

## Invasive *Haemophilus influenzae* disease in adults

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### SUMMARY

We reviewed retrospectively all invasive *Haemophilus influenzae* (Hi) infections in adults ascertained from reference laboratory records and notifications from five NHS regions over the 5 years from 1 October 1990, a period encompassing the introduction of routine Hib childhood immunization (October 1992). A total of 446 cases were identified, a rate of 0·73 infections per 10<sup>5</sup> adults per annum. Though numbers of Hib infections in adults fell after the introduction of Hib vaccines for children ( $P = 0\cdot035$ ), and there was no increase in infections caused by other capsulated Hi serotypes, total numbers of invasive Hi infections increased due to a large rise in infections caused by non-capsulated Hi (ncHi) strains ( $P = 0\cdot0067$ ). There was an unexpectedly low rate of infections in those aged 75 years or more ( $P < 0\cdot0001$ ). The commonest clinical presentations were pneumonia with bacteraemia (227/350, 65%) and bacteraemia alone (62/350, 18%) and the highest rates of disease were in the 65–74 years age group ( $P < 0\cdot0001$ ). Clinical presentation was not influenced by the capsulation status of the invading Hi strain. 103/350 cases (29%) died within 1 month, and 207/350 (59%) within 6 months of their Hi infection. Case fatality rates were high in all age groups. Pre-existing diseases were noted in 220/350 cases and were associated with a higher case fatality rate (82% vs. 21%,  $P < 0\cdot0001$ ). After the introduction of Hib immunization in children, invasive Hib infections in unimmunized adults also declined, but the overall rate of invasive Hi disease in adults increased, with most infections now caused by non-capsulated strains. Physicians and microbiologists should be aware of the changing epidemiology, the high associated mortality and high risk of underlying disease. Invasive haemophilus infections in adults should be investigated and treated aggressively.

### INTRODUCTION

*Haemophilus influenzae* (Hi) is carried in the throat of most healthy individuals and can be spread by droplet

infection [1]. Strains are classified according to the presence or absence of a polysaccharide capsule [2]. Capsulated strains, which are generally more invasive, can be categorized into six serotypes, a–f [2]; of these, type b strains (Hib) are responsible for most invasive Hi infections in populations not protected by conjugated Hib vaccines [3]. In unimmunized popula-

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tions, invasive Hib infection affects mainly infants and young children, manifesting as one or more of a range of acute pyogenic infections including meningitis, epiglottitis and cellulitis, usually accompanied by bacteraemia [3, 4]. Non-capsulated Hi (ncHi) strains have been associated mainly with respiratory infections including otitis media in infants and young children, and infections in vulnerable populations such as bronchopneumonia in the elderly and exacerbations of chronic bronchitis [5, 6].

Whereas 60–80% of children carry ncHi strains in the nasopharynx [7], carriage of Hib and other capsulated haemophili is much less frequent. Peak carriage rates of Hib are less than 5% and are observed in young children [7, 8]. Adults carry Hib strains only rarely [9], unless they are close contacts of cases of Hib disease [10].

In the United Kingdom, prior to the introduction of Hib vaccines into the infant immunization schedule in October 1992, most cases of invasive Hi disease were due to Hib and most infections occurred in children aged under 5 years, with a peak incidence in males aged between 6 and 11 months [11]. Hib infections in older children and adults were encountered infrequently and were assumed to occur as a consequence of transmission of Hib strains from pre-school children, the main pool of carriers, to the occasional susceptible older child or adult. Contact with other children is a recognized risk factor for Hib disease in young children [12], and adults may also acquire their infecting strains through close contact with young children [13].

Before 1992, 9% of Hib and 64% of ncHi infections occurred in adults in the United Kingdom, with similar numbers of the two types of infection in those aged 15 years or more [11]. A high morbidity in adult Hi infections caused by both capsulated and ncHi strains has been noted [14], together with high mortality [15, 16]. An association between pre-existing diseases and many adult cases of Hi bacteraemia was documented first by Farley and colleagues in a population-based study in the US [17] and subsequently confirmed by Kostman and colleagues [18].

When Hib vaccination in infants and children was introduced, it was not clear whether it would reduce the prevalence of nasopharyngeal carriage of Hib strains, nor, if it did so, whether other Hi strains would supplant them, maintaining or increasing rates of Hi disease in adults. Data in large UK populations on the incidence and outcome of ncHi infections in adults were also lacking. An increasing incidence of

such infections as a consequence of an ageing population and of more intensive medical treatments in the elderly was considered possible.

The objectives of this study were to document the epidemiology of adult invasive Hi disease before and after the introduction of Hib vaccine into the UK infant immunization schedule, to determine the mode of clinical presentation and outcome of adult invasive Hi infection, and to determine risk factors for these infections from recognized associations including pre-existing disease.

## SUBJECTS AND METHODS

### Participating regions

Microbiology laboratories in the NHS regions of East Anglia, North, North West, Oxford and South West participated in the study. Laboratories in these regions (together with laboratories in Wales), had been collaborating in a programme of enhanced surveillance of invasive Hi infections since 1989, designed to monitor the effects of the introduction of conjugated Hib vaccines into the childhood immunization schedule in 1992 [11].

Population sizes of the participating regions were determined by reference to Office for National Statistics (ONS) estimates for 1993.

### Ethical approval

The study was approved by the Public Health Laboratory Service (PHLS) Research Ethical Committee.

### Case definitions

*Hi infection.* Growth of *H. influenzae* from a normally sterile site, for example blood culture or cerebrospinal fluid.

*Case.* Patient aged 15 years or more at the date of infection, with isolation of *H. influenzae* from a normally sterile site by a laboratory in one of the participating HNS regions.

*Date of infection.* The date of first *H. influenzae* specimen receipt in, or report to the HRU or to the PHLS Communicable Disease Surveillance Centre (CDSC), between 1 October 1990 and 31 September 1995.

*Hi-related death.* Death occurring within 6 months of the date of Hi infection.

*Early death.* Death occurring within 1 month of the date of Hi infection.

*Late death.* Death occurring after 1 month but within 6 months of the date of Hi infection.

### Case finding

Cases were identified through intensified, population-based surveillance of invasive Hi infection in England and through passive laboratory reporting to CDSC. CDSC and HRU datasets were reconciled regularly throughout the duration of the study. Cases of invasive Hi infection reported to CDSC by participating laboratories but not reported to the HRU were included to ensure that ascertainment was as complete as possible.

### Laboratory procedures

Isolates from cases of presumptive Hi infection were sent from participating laboratories to the HRU as part of a programme of enhanced surveillance. Strains confirmed as *H. influenzae* were serotyped using slide agglutination [19] and the results validated by amplification of haemophilus-specific DNA in a polymerase chain reaction [20]. Strains which could not be typed by this method were classified as non-capsulated (ncHi) [21]. Strains serotyped by the primary laboratory but not sent to the HRU were designated 'serotype not determined'.

### Case follow-up

Between April 1993 and April 1996 the microbiologist reporting each case was contacted to provide details of the patient. Where possible, the patient's general practitioner (GP) was requested to confirm the personal details of the case, whether or not they were alive, and the date of death where this had occurred. With consent, medical details were obtained from the patient and verified wherever possible by the patient's GP and hospital clinician. In cases where patient identification was not possible due to incompleteness of microbiological records, the hospital information system of the reporting laboratory and the local Family Health Services Authority (FHSA, part of Health Authority since April 1996) were requested to provide relevant patient details, enabling contact to be made with the GP.

Data on cases already dead at the time of follow-up were ascertained from the Office of Population Censuses and Surveys (OPCS, later, ONS) and from death certificates and hospital and GP notes where these were available.

### Statistical analysis

Data were stored as a Microsoft Excel database and analysed using SPSS statistical software. The significance of differences between proportions was determined using  $\chi^2$  tests.

For comparisons of the incidence of Hi disease before and after the introduction of Hib vaccination (October 1992), the study period was divided into two parts – October 1991 to September 1993, and October 1993 to September 1995. This partition permitted a 12-month period for Hib vaccine to begin to exert its effects on vaccinated and unvaccinated populations.

## RESULTS

### Epidemiology

Among the 12 200 000 people aged 15 years or more in the study regions (48.5% male), 446 cases of Hi infection were identified, an annual incidence of 0.73 infections per  $10^5$  adults. Of 353 Hi isolates from normally sterile sites which were sent to the HRU, all were from blood or cerebrospinal fluid; there were 123 (35%) Hib strains, 6 (2%) type e, 24 (7%) type f and 200 (57%) non-capsulated strains. Strains were not received at the HRU from the remaining 93 cases.

There was a significant reduction in the number of Hib infections ascertained in the second study period compared with the first ( $\chi^2$  on 1 D.F. = 4.43,  $P = 0.035$ , Fig. 1), but a marked rise in the numbers of ncHi infections ( $\chi^2$  on 1 D.F. = 7.35,  $P = 0.0067$ ), the latter phenomenon prevailing across all study regions except East Anglia.

The attack rate of Hi infections rose significantly between the age bands of 15–24 and 65–74 years ( $\chi^2$  on 1 D.F. = 21.01,  $P < 0.0001$ , Fig. 2). A dramatic decline in incidence was then seen between those aged 65–74 and those aged 75 years or more ( $\chi^2$  on 1 D.F. = 17.76,  $P < 0.0001$ ). There were no significant differences between infections caused by capsulated and those caused by non-capsulated strains, with respect to either age or gender (Mann–Whitney  $P = 0.18$  and  $\chi^2$  on 1 D.F. = 1.15,  $P = 0.29$  respectively). In the 25–44 years age group there were more female than male cases of invasive Hi infection caused by both Hib and ncHi strains.

### Clinical presentation and outcome

Clinical manifestations and outcome of 350/446 cases were ascertained. 227 patients (65%) presented with pneumonia and bacteraemia, 62 (18%) with bac-

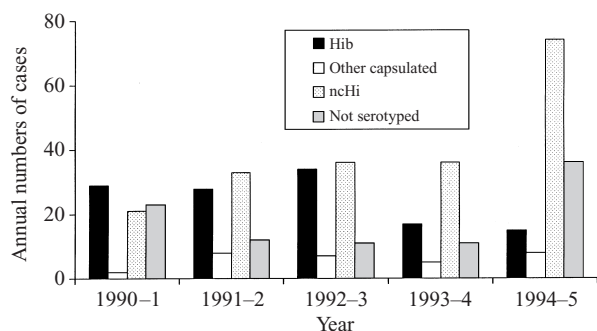


Fig. 1. Cases of invasive Hi infection by year and by strain type.

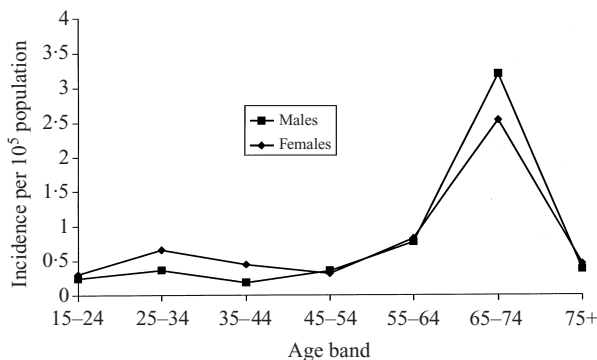


Fig. 2. Incidence of Hi infections by age band and by gender in five English regions, October 1990 to September 1995.

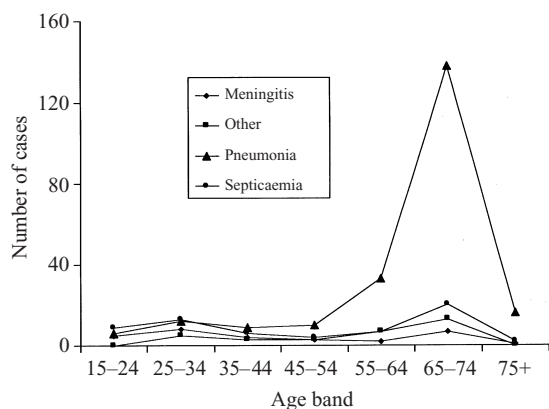


Fig. 3. Clinical presentation of invasive Hi infection by age.

teraemia alone, 30 (9%) with meningitis and 31 (9%) with other manifestations of infection. The proportions of patients with these respective clinical presentations varied with age ( $\chi^2$  on 18 D.F. = 68.91,  $P < 0.0001$ ) due to a marked increase in pneumonia cases in those aged 65–74 years (Fig. 3). The proportion of patients with each clinical presentation did not vary significantly with capsulation status of Hi strain ( $\chi^2$  on 3 D.F. = 7.8,  $P = 0.05$ ).

Six months after the onset of the infection, 207 (59%) of 350 patients in whom outcome was known, had died. Of these, 103 were early and 104 were late

deaths. Death rates were high in all age groups (Table 1). Clinical presentations were similar for infections caused by capsulated and ncHi strains. 61/69 (88%) of those with meningitis or septicaemia who died did so early, whereas most pneumonia cases who died (90/131, 69%) did so late (Table 2).

Pre-existing disease was identified in 220 patients. Diseases were: lung disease (64), malignancy (42), heart disease (39), neurological condition (14), renal disease (12), rheumatological disease (11), liver disease (9), diabetes mellitus (8), splenectomy (6), neurosurgical operation (6) and other (9). In those with pre-existing disease, the death rate within 6 months was 180/220 (82%) compared with 27/130 (21%) of those without pre-existing disease ( $\chi^2$  on 1 D.F. = 126.03,  $P < 0.0001$ , Table 3). In those without pre-existing disease and in whom strains were typed, the death rate was higher in cases due to capsulated strains, but the difference was not significant (10/40 *vs.* 9/69,  $\chi^2$  on 1 D.F. = 2.52,  $P = 0.1$ ). A greater proportion of Hi cases with meningitis and septicaemia (84/92) had pre-existing diseases recorded than those with pneumonia (125/227,  $\chi^2$  on 1 D.F. = 38.05,  $P < 0.0001$ ).

## DISCUSSION

### Patient selection; study design

This is much the largest study of adult Hi infections to be reported to date and encompassed a period when conjugated Hib vaccines were introduced into the childhood immunization schedule. Enhanced surveillance of invasive Hi infections in the five English study regions, covering 30% of the adult English population, was introduced in 1989 and was shown to have improved ascertainment [22]. In this study, patients were identified retrospectively by scrutiny of all available data sources, including routine and reference laboratory data, and hospital and general practitioner information.

Although Regional Health Authorities were re-organized in April 1994, the participating laboratories did not change, and methods of reporting remained constant throughout the study period.

### Incidence, age and gender

The overall incidence of 0.73 infections per  $10^5$  adults per annum in our study was lower than the figure of 1.7 per  $10^5$  reported by Farley and colleagues in metropolitan Atlanta, USA in 1988–90. Farley's study was undertaken prior to the introduction of routine

Table 1. Case fatality rates by age band

Age band	Total cases (A)	Total cases where outcome was known (B)	Fatal cases (C)	Case fatality rate (C/B × 100)
15–24	29	20	13	65.0
25–34	58	38	20	52.6
35–44	33	22	11	50.0
45–54	33	20	11	55.0
55–64	61	49	34	69.4
65–74	196	178	109	61.2
75+	23	19	7	36.8
Age not known	13	4	2	50.0
Total	446	350	274	59.1

Table 2. Case fatality rates by mode of clinical presentation

Clinical manifestation	Total no. of cases	No. of early deaths	No. of late deaths	No. alive at 6 months	Case fatality rate at 6 months
Pneumonia	227	41	90	96	57.8
Septicaemia	62	45	8	9	85.5
Meningitis	30	16	0	14	53.3
Other	31	1	6	24	22.6
Total	350	103	104	143	59.1

Table 3. Effect of pre-existing diseases on outcome

Pre-existing disease	No. surviving 6 months	No. of early deaths	No. of late deaths	Total
Present	40	83	97	220
Absent	103	21	6	130
Total	143	104	103	350

childhood Hib immunization in the USA, and of 40 Hi strains characterized, 20 (50%) were identified as Hib, compared with 123/353 (35%) Hib strains in our study which included 3 years of ascertainment after the introduction of routine childhood Hib immunization.

The incidence of invasive Hi infections by age remained relatively constant up to the age band 55–64 years, though the rate was higher in females than in males in the 25–44 years age group. This could have been due to greater contact with young children, the principal carriers of Hib strains. Also, some infections may have been associated with pregnancy or childbirth.

The rate of infection then rose sharply in those aged 65–74 years or more, regardless of gender, mainly due to a marked increase in the numbers of pneumonia cases, which constituted 78% of clinical presentations

in this age group. Despite increased numbers of pneumonia cases, the proportion of infections caused by non-capsulated haemophili in the elderly was unchanged by comparison with younger age groups.

Disease incidence then fell significantly in those aged 75 years or more. This was unexpected and contrasted with rapidly rising rates of systemic pneumococcal infections in the same age group [23, 24]. Possible explanations include lower ascertainment, reduced exposure to Hi carriers, lower host susceptibility and/or reduced exposure to co-factors. Further work would be needed to confirm this finding, and to explore potential underlying mechanisms.

### Deaths

The overall case fatality rate, as measured 6 months from initial presentation, was very high (59%), and

consistently so across all age groups. Most early deaths were probably related directly to Hi infection, though there was a high prevalence of pre-existing diseases amongst the fatal cases.

### Clinical presentations

The commonest clinical presentation of invasive Hi disease was pneumonia, the diagnosis being made by isolation of haemophili from blood culture and not from sputum. Though a high proportion of cases presenting with pneumonia might have been expected for nHi strains, which are commonly associated with respiratory infections, by far the most frequent manifestation of Hib infection in infants is meningitis, an unusual clinical presentation in this adult population. The frequency of different clinical presentations of invasive Hib infections is known to vary even in young children, with a relatively greater proportion of epiglottitis cases in children outside the first year of life. The reasons for these variations are not known.

The proportions of Hib and non-Hib cases with evidence of pre-existing chronic disease, which may have predisposed to Hi infection were similar.

### *Haemophilus influenzae* strains

The incidence of invasive Hib infections outside the first 5 years of life is low. Rates of Hib infections in this adult population halved in the latter 2 years of the study period when compared with the preceding 3 years. Though conjugated Hib vaccines were introduced into the routine childhood immunization schedule in October 1992, they were offered routinely only to children up to the age of 48 months. Subsequently, studies in Finland [25], the United States [26] and the United Kingdom [27] have confirmed a reduction in the prevalence and (possibly) intensity [28] of carriage of nasopharyngeal Hib in children following administration of conjugated Hib vaccine. Thus a reduction in the incidence of Hib infections in those aged 15 years and over in our study may have been attributable to a reduction in exposure.

In contrast, and with the exception of East Anglia, all participating regions showed a large rise in the numbers of nHi infections in the last year of the study period. Invasive infections caused by nHi have

been associated with old age, immunodeficiency and chronic underlying chest disease [6]. With continued ageing of the population and increases in the numbers of patients receiving immunosuppressive therapy, some increase in numbers of nHi infections might have been predicted over a 5-year period, but the large and abrupt rise observed in the last year of this study was unexpected. Numbers of nHi infections, for which vaccines are not currently available, will require careful ascertainment and monitoring in the coming years to document trends. Hi strains whose serotype was not determined (i.e. those not sent to the HRU) were distributed approximately evenly across the participating regions and across the 5 years of the study period, and were therefore unlikely to have biased the proportions of infections caused by confirmed capsulated and non-capsulated Hi strains.

A small number of infections were caused by capsulated Hi strains other than Hib, namely Hie and Hif, but numbers remained very low throughout. Though concerns have been expressed that a rise in the prevalence of immunity to Hib strains engendered by population-wide immunization of children might open an ecological niche for such closely related capsulated haemophili, we found no evidence in our study population in the first 3 years following introduction of Hib immunization.

We studied invasive Hi infections in a sample of over 30% of the adult English population over a 5-year period, documenting a declining rate of Hib infections in adults after the introduction of Hib vaccines in children, a large and unexplained rise late in the study period in the incidence of invasive infections due to non-capsulated Hi strains, and a very high case fatality rate in adults of all ages regardless of the nature of the infecting Hi strain.

Physicians need to be aware of the very serious prognosis associated with invasive Hi infections, the high risk of underlying disease and thus the need to investigate and treat vigorously. Invasive Hi infection in apparently previously healthy adults should prompt a careful search for underlying diseases.

The large and unexplained rise in incidence of nHi invasive infections at the end of the study period warrants further investigation and indicates a need to maintain enhanced surveillance. Though work on vaccines for nHi infections is in progress, their early introduction into immunization schedules is not expected.

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