AN EVALUATION OF *HAEMOPHILUS INFLUENZAE* TYPE B (HIB) VACCINATION AND DESCRIPTION OF RISK FACTORS FOR HIB VACCINE FAILURE IN EUROPE 1996-1998

Final report

October 1999

Project coordinator: Mary Ramsay,
PHLS Communicable Disease Surveillance Centre
London

Contributors: ***Sarah Handford, Nick Andrews, Amal Rushdy***
PHLS Communicable Disease Surveillance Centre
Mary Slack, PHLS Haemophilus Reference Unit, Oxford
Paul Heath, St George's Hospital Medical School, London

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

During the past decade, conjugate vaccines against *Haemophilus influenzae* type b (Hib) infection have been introduced for routine use in infants into several countries in Europe. Currently, the vaccination programmes in these countries differ with respect to the choice of vaccine, the schedule for primary immunisation, and the use of a booster dose in the second year of life.

Prior to licensing, controlled studies of three conjugate vaccines demonstrated good short-term protection with efficacy estimates of between 83% and 100%.[1-4]Two post marketing studies with one of these vaccines, however, obtained substantially lower estimates of vaccine efficacy in US children aged 18-59 months[5] and in native Alaskan infants.[6] In Europe, post-marketing surveillance suggests that the current Hib vaccination programmes are highly effective in controlling Hib disease.[7] No comparative estimates of vaccine efficacy, however, from each programme are available.

Studies in the US have suggested that vaccine failure after a conjugate vaccine can indicate an underlying problem with immune responsiveness. More information is needed to describe risk factors in different populations and with different vaccines and schedules. This information could lead to changes in recommendations for vaccination of high-risk groups or contribute to the choice of an appropriate vaccine and schedule for all children.

Vaccines are now becoming licensed in several other countries. The implementation of mass vaccination campaigns, however, into other European member states will require additional health care resources and would need to be targeted at the most appropriate choice of vaccination policy, including the choice of the most effective vaccine and schedule.

Many studies have been undertaken in developed countries to look at the epidemiology of invasive Hib infection within their populations and thus to allow informed decisions on the introduction of Hib vaccination programmes. Due to different methodologies (study types, case definitions, study populations, age group stratification, studies confined to meningitis etc.) true comparisons cannot always be drawn.

This collaborative study between six European countries, (Finland, Ireland, Italy, the Netherlands, Spain (Valencia) and England & Wales (United Kingdom)), and Australia allows control over study design and hence comparative data will be produced for the large population under study. This will be the first controlled, inter-country study of the epidemiology of Hib, and the impact of conjugate vaccines on it, to be undertaken.

1.1. The project

This collaborative BIOMED II funded three year study (1996-99) aims to describe the epidemiology of invasive *H. influenzae* in these countries, the impact of vaccination programmes on the epidemiology of *H. influenzae* and to describe the risk factors associated with vaccine failure using different vaccines and schedules. Obtaining comparative data will inform European licensing authorities and public health policy in countries considering the introduction of Hib vaccine, and facilitate the eventual harmonisation of vaccine schedules.

Prior to the use of vaccine, Hib infection was a major cause of childhood morbidity and mortality and a major burden on health care expenditure. The project aims to evaluate and compare the performance of Hib prevention strategies in several countries. The introduction of vaccine into other member states will require additional health care resources and this project will help to ensure that such new expenditure is targeted towards the most appropriate choice of vaccination policy, including the choice of the most effective vaccine and schedule.

Several European countries have established programmes for vaccination against Hib infection. Other countries are developing surveillance to describe the epidemiology of the disease prior to the introduction of vaccines. By this collaboration, countries with established programmes can compare the performance of their own vaccination campaigns with others. This will inform decisions about setting coverage targets, need for booster vaccinations, choice of vaccine and methods of post marketing surveillance. Countries

without existing programmes can learn from models of good practice in states with established policies. This will inform the establishment of surveillance schemes and decisions about future implementation of Hib vaccination.

The project aims to provide a network resource to provide genotyping of strains from vaccine failures and quality assurance of laboratories performing serotyping for the population under surveillance. The justification for this is that the accuracy of serotyping has been questioned.[8; 9] A Hib vaccine failure can only be a true failure if the infecting organism is truly a type b *H. influenzae* and efficacy estimates can be biased by use of a non-specific case definition.[10] Invasive disease can be caused by *H. influenzae* with other capsular type (a,c,d,e,f) or by non-capsulated organisms. Some problems with mistyping are due to non-encapsulated variants of *H. influenzae*, denoted 'b-' strains.[11] The relative importance of 'b-' strains is likely to increase with reduced incidence of Hib disease following the introduction of mass vaccination. (A proportion of non-capsulated strains cross-react with specific anti-sera; such strains can only be accurately detected by genotyping). Achievement of both objectives will therefore depend upon accurate serotyping of a high proportion of strains (particularly from cases in countries with established vaccine programmes). Therefore, a central resource will be established in one reference laboratory in England.

In addition to providing standardised laboratory protocols for growing and serotyping *H. influenzae*, and coordination of the exchange of strains of the organism to allow consistency of results, the laboratory will provide genotypic confirmation of capsular type for cases arising in countries with established vaccine programmes and training fellowships for microbiologists from countries without established reference facilities. Training workshops will be offered to microbiologists from countries without existing reference facilities at the English reference laboratory in Oxford.

1.2. Aims and objectives

The objectives of the project are:

1. To obtain comparable estimates of age-specific vaccine efficacy of Hib vaccine in countries using different vaccines and schedules

2. To describe the risk factors associated with vaccine failure using different vaccines and schedules.

1.3. The tasks

Task 1. To describe the methods of surveillance and to compare epidemiology of invasive *H. influenzae* infections in each country

Task 2. Establish and compare the accuracy and reliability of serotyping of strains of *H. influenzae* in children.

Task 3. Determine the vaccination status of all invasive *H. influenzae* infections in children

Task 4: Description of risk factors for vaccine failure

Task 5. Obtaining the age-specific estimates of Hib vaccination coverage.

Task 6. Calculating age-specific estimates of vaccine efficacy.

2. BACKGROUND

Since it's recognition, Hib has been shown to be the most common cause of serious infection and mortality in children under five years of age in industrialised countries. The risk of invasive Hib disease was comparable to the risk of contracting polio before polio vaccines were introduced.[12] World-wide, the age-specific incidence and type of disease varied from one area to the next, but, regardless of location, approximately 80% of disease occurred before the age of five years. The age-relationship and the relative attack rates of meningitis and epiglottitis are not uniform in all countries.[13] The case attack rate per 100,000 children less than five years of age was 25 in Ireland,[14]31 in United Kingdom (England and Wales),[15] between 40 and 60 in Australia, New Zealand[16] and Scandinavia,[17; 18] and between 60 and 130 in USA.[19; 20] Indigenous populations in USA and Australia display case attack rates as high as 450/100,000 children under 5 years of age.[21]

The past decade has seen the development of the protein conjugate vaccines and the subsequent introduction of routine vaccination programmes into a number of developed countries. Protection through vaccination of young children has rapidly changed the epidemiology of *H. influenzae* infection. Hib disease is a global problem, and so the successful implementation of conjugate vaccines in industrialised countries can pave the way for the use of Hib vaccine in developing countries. We are now in the position to look at the epidemiology of *H. influenzae* in the pre-vaccine era and during current vaccine implementation in a number of countries.

2.1. Hib vaccine development

Haemophili were first observed by Koch in 1883 in conjunctivitis. Robert Pfeiffer isolated, described, and cultured "influenzae-bacillus" using blood in 1892-1893.[22; 23] In 1917 it was named "*Haemophilus influenzae*" by the American Society of Bacteriologists.[22]

In the 1930s, Margaret Pittman defined two major strains of *Haemophilus influenzae*, namely encapsulated and non-encapsulated strains.[22-24] Among encapsulated strains there were six antigenically distinct serotypes: a, b, c, d, e, f. Pittman showed experimentally in rabbits that antibodies to type b capsules gave type-specific protection against Hib infection. There was a need to develop a vaccine that assisted acquisition of antibody against Hib capsule - polyribosylribitol phosphate (PRP) - and thus give protection against infection.[24] In 1972 anti-capsular antibodies were first shown to be protective in humans.[22]

The polysaccharide vaccines against Hib were first tested in clinical trials in the 1970s.[25] A Finnish study in a population of 100,000 children showed that Hib polysaccharide vaccine was 90% efficacious in the prevention of invasive Hib infection. However, the immunogenicity of this vaccine was strongly age-dependent. Vaccination only gave sufficient protection when the recipients were aged at least 18-24 months.[25]

2.1.1. *H. influenzae conjugate vaccines*

As the incidence of invasive Hib disease generally peaked around the first birthday, vaccines that could provide protection in this vulnerable period were required. The PRP conjugate vaccines were developed as a means to enhance the immunogenicity of the PRP polysaccharide by utilising the immunological principles of hapten-carrier linkage. The PRP polysaccharide hapten is covalently linked to an immunogenic T-cell-dependent protein carrier. Compared with the PRP polysaccharide vaccine all four PRP-conjugate vaccines developed demonstrated improved immunogenicity characteristic of most T-cell-dependent immunogens.

The four currently available vaccines, although using the same immunological approach, are chemically and structurally distinct, and appear to induce immune responses with different immunological characteristics. The vaccines differ in the following aspects: 1) the type of protein carrier; 2) the size of the polysaccharide; 3) the chemical linkage of the polysaccharide; and 4) the three-dimensional structure of the conjugate.[23; 26]

1. PRP-Diphtheria toxoid conjugate vaccine (PRP-D) (manufactured by Connaught Laboratories, Inc., USA). Hib polysaccharide conjugated to diphtheria toxoid.

2. Haemophilus b Oligosaccharide Conjugate vaccine (HbOC) (manufactured by Wyeth Lederle Vaccines, USA). Hib oligosaccharide conjugated to CRM197 protein.

3. PRP-Tetanus toxoid conjugate vaccine (PRP-T) (manufactured by Pasteur-Merieux Serums & Vaccines, France, and by SmithKline Beecham Biologicals, Belgium). Hib polysaccharide conjugated to tetanus toxoid.

4. PRP-outer membrane protein complex conjugate protein vaccine (PRP-OMP) (manufactured by Merck Sharp & Dohme, USA). Hib polysaccharide conjugated to an outer membrane protein complex of Group B meningococci.[23; 27]

Efficacy studies have shown that PRP-D, HbOC, and PRP-OMP can prevent more than 90% *of H. influenzae* type b disease. A formal study of PRP-T was not completed due to the licensing of the other vaccines, but this vaccine is currently being offered in immunisation programmes in Europe.[28]

As a result of immunogenicity studies that have been carried out on the four conjugate vaccines, PRP-D appears to be the least immunogenic. PRP-OMP elicits the greatest immune response after a single dose, especially in young infants.[23] PRP-T and HbOC both induce antibody responses after the second or third dose in infancy, and the final antibody concentrations are generally higher than they are with the other two conjugates.[27]

A vaccine which is appropriate for a population with a high mean age of disease (viz. Australian Caucasians, some European populations) may not be appropriate for a population with a lower mean age of disease (Australian Aboriginals).[24] This has been suggested by the poor efficacy of the PRP-D vaccine demonstrated in native Alaskan infants, a population with high incidence of disease in infancy.[29]

2.2. Epidemiology - pre-vaccination

2.2.1. Incidence

The overall incidence of invasive Hib disease in children under 5 years of age shows wide variation between countries/regions, ranging from 12/100,000 in Athens, Greece, [30] to 237/100,000 in Northern Territory, Australia[21] (Table 1). Epidemiological studies in Denmark, England and Wales, Finland, Italy, the Netherlands, Ireland, Scotland, Sweden, Switzerland, New Zealand, and Australian states/territories (other than Northern Territory) have shown the annual incidence rate of invasive Hib in children under five years of age to be between 20 and 60 per 100,000.

Hib meningitis and Hib epiglottitis comprise different proportions of all invasive Hib in different countries. Meningitis always appears to comprise at least 30% of the presenting illness in the 0-5 years age group (range 30-75%; inter-country median 57%), whilst the proportion of Hib caseload due to epiglottitis can range from 0 - 47% (inter-country median 25%).

Epiglottitis is reported as a major component of all studies of invasive Hib disease in Western Europe.[31] Several states in Australia have reported epiglottitis as the presenting disease for approximately 30% of the Hib cases, while the corresponding percentages in Australian Aboriginal and Israeli populations are zero and approximately 3%, respectively (Table 1).

Epiglottitis is rare in populations in which the overall incidence of invasive Hib disease is very high and where it occurs very early in life, such as Australian Aboriginals.[21] Such populations show a high percentage of invasive Hib disease presenting as meningitis and pneumonia. Whether the low incidence of epiglottitis in such populations is a matter of genetic predisposition or simply reflects age-specific susceptibility to the disease is yet unclear. Dagan's[32] study in Israel presented a unique epidemiological pattern: the age distribution resembled that of a developing country, but the incidence of disease was shown to be similar to that of a developed country. For example, the case attack rate of invasive Hib disease is 34/100,000 (a rate similar to that of England and Wales, Denmark, and New Zealand) but

93% of cases occurred before the age of 2 years, and the incidence of epiglottitis in children less than 5 years of age was <1/100,000.

The case definition of invasive Hib disease varies considerably between studies, especially with respect to the criteria for diagnosis of epiglottitis. This will have resulted in over- or under-estimates of the population incidence of epiglottitis being made in studies in different countries. For example, in Australia, the case definition for Hib epiglottitis includes cases which are clinically diagnosed without microbiological evidence of Hib infection, and while the rates of epiglottitis may truly be higher than those in other countries, caution has to be taken when interpreting study results.

Table 1: Reported incidence of Hib meningitis, Hib epiglottitis and all invasive Hib disease in children less than 5 years of age in developed countries (% of total) pre-vaccination programmes

	Annual incidence (%) per 100,000 children			
Country (Area/Region)	Years	Hib meningitis	Hib epiglottitis	All invasive Hib disease
Australia (Australian Capital Territory)[33]	1984-1990	31 (49)	20 (32)	63
Australia (Northern Territory) - all[21]	1985-1988	88 (37)	9 (4)	237
- Aboriginal		159 (30)	0 (0)	529
- non-Aboriginal		53 (58)	13 (14)	92
Australia (Sydney)[34]	1985-1987	21 (54)	13 (33)	39
Australia (Victoria)[35]	1985-1987	25 (42)	28 (47)	59
Australia (Western Australia)[36]	1984-1988	-	-	-
-Aboriginal		150	-	-
- non-Aboriginal		27	-	-
Denmark[37]	1985-1986	27 (68)	8 (20)	40
Finland[17]	1985-1986	26 (50)	13 (25)	52
France[13]	1980-1989	15 (71)	2 (10)	21
Greece - (Athens)[30]†	1992-1994	8 (67)	-	12
Iceland[38]	1974-1988	43	-	-
Israel†[32]	1988-1990	18 (53)	<1(~ 3)	34
Netherlands[39]		22	-	-
New Zealand - (Auckland)[40]	1981-1987	27 (66)	-	41
Ireland†[14]	1991-1993	12 (48)	4 (16)	25
Sweden†[18]	1987-1992	31 (57)	15 (28)	54
Belgium[41]	1990-1992	30 (69)	6 (14)	44
Spain (J Campos, personal communication)	1993-1994	8 (67)	-	12
Switzerland[42]	1976-1989	25 (42)	19 (32)	60
United Kingdom (England and Wales)†[15]	1991-1992			31
United Kingdom, Scotland[43]	1991	14 (54)	-	26
United Kingdom, Wales†[44]	1988-1990	22 (63)	-	35

† denotes prospective studies

2.2.2. Seasonality

The majority of countries/regions show peak incidence of invasive Hib disease in the winter months[14; 17; 32-35; 42; 45] and some have a bimodal peak of incidence (e.g. Italy, Finland, Israel, Switzerland).[17; 32; 41; 42; 45] In Auckland, New Zealand, however, no distinct seasonal distribution in the incidence of invasive Hib disease was observed,[40] and in central Australia significantly fewer cases were diagnosed in the winter months than the non-winter months.[21]

2.2.3. Age distribution

Among children less than 5 years of age living in industrialised countries, up to 40% of the invasive Hib disease infections occur before 12 months of age (**Table 2**). In contrast, in indigenous minority populations such as the Australian Aboriginals, a majority of invasive Hib infections occur during the first year of life.[21] A similar age distribution of infection is shown in Israeli children.[32; 46]

Table 2: Proportion of cases (%) of invasive Hib disease in children under 5 years of age: by age and country

Country (Area/Region)	**< 12 months**	**< 18 months**	**< 24 months**
Australia - (Northern Territory)[21]			
- All		76	
- Aboriginal	71	85	
- Non-Aboriginal	39	47	
Australia - (Sydney)[34]	30	47	60
Australia - (Victoria)[35]	22	38	54
Finland[17]			
Greece - (Greater Athens)[30]	36		84
Iceland[38]			73
Israel[32]	70	89	95
New Zealand - (Auckland)[40]		66	70
Spain (J Campos, personal communication)	43		78
Switzerland - (Geneva)[42]	32		58
England & Wales[47]	42		71

2.2.4. Mortality

The case fatality rate for invasive Hib has been reported in the range 0.5% - 5.0%. However, caution has to be taken when looking at these published case fatality rates as they are given for different study populations, age categories, and some are quoted for invasive *H. influenzae* disease while others are given for only for invasive Hib. Table 3 gives figures from published literature.

Table 3: Case fatality rates for invasive Hib: by Country / Region

Country – Area/Region	Year	Age of study population	Case-fatality (%)
Australia - Australian Capital Territory [33]	Jan 84 - Dec 90	Paediatric	0.7†
Australia - Northern Territory[21]	mid 85 - mid 88	0-5 years	3.7
Australia – Victoria[35]	Jan 85 - Dec 97	< 16 years	2.6
Australia- Sydney[34]	1985 - 1987	0-14 years	2.1
Belgium[41]	1990 - 1992	< 5 years	2.1
Denmark[48]	1985 - 1986	0-14 years	2.0
Finland[17]	Feb 85 - Dec 86	0-15 years	1.8
France[13]	Jan 80 - Dec 89	1-59 months	3.0
Greece[30]	Nov 92 - Nov 94	0-14 years	2.2
Iceland[38]	1974 - 1988	all ages	0.7
Israel[32]	Oct 88 - Sept 90	≤ 12 years	2.1
New Zealand – Auckland[40]	Jan 81 - Apr 87	< 15 years	0.5
Ireland[49]	Sept 91 - Sept 93	< 14 years	1.3
Spain (J Campos, personal communication)	Jan 93 - Dec 94	< 5 years	4.7
Sweden[18]	Jan 87 - Dec 92	all ages	2.9†
Switzerland[42]	1976 - 1989	0-16 years	1.1
England & Wales[47]	Oct 90 - Sept 92	all ages	3.9
United Kingdom – Oxford[50]	1985 - 1991	< 10 years	4.3

† all *H. influenzae*

2.3. Country profiles - pre-vaccination

2.3.1. Australia

Population-based studies in Victoria, Australian Capital Territory, and Sydney, New South Wales prior to introduction of the Hib immunisation programme showed invasive Hib infection rates of approximately 40-60 per 100,000 children under the age of five years.[33-35] Epiglottitis accounts for a relatively high proportion of cases, but this is variable between studies and may partly reflect the different case definitions. Overall, nearly 50% of cases occur in children over two years of age.

Amongst Aboriginal children in the Northern Territory the epidemiology of *H. influenzae* is very different. The estimated annual attack rates (annual attack rate) in the Northern Territory were approximately 529/100,000 Aboriginal children under five years of age compared to 92 in non-Aboriginal children.[21] Forty percent of cases occur in Aboriginal children in the first 6 months of life, and meningitis and pneumonia are the dominant manifestations of infection. Epiglottitis is relatively

rare.[21] The annual attack rate for non-Aboriginal children in the Northern Territory is higher than elsewhere in Australia.

2.3.2. Belgium

The incidence of invasive Hib infections in Belgium[41] over the years 1990-1992 inclusive was shown, by retrospective study, to be 44 per 100,000 children under the age of five years. Meningitis accounted for 69% (30/100,000) of cases and epiglottitis for 14% (6/100,000). Twenty one percent of the Hib cases in this study population occurred in children aged less than six months. The case fatality over this period was 2.1% (2 deaths in 101 cases).

The incidence of cases of Hib displayed a bimodal pattern, peaking in April and October-November.

2.3.3. Denmark

A retrospective study of Danish children in 1985-1986 showed an annual attack rate of invasive Hib of 40/100,000 in children less than 5 years of age, with 68% of cases occurring in children less than 2 years of age.[48] The annual incidence of Hib meningitis was found to be 27/100,000 in children less than five years of age.

2.3.4. Ireland

In the 4 year period prior to introduction of vaccine in 1992 to Ireland a retrospective study was undertaken and the average Hib disease incidence was 35/100,000 in children less than five years of age. During the period of active surveillance (1991-1993) the incidence rate was 25/100,000 in this age group[14] with a peak incidence in the 6-11 month age group (included part of the post-vaccination epidemiology as vaccine was introduced in 1992).

2.3.5. Finland

Intensified surveillance of invasive Hib disease between 1985 and 1986 showed that the annual attack rate in children under 15 years of age was 19/100,000, and in children less than five years of age it was 52/100,000. The annual attack rate for meningitis in children under five was 26/100,000.[17] Forty five percent of cases were in children under 2 years of age. The disease occurs more amongst older children compared with data from many other industrialised countries. The annual attack rate of Hib meningitis in children under 5 years was shown to be 27/100,000 in 1978, [51] and 26/100,000 in 1985-86.[52] Forty-seven percent of cases occurred before 18 months of age, and 59% before two years of age.

Cases of Hib meningitis and epiglottitis occurred more often in boys than girls, whereas the opposite was found for other types of invasive Hib disease (p=0.015), even when age was controlled for as a confounder.

Bimodal seasonal peaks were shown in the incidence in invasive Hib disease in Finland.

2.3.6. France

Children aged 0-4 years from two French departments were studied over the 10-year period 1980-89 to determine the incidence of meningitis and other systemic disease due to *H. influenzae.*[13] The incidence of invasive Hib infections was found to be 21/100,000 in children less than 5 years of age. The Hib meningitis infection rate was 15/100,000, and for other systemic disease it was 17/100,000 (of which epiglottitis was 2/100,000). Most meningitis cases occurred in the 0-5 year age group; 6% of cases were observed before 6 months of age, 42% before 12 months, 68% before 18 months, and 78% before two years.

Over the ten-year study period, the number of observed cases was stable with peak incidence in October. As noted in many other studies, there was a slightly greater incidence in boys. Mortality was 3%.

2.3.7. Germany

Estimates of the incidence of *H. influenzae* meningitis in children under 5 years of age in pre-vaccination periods in Germany gave a rate of 23/100,000.[53] Nationwide immunisation was introduced in Germany in 1990; the German recommendations are for two vaccinations during the first 6 months of life plus a booster in the second year with a free choice of the four vaccines (PRP-D, PRP-OMP, HbOC, PRP-T) marketed in Germany. There was, however, no serotyping of the *H. influenzae* specimens.[54]

2.3.8. Greece

A prospective study was undertaken in the Greater Athens area for two years, 1992-1994. The annual attack rate of invasive Hib disease among children under five years of age was 12/100,000. Including clinical cases of epiglottitis, this rate increased to 16.25/100,000.[30] Hib meningitis accounted for 69% of cases, with an annual attack rate of 8/100,000. The incidence of culture confirmed epiglottitis was 1.7/100,000, and including clinically diagnosed cases, the overall epiglottitis incidence was 6/100,000.

2.3.9. Iceland

A retrospective study of Iceland's records of *H. influenzae* meningitis and septicaemia cases between 1974 and 1988 gave an annual attack rate of 43/100,000 children under five years of age.[38] Approximately 70% of these cases were in children under the age of two years.

2.3.10. Israel

A nationwide prospective study of children aged 0-12 years was conducted between October 1988 and September 1990 in Israel[32; 46] to inform decisions regarding the need for a Hib conjugate immunisation programme. The incidence of invasive Hib disease in children under the age of five years was 34/100,000 with 22% of cases $\leq$ 6 months, 69% of cases $\leq$ 12 months, 87% of cases $\leq$ 18 months, and 93% $\leq$ 24 months of age. In children under 5 years of age, meningitis accounted for 53% of cases, pneumonia for 21%, cellulitis for 12%, septicaemia for 9%, and epiglottitis for less than 3%. During the first year of life, the incidence of invasive Hib was 117/100,000 children.

Israel shows a unique epidemiological pattern for invasive Hib disease in children. The age distribution of cases is similar to that of a developing country, but the overall incidence is similar to that found in Western Europe. As a result of this study, the Israeli Ministry of Health licensed conjugate vaccines for immunisation of infants beginning at two months of age. The prospective surveillance system established for this study has been continued to enable determination of the impact of the Hib immunisation programme on the incidence rate.

2.3.11. Italy

The epidemiology of Hib infection in Italy is poorly understood and has essentially been derived from hospital-based studies focused on the proportion of Hib meningitis among the total meningitides in childhood.[45] Prior to vaccine licensure, Tozzi and associates undertook a population-based study to estimate the incidence of preventable Hib infection. This study used a prospective cohort of 15,601 children born 1992-93 in 4 of the 21 regions within Italy, and results obtained were limited due to truncation of the study when children were aged from 17-30 months. Estimates of the incidence of invasive Hib disease in children under five years of age were made from these results by using age distribution patterns of Hib shown by other European studies. Estimates of invasive Hib disease of 36.1 to 44.5 per 100,000 person years in children under five years of age and annual attack rate of 28.7 per 100,000 for the first two years of life were obtained.

2.3.12. Netherlands

A study of bacterial meningitis from 1977-1982 estimated the annual attack rate of Haemophilus meningitis in children under five years of age at 22/100,000.[55] It was estimated that in the Netherlands about 1 of 250 children acquired invasive Hib disease below the age of 5 years before 1993.[56]

2.3.13. New Zealand

A retrospective, and for a short period prospective, study over 1981-1987 in the Auckland paediatric population showed rates of invasive Hib disease to be 41/100,000 and meningitis to be 27/100,000 (63% of total cases) in children under 5 years of age.[40] Most disease (91%), occurred in children under 5 years of age and 64% under 2 years of age. Epiglottitis accounted for 14 % of invasive Hib disease cases. The peak incidence of invasive Hib was seen in children 6-24 months old but no seasonal variation was seen.

2.3.14. Spain

A retrospective study from 1993 to 1994 of invasive Hib disease in children aged 0-4 years in Spain identified 302 cases of Hib disease (192 Hib meningitis) from 97 hospitals in 12 of Spain's autonomous regions. The annual attack rate for all invasive Hib disease was 12.4/100,000 (regional range 4.7-20.9/100,000) and for Hib meningitis (64% of all cases) 8.0/100,000 (regional range 4.7-14/100,000) in children under five years of age. Children under one year of age accounted for 43% of cases and children less than two years 78%. The case fatality rate was 4.7%. *(Jose Campos, Madrid, Spain, personal communication).*

2.3.15. Sweden

A prospective study in a county population in Sweden[18] between 1987 and 1992 showed the incidence rate of invasive Hib in children under the age of five years to be 54/100,000. *H. influenzae* meningitis and *H. influenzae* epiglottitis showed an incidence of 31/100,000 and 15/100,000, respectively, in children under five years of age. Note must be made, however, that in the meningitis and epiglottitis cases, *H. influenzae* has not been typed. The case-fatality rate, across all ages, was 2.9% for *H. influenzae*.

2.3.16. Switzerland

The annual average incidence rate of invasive Hib disease in children under the age of five years was shown to be 60/100,000 children over the period 1976-1989.[42] This was a retrospective study, and the incidence showed statistically significant increases within this time; increasing to 122/100,000 and 92/100,000 in 1988 and 1989, respectively. However, caution needs to be taken with regard to the large fluctuations in the incidence rate, as this study population was small and solely urban, consisting of only the city and canton of Geneva.

The age distribution of all cases showed that 92% of cases occurred in children under five years of age; 8% less than 6 months of age; 30% less than 12 months and 54% less than 24 months. During the study period, rates of Hib meningitis (25/100,000) and epiglottitis (19/100,000) were constant, but an increase in the rate of other invasive Hib infections was found.

2.3.17. United Kingdom

Active surveillance of *H. influenzae* in the Oxford region for seven years (1985-91) showed the annual incidence of invasive Hib in children less than five years of age to be 35.5/100,000 with a mortality of 4.3%. The annual incidence of Hib meningitis in this same age group was 25.1/100,000 with a mortality of 4.8%.[50]

The epidemiology of *H. influenzae* disease in the pre-vaccine era was studied for the two years immediately prior to the introduction of vaccine to the United Kingdom in 5 regions of England and Wales (1990-1992). Hib was shown to make up 82% of the 772 cases, and of these cases, 88% of them occurred in children less than five years of age, and of these 42% in the first year of life.[47] The annual attack rate in children less than five years of age was 30.9/100,000.[15]

The annual attack rate of invasive Hib disease in Scotland in 1991 was 25.5/100,000 in children less than five years of age; a rate that is less than that from other United Kingdom studies, but age-sex and seasonal distribution is consistent with that of other studies.[43]

2.4. Epidemiology - post-vaccination

2.4.1. Incidence

Hib vaccination programmes have now been introduced in a number of developed countries, and rapid reductions in the annual attack rate of Hib have been seen. For example, England & Wales experienced a decrease of approximately 90% in the incidence of Hib in children less than 5 years of age, within the space of 1-2 years.[15] The following section will discuss in brief the various immunisation strategies and the published outcomes of these programmes.

Sharp reductions in the incidence of invasive Hib disease have been seen in countries with a high vaccination coverage. Countries such as New Zealand and Australia[57; 58] with considerably lower coverage rates, did not appear to have such sudden reductions in incidence, but vaccine has still had a significant impact on disease burden. In the year following introduction of routine Hib immunisation, New Zealand had reduced the rate of infection by 50% (this should be regarded as a transitional year). In the Netherlands, (where a catch-up programme was not conducted), it has taken 4-5 years to achieve an 88% reduction in annual attack rate in children under the age of five years, (even though a high vaccine coverage rate has been achieved).[39]

Table 4: Incidence of invasive Hib disease in children under five years of age following introduction of routine Hib immunisation programmes

Country	Date of introduction	Year of study	Cases/100,000	Percent reduction
Australia[58]	01/04/93	1996		94%
Iceland*[59]	01/05/89	Oct 1989-93		100%
Netherlands*[39]	01/04/93	1993-6		88%
New Zealand[57]	01/01/94	1994	23.5/100,000	50%
Ireland[49]	01/10/92	1995	2.6/100,000	90%
Sweden[60]	01/01/93	1994	3.5/100,000	90%
England & Wales[15]	01/10/92	1993-4	2.0/100,000	94%

* Refers only to Hib meningitis

Iceland introduced routine immunisation against Hib using PRP-D in May 1989. Children were scheduled to receive the first three doses at age 3, 4, and 6 months and a booster at 14 months. In 1994, no cases of Hib meningitis had been diagnosed since October 1989. Hib bacteraemia was confirmed in 1989-1991 in 4 unvaccinated and 3 vaccinated children, two having received one dose and one 3 doses.[59]

After the introduction of routine vaccination programmes, several countries have shown the relative distribution and type of invasive disease to be similar to that of the pre-vaccination period.[58; 61] Shifts to a higher incidence in older children and adults were seen in the Netherlands, and Sweden.[39; 60]

Seasonal peaks in the incidence of Hib were seen to disappear after establishment of vaccination programmes in a number of countries.[39; 60]

2.4.2. Vaccine failures

In England & Wales between 1 October 1992, and 1 October 1993, there were 164 reports of invasive infection, and of these 43 were true vaccine failures.[62] Analysis of cases by ethnic group fits the racial mix of the United Kingdom population, and suggests that the PRP-T vaccine is protective for all racial groups in the United Kingdom. The relative distribution and types of invasive Hib disease among the United Kingdom vaccine failures appeared similar to that seen before introduction of the immunisation programme. Epiglottitis is now more prominent, which is probably related to the fact that epiglottitis is more common between 1 and 3 years of age. The case-fatality rate (one death amongst the vaccine failures) has also been shown to be consistent with that shown in the pre-vaccination period.[62]

Over three and a half years (Oct 1992-Mar 1996) Ireland had seven true vaccine failures amongst the 27 reported cases of invasive Hib disease.[49]

Between 1993 and 1996, Australia, had 34 cases of true vaccine failures (according to the Australian definition). There were 58 cases, however, which fulfilled the United Kingdom and Ireland definition of true vaccine failures. The spectrum of invasive illness remained similar to the earlier period, with meningitis and epiglottitis the most commonly reported presentations. Surveillance information suggests that the Aboriginal and Torres Strait Islanders may still remain at increased risk of invasive disease. The proportion of vaccine failures and deaths in this population was higher than for the Australian population overall.[58]

In the 3 years April 1993 - April 1996 there were 22 cases of Hib meningitis in the Netherlands. Of these only 2 were vaccine failures.[39] Results from the three year post-implementation Hib surveillance study in the Netherlands from 1993-1996 showed 13 vaccine failures occurring in this time using the British Paediatric Surveillance Unit case definitions of which 7 were true vaccine failures.[63]

2.4.3. Underlying medical conditions

Based on British Paediatric Surveillance Unit (BPSU) surveillance of true vaccine failures in the United Kingdom and Ireland through December 1995, 30% of such cases had an associated medical (e.g. prematurity, chromosomal abnormality, malignancy) or immunological condition.[49]

In Australia, the Hib Case Surveillance Scheme does not provide information on risk factors for vaccine failures.[58] However, since January 1998 the Australian Paediatric Surveillance Unit (APSU), a scheme based on the BPSU, has included *H. influenzae* disease on its card *(P McIntyre, personal communication).*

Underlying conditions were present in two of the seven cases (29%) reported as true vaccine failures in the Netherlands, one with a chromosomal abnormality and prematurity and another with immunodeficiency.[63]

2.4.4. Nasopharyngeal carriage rates

Hib also colonises the upper respiratory tract of healthy individuals and before the widespread use of vaccination the peak age of carriage was 2-3 years.[64] Several studies have indicated that Hib carriage is reduced by vaccination with conjugate vaccine.[59; 62; 65; 66] The effect of the reduction in Hib carriage rates in vaccinated children on the pattern of disease in both vaccinated and unvaccinated populations is unclear, and surveillance of this needs to be maintained. Although Hib is predominantly a disease of childhood, Hib infection can occur in the adult population, especially the elderly, and adult cases and carriers may therefore become a continuing reservoir of infection for susceptible individuals.[61]

A study was undertaken in England & Wales to look at Hib carriage in the population offered the "catch-up" programme when routine childhood Hib immunisation was introduced.[67] Throat swabs were taken before the programme was introduced in 1992 and the survey was repeated, where possible in the same geographical sites, in mid 1994. In 1992, 1,536 children aged 1-4 years were swabbed in 75 centres, and the overall Hib carriage rate was shown to be 3.97% (61/1,536). In 1994, 1,563 children were swabbed in 76 centres (including 61 that were in the first survey). The Hib carriage rate had fallen

significantly to 0.70% (11/1,563) ($p<0.0001$). In this second survey, Hib vaccine coverage was high (88.6%) and Hib carriage rates were lower (0.54% [7/1,303]) amongst vaccinated than unvaccinated (1.80% [3/167]) children, but this difference was not statistically significant. In view of the reduced potential for boosting by natural infection and the absence of a fourth dose in the second year of life, the persistence of protection from Hib vaccination must continue to be monitored in the United Kingdom.

In Iceland, Hib strains isolated from throat, nasopharynx, ears and eyes of children aged 0-5 years with clinical signs of non-invasive infection (e.g. pharyngitis, ophthalmic infections), disappeared when the programme had run for about 2 and a half years. No Hib strains were isolated from nasopharyngeal swabs of 219 children aged 0-5 years attending day-care centres in 1992.[59]

Because the Hib conjugate vaccines differ in biochemical composition and immunogenicity[26] they may vary in their long-term efficacy and effect on Hib carriage and transmission. In addition, different immunisation schedules between countries may impact on herd immunity.[65] For example, administration of a booster dose of conjugate Hib vaccine after 12 months of age may prolong high titre anti-PRP antibody level in children, thereby enhancing the potential to limit transmission of Hib in the population. This reinforces the need to maintain surveillance of nasopharyngeal carriage of Hib in the populations where routine immunisation programmes exist.

2.4.5. Herd immunity

Finland has served not only as a testing ground for the concept of protection through immunisation but also has benefited as invasive Hib disease has almost been eradicated in children. Since 1993 all the Hib conjugate vaccines have been registered and nationwide immunisation has become routine. HbOC was used exclusively in Finland during 1993, 1994, and 1995. The result has been that only one case of Hib disease per year has been reported in children under 5 years of age in 1993 (pneumonia) and 1994 (cellulitis).[26] There has been no increase in meningitis or epiglottitis caused by other pathogens.[68]

In Finland, Hib disease has also started to disappear from older, unvaccinated children; a pattern consistent with herd immunity due to decreased transmission in the population.[27] Booy and colleagues[69] have also provided evidence of the herd immunity effect in England and Wales: the virtual disappearance of Hib disease in infants aged 2 months who have only received one dose of PRP-T vaccine and the fall in rates of invasive disease in children under two months.[70; 71] Similarly in Israel, a fall in cases in children below the age of vaccination has been attributed to herd immunity.[72] The Netherlands, which did not introduce a catch-up programme for children under 5 years of age, has seen little reduction in cases outside of the vaccinated cohorts so far.[39]

2.5. Country Profiles - post-vaccination

2.5.1. Australia

The conjugate Hib vaccines PRP-OMP, HbOC, and PRP-T became free to all children under the age of five from April 1993 in Australia. [58] The routine vaccination schedule offers vaccine at 2,4,6, and 18 months of age, and a catch-up programme was undertaken at the outset.

Between 1992 (549 cases) and 1996 (53 cases) there has been a 94% reduction in cases in children under the age of five years.[58] In the three-year period July 1993-June 1996, meningitis and epiglottitis were the dominant manifestations of disease, 39% and 30% respectively, following similar distribution to pre-vaccination period.

The number of vaccine failures increased over time, while the number of invasive Hib cases fell. Thirty-four cases were registered as vaccine failures. However, while these 34 cases met the Australian case definition of a vaccine failure, a further 24 cases would meet the United Kingdom definition, thus making it 58 vaccine failures (18% of cases under 6 years of age).

Hib coverage has been difficult to measure, and the best national estimate is 50% coverage in April 1995 from the Australian Bureau of Statistics. Also, no studies have identified the proportion each type of vaccine contributes to the overall coverage, and hence estimates of vaccine efficacy for individual vaccine types cannot be produced.

2.5.2. Finland

Hib immunisation was officially made routine in 1993, and is now offered to children at 4, 6, and 14-16 months of age. However, as large scale vaccine trials with the conjugate vaccines had been running since 1986 in Finland, the scale of decrease in infection rate in children was not as dramatic as in those countries introducing Hib vaccination straight into routine programmes.[27] HbOC has been used exclusively in Finland during 1993, 1994, and 1995. Only one case of Hib disease has been reported in children under 5 years of age in 1993 (pneumonia) and 1994 (cellulitis). (J Eskola, personal communication)[26] There has been no increase in meningitis or epiglottitis caused by other pathogens.[68]

The disease has almost been eradicated in children. The number of cases of Hib meningitis in children under 5 years of age in Finland fell from 30 cases in 1986 to nine in 1988, to three in 1990, to none in 1993, 1994, and 1995.[7; 26] Cases in older children have also declined.[27]

Despite the decline in children, in 1991 the incidence of Hib disease amongst adults suggested that Hib infection pressure continues.[73]

2.5.3. Germany

Active surveillance for systemic *H. influenzae* infections was initiated in July 1992. From July 1992 to June 1993, the total number of reported cases was 84. This yields an incidence in children under 5 years of age in Germany of 1.9 per 100,000; furthermore this figure is probably an underestimate because the average monthly surveillance response rate was only 66% in that year.[53]

Twenty-four cases had been vaccinated at least once more than 14 days before the onset of *H. influenzae* meningitis and fifteen cases after at least two vaccinations were observed in German children. Additionally, one case had been vaccinated 3 times and two cases had received their first vaccine at over 18 months of age.[54] Sixteen of these 18 cases (88%) had been given PRP-D vaccine, which, according to sale figures, has a market share of about 70%. Unfortunately, serotyping of *H. Influenzae* was not done in most of these patients.[54]

2.5.4. Iceland

Hib conjugate vaccine (PRP-D) was introduced nationwide in Iceland[59; 74] for children aged 3 months to 3 years in May 1989. This immunisation program has eliminated invasive Hib disease in children 1 month to 10 years of age.[26; 59; 74] The percentage of the type b strains isolated from children in Iceland under 6 years of age with respiratory, throat, ear, conjunctival infections declined after mid-year 1991.[74]

In 1994, no cases of Hib meningitis had been diagnosed since October 1989. Hib bacteraemia was confirmed in 1989-1991 in 4 unvaccinated children and 3 vaccinated, two having received one dose and one 3 doses.[59]

2.5.5. Israel

The effectiveness of Hib vaccination in Israel was assessed three years after implementation of vaccine.[72] It was estimated that the vaccine had been 95% effective against all invasive Hib and 97% effective against Hib meningitis. A reduction in cases too young to be immunised was attributed to herd immunity.[72]

2.5.6. Netherlands

Since April 1993, Hib vaccination using PRP-T vaccine has been routinely offered to all children in the Netherlands. The vaccination schedule is for ages 3, 4, 5, and 11 months and there was no catch-up programme for children under five years of age.

Van Alphen and colleagues have looked at the impact of the Hib vaccination programme on the incidence of *H. influenzae* meningitis in the first 3 years of the immunisation programme.[39] A steady reduction in the number of cases was shown, and the seasonal variation in incidence disappeared. Two

and a half years after introduction of the programme there was an 88% decline in the number of cases in the study cohort. After this, the rate decreased no further. Like the United Kingdom, the Netherlands has a high Hib vaccine uptake, but the decline in incidence of Hib in the under 5 year olds was not as dramatic, and herd immunity was not observed. This may be reflective of the lack of a catch-up programme in the Netherlands.

During the 3-year study period, a shift to higher ages occurred in the age-specific incidence of Hib meningitis because of the gradual disappearance of cases in younger age groups.

2.5.7. New Zealand

Hib vaccination of infants became routine in New Zealand[57] in January 1994. The vaccine schedule is 6 weeks, 3 months, 5 months, and 18 months of age. In addition, a catch-up programme offered Hib vaccine to all children up to the age of five years. The rate of invasive Hib disease in those under five years of age decreased from 43.6/100,000 in the 1991-93 period (pre-vaccination) to 23.5 in 1994. This year was regarded as a transitory year, and it is acknowledged that to achieve elimination of the disease New Zealand will have to achieve and maintain high immunisation coverage levels.[57]

2.5.8. Sweden

Conjugate Hib vaccines were introduced in Swedem[60] in 1992, and all children born after December 31, 1992, were offered vaccine free of charge. A rapid decline of *H. influenzae* meningitis and bacteraemia was observed in the autumn of 1993, when the expected peak incidence failed to appear.[60] In the pre-vaccination period 1987-1991, the average annual incidence was 34/100,000 in children aged 0-4 years. In 1994, the annual incidence fell to 3.5/100,000 (a 90% decrease). No significant decline was observed in older children or adults. There was a 92% reduction in the number of meningitis cases and an 83% reduction in the cases of bacteraemia. A similar decline was noted in two regions that followed different strategies for the introduction of the vaccination programme (one where vaccine was not free, and another where immunisation was offered to all children aged 0-4 years).

The vaccination of younger children may explain the earlier decrease in the number of meningitis cases compared with bacteraemic cases.

2.5.9. United Kingdom and Ireland

The United Kingdom and Ireland[15] made Hib conjugate vaccine part of their routine immunisation schedules on 1st October 1992. The United Kingdom provided immunisation for infants at the ages of 2, 3, and 4 months of age, and a catch-up programme for all children under five years age was implemented. The Ireland vaccinates infants at 2,4, and 6 months age, and it also provided a catch-up programme for under five year old children.

Since October 1992 there has been a rapid reduction in the number of cases of invasive Hib disease. In England & Wales, the annual attack rate for Hib disease in children under 5 years of age fell from 30.9 per 100,000 population in 1991-2 (369 cases recorded) to 2.0 per 100,000 in 1993-1994 (24 cases).[15] The risk of acquiring the disease in the pre-vaccine period (1991-1992) was 1:3200, whilst the risk after introduction of the routine vaccine programme reduced to 1:50,000.[15] A dramatic decrease has also been seen in Ireland; the rate has dropped from 25/100,000 children under the age of five years in 1987-1990, to 2.6/100,000 in 1995. These decreases in incidence are both over 90%. True vaccine failures have been observed in both United Kingdom[69] and Ireland. Between Oct 1 1992 and Oct 1 1995 43 true vaccine failures have been recorded in England & Wales. One death (2%) has been seen in these vaccine failures, which is consistent with the pre-vaccination case fatality rate. Ireland has had seven true vaccine failures between Oct 1 1992 and March 1996.

The relative distribution of type of invasive Hib disease among vaccine failures is similar to that seen before introduction of the immunisation programme. Only epiglottitis is more prominent which is consistent with the fact that epiglottitis is more common between 1 and 3 years of age and with the slight fall-off in vaccine efficacy in older children.[69]

Vaccine uptake in the United Kingdom has been very high and the decline of Hib disease rapid. The estimated overall efficacy for three doses of PRP-T was 98.1% (95% CI 97.3-98.7%) in the United Kingdom. Data on Hib vaccine coverage are not readily available in Ireland and hence no reliable estimates can be made of vaccine efficacy. Analysis of cases by ethnic group suggests that PRP-T vaccine is protective for all racial groups in the United Kingdom.[69]

Evidence has been provided for herd immunity in the United Kingdom by the virtual disappearance of Hib disease in infants aged 2 months who have received only one dose of PRP-T vaccine and are not likely to be immune.

2.6. Other International initiatives

Globally and at the European level, there have been several initiatives on the surveillance of vaccine preventable disease and on vaccination programmes in the past few years which have included information on Hib vaccine or disease.[75-79]

A recent position statement from World Health Organisation now recommends the incorporation of Hib vaccine in infant immunisation programmes.[80] The World Health Organisation has also produced a 'generic protocol for population-based surveillance of *Haemophilus influenzae* type b' as part of the Global Programme for Vaccines and Immunisation. This document aims to encourage developing countries to establish the burden of disease and to inform the addition of Hib conjugate vaccine into infant immunisation schedules.[75] The protocol suggests that surveillance of Hib meningitis is the most cost-beneficial approach. Meningitis was chosen as the laboratory diagnosis is fairly simple, and the yield from microbiological testing of cases with meningitis is expected to be higher than fluid culture in septicaemia or pneumonia. The document emphasises that it is essential that cerebrospinal fluid (CSF) samples are submitted to a single laboratory with the ability to culture CSF for *H. influenzae* or to perform Hib antigen detection tests on CSF. Although meningitis is only a proportion of all invasive Hib disease, estimation of the incidence of meningitis will allow extrapolation to give estimates of the true incidence of Hib disease.

Surveillance of bacterial meningitis in Europe[76] has been performed over many years. This project mainly collects information on meningococcal disease although some countries contribute information on *H. influenzae* meningitis. The main outputs of this system are descriptive epidemiology of *H. influenzae* meningitis in countries that report and incidence rates of this disease by age and season. This surveillance system is not limited to the European Community and includes many countries of Eastern Europe and some non-European countries.

The European Sero-Epidemiology Network, begun in 1996, is also a European network for serosurveillance across Europe[81] which has collected information on vaccination programmes throughout Europe focusing mainly on measles, mumps, rubella, pertussis and diphtheria serology. There is no plan to perform Hib serology at present but the mechanism for extension to other infections is available.

Three main reports published during the period 1993-1996 have looked at vaccination programmes and surveillance of vaccine preventable diseases in Europe including Hib.[77-79] All have been funded by the European Commission.

The first was the EUREPI project.[77] This aimed to give accurate and standardised information on immunisation programmes in Europe and to evaluate each country's ability to meet the common objectives by 1995. These objectives were the achievement of elimination targets for certain vaccine preventable disease set for European countries by World Health Organisation. The study focused on four key areas; quality assurance for immunisation coverage assessment, outbreak investigation and research on the epidemiology of vaccine preventable diseases close to elimination, monitoring of adverse events following immunisation, and cold chain of vaccine supply. It was concluded that surveillance systems (using measles as an example) should allow for data centralisation ultimately at a European level to allow for Europe-wide and World Health Organisation studies on disease. To determine the most cost-effective method for assessing vaccine coverage and to assess vaccine wastage it was concluded that for countries where the private sector was predominant in vaccine delivery the

reliability and comparability of data available for assessing vaccination coverage (doses distributed) needed to be evaluated against more reliable systems using the number of children immunised.

The second report was produced by the European Vaccine Manufacturers[78] with the aim of rationalising the use of vaccines in Europe and worldwide. The main recommendations included increasing efforts to co-ordinate surveillance and the further development of epidemiological systems and methodologies between European countries. They also recommended the reinforcement of vaccine coverage rates throughout the European Community with a proposed European Advisory Committee that could propose possible harmonisation of immunisation policies.

The third was undertaken by the joint expert panels of 'European surveillance system for infectious disease' and 'Harmonisation of European Vaccination Programmes' of the COST/STD-3 initiative.[79] This was an initiative to improve collaboration between scientists and the vaccine manufacturing industry in the field of European vaccine research. The panel concluded that surveillance played a crucial role in the development and implementation of effective vaccine policies and was essential for evaluating vaccination programmes. They recommended Europe-wide disease specific surveillance guidelines, the development of uniform, appropriate case definitions, a commonality of diseases for universal vaccination, the concept of an acceptable schedule range for each vaccine and recommended priorities for epidemiological research. Several research priorities identified included studies on vaccine failures, need for booster doses, mathematical modelling to understand the effect of vaccination programmes on disease epidemiology, exchange of comparable data between countries, comparable methodologies for determining age-specific coverage across Europe, and collaboration between laboratories to enhance comparability between laboratory based surveillance data.

3. METHODS

3.1. Surveillance of Hib vaccination programmes

Surveillance of *H. influenzae* type b, like other vaccine preventable diseases, should aim to measure the burden of the disease in the population, to define the target population for vaccination, to evaluate the impact of the vaccination programme and to detect problems that may require alterations to the vaccination strategy.[82] Surveillance of vaccination programmes should involve gathering information on disease incidence and prevalence, on vaccination coverage, vaccine failures, and adverse events to provide information for vaccine policy.

As can be seen from the review of published literature, many European and Australasian countries have reported on Hib infection prior to and after the implementation of a vaccination programme. Some comparisons can be made on the epidemiology of Hib from published data but as different methods are used and the results presented are in an aggregated form, more detailed comparative analyses cannot be undertaken. It can be seen that differences in surveillance systems, in vaccination programmes and in laboratory methods can impact on comparison of the epidemiology of Hib between countries.

At the start of this study it was therefore essential to describe the similarities and differences between countries to establish areas where valid comparisons can be made, to recommend changes that could be simply undertaken and to determine where the concerted action would be most effective. This information can be elicited from the national/regional responsible centres for Hib surveillance and Hib laboratory reference facilities using detailed questionnaires. The questionnaires were developed after reviewing the key literature on surveillance of vaccine preventable disease[82-84] and of previous reports on vaccination programmes in Europe.[77-79]

3.2. Development of the questionnaire on the surveillance of Hib disease

Information on surveillance systems in participant countries was obtained using a questionnaire (Appendix 1). The content of the questionnaire included the objectives of surveillance, the types of surveillance undertaken, the case definition used, the laboratory methods used, the population under surveillance, the variables gathered, the dissemination of findings, evaluation of the surveillance systems and any special studies or developments within the surveillance system. The rationale for the inclusion of these areas is discussed below.

3.2.1. Objectives of surveillance

The overall aims and objectives of a surveillance system will depend on what stage a particular region or country is at in implementing a vaccination programme. For countries that have yet to implement Hib vaccination programmes, the surveillance objectives will be different than those that have routine Hib immunisation and this can also affect how the surveillance system operates and the information it collects.

3.2.2. Case definitions

The case definitions used for a vaccine preventable disease may also vary with the stage of the vaccination programme.[85] Invasive Hib disease is usually severe and requires hospitalisation; many of the presenting clinical conditions can be caused by other organisms. For surveillance of invasive Hib disease, therefore, microbiological diagnosis is required both before and after implementation of a vaccination programme to establish the diagnosis.[75] Rates of disease would be increased by including clinically defined cases which are not confirmed (e.g. of epiglottitis). After the vaccination programme has been implemented, the specificity of the case definition becomes more important.[82]

3.2.3. Population under surveillance

Surveillance may be exhaustive or restricted to defined population groups (e.g. children) or performed in sentinel regions. Although restricted or sentinel surveillance can provide useful trend information

within one country, a description of the population under surveillance is required to inform comparisons between countries.

3.2.4. Types of surveillance

Reporting systems can be passive and/or active and the type of reporting can affect the proportion of total disease ascertained. Active surveillance is felt to increase reporting and many countries now have some form of active paediatric surveillance schemes for a number of communicable diseases of childhood.[63; 86] These schemes are useful for surveillance provided the disease is rare enough so that reporting fatigue is minimised. Comparison of the types of surveillance and of the data obtained can inform future surveillance in participant countries.

3.2.5. Variables collected

Information gathered on individual cases needs to include variables that meet the objectives of the surveillance system and the case definition. Common variables and the definition and coding of variables needs to be known to enable comparison between countries.

3.2.6. Laboratory methods

Information on laboratory methods in all participating countries for diagnosis and reference facilities for *H. influenzae* or Hib is required. The clinical and microbiological practice in a country, in relation to diagnosis of Hib disease, can impact on establishing the disease burden and how comparisons are made between countries. If laboratories in some countries do not routinely test blood cultures or other sterile site specimens for *H. influenzae* in cases with compatible clinical disease, invasive *H. influenzae* and Hib disease will not be diagnosed. For comparisons to be made between countries it is important to know how cases of Hib disease are ascertained. This questionnaire therefore included information on the proportion of local laboratories able to detect Hib or *H. influenzae* infection.

The ability and quality of laboratory facilities to serotype isolates as Hib either locally, regionally or nationally is also crucial to surveillance. If samples are serotyped at a central laboratory the proportion of laboratories sending isolates to the reference laboratories is required. If serotyping is not undertaken locally or specimens are not referred to reference laboratories, the contribution of Hib to all *H. influenzae* may not be ascertained.

3.2.7. Dissemination of surveillance findings

An important component of surveillance systems is for 'information for action'.[82; 83] Vaccine policy decision-makers need to have the available information to decide on implementing or reviewing a vaccination programme. Local public health and clinical professionals need feedback for evaluating local and national initiatives and to encourage continued reporting.

3.2.8. Evaluation of surveillance

Evaluation of surveillance systems is an integral part of surveillance and should lead to developments to improve or revise these systems. Often under-reporting, sensitivity and specificity are assessed but other aspects such as timeliness and cost-effectiveness are equally important. There are published guidelines for evaluating surveillance systems.[83]

3.2.9. Additional studies and developments

Special studies may sometimes be required to supplement surveillance of vaccine preventable diseases such as carriage, serological or other epidemiological surveys. In the surveillance of Hib disease, carriage studies before and after implementation of vaccination programmes can assist in understanding the dynamics of the disease and allows models of infection to be developed for mathematical modelling to determine patterns of future disease.

3.3. Development of the questionnaire on vaccination programmes

The World Health Organisation has recommended[80] that 'Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunisation programmes. The decision to implement a vaccination programme in a country will depend on the disease burden, the costs of the programme, the political will, and professional and other pressures. Where the burden of disease is unclear, efforts should be made to establish this.

With the exception of Greece, Portugal, Italy and Spain, Hib is included in national infant immunisation schedules in all EC countries.[87; 88] The vaccination programme implemented, however, depends upon many factors; the epidemiology of the disease in the population, the type of vaccine licensed and available, the efficacy and performance of the vaccine in local or international vaccine trials, the organisation of vaccination delivery, and the recommendations of experts and of vaccine manufacturers. There can, therefore, be very marked differences between countries, and occasionally within countries in vaccines used and vaccination schedules.

Comparison of the epidemiology of Hib and of Hib vaccine efficacy between countries needs to take account of these programme differences. Information on the current vaccination programmes for Hib was also obtained by questionnaire (Appendix 1). Questions were included on the introduction of the vaccine nationally, the target population, the immunisation schedule and number of booster doses, the delivery and organisation of the programme, methods for estimating vaccination coverage and surveillance of adverse events. The rationale for including these aspects of the vaccination programme is discussed below.

3.3.1. Delivery and organisation of vaccination programmes

Vaccine delivery and organisation of health services will impact on the programme chosen and on its outcome. Compulsory vaccination, such as requirements for completion prior to school admission, may ensure high coverage. The timing of the requirement, however, might encourage children to complete vaccination late, after the targeted age. The method of funding for vaccine programmes and the method of reimbursement for vaccine and for administration can also affect vaccine delivery and coverage.

Effectively delivering a vaccine to the target population is also affected by how the programme is co-ordinated and administrated at different levels. Ensuring that the target population has access to vaccination services is essential. Children eligible for vaccination may be registered and scheduled for vaccination based on this registration. A call and recall system for children to prompt attendance for vaccination may exist. Flexible access to vaccination services for their children by outreach or at clinics held in more accessible areas and at more accessible times may encourage higher coverage and more prompt vaccination.

3.3.2. Implementation of national vaccination

How and when an immunisation programme is introduced can also explain some of the impact on disease. The date of introduction of a vaccine nationally is usually taken as the beginning of the post-implementation period. Interpretation of the epidemiology before and after vaccine implementation has to be conducted with caution. Some countries may have had extensive vaccination use through pre-implementation trials or from private/independent use of vaccine after license but before the vaccine is incorporated into national programmes. At introduction of a programme, the vaccine may also be offered to a wider age group than routinely scheduled as part of a 'catch-up' campaign.

3.3.3. Vaccine schedule

Differences in Hib vaccination schedules need to be allowed for in comparing different countries and interpreting the results. Differences in age of the first and second dose may affect disease rates in certain age groups. Booster doses may also be scheduled in some countries and this may also impact on the epidemiology of the disease both by direct and indirect effects.

3.3.4. Choice of vaccine

Different vaccines may have different efficacy (either in the whole population or in specific groups). It is important, therefore, to be able to evaluate individual vaccines within a programme. This may be difficult if information on type of vaccine administered to an individual and the total doses of that type of vaccine administered is not available.

3.3.5. Coverage assessment

An estimate of coverage is needed to determine the effectiveness of vaccine delivery programme and to estimate vaccine efficacy. The characteristics of those not vaccinated can also be assessed and vaccination strategies targeted. Differences in the organisation and administration of a vaccination programme can affect how coverage rates can or cannot be assessed.

Total population assessment involves measuring either total doses or courses administered or doses distributed. Doses administered can be used to estimate coverage with the denominator usually taken as the resident population. This is usually the most accurate method but factors that affect the numerator or denominator can lead to bias. Lower coverage levels may be estimated due to population migration outside whilst remaining on the 'resident list' or by failure to or delays in recording administered doses. Doses distributed can also be biased, usually towards higher coverage estimates, from failure to record doses discarded and doses given outside of the target age. Sample population assessment can be made in a selected sample of 'settings' such as public health clinics or by coverage surveys such as the World Health Organisation cluster samples.[89]

Coverage levels may also not be directly measured for particular antigens and estimates are made using other antigens given at the same time.

3.3.6. Adverse events surveillance

Surveillance of adverse events is part of the post-marketing surveillance of vaccines. Often it is reliant on passive physician reporting and events are known to be under-reported.[90] Few countries have active surveillance systems for adverse events. Adverse events in relation to Hib vaccine have rarely been reported.[90] Although it is an important part of the evaluation of a vaccination programme it is not a direct part of this study and a current European Vaccine Inventory study is looking at these issues.

3.4. Vaccination coverage

Age-specific estimates of Hib vaccination coverage were requested annually from participant countries by questionnaire. In those countries without routinely collated coverage data, this could be determined by using established methods (e.g. World Health Organisation cluster sampling) or case control techniques.[6]

3.5. Collection of epidemiological data

A project workshop was held, enabling collaborators to consult on and review the tasks, present the results of the study annually, and to make recommendations on the future progress of the study.

The first workshop was held at CDSC, Colindale, in November 1996 where the findings of the questionnaires on methods of surveillance, laboratory diagnosis of *H. influenzae* and Hib, and the vaccination programmes were presented and discussed. At this workshop, agreement was gained on the case definitions for invasive *H. influenzae* disease and vaccine failures, the minimum data set for *H. influenzae* cases, and the methods for the annual data collection from participating countries, including information on vaccination coverage and pre-vaccination incidence of disease.

3.5.1. Invasive H. influenzae cases

For each case of invasive *H. influenzae*, participant countries were required to establish basic clinical and socio-demographic data and vaccine history including dates, make and batch of vaccine.

Information on age, sex, vaccination status and clinical and laboratory features of all cases were to be obtained from each partner country annually over the three years. Where possible, estimates of the pre-vaccination incidence of *H. influenzae* were requested from participant countries.

3.5.2. Case Definition for the surveillance of invasive H. influenzae disease

Isolation of *H. influenzae* from normally sterile site e.g. blood/CSF/joint aspirate with a clinical picture compatible with invasive disease.

3.6. Laboratory identification

It was felt that, whilst in most countries referring laboratories were able to identify *H. influenzae*, confirmation, or otherwise, should be performed by the reference laboratory. For countries where not all laboratories could identify *H. influenzae*, it was agreed that it would be advisable to have enhanced or sentinel surveillance based around those laboratories that were able to do primary identification.

Achievement of both study objectives depends upon accurate serotyping of a high proportion of strains; particularly from countries with established vaccine programmes. It was agreed that the United Kingdom would co-ordinate a quality control programme, sending out strains for typing on an annual basis. By collaboration between reference laboratories in each country, standardised protocols were to be developed for serotyping and exchange of strains.

Laboratories in countries with established vaccination programmes were asked to freeze all strains of *Haemophilus influenzae*, for future exchange of strains. It was seen as imperative for all vaccine failure strains to be genotyped by PCR and for a sample of strains from unvaccinated children to be genotyped.

A central resource was established in the United Kingdom to genotype strains from countries with established vaccination programmes or to train country reference laboratories to use PCR genotyping. Protocols for PCR genotyping would be supplied by United Kingdom (Oxford) for laboratories to establish their own method. For those countries not wishing to establish or use a method, Oxford would genotype strains from vaccine failures. Emphasis needs to be placed on quality assurance; when other laboratories are running their own PCR genotyping there is need for exchange of strain inter alia to check comparability of the results.

3.6.1. Laboratory training

A laboratory workshop was held at the Haemophilus Reference Laboratory, Oxford Public Health Laboratory in November 1997.

3.6.2. Quality assurance scheme

During the study period the PHLS Haemophilus Reference Unit (HRU) Oxford has distributed 3 sets of Quality Assurance strains to participating laboratories. The laboratories were asked to identify and type the strains using their usual laboratory methods. The strains were derived from the collection of the PHLS HRU. Prior to distribution the strains were re-tested to confirm their identity and type.

The first distribution was sent out on 25.2.97 to 8 centres. The strains were sent on chocolate agar slopes, by courier. The second set of strains was distributed on 4.9.98 to 12 laboratories. The third distribution was sent out on 22.3.99 to 11 laboratories.

3.7. Vaccine failures

Data variables to be collected on cases of vaccine failure were also determined at the meeting of 27/28 November 1996, including risk factors for vaccine failure. For each case of vaccine failure, data on birth weight, gestation, dates and type of vaccine administered, and details of any underlying medical condition were requested. Where possible, determination of specific antibody levels to Hib, diphtheria and tetanus, and total immunoglobulins and IgG subclasses should be measured. Vaccine failures were

categorised as True Vaccine Failure (TVF), Apparent Vaccine Failure (AVF), or Possible Vaccine failure (PVF).

3.7.1. Case definition for vaccine failures

a) True Vaccine Failure (TVF)

Invasive Hib disease occurring:

(i) >2 weeks after dose 1 of Hib vaccine given at age > 1 year, or,
(ii) > 1 week after 2 doses given at age < 1 year.

b) Apparent Vaccine Failure (AVF)

Invasive Hib disease occurring after 1 or 2 doses of Hib vaccine but before sufficient time has elapsed to become a TVF e.g. after 1 dose of vaccine in the first year of life.

c) Possible Vaccine Failure (PVF)

Invasive *H. influenzae* disease in a vaccinated child but the isolate was not serotyped. These are further classified as Possible TVF (PTVF) and Possible AVF (PAVF).

3.8. Estimating Hib Vaccine Efficacy

Before a vaccine is recommended for routine use, it's safety and efficacy are usually established in clinical trials. Prior to licensing of Hib conjugate vaccine in Europe, such trials had demonstrated good short-term protection with efficacy estimates of between 83% and 100%.[1-4] On the basis of this, over the past decade conjugate vaccines against Hib infection have been introduced into several countries in Europe for routine use in infants. Currently, the vaccination programmes in these countries differ with respect to the choice of vaccine, the schedule for primary immunisation, and the use of a booster dose in the second year of life. Although the impact of vaccination has been reported from several countries, no comparative estimates of the effectiveness of Hib vaccination under each programme are available.

There are many methods of assessing vaccine efficacy in the field.[91-93] Such measurement is important where concern exists about the effectiveness of the vaccine. One such concern for Hib vaccine relates to the possibility of low vaccine efficacy in certain ethnic groups,[29] but more general concerns relate to potential cold-chain failures or outbreaks in highly vaccinated communities. Evaluation of vaccine efficacy in the field becomes more important when vaccine coverage increases, as more cases in vaccinated individuals are expected.

We have chosen to use the screening method as it can be performed using routinely generated data and only requires individual vaccination status to be determined on the small number of cases. Like all methods of estimating vaccine efficacy from observational data, there is potential for both under- and over-estimation of vaccine efficacy depending upon the data used. This report introduces the screening method and discusses the potential problems with estimates obtained by using this method. We have then used data provided as part of the EU collaboration to make provisional estimates of Hib vaccine efficacy (VE).

3.8.1. The screening method: Definition and Formulae

The screening method, described by Farrington,[94] uses population vaccine coverage data and case vaccine history data to estimate vaccine efficacy (VE).

The definition of VE is the reduction in the attack rate of a disease in unvaccinated (ARU) compared to vaccinated (ARV) individuals. As a formula this is (ARU-ARV)/ARU. VE is often quoted as a percentage, although it can be negative if ARV is greater than ARU.

VE can be estimated from clinical trials, cohort studies and case control studies[92; 93] as well as by the screening method. The screening method relies on the fact that information on coverage (proportion of

the population vaccinated or PPV) and the proportion of cases vaccinated (PCV) is sufficient to estimate VE. This is demonstrated below:

Suppose we know there are '**a**' cases vaccinated, '**b**' members of the population vaccinated, '**c**' cases unvaccinated and '**d**' members of the population unvaccinated.

$VE = (c/d - a/b)/(c/d) = 1 - (a/c \times d/b)$

Now it can easily be shown that a/c is the same as PCV/(1-PCV) and d/b is the same as (1-PPV)/PPV.
So $VE = 1 - (PCV/(1-PCV) \times (1-PPV)/PPV) =$ **$1 - [PCV(1-PPV)]/[(1-PCV)PPV]$**

To model this statistically we take coverage as a fixed value (called an offset in the model) and use logistic regression on the data for cases. For coverage we only need to know the proportion vaccinated (not the numerator and denominator), whereas for cases we need to know the total number and number of cases vaccinated. Note that a random subset of cases could be used rather than all cases.

3.8.1.1. Simple Example:

VE for the UK Hib data in 1-2 year olds during 96/97

Proportion of the cases fully vaccinated (excluding partially vaccinated)
PCV = 22/26 = 84.6%
Proportion of the population fully vaccinated (adjusted to exclude partially vaccinated)
PPV = 98.96%

$$VE = 1 - 0.846 \times 0.0104/(0.9896 \times 0.154) = 94.2\%$$

From the statistical model the 95% CI is 82.9% to 98.0%, note that this confidence interval is approximate. It is possible in this simple example to calculate an exact confidence interval using the binomial distribution – this gives a 95% CI of 76.9% to 98.0%, so the model has over estimated the lower limit. With larger numbers than four unvaccinated cases out of 26 the model estimate of the 95% CI will be more accurate.

Despite nearly all the cases being vaccinated the VE is estimated as over 70%, this is a result of the high coverage (98.96%). The coverage is higher than published data because partially vaccinated children have been excluded (based on a small study that is now being repeated). Based on this coverage, if in fact the vaccine had zero efficacy, we would expect only 0 or 1/26 cases to be unvaccinated.

3.8.2. Assumptions, Biases and Interpretation of Vaccine Efficacy

3.8.2.1. Case definition: Sensitivity and Specificity

The sensitivity and specificity of the definition chosen for the cases can affect vaccine efficacy estimates. In general, a lack of sensitivity (i.e. true cases are missed) in the case definition will mean we have fewer cases in the study and would reduce the precision of the estimate of vaccine efficacy. Lack of sensitivity can only bias the point estimate of efficacy if the sensitivity differs between vaccinated and unvaccinated groups.

Low specificity (i.e. some cases are not really cases) can result in a substantial under-estimate of vaccine efficacy (as Hib vaccine cannot be expected to protect against disease not due to Hib infection).

For the European Hib project, the analysis is based upon cases confirmed by isolation of *Haemophilus influenzae* type b from a normally sterile site (see case definition for European surveillance). Where possible, typing has been confirmed in national or regional reference laboratories. Clearly where typing results have not been confirmed, there is potential for misclassification of other types of *H. influenzae* as type b. This misclassification would reduce the estimate of vaccine efficacy produced.

3.8.2.2. Cases which occur close to the time of vaccination

Ideally, cases that occur close to the time of vaccination should be excluded from the analysis. This is because the vaccine could not be expected to produce protection immediately. In addition, when using the screening method, it may be difficult to assess vaccination coverage in the population at an age very soon after the vaccine is scheduled. Where there are a small number of cases, however, a large amount of the data would be lost if all such cases were excluded.

For Hib, as infection is common in infants, it would be desirable to include cases occurring in children under one year. If such cases are included, then care is required to ensure that the coverage data in this age group matches the coverage expected of the cases. Where routine coverage data is evaluated at one year, but where vaccination is scheduled in the first six months of life, estimates of coverage at various points throughout the first year of life are required. For example, in Australia in 1996 there was 1 case aged 3-4 months, 2 aged 4-6 months, 2 aged 7-8 months, 2 aged 9-10 months and 1 aged 11-12 months. The estimated full coverage in these age groups was 0%, 40%, 50%, 62%, and 62% (to allow for delays in completion of the vaccination schedule). The estimated overall coverage in this group of cases is therefore (1*0% + 2*40% + 2*50% + 2* 62% + 1* 62%)/8 = 45.75%. Errors in estimating coverage can bias efficacy estimates in either direction (see misclassification of vaccination status).

3.8.2.3. Case finding / ascertainment

The method of case finding can potentially affect the estimate of vaccine efficacy. For example reports from health care providers may be biased towards persons who seek medical care, including vaccination, and may therefore lead to an under-estimate of efficacy. This is less likely to be a problem, however, for a severe disease such as invasive Hib infection, which would be expected to present for hospital admission, and where a laboratory definition is used. In the UK, however, special surveillance schemes have been established to enhance the reporting of vaccine failures. Estimation of efficacy based on a vaccine failure reporting system alone would therefore lead to a low estimate of vaccine efficacy.

3.8.2.4. Misclassification of vaccine history

Misclassification of vaccination status can severely affect estimates of vaccine efficacy in either direction. If vaccine status is misclassified in the cases and misclassification is equally likely to be falsely vaccinated and falsely unvaccinated then this will bias VE towards zero.

With the screening method, ascertainment of vaccination status in the cases can usually be performed with high accuracy. The estimate of vaccination status in the population is usually available from routine coverage data, and is therefore more subject to problems of accuracy. In this study, routine coverage has been provided using a variety of methods, and collected at standard evaluation ages (see interim report). To estimate age-specific coverage during a certain year, extrapolations have been made which assume that a child's vaccination status does not change after the evaluation date. In most countries, the routine method of coverage estimation is likely to underestimate vaccination coverage in the population. This would lead to an underestimation of vaccine efficacy.

The accuracy of coverage data is very important. From the first example the effect of varying coverage in the population on the estimate of vaccine efficacy is as follows (**Table 5**):

Table 5: Example of the effect of varying coverage on estimates of vaccine efficacy

Coverage	Vaccine efficacy
99.5	97.2%
98.96	**94.2%**
97	83.0%
95	71.1%
90	39.0%

The screening method does not allow for uncertainty in coverage, it is taken as a fixed offset in the statistical model. This means the confidence intervals around the estimates of vaccine efficacy do also not allow for uncertainty in coverage. To incorporate uncertainty in coverage into the analysis, a sensitivity analysis needs to be carried out with a range of possible values for coverage.

3.8.2.5. Definition of vaccinated

The definition of complete vaccination may not be clear. For many vaccines, such as Hib, multiple doses and boosters are given. In addition, for Hib vaccine the schedule differs with age (so that only a single dose of vaccine is required above the age of one year, whereas 2 or 3 doses may be required in infants). The definition of vaccinated may therefore be any of the following (**Table 6**):

Table 6: Possible definition of full vaccination

Vaccinated	Unvaccinated
1.Three doses <1yr and/or a booster when over 1yr	No vaccine at all
2.Three doses <1yr and/or a booster when over 1yr	No more than 1 dose under 1
3.Three doses <1yr and/or a booster when over 1yr	No more than 2 doses under 1
4.At least 2 doses <1yr and/or a booster over 1yr	No vaccine at all
5.At least 2 doses <1yr and/or a booster over 1yr	No more than 1 dose under 1

The VE can vary quite considerably depending on which definition is used.

If the definition of vaccination used is different in the cases and the population then this will bias the VE. To estimate efficacy for a complete schedule using the screening method, it is important that children who are partially vaccinated are excluded. If partially vaccinated cases are omitted from the cases, however, they must also be omitted from the calculation of coverage. If, for example, coverage is 95% full, 4% partial and 1% none, then after omitting the 4% with partial coverage, the coverage is now 95%/96% = 98.96% (the value used for UK one year olds).

It is therefore important that age-specific partial and full coverage estimates are available. In the analysis of the European Hib data, where estimates of partial coverage have been provided, these have been used to correct estimates as appropriate. The effect of inclusion of partially vaccinated cases and controls is also presented.

3.8.2.6. Confounding variables - age, year and country

Confounding is always a problem in observational studies, and can bias estimates in either direction. Common confounders in observational studies include age, time period and geographical area. When using the screening method, it is usually necessary to stratify by (or adjust for) these variables. The reason for adjusting for factors such as these is because they are likely to be associated with disease as well as with vaccination status. In the European study, analysis should adjust for age, country, and year; without this adjustment there is the possibility of statistical confounding. This is illustrated in the following example:

Consider the following data (note that partially vaccinated cases are excluded and coverage has been adjusted to remove partially vaccinated children). (**Table 7**)

Table 7: Example of the effect of confounding on vaccine efficacy estimates

Country	Year	Age	Vaccinated cases/ total cases	Adjusted coverage**	(Full, Partial)
UK	96	1	9/11	98.96%	(95%,4%)
	96	2-4	9/10	98.96%	(95%,4%)
	96	5-9	2/4	77%	(77%,0%)
	97	1	3/3	98.96%	(95%,4%)
	97	2-4	11/12	98.96%	(95%,4%)
	97	5-9	0/1	77%	(77%,0%)
Netherlands	96	1	1/3	97.94%	(95%,3%)
	96	2-4	2/2	58.2%	(56.7%,2.6%)
	96	5-9	0/0*	0%*	(0%,0%)
	97	1	0/0*	97.94%	(95%, 3%)
	97	2-4	2/3	94.95%	(88.3%,7%)
	97	5-9	0/0*	0%*	(0%,0%)

* no data to contribute to the analysis
** = Full coverage/(100-Partial coverage)

Clearly, coverage varies greatly with age, as does the frequency of cases. This needs to be accounted for in the analysis. For example in the UK, it would be wrong to take the average coverage in 1-9 year olds (86.8%) and take the total cases vaccinated/total (34/41 = 82.9%). This would give a VE = 26.3%. The correct analysis, adjusting for age, is shown below.

Note that because the numbers are quite low, it is useful to estimate VE from different years. Differences in VE between years can be statistically tested (using analysis of deviance between statistical models). If no statistical difference is detected results can be pooled to give more accurate estimates. For example, we have looked for evidence of differences in efficacy by year, age, and country.

The results of analysing this data in a multivariable model are as follows:

Test for a year effect on VE	change in deviance= 0.45	d.f.=1	p-value =0.50
Test for an age effect on VE	change in deviance= 4.60	d.f.=2	p-value =0.10
Test for difference between countries	change in deviance= 0.01	d.f.=1	p-value =0.92

So, according to this analysis, we can summarise VE across years and age groups and even across countries. Note that with the addition of more data (from more years or countries) an age effect may be detected.

So summarising the efficacy across age groups and years the following estimates of efficacy are produced:

	VE	**95% CI**
UK	89.6%	(59.9% to 98.2%)
Netherlands	87.2%	(23.3% to 97.9%)
Overall	89.0%	(73.5% to 95.5%)

The correct estimate for VE for the UK is 89.6%, very different from the estimate that was obtained by pooling all cases and taking an average coverage (VE=26.3%), this effect is called confounding.

3.8.2.7. Other confounding variables

There are many other potential variables that could confound the estimates of efficacy. Ideally, any variables that may be associated with disease and vaccination need to be adjusted for in this way. Using the screening method, this requires that coverage data is available for each level of that variable. Because routine coverage data is not generally available stratified for each variable it can be difficult to control for many variables.

The most important variables are those which are strongly associated with exposure to infection. If a vaccine protects against infection (as well as disease) and vaccine coverage is high, then unvaccinated children are protected from exposure to infection (herd immunity). Differential exposure in vaccinated and unvaccinated individuals seems quite likely because unvaccinated children may mix with other unvaccinated children and therefore be more likely to be exposed to infection. This is particularly problematic when vaccine coverage is variable and where pockets of unimmunised children occur. Although there may be some explanatory variables (e.g. district of residence) which can be used to adjust for this, it will always be difficult to fully adjust for this potential bias.

Whether variations in vaccination coverage with Hib vaccine are likely to lead to marked variations in exposure to Hib is unclear. Mathematical models of Hib suggest that transmission of Hib is maintained by carriage in older individuals and adults.[10] If Hib vaccination does markedly reduce transmission of infection in the population, then it seems plausible that unvaccinated children would be at greater risk of exposure than vaccinated children. This bias would lead to an overestimation of vaccine efficacy.

3.8.2.8. Risk factors for vaccine failure

When cases are rare it is important to check for similarities between the cases which may suggest that there are particular risk groups in which the vaccine is more likely to fail. For example, if most of the vaccinated cases tended to be of a particular ethnic origin this may suggest that ethnic status is a risk group for vaccine failure. For Hib, certain immunological and medical disorders do seem to be over-represented amongst cases of vaccine failure.[11] For other factors, it is difficult to determine whether such variables are actually over-represented amongst vaccine failures, or whether such variables are associated with a high risk of infection. Any factors that are associated with a higher risk of infection or with a higher risk of vaccination failure could confound the estimation of vaccine efficacy if they are also associated with vaccination status. This could bias the estimate in either direction. Many of the factors described in vaccine failures (immunological abnormalities, underlying medical conditions, and prematurity) are more likely to be associated with lower vaccination coverage. Such an association would lead to an over-estimation of vaccine efficacy using the screening method.

3.8.2.9. Types of vaccine action

When vaccine efficacy is estimated at a single point in time it is common to observe a fall off in efficacy with age. Supposing that, in this study, vaccine efficacy in 1 year olds was estimated to be 94%, but in 5-9 year olds it was 80%, what does this mean? Depending on the vaccine action two possible explanations are as follows:

a) If the vaccine is given to children under one and truly gives full protection to 95% of those vaccinated but no protection to 5% (VE=95%). From the data presented we conclude that, over time, there is loss of protection so that VE drops to 80% in 5-9 year olds.

b) If the vaccine reduces the risk of infection in each individual (after they have been exposed) by 95%. In this scenario, children in the 5-9 year old age group may have been exposed to infection at a younger age and, therefore, many of the unvaccinated individuals will have acquired natural immunity. Even without an actual decline in protective efficacy, unless individuals who have had past infection could be excluded from the study, this phenomenon would explain the lower apparent VE observed in 5-9 year olds.

In reality, the effect of any vaccine may be a combination of the above. For Hib, as invasive infection is rare, it is unlikely that past invasive infection has produced a significant proportion of individuals who are “immune”. As vaccine protects against carriage, however, and if carriage does lead to protection against disease then one might expect a high proportion of unimmunised children to be “immune” by a certain age. This could lead to an apparent fall in efficacy with age. A similar problem has been discussed in relation to pertussis.[95]

3.8.2.10. Small numbers

If the vaccine coverage and efficacy are high there are likely to be very few cases in the population under surveillance. For example, in Finland in 1996/1997 only one case was reported. This makes the

estimation of vaccine efficacy difficult and yields imprecise estimates. One advantage of a European study is the larger amount of data available.
As described in the first example, a further problem with small amounts of data is that the confidence interval around the VE estimate will become biased when the number of cases (or the number of unvaccinated cases) is small.

The possible and likely effects of each problem are summarised below. (**Table 8**)

Table 8: Summary of likely problems in Hib data and the potential effect on vaccine efficacy estimates

Likely problem	**Likely effect**
Non-specific case definition	Reduce efficacy
Preferential reporting of cases in vaccinated children	Reduce efficacy
Vaccination coverage under-estimated	Reduce efficacy
Proportion partially vaccinated under-estimated	Reduce efficacy
Unvaccinated more likely to be exposed	Raise efficacy
Risk factors for vaccine failure are associated with low vaccine coverage	Raise efficacy
Past infection in unvaccinated	Efficacy falls with age
Very high vaccine coverage	Estimate less precise

4. RESULTS

4.1. Questionnaire Surveys

Questionnaires on surveillance systems and vaccination programmes were returned from 12 countries; 9 in Western Europe (Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain (Valencia), Sweden, and UK (England and Wales)) and three from outside (Australia, Israel, Poland). The findings are summarised in Appendix 2.

4.1.1. Surveillance systems

4.1.1.1. Objectives

For countries with vaccination programmes the objective of surveillance was to monitor the impact of vaccination by universal case ascertainment of invasive Hib disease. In Italy, Spain, Poland and Greece the principal objective was the assessment of the disease burden to inform decisions about the introduction of Hib vaccine.

4.1.1.2. Case definitions

The case definition used in each country, except Italy and Poland, included all cases of invasive Hib disease with isolates from a normally sterile site. Italy limited surveillance to cases of Hib meningitis but from 1997 onwards surveillance in sentinel regions was enhanced to include all invasive infections. Retrospective data was obtained from three regions for 1996 to provide consistent data. Surveillance in Poland was also limited to meningitis.

Antigenic diagnosis was included in the case definitions used by Australia 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 European data set).

Data on other serotypes of invasive *H. influenzae* was also collected in Finland, Ireland, Germany, Greece, Spain, Sweden, the Netherlands, Poland and UK (England & Wales).

4.1.1.3. Population under surveillance

All participant countries, except Spain, Sweden, Germany, Greece, Poland and Israel, had a national surveillance system across all ages. In Sweden, Germany and Israel cases were only reported nationally in the paediatric population (under 15 years in Sweden, under 13 years in Israel, and under 10 years in Germany). In Spain (Valencia) and Greece (Attiki) surveillance was limited to the paediatric population (under 15 years) of a single region. In Poland, surveillance was confined to seven districts, to children under five years and to cases of meningitis only.

The Italian national surveillance system was limited to Hib meningitis only. However, a retrospective survey was performed in laboratories reporting Hib meningitis in three regions to ascertain other cases of invasive disease and this was used to augment the routine data in 1996. From 1997 eight regions were involved in sentinel surveillance of all Hib infections.

4.1.1.4. Method of surveillance

Laboratory reporting of confirmed cases of Hib, and clinical reporting of cases, were the two forms of surveillance relied on by Australia, Finland, Greece (Attiki), Israel, the Netherlands, Spain (Valencia), Germany, Sweden, Poland and UK (England & Wales). Linked reporting systems or individual case collation, and duplicate elimination, was undertaken by the national public health institute, reference laboratory, academic paediatric department, ministry of health or vaccine institute.

Ireland and Italy relied solely on laboratory reporting of confirmed Hib cases. However, the Irish surveillance system was active for laboratories serving paediatric populations, whereas the Italian

system relied on voluntary notification of meningitis with laboratory confirmation. In 1997, more active surveillance was established via laboratories in eight Italian regions.

4.1.1.5. Type of surveillance

Australia, Germany, Italy, the Netherlands, Poland, Spain (Valencia), and the United Kingdom have some form of active surveillance. This included enhanced paediatric surveillance systems with monthly reports including nil returns in four countries (Australia, England and Wales, Netherlands (1996-7 only), Germany (1998)). Since 1997 active sentinel surveillance has been conducted in 8 regions in Italy, where hospital microbiological laboratories are contacted monthly to verify zero reporting.

4.1.1.6. Data collection - variables and methods

Basic personal, clinical and laboratory variables were collected for Hib cases, and vaccination status and risk factors for cases of vaccine failure (Appendix 3). Data were provided by clinicians and/or laboratories in all of the participant countries, except in Italy, where data were obtained from the hospitals (within the national bacterial meningitis surveillance system) and from laboratories (within the active surveillance system in 8 regions).

Finland, Italy, Spain (Valencia), UK (England & Wales), and Sweden report cases from source as they occur, Poland reported twice weekly, Greece reported weekly, Australian and Ireland reported cases fortnightly, and the Netherlands, Israel and Germany reported monthly.

Each participant country with an established vaccination programme except Germany had Hib surveillance data for at least one year prior to the national programme's introduction.

4.1.1.7. Data analysis

All countries analysed their Hib case data by age, and all except Spain (Valencia) also analysed by sex. The distribution of cases by clinical diagnosis was analysed by Australia, Ireland, the Netherlands, and Spain (Valencia), and the majority of countries could at least give rates for Hib meningitis in children under five years of age. Geographical distribution of cases was analysed in Australia, Finland, Italy, and Spain (Valencia). Vaccination status was analysed in Australia, the Netherlands, and the United Kingdom.

These analyses were done with differing frequency in the participant countries. All countries analysed their data annually, and in addition to this Finland and Greece did analyses weekly and monthly, UK (England & Wales) did monthly analyses, Germany and Sweden quarterly, whereas Australia, Spain and Poland analysed their surveillance system data six-monthly.

4.1.1.8. Data dissemination

Each participant country produced regular reports that were aimed at health care professionals and health authorities, and all had published results of Hib surveillance in their country, or were in the process of doing so. The frequency of the reports varied between countries: Australia and Poland reported fortnightly and annually; Finland weekly, monthly, and annually; Germany quarterly; Ireland and the Netherlands annually; Spain six-monthly; Greece and UK (England & Wales) monthly and annually; Italy (within active sentinel surveillance) quarterly and annually.

4.1.1.9. Evaluation of Hib surveillance

Seven countries (Australia, Greece, Finland, Netherlands, Spain, Sweden and UK (England & Wales)) were currently, or had recently, evaluated their surveillance systems, with particular reference to under-reporting.[56; 96] Subsequently, Australia, Italy, Netherlands, and UK (England & Wales) were proposing elements within their surveillance systems to assess and reduce under-reporting. In Poland an external evaluation was performed by WHO. In Greece, an evaluation of the proportion of meningitis with no bacterial isolates (as recommended by WHO[75] had been undertaken.[30] In Italy an evaluation of the enhanced regional surveillance scheme was undertaken to attempt to explain the low rates of disease

observed and the variation between regions. They concluded that the low rates could not be fully explained by under-diagnosis, under-reporting, or by vaccine coverage.[97]

4.1.2. Hib vaccination programmes

4.1.2.1. Vaccination programme introduction

National vaccination programmes commenced in most participant countries between 1991 and 1994. At the start of the project in 1996, Italy, Greece, Poland and Spain did not have national immunisation programmes. In Valencia, an autonomous region of Spain, immunisation of children with Hib vaccine was encouraged, and vaccine supplied free on prescription between 1996 and 1998. Hib vaccine was incorporated into the regional programme in Valencia in 1998. In Greece, children with one insurance provider were eligible for Hib vaccine; this covered approximately 40% of the population. The Hib vaccine was licensed before national/regional implementation in Spain, Greece, Israel and Italy for use in private practice. Vaccination was not compulsory in any country.

4.1.2.2. Vaccination programme schedules

The countries with national Hib vaccination programmes differed in the choice of immunisation schedules used and in how the programme was introduced. Catch-up immunisation of all children less than five years of age was introduced with the programme in Australia, Ireland and the United Kingdom. Booster doses were used with a three-dose schedule in Australia, Greece, Italy, Spain and the Netherlands and with a two-dose schedule in Germany, Israel, Sweden and Finland. In two countries (UK and Ireland), three doses were used in infancy with no subsequent booster.

Australia, Ireland, Greece, Germany, Israel and the United Kingdom administered the first dose of Hib vaccine to infants at two months of age, while the Netherlands and Sweden administered the first dose at 3 months of age, and Finland at 4 months of age.

4.1.2.3. Vaccines used

The details of the type of vaccine used and the immunisation schedule in the ongoing programmes are given below (**Table 9**).

In addition to changes in the schedule, several countries had used more than one type of vaccine. For example, the start of the programme in the UK, HbOC had been used for catch-up vaccination with PRP-T for infant vaccination. After implementation, the main type of vaccine used had varied because of supply problems and to allow of mixing of DTP and Hib vaccines and combination vaccines (with DTP). Similarly, in Germany the schedule and vaccine used had changed as new combination vaccines (with DTaP) had been introduced. In other countries, different makes of vaccines had been available via the private sector. In Australia, a different vaccine was used in aboriginal and non-aboriginal populations. This decision was made on the grounds that PRP-OMP appeared to be protective with one dose in populations with a very high incidence and where disease is contracted at a very young age.[4] For this reason PRP-OMP had been chosen for the aboriginal population.

4.1.2.4. Vaccines storage and distribution

Vaccines were stored nationally or regionally, and distributed to local health centres/pharmacists in most countries. Vaccine was supplied free of charge by the state or through general insurance (Netherlands and Germany) in all countries with national immunisation programmes. In Greece, vaccine costs were reimbursed only for children in one insurance system. Other parents would be able to pay privately for the vaccine. In Italy the parents usually paid for the vaccine, except for some high-risk groups who were eligible for free vaccine. In Spain (Valencia) until 1998, when the regional programme was implemented, parents paid a proportion of the costs of vaccinating their children.

Table 9: Type of Hib conjugate vaccine and immunisation schedule used in the study participant countries

Country/Region	Type of Vaccine	Immunisation schedule
Australia	HbOC (90%)	2 months 4 months 6 months 18 months
	PRP-OMP (10%)	2 months 4 months 12 months
Finland	HbOC	4 months (with DTP) 6 months (with IPV) 14-18 months (with MMR)
Germany	DTaP/PRP-T/IPV (90%) PRP-OMP } PRP-T } (10%) HbOC }	2, 3, 4 & 12 months 3, 5, 12 months
Greece	PRP-T HbOC	2 months 4 months 6 months 15-18 months
Ireland	HbOC	2 months (with DTP/DT + OPV) 4 months (with DTP/DT + OPV) 6 months (with DTP/DT + OPV)
Israel	1994 - 97 PRP-OMP(≈90%) HbOC/PRP-T From July 97 PRP-T	2, 4 & 12 months 2, 4, 6 & 12 months
Italy	PRP-T HbOC for a few months in 1996	< 6 mths - 3 doses + booster > 12 mths - 1 dose 6-12 mths - 2 doses + booster > 12 mths - 1 dose
Netherlands	PRP-T	3 months (DTP-IPV in other limb) 4 months (DTP-IPV in other limb) 5 months (DTP-IPV in other limb) 11 months (DTP-IPV in other limb)
Spain (Valencia)	PRP-T (30%) HbOC (70%)	As recommended by the manufacturers (4 doses < 12 mths, 1 dose > 12 mths
Sweden	PRP-T`	3 months 5 months 12 months
United Kingdom	HbOC PRP-T DTP/PRP-T	2 month (combined/mixed with DTP) 3 months (combined/mixed with DTP) 4 months (combined/mixed with DTP)

4.1.2.5. Vaccination scheduling and call/recall

Computerised registration for immunisation, and vaccination scheduling based on this, was the procedure in Ireland, Netherlands, Sweden and United Kingdom; call and recall was run through the same system in Netherlands, Sweden and United Kingdom. Australia had a variable call/recall system and commenced a new national computerised immunisation register in 1996. Ireland was also introducing call/recall with a new system in 1997/8. Vaccine was administered either by doctors in their practice or clinic and/or by public child health centres. Vaccination status of the children was recorded in all countries, either on computer or paper records.

4.1.2.6. Vaccination coverage

Hib vaccination coverage was measured or estimated nationally in Australia, Finland, the Netherlands, Sweden and UK (England & Wales). Different methods for estimation of coverage were used: sentinel surveys (Finland), estimation using DTP as an indicator (the Netherlands), or total population assessment (Australia, Sweden, United Kingdom). The United Kingdom measures coverage quarterly by district; the Netherlands and Sweden do yearly estimates; Finland does biennial estimates; and Australia has done estimates every few years, but from 1996 introduction of a new system will enable quarterly estimates.

Ad-hoc surveys were used to assess coverage in Greece (Attiki) and Spain (Valencia). Germany had sporadic surveys conducted in several regions. Ireland had no system in place to give data at regional or national level until 1998. In Italy, where there is no national immunisation programme, vaccination centres make six-monthly reports to the Ministry of Health, giving the number of doses administered by age. To improve data on coverage, a cluster sample survey was performed in 1998, at that stage coverage in children born in 1996 was 19.8% (range 1.9-41.4%).[98]

The age at which vaccination coverage was assessed was variable. In Germany coverage was assessed at school entry, but in most other countries assessment occurred at least once at the age of between one and two years. Four countries assessed coverage at 12 months of age (for three doses in UK (England & Wales), Australia and the Netherlands, and for two doses in Finland). Three countries assessed vaccination coverage at older ages (aged two years in the UK and Sweden, at three years in Finland and at five years in the UK). In 1998, Ireland reported the first national estimate of vaccine coverage in two-year-old children using a newly implemented computerised system. In Germany, coverage data was available from surveys of children under five in different regions between 1996 and 1998. More recent unpublished data from Germany suggests that vaccination coverage has now improved to greater than 95%.

In an attempt to compare coverage data provided, the corresponding birth cohort and year of study have been determined for each estimate provided (**Table 10**). Although data is difficult to compare because of different methods of measurement, coverage was extremely high (above 95%) in Sweden, Finland and the Netherlands. Coverage was also high (over 90%) in Israel, UK and Spain (after introduction in 1998). Poorer coverage (70-90%) was achieved in Australia, Ireland and Germany although participants in both Australia and Ireland felt that these estimates were below the actual level reached. Coverage was low (below 50%) in the two countries with no national programme (Greece and Italy).

Additional data on coverage by dose was provided by Greece (**Table 11**) and UK (**Table 12**) and has been used for efficacy calculations. Data on children under the age of one was also provided by Greece (**Table 11**). For the UK data on coverage in children under one was assessed by a one off computer run in 22 trusts. Data was generated for children born between 1/1/96-31/1/1996 as at 31/7/96; these children would be aged between 6 and 7 months. The coverage for three doses at this age was 4,357/4,897 (88.9%).

Coverage was also assessed for the one-off catch-up vaccination programme in one region in UK (England & Wales) in 1993/4.[99] Coverage reached 89% in children born in 1992, 87% for those born in 1991, 77% for those born in 1990 and was only 39% in children born in 1989. Estimates of coverage in the catch-up were lower in Australia, but no estimate was available from Ireland.

Table 10: Hib vaccination coverage estimates in study participant countries

Country	Year started	Vaccine Programme	Schedule*	1996					1997					1998				
				Birth cohort					Birth cohort					Birth cohort				
				1995	1994	1993	1992	1991	1996	1995	1994	1993	1992	1997	1996	1995	1994	1993
Australia	1992-3	Primary	2, 4, (6) mths						78%					87%				
	1992-3	Booster	12/18 mths		62%	52%									83%			
	1992-3	Catch-up	One dose				26%	26%					26%					
Ireland	1992	Primary	2,4,6 mths												84%			
	1992-3	Catch-up	One dose															
Finland	1993	Primary	4,6 mths	99%		98%	In trials						In trials	99%				
	1993	Booster	14-18 mths	99%		97%								98%				
Germany	1991	Primary	2,3,4 mths	55-75%					65-79%					65-78%				
	1991	Booster	12 mths		55-75%					65-79%					65-78%			
Greece	1994	Primary	2, 4, 6 mths						38%	29%				38%	29%			
	1994	Booster	15-18 mths							16%					16%			
Israel	1994	Primary	2,4 mths	90%	90%				90%	90%				90%	90%			
	1994	Booster	12 mths	90%	90%				90%	90%				90%	90%			
	1992	Private				40%	25%	0%				40%	25%					
Italy	1995	Private	under 5y	0%	0%	0%	0%								20%			
Netherlands	1993	Primary	3,4,5 mths	96%		97%	0%							98%				
	1993	Booster	11 mths		96%	93%								95%				
Sweden	1992-3	Primary	3,5 mths		99%					99%				99%	99%			
	1992-3	Booster	12 mths															
Spain	1998	Primary	3 doses	33%	33%	33%			57%	57%	33%			95%	65%			33%
		Booster	> 12 mths	33%`	33%	33%			57%	57%	33%			95%	65%			
UK	1992	Primary	2,3,4 mths	93%	95%	95%			92%	95%	95%			92%	95%			95%
	1992-3	Catch-up	One dose				89%	87%					89%					

* Ages in brackets represent changes to the initial schedule

Table 11: Estimates of Hib vaccination coverage by dose, Greece 1997/8 (sample of 1728 children) [100]

Age (months)	1 dose	2 doses	3 doses	4 doses
3	19	0	0	0
5	295	17	0	0
7	16	32	7	0
12	10	18	38	0
15	11	21	30	2
18	12	19	30	7
23	11	10	29	16

Table 12: Estimates of Hib vaccination coverage by dose, UK (children born 1/10/92-31/10/96 as at 1/1/99)

Cohort	Dose 1	%	Dose 2	%	Dose 3	%
119,363	116,599	97.7%	115,912	97.1%	115,104	96.4%

4.1.3. Laboratory methods

The questionnaire on laboratory methods was returned by ten countries: Australia (Melbourne and Sydney), Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain (national and Valencia), Sweden, and UK.

4.1.3.1. Laboratory Hib identification and reference facilities

All countries had reference laboratory facilities for *Haemophilus influenzae.* Spain (Valencia) and all countries with national vaccination programmes had primary identification in over 80% of laboratories, and between 80 to 100% referred Hib isolates to the reference laboratory. In Sweden, a lower proportion of isolates would be referred – mainly those from vaccine failures. In countries with vaccination programmes, those hospital laboratories that could identify *H. influenzae* would normally test all specimens from cases of suspected bacterial meningitis and all blood cultures for *H. influenzae*. In Spain (Valencia), hospital laboratories would look for *H. influenzae* in all sterile site specimens, but only in children.

In Italy between 50 and 80% of hospital laboratories had facilities to identify *Haemophilus influenzae*, and would only test specimens from cases of meningitis. In addition, in Italy only 20% to 50% of laboratories would refer isolates of Hib to the reference laboratories. For this reason, cases confirmed by antigen detection have been included in the case definition for Italy and in some of the results tables for Italy. Enhanced laboratory surveillance is also being established. In the eight regions paticipating in the active surveillance, guidelines for identification from sterile sites were distributed in 1997 to all microbiological laboratories.

4.1.3.2. Specimen transport, receipt and storage

All reference laboratories either subbed the strains immediately on receipt or in batches. All the media used to transport the strains to the reference laboratory and to subculture the strains were able to sustain the growth of *Haemophilus influenzae*. All laboratories could store the strains long term in viable media at -80ºC.

4.1.3.3. Hib-serotyping and genotyping

There were some minor differences in identification methods that could lead to misclassification of non type-b *Haemophilus influenzae*.

The main differences in the identification methods used by the laboratories related to the ability to genotypically confirm vaccine failures as *H. influenzae* serotype b. At the start of the project Ireland, Spain (Valencia) and Italy did not have these facilities and for Ireland and Spain (Valencia) the strains from vaccine failure cases were sent to the Oxford reference laboratory (United Kingdom). In Italy, PCR capsular typing has been performed by the central reference laboratory since 1998.

4.2. Data on invasive *Haemophilus* infection 1996-1998

4.2.1. Overall incidence of invasive Hib *disease*

Data on cases in all age groups was provided by five European countries (Finland, Ireland, Italy, Netherlands, and UK (England & Wales)) and Australia for each year of the study (Table 13). The crude incidence was low in 1996 (0.20 cases per 100,000 population) and fell in both 1997 and 1998. In 1996, the highest incidence was observed in Italy - the only country without a national vaccination programme. Of those countries with a national vaccination programme, the incidence was highest in Ireland in each year of the study.

4.2.2. Age distribution of cases

Amongst those countries with surveillance in all age groups, the majority of cases in each year (63%-75%) were in children under five years of age. The proportion of cases in under fives was highest in Italy. The proportion in under fives did not change over the period of the study but the proportion in

children under one increased from 19% to 36% with a consequent decrease in the proportion of cases in children aged one to four years.

4.2.3. Incidence of invasive Hib *disease in childhood*

Data on all cases in children under 15 years was provided by eight European countries (Finland, Greece (Attiki), Ireland, Italy, Netherlands, Spain (Valencia), Sweden, and UK (England & Wales)) and two from outside Europe (Australia and Israel) for each year of the study. Data from Germany for children under 10 years of age became available in 1998 (Table 15). The annual incidence in children under 15 fell from 0.76 per 100,000 in 1996 to 0.45 per 100,000 in 1998. In each year, the highest incidence was observed in Italy – the country with the lowest reported coverage for Hib vaccine.

4.2.4. Age distribution of childhood cases

Over 80% of cases in children were in those aged under five years, with more than 25% in children under one. The proportion under one year of age increased from 28% in 1996 to 41% in 1998, and the proportion of cases in children aged 1-4 years and 5-14 years decreased (Table 16).

4.2.5. Age-specific incidence

In 1996, the crude incidence for invasive Hib in children under five was 2.04 per 100,000 and ranged from zero in Finland, to 9.37 per 100,000 in Spain (Valencia). The overall incidence in this age group fell in both 1997 and 1998 but remained high in Italy (Table 17). The incidence of Hib meningitis was 1.20 per 100,000 in 1996 (Table 18) and fell to 0.81 by 1998.

Despite the increase in the proportion of cases observed in children under one the overall incidence in this age group fell with each successive year (Table 19). The biggest fall was observed in Spain (Valencia) who introduced routine vaccination during the period of the study. By the end of the study the incidence in infants was highest in Italy. Although the number of cases in children under one was small, most of the decrease in this age group occurred in cases in children aged 6-11 months – the age group who would be scheduled to have received at least two doses of Hib vaccine. The incidence in younger children did not show a consistent decline.

Table 13: Numbers of cases and crude incidence (per 100,000 population) of invasive Hib disease by country for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	5	5140323	0.10	2	5140323	0.03	4	5140323	0.08
Ireland	8	3539000	0.23	10	3539000	0.28	10	3539000	0.28
Italy (routine)*	88 (32)	57332996	0.15	116 (85)	57332996	0.20	110 (80)	57332996	0.19
Italy (enhanced)*	50 (50)	14126905	0.35	87 (68)	33135024	0.26	81 (64)	33135024	0.24
Netherlands	32	15493889	0.21	20	15493889	0.13	19	15493889	0.12
UK	55	51911175	0.11	61	51911175	0.12	37	51911175	0.07
EUROPE†*	150 (150)	90211292	0.17	180 (161)	109219411	0.16	152 (134)	109219411	0.14
Australia*	36 (35)	18311486	0.20	45 (44)	18311486	0.25	21 (20)	18311486	0.11
TOTAL†*	186 (185)	92042778	0.20	225 (205)	127530897	0.18	173 (154)	127530897	0.14

Numbers in parentheses indicate cases confirmed by isolation in countries where antigen detection is included
* including antigen detection
† including enhanced surveillance data from Italy

Table 14: Age distribution of cases of invasive Hib disease by country for 1996, 1997 and 1998

	1996								1997								1998							
	Under one		1-4 years		5-14 yrs		Over 15		Under one		1-4 years		5-14 yrs		Over 15		Under one		1-4 years		5-14 yrs		Over 15	
Australia	11	31%	11	31%	10	28%	4	11%	12	27%	17	38%	7	16%	9	20%	7	33%	10	48%	1	5%	3	14%
Finland	0	0%	0	0%	0	0%	5	100%	0	0%	0	0%	2	100%	0	0%	2	50%	0	0%	0	0%	2	50%
Ireland	1	13%	5	63%	0	0%	2	25%	3	30%	3	30%	0	0%	4	40%	3	27%	6	55%	1	9%	1	9%
Italy*	7	14%	36	73%	2	4%	4	8%	31	36%	36	42%	5	6%	14	16%	36	46%	33	42%	4	5%	6	8%
Netherlands	6	19%	18	56%	1	3%	7	22%	5	25%	6	30%	0	0%	9	45%	5	26%	5	26%	3	16%	6	32%
UK	9	17%	21	57%	7	19%	16	43%	14	23%	15	25%	3	5%	29	48%	8	22%	14	38%	2	5%	13	35%
Total	34	19%	91	50%	20	11%	38	21%	65	29%	77	34%	17	8%	65	29%	61	36%	68	40%	11	6%	31	18%

*Enhanced surveillance data for Italy

Table 15: Numbers of cases and incidence (per 100,000 population) of invasive Hib disease in children under 15 years by country for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	0	971570	0.00	2	971570	0.21	2	951145	0.21
Germany	-	-	-	-	-	-	28[#]	13098411	0.33[#]
Greece	7	558558	1.25	3	558558	0.54	4	558558	0.72
Ireland	6	939000	0.64	6	939000	0.64	10	911000	1.10
Italy (routine)*	83 (29)	8517091	0.97	101 (74)	8517091	1.19	99 (72)	8620500	1.15
Italy (enhanced)*	45 (45)	1816128	0.64	72 (57)	4832819	1.49	73 (57)	4832819	1.51
Netherlands	25	2847820	0.0	11	2847820	0.39	13	2882000	0.45
Spain	19	778105	0.88	5	778105	0.64	1 (0)	778105	0.13
Sweden	3	1626178	2.44	4	1626178	0.25	4	1648462	0.24
UK	37	9733595	0.18	32	9733595	0.33	24	10033595	0.24
EUROPE†*	142 (142)	19270954	0.73	135 (120)	22595684	0.60	159 (141)	35694095	0.45
Australia*	32 (31)	3911737	0.82	36 (35)	3911737	0.92	18 (17)	3911737	0.46
Israel	14	1671000	0.84	4	1671000	0.24	7	1671000	0.42
TOTAL†*	188 (187)	24853691	0.76	175 (159)	28178421	0.62	184 (165)	41276832	0.45

Numbers in parentheses indicate cases confirmed by isolation in countries where antigen detection is included
* including antigen detection
† including enhanced surveillance data from Italy
# relates only to children under 10 years of age

Table 16: Age distribution of cases of invasive Hib disease in children under 15 years by country for 1996, 1997 and 1998

	1996							1997							1998						
Age group	Under 1		1-4 years		5-14 yrs		All	Under 1		1-4 years		5-14 yrs		All	Under 1		1-4 years		5-14 yrs		All
Australia	11	34.38%	11	34.38%	10	31.25%	32	12	33.33%	17	47.22%	7	19.44%	36	7	38.89%	10	55.56%	1	5.56%	18
Finland	0		0		0		0	0	0.00%	0	0.00%	2	100.00%	2	2	100.00%	0	0.00%	0	0.00%	2
Germany[#]	0		0		0		0	0		0		0		0	5	17.86%	20	71.43%	3	10.71%	28
Greece	2	28.57%	4	57.14%	1	14.29%	7	1	33.33%	2	66.67%	0	0.00%	3	1	25.00%	2	50.00%	1	25.00%	4
Ireland	1	16.67%	5	83.33%	0	0.00%	6	3	50.00%	3	50.00%	0	0.00%	6	3	30.00%	6	60.00%	1	10.00%	10
Israel	6	42.86%	6	42.86%	2	14.29%	14	3	75.00%	1	25.00%	0	0.00%	4	4	57.14%	1	14.29%	2	28.57%	7
Italy*	7	15.56%	36	80.00%	2	4.44%	45	31	43.06%	36	50.00%	5	6.94%	72	36	49.32%	33	45.21%	4	5.48%	73
Netherlands	6	24.00%	18	72.00%	1	4.00%	25	5	45.45%	6	54.55%	0	0.00%	11	5	38.46%	5	38.46%	3	23.08%	13
Spain	10	52.63%	9	47.37%	0	0.00%	19	0	0.00%	5	100.00%	0	0.00%	5	0	0.00%	1	100.00%	0	0.00%	1
Sweden	1	33.33%	0	0.00%	2	66.67%	3	0	0.00%	2	50.00%	2	50.00%	4	4	100.00%	0	0.00%	0	0.00%	4
UK	9	24.32%	21	56.76%	7	18.92%	37	14	43.75%	15	46.88%	3	9.38%	32	8	33.33%	14	58.33%	2	8.33%	24
Total	53	28.19%	110	58.51%	25	13.30%	188	69	39.43%	87	49.71%	19	10.86%	175	75	40.76%	92	50.00%	17	9.24%	184

* enhanced surveillance data
# relates only to children under 10 years of age

Table 17: Numbers of cases and incidence (per 100,000 population) of invasive Hib disease in children under 5 years by country for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	0	323175	0.00	0	323175	0.00	2	304936	0.66
Greece	6	169648	3.54	3	169648	1.77	3	169648	1.77
Germany	-	0	-	-	0	-	25	3973913	0.63
Ireland	6	268000	2.24	6	268000	2.24	9	240000	3.75
Italy (routine)*	78 (29)	2740019	2.85	95 (70)	2740019	3.47	93 (67)	2769531	3.36
Italy (enhanced)*	43 (43)	593726	7.24	67 (53)	1564678	4.28	69 (53)	1564678	4.41
Netherlands	24	980906	2.45	11	980906	1.12	10	969000	1.03
Spain	19	202697	9.37	5	202697	2.47	1 (0)	202697	0.49
Sweden	1	566906	0.18	2	566906	0.35	4	491356	0.81
UK	30	2982743	1.01	29	2982743	0.97	22	3282743	0.67
EUROPE†*‡	129 (129)	6087801	2.12	123 (109)	7225058	1.70	145 (127)	11198971	1.29
Australia*	22 (21)	1297534	1.70	29 (28)	1297534	2.24	17 (16)	1297534	1.31
Israel	12	596000	2.01	4	596000	0.67	5	596000	0.84
TOTAL†*‡	163 (162)	7981335	2.04	156 (141)	9118592	1.71	167 (148)	13092505	1.28

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

* including antigen detection

† including enhanced surveillance data from Italy

Table 18: Numbers of cases and incidence (per 100,000 population) of invasive Hib meningitis in children under 5 years by country for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	0	323175	0.00	0	323175	0.00	1	304936	0.33
Greece	2	169648	1.18	1	169648	0.59	0	169648	0.00
Germany	-	0	-	-	0	-	15	3973913	0.38
Ireland	1	268000	0.37	5	268000	1.87	3	240000	1.25
Italy (enhanced)	37	593726	6.23	53	1564678	3.39	52	1564678	3.32
Netherlands	13	980906	1.32	6	980906	0.61	10	969000	1.03
Spain	14	202697	6.91	2	202697	0.99	1	202697	0.49
Sweden‡	1	566906	0.18	2	566906	0.35	2	491356	0.41
UK	16	2982743	0.53	17	2982743	0.57	11	3282743	0.34
EUROPE	84	6087801	1.38	86	7225058	1.19	95	11198971	0.85
Australia	7	1297534	0.54	16	1297534	1.23	9	1297534	0.69
Israel	5	596000	0.84	2	596000	0.34	2	596000	0.34
TOTAL	96	7981335	1.20	104	9118592	1.14	106	13092505	0.81

Table 19: Numbers of cases and incidence (per 100,000 population) of invasive Hib disease in children under 1 year by country for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	0	60448	0.00	0	60448	0.00	2	56768	3.52
Germany	-	0	-	-	0	-	5	811285	0.62
Greece	2	32856	6.09	1	32856	3.04	1	32856	3.04
Ireland	1	48000	2.08	3	48000	6.25	3	48000	6.25
Italy (routine)*	33 (14)	522980	6.31	51 (38)	522980	9.75	50 (34)	533606	9.37
Italy (enhanced)*	7	117707	5.95	31 (26)	302125	10.26	36 (28)	302125	11.92
Netherlands	6	190736	3.15	5	190736	2.62	5	192000	2.60
Spain	10	39160	25.54	0	39160	0.00	0	39160	0.00
Sweden	1	99028	1.01	0	99028	0.00	4	89234	4.48
UK	9	651112	1.38	13	651112	2.00	8	651112	1.23
EUROPE†*	36	1239047	2.91	54 (49)	1411255	3.83	64 (56)	2222540	2.88
Australia*	11	255792	4.30	12	255792	4.69	7 (6)	255792	2.74
Israel	6	125000	4.80	3	125000	2.40	4	125000	3.20
TOTAL†*	53 (53)	1619839	3.27	69 (64)	1792047	3.85	75 (66)	2603332	2.88

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

* including antigen detection

† including enhanced surveillance data from Italy

Table 20: Numbers of cases and incidence (per 100,000 population) of invasive Hib disease in children under 1 year for all countries combined, for 1996, 1997 and 1998

	1996			1997			1998		
	N	Population	Incidence**	N	Population	Incidence	N	Population	Incidence
Under 3 months	10	404960	2.85	13	448012	2.90	11	650833	1.69
3-5 months	11	404960	3.13	25	448012	5.58	27	650833	4.15
6-11 months	25	809919	3.56	31	896023	3.46	37	1301666	2.84
Not known	7			0			0		
TOTAL†*	53 (53)	1619839	3.27	69 (64)	1792047	3.85	75 (66)	2603332	2.88

* including antigen detection
† including enhanced surveillance data from Italy
** children under one with precise age unknown are divided amongst age groups in proportion to cases with known age

4.2.6. Clinical diagnosis

Meningitis remains the dominant clinical diagnosis amongst cases reported in each year and no real change in the distribution of diagnoses occurred over the period of the study (Table 21). Other than meningitis, septicaemia was the prominent other clinical diagnosis. The proportion of meningitis was high in all countries (Table 22) and highest in Italy.

The proportion of cases with meningitis was much lower amongst cases in adults than in children (Table 23). Epiglottitis was more common in older children (aged 1-14) than in infants and adults. Pneumonia and septicaemia were more common amongst adult cases, whereas pneumonia was an extremely rare diagnosis in children.

4.2.7. Sex distribution of Hib *cases*

An excess of male cases was observed in 1996 but this excess was not apparent in 1997 and 1998 (Table 24). The excess in 1996 was largely confined to children under fifteen and appeared to have declined in children under five by 1997 and in children under 10 years of age by 1998.

Table 21: Cases of Invasive Hib disease by clinical diagnosis and year in children under 15 years

Diagnosis	1996		1997		1998		1996-8	
Meningitis	106	56%	113	65%	115	63%	334	61%
Epiglottitis	21	11%	19	11%	14	8%	54	10%
Pneumonia	10	5%	6	3%	4	2%	20	4%
Septicaemia	30	16%	25	14%	23	13%	78	14%
Other	18	10%	7	4%	25	14%	50	9%
Not known	3	2%	5	3%	3	2%	11	2%
Total	188	100%	175	100%	184	100%	547	100%

Table 22: Cases of Invasive Hib disease in children under 15 years by clinical diagnosis and country : 1996, 1997 and 1998 combined

Diagnosis	Meningitis		Epiglottitis		Pneumonia		Septicaemia		Other		Not known		Total
Australia	40	47%	17	20%	3	3%	17	20%	9	10%	0	0%	86
Finland	1	25%	1	25%	1	25%	1	25%	0	0%	0	0%	4
Germany[#]	17	61%	3	11%	1	4%	3	11%	1	4%	3	11%	28
Greece	3	21%	0	0%	0	0%	11	79%	0	0%	0	0%	14
Ireland	9	41%	3	14%	1	5%	5	23%	4	18%	0	0%	22
Israel	11	44%	0	0%	5	20%	8	32%	1	4%	0	0%	25
Italy	150	79%	8	4%	5	3%	8	4%	17	9%	2	1%	190
Netherlands	32	65%	8	16%	0	0%	3	6%	2	4%	4	8%	49
Spain	17	68%	0	0%	2	8%	6	24%	0	0%	0	0%	25
Sweden	6	55%	2	18%	0	0%	2	18%	1	9%	0	0%	11
UK	48	52%	12	13%	2	2%	14	15%	15	16%	2	2%	93
Total	334	61%	54	10%	20	4%	78	14%	50	9%	11	2%	547

relates only to children under 10 years of age

Table 23: Cases of Hib disease in children by clinical diagnosis and age : 1996, 1997 & 1998 combined

Diagnosis	Under 1		1-4 years		5-9 years		10-14 years		15 years or more		Not known	
Meningitis	114	71%	143	61%	16	43%	7	64%	18	13%	3	50%
Epiglottitis	0	0%	37	16%	10	27%	2	18%	12	9%	1	17%
Pneumonia	5	3%	2	1%	5	14%	0	0%	24	18%	0	0%
Septicaemia	19	12%	25	11%	2	5%	2	18%	40	30%	0	0%
Other	19	12%	25	11%	3	8%	0	0%	25	19%	2	33%
Not known	3	2%	4	2%	1	3%	0	0%	15	11%	0	0%
All diagnoses	160	100%	236	100%	37	100%	11	100%	134	100%	6	100%

Table 24: Age-sex distribution of Hib cases: by year and age

Year	1996				1997				1998			
Sex	Male		Female		Male		Female		Male		Female	
Under 1	37	61%	24	39%	54	47%	62	53%	53	50%	52	50%
1-4 years	55	59%	38	41%	63	52%	58	48%	61	55%	50	45%
5-9 years	11	65%	6	35%	14	70%	6	30%	5	56%	4	44%
10-14 years	5	83%	1	17%	1	33%	2	67%	6	75%	2	25%
15 years or more	18	47%	20	53%	39	49%	40	51%	20	50%	20	50%
All ages	126	59%	89	41%	171	50%	168	50%	145	53%	128	47%

* includes only cases with sex and age specified

4.3. Other serotypes of *Haemophilus influenzae*

Data on all types of *Haemophilus influenzae* was provided by five European countries (Finland, Ireland, Italy, Netherlands and UK (England & Wales)) for all age groups (Table 25), for Greece (Attiki), Spain (Valencia) and Sweden in children under fifteen years of age, and for Germany in children under 10 years of age (1998 only) (Table 26).

During the study period 1996-1998 a total of 1,930 cases of invasive *H. influenzae* disease due to all serotypes was reported from all the participating countries. Type b infection formed 25% (range 14-63%) of all invasive *H. influenzae* disease isolates in total populations under surveillance, and 52% (range 32-86%) amongst children under fifteen.

Although not all participating countries performed typing on all strains, there were few *H. influenzae* infections due to capsulated serotypes other than type b. The vast majority of non-b strains were non-capsulated organisms. The latter formed 45% of infections reported in populations including adults and 32% of cases in childhood populations. The proportion of cases known to be caused by non-capsulated strains was high in the Netherlands, Finland and the UK. A small number of cases were determined not to be due to type b organisms but further typing was not performed (Table 25, Table 26).

4.3.1. Non-capsulated Haemophilus influenzae

Between 1996 and 1998, 838 cases of non-capsulated (nc) (n=819) or non-b/not further typed (nb) (n=19) *H. influenzae* disease were reported (Table 25,Table 26). The annual breakdown is as follows: 229 cases in 1996; 279 in 1997; 330 in 1998 (Table 27,Table 28). 258 cases were notified in children under 15 years of age. The annual breakdown of isolates from children under 15 years of age is as follows: 72 in 1996; 83 in 1997, 103 in 1998. All countries reported for all 3 years except Italy (1997 and 1998 only). The majority of reports came from the UK (552) and Netherlands (183).

The number of non-capsulated strains increased slightly over the period of the study but the incidence in all age groups remained fairly constant. The overall annual incidence of non-capsulated or non-b (not further typed) *H. influenzae* disease was 2.5/1,000,000 whole population in 1996, 2.5/1,000,000 in 1997 and 3.06/1,000,000 in 1998 (Table 29). The incidence of non-capsulated infection was higher than that for type b infections in the same countries which was 1.7, 1.6 and 1.4/1,000,000 in 1996, 1997 and 1998 respectively (Table 13).

In childhood populations, the incidence of non-capsulated infection (Table 30) was lower than the incidence of type b infection (Table 15). For children under 15 years of age the annual incidence of nc or nb *H. influenzae* disease was 3.6/1,000,000 in 1996, 3.7/1,000,000 in 1997 and 2.6/1,000,000 in 1998 (Table 30). This compares to an incidence of type b infection of 7.3, 6.0 and 4.5/1,000,000 in the same years. The highest incidence of non-capsulated infections was observed in Finland, the Netherlands and the UK (England & Wales).

4.3.2. Non-b capsulated Haemophilus influenzae

The numbers of capsulated Hi infections other than type b was low – much lower than that for type b and non-capsulated infections. There were 114 cases of non-b capsulated *H. influenzae* infection in 1996-1998, compared to 830 non-capsulated and 522 type b isolates reported. Twenty-nine cases occurred in children aged less than 15 years, and 85 occurred in patients aged over 15 years. The majority of reports came from the UK (83) and Netherlands (18) (Table 31,Table 32). There were 4 Hi type a cases, 1 Hic, 1Hid, 25 Hie, and 83 Hif. The overall average annual incidence of non-b capsulated *H. influenzae* was 0.35/1,000,000 in the whole population and 0.37/1,000,000 in children aged less than 15 years.

Table 25: Numbers (%) of *Haemophilus influenzae* isolates reported in Finland, Ireland, Italy, Netherlands, and United Kingdom by serotype (all age groups and years combined)

Country	**Type b**	**Other capsulated strains**	**Non-capsulated**	**Non-b (not further typed)**	**Not typed/ not known**	**Total**
Finland	11 (16)	5 (7)	41 (51)	13 (19)	0 (0)	70
Ireland	28 (50)	1 (2)	19 (34)	0 (0)	8 (14)	56
Italy (enhanced)	182 (63)	2 (1)	24 (8)	6 (2)	73 (25)	287
Netherlands	71(26)	18 (7)	183 (67)	0 (0)	0 (0)	272
United Kingdom	153 (14)	83 (7)	552 (49)	0 (0)	335 (30)	1123
Total	445 (25)	109 (6)	819 (45)	19 (1)	416 (23)	1808

Table 26: Numbers (%) of *Haemophilus influenzae* isolates reported in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, and United Kingdom from children under 15 years (1996, 1997 and 1998 combined)

Country	**Type b**	**Other capsulated strains**	**Non-capsulated**	**Non-b (not further typed)**	**Not typed/ not known**	**Total**
Finland	4 (33)	2 (17)	5 (42)	1 (8)	0 (0)	12
Germany[#]	28 (55)	0 (0)	1 (2)	10 (20)	12 (24)	51
Greece	14 (93)	0 (0)	1 (7)	0 (0)	0 (0)	15
Ireland	21 (68)	1 (3)	9 (29)	0 (0)	0 (0)	31
Italy (enhanced)	159 (77)	1 (0)	1 (0)	0 (0)	45 (22)	206
Netherlands	49 (46)	4 (4)	54 (50)	0 (0)	0 (0)	107
Spain	24 (86)	0 (0)	1 (4)	0 (0)	3 (11)	28
Sweden	11 (39)	5 (18)	8 (29)	0 (0)	4 (14)	28
United Kingdom	93 (32)	16 (5)	167 (57)	0 (0)	19 (6)	295
Total	403 (52)	29 (4)	247 (32)	11 (1)	83 (11)	773

relates to only children under 10 years of age

Table 27: Annual numbers of non-capsulated and non-b (not further typed) *Haemophilus influenzae* isolated in Finland, Ireland, Italy, Netherlands, United Kingdom

Country	1996			1997			1998		
	nc	Nb	total	nc	nb	total	nc	nb	total
Finland	9	5	14	11	3	14	21	5	26
Ireland	5	0	5	11	0	11	3	0	3
Italy (enhanced)	0	0	0	8	6	14	16	0	16
Netherlands	58	0	58	60	0	60	65	0	65
United Kingdom	152	0	152	180	0	180	220	0	220
Total	224	5	229	270	9	279	325	5	330

Table 28: Annual numbers of non-capsulated and non-b (not further typed) *Haemophilus influenzae* isolated in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom in children under 15

Country	1996			1997			1998		
	Nc	nb	total	nc	nb	total	nc	nb	total
Finland	3	1	4	0	0	0	2	0	2
Germany[#]	0	0	0	0	0	0	1	10	11
Greece (Attiki)	1	0	1	0	0	0	0	0	0
Ireland	2	0	2	7	0	7	0	0	0
Italy (enhanced)	0	0	0	1	0	1	0	0	0
Netherlands	17	0	17	16	0	16	21	0	21
Spain (Valencia)	1	0	1	0	0	0	0	0	0
Sweden	5	0	5	2	0	2	1	0	1
United Kingdom	42	0	42	57	0	57	68	0	68
Total	71	1	72	83	0	83	93	10	103

relates to only children under 10 years of age

Table 29: Incidence (per 100,000) of non-capsulated *Haemophilus influenzae* in Finland, Ireland, Italy, Netherlands, and United Kingdom

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	9	5135323	0.18	11	5135323	0.21	21	5159646	0.41
Ireland	5	3539000	0.14	11	3539000	0.31	3	3539000	0.08
Italy (enhanced)	0	14126905	0.00	8	33135024	0.02	16	33135024	0.05
Netherlands	58	15493889	0.37	60	15493889	0.39	65	15493889	0.42
United Kingdom	152	52211175	0.29	180	52211175	0.35	220	52211175	0.42
Total	**224**	**90506292**	**0.25**	**270**	**109514411**	**0.25**	**325**	**109538734**	**0.30**

Table 30: Incidence (per 100,000) of non-capsulated *Haemophilus influenzae* in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, and United Kingdom in children under 15 years

	1996			1997			1998		
	N	Population	Incidence	N	Population	Incidence	N	Population	Incidence
Finland	3	971570	0.31	0	971570	0.00	2	951145	0.21
Germany[#]	-	-	-	-	-	-	1	13098411	0.01
Greece	1	558558	0.18	0	558558	0.00	0	558558	0.00
Ireland	2	939000	0.21	7	939000	0.75	0	939000	0.00
Italy (enhanced)	0	1816128	0.00	1	4832819	0.02	0	4832819	0.00
Netherlands	17	2847820	0.60	16	2847820	0.56	21	2847820	0.74
Spain	1	778105	0.13	0	778105	0.00	0	778105	0.00
Sweden	5	1626178	0.30	2	1626178	0.12	1	1626178	0.06
United Kingdom	42	10033595	0.42	57	10033595	0.57	68	10033595	0.67
Total	**71**	**19570954**	**0.36**	**8383**	**22587645**	**0.37**	**93**	**35665631**	**0.26**

relates to only children under 10 years of age

Table 31: Average annual incidence (per million person-years) of non-b capsulated *Haemophilus influenzae* in Finland, Ireland, Italy, Netherlands, and United Kingdom 1996-8

Country	**Type a**	**Type c**	**type d**	**type e**	**type f**	**Total**	**Person years**	**Annual incidence per million**
Finland	0	0	0	1	4	5	15430292	0.32
Ireland	0	0	0	0	1	1	10617000	0.09
Italy (enhanced)	1	0	0	0	1	2	80396953	0.02
Netherlands	0	0	1	1	16	18	46481667	0.39
United Kingdom	1	1	0	23	58	83	156633525	0.53
Total	**2**	**1**	**1**	**25**	**80**	**109**	**309559437**	**0.35**

Table 32: Average annual incidence (per million person-years) of non-b capsulated *Haemophilus influenzae* in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom in children under 15, 1996-8

Country	**type a**	**Type c**	**type d**	**type e**	**type f**	**Total**	**Person years**	**Incidence**
Finland	0	0	0	0	2	2	2914710	0.69
Germany[#]	0	0	0	0	0	0	13098411	0.00
Greece	0	0	0	0	0	0	1675674	0.00
Ireland	0	0	0	0	1	1	2817000	0.35
Italy (enhanced)	1	0	0	0	0	1	11481766	0.09
Netherlands	0	0	0	1	3	4	8543460	0.47
Spain	0	0	0	0	0	0	2334315	0.00
Sweden	2	0	0	0	3	5	4878534	1.02
United Kingdom	0	1	0	2	13	16	30100785	0.53
Total	**3**	**1**	**0**	**3**	**22**	**29**	**77844655**	**0.37**

relates to only children under 10 years of age

4.3.3. Age distribution of Haemophilus influenzae

The age distribution of cases of non-capsulated and non-b capsulated *H. influenzae* infection (Table 33,Table 34) reveals that 70% of cases of nc Hi occurred in adults (15 years or over) with only 24% in children under five years. Combining data for other capsulated infections, 74% of non-b Hi capsulated occurred in patients aged 15 years or more, with only 10% in children under one year and only 21%in children under five. This is in marked contrast to the picture seen in Hib disease, prior to the introduction of routine Hib immunisation where 79% of infection occurred in children aged less than 5 years.

4.3.4. Clinical diagnosis of Haemophilus influenzae

Meningitis was an uncommon clinical diagnosis in non-capsulated infections causing only 14% of disease in all age groups; septicaemia was the most common diagnosis followed by pneumonia (Table 35). In children under fifteen the distribution of diagnoses was similar, meningitis was also uncommon causing less than 20% of disease (Table 36). Septicaemia was the commonest diagnosis, but unlike adult infections, pneumonia was rare.

Amongst capsulated infections other than type b in total populations under surveillance, the distribution of diagnoses was similar to that for non-capsulated infections (Table 37). Amongst children under fifteen, however, the proportion of cases with a diagnosis of meningitis was higher than for non-capsulated infections (Table 38). Numbers were too small to determine any differences in the distribution of diagnoses between each of the capsular serotypes (**Table 39**).

The distribution of diagnoses for both nc infections varied from that described for type b infections (Table 40). In children under 15 years the clinical breakdown for ncHi differs considerably from that of Hib and non-b capsulated strains. In children, the distribution of clinical diagnoses for types a-e infections was more similar to that described for type b infections (Table 41).

4.3.5. Mortality / case fatality rate

Data on the outcome of infection was routinely available for nine countries for 1997 and 1998 (**Table 42**). The estimated case-fatality ratio for Hib infections was 5.4%. In contrast, the estimated case fatality for both non-capsulated infections and for capsulated infections other than type b was much higher. The mortality rates for ncHi and non-b capsulated Hi were both 23% (107/465 ncHi, 15/66 non-b capsulated Hi). Numbers were too small to compare case-fatality rates for the individual countries.

Table 33: Age distribution of cases of non-capsulated infection in Ireland, Finland, Italy, Netherlands, and United Kingdom for 1996, 1997 and 1998 combined

	Under 3 mths	3-11 mths	1-4 years	5-9 years	10-14 years	15 or more	NK	Total
Finland	2	0	2	1	0	36	0	41
Ireland	2	4	1	0	2	10	0	19
Italy (enhanced)	0	0	1	0	0	22	1	24
Netherlands	11	8	25	5	5	129	0	183
United Kingdom	57	29	52	19	10	376	9	552
Total	**75 (9%)**	**33 (5%)**	**78 (10%)**	**21 (3%)**	**13 (2%)**	**588 (70%)**	**10 (1%)**	**819**

Table 34: Age distribution of cases of non-b capsulated infection in all countries 1996, 1997 and 1998 combined

	Under 1 year	1-4 years	5-9 years	10-14 years	15 or more	NK	Total
A	1	1	0	1	1	0	4
C	1	0	0	0	0	0	1
D	0	0	0	0	1	0	1
E	1	2	0	0	22	0	25
F	8	10	2	2	60	1	83
Total	11 (10)	13 (11)	2 (2)	3 (3)	84 (74)	1 (1)	114

Table 35: Numbers (%) of cases of all ages with non-capsulated *Haemophilus influenzae* isolated in Finland, Ireland, Italy, Netherlands, and United Kingdom (all age groups, 1996, 1997 and 1998 combined) by diagnosis

	meningitis	epiglottitis	septicaemia	pneumonia	other	nk	total
Finland	7	0	7	1	0	26	41
Ireland	4	0	10	4	1	0	19
Italy (enhanced)	1	0	7	1	14	1	24
Netherlands	37	1	48	16	13	68	183
United Kingdom	67	2	198	85	187	13	552
Total	116 (14)	3 (0)	270 (33)	107 (13)	215 (26)	108 (13)	819

Table 36: Numbers (%) of cases in children under 15 years with non-capsulated *Haemophilus influenzae* isolated in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden and United Kingdom (all age groups, 1996, 1997 and 1998 combined) by diagnosis

	Meningitis	Epiglottitis	Septicaemia	Pneumonia	Other	Nk	Total
Finland	1	0	2	0	0	2	5
Germany[#]	0	0	0	0	0	1	1
Greece	0	0	1	0	0	0	1
Ireland	0	0	6	2	1	0	9
Italy (enhanced)	0	0	0	0	1	0	1
Netherlands	15	1	13	2	7	16	54
Spain	1	0	0	0	0	0	1
Sweden	2	0	5	0	1	0	8
United Kingdom	25	2	56	10	73	1	167
Total	44 (18)	3 (1)	83 (34)	14 (6)	83 (34)	20 (8)	247

relates to only children under 10 years of age

Table 37: Numbers (%) of cases of all ages with type a, c, d, e or f *Haemophilus influenzae* isolated in Finland, Ireland, Italy, Netherlands, and United Kingdom (all age groups, 1996, 1997 and 1998 combined) by diagnosis

	Meningitis	Epiglottitis	Septicaemia	Pneumonia	Other	Not known	Total
Finland	2	0	0	0	1	2	5
Ireland	0	0	1	0	0	0	1
Italy (enhanced)	0	0	1	0	0	1	2
Netherlands	6	0	3	1	1	7	18
United Kingdom	12	1	22	26	19	3	83
Total	20 (18)	1 (1)	27 (25)	27 (25)	21 (19)	13 (12)	109

Table 38: Numbers (%) of cases in children under 15 years with type a, c, d, e or f *Haemophilus influenzae* isolated in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden and United Kingdom (1996, 1997 and 1998 combined) by diagnosis

	Meningitis	Epiglottitis	Septicaemia	Pneumonia	Other	Not known	Total
Finland	1	0	0	0	0	1	2
Ireland	0	0	1	0	0	0	1
Germany[#]	0	0	0	0	0	0	0
Greece	0	0	0	0	0	0	0
Italy (enhanced)	0	0	1	0	0	1	2
Netherlands	2	0	0	0	0	2	4
Spain	0	0	0	0	0	0	0
Sweden	3	0	2	0	0	0	5
United Kingdom	9	0	3	1	2	0	15
Total	15 (52)	0 (0)	7 (24)	1 (3)	2 (7)	4 (14)	29

relates to only children under 10 years of age

Table 39: Numbers (%) of cases with type a, c, d, e or f *Haemophilus influenzae* isolated in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden and United Kingdom (all age groups, 1996, 1997 and 1998 combined) by diagnosis

	Meningitis	**Epiglottitis**	**Septicaemia**	**Pneumonia**	**Other**	**Not known**	**Total**
Type a	1	0	1	1	0	1	4
Type c	0	0	1	0	0	0	1
Type d	1	0	0	0	0	0	1
Type e	1	0	5	11	7	1	25
Type f	20 (24)	1 (1)	22 (26)	15 (18)	14 (16)	11 (13)	83
All	**23 (20)**	**1 (1)**	**29 (25)**	**26 (24)**	**21 (18)**	**13 (11)**	**114**

Table 40: Numbers (%) of cases of all ages with *H. influenzae* isolated in Finland, Ireland, Italy, Netherlands, UK (all age groups, 1996, 1997, 1998 combined) by diagnosis.

	Meningitis	Epiglottitis	Bacteraemia	Pneumonia	Other	NK	Total
NcHi	117 (14)	3 (0)	270 (33)	107 (13)	215 (26)	108 (13)	819
Non b capsulated	20 (18)	1 (1)	27 (25)	27 (25)	21 (19)	13 (12)	109
Hib	228 (31)	41 (9)	64 (14)	32 (7)	59 (13)	22 (5)	446
TOTAL	**365**	**45**	**361**	**166**	**295**	**143**	**1374**

Table 41: Numbers (%) of cases of ncHi, non-b capsulated Hi and Hib isolated in children under 15 years in Finland, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden & UK (1996, 1997 and 1998 combined) by diagnosis.

	Meningitis	Epiglottitis	Bacteraemia	Pneumonia	Other	NK	Total
NcHi	44 (18)	3 (1)	83 (34)	14 (6)	83 (34)	20 (8)	247
Non b capsulated	15 (52)	0 (0)	7 (24)	1 (3)	2 (7)	4 (14)	29
Hib	260 (63)	36 (9)	54 (13)	12 (3)	37 (9)	15 (4)	414
TOTAL	**319**	**39**	**144**	**27**	**122**	**39**	**690**

Table 42: Outcome of infection in Australia, Finland, Germany, Greece, Ireland, Israel, Italy, Netherlands, Spain, Sweden, and United Kingdom for 1997 and 1998

	Type b			Type nc			Type a, c, d, e or f		
	Died	**Total**	**%**	**Died**	**Total**	**%**	**Died**	**Total**	**%**
Australia	3	55	5.5	-	-		-	-	-
Finland	-	-		-	-		-	-	-
Germany[#]	2	19	11	-	-		-	-	-
Greece	0	14	0	-	-		-	-	
Ireland	0	9	0	0	2	0	1	1	100
Israel	0	7	0	-	-		-	-	-
Italy (enhanced)	4	126	3.2	3	22	14	1	1	100
Netherlands	-	-		-	-		-	-	-
Spain	0	1	0	-	-		-	-	-
Sweden	1	4	25	0	1	0	1	3	33
United Kingdom	9	118	7.6	104	440	24	12	61	20
Total	**19**	**353**	**5.4**	**107**	**465**	**23**	**15**	**66**	**23**

relates only to children under 10 years of age*8.3.6.*

4.4. Laboratory quality assurance

4.4.1. Distribution 1

Of the 8 centres 1 laboratory failed to return their results, 1 laboratory experienced a delay in receiving the strains, and only 1 was viable on testing. We were unable to send the isolates to 1 centre due to postal problems beyond our control. Thus a total of 5 sets of complete or nearly complete results were received.

Strain 1was a non typeable strain of *Haemophilus influenzae* (biotype I)
3 centres correctly identified this strain. 2 centres incorrectly identified this strain as serotype d. (It was non viable on receipt in 1 centre). **Comments:** On re-testing, The HRU, Oxford was unable to get this strain to cross react with d antisera.

Strain 2 was *Haemophilus haemolyticus*
1 centre correctly identified this strain. 3 centres incorrectly identified this strain as *H. influenzae* non typeable. (The strain was non viable in 2 centres). **Comments:** *H.haemolyticus* requires the same growth factors as *H. influenzae* but is haemolytic on blood agar in 10% CO_2. PCR with OMP P2 primers will be negative for *H.haemolyticus*.

Strain 3 was *Haemophilus influenzae* serotype b (biotype II)
5 centres correctly identified this strain (non viable in 1 centre). **Comments:** No problems were encountered with this strain.

Strain 4: *Haemophilus influenzae* serotype b- (biotype I) - This strain is genetically a type b but lacking part of the locus for expression of capsule.1 centre correctly identified this strain. 1 centre identified this strain as serotype b, not the capsule deficient variant b-. 1 centre incorrectly identified this strain as non-typeable. 1 centre incorrectly identified this strain as serotype f. 1 centre found 2 strains, the predominant strain showing autoagglutination.
Comments: b- strains often display colonial variation, and autoagglutinate on slide agglutination. The colonies appear “rough” and irregular, and do not look capsulate. Genotyping is one way to detect capsule deficiency in these strains.

Strain 5 *Haemophilus influenzae* serotype f (biotype I)
6 centres correctly identified this strain. **Comments:** There were no problems with this strain.

Strain 6: *Haemophilus influenzae* non typeable (biotype VI) - cross-reacts with b and c antiserum.
3 centres correctly identified this strain. 1 centre incorrectly identified this strain as serotype b. 1 centre incorrectly identified this strain as serotype c. (Non viable in 1 centre). **Comments:** The incorrect results for this strain were understandable, however genotyping strains that give non-specific agglutination results overcomes this problem.

4.4.2. Distribution 2

Of the 12 centres participating in the quality assurance scheme 2 laboratories failed to return their results. 1 laboratory only returned preliminary results. 1 laboratory identified the strains to species level only, and did not provide serotypes. A total of 8 sets of complete results were received.

Strain 7 was *Haemophilus influenzae* non-typeable (biotype IV)
6 centres correctly identified this strain. 1 centre incorrectly identified this strain as serotype d. 1 centre incorrectly identified this train as serotype a. 1 centre returned biotyping results only. 1 centre identified this strain to species level only. **Comments:** The HRU, Oxford found this strain cross-reacted with type d antisera.

Strain 8 was *Haemophilus haemolyticus*
5 centres correctly identified this strain to species level. 2 centres correctly identified this strain as *Haemophilus sp.* not *H. influenzae*. 2 centres incorrectly identified this strain as *H. influenzae*, one found it to be non-typeable, and the other did not provide a serotype. 1 centre returned biotyping results only, but had preliminarily incorrectly identified this strain as *H. influenzae*. **Comments**: *H.*

haemolyticus requires the same growth factors as *H. influenzae* but is haemolytic on blood agar in 10% CO_2. PCR with OMP P2 primers will be negative for *H. haemolyticus*.

Strain 9 was *Haemophilus influenzae* non-typeable (biotype III)
3 centres correctly identified this strain. 2 centres found this strain autoagglutinated and were unable to serotype it. 2 centres incorrectly identified this strain as *Haemophilus spp*, not *H. influenzae*. However, understandable due to OMP PCR negative result. 1 centre identified this strain as *H. influenzae* biogroup *aegyptius*. 1 centre returned biotyping results only. 1 centre identified this strain to species level only. **Comments**: The HRU was unable to get this strain to emulsify in saline for slide agglutinations. On PCR, we were unable to obtain a product with the OMP primers, however the strain was non-haemolytic. HRU, Oxford is confident this strain is *H. influenzae* on the basis of the biochemical and morphological results obtained.

Strain 10 was *Haemophilus influenzae* serotype e (biotype IV)
8 Centres correctly identified this strain. 1 centre identified this strain to species level only. 1 centre returned biotyping results only. **Comments**: There were no problems with this strain.

Strain 11 was *Haemophilus influenzae* serotype b (biotype I)
4 centres correctly identified this strain. 2 centres incorrectly identified this strain as non-typeable. 2 centres found this strain cross-reacted and were unable to type it. 1 centre identified this strain to species level only. 1 centre returned biotyping results only. **Comments**: This strain cross reacted with type c antiserum, therefore further typing was required to determine the serotype, e.g. PCR.

Strain 12 was *Haemophilus influenzae* serotype b- (biotype I) This strain is genetically a type b but lacking part of the locus for expression of capsule.
4 centres correctly identified this strain as serotype b. 2 centres incorrectly identified this strain as non-typeable. 2 centres found this strain cross-reacted and were unable to serotype it. 1 centre identified this strain to species level only. 1 centre returned biotyping results only. **Comments**: b- strains often display colonial variation and autoagglutinate on slide agglutination. The colonies appear "rough" and irregular, and do not look capsulate. Genotyping is one way to detect capsule deficiency in these strains.

4.4.3. Distribution 3

Of the 11 centres participating in the quality assurance scheme 3 laboratories failed to return their results, 1 laboratory lost the strains prior to testing because of a power failure, 1 laboratory returned results without identifying which laboratory they were from. A total of 8 sets of complete results were returned.

Strain 13 was *Haemophilus influenzae* serotype a (biotype IV)
7 centres correctly identified this strain as serotype a, 1 centre identified this strain as serotype a-f, cross-reacting with a and d antisera, 4 centres correctly identified this strain as biotype IV. **Comments**: In general there were no problems with this strain. HRU, Oxford was unable to get this strain to cross react with d antisera.

Strain 14 was *Haemophilus influenzae* non typeable (biotype I)
7 centres correctly identified this strain, 1 centre found this strain cross-reacted with type b, d, e antisera, 5 centres identified this strain as biotype I. **Comments**: With one exception there were no problems with this strain. HRU, Oxford was unable to get this strain to cross-react with type b, d, and e antisera. PCR will confirm the identity of a strain giving apparent cross-reaction on slide agglutination.

Strain 15 was *Haemophilus parainfluenzae* (Biotype I)
8 centres correctly identified this strain as *H. parainfluenzae*. 5 centres correctly identified this strain as biotype I. **Comments**: There were no problems with this strain.

Strain 16 was *Haemophilus influenzae* serotype b (biotype I)
7 centres correctly identified this strain as *H. influenzae* type b. 1 centre incorrectly identified this strain as non-typeable. 4 centres correctly identified this strain as biotype. **Comments**: This strain

cross-reacted with type c antiserum on slide agglutination. PCR may be required to determine the serotype.

Strain 17 was *Haemophilus influenzae* non-typeable (biotype III)
7 centres correctly identified this strain as non-typeable. 1 centre found this strain cross-reacted with type a and e antisera. 4 centres correctly identified this strain as biotype III. 1 centre incorrectly identified this strain as biotype IV. **Comments**: HRU, Oxford was unable to get this strain to cross-react with type a and e antisera. Biotype III is I-ve, urease +ve, and ODC -ve. Biotype IV is I-ve, urease +ve, and ODC +ve.

Strain 18 was *Haemophilus influenzae* serotype b (biotype I)
7 centres correctly identified this strain as serotype b. 1 centre incorrectly identified this strain as non-typeable. 1 centre identified this strain as cross-reacting with type b and c antisera. 4 centres correctly identified this strain as biotype I. 1 centre incorrectly identified this strain as biotype IV. **Comments**: HRU, Oxford was unable to get this strain to cross-react with a antiserum. Genotyping would overcome the problem of cross-reacting agglutination.

Table 43: Results of the first quality assurance scheme (25/2/97)

ID	UK results	Centre 1	*Centre 2*	*Centre 3*	*Centre 4*	*Centre 5*	*Centre 6*
Strain 1	FF 7253 Non-typeable Biotype I	Non viable	*H. influenzae* non-typeable Biotype I	*H. influenzae* non-typeable beta-lact neg	*H. influenzae* Serotype d	*H. influenzae* non-typeable Biotype I	*H. influenzae* Serotype d AB sens
Strain 2	FF 7094 *Haemophilus haemolyticus*	Non viable	*H. influenzae* non-typeable Biotype III	*H. influenzae* non-typeable Beta-lact pos	*H. influenzae* non-typeable	*H. haemolyticus*	Non viable
Strain 3	FF 7234 Serotype b Biotype II	Non viable	*H. influenzae* Serotype b Biotype II	*H. influenzae* Serotype b beta-lact neg	*H. influenzae* Serotype b	*H. influenzae* Serotype b Biotype II	*H. influenzae* Serotype b
Strain 4	FF 7166 Serotype b- Biotype I	Non viable	*H. influenzae* nontypeable Biotype I	*H. influenzae* Serotype b beta-lact neg	*H. influenzae* Serotype f	*H. influenzae* Serotype b- Biotype I	Two strains- Predominant strain autoagglutinates
Strain 5	FF 7229 Serotype f Biotype I	*H. influenzae* Serotype f Biotype I	*H. influenzae* Serotype f Biotype I	*H. influenzae* Serotype f beta-lact neg	*H. influenzae* Serotype f	*H. influenzae* Serotype f Biotype I	*H. influenzae* Serotype f AB sensitive
Strain 6	FF 5615 (cross reacts with b&c) Biotype VI	Non viable	*H. influenzae* Biotype VI	*H. influenzae* beta-lact neg	*H. influenzae*	*H. influenzae* Biotype VI	*H. influenzae* AB sensitive

Table 44: Results of the second quality assurance scheme

Distribution ID UK Results)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**11**	**12**
Strain 7 *H. influenzae* Non-typeable (cross reacts with d) Bioytpe IV	*H. influenzae* non-typeable biotype IV	*H. influenzae* biotype IV	*H. influenzae* non-typeable	*H. influenzae* serotype d ?wk c cross reaction	*H. influenzae* non-typeable biotype IV	*H. influenzae* non-typeable	*H. influenzae* serotype a biotype IV	*H. influenzae* non-typeable biotype IV	*H. influenzae* biotype IV	*H. influenzae*	*H. influenzae* non-typeable biotype IV
Strain 8 *H. haemolyticus*	*H. haemolyticus*	*H.. influenzae* biotype II	*H.* not influenzae non-typeable	*H. haemolyticus*	*H. haemolyticus*	*H.* not *influenzae*	*H. haemolyticus*	*H. haemolyticus*	Strain lost	*H. influenzae*	*H. influenzae* non-typeable biotype I
Strain 9 *H. influenzae* Non-typeable (won't emulsify in saline) Bioytpe III	*H. influenzae* non-typeable biotype III	*H. influenzae* biotype III	*Haemophilus* not influenzae non-typeable	*H. influenzae* autoagglutinating	*H. influenzae* autoagglutinating biotype III	*Haemophilus spp* not *H. influenzae*	*H. influenzae* non-typeable biotype III	*H..influenzae* Non-typeable Biotype III	Strain lost	*H. influenzae*	*H. influenzae* non-typeable biotype III (biogroup aegyptius)
Strain 10 *H. influenzae* Serotype a Biotype IV	*H. influenzae* type e biotype IV	*H. influenzae* biotype III	*H. influenzae* serotype e	*H. influenzae* serotype e	*H. influenzae* serotype e biotype IV	*H. influenzae* serotype e	*H. influenzae* serotype e biotype IV	*H. influenzae* serotype e biotype IV	*H. influenzae* serotype e biotype IV	*H. influenzae*	*H. influenzae* serotype e
Strain 11 *H. influenzae* Serotype b (cross reacts with c) Bioytpe I	*H. influenzae* non-typeable biotype I	*H. influenzae* biotype IV	*H. influenzae* serotype b	*H. influenzae* cross reacts with c & f	*H. influenzae* serotype b biotype I	*H. influenzae* serotype b	*H. influenzae* serotype b biotype I	*H. influenzae* cross reacts biotype I	*H. influenzae* biotype I	*H. influenzae*	*H. influenzae* non-typeable biotype I
Strain 12 *H. influenzae* Serotype b Biotype I	*H. influenzae* serotype b biotype I	*H. influenzae* biotype IV	*H. influenzae* serotype b	*H. influenzae* cross reacts with a & f	*H. influenzae* non-typeable biotype I (a, b, c, d pos)	*H. influenzae* serotype b-	*H. influenzae* non-typeable biotype I	*H. influenzae* cross reacts biotype I	*H. influenzae* biotype I	*H. influenzae*	*H. influenzae* serotype b biotype I

Table 45: Results of the third quality assurance scheme (22/3/99)

Strain no:	**U.K. Results**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
13	*H. influenzae* serotype a biotype IV	*H. influenzae* serotype a biotype IV	*H. influenzae* types a, c-f biovar IV	*H. influenzae* type a	*H. influenzae* a-f x reacts a+d	*H. influenzae* a	*H. influenzae* a	*H. influenzae* a,c,f biotype IV	*H. influenzae* type a biotype IV
14	*H. influenzae* non-capsulated biotype I	*H. influenzae* non-typeable biotype I	*H. influenzae* non-typeable biotype I	*H. influenzae* non-typeable	*H. influenzae* x reacts b, d, e	*H. influenzae* non-typeable	*H. influenzae* non-typeable biotype I	*H. influenzae* non-typeable biotype I	*H. influenzae* non-typeable biotype I
15	*H. para influenzae* biotype I	*H. para influenzae* biotype I	*H. para influenzae* biotype I	*H. para influenzae*	*H. para influenzae*	*H. para influenzae*	*H. para influenzae* biotype I	*H. para influenzae* biotype I	*H. para influenzae* biotype I
16	*H. influenzae* serotype b biotype I	*H. influenzae* serotype b biotype I	*H. influenzae* serotype b biotype I	*H. influenzae* type b	*H. influenzae* type b	*H. influenzae* type b	*H. influenzae* type b	*H. influenzae* non-typeable biotype I	*H. influenzae* type b biotype I
17	*H. influenzae* non-capsulated biotype III	*H. influenzae* non-typeable biotype III	*H. influenzae* non-typeable biotype III	*H. influenzae* non-typeable	*H. influenzae* x reacts a + e	*H. influenzae* non-typeable	*H. influenzae* non-typeable biotype III	*H. influenzae* non-typeable biotype IV	*H. influenzae* non-typeable biotype III
18	*H. influenzae* serotype b biotype I	*H. influenzae* serotype b biotype I	*H. influenzae* serotype b biotype I	*H. influenzae* type b	*H. influenzae* b/c	*H. influenzae* type b	*H. influenzae* type b	*H. influenzae* non-typeable biotype IV	*H. influenzae* type b biotype I

4.5. Vaccination programme effectiveness

Estimates of the pre-vaccination rates of invasive Hib disease were available from published studies in nine countries. In Germany, published rates were confined to Hib meningitis (23/100,000 children less than five years). Data was available from some localised studies in Spain but rates varied substantially between studies in different autonomous regions and the study participants had some concern about the validity of the only study from Valencia. A single study in Italy had estimated rates of Hib disease from follow up in a study cohort for a pertussis vaccine trial and therefore rates in children under five were extrapolated from the age group followed. Subsequent surveillance has also demonstrated wide variation in rates between districts and therefore it is not clear how generalisable this pre-vaccine data is to the whole Italian population.

In comparison to all published data, incidence rates in the seven countries with national programmes were substantially lower in 1996 and rates remained low in 1997 and 1998. The percentage fall in estimated rates ranged from 78% in Ireland to 100% in Finland with five countries experiencing greater than a 95% fall in rates. By 1998, eight countries had implemented national immunisation and the range of fall in incidence from pre-vaccine rates was between 89% and 99% (Table 46). In Germany rates of Hib meningitis were 0.38/100,000 children under five in 1998; this represented a 98% fall in incidence from the pre-vaccine era.[53]

Six countries were able to provide comparable data from the existing surveillance scheme for each year since the pre-vaccine era (Table 47). This data indicated that one country (Finland) had seen a major reduction (more than 90%) in disease prior to national introduction of vaccine, this was attributed to widespread use of Hib vaccine as part of trials. Of the remaining countries, all except Greece (Attiki) had achieved over 90% reduction in rates by the third year after vaccine introduction. Three countries had achieved more than a 95% reduction, but in Ireland the reduction in the rate seems to have stabilised at around 90%. A similar fall in incidence was achieved around two years earlier in the UK (England & Wales) than in the Netherlands. Vaccine was introduced in the latter country around six months after the introduction in the UK although without a “catch-up” programme in all children under five years of age. In both Israel and Greece (Attiki) vaccine had been widely used in private practice prior to implementation and so pre-vaccine rates may have been lower than expected.

Table 46: Rates of invasive Hib disease in children under 5 years of age pre- and post-vaccination programme

Country	Year of introduction	Invasive Hib /100,000						
		Pre-vaccination	1996	% reduction	1997	% reduction	1998	% reduction
Australia[58]	1992/1993	39.0	1.70	96	2.24	94	1.31	97
Finland[17]	1993	52.0	0.00	100	0.00	100	0.33	99
Germany	1991	-	-	-	-		0.63	-
Greece	May 1994 (for 40% of population)	16.25	3.54	78	1.77	89	1.77	89
Ireland[14]	October 1992	25.4	2.24	91	2.24	91	3.33	87
Israel[32]	1994	34	2.01	94	0.67	98	0.84	98
Italy[101]	Not yet		7.24		4.28		4.41	
Netherlands[56]	April 1993	63.0	2.45	96	1.12	98	1.03	98
Spain	1996 (Valencia)	-	9.37	-	2.47	-	0.49	-
Sweden	1992-1993	54.0	0.18	100	0.35	99	0.61	99
England & Wales[67]	October 1992	31.0	1.01	97	0.97	97	0.67	98

Table 47: Annual incidence (per 100,000 population) of invasive Hib disease in countries with surveillance over the period of vaccine introduction

Country	Finland		Greece		Ireland		Israel		Netherlands		UK	
Year of national Introduction	1993		May 1994 (40% of population)		Oct 1992		1994		Apr 1993		Oct 1992	
Catch-up	In trials		Private practice		Under fives		Private practice		No		Under fives	
	Rate	% change*	Rate	% change*	Rate	% change*	Rate	% change*	Rate	% change*	Rate	% change*
1986	53.6											
1987	34.4	-36%										
1988	22.0	-77%	-		-		-		-		-	
1989	9.60	-82%	-		-		-		33.4		-	
1990	2.20	-96%	-		-		31.5		27.4	-18%	22.5	
1991	0.90	-98%	-		32.8		28.5	-10%	20.3	-39%	23.5	+4%
1992	0.90	-98%	10.0		31.4	-4%	30.2	-4%	23.9	-28%	20.2	-10%
1993	0.40	-99%	9.43	-6%	13.4	-59%	26.0	-17%	23.4	-30%	6.34	-72%
1994	0.40	-99%	8.84	-12%	5.20	-84%	9.10	-71%	13.3	-60%	1.10	-95%
1995	0.40	-99%	2.35	-77%	2.20	-93%	3.80	-88%	5.00	-85%	1.00	-96%
1996	0.00	-100%	3.54	-65%	2.24	-93%	2.01	-94%	2.45	-93%	1.01	-96%
1997	0.00	-100%	1.77	-82%	2.24	-93%	0.67	-98%	1.12	-97%	0.97	-96%
1998	0.66	-99%	1.77	-82%	3.75	-89%	0.84	-97%	1.03	-97	0.67	-97%

* from baseline year

4.6. Vaccine efficacy

4.6.1. Preliminary analysis of the vaccine efficacy of Hib vaccine in eight countries 1996-1998

This analysis uses the screening method to estimate vaccine efficacy in eight countries. To estimate efficacy the following information was required for each country in each year.

1. Age and vaccination status of Hib cases.
2. Vaccine coverage by age (eight age groups were used).

Only cases aged 6 months to 9 years with a known vaccination status were included. Information on partial vaccination and partial coverage was also obtained or estimated.

Table 48: Summary of the case data used in the analysis of vaccine efficacy (by year)

	Year			
COUNTRY	1996	1997	1998	1996-8
Australia	26	22	15	63
Ireland	6	6	7	19
Finland	0	1	1	2
Israel	0	0	6	6
Netherlands	14	8	9	31
Sweden	2	2	2	6
UK	31	18	15	64
Spain	14	4	1	19
Total	93	61	56	210

Table 49: Summary of the case data used in the analysis of vaccine efficacy (by age)

	Age group								
COUNTRY	6–8 mths	9-11 mths	12-17 mths	18- 23 mths	2 yr olds	3 yr olds	4 yr olds	5-9 yrs	Total
Australia	7	4	14	7	5	8	3	15	63
Ireland	4	2	4	2	5	2	0	0	19
Finland	1	0	0	0	0	0	0	1	2
Israel	1	2	0	0	0	1	0	2	6
Netherlands	3	3	4	3	6	5	7	0	31
Sweden	2	0	0	0	1	0	0	3*	6
UK	4	3	9	10	18	10	3	7	64
Spain	5	2	5	1	3	1	2	0	19
Total	27	16	36	23	38	27	15	28	210

* these 3 cases were too old to have been vaccinated so they are not included in the analysis.

Table 50: Summary of the case data used in the analysis of vaccine efficacy (by vaccination status)

	Vaccine status					
COUNTRY	none	1+ dose	2+ doses	Full	Full + booster	Total
Australia	20	7	6	23	7	63
Ireland	7	3	1	8	0	19
Finland	1	0	0	1	0	2
Israel	1	1	0	4	0	6
Netherlands	20	1	1	4	5	31
Sweden	3	0	2	1	0	6
UK	13	1	0	50	0	64
Spain	16	1	0	2	0	19
Total	81	14	10	93	12	210

4.6.2. Definitions

1+ dose: at least 1 partial dose given to an under one year old.
2+ doses: at least 2 partial doses given to an under one year old.
Full: at least 3 doses given to an under one year old or one dose to an over one year old.
Full + booster: A booster dose given as a 4th dose to a child of at least 11 months.

4.6.3. Results

Those with two partial doses are counted as vaccinated, those with one partial dose are omitted and the coverage is adjusted to remove these. For example if coverage for at least 2 partial is 95% and for at least 1 partial is 96% then estimated coverage omitting those with just one partial is 95%/99% = 95.96%.

Age was grouped into four groups after an initial analysis.

Factors in the analysis are Country + Age + Year.

Table 51: Multi-variable logistic regression analysis by country, age and year, for the odds of vaccination after adjusting for population coverage

Factor	Factor level	Odds Ratio	P-value
Country	Australia	1.00	<0.00001
	Ireland	0.76	
	Finland	*	
	Israel	*	
	Netherlands	0.03	
	Sweden	*	
	UK	0.43	
	Valencia	0.18	
Age	6months – 11.99 months	1.00	<0.0001
	1 yr	2.41	
	2/3 yrs	16.1	
	4+	6.2	
Year	1996	1.00	0.50
	1997	0.65	
	1998	0.60	

* - not enough data for an accurate estimate
Note that an odds ratio of less than one equates to a higher vaccine efficacy.

Both country and age had a significant effect upon vaccine efficacy . There was no difference in efficacy between years of the study. Therefore, to estimate vaccine efficacy for each country we can calculate unadjusted estimates averaged across years.

Table 52: Summary of vaccine efficacy by country

Country	VE	95% CI
Australia	39.9%	(-17% to 69.3%)
Ireland	65.7%	(7.9% to 87.2%)
Finland	-	-
Israel	-	-
Netherlands	97.9%	(95.2% to 99.1%)
Sweden	-	-
UK	74.2%	(50.2% - 86.7%)
Valencia	88.0%	(46.4% to 97.3%)
Total	76.2%*	(65.9 to 83.4)

* this includes the Finnish, Swedish and Israel data – individual estimates were not possible due to low numbers.

Significant variations were observed by country, most notably the low efficacy in Australia and high efficacy in the Netherlands.

Table 53: Summary of vaccine efficacy by age (averaged across country and year).

Age	VE	95% CI
6m – 11.99m	94.0	(86.8 to 97.3)
1yr olds	86.8	(75.9 to 92.8)
2/3yrs	31.6	(-42.8 to 67.2)
4-9yrs	43.6	(-25.0 to 73.6)

A significantly lower efficacy was observed in older children.

Table 54: Summary of vaccine efficacy by year (averaged across country and age).

Year	VE	95% CI
1996	67.6	(43.0 to 81.6)
1997	78.9	(60.4 to 88.7)
1998	82.8	(66.4 to 91.1)

No significant differences were observed by year.

The main variations are by country and by age. Where possible (if sufficient numbers) we can estimate efficacy split by country and in two age groups.

Table 55: Summary of vaccine efficacy by country and age group (6m-23.99m and 2-9 yrs)

Country	Age	VE	95% CI
Australia	<2	77.1%	(44.8% to 90.5%)
	2+	-14.4%	(-157% to 49.6%)
Ireland	<2	88.6%	(55.8% to 97.0%)
	2+	-	-
Netherlands	<2	99.0%	(96.6%to 99.7%)
	2+	95.4%	(83.7% to 98.7%)
UK	<2	86.2%	(67.0% - 94.3%)
	2+	54.2%	(-20% to 82.6%)
Valencia	<2	100%	-
	2+	32.6%	(-290% to 88.4%)

4.6.4. Comments

Note that there were no significant differences between the years, also there were no significant interactions between country and age, or country and year.

The pattern of a lower efficacy in the older age groups is seen in all countries where this could be assessed. The overall age effect (for all countries combined) is significant in most analyses, the general pattern shows a higher efficacy in under ones and the lowest efficacy in the 2-4 year olds, then the 5-9 year olds. This may be associated with waning immunity, the effect of vaccine action or may be due to under-estimates of coverage for older children. In particular, the efficacy in older children in Australia seems low and this may be explained by the poor accuracy for coverage estimates in this age group. The highest efficacy is seen in the Netherlands and this effect is most marked in the older age group - further analysis is required to determine if this could be the effect of a booster dose.

4.7. Vaccine failures

4.7.1. Cases in vaccinated children

Vaccination status was reported for 400/547 (73%) of cases in children under 15 years (Table 56). The proportion of cases of invasive Hib disease which occurred in vaccinated children was 31% overall (range 0-64%). The proportion of cases in vaccinated children was high (50% or more) in Australia, Germany, Ireland, and the UK. Of the 170 cases which occurred in vaccinated children, 33 (19%) were reported after only receiving the first dose of vaccine (given under 12 months of age). The remaining 118 (69%) cases represent true vaccine failure (TVF): 91 after 3 doses of vaccine, 10 after 4 doses, 28 after 2 doses in the 1st year of life and 9 after 1 dose given in the 2nd year of life.

The majority of reports of cases in vaccinated children came from four countries: England, Australia, The Netherlands, and Ireland. Meningitis was the main clinical presentation (53%) followed by bacteraemia (20%). Thirty-three cases constituted apparent vaccine failures (AVF) (after 1 dose given in the 1st year of life). Although the majority of TVF were reported from the UK (52 versus 21 Australia), the majority of AVF were reported from Australia (15) versus four in the UK.

4.7.2. True vaccine failures

Concentrating on the infections which occurred despite three or four doses of vaccine, the major clinical presentation was again meningitis (57%) but epiglottitis was next most common (14%). The median age of presentation with vaccine failure was 28 months (range 4-97) with 77 of 96 (80%) occurring in the 12-47 month age groups. Age of presentation was not significantly different between countries.

4.7.3. Possible vaccine failures

A further 8 cases of Hi infection were reported in vaccinated children but the isolate was not serotyped (possible vaccine failures).

4.7.4. Risk factors for vaccine failure

Completed proformas were received from 68/96 (71%) of the true vaccine failures where 3 or 4 doses had been received. This revealed that the sex distribution was equal, 13% were born prematurely and 3/62 had an underlying illness (2/3 malignancy).

Acute serology was obtained in 14 cases, was < 1.0 ug/ml in 13/14 and undetectable in 10/14 cases.

Convalescent serum was obtained in 55 individuals and suggested a poor antibody response to PRP in 26% i.e. < 1.0 ug/ml. However of those who then received a further dose of vaccine, the response was satisfactory in all.

Immunoglobulins were assayed in 52 and were low for age in 25% (9 low total immunoglobulins, 3 low IgG subclass levels and 1 low total and subclass levels). Therefore, of those who had both clinical and immunological data available, 40 % were shown to have a clinical and / or immunological abnormality. If we include those who also had a poor convalescent antibody response, then 28/50 (56%) children appear to have an underlying abnormality

The numbers of true vaccine failures fully investigated was too small to determine any differences between countries or vaccines.

Table 56: Vaccination status of cases of invasive Hib disease in children under 15 years by country

	Australia		Finland		Germany[#]		Greece		Ireland		Israel		Italy		Netherlands		Spain		Sweden		UK		Total	
Vaccinated	50	58%	1	25%	14	50%	0	0%	14	64%	9	36%	3	2%	14	29%	3	12%	4	36%	58	62%	170	31%
One	15	17%	0	0%	1	4%	0	0%	4	18%	1	4%	2	1%	3	6%	2	8%	1	9%	4	4%	33	6%
Two	10	12%	0	0%	8	29%	0	0%	1	5%	4	16%	0	0%	1	2%	0	0%	2	18%	2	2%	28	5%
Three	16	19%	1	25%	5	18%	0	0%	9	41%	4	16%	1	1%	5	10%	0	0%	1	9%	49	53%	91	17%
Four	4	5%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	5	10%	1	4%	0	0%	0	0%	10	2%
Catch-up	5	6%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	0	0%	3	3%	9	2%
Not vaccinated	29	34%	3	75%	14	50%	14	100%	8	36%	16	64%	62	33%	26	53%	18	72%	5	45%	35	38%	230	42%
Not known	7	8%	0	0%	0	0%	0	0%	0	0%	0	0%	125	66%	9	18%	4	16%	2	18%	0	0%	147	27%
Total under 15	86	100%	4	100%	28	100%	14	100%	22	100%	25	100%	190	100%	49	100%	25	100%	11	100%	93	100%	547	100%

relates to only children under 10years of age

5. DISCUSSION

5.1. Vaccination programmes

Considerable variation was demonstrated between the participant countries in their vaccination programmes: the vaccines used, the vaccination schedule, the programme implementation strategies, and the coverage achieved. The number and type of Hib vaccines licensed varied between countries.

Vaccines used also varied within countries for practical reasons. Examples of such scenarios reported to the project included the use of two different vaccines for a large catch-up campaign, or changing manufacturer to allow administration of combination vaccine (with DTP/DtaP) or mixing of vaccines (with DTP) in a single syringe. Most of the larger countries have not relied solely upon one vaccine - this may reflect concern about the sustainability of a supply from a single manufacturer. In addition, some vaccine choices have been made for epidemiological reasons. Two countries in which pre-vaccine studies had demonstrated that a substantial proportion of Hib disease occurred in young infants chose to use PRP-OMP vaccine. This choice was probably due to excellent protection offered by this vaccine in young infants with only one dose.[4] This vaccine was targeted at Aboriginal populations in Australia and was the first vaccine used in Israel, although the latter country has subsequently switched to PRP-T.

The schedules used also vary enormously; with differences both in number of doses, the age at first dose, and the use of a booster. Although the reasons for the choice of schedule were not explicitly requested in this survey, in general, Hib vaccination was administered with other antigens and therefore the choice of schedule reflected those currently in use for DTP and polio vaccines. In UK (England & Wales), Ireland and Australia the infant programme was also implemented alongside catch-up immunisation of all children under five years of age. In Sweden, this catch-up occurred in some regions only. The decision to use a catch-up was based upon the desire to have a rapid effect on the disease epidemiology. In Israel, because of a younger age distribution of disease, catch-up was not considered necessary. In many countries, prior to national implementation, vaccine had been used quite widely in pre-implementation trials or in private practice and therefore the need for catch-up was less clear.

5.2. Vaccine coverage

Methods for assessing Hib vaccine coverage were generally the same as those in use for other vaccines. The methods used, the age at evaluation and the timeliness of the measurement was very variable. The vaccination coverage achieved by the participant countries with national programmes ranged from between 65% to 99% over the period of the study. Apart from Germany, however, all countries with a national programme had achieved 80% or higher coverage for their infant programme by 1998; most countries had achieved over 90% coverage in infants. In Germany, data was only available from ad-hoc regional studies and was evaluated in all ages under five. It is possible, therefore, that coverage in the younger cohorts was closer to that achieved in other countries, and recent unpublished data suggest that vaccination coverage is now greater than 95%. In general, countries with high vaccination coverage for other antigens were able to reach similar levels for Hib vaccine coverage. Where coverage was reported as low, this was usually attributed to problems with data collection rather than to refusal of vaccines.

Three countries without routine programmes at the start of the programme had attempted to estimate vaccine coverage. In Spain (Valencia), Greece (Attiki) and Italy ad-hoc coverage surveys had been performed and coverage of between 20-50% achieved. When Spain implemented a regional programme in 1998 coverage quickly improved to over 90%.

5.3. Surveillance methods

In addition to variations in vaccination policy, surveillance methods varied between countries. There were, however, many common factors. Firstly, all countries with routine vaccination programmes shared the same objectives for their surveillance systems: to evaluate the impact of the vaccination programme. Secondly, all these countries had aimed to ascertain all cases of invasive Hib disease in the whole or the paediatric population. In addition, because all of the countries had experienced a fall in the incidence of disease to very low levels, concern about avoiding under-reporting had been expressed.

In the four countries that had not implemented routine vaccination at the start of the project, however, surveillance was more limited. Surveillance was confined to cases of meningitis (Italy and Poland) or to the population under five (Poland), or to one region (Spain and Greece).

In the pre-vaccine era, where the main objective of surveillance is to assess burden, it is probably a reasonable approach to monitor cases in children (who are likely to be the target population). In the post vaccine era, because of the concern about persistence of protection or the effects of reductions in carriage on the maintenance of herd immunity, surveillance in older people may be recommended. Those countries where surveillance in adults is performed, however, have not shown any increase in disease rates in older age groups. The number of cases, however, is likely to be very small and therefore, should an increase occur, it may take some time for the smaller countries to detect this change. By pooling data from several countries as part of the European project, we have a large adult population under surveillance. Any suggestion of an increase in Hib incidence outside of the age groups targeted for vaccination should be more easily detected and changes in surveillance recommended.

Surveillance of meningitis alone is likely to substantially under-estimate the burden of Hib infection. Adjustments need to be made to burden estimates to inform the introduction of routine vaccination.[102] To attempt to circumvent this, in 1996 Italy augmented its meningitis data by retrospective ascertainment in three regions of all culture-confirmed cases of invasive Hib with other clinical diagnoses. Sentinel surveillance of all invasive infections was then continued in 1997 and 1998. Despite this, rates in Italy were below those described in other countries pre-vaccine. This may reflect a genuinely low incidence, the impact of use of Hib vaccine in the private sector, or poor laboratory ascertainment. These possibilities have been discussed in the evaluation of the surveillance system.[97]

It is accepted that Hib meningitis surveillance is simpler and more cost-effective than surveillance of all invasive disease where resources are limited; this approach has been recommended by the World Health Organisation.[75] The other advantage with meningitis surveillance is that data on other causes of infection may be obtained and can be used to inform decisions about the use of other vaccines – including meningococcal and pneumococcal conjugate vaccines.[102] Surveillance of Hib meningitis has also been recommended as a feasible means of monitoring the impact of vaccination.[102] As we have shown, the pattern of clinical diagnosis in invasive Hib disease does not seem to have changed following implementation of routine vaccination programmes and meningitis is still the predominant diagnosis for Hib infection in children. Hib meningitis surveillance may therefore be adequate to monitor the impact of vaccination in children, but in adult populations under surveillance the inclusion of other diagnoses is desirable.

Another interesting difference in case disease categories is the inclusion of cases of epiglottitis where no microbiological evidence of Hib infection is found. Although data on such cases was excluded from our data set for comparison purposes, cases with a clinical diagnosis of epiglottitis are included in the surveillance of Hib disease in Australia. In the pre-vaccine era, the vast majority of cases of clinical epiglottitis are due to Hib[37; 103] and the reduction in cases of clinical epiglottitis from pre-vaccine levels [104-108] suggests that clinically defined cases of epiglottitis can be used to augment case ascertainment of Hib disease. The predictive value of epiglottitis, however, as a marker of Hib infection in the post-vaccine era has not been evaluated. It may be expected that when true Hib infection declines, the proportion of clinical epiglottitis due to other infections will increase. This aspect needs to be evaluated before the inclusion of clinical cases of epiglottitis can be recommended.

5.4. Laboratory methods

In all of the countries with established national vaccination programmes, a high proportion of laboratories were able to identify *H. influenzae* and would test specimens from most cases of invasive disease. Although in some countries a minority of laboratories would type all isolates, in most countries with national programmes, apart from Sweden, a very high proportion of isolates were referred to the national or regional reference laboratory. In Sweden, only isolates from vaccine failures were consistently referred to the reference laboratory. In Spain (Valencia) and Greece (Attiki) surveillance was based in a single region and a small number of laboratories – this enabled a high proportion of isolates to be typed in a reference laboratory.

In Italy, at the time the project started, a low proportion of laboratories were able to identify *H. influenzae*, and most would normally only look for the organism in cases of meningitis. In addition, few laboratories would refer isolates to a national reference laboratory. This failure of identification at primary sites is likely to lead to substantial under-ascertainment of cases of invasive Hib disease. An active surveillance project in Italy did suggest that the rate of disease obtained from routine surveillance would substantially under-estimate the true burden of infection.[45] As previously discussed, this may have explained the low rates of disease observed in Italy in 1996.[45] As part of the enhanced regional surveillance, identification capacities from sterile sites and referral of isolates to the national reference laboratory have improved in 1997 and 1998.

Once an isolate reaches the reference laboratory, different methods for identifying the organism were being employed by the study participants. At the first workshop it was concluded that all methods were adequate for the majority of specimens, but that a quality assurance exercise should be conducted. The results of the first quality assurance round of

specimens did show some organism misidentification but the errors were felt unlikely to lead to substantial misclassification of *H. influenzae* as b or non-b. A second round was conducted in 1998 and a third in 1999. Following the laboratory workshop on the identification of isolates held in 1997, substantial improvement was observed in the final QA round.

5.5. Epidemiology of Hib during the study period

Retrospective data was provided from pre-vaccine era for six countries. Pre-vaccine rates compare with published studies for all countries. For the three countries that did not have a programme at the start of the project, rates of disease in 1996 were lower than pre-vaccine rates and published rates in other countries. All three countries were in southern Europe and it has been suggested that rates in such countries are genuinely lower.[109] Other explanations include problems with ascertainment and the effect of vaccine use in the private sector.

In most countries, national vaccination had been implemented between two and five years before data collection occurred in this project. Despite this, over the period of the study, the incidence of Hib infection continued to decline in all age groups, in children under 15 and in children under 5 years with each year of the study. An increase was noted in the proportion of cases in children under one year of age, but the actual incidence also declined in each year of the study. This proportionate increase therefore reflected the greater reduction in cases in children aged 1-4 years – the main age groups eligible for vaccination. Even in children aged less than three months, although numbers of cases were fairly small, the incidence declined in each year. These young children, who are either not scheduled for vaccination or may have received a single dose, may be getting indirect protection from reduced exposure to infection transmitted by older children.

By 1998, the lowest rates of disease in children under fifteen years and under five years were observed in countries with high vaccine coverage (above 90%). In Ireland, and Australia rates were slightly higher –probably due to coverage being between 80 and 90%. Rates were also high in Greece and Italy – but perhaps lower than expected given the substantially lower coverage in these countries. Pre-vaccine rates in Greece were lower than observed in northern Europe,[30; 107] and similar to those observed in many parts of Spain (J Campos personal communication). It has been suggested that rates of Hib are lower in southern than northern Europe,[72]and this may explain the low baseline rates in both Italy and Greece. This may, in turn, explain why the rates observed in both Greece and Italy in 1998 are not substantially higher than in countries with national programmes.

In 1996, the sex distribution of cases reported in the project reflected that described in Europe in the pre-vaccine era.[14; 17; 47] In 1997 and 1998, however, the number of male and female cases was even. A lower male:female ratio was observed in Australia in the pre-vaccination period,[33-35] but this was not seen during this project. A study of *H. influenzae* in the under five year old population before the introduction of the programme in the Northern Territory, Australia, showed that, although an equal number of cases occurred in males and females, there was a predominance of cases in Aboriginal girls and in non-Aboriginal boys.[21] The different sex ratio in Australia may have reflected a different epidemiology in the Aboriginal population. The absence of a sex difference in the latter two years of the study suggests that any excess risk associated with gender has become largely unimportant following the dramatic impact of vaccination.

5.6. Clinical features of Hib disease

In 1996-8, the distribution of Hib cases by clinical diagnosis shows meningitis remains the dominant clinical diagnosis. Septicaemia was the next commonest presenting disease followed by epiglottitis. Little difference was observed between countries in the distribution of diagnoses. A slightly higher proportion of cases of epiglottitis was observed in Australia than elsewhere. Considerable published literature has shown the dominance of epiglottitis in the Hib disease clinical diagnoses in children under five years of age in Australia, [33-35] and no full explanation appears to yet be available for this occurrence. It may reflect inclusion of cases of epiglottitis that are not confirmed as Hib infection by laboratory criteria. In this study, such cases were excluded but a high proportion of cases of epiglottitis was still observed in Australia. The distribution of diagnoses, however, was strongly related to age; meningitis was the commonest presenting diagnosis in children, whereas septicaemia and pneumonia predominate in adults. Epiglottitis is most common in older children between 1 and 14 years. This may partly explain differences between countries and differences in the distribution of diagnoses may be explained by different vaccine coverage in certain age groups. Unfortunately the numbers of cases are too small to fully examine this hypothesis.

5.7. Impact of Hib vaccination programmes

Published studies from all countries in the period prior to introduction of the Hib vaccination programmes enable incidence rates at that time to be compared to the rates seen after introduction of the programmes. Dramatic reductions in the rates (at least ten-fold) were observed in all countries[14-17; 21; 33; 35; 110]

Our study confirms that the epidemiology of invasive Hib disease in Australia, Finland, Ireland, Israel, the Netherlands, Sweden and UK (England & Wales), has changed dramatically since the introduction of national immunisation programmes. Compared with pre-vaccine publications, all countries that had introduced vaccination, had experienced huge reductions (between 87-99%) in the incidence of infection. The magnitude of the decreases in the incidence of Hib varied between the participant countries, and appeared largely to reflect the proportion of the pre-school population who have been vaccinated. Overall, the control of the disease (% reduction, current incidence) is not shown to be any greater in those countries using 4 doses than in those using 3 doses.

Several countries were able to provide sequential data from pre- to post-vaccine eras. This data indicated that in Finland, a dramatic fall in disease incidence was observed prior to vaccine implementation. This was attributed to widespread use of vaccine as part of pre-licensure trials. The fall in disease incidence occurred within two or three years of implementation in all other countries. There was a suggestion that reduction occurred slightly more quickly in the UK than in the Netherlands – this was probably due to the additional benefit of catch-up vaccination. The rapid fall in disease incidence also occurred quickly in Israel – this may have been due to use of vaccine in the private sector prior to implementation of the national programme. Alternatively, it may reflect the different age distribution of invasive disease prior to vaccine implementation and the rapid achievement of high coverage in the age group at most risk. In contrast, in the Netherlands, where the peak age of disease prior to vaccine implementation was expected to be similar to the pattern in Western Europe, it would take longer for vaccinated cohorts to reach the time of peak incidence.

5.8. Other Haemophilus infections

Following the introduction of routine Hib immunisation into a country there is a dramatic fall in the number of cases of invasive Hib disease. Hib vaccine does not prevent infections caused by non-capsulated *H. influenzae* (ncHi) or non-b capsulated strains of *H. influenzae*. Theoretically the incidence of such infections might increase as these strains fill the ecological niche vacated by Hib.

We have therefore studied the epidemiology of non-b *H. influenzae* infections in Europe during the course of our collaborative study. All of the strains included in the report are derived from invasive infections i.e. the organisms were recovered from a normally sterile site. All of the strains have been confirmed by a national reference laboratory and serotyped, and in some cases typed using molecular methods.

From the countries that serotyped a high proportion of non-type b *H. influenzae* cases, non-capsulated organisms formed the vast majority of non-type b infections. There was a slight increase in such cases over the study period but the estimated incidence of non-capsulated infections remains low and is still lower than the pre-vaccine incidence of type b infection (particularly in children). Amongst non-capsulated infections a different distribution of clinical diagnoses was seen. Whilst meningitis comprised 56% of the clinical diagnoses in the cases of type b *H. influenzae*, it made up a smaller proportion of non-capsulate infections. In addition, the age breakdown of cases was different - particularly for meningitis - with the majority of cases occurring in older children and adults.

Amongst infections due to capsulated organisms other than type b, type f was the predominant capsular serotype with very small numbers of types a, c, d and e. In children, the clinical picture of these infections resembled those for type b and differed from those of non-capsulated infections. The numbers of such infections were small and the incidence remained extremely low over the study period.

Case fatality rates were also higher for non-capsulated and non-b capsulated Hi infections than they were for Hib infections. It is possible that this reflects a higher rate of underlying disease in those who develop disease due to non-capsulated and non b capsulated Hi. This was not specifically addressed in this study.

5.9. Laboratory quality assurance

The laboratory quality assurance scheme demonstrated that some laboratories provided excellent results throughout the study. Other laboratories showed a marked improvement as the study has proceeded. The majority of laboratories are now reporting a very high standard of identification. The scheme has identified some problems, with the use of slide

agglutinations for serotyping. The results are easy to misinterpret because of the problems with non-specific agglutination, cross-reactions and auto-agglutination. The use of a PCR-based genotyping method will provide a serotype/genotype for strains giving inconclusive results on slide agglutination. Ideally a genotyping method should be used for all *H. influenzae* isolates from cases of Hib vaccine failure.

5.10. Vaccine efficacy

As part of this EU funded collaboration, comparable data on the epidemiology of Hib before and after the introduction of vaccination has been obtained from several countries. All countries that have used Hib vaccine have shown a substantial reduction in the incidence of Hib infection from pre-vaccine levels. Comparison of the impact of vaccine between countries is difficult for three main reasons. Firstly, prior to the introduction of Hib vaccine the incidence of Hib infection varied substantially between countries. Secondly, routine vaccination coverage of Hib vaccine, where it is known, ranged widely. Thirdly, differences in the length of time since vaccine introduction and the method of vaccine introduction means that the number of cohorts of children immunised in each country differs. These differences mean that a straightforward comparison of incidence rates in a given year is problematic. In three countries an attempt to measure efficacy has been made by comparing observed cases in vaccinated children with those expected from pre-vaccine rates.[39; 69; 72] This has consistently demonstrated high efficacy but the method cannot separate the direct protection from vaccination from the indirect effect of high herd immunity. Without such separation, the potential for comparison between vaccines and schedules used in different countries is impossible.

To circumvent this, an attempt was made to estimate the direct effect of vaccination by comparison of the current incidence rate of disease in vaccinated and unvaccinated individuals. We chose to use the screening method because it is a useful, economical way of estimating vaccine efficacy from routine data. Case control studies are more expensive, and have potential biases due to the selection of controls. Cohort studies are very expensive for rare diseases and are the most appropriate method in outbreak investigations only in defined communities (such as schools) - this type of outbreak is unlikely to occur with Hib infection.

When using this method it is important to be aware of the possible biases and to adjust for them or to minimise them where possible. Many of the potential biases mentioned are not specific to the screening method; they also apply to case control and cohort studies. The main biases specific to the screening method are those concerned with estimating coverage. The vaccine efficacy estimates obtained should therefore be interpreted carefully in the context of the accuracy of the coverage data.

Using the screening method, Hib vaccine efficacy both overall and in those five countries with a sufficient number of cases to make analysis valid was high. Efficacy was slightly lower than pre-licensure evaluations and than estimated by comparing the number of observed cases with the number of cases expected from pre-vaccine rates.[39; 69; 72] Lower efficacy was observed in Australia and Ireland, but this may be explained by problems with the coverage estimates provided for the study. More credible estimates of efficacy were obtained in younger children in Australia where the coverage estimates had been improved by the introduction of a national register.

The importance of using accurate estimates of coverage and of partial coverage for this analysis cannot therefore be over-emphasised. More accurate vaccination coverage data, by dose and at various ages under the age of one would allow more sophisticated evaluation of efficacy. Pooling of data on vaccine failures and knowledge of factors associated with vaccine coverage will also facilitate a more valid interpretation of the data generated. Bearing in mind the potential problems, further analysis is required to determine if there may be additional benefit from a booster dose of vaccine. Numbers are small, however, and findings should therefore be interpreted with caution. The data does suggest, however, that vaccine efficacy may decline with age, but this finding may be explained by the mechanism of vaccine action.

Participants have reviewed the data presented and, where possible, improvements to existing data sources (in particular to the estimates of coverage) are planned. Future analysis may be restricted to age groups in which coverage data is felt to be accurate. Data on the likely magnitude of any errors will also be provided by study participants and used to modify estimates or to perform sensitivity analysis.

By continuing data collection prospectively, it is hoped that sufficient numbers of cases will be accrued to re-analyse the vaccine efficacy in cohorts where accurate coverage is known. This will then allow comparison of different vaccines and schedules to inform all countries using or planning to use Hib vaccine.

5.11. Vaccine failures

Other than in UK (England & Wales) and Australia the numbers of cases of vaccine failure are small and it is too early to generalise about the impact of different schedules. Similar numbers of cases of Hib disease in vaccinated children have been reported over the 3 years of the surveillance study. Amongst those countries with national vaccination programmes, the incidence of vaccine failures is greatest in Australia. Australia also had the largest numbers of apparent vaccine failures (children infected after one dose of vaccine) which may be a reflection of a higher circulation of Hib in this population. This in turn will be affected by how long a vaccination programme has been in place, the coverage achieved and the schedule used. These factors also dictate the different proportion of total Hib cases which occur in vaccinated individuals so that this figure is highest in those countries where a larger proportion of children have been vaccinated. This proportion is likely to increase in future years and collection of risk factor information on such cases will form an important component of the future work of this network.

It is of interest to note that even three doses of Hib vaccine in infancy plus a booster in the 2nd year of life can be associated with vaccine failure. This supports the suggestion that host factors may be important in vaccine failure. Vaccine failure appears to occur because of inadequate concentrations of circulating anti-PRP antibody when Hib is encountered. Underlying clinical and immunological factors are present in a proportion of cases and may predispose to vaccine failure. The convalescent antibody response to Hib disease is poor in a proportion suggesting an underlying problem with anti-polysaccharide antibody responses and a theoretical risk of further episodes of Hib disease. Fortunately the response to a booster dose of conjugate vaccines in such individuals is satisfactory and therefore, it seems reasonable to offer an additional dose of vaccine to those children who develop disease despite prior vaccination.

6. OUTCOMES OF THE STUDY

6.1. Laboratory standards

This project has been successful in improving laboratory standards in participant countries. This has been achieved through the provision of training fellowships and a laboratory workshop and has been demonstrated by the improvement in the performance in the quality assurance. The QA has also demonstrated the importance of using molecular techniques to confirm typing results – particularly in vaccine failures. Many of the participant countries have now established such techniques in their own laboratories.

6.2. Establishment of network

This project has established an active network of individuals from different disciplines (epidemiology, paediatrics, and microbiology) with an interest in Hib and Haemophilus infections. This provides a basis for future work and for further research collaboration. This network could also act as a model for networks focussing on other vaccine preventable infections or other invasive infections such as meningococcal and pneumococcal disease. The likely availability of conjugate vaccines for the latter two infections makes the development of such networks important.

6.3. Dissemination of study results

Study results have been disseminated at international conference and informally by study participants and via international organisations such as the World Health Organisation. Further peer-reviewed publications are planned.

6.4. Added value for participant countries

Comparison of data and discussion of methods has lead to the evaluation and developments in both surveillance and laboratory methods in many participant countries. Information has also been provided for vaccine policy, and access to network resources and training will improve the quality of surveillance in each country.

6.5. Other developments

The project has also generated European added value by increased collaboration in the field of public health and by improved knowledge (via the dissemination of information). The harmonisation of surveillance methods by the adoption of agreed case definitions, laboratory techniques and comparable analysis will benefit other countries outside the collaboration who may be establishing new surveillance schemes or considering introduction of vaccine.

7. RECOMMENDATIONS

7.1. Continuation of prospective surveillance

Despite the different methods of surveillance of Hib disease and different implementation of vaccination programmes, invasive Hib disease in children in these countries has fallen. The ability to compare the impact of vaccination in different countries will require on-going data collection and expansion of the network to include other EU and non-EU countries. This will increase the population under surveillance, the number of cases identified and the power of any future analysis. Further analysis may enable comparison of vaccines and schedules but will require accurate estimates of vaccine coverage.

7.2. Improvement of data on vaccine coverage

One of the major weaknesses demonstrated in this project has been in the quality of information on vaccine coverage. It is disappointing that some countries had no data on vaccine coverage at all. Improved data on vaccine coverage would be useful for all vaccine preventable infections. As part of future DGV projects on vaccine preventable disease, data on coverage will be collected for all EU countries. It is hoped that this may encourage improvements in the accuracy of information available.

7.3. Establishment of similar networks for other infections

Collaboration in this study has helped in the evaluation and development of surveillance for Hib. In retrospect, it would have been better if standard collection of data had preceded the implementation of vaccination programmes. With this is mind, a DGV proposal has been submitted to collect information on meningococcal and Hib infections. The proposal builds on the existing data collection for meningococcal disease but follows the model of this Hib project by including components on describing the surveillance system and improving laboratory capacity. In future, this network could easily be expanded to collect information on pneumococcal infection. Collection of baseline data prior to the implementation of conjugate vaccination against meningococcal and pneumococcal infection will allow better comparison of the impact of implementation in member states.

7.4. Dissemination of the study results to a wider audience

We hope that the results of the Hib project so far will be disseminated via several publications. In addition, copies of the report will be circulated widely to participant countries, to non-participant countries and to international organisations.

8. ACKNOWLEDGEMENTS

The co-ordinating team would like to thank all of the participants and the participating organisations for providing data, attending meetings and contributing to the success of the project.

In addition we would like to acknowledge the support of Wyeth-Lederle, Pasteur Merieux and WHO Geneva who helped to finance attendance from countries outside of the European Union.

9. PARTICIPANTS

UNITED KINGDOM (GB)

Dr Mary Ramsay
PHLS CDSC
61 Colindale Avenue
LONDON NW9 5EQ
Tel: 020-8200 6868 Ext 4085
Fax: 020-8200 7868
E-mail: mramsay@phls.org.uk

Ms Shirley Boland
PHLS CDSC
61 Colindale Avenue
LONDON NW9 5EQ
Tel: 020-8200 6868 Ext 4084
Fax: 020-8200 7868
E-mail: sboland@phls.org.uk

Dr Amal Rushdy
PHLS CDSC
61 Colindale Avenue
LONDON NW9 5EQ
Tel: 020-8200 6868 Ext 4459
Fax: 020-8200 7868
E-mail: arushdy@phls.nhs.uk

Mr Nick Andrews
PHLS CDSC
61 Colindale Avenue
LONDON NW9 5EQ
Tel: 020-8200 6868 Ext 4419
Fax: 020-8200 7868
E-mail: nandrews@phls.org.uk

Ms Sarah Handford
PHLS CDSC
61 Colindale Avenue
LONDON NW9 5EQ
Tel: 020-8200 6868 Ext 4499
Fax: 020-8200 7868
E-mail: shandfor@phls.org.uk

Dr Mary Slack
Consultant Microbiologist
PHLS Haemophilus Reference Laboratory
Public Health Laboratory
John Radcliffe Hospital
OXFORD OX3 9DU
Tel: 01865-220859
Fax: 01865-220890
E-mail: mary.slack@ndp.ox.ac.uk

Dr Paul Heath
Senior Lecturer/Honorary Consultant
Department of Child Health
St. George's Hospital Medical School
Tooting
London SW17 ORE
Tel: 020-8725 5980
Fax: 020-8725 2858
E-mail: pheath@sghms.ac.uk

Miss Jane Moore
Medical Laboratory Scientific Officer (2)
University of Oxford
John Radcliffe Hospital
Oxford OX3 9DU
Tel: 01865-220879
Fax: 01865-220890

ITALY (IT)

Dr Alberto Eugenio Tozzi
Reparto Malattie Infettive
Laboratorio di Epidemiologia e Biostastitica
Istituto Superiore di Sanita — Tel: +390-6-4938-7215
Viale Regina Elena, 299 — Fax: +390-6-4938-7292
ROME 00161 — E-mail: tossi@iss.it

Dr Marta Ciofi delli Atti
Reparto Malattie Infettive
Laboratorio di Epidemiologia e Biostastitica
Istituto Superiore di Sanita — Tel: +390-6-4938-7212
Viale Regina Elena, 299 — Fax: +390-6-4938-7292
ROME 00161 — E-mail: ciofi@iss.it

Dr Marina Cerquetti
Laboratorio di Bacteriologiae Micologia Medica
Istituto Superiore di Sanita — Tel: +390-6-4990-2343
Viale Regina Elena, 299 — Fax: +390-6-4938-7112
ROME 00161 — E-mail: mcerquet@iss.it

Dr Marina Casini Lemmi
Ospedale Galliera
Laboratoy Centrale
Via Mura Delle Cappuccine 14 — Tel: +390-10-563-2327
16128 Genova — Fax: +390-10-563-2699
ITALY — E-mail: romano@galliera.it

Dr Paola Mastrantonio
Laboratorio di Bacteriologia e Micologia Medicale
Istituto Superiore di Sanita — Tel: +390-6-4990-2335
Viale Regina Elena, 299 — Fax: +390-6-4938-7112
ROME 00161 — E-mail: pmastran@iss.it

SPAIN (ES)

Dr Javier Diez Domingo
G.V. FDO.
Catolico 76 E6
IZDA 46008
VALENCIA
Tel: +349-6-367-5562
Fax: +349-6-367-5562
E-mail: jdiez@ctv.es

Dr Concha Gimeno
Instituto Valenciano de Microbiologia
Masia El Romeral
Ctra. de Betera a San Antonio
de Benageber, Km 0.3
Betera
VALENCIA 46117
Tel: +349-6169-1702
Fax: +349-6169-1637
E-mail: -

Dr Jose Campos
Jefe de Area de Diagnostico
Centro Nacional de Microbiologia
Ctra. Majahonda-Pozuelo Km 2.5
Majahonda
MADRID 28220
Tel: +349-1509-7901 Ext 3643
Fax: +349-1509-7966
E-mail: jcampos@isciii.es

Dr Nuria de la Muela
c/Actor Mora 26
46009 Valencia
SPAIN
Tel: +346-1691702
Fax: +346-1691637
E-mail: concepcion.gimeno@uv.es

Dr Victoria Domingues
c/Actor Mora 26
46009 Valencia
SPAIN
Tel: +346-1691702
Fax: +346-1691637
E-mail: concepcion.gimeno@uv.es

Dr Amparo Morant
Direccio General dei Servie Valcia de Salud
Direccio Atencio Primaria Arees
C/Flora, 7-acc.dupl
VALENCIA 46010
Tel: +349-6362-4792
Fax: +349-6393-1229
E-mail: ipereiro@san.gva.es

THE NETHERLANDS (NL)

Dr Marina Conyn-van Spaendonck
Department of Infectious Diseases Epidemiology
National Instit. of Public Health & Environ. Protection
P.O. Box 1
Antonie van Leeuwenhoeklaan 9
BILTHOVEN BA-3720
Tel: +31-30-274-3018
Fax: +31-30-274-4409
E-mail: ciemc@rivm.nl

Dr Lodewijk Spanjaard
Academic Medical Center
Department Medical Microbiology and
Netherlands Reference Laboratory
for Bacterial Meningitis
P.O. Box 22660
1100 DD AMSTERDAM
Tel: +31-20-566-9111 tracer 59 143
Fax: +31-20-697-9271
E-mail: L.spanjaard@amc.uva.nl

FINLAND (FI)

Leena Kuisma
National Public Health Institute
310 90101 Oulu
FINLAND
Tel: +358-8-537-6246
Fax: +358-8-537-6251
E-mail: leena.kuisma@ktl.fi

Tarja Kaijalainen
National Public Health Institute
PL 310 90101 Oulu
FINLAND
Tel: +358-8-537-6249
Fax: +358-8-537-6251
tarja.kaijalaine@ktl.fi

Dr Juhani Eskola
Department of Infectious Diseases Epidemiology
National Public Health Institute
Mannerheimintie 166
HELSINKI FIN-00300
Tel: +358-9-474-4231
Fax: +358-9-474-4675
E-mail: juhani.eskola@ktl.fi

Dr Marja Leinonen
National Public Health Institute
Oulu Osasto
PO Box 310
Aapistie 1
OULU FIN-90101
Tel: +358-8-537-6235
Fax: +358-8-537-6251
E-mail: maija.leinonen@ktl.fi

Eija Kela
National Public Health Institute
Mannerheimintie 166
HELSINKI FIN-00300
Tel:
Fax: +358-9474-4468
E-mail: eija.kela@ktl.fi

Dr Elja Herva
National Public Health Institute
Oulun Osasto, Box 310
Aapistie 1
FIN - 90101
Oulu
FINLAND
Tel: +358-8-537-6251
Fax: +358-8-537-6210
E-mail: elja.herva@ktl.fi

GERMANY (DE)

Dr Anette Siedler
Robert Koch-Institute
FG21/Epidemiologisches Datenzentrum
General-Pape-Str. 62
D-1210 Berlin
GERMANY
Tel: +49-30-4547-3452
Fax: +49-30-4547-3514
E-Mail: siedlera@rki.de

GREECE (GR)

Professor Marie Theodoridou
Paediatric Clinic of the University of Athens
Aghia Sophia Children's Hospital
ATHENS 115 27
Tel: +30-1-7467-669
Fax: +30-1-7797-649

Dr Anastasia Pangalis
Department of Clinical Microbiology
Aghia Sophia Children's Hospital
ATHENS 115 27
Tel: +30-1-17770-152
Fax: +30-1-17770-152
E-mail: mecha.23@otenet.gr

IRELAND (IE)

Dr Jerry Fogarty
Department of Public Health Medicine
Western Health Board — Tel: +353-917-51131
Merlin Park Hospital — Fax: +353-917-55632
GALWAY

Dr Anne Moloney
Consultant Microbiologist
Regional Hospital — Tel: +353-5187-3321
Dunmore Road — Fax: +353-5187-9950
WATERFORD — E-mail: WalshMA@Sehb.ie

Dr Pat Mullhare
Microbiology Department
Waterford Regional Hospital
Waterford — Tel: +353-51-73321
IRELAND — Fax: +353-51-79950

SWEDEN (SE)

Professor Per Olcen
Department of Clinical Microbiology & Immunology
Orebro Medical Center Hospital — Tel: +46-19-15-1520
SE - 70185 — Fax: +46-19-12-7416
Orebro — E-Mail: per.olcen@orebroll.se

Dr Orjan Garpenholt
Department of Clinical Microbiology & Immunology
Orebro Medical Center Hospital — Tel: +46-19-15-1520
SE - 70185 — Fax: +46-19-12-7416
Orebro — E-Mail: per.olcen@orebroll.se

WHO

Dr Colette Roure
WHO Regional Office for Europe — Tel: +45-3917-1534
Scherfigsuej 8 — Tel: +45-3917-1851
COPENHAGEN DK-2100 — E-mail: cro@who.dk

COUNTRIES NOT FINANCED BY THE COMMISSION

AUSTRALIA (AU)

Dr Peter McIntyre
National Centre for Immunisation Research & Surveillance
P.O. Box 3515
Paramatta
NSW 2124 E-mail: peterm@nch.edu.au

Professor Geoff Hogg
Microbial Diagnostic Unit
Department of Microbiology
University of Melbourne Tel: +61-39-344-5685
Parkville Fax: +61-39-344-7833
VICTORIA 3052 E-mail: g.hogg@mdu.unimelb.edu.au

Professor Lyn Gilbert
ICPMR & New Children's Hospital
Level 3, ICPMR Tel: +61-2-9845-6238
Westmead Hospital Fax: +61-2-9893-8659
WESTMEAD NSW 2145 E-mail: lyng@cidm.wh.su.edu.au

Dr Anna Herceg
Public Health Division
Commonwealth of Australia Tel: +61-6289-8638
GPO Box 9848 Fax: +61-6281-7791
CANBERRA ACT 2601 E-mail: ana.herceg@hhlgcs.ausgovhhcs.telememo.au

POLAND (PL)

Dr Anna Skocynska
Sera and Vaccines Research
Central Laboratory
Ul. Chelmska 30/34 Tel: +48-22-625-4647
00-725 Warsaw Fax: +48-22-41-2949
POLAND E-mail: skozek@urania.il.waw.pl

ISRAEL (IL)

Professor Ron Dagan
The Paediatric Infectious Disease Unit
Soroka University Medical Centre
Beer Sheva 84101 Tel: 972-7-6400547
PO Box 151 Fax: 972-7-6232334
Israel E-mail: rdagan@bgumail.bgu.ac.il

PARTICIPATING INTERNATIONAL ORGANISATIONS

UK: Public Health Laboratory Service Communicable Disease Surveillance Centre
Public Health Laboratory Service Haemophilus Reference Unit
Oxford Vaccine Group

DE: Robert Koch-Institute

GR: Aghia Sophia Children's Hospital

IT: Istituto Superiore di Sanita (ISS)

ES: Unidad de Investigacion de Atencion Primaria (UIAP)
Centro Nacional de Microbiologia

NL: National Institute of Public Health & Environmental Health (RIVM)

FI: National Public Health Institute (NPHI)

IE: Western Health Board (WHB)

IL: The Paediatric Infectious Disease Unit

AU: National Centre for Immunisation Research & Surveillance

Observers

WHO: World Health Organisation Regional Office for Europe (WHO)

10. REFERENCES

1. Booy R, Hodgson S, Carpenter L, et al. Efficacy of *Haemophilus influenzae* type b conjugate vaccine PRP-T. *Lancet* 1994;**344**:362-366.

2. Eskola J, et al. Efficacy of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. *New England Journal of Medicine* 1987;**317**:717-722.

3. Black S, Shinefield H, Fireman B, Hiatt R, Polen M, Vittinghoff E. Efficacy in infancy of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in a United States population of 61 080 children. *Pediatric Infectious Disease Journal* 1991;**10**:97-104.

4. Santosham M, Wolfe M, Reid R, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of haemophilus influenzae type b polysaccharide and neisseria meningitidis outer-membrane protein complex. *New England Journal of Medicine* 1991;**324**:1767-1772.

5. Wenger J, Pierce R, Deaver K, Plikaytis B, Facklam R, Broome C. Efficacy of haemophilus influenzae type b polysaccharide- diphtheria toxoid conjugate vaccine in US children aged 18-59 months. *Lancet* 1991;**338**:395-398.

6. Ward J, Brenneman G, Letson G, Heyward W, and the Alaska H.Influenzae Vaccine Study Group. Limited efficacy of a *Haemophilus Influenzae* type b conjugate vaccine in Alaska native infants. *New England Journal of Medicine* 1990;**323**:1393-1401.

7. Peltola H, Kilpi T, Anttila M. Rapid disappearance of Haemophilus influenzae type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet* 1992;**340**:592-594.

8. Wallace R, Musher D, Septimus E, et al. *Haemophilus influenzae* infections in adults: charaterization of strains by serotypes, biotypes and B-lactamase production. *Journal of Infectious Diseases* 1985;**144**:101-106.

9. Shivley R, Shigei J, Peterson E, de la Masa L. Typing of *Haemophilus influenzae* by conventional slide agglutination. *Journal of Clinical Microbiology* 1985;**14**:706-708.

10. Blackwelder W, Storsaeter J, Olin P, Hallander H. Acellular pertussis vaccines. Efficacy and evaluation of clinical case definitions. *American Journal of Disease in Childhood* 1991;**145**:1-6.

11. Falla T, Anderson E, Chappell M, Slack M, Crook D. Cross-reaction of spontaneous capsule-deficient *Haemophilus influenzae* type b mutants with type-specific antisera. *Eur.J.Clin.Microbiol.Infect.Dis* 1993;**12**:147-147.

12. Murphy J. The introduction of Haemophilus influenzae type b (Hib) vaccine. *Irish Medical Journal* 1992;**85**:123-123.

13. Reinert P, Liwartowski A, Dabernat H, Guyot C, Boucher J, Carrere C. Epidemiology of *Haemophilus influenzae* type b disease in France. *Vaccine* 1993;**11**:S38-S42

14. Fogarty J, Moloney AC, Newell JB. The epidemiology of haemophilus influenzae type b disease in the Republic of Ireland. *Epidemiology & Infection* 1995;**114**:451-463.

15. Hargreaves R, Slack M, Howard A, Anderson E, Ramsay M. Changing patterns of invasive haemophilus influenzae diseases in England and Wales after introduction of the Hib vaccination programme. *BMJ* 1996;**312**:160-161.

16. Gilbert G. Epidemiology of *Haemophilus influenzae* type b disease in Australia and New Zealand. *Vaccine* 1991;**9**:S10-S13

17. Takala A, Eskola J, Peltola H, Makela H. Epidemiology of invasive *Haemophilus influenzae* type b disease among children in Finland before vaccination with *Haemophilus influenzae* type b conjugate vaccine. *Pediatric Infectious Disease Journal* 1989;**8**:297-301.

18. Hugosson S, Silfverdal S, Garpenholt O, et al. Invasive Haemophilus influenzae disease: Epidemiology and clinical spectrum before large-scale H. influenzae type b vaccination. *Scandinavian Journal of Infectious Diseases* 1995;**27**:63-67.

19. Broome C. Epidemiology of *Haemophilus influenzae* type b infections in the United States. *Pediatric Infectious Disease Journal* 1987;**6**:779-782.

20. Murphy T, Osterholm M, Pierson L. Prospective surveillance of H. influenzae type b disease in Dallas County, Texas and Minnesota. *Pediatrics* 1987;**79**:173-180.

21. Hanna J. The epidemiology of invasive *Haemophilus influenzae* infections in children under five years of age in the Northern Territory: a three-year study. *Medical Journal of Australia* 1990;**152**:234-240.

22. Jordens J, Slack M. Haemophilus influenzae: then and now. *Eur.J.Clin.Microbiol.Infect.Dis* 1995; **14**:935-948.

23. Shapiro E, Ward J. The epidemiology and prevention of disease caused by *Haemophilus influenzae* type b. *Epidemiologic Reviews* 1991;**13**:113-142.

24. Clements D, Gilbert G. Immunisation for the prevention of *Haemophilus influenzae* type b infections: a review. *Australian and New Zealand Journal of Public Health* 1990;**24**:828-834.

25. Peltola H, Kayhty H, Sinoven A, Makela P. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vacinnees 3 months to 5 years of age in Finland. *Pediatrics* 1997;**60**:730-737.

26. Madore D. Impact of immunization on haemophilus influenzae type b disease. *Infectious Agents and Disease* 1996;**5**:8-20.

27. Eskola J, Kayhty H. Ten years' experience with *Haemophilus influenzae* type (Hib) conjugate vaccines in Finland. *Reviews in Medical Microbiology* 1996;**7**:231-241.

28. Booy R, Moxon E. Immunisation of infants against *Haemophilus influenzae* type b in the UK. *Archives of Disease in Childhood* 1991;**66**:1251-1254.

29. Ward J, Brenneman G, Letson G, Heyward W. Limited protective efficacy on an H influenzae type b conjugate vaccine (PRP-D) in native Alaskan infants. *New England Journal of Medicine* 1990;**323**:1393-1401.

30. Tsolia MN, Theodoridou MN, Mostrou GJ, et al. Epidemiology of invasive Haemophilus influenzae type b infections among children in Greece before the introduction of immunization. *Scand J Infect Dis* 1998;**30**:165-168.

31. Sepkowitz S. Hair loss after immunization. *JAMA* 1998;**279**:117-118.

32. Dagan R. Epidemiology of invasive *Haemophilus influenzae* type b (Hib) disease in Israel. *Vaccine* 1993;**11**:S43-S45

33. McGregor A, Bell J, Abdool I, Collignon P. Invasive *Haemophilus influenzae* infection in the Australian Capital Territory region. *Medical Journal of Australia* 1992;**156**:569-572.

34. McIntyre P, Leeder S, Irwig L. Invasive *Haemophilus influenzae* type b disease in Sydney children 1985-1987: a population-based study. *Medical Journal of Australia* 1991;**154**:832-837.

35. Gilbert G, Clements D, Broughton S. *Haemophilus influenzae* type b infections in Victoria, Australia, 1985 to 1987. *Pediatric Infectious Disease Journal* 1990;**9**:252-257.

36. Hanna J, Wild B. Bacterial meningitis in children under five years of age in Western Australia. *Medical Journal of Australia* 1991;**155**:160-164.

37. Hugosson S, Olcen P, Ekedahl C. Acute epiglottitis - aetiology, epidemiology and outcome in a population before large-scale *Haemophilus influenzae* type b vaccination. *Clin.Otolaryngol.* 1994;**19**:441-445.

38. Olafsson O, Jonsdottir K, Barreto L, Hansen H, Sigthorsson T. The launch of an infant *Haemophilus influenzae* type b immunisation programme in Iceland. *Circumpolar Health 90* 1990;341-343.

39. van Alphen L, Spanjaard L, van der Ende A, Schuurman I, Dankert J. Effect of nation wide vaccination of 3-month-old infants in The Netherlands with conjugate *Haemophilus influenzae* type b vaccine: High efficacy and lack of herd immunity. *Journal of Pediatrics* 1997;**131**:869-73.

40. Voss L, Lennon d, Gillies M. Haemophilus influenzae type b disease in Auckland children 1981-87. *New Zealand Medical Journal* 1989;**102**:149-151.

41. Van Loock F, Rubbens C, Bauche P. Enquete sur I'incidence des infections invasives a haemophilus influenzae on communaute francaise de Belgigue 1990-1992. *Ministere de la Culture et des Affaires Sociales* 1993;1-10.

42. Gervaix A, Suter S. Epidemiology of invasive *Haemophilus influenzae* type b infections in Geneva, Switzerland, 1976 to 1989. *Pediatric Infectious Disease Journal* 1991;**10**:370-374.

43. Brewster D. The epidemiology of *Haemophilus influenzae* invasive disease in Scotland prior to immunisation. *Health Bulletin* 1993;**51**:385-393.

44. Howard A, Dunkin K, Musser J, Palmer S. Epidemiology of *Haemophilus influenzae* type b invasive disease in Wales. *BMJ* 1991;**303**:441-445.

45. Tozzi A, Salmaso S, Ciofi degli Atti M, et al. Incidence of invasive *Haemophilus influenzae* type b disease in Italian children. *European Journal of Epidemiology* 1997;**13**:73-77.

46. Dagan R, and The Israeli Pediatric Bacteremia and Meningitis Group. A two-year prospective, nationwide study to determine the epidemiology and impact of invasive childhood *Haemophilus influenzae* type b infection in Israel. *Clinical Infectious Diseases* 1992;**15**:720-725.

47. Anderson E, Begg N, Crawshaw S, Hargreaves R, Howard A, Slack M. Epidemiology of invasive *Haemophilus influenzae* infections in England and Wales in the pre-vaccination era (1990-2). *Epidemiology & Infection* 1995;**115**:89-100.

48. Kristensen K, Kaaber K, Ronne T, Larsen S, Henrichsen J. Epidemiology of *Haemophilus influenzae* type b infections among children in Denmark in 1985 and 1986. *Acta Paediatr* 1990;**79**:587-592.

49. Fogarty J. Moving towards elimination of Hib disease in Ireland. *Forum* 1996;3-4.

50. Booy R, Hodgson SA, Slack MPE, Anderson EC, Mayon-White RT, Moxon ER. Invasive Haemophilus influenzae type b disease in the Oxford region (1985-91). *Arch Dis Child* 1993;**69**:225-228.

51. Valamri P, Kataja M, Peltola H. Invasive *Haemophilus influenzae* and meningococcal infection in Finland. A climatic, epidemiological and clinical approach. *Scandinavian Journal of Infectious Diseases* 1987;**19**:19-27.

52. Claesson B. Epidemiology of invasive *Haemophilus influenzae* type b disease in Scandinavia. *Vaccine* 1993;**11**:S30-S33

53. von Kries R, Windfuhr A, Lucking A, Helwig H. Preventing *Haemophilus influenzae* meningitis: Germany's experience. *Lancet* 1994;**344**:469-469.

54. Zielen S, Ahrens P, Hofmann D. Efficacy of Hib vaccine. *Lancet* 1994;**344**:828-828.

55. Spanjaard L, Bol P, Ekker W, Zanen H. The incidence of bacterial meningitis in the Netherlands - a comparison of three registration systems, 1977-1982. *Journal of Infection* 1985;**11**:259-268.

56. Talsma E, Conyn van Spaendonck M, Geubbels E, Suijkerbuijk A. *Paediatric surveillance of invasive infections by Haemophilus influenzae in 1995 in the Netherlands*. Netherlands: National Institute of Public Health and the Environment, 1996;1-35

57. Baker M, Martin D. Hib disease rate plummets following immunisation programme. *The New Zealand Public Health Report* 1995;**2**:13-14.

58. Herceg A. The decline of *Haemophilus influenzae* type b disease in Australia. *Communicable Diseases Intelligence* 1997;**21**:173-176.

59. Jonsdottir K, Hansen H, Guobjornsdottir H, et al. Epidemiology of invasive *Haemophilus influenzae* type b (Hib) disease in Iceland from 1974 and impact of vaccination programme launched in 1989. *Arctic Medical Research* 1994;**53**:619-621.

60. Garpenholt O, Silfverdal S, Hugosson S, et al. The Impact of Haemophilus influenzae type b vaccination in Sweden. *Scandinavian Journal of Infectious Diseases* 1996;**28**:165-169.

61. Hargreaves R, Slack M, Howard A, Ramsay M. *Report of the PHLS Regional Survey of invasive haemophilus Influenzae Disease in England and Wales 1990-1994*. PHLS, 1996;1-8

62. Heath P, Bowen-Morris J, Griffiths D, Griffiths H, Crook D, Moxon E. Antibody persistence and *Haemophilus influenzae* type b carriage after infant immunisation with PRP-T. *Archives of Disease in Childhood* 1997;**77**:488-492.

63. Veldhuijzen I, Conyn van Spaendonck M, Suijkerbuijk A, van Alphen L, Dankert J. *Three years of surveillance of invasive infections by Haemophilus influenzea after introducation of immunisation in the National Immunisation Programme*. Netherlands: 1997;1-36

64. Howard AJ, Dunkin KT, Millar GW. Nasopharyngeal carriage and antibiotic resistance of Haemophilus influenzae in healthy children. *Epidemiology & Infection* 1988;**100**:193-203.

65. Barbour ML, Mayon-White RT, Coles C, Crook DW, Moxon ER. The impact of conjugate vaccine on carriage of Haemophilus influenzae type b. *Journal of Infectious Diseases* 1995;**171**:93-98.

66. Takala A, Eskola J, Leinonen M. Reduction of oropharyngeal carriage of *Haemophilus influenzae* type b (Hib) in children immunised with an Hib conjugate vaccine. *Journal of Infectious Diseases* 1991;**164**:982-986.

67. Ramsay M, Slack M, Howard T, et al. *The impact of catch-up vaccination on pharyngeal carriage rate of Haemophilus influenzae type b*. 1996;1-4

68. Takala A, Peltola H, Eskola J. Disappearance of epiglottitis during large-scale vaccination with *Haemophilus influenzae* type b conjugate vaccine among children in Finland. *Laryngoscope* 1994;**104**:731-735.

69. Booy R, Heath P, Slack M, Begg N, Moxon E. Vaccine failures after primary immunisation with ***Haemophilus influenzae*** type-b conjugate vaccine without booster. *Lancet* 1997;**349**:1197-1202.

70. Teare E, Fairley C, White J, Begg N. Efficacy of Hib vaccine. *Lancet* 1994;**144**:828-829.

71. Rushdy A, Ramsay M, Heath P, Azzopardi H, Slack M. Infant Hib vaccination and herd immunity. *Journal of Pediatrics* 1998;

72. Dagan R, Fraser D, Roitman M, et al. Effectiveness of a nationwide infant immunization program against Haemophilus influenzae b. The Israeli Pediatric Bacteremia and Meningitis Group. *Vaccine* 1999;**17**:134-141.

73. Eskola J, Takala A, Kayhty H, Peltola H, Makela H. Experience in Finland with *Haemophilus influenzae* type b vaccines. *Vaccine* 1991;**9**:S14-S16

74. Jonsdottir K, Steingrimsson O, Olafsson O. Immunisation of infaants in Iceland against *Haemophilus influenzae* type b. *Lancet* 1992;**340**:252-253.

75. Levine O, Schuchat A, Schwartz B, Wenger J, Elliott J. *Generic protocol for population-based surveillance of Haemophilus influenzae type B*. Geneva: World Health Organization, 1996;1-25

76. Noah N, Connolly M. *Surveillance of Bacterial Meningitis in Europe 1995*. UK: Lederle-Praxis, 1996;1-43

77. Guerin N, Thiers G. *EUREPI: Research in Methodologies of Immunization Programmes Management in Europe Funded by the EC Medical Research Programme - Health Services Research*. Brussels: 1993;1-99

78. European Vaccine Manufacturers. *Study on vaccines for human use and their rational use in Europe and Worldwide* . European Commission, 1994;1-106

79. Anonymous. The European Commission COST/STD-3 Initiative on European Vaccine Research
Reports of the Expert Panels
Harmonisation of European Vaccination programmes. *Vaccine* 1996;**14**:611-623.

80. Banatvala J. Rubella - could do better. *Lancet* 1998;**351**:849-850.

81. Osborne K, Weinberg J, Miller E. The European Sero-Epidemiology Network. *Eurosurveillance* 1997; **2**:29-31.

82. Orenstein W, Bernier R. Surveillance in the control of vaccine-preventable diseases. In: Halperin W, Baker E, Monson R, eds. *Public Health Surveillance*. 1990;76-107.

83. Klaucke DN, Buehler JW, Thacker SB, et al. Guidelines for evaluating surveillance systems. *MMWR* 1988;**37**:1-18.

84. Declich S, Carter A. Public health surveillance: historical origins, methods and evaluation. *Bulletin of the World Health Organization* 1994;**72**:285-304.

85. Begg N, Miller E. Role of epidemiology in vaccine policy. *Vaccine* 1990;**8**:180-189.

86. Hall S, Nicoll A. The British Paediatric Surveillance Unit - a pioneering method for investigating the less common disorders of childhood. Report of a seminar held in June 1995. *Child: Care, Health and Development* 1998;**24**:129-143.

87. Anonymous. Expanded Programme on Immunization
Immunization schedules in the WHO European Region, 1995. *Weekly Epidemiological Record* 1995;**70**:221-227.

88. Guerin N, Roure C. Immunisation schedules in the countries of the European Union. *Eurosurveillance* 1995;5-7.

89. Henderson R, Sundaresan T. Cluster sampling to assess immunization coverage: a reveiw of experience with a simplified ampling method. *Bull WHO* 1982;**60**:253-260.

90. Dittmann S. Immunobiological preparations. In: Anonymous*Meyler's Side Effects of Drugs, 13th Edition*. Elsever Sceince B.V., 1996;918-961.

91. Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. *Bulletin of the World Health Organization* 1985;**63**:1055-1068.

92. Orenstein W, Bernier R, Hinman A. Assessing vaccine efficacy in the field
Further observations. *Epidemiologic Reviews* 1988;**10**:212-241.

93. Smith P, Rodrigues L, Fine P. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *International Journal of Epidemiology* 1984;**13**:87-93.

94. Farrington CP. Estimation of vaccine effectiveness using the screening method. *International Journal of Epidemiology* 1995;**22**:742-746.

95. Farrington C. Quantifying misclassification bias in cohort studies of vaccine efficacy. *Statistics in Medicine* 1990;**9**:1327-1337.

96. Macleod C. *Haemophilus influenzae*: the efficiency of reporting invasive disease in England and Wales. *Communicable Disease Report* 1994;**4**:R13-R16

97. Handysides S, Handford S. Unexplained low incidence of invasive Haemophilus influenzae type b infections in Italy. *Eurosurveillance Weekly* 1999;**3**:990616 http://www/eurosurv.org/1999/990616.html

98. Salmaso S, Rota MC, Ciofi DAM, Tozzi AE, Kreidl P. Infant immunization coverage in Italy: estimates by simultaneous EPI cluster surveys of regions. ICONA Study Group [In Process Citation]. *Bull WHO* 1900;**77**:843-851.

99. O'Brien H. Hib immunisation catch up programme in North East Thames. *Communicable Disease Report* 1994;**4**:R17-R18

100. Syrogiannopoulos G, Griva I, Beratis N. Haemophilus influenzae type B (Hib) vaccination and meningitis cases during the first two years in life in Southwestern Greece. *ESPID 99' Abstract Book of the 17th Annual Meeting of the European Society for Paediatric Infectious Diseases* 1999;**1999**:94(Abstract)

101. Tozzi, A., Salmaso, S., degli Atti, M., Panei, P., Anemona, A., Wassilak, S., and Greco, D. Incidence of invasive Haemophilus influenzae type b disease in Italy. 1-11. 1995. (GENERIC)
Ref Type: Report

102. Levine OS, Schwartz B. The rationale for population-based surveillance for Haemophilus influenzae type b meningitis. *Pediatr Infect Dis J* 1998;**17**:Suppl-8

103. Hanna J, Wild B, Sly P. The epidemiology of acute epiglottitis in children in Western Australia. *J.Paediatr.Child Health* 1992;**28**:459-464.

104. Wurtele P. Acute epiglottitis in children: Results of a large-scela anti-*Haemophilus* type B immunization program. *The Journal of Otolaryngology* 1995;**24**:92-97.

105. Hickerson S, Kirby R, Wheeler G, Schutze G. Epiglottitis: A 9-year case review. *Southern Medical Journal* 1996;**89**:487-490.

106. Gorelick M, Baker D. Epiglottitis in children, 1979 through 1992:
Effects of Haemophilus influenzae type B immunization. *Arch Pediatr Adolesc Med* 1994;**148**:47-50.

107. Valdepena H, Wald E, Rose E, Ungkanont K, Casselbrant M. Epiglottitis and *Haemophilus influenzae* immunization: The Pittsburgh experience-A five-year review. *Pediatrics* 1995;**96**:424-427.

108. Alho O, Jokinen K, Pirila T, Ilo A, Oja H. Acute epiglottitis and infant conjugate Haemophilus influenzae type B vaccination in Northern Finland. *Arch Otolaryngol Head Neck Surg* 1995;**121**:898-902.

109. Peltola H. Haemophilus influenzae type b disease and vaccination in Europe: lessons learned. *Pediatr Infect Dis J* 1998;**17**:Suppl-32

110. AnonymousHepatitis A and drug misuse in the West Midlands. *Commun Dis Rep Weekly* 1999;**9**:461& 464

11. APPENDICES

APPENDIX 1 - Questionnaires for surveillance, vaccination and laboratory methods

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 from each system?
(e.g. individual case collation, comparison of aggregate data, none etc.)

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?
(specifically is it Hib or all *H. influenzae,* meningitis or all invasive disease?)

1.3 Population

What is the population under surveillance?
(please specify by age and if not national by geographic distribution/proportion of population)

1.3 Type of surveillance system

What type of surveillance system is this?
(please specify if this is an active surveillance system or passive)

1.4 Start of surveillance system

When did this surveillance system start?
(please specify for how many years data is available)

Part B

2 Data collection

2.1 Information collected

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

2.2 Reporting sources

Who provides the data?
(please specify who reports the data used and where it is received from)

2.3 Time period

How frequently is the data collected?
(Please specify over what time period the data is collected e.g. weekly, monthly, annually etc.)

2.4 Data handling

How is the data handled from source to surveillance system?
(please specify how data is transmitted from source to surveillance system e.g. fax, phone, electronic etc..)

2.5 Duplicate reports

Are duplicates routinely detected and eliminated?

Part B

3 Data analysis

3.1 Analysis

Who analyses the data?

3.2 Frequency

How often is the data analysed?

3.3 Variables analysed

What variables are used in the analysis?
(please state what variables collected for the surveillance system are used in the analysis and what variables from outside the surveillance system are used e.g. denominator data)

3.4 Results of analysis

What results of the analysis are produced and how is the data presented?
(please specify standard tables, text, graphs etc.)

Part B

4 Data dissemination

4.1 Regular reports

4.1a Frequency

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

4.1b Method of reporting

How are the reports disseminated?
(please state if this is paper, fax, electronic etc.)

4.1c Audience

Who are the reports disseminated to?

4.2 Recent publications

Are there recent or relevant publications demonstrating application(s) of the surveillance system?
(please list any recent or relevant publications)

Part B

5 Evaluation and Development

5.1 Evaluation

Has the surveillance system undergone recent evaluation?
(please include a summary of any recent evaluation)

5.2 Development

Are any developments with the existing surveillance system planned in the next few years?

Hib Vaccination in Europe - Invasive *Haemophilus influenzae* infections
Hib vaccination programme questionnaire

Country: .....

Name of respondent: .....

Position: .....

Centre: .....

Address: .....
.....
.....

_____

The purpose of this questionnaire is to describe the Hib vaccination programmes in Europe.

Please attach any relevant reports and publications that illustrate the programmes or answers to questions.

1 Hib vaccination programme

1.1 Level of vaccination programme

Is Hib vaccination included in the national immunisation programme?
(please specify how it is given if it is not a national programme)

1.2 Incentives for vaccination

1.2a Legal requirement

Is Hib vaccination compulsory (by law) ?

1.2b Other incentives

Are there other incentives to Hib vaccination?
(please specify e.g. prohibited school entry etc..)

1.3 Introduction of Hib vaccination

When was Hib vaccination introduced?
(please state if this was graduated or all at once)

1.4 Target population

Who are the target population for Hib immunisation?
(please specify the age groups)

1.5 'Catch-up' population

Was there a 'catch-up' programme at the time of introduction of Hib vaccination?
(please specify the age groups that were targeted for the 'catch-up'?

1.6 Immunisation schedules

What immunisation schedule is followed for Hib vaccination in your country?
(please also state timing in relation to other vaccinations)

1.7 Immunisation co-ordinators

Are there nominated persons at designated geographical levels with responsibility administrating and co-ordinating the Hib immunisation programme?

2 Vaccine

2.1 Type of Hib vaccine

What Hib vaccine(s) is(are) currently in use?
(please specify the type of Hib vaccine, the manufacturer and the approximate proportion of the target population receiving each type if more than one)

2.2 Vaccine storage and distribution

Who is responsible for the storage and the distribution of the Hib vaccine?
(please specify responsibility at each level, local, regional, national etc., and how this is co-ordinated especially in maintaining the cold chain)

2.3 Registration for and scheduling of Hib vaccination

2.3a Registration for vaccination

Are children registered on for vaccination soon after birth?
(please specify if paper, computerised etc..)

2.3b Scheduling for Hib vaccination

Are children scheduled for vaccination based on this registration?

2.3c 'Call/recall' for Hib vaccination

Are children called and recalled for vaccination based on this registration?

2.4 Hib vaccine prescription

Who prescribes the Hib vaccine?

2.5 Hib vaccine administration

Who gives the Hib vaccine and where is it available?

2.6 Hib vaccine charges

Who pays for the Hib vaccine?
(please state if this is the state/public health system, insurance companies or parents)

3 Hib vaccination coverage

3.1 Vaccination status

Is data on an individuals Hib vaccination status held at local, regional or national level?
(please specify how these records are held e.g. paper, computerised etc.)

3.2 Vaccination coverage

3.2a Calculation methods

What method(s) are used to estimate/calculate vaccination coverage of Hib?

3.2b Data sources

What numerator and denominator data is used to estimate Hib vaccination coverage for each method?
(please state if this is routinely collected, special surveys etc.)

3.2c Frequency

How often is Hib vaccination coverage estimated?
(please state how often and to whom this information is disseminated.
please also specify to what smallest denominator this is done i.e. geographical breakdown/size of population)

3.2d Age and dosage

At what age is Hib vaccination coverage assessed and at how many dosages in the schedule?

3.3 Hib vaccination coverage

What are the Hib vaccine coverage estimates since the vaccination programme started?
(please state the yearly mean and range for geographical areas if possible)

4	Vaccine impact
Has the impact of the vaccination programme on cases of Hib been evaluated? (please specify the methods used to determine this or a summary of such an evaluation)	
5	**Adverse events**
Is there surveillance of adverse events of Hib vaccination? (please summarise if and how this is done)	

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.

Please return both sections of completed questionnaire to:-

Dr. Mary P.E. Slack
Haemophilus Reference Laboratory
Public Health Laboratory,
Level 6/7, John Radcliffe Hospital,
Headington,
Oxford, OX3 9DU
U.K.

(Tel: +44-1865-220879/220884 Fax: +44-1865-220890)

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 national/area 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 (please state origin
of blood used i.e. horse, sheep)
.....
.....
.....

Haemolysis (please state origin of blood used)
.....
.....
.....

Nitrate
If Yes, please state method
.....
.....
.....

Yes No
O.N.P.G.

Commercially available identification kit
(Please give details)
.....
.....
.....

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

2.3 Are the strains biotyped using the following tests?

Indole
Urease
Ornithine decarboxylase

2.4 Are the strains serotyped?

If so, which of the following methods are used:

Slide agglutination with polyvalent antisera
If yes, give details of antisera used
.....
.....
.....

Yes No

Slide agglutination with type specific antisera
If yes, give details of antisera used
.....
.....
.....
Counter current immunoelectrophoresis
PCR
If yes, give details of primers used
.....
.....
.....

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

Yes No

2.5 Are the strains further subtyped?
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?

Broth dilution
Agar incorporation
E-test (AB BIODISK)
Commercially prepared MIC microtitre trays
(If so, please give details of kit used)
.....
.....
.....
Other, please specify
.....
.....
.....

Yes No

2.7 Do you test for beta-lactamase production?
If yes, please state method used
.....
.....
.....

2.8 Do you test for chloramphenicol acetyltransferase (CAT) production?
If yes, please state method used
.....
.....
.....

2.9 Long term storage
How do you store strains long term?
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)

APPENDIX 2 - Summary results of the surveillance, vaccination and laboratory methods questionnaires

Hib Surveillance Systems in Europe - Results of Survey -November 1996

Country	Australia	Finland	Ireland	Italy	Netherlands	Spain (Valencia)	United Kingdom
Part A - 1. Surveillance methods							
1.1. Main surveillance methods	Laboratory and clinical	National Infectious Disease Surveillance - notif from microbiology labs and physicians (1985-1994 special surveillance for invasive infections in children from all labs)	Laboratory based system	Voluntary notification of meningitis with laboratory confirmation	Laboratory surveillance Paediatric (clinical) surveillance	No National System Valencia - vaccine institute has set up a surveillance system	Laboratory based Paediatric
1.2. Data Collation	Linked systems	Individual case collation		-	Anonymous record linkage at individual level		Individual case collation
Part B - 1. Hib Surveillance System							
1.1. Objectives	Hib Case Surveillance Scheme (HCSS) -To obtain information on invasive Hib disease not available to the National Notifiable Diseases Surv System (NNDSS) including outcome, vaccination status, to record vaccine failures and estimate vaccine efficacy	Universal case ascertainment	Universal case ascertainment. Burden of disease prior to national programme, now also vaccine failures.	Evaluation of incidence of Hib meningitis Evaluation of incidence rates by age-groups and geographical area	Universal case ascertainment. Registration of all paediatric cases of invasive disease (meningitis, sepsis, epiglotitis, arthritis, osteomyelitis, cellulitis) caused by H inf all serotypes (Jan 95)[type b since 10/93)	To know the incidence of Hib disease. To study risk factors. To study vaccine failures.	Universal case ascertainment. Epidemiological and microbiological impact of Hib vaccination. Antibiotic susceptibility of Hib.
1.2. Case Definition	Isolation of Hib from a normally sterile site **and/or** Identification of Hib antigen in CSF, urine or joint fluid with clinical features compatible with invasive Hib disease **and/or** A confident diagnosis of epiglotitis by direct vision, laryngoscopy or X-ray.	Positive culture of Hib from blood, CSF or other usually sterile site	All H. influenzae invasive disease	Clinical meningitis + Hib isolation	All invasive Hib disease from 1994 Hib meningitis before 1994 Registration of all paediatric cases of invasive disease (meningitis, sepsis, epiglotitis, arthritis, osteomyelitis, cellulitis) caused by H inf all serotypes (Jan 95)[type b since 10/93	All Haemophilus influenzae grown from normally sterile sites	Positive culture of Hib from a sterile site
1.3. Population under Surveillance	Whole Australian population	All ages, whole country	Population of Republic of Ireland (3.5M). Emphasis on <14 yrs.	Countrywide population (~57M)	All ages, whole country 1-14 years, national	Children under 15 yrs Valencian county (3.5M people)	Whole population
1.4. Type of Surveillance	NNDSS passive. Once reported, HCSS is active	Passive	Active surveillance for laboratories serving paediatric populations	Passive	Passive laboratory Active paediatric	Active	Passive mostly, active for <16yrs
1.5. Period of Surveillance	Hib on NNDSS since 1991 HCSS commenced 1993 Both ongoing	Special surveillance 1976-1994 National register from 1995	1/10/91 and is ongoing (retrospective data available nationally since 1987	January 1994	10/93 (type b) since 1/95 all serotypes still ongoing	1/12/95	National from 1978 Paediatric 1/10/95

Hib Surveillance Systems in Europe - Results of Survey -November 1996

Country	Australia	Finland	Ireland	Italy	Netherlands	Spain (Valencia)	United Kingdom
2. Data Collection							
2.1. Variables Collected	See attached HCSS form.	Personal identifiers Source of culture and date. hospital and lab identifiers	Name, age sex, DOB, date and site of isolate, clinical, outcome, vaccine history and batch, ant-PRP antibody, analysis of organism	See attached	Personal, hospital, clinical, vaccination, specimens, cultures, serotyping, ref lab.	From microbiologist: name, age disease, serotype if available From Paediatrician: clinical course, outcome and risk factors. Previous treatment.	Personal, laboratory, clinical and vaccination details (see attached)
2.2. Reporting Sources	Drs, Hosps, Labs report to Health Authorities who forward on to the Department of Health and Family Services (DHFS)	Physicians and labs	Microbiologists from labs	Hospital director where the patient was admitted	Hospital labs Paediatrician, data available from patient records	Paeds and microbiologists from all hospitals in Valencia	Laboratories Paediatricians
2.3. Time period	National reporting every two weeks	Ongoing	Twice monthly	Each time a case occurs	Monthly	Each time a micro-organism is collected	Ongoing
2.4. Data handling	NNDSS electronic HCSS paper	Physicians to the register- paper Lab to register- paper or electronic	Phone primarily	Diskette;fax;mail.	Initial report on postcard by paediatrician to surveillance centre, questionnaire sent to paed, returned by post.	Microbiologists fill in a questionnaire that is sent with the strain to the ref. lab. Paeds post their questionnaires	Paediatric- phone or card to centre and then questionnaire filled. Labs - electronic, paper
2.5. Duplicates eliminated	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Data Analysis							
3.1. Analysis - Who analyses	DHFS	KTL	Dr Fogarty	The Ministry of Health, the Instituto Superiore di Sanita	Investigator at RIVM reference laboratory	Vaccine Institute of Valencia - Drs Diez and Morant	PHLS CDSC and Ref Lab
3.2. Frequency of analysis	NNDSS every two weeks HCSS annually	Weekly, monthly and annually	Annually	Yearly	Yearly	Six monthly	Monthly reports Annual reports
3.3. Variables analysed	All variables analysed. Australian population estimates used to estimate rates	Age, sex, place of residence population statistics	Age, sex, clinical diagnosis, survival status. national population <5yrs from census data.	From the surveillance system: age, sex, residence, exposure to other cases Denominator data: Italian population by age, residence	Age, sex, clinical picture, data on serotyping, immunisation status	Number of cases, age, geographical distribution and disease (to date) Denominator: Number of official children <5yrs Number of vaccinated children will be obtained next month.	Age, sex, vaccination status
3.4. Results of analysis	Examples of reports attached	Cross tabulations (Hib cases by age, sex, presented in different districts)	See attached papers	Standard tables	Written report with tables and figures	Tables and Graphs. Data analysed once so far.	See attached

Hib Surveillance Systems in Europe - Results of Survey - November 1996

Country	Australia	Finland	Ireland	Italy	Netherlands	Spain (Valencia)	United Kingdom
4. Data Dissemination from the Hib Surveillance System							
4.1a. Regular Reports - Frequency	Fortnightly and annually	a) weekly Internet update b)monthly tables in KTL bulletin c) annual KTL reports	Annually	No regular reports	Yearly	Six monthly	Monthly - Communicable Disease Report(CDR) Annually - Paediatric report
4.1b. Method of reporting	Published in Communicable Disease Intelligence and presented at meetings	a) WWW b) Mthly newsletter c) Booklet	Paper and scientific meetings	-	Paper	Mailed	Paper
4.1c. Audience	Those involved in communicable disease control and a wider group of professionals	a) mainly physicians, all b) health care workers c) health administrators	Medical (GP, Paediatric, Public health, microbiologists) and paramedical nurse, technologists)	-	Health authority colleagues	Local co-ordinators Annual report will go to health authorities First report presented at a local meeting	CDR - labs, public health, paeds
4.2. Recent publications	Attached	New surveill system WWW Special Surveys - attached	See attached	Pattern of bacterial meningitis in Italy 1994 (in press)	Annual report 1994 Annual report 1995 due November. Publication in Dutch Journal	No	See attached
5. Evaluation and Development of the Hib Surveillance System							
5.1. Evaluation	Not recently	New system being evaluated	No	No	Yes, annual report 1995	System has been evaluated in relation to meningococcal disease with an under-reporting estimate of 4% Yearly the databases of the system and those to different microbiology and paediatric services will be compared	Yes, under-reporting - see attached
5.2. Development	Proposed to include Hib in the Australian Paediatric Surveillance Unit system to collect information from paediatricians on cases of invasive Hib and refer isolates.	No major revisions		Yes - check of hospital discharge diagnosis vs notifications.	-Immunological evaluation of vaccine failures -Intensified feedback to paeds in order to reach higher coverage		Lab developments -enhancing surveillance through labs -nontypable strains Other -extend childhood surv to all invasive strains not just vaccine failures

Netherlands

Paediatric Surveillance of Invasive infections by Haemophilus influenzae serotype b in 1994 in the Netherlands. ELPE Geubbels, MAE Conyn-van Spaendonck, AWM Suijkerbuijk. July 1995 RIVM

Finland

Ten Years' experience with Haemophilus type b (Hib) conjugate vaccines in Finland. Juhani Eskola and Helena Kayhty. Reviews in Medical Microbiology 1996; 7(4):231-241

Hib Vaccination Programmes in Europe - Results of Survey - November 1996

Country	Australia	Finland	Ireland	Italy	Netherlands	Spain (Valencia)	United Kingdom
1. Hib Vaccination Programme							
1.1. National programme	Yes	Yes	Yes	No national programme. Hib is recommended, some regions planning to implement local policies.	Yes	No - (one county only) Free on prescription	Yes
1.2a. Compulsory	No	No	No	No	No	No	No
1.2b. Other incentives to parents	Education programmes	No	No	No	No	No	No
1.3. Year of introduction	1992/93	1993 national (1986 trials)	October 1992	Hib vaccine licensed in 1995	April 1993	-	October 1992
1.4. Target population	<5 yrs	All infants at 4/12	<5 yrs	<5 yrs + hi risk groups	Born after 1/4/93 at 3,4,5 & 11 mths of age	-	<5 yrs
1.5. Catch-up programme	Yes	No	Yes	No	No	-	Yes
1.6. Immunisation Schedule	2,4,6,18 mths	4 (with DTP), 6 (with IPV), 14-18 mths (with MPR)	2,4,6 mths (DTP/DT+Hib+OPV)	Regions using it are: <6/12 - 3 doses + bdose 6-12/12 - 2 doses+bdose >12/12 - 1 dose	3,4,5,11 mths together with DTP-Polio (IPV) but in other limb	As recommended by the manufacturers (4 doses <12/12, I dose >12/12)	2,3,4 mths (DTP/DT+Hib+OPV)
1.7. Immunisation Co-ordinator	Yes	No	No, informal ones currently	No	Yes	-	Yes
2. Vaccines							
2.1. Type of Vaccine	2 (HbOC - Lederle 90%, PRP-OMP Merk Sharp)	1 (HbOC - Wyeth-Lederle)	1 (HIBTITER - Wyeth-Lederle)	2 (PRP-T > HbOC)	1 (PRP-T - Merieux)	2 (PRP-T Pasteur-merieux - 30%, HbOC - Lederle 70%)	3 (HibTiter, HibDTP-Pasteur Merieux 55%)
2.2. Storage and Distribution	State/Terr HA's distribute to providers who store on site.	KTL national storage & distribution, Local Public Health(PH) centres		Regional and local pharmacies, local vaccination centres	SVM/RIVM national distrib to provincial immunisation 'ent' administration. Local centres delivered on quarterly basis. Continuous temp. regulation	Pharmacists	NCIP national storage and distrib to local health centres and pharmacies.
2.3a. Registration for vaccination	Yes register for Medicare soon after birth onto the Australian Childhood Immunisation Register (ACIR) from 1996.	No	Yes - computerised	No	Yes - computerised after birth at municipality	-	Yes - computerised
2.3b. Vaccination Scheduling based on register	Not based on the register	No	Yes	No	Yes	-	Yes
2.3c. Call/recall	Reminders and recalls sent - varies by State	No	No -currently. Yes-with new system being introduced	No	Yes - invited to special healthy baby clinics	-	Yes
2.4. Vaccine prescription	National Programme. Occas. Med. pract.	National programme	-	Local vaccn centres Family paediatrician	Vaccine delivered to clinics from provincial 'ent' adminisn	Paediatricians, private or NHS	National programme
2.5. Vaccine administration	GP's, Public immn clinics, some hosps, Aborig. Med.Servs depending on the state.	Public Health Nurses at child health centres (CHC's)	GP's at GP surgeries and clinics	Local vaccination centres or Family Paediatrician after parents buy the vaccine from the pharmacy.	Doctors at clinics	By Paediatrician. Bought in chemists and admin by nurses in NHS. Some private paed have vaccine in their clinics	Nurses/GP's at GP surgeries Doctors at Child Health centres
2.6.Vaccine charges	Free<5yrs - Commonwealth Dept. of Hlth and Family Services	KTL (government), Free to PH centres and families	Health Board (state provision)	Parents usually pay. Some free of charge to hi-risk groups	General insurance (not private).	60% parents 40% state	Free state provision

Hib Vaccination Programmes in Europe - Results of Survey - November 1996

Country	Australia	Finland	Ireland	Italy	Netherlands	Spain (Valencia)	United Kingdom
3. Hib Vaccination Coverage							
3.1. Vaccination status recorded	Personal Health Record at clinic where vaccine given and on the ACIR.	Yes - Paper records at local level	Being computerised at local level	Public vaccn centres - Yes- paper and computer Paeds - certif. to parents (some paeds notify vaccn at a regional level)	Yes - computerised at regional level (ent administration)	No	Yes - computerised
3.2a. Vaccination coverage estimates - method	Past surveys relied on parent recall. ACIR from 1996 will be more accurate	Sentinel method (special surveys)	Data not usually available at national or regional level. systems being developed	No methods in use	Collation of data from 'ent' administr in a national report at specified municipal level	Clustering method - WHO	Hib doses given to children at district level
3.2b. Data sources: Numerator Denominator	National surveys. 1996- ACIR>98% of the Australian population are covered by Medicare	Special surveys in connection with sentinel surveys	Data not available	Doses administered by age at vaccination centre - data held regionally	Hib doses(3) by age(12/12) No. of children per birth cohort	-	 Doses given by age Birth cohorts
3.2c. Frequency of estimation and geographic region	Surveys every few years ACIR - will be able to do quarterly estimates	Every two years. Random sample of 34/1057 CHC's	Data not available	Vaccination centre reports to Ministry of Health biannually	Yearly report from Medical Inspectorate of Health	Not done before	Quarterly by district
3.2d. Age and Dosage of VC	Will be done with ACIR based on the immunisation schedule at different ages	Hib 2 at 12mths Hib 3 at 3yrs	Data not available	No methods in use	Hib 3 at 12mths	-	Hib 3 at 12 mths & 24 mths
3.3. Current coverage	National surveys 1995 1yr - 62%, 2yrs - 52% Sydney 1994, 3-59mths-77%	Hib 2 at 12mths - 98.8% Hib 3 at 3yrs - 96.6%	Data not available	Only recently licensed with no national programme - 0%	First report awaited. Currently using DTP/Polio as an estimate: 97%	-	Hib 3 at 12 mths - 94.8% Hib 3 at 24 mths - 95.2%
4. Hib Vaccine Programme Evaluation							
Evaluation of Hib Vacc Prog	Hib cases have declined see refs.	Yes, see ref.	Yes. See attached	No	Yes - based on surveillance	No	Yes see attached
5. Adverse Events of Vaccination							
Adverse Events monitoring	2 systems with under-reporting -Adverse Drug Reactions -Serious Adverse Events Following Vaccination	Notifications from vaccns (serious and unexpected adverse events)	Yes, as part of a general system - passive.	Passive surveillance, all physicians invited to notify adverse events to Ministry of Health	Report by phone to paed at RIVM who evaluates each report. All reports are reviewed and reported by the National Health Council	No	Passive via 'Yellow card scheme' reporting of adverse events to medicines.

Hib VACCINATION IN EUROPE

INVASIVE *HAEMOPHILUS INFLUENZAE* INFECTIONS.

	LABORATORY FACILITIES	**COUNTRIES PARTICIPATING IN STUDY**							
		AUSTRALIA (MELB.)	**AUSTRALIA (SYDNEY)**	**FINLAND**	**IRELAND**	**ITALY**	**NETHERLAND**	**SPAIN (MADRID)**	**SPAIN (VALENCIA)**	**UNITED KINGDOM**
I	What proportion of hospitals in your country/area have the facilities to do primary identification of *H. influenzae* strains?	100%	80-100%	100%	100%	c50-80%	100%	80-100%	100%	80-100%
II	For those hospitals which can identify *H. influenzae*, what type of cases/specimens would be tested.									
	All CSF's from suspected bacterial meningitis	YES	YES	YES	YES	YES	YES	YES	YES	YES
	All CSF's from suspected bacterial meningitis in children		YES	YES			YES	YES	YES	YES
	All blood cultures	YES	YES	YES	YES		YES	YES	YES	YES
	All blood culture in children		YES	YES			YES	YES	YES	YES
	Blood cultures from cases of epiglottitis		YES	YES	YES		YES	YES	YES	YES
	Blood cultures from cases of epiglottitis in children		YES	YES			YES	YES	YES	YES
	Other conditions, please describe.	YES All pneumon Osteo,SA,in children	YES	YES	YES Sterile sites		YES	YES	YES Sterile sites	YES Sterile sites
III	What proportion of hospitals would be able to perform serotyping on isolates of :-									
	H. influenzae type b	20-50%	<20%	100%	80-100%	50-80%	<20%	50-80%	80-100%	50-80%
	Other *H. influenzae*	<20%	<20%	<20%	20-50%	<20%	<20%	<20%	20-50%	<20%
IV	What proportion of hospitals refer isolates to the national / area reference laboratory (ie your lab)?	100%	80-100%	100%	100%	20-50%	80-100%	<20%	80-100%	100%

		AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
V	For those hospitals which do refer isolates to your lab, what type of cases are they referred for?									
	All invasive *H. influenzae*	YES	YES	YES	YES	NO	YES	YES	NO	YES
	All invasive *H. influenzae* in children					NO			YES	
	H. influenzae meningitis					YES				
	H. influenzae meningitis in children									
	H. influenzae epiglottitis in children									
	Other, please describe							Chronic inf., otitis, conj.		Invasive disease
	REFERENCE LABORATORY METHODS									
1.1	**Receipt of strains**									
	1.11 Are the strains subbed immediately on receipt?	YES	YES	YES	YES	YES	YES	YES	YES	NO
	1.12 Are the strains tested on receipt?	YES	YES (S.typ)	YES	YES	YES	YES	YES		YES
	1.13 Are the strains stored and tested in batches?	NO	YES	YES	YES	NO	NO	NO	YES	YES
2.1	**Media**									
	2.11 What media is used to transport strains to the lab ?	Choc	Choc	Modified Stuart's	Choc	Choc	Choc	Choc	Transgrow	Choc
	2.12 What media is used to subculture the strains?	Choc	Choc	Choc	Choc	Thayer Martin	Choc	Choc	Choc	Choc
	2.13 What media is used to test growth factor requirement?	NA	NA	TSB+YEA+ Horse serum	NA	Mueller Hinton	Mueller Hinton	Mueller Hinton	Mueller Hinton	Columbia
	2.14 What media is used for susceptibility testing?	HTM	HTM		HTM	HTM	HTM	HTM &/or Choc	HTM	NAD

	AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
2.15 What media is used for long term storage of strains?	Protect bead	10% Glyc.	Skimmed milk	Protect bead	Microbank	15%glycerol peptone	Skimmed milk	Protease pep & glycerol	15% glcerol TSB
2.16 Please state atmosphere of incubation	5%CO2	5%CO2 36C	5%CO2 37C	CO2	Air	5%CO2	5%CO2	5%CO2 35-37C	5% CO2 37C
2.17 Please state duration of incubation	18-24HRS	24-48HRS	24-48HRS	48HRS	24HRS	24HRS	24HRS	24-48HRS	24HRS
2.2 **Identification Methods**									
Are the following tests performed?									
Catalase	YES	YES	NO	NO	NO	NO	NO	YES	YES
Oxidase	NO	YES	NO	NO	YES	NO	NO	YES	YES
Dependence on growth factors: i) disc method	YES	YES	YES	YES	YES	YES	YES	YES	YES
ii) plate incorporation	NO	NO	NO	NO	NO	noncaps	NO	NO	NO
Porphyrin	YES	YES	NO	YES	NO	YES noncaps	YES	YES	YES
Satellitism on blood agar (please state origin of blood)	YES Horse	YES Horse	YES Sheep	NO	NO	NO	NO	NO	YES Horse
Haemolysis (Please state origin of blood)	YES Horse	YES Horse	NO	YES Horse	NO	YES	NO	YES Horse	YES Horse in 10%CO2
Nitrate (Please state method used)	NO	YES Rapid ferm. or tube test	NO	NO	NO	YES	NO	YES API system	YES Cook's method
ONPG	NO	NO	NO	NO	NO	NO	YES	YES	YES
Commercially available ID kit	NO	NO	NO	YES RapID NH	NO	NO	YES ROSCO	NO	YES RapID NH

	AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
Other, specify						Gluc, Suc, Lact, Xyl on caps strains	Sugars homemade		ROSCO ID sugars
2.3 Are the strains biotyped using the following tests?									
Indole	YES	YES	NO	YES	NO	YES	YES	YES	YES
Urease	YES	YES	NO	YES	NO	YES	YES	YES	YES
Ornithine decarboxylase	YES	YES	NO	YES	NO	YES	YES	YES	YES
2.4 Are the strains serotyped?	YES	YES	YES	YES	YES	YES (If noncaps)	YES	YES	YES
If so, which of the following methods are used;									
Slide agglutination with polyvalent antisera (If yes, give details of antisera used)	YES Difco	NO	NO	NO	YES Difco If type b neg	NO	YES In house	YES Phadebact	YES Difco
Slide agglutination with type specific antisera (If yes, give details of antisera used)	YES Murex Diag.	YES Murex Diag.	NO	YES Wellcome	YES DIFCO	NO	YES a-f	YES Difco	YES Murex
Counter current immunoelectrohoresis	NO	NO	YES DIFCO a-f	NO	YES If type b neg	NO	NO	YES	NO
PCR (If yes, give details of primers used)	NO	Under development	NO	NO	NO	NO	NO	NO	YES H.i OMP(P2) primers
Other, specify	Phadebact		Latex agg			Coagg with			VK primers

	AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
	Haemophilus Test type sp. reagents		Antiserum plate method			polyclonal type specific antisera			for capsule a-f primers ISLOUT BEXb for b-strains
2.5 Are the strains further subtyped?	YES	YES	NO	NO	NO	YES	YES	NO	YES (OCC)
If yes, which typing method is used?									
OMP	YES	YES				YES	YES		YES
Ribotyping	NO	NO				NO	YES		YES
LPS	NO	NO				YES	NO		NO
PFGE	YES	YES				NO	YES		NO
Other, specify	Probes for capsule genes.	NO		Strains for BPASU survey sent to Oxford HRL			Not performed routinely		REP PCR These methods of little value for caps strains
2.6 Susceptibility Testing									
2.61 Please list antimicrobial chemotherapeutic agents tested, and concentrations	AMP 10 CTX 30 Chlor 30 RD 5 ATCC49247	Not done routinely on referred isolates Batch testing periodically by agar dil.	Surveillance of antibiotic sens testing being done by research group in collab with us	AMP 2ug CTX 10ug CHLOR 10ug RIF 5ug	AMP CFTX ERY		AMP, AMC CXM, CTX CHLOR, CIP RIF and others when required	CXM 30mcg CTX 30mcg CAZ 30mcg IMP 10mcg AZM 15mcg CIP 5mcg SXT AML 20mcg CFTX 30mcg	TRIM 1.25u AMP 2ug CHLOR 10ug CTX 30ug RIF 2ug TET 10ug CXM 30ug AMC 3ug CAZ 30ug

	AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
								AMP 10mcg	GENT 10ug
								CLAR 15mcg	CIP 1ug
								CEFIX 30mcg	NEO 30ug
2.62 Which method of susceptibility testing is used?									
Disc diffusion: Control org on same plate	NO	NO		YES	NO		NO	YES	NO
Control org on separate plate	NO	YES		NO	NO		YES	YES	YES
Break points	NO	NO		NO	NO		NO	YES	NO
Other, specify		CDS Method							
2.63 If MIC's are required, which method is used?									
Broth dilution	NO	NO		NO	YES	YES	NO	YES	NO
Agar incorporation	NO	NO		YES	NO	NO	NO		NO
E-test (AB BIODISK)	YES	YES		YES	YES	YES	YES		YES
Commercially prepared MIC microtitre trays	NO	NO		NO	NO	NO	YES		NO
Other, specify							Sensititre	Sensititre	
2.7 Do you test for beta lactamase production?	YES	YES		YES	YES	YES	YES	YES	YES
If yes, state method.	Nitrocefin	Nitrocefin		Nitrocefin	Nitrocefin		Ref Lab homemade	Nitrocefin	Intralactam strips
2.8 Do you test for chloramphenicol acetyltransferase (CAT) production?	YES	NO		NO	NO	NO	YES	NO	YES
If yes, state method.	Double disc method, not routine.						Ref Lab homemade		Commercial kit- REMEL KANSAS

	AUSTRALIA (MELB.)	AUSTRALIA (SYDNEY)	FINLAND	IRELAND	ITALY	NETHERLAND	SPAIN (MADRID)	SPAIN (VALENCIA)	UNITED KINGDOM
2.9 Long term storage How do you store strains long term?									
Agar slopes	NO	NO	NO	NO	NO	YES	NO	YES	NO
Frozen at -80C	YES .-70C	10% Glycerol .-70C	YES	YES	YES	YES	YES	YES	YES
Other, specify									
Please give any other information not covered above.							For QC use 5 reference strains, 3 external ATCC 49247 ATCC 49766 ATCC 10011 & 2 internal		

APPENDIX 3 - Hib case data collection proforma

Hib surveillance and vaccination Variables to be collected on cases of invasive Hib

Personal:
Identifier
Date of birth
Date of onset
Sex of patient
Geographic location

Clinical condition:

Meningitis
Epiglottitis
Cellulitis
Septic arthritis/osteomyelitis
Pneumonia
Septicaemia (no other focus)
Other (specify if known)
Not known

Method of confirmation

If culture, give site(s).

Organism:

H influenzae type b
H influenzae type a
H influenzae type e
H influenzae type f
H influenzae non typeable/non-capsulated
H influenzae not typed
If culture, give site(s).

Vaccination status:

Vaccinated? yes / no / NK
If vaccinated, number of doses/dates of vaccine.