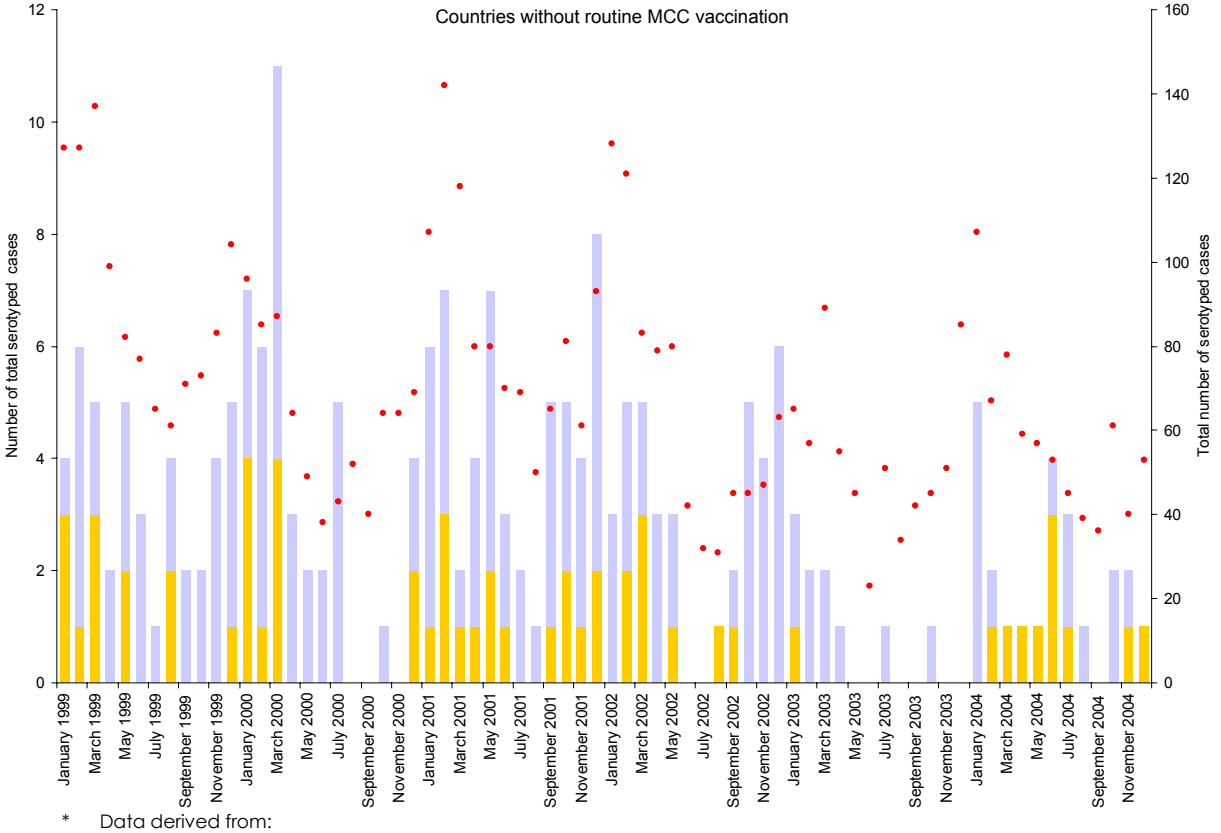
Figure 12 indicates a decreasing proportion in 2003 and 2004 of serogroup C strains which are of serotype P2.2a across Europe. Table 4 shows that this is primarily within the MCC countries, changes in non-MCC countries occurring in both directions, and with the exception of a brief increase in 2001 and 2002, overall remaining relatively stable over time.

B2a/B2b rapid surveillance project

The number of cases of B:2a and B:2b in each of the sentinel countries is shown in Table A20, and the proportion of cases which are of this phenotype with respect to the total number of serotyped cases is shown for countries with and without routine MCC vaccination in Figure 15.

Figure 15 Number of serogroup B serotyped cases which are of phenotype B:P2.2a or B:P2.2b in countries submitting consistent data with and without routine MCC vaccination, by month and year, 1999 - 2004*





* Data derived from:
Countries without routine MCC vaccination: Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Malt
Norway, Poland, Portugal, Slovak Republic, Slovenia, Sweden, Switzerland
Countries with routine MCC vaccination: Belgium, Ireland, Netherlands, Spain, United Kingdom

There appears to be natural variability in the overall number of cases caused by isolates of phenotype B:P2.2a and B:P2.2b without any clear trends in either countries with or without routine MCC vaccination. Thus, there appears to be no evidence to date that any capsule switching or expansion of B:2.2a or B2.2b cases is occurring in MCC countries, though Spain continues to see higher numbers than were present before the introduction of MCC vaccination. The situation continues to be monitored.

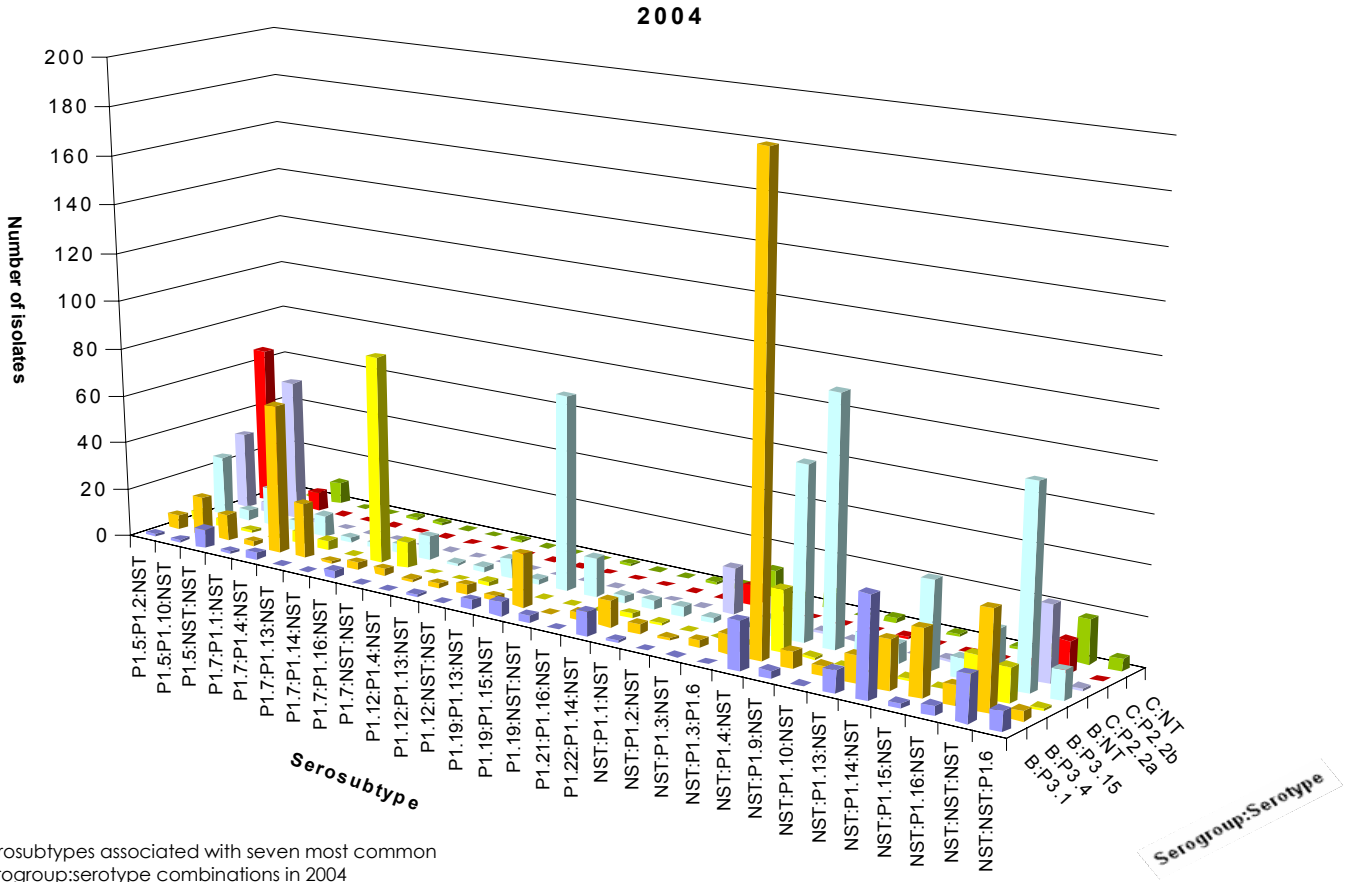
Distribution of serosubtypes

The association of various serosubtypes with serogroup and serotype is shown graphically in Figures 16 and 17 and in Tables A21 to A24. The seven most common serogroup:serotype combinations were determined for 1999 and for 2004, and these were found to be the same for both years, though their relative frequency did change slightly. The phenotypes were B:P3.4, B:NT, C:P2.2a, B:P3.15, C:P2.2b, B:P3.1, C:NT, and the serosubtypes combinations associated with each of these in 2004 are shown graphically in Figure 16. As can be seen, certain serosubtypes do tend to cluster with certain serogroup:serotype combinations, most noticeably serosubtype NST:P1.4:NST with B:P3.4 strains. The number of isolates having the most common serogroup:serotype:serosubtype phenotypes in 1999 and 2004 are shown in Figure 17, these being present in more than 60 isolates in either year. Generally, there were less isolates of a particular phenotype present in 2004 than in 1999, though this might be in part due to the increase in genotyping technologies in 2004 to determine PorA (serotype) but not PorB (serosubtype) variants. This is illustrated by the presence of the B:NT:P1.19:P1.15:NT phenotype in more than 60 isolates in 2004, but none in 1999.

The epidemiology of different serosubtype variants is becoming increasingly important due to the failure to produce an effective vaccine based on the meningococcal serogroup B polysaccharide. This is thought to be due to similar antigenicity between serogroup B strains and host tissue, particularly brain tissue. Therefore, attention has switched to developing vaccines directed against OMPs, such as the Por A protein. Vaccines of this type have been developed by the Finlay Institute in Cuba and by the National Institute of Public Health (NIPH) in Norway, the latter also being adapted to tackle an epidemic of meningococcal serogroup B disease in New Zealand. The Cuban vaccine was produced using a B:P3.4:P1.15 strain, and the Norwegian one using a B:P3.15:P1.7,16 strain (Bjune *et al* 1991, Jodar *et al* 2002, Rodriguez *et al* 1999, Sierra *et al* 1991). The National Vaccine Institute in the Netherlands has produced recombinant PorA vaccines using two or three strains that each express three different sets of PorA proteins and do not express the capsular B protein. The hexavalent vaccine produces P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4 and the nonavalent produces these plus P1.22,14; P1.7-1,1; P1.18-1,3,6 (Claassen *et al* 1996, van der Ley *et al* 1995)

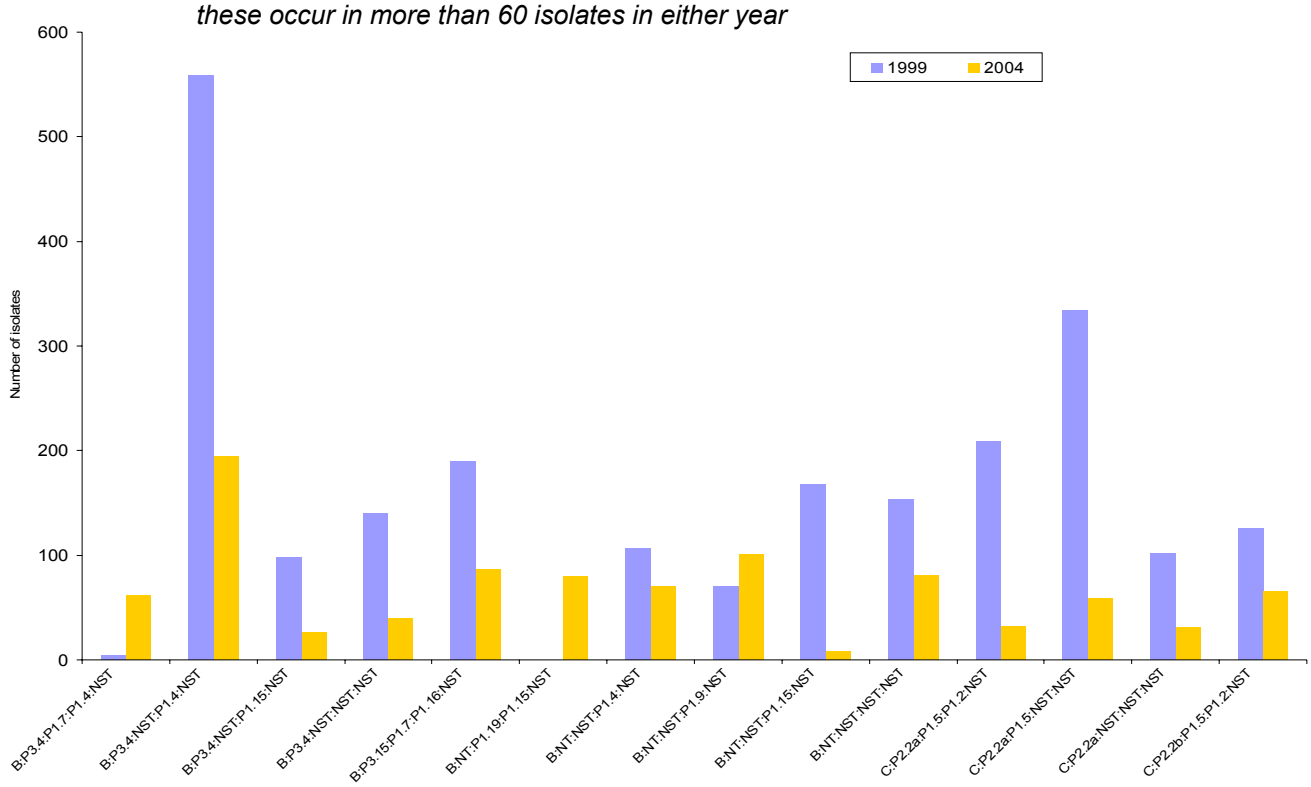
Assuming that each of the vaccines can protect against any strains containing any of the PorA gene variants against which that vaccine was produced, the percentage of cases that would theoretically would be covered in the countries which serosubtype their isolates is given in Table 5 in 2004. Not surprisingly, the RIVM hexavalent and nonavalent vaccines afford by far the greatest coverage.

Figure 16 Most common associations between serosubtype variants and serogroup/serotype, countries with consistent data, 2004*



Serosubtypes associated with seven most common serogroup:serotype combinations in 2004

Figure 17 Distribution of serogroup:serotype:serosubtype combinations in 1999 and 2004 where these occur in more than 60 isolates in either year



- Data used fro: Austria, Belgium, Czech Republic, Denmark, Finland, Greece, Ireland, Italy, Malta, Netherlands, Norway, PolandP, Slovenia, Switzerland, United Kingdom

Table 5 Theoretical percentage coverage afforded by different vaccines raised against PorA gene products in 1999 and 2004 (assuming no cross protection)

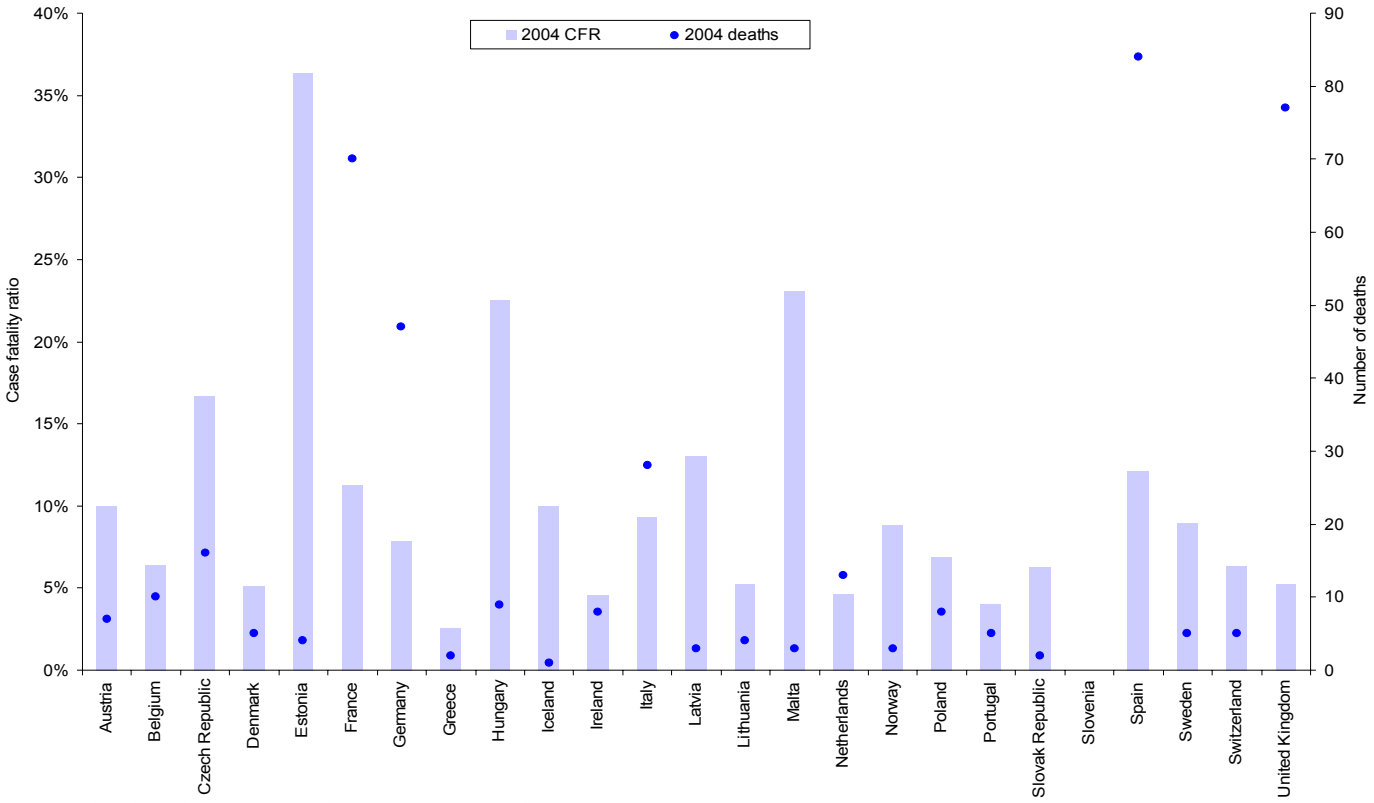
Vaccine developed by	PorA variants	Year	No of cases prevented	Total number of cases	% coverage
Finlay Institute, Cuba	P1.15	1999	457	3234	14.1%
NIPH, Norway	P1.7,16	1999	577	3234	17.8%
RIVM, Netherlands	P1.5,7,12,19 P1.2,4,10,13,15, 16	1999	2299	3234	71%
RIVM, Netherlands nonavalent	P1.5,7,12,18,19,22 P1.1,2,3,4,10,13,14,15, 16 P1.6	1999	2601	3234	80.4%
Finlay Institute, Cuba	P1.15	2004	204	2065	9.8%
NIPH, Norway	P1.7,16	2004	506	2065	24.5%
RIVM, Netherlands hexavalent	P1.5,7,12,19 P1.2,4,10,13,15, 16	2004	1391	2065	67.4%
RIVM, Netherlands nonavalent	P1.5,7,12,18,19,22 P1.1,2,3,4,10,13,14,15, 16 P1.6	2004	1695	2065	82.1%

- Data used from: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom

Case fatality

The overall case fatality ratio (CFR) in Europe was 7.05% in 2003 and 8.01% in 2004. The case fatality ratio (CFR) for laboratory confirmed meningococcal disease in different European countries in 1999, 2003 and 2004 is shown in Figure 18, and for all years 1999–2004 in the Table A25.

Figure 18 Case fatality ratio due to laboratory-diagnosed confirmed and probable meningococcal disease, and total number of deaths, in 2004, in all countries for which outcome data is available



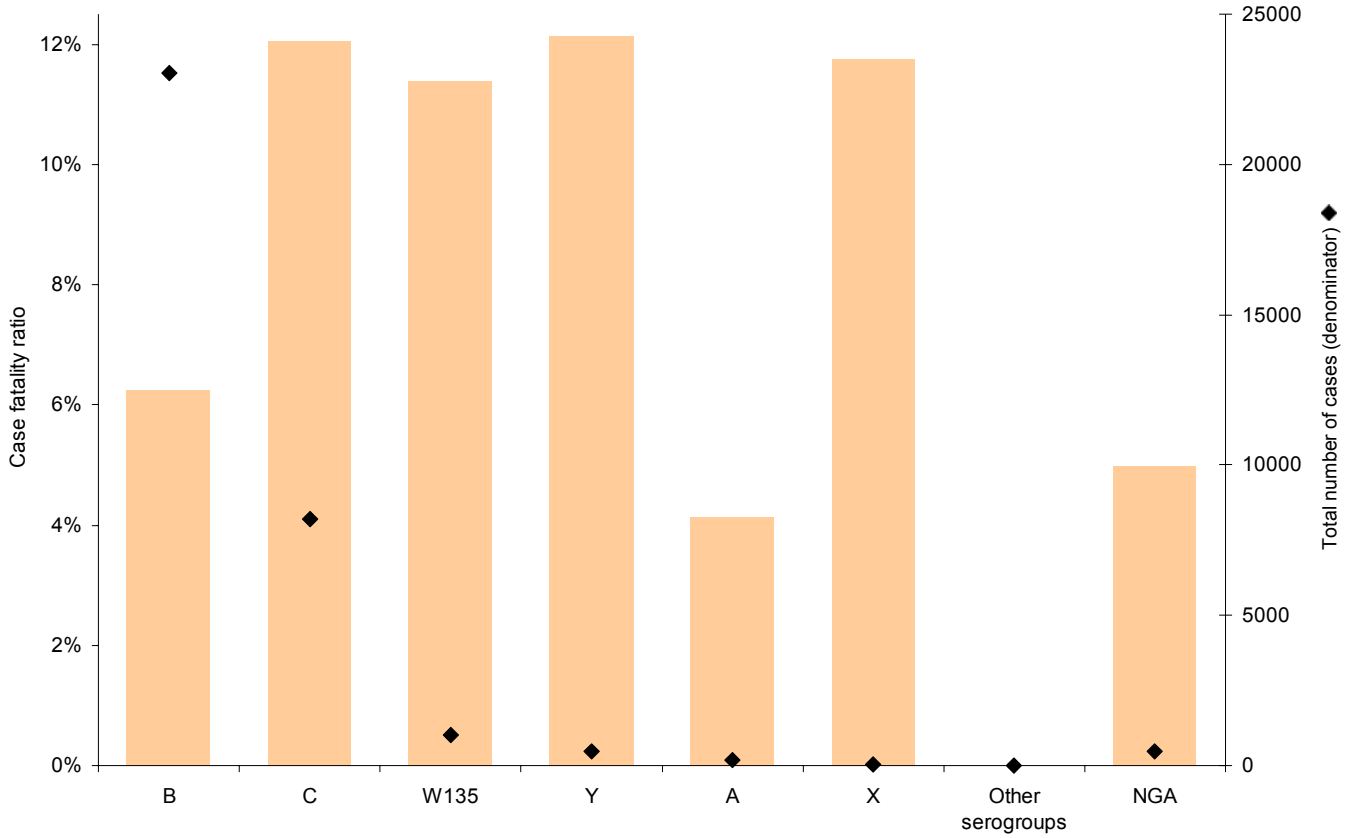
Case fatality ratio calculated using all laboratory-confirmed cases as denominator

The ratios are remarkably consistent across Europe, with half of the countries' CFRs in the range 5.19% to 11.2% (the interquartile range was 6.01). The highest CFRs were found in Estonia (36%) and Malta (23%), the lowest in Slovenia (no deaths) and Greece (3%). However, there were in Estonia and Malta respectively four and three deaths in 2004, and no deaths in either country in the previous year, indicating that due to the small overall number of meningococcal cases occurring in these countries, a small variation in the number of deaths will lead to large variation in the calculated CFR. The overall annual case fatality rate across Europe has remained stable with time, varying only between 6.5% and 9% in the period 1999-2004.

One continual problem in comparing CFRs across Europe is that different countries have a different proportion of cases where they know the outcome (survival or death) of a meningococcal case. However, since it is more likely that an epidemiology centre/reference laboratory would be informed of a patient's death than of their survival, this analysis was conducted assuming that those cases whose outcome is unknown have survived. This means that CFR could be under-estimated in some countries assuming that all cases of unknown outcome survive but, as the likelihood of survival is much higher than that of death, this is the smaller risk.

The effect of serogroup on case fatality is shown in Figure 19 and in Table A26.

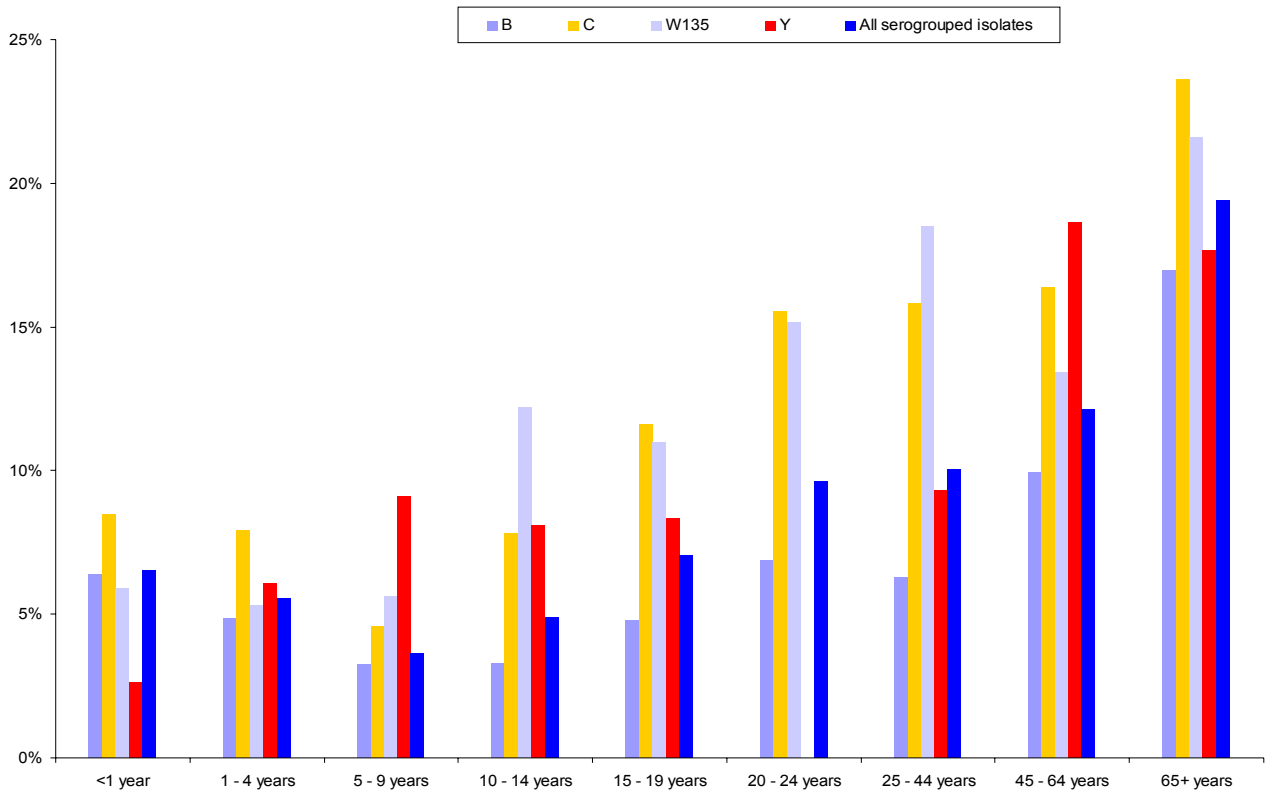
Figure 19 Serogroup specific confirmed and probable case fatality ratios and total number of deaths due to each serogroup in all countries for which outcome data is available, 1999-2004 combined



While serogroup B contributed by far the largest number of overall deaths for the period 1999-2004, the CFR of cases due to serogroups C, W135 and Y were higher than that of serogroup B. The CFR of other serogroups *ie* serogroups A, X, Z, and 29E, tends to be high in certain years, but this is due to the very small number of overall cases.

The effect of age and serogroup on case fatality is illustrated in Figure 20.

Figure 20 Age and serogroup specific case fatality ratios in all countries for which outcome data is available, 1999-2004 combined



Overall, CFR increases with age, the 65+ year age group suffering an overall CFR of just under 20%, and the lowest overall CFR, of just under 4%, being found in the 5 – 9 year old age group. CFRs associated with serogroups B, C, W135 and Y appear to follow this general pattern.

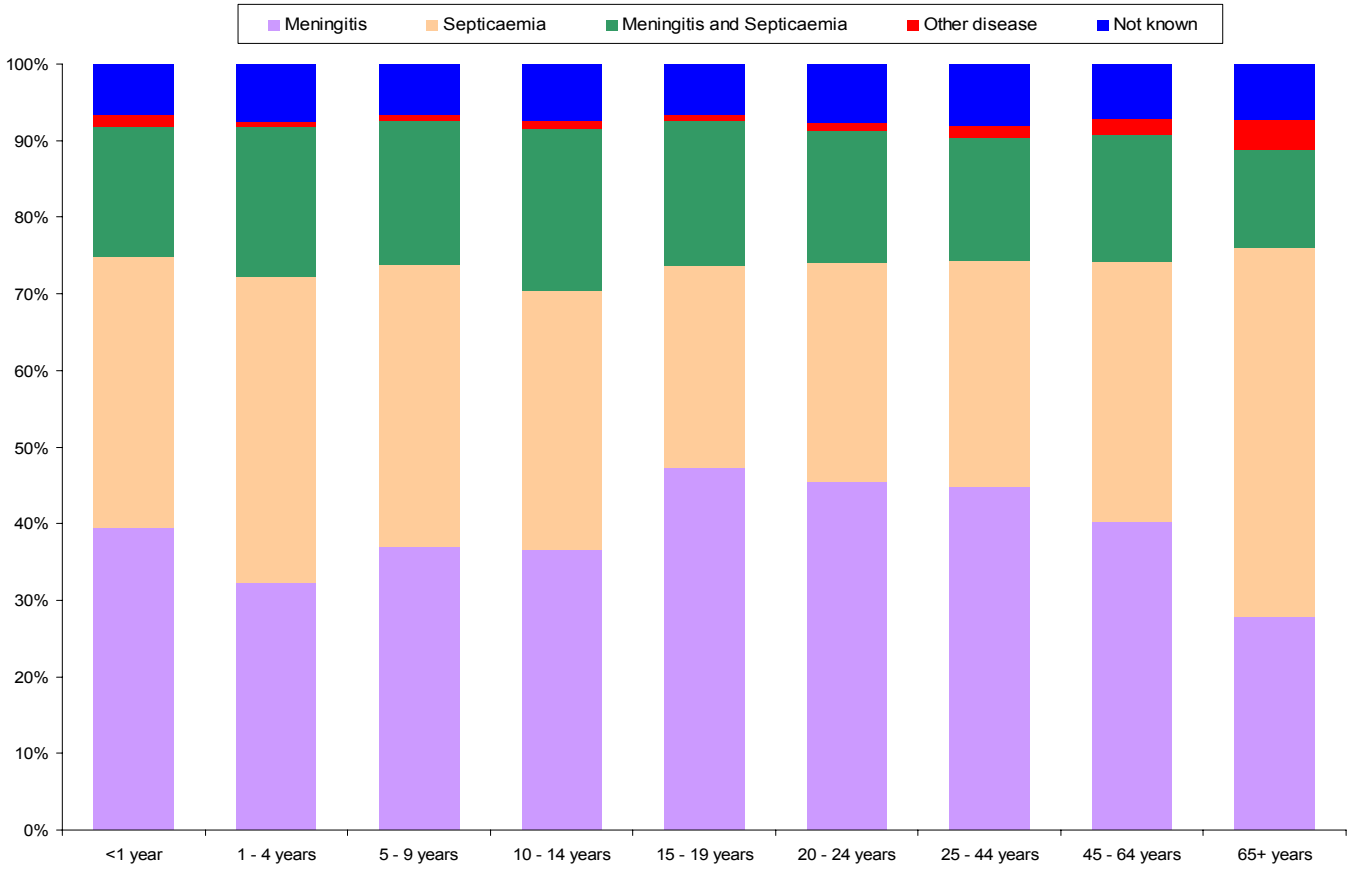
Disease presentation

The association between disease presentation and age for years 1999 to 2004 is shown in Figure 21.

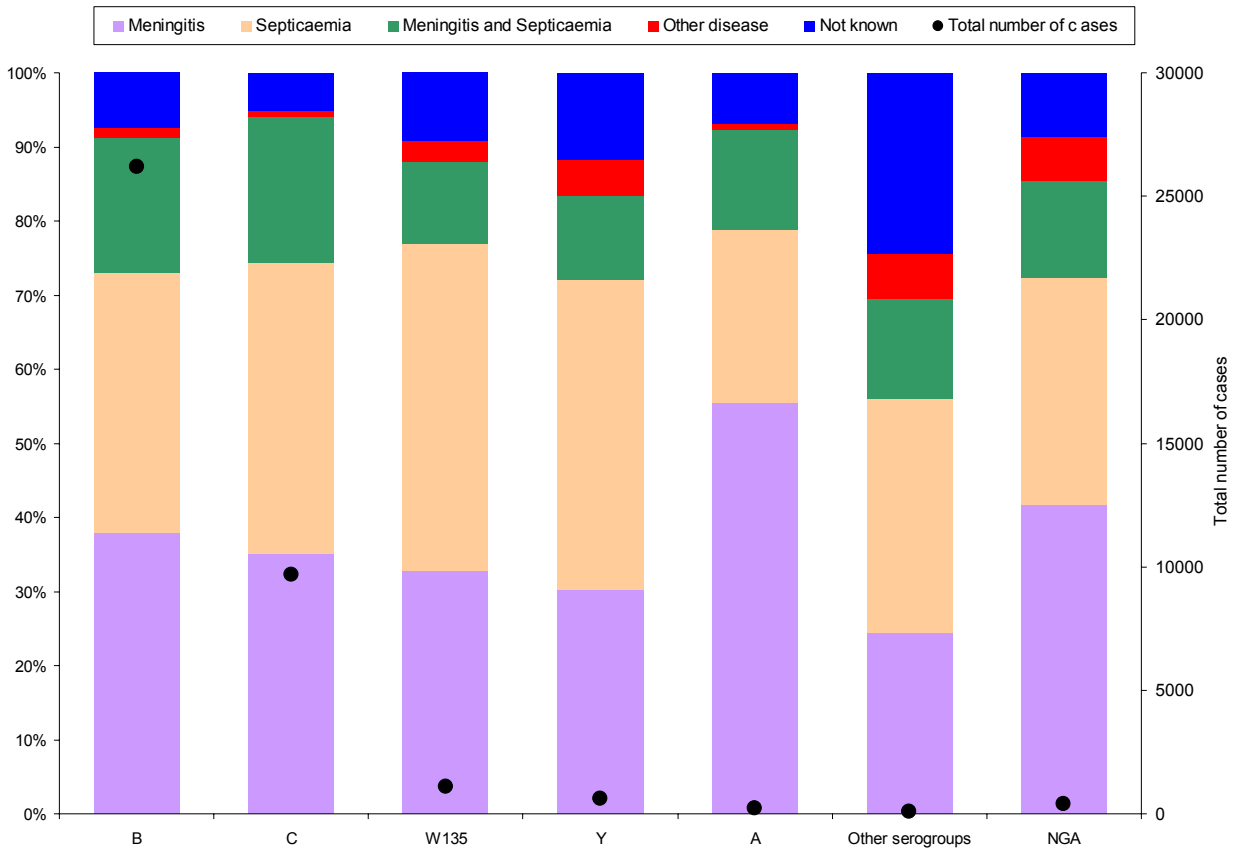
There is an age-specific distribution of disease presentation, with the proportion of cases of meningitis highest in the 15 – 44 year age group, and that of septicaemia and other diagnoses highest in the 65+ age group. In the <15's, the proportion of cases due to meningitis and septicaemia are approximately equal, and the proportion of cases presenting with both meningitis and septicaemia varies within 5–10% for all age groups.

The relationship between serogroup and disease presentation is shown in Figure 22.

Figure 21 Association between disease presentation and age group, all countries and years combined



`Figure 22 Association between disease presentation and serogroup, all countries and years combined



There seems to be little association between the two, with possibly the exception of serogroup A; over 50% of these cases present as meningitis. With respect to the other serogroups, meningitis and septicaemia present in fairly equal proportions, with a lower number of cases presenting with both symptoms.

The association between case fatality and disease presentation is shown in Figure 23.

Figure 23 Association between disease presentation and case fatality in all countries for which outcome data is available, 1999-2004

The CFR is highest in septicaemic presentations in all years, with a slightly lower CFR evident in those which present with both septicaemia and meningitis. Those who present with meningitis alone have an appreciably better chance of survival.

As apart of the EU-MenNet collaboration, the associations between phenotype and genotype and outcome have been examined, and this is still ongoing. The preliminary results suggest that a significantly higher odds of death was found if the infecting organism was C:2a or W135:2a. Using the subset of cases with MLST results (obtained through matching the EU-IBIS dataset with EMMC), it was shown that strains of the ST-11 clonal complex were significantly associated with a higher odds of death than compared to the baseline (ST-44 clonal complex). The results will be explored in more depth in the 2005 Annual Report.

C. Website

http://www.euibis.org

The website has been developed substantially, and now features:

- a number of dynamically generated graphs,
- Presentations from pertinent meetings
- MCC vaccine schedules used in different countries
- Postal, telephone and email contacts for participating countries
- A participant only area which includes a bulletin board and meeting presentations that are not suitable to be placed in the public domain.

CONCLUSIONS AND PROJECT ACHIEVEMENTS

EU-IBIS has collected data on meningococcal disease in Europe since 1999. Now, with six years of data, the benefits of such a project are very clear. The amalgamation of data from different countries provides a very large dataset, and subsequent analyses of temporal and geographical trends may be very powerful.

Since the earlier EU-IBIS reports, the main changes to the data include the addition of some of the EU accession countries (Estonia, Hungary, Latvia, Lithuania, Poland, Slovak Republic, Slovenia) to the network and the increasing use of PCR in identification of *N meningitidis* (18 out of 27 countries used PCR to some extent in 2004). The wide range in incidence of probable and confirmed meningococcal disease across Europe is still apparent. There are inevitably differences in how meningococcal disease surveillance is conducted between countries, and while this may account for some of the observed differences in disease epidemiology there are clearly real differences, *eg* in age distribution, serogroup distribution. A review of the ascertainment of meningococcal disease in Europe has recently been conducted, and the methods highlighted in this paper may help to define the level of under-reporting of meningococcal disease and suggest areas where disease surveillance can be improved (Trotter *et al* 2005).

The data clearly demonstrate the continuing impact of meningococcal C (MenC) vaccination on reduction of meningococcal disease, and important insights have been gained made through comparisons of the impact of different vaccine schedules and catch-up campaigns. Although incidence rates do fluctuate with time within country (Jones 1995), the consistent impact of MenC vaccination has been seen only in serogroup C epidemiology in a range of different countries and has been sustained over time. This has been demonstrated by the incidence of meningococcal C disease decreasing markedly throughout 1999-2004 in the countries which have introduced routine MenC vaccination (Belgium, Iceland, Ireland, Netherlands, Spain, UK), but remaining stable in those countries which have not (yet) done so.

Serogroups B and C continue to account for the majority of meningococcal isolates recorded, though there is variation in individual countries, *eg* in Sweden in 2004, 12 of 52 cases were either of serogroup W135 or Y. Serogroup distribution is also affected by age, with serogroup B predominating in the younger age groups, and W135 and Y much more in evidence in the 65 years and older age group. The risk of acquiring a serogroup C infection tends to increase gradually with age until about 20-25 years of age.

The greatest risk of acquiring a meningococcal B infection is present in those under five years of age, in which age group is present about 50% of all invasive meningococcal disease. In contrast, certainly in more recent years, only around 25% of serogroup C meningococcal infections occur in the under fives (around 10% lower than in earlier years). This is probably explained by the routine use of MenC vaccination in young children in some countries. Not surprisingly, the highest incidence of serogroup

B disease occurs in the <1's, with both serogroups showing a second, smaller peak in incidence in the 15 – 19 age group. For serogroup C the same pattern is observed although the adolescent peak is relatively more important. There appears to have been a small decrease in serogroup B incidence over time in all age groups below 25. The larger decrease in serogroup C incidence over the same time period is much more evident in the under fives than in the older age groups.

There is much less variability in serotype for serogroup C than for serogroup B, and the predominant serotypes found with each serogroup are different. Serotypes P3.1, P3.4 and P3.15 tend to cluster with serogroup B isolates, whereas serotypes P2.2a and P2.2b are found in around 80% of serogroup C isolates. However, the proportion of serotype P2.2a has declined consistently since 2002, but without any change in the proportion of P2.2a associated with serogroup B strains. This may reflect the use of MenC vaccine in countries where P2.2a was the most common serogroup C serotype, this particular strain appearing to be associated with high incidence and high case-fatality ratios.

Serosubtypes also show great variability in their association with different serogroup/serotype combinations, although the individual associations do tend to remain stable over time, at least between 1999 and 2004. Serosubtyping is becoming more important, particularly in relation to serogroup B strains, with the development and introduction of meningococcal B outer membrane vesicle/protein (OMV/OMP) vaccines, as the distribution of different serosubtypes within the *N meningitidis* population directly affects how much protection any such vaccine might afford. Data on the subtyping of strains is increasing due to the adoption of molecular technologies in more and more countries, and during the bi-annual EMGM meeting at Dublin in September 2005, members agreed to implement PorA antigen sequencing until 2007.

Case fatality analyses are probably more robust when comparing the effect of age, serogroup or disease presentation than when comparing rates across countries, as the ability to accurately capture outcome data on all cases of invasive meningococcal disease differs considerably between countries. Case fatality ratios appear to be highest in serogroup C, W135 and Y infections. Case fatality across all serogroups increases with age, with the lowest rates being found in <10's, and the highest in the 65+ age group. A disease presentation of septicaemia is much more likely to result in death than one of meningitis, and while there does not appear to be a noticeable association between serogroup and disease presentation, it is very evident that septicaemia is a more common presentation than meningitis in those aged 65 years and above,

Finally, the website continues to be developed, with better navigation, presentations from past meetings, dynamically-generated data charts, and a participant only area all now part of the improved website.

FUTURE DIRECTIONS

With the establishment of the European Centre for Disease Prevention and Control (ECDC, http://www.ecdc.eu.int/) in summer 2003, and its assumption of the EU's responsibility to develop epidemiological surveillance at the European level, including oversight of Dedicated Surveillance Networks (DSNs) such as EU-IBIS, the future direction of the network will be carefully evaluated and possibly new priorities will be set. The current contract with the EU finishes in September 2006, before which time an independent team working for the ECDC will evaluate the aims, objectives, and functioning of the network, and formulate appropriate recommendations. The future of the network is very much dependant on those recommendations and how the ECDC implement them.

Another factor to consider is the evolution of the European Monitoring Group on Meningococci, with whom EU-IBIS has worked closely in the past, into a Society, with an agreed constitution and may be different ways of working. EU-IBIS would be keen to work as closely as possible with the new Society, both to prevent duplication of work, and to increase the amount of integrated data on the epidemiology of invasive meningococcal disease from which evidence-based conclusions and recommendations might be drawn.

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APPENDIX I - Data Variables submitted to EU-IBIS

Data variable	Data type	Possible values
Year	Number	
Country	Text	
IDNo	Text	
Date of birth Or Age (year/month/days	DD/MM/YY 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	A, B, C, W135, X, Y, Z, Z/29E, 29E, Other (please specify), NGA (not groupable) NK = Not known/Not typed
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, W135, X, Y, Z, Z/29E, 29E, NGA (not groupable), Other (Specify), NK (not known)
Serotype	Text	P2.2a, P2.2b, P3.1, P3.4, P3.14, P3.15, P3.16, P3.21, P3.22, P3.23, NT (not typable), NK (not known)
VR1/PorA1	Text	P1.5, P1.7, P1.12, P1.17, P1.18, P1.19, P1.20, P1.21, P1.22, NST (not typable), NK (not known)
VR2/PorA2	Text	P1.1, P1.2, P1.3, P1.4, P1.9, P1.10, P1.13, P1.14, P1.15, P1.16, P1.19, P1.23, P1.24, P1.25, P1.27, NST (not typable) NK (not known)
VR3/PorA3	Text	P1.6, NST (not typable), NK (not known)
Data variable	Data type	Possible values
Vaccination status	Number	1=yes, 2=no, 3=not known

Data variable	Data type	Possible values
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	
Chloramphenicol 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	

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APPENDIX III – GLOSSARY AND DEFINITIONS

Glossary

ECDC	European Centre for Disease Prevention and Control
EMGM	European Monitoring Group for Meningococci
EQAS	External quality assurance scheme
EU	European Union
EU-IBIS	European Union Invasive Bacterial Infection Surveillance
HPA	Health Protection Agency
MCC	Meningococcal serogroup C conjugate [vaccine]
MLST	Multi-locus sequence typing
PCR	Polymerase chain reaction
ST	sequence type
OMP	outer membrane protein
OMV	outer membrane vesicles
MCC	Men C conjugate vaccine
Men C	Meningococcal disease caused by serogroup C strains

Definition of terms used in the report

CFR	Case fatality ratio: with respect to a particular pathogen, the ratio of number of resulting deaths to the total number of invasive cases
Chemoprophylaxis	Adminstration of antibiotics to close (*eg* household) contacts of a person with invasive meningococcal disease to prevent outbreaks
Confirmed case	A case with appropriate clinical presentation where presence of *N meningitidis* has been identified by culture, PCR or latex from a normally sterile site, or where presence of diplococci in a normally sterile site has been identified by microscopy.
Genotypic	Refers to characterisation made by DNA analysis techniques
Laboratory-diagnosed	Refers to a case in which the presence of *N meningitidis* has been detected, by culture diagnosis, PCR, latex agglutination, serology or microscopy
Mab	Monoclonal antibody, used in serological typing to identify meningococci phenotypic markers such as serogroup and serotype
MCC countries	Countries who have introduced MenC conjugate vaccine into their routine schedule
Non-culture	Refers to laboratory methods that do not require growth of meningococcal isolates for confirmation and / or characterisation.
Phenotype	Refers to serological characterisation by serogroup, serotype and serosubtype
Probable case	A case with appropriate clinical presentation where presence of *N meningitidis* organism, DNA or antigen has been identified in a non-sterile site, or high levels of meningococcal antibody have been found in convalescent serum, or a case presenting with a clinical picture compatible with meningococcal disease

APPENDIX IV – Data Tables

Table A1 National institutions supplying data

Country	Epidemiology/Surveillance Centre	Laboratory Reference/Microbiology Centre
Austria	General Directorate Public Health, Vienna	Austrian Agency for Food and Health Safety, Graz
Belgium	Epidemiology Section, Scientific Institute of Public Health, Brussels	National Meningococcal Reference Laboratory , Scientific Institute of Public Health, Brussels
Czech Republic	National Institute of Public Health, Prague	National Institute of Public Health, Prague
Denmark	Department of Epidemiology, Statens Serum Institut, Copenhagen	Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut, Copenhagen
Estonia	Health Protectorate Inspectorate, Tallinn	Health Protectorate Inspectorate, Tallinn
Finland	Epidemiology, National Public Health Institute, Helsinki	Vaccine Immunology Laboratory, National Public Health Institute, Helsinki
France	Institut de Veille Sanitaire, Saint Maurice	Institut Pasteur, Paris
Germany*	Robert Koch Institute, Berlin	Institute for Hygiene and Microbiology, Würzburg
Greece	Public Health Department, National School of Public Health, Athens	National Meningococcal Reference Laboratory, National School of Public Health, Athens
Hungary	Johan Bela National Centre for Epidemiology, Budapest	Johan Bela National Centre for Epidemiology, Budapest
Iceland	Centre for Infectious Disease Control, Seltjarnarnes	Landspitali University Hospital, Reykjavik
Ireland	Health Protection Surveillance Centre, Dublin	Children's University Hospital, Dublin
Italy	Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Rome	Department of Infectious, Parasitic and Immune-mediated Disease, Istituto Superiore di Sanità, Rome
Latvia	State Agency "Public Health Agency"	
Lithuania	Centre for Communicable Disease Prevention and Control, Vilnius	National Public Health Laboratory Center, Vilnius
Luxembourg	Inspection Sanitaire	Laboratoire National de Santé
Malta	Department of Public Health, Msida	
Netherlands	National Institute of Public Health and the Environment (RIVM), Bilthoven	Academic Medical Centre, Amsterdam
Norway	Norwegian Institute of Public Health, Oslo	Norwegian Institute of Public Health, Oslo
Poland	National Institute of Hygiene, Warsaw	National Institute of Public Health, Warsaw
Portugal	Direcção-Geral da Saúde, Lisbon	Instituto Nacional de Saúde Dr Ricardo Jorge, Lisbon
Slovak Republic	Section of Epidemiology, Public Health Authority, Bratislava	National Reference Centre for Meningococci, Public Health Authority, Bratislava
Slovenia	Communicable Diseases Centre, Institute of Public Health Slovenia, Ljubljana	Laboratory for Immunology and Molecular Diagnostics, National Reference Centre for Meningococci, Institute of Public Health Slovenia, Ljubljana
Spain	Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid	Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Madrid
Sweden	Swedish Institute for Infectious Disease Control (SMI), Solna	Department of Clinical Microbiology and Immunology, Orebro
Switzerland	Swiss Federal Office of Public Health, Berne	Laboratoire Central de Bactériologie, Geneva
United Kingdom	Health Protection Agency, London / Stobhill Hospital, Glasgow	Manchester Medical Microbiology Partnership, Manchester / Stobhill Hospital, Glasgow

Countries with consistent data 1999 – 2004

*Data from Institute of Hygiene and Microbiology consistent across 1999 to 2004, used in serogroup and typing analyses; Robert Koch Institute data available only from 2001, used in all other analyses

Table A2 Total population data, by country, 1999 - 2004

Country	1999	2000	2001	2002	2003	2004	Source
Austria	8,094,156	8,113,413	8,131,690	8,148,312	8,162,656	8,174,762	www.census.gov/cgi-bin/ipc/idbagg (for Austria)
Belgium	10,226,419	10,251,250	10,286,570	10,332,785	10,376,133	10,421,137	www.iph.fgov.be/epidemio/spma/index.htm
Czech Republic	10,278,098	10,266,546	10,206,436	10,203,269	10,211,455	10,211,455	www.czso.cz/eng/edicniplan.nsf/t/79005D6975/$File/40270301.pdf
Denmark	5,319,111	5,337,344	5,355,082	5,374,255	5,387,174	5,401,177	www.statbank.dk/statbank5a/default.asp?w=1024
Estonia	1,379,237	1,372,071	1,366,959	1,361,242	1,356,045	1,351,069	http://pub.stat.ee/px-web.2001/I_Databas/Population/Population.asp
Finland	5,158,097	5,168,595	5,180,309	5,193,039	5,204,405	5,214,512	www.census.gov/cgi-bin/ipc/idbagg (for Finland)
France	60,158,533	60,434,492	60,754,024	61,078,533	61,391,033	61,684,291	www.insee.fr
Germany	82,074,778	82,187,909	82,280,551	82,350,671	82,398,326	82,424,609	www.census.gov/cgi-bin/ipc/idbagg (for Germany)
Greece	10,882,607	10,917,457	10,949,953	10,987,559	11,023,532	11,040,650*	www.statistics.gr/eng_tables/S201_SPO_5_TS_91_03_2_Y_EN.pdf
Hungary					10,142,362	10,116,742#	portal.ksh.hu/portal/page?_pageid=38,119917&_dad=portal&_schema=PORTAL
Iceland	277,184	281,154	285,054	287,559	289,272	292,587	www.statice.is/?pageid=1178&src=/temp_en/mannfjoldi/midarsmannfjoldi.asp
Ireland	3,741,400	3,789,500	3,847,100	3,917,200	3,978,800	4,043,700	http://www.cso.ie/px/pxeirestat/database/eirestat/Population.asp
Italy	56,909,109	56,923,524	56,960,692	56,993,742	57,321,070	57,888,245	demo.istat.it/index_e.html
Latvia					2,331,480	2,319,203	data.csb.lv/EN/Database/annualstatistics/04.%20Population/04.%20Population.asp
Lithuania			3,486,998	3,475,586	3,462,553	3,445,857	epp.eurostat.cec.eu.int/extraction/evalight/EVAlight.jsp?A=1&language=en&root=/theme3/demo/dpop/ppavg (for Lithuania)
Luxembourg	433,600	439,000	439,000	444,050	448,300	451,600	http://www.statistiques.public.lu/stat/TableViewer/tableView.aspx?ReportId=1059
Malta	391,415~	391,415	394,641	397,242	399,867	399,867~	http://www.nso.gov.mt/statbase/data_table_options.aspx?id=19
Netherlands	15,760,225	15,863,950	15,987,075	16,105,285	16,192,572	16,258,032	statline.cbs.nl/StatWeb/start.asp?LA=en&DM=SLEN&lp=Search/Search
Norway	4,445,329	4,478,497	4,503,436	4,524,066	4,552,252	4,577,457	statbank.ssb.no/statistikkbanken/default_fr.asp?PLanguage=1
Poland	38,653,625	38,646,201	38,641,046	38,232,301	38,195,177	38,180,249	www.stat.gov.pl and National Institute of Hygiene, Poland
Portugal	10,195,014	10,262,877	10,335,559	10,407,465	10,474,685	10,529,255	www.ine.pt/prodserv/quadros/periodo.asp and Direcção-Geral da Saúde (Portugal)
Slovak Republic					5,379,161	5,380,053	www.census.gov/cgi-bin/ipc/idbagg (for Slovak Republic)
Slovenia	1,985,557	1,990,272	1,992,035	1,995,718	1,996,773	1,997,004	www.stat.si/eng/tema_demografsko_prebivalstvo.asp
Spain	39,802,827	40,049,708	40,476,723	40,964,244	41,663,702	42,345,342	www.ine.es/inebase/cgi/um?M=%2Ft20%2Fp251%2Fproy_2001%2F&O=pcaxis&N=&L=1 www.ine.es/inebase/cgi/um?M=%2Ft20%2Fp263%2Fpob_01%2F&O=pcaxis&N=&L=1
Sweden				8,940,788	8,946,957	9,011,392	www.ssd.scb.se/databaser/makro/MainTable.asp?yp=tansss&xu=C9233001&omradekod=BE&omradetext=Population&lang=2&langdb=2
Switzerland	7,164,444	7,204,055	7,261,210	7,313,853	7,364,148	7,415,102	www.bfs.admin.ch/bfs/portal/fr/index/infothek/lexikon/bienvenue___login/blank/zugang_lexikon.topic.1.html
United Kingdom	58,481,070	58,643,230	58,836,674	59,206,731	59,553,759	59,834,946	Office for National Statistics, www/statistics.gov.uk/
Year total	431,811,835	433,012,460	437,958,817	448,235,495	468,203,649	470,410,295	

* 1 Jan estimate; others for Greece are mid-year, (http://www.statistics.gr/eng_tables/S201_SPO_5_TS_91_04_4_Y_EN.pdf)

\# from National Centre for Epidemiology, Budapest, Hungary ~ 2000 figures used for 1999, and 2003 figures used for 2004

Table A3 Percentage age distribution of population, by country, 1999 – 2004 combined

Country	<1	1 - 4	5 – 9	10 - 14	15 - 19	20 – 24	25 - 44	45 – 64	65+
Austria	1.00	3.94	5.67	5.83	5.91	5.93	31.60	24.47	15.65
Belgium	1.10	4.48	5.86	6.04	5.92	6.19	29.20	24.28	16.94
Czech Republic	0.90	3.52	5.13	6.24	6.60	7.83	28.92	26.98	13.88
Denmark	1.22	5.03	6.46	5.94	5.33	5.91	29.21	26.03	14.87
Estonia	0.93	3.62	5.42	7.47	7.68	7.08	27.69	24.69	15.42
Finland	1.20	4.83	6.14	6.23	6.29	6.31	27.01	27.24	14.75
France	1.29	5.00	6.16	6.51	6.64	6.43	28.48	23.51	15.97
Germany	0.93	3.73	4.98	5.61	5.65	5.62	30.40	25.96	17.13
Greece	0.93	3.73	4.96	5.34	6.30	7.45	30.12	24.02	17.14
Hungary*	0.93	3.78	5.24	6.04	6.34	7.22	28.13	26.88	15.43
Iceland	1.47	5.95	7.79	7.79	7.37	7.64	29.40	20.95	11.64
Ireland	1.45	5.63	6.90	7.42	8.19	8.30	29.80	21.13	11.18
Italy	0.93	3.69	4.72	4.91	5.23	6.14	30.67	25.15	18.55
Latvia*	0.88	3.33	4.44	7.02	8.04	7.21	28.27	24.78	16.02
Lithuania~	0.90	4.02	6.07	7.66	7.90	6.95	29.31	22.61	14.57
Luxembourg~	1.20	5.00	6.42	6.16	5.71	5.78	31.74	23.87	14.12
Malta	1.03	4.45	6.37	7.13	7.27	7.58	27.51	25.96	12.69
Netherlands	1.26	4.99	6.19	6.13	5.88	6.03	31.02	24.85	13.65
Norway	1.28	5.32	6.82	6.55	5.97	6.13	29.37	23.52	15.04
Poland	0.95	4.07	6.06	7.30	8.48	8.34	28.27	24.02	12.52
Portugal	1.10	4.24	5.13	5.43	6.27	7.41	29.93	23.92	16.58
Slovak Republic*	0.95	3.97	5.74	7.17	8.02	8.58	29.89	24.18	11.49
Slovenia	0.88	3.66	4.97	5.87	6.72	7.50	30.35	25.60	14.45
Spain	0.98	3.74	4.75	5.24	6.22	7.76	32.02	22.46	16.81
Sweden#	1.10	4.18	5.50	6.93	6.17	5.80	27.08	26.02	17.21
Switzerland	1.02	4.23	5.69	5.94	5.80	5.86	30.64	25.26	15.56
United Kingdom	1.15	4.71	6.30	6.55	6.32	6.09	29.05	23.90	15.92
Overall	1.05	4.21	5.53	6.00	6.27	6.55	29.79	24.50	16.10

* 2003 and 2004 figures used # 2002 – 2004 figures used ~ 2001 – 2004 figures used

Table A4 Confirmed, probable and confirmed, and laboratory-diagnosed, incidences (all per 100,000), by country 1999, 2003, 2004

Country	1999			2003			2004		
	Confirmed	Probable and confirmed	Laboratory-diagnosed	Confirmed	Probable and confirmed	Laboratory-diagnosed	Confirmed	Probable and confirmed	Laboratory-diagnosed
Austria	1.14	1.20	1.20	0.82	1.00	0.89	0.84	1.08	0.86
Belgium	2.90	2.90	2.90	2.18	2.20	2.20	1.49	1.51	1.51
Czech Republic	0.90	1.00	0.90	0.87	0.98	0.90	0.92	1.03	0.94
Denmark	3.33	3.50	3.33	1.91	1.95	1.91	1.81	1.85	1.81
Estonia	0.22	0.44	0.22	0.59	0.74	0.59	0.74	0.81	0.81
Finland	1.11	1.11	1.11	0.81	0.81	0.81	0.86	0.86	0.86
France	0.74	0.74	0.74	1.06	1.31	1.06	1.01	1.13	1.01
Germany*	0.49	0.49	0.49	0.93	0.94	0.93	0.72	0.73	0.72
Greece	1.77	1.94	1.19	1.08	1.19	1.08	0.65	0.65	0.65
Hungary	-	-	-	0.40	0.42	0.40	0.43	0.43	0.43
Iceland	7.58	7.58	7.58	2.07	2.77	2.77	2.73	3.42	3.42
Ireland	11.89	14.33	11.89	5.53	5.96	5.55	4.30	4.92	4.35
Italy	0.45	0.48	0.45	0.47	0.48	0.47	0.52	0.55	0.54
Latvia	-	-	-	0.64	1.03	0.69	0.78	1.03	0.99
Lithuania	-	-	-	0.87	1.27	0.87	1.54	2.67	1.54
Luxembourg	1.53	5.68	4.15	0.25	0.70	0.22	0.25	0.25	0.00
Malta	4.34	5.88	4.34	4.00	4.25	4.00	3.00	3.25	3.25
Netherlands	3.65	3.65	3.65	2.19	2.19	2.19	1.71	1.75	1.71
Norway	1.73	1.80	1.73	1.08	1.12	1.12	0.70	0.74	0.74
Poland	0.17	0.17	0.17	0.15	0.15	0.15	0.30	0.31	0.30
Portugal	-	-	-	1.34	1.93	1.34	1.18	1.73	1.18
Slovak Republic	-	-	-	0.91	0.91	0.91	0.59	0.59	0.59
Slovenia	0.30	0.30	0.30	0.80	0.80	0.80	0.45	0.45	0.45
Spain	2.38	3.52	2.38	1.08	1.19	1.18	1.64	2.11	1.64
Sweden	-	-	-	0.61	0.63	0.61	0.62	0.65	0.62
Switzerland	2.09	2.36	2.09	1.02	1.19	1.02	1.07	1.16	1.07
United Kingdom	4.72	5.39	5.24	2.85	3.10	3.03	2.31	2.55	2.46

* Data for 1999 from **Institute for Hygiene and Microbiology** Reference Laboratory; other years from Robert Koch Institute

Table A5 Number of cases of confirmed and probable laboratory-diagnosed (% culture-diagnosed) invasive meningococcal disease, by country, 1999 – 2004

Country	1999	2000	2001	2002	2003	2004
Austria	97 (82%)	83 (70%)	106 (86%)	81 (74%)	73 (78%)	70 (77%)
Belgium	297 (100%)	267 (100%)	380 (100%)	262 (100%)	228 (100%)	157 (100%)
Czech Republic	93 (96%)	61 (93%)	93 (97%)	113 (74%)	92 (71%)	96 (97%)
Denmark	177 (85%)	151 (80%)	161 (83%)	98 (89%)	103 (82%)	98 (81%)
Estonia	3 (67%)	9 (100%)	20 (95%)	8 (100%)	8 (88%)	11 (91%)
Finland	57 (100%)	48 (100%)	49 (98%)	49 (98%)	42 (100%)	45 (91%)
France	448 (100%)	489 (95%)	559 (94%)	648 (94%)	650 (99%)	625 (85%)
Germany*	402 (100%)	452 (100%)	770 (69%)	730 (74%)	768 (73%)	596 (74%)
Greece	130 (55%)	174 (36%)	185 (31%)	196 (26%)	119 (33%)	72 (54%)
Hungary					41 (83%)	43 (93%)
Iceland	21 (100%)	18 (89%)	19 (89%)	15 (87%)	8 (100%)	10 (100%)
Ireland	445 (42%)	411 (41%)	297 (34%)	225 (36%)	221 (34%)	176 (40%)
Italy	254 (63%)	243 (67%)	201 (67%)	214 (72%)	271 (77%)	314 (67%)
Latvia					16 (100%)	23 (100%)
Lithuania			35 (49%)	29 (66%)	30 (57%)	53 (60%)
Luxembourg	18	1	1	1	1	0
Malta	17 (71%)	20 (80%)	13 (92%)	14 (71%)	16 (94%)	13 (92%)
Netherlands	576 (98%)	542 (100%)	721 (100%)	616 (100%)	354 (100%)	278 (95%)
Norway	77 (95%)	85 (87%)	77 (87%)	51 (92%)	51 (84%)	34 (85%)
Poland	67 (100%)	43 (100%)	37 (100%)	35 (100%)	57 (93%)	116 (98%)
Portugal		59 (100%)	106 (100%)	185 (79%)	140 (66%)	124 (91%)
Slovak Republic					49 (86%)	32 (78%)
Slovenia	6 (100%)	8 (100%)	10 (100%)	8 (100%)	16 (100%)	9 (100%)
Spain#	947 (0%)	971 (0%)	643 (0%)	834 (0%)	493 (95%)	696 (100%)
Sweden				46 (93%)	55 (80%)	56 (89%)
Switzerland	150 (99%)	149 (97%)	147 (98%)	91 (92%)	75 (97%)	79 (82%)
United Kingdom	3064 (61%)	2993 (56%)	2570 (52%)	1948 (54%)	1807 (54%)	1474 (53%)
Total	7346 (64%)	7277 (61%)	7200 (64%)	6497 (62%)	5784 (74%)	5300 (75%)

* Data for 1999 and 2000 from **Institute for Hygiene and Microbiology** Reference Laboratory; other years from Robert Koch Institute

\# Data for 2003 from Centro Nacional de Microbiologia; all other years from Centro Nacional de Epidemiología

Table A6 Incidence (per 100,000) of confirmed and probable culture-diagnosed cases of invasive meningococcal disease, by country, 1999 - 2004

Country	1999	2000	2001	2002	2003	2004
Austria	0.99	0.71	1.12	0.74	0.70	0.66
Belgium	2.90	2.60	3.69	2.54	2.20	1.51
Czech Republic	0.87	0.56	0.88	0.82	0.64	0.91
Denmark	2.84	2.27	2.50	1.62	1.56	1.46
Estonia	0.15	0.66	1.39	0.59	0.52	0.74
Finland	1.11	0.93	0.93	0.92	0.81	0.79
France	0.74	0.77	0.86	1.00	1.05	0.87
Germany*	0.49	0.55	0.64	0.65	0.68	0.54
Greece	0.65	0.57	0.53	0.46	0.35	0.35
Hungary					0.34	0.40
Iceland	7.58	5.69	5.96	4.52	2.77	3.42
Ireland	5.05	4.46	2.60	2.09	1.88	1.76
Italy	0.28	0.29	0.24	0.27	0.36	0.36
Latvia					0.69	0.99
Lithuania			0.49	0.58	0.49	0.93
Malta	3.07	4.09	3.04	2.52	3.75	3.00
Netherlands	3.60	3.40	4.50	3.82	2.19	1.62
Norway	1.64	1.65	1.49	1.04	0.94	0.63
Poland	0.17	0.11	0.10	0.09	0.14	0.30
Portugal		0.57	1.03	1.41	0.89	1.07
Slovak Republic					0.78	0.46
Slovenia	0.30	0.40	0.50	0.40	0.80	0.45
Spain#	1.51	1.73	0.97	1.37	1.57	1.64
Sweden				0.48	0.49	0.55
Switzerland	2.08	2.00	1.98	1.15	0.99	0.88
United Kingdom	3.17	2.86	2.29	1.77	1.64	1.31
Total~	1.43	1.31	1.30	1.09	0.98	0.85

* Data for 1999 and 2000 from Institute for Hygiene and Microbiology Reference Laboratory; other years from Robert Koch Institute

Data for 2004 from Centro Nacional de Epidemiología; all other years from Centro Nacional de Microbiologia

~ Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

Table A7 Incidence (per 100,000) of laboratory-diagnosed confirmed and probable cases of invasive meningococcal disease, by country, 1999 - 2004

Country	% PCR* (years done)	1999	2000	2001	2002	2003	2004
Austria	23.53% (1999-2004)	1.20	1.02	1.30	0.99	0.89	0.86
Belgium	1.00% (2000-2004)	2.90	2.60	3.69	2.54	2.20	1.51
Czech Republic	23.72% (1999-2004)	0.90	0.59	0.91	1.11	0.90	0.94
Denmark		3.33	2.83	3.01	1.82	1.91	1.81
Estonia		0.22	0.66	1.46	0.59	0.59	0.81
Finland	0.69% (2004)	1.11	0.93	0.95	0.94	0.81	0.86
France	3.60% (2002-2004)	0.74	0.81	0.92	1.06	1.06	1.01
Germany~	7.40% (2001-2004)	0.49	0.55	0.94	0.89	0.93	0.72
Greece	70.43% (1999-2004)	1.19	1.59	1.69	1.78	1.08	0.65
Hungary	13.10% (2003-2004)					0.40	0.43
Iceland	8.79% (2001-2004)	7.58	6.40	6.67	5.22	2.77	3.42
Ireland	63.77% (1999-2004)	11.89	10.85	7.72	5.74	5.55	4.35
Italy		0.45	0.43	0.35	0.38	0.47	0.54
Latvia	2.56% (2004)					0.69	0.99
Lithuania				1.00	0.83	0.87	1.54
Luxembourg		4.15	0.23	0.23	0.23	0.22	0.00
Malta	2.15% (2001-2002)	4.34	5.11	3.29	3.52	4.00	3.25
Netherlands	0.75% (2003-2004)	3.65	3.42	4.51	3.82	2.19	1.71
Norway	9.60% (1999-2004)	1.73	1.90	1.71	1.13	1.12	0.74
Poland	4.79% (2002-2004)	0.17	0.11	0.10	0.09	0.15	0.30
Portugal	8.63% (2002-2004)		0.57	1.03	1.78	1.34	1.18
Slovak Republic						0.91	0.59
Slovenia		0.30	0.40	0.50	0.40	0.80	0.45
Spain#		2.38	2.42	1.59	2.04	1.18	1.64
Sweden	15.29% (2002-2004)				0.51	0.61	0.62
Switzerland	3.62% (1999-2004)	2.09	2.07	2.02	1.24	1.02	1.07
United Kingdom	64.56% (1999-2004)	5.24	5.10	4.37	3.29	3.03	2.46
Total**		2.00	1.93	1.87	1.55	1.38	1.21

* of all cases used to calculate laboratory-diagnosed incidence

** Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

~ Data for 1999 and 2000 from Institute for Hygiene and Microbiology Reference Laboratory; other years from Robert Koch Institute

Data for 2004 from Centro Nacional de Epidemiología; all other years from Centro Nacional de Microbiologia

Table A8 Age distribution (number and % distribution) of cases of confirmed and probable laboratory-diagnosed meningococcal disease, all countries, 1999 - 2004

Age Group	1999	2000	2001	2002	2003	2004
Number of cases						
<1 year	978	981	960	810	761	706
1 - 4 years	1580	1542	1400	1243	1132	926
5 - 9 years	637	586	553	453	357	299
10 - 14 years	498	399	444	312	314	209
15 - 19 years	878	725	784	602	534	510
20 - 24 years	289	341	293	244	229	182
25 - 44 years	430	511	518	409	350	312
45 - 64 years	355	427	399	322	296	298
65+ years	260	268	272	267	202	225
Not known	74	14	22	10	16	10
% distribution						
<1 year	16.36%	16.93%	17.01%	17.34%	18.16%	19.20%
1 - 4 years	26.43%	26.61%	24.80%	26.61%	27.01%	25.18%
5 - 9 years	10.65%	10.11%	9.80%	9.70%	8.52%	8.13%
10 - 14 years	8.33%	6.89%	7.87%	6.68%	7.49%	5.68%
15 - 19 years	14.68%	12.51%	13.89%	12.89%	12.74%	13.87%
20 - 24 years	4.83%	5.89%	5.19%	5.22%	5.46%	4.95%
25 - 44 years	7.19%	8.82%	9.18%	8.75%	8.35%	8.49%
45 - 64 years	5.94%	7.37%	7.07%	6.89%	7.06%	8.10%
65+ years	4.35%	4.63%	4.82%	5.71%	4.82%	6.12%
Not known	1.24%	0.24%	0.39%	0.21%	0.38%	0.27%

Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

Table A9 Age-specific incidence (per 100,000) of confirmed and probable laboratory-diagnosed meningococcal disease, by country, 2003

Country	<1 year	1 - 4 years	5 – 9 years	10 - 14 years	15 - 19 years	20 - 24 years	25 - 44 years	45 - 64 years	65+ years
Austria	7.77	5.83	1.11	2.92	2.52	0.81	0.31	0.24	0.08
Belgium	26.83	14.34	4.22	3.93	5.43	1.24	0.64	0.55	0.45
Czech Republic	17.08	3.59	0.64	1.28	4.37	0.41	0.50	0.14	0.07
Denmark	15.76	11.24	3.44	4.48	5.86	1.33	0.19	0.49	0.62
Estonia	0.00	2.03	1.54	0.00	1.87	1.02	0.27	0.30	0.46
Finland	3.41	1.42	0.64	0.30	2.49	1.52	0.43	0.48	0.77
France	10.86	4.43	1.48	1.21	2.87	1.49	0.31	0.29	0.50
Germany	14.14	5.97	1.59	1.43	3.80	1.10	0.21	0.22	0.18
Greece	16.74	7.38	6.05	2.64	1.55	0.50	0.15	0.15	0.10
Hungary	15.79	2.09	0.37	0.32	0.62	0.53	0.14	0.04	0.06
Iceland	0.00	23.72	4.59	0.00	0.00	0.00	1.19	0.00	5.89
Ireland	100.66	32.13	5.97	4.63	8.47	2.08	1.00	1.29	0.68
Italy	5.44	2.60	0.79	0.67	1.11	0.82	0.25	0.20	0.11
Latvia	9.98	7.84	0.00	1.77	0.00	0.00	0.45	0.17	0.27
Lithuania	43.61	7.29	0.00	0.38	0.36	0.41	0.30	0.13	0.00
Malta	49.66	12.09	8.23	10.71	7.04	6.62	1.82	0.94	0.00
Netherlands	31.62	11.83	3.76	2.79	2.92	1.64	0.65	0.68	1.08
Norway	10.79	3.80	1.94	1.62	4.04	1.46	0.15	0.46	0.45
Poland	3.43	1.14	0.09	0.30	0.19	0.03	0.03	0.03	0.04
Portugal	31.09	11.92	3.79	0.53	0.97	0.27	0.22	0.20	0.23
Slovak Republic	21.77	6.92	0.63	0.26	2.30	0.65	0.25	0.08	0.32
Slovenia	11.51	5.57	0.00	0.91	4.63	0.67	0.17	0.19	0.00
Spain	10.77	5.64	2.33	1.76	2.28	0.55	0.34	0.40	0.54
Sweden	7.05	0.80	0.85	1.76	1.45	0.77	0.33	0.26	0.26
Switzerland	12.58	2.70	2.21	0.91	3.04	1.60	0.36	0.53	0.61
United Kingdom	60.05	20.83	3.51	2.75	4.77	2.02	0.78	0.86	0.81

Table A10 Age-specific incidence (per 100,000) of confirmed and probable laboratory-diagnosed meningococcal disease, by country, 2004

Country	<1 year	1 - 4 years	5 – 9 years	10 - 14 years	15 - 19 years	20 - 24 years	25 - 44 years	45 - 64 years	65+ years
Austria	13.17	4.94	1.60	0.83	3.77	0.60	0.24	0.24	0.15
Belgium	22.79	8.93	3.05	0.63	3.41	0.62	0.57	0.50	0.73
Czech Republic	16.01	4.97	2.12	0.80	2.56	1.35	0.33	0.32	0.14
Denmark	16.95	6.08	2.31	4.09	7.02	0.68	0.32	0.63	1.48
Estonia	0.00	3.97	0.00	0.00	0.00	0.99	0.27	1.49	0.91
Finland	16.05	2.23	0.00	0.30	1.57	0.60	0.36	0.89	0.61
France	11.54	3.14	1.60	0.82	3.25	1.46	0.31	0.34	0.50
Germany	14.02	3.88	1.30	0.77	2.80	0.93	0.17	0.20	0.22
Greece	13.76	4.91	2.26	0.88	1.24	0.50	0.12	0.15	0.05
Hungary	15.06	3.39	0.19	0.00	0.78	0.28	0.07	0.18	0.06
Iceland	23.45	23.90	4.65	0.00	0.00	0.00	0.00	3.07	5.83
Ireland	68.18	32.24	5.46	2.88	5.98	3.25	0.24	0.34	0.44
Italy	5.37	3.49	0.94	1.05	1.32	0.55	0.30	0.23	0.09
Latvia	9.54	7.64	1.00	1.27	2.14	1.17	0.15	0.52	0.53
Lithuania	62.48	15.33	0.52	1.56	0.72	0.40	0.30	0.38	0.00
Malta	49.66	12.09	4.11	10.71	7.04	0.00	0.91	1.88	0.00
Netherlands	25.40	9.39	2.74	1.49	3.29	0.52	0.43	0.55	1.20
Norway	19.43	0.85	0.00	0.32	3.57	1.09	0.15	0.27	0.30
Poland	8.22	1.99	0.38	0.27	0.69	0.09	0.06	0.04	0.06
Portugal	38.41	11.03	2.42	0.90	0.67	0.14	0.12	0.12	0.17
Slovak Republic	21.41	3.32	0.66	0.52	1.40	0.22	0.12	0.08	0.00
Slovenia	11.51	4.18	0.00	0.94	2.36	0.00	0.00	0.00	0.00
Spain	29.69	9.40	3.13	1.66	3.13	1.35	0.53	0.55	0.97
Sweden	5.94	2.08	0.42	0.49	2.44	1.15	0.21	0.30	0.32
Switzerland	16.47	2.39	1.74	1.60	4.61	1.13	0.27	0.57	0.34
United Kingdom	49.81	16.28	2.77	1.86	3.70	1.37	0.69	0.74	0.92

Table A11 Serogroup distribution of cases of confirmed and probable laboratory-diagnosed meningococcal disease, by country, 2003

Country	Serogroup B	Serogroup C	Serogroup W135	Serogroup Y	Other serogroups	Non-groupable	Not known	Serogroup C vaccination (year of introduction)
Austria	52	14	1	1	1	2	2	
Belgium	166	47	3	2	1	0	9	Yes (2002)
Czech Republic	39	40	3	2	1	0	7	
Denmark	59	20	2	4	0	0	18	
Estonia	6	1	0	0	0	0	1	
Finland	28	5	0	8	0	1	0	
France	209	111	16	13	1	0	300	
Germany	365	165	12	23	1	0	2	
Greece	53	2	5	1	17	23	18	
Hungary	35	4	0	1	0	0	1	
Iceland	5	2	1	0	0	0	0	Yes (2002)
Ireland	206	5	3	2	0	4	1	Yes (2000)
Italy	89	67	3	0	1	0	111	
Latvia	3	0	0	0	0	0	13	
Lithuania	10	3	0	0	0	0	17	
Luxembourg	1	0	0	0	0	0	0	
Malta	5	1	0	0	0	0	10	
Netherlands	297	44	6	5	2	0	0	Yes (2002)
Norway	36	9	2	1	0	2	1	
Poland	33	21	1	0	0	0	2	
Portugal	67	50	6	0	1	2	14	
Slovak Republic	28	11	1	0	1	0	8	
Slovenia	6	3	3	2	0	2	0	
Spain	357	93	14	21	1	7	0	Yes (2000)
Sweden	29	13	2	2	0	0	9	
Switzerland	37	23	4	5	0	2	4	
United Kingdom	1523	106	46	22	7	7	96	Yes (1999)
Total	3744	860	134	115	35	52	644	

Table A12 Incidence (per 100,000) of confirmed and probable laboratory-diagnosed meningococcal disease, by serogroup and country, 2003

Country	Serogroup B	Serogroup C	Serogroup W135	Serogroup Y	Other serogroups	Non-groupable	Not known	Serogroup C vaccination (year of introduction)
Austria	0.64	0.17	0.01	0.01	0.01	0.02	0.02	
Belgium	1.60	0.45	0.03	0.02	0.01	0.00	0.09	Yes (2002)
Czech Republic	0.38	0.39	0.03	0.02	0.01	0.00	0.07	
Denmark	1.10	0.37	0.04	0.07	0.00	0.00	0.33	
Estonia	0.44	0.07	0.00	0.00	0.00	0.00	0.07	
Finland	0.54	0.10	0.00	0.15	0.00	0.02	0.00	
France	0.34	0.18	0.03	0.02	0.00	0.00	0.49	
Germany	0.44	0.20	0.01	0.03	0.00	0.00	0.00	
Greece	0.48	0.02	0.05	0.01	0.15	0.21	0.16	
Hungary	0.35	0.04	0.00	0.01	0.00	0.00	0.01	
Iceland	1.73	0.69	0.35	0.00	0.00	0.00	0.00	Yes (2002)
Ireland	5.18	0.13	0.08	0.05	0.00	0.10	0.03	Yes (2000)
Italy	0.16	0.12	0.01	0.00	0.00	0.00	0.19	
Latvia	0.13	0.00	0.00	0.00	0.00	0.00	0.56	
Lithuania	0.29	0.09	0.00	0.00	0.00	0.00	0.49	
Luxembourg	0.22	0.00	0.00	0.00	0.00	0.00	0.00	
Malta	1.25	0.25	0.00	0.00	0.00	0.00	2.50	
Netherlands	1.83	0.27	0.04	0.03	0.01	0.00	0.00	Yes (2002)
Norway	0.79	0.20	0.04	0.02	0.00	0.04	0.02	
Poland	0.09	0.05	0.00	0.00	0.00	0.00	0.01	
Portugal	0.64	0.48	0.06	0.00	0.01	0.02	0.13	
Slovak Republic	0.52	0.20	0.02	0.00	0.02	0.00	0.15	
Slovenia	0.30	0.15	0.15	0.10	0.00	0.10	0.00	
Spain	0.86	0.22	0.03	0.05	0.00	0.02	0.00	Yes (2000)
Sweden	0.32	0.15	0.02	0.02	0.00	0.00	0.10	
Switzerland	0.50	0.31	0.05	0.07	0.00	0.03	0.05	
United Kingdom	2.56	0.18	0.08	0.04	0.01	0.01	0.16	Yes (1999)
Total	0.80	0.18	0.03	0.02	0.01	0.01	0.14	

Table A13 Serogroup distribution of cases of confirmed and probable laboratory-diagnosed meningococcal disease, by country, 2004

Country	Serogroup B	Serogroup C	Serogroup W135	Serogroup Y	Other serogroups	Non-groupable	Not known	Serogroup C vaccination (year of introduction)
Austria	43	18	3	2	0	0	4	
Belgium	124	21	5	3	1	1	2	Yes (2002)
Czech Republic	54	32	2	2	1	0	5	
Denmark	58	14	2	3	1	0	20	
Estonia	3	2	0	0	1	0	5	
Finland	30	5	2	4	0	0	4	
France	348	188	25	17	8	2	37	
Germany	306	122	4	14	1	0	0	
Greece	43	0	0	0	3	1	25	
Hungary	37	3	0	0	0	0	3	
Iceland	6	3	1	0	0	0	0	Yes (2002)
Ireland	163	5	1	2	0	1	4	Yes (2000)
Italy	73	99	3	6	0	0	133	
Latvia	9	0	0	1	0	0	13	
Lithuania	32	5	0	0	0	0	16	
Malta	6	0	0	0	1	0	6	
Netherlands	238	17	4	6	1	0	12	Yes (2002)
Norway	25	4	1	1	0	0	3	
Poland	72	41	0	2	0	1	0	
Portugal	92	15	4	4	2	0	7	
Slovak Republic	18	6	0	0	1	0	7	
Slovenia	7	0	2	0	0	0	0	
Spain	474	146	19	3	2	45	7	Yes (2000)
Sweden	28	11	6	6	0	1	4	
Switzerland	36	18	2	2	0	1	20	
United Kingdom	1253	65	39	35	7	2	73	Yes (1999)
Total	3578	840	125	113	30	55	410	

Table A14 Incidence (per 100,000) of confirmed and probable laboratory-diagnosed meningococcal disease, by serogroup and country, 2004

Country	Serogroup B	Serogroup C	Serogroup W135	Serogroup Y	Other serogroups	Non-groupable	Not known	Serogroup C vaccination (year of introduction)
Austria	0.53	0.22	0.04	0.02	0.00	0.00	0.05	
Belgium	1.19	0.20	0.05	0.03	0.01	0.01	0.02	Yes (2002)
Czech Republic	0.53	0.31	0.02	0.02	0.01	0.00	0.05	
Denmark	1.07	0.26	0.04	0.06	0.02	0.00	0.37	
Estonia	0.22	0.15	0.00	0.00	0.07	0.00	0.37	
Finland	0.58	0.10	0.04	0.08	0.00	0.00	0.08	
France	0.56	0.30	0.04	0.03	0.01	0.00	0.06	
Germany	0.37	0.15	0.00	0.02	0.00	0.00	0.00	
Greece	0.39	0.00	0.00	0.00	0.03	0.01	0.23	
Hungary	0.37	0.03	0.00	0.00	0.00	0.00	0.03	
Iceland	2.05	1.03	0.34	0.00	0.00	0.00	0.00	Yes (2002)
Ireland	4.03	0.12	0.02	0.05	0.00	0.02	0.10	Yes (2000)
Italy	0.13	0.17	0.01	0.01	0.00	0.00	0.23	
Latvia	0.39	0.00	0.00	0.04	0.00	0.00	0.56	
Lithuania	0.93	0.15	0.00	0.00	0.00	0.00	0.46	
Malta	1.50	0.00	0.00	0.00	0.25	0.00	1.50	
Netherlands	1.46	0.10	0.02	0.04	0.01	0.00	0.07	Yes (2002)
Norway	0.55	0.09	0.02	0.02	0.00	0.00	0.07	
Poland	0.19	0.11	0.00	0.01	0.00	0.00	0.00	
Portugal	0.87	0.14	0.04	0.04	0.02	0.00	0.07	
Slovak Republic	0.33	0.11	0.00	0.00	0.02	0.00	0.13	
Slovenia	0.35	0.00	0.10	0.00	0.00	0.00	0.00	
Spain	1.12	0.34	0.04	0.01	0.00	0.11	0.02	Yes (2000)
Sweden	0.31	0.12	0.07	0.07	0.00	0.01	0.04	
Switzerland	0.49	0.24	0.03	0.03	0.00	0.01	0.27	
United Kingdom	2.09	0.11	0.07	0.06	0.01	0.00	0.12	Yes (1999)
Total	0.76	0.18	0.03	0.02	0.01	0.01	0.09	

Table A15 Age distribution of cases of confirmed and probable laboratory-diagnosed serogroup B meningococcal disease, all countries, 1999 – 2004

Age group	1999	2000	2001	2002	2003	2004
Number of cases						
<1 year	692	770	741	632	622	587
1 - 4 years	992	1006	992	907	858	729
5 - 9 years	375	331	341	296	240	198
10 – 14 years	255	189	262	196	202	131
15 – 19 years	446	413	442	340	335	332
20 – 24 years	155	175	151	124	119	127
25 – 44 years	214	250	255	206	200	165
45 – 64 years	179	234	192	174	176	184
65+ years	125	112	101	106	90	120
Not known	53	10	7	7	8	9
Total	3486	3490	3484	2988	2850	2582
% distribution						
<1 year	19.85%	22.06%	21.27%	21.15%	21.82%	22.73%
1 - 4 years	28.46%	28.83%	28.47%	30.35%	30.11%	28.23%
5 - 9 years	10.76%	9.48%	9.79%	9.91%	8.42%	7.67%
10 – 14 years	7.31%	5.42%	7.52%	6.56%	7.09%	5.07%
15 – 19 years	12.79%	11.83%	12.69%	11.38%	11.75%	12.86%
20 – 24 years	4.45%	5.01%	4.33%	4.15%	4.18%	4.92%
25 – 44 years	6.14%	7.16%	7.32%	6.89%	7.02%	6.39%
45 – 64 years	5.13%	6.70%	5.51%	5.82%	6.18%	7.13%
65+ years	3.59%	3.21%	2.90%	3.55%	3.16%	4.65%
Not known	1.52%	0.29%	0.20%	0.23%	0.28%	0.35%

Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

Table A16 Age distribution of cases of confirmed and probable laboratory-diagnosed serogroup C meningococcal disease, all countries, 1999 – 2004

Age group	1999	2000	2001	2002	2003	2004
Number of cases						
<1 year	174	89	92	77	40	50
1 - 4 years	413	346	222	179	99	100
5 - 9 years	181	164	103	82	41	48
10 – 14 years	171	136	98	73	44	42
15 – 19 years	338	214	236	175	82	99
20 – 24 years	93	127	101	84	47	29
25 – 44 years	125	169	166	132	69	74
45 – 64 years	122	114	144	94	56	53
65+ years	74	96	85	82	41	36
Not known	20	3	9	1	2	1
Total	1711	1458	1256	979	521	532
% distribution						
<1 year	10.17%	6.10%	7.32%	7.87%	7.68%	9.40%
1 - 4 years	24.14%	23.73%	17.68%	18.28%	19.00%	18.80%
5 - 9 years	10.58%	11.25%	8.20%	8.38%	7.87%	9.02%
10 – 14 years	9.99%	9.33%	7.80%	7.46%	8.45%	7.89%
15 – 19 years	19.75%	14.68%	18.79%	17.88%	15.74%	18.61%
20 – 24 years	5.44%	8.71%	8.04%	8.58%	9.02%	5.45%
25 – 44 years	7.31%	11.59%	13.22%	13.48%	13.24%	13.91%
45 – 64 years	7.13%	7.82%	11.46%	9.60%	10.75%	9.96%
65+ years	4.32%	6.58%	6.77%	8.38%	7.87%	6.77%
Not known	1.17%	0.21%	0.72%	0.10%	0.38%	0.19%

Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

Table A17 Percentage distribution of confirmed and probable laboratory-diagnosed cases due to serogroup C, by country (total serogroup cases), 1999 - 2004

	1999	2000	2001	2002	2003	2004
No Serogroup C	Estonia (3)	Estonia (9)	Luxembourg (1)	Estonia (8)	Luxembourg (1)	Greece (72)
	Slovenia (6)					Luxembourg (0)
						Malta (13)
						Slovenia (9)
<10%		Malta (20)	Greece (185)	Greece (196)	Greece (119)	Ireland (176)
			Malta (13)	Ireland (225)	Ireland (221)	Netherlands (278)
				United Kingdom (1948)	Malta (16)	United Kingdom (1474)
					United Kingdom (1807)	
10 - 19%	Austria (97)	Austria (83)	Denmark (161)	Denmark (98)	Austria (73)	Belgium (157)
	Denmark (177)	Czech Republic (61)	Estonia (20)	Finland (49)	Denmark (103)	Denmark (98)
	Finland (57)	Denmark (151)	Finland (49)	Malta (14)	Estonia (8)	Estonia (11)
	Italy (254)	Greece (174)	Ireland (297)	Slovenia (8)	Finland (42)	Finland (45)
	Malta (17)	Italy (243)	Italy (201)		France (650)	Norway (34)
	Netherlands (576)	Norway (85)	Norway (77)		Netherlands (354)	
	Norway (77)	Poland (43)	Poland (37)		Norway (51)	
	Poland (67)	Slovenia (8)	Slovenia (10)		Slovenia (16)	
			United Kingdom (2570)			
20 - 29%	Belgium (297)	Finland (48)	Germany (530)	Austria (81)	Belgium (228)	Austria (70)
	France (448)	France (489)		Italy (214)	Germany (567)	Germany (447)
	Germany (402)	Germany (452)		Norway (51)	Iceland (8)	Switzerland (79)
	Greece (130)	Netherlands (542)			Italy (271)	
	Luxembourg (18)	United Kingdom (2993)				
30 - 39%	Ireland (445)	Belgium (267)	Austria (106)	Belgium (262)	Poland (57)	Czech Republic (96)
	Switzerland (150)	Ireland (411)	Czech Republic (93)	Czech Republic (113)	Switzerland (75)	France (625)
	United Kingdom (3064)		France (559)	France (648)		Iceland (10)
			Netherlands (721)	Germany (580)		Italy (314)
				Netherlands (616)		Poland (116)
				Poland (35)		
>=40%	Czech Republic (93)	Iceland (18)	Belgium (380)	Iceland (15)	Czech Republic (92)	
	Iceland (21)	Luxembourg (1)	Iceland (19)	Luxembourg (1)		
		Switzerland (149)	Switzerland (147)	Switzerland (91)		

Calculated using data from countries submitting consistent data 1999 - 2004 (see Table A1)

Table A18 Dominant serotype of confirmed and probable laboratory-diagnosed serogroup C invasive meningococcal disease (number of serotyped C cases), by country, 1999 - 2004

Serotype	1999	2000	2001	2002	2003	2004
P2.2a	Czech Republic (26)	Austria (10)	Austria (34)	Austria (17)	Belgium (46)	Belgium (20)
	Denmark (21)	Belgium (85)	Belgium (178)	Belgium (89)	Czech Republic (23)	Czech Republic (25)
	Greece (17)	Czech Republic (10)	Czech Republic (23)	Czech Republic (28)	France (109)	France (127)
	Ireland (42)	Denmark (16)	Denmark (24)	Denmark (16)	Greece (2)	Ireland (1)
	Italy (16)	Greece (9)	France (126)	Finland (6)	Ireland (2)	Netherlands (17)
	Malta (1)	Ireland (54)	Greece (8)	France (172)	Malta (1)	Norway (1)
	Netherlands (81)	Italy (24)	Ireland (6)	Greece (6)	Netherlands (44)	Switzerland (18)
	Norway (10)	Netherlands (106)	Italy (15)	Ireland (4)	Norway (9)	United Kingdom (33)
	United Kingdom (713)	Norway (12)	Netherlands (277)	Netherlands (222)	Switzerland (23)	
		Slovenia (1)	Norway (13)	Slovenia (1)	United Kingdom (65)	
		United Kingdom (514)	Slovenia (1)	Switzerland (39)	Austria (12)	
			United Kingdom (220)	United Kingdom (128)		
P2.2b	Austria (14)	Malta (1)	Switzerland (69)	Italy (32)	Italy (55)	Italy (83)
	Belgium (77)	Switzerland (83)				
	France (100)					
	Switzerland (57)					
P3.15				Norway (3)	Denmark (19)	Denmark (14)
P3.22	Poland (8)					
P3.4			Poland (4)	Norway (3)		
NT	Finland (9)	Finland (10)	Finland (9)	Greece (6)	Finland (5)	Austria (15)
	Poland (8)	Poland (7)	Malta (1)	Norway (3)	Poland (21)	Finland (5)
			Norway (13)	Poland (11)	Slovenia (3)	Poland (40)

Table A19 Dominant serotype of confirmed and probable laboratory-diagnosed serogroup B invasive meningococcal disease (number of serotyped B cases), by country, 1999 – 2004

Serotype	1999	2000	2001	2002	2003	2004
P3.14	Italy (60)					
P3.15	Austria (60)	Austria (45)	Denmark (92)	Denmark (65)	Czech Republic (20)	Austria (32)
	Denmark (126)	Denmark (98)	Italy (46)		Denmark (57)	Denmark (56)
	Norway (57)	Norway (49)	Norway (32)		Italy (66)	Italy (48)
		Slovenia (4)	Slovenia (8)			Norway (19)
P3.22			Poland (29)		Slovenia (6)	
P3.4	Belgium (198)	Belgium (165)	Belgium (169)	Belgium (161)	Belgium (164)	Belgium (122)
	Finland (33)	Finland (29)	Finland (34)	Czech Republic (37)	Finland (28)	Czech Republic (40)
	Ireland (86)	Greece (20)	Greece (35)	Greece (37)	Greece (28)	Finland (29)
	Malta (6)	Ireland (86)	Ireland (55)	Italy (47)	Malta (3)	Greece (29)
	Netherlands (466)	Italy (61)	Malta (9)	Malta (6)	Netherlands (293)	Ireland (45)
	United Kingdom (1020)	Malta (13)	Netherlands (417)	Netherlands (371)	Norway (31)	Netherlands (232)
		Netherlands (413)		Norway (24)		Norway (19)
						Switzerland (36)
NT	Czech Republic (36)	Austria (45)	Austria (46)	Austria (39)	Austria (37)	France (233)
	France (302)	Czech Republic (34)	Czech Republic (34)	Finland (35)	Finland (28)	Ireland (45)
	Greece (30)	Poland (33)	France (194)	France (224)	France (205)	Malta (4)
	Poland (55)	Switzerland (48)	Slovenia (8)	Ireland (51)	Ireland (49)	Poland (71)
	Slovenia (6)	United Kingdom (1018)	Switzerland (52)	Poland (23)	Poland (31)	Slovenia (5)
	Switzerland (59)		United Kingdom (964)	Slovenia (5)	Slovenia (6)	United Kingdom (631)
				Switzerland (34)	Switzerland (37)	
				United Kingdom (796)	United Kingdom (779)	

Table A20 Number of cases of phenotype B:P2.2a or B:P2.2b in sentinel countries involved in the rapid surveillance project by year and month, 1999-2004

Year	Month	Countries without routine MCC vaccination						Countries with routine MCC vaccination			
		Austria	Czech Republic	Denmark	France	Greece	Italy	Ireland	Nether-lands	Spain	United Kingdom
1999	January					1				1	6
	February	1	1	1		1				2	2
	March				1	2			1	1	2
	April				1					1	3
	May		1						1		1
	June				1				1		1
	July				1					2	1
	August	1									
	Septembe										
	October				1				1		1
	November					1				1	2
	December		1								2
2000	January		1			1					10
	February			1		1				1	2
	March	1				2				2	1
	April									1	2
	May					2				2	
	June									1	
	July						1		1	1	1
	August									1	1
	Septembe										
	October	1								2	2
	November									1	4
	December		2			1					2
2001	January										4
	February		1		1	2				1	3
	March								1	1	5
	April				1				1	1	4
	May					1	2		2		1
	June										1
	July										
	August								1		2
	Septembe					1		1		1	
	October			2		1			1	1	1
	November	1								1	4
	December				2					3	3

Year	Month	Countries without routine MCC vaccination						Countries with routine MCC vaccination			
		Austria	Czech Republic	Denmark	France	Greece	Italy	Ireland	Nether-lands	Spain	United Kingdom
2002	January				1			1		8	2
	February				1	1	1			6	2
	March		1							3	3
	April				1		1	1	1	3	
	May					1				2	3
	June									1	
	July									1	
	August	1							1		2
	Septembe	1								2	1
	October									3	
	November	1									
	December	3							1	1	
2003	January	1			1					7	
	February	1								4	2
	March				1					6	
	April						1			4	
	May									2	2
	June										3
	July										1
	August										
	Septembe									2	
	October									1	
	November									2	1
	December									2	1
2004	January				3		1		2	2	3
	February				1						1
	March		1					1		1	
	April				1					1	2
	May				1					2	
	June		2		1					1	1
	July		1		1						2
	August										
	Septembe								1		
	October										
	November		1				1				
	December							1			

Shaded boxes indicate year of introduction of routine MCC vaccination

Table A21 Frequency of phenotype/genotype present in invasive meningococcal serogroup C isolates, by country, 2003

Present in more than 10 isolates														
	C:P2.2a: P1.5,2	**C:P2.2a: P1.5,10**	**C:P2.2a: P1.5**	**C:P2.2a: P1.2**	**C:P2.2a: NST:NST**	**C:P2.2b: P1.5,2**	**C:P2.2b: P1.5**	**C:P2.2b: P1.2**	**C:P2.2b: NST:NST**	**C:P3.15: P1.7,16**	**C:NT: P1.5,2**	**C:NT: P1.5**	**C:NT: NT**	**Total listed (% total known)**
Austria (A)			2		2	2		2	1				1	10 (83%)
Belgium (B)	14		10	2	4	6		1	1				3	41 (89%)
Czech Republic (CR)	10			8							3		1	22 (96%)
Denmark (D)	1				2	1		1	2	5	1		1	14 (74%)
Finland (Fi)									1				2	3 (60%)
France (Fr)	10		30	5	1	20		4			17	4	1	92 (95%)
Germany (Ge)	47	31				26								104 (86%)
Greece (Gr)		2												2 (100%)
Ireland (Ir)				1	1									2 (100%)
Italy (It)			9			2	25		5				5	46 (84%)
Malta (M)			1											1 (100%)
Netherlands (Ne)	7		15		5	3		2			2	4		38 (86%)
Norway (No)	3		1						1	1	1			7 (78%)
Poland (Pl)	1		1			6		1			1		3	13 (62%)
Portugal (Pt)			2			1	18	1	1					23 (82%)
Slovak Republic (SR)	8			2	1									11 (100%)
Slovenia (Sl)											1		2	3 (100%)
Spain (Sp)			57			7	4	1			4	1	1	75 (91%)
Sweden (Se)	1									5	1			7 (58%)
Switzerland (Si)	6		3	1	1	6		2	1					20 (87%)
United Kingdom (UK)	6		30	2	12	1						3	2	56 (86%)
Total	114	33	161	21	29	81	47	15	12	11	31	12	22	589 (86%)

Present in 2 – 9 isolates (Country)						
C:P2.2a:P1.7,1	(D, Fr, Ge, It)	C:P3.4:P1.7,16	(It, Se)	C:NT:P1.7,16	(Se)
C:P2.2aP1.22,9	(Ge)	C:P3.4:P1.15	(Sp)	C:NT:P1.12	(Pl)
C:P2.2a:P1.15	(B, Sp)	C:P3.4:NST:NST	(D, It, UK)	C:NT:P1.19,15	(UK)
		C:P3.4:P1.4	(It, Si)	C:NT:P1.2	(CR, Fr)
C:P2.2b:P1.7,1	(B)			C:NT:P1.3	(Pl, UK)
		C:P3.14:P1.5,2	(Sp, Se)		

No of isolates of each C:serotype:vr1:vr2 combination was determined, and the geographical distribution of each combination present in more than one isolate identified. Both genotypic and phenotypic data were analysed

Table A22 Frequency of phenotype/genotype present in invasive meningococcal serogroup C isolates, by country, 2004

Present in more than 10 isolates															
	C:P2.2a: P1.5,2	**C:P2.2a: P1.5,10**	**C:P2.2a: P1.5**	**C:P2.2a :P1.2**	**C:P2.2a: NST:NST**	**C:P2.2b: P1.5,2**	**C:P2.2b: P1.5**	**C:P2.2b: P1.2**	**C:P2.2b: NST:NST**	**C:NT: P1.5,2**	**C:NT: P1.5**	**C:NT: P1.2**	**C:NT: P1.3**	**C:NT: NST:NST**	**Total listed (% total known)**
Austria (A)			1		4			2				5		1	13 (93%)
Belgium (B)	4		4	2	2	3								1	16 (80%)
Czech Republic (CR)	8			11	2							2		2	25 (100%)
Denmark (D)			1		2	1	1		1						6 (43%)
Finland (Fi)									1				2		3 (60%)
France (Fr)	11		38	5	14	12	1	4	3	11	4	5		10	118 (91%)
Germany (Ge)	43	10				15									68 (91%)
Ireland (Ir)	1														1 (100%)
Italy (It)	1		4		1	41	9	4	12	2				2	76 (92%)
Netherlands (Ne)	2	4				5				1					12 (71%)
Poland (Pl)	1		1			12					2		8	4	28 (70%)
Portugal (Pt)							4		3		1				8 (100%)
Slovak Republic (SR)	1			2						1		1			5 (100%)
Spain (Sp)	1		15	1	5	1	1		1	1				3	29 (94%)
Sweden (Se)	1	1				1				2					5 (45%)
Switzerland (Si)	3		4	1	2	4		1	1					2	18 (100%)
United Kingdom (UK)	1		12		6	1				4	3			1	28 (85%)
Total	78	15	80	22	38	96	16	11	22	22	10	13	10	26	459 (87%)

Present in more than 2 - 9 isolates (Country)					
P2.2a:P1.22,9	(Ge)	P3.14:NST:NST	(Pl)	NT:P1.12,4	(A, Se)
				NT:P1.1	
P2.2b:P1.5,4	(B)	P3.15:P1.7,16	(Se)	NT:P1.4	(It)
		P3.15:P1.7	(D)	NT:P1.9	(Pl, UK)
P3.4:P1.9	(Pl)	P3.15:P1.19,15	(Se)	NT:P1.16	(Pl, UK)
P3.4:NST:NST	(It, Pl)	P3.15:NST:NST	(D)		

No of isolates of each C:serotype:vr1:vr2 combination was determined, and the geographical distribution of each combination present in more than one isolate identified. Both genotypic and phenotypic data were analysed

Table A23 Frequency of serosubtypes present in invasive meningococcal serogroup B isolates, by country, 2003

Present in more than 30 isolates																		
	B:P1.5,2	**B:P1.5,10**	**B:P1.5**	**B:P1.7,4**	**B:P1.7,16**	**B:P1.7**	**B:P1.19,15**	**B:P1.22,14**	**B:P1.3**	**B:P1.4**	**B:P1.9**	**B:P1.10**	**B:P1.13**	**B:P1.14**	**B:P1.15**	**B:P1.16**	**B:NST: NST**	**Total listed (% total known**
Austria (A)	1		2		8	4			1	3			1	1	1	1	12	35 (95%)
Belgium (B)	10		3	2	4	4				86	2	5	6	6	9	2	18	157 (96%)
Czech Republic (CR)	2		5		1					1				2	3		5	19 (95%)
Denmark (D)	5		1		31				3		1		1	3	6	4	2	57 (100%)
Finland (Fi)	3		2	1	2	5			1	3	1			3	1		5	27 (96%)
France (Fr)	6		9		23	7				51	5	3	6	7	13	5	11	146 (89%)
Germany (Ge)	22	31		62	69		23	29				2	1	1				240 (70%)
Greece (Gr)	1	1		1	2	1	6	11			1			1				25 (89%)
Ireland (Ir)			1			1	4		1	20	1	1		6		2	7	44 (90%)
Italy (It)			8		4	2			3	16	1	2	9	3	2	5	11	66 (100%)
Malta (M)							3											3 (100%)
Netherlands (Ne)	8		4	2	9	6				107	7	22		29	19	12	64	289 (98%)
Norway (No)	1				5	3				13	1		1		2	3	6	35 (97%)
Poland (Pl)	1		2		3				2	2		2	1	9			5	27 (87%)
Portugal (Pt)			3		1	2				3			2	8	6		16	41 (91%)
Slovak Republic (SR)			1		1	2			1		1	1	1		2	3	10	23 (92%)
Slovenia (Sl)			1		1				2						1			5 (83%)
Spain (Sp)	8		35		4	10			5	35	32	3	12	34	144	19	41	382 (93%)
Sweden (Se)		2		3	3		4	1										13 (46%)
Switzerland (Si)	2		4		2				2	5		1		2		3	13	34 (100%)
United Kingdom (UK)	26	2	29	12	24	7	125	12	14	199	86	5	4	102	8	33	75	763 (91%)
Total	96	36	110	83	197	54	165	53	35	544	139	47	45	217	217	92	301	2431 (90%)

Present in between 30 and 10 isolates (Country)

B:P1.7,1	(A, Fr, Ge, Ne, Pl, Sp, UK)	B:P1.18,3	(Ge, Gr)	B:P1.22,9	(Ge, Se, UK)
B:P1.7,13	(Fr, Ge, Se, UK)	B:P1.18,25	(Ge, Se, UK)	B:P1.1	(Fr, Ne, Pl, SR, Sp, UK)
B:P1.12,13	(Fr, Ge, Sp, Se, UK)	B:P1.19,13	(Ge, Ir, UK)		
B:P1.17,9	(Ge, Se)	B:P1.19	(Ir, UK)	B:P1.2	(A, B, Fr, SR, Sp, UK)
		B:P1.21,16	(Ge, Gr, Se, UK)	B:P1.12	(B, Fi, Fr, Pl, Pt, Sl, Sp, UK)

Present in between 9 and 2 isolates (Country)					
B:P1.7,2	(Ge, UK,)	B:P1.12,4	(Ge,)	B:P1.18,9	(Ge,)
B:P1.7,9	(No, Pt, Sp,)	B:P1.12,9	(Sp, UK,)	B:P1.18,13	(Ge,)
B:P1.7,14	(B, CR, Ge, Pt, Sp,)	B:P1.12,16	(Ge,)		
B:P1.7,15	(Fr, UK,)			B:P1.19,2	(UK,)
B:P1.7,30	(Ge, Se,)	B:P1.17,16	(Ge, UK,)	B:P1.19,3	(UK,)
				B:P1.19,16	(UK,)

No of isolates of each B:vr1:vr2 combination was determined, and the geographical distribution of each combination present in more than one isolate identified. Both genotypic and phenotypic data were analysed

Table A24 Frequency of serosubtypes present in invasive meningococcal serogroup B isolates, by country, 2004

Present in more than 30 isolates																	
	B:P1.5, 2	**B:P1.5, 10**	**B:P1.5**	**B:P1.7, 4**	**B:P1.7, 13**	**B:P1.7, 16**	**B:P1.7**	**B:P1.19 ,15**	**B:P1.22 ,14**	**B:P1.4**	**B:P1.9**	**B:P1.13**	**B:P1.14**	**B:P1.15**	**B:P1.16**	**B:NST: NST**	**Total listed (% total known**
Austria (A)						13	1				1		2	3		8	28 (88%)
Belgium (Be)	5		4	1		4	1			47	2	8	8	13	6	16	115 (94%)
Czech Republic (CR)	2		4			4							7	5	2	9	33 (85%)
Denmark (D)	2		1		1	28				2	2		5	8	2	2	53 (95%)
Finland (Fi)			3				3			4	1	1		2	1	9	24 (83%)
France (Fr)	3		10	1		19	10			68	11	7	12	2	8	70	221 (94%)
Germany (Ge)	14	27		82	8	49		18	26								224 (76%)
Greece (Gr)		1	3			4	3	2	3	3	2		3			1	25 (89%)
Ireland (Ir)			3					4		15	3	1	4	1	1	1	33 (75%)
Italy (It)	2		2			2				13	4	8		3	3	6	43 (91%)
Malta (M)								1		1							2 (50%)
Netherlands (Ne)	4	28		80	28	17		13	29				1				200 (85%)
Norway (No)	1					4	1			6	1			2	2		17 (100%)
Poland (Pl)	9		6	1		9	1			2		1	13		1	12	55 (77%)
Portugal (Pt)			4			1				7	3	1	5	3	1	24	49 (88%)
Slovak Republic (SR)							1						1	5		2	9 (64%)
Slovenia (Sl)	1					1				1						1	4 (80%)
Spain (Sp)	2		10				2			10	14	1	2	15	8	15	79 (94%)
Sweden (Se)		1		3	6	8		2	1								21 (78%)
Switzerland (Si)	1					2				8	4	1	4	3	5	5	33 (92%)
United Kingdom (UK)	19		27	17	1	14	8	101	14	163	85	8	67		23	71	618 (89%)
	65	57	77	185	44	179	31	141	73	350	133	37	134	65	63	252	1886 (87%)

Present in between 30 and 10 isolates (Country)					
B:P1.7,1	(A, Be, CR, Ge, Ne, Pl, Pt, SR, UK)	B:P1.21,16	(Ge, Ne, UK)	B:P1.3	(A, Be, D, Fi, Ir, It, Pl, Sl, UK)
B:P1.18,3	(Ge, Ne, Se, UK)	B:P1.22,9	(Ge, Ne, Se, UK)	B:P1.10	(A, Be, Fi, Fr, Ir, It, Pl, Sp, UK)
B:P1.19,13	(Ge, Ir, Ne, UK)	B:P1.1	(D, Fr, It, Pt, SR, Sp, Si, UK)	B:P1.12	(CR, Fi, Fr, Pl, Pt, Sp, Si, UK)
B:P1.19	(Ir, UK)				

Present in between 9 and 2 isolates (Country)					
B:P1.5,14	(Fr, Pl)	B:P1.17,9	(Ge, Ne)	B:P1.19,3	(M, UK)
		B:P1.17,16	(Ge)	B:P1.19,14	(Ne, UK)
B:P1.7,2	(Ge, Ne)	B:P1.17,23	(Se, UK)	B:P1.19,16	(UK)
B:P1.7,14	(Fi, UK)				
B:P1.7,30	(Ge, Ne)	B:P1.18,2	(Ge)	B:P1.31,16	(Ne)
		B:P1.18,9	(Ge, Ne, Se)		
B:P1.12,4	(Ge, Ne, Pl)	B:P1.18,25	(Ne, Se, UK)	B:P1.2	(CR, Fr, Gr, UK)
B:P1.12,13	(D, Fr, Ge, Ne, UK)	B:P1.18,30	(Ge, Ne)		
B:P1.12,16	(Ge)			B:P1.14	(Pt)
B:P1.12,4	(Ge, Ne, Pl)				

No of isolates of each B:vr1:vr2 combination was determined, and the geographical distribution of each combination present in more than one isolate identified. Both genotypic and phenotypic data were analysed

Table A25 Case fatality ratio in confirmed and probable laboratory-diagnosed cases of meningococcal disease, by country, 1999 – 2004

	1999			2000			2001			2002			2003			2004		
	Deaths	Cases	Case fatality	Deaths	Cases	Case fatality	Deaths	Cases	Case fatality	Deaths	Cases	Case fatality	Deaths	Cases	Case fatality	Deaths	Cases	Case fatality
Austria	7	97	7.22%	5	83	6.02%	7	106	6.60%	6	81	7.41%	5	73	6.85%	7	70	10.00%
Belgium	16	297	5.39%	13	267	4.87%	27	380	7.11%	15	262	5.73%	9	228	3.95%	10	157	6.37%
Czech Republic	7	93	7.53%	5	61	8.20%	10	93	10.75%	18	113	15.93%	8	92	8.70%	16	96	16.67%
Denmark	14	177	7.91%	11	151	7.28%	10	161	6.21%	7	98	7.14%	8	103	7.77%	5	98	5.10%
Estonia	1	3	33.33%	0	9	0.00%	2	20	10.00%	0	8	0.00%	0	8	0.00%	4	11	36.36%
Finland	10	57	17.54%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
France	35	411	8.52%	59	489	12.07%	73	559	13.06%	94	648	14.51%	63	650	9.69%	70	625	11.20%
Germany	-	-	-	-	-	-	53	770	6.88%	67	730	9.18%	68	768	8.85%	47	596	7.89%
Greece	8	130	6.15%	11	174	6.32%	7	185	3.78%	8	196	4.08%	3	119	2.52%	2	72	2.78%
Hungary	-	-	-	-	-	-	-	-	-	-	-	-	6	41	14.63%	9	43	20.93%
Iceland	2	21	9.52%	2	18	11.11%	2	19	10.53%	1	15	6.67%	0	8	0.00%	1	10	10.00%
Ireland	17	445	3.82%	25	411	6.08%	12	297	4.04%	8	225	3.56%	12	221	5.43%	8	176	4.55%
Italy	13	254	5.12%	20	243	8.23%	14	201	6.97%	24	214	11.21%	22	271	8.12%	30	314	9.55%
Latvia	-	-	-	-	-	-	-	-	-	-	-	-	4	16	25.00%	3	23	13.04%
Lithuania	-	-	-	-	-	-	2	35	5.71%	3	29	10.34%	4	30	13.33%	4	53	7.55%
Malta	5	17	29.41%	3	20	15.00%	0	13	0.00%	2	14	14.29%	0	16	0.00%	3	13	23.08%
Netherlands	23	576	3.99%	29	542	5.35%	41	721	5.69%	24	616	3.90%	8	354	2.26%	13	278	4.68%
Norway	9	77	11.69%	7	85	8.24%	3	77	3.90%	5	51	9.80%	5	51	9.80%	3	34	8.82%
Poland	1	67	1.49%	0	43	0.00%	2	37	5.41%	0	35	0.00%	8	57	14.04%	8	116	6.90%
Portugal	-	-	-	-	-	-	-	-	-	6	185	3.24%	11	140	7.86%	5	124	4.03%
Slovak Republic	-	-	-	-	-	-	-	-	-	-	-	-	5	49	10.20%	2	32	6.25%
Slovenia	0	6	0.00%	2	8	25.00%	2	10	20.00%	1	8	12.50%	1	16	6.25%	0	9	0.00%
Spain	74	947	7.81%	-	-	-	59	643	9.18%	107	834	12.83%	-	-	-	84	696	12.07%
Sweden	-	-	-	-	-	-	-	-	-	9	46	19.57%	9	55	16.36%	5	56	8.93%
Switzerland	11	150	7.33%	10	149	6.71%	11	147	7.48%	15	91	16.48%	4	75	5.33%	5	79	6.33%
United Kingdom	219	3064	7.15%	230	2993	7.68%	211	2570	8.21%	130	1948	6.67%	107	1807	5.92%	77	1474	5.22%
Total	472	6889	6.85%	432	5746	7.52%	548	7044	7.78%	550	6447	8.53%	370	5248	7.05%	421	5255	8.01%

Table A26 Serogroup-specific case fatality rate in confirmed and probable laboratory-diagnosed cases of meningococcal disease, by country, 1999 – 2004 combined

Country	C deaths	C cases	C case fatality	B deaths	B cases	B case fatality	Other deaths	Other cases	Other case fatality
Austria	6	143	4.20%	29	394	7.36%	4	30	13.33%
Belgium	46	498	9.24%	41	988	4.15%	2	44	4.55%
Czech Republic	29	190	15.26%	24	294	8.16%	6	30	20.00%
Denmark	12	117	10.26%	40	511	7.83%	2	26	7.69%
Estonia	0	7	0.00%	2	31	6.45%	1	8	12.50%
Finland	2	9	22.22%	6	35	17.14%	1	9	11.11%
France	155	917	16.90%	143	1691	8.46%	50	277	18.05%
Germany	134	1425	9.40%	264	3779	6.99%	27	415	6.51%
Greece	9	75	12.00%	22	388	5.67%	3	301	1.00%
Iceland	3	49	6.12%	3	33	9.09%	2	3	66.67%
Ireland	21	333	6.31%	59	1363	4.33%	2	64	3.13%
Italy	43	297	14.48%	45	484	9.30%	2	21	9.52%
Netherlands	33	755	4.37%	102	2224	4.59%	3	94	3.19%
Norway	4	65	6.15%	27	260	10.38%	1	43	2.33%
Poland	3	92	3.26%	11	246	4.47%	3	14	21.43%
Portugal	5	143	3.50%	13	221	5.88%	3	28	10.71%
Slovenia	1	6	16.67%	2	37	5.41%	3	14	21.43%
Spain	144	867	16.61%	160	2002	7.99%	13	138	9.42%
Sweden	9	51	17.65%	12	107	11.21%	6	33	18.18%
Switzerland	23	289	7.96%	19	266	7.14%	6	57	10.53%
United Kingdom	362	2582	14.02%	504	9450	5.33%	85	776	10.95%
Total	1044	8910	11.72%	1528	24804	6.16%	225	2425	9.28%

Table A27 Proportion of meningitis in confirmed and probable laboratory-diagnosed cases of invasive meningococcal disease, 1999 – 2004

% meningitis	1999	2000	2001	2002	2003	2004
< 50%	Greece	Ireland	Ireland	Ireland	Lithuania	Iceland
	Ireland	United Kingdom	United Kingdom	Spain	Sweden	Ireland
	Malta			Sweden		Malta
	United Kingdom			United Kingdom		Spain
50% - 70%	Belgium	Belgium	Belgium	Belgium	Austria	Austria
	Estonia	Finland	Finland	Denmark	Belgium	Belgium
	Iceland	Greece	Iceland	Finland	Denmark	Czech Republic
	Netherlands	Iceland	Lithuania	France	Finland	Finland
	Norway	Malta	Norway	Malta	Iceland	Greece
	Slovenia		Spain	Netherlands	Ireland	Latvia
	Spain			Norway	Latvia	Lithuania
				Portugal	Malta	Netherlands
				Slovenia	Netherlands	Norway
				Switzerland	Poland	Slovenia
					Spain	Sweden
					United Kingdom	United Kingdom
> 70%	Austria	Austria	Austria	Austria	Czech Republic	Denmark
	Czech Republic	Czech Republic	Czech Republic	Czech Republic	Estonia	Estonia
	Denmark	Denmark	Denmark	Estonia	France	France
	Finland	Estonia	Estonia	Greece	Greece	Hungary
	France	France	France	Iceland	Hungary	Italy
	Italy	Italy	Greece	Italy	Italy	Poland
	Poland	Netherlands	Italy	Lithuania	Norway	Portugal
	Switzerland	Norway	Malta	Poland	Portugal	Slovak Republic
		Poland	Netherlands		Slovak Republic	Switzerland
		Slovenia	Poland		Slovenia	
		Spain	Portugal		Switzerland	
		Switzerland	Slovenia			
			Switzerland			