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Epidemiology of invasive *Haemophilus influenzae* infections in England and Wales in the pre-vaccination era (1990–2)

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SUMMARY

This survey defined the pattern of invasive *Haemophilus influenzae* infections during 1990–2 in six regions in England and Wales during the pre-vaccination era providing a baseline against which any changes in patterns of disease due to the introduction of the *Haemophilus influenzae* type b vaccination programme can be monitored. A total of 946 cases of invasive *Haemophilus influenzae* were recorded during the survey period of which almost 90% were due to type b and most of the remainder were non-typeable. Type b infections occurred predominantly in children less than 5 years of age (88%) with the highest attack rate in male infants in the 6–11 month age group. Diagnostic category varied with both age and serotype; meningitis was the commonest presentation overall but pneumonia and bacteraemia were more common in adults and non-typeable isolates. Mortality was highest in neonates and the elderly (over 65 years of age) who were more likely to have an underlying predisposing condition than older children and adults. Children under 5 years of age had a higher case fatality rate for non-typeable than for type b infections. Ampicillin resistance was 15% and there were no cefotaxime resistant type b isolates.

INTRODUCTION

Haemophilus influenzae can cause a severe life-threatening infection in previously healthy individuals occurring particularly in children under 5 years of age [1]. In the UK it occurs with a peak incidence in infants less than 12 months of age [2, 3], hence the introduction of an early childhood vaccination programme against the disease. Its commonest clinical manifestation in children is meningitis occurring in more than 50% of cases with a mortality of 5% [2]. In children over 2 years it also presents as epiglottitis; less frequent manifestations of infection include cellulitis, septic arthritis, osteomyelitis and pneumonia. In adults the pattern of clinical disease differs with pneumonia being the commonest presentation [4].

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The majority of childhood isolates are capsular type b with a greater proportion of non-capsulate isolates, usually referred to as non-typeable [NT], in adults [4]. Typing methods are essential for epidemiological purposes and are based on capsular serotyping (a–f and non-typeable), biotyping, and more sophisticated molecular methods such as polymerase chain reaction (PCR). PCR can detect less common variants such as 'b minus' strains which are type b strains with a deficient capsular structure [5]. Following introduction of the *H. influenzae* type b (Hib) vaccine and the reduction in childhood type b infections, accurate typing of all isolates from cases of invasive disease becomes essential to detect any shift in the pattern of infecting organisms in the different age groups that may occur.

There have been a number of epidemiological studies of *H. influenzae* infections worldwide; populations studied have included the UK [2, 3], Northern Europe [6], the USA [7], Australia [8, 9] and some developing countries [10]. They have shown wide variations in the annual incidence of invasive Hib disease but the consistent finding between the populations studied has been the increased risk of invasive disease in children less than 2 years of age (which correlates with their inability to produce anticapsular polysaccharide antibody) and the predominance of meningitis as the presenting condition. The age of highest disease incidence correlates with the prevalence of the disease in the community under study: the higher the disease prevalence the younger the age of highest disease incidence [1]. Polyribosyl-ribitol phosphate (PRP) conjugate vaccines were introduced into the UK in October 1992 and have been shown to be both highly immunogenic in terms of their measurable antibody response and effective in reducing invasive Hib infection in immunised populations [11, 12]. Immunogenicity has been demonstrated in field trials in the UK using the regime of primary vaccination at 2, 3 and 4 months of age [13]. A catch-up programme for children under 5 years of age who did not receive a primary course, comprising a single booster dose for those over 12 months of age and a full three-dose course for those less than 12 months, has ensured rapid coverage of the susceptible age group.

The Regional Survey of invasive *H. influenzae* type b (Hib) disease in children under 10 years of age was established in the Oxford region in 1985 [2] and in Wales in 1988 [3]. These two regions were the basis for an extended Regional Survey which started in 1990 and also included four other regions (East Anglia, Northern, North-Western and South-Western). All invasive *H. influenzae* infection (all types and all ages) was monitored. The population covered by the survey was approximately 35% of the total population of England and Wales. Before this survey, incidence data were unreliable because of both a lack of typing facilities and also incomplete reporting. Cases may be reported to any or all of three sources: the Office of Population Census and Surveys (which requires only meningitis and not other forms of invasive *H. influenzae* disease to be notified), the Public Health Laboratory Service Communicable Disease Surveillance Centre (PHLS CDSC) and to the Regional Survey. An unidentifiable number of cases are never reported to any source. In a recently reported study these deficiencies in reporting were illustrated by a comparison of reports to the Regional Survey and to the PHLS CDSC. It recommended comparison of reporting databases to minimize under-reporting error [14]. Despite this error, the Regional survey remains the most accurate source of data available at the present time.

The regional survey was set up to obtain as comprehensive and accurate a baseline for the surveillance of invasive *H. influenzae* infections before the introduction of Hib vaccine as possible. This allowed effective surveillance to be in place from which the pattern of infection after introduction of the vaccination programme could be measured. The preliminary results of the first year of the survey have already been reported [15]. We now present the combined results for the first 2 years, October 1990 to September 1992 inclusive.

METHODS

During the period of the survey data were collected on all invasive. *H. influenzae* infections which were identified in the regions under study. The organisation of the surveillance was as previously described for the Oxford [2] and Wales [3] surveys. Ethical Committee approval was sought and obtained from the Public Health Laboratory Service Ethical Committee and local Ethical Committees. One district in the Northern Region refused ethical consent and was excluded from the survey. The case definition was systemic infections in which culture of normally sterile tissue or body fluid revealed *H. influenzae*, or in which haemophilus-like Gram negative organisms were seen on Gram stain in conjunction with detection of Hib antigen (the latter group were classified as serotype not determined). Cases of pneumonia and epiglottitis were included only when present in association with bacteraemia. Local microbiologists identifying a suspected case sent a report form and questionnaire containing brief clinical details and the isolate to their Haemophilus Reference Laboratory (Oxford Public Health Laboratory in the case of the five English regions and Gwynedd Hospital, Bangor, for Wales). Each region had a coordinating medical microbiologist who was responsible for surveillance in their region. The PHLS CDSC database was compared with the Regional Survey data and any cases from the participating regions not notified to the Regional Survey were followed up. The data collected is shown in Table 1.

At the reference laboratory the organism identification and antibiotic sensitivity pattern were investigated using a routine disk diffusion method and NCTC *H. influenzae* strain 11931 as a fully sensitive control. Beta lactamase production was tested using a routine acidometric method [4]. Strains confirmed as *H. influenzae* were serotyped using standard slide agglutination techniques with specific antisera to capsular types a–f; countercurrent immunoelectophoresis (CIE) was used for strains which did not agglutinate with antisera. Strains which could not be typed by either method were defined as non-typeable; a PCR technique was used in validation of the serotyping and CIE results [5].

All data collected, both clinical and microbiological, were entered onto a database in *Dataease* and analysed to provide information on age, sex, regional and seasonal incidence of the disease, mortality, organism type and antibiotic sensitivity pattern of confirmed invasive *H. influenzae* infections.

Statistical methods

Variations in attack rates by regional, calendar period, age and sex were analysed using log-linear models with population figures based on the 1991 census [16]. Age distribution of Hib and non-typeable infections in different diagnostic

Table 1. *Questionnaire data*

1. Data collected on all cases of invasive *H. influenzae*
   - Date of birth
   - Sex
   - Clinical diagnosis

   If an organism isolated:
   - Date of specimen*
   - Type of specimen
   - Gram stain and Hib antigen testing when appropriate
2. Data collected on 'culture negative' or 'bacteraemia without a primary focus' cases (in order to define the disease more clearly)
   - Presence of pyrexia
   - Any pre-existing chest disease known
   - Any other localizing signs
2. Mortality questionnaire (sent to all cases in which death was recorded within 3 months of diagnosis of infection to examine the contribution of the infection to death)
   - Onset date of illness
   - Perceived contribution to death
   - Any underlying predisposing conditions

* Date of specimen was not available on all specimens, so date specimen received in reference laboratory was taken as an alternative.

categories and case fatality rates were compared using χ^2 test of Fisher's exact test (two-tailed) where appropriate. Case fatality rates and 95% confidence limits were estimated assuming all fatalities were identified.

RESULTS

There were 946 cases of invasive *H. influenzae* disease recorded between 1 October 1990 and 30 September 1992. Infections due to Hib accounted for 772 (82%) of these infections; 95 (10%) were due to non-typeable *H. influenzae*, 4 to serotype e and 8 to serotype f. In 67 cases the serotype was not determined as no isolate was available. This included five cases in which no organism was cultured and the diagnosis was based on the results of antigen testing only. All isolates which were non-typeable by conventional typing methods were confirmed as non-typeable by PCR; no b-minus strains were identified.

The Hib attack rates in children under 5 years of age divided by region for the study period are shown in Figure 1. There were significant differences between regions ($P = 0{\cdot}03$). Attack rates were generally higher in the second year of the study ($P = 0{\cdot}03$).

Age distribution

The majority of infections were due to Hib and occurred in childhood. The distribution of invasive haemophilus infections by age and serotype is shown in Table 2. There were substantial age differences in attack rates for both Hib and NT infections ($P < 0{\cdot}0001$).

H. influenzae *type b*

Most infections with Hib occurred in children under 5 years of age; 680 (88%) out of a total of 772 infections. Of these childhood infections, 285 (42%) occurred

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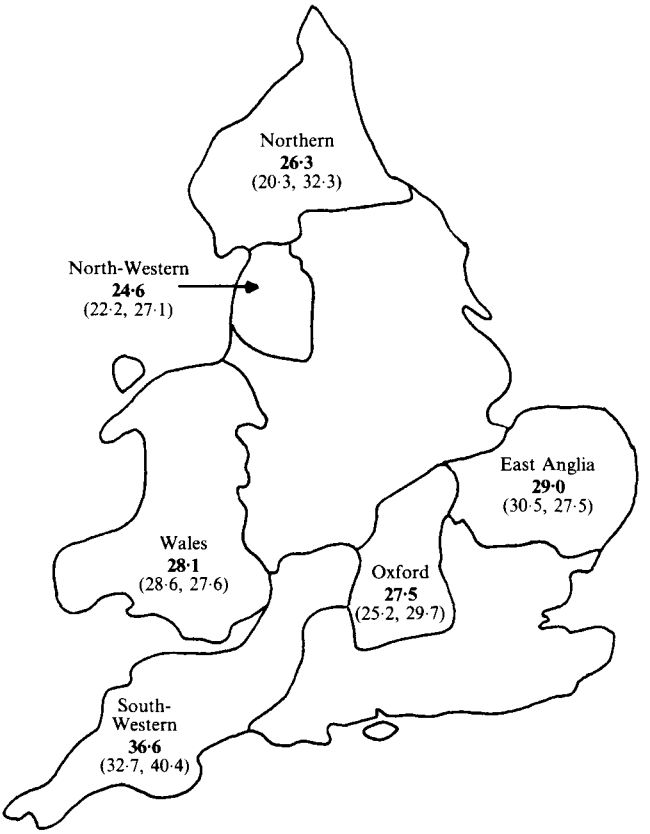

Fig. 1. Regional variation in Hib infection rates in children under 5 years of age (rates per 100000 population at risk). Figure shown in **bold** indicates overall regional rate for study; figures in parentheses indicate individual annual rates for 1990/1 and 1991/2 respectively.

in the first year of life and 484 (63%) in children less than 2 years of age. Age specific annual attack rates for Hib per 100000 population at risk are illustrated in Table 2 and demonstrate the highest attack rate in the 6–11-month age group. The number of infections recorded in infants less than 12 months of age is illustrated graphically in Figure 2.

Although most Hib infection occurred in children, 67 (9%) Hib cases occurred in adults. Twenty-seven of these adult cases of infection (40%) occurred in the age group over 65 years; in eight cases the age was not known.

Non-typeable (*NT*)

There were 95 cases of invasive infection due to non-typeable *H. influenzae*, of which 22 (23%) occurred in children under 5 years of age. Nine childhood infections were in infants less than 6 months of age and six were in neonates (less than 1 month age). Fifty-nine (62%) infections occurred in adults, 23 (39%) of which were in the age group over 65 years of age. The age group was unknown for six cases.

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Table 2. *Annual attack rate (AAR) Hib and non-typeable (NT) isolates broken down by age and sex*

Age	Total population at risk (× 1000)	Number of cases Hib	Number of male cases Hib	Number of female cases Hib	AAR Hib per 100000 population	Number of cases NT	Number of male cases NT	Number of female cases NT	AAR NT per 100000 population
< 1 month	20·1	6	3	3	14·9	6	4	2	14·9
1–5 months	100·7	86	43	43	42·7	3	3	0	1·49
6–11 months	120·8	193	109	84	80·0	1	1	0	0·41
1–2 years	238·7	199	111	88	41·7	9	4	5	1·89
2–5 years	715·8	196	103	93	13·7	3	2	1	0·21
5–15 years	2245·9	17	9	8	0·38	8	4	4	0·18
15–44 years	7669·2	25	7	18	0·16	22	6	16	0·14
45–64 years	3896·2	15	4	11	0·19	14	8	6	0·18
> 65 years	2913·4	27	17	10	0·46	23	10	13	0·39
Age not known	—	8	5	3	—	6	4	2	—
Total	17920	772	411	361	2·15	95	44	51	0·27

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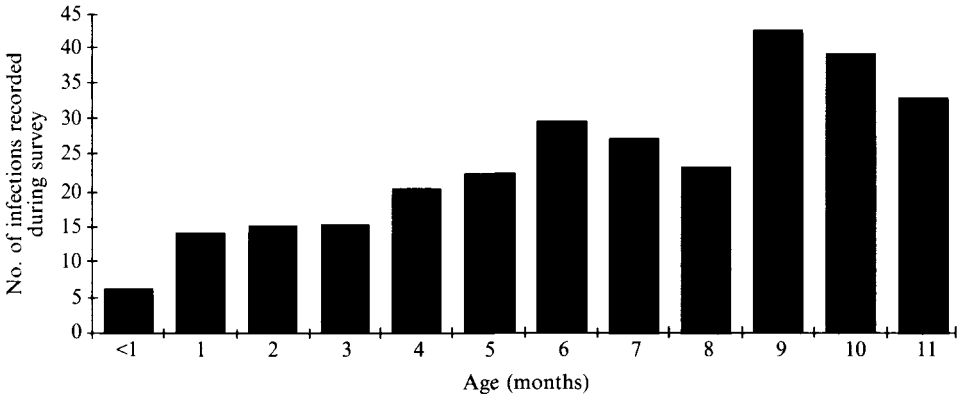

Fig. 2. Hib infections in infants < 12 months of age.

Infections due to other serotypes

There were 4 infections due to serotype e and 8 due to serotype f *H. influenzae*. Three of these infections were in childhood: 2 serotype f in the 1–5-month age group and 1 serotype e in the 5–14 years age group. The remaining 9 infections (75%) occurred in adults.

Sex distribution

There were 411 cases of Hib infection in males (53%) compared to 361 in females. Assuming equal numbers of males and females at risk, the excess of males was significant for children under 5 years of age ($P = 0{\cdot}025$). Within the 15–64 years age group there was a slight, though not significant, excess of females.

There were more non-typeable infections in females (51) than males (41), though the difference was only significant in the 15–44 years age group ($P = 0{\cdot}03$).

There were no substantial differences in diagnostic category between the sexes for Hib or non-typeable infections.

Seasonal variation in infection

Hib infection was more common in the cooler months of the year, 451 cases (58%) occurring in the period October–March ($P < 0{\cdot}001$). Overall, *H. influenzae* did not show a marked seasonal pattern.

Diagnostic category

H. influenzae *type b*

Meningitis was the commonest presenting condition, accounting for 437 cases (57%). Other clinical presentations included epiglottitis in 111 (14%), cellulitis in 54 (7%), bone and/or joint infections (septic arthritis and osteomyelitis) in 43 (5%), and pneumonia in 41 (5%). Sixty-three cases presented with bacteraemia without an obvious focus. Twenty patients presented with other less common diagnoses and in three cases the diagnostic category was not stated. Breakdown by diagnostic category and age is shown in Table 3 and shows that age has an important bearing on the clinical manifestation of infection. Hib meningitis accounted for 65% of cases in children less than 2 years of age; epiglottitis was

Table 3. *Hib breakdown by clinical diagnosis and age*

Clinical diagnosis	Total number of cases	%	Under 2 years (no. of cases)	%	2–15 years (no. of cases)	%	Adult 15+ years (no. of cases)	%
Meningitis	437	56	314	65	111	52	8	12
Epiglottitis	111	14	34	7	66	31	10	15
Pneumonia	41	5·5	13	3	7	3	21	31
Cellulitis	54	7	50	10	3	1·5	1	1·5
Septic arthritis	37	5	24	5	11	5	2	3
Osteomyelitis	6	< 1	6	1	0	0	0	0
Bacteraemia	63	8	27	6	15	7	18	27
Other*	20	2·5	13	3	0	0	7	10
Unknown diagnosis	3	< 1	2	< 1	1	< 1	0	0
Total	772†	100	483†	100	214†	100	67†	100

* 'Other' diagnoses included miscellaneous upper respiratory tract conditions (7), lung abscess (2), empyema (2), thyroid abscess (1), PUO (3), febrile convulsion (1), endocarditis (1). pericarditis (1), infected aortic aneurysm (1), liver failure (1).

† Age unknown in eight isolates so column totals do not equal total number of cases.

Table 4. *Non-typeable isolates: breakdown by clinical diagnosis and age*

Clinical diagnosis	Total number of cases	%	Cases < 15 years (no. of cases)	%	Cases > 15 years (no. of cases)	%
Pneumonia	26	27	4	13	20	34
Meningitis	12	13	3	10	9	15
Cellulitis	4	4	2	6·5	1	2
Epiglottitis	2	2	2	6·5	0	0
Septic arthritis	2	2	0	0	2	3
Bacteraemia	35	37	14	47	20	34
Other*	14	15	5	17	7	12
Total	95†	100	30†	100	59†	100

* 'Other' diagnoses included sudden infant death syndrome (2), PUO (1), haematospermia (1), tubo-ovarian abscess (1), pyosalpingitis (1), septic abortion (1), skull fracture with cerebrospinal fluid leak (1), miscellaneous respiratory tract conditions (2), right iliac fossa pain (1), peritonitis (1).

† Age unknown in six isolates so column totals do not equal total number of cases.

uncommon in this age group (7%) but accounted for 31% of cases in the 2–5 years age group. Cellulitis, septic arthritis and osteomyelitis accounted for similar proportions of infections in the two age groups. In contrast, in adults pneumonia (31%) and bacteraemia (27%) accounted for the majority of cases.

Non-typeable infections

Bacteraemia with no detectable focus of infection was the predominant diagnosis occurring in 35 (37%) infections. Pneumonia accounted for 26 (27%) and meningitis for 12 (13%) cases. Other uncommon diagnoses and breakdown by age and diagnostic category are shown in Table 4. The age distribution for infections presenting as meningitis, pneumonia, septic arthritis and bacteraemia

were significantly different for Hib and non-typeable infections (χ^2 test). There were no significant differences for epiglottitis and cellulitis.

Other capsular types

There were four infections due to serotype e organisms: meningitis (2); pneumonia (1); and epiglottitis (1). The eight infections caused by serotype f organisms presented as meningitis (4), epiglottitis (1), pneumonia (1), appendicitis (1) and PUO (1).

Antibiotic resistance

H. influenzae *type b*

Ampicillin resistance was found in 115 (15%) of 764 isolates tested, and 12 of 761 (2%) isolates were resistant to chloramphenicol. Ten isolates were resistant to both ampicillin and chloramphenicol. Ampicillin sensitivity was unknown for 8 isolates and chloramphenicol sensitivity was unknown for 11 isolates. None of the isolates tested were resistant to cefotaxime. All ampicillin resistant isolates were beta lactamase positive confirming beta lactamase production as the predominant mechanism of antibiotic resistance in *H. influenzae*.

Non-typeable infections

Ampicillin resistance was found in 11 of 95 (12%) isolates tested, and resistance to chloramphenicol was found in 2 (2%). One isolate was resistant to both ampicillin and chloramphenicol and another isolate was resistant to ampicillin and cefotaxime (but sensitive to chloramphenicol).

Other capsular types

All isolates of serotypes e and f were sensitive to ampicillin, chloramphenicol and cefotaxime.

Mortality

Fifty-three (5·6%; 95% CI 4·2–7·3%) of all reported infections proved to be fatal, 772 (81%) cases survived and for 121 (13%) the outcome was unknown. Mortality questionnaires were sent to all doctors who reported fatal cases and replies were received from 45 (85%).

Thirty (57%) of the fatal infections were due to Hib, 14 (25%) were non typeable, 1 (2%) was type e and in 8 (14%) the serotype had not been determined. The case fatality rate for Hib was 3·9% (95% CI 2·6–5·5%). For non-typeable infections the case fatality rate was 15% (95% CI 8·3–24%). The case fatality rate in children under 5 years of age was significantly higher ($P < 0·0001$) for non-typeable infections (7/22, 32%) than for Hib cases (16/680, 2·4%). For individuals over 5 years age, the difference was not significant (14/85 Hib, 6/67 NT: $P = 0·26$). Mortality rates were highest for type b and non typeable infections in neonates and the elderly (over 65 years of age). The data is shown in Table 5. There was no significant difference in mortality rates between the sexes; there were 25 deaths in males and 28 deaths in females.

Details of contribution of infection to death was available on 38 of the 45 mortality questionnaires returned: in 33 cases (87%) infection was considered to be the 'sole' or 'major' contributory factor; in the remaining 5 cases (which did not include any type b isolates) it was considered 'minor' or 'coincidental'. In 25

Table 5. *Case fatality rates: Hib and non-typeable by age*

	Total cases		Fatal cases		Case fatality rate (%)	
Age group	Hib	Non-typeable	Hib	Non-typeable	Hib (fatal/all cases)	Non-typeable (fatal/all cases)
< 1 month	6	6	1	4	16·7	66·7
1–5 months	86	3	1	1	1·2	33·3
6–11 months	193	1	2	1	1·0	100
1 year	199	9	4	1	2·0	11·1
2–5 years	196	3	7	0	3·6	0
5–14 years	17	8	1	0	5·9	0
15–44 years	25	22	2	1	8·0	4·5
45–64 years	15	14	2	1	13·3	7·1
> 65 years	27	23	9	4	33·3	17·4
Age unknown	8	6	1	1		
Total	772	95	30	14	3·9	14·7

(46%) fatal cases underlying conditions which predisposed to infection and/or death were identified, such as prematurity (4 cases), congenital abnormality (3), chronic cardio-pulmonary disease (9), malignancy (5), diabetes (1), chronic renal disease (1), alcoholism (1), and previous splenectomy (1).

There were 17 deaths in the elderly (over 65 years age). Nine were associated with an identified underlying predisposing condition: these included chronic respiratory condition (4 cases); cardiovascular condition (2); and malignancy (3). An underlying condition associated with death was more common in cases less than 12 months age (7 out of 10 (70%) in whom a response was provided) and over 65 years of age (9 out of 11 (82%)) than in the 1–64 years age group (9 out of 20 (45%)).

Diagnostic categories for deaths

H. influenzae *type b*

The mortality rates were highest for bacteraemia (14·3%) and pneumonia (4·9%) compared to meningitis (2·7%) and epiglottitis (3·6%). This reflected the predominant clinical diagnoses in the age groups with the highest mortality rates, that is neonates and the elderly, who were more likely to present with these less common clinical features.

Non-typeable/other serotypes

There were too few deaths to comment on significance of diagnostic category.

Antibiotic resistance for deaths

Data on antibiotic sensitivity was available in 47 isolates; 6 isolates (13%) were resistant to ampicillin and 2 isolates (4%) were resistant to chloramphenicol as well as ampicillin. There were no cefotaxime resistant isolates.

DISCUSSION

This survey has provided the most detailed information available to date on the epidemiology of invasive *H. influenzae* infection in England and Wales prior to the introduction of Hib vaccine serving as a baseline against which to measure any

change in pattern of the disease by infecting type, age distribution and clinical presentation as a consequence of vaccine efficacy. It included a large metropolitan area (Greater Manchester, North-Western region), other large urban areas and rural areas and it is reasonable to assume that a representative subpopulation against which to judge events in the UK overall was covered. However, as with any survey relying on disease reports, it must be assumed that despite vigilance in recording it was incomplete. The introduction of Hib conjugate vaccine into four of the eight districts of the Oxford region on a staged basis commencing in May 1991 may have reduced the total numbers of cases recorded in that region during the latter part of the survey but is unlikely to have produced a significant impact on total numbers recorded.

Recent data from the UK [12] and Finland [11] suggest that introduction of Hib vaccine will result in a rapid and dramatic decline in the incidence of Hib infection in this susceptible childhood population. Although Hib is predominantly a disease of childhood, a significant number of cases occurred in the adult population, especially the elderly who may become important in acting as a continuing reservoir of infection for susceptible persons such as unvaccinated neonates. Alternatively, the removal of the childhood reservoir may result in a reduction in the number of recorded Hib infections in adults through herd immunity. Non-typeable *H. influenzae* disease accounted for only 10% invasive infections overall, but this group may assume increasing importance in the future if the proportion of infections due to non-Hib serotypes increases because they are not covered by the vaccine.

This survey has confirmed the findings of previous epidemiological surveys of invasive *H. influenzae* disease amongst comparable populations in other countries, and validates the expected pattern of infection on which the vaccine programme was based. The survey now takes on a new role in post vaccine surveillance to monitor not only the expected reduction in overall numbers of cases of invasive Hib disease but also to detect any changes in the pattern of disease. The continuation of the survey will allow ongoing monitoring of vaccine efficacy and early anticipation of any changes which might be required in the vaccination programme in the future.

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