Prospective study of bacterial meningitis in North East Thames region, 1991-3, during introduction of *Haemophilus influenzae* vaccine

Gillian Urwin, Mei F Yuan, Roger A Feldman

Abstract

Objective—To describe the epidemiology of primary bacterial meningitis in the North East Thames region over a three year period before and during the introduction of the vaccine for *Haemophilus influenzae* type b.

Design—Analysis of information on cases of primary bacterial meningitis identified by microbiology laboratories in the region, with collection of case data by questionnaire.

Main outcome measures—Annual incidence rates for types of meningitis according to age and ethnic group.

Results—The annual incidence rates for the three major causes of bacterial meningitis in the general population were 1.9/100 000 for *Neisseria meningitidis*, 1.6/100 000 for *Haemophilus influenzae* before vaccination, and 1.0/100 000 for *Streptococcus pneumoniae*. Higher rates of *H influenzae* meningitis were found in Asians compared with white people (3.6/100 000 v 1.5/100 000, $P=0.01$). As a result of the vaccine programme introduced in October 1992 the number of cases of *H influenzae* meningitis in children under 5 years has fallen by 87%.

Conclusions—Bacterial meningitis is a serious problem especially in preschool children. There are differences in the incidence of some causes of bacterial meningitis in different ethnic groups; with *H influenzae* type b being significantly more common among black and Asian people than among white people. The immunisation programme for *H influenzae* type b in the North East Thames region has been successful in reducing the incidence of this type of meningitis in Asian and white populations. The numbers were too small to evaluate in the black population.

microbiology laboratories, public health facilities, and hospital consultants.

We organised a prospective study to evaluate the effect of the new *H influenzae* vaccine in the North East Thames region, a population of over 3.7 million with a large proportion of people from different ethnic groups. Consultant microbiologists in the region agreed to participate to identify cases of primary bacterial meningitis. The 1991 census provided up to date figures on the regional population, including data on ethnicity. Early infant immunisation against disease due to *H influenzae* was introduced in the second year of the study and allowed documentation of the impact of the immunisation programme on occurrence of the disease.

Methods

The microbiology consultants in the 19 microbiology laboratories in the region identified all clinical cases of bacterial meningitis in which there was documented microbiological evidence of the pathogen responsible for the disease by at least one of the following investigations: culture of blood or cerebrospinal fluid, cerebrospinal fluid Gram stain, or antigen detection.

Not included in the study were cases of septicaemia when there were no symptoms or clinical signs of meningitis; cases of proved bacterial meningitis associated with HIV infection; and bacterial meningitis related to neurosurgery and neurosurgical devices. The microbiologist at each centre forwarded the laboratory results of culture of blood and cerebrospinal fluid, with the organism, to the coordinating hospital.

Clinical and epidemiological details were collected by a questionnaire completed by the microbiologist or clinician in charge of the case. When this information was not returned within three months, an additional letter was sent. When there was no response to this, the details were collected from the case notes with permission from the consultant clinician. Laboratories were contacted on a regular basis to ensure that reporting of cases was maintained throughout the study period. The questionnaire and laboratory data were entered on a computer file and analysed by using EpiInfo 5.1.

Results

Over the three year period a total of 518 cases of bacterial meningitis were identified (table I). *Neisseria meningitidis*, *H influenzae*, and *Streptococcus pneumoniae* were responsible for 87.6% of cases. These three major causes of bacterial meningitis were most common in children under 5 years, and especially in infants over 1 month of age (figure). For *N meningitidis* there are two

Department of Medical Microbiology, The London Hospital Medical College, London E1 2AD

Gillian Urwin, lecturer in medical microbiology
Mei F Yuan, research assistant

Department of Epidemiology and Medical Statistics, The London Hospital Medical College at QMW, London E1 4NS
Roger A Feldman, professor of clinical epidemiology

Correspondence to: Professor Feldman.

BMJ 1994;309:1412-4

Introduction

Bacterial meningitis remains an important cause of morbidity and mortality, especially in children, with three agents causing most reported illness. In children *Haemophilus influenzae* type b has been the major cause of bacterial meningitis.^{1,2} Vaccination to prevent disease induced by *H influenzae* type b has led to a substantial reduction in the incidence of invasive disease in children in the United States³ and virtual elimination from Finland.⁴

Although meningitis is a notifiable disease, available case data have been incomplete. Reporting of *H influenzae* infections to the Public Health Laboratory Service was recently found to be 24% incomplete.⁵ During an outbreak of meningococcal meningitis in Gloucester, only 57% of cases were formally notified.⁶ For any study of bacterial meningitis active surveillance is essential and can be organised with the help of

peaks of disease, the first in children under 5 and a second smaller peak in 15-20 year olds. Only 6.5% of *H influenzae* meningitis occurred in those over the age of 15 years. *S pneumoniae* was most prevalent in children under the age of 5 years but continued as a cause of meningitis throughout adult life.

In the third year of the study there was a striking decline in the number of cases of *H influenzae* in

Cases of bacterial meningitis in 5 year age groups, North East Thames region, 1991-3

TABLE I—Cases of bacterial meningitis by causative agent and year, North East Thames region, 1991-3

Diagnosis of causative agent	Cases in 1991	Cases in 1992	Cases in 1993
<i>Neisseria meningitidis</i>	78	68	67
<i>Haemophilus influenzae</i>	59	59	9
<i>Streptococcus pneumoniae</i>	37	45	32
<i>Escherichia coli</i>	1	2	5
Group B streptococcus	6	6	9
<i>Streptococcus</i> spp	2*	3†	2‡
<i>Listeria monocytogenes</i>	3	3	2
<i>Mycobacterium tuberculosis</i>	3	1	1
<i>Staphylococcus aureus</i>	2	0	2
Enterobacteriaceae	5	2	2
<i>Pseudomonas</i> spp	1	1	0
Total	197	190	131

**S suis* 1; group C streptococcus 1.

†Group A streptococci 2; group F streptococcus 1.

‡*S salivarius* 1; group F streptococcus 1.

TABLE II—Age specific annual incidence of bacterial meningitis for major causative agents, North East Thames region, 1991-3

Detail	Cases per 100 000/year (number)								
	1991			1992			1993		
	Overall	Age < 1 year	Age < 5 years	Overall	Age < 1 year	Age < 5 years	Overall	Age < 1 year	Age < 5 years
Pathogen:									
<i>N meningitidis</i>	2.1 (78)	39 (22)	17 (44)	1.8 (68)	30 (17)	11 (30)	1.8 (67)	25 (14)	11 (31)
<i>H influenzae</i>	1.6 (59)	55 (31)	22 (57)	1.6 (59)	37 (21)	18 (50)	0.2 (9)	0	3 (7)
<i>S pneumoniae</i>	1.0 (37)	18 (10)	7.4 (19)	1.2 (45)	18 (10)	5 (13)	0.8 (32)	13 (7)	4 (11)
Denominator*	3 693 000	56 800	258 000	3 798 532	56 692	272 037	3 799 270	54 932	272 82

*Mid-year population estimates from Office of Population Censuses and Surveys based on 1991 census.

TABLE III—Incidence of bacterial meningitis by ethnic group and causative agent for all cases and those in children aged under 1 year, North East Thames region, 1991 and 1992

Ethnic group	Cases/100 000/year (number)		
	<i>N meningitidis</i>	<i>H influenzae</i>	Denominator*
All cases:			
White	1.6 (52)	1.5 (46.5)	3 180 000
Black	1.7 (3.5)	1.2 (2.5)	206 830
Asian	2.4 (5)	3.6 (7.5)	210 520
Cases in children aged < 1 year:			
White	33 (15)	41 (19)	45 820
Black	21 (0.5)	83 (2)	2412
Asian	26 (1.5)	78 (4.5)	5797

*Denominator data for cases in children adapted from regional interactive child health system dataset by Dr L. Hilder, department of epidemiology, London Hospital Medical College (Differences were not significant for Asians and black population v white populations for both *N meningitidis* and *H influenzae*).

*Denominator data for all cases taken from 1991 census; $P=0.01$, χ^2 test, comparing incidence of *H influenzae* in Asians with white population.

children under 5 (table II). There were over 50 cases in 1991 and 1992. In 1993 there were seven cases in this age group, an 87% decline.

There were no significant differences in the rates of meningitis due to *N meningitidis* among white people, Asians, and black people. In contrast, rates of *H influenzae* meningitis were significantly greater among Asians compared with white people ($P=0.01$, table III). Although there were higher rates of *H influenzae* meningitis in children under 1 year of age in both black and Asian children than in white children, the difference was not significant (table III).

Discussion

Although every effort was made to collect data on all cases of bacterial meningitis, the number of cases is an underestimate; patients presenting to hospitals outside the region and those dying before being admitted to hospital have not been included. In addition, clinical cases of pyogenic meningitis, when there is no microbiological evidence of the pathogen involved, have not been included in the study.

Data reported to the meningococcal reference laboratory gave annual incidence rates for the region of 1.0-2.8/100 000.⁷ The incidence of 1.8-2.1/100 000 in our study did not include cases of meningococcal septicaemia or other disease due to *N meningitidis*, which could have added 15% to the total. There was no significant difference in the annual number of cases of meningococcal meningitis identified in each of the three years. Age specific attack rates for meningococcal meningitis show an increased risk of bacterial meningitis in preschool children, with those under the age of 1 year at greatest risk. Prospective surveillance studies from the United States have found the highest attack rates to be in infants under 4 months (26.4/100 000), with 29% of cases of meningococcal disease in children under 1 year.¹⁰

Meningitis accounts for 60% of invasive *H influenzae* type b disease,^{7,8} which in our region represents an annual incidence of 34.2 cases/100 000 in children under 5. In Scotland, passive reporting gave an

Epidemiological implications

- Before immunisation was introduced *Haemophilus influenzae* type b was the most common cause of bacterial meningitis in preschool children in the North East Thames region
- The Asian population had significantly higher rates of *H influenzae* disease than white people
- A substantial reduction in the incidence of *H influenzae* meningitis was observed with the introduction of immunisation of infants with conjugate vaccine
- *Neisseria meningitidis* is now the most common cause of meningitis in preschool children in the North East Thames region

incidence of 22-25/100 000/year in the under 5 age group,^{11 12} Wales had an incidence of 34.6/100 000/year, Oxford 33.4/100 000/year, and five regions of England 20-33/100 000/year.^{7-9 13}

Denominator data concerning ethnicity were obtained from the 1991 census, which undercounted ethnic minorities more than other groups and undercounted urban areas, especially in London, more than other areas.¹⁴ The largest undercounting was in young adults. In comparing rates of *H influenzae* type b meningitis in various ethnic groups in infants, when undercounting is minimal, the rates were highest in the black and Asian groups, but the numbers were too small to show significance. In the population as a whole in the North East Thames region there was a significantly increased risk in the Asian population of *H influenzae* type b meningitis compared with that in white groups but no difference in the rates of meningococcal meningitis. Even if there were undercounting of 10% overall in the Asian subgroup the difference would be significant ($P=0.02$). Native American Indian and Inuit children under 5 years have high rates (254-282/100 000/year) of *H influenzae* type b disease.¹⁵ In the United states, black and Hispanic people have a higher rate of this disease than white populations.¹ Factors such as poverty, overcrowding, and use of health care¹⁶ may account for the increase in incidence in the Asian population but do not seem to affect the incidence of meningococcal meningitis in children under 1 year of age in this region.

The data from 1993 show the success of the *H influenzae* vaccine programme in the region. Uptake

of immunisation in children at 2, 3, and 4 months has been 87-89%. In older children, the catch up programme has achieved uptake rates of 34% in children born in 1989, and 77% in children born in 1990.¹⁷ The seven cases of meningitis in children under 5 years is a significantly lower incidence than in previous years. This study highlights the success of the immunisation programme and the varying incidence of *H influenzae* disease in the different ethnic groups of the region.

We are most grateful to our colleagues in the North East Thames region, without whose help this study would not have been possible. We thank Dr D R Jones for allowing access to the typing results of the meningococcal isolates from the region; Professor J D Williams and Dr M Powell for assistance in development of the project; and Dr N Banatvala and Mr A McIntosh for their help with statistical analysis and data management. The project is funded by a grant from the Wolfson Foundation.

- 1 Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV and the Bacterial Meningitis Study Group. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. *J Infect Dis* 1990;162: 1316-23.
- 2 Schlech WF III, Ward J, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States 1978 through 1981. *JAMA* 1985;253:1749-54.
- 3 Adams WG, Dever KA, Cochis SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993;269:221-6.
- 4 Peltola H, Kilpi T, Anttila M. Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet* 1992;340:592-4.
- 5 MacLeod CA. *Haemophilus influenzae*: the efficacy of reporting invasive disease in England and Wales. *Commun Dis Rep CDR Rev* 1994;2:R13-6.
- 6 Cartwright KAV, Stuart JM, Noah ND. An outbreak of meningococcal disease in Gloucestershire. *Lancet* 1986;ii:558-61.
- 7 Howard AJ, Dunkin KT, Musser JM, Palmer SR. Epidemiology of *Haemophilus influenzae* type b invasive disease in Wales. *BMJ* 1991;303:441-5.
- 8 Jones DM, Kaczmarek EB. Meningococcal infections in England and Wales: report of the meningococcal reference laboratory for 1990. *Commun Dis Rep CDR Rev* 1991;1:R76-8.
- 9 Tudor-Williams G, Frankland J, Isaacs D, Mayon-White RT, MacFarlane JA, Slack MPE, et al. *Haemophilus influenzae* type b disease in the Oxford region. *Arch Dis Child* 1989;64:517-9.
- 10 Jackson LA, Wenger JD, and the Meningitis Disease Study Group. Laboratory based surveillance for meningococcal disease in selected areas, United States, 1989-91. *MMWR* 1993;42:21-30.
- 11 Fallon RJ, Reid D. *Haemophilus influenzae* type b invasive disease (letter). *BMJ* 1991;303:1203-4.
- 12 Brewster D. The epidemiology of *Haemophilus influenzae* invasive disease in Scotland prior to immunisation. *Health Bull (Edinb)* 1993;56:385-93.
- 13 Nazareth B, Slack MPE, Howard AJ, Wright PA, Begg NT. A survey of invasive *Haemophilus influenzae* infections. *Commun Dis Rep CDR Rev* 1992;2:13-6.
- 14 Raleigh VS, Balarajan R. Public health and the 1991 census: non random underenumeration complicates interpretation. *BMJ* 1994;309:287-8.
- 15 Ward JL, Lum MKW, Hall DB, Silimperi DR, Bender TR. Invasive *Haemophilus influenzae* type b disease in Alaska: background epidemiology for a vaccine efficacy trial. *J Infect Dis* 1986;153:17-26.
- 16 Gillam S. Ethnicity and the use of health services. *Postgrad Med J* 1990;66: 989-93.
- 17 O'Brien H. Hib immunisation catch up program in north east Thames. *Com Dis Rep CDR Rev* 1994;2:R17-8.

(Accepted 11 October 1994)

A MEMORABLE PATIENT

An exercise in humility

She was old, with the diseases of age: angina, incontinence, arthritis, myxoedema. When I called she gave me cake and when I left she would kiss me. Her late husband had been a wildfowler and some of my visits were social calls in memory of his kindness to me and my table.

Then she developed headaches and visits became serious. The pain was worst in the morning and the evening, with a clear period between. No, it did not waken her. She was flushed and nauseous but did not vomit. Neither history nor examination revealed any pointers and investigations were normal save that she was hypothyroid again. I increased the dose without benefit. Simple analgesics were ineffective and I fell back on the physician's oldest friend: time.

This was ineffective and on one of my visits she also observed that her angina was worsening. At about this

time she fell and spent some time as an inpatient but baffled me further on her return by volunteering that both her headache and angina had improved while in hospital. A wild flash of insight led me to wonder if a blocked flue on her boiler could account for her twice daily headache but this theory was rapidly disproved by the plumber.

When a doctor has nothing left to give he must give of himself. This is what I did and it gave me the answer. All I had to offer was continued social calls and during one of these she developed angina. She groped for her tablets and put one under her tongue. As she handed me the bottle a great light shone and I started to laugh. Of course she had improved in hospital. Her syndrome was caused by taking thyroxine sublingually for angina and swallowing glyceryl trinitrate for hypothyroidism twice daily.—MICHAEL EBDY is a general practitioner in Lancashire