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EU-IBIS

European Union Invasive Bacterial Infections Surveillance Network

INVASIVE *HAEMOPHILUS INFLUENZAE* IN EUROPE - 2002

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Decision No. 2119/98/EC for setting up a network for the epidemiological surveillance and control of communicable diseases in the Community stated as a priority "Diseases prevented by vaccination". *H. influenzae* infection comes within this priority. Using the framework already established in a BIOMED II Hib surveillance project (1996-1999), the DG SANCO surveillance network project for invasive *H.influenzae* disease was established in all 15 EU countries and 5 non-EU countries in 2000. Further funding for the network was granted for the period October 2001- October 2003.

Aims

- To improve the epidemiological information on invasive *Haemophilus influenzae* disease within the European Union.
- To improve the laboratory capacity to accurately characterise the isolates *of H. influenzae*.
- To form a focus for wider collaboration with non European Union countries and candidate European Union countries.

Methods

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

Improvements in the laboratory capacity within the EU to accurately identify *H. influenzae* have been achieved through gaining information on systems in use by participants, by running a laboratory workshop for new members to the network, and by undertaking an External Quality Assurance Scheme (EQAS) in 2002 with the participant reference laboratories. The EQAS helped identify any existing problems in correctly serotyping *H. influenzae* isolates, and enabled corrections/assistance in laboratory methods to be made, hence improving comparability of data between countries. The laboratory workshop run for new members ensures standardised methods are being used, adding further to correct identification of isolates within the EU.

Results and Conclusions

Prior to introduction of Hib vaccination programmes the epidemiology of invasive Hib disease differed between the EU countries, with incidence rates in children under five varying between 12 and 60 per 100,000. All EU countries now have national immunisation programmes, and therefore the incidence in children under five years, the age group with the highest incidence pre-vaccine, is now very low. Countries are at different stages of vaccine implementation, have different vaccines and schedules and have achieved different levels of coverage. Despite all of these considerations, the incidence of Hib infection in the EU is much lower than in the pre-vaccine era (between 0 and 4 per 100,000).

Surveillance systems varied slightly amongst the participating countries. As most countries include all invasive Hib disease in children under fifteen years, comparison of rates in under fives and under fifteens can be made. Differences may be explained by many factors, including different methods of surveillance and completeness of ascertainment. One of the most important factors is the microbiological practice in relation to the diagnosis of Hib disease. This practice can impact on the establishment of disease burden and on comparisons between countries. The importance of continued improvement of laboratory techniques and laboratory-based surveillance cannot be over-emphasised.

Although the incidence has fallen in countries using vaccine, the clinical presentation of Hib disease has not changed. Meningitis remains the predominant diagnosis, causing over 54% of disease in under two year olds, with epiglottitis being the second most common diagnosis in pre-school children. Pneumonia and bacteraemia are more common presentations in adults. Apparent differences between countries may be explained by different age distributions of cases and the small numbers of cases.

Amongst children under five in the EU countries, the highest incidence rates in 2002 were in Ireland (2.58), Netherlands (1.60), and the UK (4.34). One of the major differences between the UK and Ireland and the remaining EU countries is the absence of a booster (third or fourth dose) in the second year of life. Over the 1999-2002 period the incidence rate has increased steadily from 0.94 to 4.34 per 100,000 in the UK in children under five years of age. Rates between years in each participant country vary due to small numbers, but the increase observed in the UK, one of the largest populations under surveillance, was responsible for a considerable increase in incidence seen in 2002. Changes in vaccination programmes have occurred over time and may be responsible for changes in incidence observed. Much of the increase observed in the UK is attributable to changes in the vaccine, and continued vigilance to detect changes in other EU countries is required. The importance of continued observation over the whole of the EU is the best way to detect changes at the earliest possible stage.

Rates of non-b capsulated *H. influenzae* infection are low and no evidence of serotype replacement has been observed despite many years of vaccination in many of the EU countries. Rates of non-capsulate infection are now similar to those for type b and emphasises the importance of ensuring accurate identification of the organism in a national reference centre. The low rates observed in some countries, probably reflects the low proportion of strains that are referred and highlights the potential for improving ascertainment of such cases.

1. INTRODUCTION

Decision No. 2119/98/EC for setting up a network for the epidemiological surveillance and control of communicable diseases in the Community stated as a priority "Diseases prevented by vaccination". *H. influenzae* infection comes within this priority.

The BIOMED II Hib surveillance project in 9 EU countries and 2 non EU countries (1996-99) was established to describe the epidemiology of invasive *Haemophilus influenzae* and describe the risk factors associated with vaccine failure using different vaccines and schedules. Using the framework already established in the above project, a DG SANCO surveillance network project for invasive *H.influenzae* disease was established in all 15 EU countries and 5 non-EU countries in 2000 to improve epidemiological information and laboratory capacity to characterise isolates of these two invasive bacterial infections. This report is on the cases of invasive *Haemophilus influenzae* reported in 1999-2002

Aims

To improve the epidemiological information on invasive *Haemophilus influenzae* disease within the European Union.
To improve the laboratory capacity to accurately characterise the isolates *of H. influenzae*.
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 European Union countries and candidate European Union countries.

A European Union network for the surveillance of *Haemophilus influenzae* is important for the following aspects within the Community: pooling of case data; pooling of vaccine failure data; rapid alert of changes in the epidemiology of infection strains; setting standards. The collection of data at European level will be available to member states to inform policy development within each country. This may therefore contribute to the harmonisation of European Hib vaccine policy and schedules.

As *Haemophilus influenzae* disease in a vaccinated community is rare, this project allows pooling of such data to increase the power of any epidemiological analysis. Hib vaccine has been demonstrated to reduce nasopharyngeal carriage of Hib and it has been postulated that one consequence of reduced exposure to this organism could be the early waning of vaccine induced immunity. In addition, the potential emergence of non-vaccine preventable strains of *H. influenzae* has been suggested. European wide analysis should be able to detect an increase in cases of Hib in older children or adults, or an increase in the incidence of non-b *Haemophilus influenzae* at an earlier stage than analysis of a single country's data. In addition, by pooling data from all countries, the populations under surveillance will become sufficient to provide more precise estimates of vaccine efficacy and will be composed of a wide variety of ethnic groups. These estimates based on pooled data may be able to assess the potential decline in vaccine efficacy with age or in certain groups.

Hib disease in vaccinated children is extremely rare. Pooling of data on vaccine failures at European level is the only reliable means of describing potential risk factors specific to certain social situations or ethnic groups, and collection of data at a European level will also increase the ethnic and social diversity of the population under surveillance.

An established network is needed for the rapid dissemination of changes in the epidemiology of an infection which may have public health significance. In addition, it will facilitate the rapid exchange of information on imported strains *of H. influenzae* infections.

This project, which has included all 15 EU countries, Iceland and Norway, and 3 countries from outside the EU, will be able to set standards for the epidemiological surveillance of *H. influenzae* and for methods used in reference laboratories. Countries are able to learn from models of good practice in other member states and these standards can also be applied in other countries, especially candidate EU and non-EU countries. In addition, establishment of this network may facilitate early dissemination of advances in therapy and in public health control measures and lead to the harmonisation of guidance on meningococcal disease. This project will also provide a model and focus for future research and public health collaborations, for example the evaluation of other new vaccines such as conjugate pneumococcal vaccines.

In this report a summary is given of the up-to-date epidemiological information gained by collecting and analysing *H. influenzae* disease case data from the network participants for 2002, with use of data from earlier years to make comparative comment. This displays the ability of the now established system to monitor changes in the epidemiology of the disease.

Finally, this project will provide substantial and up-to-date epidemiological information from which *H. influenzae* vaccination policy can be developed within individual countries introducing vaccination programmes, and help the development of guidance on prevention and control of meningococcal infection. It may also facilitate the eventual harmonisation of vaccine schedules in the European Union.

2. METHODS

Questionnaires on the surveillance system(s) and the laboratory diagnostic methods were sent to all new participant countries, and updates gained from countries already established as members of the network. The information from both these questionnaires is important for correct interpretation of the data which is gained from each individual country. A vaccination programme questionnaire was also administered to each new participating country, and updates obtained, where necessary, from existing members.

A minimum data set was received from the majority of countries for 2002. The minimum data set includes age, sex, date of onset, method of confirmation, site of identification, grouping, typing and subtyping results (as appropriate) (Refer Appendix 2). These datasets were in most cases electronically transferred to PHLS Communicable Disease Surveillance Centre, where they were entered onto the main Access database. In some instances paper listings of cases were received. The standardised case definitions developed as part of the DG XII project are used, and where surveillance is performed using other definitions, datasets are re-coded to provide comparable data for all participating countries.

Descriptive epidemiology is analysed using standard statistical packages on the minimum data set. Analysis of age-specific incidence rates, temporal trends and diversity of *H. influenzae* infections are compared. In countries with vaccination programmes, coverage data will also be requested and comparison of rates of infection in both vaccinated and unvaccinated cohorts will be interpreted in conjunction with coverage, schedule and vaccine used, since implementation and method of introduction

An External Quality Assurance Scheme was undertaken in 2002 amongst the reference laboratories of the participating countries. The EQAS was lead by the Oxford laboratory.

A central resource was provided in the UK to genotype *H. influenzae* strains from countries with established Hib vaccination programmes. Protocols for PCR genotyping were supplied by the Health Protection Agency UK, for laboratories wishing to establish their own system for genotyping strains of *H.influenzae.* For those countries not wishing to establish or use this method the Oxford laboratory offered to genotype any strains isolated from vaccine failure cases.

Dissemination of results from the surveillance of invasive *H. influenzae* disease in the EU occurs through annual reports to the network participants of the epidemiological data analyses, and presentation of results at meetings and scientific conferences. Feedback reports are given to microbiologist network participants when External Quality Assurance Schemes (EQAS) are undertaken.

A presentation on the epidemiology of *H. influenzae* type b in the EU countries was made at a international conference/workshop in Phoenix, Arizona in September, 2002. A two-day EU-IBIS/H.influenzae network workshop was held in February 2003 at HPA CDSC, Colindale, London.

3. RESULTS

Disaggregated data for 2002 was supplied by 15 countries in the network: Austria, Czech Republic, Denmark, England & Wales, Finland, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Sweden, Israel, and Australia. No disaggregated data was supplied by Belgium, France, Iceland, Luxembourg, and Spain.

3.1 Questionnaire surveys

3.1.1 Surveillance systems

3.1.1.1 Objectives

For countries with vaccination programmes, the objective of the surveillance was to monitor the impact of vaccination by universal case ascertainment of invasive Hib disease. In Portugal the additional objective was to monitor antibiotic resistance in cases of *Haemophilus influenzae* infection

3.1.1.2 Case definitions

The case definition used in each country, except Denmark and Finland, included all cases of invasive Hib disease with isolates from a sterile site. Denmark limited surveillance to meningitis. In Finland the case definition of 'invasive infection' for *H. influenzae* disease consists of blood and CSF isolations, but not isolations from other usually sterile sites.

Antigenic diagnosis was included in the case definitions used by Australia, Czech Republic, Finland and Italy (although some other countries reported such cases to the European data set). Australia was the only country to accept a clinical, non-microbiological diagnosis of epiglottitis (although these were not included in the study data set).

Data for other serotypes was also collected in Finland, Germany, Greece, Iceland, Ireland, Italy, Portugal, Sweden, the Netherlands, Norway and the UK (England & Wales), and Israel.

3.1.1.3 Population under surveillance

All participant countries, except Germany, Greece, and Israel, had a surveillance system across all ages. In Germany, and Israel, cases were only reported in the paediatric population. Prior to 2002, Austria and Sweden were likewise only reporting paediatric cases. In Greece (Attiki) surveillance was limited to paediatric population (under 15 years) in a single region and in Italy enhanced surveillance was performed in seven regions.

3.1.2 Hib vaccination programmes

The details of the type of vaccines used and the immunisation schedules in the ongoing programmes are given below (Table 1). There is considerable variation between countries in the vaccines and schedules used. As well as countries concurrently using more than one vaccine type, the type(s) and schedules being used by a country has changed over time with the continual emergence of new Hib vaccines from the range of manufacturers. Also, a high proportion of the Hib vaccines used are now combination vaccines; possible components being DTaP, DTwP, IPV, or Hepatitis B.

Table 1 : Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries

Country/region	Type of vaccine	Combined with	Immunisation schedule
Australia	**Pre 2001**		
	HbOC (95%)		2, 4, 6, 18 months
	PRP-OMP (5%)		2, 4, 12 months
	2001:		
5 states/territories	Pedvax Hib	DTPa, HepB, OPV	2, 4, 12 months
3 states	PRP-OMP (Comvax)	Hep B	2, 4, 12 months
Austria	**2000**		
	Infanrix + Hib (SKB)	DTaP	3, 4, 5 months & 2nd year of life
	Infanrix-IPV+Hib (SKB)	DTaP, IPV	3, 4, 5 months & 2nd life of life
	Procomvax (Aventis Pasteur MSD)	HBV	3, 4, 5 months & 2nd year of life
	2001		
	As in 2000,		
	plus Hexavac (DTaP-Hib-IPV-HBV)	DTaP, IPV, HBV	3, 4, 5, months and 2nd year of life
	2002		
	Infanrix + Hib (SKB)	DTaP, IPV	3, 4, 5, months and 2nd year of life
	Procomvax	HBV	3, 4, 5, months and 2nd year of life
	Hexavac (Aventis Pasteur MSD)	DTaP, IPV, HBV	3, 4, 5, months and 2nd year of life
	2003		
	As in 2002		
Belgium	**2003**		
	Hib-PRP-T (Hiberix & Act-Hib)	Not combined	2,3,4 months & 13-18 months
	Hib-HBOc	Not combined	2,3,4, months & 13-18 months
Czech Republic	**Jul 2001**		
	Hib-PRP-T (TETRACTHIB) – children <1 year	DTwP,	2,3,4 months & 18-20 months
Denmark	**1/6 1993 –1995**		
	PRP-T (Act-HIB Pasteu Merieux)	Not combined	5, 6, 16 months
	1996		
	PRP-T (Act-HIB Pasteur Merieux)	Not combined	5, 6, 15 months
	1997-2002		
	PRP-T (Act-HIB Pasteur Merieux)	Not combined	3, 5, 12 months
	1/7 2002		
	PRP-T (Act-HIB Pasteur Merieux)	DTaP-IPV/HIB	3, 5, 12 months

Table 1 : Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries (continued)

Country/region	Type of vaccine	Combined with	Immunisation schedule
Finland	**1993 Act-Hib** (Pasteur Merieux) **1994- Sep 2002 HibTITER** (Wyeth-Lederle) **Oct. 2002** Hiberix (GSK)	Combined with DTwP Not combined Not combined	4, 6 & 14-18 months
France	**1993** Hib PRP-T **1998** Hib PRP-T **2002 :** Hib-PRP-T **2003 : (not yet but should start this year)** Hib-PRP-T	 DTwP, IPV DTwP, DTaP, IPV DTwP, DTaP, IPV DTwP, DTaP, IPV, Hep B	 Pentacoq 2, 3, 4, 18 months Pent hibest 2, 3, 4, 18 months Pentacoq 2, 3, 4, 18 months Pent hibest 2, 3, 4, 18 months Pentavac 18 months Infanrix Polio Hib 18 months Pentacoq 2, 3, 4, 18 months Pentavac 2, 3, 4, 18 months Infanrix Polio Hib 2, 3, 4, 18 months Hexavac 2, 4, 18 months (vaccine with 5 antigens at 3 months of age)
Germany (In 2001, all the vaccines listed were available and in use)	**Since 1992/1993** Hib-PRP-T-CRM_{197} Hib-PRP-T **Since 1996** Hib-PRP OMPC Hib-PRP-T **Since 1997/1998** Hib-PRP-T **Since 1999** Hib PRP-OMPC **Since 2000/2001**	 Not combined Not combined DTaP DTaP-IPV Hep B DtaP-IPV-HBV	 2, 4 months, plus 11-14 months 2, 4 months, plus 11-14 months 2, 3, 4 months, plus 11-14 months* 2, 3, 4 months, plus 11-14 months* 2, 4 months, plus 11-14 months 2, 3, 4 months, plus 11-14 months*

Table 1 : Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries (continued)

Country/region	Type of vaccine	Combined with	Immunisation schedule
Germany cont'd	Hib-PRP-T		* Given at least 4 weeks apart with a min. of 6 months between last dose (11-14 mth dose) and previous dose
Greece	**1999** PRP-T HbOC **2003** PRP-T (Act-Hib, Hiberix) HbOC (Hibtiter) HibOMP (Procomvax)	 DTaP, IPV DtaP, IPV, Hep B Not combined Hep B	 2, 4, 6, 18 months 2, 4, 6, 15-18 months 2, 4, 6, 15-18 months On special occassions, by case
Iceland	PRP-D ProHIBit **Jan 2000 onwards** PRP-T (Pentavac)	 DTaP, IPV	3, 4, 6, 14 months 3, 5, 12 months
Ireland	**Pre August 2001** PRP-T (ACTHib or HibTITRE(60%), Hiberix(30%) **Post August 2001** PRP-T (Pentavac) (100%) **2002** PRP-T (Infanrix) (70%) PRP-T (Pantavac) (30%)	 DTaP, IPV DTaP, IPV DTaP, IPV	 2, 4, 6 months 2, 4, 6 months 2, 4, 6 months 2, 4, 6 months
Israel	**1994-1997** PRP-OMP (90%) HbOC/PRP-T **Jul 1997 onwards** PRP-T 1999 PRP-T HboC **May 2002 onwards** PRP-T plus PRP-T	 DTwP DTwP DTaP, IPV plus DTaP	 2, 4, 12 months 2, 4, 6, 12 months 2, 4, 6, 12 months 2,4,12 months 6 months

Table 1 : Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries (continued)

Country/region	Type of vaccine	Combined with	Immunisation schedule
Italy	**1995-March 1999**		For all vaccines :
	PRP-T	Not combined	<6 months (3 doses + booster)
	HbOC	Not combined	6-12 months (2 doses + booster)
			>12 months (1 dose)
	April 1999 onwards		
	PRP-T	Not combined	For all vaccines :
	HbOC (not available in 1997)	Not combined	3, 5, 11-12 months
	PRP-T (since 1999)	DTaP, IPV	
	OMP (since 2000)	HepB	
	PRP-T (since 2001)	DTaP, IPV, HepB	
Netherlands	PRP-T	DTP, IPV (in other limb)	3, 4, 5, 11 months
	1999 PRP-T		2, 3, 4, 11 months
	Since 2003		
	Hib-PRP-T	DTwP, IPV	2, 3, 4, 11 months
Norway	**2001 onwards**		
	PRP-T (100%) (Infanrix-Polio+Hib)	DTaP, IPV	3, 5, 11-12 months
Portugal	**2000-2001**		
	HbOC (Hibtiter)	Not combined	
	2002		
	HbOC (Hibtiter)	Not combined	2, 4, 6, 15-18 months
	PRP-T (Tetract-Hib)	DTwP	
	2003		
	PRP-T (Hiberix)	Not combined	
	PRP-T (Tetract-Hib)	DTwP	
Spain	**2002**		
	Hib-PRP-T (Hiberix, ACT-Hib)	Not combined	2, 4, 6, 15-18 months
	Hib-PRP-T (Infanrix-Hib)	DTaP	2, 4, 6, 15-18 months
	Hib-PRP-T (TETRACT-Hib)	DTwP	2, 4, 6, 15-18 months
	Hib-PRP-T (PENTACT-Hib)	DTwP, IPV	2, 4, 6, 15-18 months
	CRM-197 (HibTitre)	Not combined	2, 4, 6, 15-18 months
	Note : Infanrix-Hib-IPV & Infanrix-Hexa-Hexavac are sold in pharmacies, but are not included in the official vaccination schedule.		

Table 1 : Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries (continued)

Country/region	Type of vaccine	Combined with	Immunisation schedule
Sweden	**1992-1993** PRP-OMP (PedvaxHIB) or PRP-T (Act-Hib)	DT separately, IPV separately or mixed with PRP-T	3, 5, 12 months
	1993-1995 PRP-T (Act-Hib)	As above	3, 5 12 months
	1996-1997 PRP-T (Act-Hib)	DTaP separately, IPV separately or mixed with PRP-T	3, 5, 12 months
	1998-1999 PRP-T (Act-Hib or Pentavac)	As above or in 5-valent combination vaccine	3, 5, 12 months
	1999 PRP-T (Pentavac or Infanrix-Polio+Hib)	In 5-valent combination vaccines	3, 5, 12 months
United Kingdom	**Pre 1996** HBOC (Hib only) PRP-T (Hib only) **Since 1996** DTwP/PRP-T (some DTaP used in 2000)	 DTwP	 2, 3, 4 months 2, 3, 4 months 2, 3, 4 months

3.1.2 Laboratory questionnaire

Information on laboratory methods was previously supplied by nineteen countries: Australia, Austria, Belgium,Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and the UK). Refer to the 2001 report for information on: the laboratory Hib identification and reference facilitites used in the countries; the means of specimen transport, receipt and storage; identification methods, serotyping and gentyping of strains; and access to a central laboratory facility.

3.2 Laboratory External Quality Assurance Scheme (EQAS) for *Haemophilus influenzae*

20 laboratories were contacted and invited to participate in the EQA distribution. Four laboratories did not reply to the invitation to participate. Sixteen sets of lyophilised EQA samples were distributed by courier. Two laboratories failed to return any results. There were therefore 14 sets of results available for review. (Table 2)

Strain 19 was *Haemophilus influenzae* type b (biotype I). This was a β-lactamase producing strain that was resistant to ampicillin, but susceptible to chloramphenicol, tetracycline, rifampicin, trimethoprim and ceftriaxone.
Every laboratory correctly identified the strain as Hib. Three laboratories did not perform a beta-lactamase test (these laboratories did not carry out any antimicrobial susceptibility tests on the EQA strains). One laboratory recorded the strain as β-lactamase negative and resistant to ampicillin, co-amoxyclav, cefuroxime and ceftriaxone.
Comments: Rarely strains of *H.influenzae* can exhibit both intrinsic resistance to β-lactams (BLNAR) and resistance due to β-lactamase activity. This strain was re-tested in the HRU but we were unable to demonstrate resistance to co-amoxyclav or cephalosporins.

Strain 25 This was *Haemophilus influenzae* - a non-capsulated strain (Biotype IV). The strain was β-lactamase negative and fully sensitive to the antimicrobials tested.
10 laboratories correctly identified this strain. 3 laboratories identified it as serotype d. One laboratory identified it as serotype a. One laboratory commented that it gave agglutination with type a, b and d antisera.
Comments: this strain agglutinates with polyvalent *H.influenzae* antiserum and with type d antiserum. It looks non-capsulated on the culture plate, the colonies being amall and non-mucoid. Type d strains are extremely rare. Using molecular methods (PCR) the strain is OMP positive (confirming that it is *H.influenzae) and VK negative (confirming that it is non-capsulated.*.

Strain 28 was *H.influenzae,*- a non-capsulated strain (biotype II). This strain was β-lactamase negative and resistant to trimethoprim.
12 laboratories correctly identified this strain. 1 laboratory identified it *as* H.influenzae *type f.* 1 laboratory identified it as serotype c. 3 stated that it was trimethoprim resistant. 1 laboratory reported that it was "less susceptible " to ampicillin.
Comments The strain looked non-capsulated on the culture plates. The HRU could not confirm any agglutination with polyvalent or monospecific *H.influenzae* antisera. PCR-based genotyping confirmed the strain was non-capsulated (OMP +, VK -, b-,c-, f-) The trimethoprim MIC was >32 μg/ml.= resistant. Ampicillin MIC was 1 μg/ml =sensitive

Strain 32 was *H.influenzae* type e (biotype IV). This strain was β-lactamase negative and susceptible to all the antibiotics tested.
12 laboratories correctly identified this strain. 2 laboratories found it to be non-typable. One laboratory said that it gave agglutination with polyvalent and type a,b, e antisera. One laboratory commented that it was auto-agglutinating. 13 laboratories found it to be β-lactamase negative, 1 found it to be β-lactamase positive.
Comments This strain looks capsulated on the culture plates. The colonies are larger and mucoid compared to the non-capsulated strains.
Agglutination with more than one type-specific antiserum cannot be interpreted and requires confirmatory capsular genotyping. Auto-agglutinating strains need to be further tested using capsular genotyping.

Strain 33 was *H.influenzae* – a non-capsulated strain (biotype III). It was β-lactamase negative and resistant to trimethoprim and rifampicin.
11 laboratories correctly identified this strain.(1 commented that it agglutinated with polyvalent antiserum and gave equivocal reactions with type d and e monovalent antisera). 3 laboratories identified it as Hib(1 commented on "discrete auto-agglutination"). 6 laboratories found it to be rifampicin resistant .5 found it to be trimethoprim resistant.
Comments This strain looked non-capsulated on the culture plates. Any reaction with more than one type-specific antiserum should be checked by capsular genotyping. Any auto-agglutination renders slide agglutination uninterpretable. PCR capsular genotyping is required. In our hands this strain was clearly resistant to trimethoprim (MIC > 32 μg/ml and rifampicin (MIC>32 μg/ml)

Strain 34 was *Haemophilus paraphrophilus*. It was β-lactamase negative.
6 laboratories correctly identified this strain. 3 identified it as *H.parainfluenzae,* 2 identified it as *H.aphrophilus,* and 1 identified it as *Haemophilus sp.* And 2 stated that it was not *H.influenzae.*
Comments The strain was V-factor dependent, oxidase positive, catalase negative. The colonies looked slightly yellow and were variable in size. RapID NH gave a 99% implicit identification of *H.paraphrophilus.* It is difficult to distinguish *H.paraphrophilus* from *H.parainfluenzae* following primary isolation. *H.paraphrophilus* tends to lose its requirement for CO2 after subculturing and most laboratories routinely incubate haemophilus cultures in CO2 .

Conclusions:
All of the participating laboratories correctly identified Hib.
Some of the non-capsulated strains gave problems to some of the laboratories.
PCR-based capsular genotyping is recommended for the investigation of all Hib vaccine failure strains. No laboratory performed less well than the others.

Table 2: Laboratory External Quality Assurance Scheme (EQAS) for *Haemophilus influenzae*

Strain Number	Intended Result	Lab Number 1	Lab Number 2	Lab Number 3	Lab Number 4	Lab Number 5
19	Hib biotype I β-lactamase +ve AMP R CHLOR,CRO,TRIM,RIF, TET S	Hib biotype I	Hib biotype I β-lactamase +ve AMP R CTX,TET,CHLOR S	Hib biotype I β-lactamase +ve AMP R	Hib biotype I β-lactamase +ve AMP R CTX,CHLOR,TET, CMX S	Hib biotype I βlactamase –ve P , AMP R
25	Hi non-typable Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM, RIF,TET S	Hi non-typable Biotype IV Weak agglutination with type d Would check with PCR	Hid β-lactamase –ve AMP,CTX,TET,CHLOR S	Hi ? a,b,d biotype IV AMP S a+ b+ d+ unusual agglutination in 3 antisera	Hi non-typable Biotype IV β- lactamase –ve AMP,CTX,CHLOR,TET, CMX S	Hia (?result tippexed over?) Biotype I β- lactamase –ve P I, AMP S
28	Hi non-typable Biotype II β-lactamase –ve AMP.CHLOR,CRO,RIF, TET S TRIM R	Hi non-typable biotype II	Hif β-lactamase –ve AMP R therefore also CO- AM, cephalosporin R TET,CHLOR S	Hi non-typable Biotype II AMP S	Hi non-typable Biotype II β-lactamase –ve AMP, CTX,CHLOR, TET S CMX R	Hic Biotype II B-lactamase –ve P R, AMP S
32	Hie Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM, RIF, TET S	Hie Biotype IV	Hi non-typable β-lactamase –ve PV+ve a, b, e+ve determine serotype by PCR AMP,CTX,CHLOR,TET S	Hie Biotype IV AMP S	Hie biotype IV β-lactamase –ve AMP,CTX,CHLOR,TET, CMX S	Hie Biotype IV B-lactamase –ve P I, AMP S
33	Hi non-typable biotype III weak PV +ve, a,b,c,d,e,f - ve, β-lactamase –ve AMP,CRO,CHLOR,TET S RIF R, TRIM R	Hi non-typable Biotype III	Hi non-typable β-lactamase –ve, PV+ve, d e +/- Determine serotype by PCR AMP,CTX,TET,CHLOR S	Hib Biotype III SXT R, AMP S Discrete autoagglutination	Hi non-typable Biotype III β-lactamase –ve AMP,CTX,CHLOR, TET S CMX R	Hib III B-lactamase –ve P R, AMP I

Strain Number	Intended Result	Lab Number 1	Lab Number 2	Lab Number 3	Lab Number 4	Lab number 5
34	H.paraphrophilus AMP,CHLOR,CRO,TRIM, RIF, TET S	H.paraphrophilis	H ? autoagglutination PV+ve β-lactamase _ve determine serotype by PCR AMP,CTX,CHLOR, TET S	H.parainfluenzae ?atypical biotype ODC ++, urease ++, indole ++	Non H.influenzae β-lactamase –ve needs RapIDNH AMP,CTX,CHLOR,TET CMX S	H.aphrophilus P S, AMP S
Strain Number	**Intended Result**	**Lab Number 6**	**Lab Number 7**	**Lab Number 8**	**Lab Number 9**	**Lab number 10**
19	Hib biotype I β-lactamase +ve AMP R CHLOR,CRO,TRIM,RIF, TET S	Hib	Hib Biotype I β-lactamase +ve	Hib biotype I	Hib β-lactamase +ve AMP R CRO S CMX S	Hib β-lactamase +ve AMP R
25	Hi non-typable Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM , RIF,TET S	Hi not capsulated	Hi non-typable Biotype IV Antibiotic susceptible strain	Hid (by serum agglutination) Biotype IV Negative by PCR	Hi non-typable β-lactamase –ve AMP ,CRO, CMX S	Hi Non-encapsulated AMP S
28	Hi non-typable Biotype II β-lactamase –ve AMP.CHLOR,CRO,RIF,T ET S TRIM R	Hi not capsulated	Hi non-typable Biotype II AMP less susceptible- needs MIC	Hi non-typable biotype I	Hi non-typable β-lactamase –ve AMP ,CRO S CMX I	Hi non-encapsulated AMP S
32	Hie Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM ,RIF, TET S	Hie	Hie Biotype IV Antibiotic susceptible	Hie Biotype IV	Hie β-lactamase –ve AMP ,CRO, CMX S	Hi Non-encapsulated Autoagglutinating β-lactamase +ve AMP R
33	Hi non-typable biotype III weak PV +ve, a,b,c,d,e,f - ve, β-lactamase –ve	Hi not capsulated	Hi non-typable Biotype III RIF,CMX R AMP less susceptible- needs MICI	Hi non-typable Biotype II	Hi non-typable β-lactamase –ve AMP ,CRO S CMX R	Hib B-lactamase +ve AMP R

	AMP,CRO,CHLOR,TET S RIF, TRIM R					
34	H.paraphrophilus AMP,CHLOR,CRO,TRIM ,RIF, TET S	Not Hi	H.parainfluenzae ONPG +	H.parainfluenzae	H.aphrophilus β-lactamase –ve AMP,CRO,CMX S	H.parainfluenzae AMP S
Strain Number	**Intended Result**	**Lab Number 11**	**Lab Number 12**	**Lab Number 13**	**Lab Number 14**	
19	Hib biotype I β-lactamase +ve AMP R CHLOR,CRO,TRIM,RIF, TET S	Hib biotypeI β-lactamase +ve AMP R , CO-AM , CRO, CXM R AZT,IM,CHLOR,RIF, TET,CLAR,CIP, CMX S	Hib Biotype I β-lactamase +ve	Hib Biotype I β-lactamase +ve AMP R COAM,CTX,CEC,CXM,TET,CHLOR, CMX, RIF,CIP,AZT S	Hib Biotype I β-lactamase +ve AMP R COAM,CXM,CEF,CTX CMX,CHLOR,RIF,CIP S	
25	Hi non-typable Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM , RIF,TET S	Hid Biotype IV AMP,COAM,CRO,CXM,AZT,IM,CHLOR,RIF, TET,CLAR,CIP,CMX S	Hi non-typable Biotype IV	Hi non-typable Biotype IV β-lactamase –ve AMP COAM,CTX,CEC,CXM,TET,CHLOR, CMX, RIF,CIP,AZT S	Hi non-typable Biotype IV β-lactamse –ve AMP , COAM,CXM,CEF,CTX CMX,CHLOR,RIF,CIP S	
28	Hi non-typable Biotype II β-lactamase –ve AMP.CHLOR,CRO,RIF, TET S TRIM R	Hi non-typable Biotype II AMP,COAM,CRO,CXM,AZT,IM,CHLOR,RIF, TET S ,CLAR I ,CIP S ,CMX R	Hi non-typable Biotype II	Hi non-typable Biotype II B-lactamase –ve AMP COAM,CTX,CEC,CXM,TET,CHLOR, RIF,CIP,AZT S CMX R	Hi non-typable Biotype II β-lactamase –ve AMP , COAM,CXM,CEF,CTX CMX,CHLOR,RIF,CIP S	
32	Hie Biotype IV β-lactamase –ve AMP,CHLOR,CRO,TRIM ,RIF, TET S	Hie Biotype IV AMP,COAM,CRO,CXM,AZT,IM,CHLOR,RIF, TET,CLAR,CIP,CMX S	Hie Biotype IV	Hie Biotype IV β-lactamase –ve AMP, COAM,CTX,CEC,CXM,TET,CHLOR, CMX, RIF,CIP,AZT S	Hie Biotype IV β-lactamase –ve AMP , CO-AM,CXM,CEF,CTX CMX,CHLOR,RIF,CIP S	
Strain Numb	**Intended Result**	**Lab Number 11**	**Lab Number 12**	**Lab Number 13**	**Lab Number 14**	

er					
33	Hi non-typable biotype III weak PV +ve, a,b,c,d,e,f -ve, β-lactamase –ve AMP,CRO,CHLOR,TETS RIF, TRIM R	Hi non-typable Biotype III AMP,COAM,CRO,CXM,AZT,IM,CHLORTET,CLAR,CIPS,CMX R RIF R	**HI NON-TYPABLE** **BIOTYPE III**	Hi non-typable Biotype III β-lactamase –ve AMP, COAM,CTX, ,CXM,TET,CHLOR,CIP, AZT S CEC R RIF,CMX R possible BLNAR	Hi non-typable biotype III β-lactamase –ve AMP , CO-AM,CXM,CEF,CTX CMX,CHLOR,CIP S RIF R
34	H.paraphrophilus AMP,CHLOR,CRO,TRIM,RIF, TET S	H.paraphrophilus AMP,COAM,CRO,CXM,AZT,IM,CHLOR,RIF, TET,CLAR,CIP,CMXS	H.paraphrophilus	H.paraphrophilus AMP, COAM,CTX,CEC,CXM,TET,CHLOR, CMX, RIF,CIP,AZT S	*H.aphrophilus/* *H.paraphrophilus* *16s RNA fraction sequence*

Antibiotic Code:

AMP	**= Ampicillin**	**CMX**	**= Co-Trimoxazole**
COAM	**= Co-Amoxyclav**	**CLAR**	**= Clarithromycin**
CHLOR	**= Chloramphenicol**	**CIP**	**= Ciprofloxacin**
CTX	**= Cefotaxime**	**RIF**	**= Rifampicin**
CRO	**= Ceftriaxone**	**TET**	**= Tetracycline**
CXM	**= Cefuroxime**	**P**	**= Penicillin**
CEC	**= Cefaclor**	**AZT**	**= Aztreonam**
CEF	**= Cefixime**	**IM**	**= Imipenem**

Concordant antimicrobial susceptibilities shown in red
Discrepant typing and antimicrobial susceptibility results shown in blue

Laboratory Number	1.1.1.1. Methods Used
1.1.1.2. Oxford	
1	Phadebact "Hi", Difco-Bacto polyvalent a-f, Murex monovalent, ALA(remel), Biotyping, X&V on NA, Satellitism, Urease, Indole, ODC (+ Cysteine tryptase agar, G/lactose/maltose/sucrose, CO_2 requirement, ALA weak+ve, no 34), PCR available, bex A + b cap, no routine antibiotic sens)
2	Slide aggs, E-test, NCCLS
3	Rosco tabs, Difco AS, NCCLS
4	Porphyrin, I Urease ODC, H_2S production, Glucose, lactose, mannose, sucrose, Murex monovalent AS, PCR, RapID NH, Nitrocefin, E-test
5	Rosco tabs, E-test, Cefinase
6	X&V, latex agglutination + CIE, PCR, OMP2 VK a-f
7	X&V, API 10S
8	API NH, serum agglutination, PCR
9	NCCLS
10	X&V, API NH, E-test, Cefinase, PCR, Serotyping
11	Murex Antisera, API 10S, API NH
12	X&V, Coagglutination, ALA, I Ure ODC, Haemolysis
13	API NH, Porphyrin, PCR, Slide agglutination, Nitrocefin, Oxidsae, Microdilution MICs (Dade Behring)
14	PCR

3.3 Data on invasive *Haemophilus influenzae* infection 1999-2002

3.3.1 Overall incidence of invasive Hib disease

Data for cases in all age groups was provided by 10 European countries (Austria, Czech Republic, Finland, Ireland, Italy, Netherlands, Norway, Portugal, Sweden and the UK) and by Australia, for 2002 (Table 3). Data for meningitis cases in all age groups was supplied by Denmark. The crude incidence was low in the European Union countries in 2002 (0.27 per 100,000 population), but increased considerably from 2001 (0.16 per 100,000 population). All these EU countries have vaccination programmes established. Of those countries with a vaccination programme well-established, the UK had the highest incidence rate (0.52) in 2001. This higher rate in the UK was the major contributor to the increased incidence rate seen in the combined European Union countries. Increases have also been seen in Ireland (0.21 to 0.26) and the Netherlands (0.11 to 0.19) from 2001 to 2002. The number of confirmed adult cases in Australia is greater than the number for which case details are held by EU-IBIS (personal communication). When these cases are added to the totals in Table 3, the rate in Australia becomes the noticeably higher. However, only cases for which case details are provided are included in tables in this report.

In July 2001 the Czech Republic introduced a routine Hib vaccination programme to children under one year of age, and a decrease of 1.02 to 0.44 per 100,000 population can be seen in this country between 2000 and 2002.

3.3.2 Age disribution of cases

Amongst those EU countries with surveillance in all age groups, the overall percentage of cases in children under 5 years of age was 57%. Comparative figures for 1999, 2000 and 2001 were 58%, 63% and 57%, respectively. (Table 4) This percentage ranged widely between all the reporting countries (0-70%) over 2002. However, account must be taken of the very low number of cases some countries are experiencing now they have had vaccination programmes running for a substantial period of time. The Czech Republic, which did not have a vaccination programme instituted until mid 2001, had an age distribution similar to all the other countries in the network prior to vaccination introduction: over 75% of the cases in children under 5 years of age.

The overall percentage of cases in children under one year of age in EU countries reporting Hib cases in all age groups was 10% in 2002, a decrease from the percentages for this age group in 1999, 2000 and 2001 (27%, 20% and 16%, respectively).

3.3.3 Incidence of invasive Hib disease in childhood

Data on all cases in 2002 children under 15 years was provided by 11 European Union countries (Austria, Ireland, Finland, Germany, Greece, Italy, Netherlands, Norway, Portugal, Sweden, UK), and by three countries outside the EU (Australia, Czech Republic, Israel). (Table 5) Denmark provided data on meningitis only. The annual incidence in the EU was 0.65 per 100,000 population. This value has seen a steady increase since 1999. In 1999 the rate was 0.30, in 2000 it was 0.39, and in 2001 it had increased to 0.43 per 100,000 population. Of the EU countries, the UK has the highest rate (1.76 per 100,000 population), and as a result of being a large population country, has impacted on the rate seen in the combined EU countries. The incidence in the EU was higher in children under five than in those under fifteen, and increased over 1999 (0.84), 2000 (1.08), 2001 (1.71) and 2002 (1.77). (Table 6) The highest rate in 2002 in the under fives was in the United Kingdom (4.34), with rates above one per 100,000 observed in Ireland, Greece (Athens only), Netherlands, Sweden and Israel. In contrast to all other participating countries, the UK showed a steady increase in incidence rate in the under five year olds between 1999 and 2002. This formed the major contribution to the overall increase. The Netherlands has also experienced an increase in the rate in under five year olds over this period, but the magnitude has been less (0.72 – 1.60).

The Czech Republic, having only introduced the vaccination programme half way through 2001, has experienced a decrease from 18.55 per 100,000 children under 5 years in 2000, to 8.17 in 2002.9+

Overall incidence in the EU for Hib meningitis in children under 5 years of age saw a increase from 2001 (0.54) to 2002 (0.69) (Table 7) The one major contributor to this increase was the UK (England & Wales) . Meanwhile, several countries have seen decreases in Hib meningitis incidence in under fives.

Table 3 : Numbers of cases and crude incidence (per 100,000 population) of invasive Hib disease for all age groups, by country : 1999-2002

Country	Year	<1 y	1 yr	2 yrs	3 yrs	4 yrs	5-9 yrs	10-14 yrs	15+yrs	NK	Total cases	Population	Rate
Austria	2002	0	1(0)	0	0	0	1(0)	0	1(0)	0	3(0)	7,795,788	0.04
Denmark*	1999	1	0	0	0	0	0	0	2	0	3	5,313,577	0.06
	2000	0	0	0	0	0	0	0	0	0	0	5,330,020	0.00
	2001	0	0	0	0	0	1	0	0	0	1	5,349,212	0.02
	2002	0	0	0	0	0	0	0	0	0	0	5,349,212	0.00
Finland	1999	2	0	0	0	0	0	1	4	0	7	5,116,826	0.14
	2000	1	0	0	0	1	0	0	0	0	2	5,116,826	0.04
	2001	0	0	0	0	0	0	0	3	0	3	5,116,826	0.06
	2002	0	0	0	0	0	0	0	4	0	4	5,116,826	0.08
Iceland	1999	0	0	0	0	0	0	0	0	0	0	278,702	0.00
	2000	0	0	0	0	0	0	0	0	0	0	278,702	0.00
	2001	1	0	0	0	0	0	0	0	0	1	278,702	0.36
	2002	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	278,702	
Ireland	1999	1	2	0	0	0	1	0	3	0	7	3,744,700	0.19
	2000	2	1	0	1	0	1	0	2	0	7	3,787,100	0.18
	2001	1	1	0	1	0	2	0	3	0	8	3,839,000	0.21
	2002	0	2	3	0	2	0	0	3	0	10	3,839,000	0.26
Italy (enhanced)	1999	17(7)	6(3)	9(2)	2(0)	0(0)	2(0)	0(0)	8(5)	0(0)	44(17)	27,880,793	0.16
	2000	9(8)	2(0)	4(2)	1(1)	2(2)	0(0)	1(1)	2(2)	0(0)	21(16)	27,880,793	0.08
	2001	2(0)	3(2)	1(1)	3(3)	1(1)	1(0)	0(0)	6(3)	0(0)	17(10)	27,880,793	0.06
	2002	5(4)	0	0	2(1)	0	1(0)	0	1(0)	0	9(5)	27,880,793	0.03
Netherlands	1999	5	0	1	1	0	1	0	4	0	12	15,760,225	0.08
	2000	3	3	2	0	0	0	0	7	0	15	15,863,950	0.09
	2001	3	1	2	1	1	0	1	8	0	17	15,987,075	0.11
	2002	7	3	1	5	0	0	0	15	0	31	15,987,075	0.19
Norway	1999	0	2	0	0	0	0	0	3	0	5	4,445,329	0.11
	2000	0	0	1	0	0	0	0	6	0	7	4,478,497	0.16
	2001	0	0	0	0	0	0	0	2	0	2	4,503,436	0.04
	2002	2	0	0	0	0	0	0	6	0	8	4,503,436	0.18

Country	Year	<1 y	1 yr	2 yrs	3 yrs	4 yrs	5-9 yrs	10-14 yrs	15+yrs	NK	Total cases	Population	Rate
Portugal	1999	2	0	0	0	0	0	0	0	2	4	9,920,762	0.04
	2000	0	0	1	1	0	0	0	0	1	3	9,920,762	0.03
	2001	1	0	0	0	0	0	0	1	0	2	9,920,762	0.02
	2002	1	1	0	0	0	0	0	0	0	2	9,920,762	0.02
Sweden	2002	3	0	1	1	2(1)	1	0	14(11)	0	22(18)	8,846,625	0.25
UK	1999	12	6	5	4	5	4	0	30	0	66	51,820,200	0.13
	2000	15	10	12	15	9	5	2	31	2	101	51,820,200	0.19
	2001	23	30	19	14	4	9	2	44	0	145	51,820,200	0.28
	2002	21	59	56	0	11	26	3	93	2	271	51,820,200	0.52
EU TOTAL*	**1999**	**39**	**16**	**15**	**7**	**5**	**8**	**1**	**52**	**2**	**145**	**118,967,537**	**0.12**
	2000	**30**	**16**	**20**	**18**	**12**	**6**	**3**	**48**	**3**	**156**	**119,146,830**	**0.13**
	2001	**31**	**35**	**22**	**19**	**6**	**12**	**3**	**67**	**0**	**195**	**119,346,794**	**0.16**
	2002	39	66	61	8	15	29	3	137	2	360	**135,710,505**	**0.27**
Australia	1999	10	8	2	0	0	1	1	5	0	27	18,925,855	0.14
	2000	6(4)	2	1(0)	1	0	3	1	0	0	14(11)	19,153,380	0.07
	2001	5	3	2	1	2	3	1	0	0	17	19,413,240	0.09
	2002	5(4)	5(4)	1	0	0	3	1(0)	0	0	15(12)	19,413,240	0.08
Czech Rep.	1999	17	18	16	13	14	9	0	5	0	92	10,282,784	0.89
	2000	14	29(27)	10	16(15)	15(13)	13	1	7	0	105(100)	10,272,503	1.02
	2001	14(13)	18(17)	12(12)	15(14)	18(17)	9(6)	1(1)	7(4)	0	94(84)	10,272,503	0.92
	2002	3	8(7)	16(14)	10	3(2)	3	0	2	0	45(41)	10,272,503	0.44

* Denmark reports only meningitis and is therefore excluded from the EU totals
* Numbers in parentheses indicate cases confirmed by isolation in countries where antigen detection is included

Table 4 : Age distribution of cases of invasive Hib disease by country for 1999-2002

Country	Year	Under 1		1-4 years		0-4 years		5-14 years		15+ years		Total
		No	%	No	%	No	%	No	%	No	%	
Austria	2002	0	0%	1	33%	1	33%	1	33%	1	33%	3
Denmark*	1999	1	33%	0	0%	1	33%	0	0%	2	67%	3
	2000	0	0%	0	0%	0	0%	0	0%	0	0%	0
	2001	0	0%	0	0%	0	0%	1	100%	0	100%	1
	2002	0		0		0		0		0		0
Finland	1999	2	29%	0	0%	2	29%	1	14%	4	57%	7
	2000	1	50%	1	50%	2	100%	0	0%	0	0%	2
	2001	0	0%	0	0%	0	0%	0	0%	3	100%	3
	2002	0	0%	0	0%	0	0%	0	0%	4	100%	
Iceland	1999	0	-	0	-	0	-	0	-	0	-	0
	2000	0	-	0	-	0	-	0	-	0	-	0
	2001	1	100%	0	0	1	100%	0	0	0	0	1
	2002	N/A		N/A		N/A		N/A		N/A		N/A
Ireland	1999	1	14%	2	28%	3	43%	1	14%	3	43%	7
	2000	2	29%	2	29%	4	57%	1	14%	2	29%	7
	2001	1	13%	2	25%	3	38%	2	25%	3	38%	8
	2002	0	0%	7	70%	7	70%	0	0%	3	30%	10
Italy (enhanced)	1999	17	39%	17	39%	34	77%	2	5%	8	18%	44
	2000	9	43%	9	43%	18	86%	1	4.8%	2	10%	21
	2001	2	12%	8	47%	10	59%	1	6%	6	35%	17
	2002	5	56%	2	22%	7	78%	1	11%	1	11%	9
Netherlands	1999	5	42%	2	17%	7	58%	1	8.3%	4	33%	12
	2000	3	20%	5	33%	8	53%	0	0%	7	47%	15
	2001	3	18%	5	29%	8	47%	1	6%	8	47%	17
	2002	7	23%	9	29%	16	52%	0	0%	15	48%	31
Norway	1999	0	0%	2	40%	2	40%	0	0%	3	60%	5
	2000	0	0%	1	14%	1	14%	0	0%	6	86%	7
	2001	0	0%	0	0%	0	0%	0	0%	2	100%	2
	2002	2	25%	0	0%	2	25%	0	0%	6	75%	8
Portugal	1999	2	100%	0	0%	2	100%	0	0%	0	0%	2
	2000	0	0%	2	100	2	100%	0	0%	0	0%	2
	2001	1	50%	0	0%	0	50%	0	0%	1	50%	2
	2002	1	50%	1	50%	2	100%	0	0%	0	0%	2
Sweden	2002	3	14%	4	18%	7	32%	1	5%	14	64%	22
UK	1999	12	18%	20	30%	32	48%	4	6.1%	30	45%	66
	2000	15	15%	46	46%	61	62%	7	7.0%	31	31%	99
	2001	23	16%	67	46%	90	62%	13	9%	44	30%	147
	2002	21	8%	126	47%	147	55%	29	11%	93	35%	269
EU TOTAL*	**1999**	**39**	**27%**	**43**	**30%**	**82**	**58%**	**9**	**6%**	**51**	**36%**	**143**
	2000	**30**	**20%**	**66**	**43%**	**96**	**63%**	**9**	**6%**	**48**	**31%**	**153**
	2001	**31**	**16%**	**82**	**42%**	**112**	**57%**	**17**	**9%**	**67**	**34%**	**196**
	2002	**42**	**10%**	**187**	**46%**	**229**	**57%**	**35**	**9%**	**139**	**34%**	**403**

Table 4 : Age distribution of cases of invasive Hib disease by country for 1999-2002

Country	Year	Under 1 yr		1-4 years		0-4 years		5-14 years		15+ years		Total
		No.	%	No.	%	No.	%	No.	%	No.	%	
Australia	1999	10	37%	10	37%	20	74%	2	7.4%	5	19%	27
	2000	6	43%	4	29%	10	71%	4	29%	0	0%	14
	2001	5	29%	8	47%	13	76%	4	24%	0	0%	17
	2002	5	33%	6	40%	11	73%	4	27%	0	0%	15
Czech Rep.	1999	17	18%	61	66%	78	85%	9	9.8%	5	5.4%	92
	2000	14	13%	70	67%	85	81%	14	13%	7	7.0%	105
	2001	14	15%	63	67%	77	82%	10	11%	7	7%	94
	2002	3	7%	37	82%	40	89%	3	7%	2	4%	45

*** Denmark reports only meningitis and is therefore excluded from the EU totals**

Table 5 : Numbers of cases and crude incidence (per 100,000 population) of invasive Hib disease in children under 15 years of age, by country : 1999-2002

Country	Year	<1 yr	1-4 yrs	5-9 yrs	10-14 yrs	Total cases	Population	Rate
Austria	1999					12	1,356,807	0.88
	2000&2001	N/A	N/A	N/A	N/A	N/A		N/A
	2002	0	1(0)	1(0)	0	2(0)	1,356,807	0.15
Denmark*	1999	1	0	0	0	1	967,643	0.10
	2000	0	0	0	0	0	981,148	0.00
	2001	0	0	1	0	1	998,305	0.10
	2002	0	0	0	0	0	998,305	0.00
Ireland	1999	1	2	1	0	4	829,300	0.49
	2000	2	2	1	0	5	824,400	0.61
	2001	1	2	2	0	5	821,700	0.61
	2002	0	7	0	0	7	821,700	0.85
Finland	1999	2	0	0	1	3	971,770	0.31
	2000	1	1	0	0	2	971,770	0.21
	2001	0	0	0	0	0	971,770	0.00
	2002	0	0	0	0	0	971,770	0.00
Germany	1999	2	8	3	0	13	12,897,014	0.10
	2000	10	11	2	2	25	12,777,242	0.20
	2001	9	7	1	3	20	12,618,844	0.16
	2002	6	6	0	2	14	12,420,866	0.11
Greece	1999	1	0	0	0	1	558,558	0.18
	2000	2	1	0	0	3	558,558	0.54
	2001	1	0	0	0	1	558,558	0.18
	2002	0	3	1	0	4	558,558	0.72
Iceland	1999	0	0	0	0	0	64,711	0.0
	2000	0	0	0	0	0	64,711	0.0
	2001	1	0	0	0	1	64,711	1.55
	2002	N/A	N/A	N/A	N/A	N/A	64,711	N/A
Italy (enhanced)	1999	17(7)	17(5)	2(0)	0(0)	36(12)	3,595,194	1.00
	2000	9(8)	9(5)	0(0)	1(1)	19(14)	3,595,194	0.53
	2001	2(0)	8(7)	1(0)	0(0)	11(7)	3,595,194	0.31
	2002	5(4)	2(1)	1(0)	0	8(5)	3,595,194	0.22
Netherlands	1999	5	2	1	0	8	2,915,911	0.27
	2000	3	5	0	0	8	2,945,543	0.27
	2001	3	5	0	1	9	2,977,428	0.30
	2002	7	9	0	0	16	2,977,428	0.54
Norway	1999	0	2	0	0	2	882,408	0.23
	2000	0	1	0	0	1	894,717	0.11
	2001	0	0	0	0	0	902,431	0.00
	2002	2	0	0	0	2	902,431	0.22
Portugal	1999	2	0	0	0	2	1,744,600	0.11
	2000	0	2	0	0	2	1,744,600	0.11
	2001	1	0	0	0	1	1,744,600	0.06
	2002	1	1	0	0	2	1,744,600	0.11
Sweden	1999	1	4	0	1	6	1,654,452	0.36
	2000&2001	N/A	N/A	N/A	N/A	N/A		N/A
	2002	3	4(3)	1	0	8(7)	1,654,452	0.48
UK	1999	12	20	4	0	36	10,001,300	0.36
	2000	15	46	5	2	68	10,001,300	0.68
	2001	23	67	9	2	101	10,001,300	1.01
	2002	21	126	26	3	176	10,001,300	1.76

Country	Year	<1 yr	1-4 yrs	5-9 yrs	10-14 yrs	Total cases	Population	Rate
EU TOTAL*	**1999**	**43**	**55**	**11**	**2**	**111**	**37,472,025**	**0.30**
	2000	**42**	**78**	**8**	**5**	**133**	**34,378,035**	**0.39**
	2001	**41**	**89**	**13**	**6**	**149**	**34,256,536**	**0.43**
	2002	**45**	**159**	**30**	**5**	**239**	**37,005,106**	**0.65**
Australia	1999	10(10)	10(10)	1(1)	1(1)	22(22)	3,950,872	0.56
	2000	6(4)	4(3)	3(3)	1(1)	14(11)	3,966,067	0.35
	2001	5(5)	8(7)	3(3)	1(1)	17(16)	3,987,198	0.43
	2002	5(4)	6(5)	3	1(0)	15(12)	3,987,198	0.38
Czech Republic	1999	17(17)	61(61)	9(9)	0(0)	87(87)	1,728,678	5.03
	2000	14(14)	70(65)	13(13)	1(1)	98(93)	1,685,398	5.81
	2001	14(13)	63(59)	9(6)	1(1)	87(79)	1,685,398	5.16
	2002	3	37(33)	3	0	43(39)	1,685,398	2.55
Israel	1999	3	3	0	0	6	1,638,400	0.37
	2000	6	3	2	0	11	1,798,200	0.61
	2001	4	2	1	0	7	1,853,400	0.38
	2002	0	0	2	0	2	1,864,900	0.11

* Denmark reports only meningitis and is therefore excluded from the EU totals

* Numbers in parentheses indicate cases confirmed by isolation in countries where antigen detection is included

Table 6 : Numbers of cases and crude incidence rate (per 100,000 population) in children under 5 years of age, by country : 1999-2002

Country	Year	<1 yr	1 yrs	2 yrs	3 yrs	4 yrs	Total cases	Population	Rate
Austria	2002	0	1(0)	0	0	0	1(0)	453,283	0.22
Denmark*	1999	1	0	0	0	0	1	344,685	0.29
	2000	0	0	0	0	0	0	340,593	0.00
	2001	0	0	0	0	0	0	341,381	0.00
	2002	0	0	0	0	0	0	341,381	0.00
Ireland	1999	1	2	0	0	0	3	259,400	1.16
	2000	2	1	0	1	0	4	265,100	1.51
	2001	1	1	0	1	0	3	270,800	1.11
	2002	0	2	3	0	2	7	270,800	2.58
Finland	1999	2	0	0	0	0	2	324,870	0.62
	2000	1	0	0	0	1	2	324,870	0.62
	2001	0	0	0	0	0	0	324,870	0.00
	2002	0	0	0	0	0	0	324,870	0.0
Germany	1999	2	2	5	1	0	10	3,947,634	0.25
	2000	10	6	3	2	0	21	3,943,844	0.53
	2001	9	3	2	2	0	16	3,892,984	0.41
	2002	6	3	1	1	1	12	3,804,787	0.32
Greece	1999	1	0	0	0	0	1	169,648	0.59
	2000	2	1	0	0	0	3	169,648	1.77
	2001	1	0	0	0	0	1	169,648	0.59
	2002	0	1	1	1	0	3	169,648	1.77
Iceland	1999	0	0	0	0	0	0	20,981	0.00
	2000	0	0	0	0	0	0	20,981	0.00
	2001	1	0	0	0	0	1	20,981	4.77
	2002	N/A	N/A	N/A	N/A	N/A	N/A	20,981	N/A
Italy (enhanced)	1999	17(7)	6(3)	9(2)	2(0)	0(0)	34(12)	1,147,352	2.96
	2000	9(8)	2(0)	4(2)	1(1)	2(2)	18(13)	1,147,352	1.57
	2001	2(0)	3(2)	1(1)	3(3)	1(1)	10(7)	1,147,352	0.87
	2002	5(4)	0	0	2(1)	0	7(5)	1,147,352	0.61
Netherlands	1999	5	0	1	1	0	7	976,175	0.72
	2000	3	3	2	0	0	8	983,491	0.81
	2001	3	1	2	1	1	8	1,001,085	0.80
	2002	7	3	1	5	0	16	1,001,085	1.60
Norway	1999	0	2	0	0	0	2	301,963	0.66
	2000	0	0	1	0	0	1	302,387	0.33
	2001	0	0	0	0	0	0	300,954	0.00
	2002	2	0	0	0	0	2	300,954	0.66
Portugal	1999	2	0	0	0	0	2	555,730	0.36
	2000	0	0	1	1	0	2	555,730	0.36
	2001	1	0	0	0	0	1	555,730	0.18
	2002	1	1	0	0	0	2	555,730	0.36
Sweden	1999	1	3	1	0	0	5	518,532	0.96
	2000	N/A	N/A	N/A	N/A	N/A	N/A		N/A
	2001	N/A	N/A	N/A	N/A	N/A	N/A		N/A
	2002	3	0	1	1	2(1)	7(6)	518,532	1.35
UK	1999	12	6	5	4	5	32	3,387,800	0.94
	2000	15	10	12	15	9	61	3,387,800	1.80
	2001	23	30	19	14	4	90	3,387,800	2.66
	2002	21	59	56	0	11	147	3,387,800	4.34

Country	Year	<1 yr	1 yrs	2 yrs	3 yrs	4 yrs	Total cases	Population	Rate
EU TOTAL*	**1999**	**43**	**21**	**21**	**8**	**5**	**98**	**11,610,085**	**0.84**
	2000	**42**	**23**	**23**	**20**	**12**	**120**	**11,101,203**	**1.08**
	2001	**41**	**38**	**24**	**21**	**6**	**130**	**11,072,204**	**1.17**
	2002	**45**	**70**	**63**	**10**	**16**	**204**	**11,934,841**	**1.71**
Australia	1999	10(10)	8(8)	2(2)	0(0)	0(0)	20(20)	1,284,153	1.56
	2000	6(4)	2(2)	1(0)	1(1)	0(0)	10(7)	1,282,357	1.01
	2001	5(5)	3(2)	2(2)	1(1)	2(2)	13(12)	1,297,534	1.00
	2002	5(4)	5(4)	1	0	0	11(9)	1,297,534	0.85
Czech Republic	1999	17(17)	18(18)	16(16)	13(13)	14(14)	78(78)	463,569	16.83
	2000	14(14)	29(27)	10(10)	16(15)	15(13)	84(79)	452,761	18.55
	2001	14(13)	18(16)	12(12)	15(14)	18(17)	77(72)	452,761	17.01
	2002	3	8(7)	16(14)	7	3(2)	37(33)	452,761	8.17
Israel	1999	3	1	2	0	0	6	567,000	1.06
	2000	6	0	3	0	0	9	645,900	1.39
	2001	4	1	1	0	0	6	661,800	0.91
	2002	0	0	0	0	0	0	674,500	0.00

* Denmark reports only meningitis and is therefore excluded from the EU totals

- Numbers in parentheses indicate cases confirmed by isolation in countries where antigen detection is included

Table 7 : Numbers of cases and incidence (per 100,000 population) of invasive Hib meningitis in children under 5 years by country : 1999-2002

Country	Year	< 1 yr	1 yr	2 yrs	3 yrs	4 yrs	Total cases <5 years	Population	Rate	
Austria	2002	0	1	0	0	0	1	453,283	0.22	
Denmark	1999	1	0	0	0	0	1	344,685	0.29	
	2000	0	0	0	0	0	0	340,593	0.00	
	2001	0	0	0	0	0	0	341,381	0.00	
	2002	0	0	0	0	0	0	341,381	0.0	
Ireland	1999	0	1	0	0	0	1	259,400	0.39	
	2000	1	1	0	1	0	3	265,100	1.13	
	2001	1	1	0	0	0	2	270,800	0.74	
	2002	0	1	1	0	1	3	270,800	1.11	
Finland	1999	0	0	0	0	0	0	324,870	0.00	
	2000	1	0	0	0	1	2	324,870	0.62	
	2001	0	0	0	0	0	0	324,870	0.00	
	2002	0	0	0	0	0	0	324,870	0.00	
Germany	1999	1	1	4	1	0	7	3,947,634	0.18	
	2000	7	3	2	1	0	13	3,943,844	0.33	
	2001	7	2	1	2	0	12	3,892,984	0.31	
	2002	3	3	0	1	1	8	3,804,787	0.21	
Greece	1999	0	0	0	0	0	0	169,648	0.00	
	2000	1	1	0	0	0	2	169,648	1.18	
	2001	1	0	0	0	0	1	169,648	0.59	
	2002	0	0	0	0	0	0	169,648	0.00	
Iceland	1999	0	0	0	0	0	0	20,981	0.00	
	2000	0	0	0	0	0	0	20,981	0.00	
	2001	0	0	0	0	0	0	20,981	0.00	
	2002	N/A	N/A	N/A	N/A	N/A	N/A	20,981	N/A	
Italy (enhanced)	1999	16	6	9	2	0	33	1,147,352	2.88	
	2000	7	2	4	1	2	16	1,147,352	1.39	
	2001	1	3	1	2	1	8	1,147,352	0.70	
	2002	3	0	0	2	0	5	1,147,352	0.44	
Netherlands	1999	3	0	1	1	0	5	976,175	0.51	
	2000	3	3	2	0	0	8	983,491	0.81	
	2001	3	0	1	0	0	4	1,001,085	0.40	
	2002	3	0	0	0	0	3	1,001,085	0.30	
Norway	1999	0	1	0	0	0	1	301,963	0.33	
	2000	0	0	0	0	0	0	302,387	0.00	
	2001	0	0	0	0	0	0	300,954	0.0	
	2002	1	0	0	0	0	1	300,954	0.33	
Portugal	1999	1	0	0	0	0	1	555,730	0.18	
	2000	0	0	1	0	0	1	555,730	0.18	
	2001	0	0	0	0	0	0	555,730	0.00	
	2002	1	0	0	0	0	1	555,730	0.18	
Sweden	1999	0	2	0	0	0	2	518,532	0.39	
	2000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
	2001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
	2002	1	0	0	0	0	1	518,532	0.19	
United Kingdom	1999	6	3	2	2	2	15	3,387,800	0.44	
	2000	7	4	5	5	2	23	3,387,800	0.68	
	2001	10	11	6	5	1	33	3,387,800	0.97	
	2002	8	32	16	0	3	59	3,387,800	1.74	

Country	Year	< 1 yr	1 yr	2 yrs	3 yrs	4 yrs	Total cases <5 years	Population	Rate	
TOTAL EU	**1999**	**27**	**14**	**16**	**6**	**2**	**65**	**11,610,085**	**0.56**	
	2000	**27**	**14**	**14**	**8**	**5**	**68**	**11,101,203**	**0.61**	
	2001	**23**	**17**	**9**	**9**	**2**	**60**	**11,072,204**	**0.54**	
	2002	**20**	**37**	**17**	**3**	**5**	**82**	**11,934,841**	**0.69**	
Australia	1999	6	5	1	0	0	12	1,284,153	0.93	
	2000	5	0	0	0	0	5	1,278,970	0.39	
	2001	2	1	0	0	0	3	1,282,357	0.23	
	2002	4	2	1	0	0	7	1,282,357	0.55	
Czech Republic	1999	13	14	6	6	8	47	463,569	10.14	
	2000	11	23	5	8	4	51	452,761	11.26	
	2001	11	12	9	5	5	42	452,761	9.28	
	2002	26	2	6	10	6	50	452,761	11.04	
Israel	1999	2	0	0	0	0	2	567,000	0.35	
	2000	4	0	0	0	0	4	645,900	0.62	
	2001	1	0	0	0	0	1	661,800	0.15	
	2002	0	0	0	0	0	0	674,50	0.00	

3.3.4 Clinical diagnosis

Meningitis remains the dominant clinical diagnosis amongst cases in children. However, the distribution of cases between the clinical diagnoses has changed between 1999 and 2002. (Table 8) The percentage of cases reported as meningitis has decreased from 60% to 45%. The percentages of cases reported as epiglottitis and septicaemia have also shown decreases from 1999 to 2002 whereas the percentage of cases with 'other' diagnoses has increased from 2% to 14% over the period.1999-2002. These changes in the clinical diagnosis distribution reflect the reduced incidence of invasive Hib disease in children since introduction of vaccination programmes, as other diagnoses are more common in adults.

The proportion of meningitis was highest in all countries except Greece(Athens) and Sweden . (Table 9c) Caution has to be taken with these proportions, however, as the number of cases with known clinical diagnosis are low in some countries.

In 2002, the proportion of cases with meningitis was much lower amongst adult cases than in children.(Table 10c) Epiglottitis was more common in older children (aged 2-9 years), than in infants and one year olds. Pneumonia and septicaemia/bacteraemia were more prevalent among adult cases.

Table 8 : Cases of invasive Hib disease by clinical diagnosis and year in children under 15 years of age, 1999-2001 inclusive.

	1999		**2000**		**2001**		**2002**	
Meningitis	138	59.5%	145	55.3%	118	38.9%	132	44.9%
Epiglottitis	42	18.1%	46	17.6%	59	20.2%	31	10.5%
Cellulitis	3	1.3%	7	2.7%	7	2.1%	7	2.4%
Osteomyelitis / septic arthritis	2	0.9%	7	2.7%	8	2.4%	10	3.4%
Pneumonia	9	3.9%	8	3.1%	6	7.2%	12	4.1%
Septicaemia / bacteraemia	29	12.5%	33	12.6%	40	19.9%	49	16.7%
Other	5	2.2%	13	5.0%	27	8.1%	40	13.6%
Not known	4	1.7%	3	1.1%	2	1.2%	13	4.4%
TOTAL	**232**	**100%**	**262**	**100%**	**267**	**100%**	**294**	**100%**

Table 9a : Cases of invasive Hib disease in children under 15 years of age by clinical diagnosis and country : 1999 & 2000 combined

Country	**Meningitis**		**Epiglottitis**		**Cellulitis**		**Osteomyelitis/ septic arthritis**		**Pneumonia**		**Septicaemia/ bacteraemia**		**Other**		**Not known**	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%%	No.	%
Australia	18	51%	2	6%	2	6%	0	0%	2	6%	9	26%	1	3%	1	3%
Czech Republic	119	58%	63	31%	0	0%	4	2%	4	2%	14	7%	0	0%	2	1%
Ireland	4	44%	0	0%	0	0%	1	11%	0	0%	3	33%	0	0%	1	11%
Finland	3	60%	0	0%	0	0%	0	0%	0	0%	2	40%	0	0%	0	0%
Germany	23	61%	7	18%	0	0%	0	0%	0	0%	6	16%	2	5%	0	0%
Greece	2	50%	0	0%	0	0%	0	0%	0	0%	2	50%	0	0%	0	0%
Israel	6	35%	0	0%	2	12%	0	0%	6	35%	3	18%	0	0%	0	0%
Italy(enhanced)	52	95%	0	0%	0	0%	0	0%	0	0%	1	2%	0	0%	2	4%
Netherlands	14	89%	0	0%	0	0%	0	0%	0	0%	2	13%	0	0%	0	0%
Norway	1	33%	0	0%	0	0%	0	0%	1	33%	0	0%	1	33%	0	0%
Portugal	1	25%	1	25%	0	0%	0	0%	0	0%	0	0%	0	0%	2	50%
Sweden	2	33%	1	17%	0	0%	1	17%	0	0%	2	33%	0	0%	0	0%
UK	43	41%	14	13%	5	5%	3	3%	4	4%	21	20%	14	13%	0	0%
TOTAL	**288**	**57%**	**88**	**18%**	**9**	**2%**	**9**	**2%**	**17**	**3%**	**64**	**13%**	**18**	**4%**	**8**	**2%**

Table 9b : Cases of invasive Hib disease in children under 15 years of age by clinical diagnosis and country : 2001

Country	Meningitis		Epiglottitis		Cellulitis		Osteomyelitis/ septic arthritis		Pneumonia		Septicaemia/ bacteraemia		Other		Not known	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Australia	3	18%	3	18%	1	6%	0	0%	0	0%	6	35%	4	24%	0	0%
Czech Republic	48	55%	29	33%	0	0%	2	2%	3	3%	5	6%	0	0%	0	0%
Ireland	2	40%	1	20%	0	0%	0	0%	0	0%	1	20%	0	0%	1	20%
Finland	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Germany	14	74%	2	11%	0	0%	0	0%	1	5%	2	11%	1	0%	0	0%
Greece	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Iceland	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	0	0%
Israel	2	29%	0	0%	0	0%	0	0%	1	14%	4	57%	0	0%	0	0%
Italy(enhanced)	9	81%	1	9%	0	0%	0	0%	0	0%	1	9%	0	0%	0	0%
Netherlands	4	44%	0	0%	0	0%	0	0%	0	0%	5	56%	0	0%	0	0%
Norway	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Portugal	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	0	0%	0	0%
Sweden	N/A		N/A		N/A		N/A		N/A		N/A		N/A		N/A	
UK	35	35%	23	23%	5	5%	6	6%	1	1%	15	15%	15	15%	1	1%
TOTAL	**118**	**45%**	**59**	**23%**	**6**	**2%**	**8**	**3%**	**6**	**2%**	**40**	**15%**	**21**	**8%**	**2**	**1%**

Table 9c : Cases of invasive Hib disease in children under 15 years of age by clinical diagnosis and country : 2002

Country	Meningitis		Epiglottitis		Cellulitis		Osteomyelitis/ septic arthritis		Pneumonia		Septicaemia/ bacteraemia		Other		Not known	
Australia	7	47%	0	0%	0	0%	0	0%	3	20%	4	27%	1	7%	0	0%
Austria	2	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Czech Republic	29	67%	7	16%	0	0%	1	2%	1	2%	5	12%	0	0%	0	0%
Ireland	3	43%	1	14%	0	0%	0	0%	2	29%	1	14%	0	0%	0	0%
Finland	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Germany	9	64%	1	7%	1	7%	0	0%	1	7%	2	14%	0	0%	0	0%
Greece	0	0%	0	0%	1	25%	0	0%	1	25%	1	25%	1	25%	0	0%
Iceland	N/A		N/A		N/A		N/A		N/A		N/A		N/A		N/A	
Israel	1	50%	0	0%	0	0%	0	0%	1	50%	0	0%	0	0%	0	0%
Italy(enhanced)	6	75%	0	0%	1	13%	0	0%	0	0%	1	13%	0	0%	0	0%
Netherlands	3	19%	2	13%	0	0%	2	13%	0	0%	2	13%	1	65	6	38%
Norway	1	50%	0	0%	0	0%	0	0%	0	0%	0	0%	1	50%	0	0%
Portugal	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	00	0%	0	0%
Sweden	1	13%	1	13%	1	13%	0	0%	2	25%	0	0%	0	0%	3	38%
UK	67	38%	20	11%	4	2%	7	4%	2	1%	33	19%	36	20%	7	4%
TOTAL	127	43%	32	11%	8	3%	10	3%	13	4%	49	17%	40	14%	16	5%

Table 10a : Cases of invasive Hib disease by clinical diagnosis and age group : 1999 & 2000 combined

Diagnosis	< 1 yr	1 yr	2 yrs	3 yrs	4 yrs	5-9 yrs	10-14 yrs	15+ yrs	NK
Meningitis	93 (67%%)	66 (66%)	42 (55%)	29 (45%)	19 (41%)	21 (42%)	4 (44%)	14 (12%)	1 (14%)
Epiglottitis	2 (1%)	12 (12%)	18 (23%)	23 (36%)	16 (35%)	18 (36%)	1 (11%)_	12 (10%)	1 (14%)
Cellulitis	5 (4%)	1 (1%)	1 (1%)	1 (2%)	0 (0%)	1 (2%)	1 (11%)	1 (1%)	0 (0%)
Osteo/SA	3 (2%)	2 (2%)	2 (3%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Pneumonia	5 (4%)	3 (3%)	2 (3%)	0 (0%)	3 (7%)	1 (2%)	1 (11%)	26 (22%)	1 (14%)
Septicaemia	25 (18%)	10 (10%)	8 (10%)	7 (11%)	5 (11%)	6 (12%)	2 (22%)	32 (28%)	1 (14%)
Other	2 (1%)	4 (4%)	4 (5%)	3 (5%)	2 (4%)	3 (6%)	0 (0%)	17 (15%)	0 (0%)
Not known	4 (3%)	2 (2%)	0 (0%)	0 (0%)	1(2%)	0 (0%)	0 (0%)	10 (9%)	3 (43%)
All diagnoses	**139**	**100**	**77**	**64**	**46**	**50**	**9**	**116**	**7**

Table 10b : Cases of invasive Hib disease by clinical diagnosis and age group : 2001

Diagnosis	< 1 yr	1 yr	2 yrs	3 yrs	4 yrs	5-9 yrs	10-14 yrs	15+ yrs
Meningitis	37 (58%)	30 (50%)	18 (46%)	14 (38%)	7 (27%)	11 (44%)	2 (25%)	10 (14%)
Epiglottitis	3 (5%)	10 (17%)	12 (31%)	17 (46%)	13 (50%)	4 (16%)	0	8 (11%)
Cellulitis	3 (5%)	1 (2%)	1 (3%)	1 (3%)	0	0	0	1 (1%)
Osteo/SA	1 (2%)	4 (7%)	0	2 (5%)	1 (4%)	0	0	
Pneumonia	1 (2%)	0	4 (10%)	0	0	1 (4%)	0	18 (25%)
Septicaemia	13 (20%)	7 (12%)	1 (3%)	3 (8%)	4 (15%)	7 (28%	4 (50%)	26 (37%)
Other	5 (8%)	8 (13%)	3 (8%)	0	1 (4%)	2 (8%)	2 (25%)	6 (8%)
Not known	1 (2%)	0	0	0	0	0	0	2 (3%)
All diagnoses	**64**	**60**	**39**	**37**	**26**	**25**	**8**	**71**

Table 10C : Cases of invasive Hib disease by clinical diagnosis and age group : 2002

Diagnosis	< 1 yr	1 yr	2 yrs	3 yrs	4 yrs	5-9 yrs	10-14 yrs	15+ yrs
Meningitis	29 (48%)	46 (55%)	28 (35%)	10 (50%)	7 (37%)	14 (36%)	2 (29%)	8 (6%)
Epiglottitis	0 (0%)	3 (4%)	20 (25%)	3 (15%)	3 (16%)	3 (8%)	0 (0%)	21 (15%)
Cellulitis	5 (8%)	3 (4%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)
Osteo/SA	3 (5%)	5 (6%)	1 (1%)	0 (0%)	1 (5%)	1 (3%)	0 (0%)	4 (3%)
Pneumonia	1 (2%)	4 (5%)	2 (3%)	0 (0%)	4 (21%)	4 (10%)	0 (0%)	21 (15%)
Septicaemia	10 (17%)	13 (15%)	15 (19%)	2 (10%)	6 (32%)	6 (15%)	2 (29%)	26 (18%)
Other	7 (12%)	6 (7%)	12 (15%)	1 (5%)	9 (47%)	9 (23%)	2 (29%)	33 (23%)
Not known	5 (8%)	3 (4%)	1 (1%)	4 (20%)	2 (11%)	2 (5%)	1 (14%)	26 (18%)
All diagnoses	**60**	**83**	**80**	**20**	**19**	**39**	**7**	**142**

3.3.5 Non capsulated H. influenzae infection

Except in Norway and Israel, the incidence of non-capsulated invasive *H. influenzae* disease in children under fifteen was generally less than or similar to that of type b infection in 2002. Overall type b infection in children under 15 years of age has increased over 2001-2002, the incidence of non-capsulated invasive *H.influenzae* has shown a decrease.(Table 11) This emphasises the importance of accurate identification of strains of *H. influenzae* in children. The range of incidence observed, however, ranged widely between countries, suggesting that ascertainment may be more variable than for type b infections. In view of the technical expertise required to identify non-capsulate infections and the varying use of national reference centres described in the laboratory questionnaire, this is not surprising.

3.3.6 Other capsulated serotypes of H.influenzae

Compared to both type b and non-capsulate infections, invasive disease due to other capsulated organisms was rare. (Table 12) Type f infections were the most common serotype observed and little change occurred between years of the study.

Table 11 : Incidence of non-capsulated and type b *H. influenzae* in children under 15 years of age, 1999-2002

Country	Year	Non capsulated	Incidence	Type b	Incidence	Population
Denmark*	1999	1	0.10	1	0.1	967,643
	2000	2	0.20	0	0.0	981,148
	2001	0	0.00	1	0.10	998,305
	2002	0	0.00	0	0.00	998,305
Finland	1999	1	0.11	3	0.31	971,770
	2000	1	0.10	2	0.21	971,770
	2001	0	0.00	5	0.51	971,770
	2002	0	0.00	0	0.00	971,770
Germany	1999	12	0.09	13	0.10	12,897,014
	2000	28	0.22	25	0.19	12,897,014
	2001	20	0.16	20	0.16	12,897,014
	2002	17	0.13	14	0.11	12,897,014
Iceland	1999	2	3.09	0	0	64,711
	2000	0	0.0	0	0	64,711
	2001	1	1.55	0	0.00	64,711
	2002	N/A		N/A		64,711
Ireland	1999	1	0.12	4	0.48	829,300
	2000	2	0.24	5	0.61	824,400
	2001	3	0.36	5	0.61	821,700
	2002	0	0.00	7	0.84	821,700
Italy (enhanced)	1999	1	0.03	36	1.00	3,595,194
	2000	0	0.0	19	0.53	3,595,194
	2001	2	0.06	11	0.31	3,595,194
	2002	0	0.00	8	0.22	3,595,194
Netherlands	1999	19	0.65	8	0.27	2,915,911
	2000	7	0.24	8	0.27	2,945,543
	2001	12	0.40	9	0.31	2,977,428
	2002	15	0.50	16	0.54	2,977,428
Norway	1999	7	0.79	2	0.23	882,408
	2000	6	0.67	1	0.11	894,717
	2001	4	0.44	0	0.0	902,431
	2002	5	0.55	2	0.22	902,431
Portugal	1999	1	0.06	2	0.11	1,744,602
	2000	2	0.11	2	0.11	1,744,602
	2001	6	0.34	1	0.06	1,744,602
	2002	2	0.11	0	0.00	1,744,602
UK	1999	39	0.39	36	0.36	10,033,595
	2000	55	0.55	68	0.68	10,033,595
	2001	58	0.58	101	1.01	10,033,595
	2002	57	0.57	176	1.75	10,033,595
EU TOTAL*	**1999**	**82**	**0.24**	**104**	**0.31**	**33,934,505**
	2000	**101**	**0.30**	**130**	**0.38**	**33,971,546**
	2001	**139**	**0.40**	**150**	**0.43**	**35,006,750**
	2002	**96**	**0.28**	**223**	**0.66**	**33,943,734**
Israel	2000	1	0.06	11	0.61	1,798,200
	2001	16	0.86	7	0.38	1,853,400
	2002	6	0.32	2	0.11	1,864,900

***Denmark reports only meningitis and is therefore excluded from the EU totals**

Table 12 : Other *H. influenzae* serotypes in children under 15 years: all countries combined : 1999-2002

Year	Type a	Type c	Type e	Type f	Non-b
1999	1	0	3	10	1
2000	4	2	1	13	4
2001	1	0	3	14	2
2002	2	0	4	10	1

4. CONCLUSIONS

Prior to introduction of Hib vaccination programmes the epidemiology of invasive Hib disease differed between the EU countries, with incidence rates in children under five varying between 12 and 60 per 100,000. The Czech Republic only introduced a vaccination programme in mid 2001, and demonstrated a pre-vaccination programme incidence rate in the same range for 2001 (17/100,000). All EU countries now have national immunisation programmes, and therefore the incidence in children under five years, the age group with the highest incidence pre-vaccine, is now very low. Countries are at different stages of vaccine implementation, have different vaccines and schedules and have acheived different levels of coverage. Despite all of these considerations, the incidence of Hib infection in the EU is much lower than in the pre-vaccine era (between 0 and 4.0 per 100,000) in all participating countries.

With the falling incidence of Hib disease, the clinical presentation of Hib disease has also shown changes. Meningitis still remains the predominant diagnosis, but the proportion of cases presenting with meningitis in each year age group under five has decreased. Pneumonia and bacteraemia are more common presentations in adults. Apparent differences between countries may be explained by the different age distribution of cases and the small numbers of cases.

Amongst children under five in the EU countries, the highest incidence rates in 2002 were in the UK, Ireland and Netherlands. In 2002, the highest incidence was observed in the UK, which has experienced a quadrupling of the number of cases over the years 1999-2002 in children under five years of age. One of the major differences between the UK and Ireland and the remaining EU countries is the absence of a booster (third or fourth dose) in the second year of life, but increases have also been observed in the Netherlands – a country with a booster at 11 months. Both Ireland and the Netherlands have seen an approximate doubling of the number of cases over the four years of the study and continued vigilance for increases in other countries is required. Rates between years in each participant country vary due to small numbers but the increase observed in the UK, one of the largest populations under surveillance, was mainly responsible for an overall increase in incidence in the EU in 2001. Between 1999 and 2000, Germany had seen a doubling in the incidence rate in the under fives, but has since returned to the original rate.

Changes in vaccination programmes have occurred over time, and, in particular, the change from using Hib alone or in combination with DTwP to using combinations with DTaP has occurred in many countries. As Hib-DTaP combined vaccine is associated with lower post-vaccination antibody levels to Hib, it has been important to continue monitoring Hib incidence with this new vaccine. In the UK, DTwP vaccine combinations are recommended but during 2000 and 2001, DTaP combinations were used because of a supply problem. Studies in the UK suggest that this change has contributed to the increase in incidence rate observed. Although this phenomenon has not yet been observed in other countries, possibly due to different schedules in use, the importance of continued observation over the whole of the EU is therefore essential. For smaller countries, pooling data at an EU level may help to ensure that such changes can be detected at the earliest possible stage.

Surveillance systems varied slightly amongst the participating countries. As most countries include all invasive Hib disease in children under fifteen years, comparison of rates in under fives and under fifteens can be made. Differences may be explained by many factors, including different methods of surveillance and completeness of ascertainment. One of the most important factors is the microbiological practice in relation to the diagnosis of Hib disease. This practice can impact on the establishment of disease burden and on comparisons between countries. If laboratories in some countries do not routinely test blood cultures or specimens from other sterile sites for *H. influenzae* in cases with clinical disease compatible with Hib infection then *H. influenzae* and Hib disease will not be diagnosed. The importance of continued improvement of laboratory techniques and laboratory based surveillance cannot be over-emphasised.

Rates of non-b capsulated *H. influenzae* infection are low and no evidence of serotype replacement has been observed despite many years of vaccination in many of the EU countries. Rates of non-capsulate infection are now similar to(or less than) those for type b and emphasises the importance of ensuring accurate identification of the organism in a national reference centre. The low rates observed in some countries, probably reflects the low proportion of strains that are referred and highlights the potential for improving ascertainment of such cases. Information on the underlying variability in rates of non-capsulate infection are not known, but the ability to detect such infections may be a useful indicator of the quality of microbiological services in that country.

5. PROJECT ACHIEVEMENTS

This project has made considerable contributions to:

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

5.1 Improvements in the epidemiological information on *H. influenzae* within the EU

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

Changes in vaccination programmes have occurred over time, and, in particular, the change from using Hib alone or in combination with DTwP to using combinations with DTaP has occurred in many countries. As Hib-DTaP combined vaccine is associated with lower post-vaccination antibody levels to Hib, this project has maintained the important monitoring of Hib incidence with this new vaccine.

5.2 Improvements in the laboratory capacity within the EU to accurately identify *H. influenzae* isolates

These improvements will be achieved through gaining information on systems in use by participant countries, and by feedback of information from the External Quality Assurance Scheme (EQAS) with the participant reference laboratories. Questionnaires completed by network members on the laboratory methods used in the identification of *H. influenzae* gave information that, and, as with the surveillance system questionnaire results, allowed greater understanding of any limitations that could impact on the data individual countries supplied. The EQAS helped identify any existing problems in correctly serotyping *H. influenzae* isolates, and enabled corrections/assistance in laboratory methods to be made, hence improving comparability of data between countries. A central resource was provided in the UK to genotype *H. influenzae* strains from countries with established Hib vaccination programmes.

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

Through establishment of this *H. influenzae* disease surveillance network in the European Union, with standard case definitions, minimum dataset, and laboratory quality assurance scheme, and a website, a focus for wider collaboration with non-EU and candidate EU countries is provided. Involvement of the Czech Republic and Israel and Australia in this collaboration has increased the population under surveillance. The population under surveillance will increase markedly in 2004 when Transition EU countries join the network. It is hoped that other non-EU countries will also join the collaboration later.

5.4 Establishment of web-site

Data and reports on EU-IBIS and on *H. influenzae* infection in Europe is now presented on the EU-IBIS web-site (www.euibis.org).

6. APPENDICES

6.1 Appendix 1 : *H. influenzae* surveillance network collaborators

Dr Sigrid Heuberger	Austria
Dr Reinhild Strauss	Austria
Dr Francoise Crokaert	Belgium
Dr Germaine Hanquet	Belgium
Dr Helle Bossen Konradsen	Denmark
Dr Susanne Samuelsson	Denmark
Pr Henri Dabernat	France
Dr Anne Perrocheau	France
Prof Maija Leinonen	Finland
Dr Petri Ruutu	Finland
Prof H J Schmitt	Germany
Dr Anette Siedler	Germany
Dr Anastasia Pangalis	Greece
Prof Marie Theodoridou	Greece
Dr Hjordis Hardartottir	Iceland
Dr Haraldur Briem	Iceland
Dr Mary Cafferkey	Ireland
Dr Joan O'Donnell	Ireland
Dr Marina Cerquetti	Italy
Dr Marta Ciofi degli Atti	Italy
Dr Francois Schneider	Luxembourg
Dr Pierette Huberty-Krau	Luxembourg
Dr Lodewijk Spanjaard	Netherlands
Dr Hester de Melker	Netherlands
Dr Arne E Hoiby	Norway
Dr Oistein Lovoll	Norway
Dr Manuela Canica	Portugal
Dr Paula Lavado	Portugal
Dr Jose Campos	Spain
Dr Brigitta Henrigues	Sweden
Dr Margareta Lofdhal	Sweden
Dr Mary Slack	United Kingdom
Dr Mary Ramsay	United Kingdom

Prof Geoff Hogg	Australia
Prof Lyn Gilbert	Australia
Dr Peter McIntyre	Australia
Professor Ron Dagan	Israel
Dr. Vera Lebedova	Czech Republic
Dr. Paula Kriz	Czech Republic

6.2 Appendix 2 : Minimum dataset

Variable name	**Further description**	Field type	Coding
Country		Text	
Year		Number	
IDNO	Identification numbers/letters	Text	
INIT	Initials	Text	
Firstname		Text	
DOB	Date of birth	DD/MM/YY	
DOO	Date of onset	DD/MM/YY	
AgeYr1	Age in years	Number	
Agemth	Age in months if <1 year	Number	
Sex		Number	1=male 2=female 3=not known
Geog	Geographical area/region	Text	
Clin	Clinical diagnosis	Number	1=meningitis 2=epiglottitis 3=cellulitis 4=osteomyelitis/septic arthritis 5=pneumonia 6=septicaemia 7=other (specify in 'OthClin') 9=not known
OthClin	Other clinical diagnosis, if specified	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	
Othisol	Other method of confirmation, if specified	Text	
Site	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) 8=other (Ag)
OthSite	Other site, if specified	Text	
Serotype	Serotype if known	Text	B = *H. influenzae* type b A = *H. influenzae* type a C = *H. influenzae* type c E = *H. influenzae* type e F = *H. influenzae* type f NC = *H. influenzae* non-capsulated/not typeable NT = *H. influenzae* un-typed NK = not known

Vacc	Vaccination status	Number	1= vaccinated 2=not vaccinated 3=not applicable 4=not known
Doses	No. of doses of vaccine given pre-onset	Text	99=not known
VF	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	Booster vaccine type	Text	
Bdate	Date booster given	DD/MM/YY	
Outcome		Number	1=alive 2=died 3=not known

6.3 Appendix 3 : H. influenzae Surveillance systems questionnaire

Hib Vaccination in Europe - Invasive *Haemophilus influenzae* infections

Surveillance systems questionnaire

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

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

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

Part A
1 Surveillance methods
1.1 Methods
What methods of surveillance of *Haemophilus influenzae* are used in your country?
(please list the methods used and complete Part B of the questionnaire once for each system)

1.2 Data collation
If more than one system: How is the data collated at a national or regional from each system?

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

* "reconciliation" - cases in one system merged with cases in another system and duplicates removed.

For each method of surveillance please complete one questionnaire Part B.

Part B

1 Surveillance system

1.1 Objectives

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

1.2 Case definitions

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

H. influenzae type b ☐ *H.influenzae* ☐ Other ☐
Please specify "Other" .....
.....

Meningitis ☐ All invasive ☐ Other ☐
Please specify "Other" .....
.....

1.3 Population

What is the population under surveillance?

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

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

1.4 Type of surveillance system

What type of surveillance system is this?

Type of system
Active ☐
Passive ☐

Characteristics of system
Stimulated ☐ Not stimulated ☐
Statutory reporting ☐ Voluntary reporting ☐

Zero-reporting ☐ / No zero reporting ☐

1.5 Start of surveillance system

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

2 Data collection

2.1 Information collected

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

Age ☐
Sex ☐
Date of onset ☐
Geographic location ☐
Clinical condition ☐
Organism ☐
Method of confirmation ☐
Vaccination status ☐
Other ☐ Please specify "Other" .....
.....
.....

2.2 Reporting sources

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

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

2.3 Time period

How frequently is the data reported locally?
Weekly ☐ Monthly ☐ Quarterly ☐
Six-monthly ☐ Annually ☐ Other .....….

How frequently is the data aggregated nationally?
Weekly ☐ Monthly ☐ Quarterly ☐
Six-monthly ☐ Annually ☐ Other .....

2.4 Duplicate reports

Are duplicates routinely detected and eliminated?

3 Data analysis

3.1 Analysis

Who analyses the data at a national level?

Clinicians ☐
Paediatricians ☐
Microbiologists ☐
Epidemiologists ☐
Scientific staff ☐
Adminstrative staff ☐
Other, please specify .....
.....

4 Data dissemination

4.1 Regular reports

4.1a Frequency

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

Weekly ☐
Monthly ☐
Quarterly ☐

Six-monthly ☐
Annually ☐
Other .....

4.1b Method of reporting

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

4.1c Audience

Who are reports disseminated to?

4.2 Recent publications

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

6.4 Appendix 4 : Laboratory diagnostic methods questionnaire

Hib Vaccination in Europe - Invasive *Haemophilus influenzae* infections

Laboratory Diagnostic Methods Questionnaire

Country :.....

Name of respondent .....

Position .....

Centre .....

Address .....
.....
.....
.....

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

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

SURVEY OF LABORATORY FACILITIES FOR THE IDENTIFICATION OF HAEMOPHILUS INFLUENZAE IN.....

I)What proportion of hospitals in your country/area have the facilities to do the primary identification of H.influenzae strains?

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

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

All CSFs from suspected bacterial meningitis	☐
All CSFs from suspected bacterial meningitis in children	☐
All blood cultures	☐
All blood cultures in children	☐
Blood cultures from cases of epiglottitis	☐
Blood cultures from cases of epiglottitis in children	☐
Other conditions, please describe	☐
(e.g. osteomyelitis, septic arthritis, pneumonia)	_____

_____

III) What proportion of hospitals would be able to perform serotyping on isolates of :

H.influenzae type b

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

Other H.influenzae

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

IV) What proportion of hospitals refer isolates to the reference lab (i.e. your lab)?

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

V) For those hospitals which do refer isolates to your lab, what type of cases are they referred for?

All invasive H.flu	☐
All invasive H.flu in children	☐
H.flu meningitis	☐
H.flu meningitis in children	☐
H.flu epiglottitis in children	☐
Other, please describe	☐

REFERENCE LABORATORY METHODS

1.1 Receipt of strains

		yes	no
1.11	Are the strains subbed immediately on receipt?	☐	☐
1.12	Are the strains tested on receipt, or batched?	☐	☐
1.13	Are the strains stored and tested in batches?	☐	☐

2.1 Media

2.11 What media is used to transport strains to the laboratory?
.....……

2.12 What media is used to subculture the strains?
.....

2.13 What media is used to test growth factor requirement?
.....

2.14 What media is used for susceptibility testing?
.....

2.15 What media is used for long term storage of strains?
.....

2.16 Please state atmosphere of incubation.
.....

2.17 Please state duration of incubation.
.....

2.2 Identification Methods

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

	yes	no
Catalase	☐	☐
Oxidase	☐	☐
Dependence on growth factors		
i) by disc method	☐	☐
ii) by plate incorporation method	☐	☐
Porphyrin	☐	☐

Satellitism on blood agar yes ☐ no ☐
(please state origin of blood used i.e. horse, sheep) .....
.....

Haemolysis yes ☐ no ☐
(please state origin of blood used).....
.....

Nitrate yes ☐ no ☐
If Yes, please state method
.....
.....

O.N.P.G. yes ☐ no ☐

Commercially available identification kit yes ☐ no ☐
(Please give details).....
.....
.....

Other, please specify yes ☐ no ☐
.....
.....

2.3 Are the strains biotyped using the following tests?

Indole	yes	☐	no	☐
Urease	yes	☐	no	☐
Ornithine decarboxylase	yes	☐	no	☐

2.4 Are the strains serotyped?

If so, which of the following methods are used:

Slide agglutination with polyvalent antisera yes ☐ no ☐
If yes, give details of antisera used
.....
.....

Slide agglutination with type specific antisera yes ☐ no ☐
If yes, give details of antisera used
.....
Counter current immunoelectrophoresis yes ☐ no ☐
PCR yes ☐ no ☐
If yes, give details of primers used
.....
.....
Other yes ☐ no ☐
If yes, give details
.....

2.5 Are the strains further subtyped? yes ☐ no ☐

If yes, which typing method is used?

OMP ☐
Ribotyping ☐
LPS ☐
PFGE ☐
Other, please specify ☐

2.6 Susceptibility testing.

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

2.6.2 With method of susceptibility testing is used?

	yes	no
Disc diffusion - please state method e.g.		
Control organism on the same agar plate		
Control organism on a separate agar plate		
Break points		
Other, please specify		

2.6.3 If MICs are required, which method is used?

	yes	no
Broth dilution		
Agar incorporation		
E-test (AB BIODISK)		
Commercially prepared MIC microtitre trays		
If so, please give details of kit used		
.....		
Other		
Please specify		
.....		
.....		

2.7 Do you test for beta-lactamase production? yes ☐ no ☐

If yes, please state method used

.....

.....

.....

2.8 Do you test for chloramphenicol acetyltransferase (CAT) production? yes ☐ no ☐

If yes, please state method used

.....

.....

.....

2.9 Long term storage

How do you store strains long term?

	yes	no
Agar slopes		
Frozen at -80oC		
Other		
Please specify		
.....		

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