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EU-IBIS
European Union Invasive Bacterial Infections Surveillance Network

INVASIVE *HAEMOPHILUS INFLUENZAE* IN EUROPE 2003/2004

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SUMMARY

Introduction

EU-IBIS, a surveillance network for invasive *Haemophilus influenzae* (Hi) infections, continues to fulfil its aims to gather and improve epidemiological information about the disease, to integrate and analyse vaccination and molecular data, and to form the focus for a wider collaboration. The project has been collecting data since its inception in 1999, and is now accepting data from 24 European countries and two non-European ones, the former including seven of the ten countries which joined the European Union in May 2004, two of the others already being EU-IBIS participants. The countries which participate are Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Sweden, UK, and Australia and Israel. In addition, Spain does not submit data but contributes in other ways *eg* attendance at network meetings.

Methods

Participants have continued to submit a minimum dataset covering epidemiological, molecular and vaccination characteristics to the network, according to the EU agreed case definitions. The data was checked for internal consistency, then pooled and analysed for trends and for any notable geographical or temporal traits.

Results

Countries differed quite widely as to the extent of the serotype, clinical presentation and age group information captured by their respective surveillance systems. The most consistent indicator, and therefore the best comparator of disease burden between different countries, was the incidence of Hib meningitis in children. This varied in 2004 between 0.00 per 100,000 in children under 5 years of age in Finland, Iceland, Italy, Slovenia and Sweden, to 20.52 per 100,000 (12 cases) in Estonia, with the next highest incidences being 4.86 (1 case) in Malta and 1.37 (3 cases) in Ireland. The European average incidence in those under five years of age in 2004 was 0.64 per 100,000 population.

Overall Hi incidence continued to be low, averaging 0.50 per 100,000 across Europe in 2004 for the whole population (derived from countries collecting all Hi cases across all age groups) and 1.07 per 100,000 in the <15 year age group (derived from countries collecting all Hi cases occurring in <15's). Estonia experienced a much higher incidence of 8.34 per 100,000 in the latter category, but it, along with Poland, only introduced Hib vaccination into its routine childhood immunisation schedule in 2005. Although the burden of disease did decrease between 1999 and 2004 for most countries, there were some notable exceptions, particularly UK and Netherlands.

Invasive infections due to non-capsulated strains were common, particularly in those aged 15 years and above, though the highest incidence of non-capsulated infections occurred in children under five

years. Amongst non-b capsulated strains, serotype f and, to a lesser extent, serotype e were the most common.

For most countries, meningitis was generally the most common clinical presentation of Hi disease, presenting more often in <15y age group and particularly the <5 year olds. The proportion of cases presenting as bacteraemia was also high, and epiglottitis, which was rarely present in infants, became more common in toddlers. Serotype b infections were much more likely to cause meningitis, epiglottitis and cellulitis, while non-capsulated strains predominated in cases of pneumonia and septicaemia.

The case fatality ratio tended to vary quite markedly within countries over time, but this was due to the small number of cases involved. The European average between 1999 and 2004 was 8.34%. The case fatality ratio was highest in non-capsulated infections, and in cases of pneumonia and septicaemia.

Numbers of vaccine failure cases changed quite notably in Netherlands and UK between 1999 and 2004, over and above the changes seen in the number of overall Hi infections. The largest number of VF cases were found in the 5 – 9 year age group, though the numbers found in the 10 – 14 year age group increased with time, probably as an increasing proportion of this cohort would have received a full course of vaccination.

Conclusions

This project has demonstrated the successful development of existing networks towards the objective of providing high quality surveillance information on *Haemophilus influenzae* 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.

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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 European countries participating in the *H influenzae* (Hi) network are: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Spain, Slovak Republic, Slovenia, Sweden and UK. In addition, Australia and Israel have been contributing data to the Hi network, the former since 1996, and the latter since 1998.

Both countries participated in the BIOMED II project which was a predecessor of the EU-IBIS Hi network, alongside Finland, Germany, Greece, Ireland, Italy, Netherlands, Poland, Spain, Sweden, UK. The project ran from 1996-1998, and had very similar aims to that of the current network, namely to describe the epidemiology of invasive Hi disease, to evaluate the impact of vaccination programmes, to explore the risk of vaccine failure associated with different vaccine formulations/schedules, and to improve laboratory capacity to diagnose and characterise Hi infections.

Project aims related to *H influenzae* network

- To improve the epidemiological information on invasive disease caused by *H influenzae* within the EU
- To improve the laboratory capacity to accurately characterise the isolates of *H influenzae* using standardised methods
- To evaluate the impact of vaccination with conjugate vaccines on the epidemiology of *H influenzae*
- 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

The disease and the causative organism

Haemophilus influenzae (Hi) is a Gram negative bacterium exclusively pathogenic to humans and thus is in theory open to complete eradication. The organism is commonly present asymptomatically in the nasopharynx, where it may persist for months, and is generally spread by carriers *via* direct contact with oral secretions or respiratory droplets. In a susceptible host, certain strains can invade the bloodstream from the nasopharynx and disseminate to cause meningitis, septicaemia and other systemic illnesses. Hi infections can also present as pneumonia, epiglottitis, and other lower and upper respiratory tract infections. Hi strains are classified according to the presence or absence of a capsule, the main component of which is the polysaccharide polyribosylribitol phosphate (PRP), and which is a major determinant of virulence. Capsulated strains are further categorised on the basis of their biochemistry, antigenicity and reaction to specific antisera, serotypes a – f having been identified to date. Rates of infection and the burden of Hi disease worldwide might be significantly under-estimated due to unreliable reporting, undiagnosed sequelae and lack of healthcare and microbiological resources (Centers for Disease Control and Prevention. 2002, McVernon and Heath 2003, Peltola 2000, Shapiro and Ward 1991, World Health Organisation 1998a).

H influenzae serotype b (Hib) is an important cause of global invasive disease, with the vast majority of cases affecting children under 5 years of age, and about half these cases resulting in death or incurring significant sequelae. In the pre-vaccination era, Hib was responsible for almost all systemic disease caused by *H influenzae*, having been the most common cause of bacterial meningitis in those under five years of age, almost the sole cause of epiglottitis, and responsible for many cases of cellulitis and joint infections. In economically underdeveloped countries, Hib is also responsible for much acute respiratory illness, particularly pneumonia. In the developed world, the highest risk of acquiring an invasive Hib infection occurs between 6 and 18 months of age, younger infants being protected by passively-acquired maternal antibodies. Incidence peaked between the months October – November and March – May in the US and between November to January in Sweden. The few cases of non-type b infections in children tend to occur at a younger age and are more likely to present with pneumonia and bacteraemia. Incidence of overall Hi disease does not appear to have increased in countries in which Hib vaccine (see below) has been introduced, suggesting that the latter event has not opened an ecological niche that could be filled by non-type b strains, nor that serotype replacement is occurring. However, with increasing reports of virulent Hia and Hif strains isolated from different parts of the world, and the planned, hoped-for and actual expanding global use of conjugate vaccines, it is important to have systems in place to detect any emerging serotype replacement (Farhoudi *et al* 2005, McVernon and Heath 2003, Peltola 2000, Ribeiro *et al* 2003, Sarangi *et al* 2000, Shapiro and Ward 1991, World Health Organisation 1998b)

Another major cause of disease, albeit less often presenting as invasive infection, is non-capsulated Hi (ncHi). This affects both children and adults, but with age-related differences in disease presentation; otitis media tends to predominate in children, pneumonia in adults, and sinusitis occurring across all ages, though ncHi also causes pneumonia in children in underdeveloped

countries. Otitis media in children has been associated with deficits in language acquisition, speech development and cognitive function. People suffering from antibody deficiency are particularly susceptible to persistent and recurrent ncHi infections, and there is evidence that rates of recognised invasive ncHi infection are increasing (Barenkamp 2004, McVernon and Heath 2003, Murphy 2003, Sarangi *et al* 2000, World Health Organisation 1998c).

With regard to carriage, both Hib and ncHi strains are commonly carried in the nasopharynx, particularly in young children. Generally Hib carriage in adults is acquired by contact with young children, particularly preschool children, and the greater contact by mothers and other female relatives with such children has been suggested as a reason for the higher incidence of Hib infections seen in females as compared to males in the 25 – 44 year age group. Carriage rates of Hib can be higher than average in places of continual close contact, such as day-centres and households (Sarangi *et al* 2000, Shapiro and Ward 1991).

Case fatality rates vary with age, strain, region and pre-existing condition: invasive Hib case fatality rate is highest in the developing countries at around 25% for all ages, compared with about 5-10% for all ages in the developed countries. In older adults and immunocompromised individuals, invasive Hib infections can cause case fatality rates as high as 26%, and ncHi infections in adults with chronic obstructive pulmonary disease can also cause significant mortality (Bijlmer 1991, Murphy 2003, Peltola 2000, Shapiro and Ward 1991).

Antibiotics are essential for treatment, but have only a minor part to play in control. Development of bacterial resistance to some of the most efficient antibiotics underlines the need for prevention (World Health Organisation 1998d).

The characterisation of the organism

Identifying a case of Hi requires isolating the bacterium from a normally non-sterile body site, such as CSF, blood, joint fluid, pleural effusion or pericardial effusion, and a positive culture establishing the diagnosis. PCR and DNA sequencing strategies can also be very effectively used in laboratory diagnosis of an Hib infection. Antigen detection may be used as an adjunct to culture, particularly in diagnosing Hib infections in patients who have been partially treated with an antibiotic, which may result in the organism not being viable on culture. There are a number of options: latex agglutination, a rapid, sensitive, and specific method to detect Hib capsular polysaccharide antigen in CSF, or antigen testing of serum or urine. A negative result from the latex agglutination or antigen testing is not definitive, and false positives can occur, particularly when testing serum or urine. Hib meningitis is the form of invasive Hi disease most easily diagnosed in the laboratory (Centers for Disease Control and Prevention. 2002, Taha and Olcen 2004, World Health Organization 2001).

The polysaccharide and conjugate vaccines

The introduction of Hib conjugate vaccines has substantially reduced levels of Hib incidence in the countries which use them. In 2005, the conjugate vaccine was part of the routine childhood vaccination programme covering at least 80% of the population in more than 83 countries, and has resulted in the disease largely disappearing from Western Europe, North America, Australia and New Zealand.

Initially, polysaccharide vaccines consisting of the polysaccharide PRP derived from the Hib capsule were developed. Subsequently, conjugate vaccines were made by attaching this polysaccharide to a carrier protein to produce a more immunogenic vaccine. The proteins that have been used as conjugates include the diphtheria toxoid (PRP-D), the tetanus toxoid (PRP-T), the mutant diphtheria toxoid (HbOC (Hib oligosaccharide linked to CRM_{197}, or cross-reacting mutant diphtheria toxoid)), and the meningococcal outer membrane protein (PRP-OMP). The advantage of these conjugate vaccines is that, unlike their polysaccharide cousins, these vaccines are efficacious in early infancy, induce immunological memory, and lessen the extent of Hib carriage. Conjugate vaccines are given either singly, or in combination with other vaccines, for example the DTaP (diphtheria, tetanus, acellular pertussis) / IPV (inactivated polio) / Hib vaccine, the DTwP (diphtheria, tetanus, whole cell pertussis) / HbOC (Hib) vaccine, and the HBV (Hepatitis B virus) / Hib vaccine (Leino *et al* 2002, McVernon and Heath 2003, Peltola 2000, World Health Organization 1998).

Routine childhood vaccine schedules differ quite markedly from country to country, with some countries using 2 doses in the first year of life and a booster in late infancy or later, others using 3 doses in the first year of life with a booster in the second, and a few giving 3 doses in the early infancy and no booster dose. Schedules within countries have changed with time, both in terms of timing of doses, and the actual vaccines used. This is due either to the availability of vaccine, or because of movement towards an optimised overall schedule ((Hviid and Melbye 2004, McVernon *et al* 2004).

Despite the high reported vaccine effectiveness of Hib conjugate vaccination, a resurgence of Hib disease has been seen in both UK and, to a smaller extent, Netherlands. The rise in the former, which began in 1999, about seven years after introduction of Hib conjugate vaccination, peaked in 2002, and was ascribed to a combination of factors. These included waning immunity in the absence of a booster dose in the second year of life, and use of acellular pertussis vaccine, which has been associated with lessened immunogenecity of the Hib component. Neither of these conditions apply to the Netherlands, which saw a sudden increase in Hib incidence in 2002, 3-fold greater than that seen in the 6 previous years and that has been sustained in the years following. It has been suggested that changes in population immunity may be the most important factors in both countries. For example, reduction of Hib carriage in children caused by Hib conjugate vaccination has resulted in a lack of natural boosting of immunity in adults. This in turn has led to accumulation of susceptibles sufficient to allow increased Hib transmission and thus a much greater level of exposure to potentially invasive Hib

strains by highly susceptible individuals. There is evidence of an abrupt increase in the genetic diversity of Hib strains after introduction of the vaccine (Heath and Ramsay 2003, Schouls *et al* 2005).

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 invasive *Haemophilus influenzae* annually, using the currently agreed EU case definition (see Table 1), except that information on all serotypes is collected, rather than just serotype b.

Table 1 EU standard case definition

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

Confirmed case

A clinically compatible case diagnosed by one of the following laboratory criteria:

Isolation of *Haemophilus influenzae* b from a normally sterile site

Detection of *H influenzae* nucleic acid from a normally sterile site

Probable case

A clinically compatible case diagnosed by the following laboratory criteria:

Detection of *H influenzae* antigen from normally sterile site.

Possible case

A case with clinical epiglottitis without any laboratory confirmation or with identification only from non-sterile site

The agreed minimum dataset comprises information on age, sex, date of onset, method of laboratory confirmation, site of identification, serotype and vaccination status. However, not all countries record all cases of invasive *Haemophilus influenzae*; for example, Australia and Czech Republic report only cases of serotype b *H influenzae* (Hib) disease, and not Hi disease caused by other serotypes; Germany and Israel do not report adult cases; Poland and Denmark report primarily cases of meningitis and much more rarely those with other disease presentations. In addition, some countries, such as Belgium and France, have two separate reporting systems, one based on surveillance data and the other on samples being submitted to the Reference Laboratory. The surveillance reporting system in each country has better ascertainment, but does not record information such as serotype or vaccination status. A further complication arises when considering temporal trends due to the changes that some countries have made over time with regard to the data being captured. For example before 2002, Sweden reported only invasive Hi cases present in those under 15 years of age, but since then all ages have been monitored, and before 2003 Estonia recorded cases of only of Hi septicaemia, but since then all presentations are reported. Thus, when comparing records across Europe, caution needs to be taken. Table 2 indicates the sources and coverage of the data submitted to EU-IBIS, and Appendix I outlines the data variables requested.

Table 2 Sources and coverage of data submitted to EU-IBIS

Country	Primary source of data to EU-IBIS	Years for which data available	Serotype	Geographic coverage	Age coverage	Disease presentation
Australia	National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (Surveillance Centre)	1996 – 2004	b	All	1996 – 1999: All 2000 – 2004 < 15 years	All
Austria	National Reference Centre for Meningococci, Pneumococci and Haemophilus influenzae (Reference Laboratory)	2002 – 2004	All	All	All	All
Belgium	Scientific Institute of Public Health (Surveillance Centre)	2000 – 2004	Not determined	All	All	All
	Institut Jules Bordet (Reference Laboratory)	2003	Not determined	All	All	All
Czech Republic	Center of Epidemiology and Microbiology (Surveillance Center and Reference Laboratory)	1999 – 2004	b	All	All	All
Denmark	Statens Serum Institut (Surveillance Centre and Reference Laboratory)	1999 – 2004	All	All	All	Meningitis
Estonia	Health Protection Inspectorate (Surveillance Centre and Reference Laboratory)	1999 – 2004	All	All	<15 years	1999-2003: Septicaemia 2004: All
Finland	National Public Health Institute (Surveillance Centre and Reference Laboratory)	1996 – 2004	All	All	All	All
France	Institut de Veille Sanitaire (Surveillance Centre)	1999 – 2004	Not determined	All *	All	Meningitis, septicaemia
	Centre Hospitalier Universitaire de Toulouse (Reference Laboratory)	1999 – 2004	All	All (known to be under-reported)	All	All
Germany	Robert Koch Institute (Surveillance Centre) ESPED (Reference Laboratory)	1998 – 2004	All	All	<15 years	All
Greece	“Aghia Sophia” Children’s Hospital (Surveillance Centre and Reference Laboratory)	1996 – 2004	mainly b, non-b	1996 - 2002 Attiki, 2003 - 2004 All	All	All
Hungary	Johan Bela National Centre for Epidemiology	2003 – 2004	Not determined	All	All	Meningitis, septicaemia
Iceland	Centre for Infectious Disease Control (Surveillance Centre)	1999 – 2004	All	All	All	All
Ireland	Health Protection Surveillance Centre	1996 – 2004	All	All	All	All
Israel	Paediatric Infectious Disease Unit (Surveillance Centre and Reference Laboratory)	1998 – 2004	All	All	<13 years	All
Italy	Istituto Superiore di Sanità (Surveillance Centre and Reference Laboratory)	1996 – 2004	All	1996 - 2002 All routine; enhanced 7 regions 2003 - 2004 All	All	All
Latvia	State Public Health Agency (Surveillance Centre)	2003 – 2004	Not determined	All	All	All
Lithuania	Centre for Communicable Diseases Prevention and Control	2003 – 2004#	Not determined	All	All	Meningitis, septicaemia
Malta	Disease Surveillance Unit (Surveillance Centre)	1999 – 2004	All	All	All	Meningitis, septicaemia

Country	Primary source of data to EU-IBIS	Years for which data available	Serotype	Geographic coverage	Age coverage	Disease presentation
Netherlands	National Institute for Public Health and the Environment (Surveillance Centre)	1996 – 2004	All	All	All	All
Norway	Norwegian Institute of Public Health	1999 – 2004	All	All	All	All
Poland	National Institute for Public Health (Reference Laboratory)	1997 – 2004	All	All	All	Mainly meningitis
Portugal	Instituto Nacional de Saúde Dr Ricardo Jorge (Reference Laboratory)	1999 – 2004	All	All	All	All
Slovak Republic	Public Health Authority of the Slovak Republic (Surveillance Centre)	1999 – 2004	Not determined	All	All	All
Slovenia	Institute of Public Health Slovenia (Surveillance Centre and Reference Laboratory)	2000 – 2004	All	All	All	All
Spain	Instituto de Salud Carlos III (Surveillance Centre and Reference Laboratory)	1996 – 1998	mainly b	Valencia	<5 years	All
Sweden	Swedish Institute for Infectious Disease Control (Surveillance Centre and Reference Laboratory)	1999 – 2004	b	All	1999 <15 years 2000 – 2004: All~	All
United Kingdom	Health Protection Agency (Surveillance Centre and Reference Laboratory (not Scotland)	1996 – 2004	All	All	All	All
	Health Protection Scotland (Surveillance Centre) (Scotland)	1999 – 2004	All	All	All	All

* Aggregated data corrected for under-reporting and under-coverage
~ 2000 – 2001 Aggregated data
# 2003 – Case-based data for meningitis only; otherwise aggregate

External Quality Assurance Scheme (EQAS)

An EQAS was carried out in 2005/2006, and the results of this will be reported in the 2005 Annual Report.

Website development

Work to upgrade the existing EU-IBIS website (www.euibis.org) has been ongoing since August 2003, and now includes better navigation and links to general information for *Haemophilus influenzae* and meningitis in general.

Dissemination of results/meetings

A three day Hi workshop and business meeting was held in February 2006, and this will be reported on in the 2005 Annual Report.

RESULTS

The EU-IBIS database now holds just under 13,500 case reports of Hi disease occurring between 1996 and 2004. Of these, about 7,300 were submitted by 8 countries (Australia, Finland, Greece, Ireland, Italy, Netherlands, Sweden and UK) covering the years 1996 – 2004; just under 5,500 cases were reported by a further 12 countries (Czech Republic, Denmark, Estonia, France, Germany, Iceland, Israel, Malta, Norway, Poland, Portugal, Slovak Republic) for the years 1999 – 2004; and 540 cases have been reported by another 7 countries (Austria, Belgium, Hungary, Latvia, Lithuania, Slovenia, Spain).

As can be seen from Table 1, great care must be taken when comparing incidence rates and trends across countries, as only 9 countries collect and serotype all cases of invasive Hi disease, a further three countries collecting all data but not determining serotype of the causative Hi organism. Thus, most analyses are restricted by age (those under 5 years of age, those under 15 years of age, and those 15 years and above), serotype (b, non-b capsulated, non-capsulated), and/or clinical presentation. Care must also be taken when analysing trends from 1999 to 2004, as the data from six countries do not completely cover this period. The populations used to calculated incidence rates are given in the Appendix IV.

A. Vaccination schedules

Table 3 indicates for each country the year of introduction of conjugate Hib vaccine, and the childhood immunisation schedule in place in 2004. Further information is given on the EU-IBIS website at http://www.euibis.org/haemoph/vacc_sched_hib.htm.

Table 3 Year of introduction of conjugate Hib vaccination and childhood immunisation schedule in 2004

Country	Year of Hib introduction	Vaccine given	Combined with	Immunisation schedule
Austria	1994	Hib-PRP-T (Infanrix hexa, GSK) Hib-PRP-T (Hexavac, Aventis Pasteur)	DTaP, IPV, HBV DTaP, IPV, HBV	3, 4, 5 months & 2nd year of life 3, 4, 5 months & 2nd year of life
Belgium	1993	Hib-PRP-T (Infanrix hexa GSK)	DTaP, IPV, HBV,	2,3,4 months & 13-18 months
Czech Republic	2001	Hib-PRP-T (TetrAct-HIB, Aventis Pasteur)	DTwP	2, 3, 4 months & 18-20 months
Denmark	1993	Hib-PRP-T (ActHIB, Aventis Pasteur)	DTaP, IPV	3, 5, 12 months
Estonia	2005			
Finland	1986	Hib-PRP-T (Hiberix, GSK)		4, 6 & 14-18 months
France	1992	Hib-PRP-T (Hexavac, Aventis Pasteur)	DTaP, IPV, HBV	2, 4, 18 months (vaccine with 5 antigens at 3 months of age)

Country	Year of Hib introduction	Vaccine given	Combined with	Immunisation schedule
Germany	1990	Hib-PRP-T (Infanrix hexa, GSK)	DTaP, IPV, HBV	2, 3, 4 months, plus 11-14 months
		Hib-PRP-T (Hexavac, Aventis Pasteur)	DTaP, IPV, HBV	2, 3, 4 months, plus 11-14 months
Greece	1999	Hib-PRP-T (ActHIB, Aventis Pasteur Hiberix, GSK)	(DTaP, IPV/OPV, HBV also given)	2, 4, 6, 15-18 months
Hungary	1999	Hib-PRP-T (ActHIB, Aventis Pasteur Hiberix, GSK)	DTaP, IPV, HBV	2, 4, 6, 15-18 months
		HbOC (HibTITER, Wyeth Lederle)		2, 4, 6, 15-18 months
		Hib-PRP-OMP (Procomvax, Sanofi Pasteur)	HBV	On special occasions, by case
Iceland	1989	Hib-PRP-T (Pentavac, Aventis Pasteur)	DTaP, IPV	3, 5, 12 months
Ireland	1992	Hib-PRP-T (Infanrix-IPV+Hib, GSK) (75-80%) (Pentavac, Aventis Pasteur) (20-25%)	DTaP, IPV	2, 4, 6 months
Italy	1995 (1999 included in routine schedule)	Hib-PRP-T	DTaP, IPV, HBV	3, 5, 11-12 months
Latvia	1994		DTaP, IPV (1st, 2nd dose) DTaP, IPV, HBV (3rd dose)	3, 4-5, 6 months
Lithuania	2004	Hib-PRP-T (PentAct-Hib, Aventis Pasteur)	DTaP, IPV (1st, 2nd dose) DTaP, IPV, HBV (3rd dose)	2, 4, 6, 18 months
Malta	1996	Hib-PRP-T (ActHIB, Aventis Pasteur)	DTwP (OPV also given)	2, 3, 4 months
Netherlands	1993	Hib-PRP-T	DTwP, IPV	2, 3, 4, 11 months
Norway	1992	Hib-PRP-T (Infanrix-IPV+Hib. GSK)	DTaP, IPV	3, 5, 11-12 months
Poland	2005			
Portugal	2000	Hib-PRP-T (Hiberix, GSK)		3, 5, 11-12 months
Slovak Republic	2000	Hib	DTwP, HBV,	3, 5, 11 months
Slovenia	2000	Hib	DTaP, IPV	3, 4, 5, 12-18 months
Spain	1996	Hib-PRP-T (ActHIB, Aventis Pasteur Hiberix, GSK)		2, 4, 6, 15-18 months
		Hib-PRP-T (Infanrix-Hib, GSK)	DTaP	2, 4, 6, 15-18 months
		Hib-PRP-T (TetrAct-Hib, Aventis Pasteur)	DTwP	2, 4, 6, 15-18 months
		Hib-PRP-T (PentAct-Hib, Aventis Pasteur)	DTwP, IPV	2, 4, 6, 15-18 months
Sweden	1992	Hib-PRP-T (Pentvac, Aventis Pasteur Infanrix-IPV+Hib, GSK)	In 5 valent combination vaccines	3, 5, 12 months
United Kingdom	1992	Hib-PRP-T	DTwP, changed to DTaP, IPV in September 2004	2, 3, 4 months
Australia	1993	Hib-PRP-OMP (PedvaxHIB, Merck)	DTaP, HBV (OPV also given)	2, 4, 12 months
		Hib-PRP-OMP (Comvax, Merck) (3 states)	HBV	2, 4, 12 months
Israel	1994	Hib-PRP-T	DTaP, IPV	2, 4, 12 months
		plus Hib-PRP-T	plus DTaP	6 months

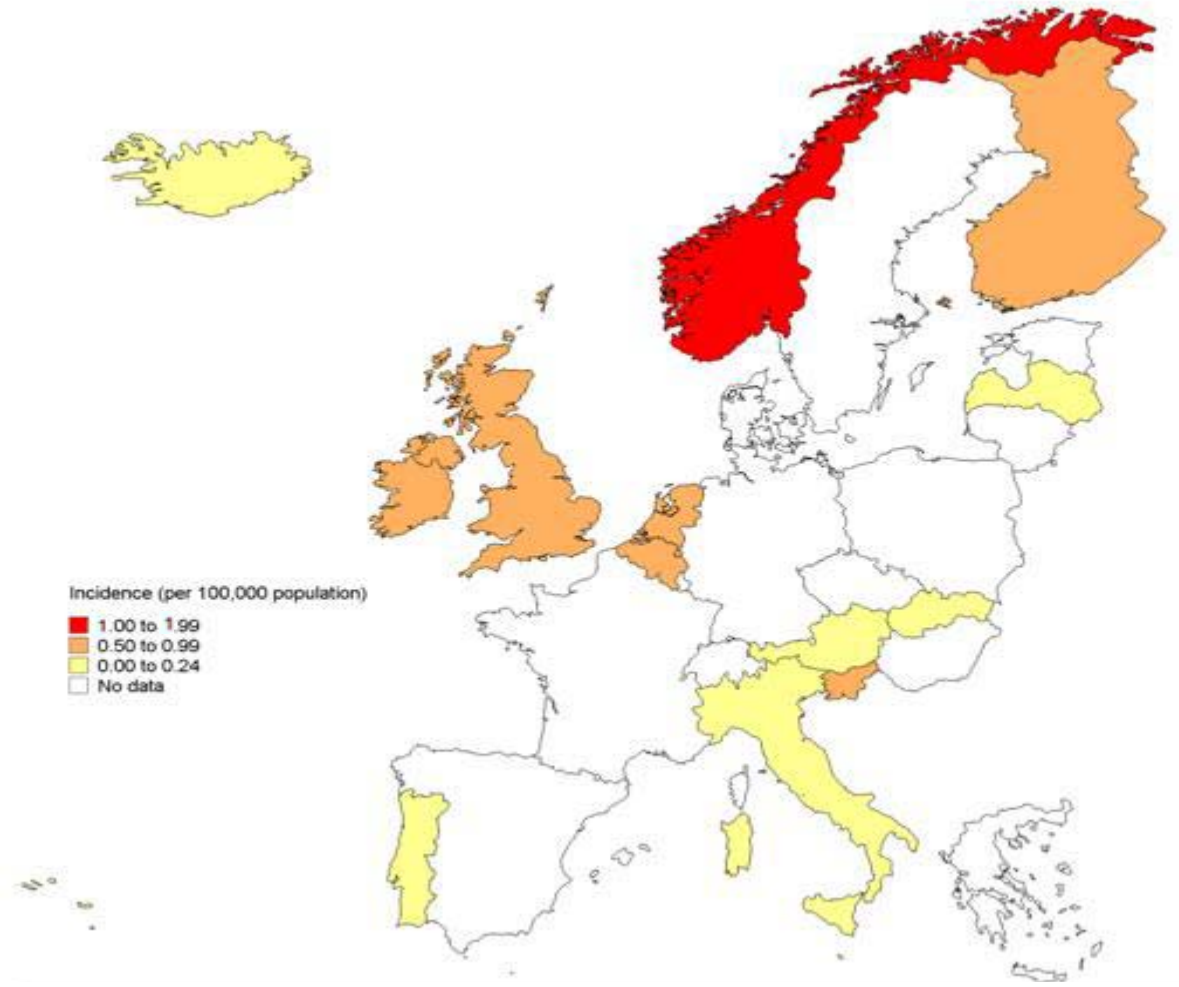
As can be seen from Table 3, there is much variety in: the particular vaccines used by different countries; the other vaccines given in conjunction with the Hib vaccine; and the ages at which the vaccine is given. Differences between countries are at least partly due to individual healthcare systems, established immunisation practice and cost (Guerin and Roure 1995), though the development and availability of new vaccine products, particularly combination vaccines, has also resulted in divergence of immunisation schedules between different countries.

B. Epidemiology

Overall *Haemophilus influenzae* incidence

Figure 1 shows the incidence of all Hi disease in participating countries which collect all cases of invasive Hi in all countries, and the incidence and number of cases of *Haemophilus influenzae* disease in all countries are shown in Table 4.

Figure 1 Total incidence (per 100,000 population) of confirmed and probable Haemophilus influenzae disease in participating countries which collect all cases of invasive Hi, 2004



There was a clear geographic trend in invasive Hi incidence, with northern European countries tending to experience higher rates than those in the south (Barquet *et al* 1996). The overall European incidence, derived from countries which collected all cases of invasive Hi in all ages groups in 2004, was 0.50. Norway had a relatively high incidence of 1.70, the rates in all the other countries being below 1 per 100,000 population.

Table 4 Incidence (per 100,000 population) (number of cases) of confirmed and probable Haemophilus influenzae disease in all participating countries, 1999 - 2004

Country	1999	2000	2001	2002	2003	2004	Comments
Austria	-	-	-	0.05 (4)	0.05 (4)	0.13 (11)	
Belgium	-	0.61 (63)	0.52 (54)	0.63 (65)	0.53 (55)	0.56 (58)	
Czech Republic	1.00 (103)	1.02 (105)	0.90 (92)	0.55 (56)	0.49 (50)	0.16 (16)	Serotype b only
Denmark	0.09 (5)	0.04 (2)	0.02 (1)	0.02 (1)	0.07 (4)	0.07 (4)	Meningitis only
Estonia	1.15 (3)	0.40 (1)	1.24 (3)	1.28 (3)	0.44 (1)	8.34 (18)	<15 years, 1999-2003 septicaemia only
Finland	0.56 (29)	0.72 (37)	0.95 (49)	0.44 (23)	0.69 (36)	0.50 (26)	
France~	0.87 (521)	0.93 (565)	0.98 (598)	0.78 (479)	0.89 (546)	0.99 (608)	Meningitis or septicaemia only
Germany	0.33 (42)	0.57 (73)	0.45 (57)	0.38 (47)	0.37 (46)	0.26 (32)	<15 years only
Greece	0.05 (2)	0.08 (3)	0.05 (2)	0.20 (8)	0.07 (8)	0.08 (9)	1999–2002 Attiki only
Hungary	-	-	-	-	0.07 (7)	0.12 (12)	Meningitis or septicaemia only
Iceland	1.44 (4)	0.36 (1)	0.70 (2)	0.00 (0)	0.00 (0)	0.00 (0)	
Ireland	0.72 (27)	0.55 (21)	0.70 (27)	0.56 (22)	0.53 (21)	0.94 (38)	
Italy	0.19 (109)	0.11 (64)	0.05 (31)	0.03 (19)	0.04 (24)	0.02 (9)	
Latvia	-	-	-	-	0.13 (3)	0.04 (1)	
Lithuania	-	-	-	-	0.17 (6)	0.23 (8)	Meningitis or septicaemia only
Malta	0.00 (0)	0.26 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.75 (3)	Meningitis or septicaemia only
Netherlands	0.43 (68)	0.49 (77)	0.57 (91)	0.67 (108)	0.82 (132)	0.78 (127)	
Norway	1.62 (72)	1.27 (57)	1.09 (49)	1.57 (71)	1.69 (77)	1.70 (78)	
Poland	0.06 (25)	0.08 (31)	0.09 (35)	0.09 (33)	0.09 (36)	0.08 (32)	Meningitis principally
Portugal	0.08 (8)	0.10 (10)	0.15 (15)	0.12 (12)	0.13 (14)	0.10 (11)	
Slovak Republic	0.35 (19)	0.28 (15)	0.20 (11)	0.13 (7)	0.17 (9)	0.07 (4)	
Slovenia	-	0.65 (13)	0.85 (17)	0.40 (8)	0.65 (13)	0.70 (14)	
Sweden#	0.37 (6)	0.34 (30)	0.21 (19)	0.25 (22)	0.27 (24)	0.41 (37)	1999 <15 years only
United Kingdom	0.68 (400)	0.85 (498)	1.03 (605)	1.28 (757)	1.26 (750)	0.92 (550)	
Overall incidence*	0.47 (736)	0.50 (780)	0.56 (880)	0.64 (1019)	0.67 (1063)	0.52 (843)	
Australia	0.14 (27)	0.07 (14)	0.09 (17)	0.08 (15)	0.06 (12)	0.06 (12)	Serotype b only
Israel	0.35 (6)	0.90 (16)	1.31 (24)	1.07 (20)	1.27 (24)	0.93 (18)	<13 years only

~ Disaggregated data # Disaggregated data for 2000, 2001

* Incidence derived from European countries with consistent data 1999-2004 and recording all cases of invasive Hi disease, these being Finland, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Slovak Republic, UK

As noted earlier, not all countries record all cases of invasive Hi disease, and the restrictions on surveillance in different countries are noted in Table 4. Allowing for the different methods of surveillance, rates of invasive Hi disease have remained fairly constant with time in most other countries, though small increases were seen in Austria, Netherlands, Ireland and UK. Estonia, however, experienced a marked increase in incidence in 2004 to 8.5 per 100,000 population (Table 4). This incidence (which occurred in those under 15 years of age) was probably explained by improved ascertainment, as prior to this only cases of bacteraemia were reported. Estonia did not introduce

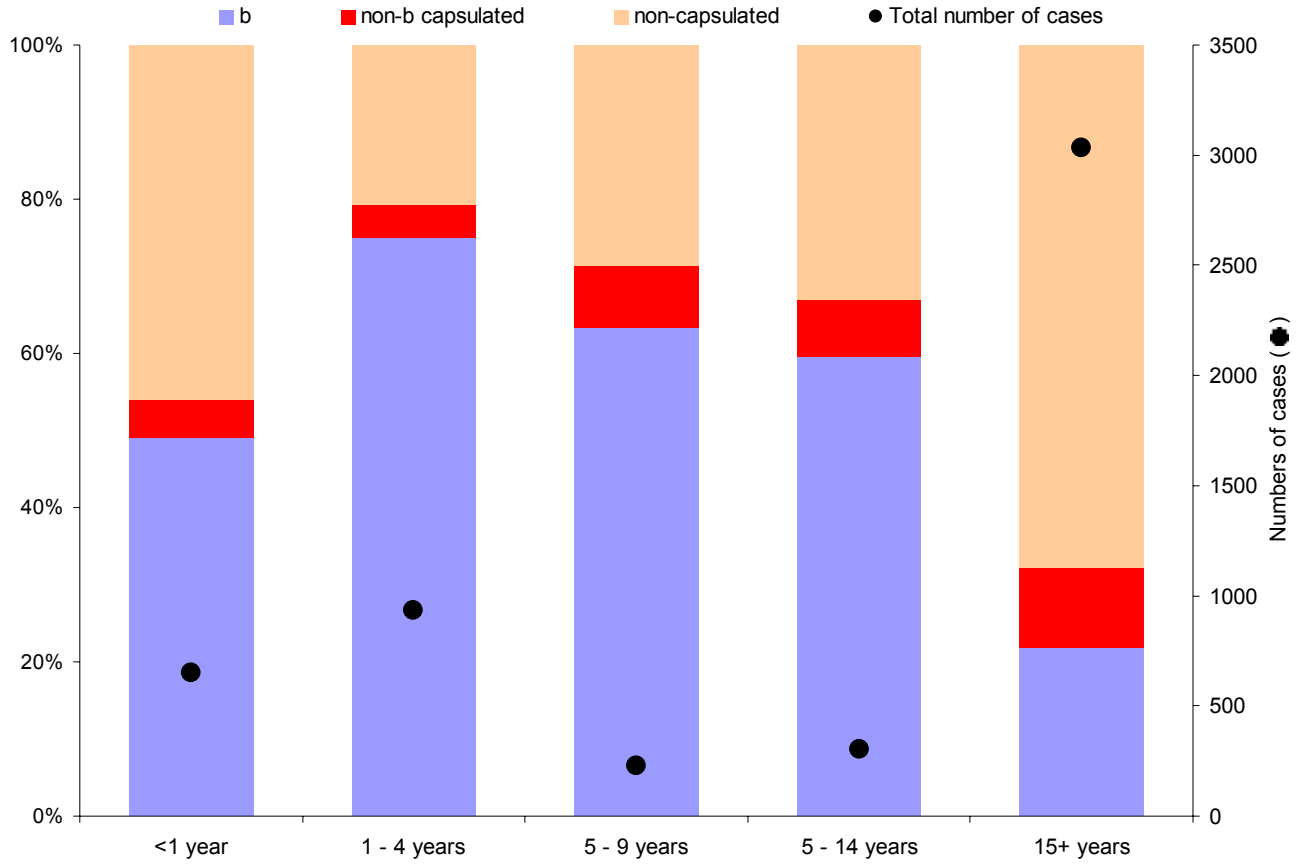
conjugate Hib vaccination until 2005, whereas most other countries have been using conjugate vaccination for at least 2 years, and for many countries much longer. Sustained reductions in incidence were seen both in the Czech Republic and in Italy.

Haemophilus influenzae serotypes

Figures 2–4 and Tables 5-6 analyse the association between serotypes causing invasive Hi infections and age.

Figure 2 indicates the distribution of serotype with age, and includes those countries which record all serotypes and ages.

Figure 2 *Serotype distribution of confirmed and probable* Haemophilus influenzae *cases by age group, all countries and years combined, 1999 - 2004*



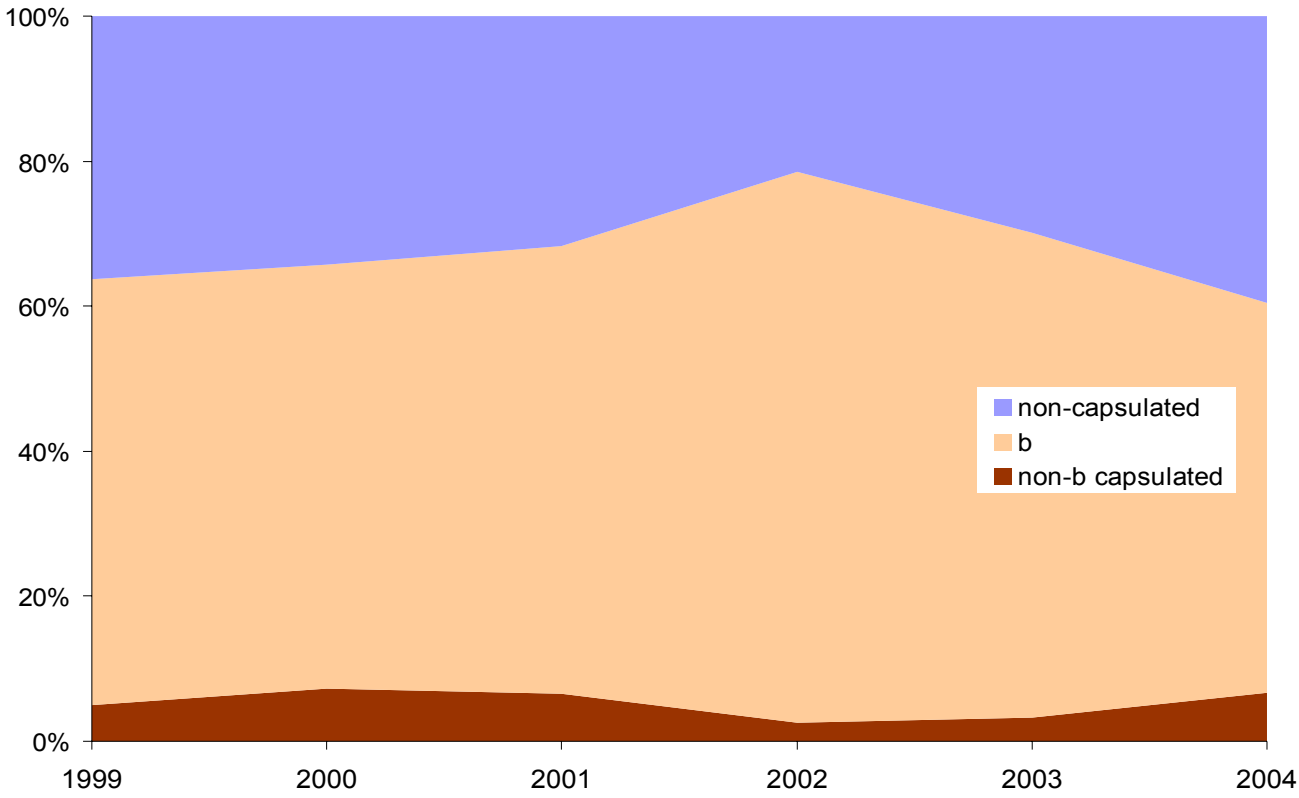
Data derived from countries which record all cases of invasive Hi disease in all age groups, these being Austria, Estonia, Finland, France (Reference Laboratory), Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, United Kingdom

Figure 2 shows that there is a clear pattern to serotype distribution with age, with a much greater proportion of non-capsulated serotypes being associated with 15 years and above (15+y) age group than in the younger age groups. In contrast, serotype b infections predominate in the younger age groups. The proportion of cases due to non-b capsulated serotypes tended to be higher in those five years of age and above, and the total number of cases was much higher in the 15+y age group than in

the <15y. Interestingly, there was a lower proportion of serotype b cases in <1y's than in either <5y's or <15y's.

Figure 3 illustrates the change in serotype distribution with time in the <15y age group. It uses the same dataset as for Figure 2.

Figure 3 Serotype distribution of confirmed and probable Haemophilus influenzae *cases in <15 year age group, all countries combined, 1999 – 2004*

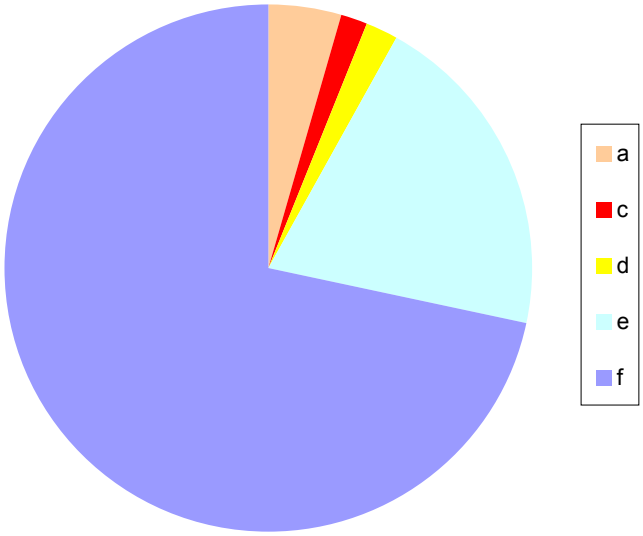


Data derived as in Figure 2

The serotype distribution changed over time, at least in the <15y's, as can be seen in Figure 3; the proportion of cases due to serotype b increased from 1999 to 2003, then decreased sharply, with the proportion of cases due to non-capsulated strains changing proportionately. The level of non-b capsulated infections did not greatly vary with time.

Figure 4 shows the distribution of non-b capsulated serotypes, these comprising mainly serotypes f and, to a lower extent, e.

Figure 4 *Non-b capsulated serotype distribution of confirmed and probable* Haemophilus influenzae *cases by age group, all countries and years combined, 1999 – 2004*



Data derived from countries as for Figure 2

Table 5 delineates the number of Hi cases caused by the different serogroups in children by country, age group and year for 1999, 2003, and 2004, and Table 6 shows the same data for adults. Table A3 in Appendix IV displays the same data for all years between 1999 and 2004

Table 5 *Serotype distribution of confirmed and probable* Haemophilus influenzae *cases in children by age and country, 1999 (or earliest year), 2003, 2004*

Country	Year	Numbers of cases									Incidence
		<5 years				5-14 years					<15 years
		b	non-b caps	non-caps	NK	b	non-b caps	non-caps	NK	Total cases	Total
Austria	2002	1	0	0	1	1	0	0	0	3	0.23
Austria	2003	1	0	0	0	0	0	0	0	1	0.08
Austria	2004	1	0	0	1	0	0	0	2	4	0.31
Czech Republic #	1999	85	-	-	-	12	-	-	-	97	5.68
Czech Republic #	2003	27	-	-	0	11	-	-	2	40	2.57
Czech Republic #	2004	7	-	-	-	8	-	-	-	15	0.96
Denmark	1999	1	0	1	0	0	0	0	0	2	0.21
Denmark	2003	1	0	1	0	0	0	0	1	3	0.30
Denmark	2004	1	0	0	0	0	0	0	0	1	0.10
Estonia	1999	2	0	0	0	1	0	0	0	3	1.15
Estonia	2003	1	0	0	0	0	0	0	0	1	0.44
Estonia	2004	17	0	0	0	1	0	0	0	18	8.34
Finland	1999	2	0	1	0	1	1	0	0	5	0.53
Finland	2003	4	0	2	0	2	0	1	0	9	0.83
Finland	2004	0	0	1	0	0	0	0	0	1	0.11

b b serotype *non-caps* non-capsulated serotype *non-b caps* non-b capsulated serotype
NK serotype not known

Country	Year	Numbers of cases									Incidence
		<5 years				5-14 years					<15 years
		b	non-b caps	non-caps	NK	b	non-b caps	non-caps	NK	Total cases	Total
France *	1999	5	3	7	1	0	0	3	0	19	0.17
France *	2003	14	1	7	0	0	1	4	0	27	0.23
France *	2004	10	1	12	1	0	1	7	0	32	0.28
Germany	1999	10	4	11	10	3	1	1	2	42	0.33
Germany	2003	18	2	10	7	1	3	3	2	46	0.37
Germany	2004	4	4	11	5	3	0	4	1	32	0.26
Greece (Attiki)	1999	1	1	0	0	0	0	0	0	2	0.12
Greece	2003	5	0	0	0	2	0	0	0	7	0.44
Greece	2004	4	0	0	0	0	0	0	1	5	0.31
Ireland	1999	3	0	1	0	1	0	0	1	6	0.72
Ireland	2003	8	0	3	0	1	0	0	0	12	1.44
Ireland	2004	9	0	1	0	0	1	2	0	13	1.54
Italy	1999	39	0	1	29	2	0	1	2	74	0.91
Italy	2003	5	0	1	0	1	0	1	0	8	0.10
Italy	2004	0	0	1	2	1	0	0	0	4	0.05
Malta	2004	1	0	1	0	0	0	0	0	2	2.74
Netherlands	1999	7	2	11	0	1	0	8	0	29	0.99
Netherlands	2003	15	2	27	0	4	1	2	0	51	1.69
Netherlands	2004	14	0	20	0	3	0	1	0	38	1.26
Norway	1999	2	0	6	0	0	0	1	0	9	1.02
Norway	2003	0	1	1	0	0	0	2	0	4	0.44
Norway	2004	1	0	2	3	0	1	1	1	9	0.99
Poland	1999	20	0	0	1	3	0	0	0	24	0.31
Poland	2003	31	0	0	0	3	0	0	0	34	0.51
Poland	2004	20	0	0	0	6	1	0	0	27	0.42
Portugal	1999	2	0	0	1	0	0	0	0	3	0.18
Portugal	2003	1	0	2	0	1	0	1	0	5	0.30
Portugal	2004	1	1	1	0	1	0	0	0	4	0.24
Slovenia	2000	4	0	3	0	1	0	0	0	8	2.52
Slovenia	2003	0	0	3	0	0	0	0	0	3	1.02
Slovenia	2004	0	0	1	0	0	0	1	0	2	0.69
Sweden #	1999	5	-	-	-	1	-	-	-	6	0.37
Sweden #	2003	5	-	-	-	2	-	-	-	7	0.45
Sweden #	2004	1	-	-	-	2	-	-	-	3	0.19
United Kingdom	1999	35	3	34	17	4	0	5	4	102	0.90
United Kingdom	2003	137	5	51	10	32	2	12	3	252	2.31
United Kingdom	2004	45	8	59	12	24	6	6	2	162	1.49
Overall European ^	1999	118	10	66	50	14	1	18	7	288	0.61
Overall European ^	2003	222	9	97	10	46	4	23	3	414	0.86
Overall European ^	2004	123	10	99	19	36	10	18	6	321	0.67
Australia #	1999	20	-	-	-	2	-	-	-	22	0.56
Australia #	2003	10	-	-	-	2	-	-	-	12	0.30
Australia #	2004	6	-	-	-	6	-	-	-	12	0.30
Israel	1999	6	0	0	0	0	0	0	0	6	0.35
Israel	2003	4	1	14	2	1	0	2	0	24	1.27
Israel	2004	10	1	5	2	0	0	0	0	18	0.93

b b serotype *non-caps* non-capsulated serotype *non-b caps* non-b capsulated serotype
NK serotype not known

Table 6 Serotype distribution of confirmed and probable Haemophilus influenzae *cases in adults (15 years of age or older) by age and country, 1999 (or earliest year), 2003, 2004*

Country	Year	Numbers of cases					Incidence
		b	non-b capsulated	non-capsulated	Not known	Total cases	
Austria	2002	1	0	0	0	1	0.01
Austria	2003	0	1	2	0	3	0.04
Austria	2004	1	1	2	3	7	0.10
Czech Republic #	1999	6	-	-	-	6	0.07
Czech Republic #	2003	5	-	-	5	10	0.12
Czech Republic #	2004	1	-	-	-	1	0.01
Denmark	1999	3	0	0	0	3	0.07
Denmark	2003	0	0	1	0	1	0.02
Denmark	2004	0	0	1	2	3	0.07
Finland	1999	4	4	12	4	24	0.57
Finland	2003	2	5	20	0	27	0.65
Finland	2004	1	0	20	4	25	0.58
France *	1999	5	6	26	0	37	0.08
France *	2003	5	4	55	1	65	0.13
France *	2004	1	6	53	0	60	0.12
Greece (Attiki)	1999	0	0	0	0	0	0.00
Greece	2003	1	0	0	0	1	0.01
Greece	2004	4	0	0	0	4	0.04
Ireland	1999	3	1	6	11	21	0.72
Ireland	2003	4	2	3	0	9	0.29
Ireland	2004	9	2	6	8	25	0.78
Italy	1999	9	0	11	15	35	0.07
Italy	2003	2	1	8	5	16	0.03
Italy	2004	1	0	3	1	5	0.01
Malta	2004	1	0	0	0	1	0.31
Netherlands	1999	4	0	35	0	39	0.30
Netherlands	2003	15	5	61	0	81	0.61
Netherlands	2004	30	6	53	0	89	0.67
Norway	1999	3	0	60	0	63	1.77
Norway	2003	4	11	27	31	73	2.00
Norway	2004	8	10	24	27	69	1.88
Poland	1999	0	0	0	0	0	0.00
Poland	2003	1	0	0	0	1	0.00
Poland	2004	1	0	4	0	5	0.02
Portugal	1999	0	0	0	3	3	0.04
Portugal	2003	2	0	7	0	9	0.10
Portugal	2004	2	1	4	0	7	0.08
Slovenia	2000	3	0	2	0	5	0.30
Slovenia	2003	1	1	8	0	10	0.59
Slovenia	2004	2	5	5	0	12	0.70
Sweden #	1999	0	-	-	-	0	0.00
Sweden #	2003	17	-	-	-	17	0.23
Sweden #	2004	34	-	-	-	34	0.46

b b serotype *non-caps* non-capsulated serotype *non-b caps* non-b capsulated serotype
NK serotype not known

Country	Year	Numbers of cases					Incidence
		b	non-b capsulated	non-capsulated	Not known	Total cases	
United Kingdom	1999	32	14	144	102	292	0.62
United Kingdom	2003	126	41	220	104	491	1.01
United Kingdom	2004	101	30	162	90	383	0.78
Overall European ^	1999	60	25	294	135	514	0.24
Overall European ^	2003	163	71	411	141	786	0.33
Overall European ^	2004	162	61	336	133	692	0.30
Australia #	1999	5	-	-	-	5	0.03
Australia #	2003	0	-	-	-	0	0.00
Australia #	2004	0	-	-	-	0	0.00

b b serotype *non-caps* non-capsulated serotype *non-b caps* non-b capsulated serotype
NK serotype not known

Total Hi numbers is for serotype b only
* Reference laboratory data
~ Total numbers of cases are for <15 years of age only
^ Data derived from countries as listed in Figure 3

The numbers of infections occurring in each country and each age group did not generally change with time, with some notable exceptions; with incidence in the Czech Republic and Italy decreased, and that in Estonia, Netherlands and UK increased. The slight increases noted earlier in Austria was not consistently reflected across any age group or serotype and might be due to random variation, and it would be interesting to note the level of the 2005 figures.

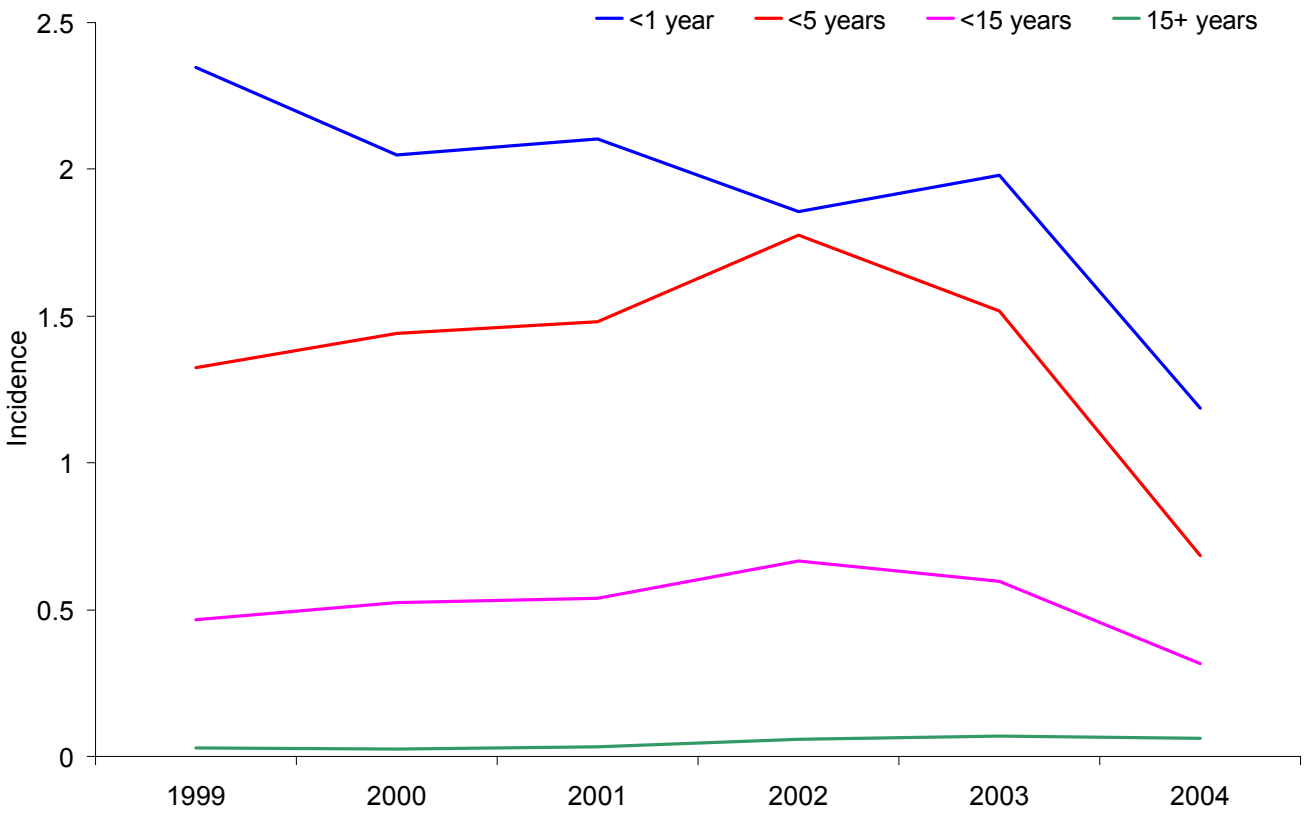
The decrease between 1999 and 2004 in incidence in the Czech Republic, which reports only Hib disease, occurred mainly in the <5y age group, though smaller reductions did occur in both the 5–14 year and 15+y age groups. The reduction in the under five's was due to the introduction in 2001 of Hib vaccination into the routine childhood immunisation schedule, and that in the older age groups was possibly due to the effect of herd immunity. The decrease seen in Italy between 1999 and 2004 was mainly reflected in Hib incidence in the <5y age group and was also probably due to the introduction of routine Hib vaccination in 1999, though the vaccine had been available on the market since 1995.

The marked increase in Hi disease incidence between 2003 and 2004 in Estonia occurred only in Hib disease in the <5y age group, and as noted earlier was probably wholly or primarily due to better ascertainment. In the Netherlands, the number of both serotype b and non-capsulated infections occurring in the <5y age group in 2003 was more than twice that of 1999, though numbers did drop slightly in 2004. There was a three-fold increase in levels of serotype b infections in the 15+y age group between 1999 and 2003, and the 2004 figure was double that of 2003. Non-capsulated infection did increase in adults between 1999 and 2003, but decreased in 2004. In UK, the number of serotype b cases in all three age groups in 2003 were about four-fold or higher that of 1999 level, though by 2004, this had dropped back down . The numbers of non-capsulated infections in <5 year age group increased between 1999 and 2004, the 2004 level being about 1.5 times that of the 1999 level while the 5 year olds and older experienced a rise between 1999 and 2003, and then a reduction in 2004.

Haemophilus influenzae serotype b infections

Figure 5 shows the overall Hib incidence for all countries submitting consistent Hib data for all ages.

Figure 5 Incidence (per 100,000 population) of confirmed and probable Haemophilus influenzae serotype b cases in different age groups, all countries combined, 1999 - 2004

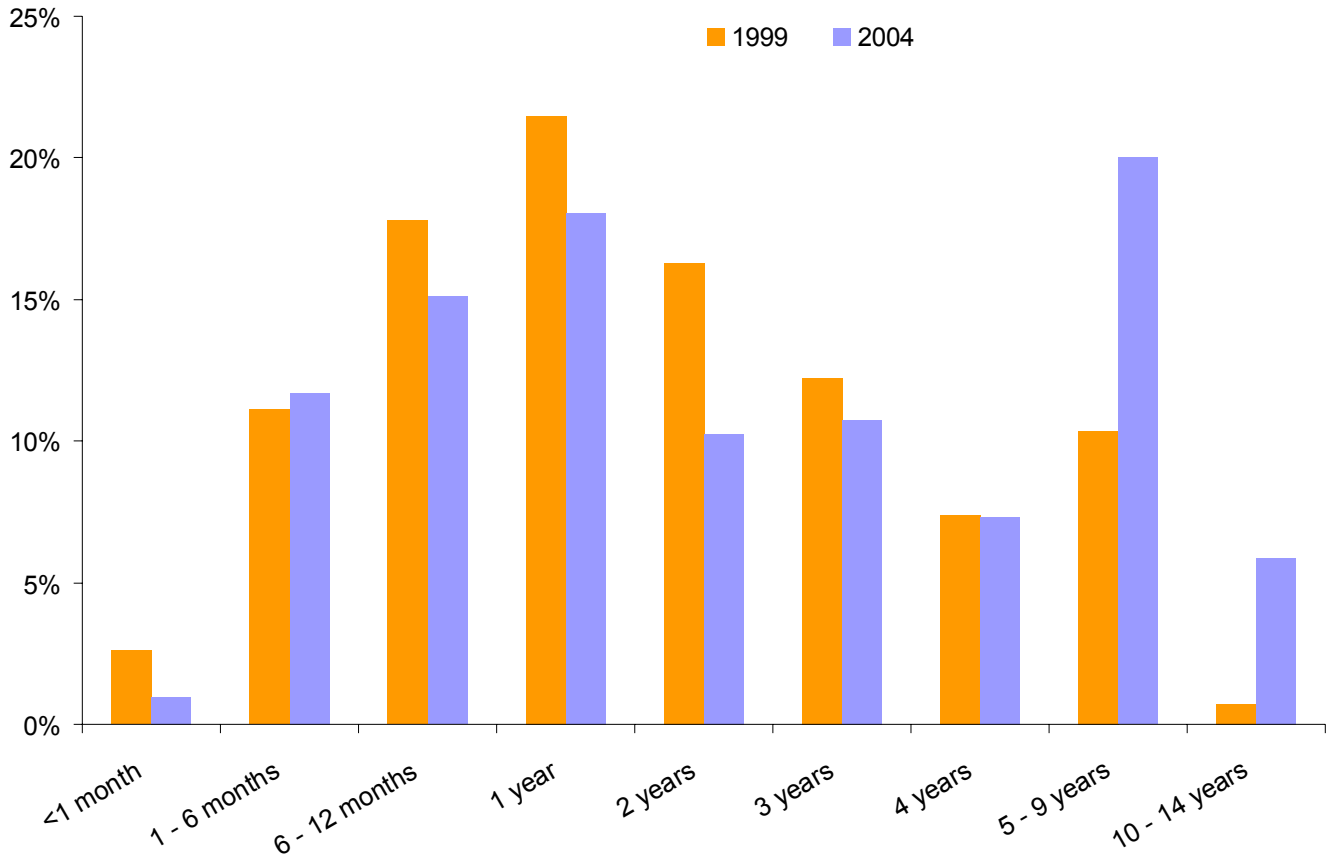


Data derived from countries which submitted consistent Hib data across all ages for 1999 – 2004, these being Australia, Czech Republic, Denmark, Finland, France (Reference Laboratory), Iceland, Ireland,, Italy, Malta, Netherlands, Norway, Poland, Portugal, United Kingdom

The graph clearly indicates that for all years, the highest Hib incidence was found in the youngest age group and decreased with increasing age. Between 2002 and 2004, however, there was a noticeable decrease in incidence in the two younger age groups, and in the <15y age group, the increase in incidence in 2002 has been reversed by 2004. By contrast, the incidence in the 15+y age group had been slowly but consistently increasing from 2000 onwards, though it might have reached a plateau by 2004. The major increase in Hib disease seen in <5y's between 1999 and 2002 was primarily due to the increase seen in the UK between these years, when the number of cases shot up from 35 to 173; the reduction in numbers of cases seen in subsequent years was due to the introduction of a booster campaign in 2003 (Heath and Ramsay 2003).

Figure 6 analyses Hib cases in children in more detail. The distribution of Hib cases between different childhood age groups is displayed for 1999 and 2004.

Figure 6 *Distribution of confirmed and probable Hib cases in different child age groups, all countries combined, 1999 and 2004*

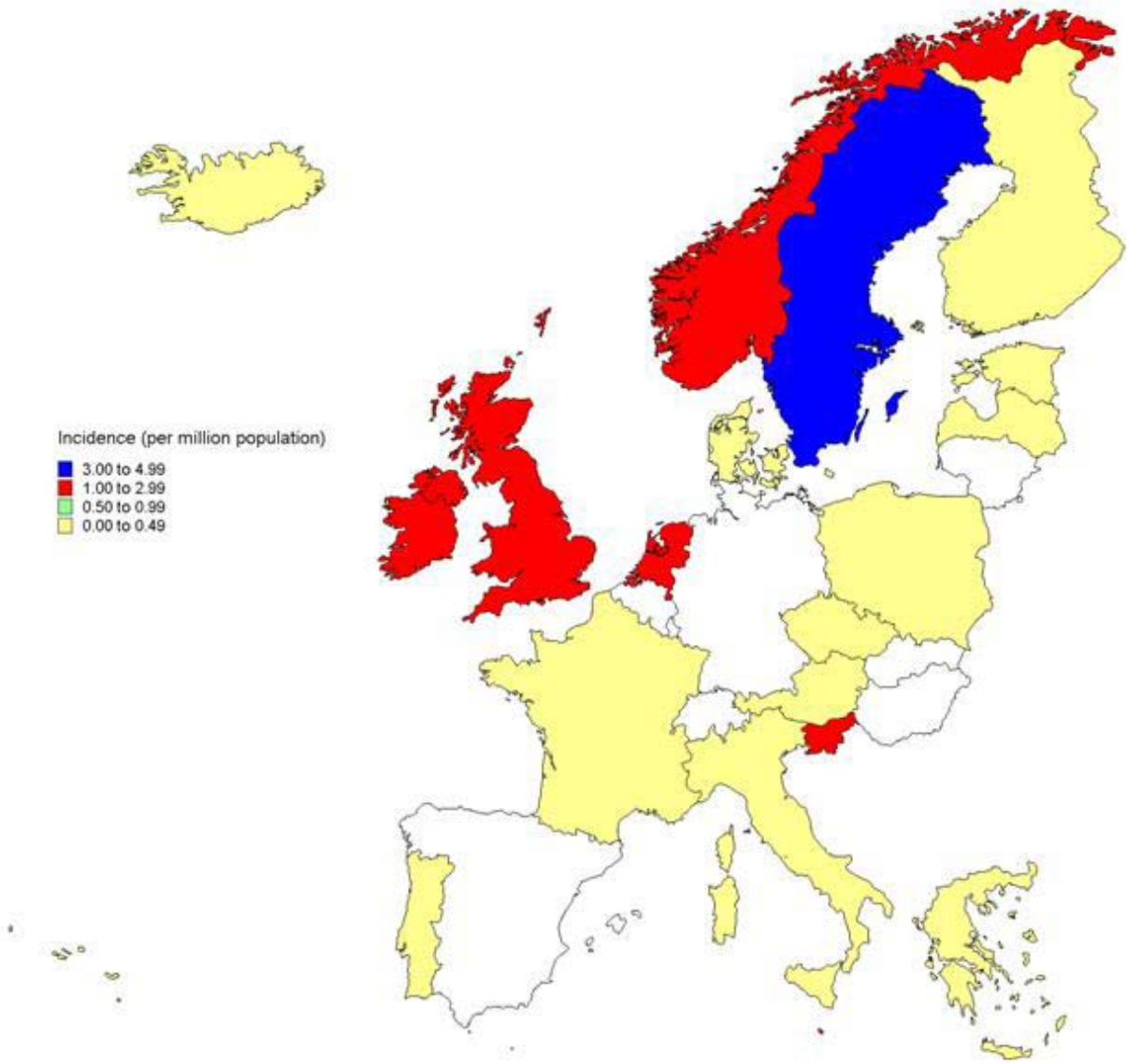


There has been a clear shift in Hib cases between 1999 and 2004 from younger to older age groups, particularly in the 5–15 years age group. This was principally due to UK, where incidence in 5–9 years age group increased over five-fold between 1999 and 2004. The increase seen in the 10-14 year olds was due to Australia and Germany as well as the UK, the latter two having had no cases at all in 1999.

Figure 7 shows the adult Hib incidence in 2004 by country.

The trend discussed earlier, of northern European countries experiencing higher *Haemophilus influenzae* incidences was reflected in adult Hib disease, with Ireland, Netherlands, Norway, Sweden and UK, and also Slovenia, all having incidences greater than 1 per million population in 2004.

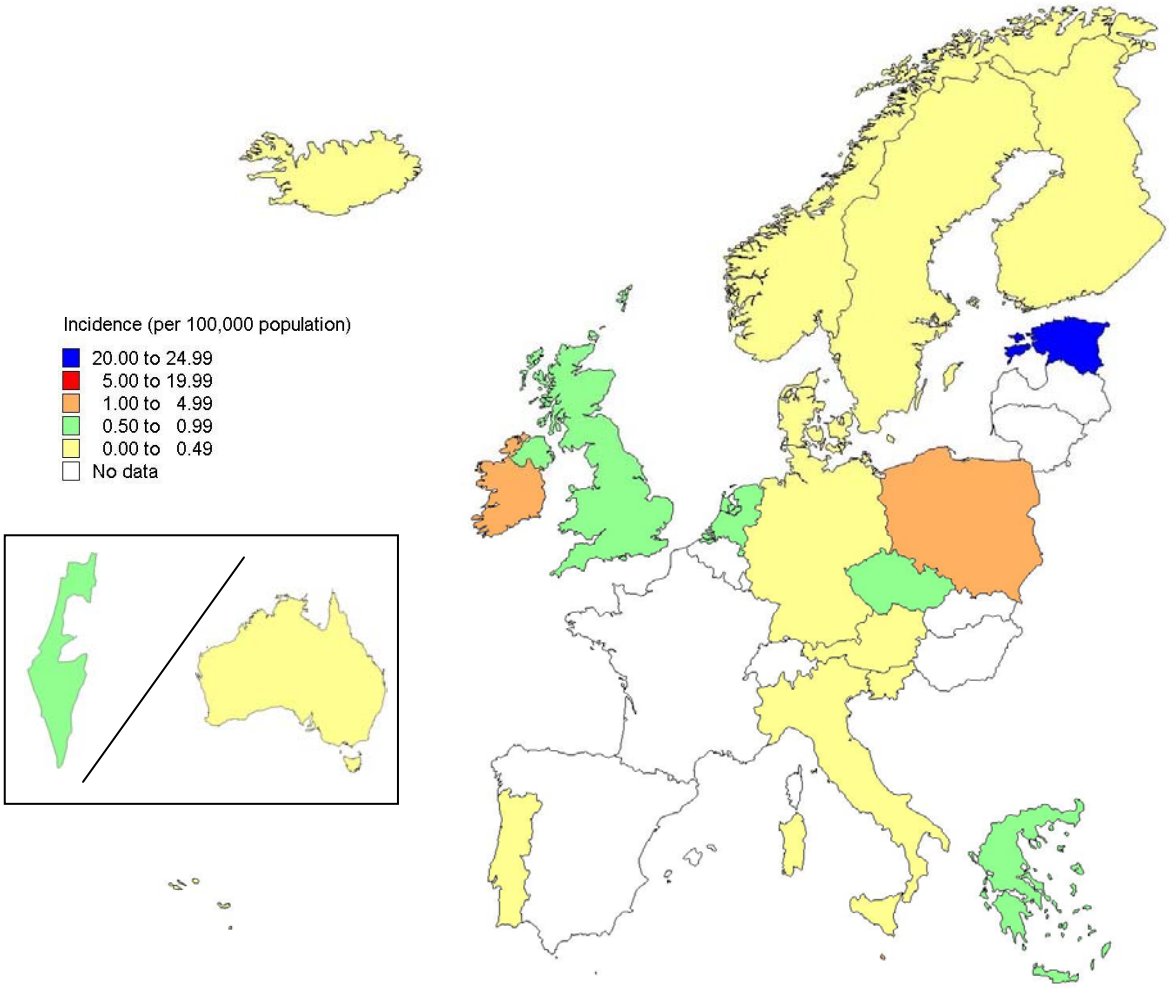
Figure 7 Incidence (per million population) of confirmed and probable Haemophilus influenzae serotype b cases in adults (15 years and older), 2004



***Haemophilus influenzae* serotype b meningitis**

The incidence of Hib meningitis in <5y age group is a good measure of disease burden across Europe as this information is captured by most participating countries. Figure 8 shows the incidence of Hib meningitis in the <5y age group in 2004, and Table 7 shows the occurrence of Hib meningitis disease in the <5y age group.

Figure 8 *Incidence (per 100,000 population) of confirmed and probable Haemophilus influenzae serotype b meningitis in <5 years age group in participating countries, 2004*



The overall European Hib meningitis incidence per 100,000 population for the <5 year age group was 0.64 in 2003 and 0.45 in 2004.

Estonia had the highest incidence in 2004 for all age groups, this being considerably higher than those of the other participating countries. The next highest incidence was in Malta, but this was due to a single case. Apart from the two countries, Hib meningitis incidence in all other participating countries was under 1 per 100,000 population in 2004.

Table 7Numbers of confirmed and probable cases and incidence (per 100,000 population) of *Haemophilus influenzae* serotype b meningitis in <5 years age group in all participating countries, 1999 – 2004

Country	Numbers of cases						Incidence		
	1999	2000	2001	2002	2003	2004	1999	2003	2004
Austria	-	-	-	1	0	1	-	0.00	0.26
Czech Republic	50	53	46	29	17	3	10.99	3.73	0.66
Denmark	1	1	0	0	1	1	0.29	0.30	0.30
Estonia	-	-	-	-	-	13	-	-	20.52
Finland	0	2	0	0	0	0	0.00	0.00	0.00
Germany	7	13	12	8	10	2	0.18	0.27	0.05
Greece	-	-	-	-	3	3	-	0.59	0.59
Iceland	0	0	0	0	0	0	0.00	0.00	0.00
Ireland	2	3	2	4	4	4	0.77	1.40	1.37
Italy	39	24	9	6	3	0	1.48	0.11	0.00
Malta	0	0	0	0	0	1	0.00	0.00	4.86
Netherlands	5	8	4	5	7	10	0.51	0.68	0.98
Norway	1	0	0	1	0	1	0.33	0.00	0.34
Poland	20	23	27	26	25	20	0.96	1.36	1.11
Portugal	0	1	0	2	1	1	0.00	0.18	0.18
Slovenia	-	2	1	0	0	0	-	0.00	0.00
Sweden	2	0	0	2	0	0	0.43	0.00	0.00
United Kingdom	16	25	39	74	50	23	0.44	1.48	0.68
Australia	12	5	3	7	0	2	0.93	0.00	0.16
Israel	2	4	1	2	3	5	0.32	0.44	0.72

The patterns reflected in the Hib meningitis incidence rates in those <5 years of age follow the overall Hib incidence very closely.

***Haemophilus influenzae* non-capsulated infections**

Figures 9–11 illustrate the association between the incidence of non-capsulated Hi (ncHi) infection and age.

Figure 9 displays the incidence of ncHi infections in different age groups between 1999 and 2004, Figure 10 demonstrates the mean annual ncHi incidence in those under 5 years of age between 1999 and 2004 for different countries, and Figure 11 indicates the ncHi incidence in the adult population across Europe.

From Figure 9, it is clear that the greatest change in incidence between 1999 and 2004 was seen in the <1y age group. Apart from a decrease in 2001, the incidence had been steadily increasing between 1999 and 2004. The pattern of incidence in <5y and <15y age groups follow a similar pattern, but to a much lower extent.

Figure 9 *Incidence (per 100,000 population) of confirmed and probable non-capsulated* Haemophilus influenzae *disease by age group, countries combined, 1999 – 2004*

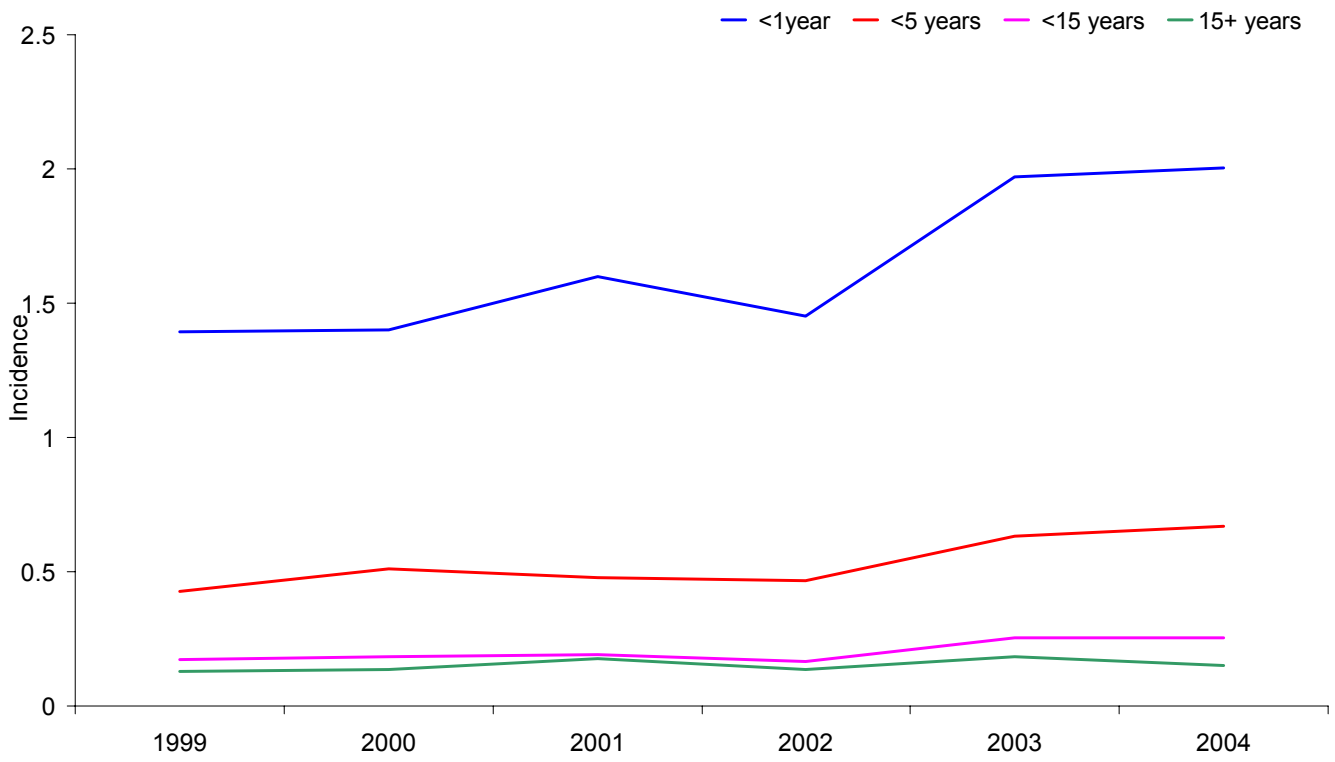


Figure 10 *Mean annual incidence (per 100,000 population) of confirmed and probable non-capsulated* Haemophilus influenzae *infections in <5 years age group by country, 1999 - 2004 combined*

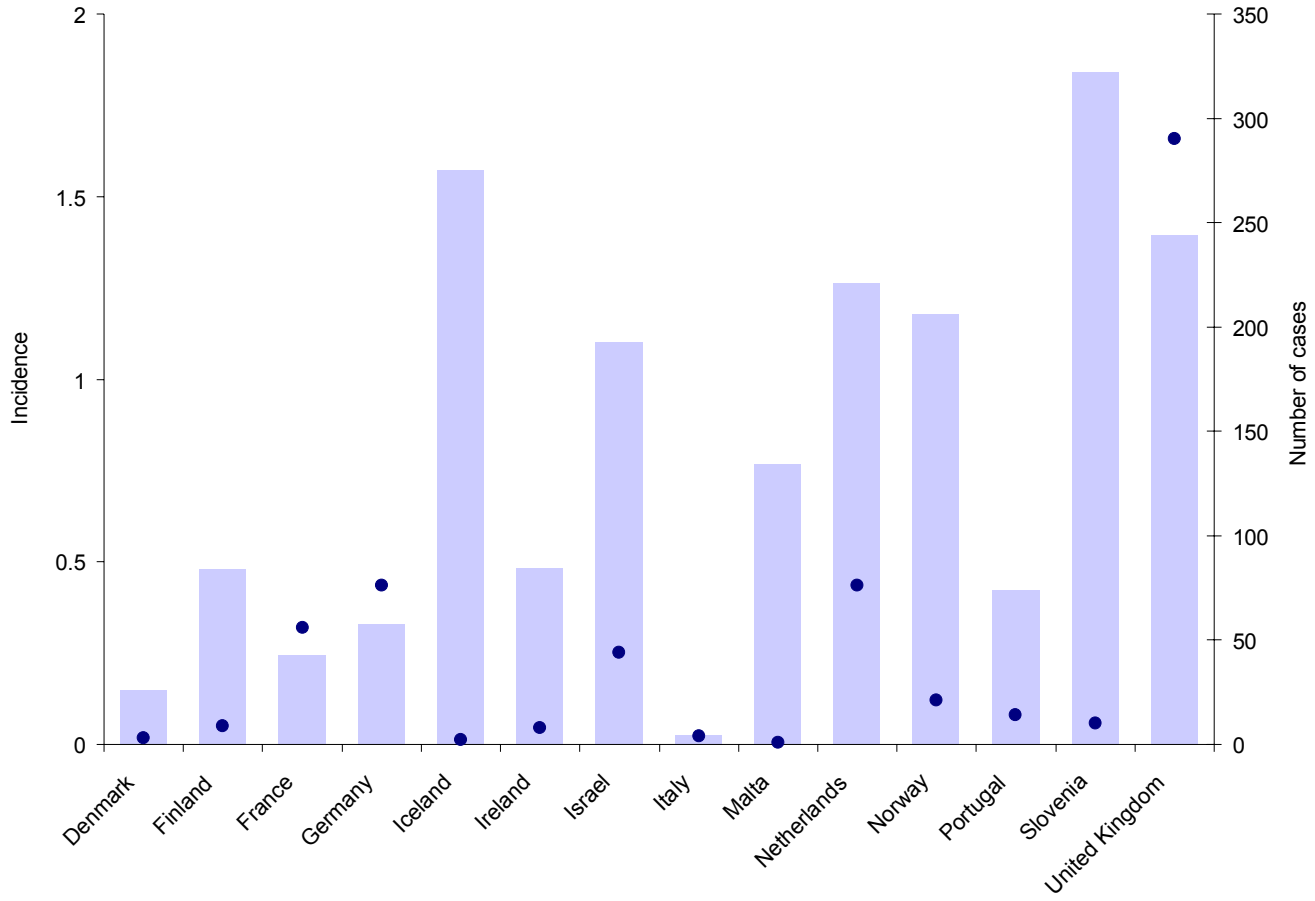


Figure 11 *Incidence (per million population) of confirmed and probable* Haemophilus influenzae *non-capsulated cases in adults (15 years and older), 2004*

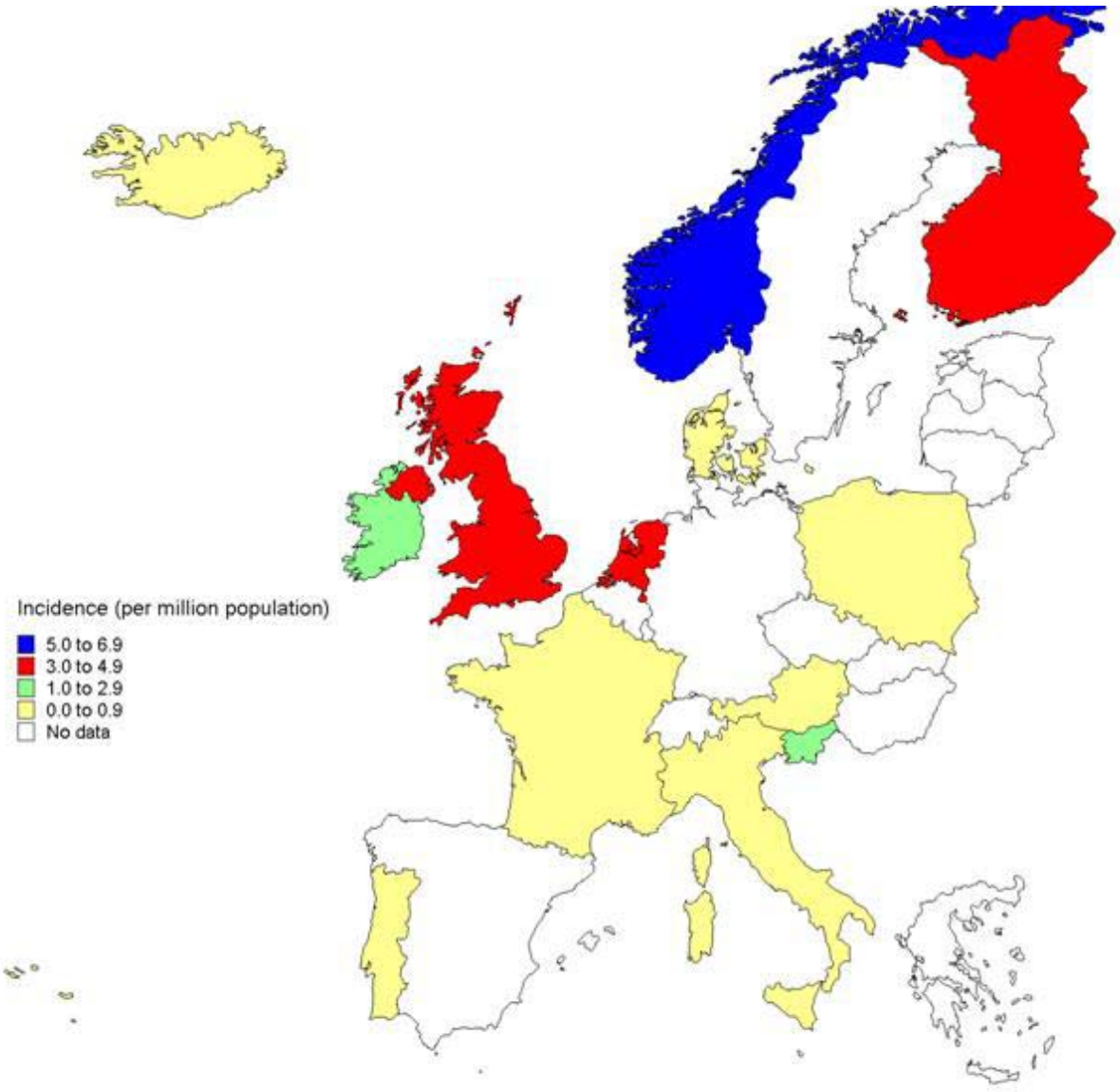


Figure 10 demonstrates that there is relatively little variability across Europe in the mean annual ncHi incidence in the <5y age group, with Slovenia experiencing the highest incidence of 1.8, and Italy the lowest of 0.03 per 100,000 population.

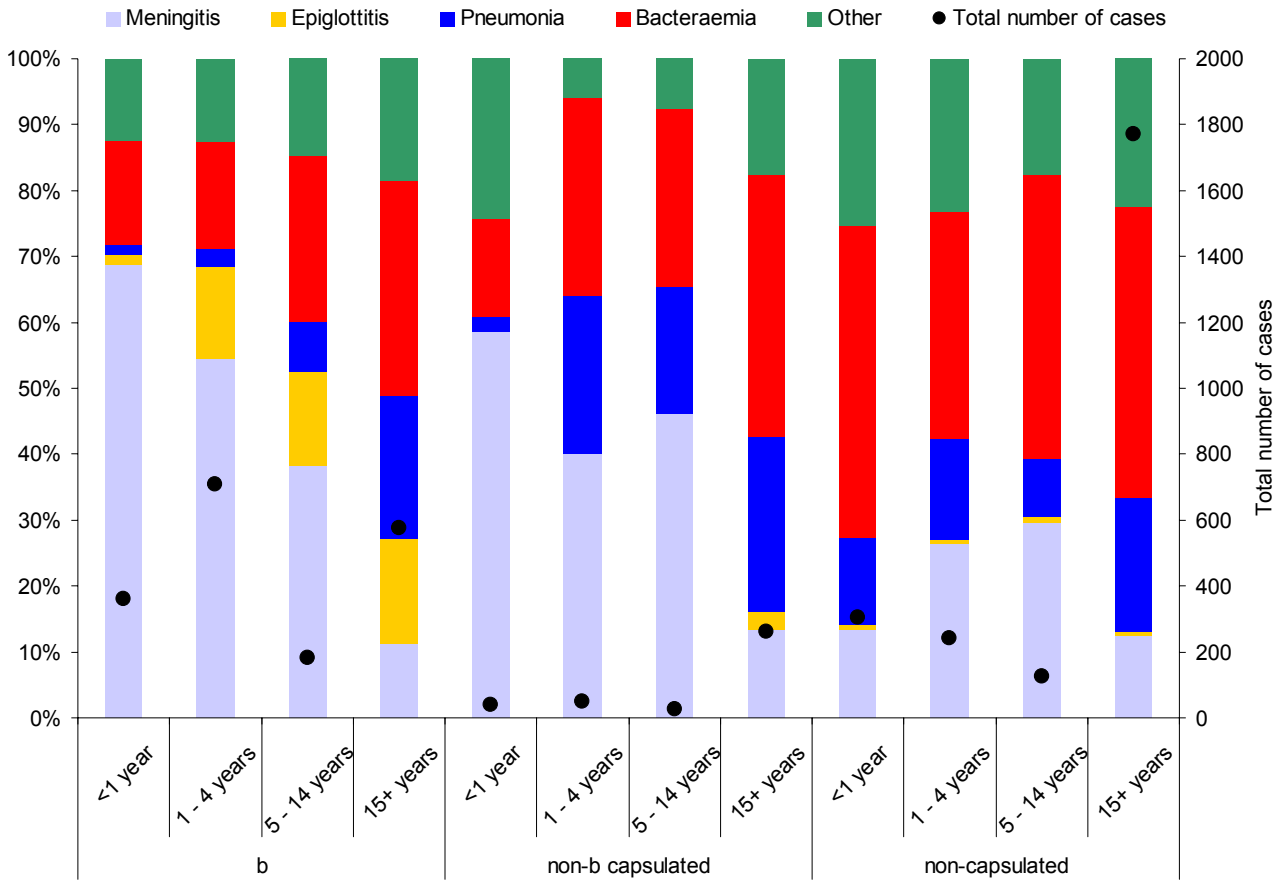
Figure 11 reflects the same trend as noted earlier for other types of Hi infection incidence, namely that the northern European rates tend to be higher than those in Southern Europe.

Clinical presentation

As discussed earlier, serotype distribution is heavily confounded by age (see Figure 2 and accompanying text). Thus any analysis of the different clinical presentations of invasive Hi disease must take into account both serotype and age.

Figure 12 shows the relationship between disease presentation, serotype and age, being derived from those countries which record all diagnoses and all serotypes. Tables A4-A6 in the Appendix detail this information on a country basis.

Figure 12 Disease presentation of confirmed and probable Haemophilus influenzae *cases by country and age group, 1999 – 2004 combined*



Data derived from countries submitting all diagnoses for all serotypes, these being: Austria, Finland, France (Reference Laboratory), Germany, Greece, Iceland, Ireland, Israel, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovenia and UK

Other includes cellulitis and osteomyelitis/septic arthritis

Hib infections demonstrated the strongest association between age and clinical presentation, with meningitis becoming markedly less common with increasing age. Epiglottitis was virtually absent in <1y age group Hib infections, and pneumonia and bacteraemia were much more common in Hib infections occurring in the 15+y age group. Overall numbers of non-b capsulated infections were small, particularly in the <15y age group, and apart from an absence of epiglottitis in the <15y's and few presentations of meningitis in the 15+y age group, there was no strong associations. Among ncHi

infections, there were few presentations of meningitis and virtually none of epiglottitis across all age groups. The frequency of bacteraemia was highest in the youngest and oldest age groups

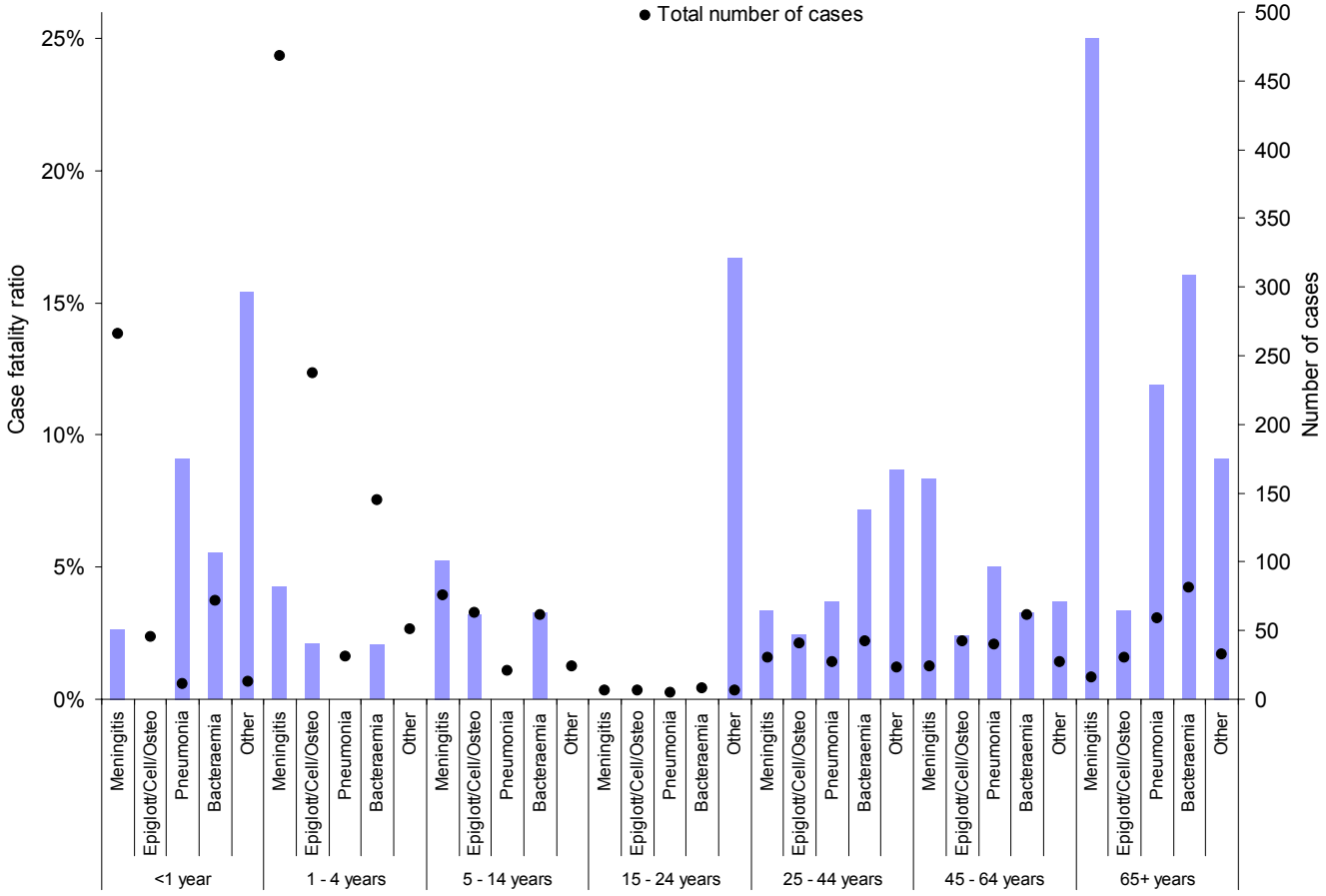
Case fatality ratio (CFR)

The overall case fatality ratio (CFR) amongst the European countries was: 1999 9.07%; 2000 8.20%; 2001 9.06%; 2002 8.18%; 2003 7.80%; 2004 8.23%, or an average annual CFR of 8.34%.

As noted earlier, valid comparisons cannot be made across different serotypes. Thus any analysis of CFR must take into account both age and serotype.

Figure 13 displays the relationship between CFR and age and clinical presentation for Hib infections. It is derived from all countries which record outcome and serotype.

Figure 13 Case fatality ratio for confirmed and probable cases of Haemophilus influenzae *serotype b, by age group and clinical presentation, all countries and years combined*



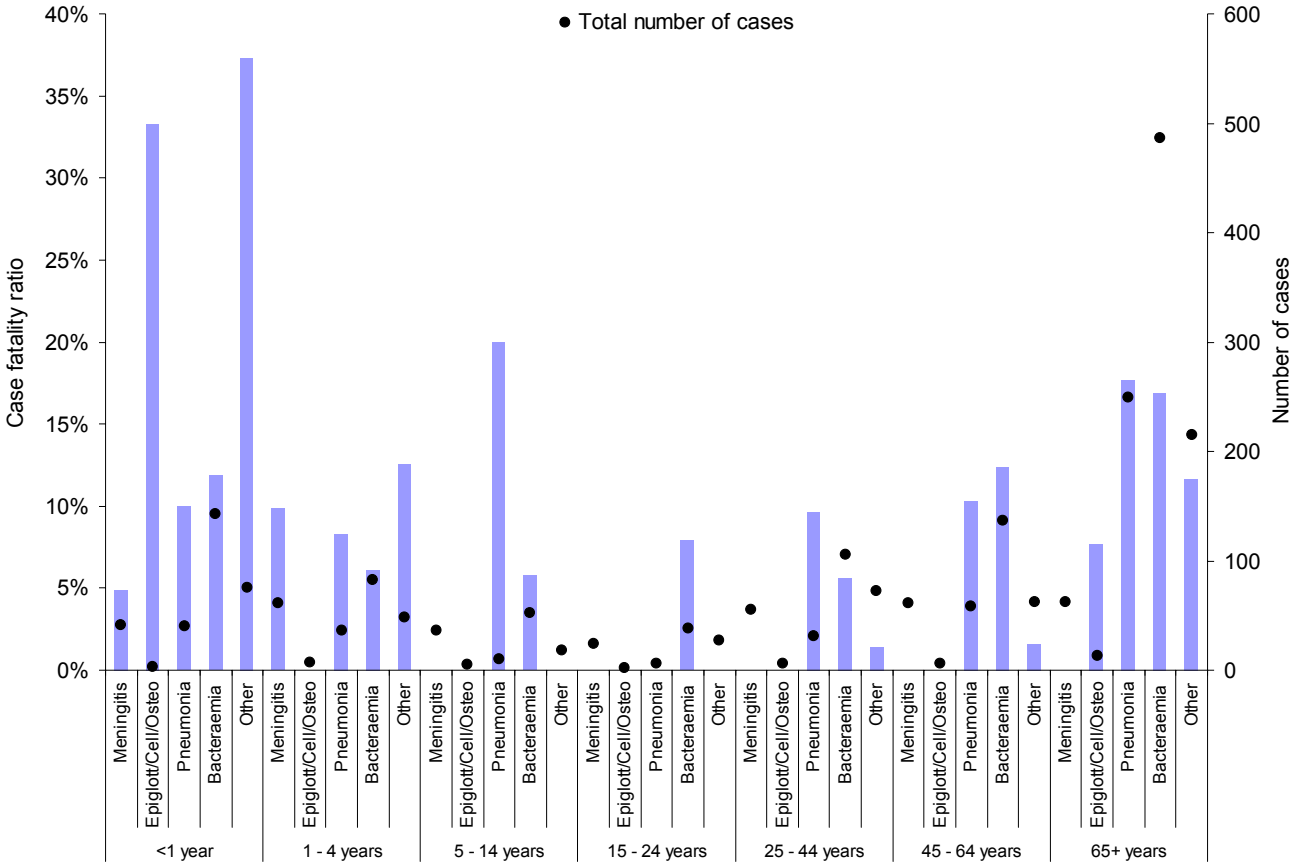
Data derived from countries which record outcome, these being: Australia, Austria, Czech Republic, Denmark, Estonia, Germany, Greece, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Slovak Republic, Slovenia, Sweden and UK

Epiglott/Cell/Osteo – Epiglottis, Cellulitis and Osteomyelitis combined
Total number of cases – Total number of alive, dead and unknown cases
Case fatality ratio calculated assuming that cases with unknown outcomes survived

Figure 13 shows that the Hib CFR was linked to both age and clinical presentation, though to differing extents. The combinations resulting in a CFR greater than 10% was the clinical presentation 'Other' in the <1 year and 15 – 24 years (indicating complicating factors including respiratory tract infections, premature baby and cardiac arrest), though total number of cases were very low in each instance. The only other occasion on which CFR rose above 10% was in the 65+ year age group, for presentations of meningitis, pneumonia and bacteraemia. It is also interesting to note that, at least in this dataset, by far the largest number of total cases, present as meningitis in the 1 – 4 year olds, and there were very few cases of any presentation in the 15 – 24 year age group.

Figure 14 displays the relationship between CFR and age and clinical presentation for ncHi infections. It is derived from all countries which record outcome and all serotypes.

Figure 14 *Case fatality ratio for confirmed and probable cases of non-capsulated* Haemophilus influenzae*, by age group and clinical presentation, all countries and years combined*



Data derived from countries which record outcome, these being: Australia, Austria, Czech Republic, Denmark, Estonia, Germany, Greece, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Slovak Republic, Slovenia, Sweden and UK

Epiglott/Cell/Osteo – Epiglottis, Cellulitis and Osteomyelitis combined

Total number of cases – Total number of alive, dead and unknown cases

Case fatality ratio calculated assuming that cases with unknown outcomes survived

It is noticeable that the highest CFR was experienced in the <1y age group with clinical presentations of pneumonia, bacteraemia and 'other' (indicating complicating factors including premature birth, respiratory tract infection, and sudden unexplained death). Although the CFR was also very high for presentation of epiglottitis in this age group, this was in fact due to a single case. As with Hib infections, some of the higher CFR's were found in the 65+y age group, although only for pneumonia, bacteraemia and 'other' (indicating complicating factors including respiratory tract infection, cancer, and chronic obstructive airways disease). There were however no deaths due to ncHi meningitis in this age group. By far the highest number of cases, at least in this dataset, occurred in the 65+y age group who presented with bacteraemia.

C. Vaccine Failures

Between 1999 and 2004, there were 931 confirmed or probable cases of Hi disease caused by either serotype b or non-serotyped strains occurring in those who had received at least one dose of Hib vaccine. Of these, 714 were classed as true vaccine failures (TVFs), that is instances where onset of invasive Hib disease occurred: (1) at least one week after the second dose of vaccine given in the first year of life, or (2) at least two weeks after the first dose of vaccine given in the second year of life or older (3) after at least three doses of vaccine had been given. A further 95 cases were classed as possible true vaccines failures (PTVFs), that is instances where the serotype of the causative organism was not determined but the other criteria as listed for a TVF had been met, or instances where vaccination was known to have taken place, but the number of doses was not known and the birth date and age of the patient was such as to make it likely that appropriate vaccination had been administered (*eg* if the birth date is with the period of routine childhood vaccination, and the age is greater than 1 year old).

The remaining 122 cases are either apparent vaccine failures (AVFs), in which vaccination has been administered but before protection could be reasonably expected to have developed (*eg* after only one dose of vaccination in the first year of life, or less than two weeks after a dose of vaccination given in the second year of life) or possible apparent vaccine failures (PAVFs), in which vaccination is known to have occurred, but the number and/or dates of vaccination are not known, and the birth date and age are such that it is unlikely that appropriate vaccination would have been administered (*eg* if the birth date is considerably prior to the period when Hib vaccination was introduced into the routine immunisation schedule, or the child was below 1 year of age).

Table 8 shows the number of vaccine TVF's occurring by country and by year, and also the percentage these cases were of the total Hib infections reported for that year. Figure 15 and Table 9 combine the data from different countries to indicate the distribution of vaccine failure by age.

Table 8 Number of vaccine failure cases and percentage these are of total cases , by country and year, 1999 - 2004

Country	Numbers of cases						% of total Hib cases					
	1999	2000	2001	2002	2003	2004	1999	2000	2001	2002	2003	2004
Czech Republic	0	0	0	0	3	1	0%	0%	0%	0%	7%	6%
Denmark	0	0	1	-	0	1	0%	0%	100%	-	0%	100%
Finland	2	1	0	0	5	0	29%	50%	0%	0%	63%	0%
France	1	0	2	4	3	4	10%	0%	13%	27%	16%	36%
Germany	6	7	5	5	6	4	46%	28%	26%	36%	32%	57%
Iceland	-	-	0	-	-	-	-	-	0%	-	-	-
Ireland	2	2	2	5	1	6	29%	29%	25%	45%	8%	33%
Italy	0	0	0	0	2	0	0%	0%	0%	0%	25%	0%
Netherlands	2	2	4	12	8	10	17%	13%	24%	40%	24%	21%
Norway	0	0	0	1	0	0	0%	0%	0%	13%	0%	0%
Portugal	0	0	0	-	0	2	0%	0%	0%	-	0%	50%
Sweden	3	-	-	4	4	3	50%	-	-	18%	17%	8%
United Kingdom	26	53	99	170	127	40	37%	50%	62%	55%	43%	23%
Australia	12	8	8	6	2	8	44%	57%	47%	40%	17%	67%
Israel	3	7	2	2	2	3	50%	64%	29%	33%	40%	30%

Figure 15 Age distribution of vaccine failure cases, all countries combined, 1999 2004

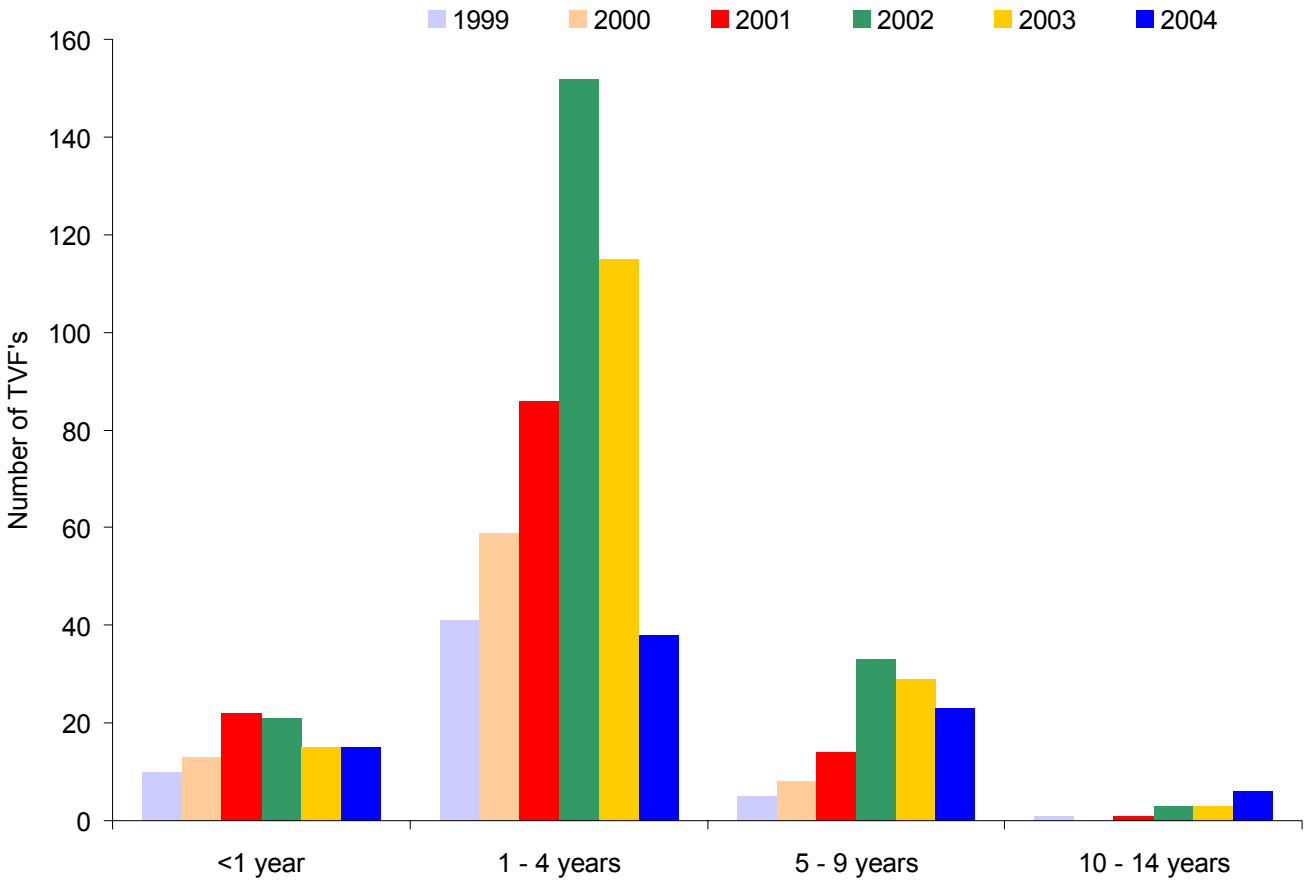


Table 9 Number of vaccine failure cases and percentage these are of total cases , by age group, 1999 - 2004

	Number of cases						% of all Hib cases					
Age group	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
<1 year	10	13	22	21	15	15	12%	15%	26%	27%	18%	26%
1 - 4 years	41	59	86	152	115	38	26%	32%	46%	62%	57%	40%
5 - 9 years	5	8	14	33	29	23	18%	25%	44%	65%	63%	53%
10 - 14 years	1	0	1	3	3	6	33%	0%	11%	27%	16%	50%

As seen in Table 8, there were two countries in which the number of TVF's changes dramatically with time, namely Netherlands and UK, with the latter experiencing by far the largest number of cases. In both countries, 2002 saw both the highest number of TVFs, and the highest proportion these were of all Hib cases. In the Netherlands, the number of TVF's continued to plateau after 2002, though the proportion these were of all Hib cases halved; in the UK, the TVF numbers dropped to less than a quarter of the 2002 value by 2004.

Figure 15 and Table 9 indicate that by far the greatest number of TVF's occurred in the 1-4 year age group for all years, though there was a noticeable decrease in 2004 on the 2002 and 2003 levels. The proportion of invasive Hi cases which were VF's in this age group was similar to that found in the 5-9 year age group, 2002 and 2003 seeing the highest proportion of cases which were VF's in both age groups. There was a slowly but steadily increasing proportion with time of cases which were VF's occurring in the 10-14 year age group, which was probably related to the increasing number in this cohort that would have received a full course of vaccination.

D. Website

http://www.euibis.org

The website has been developed substantially, and now features:

- Presentations from pertinent meetings
- The Hib conjugate 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 continues to collect all *Haemophilus influenzae* (Hi) case data as submitted by 26 countries, 24 European, and 2 non-European. In addition, it also holds data from 1996 – 1998 collected through the auspices of a predecessor project, the BIOMED II project. This dataset represents an invaluable source for monitoring and investigating the patterns of *Haemophilus influenzae* epidemiology across Europe. Countries differed quite widely in their surveillance of Hi disease, *eg* some countries track only *Haemophilus influenzae* serotype b infections, while others monitor only those under 15 years of age. Only certain types of clinical presentation might be reported, and serotyping is not always performed. Thus care should be taken when analysing patterns and detecting trends across Europe.

The average European incidence of *Haemophilus influenzae* disease in 2004 was 0.50 per 100,000 population. Of the countries which monitor all cases of Hi disease, Norway experienced the highest incidence of 1.7 per 100,000 population, and generally northern European countries had higher incidence rates than those in the South. Over the period 1999 – 2004, increase in disease was seen in Netherlands, Ireland and UK, and decreases in Czech Republic and Italy. Although a marked increase was also seen in Estonia between 2003 and 2004, this may well have been principally due to better ascertainment.

Serotype distribution is age related, with non-capsulated (ncHi) infections predominating in the 15+y age group, and serotype b infections (Hib) appearing mainly in the younger age groups. The relative proportion of infectious non-b capsulated strains in the <15y age group did not change greatly between 1999 and 2004, while that due to Hib strains peaked in 2002, and then decreased, the proportion due to ncHi strains first decreasing and then increasing accordingly. Serotype f was the most common non-b capsulated invasive Hi strain, followed by serotype e.

Hib incidence fell most dramatically in the Czech Republic, particularly in the <5y age group, due to the introduction of routine Hib vaccination into the childhood immunisation schedule in 2001. A smaller decrease was noted in the Italian <5y year population, and was probably also due to introduction of routine Hib vaccination. Increases in both Hib and ncHi infections were seen in Netherlands and in UK between 1999 and later years.

Generally, Hib incidence remained highest in the <1y age group, decreasing with increasing age. Incidence in <1y and <5y age groups in 2004 was considerably lower than its level had been in 1999, while that of the <15y age group was just lower. Incidence in the adult population remained very low, but did appear to increase slowly between 1999 and 2004. Estonia had by far the highest incidence of Hib meningitis in the <5y age group in 2004 in Europe, this being 20.52 per 100,000 population, but it introduced Hib vaccination into its childhood schedule only in 2005. Apart from Malta, whose single case of Hib meningitis in the <5 age group gave it an incidence of over 4 per 100,000, the Hib

incidence in this age group in the other European countries was less than 1 per 100,000. The average across Europe was 0.45 per 100,000 in 2004.

The ncHi incidence rate in the <1y age group increased considerably between 1999 and 2004, particularly after 2002, with those in the <5y and <15y age groups following a similar, but more muted, pattern.

Meningitis presented less commonly with increasing age in Hib infections, whereas pneumonia and bacteraemia predominated in Hib infections in those 15 years and older. Epiglottitis did not appear in Hib infections in <1y age group nor in any ncHi infections in any age group. ncHi infections also saw few presentations of meningitis, and bacteraemia was commonest in the youngest and oldest age groups.

The overall case fatality in Europe in 2004 was 8.23%. Hib CFR tended to be highest in the 65+ year age group, while that for ncHi infections was highest in the <1y age group.

There were 714 cases of Hib true vaccine failure (TVF) in Europe between 1999 and 2004. In two countries the numbers changed notably with time, that the Netherlands and UK, with 2002 seeing the highest numbers in both countries. TVF's occurred most frequently in the 1-4 year age group for all years between 1999 and 2004, peaking in 2002. There has been a steadily increasing number of cases occurring in the 10-14 year age group between 1999 and 2004.

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 implements them.

Further useful work could be done using the EU-IBIS dataset, and in collaboration if need be, for example in the investigation of genetic and other possible reasons for cases of Hib vaccine failure, and in investigating in more detail the epidemiology of, and the morbidity and mortality caused by, non-capsulated *Haemophilus influenzae* strains. Although the incidence of non-b capsulated infections does not appear to have risen (in order to fill a possible ecological niche left by the reduction of Hib disease due to the very successful introduction and continuing use of conjugate vaccine), the situation still requires continual monitoring and careful surveillance to confirm it will not happen in the future.

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APPENDIX I - Data Variables submitted to EU-IBIS

Variable	Type	Coding
Country	Text	
Year	Number	
Id No	Text	
Date of birth	DD/MM/YY	
Date of onset	DD/MM/YY	
Age in years	Number	
Age in months if <1y	Number	
Sex	Number	1=male 2=female 3=not known
Geographic location	Text	
Clinical diagnosis	Number	1=meningitis, 2=epiglottitis, 3=cellulitis, 4=osteomyelitis/septic arthritis, 5=pneumonia, 6=septicaemia, 7=other (specify in 'Other Clinical'), 9=not known
Other clinical diagnosis	Text	
Method of confirmation	Number	1=culture, 2=antigen, 3=clinical diagnosis, 9=not known
Antigen (*H. influenzae* antigen test positive for type b)	Number	
Other method of confirmation	Text	
Site of specimen	Number	1=blood, 2=CSF, 3=blood & CSF 4=other invasive, 5=not relevant 6=other (non invasive), 7=other (not known)
Other site	Text	
Serotype	Text	a, b, c, d, e, f non-b = non-b *H influenzae* non-caps = *H influenzae* non-capsulated NK = not known
Vaccination status	Number	1= vaccinated, 2=not vaccinated, 3=not applicable, 4=not known
Doses (Number of doses of vaccine given pre-onset)	Text	99=not known
Vaccine failure	Text	TVF = True Vaccine Failure, AVF = Apparent Vaccine Failure, PVF = Possible Vaccine Failure
Dose1 (Vaccine type)	Text	
Date1 (Date given)	DD/MM/YY	
Dose2 (Vaccine type)	Text	
Date2 (Date given)	DD/MM/YY	
Dose3 (Vaccine type)	Text	
Date3 (Date given)	DD/MM/YY	
Boost (Vaccine type)	Text	
Bdate (Date given)	DD/MM/YY	
Outcome	Number	1=alive, 2=died, 3=not known

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APPENDIX III – GLOSSARY AND DEFINITIONS

Glossary

<1y	Those under one year of age
<5y	Those under five years of age
<15y	Those under 15 years of age
15+y	Those 15 years old or older
DTaP	Combined diphtheria, tetanus and acellular pertussis vaccine
DTwP	Combined diphtheria, tetanus and whole cell pertussis vaccine
ECDC	European Centre for Disease Prevention and Control
EQAS	External quality assurance scheme
EU	European Union
EU-IBIS	European Union Invasive Bacterial Infection Surveillance
HBV	Hepatitis B virus (vaccine)
Hi	*Haemophilus influenzae*
HPA	Health Protection Agency
HbOC	Hib oligosaccharide conjugated to CRM197 (cross-reacting mutant diphtheria toxin) to create a vaccine
Hib	*Haemophilus influenzae* infection caused by a strain of serotype b
Hib-PRP-D	Hib PRP vaccine conjugated to diphtheria toxoid
Hib-PRP-OMP	Hib PRP vaccine conjugated to *Neisseria meningitidis* outer membrane protein complex
Hib-PRP-T	Hib PRP vaccine conjugated to tetanus toxoid
IPV	Inactivated polio vaccine
ncHi	*Haemophilus influenzae* infection caused by a non-capsulated strain
non-b capsulated Hi	*Haemophilus influenzae* infection caused by a strain of serotype a, c, d,e or f
OPV	Oral polio vaccine
PRP	Polyribosylribitol phosphate (polysaccharide present on the Hi surface)

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
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
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

APPENDIX IV – Data Tables

Table A1 Total population data, by country, 1999 – 2004

Country	1999	2000	2001	2002	2003	2004	Data source
Australia	18925855	19153380	19413240	19640979	19872646	20091504	http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3201.0Jun%202006?OpenDocument
Austria	8094156	8113413	8131690	8148312	8162656	8174762	http://www.census.gov/cgi-bin/ipc/idbagg (for Austria)
Belgium	10226419	10251250	10286570	10332785	10376133	10421137	http://www.iph.fgov.be/epidemio/spma/index.htm
Czech Republic	10278098	10266546	10206436	10203269	10211455	10211455	http://www.czso.cz/eng/edicniplan.nsf/t/79005D6975/$File/40270301.pdf
Denmark	5319111	5337344	5355082	5374255	5387174	5401177	http://www.statbank.dk/statbank5a/default.asp?w=1024
Estonia	1379237	1372071	1366959	1361242	1356045	1351069	http://pub.stat.ee/px-web.2001/I_Databas/Population/01Population_indicators_and_composition/04Population_figure_and_composition/04Population_figure_and_composition.asp
Finland	5158097	5168595	5180309	5193039	5204405	5214512	http://www.census.gov/cgi-bin/ipc/idbagg (for Finland)
France	60158533	60434492	60754024	61078533	61391033	61684291	http://www.insee.fr, from Isabelle Parent du Châltelet
Germany	82074778	82187909	82280551	82350671	82398326	82424609	www.census.gov/cgi-bin/ipc/idbagg (for Germany)
Greece	10882607	10917456	10949953	10987559	11023532	11040650	http://www.statistics.gr/eng_tables/S201_SPO_5_TS_91_04_4_Y_EN.pdf
Hungary					10142362	10116742	From Katalin Krisztalovics, National Centre for Epidemiology, Budapest, Hungary
Iceland	277184	281154	285054	287559	289272	292587	http://www.statice.is/?pageid=1178&src=/temp_en/mannfjoldi/midarsmannfjoldi.asp
Ireland	3741400	3789500	3847100	3917200	3978800	4043700	http://www.cso.ie/px/pxeirestat/Dialog/varval.asp?ma=PEAA1&ti=Population+Estimates+(Thousand)+by+Year,+Age+Group+and+Sex.&path=../Database/EireStat/Population%20Estimates/&lang=1
Israel	6125300	6289200	6439042	6569957	6689700	6809000	http://www1.cbs.gov.il/shnaton55/download/st02_10x.xls
Italy	56909109	56923524	56960692	56993742	57321070	57888245	http://demo.istat.it/index_e.html
Latvia					2331480	2319203	http://data.csb.lv/EN/Database/annualstatistics/04.%20Population/04.%20Population.asp
Lithuania			3486998	3475586	3462553	3445857	http://www.std.lt/web/main.php?parent=1094, http://epp.eurostat.cec.eu.int/portal/page?_pageid=0,1136184,0_45572595&_dad=portal&_schema=PORTAL
Luxembourg	433600	439000	439000	444050	448300	451600	http://www.statistiques.public.lu/stat/TableViewer/tableView.aspx?ReportId=1059
Malta	391415	391415	394641	397242	399867	399867	http://www.nso.gov.mt/statbase/data_table_options.aspx?id=19, 2003 data
Netherlands	15760225	15863950	15987075	16105285	16192572	16258032	http://statline.cbs.nl/StatWeb/start.asp?LA=en&DM=SLEN&lp=Search/Search
Norway	4445329	4478497	4503436	4524066	4552252	4577457	http://statbank.ssb.no/statistikkbanken/default_fr.asp?PLanguage=1
Poland	38653625	38646201	38641046	38232301	38195177	38180249	From Magda Rosinska, National Institute of Hygiene, Poland and from website www.stat.gov.pl
Portugal	10195014	10262877	10335559	10407465	10474685	10529255	http://www.ine.pt/prodserv/quadros/periodo.asp, subscribers only
Slovak Republic	5395739	5400320	5404681	5410052	5416406	5423567	http://www.census.gov/cgi-bin/ipc/idbagg (for Slovak Republic)
Slovenia	1985557	1990272	1992035	1995718	1996773	1997004	http://www.stat.si/eng/tema_demografsko_prebivalstvo.asp
Spain	39802827	40049708	40476723	40964244	41663702	42345342	http://www.ine.es/inebase/cgi/axi?AXIS_PATH=/inebase/temas/t20/p251/proy_2001/l1/&FILE_AXIS=01001.px&CGI_DEFAULT=/inebase/temas/english.opt&COMANDO=SELECCION&CGI_URL=/inebase/cgi/
Sweden	8861426	8882792	8909128	8940788	8946957	9011392	http://www.ssd.scb.se/databaser/makro/MainTable.asp?yp=tansss&xu=C9233001&omradekod=BE&omradetext=Population&lang=2&langdb=2
Switzerland	7164444	7204055	7261210	7313853	7364148	7415102	http://www.bfs.admin.ch/bfs/portal/de/index/themen/bevoelkerung/uebersicht/blank/analysen__berichte/result.ContentPar.0008.DownloadFile.tmp/bfs%20actualités%202004%20def.pdf
United Kingdom	58481070	58643230	58836674	59206731	59553759	59834946	From Office of National Statistics

Table A2 Percentage age distribution of population, by country, 1999 – 2004 combined

	<1	1 - 4	5 - 9	10 - 14	15 - 19	20 - 24	25 - 44	45 - 64	65+
Australia	1.28	5.25	6.88	6.96	6.90	6.81	29.98	23.31	12.63
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	0.92	3.70	4.90	5.26	6.22	7.43	30.24	24.04	17.29
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	1.21	5.06	6.44	6.12	5.67	5.80	32.04	23.63	14.02
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	1.05	4.21	6.18	7.29	8.05	8.61	29.86	23.21	11.53
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	1.06	4.18	6.03	6.76	5.96	5.81	27.24	25.73	17.23
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

Table A3 Numbers of confirmed and probable *Haemophilus influenzae* cases in all participating countries, 1999 – 2004

Country	Year	b				non-b capsulated				non-capsulated			
		<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years
Australia	1999	10	10	2	5	-	-	-	-	-	-	-	-
Australia	2000	6	4	4	0	-	-	-	-	-	-	-	-
Australia	2001	5	8	4	0	-	-	-	-	-	-	-	-
Australia	2002	5	6	4	0	-	-	-	-	-	-	-	-
Australia	2003	3	7	2	0	-	-	-	-	-	-	-	-
Australia	2004	2	4	6	0	-	-	-	-	-	-	-	-
Austria	2002	0	1	1	1	0	0	0	0	0	0	0	0
Austria	2003	0	1	0	0	0	0	0	1	0	0	0	2
Austria	2004	1	0	0	1	0	0	0	1	0	0	0	2
Czech Republic	1999	17	68	12	6	-	-	-	-	-	-	-	-
Czech Republic	2000	13	72	14	6	-	-	-	-	-	-	-	-
Czech Republic	2001	14	62	9	7	-	-	-	-	-	-	-	-
Czech Republic	2002	3	37	10	6	-	-	-	-	-	-	-	-
Czech Republic	2003	3	24	11	5	-	-	-	-	-	-	-	-
Czech Republic	2004	1	6	8	1	-	-	-	-	-	-	-	-
Denmark	1999	1	0	0	3	0	0	0	0	0	1	0	0
Denmark	2000	1	0	0	0	0	0	0	0	1	0	0	0
Denmark	2001	0	0	1	0	0	0	0	0	0	0	0	0
Denmark	2002	0	0	0	0	0	0	0	0	0	0	0	1
Denmark	2003	0	1	0	0	0	0	0	0	0	1	0	1
Denmark	2004	0	1	0	0	0	0	0	0	0	0	0	1
Estonia	1999	1	1	1	-	0	0	0	0	0	0	0	-
Estonia	2000	0	1	0	-	0	0	0	0	0	0	0	-
Estonia	2001	2	1	0	-	0	0	0	0	0	0	0	-
Estonia	2002	2	1	0	-	0	0	0	0	0	0	0	-
Estonia	2003	0	1	0	-	0	0	0	0	0	0	0	-
Estonia	2004	2	15	1	-	0	0	0	0	0	0	0	-
Finland	1999	2	0	1	4	0	0	1	4	1	0	0	12
Finland	2000	1	1	0	0	1	1	0	2	1	0	0	28
Finland	2001	0	0	0	3	1	0	0	7	2	2	1	30
Finland	2002	0	0	0	4	0	0	0	2	0	0	0	10
Finland	2003	1	3	2	2	0	0	0	5	1	1	1	20
Finland	2004	0	0	0	1	0	0	0	0	1	0	0	20
France	1999	4	1	0	5	2	1	0	6	4	3	3	26
France	2000	3	1	0	4	2	0	0	2	6	7	3	30
France	2001	5	2	1	7	1	3	0	5	6	1	1	74
France	2002	3	3	1	8	1	0	0	3	5	5	2	45
France	2003	5	9	0	5	0	1	1	4	4	3	4	55
France	2004	4	6	0	1	0	1	1	6	7	5	7	53
Germany	1999	2	8	3	-	2	2	1	-	5	6	1	-
Germany	2000	10	11	4	-	1	1	0	-	9	7	12	-
Germany	2001	9	7	3	-	3	0	0	-	8	8	5	-
Germany	2002	6	6	2	-	1	3	2	-	3	9	5	-
Germany	2003	10	8	1	-	0	2	3	-	5	5	4	-
Germany	2004	2	2	3	-	1	3	0	-	7	4	4	-
Greece	1999	1	0	0	0	1	-	-	-	-	-	-	-

Country	Year	b				non-b capsulated				non-capsulated			
		<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years
Greece	2000	2	1	0	0	-	-	-	-	-	-	-	-
Greece	2001	1	0	0	0	-	-	-	-	-	-	-	-
Greece	2002	2	3	1	0	-	-	-	-	-	-	-	-
Greece	2003	2	3	2	1	-	-	-	-	-	-	-	-
Greece	2004	4	0	0	4	-	-	-	-	-	-	-	-
Iceland	1999	0	0	0	0	1	0	0	0	2	0	0	0
Iceland	2000	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2001	1	0	0	0	0	0	0	0	0	0	0	1
Iceland	2002	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2003	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2004	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	1999	1	2	1	3	0	0	0	1	1	0	0	6
Ireland	2000	2	2	1	2	0	0	0	0	1	1	0	1
Ireland	2001	1	2	2	3	0	0	0	0	1	0	2	6
Ireland	2002	0	8	0	3	0	0	0	1	0	0	0	6
Ireland	2003	5	3	1	4	0	0	0	2	2	1	0	3
Ireland	2004	1	8	0	9	0	0	1	2	0	1	2	6
Israel	1999	3	3	0	-	0	0	0	0	0	0	0	-
Israel	2000	6	3	2	-	1	0	0	0	1	0	0	-
Israel	2001	4	2	1	-	0	0	0	0	3	9	4	-
Israel	2002	4	0	2	-	1	1	0	0	6	6	0	-
Israel	2003	3	1	1	-	1	0	0	0	2	12	2	-
Israel	2004	8	2	0	-	0	1	0	0	0	5	0	-
Italy	1999	19	20	2	9	0	0	0	0	0	1	1	11
Italy	2000	14	12	1	4	0	1	0	3	0	0	0	7
Italy	2001	2	8	1	6	0	0	0	3	0	1	1	5
Italy	2002	5	2	1	1	0	0	0	0	0	0	0	3
Italy	2003	4	1	1	2	0	0	0	1	0	1	1	8
Italy	2004	0	0	1	1	0	0	0	0	0	1	0	3
Malta	1999	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2000	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2001	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2002	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2003	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2004	1	0	0	1	0	0	0	0	0	1	0	0
Netherlands	1999	5	2	1	4	2	0	0	0	6	5	8	35
Netherlands	2000	3	5	0	8	2	1	1	7	4	3	0	43
Netherlands	2001	3	5	1	8	0	2	1	7	6	5	1	49
Netherlands	2002	7	9	0	14	1	1	1	10	0	0	0	4
Netherlands	2003	5	10	4	15	2	0	1	5	15	12	2	61
Netherlands	2004	8	6	3	30	0	0	0	6	11	9	1	53
Norway	1999	0	2	0	3	0	0	0	0	2	4	1	60
Norway	2000	0	1	0	6	0	0	0	0	3	3	1	43
Norway	2001	0	0	0	2	0	0	0	15	0	2	2	28
Norway	2002	2	0	0	6	0	0	0	12	1	3	1	46
Norway	2003	0	0	0	4	0	1	0	11	0	1	2	27
Norway	2004	1	0	0	8	0	0	1	10	1	1	1	24
Poland	1999	5	15	3	0	0	0	0	0	0	0	0	0

Country	Year	b				non-b capsulated				non-capsulated			
		<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years	<1 year	1- 4 years	5 – 14 years	15+ years
Poland	2000	9	14	6	0	0	1	0	0	0	0	0	0
Poland	2001	13	14	4	1	0	0	0	0	0	0	0	0
Poland	2002	5	22	6	0	0	0	0	0	0	0	0	0
Poland	2003	8	23	3	1	0	0	0	0	0	0	0	0
Poland	2004	3	17	6	1	0	0	1	0	0	0	0	4
Portugal	1999	2	0	0	0	0	0	0	0	0	0	0	0
Portugal	2000	0	2	0	0	1	0	0	1	0	2	0	0
Portugal	2001	1	0	0	1	0	0	0	1	3	1	2	6
Portugal	2002	0	0	0	0	0	0	0	0	2	3	1	6
Portugal	2003	1	0	1	2	0	0	0	0	2	0	1	7
Portugal	2004	1	0	1	2	0	1	0	1	1	0	0	4
Slovenia	2000	1	3	1	3	0	0	0	0	1	2	0	2
Slovenia	2001	1	0	0	0	0	0	1	1	0	2	0	12
Slovenia	2002	0	0	0	1	0	0	0	1	0	1	0	5
Slovenia	2003	0	0	0	1	0	0	0	1	1	2	0	8
Slovenia	2004	0	0	0	2	0	0	0	5	0	1	1	5
Sweden	1999	1	5	1	9	-	-	-	-	-	-	-	-
Sweden	2000	0	2	2	26	-	-	-	-	-	-	-	-
Sweden	2001	0	1	1	17	-	-	-	-	-	-	-	-
Sweden	2002	3	4	1	14	-	-	-	-	-	-	-	-
Sweden	2003	2	3	2	17	-	-	-	-	-	-	-	-
Sweden	2004	1	0	2	34	-	-	-	-	-	-	-	-
United Kingdom	1999	12	23	4	32	1	2	0	14	25	9	5	144
United Kingdom	2000	15	52	8	32	3	4	2	20	28	21	8	162
United Kingdom	2001	24	78	14	44	1	9	1	26	32	13	9	183
United Kingdom	2002	31	142	33	103	1	5	0	29	36	16	6	180
United Kingdom	2003	30	105	34	126	3	2	2	41	35	16	12	220
United Kingdom	2004	18	27	24	101	5	3	6	30	38	21	6	162

Table A4 Number of cases and clinical presentation of probable and confirmed cases of *Haemophilus influenzae* serotype b, by country and age group, 1999 – 2004

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Australia	1999	6	6	1	0	0	0	0	1	0	0	1	0	0	0	0	1	1	0	0	0	3	3	0	3	0	0	0	0
Australia	2000	5	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	1	0	0	0	0	1	2	0	0	1	0	0
Australia	2001	2	1	0	0	1	2	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	2	3	0	1	0	0	0
Australia	2002	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	1	1	2	0	0	0	1	0
Australia	2003	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0	2	0	0	0	0	5	1	0	0	0	1	0
Australia	2004	1	1	1	0	0	0	3	0	0	0	0	0	0	0	0	0	0	2	2	0	1	1	0	0	0	0	0	0
Austria	2002	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Austria	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Austria	2004	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Czech Republic	1999	13	37	4	0	0	28	7	3	0	0	0	0	0	0	0	0	1	2	0	2	3	1	1	1	0	0	0	0
Czech Republic	2000	10	43	8	2	0	19	4	1	0	0	0	0	1	3	0	0	0	0	1	1	2	6	1	1	0	0	0	0
Czech Republic	2001	12	34	5	4	0	24	2	2	0	0	0	0	0	2	0	0	0	0	1	1	2	2	1	0	0	0	0	0
Czech Republic	2002	2	27	7	3	0	6	1	1	0	0	0	0	0	1	0	1	0	0	1	1	1	3	1	0	0	0	0	0
Czech Republic	2003	2	15	5	1	0	7	4	0	0	0	0	0	1	0	0	1	0	2	1	2	0	0	1	1	0	0	0	0
Czech Republic	2004	0	3	1	0	0	3	5	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	1	0	0	0	0
Denmark	1999	1	0	0	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2000	1	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2001	0	0	1	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2002	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2003	0	1	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2004	0	1	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Estonia	1999	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	-	-	-	-
Estonia	2000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	1	0	-	-	-	-	-
Estonia	2001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1	0	-	-	-	-	-
Estonia	2002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1	0	-	-	-	-	-
Estonia	2003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	1	0	-	-	-	-	-
Estonia	2004	1	12	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3	1	-	-	-	-	-

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Finland	1999	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	0	0	0	1
Finland	2000	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Finland	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0	0
Finland	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
Finland	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Finland	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
France	1999	4	1	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
France	2000	3	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0	0
France	2001	5	1	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	3	0	0	0	0
France	2002	3	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	5	0	0	0	0
France	2003	4	6	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	1	0	0	0	0
France	2004	3	5	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Germany	1999	1	6	1	-	0	0	1	-	0	0	0	-	0	0	0	-	0	0	0	-	1	1	1	-	0	1	0	-
Germany	2000	7	6	2	-	0	5	1	-	0	0	0	-	0	0	0	-	0	0	0	-	2	0	1	-	1	0	0	-
Germany	2001	7	5	2	-	1	1	0	-	0	0	0	-	0	0	0	-	0	1	0	-	1	0	1	-	0	0	0	-
Germany	2002	3	5	1	-	0	1	0	-	1	0	0	-	0	0	0	-	1	0	0	-	1	0	1	-	0	0	0	-
Germany	2003	6	4	1	-	1	2	0	-	1	0	0	-	1	1	0	-	0	0	0	-	1	0	0	-	0	1	0	-
Germany	2004	1	1	0	-	0	0	0	-	0	0	0	-	0	0	0	-	1	1	2	-	0	0	1	-	0	0	0	-
Greece	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Greece	2000	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Greece	2001	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2002	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1	0	2	1	0	0	0	0	0	0
Greece	2003	1	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
Greece	2004	3	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
Iceland	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Iceland	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Ireland	1999	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0
Ireland	2000	1	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Ireland	2001	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	2	0	0	0	0
Ireland	2002	0	4	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0	1	0	1	0	0	0	0
Ireland	2003	3	1	1	0	0	0	0	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	0	1	0	0	0	0
Ireland	2004	1	3	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	2	0	3	0	3	0	0	0	0
Israel	1999	2	0	0	-	0	0	0	-	1	0	0	-	0	0	0	-	0	2	0	-	0	1	0	-	0	0	0	-
Israel	2000	4	0	0	-	0	0	0	-	1	0	0	-	0	0	0	-	1	2	1	-	0	1	1	-	0	0	0	-
Israel	2001	1	0	1	-	0	0	0	-	0	0	0	-	0	0	0	-	0	1	0	-	3	1	0	-	0	0	0	-
Israel	2002	2	0	1	-	0	0	0	-	1	0	0	-	1	0	0	-	0	0	1	-	0	0	0	-	0	0	0	-
Israel	2003	3	0	0	-	0	0	1	-	0	0	0	-	0	0	0	-	0	1	0	-	0	0	0	-	0	0	0	-
Israel	2004	5	0	0	-	0	0	0	-	3	0	0	-	0	1	0	-	0	0	0	-	0	1	0	-	0	0	0	-
Italy	1999	18	20	1	4	1	0	0	1	0	0	0	0	0	0	0	1	0	0	1	2	0	0	0	1	0	0	0	0
Italy	2000	12	12	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Italy	2001	2	7	1	5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Italy	2002	4	2	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Italy	2003	2	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Italy	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latvia	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Latvia	2004	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2004	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	1999	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	4	0	0	0	0
Netherlands	2000	3	5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	1
Netherlands	2001	3	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	5	0	0	0	1
Netherlands	2002	5	0	0	0	0	2	0	0	0	0	0	0	1	3	0	0	0	0	0	1	1	1	0	4	0	1	0	1
Netherlands	2003	3	4	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	4	0	1	0	3
Netherlands	2004	5	5	0	6	1	1	0	3	0	0	0	0	0	0	1	0	0	0	0	2	1	0	1	5	0	0	1	9

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Norway	1999	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	1
Norway	2000	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	1	0	1
Norway	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Norway	2002	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	3
Norway	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0
Norway	2004	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	1
Poland	1999	5	15	3	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2000	9	14	6	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2001	13	14	4	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2002	5	21	4	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	1	2	0	-	-	-	-
Poland	2003	6	19	3	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	3	0	0	-	-	-	-
Poland	2004	3	17	5	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	1	0	-	-	-	-
Portugal	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2000	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Portugal	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2003	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Portugal	2004	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Slovenia	2000	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slovenia	2001	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slovenia	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slovenia	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Slovenia	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	1999	0	2	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Sweden	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	2002	2	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	0	0	0
Sweden	2003	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
Sweden	2004	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
United Kingdom	1999	6	10	2	5	0	5	1	2	1	0	0	0	0	0	0	0	0	1	0	9	5	4	0	9	0	3	1	5
United Kingdom	2000	7	18	3	2	0	8	1	4	2	3	0	1	1	2	0	3	0	2	0	9	4	11	2	9	1	5	2	2
United Kingdom	2001	11	28	2	1	1	22	2	6	4	2	0	1	1	5	0	0	0	0	1	12	6	9	5	16	1	12	3	5
United Kingdom	2002	15	59	11	4	0	23	3	22	2	4	0	3	1	5	1	3	1	1	0	18	5	32	6	22	4	13	10	25
United Kingdom	2003	16	34	4	7	0	19	9	26	4	4	1	0	1	3	1	0	1	3	3	21	7	29	9	40	0	9	4	17
United Kingdom	2004	8	15	2	7	0	2	5	20	0	0	0	0	1	0	1	2	0	0	4	20	2	5	9	33	4	3	1	13

Table A5 Number of cases and clinical presentation of probable and confirmed cases of non-capsulated *Haemophilus influenzae*, by country and age group, 1999 – 2004

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Austria	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Austria	2003	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Austria	2004	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Denmark	1999	0	1	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2000	1	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2001	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2002	0	0	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2003	0	1	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Denmark	2004	0	0	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Finland	1999	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0
Finland	2000	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	1	0	0	2	0	0	0	1
Finland	2001	0	1	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	1	4	0	0	0	1
Finland	2002	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	2	0	0	0	0
Finland	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Finland	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
France	1999	0	0	1	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	1	2	10	4	1	0	6
France	2000	3	3	2	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	2	4	1	14	1	0	0	3
France	2001	2	0	1	14	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	10	1	1	0	45	2	0	0	5
France	2002	0	3	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	10	2	1	2	23	3	0	0	4
France	2003	0	2	1	14	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	10	2	0	1	25	0	0	1	0
France	2004	3	3	1	12	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	11	1	1	3	24	1	1	2	6
Germany	1999	0	3	0	-	0	0	0	-	0	0	0	-	0	1	0	-	0	0	0	-	5	1	0	-	0	0	0	-
Germany	2000	3	3	7	-	0	0	0	-	0	0	0	-	0	0	0	-	1	0	1	-	5	4	2	-	0	0	2	-
Germany	2001	1	3	3	-	0	0	0	-	0	0	0	-	0	0	0	-	3	1	1	-	3	0	0	-	1	4	1	-
Germany	2002	3	4	3	-	0	0	0	-	0	0	0	-	0	0	0	-	0	1	0	-	0	2	1	-	0	2	1	-
Germany	2003	1	2	1	-	0	0	0	-	0	0	1	-	0	0	0	-	0	0	0	-	3	2	1	-	0	0	0	-
Germany	2004	0	1	0	-	0	0	0	-	0	0	0	-	0	0	0	-	5	1	0	-	2	2	4	-	0	0	0	-

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Iceland	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Iceland	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Iceland	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Iceland	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	1999	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0	0
Ireland	2000	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Ireland	2001	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
Ireland	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Ireland	2003	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0
Ireland	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
Israel	1999	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-
Israel	2000	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	1	0	0	-	0	0	0	-	0	0	0	-
Israel	2001	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	3	8	4	-	0	1	0	-
Israel	2002	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	2	2	0	-	4	4	0	-	0	0	0	-
Israel	2003	0	1	0	-	0	0	0	-	0	0	1	-	0	0	0	-	1	4	0	-	1	7	1	-	0	0	0	-
Israel	2004	0	0	0	-	0	0	0	-	0	0	0	-	0	0	0	-	0	1	0	-	0	4	0	-	0	0	0	-
Italy	1999	0	0	1	3	0	0	0	3	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	2	0	0	0	1
Italy	2000	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	5	0	0	0	0
Italy	2001	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	1	0	0	0	0
Italy	2002	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Italy	2003	0	1	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0	0	1
Italy	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2003	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2004	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Netherlands	1999	0	4	3	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	1	5	27	0	0	0	0
Netherlands	2000	1	1	0	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	1	1	0	7	0	1	0	7
Netherlands	2001	1	1	1	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	4	0	41	0	0	0	0
Netherlands	2002	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0
Netherlands	2003	3	1	1	4	1	0	0	0	0	0	0	0	0	0	0	0	2	3	0	8	2	1	1	15	0	2	0	9
Netherlands	2004	3	2	0	8	0	0	0	0	0	0	0	0	0	1	0	0	2	2	0	7	2	1	0	13	1	3	1	8
Norway	1999	0	1	1	5	0	0	0	0	0	0	0	0	0	0	0	1	1	2	0	20	1	0	0	19	0	1	0	13
Norway	2000	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	11	1	1	0	14	2	1	0	9
Norway	2001	0	1	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0	1	0	10	0	0	0	5	0	0	0	8
Norway	2002	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	13	0	1	0	8	0	0	0	18
Norway	2003	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	10	0	0	0	3	0	0	2	5
Norway	2004	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	10	0	0	0	4	0	0	1	4
Poland	1999	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2000	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2001	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2002	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2003	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Poland	2004	0	0	0	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	-	-	-	-
Portugal	1999	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Portugal	2001	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	0	0	1
Portugal	2002	0	2	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Portugal	2003	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Portugal	2004	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Slovenia	2000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slovenia	2001	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	3
Slovenia	2002	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Slovenia	2003	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Slovenia	2004	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0

Country	Year	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
		<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
United Kingdom	1999	2	2	0	7	0	0	0	0	0	0	0	2	0	0	0	1	4	2	0	25	13	2	2	68	4	3	3	39
United Kingdom	2000	3	2	1	13	0	0	0	0	0	1	0	1					2	1	1	37	12	10	5	60	10	7	1	46
United Kingdom	2001	2	1	3	14	0	0	0	0	0	0	1	0	0	0	0	1	2	1	0	33	13	4	4	81	13	7	1	47
United Kingdom	2002	2	3	0	15	0	1	0	0	1	0	0	1	0	1	0	0	2	2	3	30	19	4	1	75	12	4	1	50
United Kingdom	2003	1	1	2	14	0	0	0	2	0	0	1	1	0	0	0	2	4	2	1	36	14	6	6	91	14	5	1	54
United Kingdom	2004	3	4	1	9	1	0	0	2	0	2	0	1	0	0	0	3	2	5	1	26	18	3	4	79	6	5	0	32

Table A6 Number of cases and clinical presentation of probable and confirmed cases of non-b capsulated *Haemophilus influenzae*, by country and age group, 1999 – 2004 combined

Country	Meningitis				Epiglottitis				Cellulitis				Osteomyelitis/septic arthritis				Pneumonia				Bacteraemia				Other			
	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years	<1 year	1 - 4 years	5 –14 years	15+ years
Austria	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Finland	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0
France	4	5	2	3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	9	0	1	0	11	2	0	0	2
Germany	6	8	2	-	0	0	0	-	0	0	1	-	1	0	0	-	0	1	2	-	1	0	1	-	0	0	0	-
Iceland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Ireland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Israel	0	0	0	-	0	0	0	-	0	0	0	-	2	0	0	-	0	2	0	-	1	0	0	-	0	0	0	-
Italy	0	1	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0	0
Netherlands	5	1	3	8	0	0	0	0	0	0	0	0	0	0	0	3	0	1	0	3	1	1	0	11	0	0	0	1
Norway	0	0	1	6	0	0	0	2	0	0	0	0	0	0	0	2	0	1	0	14	0	0	0	10	0	0	0	9
Poland	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Slovenia	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
United Kingdom	8	3	1	12	0	0	0	5	1	1	0	1	0	0	0	1	0	7	2	38	1	12	6	69	4	2	1	24

Table A7 Number of deaths from probable and confirmed cases *Haemophilus influenzae*, by country and age group, 1999 – 2004

Country	Year	b				non-b capsulated				non-capsulated			
		<1 year	1 – 4 years	5 – 14 years	15+ years	<1 year	1 – 4 years	5 – 14 years	15+ years	<1 year	1 – 4 years	5 – 14 years	15+ years
Australia	1999	0	1	0	2	0	0	0	0	0	0	0	0
Australia	2000	0	0	0	0	0	0	0	0	0	0	0	0
Australia	2001	0	0	2	0	0	0	0	0	0	0	0	0
Australia	2002	0	0	0	0	0	0	0	0	0	0	0	0
Australia	2003	1	0	0	0	0	0	0	0	0	0	0	0
Australia	2004	1	0	0	0	0	0	0	0	0	0	0	0
Czech Republic	1999	0	1	0	0	0	0	0	0	0	0	0	0
Czech Republic	2000	0	2	1	0	0	0	0	0	0	0	0	0
Czech Republic	2001	0	1	0	0	0	0	0	0	0	0	0	0
Czech Republic	2002	0	0	0	0	0	0	0	0	0	0	0	0
Czech Republic	2003	1	1	0	1	0	0	0	0	0	0	0	0
Czech Republic	2004	0	1	0	0	0	0	0	0	0	0	0	0
Denmark	1999	0	0	0	1	0	0	0	0	0	0	0	0
Denmark	2000	0	0	0	0	0	0	0	0	0	0	0	0
Denmark	2001	0	0	0	0	0	0	0	0	0	0	0	0
Denmark	2003	0	0	0	0	0	0	0	0	0	0	0	0
Denmark	2004	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	1999	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	2000	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	2001	1	0	0	0	0	0	0	0	0	0	0	0
Estonia	2002	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	2003	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	2004	0	1	0	0	0	0	0	0	0	0	0	0
France	1999	0	0	0	0	0	0	0	1	2	0	0	2
France	2000	0	0	0	0	0	0	0	0	0	0	0	0
France	2001	0	1	0	0	0	0	0	1	0	0	0	0
France	2002	0	0	0	0	1	0	0	1	0	0	0	0
France	2003	0	0	0	0	0	0	0	0	0	1	0	0
France	2004	0	0	0	0	0	0	0	0	0	0	0	1
Germany	1999	0	2	0	0	0	0	0	0	0	0	0	0
Germany	2000	1	0	0	0	0	0	0	0	0	0	0	0
Germany	2001	1	0	0	0	0	0	0	0	1	0	0	0
Germany	2002	0	1	0	0	0	0	0	0	0	1	0	0
Germany	2003	0	1	0	0	0	0	0	0	0	0	0	0
Germany	2004	0	0	0	0	1	0	0	0	0	0	0	0
Greece	1999	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2000	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2001	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2002	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2003	0	0	0	0	0	0	0	0	0	0	0	0
Greece	2004	0	0	0	0	0	0	0	0	0	0	0	0
Iceland	2001	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	1999	0	0	0	0	0	0	0	0	0	0	0	2
Ireland	2000	0	0	0	0	0	0	0	0	1	0	0	0
Ireland	2001	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	2002	0	0	0	0	0	0	0	0	0	0	0	1
Ireland	2003	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	2004	0	0	0	0	0	0	0	0	0	1	0	2

Country	Year	b				non-b capsulated				non-capsulated			
		<1 year	1 – 4 years	5 – 14 years	15+ years	<1 year	1 – 4 years	5 – 14 years	15+ years	<1 year	1 – 4 years	5 – 14 years	15+ years
Israel	1999	0	0	0	0	0	0	0	0	0	0	0	0
Israel	2000	1	1	0	0	0	0	0	0	0	0	0	0
Israel	2001	1	0	0	0	0	0	0	0	0	2	0	0
Israel	2002	0	0	0	0	0	0	0	0	0	1	0	0
Israel	2003	0	0	0	0	0	0	0	0	0	1	0	0
Israel	2004	0	0	0	0	0	0	0	0	0	0	0	0
Italy	1999	0	0	0	1	0	0	0	0	0	0	0	0
Italy	2000	0	0	0	0	0	0	0	2	0	0	0	3
Italy	2001	0	1	0	1	0	0	0	1	0	0	0	1
Italy	2002	0	0	0	0	0	0	0	0	0	0	0	0
Italy	2003	0	0	0	1	0	0	0	0	0	0	0	0
Italy	2004	0	0	0	0	0	0	0	0	0	0	0	2
Latvia	2004	0	0	0	0	0	0	0	0	0	0	0	0
Malta	2004	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	1999	0	1	0	0	0	0	0	0	1	0	1	1
Netherlands	2000	0	0	0	0	1	1	0	0	0	1	0	2
Netherlands	2001	0	0	0	1	0	0	0	0	1	0	0	4
Netherlands	2002	0	1	0	0	0	0	0	0	0	0	0	1
Netherlands	2003	0	0	0	0	0	0	0	0	0	0	0	4
Netherlands	2004	0	0	0	0	0	0	0	0	0	0	0	1
Norway	1999	0	0	0	0	0	0	0	0	0	1	0	11
Norway	2000	0	0	0	0	0	0	0	0	1	0	0	6
Norway	2001	0	0	0	0	0	0	0	1	0	0	0	5
Norway	2002	0	0	0	0	0	0	0	0	1	1	0	7
Norway	2003	0	0	0	0	0	0	0	2	0	0	0	2
Norway	2004	0	0	0	0	0	0	0	1	0	1	0	0
Portugal	1999	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2000	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2001	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2003	0	0	0	0	0	0	0	0	0	0	0	0
Portugal	2004	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	1999	0	1	0	0	0	0	0	0	0	0	0	0
Sweden	2002	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	2003	0	1	0	1	0	0	0	0	0	0	0	0
Sweden	2004	0	0	0	8	0	0	0	0	0	0	0	0
United Kingdom	1999	1	1	1	6	0	0	0	3	5	2	1	17
United Kingdom	2000	1	0	0	3	0	0	0	2	8	3	1	26
United Kingdom	2001	0	1	0	2	1	0	0	3	9	0	1	35
United Kingdom	2002	2	7	2	7	1	0	0	5	10	3	1	24
United Kingdom	2003	0	1	2	10	0	0	1	4	10	1	0	28
United Kingdom	2004	2	1	1	9	0	0	0	6	8	2	0	18

Table A8 Case fatality ratio of probable and confirmed cases *Haemophilus influenzae*, by country, 1999 – 2004

Country	Year	b		non-b capsulated		non-capsulated	
		Annual	Average annual	Annual	Average annual	Annual	Average annual
Australia	1999	11%	7%	-		-	
Australia	2000	0%		-		-	
Australia	2001	12%		-		-	
Australia	2002	0%		-		-	
Australia	2003	8%		-		-	
Australia	2004	8%		-		-	
Austria	2002	0%	0%	0%	0%	0%	0%
Austria	2003	0%		0%		0%	
Austria	2004	0%		0%		0%	
Czech Republic	1999	1%	3%	-		-	
Czech Republic	2000	3%		-		-	
Czech Republic	2001	1%		-		-	
Czech Republic	2002	0%		-		-	
Czech Republic	2003	7%		-		-	
Czech Republic	2004	6%		-		-	
Denmark	1999	25%	4%	0%	0%	0%	0%
Denmark	2000	0%		0%		0%	
Denmark	2001	0%		0%		0%	
Denmark	2002	0%		0%		0%	
Denmark	2003	0%		0%		0%	
Denmark	2004	0%		0%		0%	
Estonia	1999	0%	6%	0%	0%	0%	0%
Estonia	2000	0%		0%		0%	
Estonia	2001	33%		0%		0%	
Estonia	2002	0%		0%		0%	
Estonia	2003	0%		0%		0%	
Estonia	2004	6%		0%		0%	
France	1999	0%	1%	11%	12%	11%	2%
France	2000	0%		0%		0%	
France	2001	7%		11%		0%	
France	2002	0%		50%		0%	
France	2003	0%		0%		2%	
France	2004	0%		0%		1%	
Germany	1999	15%	6%	0%	4%	0%	2%
Germany	2000	4%		0%		0%	
Germany	2001	5%		0%		5%	
Germany	2002	7%		0%		6%	
Germany	2003	5%		0%		0%	
Germany	2004	0%		25%		0%	
Greece	1999	0%	0%	0%	0%	0%	0%
Greece	2000	0%		0%		0%	
Greece	2001	0%		0%		0%	
Greece	2002	0%		0%		0%	
Greece	2003	0%		0%		0%	
Greece	2004	0%		0%		0%	

Country	Year	b		non-b capsulated		non-capsulated	
		Annual	Average annual	Annual	Average annual	Annual	Average annual
Iceland	1999	0%	0%	0%	0%	0%	0%
Iceland	2000	0%		0%		0%	
Iceland	2001	0%		0%		0%	
Iceland	2002	0%		0%		0%	
Iceland	2003	0%		0%		0%	
Iceland	2004	0%		0%		0%	
Ireland	1999	0%	0%	0%	0%	29%	19%
Ireland	2000	0%		0%		33%	
Ireland	2001	0%		0%		0%	
Ireland	2002	0%		0%		17%	
Ireland	2003	0%		0%		0%	
Ireland	2004	0%		0%		33%	
Israel	1999	0%	5%	0%	0%	0%	5%
Israel	2000	18%		0%		0%	
Israel	2001	14%		0%		13%	
Israel	2002	0%		0%		8%	
Israel	2003	0%		0%		6%	
Israel	2004	0%		0%		0%	
Italy	1999	2%	4%	0%	14%	0%	18%
Italy	2000	0%		50%		43%	
Italy	2001	12%		33%		14%	
Italy	2002	0%		0%		0%	
Italy	2003	13%		0%		0%	
Italy	2004	0%		0%		50%	
Latvia	2003	0%	0%	0%	0%	0%	0%
Latvia	2004	0%		0%		0%	
Malta	1999	0%	0%	0%	0%	0%	0%
Malta	2000	0%		0%		0%	
Malta	2001	0%		0%		0%	
Malta	2002	0%		0%		0%	
Malta	2003	0%		0%		0%	
Malta	2004	0%		0%		0%	
Netherlands	1999	8%	3%	0%	3%	6%	8%
Netherlands	2000	0%		18%		6%	
Netherlands	2001	6%		0%		8%	
Netherlands	2002	3%		0%		25%	
Netherlands	2003	0%		0%		4%	
Netherlands	2004	0%		0%		1%	
Norway	1999	0%	0%	0%	5%	18%	13%
Norway	2000	0%		0%		14%	
Norway	2001	0%		7%		16%	
Norway	2002	0%		0%		18%	
Norway	2003	0%		17%		7%	
Norway	2004	0%		9%		4%	
Poland	1999	0%	0%	0%	0%	0%	0%
Poland	2000	0%		0%		0%	
Poland	2001	0%		0%		0%	
Poland	2002	0%		0%		0%	
Poland	2003	0%		0%		0%	
Poland	2004	0%		0%		0%	

Country	Year	b		non-b capsulated		non-capsulated	
		Annual	Average annual	Annual	Average annual	Annual	Average annual
Portugal	1999	0%	0%	0%	0%	0%	0%
Portugal	2000	0%		0%		0%	
Portugal	2001	0%		0%		0%	
Portugal	2002	0%		0%		0%	
Portugal	2003	0%		0%		0%	
Portugal	2004	0%		0%		0%	
Slovenia	2000	0%	0%	0%	0%	0%	0%
Slovenia	2001	0%		0%		0%	
Slovenia	2002	0%		0%		0%	
Slovenia	2003	0%		0%		0%	
Slovenia	2004	0%		0%		0%	
Sweden	1999	17%	12%	-		-	
Sweden	2002	0%		-		-	
Sweden	2003	8%		-		-	
Sweden	2004	22%		-		-	
UnitedKingdom	1999	13%	6%	18%	13%	14%	15%
UnitedKingdom	2000	4%		7%		17%	
UnitedKingdom	2001	2%		11%		19%	
UnitedKingdom	2002	6%		17%		16%	
UnitedKingdom	2003	5%		10%		14%	
UnitedKingdom	2004	8%		14%		13%	