The impact of Hib conjugate vaccine on the epidemiology of invasive *Haemophilus influenzae* disease in the West Midlands and the effect of deprivation and other environmental risk factors: An ecological study, 1990 - 1994

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"There I see the philosopher spending the whole day in his musty study, neglecting bodily exercise, so agape in the consumption of books that he will not grant an hour of a sunny summer day to a stroll in which his foul lungs may be refreshed by the use of fresh air. For my part you may warn, beseech, chide and importune him; you will be deceived and in the end will unhappily fall silent as you see the sage forced into immobility - his chest filled with phlegm, his joints rigid, his feet swollen with watery fluid and incapable of motion.

A glorious thing it is, of course, to die prematurely for the sake of wisdom."

Jerome Gaub (1763) (in Health Bulletin 1993; 51: 384)

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SUMMARY

Objective: To describe the epidemiology of invasive *Haemophilus influenzae* (HI) disease, and to explore the relationship between socioeconomic disadvantage and invasive HI disease in the two years immediately before (October 1990 to September 1992), and following (October 1992 to September 1994) the introduction of HI type b (Hib) conjugate vaccine.

Design: Multiple sources of case ascertainment were used to identify children with invasive HI disease in the West Midlands Health Region (WMHR) and compile a case register. An ecological study examined socioeconomic disadvantage using selected socioeconomic census data for enumeration districts, and the Townsend index of material deprivation.

Setting: WMHR, England from October 1990 to September 1994.

Subjects: Children under 5 years of age with invasive HI present on the West Midlands invasive HI case register (HICARE).

Results : The incidence of invasive HI disease in the WMHR fell from $28.3/10^5$ (95% CI=24.5 to 32.6) children <5 years of age in the pre-conjugate vaccine period to $5.4/10^5$ (3.8 to 7.4) after the vaccine had been introduced. Nine vaccine failures were identified. Those aged 6-11 months were most at risk in the pre-conjugate vaccine period (OR=2.69, 95% CI=1.14 to 6.55). In the post-conjugate vaccine period those aged 24-35 months were at most risk (OR=2.64, 1.16 to 5.94). More cases of meningitis were identified in girls than boys but the difference was not statistically significant. Significantly more cases of invasive HI seen in children of South Asian origin aged less than 12 months than in non-South Asian children (OR=2.88, 1.07 to 7.86). Children from affluent areas were at significantly reduced risk of disease compared to children from the more deprived areas (OR=0.73, 0.54 to 0.99). In the second period of the study a number of significant risk factors were identified. Children living in areas containing predominantly rented accommodation (p=0.0025), mobile populations (p=0.013) and a low density of children aged <5 years per km^2 (p=0.039) were at increased risk of invasive HI disease. Following meningitis, children from deprived areas were more likely to suffer sensorineural hearing loss (p=0.035). Case fatality was higher in the second period of the study, although not significantly so (OR=3.64, 0.88 to 15.05).

Conclusion: This four year study provides the first detailed account of the relationship between deprivation, , socioeconomic risk factors, ethnic group, and invasive HI disease in Britain. The incidence of the disease fell dramatically in the post-conjugate vaccine period. A number of socioeconomic risk factors were identified in the second period of the study. The data suggest that although Hib conjugate vaccine has greatly reduced the incidence of disease, children from deprived areas remain at greater risk than children in more affluent areas. They also indicate that the disease is still responsible for considerable sequelae and mortality.

Keywords: *H influenzae*, immunisation, deprivation, risk factors, ethnicity, West Midlands

LIST OF ABBREVIATIONS

χ^2	chi square
κ	kappa statistic
AIDS	Acquired Immune Deficiency Syndrome
ASLIB	Association of Special Libraries and Information Bureaux
ASSIA	Applied Social Science Index and Abstracts
AVF	Apparent Hib conjugate vaccine failure
BPA	British Paediatric Association
BPSU	British Paediatric Surveillance Unit
CDSC	Communicable Disease Surveillance Centre
CI	Confidence Intervals
CIE	Countercurrent Immunoelectrophoresis
CIU	Cancer Intelligence Unit
CNS	Central Nervous System
CoA	Co-Agglutination
COVER	Cover Of Vaccination Evaluated Rapidly
CRER	Centre for Research in Ethnic Relations
CsCDC	Consultants in Communicable Disease Control
CSF	Cerebrospinal Fluid
CVI	Children's Vaccine Initiative
DMF	Decayed, Missing and Filled
DT	Diphtheria and Tetanus vaccine
DTP	Diphtheria, Tetanus and Pertussis vaccine
DXM	Dexamethasone
ED	Enumeration District
ESRC	Economic and Social Research Council
ESRI	Environmental Systems Research Institute
EPI	Expanded Programme on Immunisation
GP	General Practice/Practitioner
GIS	Geographic Information System
HA	Health Authority
Hb	Haemoglobin
HbOC	*Haemophilus* type b oligosaccharide conjugate vaccine
HBV	Hepatitis B Vaccine
HI	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
HICARE	*Haemophilus Influenzae* Case Register
HIV	Human Immunodeficiency Virus
HFA 2000	Health For All by the year 2000
HLA	Human Leucocyte Antigen

ICD	International Classification of Disease
ICP	Increased Intracranial Pressure
Ig	Immunoglobulin
IL-1β	Interleukin-1 beta
IPV	Inactivated polio vaccine
ITU	Intensive Therapy Unit
JISC	Joint Information Systems Committee
LBW	Low birthweight
LGA	Local government area
LPA	Latex Particle Agglutination
MIDAS	Manchester Information Datasets and Associated Services
MMR	Measles, Mumps and Rubella vaccine
NBMRS	National Bacterial Meningitis Reporting System
NA	Not Available or not calculable from the available evidence
NAD	Nicotinamide Adenine Dinucleotide
NHS	National Health Service
NK	Not Known
NSA	Non-South Asian
ONS	Office of National Statistics
OR	Odds Ratios
OPCS	Office of Populations Census and Surveys
OPV	Oral polio vaccine
OVG	Oxford Vaccine Group
p	probability value
PCR	Polymerase Chain Reaction
PHL	Public Health Laboratory
PHLS	Public Health Laboratory Service
PXS	Prophylaxis
PRP	Polyribosyl Ribitol Phosphate
PRP-D	PRP-diphtheria toxoid conjugate vaccine
PRP-OMP	PRP-outer membrane protein conjugate vaccine
PRP-T	PRP-tetanus toxoid conjugate vaccine
RCGP	Royal College of General Practitioners
RGSC	Registrar General's Social Class
RR	Relative Risk
SA	South Asian
SAS	Small Areas Statistics
SCMO	Senior Clinical Medical Officer
SCOTDEP	Scottish deprivation (or Carstairs and Morris) score
SES	Socioeconomic status
SIDS	Sudden Infant Death Syndrome
SNHL	Sensorineural Hearing Loss
TNF	Tumour Necrosis Factor

TVF	True Hib-conjugate vaccine failure
UPA	Underprivileged Area (or Jarman) score
URTI	Upper respiratory tract infection
VAT	Value Added Tax
VTEC	Verocytotoxin-producing *Escherichia Coli*
WHO	World Health Organisation
WMHR	West Midlands Health Region
WMMC	West Midlands Metropolitan County

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1 Olowokure B, Blair I, Spencer N, Hawker J. Surveillance of *Haemophilus influenzae* disease: comparison of surveillance systems and reporting patterns in the pre-Hib and post-Hib conjugate vaccine periods. *Internationaler Kongress, Public Health: Entwicklungen und potentiale.* Freiburg, Germany: October 1999 (abstract accepted for oral presentation and will be subsequently published in the journal *Das Gesundheitswesen*).

2 Olowokure B, Blair I, Spencer N. Environmental risk factors for invasive *Haemophilus influenzae* disease identified with Geographic Information Systems in the post-Hib conjugate vaccine era. *European Public Health Association 1998 Annual Meeting.* Göteborg, Sweden: December 1998 (oral presentation).

3 Olowokure B, Blair I, Hawker J, Spencer N. Risk factors for invasive *Haemophilus influenzae* disease in the post-conjugate vaccine era. *5th conference of the Federation of Infection Societies.* Manchester, England: November 1998 (poster presentation).

4 Olowokure B, Blair I, Spencer N. Invasive *Haemophilus influenzae* disease and Hib conjugate vaccine: describing the changing epidemiology in the West Midlands. *1st annual meeting of the Royal College of Paediatrics and Child Health.* York, England: April 1997 (oral presentation).

CHAPTER 1

INTRODUCTION

INTRODUCTION

The practice of medicine in general and paediatrics in particular was altered dramatically two hundred years ago when Edward Jenner inoculated James Phipps with cowpox material taken from a dairy maid, and provided the boy with protection against smallpox.[1] Since then numerous infectious diseases have been targeted for eradication or elimination, and vaccine research and development have contributed to the decline in mortality and morbidity associated with infectious diseases among young children.

It is young children living in socioeconomically deprived conditions who are the focus of this study. The discussion which follows highlights the continuing importance of infectious diseases and then provides a brief historical and scientific background to the study. It also discusses inequalities in health and its association with infectious diseases in childhood. There is also a brief review of the epidemiology of invasive *H influenzae* disease with the focus on socioeconomic risk factors associated with the disease. The chapter concludes with an overview of the thesis.

1.1 Why communicable diseases are still important

Communicable diseases in general, and childhood communicable diseases in particular, are no longer leading causes of morbidity and mortality in 'developed' countries. Nevertheless, they still arouse considerable public interest and remain of

significant scientific, clinical, and public health importance as they continue to present a global challenge. Their continued pre-eminence is supported by evidence which may be grouped into four main areas.

Firstly, there are the phenomenal economic and human costs associated with infectious diseases. Direct and indirect costs are believed to exceed $120 billion annually worldwide.[2] The World Health Organisation (WHO) estimates that 28% of all deaths globally are attributable to infectious diseases.[3] They also estimate that 2.9 million vaccine preventable deaths occur each year, the majority of these as a result of measles.[3] In England and Wales infectious diseases are responsible for approximately 50% of consultations with general practitioners,[4] and 20% of deaths in infants and children.[5]

Secondly, there have been continuing advances and novel approaches to identifying causal pathogens, and developing vaccines in order to further reduce the burden of infectious diseases. Immunoassays and the polymerase chain reaction (PCR) are two of the more recently available microbiologic diagnostic techniques.[6] Genetic engineering in the form of genetic recombination,[7] the pursuit of methods for administering vaccines without a needle and syringe,[7] the quest for effective combination vaccines[8] (of which MMR [measles, mumps and rubella] is an established model) and microencapsulated antigens[9] are just a few examples of the results of vaccine research and development.

The third indicator of the continuing importance of communicable diseases is the availability of numerous conferences, journals and articles to inform and provide areas of debate, including a new journal dedicated to emerging infectious diseases.[10]

Finally, there is the continuing challenge provided by diseases such as tuberculosis,[11,12] and influenza,[13] as well as the recent recognition of emerging and re-emerging infectious diseases. In recognition of their importance, the WHO established a new division to monitor and co-ordinate responses to emerging and re-emerging infectious diseases in 1995.[14]

Emerging infectious diseases have been defined either as those which are genuinely new diseases or newly identified aetiologic agents of known diseases or syndromes.[2] In a recent review article, McDade identified a number of infectious diseases, syndromes and pathogens which have emerged in the last two decades.[2] These included, Hantavirus pulmonary syndrome, acquired immune deficiency syndrome (AIDS), Hepatitis E virus, *Borrelia burgdoferi,* (Lyme disease), verocytotoxin-producing *Escherichia coli* (VTEC), human immunodeficiency virus (HIV), *Helicobacter pylori* and hepatitis C virus. Recent years have also seen the resurgence (or re-emergence) of diseases and organisms thought to be under control.[2,13] Examples are tuberculosis, diphtheria, Ebola fever, cholera and invasive necrotising group A streptococci. Infectious diseases in this category are previously recognised pathogens which have typically increased in incidence, expanded into new geographic areas or threaten new populations.

Several developments may have contributed to this change in infectious disease epidemiology. These include changing microbial resistance to antibiotics, developments in agricultural and livestock practices, environmental changes, population growth, urban migration, rapid international travel, political change, armed conflict, and increasing social and material inequalities.[2,15,16]

Examination of populations living in the same geographic location however, indicates that they do not appear to be equally susceptible to infectious diseases[17-19] or chronic diseases,[20-23] and experience differences in life expectancy.[23-25]

With regard to the differential risk of acquiring communicable disease, researchers have put forward a number of theories. One of the most favoured is the relationship between the social and economic circumstances of an individual and their health. Illness is said to be related to the social and economic conditions in which a person lives, and the association between infectious disease and socioeconomic circumstance is well documented.[17,19,26-30]

1.2 Background

In the past human diseases such as tuberculosis, smallpox, plague and leprosy decimated human populations, and were thought to be the work of some supernatural power, or a divine visitation for sinful behaviour.[1,31] The Old Testament also contains several examples of disease as punishment. An example is seen in Exodus 9:16:[32]

"Suddenly lice infested the entire nation"

Epidemiology and other branches of medicine have however rapidly advanced our knowledge of infectious diseases and have made their prevention, control and eradication a possibility.

Historically, the eighteenth and nineteenth centuries are sometimes referred to as "The Golden Age of Bacteriology".[33] During this time biomedicine made great strides with many new and exciting discoveries following each other in rapid succession. Amongst these were Snow's contribution regarding cholera, Pasteur's germ theory, and Koch's discovery of the tubercle bacillus as the cause of tuberculosis.[1] From this discovery, and several others which he made, Koch showed that many diseases were the result of infection by a single specific bacteria.

This led to the famous Koch postulates which defined the conditions that must be established before a particular infective agent can be accepted as the cause of a specific disease.[1] Although valuable, especially in the study of the cause of infectious diseases, they ignored the diversity of contributing factors in the environment, and in the individual which give rise to the final manifestations of the disease process. Koch's "socially blind" model was disputed by eminent biomedical researchers such as Pasteur, Pettenkofer, and Virchow, who believed that something more than the micro-organism was involved in disease causation.[34]

Hippocrates, almost 2000 years previously, had in fact pointed out that in order to prevent disease one needed an understanding of its cause, and should consider not only individual factors but environmental influences as well.[35] In the nineteenth century Edwin Chadwick, John Snow, William Farr and others added to this by

providing the foundations for modern epidemiological research and social medicine through their work on cholera.[1] During this period there was also a rapid decline in infectious disease mortality. McKeown has argued that this occurred as a result of improvements in housing and nutrition and not specific therapeutic interventions.[36,37] However, following these social improvements, vaccination contributed to further decreases in infectious disease mortality.[36] The eradication of smallpox[38]and the potential eradication of polio in the near future[39]are more recent examples of the achievements of vaccination. As a result of the decline in infectious disease prevalence, interest in examining the role of the environment and socioeconomic circumstance in contributing to the causation of infectious diseases decreased and scientific laboratory-based medicine which concentrates on treatment rather than prevention is now dominant.

The inadequacies of the germ theory are now well recognised and disease causation is now conceptualised as being multicausal. This explanation, which takes into account many interacting variables such as demographic, biologic, ecologic, social and economic factors, is more appropriate than the simplistic monocausal model. These views are rapidly gaining ground especially with the increasing interest in examining the health experiences of different sectors of the population in relation to socioeconomic status. Almost universally there appears to be a social gradient to health, with the least affluent members of society experiencing greater morbidity and mortality.[23,40-44]

It is acknowledged that there is a third causal model which argues the case for a psychosomatic cause of infectious disease related to stressful life events or disrupted social circumstance. Several studies have investigated the role of these factors in the causation of infectious diseases. Meyer and Haggerty conducted a prospective study which demonstrated a positive association between stressful life events in children and streptococcal throat infections.[45] Boyce et al found that an increasing number of life events were associated with increasing duration of illness and illness severity in upper respiratory tract infections in children.[46] A recent case-control study by Stanwell-Smith et al in Gloucester demonstrated an association between the occurrence of meningococcal disease in children less than five years of age and a number of life events including marital arguments and change of residence.[47]

Examination of stressful life events is however beyond the scope of this particular study. The present study will concentrate on exploring the relationship between socioeconomic disadvantage and primary invasive *H influenzae* disease using an ecological approach.

1.3 Inequalities in health

A variety of health-related risk factors have been associated with being in a lower social class or a disadvantaged group. Examples are inappropriate qualitative and quantitative nutrition,[48] a dangerous environment,[49] low birth weight,[50] poor quality housing,[51] unemployment[52] and poor access to health services.[53] These risk

factors are manifested by increased morbidity and mortality rates in the poorer sections of society. The differences in health status seen between lower and higher socioeconomic groups are known as 'inequalities in health'.[21]

WHO recognised this problem and as part of its *Health For All by the year 2000* (HFA 2000) strategy launched in 1981, stated that:[54]

> "By the year 2000, the actual differences in health status between countries and between groups within countries should be reduced by at least 25%, by improving the level of health of disadvantaged nations and groups."

In 1985, WHO published targets for HFA 2000 to assist member countries in setting their own.

The, then Conservative, British government endorsed the WHO targets and in 1990 unveiled its *Health of the Nation* initiative.[55] This document was widely criticised for focusing on behavioural and lifestyle issues, and the individual, rather than addressing social and economic disadvantage and deprivation as causes of ill-health.[56,57]

Prior to this research into the relationship between illness and poor socioeconomic circumstance in the UK was given renewed emphasis with the publication of the Black report in 1980,[21] and the Health Education Authority's 'Health divide' in 1987.[21]

The Black report defined inequalities in health as:[21]

> "Health outcomes which have been socially or economically determined."

Its analysis of these inequalities were based on comparisons of mortality and morbidity using occupational status, as defined by the Registrar General, to measure socioeconomic status. The recommendations of the Black report generated intense debate on the relationships between deprivation and health, as well as a great deal of research activity.

The Black report was however criticised for a number of reasons. One criticism of relevance to this thesis relates to its use of the Registrar General's occupational classification. This has been shown to have several shortcomings.[58] These mainly centred around its validity as a measure of social affluence or deprivation, and included its inability to provide an adequate indicator of the material conditions in which a large number of families live, as well as, its inadequacy in responding to the social and economic changes in the past few decades which have resulted in an increase in single-parent families and the development of an "underclass".[59-63] These social groups, along with working mothers, children and the elderly, are not included in the Registrar General's occupational classification and may be suffering deprivation or poverty not reflected in such a measure.[63,64]

As a result of the problems associated with using the Registrar Generals classification, the examination of inequalities in health using measures of deprivation based on area characteristics has been recommended.[23,65] This type of analysis uses social, geographic and environmental data obtained from the decennial Census at various geographic levels and applies them to individuals. This approach aims to eliminate many of the problems associated with employing occupational class as an

indicator of socioeconomic circumstance, but is subject to ecological (or aggregation) bias.[66] Ecological studies are also prone to confounding and effect modification which results in the 'ecological fallacy'.[66,67] This occurs when relationships observed at aggregated area levels are attributed to individuals residing in that area.[67]

Nevertheless, area measures are being increasingly used to provide evidence for the influence of material deprivation on various aspects of health. Furthermore, reports have shown that they may be comparable with individual measures of social status especially where the smallest geographical areas are used to group individuals.[67,68] The rapid development of geographic information systems (GIS) in the past decade has facilitated this process. GIS integrate epidemiologic and environmental data allowing detailed analysis of the links between the environmental characteristics of an area and the risk of disease.[69] This technique has several applications in relation to health including epidemiologic investigations and the targeting of scarce resources to identified areas.[70,71]

Area characteristics have been shown to have a significant influence on health as residents have little or no control over their physical environment. This is especially so in the case of the poorest families living in the most deprived areas. These areas generally have high levels of unemployment, large numbers of single parent families, low owner-occupancy rates and poor housing.[21,23,73] Furthermore, when comparing the availability of medical care in affluent areas with that in deprived areas, Tudor Hart found that:[53]

> "The availability of good medical care tends to vary inversely with the needs of the population served."

This statement, known as the 'inverse care law' is still relevant more than 25 years after it was first published.

In an attempt to identify environmental characteristics of areas associated with social and economic deprivation and increased risk of disease, several researchers have devised indices of deprivation. Those of Townsend,[23] Carstairs and Morris[73] and Jarman[74]are the best known. These composite measures of deprivation use transformed social and economic data from the decennial census to provide a defined geographic area with a deprivation score.

Various explanations for how relative social and economic positioning have led to social inequalities in health have been proposed, with the artefact theory, cultural/behavioural factors, the materialist/structural explanation, and theories of natural/social selection being the most widely described.[21] Amongst these competing theories, the Black report pointed to material and social circumstances as the major contributors to inequalities in health.[21]

The Black report provided recommendations to reduce inequalities in health some of which were specifically targeted at improving the health of children and families.[21] Amongst these were recommendations regarding health education, school health and environmental changes. The report however only gave a passing mention to immunisation and neglected to mention the importance of communicable diseases as a consequence of deprivation.

British studies examining the relationship between inequalities and health have concentrated on mortality,[75-77] and health service utilisation.[52,78,79] with relatively few reports on the association between morbidity and deprivation. Although morbidity is more difficult to measure than mortality, Blaxter has argued that it is possibly a more important indicator of inequality, especially with life expectancy at birth increasing.[80]

A number of recent publications have indicated that social and economic reform are required to address the issue of inequalities in health rather than a predominantly medical approach.[81-84] The current (Labour) government appears to have placed this issue high on its agenda and has published a Green paper 'Our Healthier Nation' which attempts to tackle this area of concern.[85]

1.4 Links between socioeconomic disadvantage and infectious diseases in children

Inequalities in health between children from the most disadvantaged areas and those from the most affluent areas is acknowledged to be a major public health problem, and has been demonstrated for a number of variables including: perinatal and infant mortality rates,[21] sudden infant death syndrome (SIDS),[86] low birth weight,[87] child abuse,[88] developmental delay,[89] growth[90] and accidental injury.[49] Relatively few studies have examined the relationship between socioeconomic disadvantage and infectious diseases in childhood. Of those that have, a number indicate that tuberculosis,[18] bronchiolitis,[26] gastroenteritis,[91] dental caries,[92] meningococcal

meningitis,[47] whooping cough[93] and HIV[94] are related to living in areas of deprivation or having a low socioeconomic status. Low socioeconomic status in childhood is also believed to be linked to infectious diseases such as *Helicobacter pylori* in adult life.[95]

There are also infectious diseases, such as otitis media where the relationship with socioeconomic disadvantage is not clear.[96,97] Others, for example chickenpox, suggest that children from affluent areas appear to be at greater risk.[98]

Disadvantaged families also tend to have problems accessing and utilising health services,[99-101] have longer hospital admissions[102] and experience multiple admissions.[103] All of which may contribute to increased risk of morbidity and mortality from infectious diseases. Furthermore, they may live in adverse environmental and social conditions, which in addition to influencing their ability to use health services may increase their risk of acquiring an infectious disease. A number of studies have demonstrated an association between poor housing conditions and respiratory tract infections,[51,104,105] while overcrowded households are one of the most frequently cited risk factors for infection.[17,18,95,98]

Although there is a paucity of published literature which has examined the association between socioeconomic disadvantage and infectious diseases in children, a large amount of literature on risk factors associated with immunisation uptake is available.[106-115] However, a systematic review of the literature revealed a scarcity of British data analysing risk factors associated with the uptake of *H influenzae* type b (Hib) conjugate vaccine.

1.5 Epidemiology of *H influenzae*

Six strains (or serotypes) of *H influenzae* are responsible for the majority of cases of invasive disease attributed to this organism and these are designated 'a' through to 'f' (table 1.1).[116]

Table 1.1: *Haemophilus influenzae*: Serotypes and disease syndromes

Serotypes of *H influenzae*	Disease syndromes
Encapsulated: type b	Meningitis; epiglottitis; cellulitis; bacteraemia; septic arthritis; osteomyelitis; pneumonia; empyema; pericarditis.
Encapsulated (non-type b): types a, c, d, e, f	Rarely cause invasive disease.
Non-encapsulated	Bronchitis; otitis media; sinusitis; conjunctivits; urinary tract infections.

Adapted from Booy et al[116]

The strain which is a major cause of severe bacterial infection in young children throughout the world is type b (Hib), which may cause meningitis, epiglottitis, pneumonia and other systemic diseases.[118-120] Children aged under 5 years are particularly susceptible to invasive Hib disease.[121] The high proportion of deaths,[119,122-124] neurologic sequelae[121,125,126] and antibiotic resistance[127,128] worldwide are strong indicators of the need for an effective vaccine. In addition, there has been controversy surrounding the benefits of using dexamethasone to reduce mortality and sequelae, particularly hearing loss, in children with *Haemophilus* meningitis.[129] Furthermore, despite the advent of new and more powerful antibiotics for the treatment of meningitis there has not been an appreciable fall in mortality or morbidity resulting from Hib meningitis. These and other factors probably led to increased

vaccine research activity using the polysaccharide polyribosyl ribitol phosphate (PRP) capsule of the organism. The results of which were the production of a number of conjugate vaccines to combat invasive Hib diseases (table 1.2).

Table 1.2: *Haemophilus influenzae* type b conjugate vaccines

Conjugate vaccine		Manufacturer
PRP-D	a conjugate of PRP and diphtheria toxoid	Connaught Laboratories
PRP-T*	a conjugate of PRP and tetanus toxoid	Pasteur-Merieux
PRP-OMP	a conjugate of PRP and a meningococcal outer membrane protein	Merck, Sharp and Dohme
HbOC	a conjugate of PRP and CRM_{17} mutant diphtheria protein	Lederle-Praxis

*Hib conjugate vaccine used in the UK
Adapted from American Academy of Pediatrics[130]

In the pre-Hib conjugate vaccine era, Hib was the most common cause of bacterial meningitis in children less than 5 years of age in the United States, with incidence rates ranging from 23 to 67 per 100 000.[131-133] The introduction of Hib conjugate vaccines resulted in a rapid decline in the incidence of invasive Hib disease in this age group to 4 to 6 per 100 000 by 1991.[134,135] Other countries which have introduced Hib conjugate vaccines into their immunisation schedules have witnessed similar reductions.[136-138]

Surveys of invasive *H influenzae* meningitis in various parts of the UK in the pre-Hib conjugate vaccine period, revealed incidence rates ranging from 20 to 40 per 100 000 in children aged less than 5 years.[139-142] These were associated with mortality rates of up to 5% and complications in approximately 10% of survivors. Hib

conjugate vaccine was introduced into the UK immunisation schedule in October 1992, and by 1993-4 disease incidence had fallen to an estimated 2 per 100 000.[143]

Despite this impressive progress, the true incidence of invasive *H influenzae* disease is not known as non-meningitic diseases are not notifiable and estimates are based mainly on epidemiological studies of *Haemophilus* meningitis which have relied on passive surveillance systems. Underreporting is known to occur, and several reports indicate that *Haemophilus* meningitis suffers more from incomplete notification than meningococcal meningitis.[144,145] Furthermore, little information on preventive practices in the UK related to invasive *H influenzae* diseases such as the use of dexamethasone and chemoprophylaxis are available.

1.6 Socioeconomic disadvantage and *H influenzae*

Invasive *H influenzae* disease has been consistently linked with various markers of social and material disadvantage in several countries. These and other risk factors, all of which may be classified using the classical public health triad of host, agent and environment, interact to increase a child's risk of developing invasive *H influenzae* disease.[146,147]

Those considered to increase the risk of *H influenzae* disease in children by increasing the risk of exposure (environmental factors) include household crowding,[148,149] living in areas of high population density,[132] parental smoking,[149] low family income,[150] coming from a single parent family,[151,152] belonging to certain ethnic

groups,[119,153] having school age siblings,[154] and attending day-care outside the home.[155] Low socioeconomic status has also been associated with an increased likelihood of sequelae following *H influenzae* meningitis.[156]

Other factors operate by increasing the child's susceptibility to infection (host factors) and the following are among those implicated: low birthweight,[157] preceding viral infection,[158] age less than 5 years[134,142] and certain genetic factors.[157,159,160] In addition, non-breastfed infants have also been found to be at increased risk of disease.[148,155]

There are also factors related to the pathogenicity of the bacterium (agent factors) which may increase the likelihood of diseases occurrence, including the invasiveness of the organism.[146]

Although definitions vary and different methodologies are used, the majority of these factors have been examined in studies conducted in different parts of the world. Much of the available literature has however originated from North America, with sizeable contributions from Scandinavia and Australia. There are no comparable British data. It is important that risk factors are determined using a population-based approach, and that any changes following the introduction of Hib conjugate vaccine are evaluated.

1.7 Summary

Historically the link between socioeconomic disadvantage and infectious diseases has been well documented. An explanation of the exact nature of this relationship has however proved elusive. Today, infectious diseases still present an immense challenge to public health and child health practitioners, and the quest for effective measures to control and prevent their occurrence continues. One such measure are vaccines and of particular interest to this study, the conjugate vaccines to combat invasive Hib disease. Prior to the introduction of Hib conjugate vaccines, invasive Hib disease was one of the leading causes of bacterial meningitis in children aged less than 5 years. Young age is just one risk factor linked with invasive Hib disease. Others include various markers of poor socioeconomic circumstances. These risk factors have been determined in a number of countries. However, there are no published UK data on risk factors for invasive Hib disease either prior to the introduction of Hib conjugate vaccine or following its introduction.

1.8 Overview of thesis

This chapter has provided a brief introduction to the thesis, an overview of deprivation as well as a number of socioeconomic characteristics associated with invasive *H influenzae* disease. Chapter 2 presents the aims and objectives of the study while chapter 3 provides a more detailed review of the literature. A description of the methods used to obtain data and achieve the objectives of the study are outlined in Chapter 4. The main findings of the thesis are then presented in Chapter 5. In chapter 6 the results of the study are discussed in relation to the literature, and methodological issues are profiled. Chapter 7 summarises the thesis and concludes by providing recommendations and suggesting areas for further research. Each chapter has a brief introduction which attempts to set the chapter in the context of the general framework of the thesis.

CHAPTER 2

AIMS AND OBJECTIVES OF THE STUDY

AIMS AND OBJECTIVES OF THE STUDY

The introduction of Hib conjugate vaccine provided an ideal opportunity to examine one of the most significant additions to the UK immunisation schedule in recent times. It also provided an opportunity to determine whether the introduction of a health intervention affected existing health inequalities in a multi-ethnic area of Britain. Previous British studies have not examined this question in relation to Hib disease. This study therefore set out to provide an original contribution to knowledge in this area.

2.1 Aims of the study

Previous experience with the measles vaccine has shown that even after achieving high coverage levels, differential uptake rates are likely and that some areas will fall below the levels required to block transmission.[161,162] These areas may then act as reservoirs of infection and contain groups of susceptible children.[162] Those particularly at risk are likely to be children living in deprived circumstances as they have previously been shown to have lower immunisation uptake rates.[106,113,163] There may also be cultural or ethnic factors which reduce the acceptance of immunisation amongst certain groups.[114,164]

Prior to the introduction of Hib conjugate vaccine into the UK primary immunisation schedule a number of concerns were raised. These included whether

invasive disease would occur in those who were incompletely immunised,[165] the effect the vaccine would have on non-type b *H influenzae* serotypes,[166] the duration of protection afforded by immunisation and whether a booster dose of vaccine would be required in the second year of life.[116,167] One other question that needs to be asked is how will the vaccine perform amongst the different ethnic groups in the UK, especially in view of the poor efficacy of one of the conjugate vaccines which had been highly protective in Finland but performed poorly when given to a group of Native Americans.[168]

Given that immunisation programmes carried out at local and national levels tend to control rather than eradicate the target disease, then long-term surveillance will be required. In addition, it will be important to identify and focus on vulnerable groups of children such as those who are not immunised for various reasons. These vulnerable children are the focus of this study in relation to their area socioeconomic characteristics as previous British studies on Hib disease have not examined risk factors associated with invasive *H influenzae*.

In order to evaluate the health gain achieved by Hib conjugate vaccine, it is necessary that valid and reliable epidemiological information about patterns of infection be available, both prior to and following the introduction of the vaccine. Additionally, it is desirable to have information about which factors make some children more susceptible to the disease.

The introduction of Hib conjugate vaccine provides an opportunity to explore possible risk factors for invasive *H influenzae* and determine whether they remain the same following the introduction of Hib conjugate vaccine.

Using the GIS (Geographic Information Systems) technique, together with other epidemiologic methods, links between several potential environmental risk factors and invasive *H influenzae* disease in the period prior to and following the introduction of Hib conjugate vaccine will be examined. This method will also identify population characteristics of those areas likely to require targeting of resources in order to improve and maintain high levels of uptake for Hib conjugate vaccine, as well as for future vaccines against meningococcal, pneumococcal and other diseases of childhood.

The aim of this study is to contribute to the understanding of the relative importance of deprivation and other risk factors in the aetiology and outcome of communicable diseases in children in Britain using invasive *H influenzae* disease as a model, both before and following the introduction of a public health intervention.

The working hypothesis of this study is that following the introduction of Hib conjugate vaccine children from deprived areas will not be at increased risk of invasive *H influenzae* disease compared to children from more affluent areas.

2.2 Study objectives

The objectives of this study are to:

1. explore the relationship between invasive disease and deprivation, and determine whether children from deprived areas are at increased risk of invasive *H influenzae* compared to children from more affluent areas following the introduction of Hib conjugate vaccine.
2. identify socioeconomic and environmental factors associated with the occurrence and outcome of invasive *H influenzae* disease using GIS techniques.
3. provide a register of cases of invasive *H influenzae* disease which may be used to assess the completeness of invasive *H influenzae* surveillance and identify 'vaccine failures'.
4. describe the incidence of invasive *H influenzae* meningitis and other manifestations of *H influenzae* disease in an ethnically diverse population.
5. detect any changes in the epidemiology of invasive *H influenzae* disease following introduction of Hib conjugate vaccine.
6. describe some of the clinical, laboratory and treatment characteristics associated with the disease including the use of dexamethasone and rifampicin chemoprophylaxis.

These objectives will not only identify vulnerable groups of children and their families, but will also provide a platform for the targeting of appropriate or alternative health services and other resources to areas where social and medical inequalities exist.

CHAPTER 3

LITERATURE REVIEW

LITERATURE REVIEW

The purpose of this chapter is to provide a review of the literature relating to the surveillance of communicable diseases and to discuss the epidemiology of primary invasive *H influenzae* disease. The review will also examine the risk factors associated with primary invasive disease by focusing mainly on population-based studies. In addition, the possible role played by social class, deprivation and other parameters used to classify families on a socioeconomic scale will be examined. The final section consists of an overview of preventive measures, with particular emphasis on Hib conjugate vaccines, their impact on invasive Hib disease and the occurrence of vaccine failures.

3.1 CASE ASCERTAINMENT

3.1.1 Communicable disease surveillance

Surveillance systems for communicable diseases in the UK are primarily passive and rely to a great extent on the voluntary reporting of cases by physicians, laboratories and health care facilities to local and national health departments. Although these systems are simple and inexpensive they have been shown to be incomplete and to have different degrees of accuracy.[145,169,170]

Certain specified infectious diseases are statutorily notifiable, that is doctors have a legal obligation to notify any suspected case that they encounter. Conclusions drawn from notification data may however be flawed due to

underreporting which may occur for a number of reasons. Physicians are confused as to who should notify, which diseases are notifiable and how to fulfil their statutory duty to notify.[170-173] A study by Goldacre and Miller, in the North West region of England examined the completeness of meningitis notifications in 1976.[144] They found that notifications varied by organism, age and outcome and that only 16% of *H influenzae* meningitis cases were notified compared to 50% of meningococcal meningitis cases. Furthermore, there was a low notification rate for neonates and deaths were notified less often than survivors. Harvey et al when auditing completeness of bacterial meningitis notifications found that only 35% of *H influenzae* meningitis cases had been notified compared to 65% of meningococcal cases.[173] Almost 20 years after Goldacre and Miller's[144] study, a report from Nottingham reported similar results.[145] The investigators also showed that those more frequently notified had a shorter mean duration of hospital admission than those that were not notified.

Although *H influenzae* meningitis is statutorily notifiable, other forms of invasive *H influenzae* disease are not, consequently it is difficult to obtain reliable estimates of incidence. Few studies have examined the issue in the UK and estimates have to be extrapolated from epidemiological studies which are usually focused on local situations.

Given these shortcomings and recognising the need for accurate epidemiological data prior to the introduction of Hib conjugate vaccine, the Public Health Laboratory Service (PHLS), Communicable Disease Surveillance Centre (CDSC) initiated enhanced surveillance of invasive *H influenzae* disease in six regions (East Anglia, Northern, North Western, Oxford, South Western and Wales)

in 1990.[140] Despite using the same methodology in each of the regions, a review by Macleod of the first year of surveillance revealed underreporting to the CDSC of between 15% to 41%, while the regional survey experienced underreporting of 2% to 27%.[175]

Inaccuracies in the identification of the number of cases of meningitis and other communicable diseases not only affect the estimated incidence rates, but probably results in inadequate contact tracing and failure to offer chemoprophylaxis to all those potentially at risk.

3.1.2 Disease registers

Disease registers rely on multiple sources of data such as notifications, laboratory reports and death certificates to identify cases.[176,177] They have mainly been used for chronic conditions such as cancer[176], diabetes[178] and congenital disorders.[179] Registers are also employed to monitor children with special needs, including those with sequelae following infectious diseases.[180] Disease registers can be used to monitor, evaluate and plan health services and strategies and facilitate the estimation of educational and personnel needs.[181,182] They can also facilitate epidemiological research, act as sampling frames and provide insights into demographic risk factors.[177,183] In addition they can monitor populations at risk and provide reliable estimates of the current burden of disease and sequelae of disease.[182,183] Disease registers should however be applied to geographically defined populations.[184]

Disease registers are difficult to compile as they are dependent on the goodwill and co-operation of a variety of people in identifying cases, necessitate

the handling of a large amount of confidential data, and are time-consuming requiring extensive resources.[185] Despite these drawbacks they can provide useful information about health problems and the performance of health services.

3.2 EPIDEMIOLOGY OF INVASIVE *H INFLUENZAE* DISEASE

3.2.1 Colonisation and pathogenesis

Both encapsulated and non-encapsulated strains of *H influenzae* are found in the upper respiratory tracts of most members of the population.[186] Non-encapsulated strains are more prevalent than the capsulated strains and commonly cause otitis media, bronchitis and sinusitis.[186] Rarely are they associated with invasive disease. Encapsulated *H influenzae* type b strains are found in approximately 5% of nasopharyngeal cultures of healthy children, other capsulated strains are rarely seen.[186]

Hib is transmitted from person-to-person by respiratory droplets, or contact with secretions from carriers.[187,188] The factors that cause one child to become a carrier, and another to acquire invasive disease are poorly understood. The literature shows that approximately 95% of all invasive Hib disease occurs in children less than 5 years of age.[121,141] Systemic Hib disease is uncommon in infants under 6 months of age.[117,142] This has been attributed to decreased exposure, transplacentally acquired antibodies and the protective effect of breastfeeding.[155,186]

By 5 years of age the majority of children possess protective antibodies against Hib.[186]

Colonisation with *H influenzae* is made easier with close contact, either in the home or day-care setting. In households where a case of invasive disease has occurred, colonisation rates of up to 70% in siblings, and 20% in parents have been documented.[189,190] In day-care facilities in which a case of invasive disease has occurred, point-prevalence colonisation rates of over 55% have been reported amongst the other children.[191,192] An 18 month prospective study was carried out in a day-care centre in Dallas where no cases of invasive *H influenzae* had occurred.[193] The researchers reported that approximately 70% of children aged 18-35 months were colonised at some time during the study. This suggests that these children may be the source of colonisation in younger children.

There is also some evidence to suggest that preceding viral upper respiratory tract infection may increase Hib nasal colonisation and the possibility of bacteraemia.[158,194] The exact pathogenesis of invasive disease however, remains obscure. Much of what is known has been obtained from animal models, and it is believed that in invasive *H influenzae* disease, the organisms cross the mucosal barriers of the nasopharynx and enter the bloodstream.[195] The exact route is unknown, but they are thought to travel via the lymph system or within lymphocytes seeding all serous surfaces. This may cause meningitis, pneumonia or other invasive disease syndromes.[195]

3.2.2 Clinical disease

Although meningitis is the most common form of invasive Hib disease and the most widely reported, several other syndromes are recognised. Studies have shown that approximately 30-50% of children with culture proven invasive *H influenzae* disease have diagnoses which are non-meningitic.[117,126,196-198] These include epiglottitis, pneumonia, cellulitis, septic arthritis, osteomyelitis and septicaemia.

3.2.2.1 Meningitis

This is an inflammation of the meninges, and commonly refers to the arachnoid membrane, the subarachnoid space and the pia mater covering the brain.[199]

It is characterised by the presence of polymorphonuclear cells in the cerebrospinal fluid (CSF).

There are no particular clues to the aetiological diagnosis of *H influenzae* meningitis. History taking and clinical examination will reveal similarities to other causes of bacterial meningitis. The clinical features are well described in a recent review of the literature by Tunkel and Scheld.[200] The onset of disease may be sudden or occur insidiously, with signs and symptoms being less specific in young infants.[201] Diagnosis is primarily by isolation of *H influenzae* from either the CSF (obtained by lumbar puncture) or blood.[202]

It is recommended that suspected meningitis be treated with antibiotics prior to hospital admission.[203,204] This is believed to reduce the mortality and sequelae associated with the disease.[205,206] A study from the United States has

however indicated that the converse may actually occur as the duration and course of the disease in pretreated children may be altered.[207]

Meningitis is responsible for 40-70% of cases of invasive *H influenzae* disease, and in most populations is found mainly in children below 2 years of age.[117,123,208,209] It is a life-threatening infection which may result in neurological sequelae or death. Reports indicate that 10-40% of children suffer neurological sequelae following an episode of *H influenzae* meningitis.[121,124,125,209,210] Examples of neurological sequelae experienced by these children include learning disabilities, behavioural disorders, emotional problems, seizures and hearing loss.[210-214] These sequelae may occur alone or in any combination. Sensorineural hearing loss (SNHL) is one of the most devastating sequelae of meningitis, and may affect up to 20% of children following *H influenzae* meningitis.[156,215] SNHL may also be associated with other problems such as ataxia, developmental delay, learning disabilities and behavioural problems. It is important that all children should have an age-appropriate test for hearing loss following an episode of bacterial meningitis. Unfortunately, recent research in Britain has shown that hearing tests are not routinely carried out following an episode of bacterial meningitis.[216,217]

In recent years, dexamethasone has been advocated as adjunctive therapy for *H influenzae* meningitis.[218-221] It appears to beneficially alter the host response to infection by decreasing the inflammatory reaction, and this action is believed to reduce mortality and neurological sequelae, particularly hearing loss.[219-221] Section 3.5.4 contains more detail on this aspect of the review.

Mortality from *H influenzae* meningitis has been reported to range from 1-5% in industrialised countries.[139,209] It may however reach up to 40% in less industrialised countries.[123,124,222]

3.2.2.2 Epiglottitis

This refers to a rapidly progressive infection of the epiglottis and surrounding structures, and may cause life-threatening airway obstruction.[223]

Clinically, these children may present with sudden onset of fever, respiratory distress, dysphagia, drooling (because of inability to swallow saliva) and toxicity.[224] Visualisation of a "cherry red" oedematous epiglottis on direct or indirect laryngoscopy is said to be diagnostic. It is essential that airway patency is maintained, and nasotracheal intubation is the preferred method.[225] Research indicates that where blood cultures are performed in children, 70-90% of cases of acute bacterial epiglottitis are due to Hib.[226-229]

In mainly Caucasian populations, epiglottitis is commonly the major non-meningitic manifestation of invasive *H influenzae* disease. It has been observed in 16-37% of children with invasive disease.[209,230-232] In Britain blood culture confirmed incidence rates of up to 6.2 per 100 000 children aged less than 5 years have been reported.[121,233] These are similar to those reported from Europe and parts of the United States.[126,230,234,235]

There are several epidemiological features associated with this disease. A greater proportion of males are affected than females. Male:female ratios of between 1.4:1 and 2.1:1 have been reported for epiglottitis[209,226,231,232] compared to almost equal gender ratios for meningitis.[139,209] Also, in contrast to *H influenzae*

meningitis, children presenting with epiglottitis have been noted to be older, usually between 2 to 4 years of age with a peak incidence occurring at around the age of 3 years.[228,229] Recent reports from North America have indicated a downward shift in the age of presentation, with up to 36% of children presenting before their second birthday, compared to 20% in previous accounts.[236] In addition, there have been reports of a decrease in the incidence of the disease following introduction of Hib conjugate vaccine.[135,237,238]

Epiglottitis has been reported as absent or extremely rare in the native populations of the United States,[153] Israel[234] and Australia.[119] Similar reports have also been obtained from Africa,[196] Hong Kong[239] and South America.[222] This particular epidemiological feature is seen in populations with a high incidence of Hib disease and is thought to be related to the earlier age of disease occurrence in these populations.

A number of reports have indicated that secondary foci are uncommon.[117,226] The most common extraepioglottic infection appears to be pneumonia, which has been identified in up to 25% of patients.[223,240,241] In children the case fatality rate is low, generally between 0% and 3% in most series.[223,224,229]

3.2.2.3 Pneumonia

As a proportion of invasive *H influenzae* disease, pneumonia is usually responsible for under 15% of cases in industrialised countries.[117,209,233,242] In other parts of the world, it may contribute up to 25% of invasive *H influenzae* cases.[196,243] The relative frequency of pneumonia is high in certain populations such as the Australian Aborigines, where in one series 43% of infections were due to

pneumonia, compared with 30% for meningitis.[119] Research has indicated that up to 40% of *H influenzae* pneumonia cases may have evidence of infection elsewhere, for example meningitis or epiglottitis.[117,242]

Defining the aetiology of bacterial pneumonia has been a problem for many years, and has probably led to an underestimation of the impact of *H influenzae* pneumonia. In studies where blood culture has been used as the diagnostic tool most cases of *H influenzae* pneumonia were attributed to serotype b.[244,245] However, in these studies only a small proportion of isolates yielded positive cultures.

In a study conducted in Papua New Guinea, Shann et al reported that when lung aspiration was used only 5 of 31 (16%) strains of *H influenzae* serotyped were type b.[245] Non-serotypable strains accounted for more than half (58%, 18 of 31) of the remainder, with other serotypes contributing the remaining 8 (26%). Other reports support the finding that non-serotypable strains of *H influenzae* are important causes of pneumonia in children.[246-248]

Funkhouser and colleagues have pointed out that these contradictory results may confound the role played by Hib conjugate vaccines in the prevention of *H influenzae* pneumonia.[244]

Mortality from pneumonia due to *H influenzae* is low in Western countries, less than 5%,[242,249] it may be as high as 16% in other areas.[196,245]

3.2.2.4 Cellulitis

H influenzae is usually the cause of acute localised inflammation of the soft tissue, involving the face, head or neck.[117] The disease is generally of sudden

onset, and characterised by an area which is raised warm and tender.[120] Diagnosis depends on isolation by blood culture.[195] The literature indicates that cellulitis accounts for between 4% to 12% of invasive *H influenzae* cases.[126,197,234] Because of the accompanying bacteraemia, secondary foci such as meningitis may develop.[117,242]

3.2.2.5 Septic arthritis

Septic arthritis may occur as a result of bacteria entering the joint space from the circulation, alternatively, it may follow trauma or occur as an extension of osteomyelitis.[250] The most common pathogen in all age groups is *Staphylococcus aureus*, while *H influenzae* is predominantly seen in infants under 2 years of age.[251,252] There are however no specific features to distinguish septic arthritis due to *Staphylococcus aureus* and other bacteria from that caused by *H influenzae*. The larger joints are commonly affected, and children generally present with fever and a warm, swollen joint, which is painful when moved.[253] Diagnosis is by presenting history, physical examination, blood culture and joint aspiration, while antigen detection tests may be performed on urine and joint aspirates to identify the causative agent.[250] Surgical drainage of affected joints is performed and should be followed by long-term follow-up to detect serious sequelae such as limited joint mobility.[250,254] In studies where this manifestation of invasive *H influenzae* disease has been recorded, it represents up to 8% of cases.[119,196,231,233] Some reports group septic arthritis and osteomyelitis together as "bone and joint infections", where this is the case, together they may account for about 7% of cases.[139,198]

3.2.2.6 Osteomyelitis

H influenzae type b osteomyelitis is mainly seen in children under the age of 2 years.[117] Fever and localised bone tenderness, together with local inflammation are common symptoms.[253] In reported series of invasive *H influenzae* disease, osteomyelitis has been found in about 4% of children.[117,230]

3.2.2.7 Bacteraemia

H influenzae bacteraemia has been defined as the presence of the bacterium in the blood, without a recognisable focus of infection.[195] The child usually an infant, presents with fever, anorexia and lethargy.[255] In most series it is present in 2% to 14% of cases,[125,249,256] however more than one third of cases in a group of Australian Aborigine children were recorded as having bacteraemia.[257]

3.2.2.8 Neonatal sepsis

H influenzae is not commonly found in the maternal genitourinary tract.[258,259] However, when present the organism is associated with a high risk of neonatal infection and may lead to severe and often fatal neonatal sepsis.[260] The condition is more commonly observed in premature and low birth weight babies.[260] Obstetric complications implicated in the aetiology of this disease include maternal fever, chorioamnionitis, prolonged rupture of the membranes and vaginal discharge.[261,262] Bacterial infection is believed to occur when the neonate passes through the birth canal, and this may lead to bacteraemia and a number of systemic diseases such as meningitis, arthritis, pneumonia and septicaemia.[262] *H influenzae* type b has been identified as a cause of neonatal sepsis, although non-

typable *H influenzae* are more common.[260,261] The disease is associated with a high mortality rate, with up to 70% previously reported.[263,264]

3.2.2.9 Other systemic diseases

Uncommon disease manifestations have been reported in children with *H influenzae* disease. These include endocarditis, pericarditis, abscesses, and pyelonephritis.[120,195] Diagnosis is usually by blood culture together with the specific signs and symptoms associated with each disease entity.

3.2.3 Incidence

Much of the published data on invasive *H influenzae* (HI) disease has originated from the USA, where Hib meningitis has been the leading cause of childhood meningitis for many years. In Europe, the major pathogen in most countries is *Neisseria meningitidis*, and as such there have been few reports on the incidence of *H influenzae*. In recent years, with the development of vaccines offering protection against Hib disease, epidemiological reports have increased. However, this has mainly increased the wealth of information on Hib meningitis, while the epidemiology of other forms of invasive *H influenzae* disease remain less well characterised.

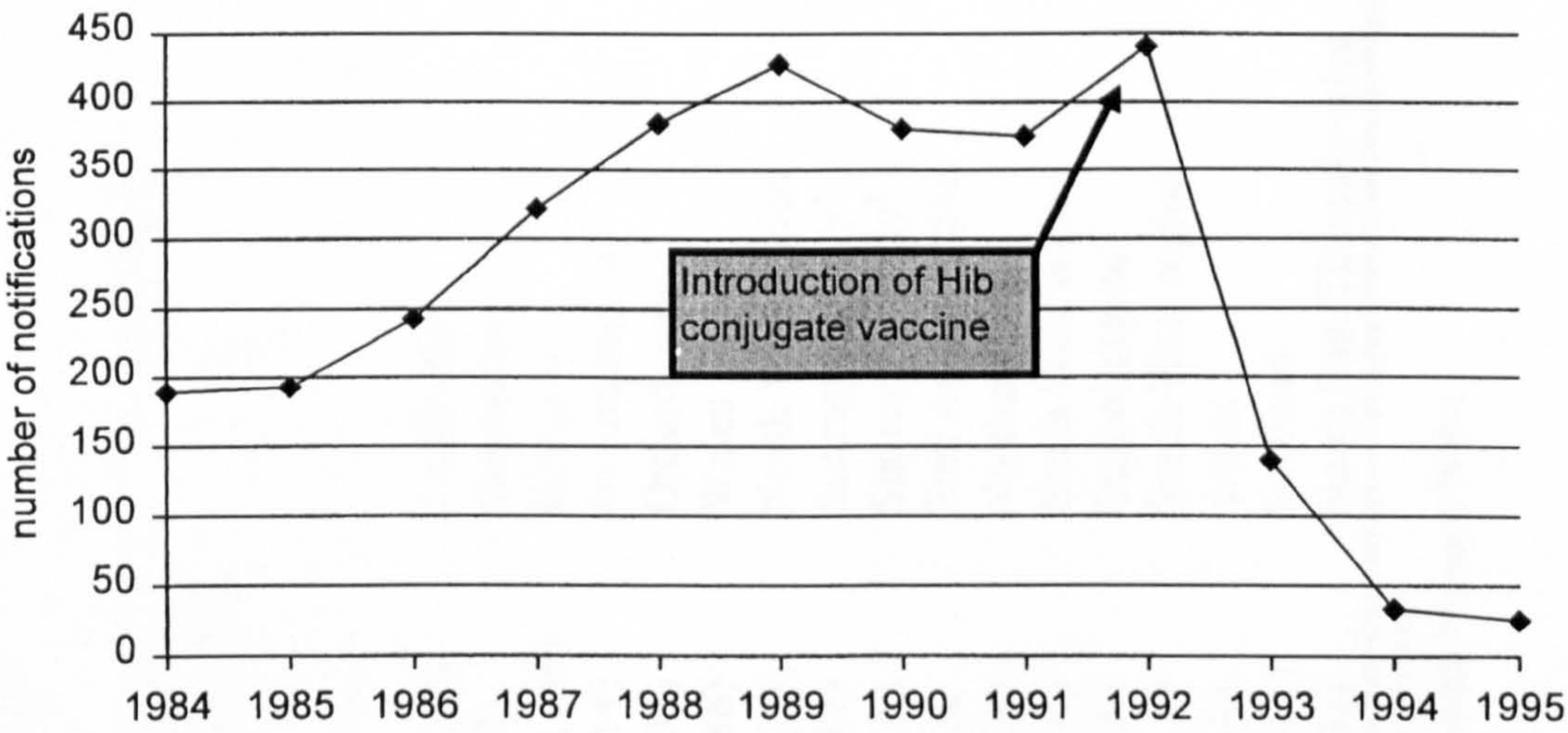
The following section will provide an overview of the epidemiological characteristics of primary invasive *H influenzae* disease in the pre-Hib conjugate vaccine period in several geographic regions utilising mainly population-based research. Firstly, the incidence of invasive *H influenzae* disease will be examined

in Britain, then the rest of Europe, the USA, other industrialised countries and finally other parts of the world.

3.2.3.1 Britain

Figure 3.1 illustrates the rise and fall, in notifications of *H influenzae* disease over several years in England and Wales.[265] The reasons for the increase are unknown but may reflect better culturing techniques, improved reporting or a true increase in incidence. The fall has occurred following the introduction of Hib conjugate vaccine to the primary immunisation schedule.

Figure 3.1: Annual notifications of H influenzae meningitis <5 years of age; England and Wales, 1984-1995



Source: PHLS, CDSC[265]

A number of retrospective and prospective population-based studies reporting on the incidence of invasive *H influenzae* disease in Britain have been published. The majority report on the incidence and characteristics of invasive *H influenzae* disease prior to the introduction of Hib vaccine, and these are summarised in table 3.1.

Table 3.1: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among children <5 years of age: UK population-based studies in the pre-Hib conjugate vaccine era

Reference	Nature of study (number <5 years old)	Location	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Broughton et al[122]	Retrospective (68)	Cambridge	1975-81	NA	18.0	1.6
Howard et al[142]	Prospective (67)	Gwynedd	1980-90	49.3	30.7	NA
Coggins et al[141]	Retrospective (239)	Glasgow	1981-90	39.0	23.8	2.9
Tudor-Williams et al[121]	Prospective (214)	Oxford region	1985-88	33.4	23.6	5.9
Booy et al[139]	Prospective (405)	Oxford region	1985-91	35.5	25.1	4.3
Howard et al[142]	Prospective (186)	Wales	1988-90	34.6	22.0	NA
Quigley et al[233]	Retrospective (83)	North West region	1989	28.3	NA	2.3
Nazareth[97]	Prospective (312)	Six region study†	1990-91	NA	26.4	NA
Hargreaves et al[140]	Prospective (NA)	Six-region study†	1990-92‡	28.4	NA	NA
Anderson et al[249]	Prospective (NA)	East Anglia region	1990-92‡	29.0	NA	NA
Anderson et al[249]	Prospective (NA)	Northern	1990-92‡	26.3	NA	NA
Anderson et al[249]	Prospective (NA)	North West region	1990-92‡	24.6	NA	NA
Anderson et al[249]	Prospective (NA)	Oxford region	1990-92‡	27.5	NA	NA
Anderson et al[249]	Prospective (NA)	South West region	1990-92‡	36.6	NA	NA
Anderson et al[249]	Prospective (NA)	Wales	1990-92‡	28.1	NA	NA
Brewster[266]	Retrospective (83)	Scotland	1991	32.2	14	NA
Urwin et al[265]	Prospective (107)	North East Thames region	1991-92	NA	20.0	NA

NA = data not available or not calculable from the evidence

† East Anglia, Northern, North Western, Oxford, South Western, Wales

The incidence can be seen to vary from region to region. Reported incidence rates for *H influenzae* meningitis range from the mean annual incidence rate of 18.0 cases per 100 000 children aged less than 5 years seen in Cambridge between 1975 and 1981,[122] to the more recent 36.6 cases per 100 000 experienced by the same age group in the South West region between 1990 and 1992.[249] The overall incidence of invasive *H influenzae* disease from 1975 to 1992 was between 24.6 and 49.3 per 100 000.[142,249]

Methodological differences may account for some of the variation. For example, prospective compared with retrospective collection of data, the sensitivity of the data sources, and the inclusion of cases of invasive *H influenzae* which are not culture-confirmed. Notwithstanding the influence these and other factors may have on the observed incidence rate, it has been noted that the six region study for England and Wales has reported interregional variation, as well as intraregional variation.[175] This is despite the use of identical methods of case identification and ascertainment in each of the centres. Differential underreporting has been cited as one possible reason for the differences noted in this multicentre study.[175]

Seasonal variation in the identification of cases has been reported. Where seasonality or monthly incidence has been examined in the literature, more cases have been found to occur in the cooler months of the year. The period from October through March usually accounts for 58% to 66% of cases.[139,249]

In case series involving children aged less than 5 years, *H influenzae* meningitis affects 41% to 49% of children aged less than 12 months.[121,139,142] As in North America and other parts of the world, age-related differences between meningitis and epiglottitis are seen. Meningitis tends to occur mainly in children

before they reach eighteen months of age, whereas epiglottitis is seen in children approaching their third birthday.[121,139]

Accounts of invasive *H influenzae* disease in children of different ethnic groups in the UK is limited. A hospital-based study carried out between 1973 and 1984 by Dyas and George provided information on 'black' and 'Asian' children without prior definition of these terms.[268] Similarly, a prospective study of bacterial meningitis by Urwin et al from the North East Thames region presented data which also included children who were designated as 'black' and 'Asian'.[267] As Bhopal et al have argued, continued usage of these 'ethnic' terms without prior definition is scientifically unsatisfactory.[269]

3.2.3.2 The rest of Europe

There are a number of population-based reports on invasive *H influenzae* disease in the English language from Europe (table 3.2), predominantly from the Scandinavian countries.

The overall incidence rate for invasive *H influenzae* disease among children aged less than 5 years, ranges from 21.0 per 100 000 in France[126] to 60.2 per 100 000 in Switzerland.[209] These rates are similar to those obtained in the UK,[142,249] but much less than those reported from the USA.[275]

H influenzae meningitis appears to occur at a similar age to that found in Britain, with 38% to 46% of cases occurring in children aged less than 12 months.[126,270,271] In contrast to the UK, most European countries have reported bimodal seasonal variation. Peaks have been noticed in autumn and spring,[126] as well as in autumn and early summer.[231]

Table 3.2: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among children <5 years of age: European population-based studies

Reference	Nature of study (number <5 years old)	Location	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Claesson et al[270]	Retrospective (122)	Sweden (Southwest)	1971-80	NA	27.0	1.6
Gervaix et al[209]	Retrospective (169)	Geneva, Switzerland	1976-89	60.2	24.9	NA
Reinert et al[126]	Retrospective (277)	France (2 departments)	1980-89	21.0	15.0	NA
Trollfors et al[271]	Retrospective (440)	Sweden	1981-83	NA	30.7	NA
Takala et al[231]	Prospective (333)	Finland	1985-86	51.9	26.0	NA
Kristensen[272]	Retrospective (210)	Denmark	1985-86	40.0	27.0	2.0
Hugosson et al[273]	Prospective (55)	Orebro County, Sweden	1987-92	55.0	31.0	NA
Fogarty et al[230]	Prospective (NA)	Republic of Ireland	1990-93	25.4	12.1	NA

NA = data not available or not calculable from the evidence

3.2.3.3 United States of America

As mentioned earlier, much of the published literature on invasive *H influenzae* disease comes from the USA. Prospective and retrospective population-based studies have reported incidence rates ranging from 68 to 113 cases per 100 000 children aged 5 years or less prior to the introduction of Hib vaccines.[131,275] The results of several population-based studies conducted in the USA are summarised in table 3.3.

When compared to reports obtained from Britain and Europe, these results indicate that the incidence of invasive *H influenzae* disease is considerably greater in the USA. There is also a striking difference in the incidence of these diseases between the Native American populations and non-native Americans. An increased incidence has also been reported for other ethnic groups in the USA, especially African Americans (table 3.4). There is still some debate as to whether these differences are genetically determined or influenced by socioeconomic risk factors.[148,278]

In the Native American populations the onset of disease occurs at an earlier age than in non-Native American, British or European children. In studies involving this population, more than 80% of cases are reported to have *H influenzae* meningitis before the age of 1 year.[281-283]

In contrast to reports on seasonality from the UK indicating one peak of disease incidence, a bimodal pattern has been observed in the USA. In the United States, invasive *H influenzae* disease peaks in late autumn, and again in early spring.[284,285]

Table 3.3: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among children <5 years of age: US population-based studies

Reference	Nature of study (number <5 years old)	Location	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Floyd et al[132]	Retrospective (107)	Tennessee	1963-71	NA	22.5	NA
Parke et al[276]	Retrospective (83)	Mecklenburg County	1966-70	NA	64.4*	NA
Tarr et al[277]	Retrospective (99)	Rhode Island	1970-74	NA	26.8	NA
Guess et al[275]	Retrospective (45)	Rochester	1975-83	113.0	64.0	2.2
Granoff et al[278]	Prospective (87)	Fresno County	1976-78	90.0	60.0	NA
Sherry et al[279]	Retrospective (418)	King County	1977-86	NA	49.6	2.1
Istre et al[155]	Retrospective (NA)	Colorado	1981-82	112.0	68.0	NA
Murphy et al[131]	Prospective (245)	Dallas County	1982-84	109.0	67.0	NA
Murphy et al[131]	Prospective (341)	Minnesota State	1982-84	68.0	45.0	NA
Rice et al[280]	Retrospective (41)	Sedgwick County	1983-87	NA	26.0	4.9
Cochi et al[148]	Prospective (102)	Atlanta	1983-84	82.0	57.0	NA

NA = data not available or not calculable from the evidence
* incidence per 100 000 <6 years of age

Table 3.4: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among ethnic minority children <5 years of age: US population-based studies

Reference	Nature of study (number <5 years old)	Population	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Parke et al[276]	Retrospective (46)	Black	1966-70	NA	130.9*	NA
Tarr et al[277]	Retrospective (14)	Black	1970-74	NA	103.6	NA
Ward et al[153]	Retrospective (60)	Native Alaskans	1971-77	490.8	409.0	6.0
Losonosky et al[281]	Retrospective/prospective (NA)	Apache	1973-82	NA	254	NA
Coulehan et al[282]	Retrospective (206)	Navajo	1974-80	214.0	152.5	NA
Granoff et al[278]	Prospective (13)	Black	1976-78	219.0	202.0	NA
Granoff et al[278]	Prospective (39)	Hispanic	1976-78	107.0	60.0	NA
Yost et al[283]	Retrospective (77)	Native Americans	1978-83	NA	136.0	6.5
Murphy et al[259]	Prospective (80)	Black	1982-84	154.0	136.0	6.5
Murphy et al[259]	Prospective (35)	Hispanic	1982-84	87.0	136.0	6.5

NA = data not available or not calculable from the evidence
* incidence per 100 000 <6 years of age

The first Hib conjugate vaccine (PRP-D) was licensed in the USA in December 1987, and superseded the polysaccharide vaccines.[286] Since then, other conjugate vaccines have been licensed and incidence rates of invasive *H influenzae* disease have fallen rapidly.[134,135,287]

Recent epidemiological reports from North America have however indicated that in some areas the incidence of invasive Hib disease was falling in children too young to have received Hib conjugate.[134,135,287] The reasons for this are yet to be clarified. It has been postulated that following vaccination of older children with conjugate vaccine reduced Hib colonisation and nasopharyngeal carriage led to decreased exposure in younger children and resulted in a herd immune effect.[288,289]

3.2.3.4 Other industrialised countries

This section contains reports from Australia, Israel, Canada, and New Zealand. Table 3.5 summarises the findings from these countries. All of these countries have native and non-native populations and considerable differences can be seen in incidence rates between the populations. The native populations tend to have a higher incidence of invasive *H influenzae* disease than the non-native population. This is especially so in the Aboriginal population of Central Australia, where an incidence rate of 1104 per 100 000 children less than 5 years of age has been reported for all invasive *H influenzae* disease.[257]

The epidemiological features of the populations in these countries differs from that seen in Europe and the United States.

Table 3.5: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among children <5 years of age: Population-based studies in other industrialised countries

Reference	Nature of study (number <5 years old)	Location (population)	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Hammond et al[290]	Prospective (NA)	Keewatin, Canada (Inuit Indians)	1981-84	NA	530.0	NA
Hammond et al[290]	Prospective (80)	Manitoba, Canada (all)	1981-84	NA	32.1	NA
Hammond et al[290]	Prospective (NA)	Manitoba, Canada (non-Indians)	1981-84	NA	25.5	NA
Hammond et al[290]	Prospective (NA)	Manitoba, Canada (Native Indians)	1981-84	NA	34.5	NA
Voss et al[198]	Retrospective (185)	Auckland, New Zealand	1981-87	41.0	27.0	0.5
Halfon-Yaniv et al[234]	Retrospective (NA)	Israel (Jews)	1984-88	48.0	NA	NA
Halfon-Yaniv et al[234]	Retrospective (NA)	Israel (Bedouins)	1984-88	58.0	NA	NA
Hanna[291]	Retrospective (146)	Western Australia (Aborigines)	1984-88	NA	149.6	10.0
Hanna[291]	Retrospective (40)	Western Australia (non-Aborigines)	1984-88	NA	26.9	4.1
McGregor et al[232]	Retrospective (118)	Capital Territory, Australia	1984-90	63.2	30.6	NA
Hansman et al[257]	Prospective (17)	Central Australia (Aborigines)	1985-86	1103.9	454.5	NA
Hansman et al[257]	Prospective (7)	Central Australia (non-Aborigines)	1985-86	345.7	NA	NA
Hanna[119]	Retrospective (22)	NT†, Australia (Aborigines)	1985-88	529.0	159.0	NA
Hanna[119]	Retrospective (14)	NT†, Australia (non-Aborigines)	1985-88	92.0	53.0	NA
Hanna[119]	Retrospective (58)	Central Australia (Aborigines)	1985-88	991.0	NA	NA
Hanna[119]	Retrospective (14)	Central Australia (non-Aborigines)	1985-88	215.0	NA	NA
Gilbert et al[242]	Retrospective (518)	Victoria, Australia	1985-87	58.5	25.4	NA
McIntyre[256]	Retrospective (264)	Sydney, Australia	1985-87	38.5	NA	1.9
Dagan[208]	Prospective (320)	Israel	1988-90	34.0	18.0	NA

NA = data not available or not calculable from the evidence

* Northern Territory

They have higher overall incidence rates, but comparable rates of meningitis. They also have a higher proportion of cases of *H influenzae* pneumonia, between 7% to 43%,[119,198,234] compared to 3% to 11% in other parts of the world.[231,249,282]

Also of interest is the age distribution in these populations. It appears to be similar to that found in other countries. In the United States and Europe, 37% to 54% of *H influenzae* meningitis cases occur in the general child population before 12 months of age.[132,267,270,280] In Israel, Canada and Australia 34% to 61% of *H influenzae* meningitis cases are seen in children before their first birthday.[242,290,291] The picture in the native populations of these countries is similar to that observed in Native Americans where a higher incidence of disease is seen in younger age groups compared to that found in the general child population.

In the main, seasonality was reported as being similar to that found in other publications, with more cases seen in the colder months of the year. A striking difference was, however, observed by researchers in Israel when they examined admissions for Bedouin children and Jewish children according to season.[292] Admissions for Bedouin children appeared to increase during the summer, whereas more Jewish children presented to hospital in the autumn. The authors then related the admissions for invasive *H influenzae* disease with admissions for respiratory infections and diarrhoeal disease. They found that there were more admissions for diarrhoeal disease in the summer and a greater number of respiratory infections during the autumn. These correlated with the admissions for Bedouin children and Jewish children respectively. Possible explanations for this observation are obscure.

3.2.3.5 The rest of the world

In several less industrialised countries of the world, the importance of endemic and epidemic meningococcal meningitis and the prominence of streptococcal meningitis, has probably contributed to the limited amount of data available on invasive *H influenzae* disease. The little that is available is mainly hospital-based and concentrates on meningitis with only sparse information on non-meningitic invasive *H influenzae* disease. This is presumably because it is easier to define and diagnose than the other disease syndromes associated with *H influenzae*.

Only a few population-based studies specifically examining invasive *H influenzae* disease in less industrialised countries were found in the English literature, and these are outlined in table 3.6. In general studies from these countries show very early onset of invasive *H influenzae* disease. Between 59% to 83% of cases of *H influenzae* meningitis occur before children reach their first birthday.[123,196,222]

The Chilean incidence rate for *H influenzae* meningitis of 15.2 per 100 000 in children aged less than 5 years is much lower than rates found in Europe.[222] However, the researchers believe this to be an underestimate. The incidence rate for *H influenzae* meningitis from one of the hospitals in the study was estimated to be 25.1 per 100 000 in children aged less than 5 years. This rate is similar to that found in Europe, and much lower than that reported for the USA.

Table 3.6: Comparison of rates of invasive *Haemophilus influenzae* (HI) disease among children <5 years of age: Population-based studies from other parts of the world

Reference	Nature of study (number <5 years old)	Location (population)	Period	All invasive disease annual incidence per 10^5	HI meningitis annual incidence per 10^5	Case fatality rate (%)
Biljmer et al[123]	Prospective (77)	The Gambia	1985-87	NA	60.0	37
Ferreccio et al[222]	Retrospective (343)	Santiago, Chile	1985-87	21.6	15.2	16
Ferreccio et al[222]	Retrospective (83)	Area Norte, Santiago, Chile	1985-87	42.5	25.1	16
Lau et al[239]	Retrospective (52)	Hong Kong (all)	1986-90	2.7	1.8	NA
Lau et al[239]	Retrospective (NA)	Hong Kong (refugees)	1986-90	42.7	NA	NA
Hussey et al[128]	Prospective (142)	Cape Town, South Africa	1991-92	54.0	35.0	NA
Hussey et al[128]	Prospective (69)	(Black)	1991-92	104.0	50.0	NA
Hussey et al[128]	Prospective (67)	(Mixed)	1991-92	38.0	27.0	NA
Hussey et al[128]	Prospective (6)	(White)	1991-92	25.0	25.0	NA

NA = data not available or not calculable from the evidence

In Hong Kong, Lau and other members of the Hib study group carried out a five year retrospective survey.[239] An average annual incidence rate of 2.7 per 100 000 children aged less than 5 years was reported for all culture-positive cases of invasive Hib disease. The researchers indicated that this was an underestimate as previous research in this area had shown that a large number of children received unprescribed antibiotics prior to admission. A sub-group of the population, children of Vietnamese refugees, had an incidence rate of 42.7 per 100 000 children aged less than 5 years.[239] These children were thought to be at increased risk because of overcrowding in the refugee camps. In addition, lack of access to non-prescription antibiotics may have increased the number of positive cultures obtained.

In contrast to accounts from Europe and North America, there were no cases of epiglottitis in the children of Hong Kong,[239] Santiago, Chile[222] or Cape Town, South Africa.[196] Instead pneumonia appears to be more important accounting for up to 25% of invasive *H influenzae* cases in one series.[196] The reasons for this are not clear, but differences in diagnostic methodology, case definitions and socioeconomic factors may be responsible.

Mortality and morbidity are also much higher in these countries when compared to the other countries previously discussed. In Africa, mortality and morbidity rates approaching 40% have been reported, with difficulty in reaching hospital facilities cited as a significant factor.[123] Lower rates have been reported from Chile,[235] but even in Hong Kong which may be regarded as highly 'Westernised' in many respects, the mortality rate is approximately 11%.[239] Case

fatality rates in these areas may be biased as only the very sick children who are more likely to die may be brought to hospital.

3.2.4 Summary of section 3.2

Incidence rates for invasive *H influenzae* vary both between and within countries. Less industrialised areas are characterised by high incidence rates and high case fatality rates. The native populations of North America and Australia are affected at a younger age and have the highest incidence rates for invasive *H influenzae* diseases. However, their mortality rates are similar to those of other communities occupying the same geographical locality. This reduced mortality in relation to other 'less developed' populations from Africa and Asia may be due to a number of reasons including easier access to medical facilities.

3.3 RISK FACTORS ASSOCIATED WITH INVASIVE *H INFLUENZAE* DISEASES

Only a handful of studies have specifically reported risk factors for invasive *H influenzae* disease or *H influenzae* meningitis. Others have hidden the examination of risk factors within the overall data analysis. The majority of these studies are from the United States with a smaller number from Western Europe. There are none from the UK.

Evidence from these studies demonstrates that a variety of risk factors appear to increase the risk of exposure or susceptibility in certain groups of infants

and young children thereby increasing their risk of developing invasive *H influenzae* disease. This section will outline several risk factors reported to be associated with an increased risk of developing primary invasive *H influenzae*.

3.3.1 Individual risk factors

3.3.1.1 Age

As noted in the previous section, a strong and consistent relationship between age and the incidence of invasive Hib disease has been observed by all researchers. Although the bacterium has been isolated in all age groups, the peak incidence of invasive *H influenzae* is primarily seen in children aged 6-11 months.[146,284] By the age of 5 years, a steep decline in incidence occurs as concentrations of protective antibody are achieved.[142,232,275] Although it is unclear how this is accomplished, it is postulated that asymptomatic nasal carriage of Hib may stimulate antibody production.[193] Another theory is that bacteria with antigenically similar surface structures, such as some strains of *Escherichia coli*, may be responsible for the production of antibodies that cross-react with Hib.[293]

Passively acquired maternal antibodies are thought to protect the young infant in the first few months of life.[196,294] However, case series have described invasive disease in up to 5% of children below the age of 3 months.[198,234,275] This would appear to indicate that not all mothers possess protective amounts of antibody.

Each type of invasive disease has a characteristic age distribution. Apart from *H influenzae* meningitis, they all tend to occur in older children. In

populations with a very high incidence of invasive *H influenzae* disease, the age-specific incidence is greatest in the younger age-groups.[119,153]

3.3.1.2 Ethnic group and 'race'

Ethnic group (or 'race') has been identified as a potential risk factor for invasive *H influenzae* disease in several population-based studies with children from certain sub-groups of the population having a much higher incidence of disease than other children living in the same geographic area (see tables 3.4, 3.5 and 3.6). There remains however, a problem with definition of ethnicity and the confounding effect of factors associated with socioeconomic status (SES).

In a recent report on acute bacterial meningitis from one of the London regions, an increased risk of *H influenzae* meningitis in 'black' and 'Asian' children was reported.[267] The authors failed to provide any rationale for the 'ethnic' categories used in their study, and incidence of disease in these groups were not reported for children less than five years of age. To my knowledge this is the only published report of the incidence of *H influenzae* in 'ethnic' groups in the UK.

The association between ethnicity and the risk of invasive *H influenzae* disease is difficult to unravel because of the confounding effects of various socioeconomic variables. This observation is supported by the inconsistent results obtained from the mainly North American literature. A prospective case-control study from Los Angeles County among children aged 18-59 months found an increased risk of disease associated with black maternal ethnicity.[149] This association remained even when other risk factors were adjusted for. In an earlier study from Atlanta, controlling for other risk factors revealed that an initial

association with 'black' children no longer held.[148] Several studies using univariate analyses have also reported contradictory results.[155,277,278,292,295]

3.3.1.3 Gender

In common with many other infectious diseases, a higher proportion of invasive *H influenzae* disease is seen in boys.[234,279] This is most vividly illustrated with epiglottitis, with reports of more than 60% of cases occurring in boys, and male:female ratios of 1.8:1 or more being described.[209,231,238]

There are however instances in the literature where the ratios are reversed. In a report from Finland, Takala et al found that girls outnumbered boys in invasive *H influenzae* disease syndromes other than meningitis and epiglottitis.[231] These other types of invasive disease were seen in 56% of girls. In Australia a significantly higher incidence of *H influenzae* meningitis was identified among Native Aborigine girls. The girls were found to have a risk five times more than that of boys (relative risk (RR)=5.12; 95% confidence interval (CI)=1.75 to 14.96).[119] Reasons for these differences in disease incidence between boys and girls are unknown.

3.3.1.4 Mode of feeding

This relates to breastfeeding, however interpretation of the available data is problematic because where this factor is considered definitions vary from study to study, and in one particular study no definition was given.[296] For instance, when using multivariate analysis to examine independent risk factors, Istre et al found that exclusive breastfeeding in the 3 months up to the time of disease was

protective (odds ratio (OR)=0.1; 95% CI=0.01 to 0.96) in children younger than 6 months of age in Colorado.[155] Another study from the United States reported similar findings for children less than one year of age, with the protective effect being most pronounced in infants aged 2-5 months.[148] A recent matched case-control study by Sherry et al from Seattle reported that breastfeeding was protective, but unlike other studies, failed to define any specific age group.[297] In this study breastfeeding was defined as the consumption of any breast milk in the month preceding disease occurrence. An Australian study with a similar definition reported contrasting results. Clements et al found that significantly more controls had been breastfed compared to cases (OR=2.2; 95% CI=1.2 to 3.9).[298] However, this association disappeared when adjusted for other risk factors.

Longer duration of breastfeeding has also been shown to be associated with protection from invasive *H influenzae* infection. A study from Finland has reported that exclusive breastfeeding for more than 6 months has been linked with a protective effect.[154]

Although the data is difficult to compare, it appears to indicate that lack of breastfeeding is a significant risk factor in developing invasive *H influenzae* disease. The immunopathology underlying this is unclear. It has been proposed that Hib anticapsular antibodies are present in human milk and evidence for this has been provided by Pichicherio et al.[294] Another study demonstrated an enhanced immune response to Hib antigen in breast fed infants who were subsequently immunised compared to immunised infants who had been formula fed.[299]

3.3.1.5 General health

Low birth weight

Low birth weight (LBW) has been defined as a birth weight of less than 2,500 grams.[300] LBW can predispose to infections in the early months of life,[157,301] and has been associated with increased susceptibility to invasive *H influenzae* disease. In one series from Finland, where specimens were taken from sterile sites, 7 of 9 neonates with invasive *H influenzae* disease were of low birth weight.[260] Similar results using the same diagnostic criteria have been reported by others.[259,262,302]

Preceding illness

It has been hypothesised that antecedent or concurrent viral respiratory infection may increase host susceptibility to invasive *H influenzae* disease, particularly meningitis. The evidence for this relationship is inconclusive. Krasinski et al could not demonstrate an association between laboratory confirmed viral infection and a recent history of upper respiratory infection in children with bacterial meningitis over a three year period in Dallas.[194] Researchers from Finland also failed to find any difference between serology samples obtained from cases with Hib disease and a group of matched controls.[158] However, they reported that case parents were more likely to report symptoms of respiratory infection, such as cough (OR=2.0; 95% CI=1.1 to 3.7) in the 4 weeks preceding Hib disease than matched controls. This study had a number of limitations. The questionnaires used were mailed to control children whereas those for cases were completed in the presence of a nurse on a visit to the family. Recall bias may also have been a

problem as questionnaires for cases were sent out 1 to 11 days (median = 3 days) after hospitalisation compared to 3 to 82 days (median 13 days) for controls. Two more recent case-control studies, one from North America and the other from Scandinavia have both failed to find any association between a history of respiratory symptoms and invasive *H influenzae* disease.[154,155]

Previous hospital admission

Takala et al reported from Finland that children with a previous history of hospitalisation were at increased risk (OR=2.04; 95% CI=1.07 to 3.89) for invasive Hib disease.[154] The researchers believed that 'unrecognised' socioeconomic factors were probably responsible for the observed association. Some support for this is provided by Spencer and colleagues.[103] Results from their study in Sheffield suggest that children from materially deprived areas are at increased risk for multiple hospital admissions. However, a relationship between SES and invasive Hib disease is yet to be reported from Finland, where socioeconomic differentials in the population are said to be minimal.[154]

Predisposing conditions

Where predisposing conditions have been considered Down's syndrome is one of the most commonly reported.[157,230,256,271] Other conditions associated with invasive *H influenzae* disease include preceding skull fracture, cystic fibrosis, phenylketonuria, and the presence of a ventriculo-peritoneal shunt.[141,157,256,271] A recent report from the Republic of Ireland has suggested that the presence of chronic illness (defined as an allergic illness such as asthma, or an illness

associated with reduced immunity, such as Down's syndrome), is a significant risk factor (OR=2.9; 95% CI=1.29 to 6.54) for invasive Hib disease.[230]

Anaemia

Kaplan and Oski retrospectively compared the haematological findings on admission of children with bacterial and aseptic meningitis.[303] After excluding possible causes of anaemia they found that 41% (45 of 109) of cases with anaemia had *H influenzae* meningitis. Of the remainder, 28% had other forms of bacterial meningitis, and 31% aseptic meningitis. Children with *H influenzae* meningitis had significantly lower mean levels of haemoglobin on admission compared to children with aseptic meningitis.[303]

A hospital based study conducted in the West Midlands reported that 31% of patients admitted with bacterial meningitis, including *H influenzae* meningitis, had anaemia.[304] Choo et al conducted a retrospective hospital-based study in Malaysia.[305] They reported that 40 of 58 (69%) children with bacterial meningitis were found to have anaemia, with haemoglobin levels below 10g%. A retrospective chart review of children with *H influenzae* disease in Bangkok using a similar case definition identified anaemia in 34 of 50 (68%) children.[243] Similarly, Bijlmer et al found that 69% of their cases of *H influenzae* meningitis in The Gambia had haemoglobin levels below the minimum threshold for healthy Gambian children.[123] The high proportion of children with anaemia and bacterial meningitis in the reports from these centres may reflect the methodology used. None of these reports indicated whether children with other possible causes of anaemia, such as haemoglobinopathies had been excluded.

Underweight for age

Children who are underweight for age also appear to be at increased risk for invasive *H influenzae* disease. Using expected weight for age to determine nutritional status, a group of researchers in Cape Town found that children with septicaemia and arthritis were significantly more malnourished than children with other *H influenzae* diagnoses.[196] Nottidge reported similar findings from his study on *H influenzae* meningitis in Nigeria, where 76% of cases were below the third centile for healthy Nigerian children.[124] Another series from The Gambia found that on admission, 27% of children aged less than 24 months were equal in weight to, or weighed less than the third centile.[123] UK data on this aspect are lacking.

3.3.1.6 Immunodeficiency

Children with deficient immune function have been identified as being at increased risk for invasive *H influenzae* disease. Among the immunological disorders associated with invasive *H influenzae* disease are sickle cell disease, HIV/AIDS and other immunodeficiency syndromes, malignancies, receiving immunosuppressive therapy and congenital or acquired asplenia.[157,195,256,284,306,412] Although the mechanisms which increase the risk of invasive disease remain obscure in this group of patients, it is believed that failure of cell-mediated immunity may be involved.[195] Current evidence indicates that these conditions do not contribute greatly to the overall incidence of invasive *H influenzae* disease.

3.3.1.7 Genetic markers

The role of genetically controlled cell surface characteristics and susceptibility to invasive *H influenzae* disease has been investigated in North America. A number of studies have indicated that certain genetic factors may be associated with an increased risk of invasive *H influenzae* disease. These include human leucocyte antigen (HLA), immunoglobulin light chain Km(1), the immunoglobulin heavy chain G2M(n) and certain blood phenotypes.[308-310] However, other studies have not been able to support these observations.[311,312] This lack of consistency may have arisen because a number of these studies carried out multiple cross-comparisons using small numbers, and therefore any significant results may have been due to chance.

3.3.2 Family and community risk factors

3.3.2.1 Family size and structure

Few studies have explicitly examined family size as a risk factor. It is often used as a proxy for, or interchangeably with, household crowding. As with other factors, conclusions are difficult to arrive at because the variable is often not well defined, but the evidence appears to point to an association.

Istre et al conducted a case-control study in Colorado and family size was one of the risk factors which they examined.[155] They reported that the total number of individuals in case households (4.3 ± 1.7), was different to that in control households (3.9 ± 1.1). Univariate analysis indicated that this difference was significant (OR=1.2; 95% CI=1.0 to 1.5) however, the authors did not enter this variable into the multivariate analysis. A prospective study conducted in Fresno

County, California looked at the relationship between family size and ethnic group. The researchers found that cases of invasive *H influenzae* involved 'white' people who were from significantly smaller households (4.27 ± 1.58) than other ethnic groups (5.22 ± 2.17; $p<0.05$).[278]

In a report from Los Angeles County, living in a household which contained more than six individuals was associated with an increased risk (OR=3.71; 95% CI=1.10 to 12.60) for invasive Hib disease.[149] Petersen et al have reported similar results for cases in households with large extended families in the native population of Southwest Alaska.[296] In contrast other reports have not been able to find an association between family size and an increased risk of invasive *H influenzae*.[148,152]

A recent case-control study conducted in Switzerland among children aged 2-16 years found that living with a lone parent was associated with an increased risk of invasive *H influenzae* disease (OR=3.52; 95% CI=1.00 to 15.37).[152] A similar observation was reported by Jafari and colleagues for children aged 2-18 months in the United States.[151]

3.3.2.2 Household crowding

Household crowding is believed to increase the exposure of the infant or young child to possible sources of *H influenzae* bacteria. The evidence for its importance as a significant factor in the development of invasive *H influenzae* disease is not convincing as contradictory reports have been published with differing definitions adding to the problem of interpretation.

In a study carried out in Atlanta household crowding was defined as more than one person per room.[148] The researchers reported that following univariate analysis, a significant association with invasive Hib disease was found and this association remained after adjusting for day-care attendance, race, breastfeeding and low family income (OR=2.7; 95% CI=1.3 to 5.7). In addition, a 'dose-response' effect was seen with the magnitude of the association increasing with increasing household crowding. The researchers also examined another index of overcrowding, the number of other people sleeping in the same room. This factor failed to demonstrate any association with increased risk of invasive *H influenzae* disease (OR=1.5; 95% CI=0.9 to 2.4).[148]

In a report from Oklahoma 3 levels of crowding were defined using a crowding index (the ratio of the number of people in the home to the number of bedrooms), these were, less than 1.5 people per bedroom, 1.5 to 1.99 and 2 or more. After adjusting for possible confounders overcrowding was a significant risk factor for invasive Hib disease only where there were 2 or more people per bedroom (OR=2.0; 95% CI=1.3 to 3.1).[295]

However, an earlier report from Colorado using a similar crowding index, found no difference between cases and controls when the number of persons per bedroom (which was 1.5 ± 0.6 for both groups), was examined as an index of crowding (OR=1.0; 95% CI=0.6 to 1.5).[155] In a more recent study from Switzerland, Mühlemann et al defined a household as crowded if two or more household members slept in the same bedroom as the child.[152] After adjusting for vaccination history, day-care, kindergarten or school attendance, and smokers in the family the researchers reported that this was not a risk factor for invasive Hib

disease (OR=1.03; 95% CI=0.57 to 1.89). Fogarty et al reported comparable results from the Republic of Ireland.[230]

Ecological analyses in Britain[19] and the United States[277] have also failed to find any differences in *H influenzae* meningitis attack rates in areas defined as having a high proportion of overcrowded households (defined as more than 1 person per room).

3.3.2.3 Siblings

A number of studies have provided data on the association between siblings and the risk of invasive *H influenzae* disease, the data are however inconsistent.

In an Alaskan Eskimo population a matched case-control study revealed that the mean number of siblings present at the time of illness was similar for cases (2.0 ± 2.1) and controls (2.2 ± 2.3) and that both cases (1.2 ± 1.1) and controls (1.1 ± 0.9) had comparable numbers of siblings less than 7 years of age.[296] Neither of these differences were statistically significant.

In Finland the presence of siblings younger than school-age (less than 7 years of age) was a risk factor for invasive Hib disease.[154] The risk remained after conducting multivariate analysis (OR=2.62; 95% CI=1.69 to 4.05) and was reported to increase with each individual sibling and to be highest among children aged less than one year. A report from the USA found that invasive *H influenzae* disease was more likely to occur in children where there was an elementary school-aged household member (OR=3.1; 95% CI=1.6 to 5.8), but that there was no increased risk with additional school-aged household members.[155] Arnold et al reporting from another part of the United States found a significantly increased risk

associated with having 3 or more siblings aged less than 5 years (OR=2.4; 95% CI=1.4 to 3.9).[295]

These findings were not replicated in a study from the Republic of Ireland.[230] This study concluded that having a child of school-age in the household was not a risk factor for invasive Hib disease. After adjusting for a number of variables, a Swiss study reported that the risk of invasive *H influenzae* disease was not associated with having siblings aged less than 4 years of age (OR=1.00; 95% CI=0.62 to 1.64).[152]

The differences noted in the literature may be related to cultural practices, socioeconomic factors and variables such as day-care attendance.

3.3.2.4 Day-care attendance

Several North American and European studies have demonstrated that children who attend day-care facilities are at increased risk for invasive *H influenzae* disease.[148,154,155,230,295,313]

One study, from Monroe County, New York State reported that Hib meningitis age-specific attack rates for children in day-care who were less than one year of age were more than ten times higher than that for children who were not attending day-care (877.2 per 100 00 and 86.2 per 100 000, respectively).[313]

A study from the Republic of Ireland suggested that children who have only recently started to attend day-care facilities are at greatest risk of invasive *H influenzae* disease (OR=1.86; 95% CI=1.02 to 3.42).[249] Takala et al reported similar results regarding day-care and invasive *H influenzae* disease in Finland.[154]

The majority of reports indicate that the risk associated with day-care attendance decreases after the age of two years.[148,154,295,313] However, Istre et al found day-care attendance to be a risk factor only for children who were aged 12 months or older.[155] Despite these differences all of these studies reported a 'dose-response' effect. That is, the risk of disease increased the longer the time spent in day-care or the greater the number of children attending the day-care facility.

A number of studies have however failed to demonstrate any association between day-care attendance and increased risk of invasive *H influenzae* disease.[149,152] This may have been due to differences in day-care practices, the number of children attending the facility and the hours spent in day-care. One study from North America reported that day-care practices differed according to ethnic group.[149] Using a case-control method, the authors found that day-care attendance was uncommon amongst Black and Hispanic cases compared to white children. The differences were reported as not reaching statistical significance. In addition, this study also reported that fewer Black case children attended day-care compared to their controls (35% *vs* 45%, respectively).[149]

Population-based studies from Britain have not reported the occurrence of cases of invasive *H influenzae* in day-care centres or crèches.

3.3.2.5 Passive smoking

Various studies have pointed to an association between passive smoking and respiratory illness in children.[314,315] The data on passive smoking as a risk factor for invasive *H influenzae* disease are however inconclusive. Contributing to

this may be differences in methodology, especially the lack of a universal definition for this risk factor.

Vadheim and colleagues reported from Los Angeles County that after adjusting for other risk factors, children aged 18-60 months from homes with two or more smokers had an increased risk (OR=6.0; 95% CI=1.49 to 24.06) of developing invasive Hib disease.[149] An earlier report from Oklahoma State found that the risk of invasive *H influenzae* remained significant for children who lived in homes where 'tobacco smoke pollution' was present after adjusting for a number of other risk factors (OR=1.4; 95% CI=1.0 to 2.1).[295] This association was only weakly significant and the researchers failed to provide a definition for 'tobacco smoke pollution'.

A case-control study carried out by Cochi et al explored this factor in metropolitan Atlanta.[148] They were unable to find an association between parental smoking and invasive *H influenzae* disease (OR=1.3; 95% CI=0.8 to 2.0). A number of other case-control studies from Western Europe and the USA have also failed to find an association between smoking in the home and invasive Hib disease.[152,154,230]

3.3.3 Environmental risk factors

3.3.3.1 Socioeconomic factors

Socioeconomic status is a difficult parameter to measure and researchers have used various proxy measures in an attempt to determine whether an association between socioeconomic factors and invasive *H influenzae* disease

exists. Some of the risk factors already discussed in sections 3.3.1 and 3.3.2, such as ethnic group and household crowding, have also been used for this purpose.

Early research in this area originated from North America and involved ecological studies which suggested that an association between increased risk of invasive Hib disease and low family income or low parental education existed.[132,150] A later study by Vadheim et al employed a number of variables to measure SES.[149] These included the annual total household income, parental education and occupation, as well as a combined SES score derived from the aforementioned characteristics. They also examined whether the usual source of payment for medical care was a risk factor for invasive Hib disease. They reported that cases tended to come from families with low incomes (35% of cases *vs*. 24% of controls, p=0.12), low parental education (39% *vs*. 32%, p=0.38) and the overall SES scores for both groups were comparable. However, the case group used Medicare/Medicaid significantly more frequently than the control group (36% vs 20%, p=0.02).[149]

The complexity of factors affecting exposure to Hib was illustrated in a case-control study from the United States. After univariate analysis Cochi and colleagues found that low family income (<$15,000) was a significant risk factor for invasive Hib disease (OR=1.8; 95% CI=1.1 to 3.0).[148] After controlling for other socioeconomic risk factors such as ethnic group, day-care attendance, household crowding and breast feeding, the association was no longer significant (OR=1.6; 95% CI=0.8 to 3.3). In a report which looked at children attending day-care centres in one New York county, Redmond and Pichichero were also unable to find an association between low family income and invasive Hib disease.[313]

Arnold et al have indicated that after adjusting for confounders such as ethnic group, maternal education, household crowding and day-care attendance, high income (annual household income of $20,000 or more) remained protective against invasive Hib disease (OR=0.4; 95% CI=0.3 to 0.7).[295] Another potential measure of SES was also examined in this study, maternal education (more than 13 years education). There was no significant difference between cases and controls for this factor (OR=0.7; 95% CI=0.4 to 1.3).[295]

European studies have generally been unable to provide any evidence to support an association between SES and invasive *H influenzae* disease. A case-control study from the Republic of Ireland used membership of social classes 4-6 (based on parental occupation), eligibility for free health services and living in housing supplied by the local authority as proxy measures for low SES.[230] None of these parameters were associated with increased risk of invasive Hib disease. An ecological study conducted in the North Thames region also failed to find an association between Hib meningitis and deprivation using the Townsend deprivation score.[19] A case-control study conducted in Finland reported no association between low level of maternal education (did not attend university or college) and risk of invasive Hib disease.[154] It has however been noted that SES in the Finnish population is relatively homogenous.[147]

The evidence on the aspects of SES examined above have been conflicting and remain unconvincing. It is, however, likely that socioeconomic factors are confounded by other host and environmental factors.

3.3.3.2 Geography

Increased incidence of disease may occur as a result of living in an urban area or area with high population density. Where these factors have been examined, the results provided have been contradictory.

Several reports have examined the differences between urban and rural populations.[132,242,272,313] A retrospective ecological study which compared the incidence of *H influenzae* meningitis in urban and rural Tennessee found a significantly increased incidence of disease ($p<0.01$) in urban residents.[132] Another study examined cases of *H influenzae* meningitis occurring in day-care centres in Monroe County, New York.[313] The geographic origin (city *vs* suburbs) of each child was analysed and, despite reporting wide socioeconomic differences geographic origin was not associated with increased risk of invasive Hib disease. A report from Victoria state, Australia divided the state into three regions, inner Melbourne, outer Melbourne and the rest of the state.[242] The researchers found that the more populous inner Melbourne region had a lower attack rate than the other two regions. The difference was however not statistically significant ($p>0.15$).[242]

Population density is another measure which has been used to describe geographic variation in invasive *H influenzae* disease. An early report by Fraser et al suggested that the incidence of *H influenzae* meningitis decreased with increasing population density in the white population but not the black population of South Carolina.[150] A later study conducted in Rhode Island reported no association between population density and the incidence of *H influenzae* meningitis.[277] However, neither of these reports provided an adequate definition of population density.

Only one British study was located which had looked at this issue.[19] The study from the Thames region of London used census data at the ward level to divide the population into 3 groups according to levels of overcrowding (which was defined as >1 person per room). The groups were then categorised as most overcrowded, intermediate and least overcrowded. The authors noted an increasing incidence of *H influenzae* meningitis with decreasing levels of overcrowding in white children aged less than 5 years.[19] This trend was however not statistically significant ([Chi-square] χ^2 for trend, p=0.13).

Another study examined the proportion of the total population aged less than 5 years in each local government area (LGA) of Sydney, Australia.[256] They placed each LGA into one of 4 classes, which ranged from low to high proportions of children aged less than 5 years. The authors reported that there were no significant differences between the four groups. However, when they compared the incidence of disease for children aged 0-1 year (19.9 per 100 000) in the group with the lowest proportion of 5 year olds with the other 3 groups combined (60.0 per 100 000), a significant difference was reported (p=0.03).[256] Their results suggest that in areas where the proportion of young children is low, exposure and development of natural immunity to Hib may be delayed.

3.3.4 Summary of section 3.3

British studies on the relationship between HI and various risk factors is lacking. However, the mainly North American and Scandinavian literature on invasive *H influenzae* disease indicates that the risk of disease is related to several factors which interact at different levels. These factors are responsible for

increasing the child's exposure and susceptibility to the organism. The most important risk factors appear to be age, ethnic origin, day-care attendance and family size. Breastfeeding appears to protect children against invasive *H influenzae* disease. However, interpretation is made difficult by the confounding effect of socioeconomic factors and the lack of clear, concise and consistent definitions for the factors examined. Despite these problems it is unlikely that socioeconomic confounding could account for the very large differences seen between the Native and non-native populations of North America, Australia and other parts of the world.

3.4 CHILDREN, DEPRIVATION AND COMMUNICABLE DISEASES

The relationship between communicable disease and socioeconomically deprived populations is clearly illustrated from the records kept during the time of the Great Plague in Britain in 1665. During this period Defoe noted that:[316]

> "The misery of that time lay upon the poor, who, being infected, had neither food nor physic, neither physician nor apothecary to assist them."

As discussed earlier in section 1.3, medical attention to the variation in disease distribution across social groups was rekindled following publication of the Black Report,[21] which stimulated research around the areas of poverty and deprivation.

Although closely related, poverty and deprivation are two concepts which are quite distinct. Townsend has defined poverty as:[317]

> "Individuals, families and groups in the population can be said to be in poverty when they lack the resources to obtain the type of diet, participate in the activities and have the living conditions and amenities which are customary, or at least widely encouraged, or approved, in the societies in which they belong. Their resources are so seriously below those commanded by the average individual that they are, in effect, excluded from ordinary living patterns, customs and activities."

He has also provided a definition of deprivation which appears to have gained wide acceptance.[332]

> "A state of observable and demonstrable disadvantage relative to the local community or the wider society or nation to which an individual, family or group belongs."

Poverty can therefore be conceptualised as arising from a lack of resources, whereas deprivation is applicable to conditions which may be independent of income.

Using available health information, it is very difficult to measure poverty or deprivation directly. However, with the increasing use of postcodes in routine statistical systems, it has become possible to examine the relationship between socioeconomic area characteristics, which may be classified as 'deprived' or 'affluent', and health events at an ecological level.

3.4.1 Measuring deprivation

From the English Registrar General's first classification of social class, through to the current plethora of social classification methods, measuring

deprivation and assessing the health effects of 'class' on individuals, geographic areas and populations has been a major challenge for researchers and social commentators. Quantifying this complex phenomenon not only enables comparisons to be made, but also facilitates the development and testing of hypotheses.

Social class has been employed as an instrument for epidemiological research for many years and is heavily reliant on the type of work an individual performs. This hierarchical system has been severely criticised for a number of reasons. One example is the lack of clear criteria for allocating occupations to social classes.[59] It has also been noted that there is a widening imperfection in the correlation between social class and income, with greater variation in income within social classes than between social classes.[318]

Commentators have also indicated that the Registrar General's Social Class (RGSC) system excludes members of the population not in formal employment, notably the elderly, women and children, and the emerging 'underclass'.[59-63] For example, married women working outside the home are excluded, even though their earnings may influence the standard of living of the household. It may therefore be concluded that epidemiological analyses utilising the Registrar General's social class classification will not reveal the full extent of social and economic inequalities.

The Black Report noted the inadequacy of social class for the measurement of health inequalities and called for:[21]

> "Study of the interaction of social factors implicated in ill-health over time, and within small areas."

This led to the formulation of alternative social classifications to quantify health differences. Many of these alternative approaches employ census data for a defined geographic area and apply them to individuals.

A census is carried out every ten years in the UK, and provides a 'snapshot' of the population at that time. A large number of details regarding the population are collected and made available for different sized areas from the countries comprising the UK, to the smallest area - the enumeration district (ED). This is an area containing an average of 500 people in urban areas and about 150 people in rural areas.[68] EDs can be identified using the postcode of address and may be aggregated to wards, wards to local authorities and so on.[68]

Increasingly, the ED is being used as the unit of geographical analysis, and individuals are being classified using aggregate data obtained from the census. EDs are employed because they are currently the smallest geographical area available, and are likely to contain more socially homogenous populations than larger areas, such as electoral wards.[66,319] Nevertheless, the problem of the 'ecological fallacy' whereby data aggregated at a particular geographic level is not necessarily representative of particular individuals or households within that area, still exists.[67] However, the use of the ED is believed to minimise the effect of social heterogeneity present among individuals or households when geographical analyses are conducted.

Although the census provides much useful information, it was only in 1991 that direct questions on ethnic origin were included for the first time. The census continues to omit questions about income which might be useful in specifically addressing the issues of poverty or deprivation. This, and the lack of routinely

collected information on wealth, income or occupation in health records, has led to the use of proxy measures of deprivation by researchers. Single indicators of deprivation such as unemployment have been used,[320,321] however many measures are indices constructed from a number of census-based variables.

Of the many composite indices claiming to measure deprivation or some aspect of it, the three most widely used in the medical literature are the Townsend material deprivation index,[23] the Jarman (or underprivileged area [UPA]) score,[74] and the Scottish deprivation (SCOTDEP or, Carstairs and Morris) score.[322] Each of these indices is composed of a different set of census small area statistics (table 3.7), each of which has various statistical procedures performed on them to ensure equal weighting, and therefore an equal contribution to the index.

Thunhurst has criticised composite scores for:[323]

"Throwing everything into a statistical melting pot and expecting to produce an answer."

Several other criticisms have been made regarding the criteria for selecting variables, the mathematical manipulations required to create an index, and their reliance on dated census information.[324-326] Despite these comments the indicators have been increasingly used as markers of deprivation when social inequalities in health are under consideration.

In assessing the value of each of these indices in explaining the relationship between deprivation and health, Morris and Carstairs concluded that although the scores correlated well with each other, the Townsend deprivation index and the Scottish Deprivation score performed better than the Jarman score.[327] This is not surprising in view of the fact that the Jarman score was originally developed to

identify factors likely to affect the workload of general practitioner's. The methodology employed to obtain the Jarman score has been criticised for its flawed approach.[326,328,329]

Table 3.7: Components of the most commonly used measures of deprivation

Census population variable (%)	Carstairs and Morris[322] (SCOTDEP*)	Jarman[74] (UPA†)	Townsend[23]
Unemployed	✓	✓	✓
Overcrowded households	✓	✓	✓
Not car owners	✓	✗	✓
Not owner-occupied	✗	✗	✓
Low social class	✓	✗	✗
Unskilled	✗	✓	✗
Single parents	✗	✓	✗
Below 5 years of age	✗	✓	✗
Lone pensioners	✗	✓	✗
One year immigrants	✗	✓	✗
Ethnic minorities	✗	✓	✗

* Scottish deprivation score
† Underprivileged area score

3.4.2 Deprivation and child health

Following publication of the Black report a plethora of published literature appeared demonstrating inequalities in health between those from poorer areas and those from more advantaged areas. Recent evidence suggests that this differential may be increasing.[77,82,330,331]

Various explanations for the association between deprivation and adverse health outcomes have been proposed. The Black report broadly classified them into four schools of sociomedical thought: artefact, natural selection, behavioural/cultural and structural/materialist (table 3.8):[21]

Table 3.8: Summary of the Black reports explanations for health inequalities

1.	Artefacts of measurement	- This suggests that health inequalities are not real but due to statistical and classification artefact.
2.	Social selection	- This accepts the existence of inequalities, but suggests that health determines social position rather than vice versa.
3.	Behavioural/cultural	- This is based on the premise that the observed health differences between social groups are accounted for by health-related behaviour.
4.	Material/structural	- This explanation suggests that the differences seen between social groups occur as a result of the unequal distribution of resources in society.

Researchers have not applied equal weight to each of these explanatory variables and have suggested that the first two explanations are of little importance in explaining the observed inequalities in health.[21,332,333] Social medicine research has been biased towards the behavioural/cultural explanation.[334] It has however been argued that the material/structural view best explains the socioeconomic

gradients seen when examining issues of inequalities in health,[21] although it is recognised that it is difficult to separate behaviour from its social context.[335]

3.4.2.1 Paediatric communicable diseases and deprivation

An extensive body of knowledge has demonstrated that paediatric mortality[21] and a number of measures of morbidity such as low birth weight,[50] child abuse,[88] diabetes,[336] sudden infant death syndrome[86] and accidents [49] are associated with socioeconomic inequalities. The health inequalities demonstrated by these measures appears to indicate that there are significant differences in health experience between children from poorer areas and those from more advantaged areas.

Examination of the relationship between paediatric infectious diseases and deprivation has however not received as much attention in the published literature. When the available literature on communicable diseases are examined, in general there appears to be an unequal burden of communicable disease among children from poorer socioeconomic backgrounds or levels of deprivation.

The definitive communicable disease of poverty is tuberculosis. Its association with socioeconomic disadvantage has been one of the factors used to explain its recent re-emergence as a major infectious cause of morbidity and mortality in both the UK and USA.[17,18,337] Other reasons given for the increase in tuberculosis include its link with HIV/AIDS and increasing antibacterial resistance.[11,12]

An ecological analysis of meningitis cases in the North East Thames region utilised the Townsend score to divide wards into three groups to carry out an

analysis of area of residence.[19] The study did not find an association between meningococcal or *Haemophilus* meningitis and deprivation. The researchers reported an increasing incidence of meningococcal meningitis from the least overcrowded wards to those classified as the most overcrowded. A similar pattern was not found for *H influenzae* meningitis. A case-control study of meningococcal disease suggested that households with 6 or more residents were a risk factor for disease in children aged less than 5 years, while cases in households where the head of household was in social class I/II were less likely to present with meningococcal disease.[47]

A study carried out in Sheffield reported that children admitted with bronchiolitis were more likely to reside in areas of deprivation (as defined by the Townsend deprivation score) than controls.[26] This relationship was still present even after excluding children from homes which contained a smoker. In the Child Health and Education Study, Taylor and colleagues employed a composite index of SES and demonstrated social class gradients for lower respiratory tract infections and gastroenteritis in children aged up to five years. Disadvantaged children were reported to be at increased risk.[91]

Helicobacter pylori is acquired at an early age and prevalence of the infection increases with age. Patel et al carried out a population-based longtitudinal study of children in Edinburgh from the age of 7 to 11 years.[95] They examined a number of socioeconomic factors and found that children from single parent families, overcrowded homes and those living in rented accommodation were at increased risk of *Helicobacter pylori* infection.

In England and Wales the fourth national study of general practice (GP) consultations rates used social class (as defined by occupation) as one of its measures of socioeconomic status. Significantly more children from (the 'lower') social classes IV and V attended GP consultations for infectious and parasitic diseases than children whose parents were in social classes I and II.[4]

A study from Glasgow reported on the relationship between deprivation and hospital admission by postcode of district of residence for a number of individual infectious diseases (measles, whooping cough, gastroenteritis) and all infectious diseases combined.[93] They found a strong and consistent relationship with deprivation for all the diseases examined.

Dental decay (or dental caries) occurs as a result of bacterial action modified by sugar in the diet and dental hygiene. In 1993-94, almost 50% of 5 year olds had dental decay in Great Britain. There is a body of evidence linking dental decay in children with material deprivation. Two ecological studies, one using the Jarman score[338] and the other using the Townsend index[92] have both shown that tooth decay (based on the decayed, missing and filled tooth (dmft) index) in children is associated with deprivation.

Lissauer et al carried out a prospective case-control study which looked at the influence of homelessness on the health of children in London.[27] The researchers found that homeless children were more likely to be admitted to hospital with infectious diseases than the control group.[27]

In a review of the literature on infectious disease in childhood and social disadvantage, Reading cited a number of studies which provided equivocal evidence of social differences in disease incidence (for example ear infections,

measles and pertussis).[5] However, it seems clear that inequalities do exist in relation to communicable diseases. The causative factors underlying the patterns observed are however disputed but centre around lifestyle or behavioural influences and structural or material influences. Although it is difficult to separate one from the other, the latter appear to exert a greater influence when moving from the individual level to the community level.

3.4.2.2 Immunisation and deprivation

Immunisation is a major public health activity, and the level of immunisation uptake can be used as a marker for the adequacy of health-care delivery or its utilisation. The main aim of immunisation is to provide immunological protection against a specific infection without exposing the recipient to the risk associated with natural infection. The procedure prevents death and disability, and is recognised as one of the most cost-effective medical strategies available. It not only provides protection for the individual but through the herd immune effect also provides protection for the community.

Such is the importance of immunisation that when the WHO set its target of 'Health For All 2000', it included amongst its goals the elimination of the major vaccine preventable diseases of childhood such as diphtheria, tetanus, measles, congenital rubella, tuberculosis and polio.[339] To achieve this goal it set a target of 90% immunisation among children aged less than two years of age by 1990. In 1992, the UK government white paper 'Health of the Nation' set immunisation targets of 95% for the health authorities.[55]

In the UK it is well documented that immunisation uptake rates exhibit inter- as well as intraregional variation,[340] and that immunisation rates are lower than in several other industrialised countries.[339] Recent years however, have seen a temporal association between improving uptake rates and several changes in immunisation policy. These changes include the introduction of immunisation targets in GP contracts,[341] the computerisation of child health records,[115] the appointment of district immunisation coordinators,[341] and the change in the national immunisation schedule from 3, 7 and 9 months of age for the 'triple vaccine' and oral polio vaccine (OPV) to an 'accelerated' schedule of 2, 3 and 4 months of age.[342]

However, for a vaccine to be effective it must reach those it is intended for, and a number of factors have been associated with poor immunisation levels in children. Factors linked with poor immunisation uptake in the UK and other countries are complex and multifactorial and maybe linked to the provision and organisation of health services and parental and health professional behaviour and knowledge.[106-108,110,343-346] International research evidence further suggests that there is a relationship between the characteristics of the population served such as low social class, living in deprived areas and certain family or social characteristics, and low immunisation uptake.[106,109,163,347-350]

Evidence from a national study of factors influencing childhood immunisation uptake rates in England and Wales indicated that districts with high social deprivation (UPA) scores were associated with lower levels of immunisation uptake.[106] Deprived areas have also been associated with inadequate access to or poor utilisation of preventive health services.[53,351] In a case-control study matching

children from a 'deprived' area for gender and age with children from an 'affluent' area, Marsh and Channing reported that there was a poor uptake of preventive care by children from deprived backgrounds, and that these children had much lower immunisation rates, and later immunisation dates than their controls.[347] A study from Liverpool indicated that parents from socially deprived areas were less likely to provide consent for immunisation of their children.[113] Lynch examined GP payments linked to immunisation rates in Glasgow.[111] It was found that practices providing health services for populations in deprived areas were less likely to reach childhood immunisation targets than those in more affluent areas. A report from Northumberland demonstrated that although an overall increase in immunisation rates had occurred in recent years, there were still inequalities in uptake between deprived and affluent areas.[352] In some cases these differences were said to have increased thereby leaving children from deprived areas at increased risk from preventable infectious disease.

Jarman et al reported that immunisation uptake was lower in urban areas and that immunisation uptake was strongly linked with social factors such as overcrowding, population density, single parent families, unemployment and ethnic minority status (New Commonwealth including Pakistan).[163] Data on children from ethnic minority groups is however conflicting. A number of studies have described children from these groups as being at increased risk for poor immunisation uptake,[114,353] while others have suggested that immunisation uptake in these populations is similar to, if not better than, that of the indigenous population.[354,355] However, it should be noted that the majority of the published UK data on ethnic minority children and immunisation uptake refers to children of

South Asian origin. There is little information regarding immunisation uptake in children from other ethnic minority groups.

Larger families are associated with several social attributes including residing in inner city or deprived areas, and ethnic minority status. Research in this area has identified children from large families as starting immunisation schedules late or being less likely to complete the recommended immunisation schedule when compared with children from smaller families.[106,108,163,348]

A number of families are highly mobile and change address several times in a year. There is some concern that children in these families may be at risk of not being vaccinated. There is, however, conflicting evidence as to whether moving between health districts during the immunisation period affects immunisation uptake. One recent report from Li and Taylor in one of the London districts, found that children who had moved into the district from outside were as adequately immunised as those resident in the district since birth.[350] Pearson et al in Liverpool reported contrasting results.[356] In their study, children who moved into the city were less likely to be fully immunised than those children who had been resident in Liverpool since birth. Among other factors, these discordant results may reflect differences in information transfer between districts, whether or not these families register with primary care services, and their utilisation of community health services.

Most of the literature reviewed appears to indicate that children from deprived areas, or families, are less likely to be up-to-date with their immunisations than their peers from more affluent areas. These children are also more likely to have a higher frequency of hospital admission.[103,347] In addition, the literature

suggests that children admitted to hospital are likely to be inadequately immunised.[357,358] However, despite WHO advice that:[359]

> "contact with the health services made for other reasons should be exploited for the purposes of immunisation"

reports indicate that the immunisation status of hospitalised children remains unchanged on discharge from hospital.[360]

Population characteristics alone however do not fully account for the variation in vaccine uptake, and the accuracy of data on immunisation uptake has been questioned.[361,362] The structure and organisation of preventive services has also been examined as a factor in differential rates of immunisation. Factors associated with missed or delayed immunisation include immunisation location, level of professional knowledge, inconvenient opening hours and failure to receive appointment letters.[106-108,346,363-365]

3.5 DIAGNOSIS AND TREATMENT OF INVASIVE *H INFLUENZAE* DISEASE

In addition to the risk factors outlined in the previous sections, there are other factors which may affect the morbidity and mortality associated with primary invasive *H influenzae* disease. Again, these factors are generally well documented for *H influenzae* meningitis, and less well for other manifestations of the organism. This part of the literature review will therefore mainly refer to approaches designed to decrease the morbidity and mortality associated with *H influenzae* meningitis.

3.5.1 Diagnostic methods

H influenzae is a small gram-negative coccobacillus indigenous to humans and found mainly in the upper respiratory tract.[255] On gram-staining clinical specimens may appear to be pleomorphic and this variable morphology may lead to misinterpretation of stained smears.[146] The organism requires two factors (X and V) for growth in vitro. The X factor is a heat-stable, iron-containing protophyrin, whereas V factor is a heat-labile coenzyme supplied by nicotinamide adenine dinucleotide (NAD).[146,255] These growth requirements distinguish *H influenzae* from other *Haemophilus* species.

H influenzae are divided into capsulated and unencapsulated strains. Encapsulated strains are further sub-divided into serotypes a through to f depending on the antigenic specificity of their polysaccharide capsule. Type b is responsible for 90% of invasive disease and antibody to the type b capsule is the basis for rapid diagnostic tests as well as the current vaccines.[146]

Detection of *H influenzae* either by Gram stain or culture from a normally sterile fluid, such as CSF or blood, is the 'gold' standard for the aetiological diagnosis of invasive *H influenzae* disease.[255,195] However, prior antibiotic treatment may decrease the probability of detecting the organism in up to 60% of patients with meningitis.[192] This figure may be higher in countries, such as Hong Kong and Thailand, where antibiotics are more freely available than they are in most Western countries.[239] Although antibiotic therapy prior to hospitalisation has been shown to reduce the frequency of positive Gram stains and bacterial cultures, it does not affect the yield of the organism or the biochemical characteristics of the CSF in bacterial meningitis.[366]

As a result of the problems caused by prior antibiotic therapy, the difficulty in establishing the precise aetiology of syndromes such as pneumonia, and the importance of starting antibiotic treatment before culture results are known, specific immunological tests have been developed to rapidly establish the presence of type b capsular polysaccharide antigen.[367-369]

Cross-reactivity with *E. coli, S. pneumoniae*, staphylococcus, meningococcus and other bacteria may also result in false positive test results. This is because these organisms possess surface structures similar to Hib antigen and therefore cross-react with Hib anti-serum.[195,369,370]

Another problem is the detection of Hib antigen in urine and CSF following vaccination. Using latex agglutination tests, Goepp et al reported that antigenuria occurred in 41% of infants up to 30 days after receiving Hib conjugate vaccine.[371] In another study, Hib antigen was detected in the CSF of a child despite negative serum and urinary antigen tests, as well as negative blood and CSF cultures twenty one days after receiving immunisation.[372]

As a consequence of these problems, and their inability to identify antibiotic bacterial resistance, rapid antigen tests are not recommended for the routine diagnosis and management of invasive disease in general, and meningitis in particular.[373]

3.5.2 Antibiotic resistance

Ampicillin has been the mainstay of treatment for invasive *H influenzae* for many years. However, in 1974 plasmid-mediated b-lactamase resistance to

ampicillin was first reported.[195] Since then, increasing resistance to ampicillin and other antibiotics has been reported.

This is dramatically illustrated by the rapid rise in ampicillin resistance found in one region of France. A ten year retrospective study reported that 4% of strains were ampicillin resistant in 1980.[126] By 1989, this had increased to 55%. During the same time period, ampicillin resistance in Britain increased from 3% to 16%.[121,141,142] A more recent report from the PHLS six region study indicates that from 1990/91 to 1993/94 the proportion of ampicillin resistant Hib strains increased from 16% to 26%.[140] This increase may however have occurred as a result of increased testing and awareness following the introduction of Hib conjugate vaccine. In Europe, the highest incidence has been reported from Spain, where 60% of isolates were found to be ampicillin resistant.[127] In the USA, two nationwide studies reported that in 1986 approximately 32% of *H influenzae* isolates were resistant to ampicillin.[128,374]

Occasional reports documenting chloramphenicol resistance have appeared in the literature. Campos et al have reported that 66% of invasive Hib isolates in Spain are resistant to chloramphenicol.[127] Contrastingly, strains resistant to chloramphenicol are rarely encountered in other parts of Europe. In Britain, Anderson et al found 2% of *H influenzae* strains to be chloramphenicol resistant in the early 1990's,[249] while in France[126] and Sweden[273] 4% and 1% (respectively) of strains were resistant to chloramphenicol. In the USA, a study in which 1025 isolates were tested reported that only 1 (0.1%) was chloramphenicol resistant.[374] A recent five year study carried out in Hong Kong where the community use of antibiotics without prescription is a recognised clinical problem, found that 23% of

isolates were chloramphenicol resistant in addition to 26% being ampicillin resistant and 16% demonstrating resistance to both antibiotics.[239] Strains resistant to both ampicillin and chloramphenicol are also a major problem in Spain where 57% of Hib isolates are resistant to both antibiotics.[127]

The emergence of strains resistant to both drugs complicates the treatment of *H influenzae* meningitis, especially in places where ampicillin and chloramphenicol are still commonly used as initial empiric therapy. Fortunately, this does not appear to be a dilemma in many countries yet, although recent reports from England and Wales indicate that up to 2% of Hib strains are resistant to both antibiotics.[142,249]

Antibiotic prescribing patterns in hospital and the community may influence the observed pattern of antibiotic resistance, as may inter-community transmission of resistant strains. Different methodologies, such as mode of collection of specimens, and the testing of isolates from sterile and non-sterile sites may also account in part for the different rates of resistance found in various countries.

3.5.3 Antibiotic therapy

Empiric treatment of meningitis in children beyond the neonatal period has traditionally been instituted with penicillin or ampicillin, and chloramphenicol. Once the organism has been positively identified as *H influenzae* and its antibiotic susceptibility is known, then treatment may be changed where appropriate.

The combination of a penicillin and chloramphenicol is both cheap and effective, and is used in many parts of the world for bacterial meningitis in the

post-neonatal period. The regimen, however, has several drawbacks including, increasing bacterial resistance to either or both of these drugs (see section 3.5.2), the interaction of chloramphenicol with other drugs, the variation in drug metabolism between individuals, as well as its potential toxicity.[375,376] It is now recommended that third-generation cephalosporins are used for the treatment of *H influenzae* meningitis.[375,377] Despite these recommendations, ampicillin and chloramphenicol may remain the drugs of choice in the treatment of invasive Hib disease especially in countries with limited resources, in areas where there are issues of cost-containment, and where paediatricians and microbiologists are reluctant to change their prescribing practice.

Prospective randomised controlled trials of cephalosporins have shown that they are efficacious when used to treat invasive *H influenzae* type diseases, including meningitis.[378-380] They penetrate well into the CSF, achieve rapid sterilisation, are active against strains resistant to penicillins and chloramphenicol, and have few toxic side effects. Furthermore, resistance to these drugs remains uncommon. However, in comparative trials with traditional therapy for *H influenzae* meningitis, they have not been shown to be superior to ampicillin and chloramphenicol, and do not appear to significantly reduce mortality and neurological sequelae.[381-383]

The duration of antibiotic therapy for meningitis is generally gauged upon the response of the child to treatment and a 7 to 10 day course is traditionally recommended.[375] Recent research in a number of different centres has examined seven day courses of antibiotic therapy in children with uncomplicated *H influenzae* meningitis.[378-380,384,385] The results have been encouraging, reporting no

significant differences in terms of morbidity, treatment failures and sequelae when compared to children treated with longer courses of antibiotics. The studies have however suffered from small numbers and the use of differing drug and dosage schedules. This makes it difficult to reach any firm conclusions as to the benefits of shorter courses of treatment. The introduction of Hib conjugate vaccines means that further evidence to support these results is unlikely.

3.5.4 Dexamethasone therapy

Despite the availability of newer antibiotics and advances in the diagnosis and management of *H influenzae* meningitis and other invasive Hib diseases, *H influenzae* meningitis is still associated with significant morbidity and mortality in children. Much of this has been attributed to the inflammatory response within the CNS.

Animal models have shown that the lysis of bacteria by antibiotics induces the release of cytokines such as tumour necrosis factor (TNF) and interleukin-1 beta (IL-1 β).[386,387] These in turn activate the inflammatory response which may lead to undesirable changes such as cerebral oedema, increased intracranial pressure (ICP) and disturbances in cerebral blood flow. The administration of dexamethasone has been shown to reduce or prevent the production of cytokines and thereby decrease the inflammatory response both in vitro and in vivo.[388-391]

A number of clinical trials in children with bacterial meningitis suggest that when dexamethasone is given before or together with the first dose of parenteral antibiotic, abnormal CSF parameters, fever and the concentrations of CSF cytokines improve significantly earlier than in those children given placebo.[219-221]

These trials also suggested that sensorineural hearing loss, and other neurological sequelae were more likely to be reduced in those who received dexamethasone.[219-221,392] Adverse side effects appeared to be minimal and were mainly related to gastrointestinal bleeding.[219,220]

Two meta-analytical studies using slightly different methodologies, and published out six years apart, examined the evidence for the routine use of dexamethasone in the treatment of bacterial meningitis.[393,394] Both reached the same conclusion, that there was insufficient evidence to recommend routine use of corticosteroids in the treatment of acute bacterial meningitis. They also found that the available evidence indicated that steroids did not significantly reduce the risk of morbidity or mortality in children with acute bacterial meningitis.[393,394]

There have been several criticisms of the dexamethasone studies. It has been pointed out that most of the initial studies were carried out by the same group of researchers, that the number of patients enrolled in the studies were small and that differing doses of corticosteroids were given. Furthermore, as the majority of children had *H influenzae* meningitis, the results were not generalisable to other types of bacterial meningitis.[129,393-395]

Nevertheless, on the basis of the initial results, in 1990, the American Academy of Pediatrics recommended that dexamethasone therapy be considered in children two months of age or older with proven or suspected bacterial meningitis.[396] The recommended regimen was 0.15 mg/kg every 6 hours for 4 days. They also recommended that the initial dose of dexamethasone be given with the initial dose of antibiotic, and that haemoglobin concentration and the

examination of stool for occult blood be performed regularly during dexamethasone administration.[396]

A questionnaire survey of directors of paediatric infectious disease training in the USA and Canada was carried out in 1992. Responses were received from 69 of 79 (87%) questionnaires sent out. Of these 50% said that they "always" or "sometimes" used dexamethasone for the treatment of bacterial meningitis.[397] Comparable data for the UK on the use of dexamethasone by paediatricians is unavailable.

The British Paediatric Immunology and Infectious Disease's Group, in a review of the published literature on dexamethasone and meningitis, believed that the introduction of *H influenzae* vaccines in the UK would significantly reduce the incidence of *H influenzae* meningitis, and that this would therefore render any debate over the issue less meaningful.[129] They concluded that research priorities should be directed towards determining the effect of dexamethasone on the course and outcome on other forms of bacterial meningitis, especially meningococcal.

3.6 PREVENTION OF INVASIVE *H INFLUENZAE* DISEASE

3.6.1 Chemoprophylaxis

Colonisation with Hib may not be eradicated or may recur after antibiotic therapy has been completed in a child with invasive Hib disease. Recolonisation and persistence of the organism are ways by which this may occur. This may be prevented by the use of chemoprophylaxis, which is used to prevent secondary transmission of meningitis following the occurrence of an index case.[195]

Rifampicin is the current drug of choice for the eradication of nasopharyngeal carriage of *H influenzae* and the prevention of secondary cases of invasive *H influenzae* disease.[398] Studies have shown that a dose of 20mg/kg/day (maximum 600mg/dose) of this antibiotic given orally once daily for 4 days is effective in eradicating nasopharyngeal carriage of *H influenzae*.[399-402] It is generally safe, but has several side effects including red coloration of sputum, urine and tears, itching and gastrointestinal upset.[403]

Despite its effectiveness, instances of prophylactic failure have been reported. Several possible explanations have been advanced for this including the emergence of rifampicin resistant *H influenzae* strains, failure of the drug to eliminate Hib from the nasopharynx and recolonisation with the organism following rifampicin prophylaxis.[398,404,405] Other problems associated with chemoprophylaxis include defining contacts, delayed contact tracing, ensuring simultaneous administration of chemoprophylaxis to all contacts and failure of compliance.[405,406]

Prophylaxis for invasive Hib disease in the UK has been recommended for all index cases, all family members who are close contacts and other close contacts with children aged less than four years of age who are unimmunised or incompletely immunised with Hib vaccine.[403] Furthermore, in order to reduce the likelihood of recolonisation all contacts should be treated simultaneously. These are similar to guidelines for chemoprophylaxis in the USA.[407]

The development and introduction of the conjugate Hib vaccines into routine immunisation programmes has probably made the issue of chemoprophylaxis less contentious. However, because the majority of secondary

cases occur within a few days of the index case, and because it takes 1 to 2 weeks for antibody concentrations to become protective following administration of Hib vaccine,[408] immunisation alone would not prevent disease occurrence during the period of greatest risk.[409,410] Additionally, treatment of invasive *H influenzae* disease does not eliminate carriage of the organism in the nasopharynx of the index case.[195,411] Following hospital discharge index cases still harbour bacteria and may be a potential source of recolonisation in household contacts. Thus, chemoprophylaxis is required by both index cases and contacts.

3.6.2 Hib vaccines

The Hib bacteria contains a polysaccharide PRP capsule which determines its virulence and invasiveness.[195] Antibodies to this capsular polysaccharide provide immunity to invasive disease by Hib, and by 5 years of age most children have protective antibody levels.[412] This immunity is thought to develop from a number of sources including asymptomatic carriage and following cross-reactivity with various gastrointestinal bacteria which have similar polysaccharide capsules to that of Hib.[412] Maternally acquired antibodies as well as antibodies obtained through breastfeeding provide protection in the first few months of life.[146,284,294] Therefore, invasive disease primarily affects children aged between 2 months and 5 years.

The identification of the key role played by the polysaccharide capsule of Hib in the pathogenesis of invasive disease by this organism has been instrumental in providing one of the most exciting advances in paediatrics, the development of conjugate vaccines to prevent Hib disease. This technology is now being applied

to the development of a number of other conjugate vaccines against group B meningitis, pneumococcal infections, malaria and *Pseudomonas aeruginosa.*[413]

The new Hib conjugate vaccines are more immunogenic and efficacious in young children than the initial Hib polysaccharide vaccine, and therefore have a greater potential to significantly reduce the incidence of severe Hib disease.[167,414-416] The reason for the greater protective efficacy afforded by the conjugate vaccines over the polysaccharide vaccine lies in the type of humoral immune response elicited.

In general, protein antigens evoke a T-cell dependent antibody response.[412] This involves the activation of T-helper lymphocytes, which then stimulate antibody production by B-lymphocytes.[412] T-cell induced immunity also results in the manufacture of B-memory cells, which provide the basis for significantly increased antibody production when the host is challenged by the same antigen at a later date (booster response).[412] The carrier protein is also said to enhance the immune response.[146]

In common with other polysaccharide vaccines (for example meningococcal and polyvalent pneumococcal), the bacterial capsular polysaccharide Hib vaccine is poorly immunogenic in infants.[417] The antigen elicits a T-cell independent immune response by acting directly on B-cells to induce the synthesis of humoral antibodies.[146,412] The T-helper lymphocytes are bypassed, and therefore the T-cell independent immune response is not associated with the production of appreciable numbers of B-memory cells, or significantly increased levels of protective antibodies in response to further exposure to the antigen, either by natural exposure or further vaccination.[146,412] T-cell independent

antigens are also associated with limited or no antibody response in children below the age of 18 months, and these are the children most at risk of morbidity and mortality.[146,412]

The following section will examine the immunogenicity and protective efficacy of the different varieties of Hib vaccine.

3.6.2.1 Polysaccharide vaccine

Polyribosyl ribitol phosphate (PRP) vaccine

Now mainly of historical interest, PRP vaccine was a T-cell independent immunogen which induced a poor immunologic response, was highly age dependent and failed to respond to booster doses. It was the first Hib vaccine to be licensed in the USA in 1985 following trials in Finland which reported an estimated protective efficacy of 90% (95% CI=56% to 96%) but only in children aged more than 18 months.[146,418]

Protective levels of antibody with this vaccine are said to be reached when anti-PRP antibody concentration is 1.0 μg/ml.[419] However, children aged less than 18 months failed to achieve this with the polysaccharide vaccine. The exact concentration of antibody required to confer protection against invasive Hib disease is unknown. Long-term protection is however reported to be associated with anti-PRP antibody concentration levels of 1.0 μg/ml,[418] while levels of ≥ 0.15μg/ml are regarded as protective if obtained in unimmunised people.[419]

In the USA, post-licensure case-control studies provided a wide variety of results, together with reports of vaccine failures. One multi-centre study reported high levels of protective efficacy in their trial, 88% (95% CI=74% to 96%).[420]

Osterholm et al were originally part of the same multi-centre trial but reported markedly different results. They found that PRP vaccine had a protective efficacy of -55% (95% CI= -238% to 29%).[410] Their results suggested that there was an increased risk of disease following vaccination. Although several explanations have been proposed, these widely conflicting results remain unexplained. The development of conjugate vaccines has now made this issue academic.

3.6.2.2 Conjugate vaccines

The limited immunogenicity of PRP vaccine in young infants, and the variable levels of protective efficacy reported from clinical trials provided the impetus for the development of the next generation of vaccines, the conjugate vaccines.

These vaccines are produced by covalent linkage (conjugation) of PRP to a protein carrier molecule.[146] This increases the immunogenicity of the vaccine as it elicits a T-cell dependent immune response, and results in improved immunogenicity.[412] Consequently, there is increased and prolonged antibody synthesis, and the production of a booster response. The vaccines have been shown to be highly effective in young infants and children with only minor adverse effects reported. These include local erythema, tenderness, irritability and fever.[421,422]

At the time of writing there are 4 conjugate Hib vaccines and although all are similar in some respects, they differ in several others. Their differences include

the type of carrier protein used, length of the polysaccharide chain (see table 3.9), and level of protective efficacy.

PRP-diphtheria toxoid conjugate (PRP-D) vaccine

This vaccine links diphtheria toxoid as the protein carrier to a medium-sized length of PRP polysaccharide.[244,423] Immune responses using this vaccine are demonstrably better than those seen after immunisation with plain PRP polysaccharide vaccine, and an increased response is seen following a second or third booster dose.[408,424,425] Although most children developed high antibody levels, the immune response in children 2 to 6 months of age was found to be poor, even after three doses.[424] While children aged 9 to 15 months responded less well to the vaccine, older children achieved high concentrations of anti-PRP antibody even after a single dose.[408,425]

Table 3.9: Properties of *Haemophilus influenzae* type b conjugate vaccines*

Conjugate vaccine	Protein carrier	Polysaccharide size	Manufacturer	Trade name
HbOC	Diphtheria toxin mutant CRM_{197}	oligosaccharide (10μg)	Lederle-Praxis	HibTITER
PRP-D	Diphtheria toxoid	whole PRP (25μg)	Connaught	ProHIBiT
PRP-OMP	Group B meningococcal outer membrane complex	whole PRP (15μg)	Merck, Sharp and Dohme	PedvaxHIB
PRP-T†	Tetanus toxoid	whole PRP (varies with lot)	Pasteur/Merieux/Connaught	ActHib

* Adapted from Force et al[412]

† Hib conjugate vaccine used in the UK primary immunisation schedule

In Finland, over 100 000 children received PRP-D vaccine at 3, 4, 6 and 14 months of age. The estimated protective efficacy of the vaccine was 89% (95% CI=70% to 96%) after 3 doses, and 100% (95% CI=82% to 100%) following the fourth booster dose.[426] An efficacy study conducted in the USA by Greenberg et al also found the vaccine to be protective.[408] They reported a protective efficacy of 88% (95% CI=42% to 97%) in children aged 18-59 months of age.

However, an efficacy trial conducted amongst a group of Native Alaskan infants, who are a high risk group, provided conflicting results.[168] Thirteen of 32 episodes of invasive disease occurred in children who had been immunised, with eight of these having received the full course of three vaccinations at 2, 4 and 6 months of age. Vaccine efficacy in this group of children was estimated to be 35% (95% CI= -57 to 73%). The reasons for this difference are yet to be clearly defined, but it has been proposed that a higher incidence or earlier development of Hib disease in this population, or other undefined factors, may be responsible.[412,423]

H influenzae type b oligosaccharide conjugate (HbOC) vaccine

HbOC is a PRP oligosaccharide conjugate vaccine whose carrier protein is a non-toxic mutant diphtheria toxin which is covalently linked to several short oligosaccharide chains of PRP.[244,423] A three dose course of the vaccine has been demonstrated to provide protective concentrations of antibody for a minimum period of a year in most young children, with reports in some series of protective levels lasting 2-4 years.[428,429]

Black et al reporting from Northern California estimated vaccine efficacy to be 84% (95% CI=59% to 94%) when infants were vaccinated at 3, 5 and 7

months of age.[416] In this study, only three vaccine failures were identified over a 1 - 3 year follow-up period. All of these occurred in children in the period following the first vaccine, but prior to the second vaccine. Further evaluation of this group of children found protective levels of antibody in 97% one month after the final dose of HbOC. This had dropped to 71% one year after completing the 3 dose course, however a fourth dose of vaccine given at 18 months of age produced a significant booster response.

Tudor-Williams et al evaluated HbOC vaccine in a group of British infants.[421] The vaccine was given in one of two doses, either 2 μg or 10 μg, at 3, 5 and 9 months of age. When reviewed one month after completing the course, regardless of the dose administered, 98% of those immunised had protective levels of antibody. No further follow-up of these children was conducted.

An efficacy trial in a group of Native American children also used a three dose series, but the children were immunised at 2, 4 and 6 months of age and doses ranged from 6.5 μg to 15 μg.[429] Evaluation of antibody levels 2 months after the first dose found no difference between control and placebo groups. However, following second and third doses of the vaccine a booster response was observed, and one month after the final dose over 90% of the children had protective concentrations of antibody. An observed decline in antibody levels in the months following administration of the final dose resulted in the authors recommending a booster dose at 15-18 months of age.

PRP outer membrane protein conjugate (PRP-OMP) vaccine

This vaccine has medium sized lengths of PRP polysaccharide linked to its protein carrier which are outer membrane protein vesicles of a strain of group B *Neisseria meningitidis*.[244,423] PRP-OMP is highly immunogenic and in contrast to other Hib conjugate vaccines, a dramatic antibody response is seen in response to the first dose, even in infants as young as 2 months of age.[419] Unlike other conjugate vaccines a significant booster response is not seen following a second dose, and antibody levels decrease significantly in the year following immunisation.[419]

Santosham et al evaluated the efficacy of this conjugate vaccine in a group of Native American infants who were immunised at 2 and 4 months of age.[430] Using an intention to treat analysis they estimated that the protective efficacy in children receiving one or two doses was 95% (95% CI=72% to 99%). A decline in antibody levels was seen in the 3-12 month period following the second vaccination in the 2 dose regimen, and the authors recommended that a booster dose should be given at 12 months of age. Other reports have also recommended that a booster dose be given at 12-15 months of age.[431,432]

PRP tetanus toxoid conjugate (PRP-T) vaccine

Large polysaccharide polymers linked to a tetanus toxoid protein carrier are used to produce the PRP-T conjugate vaccine.[244,423] The vaccine is highly immunogenic at all ages,[433-435] and has been reported to be immunogenic in children with sickle cell disease and malignancy.[436]

In 1991 Booy et al reported from Oxford that when PRP-T was administered at 2, 3 and 4 months of age, concentrations of more than 1.0 μg/ml were seen in 91% of children who had received the vaccine one month after the third dose.[437] The authors estimated that the protective efficacy of the vaccine was 95% (95% CI=75% to 100%). Only one vaccine failure was identified in immunised children compared to 18 vaccine failures in control children followed for 20 months. These results were achieved without the use of a booster dose in the second year.

Recent reports from South America and Africa indicate that PRP-T conjugate vaccine is equally immunogenic in young children from developing countries. Lagos et al reported an estimated vaccine efficacy of 92% (95% CI=65% to 100%) in Chilean children who completed a 3 dose schedule at 2, 4 and 6 months.[438] Mulholland et al conducted a double-blind randomised trial in The Gambia.[439] Children received PRP-T conjugate vaccine at 2, 3 and 4 months. The estimated vaccine efficacy in this group of children was 95% (95% CI=67% to 100%).

3.6.2.3 Combined vaccines

A combined vaccine is one which contains two or more vaccines administered in a single injection, DTP and MMR are examples of such vaccines which are already currently employed.[8,440] They have demonstrated that combined vaccines are acceptable to both health professionals and parents, and can be as safe and as effective in preventing disease as their component vaccines.

Clinical evaluation of new combination vaccines containing Hib conjugate vaccine, such as Hib-DTP, Hib-DTP-IPV and Hib-DTP-HBV-IPV have been conducted or will take place. With more and more parenteral vaccines (for example acellular pertussis, varicella, meningococcal, pneumococcal and respiratory syncitial virus vaccine) on the horizon, the reasons for combining a number of these vaccines into a single injection becomes attractive.[8,438,439,441-446] The infant and parent will not only have fewer visits and fewer injections, but from the public health perspective, a reduction in the number of inoculations would reduce the cost of administration, be more practical and contribute to improved vaccine uptake.[8,447,448]

The administration of Hib conjugate vaccines together with other childhood immunisations has been shown to be both safe and effective. Begg and colleagues compared the safety and immunogenicity of giving combined PRP-T/DTP and HbOC/DTP vaccines with giving the combinations separately at different sites. They analysed data from children recruited to previous trials and immunised using the standard UK immunisation schedule (at 2,3 and 4 months of age).[442] The results obtained indicated that protective levels of anti-PRP antibody were attained with both types of combined Hib conjugate vaccines and that no significant differences in post-vaccination titres were seen between the four different groups. They also reported that the combined vaccine did not result in increased adverse reactions. Using a randomised controlled trial approach, Jones et al reported similar results for a study conducted in a different part of the UK.[441]

Results from these studies and several others worldwide indicate that there is a reduction in the anti-PRP antibody response as well as tetanus and pertussis

antitoxin responses in combined vaccines containing PRP-T or PRP-D and DTP.[434,435,441-446] Reasons for these reduced responses are not known but it has been proposed that it may be due to carrier suppression.[449] The clinical significance of the reduced response to combined vaccines is yet to be determined.

3.7 PUBLIC HEALTH IMPACT OF Hib CONJUGATE VACCINES

The literature indicates that the use of Hib conjugate vaccines has been followed by a rapid decline in morbidity and mortality due to invasive Hib infections in all countries where they are used. The final section in this chapter will review the published literature on the impact Hib conjugate vaccine has had on invasive Hib infections and examine the factors associated with vaccine failures.

3.7.1 Effect of Hib conjugate vaccine on disease incidence

Hib conjugate vaccines were incorporated into the primary immunisation schedule of the UK and Republic of Ireland in October 1992. Three doses of PRP-T conjugate vaccine were to be given at one month intervals starting from the age of two months.[450,451] It was also recommended that children aged up to 48 months be included in a catch-up programme, which was scheduled to last one year. Children aged less than 12 months were to receive 3 doses of the PRP-T conjugate vaccine, while those aged between 12 and 48 months would receive a single dose of the HbOC conjugate vaccine. In children aged 12 months, coverage of greater

than 90% had been achieved by November 1993.[452] Following conclusion of the vaccine programme, only PRP-T conjugate vaccine was recommended for use in the UK.

In the PHLS six region laboratory-based study, Hargreaves and colleagues assessed the change in incidence of invasive *H influenzae* disease among children aged less than 5 years.[140] They reported that incidence rates fell from 26.0 to 2.0 per 100 000 children between 1990/91 and 1993/94. This represented a 92% decrease in incidence during the period of the study. Urwin et al also reported a reduction in the incidence of *H influenzae* meningitis in children aged less than 5 years in the North East Thames region, from 22.0 per 100 000 in 1991 to 3 per 100 000 in 1993, the year following the introduction of Hib conjugate vaccine.[267]

In the Republic of Ireland, a similar dramatic decline in incidence was also observed. A 90% reduction in disease incidence was seen with approximately 75% immunisation coverage.[453] Reports from other European countries indicate that comparable reductions in the incidence of invasive Hib disease have occurred following the introduction of Hib conjugate vaccines.[136,454,455]

Vaccination with Hib conjugate vaccines has also resulted in large decreases in the incidence of Hib infections in the USA, with reductions of between 82% to 95% reported in children aged less than 5 years.[134,135,287,456-460] Data from Canada,[137] Australia[138] and The Gambia[439] also demonstrate an association between the decline in the incidence of invasive Hib disease and the introduction of Hib conjugate vaccines.

Notwithstanding the temporal association between introduction of the vaccine and the decline in cases of invasive *H influenzae* disease among young

children, it is possible that other factors may be responsible. Indeed, the incidence of invasive Hib disease has been shown to vary both seasonally and interannually.[138,279,292] The results of a time-series analyses carried out in Australia suggest that these factors cannot account for the dramatic decline observed.[138] Furthermore, the vaccination effect has been seen consistently in each country where Hib conjugate vaccine has been introduced. This evidence provides further support that the introduction of the vaccine was responsible for the rapid reduction in the incidence of invasive Hib disease.

The decline in incidence seen following the introduction of the vaccine has been observed not only in immunised children but also in unimmunised children.[134,135,287,460] This phenomenon, known as the herd immune effect, occurs as a result of the presence of immune individuals in the population providing indirect protection to non-immune individuals.[461] It has been suggested that Hib conjugate vaccines reduce nasopharyngeal carriage of Hib among vaccinated children and that this provides some protection for unvaccinated children by reducing transmission of the organism or delaying its acquisition.[289,462,463] This then leads to greater than expected reductions in the incidence of invasive Hib disease.

Man is the only host for *H influenzae* type b and consequently the worldwide use of Hib conjugate vaccines has the potential to eliminate the pathogen and its resultant diseases. However, not all countries currently employ Hib conjugate vaccines. For example, in the WHO European region, only 14 of 47 (30%) member countries (as of 1995) include Hib in their immunisation programmes.[464] These countries are mainly from Northern Europe and they have different immunisation programmes and schedules. With the increased movement

across international boundaries and the likelihood of the transfer of the medical care of susceptible children, knowledge regarding the interchangeability of Hib conjugate vaccines is essential. Currently available data from studies conducted in the United States[465-467] and the United Kingdom[468] suggest that PRP-T and PRP-OMP; PRP-OMP and HbOC; PRP-T and HbOC; and PRP-OMP and PRP-D can be interchanged with each other without compromising safety, immunogenicity or efficacy. It has been demonstrated that giving different combinations of Hib conjugate vaccines may produce a better immune response than if a single Hib conjugate vaccine had been used for all three vaccinations.[465,466] Small numbers of children recruited for the studies, the use of different immunisation schedules, the exploration of only a few of the possible schedules and the lack of data on long-term protection and the interchangeability of combined vaccines limits any conclusions which may be drawn.

Despite these and other concerns, such as the cost of conjugate vaccines,[469-472] and debate as to whether Hib conjugate vaccines should be introduced into the EPI (Expanded Programme on Immunisation) programme,[473] the future elimination of Hib remains a possibility. The WHO and the Children's Vaccine Initiative (CVI) have recommended that Hib conjugate vaccines be included in infant immunisation programmes, and are currently considering how best to incorporate these vaccines into the EPI programme.[474]

3.7.2 Hib conjugate vaccine failures

Despite the success of Hib conjugate vaccines, vaccine failures have occurred and the reasons for this remain ambiguous. Holmes and Granoff

reviewed published serologic, immunologic and genetic data of children who developed culture-proven invasive Hib disease 14 or more days after immunisation with Hib conjugate vaccine.[475] Their study only looked at children aged 15 months or more at the time of immunisation. They found that some of these children had a deficiency of IgG2 and/or IgM, and were thought to represent delayed maturation of the immune system. These results were however only seen in 40% of vaccine failures, the reasons for the remainder remain unclear.

In the UK Booy et al have recently reported the findings of a national BPSU study into Hib conjugate vaccine failures from 1992-1995.[476] They reported 89 vaccine failures, of these they identified 43 true vaccine failures (TVF) and 46 apparent vaccine failures (AVF). A true vaccine failure was defined as invasive Hib disease occurring more than 2 weeks after a single dose of vaccine (PRP-T or HbOC) given to an infant of more than 1 year or more than 1 week after at least two doses had been given (at least 1 month apart) to a child younger than 1 year.[476] The majority of their TVF cases were either due to meningitis (26 of 43, 60%) or epiglottitis (10 of 43, 23%).

Frasch et al reported Hib conjugate vaccine failures following immunisation with PRP-D in 26 children in the United States over a one year period.[477] All of these children were aged less than 5 years and meningitis was the most common diagnosis (11 of 18, 61%), there was only one case of epiglottitis.

An Australian report on one year's experience with Hib conjugate vaccine usage, also found a lack of epiglottitis cases in the 9 vaccine failures identified following immunisation with one or more doses of either PRP-T, PRP-D, HbOC or PRP-OMP.[478] Among their 9 cases were 5 cases of meningitis and 1 case of epiglottitis.

There were no reported vaccine failures following immunisation with PRP-T conjugate vaccine. Vadheim et al reported on 29 vaccine failures following immunisation with one or more doses of HbOC or PRP-OMP conjugate vaccines over a two year period.[460] They found that 21 of these cases manifested as meningitis and none as epiglottitis.

The lack of epiglottitis cases seen in most series may be attributed to the herd immune effect with vaccinated younger children protecting unvaccinated older children. In the UK series the diagnostic distribution has changed with proportionally more cases of epiglottitis identified.[476] It is however difficult to draw any conclusions from this series with respect to children as ages were not given.

3.8 Summary of chapter 3

This review of the literature has shown that the current British surveillance systems reliance on voluntary reporting of cases of *H influenzae* meningitis leads to underreporting of the disease. Reliance on routine data sources may therefore underestimate the clinical, public health and economic impact of Hib disease.

Disease incidence and risk factors vary between and within countries, but are highest in 'developing' countries and among the native populations of the United States, Canada, Australia and Israel. This may reflect differing study methodologies or clinical practices, access to healthcare, socioeconomic factors or other influences.

Deprivation has an important effect on health, and the most deprived appear to suffer relatively more from ill-health than the more affluent members of the

population. Children are one of the most at risk groups, and there is a plethora of British data which has examined the issue of deprivation in relation to immunisation uptake. Given that prior to the introduction of Hib conjugate vaccines in the UK that *H influenzae* was one of the leading causes of meningitis in young children, it is surprising that there is little data on its relationship with deprivation. Furthermore, data is lacking on the incidence of the disease among the ethnic minority population in the UK.

Hib conjugate vaccines have resulted in a dramatic reduction in the incidence of disease in all countries where they have been introduced. Consequent to their success conjugate vaccines are being developed for a number of other diseases and the WHO is planning to incorporate Hib conjugate vaccines into the EPI programme. Thus eradication of this disease is potentially possible, however vaccine failures have been identified and the long-term effectiveness and safety of these vaccines is yet to be determined. This means that continued surveillance to identify at risk populations remains important.

CHAPTER 4

METHODOLOGY

METHODOLOGY

In October 1992, a descriptive study of deprivation and other socioeconomic risk factors associated with invasive *H influenzae* disease in the West Midlands Health Region (WMHR) was undertaken as Hib conjugate vaccine was introduced into the UK primary immunisation schedule.

To identify cases a comprehensive surveillance system was established by the researcher which involved retrospective and prospective identification of cases and was planned to involve all hospital laboratories and consultants in communicable disease control (CsCDC) within the region.

The surveillance effort was directed at identifying all children aged less than 5 years with invasive *H influenzae* during a four year period. This would provide a comprehensive register of cases of invasive *H influenzae* infections which could be used to determine disease incidence, provide data for epidemiological research, and measure the impact of Hib conjugate vaccine.

This chapter provides an overview of the conduct of the study from the initial literature search through to methods of data collection and analysis.

4.1 SYSTEMATIC SEARCH OF THE LITERATURE

The literature search was carried out with the aim of identifying, retrieving and critically reviewing the available published literature reporting original data or reviews describing the association between invasive *H influenzae* disease and

markers of poor socioeconomic circumstance. At the same time, a similar search was conducted for the demographic, epidemiologic, environmental and public health issues surrounding invasive *H influenzae* disease in children aged 0-59 months.

In order to conduct a comprehensive literature search, several keywords (table 4.1) were used:

Table 4.1: Keywords used in the systematic search of the literature for invasive *Haemophilus influenzae* disease

Antibiotic resistance	Infectious diseases
Cellulitis	Meningitis
Chemoprophylaxis	Neonatal sepsis
Conjugate vaccines	Osteomyelitis
Communicable diseases	Pneumonia
Co-primary disease	Race
Deprivation	Registers
Dexamethasone	Risk factors
Epidemiology	Secondary disease
Epiglottitis	Sensorineural hearing loss
Ethnic group	Septic arthritis
Haemophilus influenzae	Septicaemia
Health inequalities	Socioeconomic status
Immunisation	Vaccines

A number of computerised databases were consulted and these were:

MEDLINE[479]**:** This database contains citations to the world-wide literature on biomedicine, including research, clinical practice, management and policy. It is produced by the National Library of Medicine in the United States and over 70 per cent of the references are from English language source materials. The literature was searched for articles published in English on *H influenzae* in children from 1966-1997.

ASSIA (Applied Social Science Index and Abstracts)[480]: References to and abstracts of articles in more than 300 academic journals in the applied and social sciences from 1987 are contained in this database. There were 79 references to infectious diseases and 96 for communicable diseases. When combined with deprivation (430 references), only one citation was found. Combining infectious diseases with risk factors (2,435 citations) produced 7 references. When infectious diseases and communicable diseases were each linked with health inequalities and socioeconomic status, no citations were found.

ASLIB (Association of Special Libraries and Information Bureaux) INDEX TO THESES[481]: This database provides details of theses accepted by universities in Great Britain and Ireland from 1970. Using *H influenzae* as the keyword 21 theses were identified from 1975 to 1996 at the MSc, MD and PhD levels. The most recent of these was submitted in 1993, however all were laboratory-based and none examined the epidemiology of invasive *H influenzae* diseases.

Citations thought to be appropriate were retrieved and reviewed. The reference lists of articles obtained by this method were then examined and additional appropriate literature identified. The scope of the search for literature was further widened by requesting colleagues who had published work in the areas of epidemiology, social medicine or communicable diseases to identify published or unpublished work on health inequalities and invasive *H influenzae*.

4.2 STUDY DESIGN

Social inequalities in health are difficult to study and increasingly researchers are using "small area" census-based socioeconomic characteristics of residential areas to address the problem of inadequate socioeconomic information in individual health records.[21,23,65] Studies which use this geographic approach are called ecological studies. In these studies the unit of analysis is an aggregate of individuals within a defined geographic location.[482] An "ecological fallacy" occurs when inappropriate conclusions are made on the basis of ecological data.[482] This is because an association observed between variables at the group level is not necessarily representative of any particular individual or of all individuals in that group.

There are also problems in carrying out individual-level analyses as access to individual-level data is required. This access may be denied on the grounds of confidentiality. Furthermore, it has been argued that individual-level analysis may be less appropriate for transmissible infectious disease epidemiology in which infection risk depends on the prevalence of disease in a community.[483,484]

Ecological analyses are thought to be more appropriate for identifying community level determinants of infectious disease rates and for studying the distribution of infectious diseases in a population.[485] Transmission of infection involves direct and indirect contact between individuals and groups. Analysis of individuals is necessary but insufficient on its own to define communicable disease distribution in a population.[484,486]

It has been stated that the prime justification for the ecological approach is to study health in an environmental context.[486] The aim is to understand how the environment affects the health of persons and groups through a number of factors. It is believed that measures of individual attributes cannot account for these processes. Families, communities, cultures and other social, political and economic phenomena may affect health in ways not explicable by studies that focus exclusively on individuals.[486]

Susser has stated that ecological studies are obligate when they are the only choice available either because of the question asked (as in testing differences between groups and discovering group effects), or because of a concern with dependent happenings (as in transactions involving more than one individual), or merely because of the lack of individual data.[486] All of these reasons are relevant to this study.

This study is therefore a descriptive ecological cross-sectional study with cases of invasive *H influenzae* disease as the numerator and 1991 census population data as the denominator.

It is designed to examine the relationship between invasive *H influenzae* disease and material deprivation in the WMHR between 1 October 1990 and 30 September 1994.

In addition to analysing the relationship between disease and deprivation, the study describes the epidemiology of invasive *H influenzae* disease in children aged less than 5 years in the WMHR in the two year period before (October 1990 - September 1992), and immediately following (October 1992 - September 1994),

the introduction of Hib conjugate vaccines into the primary immunisation schedule of the United Kingdom.

Although hypotheses are not being tested in this study, the data collected should provide information for the development of hypotheses and pointers for further research.

The study was originally designed as a case-control study which would also have investigated the role of stressful life events in the onset of invasive *H influenzae* disease in children. Despite designing, testing and piloting a questionnaire, the original study design was discarded because of a number of reasons. These included insufficient funding, the length of time taken to obtain permission from the various research ethics committees and the increased probability of recall bias, especially on the part of control parents due to the long time-lag in gathering data. It was also anticipated that the introduction of Hib conjugate vaccine would greatly reduce the numbers in the post-conjugate vaccine period making a case-control study unfeasible.

4.2.1 Why invasive *H influenzae* disease ?

Initially, both invasive meningococcal and pneumococcal diseases were considered as alternatives. However, because of anticipated problems with disease definition and the imminent introduction of an effective vaccine for invasive Hib disease, it was decided to select invasive *H influenzae* diseases over the other two.

Some other factors which favoured the selection of invasive *H influenzae* diseases for this study were the defined susceptible population (children aged less than 5 years), and the opportunity to determine the epidemiology of both

meningitic and non-meningitic diseases. Furthermore, previous British studies had not reported environmental risk factors for invasive *H influenzae* disease. Most of them concentrated on other epidemiological aspects. In addition, this study could provide a model for the accurate determination of baseline incidence rates and other epidemiological changes which may be associated with the introduction of pneumococcal, meningococcal or other vaccines.

The WMHR was selected because of the researcher's academic base, and its fortuitous exclusion from the PHLS six region study of invasive *H influenzae* disease, which was carried out during the same time period as this study.

4.3 ETHICAL CONSIDERATIONS

This will be considered in two parts, ethics committees and the issue of confidentiality.

4.3.1 Ethics committees

In the NHS ethical issues relating to medical research are the responsibility of district and hospital research ethics committees. Their purpose is to maintain high ethical standards in the conduct of medical research.[487] Permission to access the medical records of children identified as eligible for inclusion in the study was sought from the research ethics committees in each of the 20 districts prior to commencing the study.

Letters were sent to chairpersons, or secretaries, in each of the districts requesting permission to carry out the study. Application forms were received,

completed and returned together with the protocol and any other documents which were requested. Several ethics committees invited the researcher to explain the purpose of the study, answer questions about the protocol, and to clarify aspects of the data collecting instruments and draft letters. Permission was eventually obtained from all of the districts, but took almost a year.

4.3.2 Confidentiality and anonymity

All correspondence, data entry and data storage were carried out at the University of Warwick, which is registered under the Data Protection Act 1984.

Once the child's medical notes had been traced and data extracted from them onto a proforma, the child was given a non-unique code number using a modification of the Soundex Code[488] (see section 4.7.2 for more details).

The data obtained were entered onto a computer directly from the proforma and stored on the hard disk, backup copies were made on floppy disks. The computer was situated in a room with a number lock. A password was needed to access the data on the computer, and this was known only to the researcher. The floppy disks were kept under lock and key in a separate room.

At the end of the study, any data which could be used to identify the child or their family will be destroyed. Results of the study will be provided in aggregated form whereby it will not be possible to identify individual children or their families.

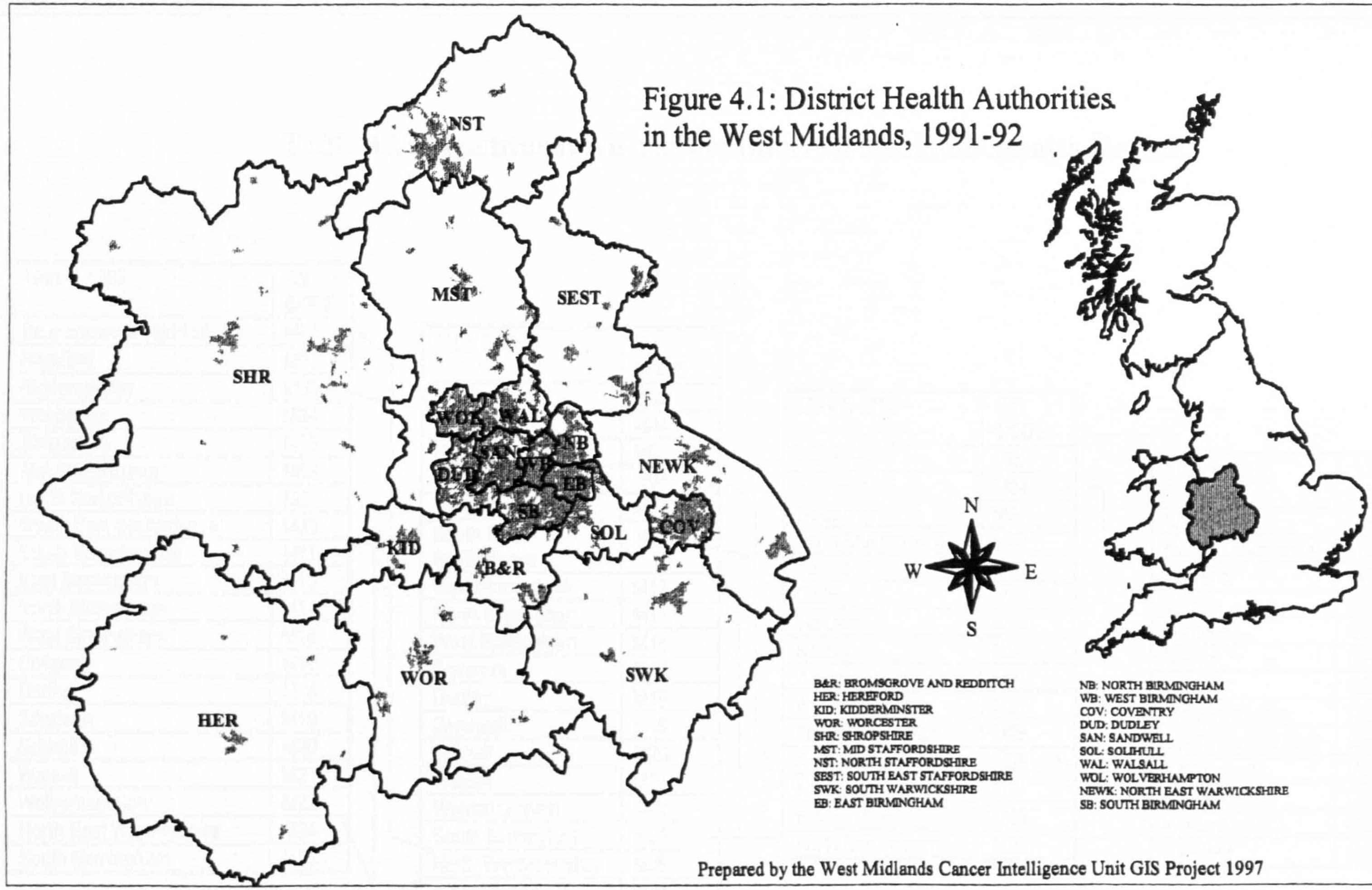
4.4 STUDY AREA

This study was carried out in the WMHR from October 1990 to September 1994. The WMHR comprised 20 health districts in 1991[489] (figure 4.1), and these have been retained for the analysis of data. Table 4.2 illustrates how the present (1997) 13 health authorities arose following changes made to district boundaries over the years.

The WMHR occupies a central geographic location within England, covering an area of 13,004 square kilometres, and has a population density of 406 persons per square kilometre (compared to 240 per square kilometre for the UK).[490] Nearly 9% of households in the West Midlands contain 5 or more people, the largest proportion in any of the English regions.[490]

The region contains England's second largest city, Birmingham, as well as cities and towns such as Coventry, Stoke-on-Trent, Wolverhampton, Stafford and Walsall. Residents of the region live within a wide range of socioeconomic conditions, from densely populated deprived inner-city areas to affluent residential districts and sparsely populated rural areas. A number of regional socioeconomic indicators are shown in table 4.3.

Figure 4.1: District Health Authorities in the West Midlands, 1991-92



Prepared by the West Midlands Cancer Intelligence Unit GIS Project 1997

Table 4.2: Constituent Districts of the West Midlands Health Region

1991 & 1992	'20' CODE
Bromsgrove & Redditch	M01
Hereford	M02
Kidderminster	M03
Worcester	M04
Shropshire	M05
Mid Staffordshire	M06
North Staffordshire	M07
South East Staffordshire	M08
South Warwickshire	M11
East Birmingham	M13
North Birmingham	M14
West Birmingham	M16
Coventry	M17
Dudley	M18
Sandwell	M19
Solihull	M20
Walsall	M21
Wolverhampton	M22
North East Warwickshire	M24
South Birmingham	M25

1993 & 1994	'18' CODE
Hereford	M02
Worcester	M04
Shropshire	M05
Mid Staffordshire	M06
North Staffordshire	M07
South East Staffordshire	M08
East Birmingham	M13
North Birmingham	M14
West Birmingham	M16
Coventry	M17
Dudley	M18
Sandwell	M19
Solihull	M20
Walsall	M21
Wolverhampton	M22
South Birmingham	M25
North Worcestershire	M26
Warwickshire	M28

1994 & 1995	'15' CODE
Hereford	M02
Worcester	M04
Shropshire	M05
North Staffordshire	M07
Coventry	M17
Dudley	M18
Sandwell	M19
Solihull	M20
Walsall	M21
Wolverhampton	M22
South Birmingham	M25
North Worcestershire	M26
South Staffordshire	M27
Warwickshire	M28
North Birmingham	M29

1995 & 1996	'13' CODE
Shropshire	QEF
North Staffordshire	QEH
Coventry	QEA
Dudley	QEC
Sandwell	QEE
Solihull	QEG
Walsall	QEK
Wolverhampton	QEM
South Staffordshire	QEJ
Birmingham	QD9
Warwickshire	QEL
Worcestershire	QEN
Hereford	QED

Prepared by the West Midlands Cancer Intelligence Unit

Table 4.3: Selected socioeconomic variables*: WMHR compared to England and the United Kingdom

		WMHR	England	UK
Proportion of workforce unemployed (spring 1993)		11.7	10.3	10.3
Proportion of claimants unemployed for over 3 and up to 5 years (1994)		8.6	7.4	7.4
Total population change (1981-1992)		1.8%	3.3%	2.9%
Proportion of male employees earning under £200 gross per week (1993)		26.0	22.4	23.4
Redundancy rates per 1,000 employees (1992)		16.1	15.6	15.1†
Day nursery places per 1,000 population aged <5 years (1992)		40.4	35.7	32.8
Household disposable income (£ per head, 1991)		93.5	101.0	100.0
Proportion of population in ethnic minority group (1991)		8.2	6.2	5.5†
Proportion of population aged <5 years (1991)		6.9	6.7	6.7
Proportion of household income from social security benefits (1992)		15.1	12.4	13.1
Average gross weekly income per household (£, 1992)		304.2	350.5	342.9
Lone parent households with dependent children as a proportion of all families (1991-92)		10.1	8.9	9.1†
Household car ownership (1992):	no car	29%	31%	33%†
	one car	47%	45%	44%†
	two or more	24%	24%	23%†
Proportion of dwellings owner-occupied (1991)		68	69	68
Social class of economically active (1993):				
professional (class I)		4.6%	5.4%	5.4%
unskilled (class V)		6.1%	5.6%	5.8%

* Adapted from reference 490

† Data relates to Great Britain and not the United Kingdom

There are 10,903 enumeration districts in the WMHR and they are distributed amongst the Health Authorities as shown in table 4.4. Almost half (47%) of all EDs in the region may be classified as deprived and great variation in the distribution by health authority can be seen. A higher proportion of deprived EDs are seen in urban/inner city areas such as Birmingham, Wolverhampton and Sandwell, whereas mainly rural areas tend to have fewer deprived EDs, for instance, Hereford and South Warwickshire. The WMHR contains some of the most deprived (Sandwell and Birmingham) as well as some of the most affluent districts (Solihull, North Worcestershire, Warwickshire and South Staffordshire) in England.[491]

Table 4.4: Health Authorities in the WMHR ranked by proportion of enumeration districts classified as deprived by the Townsend material deprivation score using 1991 census data

Health Authority*	Number of enumeration districts	Number classified as deprived†	% classified as deprived†
West Birmingham	413	322	78.0
Sandwell	562	433	77.0
East Birmingham	389	282	72.5
Wolverhampton	498	359	72.1
South Birmingham	829	566	68.3
Walsall	472	306	64.8
Coventry	601	337	56.1
North Staffordshire	939	453	48.2
Dudley	601	279	46.4
North Birmingham	318	138	43.4
North East Warwickshire	588	210	35.7
Bromsgrove & Redditch	307	103	33.6
Shropshire	970	298	30.7
South East Staffordshire	542	165	30.4
Solihull	380	115	30.3
Mid Staffordshire	637	188	29.5
Kidderminster	219	61	27.9
Hereford	489	120	24.5
Worcester	602	142	23.6
South Warwickshire	547	123	22.5
Total	10 903	5 000	45.9

* Data refers to Health Authorities and enumeration districts as at October 1992
† This refers to enumeration districts with a Townsend deprivation score of greater than zero

The West Midlands population of approximately 5 million is unevenly distributed, with approximately 50% of the population living in the urban conurbation of the West Midlands Metropolitan County (WMMC).[490] This has 2,927 people per square kilometre and is the second most populous county in England and Wales after Greater London.[490] In contrast, other areas of the WMHR, such as South Shropshire and Leominster (with 38 and 43 people per square kilometre respectively) are amongst the least populated areas in the country.[490]

Data from the 1991 Census shows that although the population of the region is predominantly white, it is ethnically diverse, with one in 12 people belonging to an ethnic minority group (only the South East has a higher proportion).[490] A high proportion of these are from the South Asian (people from India, Pakistan and Bangladesh) ethnic group (table 4.5).

Table 4.5: Population characteristics of the WMHR compared to England and Wales (1991)

	England & Wales[492] (all ages)	WMHR[492] (all ages)	WMHR[493] (0-4 years)
Total persons*	49 860 000	5 150 000	350 000
Ethnic group (%)			
White	94.1	91.8	86.2
South Asian	2.9	5.4	8.6
Black	1.8	2.0	3.2
Others	1.2	0.8	2.0

* to the nearest thousand
Adapted from Owen[492]
Adapted from the West Midlands Regional Information Unit[493]

An estimated 350,000 children aged 0-4 years of age are resident in the region,[493] and in 1992 it was estimated that the West Midlands regional annual live

birth rate of 66 per 1,000 women in all age groups was amongst the highest in the country.[490]

The regional immunisation uptake rates were comparable to those seen nationally. COVER (cover of vaccination evaluated rapidly) surveillance data indicated that in November 1993 uptake of diphtheria and pertussis immunisations in children aged 12 months, was 94% and 92% respectively in the WMHR, while measles coverage was 92% for the same period in children aged 24 months.[340] Hib uptake was reported for the first time in November 1993 by the COVER scheme.[340] The uptake of the newly introduced vaccine was also reported to be high, with overall coverage in the UK regions reaching 90% (range 86% to 95%) for 3 doses in children aged 12 months. In the WMHR the estimated average regional immunisation coverage for this period was 91% (79% to 97%).[340]

Variation in the provision of acute paediatric care exists within the region. When the study commenced there were twenty two hospitals providing acute paediatric care, with the majority having hospital-based laboratories. All districts with the exception of Solihull, had at least one hospital providing acute paediatric care within it's boundaries. Children presenting at Solihull Hospital were usually referred to the nearby Birmingham Heartlands hospital.

Children with uncomplicated meningitis and systemic diseases are usually managed in the hospital of admission. Children with complications, or those requiring diagnostic techniques which are unavailable at the admitting hospital may be referred to one of two centres, either Birmingham Children's Hospital or North Staffordshire Hospital.

4.5 OPERATIONAL DEFINITIONS

Systemic *H influenzae* disease primarily affects young children, with up to 71% of cases seen in children aged 24 months or less in European countries.[139,209,231] Furthermore, the literature indicates that after the age of 5 years, the incidence of *H influenzae* disease decreases dramatically.[142,232,275] The study was therefore restricted to collecting data on children from the age of 0 to 59 months.

Previous research has shown that where serotyping is performed, nearly all cases of invasive *H influenzae* disease in young children are due to organisms of serotype b.[121,126,233,270] Serotyping, however is not routinely performed by many laboratories in the region, nor are all specimens sent to the *Haemophilus* reference laboratory for typing and antibiotic sensitivity testing. The case definition was therefore not restricted to serotype b or those cases where serotyping had been carried out.

4.5.1 CASE DEFINITION

4.5.1.1 Primary invasive *H influenzae* disease

This study will consider primary cases of invasive *H influenzae* disease, and these are defined as an illness in which *H influenzae* was isolated from either CSF or blood culture in children who are not known to have had direct exposure to another person with an invasive *H influenzae* infection.[146,494] If onset of illness occurs in children from the same household or day-care facility within 24 hours of an index case, these will be defined as co-primary cases.[146]

Secondary cases of invasive *H influenzae* disease have been defined as those in which disease occurs 1 to 30 days following exposure to a primary case in the same household or day-care facility.[146] In the UK secondary cases are uncommon,[141,142,197] in North America and Europe they account for less than 2% of invasive *H influenzae* disease.[148] As the number of cases of secondary disease are expected to be small and because of the importance of defining risk factors for primary invasive *H influenzae* disease, children with secondary disease will be excluded from the study.

It was assumed that invasive *H influenzae* infections were serious diseases which would require hospitalisation. Children with *H influenzae* were eligible for inclusion in the study if there was clinical and laboratory evidence of infection, and if they fulfilled all of the following criteria:

- aged less than 5 years at the time of admission
- admitted to a hospital within the West Midlands Health Region
- date of onset between 1 October 1990 and 30 September 1994

The date of hospital admission was used as a proxy for the date of disease onset. Children who died prior to admission were included if a post-mortem examination was conducted in a hospital within the region, and if post-mortem isolates yielded *H influenzae*, and the recorded date of death was within the time-frame of the study. Children discharged and readmitted within a 30 day period were only counted once.

Children initially admitted to a hospital within the region, and then transferred outside the region were included in the study if cultures obtained prior to transfer had subsequently proved to be positive.

Excluded from the study were:

- children from the region admitted to hospitals outside the region
- diagnoses based solely on isolation of *H influenzae* antigen
- patients in whom the organism had been isolated from a non-sterile site
- children whose cultures were taken outside the study period
- secondary cases of invasive *H influenzae* disease
- any medical notes not obtained before June 1st 1995

The database containing all cases of invasive *H influenzae* disease eligible for this study was known as the West Midlands *H influenzae* case register (HICARE).

4.5.2 CLINICAL FEATURES

4.5.2.1 Spectrum of disease

Whenever possible the primary site of infection was identified, but it was recognised that a number of children would not have an identifiable focus, and that others might have more than one possible diagnosis. In addition, it is acknowledged that retrospective ascertainment from medical records makes a definitive diagnosis difficult in some children.

Table 4.6 contains the definitions used for this study of the most commonly encountered disease syndromes. All other diagnoses were based on a positive blood culture together with clinical signs and symptoms compatible with a specific disease syndrome.

Table 4.6: Definition of clinical syndromes used for the identification and hierarchical classification of cases of invasive *Haemophilus influenzae* disease on the HICARE register: WMHR 1990-1994

Clinical syndrome	HICARE definition
Meningitis	Clinical findings compatible with a diagnosis of meningitis together with one or more of the following: *H influenzae* isolated from the CSF, or characteristic cellular and/or biochemical changes in the CSF together with a positive blood culture
Epiglottitis	Diagnosed on the basis of a positive blood culture, with relevant clinical history and clinical features.
Pneumonia	Defined by a positive blood culture together with positive clinical chest findings, radiological signs, or both.
Cellulitis	A positive blood culture together with localised acute inflammation of the skin.
Septic arthritis	Pain and swelling around a joint together with culture of *Haemophilus influenzae* from venous blood.
Osteomyelitis	Localised bone tenderness, together with local inflammation and a blood culture which grows *Haemophilus influenzae*.
Bacteraemia	A positive blood culture without focal signs.

Where more than one invasive *H influenzae* disease entity was present in an individual, a hierarchical order of disease was established following the method of Broadhurst et al.[135] In order for each case to be counted only once, a diagnosis of meningitis took precedence over any other diagnoses, next was epiglottitis and so forth (see table 4.6).

4.5.2.2 Hearing loss and other sequelae

This was assessed from the hospital records and was based on routine paediatric follow-up as indicated in the medical notes. No attempt was made to contact community paediatricians to determine the results of developmental or hearing tests.

A diagnosis of SNHL was accepted only if the results of a hearing test, or a letter from an audiologist, Senior Clinical Medical Officer (SCMO) or other person responsible for carrying out hearing tests were present in the medical notes.

Other neurological sequelae were defined as neurological dysfunction secondary to invasive *H influenzae* disease if they were recorded in the medical notes and present at discharge, or identified during follow-up.

It is acknowledged that sequelae, especially long-term sequelae such as behavioural problems and intellectual disorders, cannot be accurately determined from a retrospective perusal of medical notes.

4.5.2.3 Clinical and laboratory definitions

The various definitions used are shown below in table 4.7.

Table 4.7: Definitions used for abstracting data from case notes of invasive *Haemophilus influenzae* disease: HICARE, WMHR 1990-1994

	HICARE definition
Antibiotic resistance	As documented in the medical notes or laboratory records.
Antibiotic therapy	The initial parenteral antibiotic(s) received by the child on admission to hospital were recorded.
Chemoprophylaxis	Documented evidence that the case child, or any contacts, had been prescribed chemoprophylaxis was sought from the medical notes.
Chloramphenicol monitoring	Children with *Haemophilus influenzae* meningitis in whom at least two recorded plasma chloramphenicol measurement were found in their medical notes.
Dexamethasone	Medical notes were examined to determine whether parenteral dexamethasone had been given following admission for *Haemophilus influenzae* meningitis. Children were divided into two groups, those who received dexamethasone and those who did not receive dexamethasone.
Duration of illness	Children were divided into three groups according to length of duration of illness before admission to hospital as ascertained from the case notes. These were short duration (≤ 24 hours), intermediate (>24 hours but <48 hours), and long (>48 hours). Where the sample size was small, these were collapsed into two groups.
Pre-admission antibiotics	This was defined as documented evidence that the child had received oral or parenteral antibiotics within one week of admission to hospital for *Haemophilus influenzae* meningitis.
Serotype	As documented in the notes or laboratory records.

4.5.3 INDIVIDUAL RISK FACTORS

4.5.3.1 Age

Age on admission was defined as the number of completed months at which the child was admitted to hospital for an episode of invasive *H influenzae* disease. This was obtained by subtracting the date of birth from the date of admission. For many analyses the ages were classified into 5 groups, namely 0-11 months; 12-23 months; 24-35 months; 36-47 months and 48-59 months. Other groups were used where appropriate to provide comparisons with other studies.

4.5.3.2 Gender

This was specified as male or female.

4.5.3.3 Ethnic group

As this study is retrospective, it is difficult to determine the ethnicity of cases. The children were therefore placed into one of two groups using their surname and forenames. One group was defined as South Asian (that is, children deemed to originate from the Indian sub-continent countries of India, Bangladesh and Pakistan) and the other as non-South Asian. This method of defining ethnicity retrospectively has been used previously by several researchers,[354,356,495] and the categories used in this study are compatible with 1991 census data.[496]

4.5.3.4 Low birthweight

This was defined as a birthweight of less than 2500 grams.[300] Where birthweight had been recorded in pounds and ounces it was converted to grams using the formula 2.2 pounds = 1,000 grams.

4.5.3.5 Nutritional status

Weight on admission for each child was evaluated using Child Growth Foundation weight charts appropriate for the gender of the child.[497,498] Children found to be below the 3rd centile for age were classified as being underweight for age.[499]

4.5.3.6 Anaemia

The WHO has recommended that a haemoglobin (Hb) concentration of less than 11 g/dl be used to identify anaemia in children aged between 6 months to 6 years.[500] This was the definition used in this study.

4.5.3.7 Chronic illness

Following the method of Fogarty et al, children with illnesses which had an allergic component (e.g. asthma and eczema), and those with illnesses associated with reduced immunity (e.g. leukaemia and Downs syndrome) were considered to have a chronic illness.[230]

4.5.4 FAMILY AND COMMUNITY RISK FACTORS

4.5.4.1 Day-care attendance

This was defined as any child care arrangement documented in the medical notes which indicated that the child was cared for inside or outside the home by a non-parent. The retrospective nature of the study precluded any consideration of the number of children cared for or the number of hours the child attended.

4.5.5 ENVIRONMENTAL RISK FACTORS

4.5.5.1 Immunisation status

Medical records were examined to determine the immunisation status of all the cases. Age-appropriate uptake was calculated according to the expected completion of the immunisation schedule (table 4.8).

Table 4.8: Recommended UK primary immunisation schedule for infants and children

Age		Vaccine
2 months	1st dose	Diphtheria, Tetanus, Pertussis (DTP) vaccine
	1st dose	*H influenzae* type b conjugate (Hib) vaccine
	1st dose	Oral Polio Vaccine (OPV)
3 months	2nd dose	DTP/Hib/OPV
4 months	3rd dose	DTP/Hib/OPV
12-15 months	1st dose	Measles, Mumps, Rubella (MMR) vaccine

A child was considered to have been completely immunised if they had received their three scheduled primary doses by the age of six months, and MMR/measles by 15 months of age. If at the time of hospital admission the child had not received the appropriate number of immunisations more than one month after the due date, the child was considered to be incompletely immunised for age.

A child was considered to have received a vaccine if specific immunisations had been noted in their records, or if their immunisation status had been documented as "up-to-date". Where immunisation status was not documented in the notes the child was excluded from this part of the data analysis.

Only children identified in the post-Hib conjugate vaccine era had their immunisation status verified in order to determine primary immunisation status, as well as, Hib immunisation status. This was achieved by contacting the appropriate district immunisation co-ordinator or public health physician. The information obtained was then utilised to determine which children could be regarded as 'vaccine failures' following the British Paediatric Surveillance Unit (BPSU) definition, and the accuracy of hospital recorded primary immunisation histories compared to that found on the child health computers.

Vaccine failures

The BPSU have classified vaccine failures into two groups, true vaccine failures and apparent vaccine failures. Invasive Hib disease occurring in a child following three doses of vaccine is defined as a true vaccine failure.[476] True vaccine failures are also said to occur if invasive Hib disease is seen more than one week after two doses of vaccine are given to a child aged up to 12 months; or if Hib disease occurs in a child aged more than 12 months two weeks or more after receiving a single dose of vaccine. Apparent vaccine failures also occur following vaccination but present before protection can be expected to develop. Therefore, children aged less than 12 months who develop invasive disease after a single vaccination, or within a week of receiving a second vaccination, are termed

apparent vaccine failures.[476] Children aged over 12 months of age who present with invasive disease within two weeks of a single dose of vaccine, are also termed apparent vaccine failures.

4.5.5.2 Urban/rural areas

In order to determine the 'urbanity' or 'rurality' of areas, the districts comprising the WMHR were divided into two groups. Those which make up the WMMC were considered to be 'mainly urban' areas, while all other districts were classified as 'mainly rural' areas. The districts comprising the WMMC are Coventry, Dudley, Solihull, Sandwell, Walsall, Wolverhampton and the Birmingham districts (see figure 4.1). It is recognised that this represents a crude classification and that within a district classified as 'mainly rural' a substantial percentage of the population may live in areas which could be classified as urban, and vice versa. For instance, North Staffordshire is one of the districts which has been placed in the 'mainly rural' category yet contains Stoke-on-Trent, a conurbation with a population of more than 250,000.

4.5.5.3 Socioeconomic census variables

The relationship between invasive *H influenzae* disease and a number of census variables was explored using univariate analysis to identify possible associations between incidence rates for invasive *H influenzae* disease and different levels of deprivation and social and economic disadvantage. The census variables selected for analysis are listed and defined in table 4.9.

Table 4.9: Sociodemographic 1991 census variables selected for the analysis of invasive *H influenzae* disease, WMHR 1990-1994

Socioeconomic variable	Definition
All movers	Proportion of residents with a different address one year before the census
Child density	Density of children aged <5 years per km^2
Children <5 years	Proportion of the total population less than 5 years of age
Deprivation	Townsend material deprivation score
Local movers	Proportion of residents with a different address one year before the census who moved between districts but within counties
Lone parent	Proportion of lone parent households
No car*	Proportion of households without a car
Not owner-occupied*	Proportion of households not owner-occupied
Overcrowded households*	Proportion of all households with more than one person per room
Unemployed*	Proportion of economically active people who are unemployed

* Components of Townsend material deprivation score

They were selected as independent variables as a number of them are recognised markers of socioeconomic disadvantage or deprivation.[23,74] Previous epidemiologic studies have also shown the majority to be either risk factors for invasive *H influenzae* disease or to be associated with poor immunisation uptake.[106,111,148,151,256,350,357]

4.6 CASE ASCERTAINMENT

Surveillance has been defined as the systematic collection, collation, and analysis of data and dissemination of the results so that appropriate control measures can be taken.[501] In communicable diseases this information is used to monitor disease trends, identify outbreaks or epidemics and evaluate control and prevention programmes.[501]

In the UK there are three main sources of surveillance data on communicable diseases,[169,501] including invasive *H influenzae* disease. Firstly there is the statutory notification system. In this system the attending clinician has a statutory duty to notify the 'proper officer' of the local authority (usually a consultant in communicable disease control) of suspected or confirmed cases of certain infectious diseases, including *H influenzae* meningitis.[169] These notifications are then collated at the regional and national level by the Office of National Statistics ([ONS] formerly Office of Populations Census and Surveys [OPCS]).[169] This source of data is however known to suffer from underreporting and a number of other drawbacks.[144,170-172]

Initially, notifications for *H influenzae* meningitis and other causes of bacterial meningitis (apart from meningococcal meningitis) were concealed within the category of 'other bacterial causes of meningitis'. Since 1982 however *H influenzae* meningitis and other forms of bacterial meningitis, have been identified separately.[502] Other manifestations of invasive *H influenzae* are however not notifiable diseases.

A second source of data is the PHLS, CDSC laboratory reporting system for microbiologically confirmed infections.[169] This system, which will include reports on both meningitic, as well as non-meningitic forms of invasive *H influenzae* disease is however subject to selection bias with regard to the taking of samples, variability in reporting by laboratories and limited demographic data on cases.[503,504]

The third system is the Royal College of General Practitioners (RCGP) 'spotter practice' scheme.[169,501] The main limitations of this system are that coverage is 'patchy' and the system is mainly targeted at diseases, such as chickenpox, scabies and influenza, which are not notifiable.[504]

In addition, these routine sources of communicable disease surveillance may be supplemented by hospital discharges and death notifications. Hospital discharge diagnoses are however subject to coding errors, and in one published audit 20% of case notes retrieved were inappropriate for the study.[505] With regard to death certificates, there is wide variation in the accuracy with which they are filled out.[503] Furthermore, it has been reported that the case notes of patients who have died in hospital are more likely to be missing than those of other patients.[506] Taking these into consideration it was decided not to employ either of these sources of information for the study.

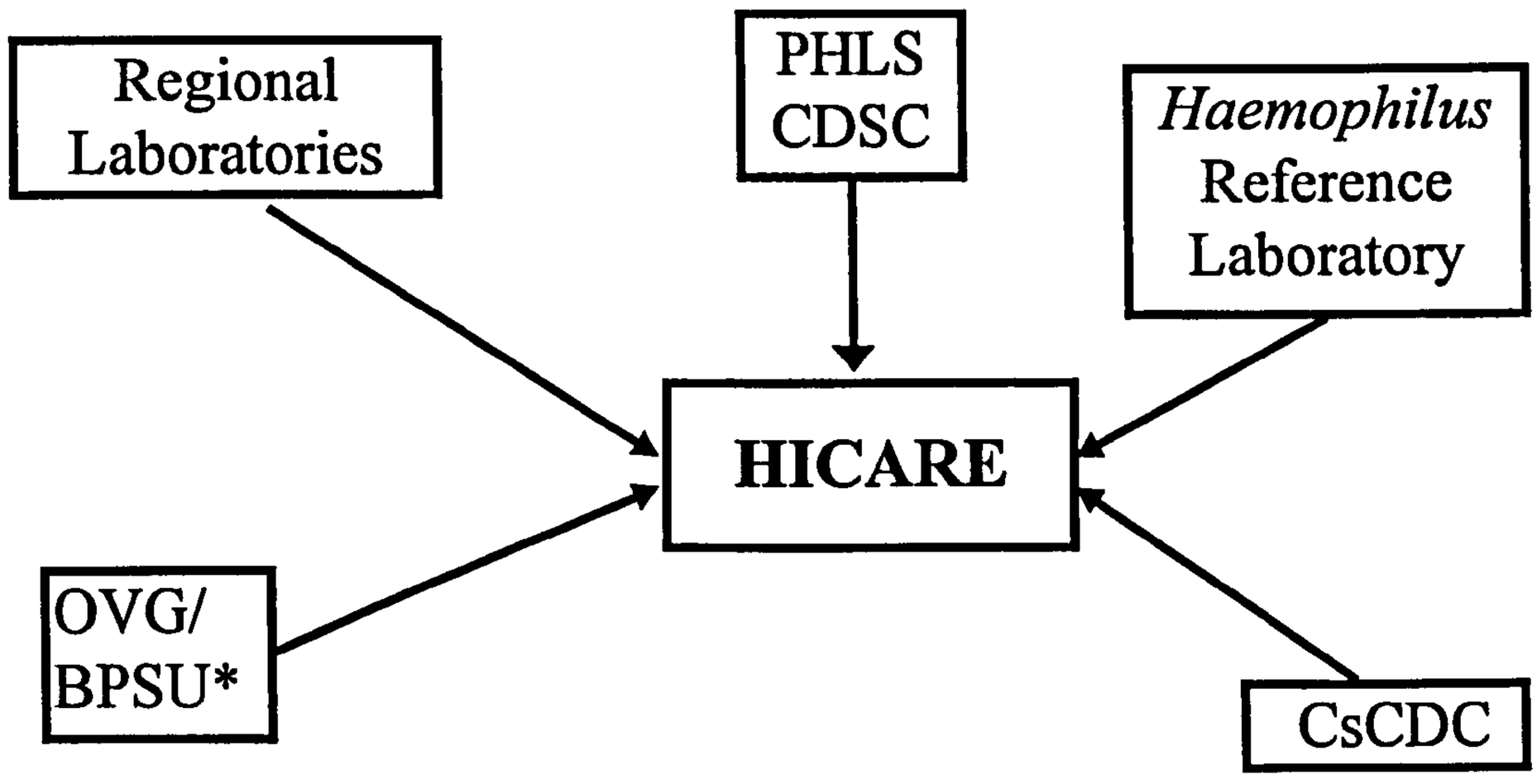
For the purposes of this study statutory notifications and laboratory reports will be used as the foundation for the construction of a register of invasive *H influenzae* cases in children aged less than 5 years who meet the case definition for inclusion in the study. Cases will also be identified from a number of other sources (see section 4.6.1).

4.6.1 Compilation of disease register

Invasive *H influenzae* meningitis produces a potentially life-threatening disease in children and is a statutorily notifiable disease, yet a number of UK studies have demonstrated that notification and reporting of this form of meningitis is more incomplete than notification for meningococcal meningitis.[144,145,173]

In order to ensure that case identification for meningitic and non-meningitic disease was as comprehensive and complete as possible, several overlapping surveillance systems were used (figure 4.2) to assemble a disease register.

Figure 4.2: Sources of case identification for invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994



*OVG/BPSU (Oxford Vaccine Group/British Paediatric Surveillance Unit)

The co-operation of the PHLS, CDSC, regional laboratories, consultants in communicable disease control and immunisation co-ordinators within the WMHR, the OVG/BPSU and *Haemophilus* reference laboratory in identifying cases and providing data was sought. For the purposes of this study, a laboratory or an

individual was considered to have participated in the study if they provided one or more of the following pieces of information:

- the name, date of birth or other demographic information related to cases
- indicated that no cases had been identified during the study period
- allowed examination of laboratory records
- provided access to medical records

4.6.1.1 PHLS, CDSC

As part of the national surveillance of communicable diseases, laboratories in the West Midlands region voluntarily report isolates of *H influenzae*, and other infectious diseases, to the PHLS, CDSC London. Computerised line listings from the PHLS, obtained with the co-operation of the regional epidemiologist, provided the primary source of retrospective data for this research. Late reporting of cases by laboratories is known to occur, and to account for this data was requested for laboratory reports from October 1990 to December 1994.

4.6.1.2 Regional PHL and NHS laboratories

The major local source of cases were the records of all hospital microbiology or pathology laboratories in the region. Laboratory directors were asked to provide information on all children aged under 5 years with positive cultures of *H influenzae* who had specimens sent to their laboratory. At the time the study was conducted, several laboratories lacked computer resources and, either provided manual reports or, were visited by the researcher who reviewed the laboratory records in order to identify cases. Thirteen (62%) of the twenty one

laboratories in the region provided data which was either retrospective and/or prospective in nature.

4.6.1.3 Consultants in communicable disease control

The third major source of cases were CsCDC. There were eighteen CsCDC in the region when the study commenced, eleven (61%) supplied information regarding cases notified to them during the study period.

4.6.1.4 BPSU/OVG

The Oxford Vaccine Group have been conducting a study on Hib conjugate vaccine failures in the Hib vaccine era on behalf of the BPSU. Sources of data for the BPSU study include over 90% of paediatricians, as well as microbiologists and public health physicians. The OVG provided the researcher with a listing of cases reported to them who were eligible for inclusion in this study.

4.6.1.5 Haemophilus reference laboratory

The *Haemophilus* reference laboratory at Oxford, which provides identification, serotyping and sensitivity testing for *H influenzae*, was also contacted via the OVG. They were asked to provide a listing of isolates sent to them from the region during the study period. This was used to ascertain specimen dates, serotypes and antibiotic sensitivities.

4.6.1.6 Consultant paediatricians

All consultant paediatricians working in hospitals in the West Midlands and listed in the British Paediatric Association (BPA) yearbook for 1992-93 were also contacted.[507] They were informed of the study and asked for permission to examine the medical notes of children who had been under their care during the study period. In cases where laboratory directors had not provided access to their laboratory records to confirm laboratory diagnosis and provide further information where required, consultant paediatricians were contacted and provided with all available information in order to obtain the child's case notes.

4.6.1.7 Immunisation co-ordinators

All the district immunisation co-ordinators within the region co-operated in providing information on children in their district. Each immunisation co-ordinator was sent a list of the cases believed to be from their district, and asked to provide the researcher with their immunisation histories.

Using the information obtained from all these sources, the West Midlands HICARE database was constructed. All sources were cross-referenced using first and second names, together with date of birth and postcode of home address to ensure maximum case ascertainment without duplication. When case identification was complete the total number of case children identified by each system was known,

Since this study does not involve sampling, the usual consideration of sample size determination does not apply. It is however expected that the study

will provide one of the largest and most comprehensive case series of invasive *Haemophilus* disease in Britain.

4.7 DATA COLLECTION

4.7.1 Access to hospital notes

Once cases were identified, letters containing a brief description of the study were sent to the consultant paediatrician responsible for the care of the child asking them for permission to look at the child's medical notes. When this was obtained, letters were then sent to managers of medical records libraries in all the hospitals informing them of the study, providing them with all the available details for each child, and asking them to locate the medical notes of children identified as cases. Ideally this information would include all or some of the following: the child's full name; gender; address at the time of admission, or last known address; date of birth, or age; date of admission, or date of specimen; and hospital number. In several instances, especially where information was obtained from the PHLS, CDSC listing, much of this information was missing. Where the identifying information was deemed insufficient by the medical records librarian, consultant paediatricians were asked to supplement the available information by searching their admission records.

Once the consultant paediatricians had given their consent for the researcher to look at the case notes, either by directly informing the researcher or through the medical records librarian, a suitable date was arranged with the librarian for the researcher to visit the hospital to look at the case notes. Many of

the hospitals collated the records, and invited the researcher to extract the required data on the hospital premises. In cases where only one or two case notes had been identified, some hospitals posted the medical notes to the researcher, and these were reviewed and returned as quickly as possible by registered post.

Any child who was eligible for the study but whose notes could not be located by the 1st June 1995 was excluded from the study.

4.7.2 Research instrument

A data collection form or proforma (appendix 1) was constructed by the researcher following the initial proposal and review of the literature. The information to be obtained using this instrument was discussed with the researcher's supervisor, chair of the advisory committee and the regional epidemiologist. Agreement was reached as to which factors should be looked at.

The form was piloted using the medical notes of twelve children who had been admitted to one of the hospitals in the region with invasive *Haemophilus influenzae* disease prior to 1 October 1990. This resulted in minor changes to the form.

The information collected for each case included the identifying hospital laboratory, confirmation of the diagnosis, date of birth, gender, name, postcode, clinical presentation, management, antibiotic therapy, laboratory results, outcome and immunisation status. After completing the proforma it was checked for errors and omissions, and when deemed complete, dated and given a serial number.

The serial number was obtained by coding the child's name using a modification of the Soundex code.[488] The Soundex code is a simple system

developed for the confidential reporting of AIDS/HIV cases which produces a non-unique three digit numeric code from a surname. In this study it was used in combination with the last two digits of the child's year of birth and forename and family name initials. These preceded the three digit code derived from the surname.

Any events or data required for this study which were not present in the notes were treated as missing data.

4.8 DATA ENTRY

Epi Info[508] was used to create a computerised version of the form. The researcher entered data directly onto the computer from the proforma, and apart from the child's identification number, most entries were pre-coded and numeric. All data was maintained on computer, and Microsoft Access for windows, Microsoft Excel for windows and SPSS[509] were used for database maintenance and manipulation.

Systematic errors were periodically checked for by printing frequency tables for each variable, and going back to the proforma where necessary to corroborate data. When data entry for all forms was complete, a sample of 20% of proformas were checked in order to minimise errors. Serial numbers of fifty two cases were selected randomly using numbers generated by Epi Info version 6. The computer-held data on each of these cases was then compared with that on the original proforma. Thirty three errors were identified and corrected.

4.9 DATA ANALYSIS

4.9.1 Sources of denominator data

The period of study (1990-94) spanned the 1991 census, therefore the 1991 population distributions and census data were thought to be appropriate for the calculation of rates and other demographic data. The population of 0-4 year olds was available at the ED level, and these were aggregated and used as denominator data for the calculation of disease rates for districts, deprivation and other socioeconomic variables derived from the census. The population counts for EDs from the 1991 Census were downloaded from the computerised Small Areas Statistics package (SAS) database held by MIDAS (Manchester Information Databases and Associated Services, University of Manchester). Aggregating the EDs revealed that there were 351,037 children aged 0-4 years in the WMHR.

Census variables, and therefore Townsend scores, were available for 10,774 of 10,903 (99%) EDs in the WMHR which contained 350,999 children aged 0-4 years. Data were therefore unavailable for 129 EDs which contained 38 children aged 0-4 years. These children were excluded from the denominator in all analyses involving census variables, but included in any other analyses. This difference may be attributed to measures to protect confidentiality especially in the case of small populations.[510] The variations identified in the denominator data were deemed too small to affect the overall results obtained.

District, age, gender and ethnic-specific incidence rates were among those calculated, and reported as cases per 100 000 children under 5 years of age.

Children from outside the region (identifiable by postcode and district of residence) were excluded from certain geographic and socioeconomic analyses.

4.9.2 Statistical analyses

Cases with data missing for a particular variable were excluded from the analysis for that variable. As a consequence, missing data for certain variables occurred and numbers therefore varied slightly.

All percentages were rounded to the nearest whole number, while all probability values were expressed to two significant figures. All statistical tests were carried out using Epi-Info version 6.

The χ^2 test with Yates' continuity correction, or Fisher's (two-tailed) exact test (where sample sizes were less than 5) were used to test for differences between categories using 2x2 tables.[511] Statistical significance was determined using probability (p) values, and odds ratios with Cornfield 95% confidence intervals. Where Cornfield estimates were deemed to be inaccurate using Epi Info version 6 'statcalc' software, Epi Info version 6 'epitable' was used. Student's *t* test for independent samples was used to compare two means, while one-way analysis of variance was used to test the equality of several means.[511]

The χ^2 test for trend was used to test for significant increase or decrease in trend across categories of deprivation or other socioeconomic variable.[511] Differences of <0.05 were considered to be significant, and <0.01 highly significant.[511] Odds ratios greater than 1 were indicative of a positive association.[511]

Confidence intervals for rates were derived from published tables of confidence intervals for Poisson counts at the 95% level.[512]

Evaluation of the strength of agreement between different sources of immunisation history in the post-Hib conjugate vaccine era was reported using the overall proportion of agreement and the kappa (κ) statistic. For the latter, the strength of agreement was determined using an adaptation of the categories suggested by Landis and Koch (table 4.10).[511]

Table 4.10: Interpreting strength of agreement of kappa statistic

κ value	Strength of agreement
<0.40	poor to fair agreement
0.40 to 0.60	moderate agreement
0.60 to 0.80	substantial agreement
0.80 to 1.00	almost perfect agreement

4.9.3 Socioeconomic analyses

Geographic Information Systems (GIS) are computerised systems for automating, storing, retrieving, manipulating, displaying and analysing mapped information.[69,72] A GIS includes spatial data in the form of maps and descriptive information in the form of relational databases associated with the mapped features.[69,72] The GIS technique can be used to associate spatial distributions of epidemiologic and environmental variables.[72,513-515]

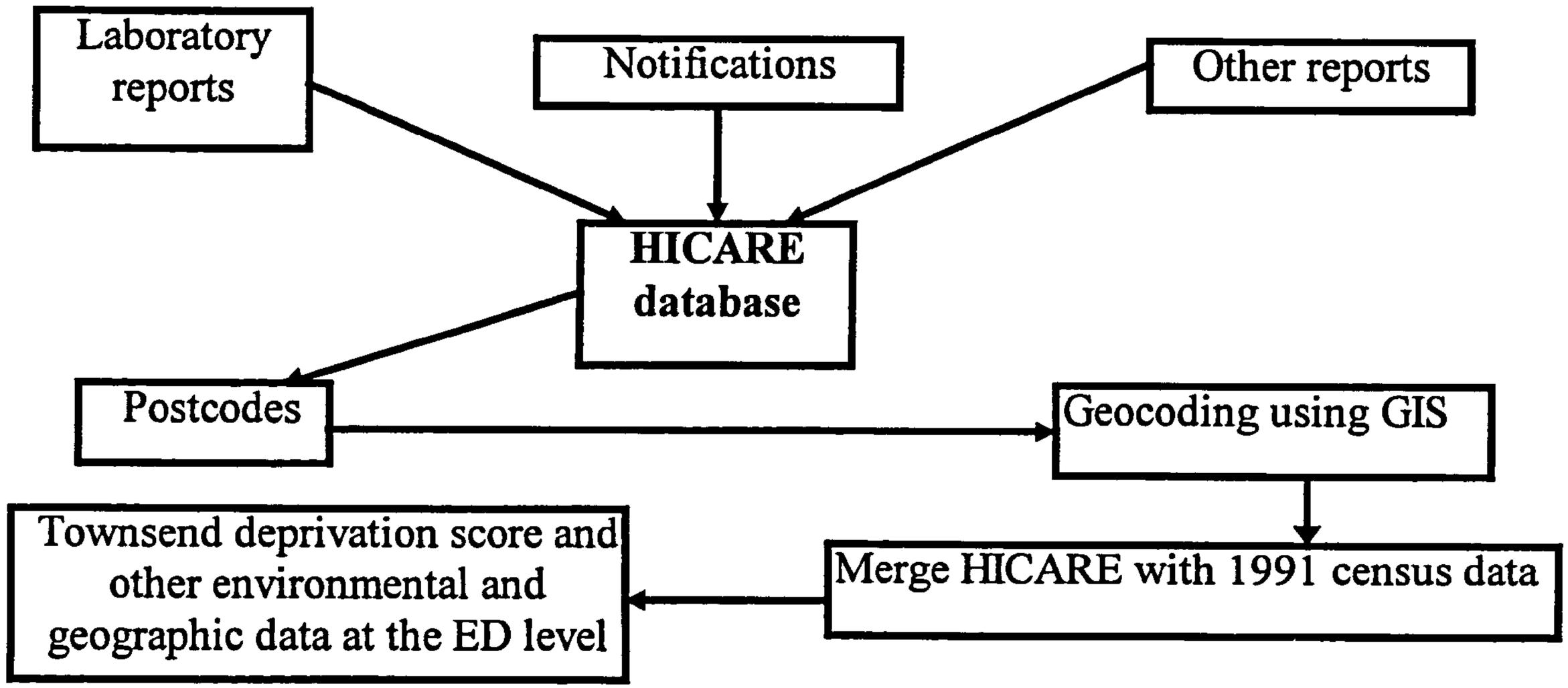
In this study the GIS used was ArcView (Environmental Systems Research Institute (ESRI), Redlands, California), this was based at the Cancer Intelligence Unit (CIU), University of Birmingham and was used to match the postcode at the time of admission to an ED for each case by computerised cross-referencing.

Computerised data on the socioeconomic characteristics of each ED were obtained from the 1991 census SAS database, held by the CIU, University of Birmingham. These were then collated and linked to data on cases from the HICARE register. Figure 4.3 illustrates how the different databases were linked via postcodes to obtain the district of residence as well as the Townsend material deprivation score and other socioeconomic data applicable to the corresponding ED.

The enumeration district is the smallest geographical unit for which census information is available (containing between 150-250 households), and is the geographic unit of analysis for this study. Justification for using EDs were concerns that the use of aggregated data from larger area units such as wards and postcode sectors would lead to aggregation bias and provide less socially homogenous populations than those found in EDs.[319]

Once the EDs were obtained they were allocated a score on the Townsend material deprivation index. The Townsend deprivation score is generated by carrying out mathematical transformations on four census variables, these are the proportions of the total resident population of each ED who are, unemployed adults, live in households with more than one person per room, do not have access to a car and are not owner-occupiers. Townsend used these as markers for lack of material resources (unemployment), wealth (owner-occupancy), income (car ownership) and living conditions (overcrowding).[23]

Figure 4.3: HICARE register: database linkage using GIS: WMHR, 1990-1994



Log transformation is carried out on the unemployment and overcrowding variables to reduce their skew. Each variable is then standardised by converting it to a Z-score and it is the sum of these standardised scores which provides the Townsend deprivation score.[23] Increasingly positive scores indicate greater deprivation.

Apart from the Townsend score the medical literature contains a number of other indices which aim to measure deprivation and there is debate about which is the most appropriate to use in analysing the relationship between health and deprivation. The most prominent of these indices are those developed by Jarman[516] and Carstairs and Morris.[327]

The Jarman index was initially designed to measure the workload of general practitioners. The scoring system used to identify underprivileged areas was generated from the subjective views of general practitioners of their patients social characteristics which they believed increased their workload.[74,516] In practice, however it rapidly gained currency as an indicator of deprivation,[517] and has also been used to identify areas for the allocation of deprivation payments to general practitioners.[326,517] This index has been criticised for its selection of variables, lack of validation and inappropriate usage.[326,328,329,517]

Amongst its 8 variables the Jarman score includes children under 5 years of age, ethnicity and single parenthood. These demographic factors make it less effective as a measure of material deprivation because they are not indicators of material deprivation *per se* and people or families in these categories are not equally deprived.[23]

Similarly, the use of social or occupational class in the construction of the Carstairs and Morris score is also thought to have disadvantages. Social classes contain groups of occupations with appreciable economic heterogeneity, and research has shown that there is greater intra-class variation than inter-class variation in income.[318] Although poor access to material resources may be related to membership of low social class, Townsend has stated that inclusion of this factor as a variable in an index of deprivation would not permit analysis of the relationship between deprivation, health and social class.[23]

The inclusion of social class in the Carstairs and Morris index and certain demographic factors in the Jarman index impair the ability of these indices to assess all aspects of material deprivation. Taking the above into consideration, it was believed that the Townsend material deprivation score would provide the best means of exploring the relationship between health and material deprivation.

The Townsend deprivation scores for EDs used in this study were provided by the Cancer Intelligence Unit (CIU). The EDs were ranked in ascending order, according to these scores, and divided into three groups (tertiles) containing approximately equal numbers of EDs, thereby grouping together areas of similar socioeconomic status (table 4.11).

Table 4.11: Townsend deprivation tertiles for the WMHR

Deprivation category	Population	Townsend deprivation score
1 (low deprivation)	98, 825	-8.50 to -2.10
2 (medium deprivation)	101,012	-2.00 to +1.70
3 (high deprivation))	151,162	+1.80 to +8.80

The deprivation map (figure 4.4) of the WMHR indicates where the three different categories of material deprivation may be found in the region. Incidence rates were calculated for each of these different levels of deprivation and differences in observed rates compared using χ^2 for trend.

The four variables used to construct the Townsend deprivation score, along with other selected census indicators of deprivation (see section 4.5.5.3), were analysed in a similar manner.

A scatter diagram was used to determine the closeness of the association between district immunisation uptake rates for Hib conjugate vaccine and the district Townsend deprivation score.

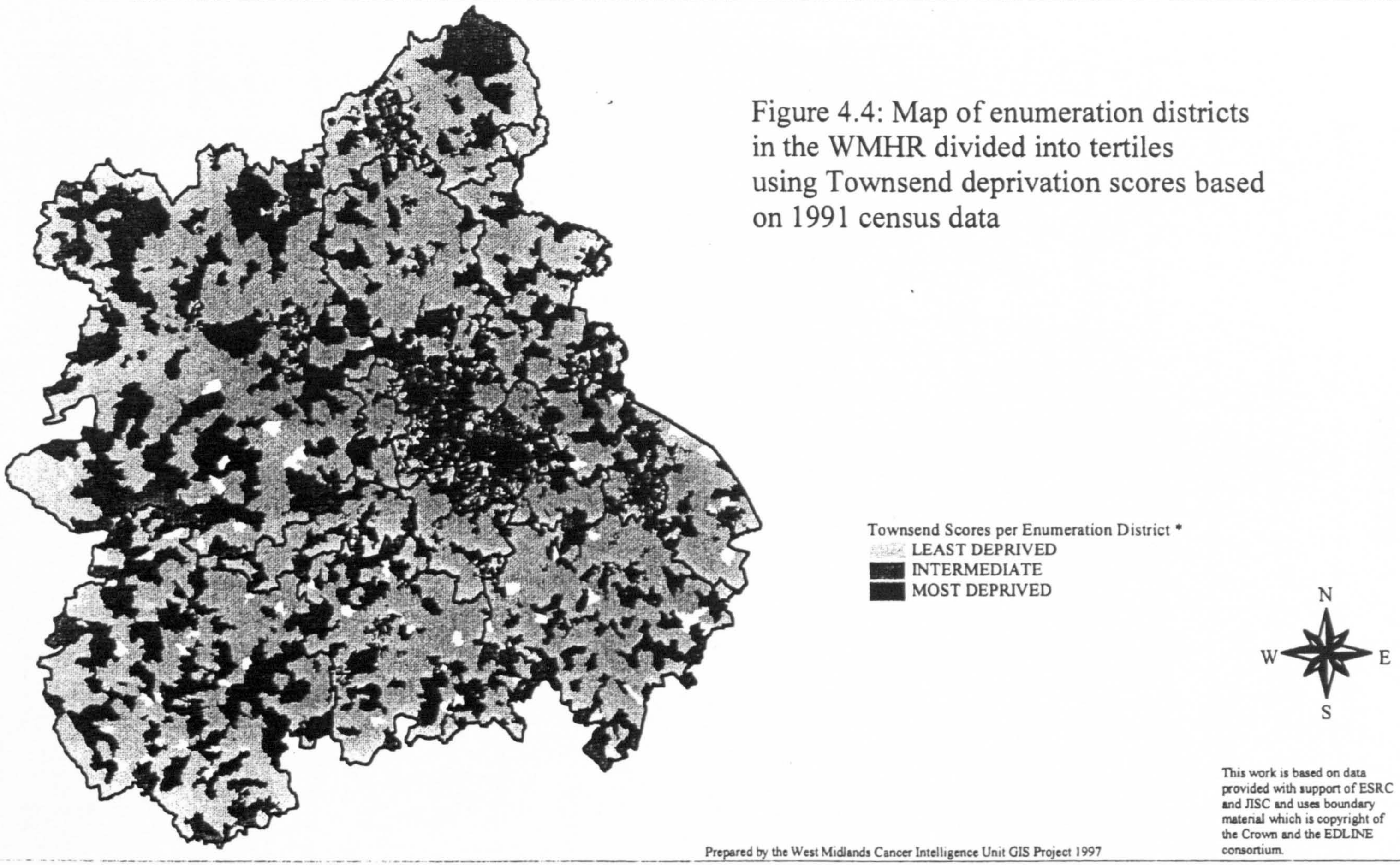


Figure 4.4: Map of enumeration districts in the WMHR divided into tertiles using Townsend deprivation scores based on 1991 census data

CHAPTER 5

RESULTS

RESULTS

Despite rigorous attempts to do so, it was not possible to collect data on all variables for all children. It is therefore inevitable that sample sizes for certain sub-analyses will vary. Because of the small number of cases identified in the non-meningitic group, especially in the second period of the study, only a limited analysis has been carried out using this sub-group. Nevertheless, this chapter presents a series of analyses which examines variations in the incidence of disease for the risk factors specified in chapter 4. Details of diagnostic categories, and selected clinical and laboratory aspects are also presented. Each section of the chapter ends with a summary of the key results obtained.

5.1 INCIDENCE OF INVASIVE *H INFLUENZAE* DISEASE

5.1.1 Case identification and comparison of surveillance systems

Using multiple sources of case ascertainment over a four year period from October 1990 to September 1994, 258 cases of invasive *H influenzae* disease were identified who fulfilled the case definition and were included on the HICARE disease register. Of these, 199 were identified in the pre-Hib conjugate vaccine era (October 1990-September 1992), and 59 in the post- Hib conjugate vaccine era (October 1992-September 1994). *H influenzae* meningitis was the most common disease entity each year, and accounted for 172 of 258 (67%) cases. Epiglottitis (32 of 258, 12%) was the second most common disease identified during the study

period. Pneumonia, septicaemia and cellulitis were the other major syndromes seen. The clinical spectrum of disease observed in the WMHR is dealt with in more detail in section 5.5.1.

Table 5.1 shows the estimated incidence rates for all cases of invasive *H influenzae* disease and *H influenzae* meningitis during each year of the study. The incidence of all invasive *H influenzae* disease and *H influenzae* meningitis showed a statistically significant decrease in both of the post-conjugate vaccine years from the pre-conjugate vaccine years. In addition, the incidence of disease seen in the second post-conjugate vaccine year of the study was statistically significantly lower than that of the first (confidence intervals did not cross).

Table 5.1: Incidence* of invasive *Haemophilus influenzae* disease and *Haemophilus influenzae* meningitis by study year, WMHR 1990-1994

Study year	Invasive HI† disease Cases	Invasive HI† disease Incidence rate (95% CI)	HI† meningitis Cases	HI† meningitis Incidence rate (95% CI)
October 1990-September 1991	97	27.6 (22.4-33.7)	64	18.2 (14.0-23.3)
October 1991-September 1992	102	29.1 (23.7-35.3)	72	20.5 (16.0-25.8)
October 1992-September 1993	53	**15.1 (11.3-19.7)**	31	**8.8 (6.0-12.5)**
October 1993-September 1994	6	**1.7 (0.6-3.7)**	5	**1.4 (0.5-3.3)**
Four yearly incidence rate	258	18.4 (15.7-20.2)	172	12.3 (10.5-14.2)

* Incidence per 100 000 children <5 years of age

† *Haemophilus influenzae*

Figures in bold indicate incidence rates significantly different from that of the previous year

A comparison of all cases identified by the case register with those reported to the CDSC and other surveillance systems is summarised in table 5.2. The table shows that 19% of cases on the register were not reported to the CDSC.

Table 5.2: Comparison of cases of invasive *Haemophilus influenzae* disease identified by multiple overlapping surveillance systems, WMHR 1990-1994

		HICARE	CDSC	Regional laboratories	CsCDC	*Haemophilus* Reference Laboratory	OVG/BPSU
Total number of cases:		258	208	176	95	46	7
October 1990-September 1992		199	170	132	73	23	-
October 1992-September 1994		59	38	44	22	23	7
Meningitis:		172	141	116	90	36	7
October 1990-September 1992		136	117	87	71	17	-
October 1992-September 1994		36	24	29	19	19	7
Other invasive disease:		86	67	60	5	10	-
October 1990-September 1992		63	53	45	2	6	-
October 1992-September 1994		23	14	15	3	4	-
Mortality:		8	6	6	5	1	-
October 1990-September 1992		4	3	3	2	-	-
October 1992-September 1994		4	3	3	3	1	-
Age group (months):							
	0-11	101	78	74	44	18	3
	12-23	87	65	55	31	15	3
	24-35	35	31	25	12	8	1
	36-47	19	18	12	4	4	-
	48-59	16	16	10	4	1	-
Gender:							
	boys	133	108	91	50	24	4
	girls	125	100	85	45	22	3
Ethnic group:							
	NSA	236	190	157	81	39	6
	SA	22	18	19	14	7	1

Underreporting to the CDSC varied with time and other parameters. Fifteen per cent of cases identified by HICARE were not reported to the CDSC in the period prior to the introduction of the vaccine. This proportion more than doubled in the period following introduction of the vaccine to 36%.

When comparing reports of meningitis and non-meningitic disease during the two study periods, a similar picture is seen. In the pre-vaccine era underreporting of 14% and 16% occurred for meningitis and non-meningitic diseases respectively, while in the post-vaccine period 31% of meningitis cases and 42% of non-meningitic HICARE cases were not reported to the CDSC. There was also apparent variation in the reporting of cases according to age. It was found that in children aged less than 2 years, approximately 24% of cases were not reported to the CDSC. This was almost four times more than the estimated 7% underreporting in children 2 years of age or older. There were no differences in reporting by gender or ethnic group.

Incidence rates based on reports to CDSC for the pre- and post-vaccine periods were found to be 24.2 (95% CI=20.7 to 28.1) per 100 000 children less than 5 years old and 5.4 (95% CI= 3.8 to 7.4) 100 000 respectively. The corresponding figures obtained utilising data for the West Midlands from the HICARE register were 28.3 (95% CI=24.5 to 32.6) 100 000 and 8.4 (95%=CI 6.4 to 10.8) 100 000 respectively. These incidence rates were 17% and 56% above those obtained using CDSC data in the pre- and post-Hib conjugate vaccine eras respectively.

5.1.2 Exclusions from HICARE

Initially 310 potential cases were identified, however, 52 (17%) of these children were excluded from the West Midlands HICARE register. Lack of traceable medical notes meant that 25 children, who apparently met the case definition, were excluded from the study (table 5.3) as it could not be determined whether their diagnosis had been laboratory confirmed. These children had similar characteristics to those included on the HICARE register.

Table 5.3: Cases of invasive *Haemophilus influenzae* disease excluded from HICARE due to lack of traceable medical records by study period and demographic characteristics, WMHR 1990-1994.

	Pre-Hib conjugate vaccine (n=19)	Post-Hib conjugate vaccine (n=6)	Total
Diagnosis:			
meningitis	7	3	10
other	5	3	8
unknown	7	0	7
Mortality	6	2	8
Age group (months)			
0-11	7	2	9
12-23	6	3	9
24-35	1	0	1
36-47	3	0	3
48-59	1	0	1
unknown	1	1	2
Gender:			
boys	11	2	13
girls	7	3	10
unknown	1	1	2
Ethnic group			
Non-South Asian	16	5	21
South Asian	3	1	4

Eight of the 25 (32%) children died. Two other children were not included on the register because their medical notes were not made available to the researcher before the deadline for data collection.

Of the remaining 27 cases, ten children had no evidence of a positive blood culture in their medical records, and their details are shown in table 5.4.

Two children were found to have non-*H influenzae* disorders. One was diagnosed with undescended testes, while another was a case of bacterial meningitis caused by another organism. Of the remaining 15 children, eight who had no record of sample dates when reported to CDSC were subsequently found to have had specimens taken outside the study period, another seven, who had no documented date of birth or age when first reported to CDSC, were found to be more than 59 months of age at the time of hospital admission.

Table 5.4: Cases of invasive *Haemophilus influenzae* disease identified by laboratory reports of isolates other than blood or CSF excluded from HICARE and ranked by month of onset, WMHR 1990-1994

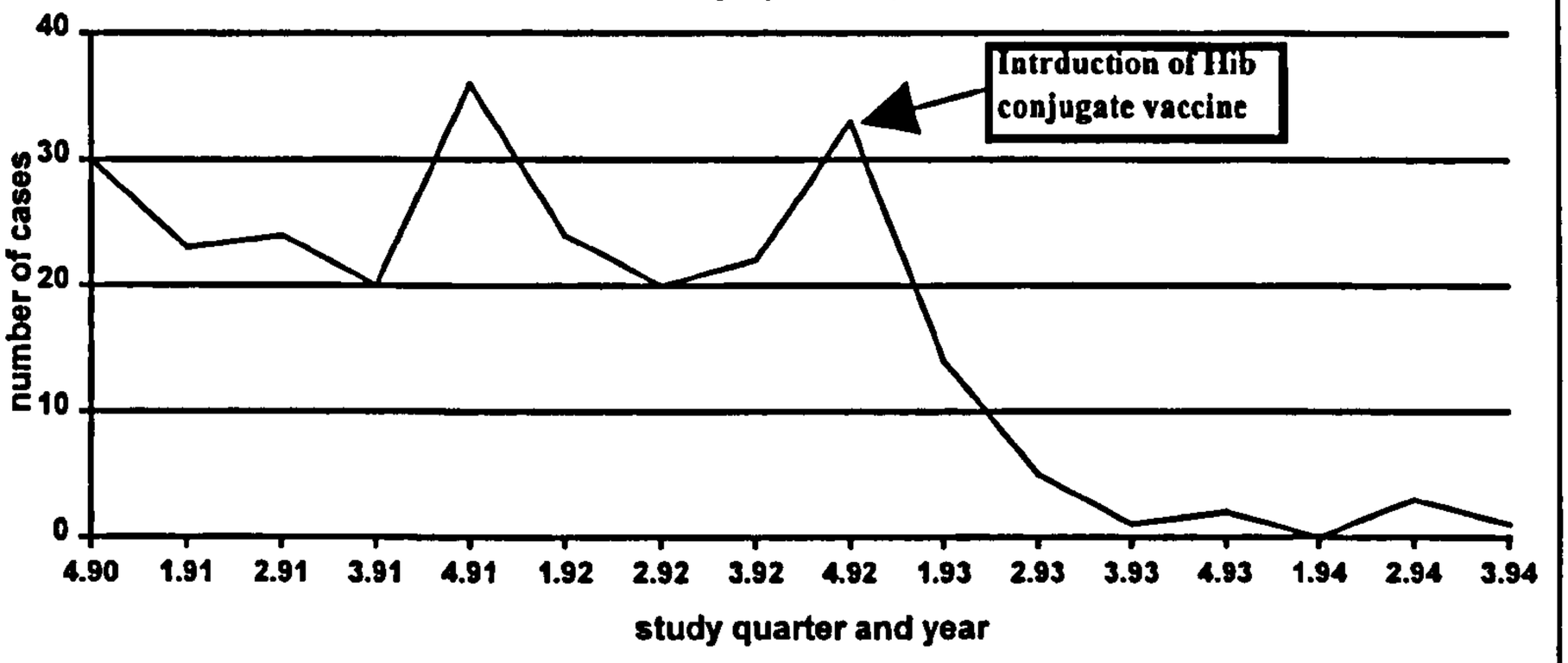
Case no.	Month of onset	Age	Gender	Ethnic group	Clinical diagnosis	Culture specimen	Serotype
1	October 1990	3 years	F	NSA	Epiglottitis	Clinical diagnosis only	unknown
2	December 1990	22 months	M	NSA	Septic arthritis	Pus	unknown
3	January 1991	11 months	M	SA	Septic arthritis/ osteomyelitis	Pus*	unknown
4	December 1991	18 months	F	NSA	Croup	Sputum	unknown
5	September 1992	2 years	F	NSA	Septic arthritis/ osteomyelitis	Pus*	unknown
6	March 1993	1 day	F	NSA	Neonatal sepsis	Ear swab; nasal swab; umbilical swab; gastric aspirate	unknown
7	September 1993	59 months	M	NSA	Tracheitis	Tip of endotracheal tube	non-capsulate
8	July 1993	NK†	F	NSA	Bronchopneumonia	Eye swab	b
9	January 1994	5 days	NK†	NSA	Neonatal sepsis	Ear swab; gastric aspirate; tip of endotracheal tube	non-capsulate
10	February 1994	12 months	F	NSA	Retropharyngeal abscess	Pus*	non-capsulate

*Each of these cases had blood cultures which were negative for *Haemophilus influenzae*
†NK - Not known

5.1.3 The impact of Hib conjugate vaccine

Figure 5.1 shows the dramatic reduction in the number of cases of invasive *H influenzae* following the introduction of Hib conjugate vaccine in the fourth quarter of 1992.

Figure 5.1: Cases of Invasive *Haemophilus influenzae* disease in the WMHR by quarter, 1990-1994



A more detailed six monthly examination of this data is shown in table 5.5. The incidence of disease can be seen to fluctuate up to the introduction of Hib conjugate vaccine in October 1992. There was little change in the first six months after the vaccines introduction, then a precipitous decrease in the observed incidence rate was seen from April 1993 onwards. The incidence of disease in this period was significantly different from that in the preceding 6 months.

Table 5.5: Six-monthly incidence* of invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994

Time period	Cases	Incidence rate	95% CI
October 1990 - March 1991	52	14.8	11.1-19.4
April 1991 - September 1991	44	12.5	9.1-16.8
October 1991 - March 1992	60	17.1	13.0-22.0
April 1992 - September 1992	43	12.2	8.9-16.5
October 1992 - March 1993	47	13.4	9.8-17.8
April 1993 - September 1993	7	**2.0**	**0.8-4.1**
October 1993 - March 1994	2	0.6	0.1-2.1
April 1994 - September 1994	3	0.9	0.2-2.5

* Incidence per 100 000 children <5 years of age
Figures in bold indicate incidence rates significantly different from that of the previous period

5.1.4 KEY POINTS FROM SECTION 5.1

- There were 199 cases identified in the pre-Hib conjugate vaccine period and 59 cases identified in the post-Hib conjugate vaccine period.
- Underreporting to CDSC increased from 15% in the pre-conjugate vaccine era to 36% n the post-conjugate vaccine period.
- Variation in reporting according to age was observed, 24% of cases aged less than 24 months of age were not reported to CDSC compared with 7% in those older than 24 months.
- Incidence rates obtained from HICARE register data were 17% and 56% above those obtained using CDSC data in the pre- and post-conjugate vaccine periods respectively.
- Seventeen per cent of cases identified were ineligible for inclusion on the HICARE register for reasons which included lack of case notes and insufficient diagnostic information.
- A significant decrease in disease incidence was seen 6 months after the vaccine was introduced.
- Introduction of Hib conjugate vaccine resulted in a precipitous decrease in the incidence of invasive *H influenzae* diseases. The most dramatic reduction was seen 6 months after the vaccine was introduced.

5.2 INDIVIDUAL RISK FACTORS

5.2.1 Age

The age distribution of cases of *H influenzae* meningitis, epiglottitis and other invasive diseases is shown in table 5.6. This shows that there was a significant association between the type of invasive *H influenzae* disease and age of presentation. Children aged 0-11 accounted for most cases of meningitis and non-epiglottic invasive disease, whereas epiglottitis was seen more commonly in older children. Age differences related to specific disease syndromes are discussed in greater detail in section 5.5.

Table 5.6: Distribution of cases of invasive *H influenzae* disease in the WMHR by age group and disease entity, 1990-1994

Age group (months)	Meningitis	Epiglottitis	Other disease	Total
0-11	74	1	26	101
12-23	58	12	17	87
24-35	20	10	5	35
36-47	11	7	1	19
48-59	9	2	5	16
Total	172	32	54	258

$\chi^2 = 33.86$; df = 8; $p<0.0001$

During the four years of the study, more than half (152 of 258, 59%) of all cases were aged less than 18 months, 39% (101 of 258) were under 12 months of age, 13% (34 of 258) were aged less than 6 months of age and 5% were under 3 months of age. More detailed examination of this data for those aged less than 3 months indicates that they accounted for 7% (13 of 199) of cases in the pre-conjugate vaccine period and 9% (5 of 59) of cases in the post-conjugate vaccine era.

Figure 5.2: Age distribution (percentage) of cases of invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994

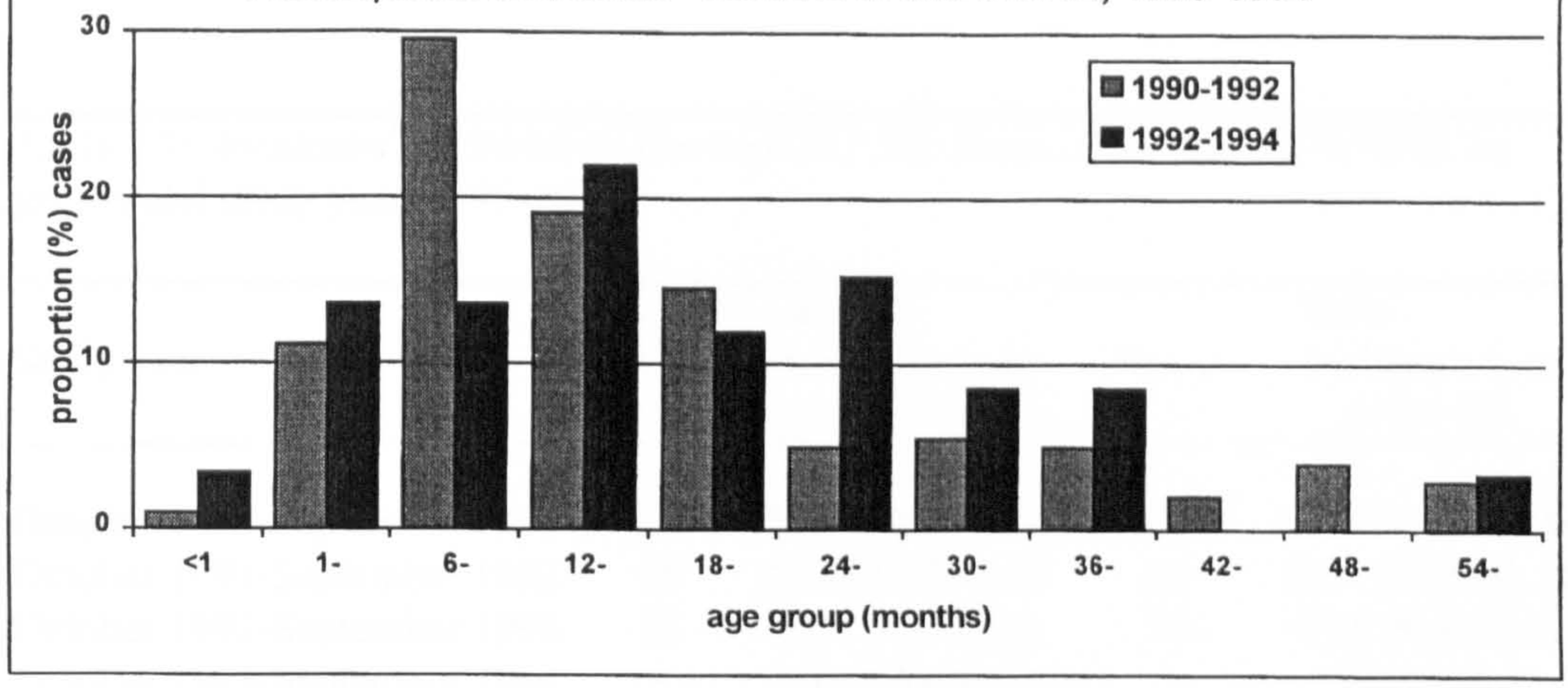


Figure 5.2 compares the proportional age distribution of cases of invasive *H influenzae* disease during the two time periods. Prior to the introduction of Hib conjugate vaccine in the WMHR, children aged 6-11 months were at greatest risk. They accounted for 30% of cases during this period and 14% in the post-vaccine era (OR=2.69, 95% CI=1.14 to 6.55; p=0.021). Following introduction of the vaccine, children over 12 months of age accounted for a slightly larger proportion of cases with those aged 24-35 being at proportionately increased risk (OR=2.64, 95% CI=1.16 to 5.94; p=0.017).

5.2.2 Gender

The ratio of boys:girls was similar (1.1:1) for the duration of the study. This slight preponderance of boys was mainly due to the large number of cases identified in boys in the first year of the study (boy:girl ratio of 1.3:1). Table 5.7 indicates that following the introduction of Hib conjugate vaccine the incidence rates for both boys and girls were similar. The incidence of disease fell

significantly in girls in both post-conjugate vaccine years. In boys, a significant decrease was not seen until the second year.

Table 5.7: Incidence* of invasive *Haemophilus influenzae* disease in the WMHR by gender and study year, 1990-1994

Study year	Boys		Girls	
	Cases	Incidence rate (95% CI)	Cases	Incidence rate (95% CI)
October 1990-September 1991	55	29.5 (23.0-39.8)	42	23.9 (17.7-33.2)
October 1991-September 1992	48	25.8 (19.7-35.3)	54	30.7 (23.7-41.2)
October 1992-September 1993	27	14.5 (9.8-21.8)	26	**14.8 (9.9-22.3)**
October 1993-September 1994	3	**1.6 (0.33-4.88)**	3	**1.7 (0.4-5.1)**

* Incidence per 100 000 children <5 years of age
Figures in bold indicate incidence rates significantly different from that of the previous year

Evaluation of the major disease syndromes by gender (table 5.8) demonstrated that overall, there was a significant difference between the occurrence of disease syndromes amongst boys and girls.

Table 5.8: Distribution of cases of invasive *Haemophilus influenzae* disease in the WMHR by gender and diagnostic category, 1990-1994

	Diagnostic category			
	Meningitis	Epiglottitis	Other	Total
Boys	82	23	28	133
Girls	90	9	26	125

$\chi^2 = 6.33$; df=2; p = 0.042

This may be due to the greater number of boys with epiglottitis than girls, the overall gender ratio for this disease was 2.6:1. This difference was statistically significant (OR=2.69, 95% CI=1.13 to 6.60; p=0.023) when gender was used to compare epiglottitis with all the other disease syndromes.

More girls were identified with meningitis than boys in both periods of the study (boy:girl ratio 0.9:1). This observation showed a trend towards increased risk for girls but just failed to reach conventional levels of statistical significance (OR=1.65, 95% CI=0.95 to 2.88; p=0.079) when meningitis was compared with all other disease syndromes.

5.2.3 Ethnic group

Only children resident in the region were used in this analysis. Overall 22 (9%) of 244 cases who were resident in the region were classified as being of South Asian origin (SA) origin (see section 4.5.3.3 for definition). The proportions obtained were similar to the demographic distribution of these groups in the paediatric population of the WMHR. Although the proportion of SA children affected increased from 8% (15 of 190) in the pre-vaccine era to 13% (7 of 54) in the post-vaccine period, this increase was not statistically significant (OR=1.74, 95% CI=0.60 to 4.93, p=0.28).

With the exception of the year prior to the introduction of the vaccine, incidence rates for children of SA origin were consistently, but not significantly, higher than those for children of non-South Asian (NSA) origin (table 5.9). A significant reduction in the incidence of disease in NSA children was seen in 1992/93 following the introduction of the vaccine.. A correspondingly significant fall was not demonstrated for SA children.

Table 5.9: Incidence* of invasive *Haemophilus influenzae* disease by study year and ethnic group, WMHR 1990-1994

Study year	Non-South Asian		South Asian	
	Cases	Incidence rate (95% CI)	Cases	Incidence rate (95% CI)
October 1990-September 1991	85	25.7 (20.5-31.8)	9	28.6 (13.0-54.4)
October 1991-September 1992	90	27.2 (21.9-33.4)	6	19.1 (7.0-41.7)
October 1992-September 1993	42	**12.7 (9.2-17.2)**	6	19.1 (7.0-41.7)
October 1993-September 1994	5	**1.5 (0.5-3.5)**	1	3.2 (0.1-17.8)

* Incidence per 100 000 children <5 years of age
Figures in bold indicate incidence rates significantly different from that of the previous year

Meningitis was responsible for 68% (15 of 22) of cases in SA children, and septicaemia (3 of 22) was the second most common disease entity. A similar proportion of meningitis cases were seen in NSA children (150 of 222, 68%), with the most common non-meningitic disease in this group of children being epiglottitis, which accounted for 28 of 222 (13%) cases. Only one case of epiglottitis was seen in a child of SA origin throughout the four year study period. This difference was not statistically significant (OR=0.38, 95% CI=0.05 to 2.76, p=0.50).

Table 5.10 shows the incidence rates for meningitis and non-meningitic diseases by gender and ethnic group. Although not statistically significant, both SA and NSA girls had a higher incidence of meningitis than boys from their respective ethnic groups.

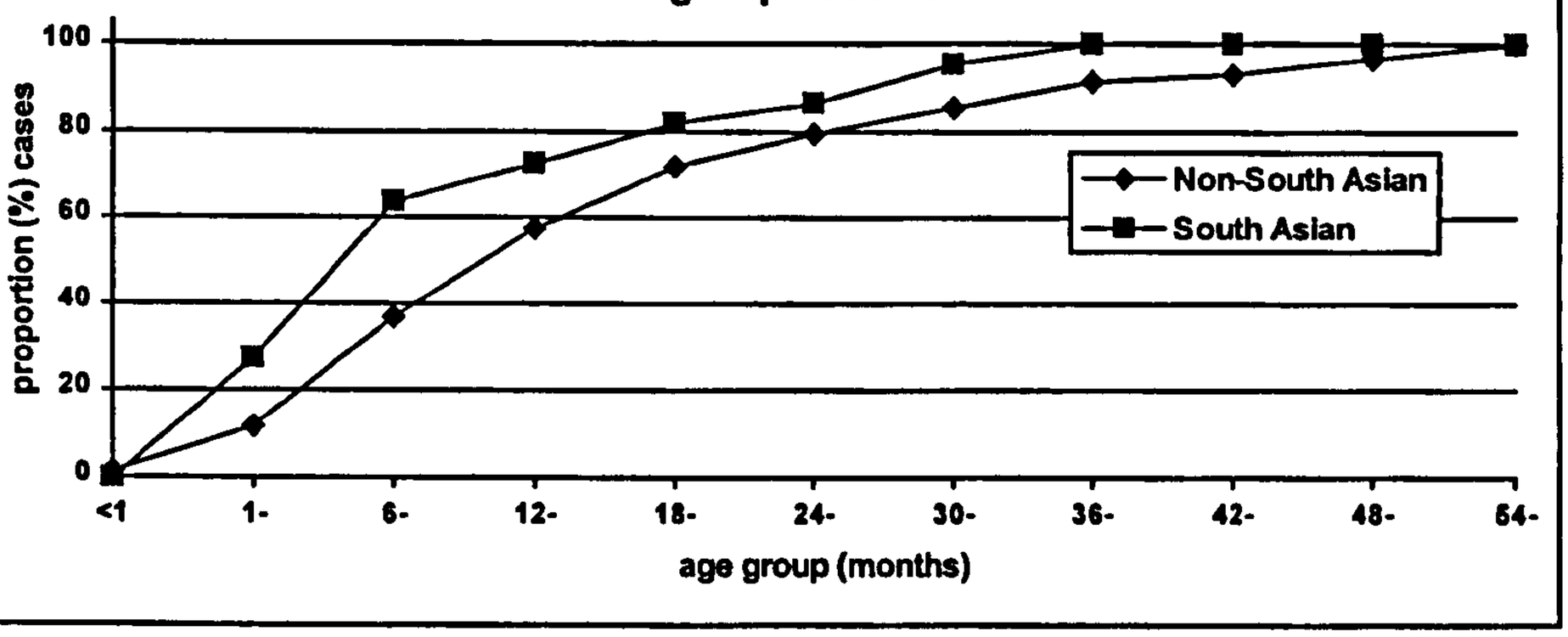
Table 5.10: Incidence* (95% CI) of invasive *H influenzae* disease in the WMHR by gender, ethnic group and disease category, 1990-1994

	South Asian		Non- South Asian	
	Boys	Girls	Boys	Girls
Meningitis	9.3 (3.4-20.4)	14.6 (6.7-27.8)	11.0 (8.7-14.0)	12.6 (10.0-15.7)
Non-meningitic	4.7 (0.9-13.7)	6.5 (1.8-16.6)	7.2 (5.2-9.3)	4.8 (3.1-6.7)

* Incidence per 100 000 children <5 years of age

In general, the age distribution of SA children differed from that of NSA children (figure 5.3). The majority of cases in SA children (14 of 22, or 64%) occurred in children less than 12 months old, compared to 38% (84 of 222) in NSA children (OR=2.88, 95% CI=1.07 to 7.86; p = 0.033). The mean age at onset for SA children was 13.1 months (median 10.0 months) and ranged from 1 to 37 months, compared with an average age of 19.0 months in children of NSA origin (median 15.0 months, range 0 to 59 months).

Figure 5.3: Cumulative frequency graph of the age distribution of invasive *Haemophilus influenzae* disease in the WMHR, by ethnic group 1990-1994



Children of SA origin were also more likely to present for admission 48 hours or more after the onset of symptoms than NSA children (OR=2.72, CI=1.01 to 7.24: p=0.046).

5.2.4 Birthweight

Low birthweight was defined as a weight of less than 2500g at birth. At the time of hospital admission, the birthweight of 164 children had been recorded, and 18 (11%) were classified as having a low birthweight. In this group of children the birthweight ranged from 1020g to 2470g (mean 1860g, median 2050g).

Disease entities identified in children who had a LBW were meningitis (11), pneumonia (2), septicaemia (2) and neonatal sepsis (3). Three cases were observed in children of SA origin and all were girls. There were 15 children from the NSA population, eight boys and seven girls.

Cases with a history of LBW had a mean age of 12.6 months (median 8.5 months, range 0-39 months) compared to 19.0 months (median 15.0 months, range 0-59 months) for children with a birthweight equal to or greater than 2500g. The difference between the mean age of disease onset in those of LBW and normal birthweight almost reached conventional levels of significance (p=0.058)

Twelve of 127 (9%) children seen during the pre-vaccine period had been of LBW compared to 6 of 37 (16%) in the post-vaccine era. (OR=0.54, 95% CI=0.19 to 1.55; p=0.24). There was no overall association between LBW and deprivation (OR=0.41, 95% CI=0.04 to 2.10; p=0.34), however LBW children were more likely to come from single parent families (OR=4.01, 95% CI=1.11 to 12.95; p=0.017).

Children who had been born with a LBW were not found to be at greater risk when examined for complications at follow-up (OR=1.87, 95% CI=0.39 to 8.88; p=0.34). They were however more likely to die following their episode of

invasive *H influenzae* disease than those of normal birthweight (OR=9.24, 95% CI=1.29 to 51.98; p=0.013).

Ten of 18 isolates were serotyped in this group of children and all were serotype b. Antibiotic resistance was seen in 5 of 17 (24%) isolates, three of which were CSF cultures and two blood cultures.

5.2.5 Nutritional status

The nutritional status of cases was determined by plotting the weight on admission on a 'Child Growth Foundation' growth chart. Children below the 3rd weight centile for age were classified as being underweight for age.

Only previously healthy children aged more than 1 month were included in this analysis, therefore neonates and children with predisposing conditions, such as Down's syndrome or congenital heart disease, were excluded.

Of the 241 cases eligible for the analysis, 228 (95%) had a documented weight at the time of admission, and 18 (8%) of these were underweight. There were 11 of 178 (6%) in the pre-conjugate vaccine period compared to 7 of 50 (14%) in the post-vaccine era. This difference failed to reach conventional levels of significance (OR=2.47, 95% CI=0.81 to 7.42; p=0.080). The most common disease encountered in this group of children was meningitis (14 of 18), there were no cases of epiglottitis.

Significant differences were found between children who were underweight for age and those within the normal weight range. Underweight children were more likely to have a history of previous hospital admissions (OR=16.07, 95% CI=4.22 to 62.32; p<0.0001). They were also more likely to have been ill for more

than 24 hours prior to admission (OR=6.24, 95% CI=1.39 to 27.98; p=0.0090), and to have been LBW babies (OR=9.71, 95% CI=2.32 to 40.09; p=0.0015).

Children who were underweight on admission spent a mean of 11.3 days in hospital compared to 9.8 days for those not classified as underweight. This difference did not reach conventional levels of statistical significance. A highly significant association was however found between being underweight on admission and coming from a highly deprived area (OR=undefined, p=0.0083).

Outcome was known in 225 of the 228 cases whose weight was known. Only one death occurred in this group of children and this was seen in a child who was underweight.

Significant associations were not found for several other variables such as disease entity, ethnicity, gender and family size and structure.

5.2.6 Anaemia

Following the WHO recommendation that a haemoglobin concentration of less than 11g/dl be taken as indicative of anaemia in children aged between 6 months and 6 years, 72 of 207 (35%) cases of invasive *H influenzae* disease aged 6 months or more were classed as anaemic. A smaller proportion of children were found to be anaemic in the second period of the study compared to the first (29% [10 of 44] vs 38% [62 of 163]). This difference was not statistically significant (OR=2.09, 95% CI=0.90 to 4.91, p=0.087).

Meningitis was the most common disease entity in this group of children accounting for 72% (52 of 72) of cases. Epiglottitis (6 cases, 8%), and septicaemia

(5 cases, 7%) were the next most common. The remaining diagnoses were pneumonia (3 cases, 4%), cellulitis (3) and septic arthritis (1).

The mean age of children with anaemia was 16.1 months (median 14.5 months, range 6-52 months), while those with normal haemoglobin levels had an average age of 23.6 months (median 20.0, range 6-59). The difference in the mean age of these two groups was statistically significant (p=0.0013). Children with anaemia were more likely to be the youngest child in the family (OR=4.63, 95% CI=1.62 to 16.17; p=0.003).

Significantly more children with anaemia were ill for 24 hours or more before admission than other children (OR=2.56, 95% CI=1.31 to 5.05, p=0.018), and spent an average of 12 days in hospital compared to 8.3 days for those with normal haemoglobin levels. This difference was statistically significant (p=0.0027).

Children with anaemia were also more likely to have complications at follow-up (OR=3.69, CI=1.05 to 14.51; p=0.022), although when hearing loss alone was examined a significant association was not found.

Significant associations were not found for several other factors such as deprivation, ethnicity, gender, and mortality.

5.2.7 Chronic illness

Table 5.11 shows that a history of chronic illness for a variety of conditions was recorded for 25 of 254 (10%) children on the register. Several of these children had more than one long-term illness.

Table 5.11: Chronic illness identified in 25 cases of invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994

Chronic illness	Number of children affected*
Asthma	9
Eczema	9
Congenital heart disease	3
Down's syndrome	3
Drug allergies	3
Others	6
Total	33

* A number of children had more than one chronic condition

The proportion of children with a documented chronic illness rose from 9% (18 of 196) in the pre-vaccine period to 12% (7 of 58) in the post-vaccine period. The increase did not reach conventional levels of significance (OR=1.41, 95% CI=0.50 to 3.88: p=0.63).

Among this group of children there were 14 cases of meningitis, 3 cases each of epiglottitis and pneumonia, and 2 of cellulitis. One case each of septicaemia, septic arthritis and bacterial endocarditis were also seen.

Twenty-three children were of NSA origin, 14 were boys and 9 girls. Only two children were of SA origin, one of each gender. No association was found between deprivation and chronic disease.

The mean age of these children was 17.4 months (median 13.0 months, range 3-58 months) compared to an average age of 18.7 months (median 15.0 months, range 0-59 months) in children who did not have a chronic illness. This difference did not reach conventional levels of significance (p=0.897).

One death occurred in this group of children, a case of meningitis in a SA infant who had Down's syndrome together with congenital heart disease.

5.2.8 KEY POINTS FROM SECTION 5.2

- ❑ Overall, almost 60% of cases identified were aged less than 18 months of age.
- ❑ A significant shift was seen in the age of those proportionately most at risk from 6-11 months of age in the pre-conjugate vaccine period to 24-35 months of age in the post-vaccine period.
- ❑ Similar numbers of boys and girls were affected in the four years studied.
- ❑ Boys were significantly more at risk for epiglottitis, however more girls were identified with meningitis in both periods of the study.
- ❑ The proportion of SA children affected increased from 8% in the pre-conjugate vaccine period to 13% in the post-conjugate vaccine period.
- ❑ SA girls had the highest rates of *H influenzae* meningitis.
- ❑ Significantly more cases of invasive *H influenzae* disease were seen in SA children at less than 12 months than in NSA children.
- ❑ Children of SA origin were more likely to present to hospital late.
- ❑ A LBW was documented for 9% of cases in the pre-conjugate vaccine era compared to 16% in the post-conjugate vaccine period.
- ❑ LBW babies were associated with single parent families and increased risk of mortality.
- ❑ Before Hib conjugate vaccine was introduced 6% of cases were underweight for age on admission, this increased to 14% of cases in the second period of the study.
- ❑ Significant associations were seen between being underweight and a history of LBW, previous hospital admissions and living in an area of high deprivation.
- ❑ More than one-third (35%) of cases were anaemic on admission.
- ❑ Children with anaemia were significantly younger when admitted, spent longer in hospital and were more at risk of neurological complications at follow-up.
- ❑ Chronic illness on admission was identified in 10% of cases over the duration of the study.

5.3 FAMILY AND COMMUNITY RISK FACTORS

5.3.1 Family size and structure

Information on family size and structure were available for 254 of the children. There were 200 children with one or more siblings at the time of admission, and 157 of 194 (81%) of these children had one or more siblings younger than 5 years of age. Significantly more cases of meningitis occurred in children who had two or more siblings aged less than 5 years (OR=4.62, 95% CI=1.28 to 25.11; p=0.019).

In cases with siblings, meningitis was responsible for the majority of cases (131 of 200, 65%) with epiglottitis (22 of 200, 11%) the next most common invasive disease.

In this study, the number of siblings ranged from 1 to 7 (mode=1), and the mean number of siblings in these families was 1.7. Children from SA families had an average of 2.7 siblings, whereas NSA children had a mean of 1.6 siblings. This difference was highly significant (p = 0.00023).

There were 54 of 254 (21%) children who were reported to be singletons, and 52 (96%) of these were NSA children. The most common invasive disease in singletons was meningitis (37 of 54, 69%), followed by epiglottitis (9 or 17%). The mean age among this group of children was 20.6 months (median 18 months, range 0-59 months) compared to 17.9 months (median 13 months, range 0-59 months) in children with siblings. This difference was not statistically significant (p=0.20).

There was one instance of co-primary disease. Two siblings aged 22 months and 7 months were admitted to hospital in the pre-vaccine era, both had septicaemia. The younger sibling was the index case and was admitted to hospital 24 hours before the older child. Both children recovered without any apparent problems. No secondary cases were identified in this case series.

5.3.2 Lone parent families

Only 234 case notes had parental details from which it was possible to identify 32 (14%) children as having a single parent. The proportion of children from lone parent families was similar in both study periods, 14% in the pre-vaccine period and 13% in the second period of the study.

As with many of the other variables examined, meningitis was the most common diagnosis, and accounted for 20 of 32 (63%) cases.

All the children identified from lone parent families were of NSA origin. (OR = undefined, p = 0.051). Deprivation was not significantly associated with coming from a lone parent family.

5.3.3 Daycare attendance

Excluding children aged less than one month of age, various forms of daycare were documented in the medical records of 39 of 252 (16%) children at the time of admission. Most children attended nursery/primary school (17 of 39, 44%), while other forms of daycare were playgroup/playschool (8), mother and toddler groups (7), and childminders (7).

Cases attending any type of daycare were aged between 2 to 59 months, and had an average age of 26.1 months (median 23.0 months) compared to a mean of 17.6 months (median 13.0 months, range 2-58 months) in children who were not attending any form of daycare. Comparison of the mean ages of the two groups revealed a significant difference (p=0.00012)

The main disease entity in children attending daycare was meningitis (24 of 39, 62%), with epiglottitis (7 or 18%) being the next most common. Other diseases encountered were cellulitis (4), septic arthritis (2), pneumonia and empyema (1 case each). There were no deaths or long term complications in children attending daycare.

Girls accounted for nearly two-thirds of children receiving day care (24 of 39, 62%). Daycare attendance was however uncommon in children of SA origin, only one child of SA origin was identified in this group. It was also uncommon for children of lone parents to attend daycare (3 of 32, 9%).

Children attending daycare were less likely to have siblings (OR=0.41, 95% CI=0.18 to 0.92; p=0.028) than those not attending daycare.

Cases attending daycare accounted for 32 of 199 (16%) cases in the pre-vaccine era, and 7 of 59 (12%) cases in the post-vaccine era. This difference was not statistically significant (OR=0.70, 95% CI=0.29 to 1.69; p=0.34). None of the children identified in the post-vaccine period who attended daycare had received Hib conjugate vaccine.

During the survey, two cases of invasive disease were identified in children who had attended the same nursery. Information on one of these children is limited as the child (the index case) died within 24 hours of admission and the medical

notes could not be located. Both children were admitted to the same hospital, the second child being admitted 46 days after the index case, and both had blood specimens identified as Hib biotype I. More detailed typing was however not available.

5.3.4 KEY POINTS FROM SECTION 5.3

- ❑ Significantly more cases of meningitis were seen in children with 2 or more siblings aged less than 5 years.
- ❑ Children from SA families had a mean of 2.7 siblings compared to 1.6 for NSA children.
- ❑ There was only one instance of co-primary disease in this series and no secondary cases were identified.
- ❑ From 1990-94 14% of cases were identified as coming from lone-parent families.
- ❑ No association was seen between deprivation and coming from a lone parent family.
- ❑ Daycare attendance was documented for 16% of cases in the pre-conjugate vaccine period and 12% in the post-conjugate vaccine era.
- ❑ Cases attending daycare were significantly younger than those who were not, and significantly less likely to have siblings.
- ❑ Daycare was uncommon amongst children of NSA origin.

5.4 ENVIRONMENTAL RISK FACTORS

5.4.1 Immunisation status

5.4.1.1 In the pre-Hib conjugate vaccine era

The primary immunisation history documented in the hospital notes at the time of admission was used to evaluate the immunisation status of the 199 children hospitalised prior to the introduction of Hib conjugate vaccine.

Children were placed in one of two categories according to their immunisation history. They were classified as having received either (i) an age-appropriate course of primary immunisation, or (ii) having received an incomplete course of primary immunisation, this category included those who had not received any immunisations. Eight children aged less than 2 months, and 24 children for whom immunisation data had not been recorded were excluded from the analysis.

Immunisation histories had been documented in the medical records of 167 (84%) children. Of these, 31 (19%) had either been incompletely immunised or not immunised at all. Seven of these children had not received any immunisations prior to admission, while fourteen of the remaining children needed one or more doses of DTP/DT. Nine required MMR alone, and one child was overdue for both DTP/DT and MMR.

When the two categories were compared, attending daycare, being underweight, having a history of chronic illness or LBW, anaemia on admission or living in a mainly urban or mainly rural area did not appear to influence

immunisation uptake. Age was not significantly related to uptake however, immunisation uptake improved with increasing age (table 5.12).

Table 5.12: Primary immunisation status of children with invasive *Haemophilus influenzae* disease in the pre-Hib conjugate vaccine period in the WMHR, 1990-1992

	Age group (months)					Total
	0-11	12-23	24-35	36-47	48-59	
Age-appropriate	48	53	13	10	12	136
Incomplete/none	17	9	3	2	0	31
Total	65	62	16	12	12	167

The mean age of cases with age-appropriate primary immunisation status compared to the other cases was 19.7 months (median 15.0 months, range 2-59 months) and 14.9 months (median 11.0 months, range 3-43 months) respectively. The difference between these two groups was not statistically significant (p=0.12).

Overall, only 12 of 19 (63%) children from lone-parent families, compared to 110 of 132 (83%) children from other families were up to date with their immunisations. This result almost reached conventional levels of significance (OR=0.34, 95% CI=0.11 to 1.09; p=0.057).

South Asian children were more likely to be overdue for their immunisations than NSA children (OR=3.54, 95% CI=1.04 to 12.03; p=0.048), while children who had three or more siblings were less likely to be adequately immunised than cases from smaller families (OR=0.22, 95% CI=0.06 to 0.72; p=0.0067).

5.4.1.2 In the post-Hib conjugate vaccine era

The Hib immunisation status of the 59 children presenting in the post-vaccine era was determined primarily by contacting the appropriate immunisation co-ordinator. Where the information was not available from this source, either because the child was not a resident of the region or had moved, the immunisation history documented in the hospital records at the time of admission was used.

Excluded from the following analysis are six children. Three were aged less than two months at the time of the study, and therefore not eligible for immunisation at the time of admission. Three other children were from outside the region and had no documented immunisation history.

There were 44 of 53 (83%) children who did not receive Hib immunisation in the two year period immediately following introduction of the vaccine. Of these 25% (11 of 44) were less than 12 months of age and 70% (31 of 44) between 12 and 47 months of age. The mean age of children who did not receive Hib immunisation was 21.4 months (median 18.5 months, range 3-59 months). When compared with the average age of children who had received the vaccine (mean 13.8 months, median 12.0 months, range 3-38 months), a statistically significant difference was not found ($p=0.11$).

Analysis of the Hib immunisation status of those children who had not been immunised before admission indicated that over one third (15 of 44, 34%) did not receive Hib conjugate vaccine following discharge. Those children who were immunised, received the first dose of vaccine on average 109.6 days (median 76 days, range 3-441 days) following discharge from hospital. None of the children received the vaccine while in hospital.

Overall 33 of 44 (75%) children who had not received Hib conjugate vaccine prior to admission, had age-appropriate immunisation status for the other vaccines in the primary immunisation schedule. Only two of these children were over 48 months of age, and would not have been targeted by the 'catch-up programme'. Excluding them would have reduced the unimmunised proportion to 70%.

Factors which did not appear to significantly influence Hib conjugate vaccine uptake included ethnic group, family size and structure, attending daycare, having a history of chronic illness or LBW, or living in an urban or rural area.

When the primary immunisation data obtained from the immunisation co-ordinators (excluding Hib immunisation) for children resident in the region admitted to hospital in the post-vaccine period were compared with the information initially recorded in the medical notes, similar results were obtained (table 5.13). Agreement between verified and documented immunisation data was seen in 37 of 42 (88%) cases. Using the kappa measure of agreement, a kappa value of 0.55 (one-tailed p-value=0.0002) was obtained. The Landis and Koch classification indicates that this represents moderate agreement between the two sources.

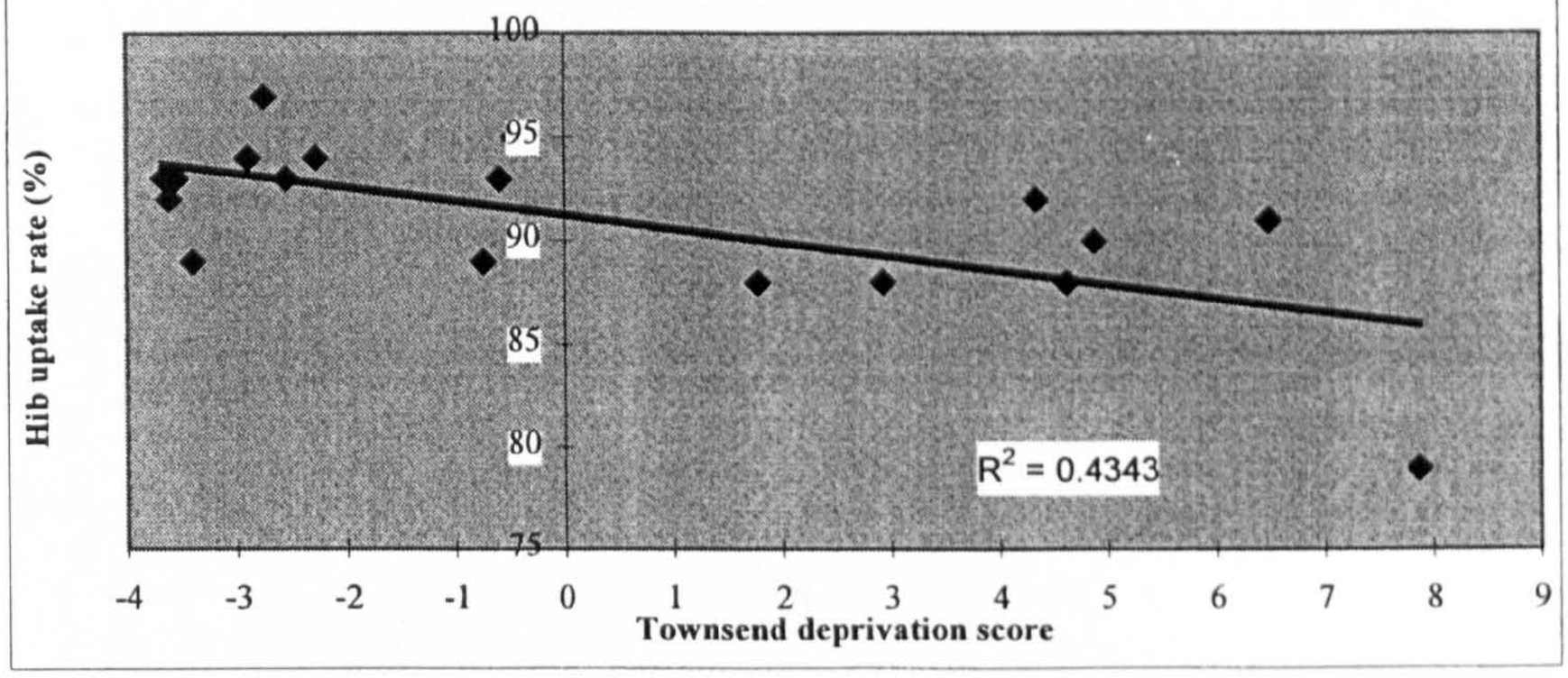
Table 5.13: Comparison of the primary immunisation status of children with invasive *Haemophilus influenzae* disease in the WMHR obtained from two independent sources in the post-Hib conjugate vaccine period, 1992-1994

Immunisation status obtained from the immunisation co-ordinator	Immunisation status documented in the medical notes at the time of admission		Total
	Age-appropriate	Incomplete/none	
Age-appropriate	33	3	36
Incomplete/none	2	4	6
Total	35	7	42

Kappa = 0.55; p=<0.001

District immunisation uptake scores for Hib conjugate vaccine first became available in November 1993.[340] Figure 5.4 shows a negative correlation between district immunisation uptake rate and the district Townsend deprivation score. The correlation was found to be highly significant (r^2 =43%, n = 18; p <0.005).

Figure 5.4: District* Hib immunisation uptake rates (Nov. 1993) related to district deprivation scores, WMHR 1992



* In November 1993 there were only 18 districts; Bromsgrove & Redditch and Kidderminster had merged to form North Worcester; and South Warwickshire and North East Warwickshire had merged to become Warwickshire (see table 4.2)

The immunisation records of individual children were examined by deprivation tertile in the post-Hib conjugate vaccine era. A significant association was not found at this level (χ^2 for linear trend =0.092, p = 0.76).

5.4.1.3 Hib conjugate vaccine failures

During the two year post-Hib conjugate vaccine period studied, nine vaccine failures were identified using the BPSU case definition. Table 5.14 shows selected characteristics of the 9 children identified, most of whom received only one dose of vaccine. There were three true vaccine failures, two occurred after 3

doses of vaccine and one after a single dose. Five apparent vaccine failures were also identified, as well as one non-vaccine failure.

Excluding the non-vaccine failure, the other vaccine failures accounted for 15% (8 of 53) cases seen during 1992/94. Five of the vaccine failures (including one true vaccine failure) occurred in the first year following the introduction of Hib conjugate vaccine, and three (including two true vaccine failures), in the second year. All the vaccine failures occurred in different health authorities.

One of the children classified as an apparent vaccine failure died. This three month old girl of SA origin had received a single dose of vaccine ten days previously, and died within a few hours of hospital admission. The other four apparent vaccine failures, as well as the three true vaccine failures, and the child who was a non-vaccine failure all survived.

Ethnic group, lone parent, family size and structure, having a history of chronic illness or LBW, living in a deprived area, anaemia or being underweight for age did not appear to influence the occurrence of Hib conjugate vaccine failure.

Table 5.14: Cases of invasive *Haemophilus influenzae* disease occurring after immunisation with Hib conjugate vaccine in the WMHR, ranked by month and year of onset, 1992-1994

Case no.	Month and year of onset	Age (months)	Sex	Ethnic group	Disease	Number of doses of vaccine received prior to hospital admission	Number of days between first vaccination and hospital admission	Serotype	BPSU classification
1	October 1992	3	M	NSA	meningitis	1	1	b	AVF*
2	October 1992	26	M	NSA	meningitis	1	4	b	AVF
3	December 1992	4	M	NSA	meningitis	1	1	b	AVF
4	January 1993	3	F	SA	meningitis	1	10	b	AVF
5	January 1993	12	F	NSA	meningitis	1	20	b	TVF†
6	February 1993	13	M	NSA	meningitis	1	23	nc¶	NVF‡
7	October 1993	5	M	NSA	meningitis	3	85	b	TVF
8	October 1993	38	M	NSA	meningitis	1	1	b	AVF
9	August 1994	20	F	NSA	meningitis	3	555	b	TVF

* Apparent Vaccine Failures
† True Vaccine Failures
‡ Non-Vaccine Failures
¶ non-capsulate

5.4.1.4 KEY POINTS FROM SUB-SECTION 5.4.1

- ❑ In the pre-Hib conjugate vaccine era immunisation histories were available for 84% of cases.
- ❑ Age-inappropriate immunisation histories were recorded for 19% of children in the pre-Hib conjugate vaccine period, the majority required one or more doses of DTP/DT.
- ❑ Deprivation was not significantly associated with poor immunisation uptake at the individual level, but a significant association was observed at the district level.
- ❑ Children of SA origin and those with 3 or more siblings were significantly more likely to have inadequate immunisation histories.
- ❑ Proportionately fewer children from lone-parents were up to date with their immunisations than children from other families.
- ❑ In the post-conjugate vaccine period, 83% of cases had not received Hib conjugate vaccine before admission despite being upto-date with other vaccines.
- ❑ Following discharge, 34% did not receive Hib conjugate vaccine, and those who did waited an average of 110 days. None received the vaccine in hospital.
- ❑ There was significant agreement between documented immunisation histories and those obtained from immunisation co-ordinators.
- ❑ There were 9 vaccine failures, 3 of which were true vaccine failures, 5 apparent vaccine failures and 1 non-vaccine failure. Two of the true vaccine failures had received full courses of Hib conjugate vaccine.

5.4.2 Socioeconomic factors

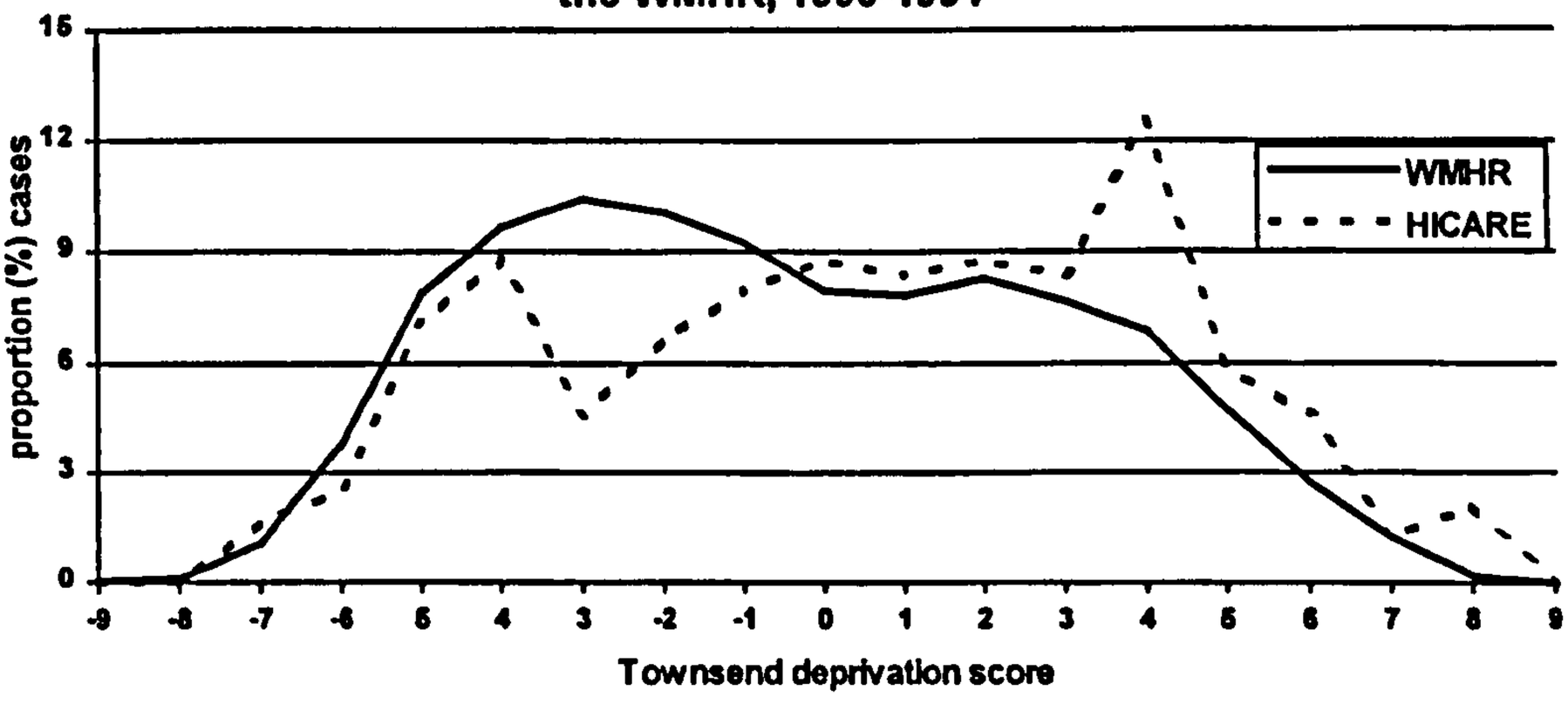
Data for figures in this sub-section may be found in appendix 2 together with the cut-off points for each of the tertiles used.

5.4.2.1 Deprivation

The database containing the postcodes obtained from the medical records of cases were linked to the West Midlands geographic database at the CIU using GIS software. This matched 236 of 258 (92%) postcodes to EDs in the region. Unmatched addresses were checked in the Royal Mail postal address book to verify the postcode. Using this technique a further 8 postcodes were matched to EDs giving an overall match of 95%. The remaining 14 (5%) postcodes could not be matched to EDs because the addresses given were outside the WMHR.

Townsend deprivation scores for cases ranged from +8.8 (most deprived) to -6.5 (least deprived), compared to +8.8 to -8.5 for the region as a whole. The proportionate distribution of deprivation amongst children with invasive *H influenzae* disease is compared with that in the WMHR (figure 5.5).

Figure 5.5: Proportional distribution of Townsend deprivation scores for cases of invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994



The figure shows that the distribution of ED deprivation scores within the region is skewed towards the more affluent end of the range, whereas the distribution amongst cases is skewed towards the more deprived end of the scale.

In table 5.15 the incidence of invasive *H influenzae* disease is shown for each of the deprivation tertiles. Although the incidence for children living in affluent areas was lower than that of the other two groups, they did not differ significantly.

Table 5.15: Annual incidence* of invasive *Haemophilus influenzae* disease by Townsend deprivation tertile, WMHR 1990-1994

Deprivation category	Population	Cases	Incidence rate (95% CI)
High	151,162	110	14.2 (10.7 - 18.4)
Medium	101,012	78	19.3 (15.3 - 24.1)
Low	98,825	56	18.2 (15.0 - 21.9)
Total	350 999	244	17.4 (15.0 - 19.4)

* Incidence per 100 000 children <5 years of age

The incidence of disease for those children in affluent areas was then compared with that of the other two groups combined (table 5.16). A significantly reduced incidence of disease was then seen in children living in the more affluent areas (p=0.0046).

Table 5.16: Analysis of the incidence of invasive *Haemophilus influenzae* disease by Townsend deprivation category, WMHR 1990-1994

Area of deprivation	OR (95% CI)	p value
High vs low	1.34 (0.96 - 1.87)	0.09
Low vs medium/high	0.73 (0.54 - 0.99)	0.046

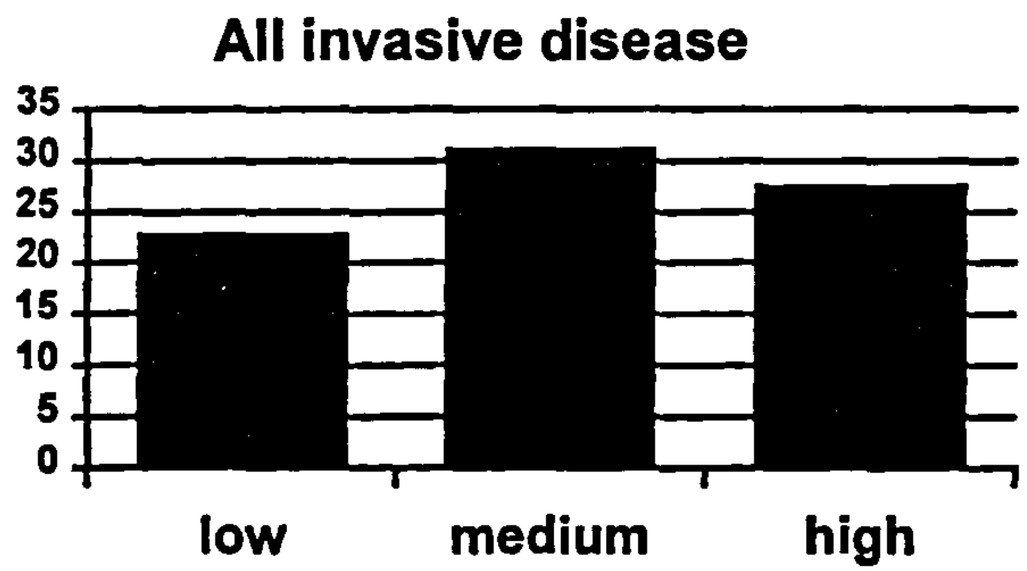
In the pre-Hib conjugate vaccine era there was a 14% difference between the incidence rates for all cases of invasive *H influenzae* disease observed for

children aged less than 5 years in low (23.3 per 100 000 [95% CI=17.0 – 31.0]) compared to high (27.1 per 100 000 [95% CI=21.6 – 33.7]) areas of deprivation (figure 5.6). The incidence rates in the post-conjugate vaccine period were 5.1 per 100 000 (95% CI=2.4 – 9.3) and 9.2 per 100 000 (95% CI=6.2 – 13.39) for low and high areas of deprivation respectively. This represented a 45% difference, and the test for linear trend failed to achieve conventional levels of significance.

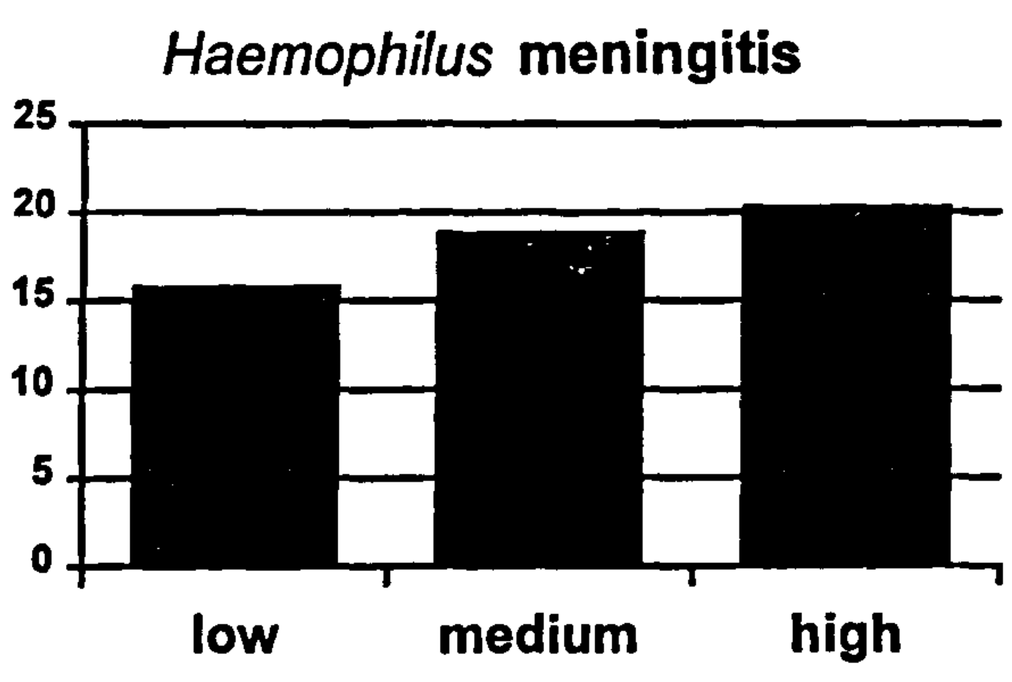
Figure 5.6 also shows a gradient in disease experience in each time period of the study when *H influenzae* meningitis cases were examined separately. Although neither gradient was significantly different, the gap in incidence between the most deprived and least deprived areas widened over the two time periods.

Figure 5.6: Incidence rates for invasive *Haemophilus influenzae* disease and *Haemophilus influenzae* meningitis by Townsend deprivation tertile, WMHR 1990-94

Pre-Hib conjugate vaccine: 1990-92

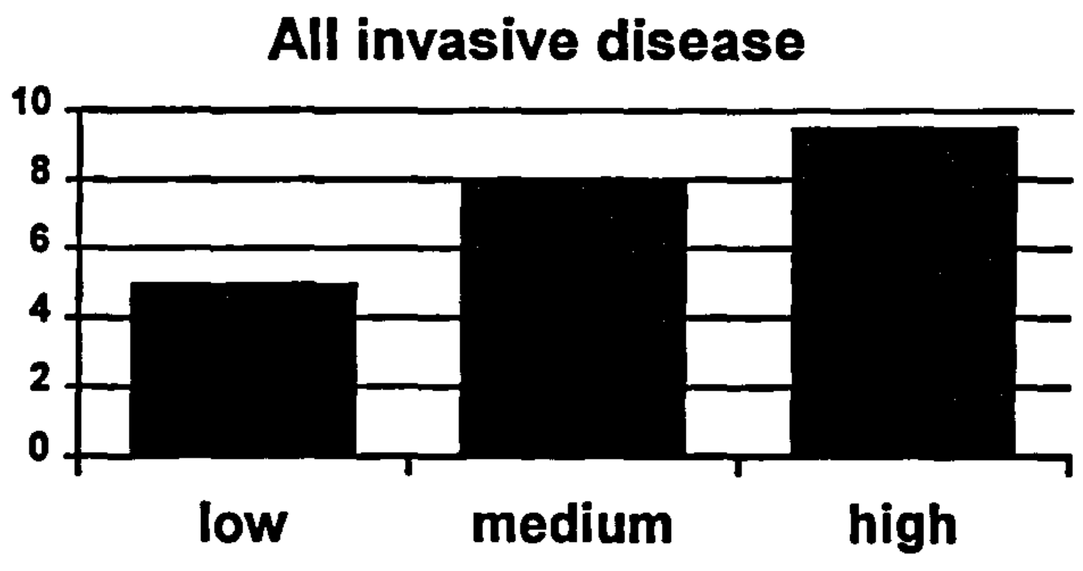


chi-square for linear trend = 0.75; p = 0.39

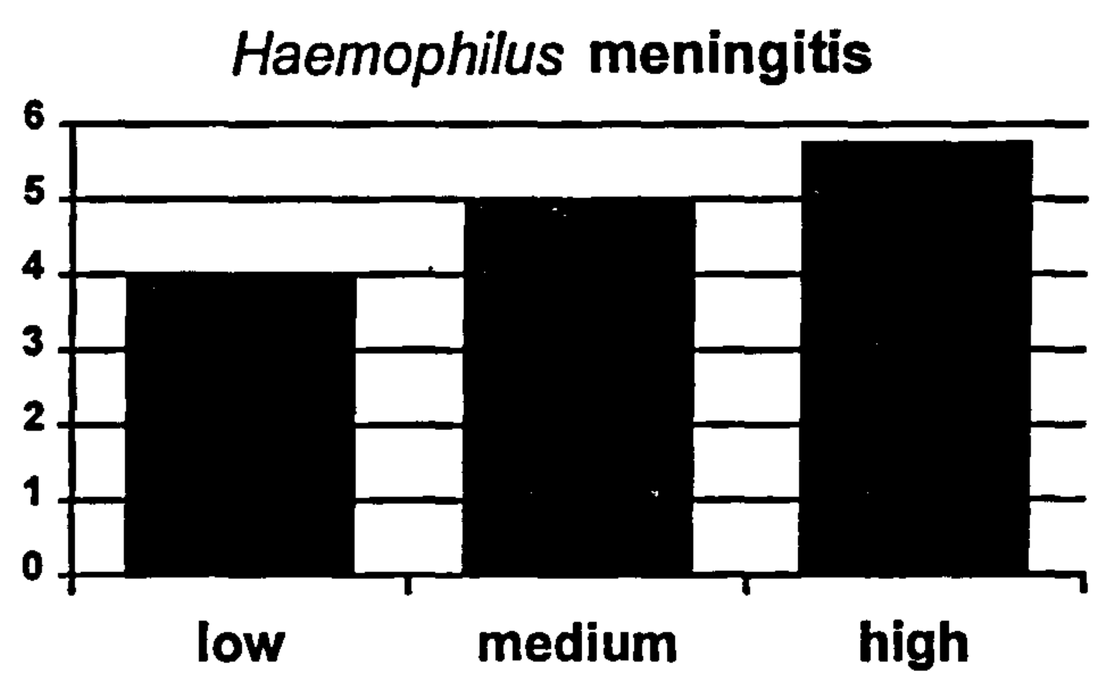


chi-square for linear trend = 1.31; p = 0.25

Post-Hib conjugate vaccine: 1992-94



chi-square for linear trend = 2.65; p = 0.10



chi-square for linear trend = 0.79; p = 0.37

In the pre-conjugate vaccine period the incidence of *H influenzae* meningitis in children living in areas of high deprivation was 48% higher than that of those from areas of low deprivation. In the post-vaccine era this had increased to 53%.

Table 5.17 compares children from the most deprived EDs with children from the least deprived EDs for several demographic, social and clinical factors. Immunisation status, gender, age-group and clinical disease were similar for both groups of children. However, cases of invasive *H influenzae* disease living in areas of high deprivation seem to be more at risk for a number of factors than cases from the most affluent areas.

When children with meningitis were analysed separately (not shown in table), several additional factors emerged. It was found that children with meningitis from the most deprived areas were more likely to be the youngest child in the family (OR=0.12, 95% CI=0.01 to 0.96; p=0.032), and more likely to come from a family with two or more siblings (OR=undefined, p=0.0030) than children from the least deprived areas.

A number of other factors did not reach conventional levels of significance but may be clinically relevant. Compared to cases from the least deprived areas, children from the most deprived areas who had been admitted with meningitis were asked to attend follow-up less often than their peers from the least deprived EDs (67/73 *vs* 39/39, OR=undefined, p=0.090). Of these, only 55 of 67 (82%) children from the most deprived areas were brought for follow-up compared to 36 of 39 (92%) children from the least deprived group (OR=0.38, 95% CI=0.10 to 1.45; p=0.24).

Table 5.17: Comparison of selected variables for cases of invasive *Haemophilus influenzae* disease by Townsend deprivation category, WMHR 1990-1994

Variable	High deprivation (n=110)	Low deprivation (n=56)	Odds ratio (95% CI)	p value
Study period:				
1990-1992	82	46	0.63 (0.26-1.50)	0.35
1992-1994	28	10		
Disease entity:				
meningitis	78	40	0.96 (0.44-2.07)	0.94
non-meningitic	32	16		
Age group (months):				
0-11	49	23	1.13 (0.56-2.29)	0.84
12-23	33	19	0.85 (0.40-1.78)	0.76
24-35	13	8	0.81 (0.29-2.32)	0.85
36-47	5	3	0.85 (0.16-5.68)	1.00
48-59	10	3	1.78 (0.43-10.49)	0.55
Gender:				
boys	58	26	1.29 (0.64-2.58)	0.55
girls	52	30		
Ethnic group				
SA	17	1	**10.16 (1.32-78.50)**	**0.0069**
NSA	93	55		
Large family (> 2 siblings):	23/88	1/38	**13.09 (1.70-100.93)**	**0.0012**
yes	65/88	37/38		
no				
Immunisation status†:				
age-appropriate	69/88	42/48	0.52 (0.16-1.50)	0.28
incomplete/none	19/88	6/48		
Underweight for age:				
yes	12/99	1/52	7.03 (0.89-55.7)	**0.035**
no	83/99	51/52		
Hearing test requested*:				
yes	56/72	30/37	0.82 (0.27-2.42)	0.86
no	16/72	7/37		
Attended hearing test*:				
yes	39/56	27/30	0.25 (0.04-1.00)	0.057
no	17/56	3/30		
Failed hearing test*:				
yes	7/36	0/24	**undefined**	**0.035**
no	29/36	24/24		

* This analysis only includes cases of meningitis
† 1990 - 1992 (primary immunisation status in the pre-Hib conjugate vaccine period)
Figures in bold indicate a statistically significantly result

In addition, children from the most deprived areas who had meningitis had more neurological problems at follow-up compared to those from the least deprived EDs (10/77 vs 1/40, OR=5.82, 95% CI=0.72 to 47.21; p=0.095), and were significantly more likely to have SNHL (OR=undefined; p=0.035).

No deaths were identified in children from the least deprived areas, whereas a case fatality rate of 5.5% (6 of 110) was found in children from the most deprived areas. This difference did not reach conventional levels of significance (OR=undefined, p=0.097).

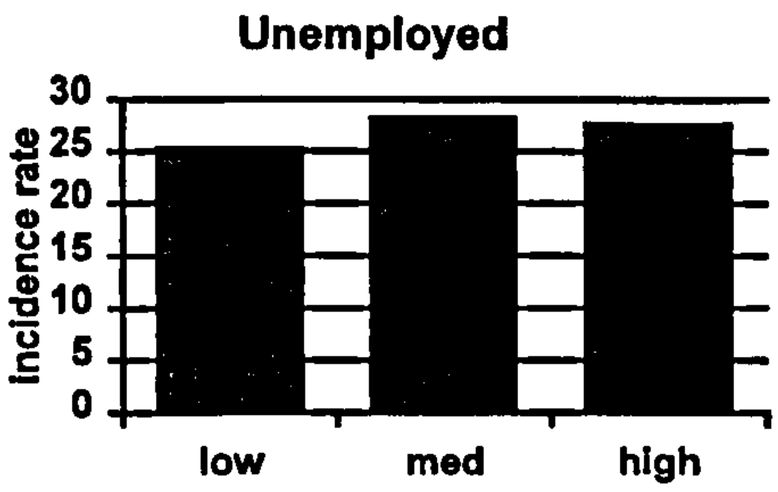
5.4.2.2 Components of the Townsend deprivation score

There were no obvious disease gradients seen for all invasive *H influenzae* disease when the components of the Townsend material deprivation score were examined individually in the two years before Hib conjugate vaccine was introduced (figure 5.7). In the post-vaccine period however, gradients from low to high areas of deprivation can be seen for all the variables with non-owner occupancy being significantly associated with disease risk.

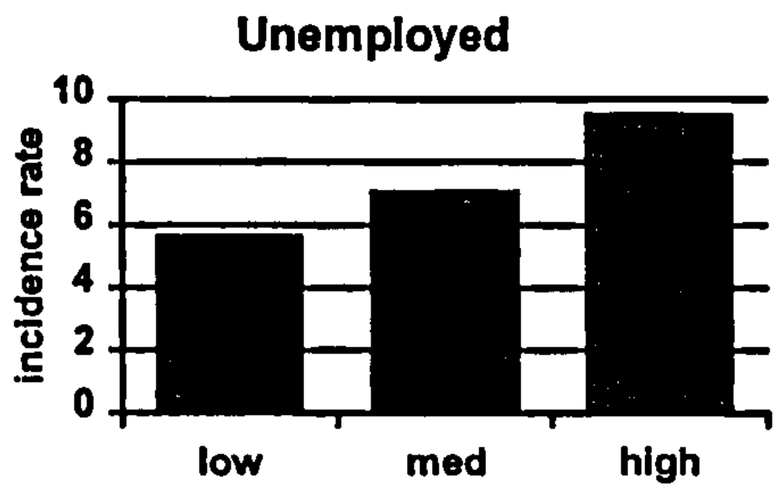
For meningitis cases a similar picture was observed in the pre-conjugate vaccine era with only lack of a car demonstrating a slight gradient. With the exception of one variable, overcrowding, figure 5.8 shows that all other components of the Townsend score demonstrated a consistent increase in incidence of disease with increasing deprivation.

Figure 5.7: Incidence rates for invasive *H influenzae* disease for components of the Townsend deprivation score in the WMHR, 1990-94

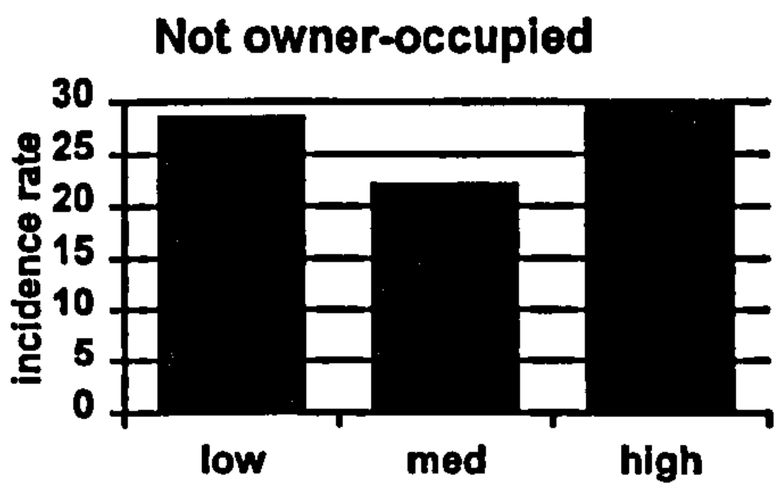
Pre-Hib conjugate vaccine: 1990-92	Post-Hib conjugate vaccine: 1992-94



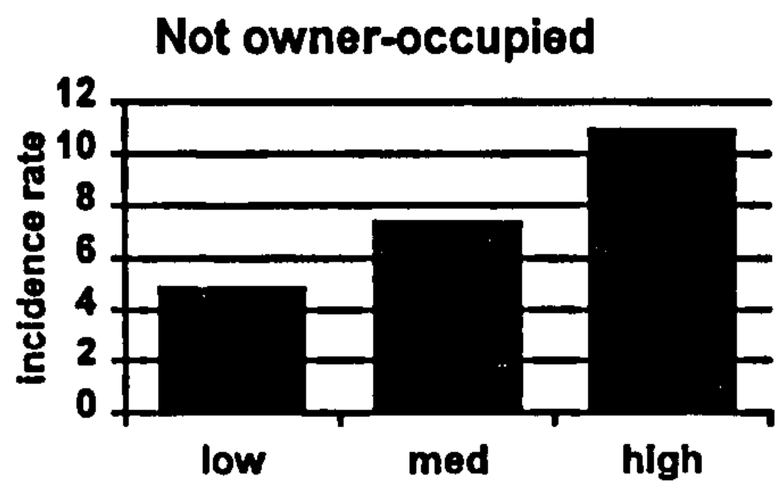
chi-square for linear trend = 0.19; p = 0.66



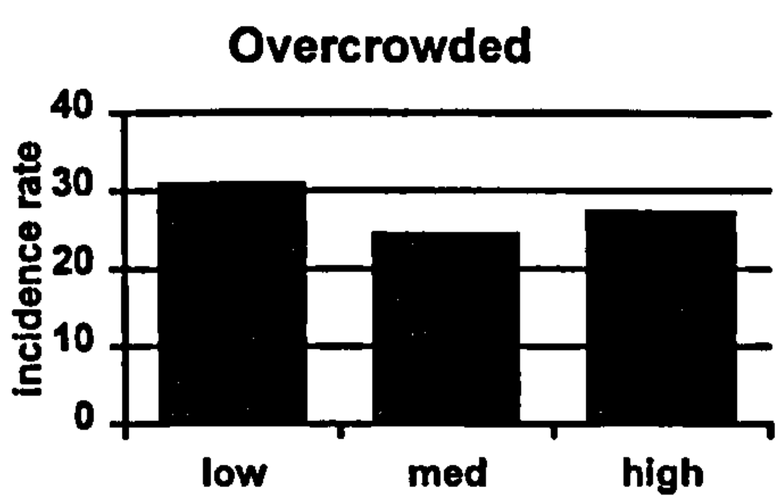
chi-square for linear trend = 2.37; p = 0.12



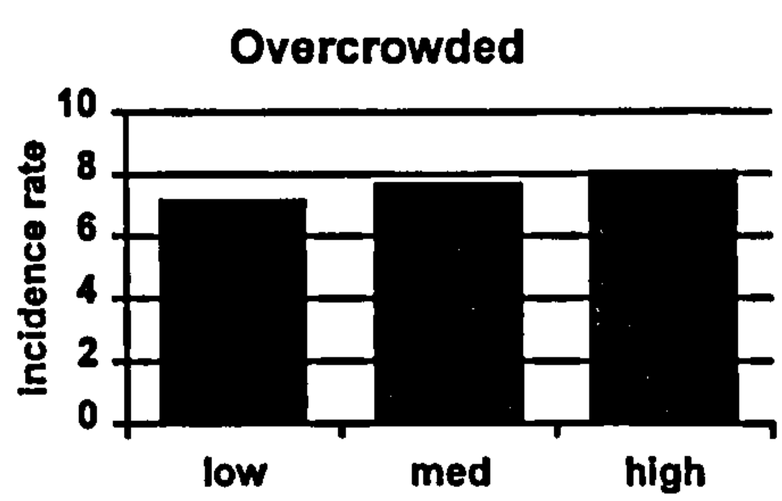
chi-square for linear trend = 0.11; p = 0.74



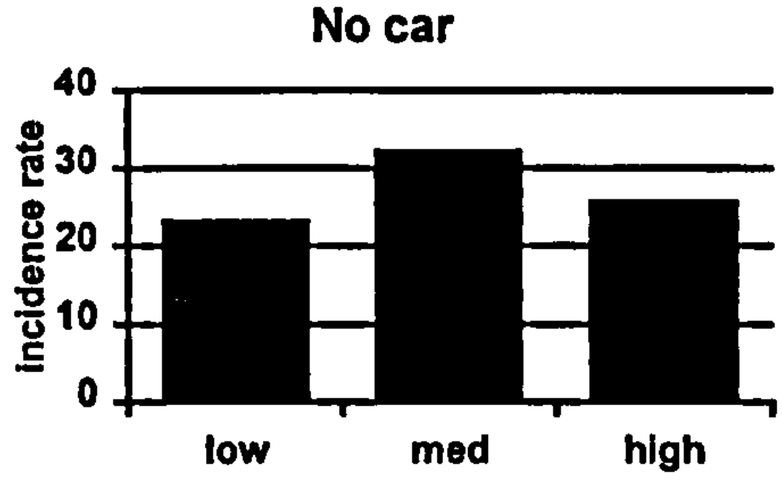
chi-square for linear trend = 5.02; p = 0.0025



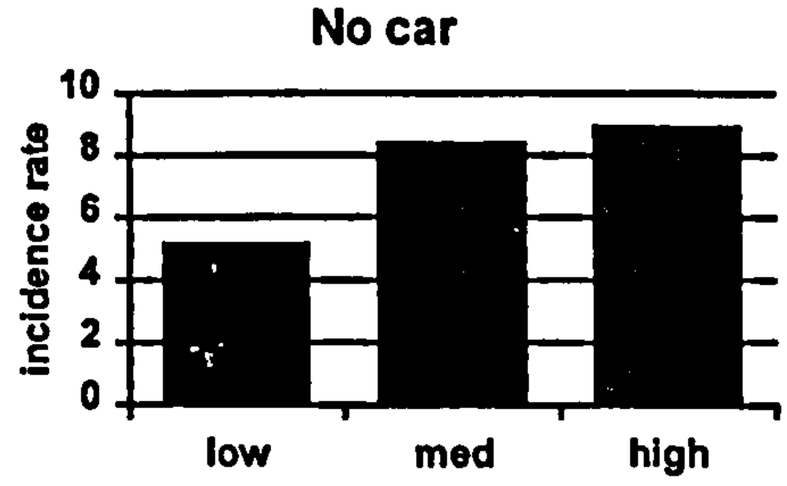
chi-square for linear trend = 0.30; p = 0.58



chi-square for linear trend = 0.12; p = 0.73



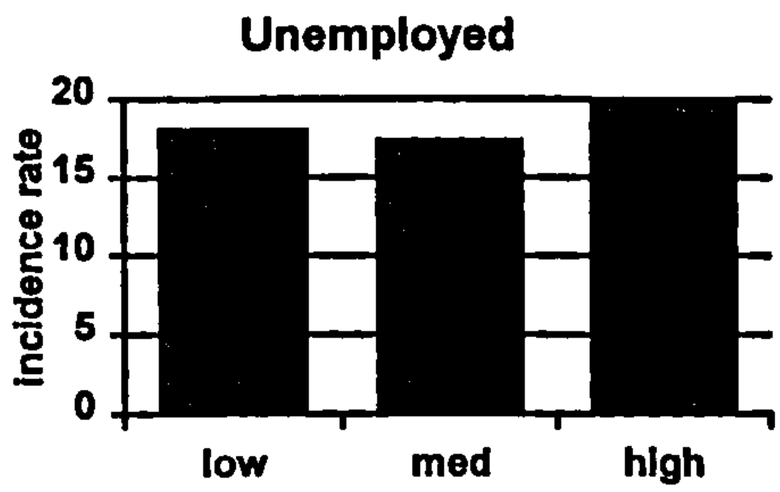
chi-square for linear trend = 0.13; p = 0.72



chi-square for linear trend = 2.00; p = 0.16

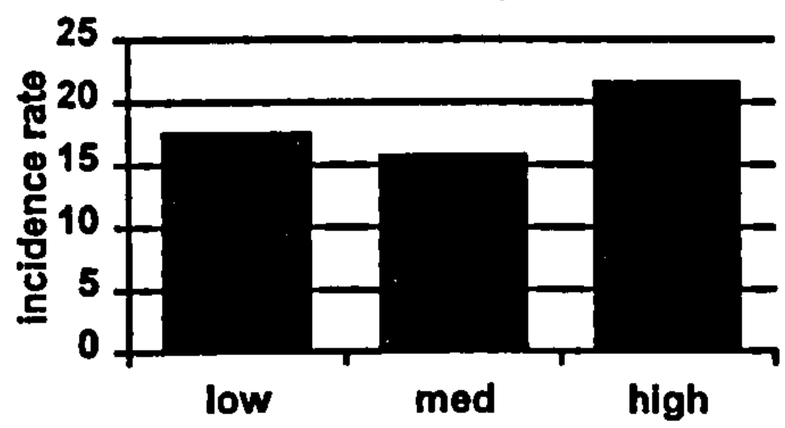
Figure 5.8: Incidence rates for *Haemophilus influenzae* meningitis for components of the Townsend deprivation score in the WMHR, 1990-94

Pre-Hib conjugate vaccine: 1990-92	Post-Hib conjugate vaccine: 1992-94

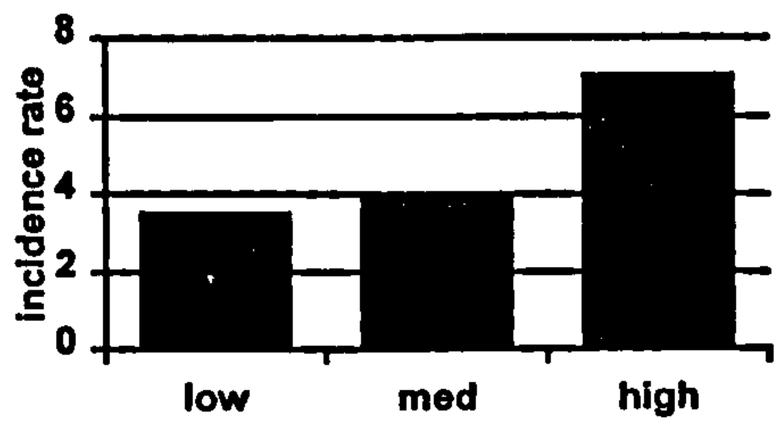


chi-square for linear trend = 0.23; p = 0.63

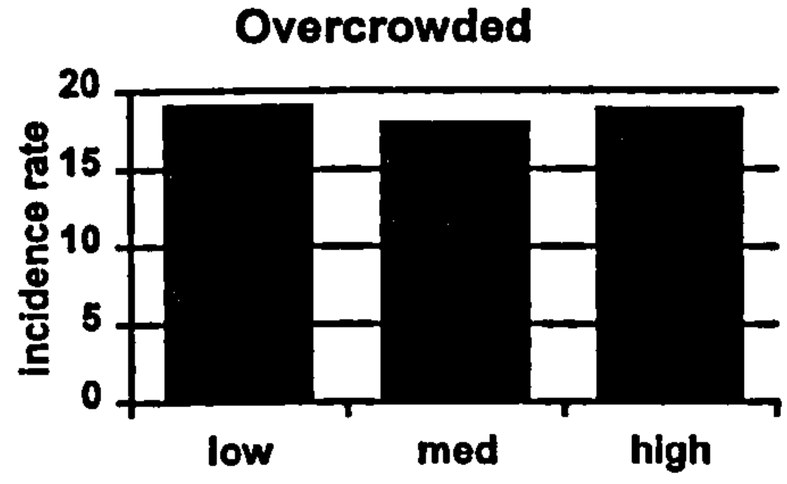
chi-square for linear trend = 0.79; p = 0.37



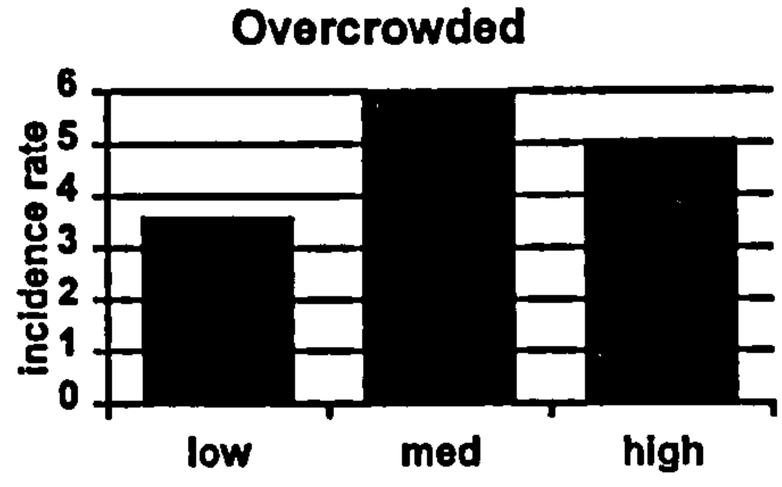
chi-square for linear trend = 1.17; p = 0.28



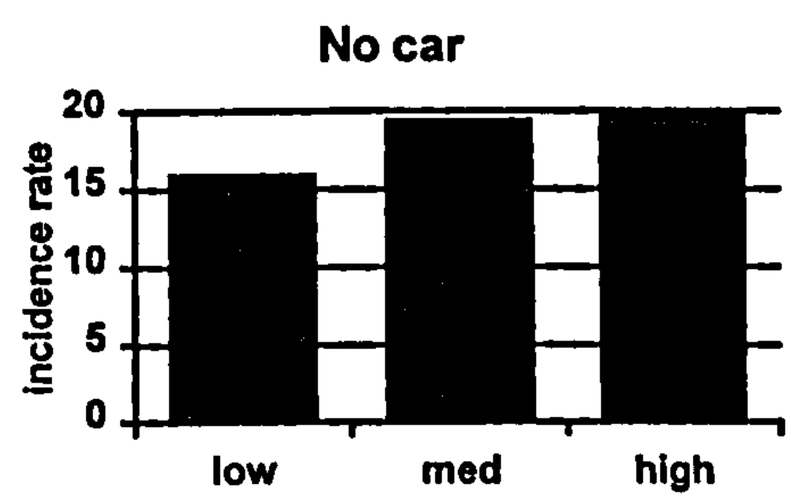
chi-square for linear trend = 3.24; p = 0.072



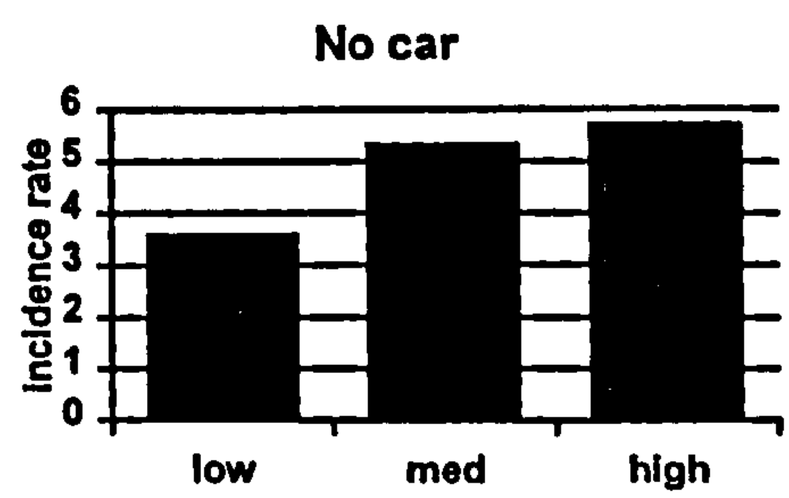
chi-square for linear trend = 0.000; p = 0.99



chi-square for linear trend = 0.30; p = 0.59



chi-square for linear trend = 0.79; p = 0.37



chi-square for linear trend = 0.98; p = 0.32

5.4.2.3 Other socioeconomic variables

For all invasive *H influenzae* diseases figure 5.9 shows that in the period prior to the introduction of Hib conjugate vaccine, population density was significantly associated with disease. However, the gradient was contrary to that seen previously, with increasing attack rates from high to low areas of population density.

A similar trend, although not reaching conventional levels of significance is seen when the proportion of children in the population are examined. Local movers show a gradient in the opposite direction, whilst all movers and lone parents did not show any gradient.

As with components of the Townsend deprivation score, there was a change in trend for all the census indicators following the introduction of Hib conjugate vaccine. Gradients are seen for most of the variables, except child population and lone parents. Population density and all movers demonstrated marked trends which were statistically significant.

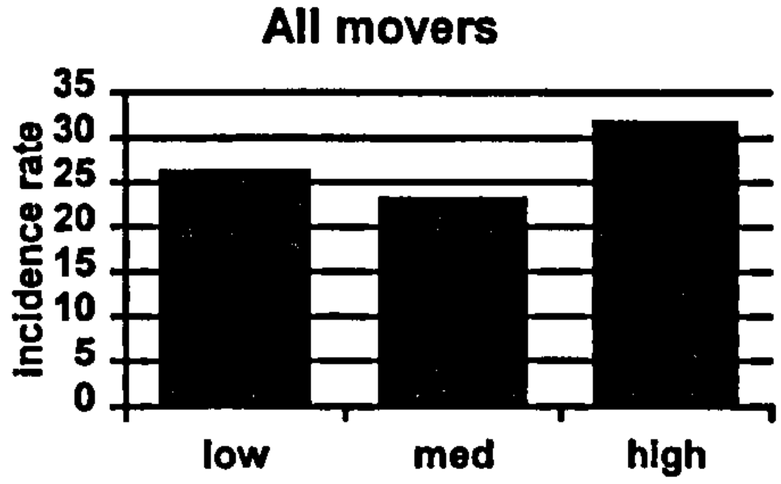
Haemophilus meningitis cases were analysed separately and gradients were seen for a number of variables (figure 5.10). The incidence of *Haemophilus* meningitis for child population and population density decreased with increasing deprivation and a significant trend was seen with population density in the pre-vaccine era. Other variables showed no trend in incidence during the same time period.

For most of the indicators examined a disease gradient was seen (figure 5.10) following the introduction of Hib conjugate vaccine. Both types of migration showed marked trends in incidence of disease from high to low and both were

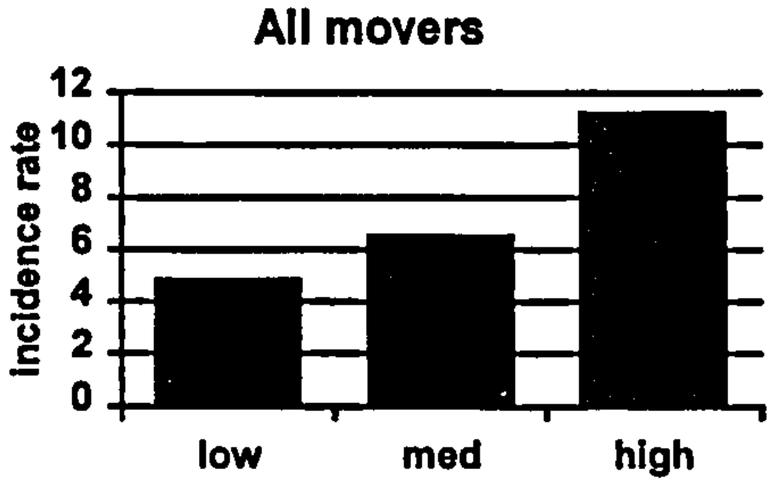
statistically significant. *Haemophilus* meningitis rates for population density continued to increase from high to low areas of deprivation and just failed to reach conventional levels of significance in the second period of the study. The variables lone parent and child population showed no trend in incidence.

Figure 5.9: Incidence rates for invasive *Haemophilus influenzae* disease for selected census variables in the WMHR, in the pre-Hib conjugate vaccine period 1990-94

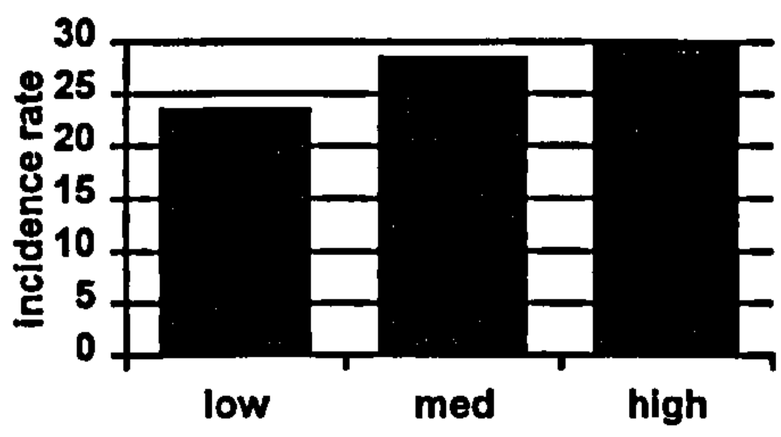
Pre-Hib conjugate vaccine: 1990-92	Post-Hib conjugate vaccine: 1992-94



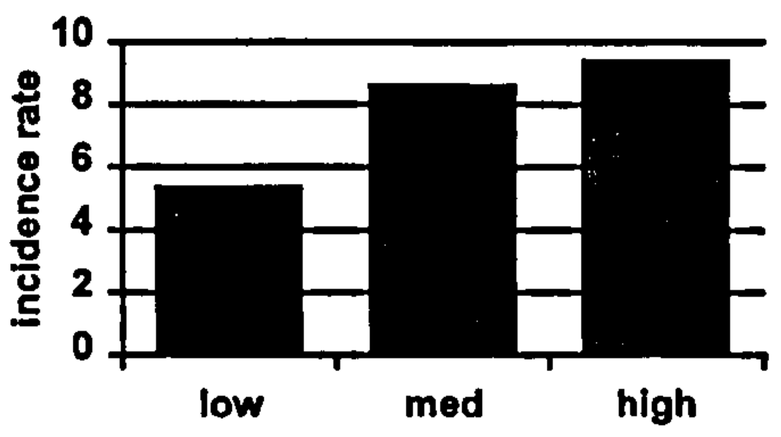
chi-square for linear trend = 1.49; p = 0.22



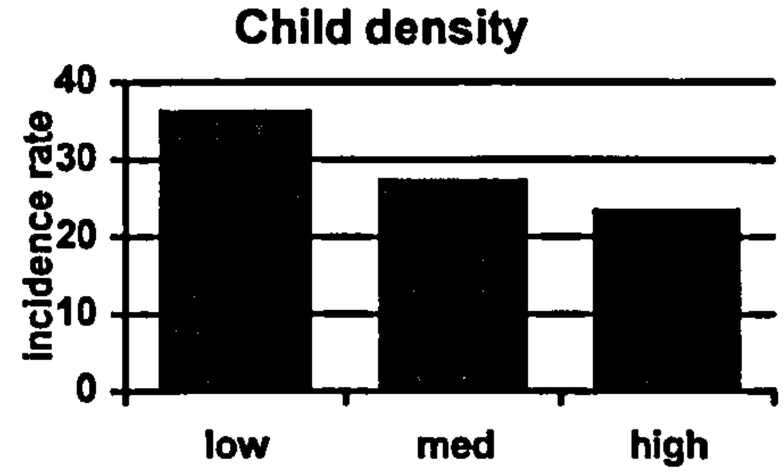
chi-square for linear trend = 6.23; p = 0.013



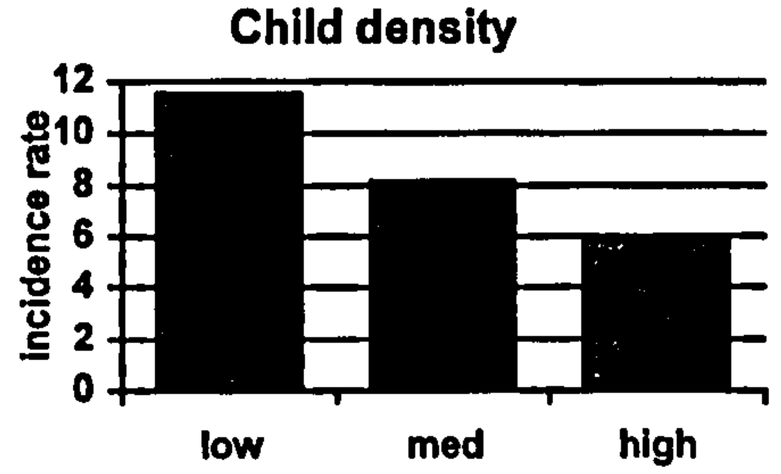
chi-square for linear trend = 1.54; p = 0.21



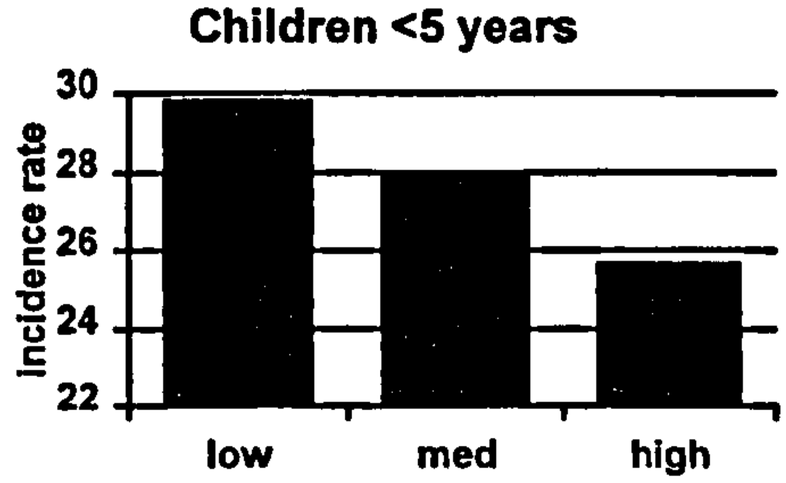
chi-square for linear trend = 2.38; p = 0.12



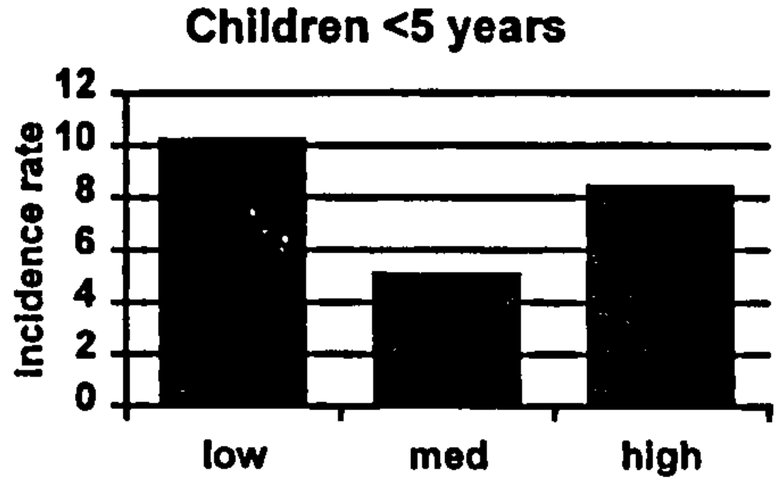
chi-square for linear trend = 5.69; p = 0.017



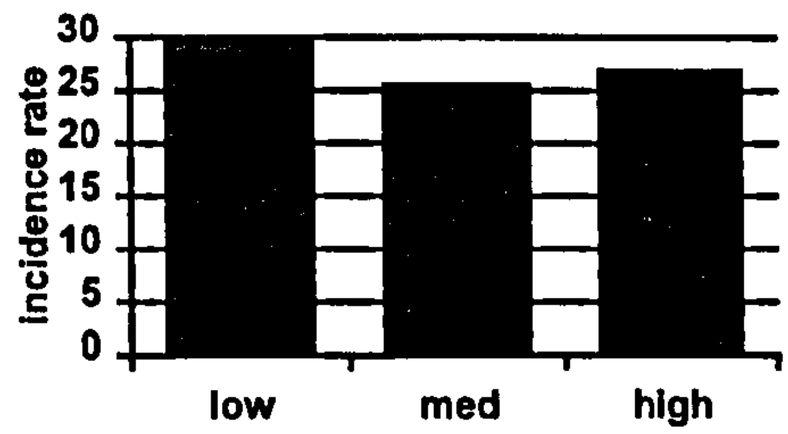
chi-square for linear trend = 4.27; p = 0.039



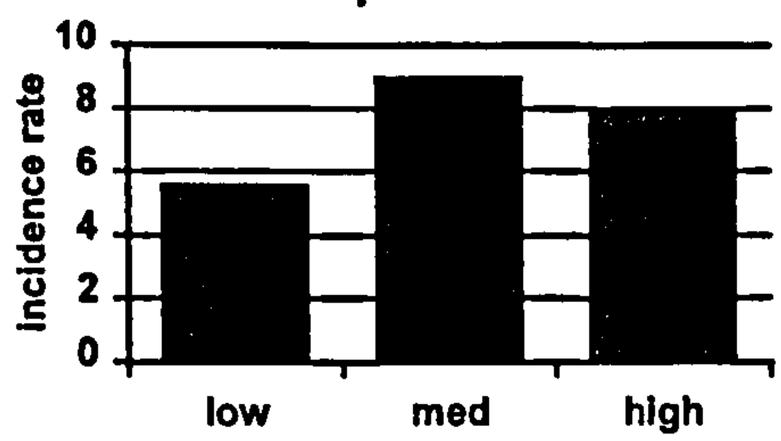
chi-square for linear trend = 0.66; p = 0.42



chi-square for linear trend = 0.001; p = 0.98



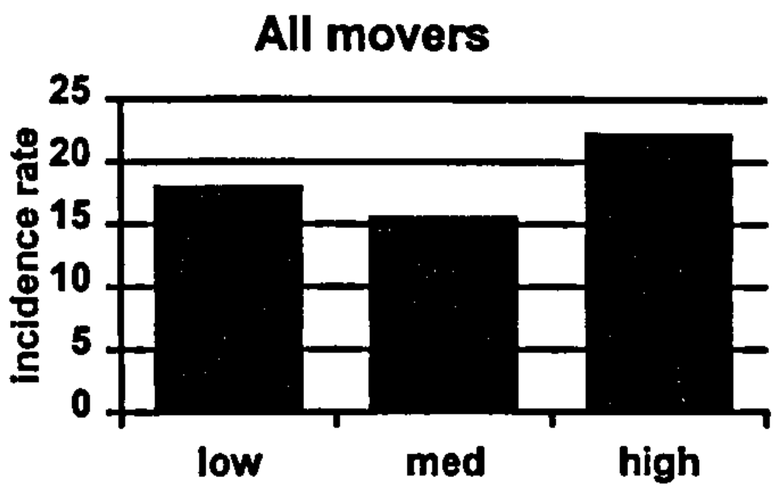
chi-square for linear trend = 0.19; p = 0.66



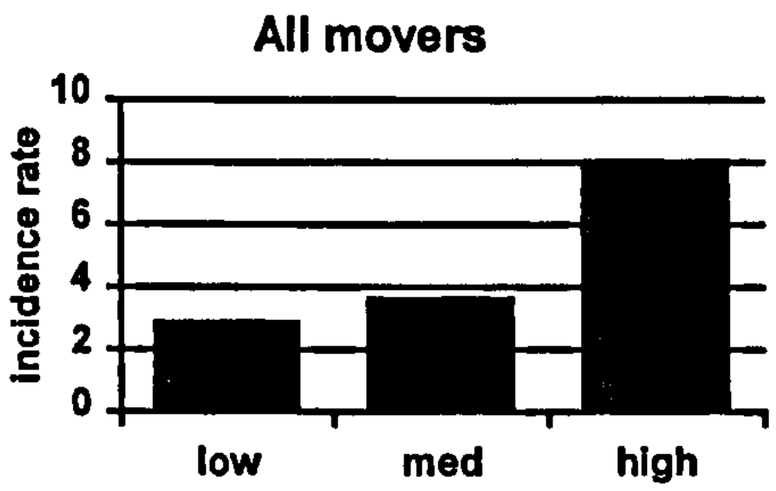
chi-square for linear trend = 0.50; p = 0.48

Figure 5.10: Incidence rates for *Haemophilus influenzae* meningitis for selected census variables in the WMHR, in the pre-Hib conjugate vaccine period, 1990-94

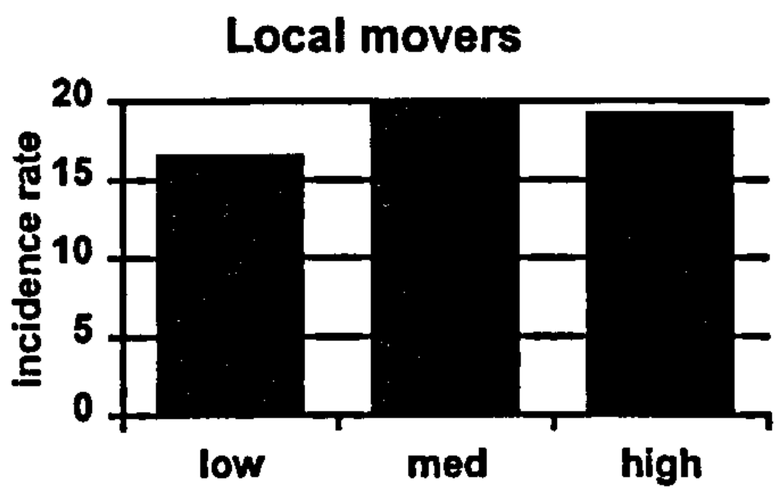
Pre-Hib conjugate vaccine: 1990-92	Post-Hib conjugate vaccine: 1992-94



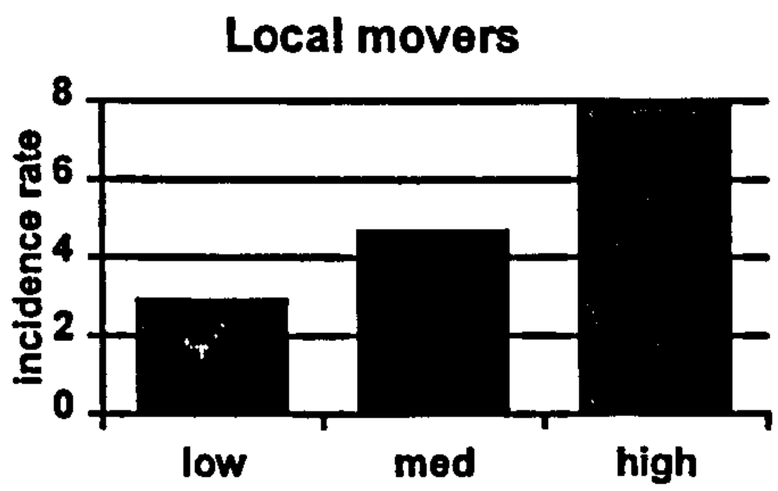
chi-square for linear trend = 1.23; p = 0.27



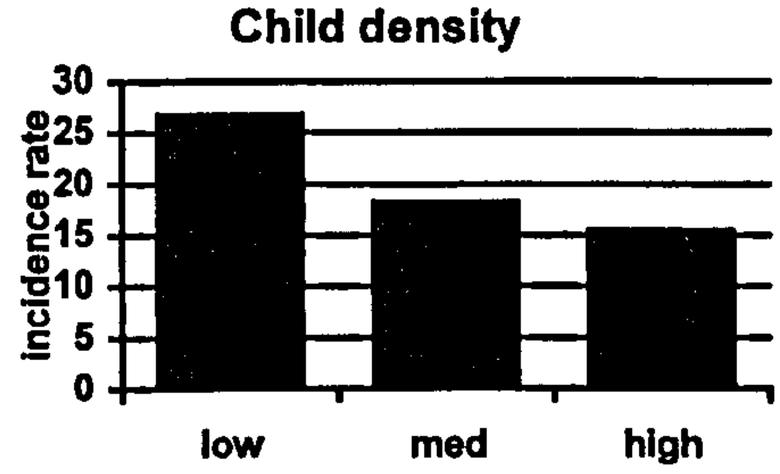
chi-square for linear trend = 6.25; p = 0.012



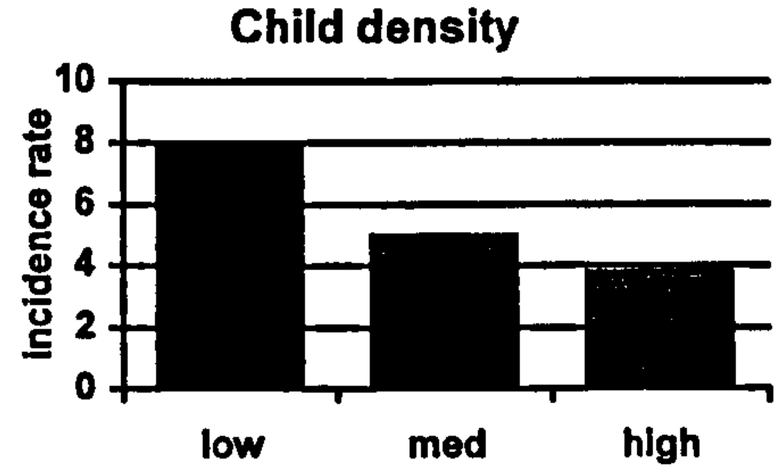
chi-square for linear trend = 0.47; p = 0.49



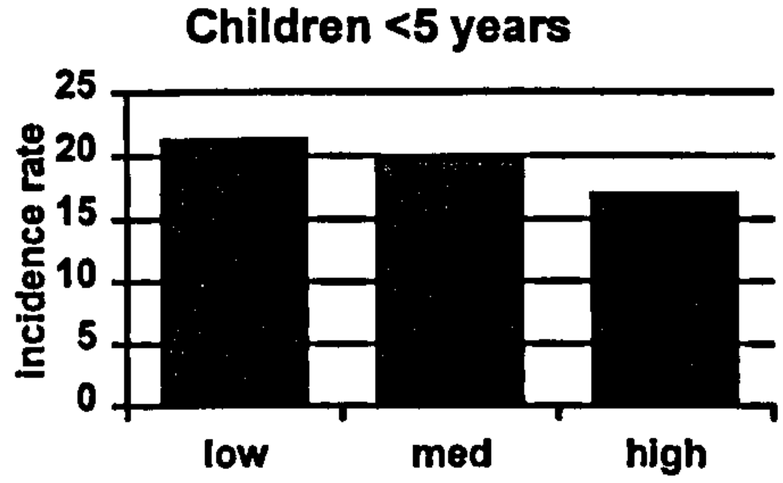
chi-square for linear trend = 5.42; p = 0.020



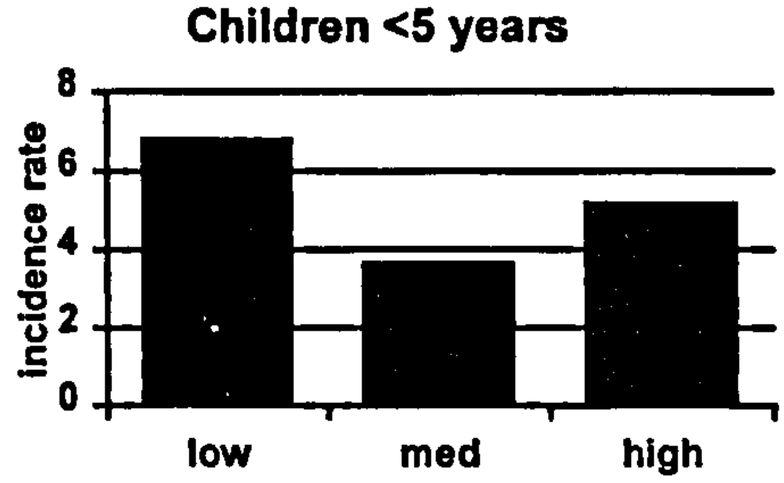
chi-square for linear trend = 6.18; p = 0.013



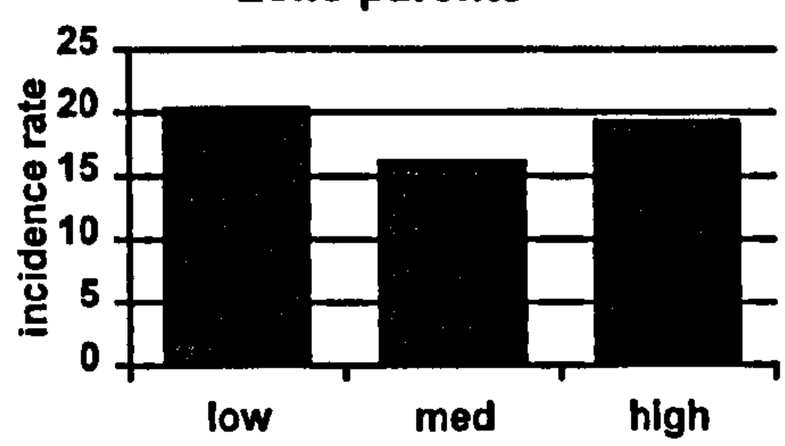
chi-square for linear trend = 3.21; p = 0.073



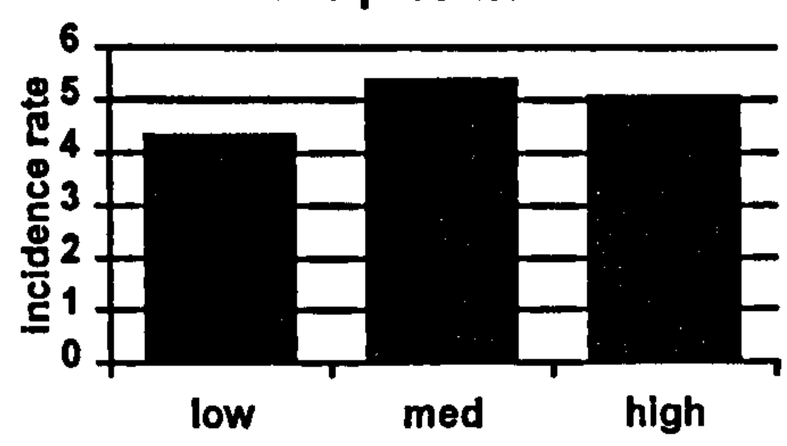
chi-square for linear trend = 1.14; p = 0.29



chi-square for linear trend = 0.10; p = 0.75



chi-square for linear trend = 0.004; p = 0.95



chi-square for linear trend = 0.076; p = 0.78

5.4.2.4 KEY POINTS FROM SUB-SECTION 5.4.2

- ❑ Using the GIS technique, 95% of postcodes were matched to enumeration districts.
- ❑ More cases of disease seen in the most deprived EDs.
- ❑ Children in areas of low deprivation were at significantly less risk compared to children from other areas.
- ❑ Living in areas of high deprivation was associated with a number of factors including being underweight on admission, being of SA origin and suffering SNHL.
- ❑ Fewer children with meningitis who lived in areas of high deprivation were asked to, or attended follow-up.
- ❑ Children with meningitis living in areas of high deprivation were significantly more likely to have SNHL.
- ❑ Difference in incidence of disease were seen between high and low areas of deprivation in both time periods. The difference increased from 18% in the pre-conjugate vaccine period to 48% in the post-vaccine era.
- ❑ Gradients were not seen for the four components of the Townsend material deprivation score before the introduction of Hib conjugate vaccine. In the post-vaccine era gradients which increased from low to high were seen for all components.
- ❑ Areas with a high proportion of non-owner occupiers was significantly associated with increased disease risk in the post-conjugate vaccine period.
- ❑ Population density was associated with disease risk but the gradient increased from high to low.
- ❑ High areas of migration was significantly associated with disease in the post-vaccine period.
- ❑ Most of the socioeconomic variables examined showed trends in the post-conjugate vaccine period.

5.4.3 Physical environment

5.4.3.1 Geographic distribution

District incidence rates

The district or health authority (HA) of residence was determined using the postcode recorded at the time of admission to hospital. The average annual incidence rate of invasive *H influenzae* disease in children according to HA of residence is shown in table 5.18 and figure 5.11. The table shows that two districts had incidence rates significantly different from that of the WMHR during the pre-conjugate vaccine period. Significant differences can also be seen between the lowest, South Warwickshire and a number of other districts.

Following the introduction of the vaccine, the majority of Health Authorities experienced a fall in the incidence of invasive *H influenzae* disease of between 42%-100%. One exception to this was Worcester HA with a 67% increase in its incidence rate in the two year period immediately following introduction of the vaccine. This may have been caused by an 'outbreak' in 1993 when four cases were identified over a 3 month period shortly after the vaccine was introduced. These four cases were found to be clustered in time, with the first and second case separated by 35 days, the second and third by 15 days and the third and fourth by 4 days.

Despite the rapid fall in disease incidence in the period after Hib conjugate vaccine was introduced, only 4 health authorities experienced significant reductions in the incidence of disease. These were West Birmingham, Solihull, Shropshire and Bromsgrove and Redditch.

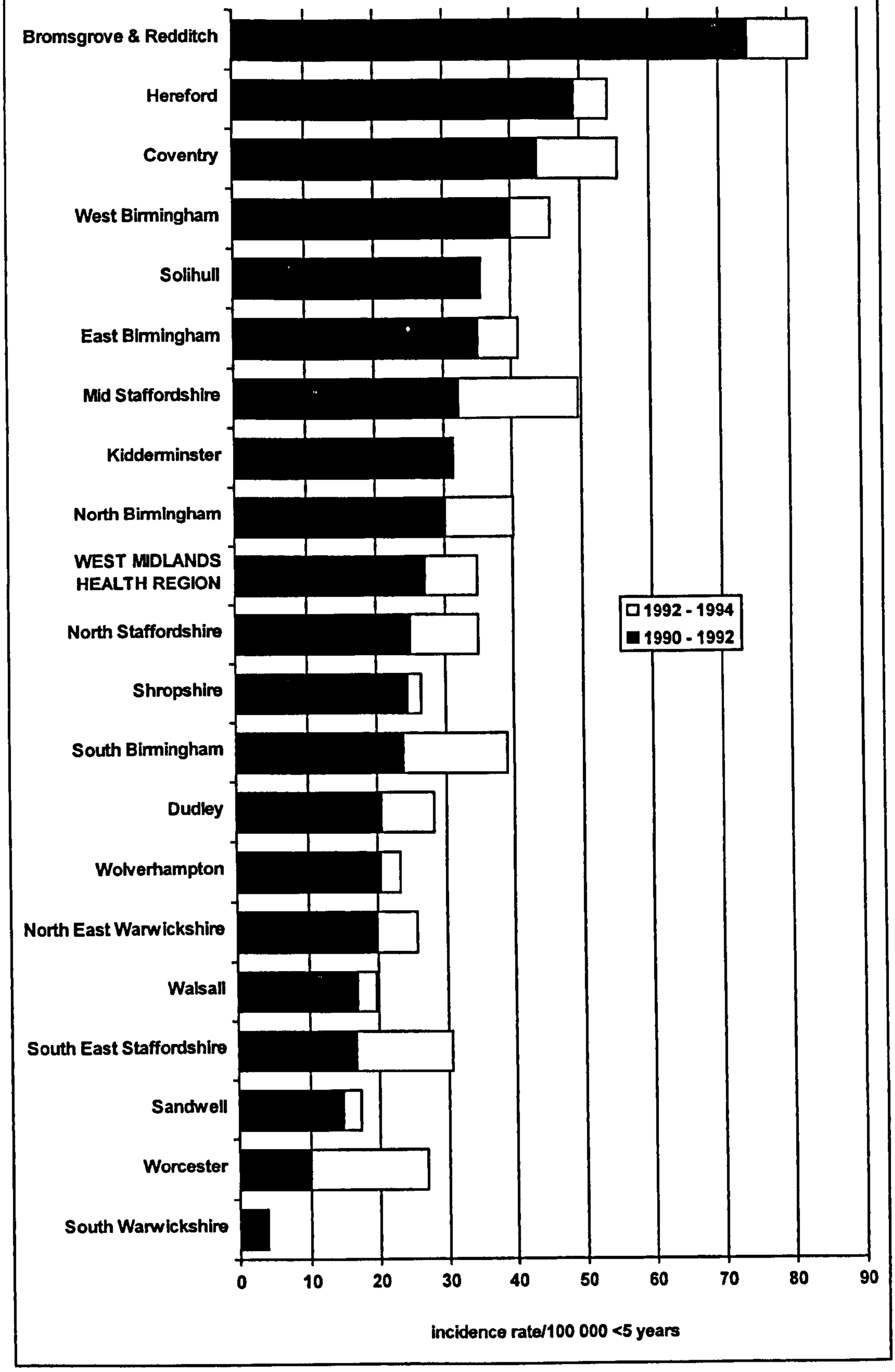
Table 5.18: Disease specific annual incidence rates of invasive *Haemophilus influenzae* disease before and following the introduction of Hib conjugate vaccine in the WMHR, 1990-1994

Health Authority	Pre-Hib conjugate vaccine		Post-Hib conjugate vaccine	
	Cases	Incidence rate* (95% CI)	Cases	Incidence rate* (95% CI)
Bromsgrove & Redditch	17	**74.2 (43.2 - 118.7)**	2	8.7 (0.9 - 31.4)
Hereford	10	49.2 (23.6 - 90.6)	1	4.9 (0.1 - 27.1)
Coventry	19	43.9 (26.3 - 68.6)	5	11.6 (3.7 - 27.0)
West Birmingham	14	40.0 (22.0 - 67.2)	1	2.9 (0.09 - 15.7)
Solihull	9	35.6 (16.2 - 67.7)	0	0.0 (0.0 - 14.6)
East Birmingham	12	35.1 (18.2 - 61.5)	2	5.9 (0.6 - 21.1)
Mid Staffordshire	13	32.2 (17.1 - 55.1)	7	17.4 (6.9 - 35.7)
Kidderminster	4	31.4 (8.6 - 80.1)	0	0.0 (0.0 - 29.1)
North Birmingham	6	30.1 (11.0 - 65.7)	2	10.0 (1.0 - 36.1)
North Staffordshire	15	24.9 (14.0 - 41.0)	6	10.0 (3.7 - 21.8)
Shropshire	13	24.5 (13.0 - 41.8)	1	1.9 (0.06 - 10.4)
South Birmingham	14	23.8 (13.1 - 40.0)	9	15.3 (7.0 - 29.1)
Dudley	8	20.5 (9.0 - 40.4)	3	7.7 (1.5 - 22.5)
Wolverhampton	7	20.4 (8.2 - 42.0)	1	2.9 (0.09 - 16.0)
North East Warwickshire	7	19.9 (8.0 - 41.0)	2	5.7 (0.06 - 20.5)
Walsall	6	16.9 (6.2 - 36.9)	1	2.8 (0.08 - 15.5)
South East Staffordshire	6	16.7 (6.1 - 36.5)	5	13.9 (4.5 - 32.6)
Sandwell	6	14.8 (5.4 - 32.3)	1	2.5 (0.07 - 13.6)
Worcester	3	10.1 (2.0 - 29.5)	5	16.8 (5.4 - 39.3)
South Warwickshire	1	**3.9 (0.1 - 21.3)**	0	0.0 (0.0 - 14.3)
WMHR	190	27.1 (23.3 - 31.2)	54	7.7 (5.8 - 10.0)

* Incidence per 100 000 children <5 years of age

Figures in bold indicate incidence rates significantly different from that of the WMHR

Figure 5.11: Incidence rates of invasive *Haemophilus influenzae* disease in the WMHR by health authority of residence in the pre- and post-Hib conjugate vaccine periods



Urban/rural districts

The definition of mainly urban and mainly rural districts has been given in section 4.5.5.2. The overall incidence rates for the mainly urban and mainly rural districts were similar, 17.5/100 000 and 17.2/100 000 respectively, over the four years of the study. Table 5.19 shows that in both years of the post-conjugate vaccine period the incidence of disease was slightly higher in the rural areas compared to the urban areas.

Table 5.19: Incidence* of invasive *Haemophilus influenzae* disease by geographic area and study year, WMHR 1990-1994

Study year	Mainly urban		Mainly rural	
	Cases	Incidence rate (95% CI)	Cases	Incidence rate (95% CI)
October 1990-September 1991	49	26.8 (19.8 - 35.4)	45	26.8 (19.5 - 35.8)
October 1991-September 1992	52	28.4 (21.2 - 37.3)	44	26.2 (19.0 - 35.2)
October 1992-September 1993	22	**12.0 (7.5 - 18.2)**	26	15.5 (10.1 - 22.7)
October 1993-September 1994	3	**1.6 (0.3 - 4.8)**	3	**1.8 (0.4 - 5.2)**

* Incidence per 100 000 children <5 years of age
Figures in bold indicate incidence rates significantly different from that of the previous year

Compared to rural areas, in urban areas the incidence of disease was significantly lower in the first year after the vaccine was introduced. The rural areas did not experience a significant decrease until the second post-conjugate vaccine year. Comparable results were obtained when *H influenzae* meningitis was analysed separately (results not shown).

Table 5.20 compares children from the WMMC (urban districts) with children from the districts classified as mainly rural, for several demographic, social and clinical factors.

Table 5.20: Comparison of selected variables for cases of invasive *Haemophilus influenzae* disease in the WMHR by geographic area of residence, 1990-1994

Variable	WMMC* (n=126)	Other districts† (n=118)	Odds ratio (95% CI)	p value
Study period:				
1990-1992	101	89	1.32 (0.69-2.52)	0.46
1992-1994	25	29		
Disease category:				
meningitis	79	86	0.63 (0.35-1.12)	0.12
non-meningitic	47	32		
Ethnic group				
SA	21	1	**23.40 (3.09-176.99)**	**<0.0001**
NSA	105	117		
Deprivation category:				
high	79/94	31/72	**6.97 (3.20-15.37)**	**<0.0001**
low	15/94	41/72		
Large family (> 2 siblings):				
yes	78/100	84/90	**0.25 (0.10-0.66)**	**0.0056**
no	22/100	6/90		
Lone parent:				
yes	20	8	2.28 (0.90-5.95)	0.090
no	101	92		
Immunisation status‡:				
age-appropriate	85/106	82/97	0.74 (0.34-1.63)	0.53
incomplete/none	21/106	15/97		
Dexamethasone given:				
yes	51/78	38/83	**2.24 (1.13-4.45)**	**0.019**
no	27/78	45/83		
Follow-up given:				
yes	90/118	98/114	0.52 (0.25-1.09)	0.086
no	28/118	16/114		
Hearing test requested¶:				
yes	57/75	68/78	0.47 (0.18-1.17)	0.11
no	18/75	10/78		
Attended hearing test¶:				
yes	48/57	51/68	1.78 (0.67-4.81)	0.30
no	9/57	17/68		
Failed hearing test¶:				
yes	8	2	4.54 (0.91-22.75)	0.090
no	37	42		

* 'mainly urban' districts
† 'mainly rural' districts
‡ 1990 - 1992 (primary immunisation status in the pre-Hib conjugate vaccine period)
¶ This analysis only includes cases of meningitis
Figures in bold indicate a statistically significant result

Living in the WMMC was significantly associated with being of SA origin, coming from a large family and experiencing deprivation. There were no gender or age differences, nor were there differences seen when nutritional status, anaemia and chronic illness were compared in these children.

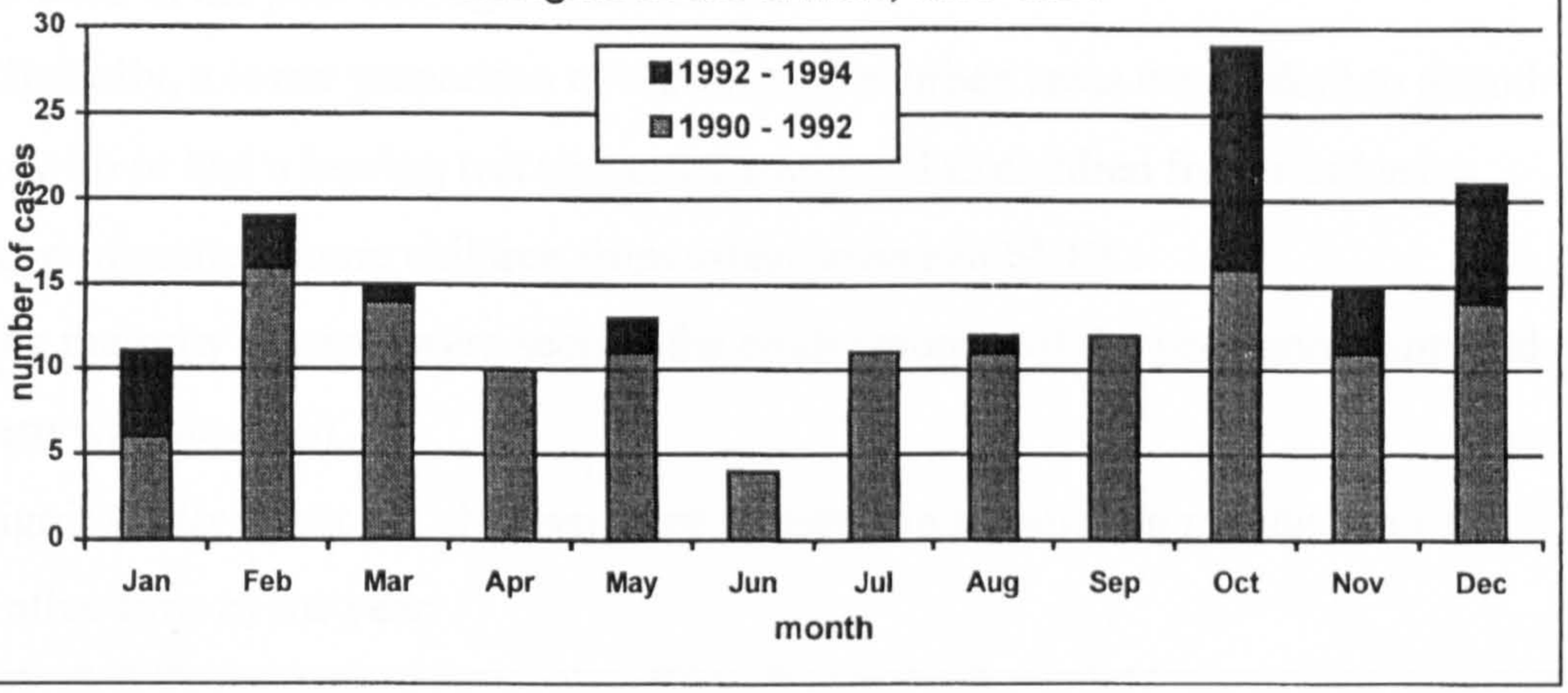
5.4.3.2 Seasonal variation

Cases of invasive *H influenzae* disease were seen throughout the year, but were more common in the colder months. The majority of cases (144 of 258, 56%) were seen between October and February, which also accounted for the highest number of fatalities (5 of 8).

A statistically significant association was seen when season of onset and ethnic group were examined. During the autumn months significantly fewer SA children were admitted to hospital than at other times of the year (OR=0.09, 95% CI=0.01 to 0.66; p=0.0018).

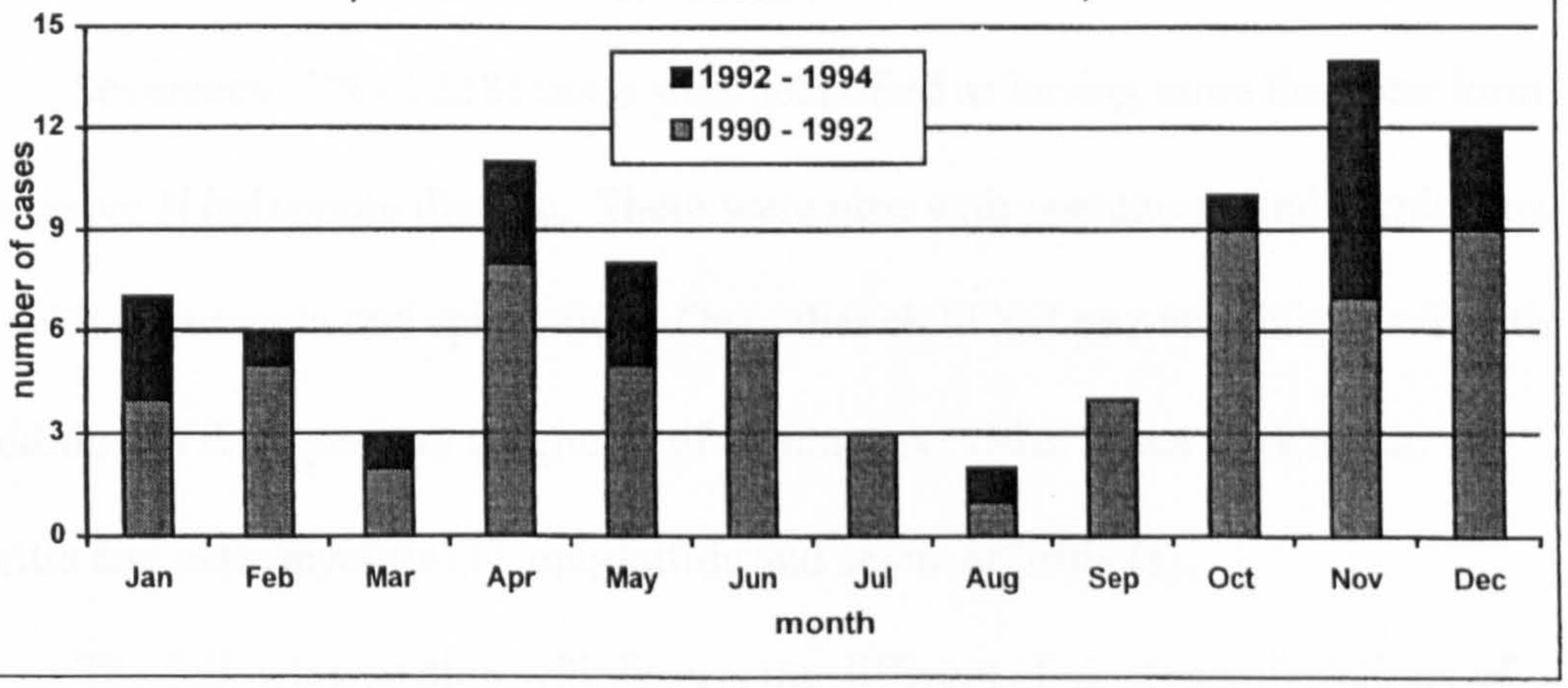
When the relationship between age of admission and season of onset was examined, children admitted during the summer months were significantly younger than those admitted during cooler months of the year (p=0.039). The children in the former group had a mean age of 14.2 months (median 11.5 months, range 0-36) compared to a mean age of 19.3 months (median 15.0, range 0-59 months).

Figure 5.12: Seasonal distribution of *Haemophilus influenzae* meningitis in the WMHR, 1990-1994



Evaluation by disease entity (figures 5.12 and 5.13) showed the occurrence of bimodal patterns for both meningitis, which peaked in mid-autumn and late winter, and non-meningitic diseases which peaked in late autumn and mid-spring.

Figure 5.13: Seasonal distribution of non-meningitic invasive *Haemophilus influenzae* disease in the WMHR, 1990-1994



5.4.3.4 KEY POINTS FROM SUB-SECTION 5.4.3

- ❑ Wide differences in incidence rates were observed for the different health authorities in the WMHR in both the pre- and post-vaccine periods.
- ❑ All districts except one, experienced a reduction in disease incidence in the post-vaccine period.

- ❑ Significant reduction in disease incidence seen in the urban areas before the rural areas in the post-conjugate vaccine era.
- ❑ Clinically, a lower proportion of children from urban areas were asked to attend follow-up or had a hearing test requested compared to children from rural areas.
- ❑ Proportionately more children from urban areas had SNHL.
- ❑ The majority of cases were seen in the colder months of the year, and a bimodal pattern was observed.
- ❑ Significantly fewer SA children were admitted in the autumn months than at any other time of the year.

5.5 CLINICAL FEATURES

5.5.1 Spectrum of disease

The distribution of disease entities was similar in both study periods with meningitis and epiglottitis responsible for the majority of cases (table 5.21).

Seventeen (7% of 258) cases were identified as having more than one form of invasive *H influenzae* disease. There were nine with pneumonia and meningitis, five with pneumonia and epiglottitis. One other child had pneumonia and cellulitis in addition to their primary diagnosis of meningitis. Other cases were septic arthritis and osteomyelitis (1), epiglottitis and septic arthritis (1).

The following section will discuss the different clinical manifestations of invasive *H influenzae* disease.

Table 5.21: Disease specific annual incidence rates of invasive *Haemophilus influenzae* disease before and following the introduction of Hib conjugate vaccine in the WMHR, 1990-1994

Disease entity	Pre-Hib conjugate vaccine (October 1990-September 1992)		Post-Hib conjugate vaccine (October 1992-September 1994)	
	Cases (%)	Incidence rate* (95% CI)	Cases (%)	Incidence rate* (95% CI)
Meningitis	136 (68)	19.4 (8.1-22.9)	36 (61)	**5.1 (3.6-7.1)**
Epiglottitis	22 (11)	3.1 (2.0-4.7)	10 (17)	1.4 (0.7-2.6)
Septicaemia	9 (5)	1.3 (0.6-2.4)	3 (5)	0.4 (0.09-1.3)
Cellulitis	14 (7)	2.0 (1.1-3.3)	1 (2)	**0.1(0.004-0.8)**
Pneumonia	10 (5)	1.4 (0.7-2.6)	3 (5)	0.4 (0.09-1.3)
Septic arthritis	4 (2)	0.6 (0.2-1.5)	3 (5)	0.4 (0.09-1.3)
Osteomyelitis	1 (0.5)	0.1 (0.004-0.8)	1 (2)	0.1(0.004-0.8)
Neonatal sepsis†	1 (0.5)	0.1 (0.004-0.8)	2 (3)	0.3 (0.03-1.0)
Other	2 (1)	0.3 (0.03-1.0)	0 (0)	0.0 (0.0-0.5)

* Incidence per 100 000 children <5 years of age

† Average annual number of live births in 1991 (74 210) used as the denominator

Figures in bold indicate incidence rates significantly different from that of the previous study period

5.5.1.1 Meningitis

Meningitis was the most common disease entity each year and accounted for 172 of 258 (67%) cases. During the four year study period, the incidence of *Haemophilus* meningitis in children aged 0-4 years fell 92% from 17.7 cases per 100 000 in the first year of the study to 1.38 cases per 100 000 in the final year of the study.

The mean age at presentation for non-neonatal cases was 17.3 months (median 13.0, range 1-59 months). During the 1990/92 period, 46% (62 of 136) of cases were under 12 months of age, and the mean age at presentation was 17 months (median 12, range 1-58 months). In the post-vaccine period the proportion aged 12 months or less fell to 36% (12 of 36), and the mean age increased to 18.2 months (median 15.5, range 1-59). When the mean age of the groups were compared for the two periods of the study, the resultant probability value (p=0.618) was not statistically significant.

Of 133 cases of meningitis fulfilling the case definition for anaemia used in this study, 52 (39%) were found to be anaemic on admission to hospital. For non-fatal cases of meningitis, the average length of hospital stay was 11.7 days (median 11 days), and ranged between 0-76 days. One child, who was very ill on admission, spent less than 24 hours before being transferred to another hospital within the region. Further information on this case was not available as the medical notes were incomplete. The child who spent 76 days in hospital was a seven month old boy who was hypertonic on admission and had seizures within 24 hours of admission. He developed a hydrocephalus which required a shunting procedure, and subsequently developed seizures and brain damage.

Ten (6%) children with meningitis had concomitant pneumonia. One of these children had meningitis and pneumonia together with cellulitis, and was one of five deaths due to meningitis in this series. Children with meningitis who had more than one recognised site of infection were affected mainly in the pre-vaccine era (8 of 10), and were young boys of NSA origin. No child was seen with concomitant meningitis and epiglottitis.

Over a third (62 of 168, 37%) of meningitis cases received antibiotics prior to admission. Those who received pre-admission antibiotics had a mean age of 19.4 months (median 15.0 months, range 3-59 months), whereas those who did not had an average age of 15.7 months (median 11.5 months, range 0-59 months). This difference just failed to reach conventional levels of significance (p=0.076). There was a decrease in the number of children who received antibiotics before admission from 39% (52 of 134) in the first period of the study to 29% (10 of 34) in the post-conjugate vaccine period. This was not statistically significant (p=0.42).

Children with meningitis were more likely to have received antibiotics prior to admission (OR=2.17, 95% CI=1.13 to 4.17; p=0.018), and to be brought to hospital later (more than 24 hours following the onset of symptoms), than children with other types of invasive disease (OR=3.29, 95% CI=1.84 to 5.93; p<0.0001).

Resistance to ampicillin was encountered in 21 of 145 (15%) CSF isolates, and 20 of 107 (16%) blood specimens.

5.5.1.2 Epiglottitis

Epiglottitis was the second most common disease identified during the study period. The incidence of disease decreased 55% from 3.1 per 100 000 cases in 1990-92 to 1.4 in 1992-94. This decrease was not statistically significant.

The mean age at admission for epiglottitis was 28.9 months (median 27.5 months, range 10-59 months), with 41% (13 of 32) of cases aged 24 months or less, compared to 17.2 months for meningitis (median 13.0 months, range 0-59 months). The difference between the mean age in children with epiglottitis and those with meningitis was highly significant ($p<0.0001$).

Children aged 24-59 months were more at risk from epiglottitis (OR=5.02, CI=2.18 to 11.64; $p<0.0001$), while children aged less than 12 months were significantly less likely to have epiglottitis than any other invasive disease (OR=undefined, $p<0.0001$).

Analysis of the severity of this manifestation of invasive *H influenzae* disease indicated that cases of epiglottitis were more likely to be admitted within 24 hours of the onset of symptoms than those with non-epiglottic disease (OR=6.78, 95% CI=2.56 to 20.90; $p<0.0001$). Using intubation as a further measure of the severity of the disease in this series, 69% (22 of 32) of the cases were intubated. The average duration of intubation was 2 days (range 0-4 days). Respiratory arrest occurred in one child at the time of admission, the child was successfully resuscitated and suffered no long term sequelae. Eighteen (56%) children were admitted to ITU or its equivalent, for between 1 to 14 days (mean 2.3, median 2 days). The mean and median length of hospital stay were 5 days (range 1-13 days), with 63% of cases spending 5 days or less in hospital.

Children with epiglottitis were less likely to receive chemoprophylaxis than children with other invasive disease during admission or on discharge (OR=0.36, 95% CI=0.14 to 0.89; p=0.024), and were also less likely to receive follow-up (OR=0.10, 95% CI=0.04 to 0.23; p<0.0001).

Six of 32 (19%) had associated invasive *H influenzae* disease. Pneumonia was present in 5 children, while the remaining child, originally admitted with septic arthritis of the knee had developed epiglottitis in hospital.

There were no deaths in this group of children, and no documented sequelae at discharge or during follow-up.

Epiglottitis was observed mainly in the colder months of the year with 20 of 32 cases (63%) identified between October and February.

Of the 32 cases of epiglottitis seen 18 (56%), were serotype b. None of the ten children hospitalised in the post-vaccine era had been immunised with Hib conjugate vaccine prior to admission.

5.5.1.3 Cellulitis

Cellulitis was the most common non-meningitic disease after epiglottitis. The most common site for cellulitis was the periorbital area which accounted for 8 of 15 cases (53%). Other sites were the head and neck (4), and the lower (2) and upper limbs (1). Eight boys and 7 girls were affected and none had more than one site involved.

This manifestation of invasive *H influenzae* disease affected children aged 3-48 months (mean 14.3 months, median 10 months). The mean age of those with periorbital cellulitis differed from that of those with other areas affected.

Periorbital cellulitis was seen more often in children with a mean age of 16.4 months (median 13.0 months, range 6-48 months), whereas children with other areas affected had a mean age of 12.5 months (median 9.5, range 3-21 months). This difference was not significant (p=0.50).

The majority (9 of 15) of these children spent less than 5 days in hospital with the average length of stay being 4.5 days (median 4 days, range 3-8 days).

5.5.1.4 Pneumonia

Pneumonia on its own accounted for 5% (13 of 258) of all invasive disease in both the pre-vaccine and post-vaccine periods of the study. However the incidence rate fell by 71% in the two years following the introduction of the vaccine, from 1.4 per 100 000 to 0.4 in 1992/94.

Pneumonia was the most frequent disease entity associated with other invasive *H influenzae* disease, and amongst 17 cases identified with more than one disease entity, pneumonia was diagnosed in 15 (88%).

Children with pneumonia were mainly NSA (11 of 13) and boys (10 of 13). The two SA children with this disease entity were both girls. The mean age of children with this form of invasive *H influenzae* was 15.4 months (median 15 months, range 2-38 months).

Two of 13 children with pneumonia as the primary diagnosis died, and a further 2 deaths occurred in children who had *Haemophilus* meningitis and concomitant pneumonia.

Only one of the 13 isolates was serotyped, and this was type b. Of the ten isolates with antibiotic sensitivity results, none were ampicillin resistant.

5.5.1.5 Septicaemia

Twelve children in this series were noted to have positive blood cultures without an associated focal infection.

The median age of children in this group was 15 months (mean 23 months, range 2-58 months). Most of the children affected were less than 2 years old (9 of 12, 75%), with three cases occurring in children aged 51, 55 and 58 months.

Equal numbers of boys and girls were affected, giving a gender ratio of 1:1. The ratio for ethnic groups however was 3:1, with 9 children of NSA origin affected.

5.5.1.6 Septic arthritis

There were 8 sites identified in 7 cases. One child had two joints involved simultaneously, the left elbow and right shoulder. In this series, the larger joints were mainly involved with the upper (two sites each for the shoulder and elbow joints), and lower (two sites each for the knee and hip joints) extremities equally affected. All children recovered without any apparent disability.

An associated invasive *Haemophilus* infection was noted in one child who had osteomyelitis in addition to septic arthritis.

Children with an average age of 18 months (median 11 months, range 10-32 months) were affected with the majority of cases (4 of 7) occurring before 12 months of age. All cases were seen in children of NSA origin, and 5 girls were affected.

Septic arthritis required an average length of hospital stay of 12.7 days (median 7 days, range 4-39 days). This was reduced to 8.3 days when the child

with the longest hospital stay was excluded from the analysis. This child had incision and drainage of the hip and open reduction of the femoral head.

During hospitalisation five of the children had X-rays of the affected joints. Only one child had radiographic evidence of a bony abnormality.

5.5.1.7 Osteomyelitis

Osteomyelitis without an associated invasive *H influenzae* disease was seen in two children. One 12 month old boy had osteomyelitis of the humerus, while the second child, a 14 month old girl had osteomyelitis of the distal end of the tibia. Both children were of NSA origin.

There was no X-ray evidence of osteomyelitis in either of these children, however, a radionuclide scan suggested the diagnosis in one child. Diagnosis in the second child appeared to be based on blood culture and clinical signs and symptoms. At discharge both were well and there were no apparent long term sequelae.

5.5.1.8 Uncommon manifestations

Two less common manifestations of invasive *H influenzae* disease were encountered in this study. One was a case of bacterial endocarditis in an 8 month old NSA girl with pre-existing congenital heart disease. The second was a case of empyema in a four year old girl of NSA origin. Both cases occurred in the pre-vaccine era and both recovered uneventfully.

5.5.1.9 Perinatal disease

During the study period, 4 neonates with invasive *H influenzae* disease were seen. This represents 1.6% of all cases identified. There were 74,210 live births in the region during this period, giving an average annual incidence of 1.4 cases per 100 000 live births (95% CI=0.37 to 3.45).

Onset of illness occurred within 24 hours of life in all of these babies. Positive bacterial cultures were obtained from blood (four specimens) and CSF (one specimen). None of the isolates were serotyped. Three were diagnosed as neonatal septicaemia, and one as neonatal meningitis.

Three of the neonates were premature, the youngest was 26 weeks and the others were delivered at 28 and 35 weeks. All three were also low birthweight babies being 1080g, 1020g and 2350g respectively. The baby born at 26 weeks was the only death in this group.

Clinical details were available for three of the mothers. *H influenzae* was isolated from the placental and vaginal cultures of one mother. Another mother had premature rupture of the membranes, but all cultures were negative, while the third mother had no clinical signs of infection. Most of the mothers were young (three were 20 years old, and one was 22 years old) and lone parents with more than one child and resident in the most deprived EDs (3 of 4).

5.5.1.10 KEY POINTS FROM SUB-SECTION 5.5.1

- ❑ Meningitis accounted for the majority of cases in both the pre-conjugate and post-conjugate vaccine periods.
- ❑ Anaemia was identified in 39% of meningitis cases on admission.
- ❑ Children with meningitis were brought to hospital significantly later than children with other types of invasive disease.
- ❑ Antibiotics prior to admission were given to 37% of cases of meningitis. These children tended to be older than those who did not receive antibiotics.
- ❑ After meningitis, epiglottitis was the second most common disease entity.
- ❑ The incidence of epiglottitis fell by 79% in the 2 years following the introduction of Hib conjugate vaccine.
- ❑ Children with epiglottitis were significantly older than those with meningitis
- ❑ Pneumonia was the disease most frequently associated with other invasive diseases.
- ❑ Only 1 of 13 isolates from children with pneumonia were serotyped, and this was type b.
- ❑ Four cases of perinatal disease identified, all developed illness within 24 hours of birth. None of the isolates were serotyped, and positive cultures were only obtained from 1 of 4 mothers.
- ❑ All 4 mothers were young, lone-parents and the majority were resident in the most deprived areas.
- ❑ Other invasive diseases encountered were septic arthritis, osteomyelitis, cellulitis, bacterial endocarditis and empyema.

5.5.2 Morbidity and mortality

5.5.2.1 Morbidity

Morbidity was assessed indirectly by determining the length of hospital stay and the presence of documented sequelae at follow-up.

Hospital stay

The median duration of hospital admission for all invasive *H influenzae* disease were the same in both periods of the study, 9 days. For the different disease manifestations, the median length of hospital stay did not differ between those who were admitted in the pre-conjugate and post-conjugate vaccine periods. Children with meningitis had median lengths of hospital stay of 11 and 10 days in the pre-conjugate and post-conjugate periods respectively. The median length of hospital admission for epiglottitis was 5 days in both time periods. Cases with non-meningitic and non-epiglottic disease had median lengths of hospitalisation of 5 and 6 days before and after the introduction of the conjugate vaccine respectively.

Sequelae

Follow-up and attendance for follow-up were evaluated by examining the medical records for evidence of the child being seen, either at the admitting hospital or another centre, at least once following discharge. Of the surviving meningitis cases, 153 of 161 (95%) were asked to return for follow-up after discharge. A similar evaluation of the non-meningitic disease entities revealed that only 45 of 82 (55%) were requested to attend for follow-up. This difference was

statistically significant (OR=15.72, 95% CI=6.39 to 40.00; p<0.0001). Similar proportions of meningitic and non-meningitic patients did not attend follow-up (12% and 13% respectively)

Seventeen children who had at least one recorded follow-up after discharge from hospital presented with a variety of sequelae, and four of these had multiple problems (table 5.22). All children identified with complications at follow-up had meningitis, and excluding fatal cases of invasive disease, a significant association between meningitis and complications at follow-up was observed (OR=undefined, p<0.001).

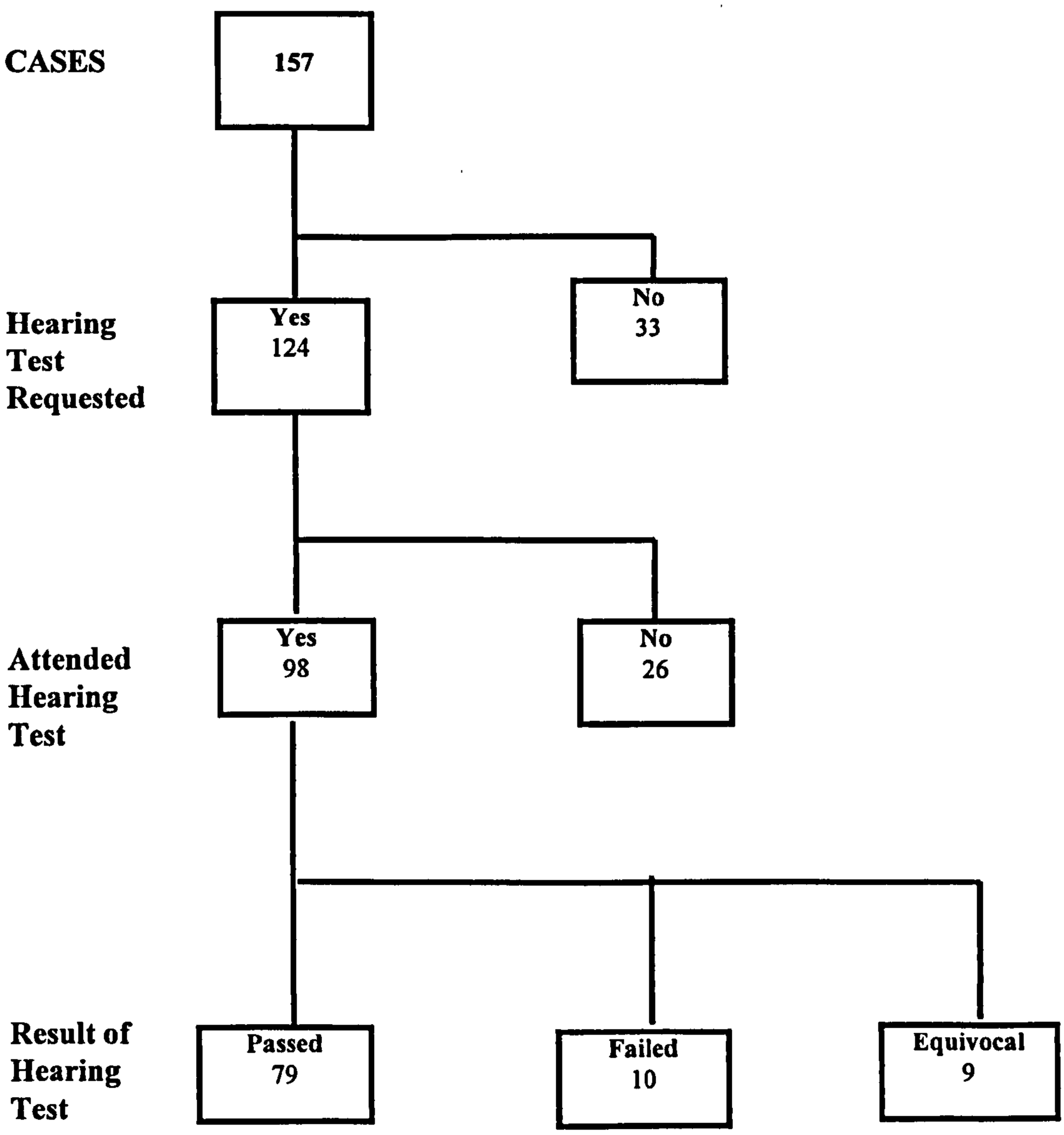
Table 5.22: Long-term sequelae in survivors of invasive *Haemophilus influenzae* meningitis resident in the WMHR and ranked by age, 1990-1994

Case no.	Age (months)	Sex	Ethnic group	Long-term sequelae
1	1	M	SA	Hydrocephalus; seizures
2	3	F	SA	Hearing loss; developmental delay
3	5	M	NSA	Hearing loss
4	6	M	NSA	Hydrocephalus; developmental delay; seizures; hemiparesis
5	7	F	NSA	Hearing loss
6	7	M	NSA	Hearing loss
7	7	M	NSA	Hydrocephalus; developmental delay; seizures
8	8	M	NSA	Hydrocephalus
9	8	M	NSA	Hearing loss
10	9	M	NSA	Hearing loss
11	16	M	NSA	Hearing loss
12*	18	F	NSA	Hearing loss
13	23	F	NSA	Hearing loss
14	25	M	NSA	Seizures
15	34	F	NSA	Hemiparesis
16	52	F	NSA	Hearing loss
17	52	F	NSA	Hearing loss

* This child was resident outside the region

SNHL was the most common post-meningitic complication. Figure 5.14 shows that of the 157 children resident in the WMHR who survived, only 124 (79%) had a hearing test requested by the hospital prior to or at the time of discharge, and only 98 of these were seen at least once.

Figure 5.14: Sensorineural hearing loss and *Haemophilus influenzae* meningitis in children resident in the WMHR, 1990-1994



Of the 98 children tested, nine children had equivocal results, either because of an upper respiratory tract infection (URTI) or being uncooperative at the time of testing. These tests were to be repeated but no definitive results were located in the medical notes at the time of data collection.

In this series 10% (10 of 98) children were diagnosed as having SNHL following audiometry. One other child with SNHL was resident outside the region and excluded from the following analysis. The hearing deficit in these children was bilateral in 6 cases and unilateral in 4, with one child requiring cochlear implants, and one other bilateral hearing aids. Similar proportions of SA (1 of 9, 11%) and NSA (9 of 80, 11%) children were affected.

The ten children resident in the region with SNHL were aged 3-52 months, with a mean age of 18.2 months (median 9.5 months) compared with an average age of 19.9 months (median 15.0 months, range 1-58 months) in those without hearing loss. Eight of 62 (13%) children aged less than 24 months of age had SNHL, while 2 of 27 (8%) aged 24 months or more failed their hearing test. This difference was not statistically significant (p=0.72). Equal numbers of boys and girls were affected.

The proportion of children identified with SNHL decreased from 13% (9 of 72) in the pre-Hib conjugate vaccine era to 6% (1 of 17) in the post-conjugate vaccine period. This reduction was not statistically significant (OR=0.44, 95% CI=0.02 to 3.93; p=0.68).

Children who had been ill for more than 48 hours before admission were found to be at greatest risk for SNHL (OR=6.49, 95% CI=1.70 to 24.77; p<0.0064).

The mean length of admission for those with SNHL was 15.4 days (median 12.0 days, range 8-54) compared to 11.3 days (median 11.0, range 4-76 days), for those who did not suffer any hearing loss. This difference failed to reach conventional levels of significance (p=0.16).

5.5.2.2 Mortality

Outcome was known in 254 cases, and there were 8 deaths, giving a case fatality ratio of 3%. Equal numbers of deaths were seen in boys and girls. Of the 8 deaths, 4 of 197 (2%) occurred during the pre-vaccine period, and 4 of 57 (7%) in the post-vaccine era. This difference almost reached conventional levels of statistical significance (OR=3.64, 95% CI=0.88 to 15.05; p=0.078).

Five children with meningitis died, two others died following an episode of pneumonia and the remaining death occurred in a case of neonatal sepsis. Five deaths were known to have occurred suddenly with the child either being found dead at home or soon after admission. The three other fatalities received hospital treatment for one, two and five days.

Of the deaths occurring in the post-vaccine era, only one child had received Hib conjugate vaccine. This 3 month old child was immunised ten days prior to hospitalisation, and was therefore classed as an apparent vaccine failure.

There were 6 of 232 (2%) children of NSA origin who died compared to 2 of 22 (9%) SA children. This difference did not reach conventional levels of significance (OR=3.77, 95% CI=0.71 to 19.90; p=0.15).

The mean age at admission of children who died was 7.9 months (median 3.0 months, range 0-29 months) with 6 of 8 deaths occurring in children aged 12

months or less. Those who survived were on average 18.9 months of age (median 15.0, range 0-59) on admission. There was a significant difference between the mean age of survivors and those who died (p=0.027)

5.5.2.3 KEY POINTS FROM SUB-SECTION 5.5.2

- ❑ Significantly more cases of meningitis were asked to return for follow-up after discharge, compared to those with non-meningitic disease.
- ❑ SNHL was the most common post-meningitic complication.
- ❑ Only 65% of children resident in the WMHR had at least one documented post-meningitic hearing test.
- ❑ SNHL was identified in 10% of post-meningitic survivors.
- ❑ Hearing loss was significantly associated with delay in being brought to hospital.
- ❑ Case fatality rate of 3% over the four years of the study, 2% in 1990-92 and 7% in 1992-94.
- ❑ Those who died were significantly younger than survivors, and the majority of deaths occurred suddenly at home.

5.5.3 Antibiotic regimens

Only the initial antibiotics prescribed on admission to children with meningitis were considered in this analysis. Dosage and duration of treatment with antibiotics were not examined. Table 5.23 shows the various antibiotics prescribed for children with *H influenzae* meningitis.

Table 5.23: Antibiotics prescribed either singly or as combined therapy for the initial treatment of *Haemophilus influenzae* meningitis before and following the introduction of Hib conjugate vaccine in the WMHR, 1990-1994

Antibiotic	Pre-Hib conjugate vaccine	Post-Hib conjugate vaccine	No.	Total
Ampicillin				28
alone	3	-	3	
combined	22	3	25	
Chloramphenicol				118
alone	6	2	8	
combined	98	12	110	
Penicillin				95
alone	-	-	-	
combined	81	14	95	
Cefotaxime				42
alone	17	12	29	
combined	5	8	13	
Ceftazidime				6
alone	1	1	2	
combined	4	-	4	
Cefuroxime				12
alone	1	-	1	
combined	10	1	11	
Other antibiotics				7
alone	-	1	1	
combined	6	-	6	
All antibiotics	254	54		308

The most common antibiotic prescribed in the pre-Hib conjugate vaccine era was chloramphenicol. Of the 254 antibiotics prescribed it was given either alone or combined with another antibiotic on 104 (41%) occasions. In the second period of the study a total of 54 antibiotics were prescribed, and chloramphenicol accounted for only 14 (26%) of these prescriptions. This reduction almost reached conventional levels of significance (OR=0.50, 95% CI=0.25 to 1.02; p=0.056).

Eight children received chloramphenicol alone as initial antibiotic therapy. Drug assays were performed for only 3 of these cases. Overall, less than half (50

of 118, 42%) of the children who were prescribed chloramphenicol had blood levels of the drug monitored.

Chloramphenicol was the most prescribed antibiotic in all age groups. In those aged less than 12 months chloramphenicol was prescribed for 53 of 142 (37%) cases of meningitis. However, less than half (47% of 53) of these had serum chloramphenicol levels measured at least twice.

Antibiotic combinations used during the pre-Hib conjugate vaccine period were compared with those employed during the post-conjugate vaccine period. Compared with other combinations, chloramphenicol and penicillin were used significantly more for the treatment of meningitis in both study periods (OR=2.55, 95% CI=1.05 to 6.35; p=0.038).

Cefotaxime was the most prescribed cephalosporin both prior to and following the introduction of Hib conjugate vaccine. There was a significant increase in the number of cases prescribed this drug as initial antibiotic therapy, either alone or in combination with another antibiotic in the immediate post-vaccine era (OR=6.20, 95% CI=3.07 to 12.05; p<0.0001). Overall there was a significant increase in the number of children who received a cephalosporin as part of initial antibiotic therapy in the post-vaccine period (OR=3.91, 95% CI=2.05 to 7.43; p<0.0001).

No association was found between the antibiotics prescribed and mortality, SNHL or other sequelae of meningitis.

5.5.4 Dexamethasone therapy

Dexamethasone is not recommended for the routine treatment of *H influenzae* meningitis in the UK, however, this study found that 93 of 168 (55%) children with meningitis received intravenous dexamethasone. Seventy one of 134 (53%) in the pre-conjugate vaccine period and 22 of 34 (65%) in post-conjugate vaccine era. The dosage and duration of steroid therapy were not examined in this analysis.

Table 5.24 compares the characteristics of children with *Haemophilus* meningitis who received dexamethasone during their hospital admission with those that did not. Both groups had similar demographic and clinical characteristics.

Slightly more children who received dexamethasone (6 of 43, 14%) were later found to have SNHL than those who did not (5 of 48, 10%).

Table 5.24: Comparison of selected variables for cases of *Haemophilus influenzae* meningitis who received dexamethasone therapy with those not receiving dexamethasone in the WMHR, 1990-1994

Variable	Received DXM* (n=93)	No DXM* (n=75)	Odds ratio (95% CI)	p value
Study period:				
1990-1992	71	63	0.61 (0.26-1.43)	0.30
1992-1994	22	12		
Age group (months):				
0-11	41	32	1.06 (0.55-2.05)	0.98
12-23	31	26	1.29 (0.66-2.53)	0.52
24-35	12	7	1.44 (0.49-4.32)	0.63
36-47	7	4	1.44 (0.35-6.99)	0.76
48-59	2	6	0.25 (0.02-1.48)	0.14
Sex:				
boys	45	36	1.02 (0.53-1.95)	0.92
girls	48	39		
Ethnic group				
SA	10	4	2.14 (0.58-9.71)	0.36
NSA	83	71		
Length of admission:				
mean	11.5	11.8		0.80
7 days or more	86/93	58/75	**3.73 (1.35-10.68)**	**0.0082**
10 days or more	58/93	43/75	1.23 (0.63-2.41)	0.61
Readmitted:				
yes	1	4	0.19 (0.00-2.02)	0.17
no	92	71		
Antibiotics before admission:				
yes	32/92	30/74	0.78 (0.39-1.55)	0.55
no	60/92	44/74		
Sequelae:				
yes	11	6	1.56 (0.50-5.41)	0.55
no	82	69		
Failed hearing test:				
yes	6/43	5/48	1.39 (0.32-6.26)	0.85
no	37/43	43/48		
Died:				
yes	0/89	2	undefined	0.21
no	89/89	73		

* Dexamethasone

Figures in bold indicate a statistically significant result

5.5.5 Prophylaxis

It is recommended that prophylaxis for the prevention of secondary cases of invasive *H influenzae* disease be given to the index case prior to discharge, and to all household members where there is another child less than 4 years of age in the index household.

During hospital admission or prior to discharge, rifampicin was prescribed for some or all contacts of 50 of 115 (43%) index children who had a sibling aged less than 4 years in their household. Chemoprophylaxis was also prescribed for 11 of 28 (39%) children who were the only child in the family or did not have siblings aged less than 4 years. In only 36 of 115 (31%) cases were some or all contacts of children with siblings aged less than 4 years prescribed rifampicin.

Contacts of index cases with meningitis who had siblings below four years of age were more likely to receive prophylaxis than those who had a non-meningitic disease (OR=6.29, 95% CI=2.20 to 21.88; p=0.00022).

Table 5.25 compares the data obtained for index cases who received rifampicin with those who did not. Several significant findings can be seen. Additional analyses revealed that amongst the group of children attending daycare, those who had meningitis were more likely to receive prophylaxis than those who had non-meningitic disease (OR=13.0, 95% CI=2.01 to 135.83; p=0.0035). Although statistically there was no difference between NSA and SA cases receiving prophylaxis, contacts of SA children were more likely (OR=3.65, 95% CI=1.32 to 10.16; p=0.0091) to be prescribed rifampicin than their NSA counterparts.

Table 5.25: Comparison of selected variables for cases of *Haemophilus influenzae* disease who were prescribed prophylaxis with those not prescribed prophylaxis in the WMHR, 1990-1994

Variable	PXS* prescribed (n=111)	No PXS* (n=135)	Odds ratio (95% CI)	p value
Study period:				
1990-1992	82	110	0.64 (0.34-1.23)	0.20
1992-1994	29	25		
Disease entity:				
meningitis	99	64	**9.15 (4.40-19.38)**	**<0.0001**
non-meningitic	12	71		
Age group (months):				
0-11	45	49	1.20 (0.69-2.07)	0.58
12-23	37	48	0.91 (0.52-1.59)	0.82
24-35	13	21	0.92 (0.32-1.60)	0.49
36-47	9	9	1.24 (0.43-3.54)	0.85
48-59	7	8	1.07 (0.34-3.38)	0.89
Gender:				
girls	62	57	**1.73 (1.01-2.97)**	**0.045**
boys	49	78		
Ethnic group				
SA	13	7	2.43 (0.86-7.02)	0.10
NSA	98	128		
Large family (> 2 siblings):	38/82	42/108	1.36 (0.73-2.53)	0.38
yes	44/82	66/108		
no				
Siblings <4 years old:				
yes	50/61	65/82	1.19 (0.47-3.00)	0.85
no	11/61	17/82		
Attended daycare				
yes	18	21	1.05 (0.50-2.20)	0.98
no	93	114		
Length of admission:				
mean	12.0	9.3		**0.021**
7 days or more	96/111	79/135	**4.54 (2.29-9.10)**	**<0.0001**
10 days or more	72/111	45/135	**3.69 (2.10-6.50)**	**<0.0001**
PXS for some/all contacts:				
yes	51	16	**6.32 (3.19-12.67)**	**<0.0001**
no	60	119		

* Prophylaxis

Figures in bold indicate a statistically significant result

When rifampicin prophylaxis was analysed against season of onset, significantly fewer cases of meningitis (OR=0.46, 95% CI=0.24 to 0.91; p=0.036), and their contacts (OR=0.38, 95% CI=0.18 to 0.81; p=0.017) received prophylaxis during the autumn months than at any other time of the year.

In addition to these findings, examination of the prescriptions contained in the medical notes indicated that there was confusion as to the duration and dosage of rifampicin required. In several instances, the index child and their contacts received prophylaxis which was appropriate for meningococcal disease (2 days) rather than for *H influenzae* (4 days).

5.5.5.1 KEY POINTS FROM SUB-SECTION 5.5.3 to 5.5.5

- ❑ Chloramphenicol was the single most commonly prescribed antibiotic.
- ❑ Only 42% of children who received chloramphenicol had assays performed.
- ❑ Penicillin and chloramphenicol were the first-line combination of choice in both study periods.
- ❑ There was a significant increase in use of cefotaxime in the second period of the study.
- ❑ Dexamethasone was prescribed for 55% of meningitis cases in the pre-conjugate vaccine period and 65% in the post-conjugate vaccine period.
- ❑ Rifampicin was prescribed for 31% of cases who had a sibling aged 4 years or less.
- ❑ Rifampicin chemoprophylaxis was prescribed for 39% of children who were singletons or did not have a sibling aged less than 4 years.
- ❑ Children with meningitis were more likely to receive prophylaxis than those who had non-meningitic disease.
- ❑ Significantly more girls received prophylaxis than boys.
- ❑ Contacts of SA children were significantly more likely to receive prophylaxis

than contacts of NSA children.

- ❑ Significantly more cases received prophylaxis if they were admitted for seven days or more.
- ❑ Significantly fewer cases of meningitis and their controls received prophylaxis in the autumn than at any other time of the year.
- ❑ There appeared to be confusion regarding the dosage and duration of chemoprophylaxis.

5.6 BACTERIAL EPIDEMIOLOGY

5.6.1 Diagnostic tests

There were 172 children with a diagnosis of meningitis in this series. In 160 cases, both CSF and blood samples were taken. The organism was isolated from both specimens in 124 (78%) cases, from CSF and not blood in 22 (14%) cases, and from blood and not CSF in 14 (9%) cases. Of the remaining 12 cases, two children who died suddenly at home had the organism isolated from post-mortem swabs of the meninges, six children had only CSF samples taken and four others had only blood samples taken. In addition, on gross examination 9 of 162 (6%) CSF specimens were reported as clear. Despite this all nine CSF cultures yielded *H influenzae*.

Of the 87 children who had non-meningitic diseases, 75 (86%) had blood cultures performed without a concomitant CSF culture, and eleven children had both blood and CSF specimens taken of which only the blood culture was positive. The remaining child died before blood or CSF specimens were taken. Diagnosis

was by a post-mortem swab of the trachea and bronchi, and a sample of lung parenchyma, all of which grew *H influenzae.*

When the effect of pre-admission antibiotics on culture results was examined, a significant association between negative blood cultures and cases who had received antibiotics prior to admission was found (OR=3.47, 95% CI=1.36 to 8.94; p=0.0064). A similar association was not seen with CSF cultures.

5.6.2 Serotype

Serotyping results were available for 154 of 258 (60%) cases, of which 152 (99%) were type b. There were two non-capsulate strains, and these accounted for less than 1% (1 of 114) and 3% (1 of 40) serotypes in the pre- and post-Hib conjugate vaccine periods respectively. Both were ampicillin resistant cases of meningitis. One occurred in a two month old boy in the pre-vaccine period, and the other in a boy of 13 months in the post-vaccine period, both were NSA and had uneventful hospital admission and follow-up.

A slight increase in the number of isolates serotyped was noted when the two main study periods were compared. In the pre-Hib conjugate vaccine era, 114 of 199 (57%) were serotyped, compared to 40 of 59 (68%) in the post-Hib conjugate vaccine era.

5.6.3 Antibiotic resistance

Ampicillin resistance was identified in 54 of 357 (15%) *H influenzae* specimens. All the isolates tested were sensitive to chloramphenicol and cephalosporins. There were 33 of 211 (16%) blood culture isolates which were

ampicillin resistant, and 21 of 146 (14%) CSF isolates resistant to ampicillin. Nineteen of the CSF specimens were serotyped and 17 (89%) of these were serotype b. Of the ampicillin resistant blood specimens, 22 were serotyped and 21 (95%) of these were serotype b.

In 16 of the 54 resistant cases, both blood and CSF isolates had been taken simultaneously. Eleven isolates exhibited ampicillin resistance in both specimens, 4 had ampicillin resistant *H influenzae* in blood but not in the CSF, while one organism demonstrated ampicillin resistance in CSF but not in blood.

Two of the children who died had isolates identified which were resistant to ampicillin. One was a blood specimen, the other CSF. However, there was not a statistically significant association between ampicillin resistance and death. Two other children whose outcome was unknown also had ampicillin resistant invasive organisms.

Significantly more children with ampicillin resistant invasive *H influenzae* were found to suffer hearing loss as a sequelae (OR=4.04, 95% CI=1.07-15.25; p=0.045). A similar association was not found for a number of other factors including age, gender, ethnic group, chronic illness, anaemia and poor nutritional status on admission. Children with a history of previous hospital admission as well as those who were discharged and readmitted following the index admission were also analysed. Both failed to produce statistically significant associations.

Ampicillin resistance increased during the post-vaccine period of the study for each type of specimen. Venous blood isolates exhibited resistance to ampicillin in 15% (24 of 163) of cases in the pre-vaccine period. This increased to 19% (9 of 48) in the post-vaccine period (OR=1.34, 95% CI=0.53 to 3.33; p=0.65). CSF

isolates demonstrated a more marked increase from 13% (15 of 116) to 20% (6 of 30) during the same time periods (OR=1.68, 95% CI=0.59 to 4.79; p=0.49). Neither of these increases were statistically significant.

5.6.4 KEY POINTS FROM SECTION 5.6

- ❑ A significant association was seen between negative blood cultures and cases who had received antibiotics before admission.
- ❑ Serotyping results were available for 60% of cases, almost all were type b.
- ❑ More isolates were serotyped in the post-conjugate vaccine period (68%) than the pre-conjugate vaccine era (57%).
- ❑ Resistance to ampicillin was seen in 15% of isolates.
- ❑ Ampicillin resistance was significantly associated with SNHL.
- ❑ There was an increase in ampicillin resistance in both CSF and blood cultures in the post-vaccine period.

CHAPTER 6

DISCUSSION

DISCUSSION

6.1 DISCUSSION

In this chapter the results of the study are placed in the context of previously published research. The present study has confirmed some previously reported risk factors, but has also identified a number of others which have not previously been described for invasive *H influenzae* disease. The chapter concludes with a description of the methodological strengths and limitations of the study.

6.1.1 Incidence of invasive *H influenzae* disease in the pre-Hib conjugate era

The average annual incidence rate of 28.4 per 100 000 children aged less than 5 years reported for this study in the pre-conjugate vaccine period is the same as that obtained for the same time period in the PHLS six region study (28.4)[140] and in other health regions of Britain (28.3 in the North West region,[233] 28.1 in Wales[249] and 26.3 in the Northern region[249]). The incidence is slightly higher than that reported from the Republic of Ireland (25.4)[230] and France (21.0),[126] but lower than those reported from Scotland (32.2)[266] and parts of Scandinavia, (51.9),[231]Switzerland (60.2),[209] Australia (58.5)[242], and North America (112.0).[155]

The case definition used in this study may have underestimated the true incidence of disease and consequently the reported rates for invasive *H influenzae*

disease in this study are considered to be minimum estimates. Other contributing factors may include children resident in the region and treated in hospitals outside the WMHR, cases without definitive bacteriological diagnoses either because specimens were not taken for laboratory diagnosis or laboratory diagnosis may have been negative because the child had received parenteral antibiotics prior to admission. Despite this the annual incidence of invasive *H influenzae* disease was within the range of 26.3 to 36.6 per 100 000 children aged less than 5 years reported by the different regions in the PHLS six region study.[249]

When comparing the incidence rates obtained for the West Midlands with those reported by the PHLS six region study it is important to bear in mind that the methodology used in the latter study was different. It was laboratory-based, prospective and employed a broader case definition, including cases detected by the presence of Hib antigen[249] The current study was mainly retrospective in nature, used several sources of case identification and did not include cases detected by Hib antigen. The inclusion of Hib antigen positive cases which are culture negative should not affect the comparability of the data as in the PHLS six region study they accounted for only a small proportion of cases (5 of 772, <1%).[249]

Two descriptive studies which overlapped in time have been carried out previously in the WMHR. Both were hospital-based studies and both were conducted in hospitals in Birmingham. Dyas and George examined the occurrence of invasive *H influenzae* disease in children admitted to Birmingham Children's Hospital during the period 1973 to 1984 and identified 83 cases in this 10 year period (8.3 cases per year).[268] In this study 20 children were admitted to the same

hospital in the 2 years (10 per year) before Hib conjugate vaccine was introduced. Davey et al reviewed cases of bacterial meningitis admitted to East Birmingham Hospital (now Birmingham Heartlands Hospital) between 1968 and 1977.[304] They identified 51 cases of *H influenzae* meningitis during this 10 year period (5.1 cases per year) compared to the 13 cases (6.5 cases per year) admitted to the same hospital in the first half of this study. Although it is difficult to compare our results it would appear that invasive *H influenzae* disease increased with time in the WMHR in the pre-Hib conjugate vaccine era. This may have occurred as a result of changes in clinical practice, improved diagnostic techniques, improved surveillance, increased susceptibility of the at risk population, increased virulence of the organism or a true increase in the prevalence of the disease.

6.1.1.1 Comparison of surveillance systems

The comparison of cases by the reporting systems which identified them revealed that underreporting varied with age and disease entity, and similar results have been reported previously. These surveys highlighted the incompleteness of meningitis notifications, particularly those due to *H influenzae* meningitis.

Using data from the PHLS six region study, Macleod specifically examined the completeness of reports of invasive *H influenzae* disease in the pre-vaccine era.[175] On average, 17% underreporting to the regional survey occurred and 24% underreporting to the CDSC. It was suggested that the introduction of Hib conjugate vaccine might improve the efficiency of reporting. Given the debate and publicity surrounding the launch of the vaccine, as well as the BPSU study of vaccine failures, this was not an unreasonable assumption. However, in this study

the finding that overall underreporting to CDSC from laboratories within the WMHR actually increased from 15% in the pre-conjugate vaccine period to 36% in the post-vaccine period contradicts this supposition. This observation has not previously been reported in the UK, and may have arisen due to complacency on the part of clinicians and microbiologists in view of the success of the vaccine.

6.1.1.2 Excluded cases

An area of concern was the exclusion from the study of 25 cases due to insufficient identifying data or missing case notes. If the 19 cases excluded in the pre-conjugate vaccine era had been included in the numerator, then the average annual incidence of invasive *H influenzae* disease would have increased by 10% to 31.1 per 100 000 (95% CI=26.0 to 34.3). Performing a similar calculation for the post-conjugate vaccine data provides an incidence rate of 9.3 (95% CI=7.2 to 11.8), this was an 11% increase on the original incidence rate. Statistically neither result was significantly different from the original HICARE rates however, comparison with CDSC data shows that these incidence rates would have been 29% and 72% greater than those obtained using CDSC data in the pre-conjugate and post-conjugate periods respectively. These large differences have social, economic and health service implications.

The problem of missing case notes has been highlighted by a number of authors and in this study contributed to a lower disease incidence.[505,506,518] This was particularly evident in this study for children who died, where 8 of 25 case notes could not be located, and to a lesser extent for children of SA origin.

6.1.1.3 Impact of Hib conjugate vaccine on public health

Following the successful introduction of Hib conjugate vaccines in several countries in Western Europe and the United States, and the results of Hib conjugate vaccine trials in Britain,[167] a dramatic reduction in the incidence of invasive Hib disease was anticipated. In this study the greatest reduction in the incidence of invasive *H influenzae* disease in the WMHR was seen six months after the conjugate vaccine was introduced, and a 95% reduction in disease incidence was seen between 1990/91 and 1993/94. This confirms the success of Hib conjugate vaccine in children in the WMHR, and this compares favourably with reductions observed in other parts of Britain,[140] Finland,[136] Australia,[138] Canada,[137] and the United States[134] following the introduction of Hib conjugate vaccine.

This observation not only indicates a definite change in the epidemiology of the disease, but is also said to be indicative of a much greater effect than would be expected from vaccination alone.[519] It has been suggested that herd immunity may be one explanatory factor.[289] Results from studies conducted in Britain and the United States suggest that vaccination with Hib conjugate vaccine reduces nasopharyngeal carriage among the vaccinated population thereby reducing or delaying transmission of the organism.[289,463]

Other factors may have been responsible for the observed decline. Changes in diagnostic and reporting practices at district and hospital level may have occurred. However, these would probably have improved reporting leading to a consequent increase in cases. Comparison of disease incidence due to meningococcal and pneumococcal meningitis in the same time period by Urwin et al in the North East Thames region did not demonstrate similar decreases for these

organisms.[267] This also indicates that changes in surveillance activity or clinical practice could not account for the dramatic decrease in invasive *H influenzae* disease. Invasive Hib disease has been shown to exhibit annual and seasonal variation.[138,279,292] McIntyre et al reported that in Sydney, Australia age-specific time-series analysis which took annual and seasonal variation into account demonstrated a significant decrease in the incidence of invasive Hib disease which was associated with the introduction of Hib conjugate vaccine.[138]

6.1.2 Individual risk factors

6.1.2.1 Age

In this study 42% of children identified with invasive disease in the pre-conjugate vaccine period were less than 12 months of age. The PHLS six region study reported a similar figure (42%).[249] Other British studies with comparable reports regarding the age of children have concentrated on *H influenzae* meningitis. The present study found that 46% of meningitis cases were less than 1 year of age prior to the introduction of Hib conjugate vaccine. Two separate reports from Oxford found that 44%[121] and 49%[139] of children with *H influenzae* meningitis were aged less than 12 months. A report from Wales indicated that 40% of children were less than 1 year of age.[142] A similar proportion of children affected at this age has been reported from Europe.[126,270,271]

Slack has suggested that Hib conjugate vaccine would shift the burden of disease to an older age group as a result of reduced or delayed transmission of the organism.[519] The results in the WMHR support this as a shift in the age

distribution of those at most risk was observed following the introduction of Hib conjugate vaccine from those aged 6-11 months to those aged 24-35 months.

6.1.2.2 Gender

The overall male:female ratio of 1.1:1 reported in this study was in keeping with previous epidemiologic reports from different parts of the world.[123,131,230,232,239,266] However differences in gender distribution were found in this study which, to the researcher's knowledge, have not previously been reported in Britain. The significance of the increased incidence of *H influenzae* meningitis in girls is uncertain and may have arisen due to chance. However the increased risk for girls just failed to reach statistical significance (OR=1.65, 95% CI=0.95 to 2.88: p=0.079) and the confidence intervals were narrow. An example of an infectious disease where a female predominance has been reported previously is whooping cough.[520] Reports regarding this phenomenon for *H influenzae* are scarce. In Finland, Takala et al reported a female predominance in *H influenzae* diseases other than meningitis and epiglottitis which was not statistically significant.[231] Hanna et al found that 65% (26 of 40) of cases of *H influenzae* meningitis observed in Aborigine children aged less than 5 years occurred in girls giving a relative risk of 1.89 (95% CI=0.99 to 3.60; p>0.05) when compared to Aborigine boys.[291] Possible explanations for these findings remain elusive.

6.1.2.3 Ethnic group

A number of population-based studies from the United States,[153,259,278] Australia[119,257,291] and Israel[234] have examined incidence rates in multi-ethnic populations. They have reported that white populations are at reduced risk compared to other ethnic groups occupying the same geographic area, and that a greater proportion of invasive *H influenzae* disease occurs at a younger age among children in ethnic minority populations.

Only one study was located that was conducted outside the UK and which provided data on invasive *H influenzae* disease in one of the major ethnic minority groups in the UK. The report was a retrospective hospital-based study which examined cases of bacterial meningitis admitted between 1987 and 1994 in Bangladesh.[118] The authors reported a similar age-distribution to that seen in children of SA ethnic origin in the WMHR. In their study, 69% (191 of 277) cases occurred in children aged less than 12 months of age.

The age distribution in children from the SA ethnic group in Britain has not previously been described. The South Asian children in this study had an age-related pattern of disease similar to that seen in Native Americans,[153,282] Australian Aborigines[2119,257] and other children from 'deprived societies'[234,290]. In this study 64% (14 of 22) of cases occurred in children of SA ethnic origin before the age of 12 months. In the places where ethnic differences have been studied, the factors responsible for ethnic age differences in disease risk are not clear. Some authors suggest that genetic differences may play a role, while others point to confounding socioeconomic factors such as household overcrowding and the number of siblings. The results of research into these factors has provided contradictory results.

One of the concerns prior to the introduction of Hib conjugate vaccine was that immunogenicity may vary according to ethnic group. However, previously published epidemiological studies conducted in Britain have consistently failed to provide ethnic-specific incidence rates, either before or following introduction of the vaccine, or to compare uptake of Hib vaccine in different ethnic groups. Where ethnic groups have been reported, the criteria used to classify children into these groups are not made clear.[267] This survey followed methods of categorisation which were compatible with the 1991 population census classification of ethnic group.

Differences in disease distribution have also been noted amongst other ethnic groups. One series involving Native Alaskan children failed to report any cases of epiglottitis.[153] Similar results have been obtained in Chile, Hong Kong and South Africa.[196,222,239] Comparable results were obtained for children of SA origin in the WMHR where, from 1990-94 only one case of epiglottitis was identified. It has been proposed that epiglottitis is more common in populations where invasive *H influenzae* disease is encountered later in childhood, and although the mechanism for this remains obscure, the results obtained for SA children in the WMHR would appear to support this view.

Although immunisation rates for the different ethnic groups living in the WMHR are unavailable, this study found that children of SA origin were significantly less likely to have age appropriate immunisation histories. Support for this appears to be provided by other results obtained in this study. The incidence of disease fell by 89% in SA children compared to 94% in NSA children, causing the proportion of children of SA origin to increase from 8% in the first

period of the study to 13% in the second. Although neither of these observations reached statistical significance they are compatible with a problem with immunisation uptake in this group of the population, or vaccine immunogenicity. Further support is provided by a recent report by Bedford et al.[353] They examined the immunisation status of 1,411 at primary school in an inner London district. They found that 50 of 54 children who had no immunisations were of 'Asian' origin.

Ethnic differences have also been noted in the USA following introduction of Hib conjugate vaccines. Using data from the National Bacterial Meningitis Reporting System (NBMRS), Adams et al reported a significant increase ($p<0.001$) in the proportion of Black American children aged less than 5 years with invasive *H influenzae* disease following the introduction of Hib conjugate vaccine.[134] The proportion affected increased from 27% in 1989 (pre-conjugate vaccine) to 37% in 1991 (post-conjugate vaccine). As with the HICARE study, one reason for this may be the lower immunisation uptake rates in this ethnic minority group.

6.1.2.4 Nutritional status

It is well known that malnutrition reduces a host's resistance to infection and that infection is a major cause of morbidity and mortality in malnourished children.[521] In this study 8% (18 of 228) of cases were below the third centile for weight of a population growth chart.[497,498] This proportion increased from 6% (11 of 178) in the pre-conjugate vaccine era to 14% (7 of 50) in the second period of the study. Although information on nutritional status as a predisposing factor is not mentioned in the majority of studies, two studies from 'developing' countries

have reported an association between *H influenzae* meningitis and being underweight for age on admission. Nottidge reported from an urban centre in Nigeria that 76% of children admitted with *H influenzae* meningitis were below the 3rd centile of a weight chart.[124] In Malaysia, Choo et al found that 17% of children admitted with *H influenzae* meningitis were below the 3rd centile.[305] Although the results obtained in Nigeria and Malaysia are not strictly comparable with those obtained in the WMHR, the results in the second period of the study approach those reported from Malaysia. The increase in the WMHR may reflect increasing deprivation within the study group as this factor just failed to reach statistical significance when the two time periods were compared (OR=2.47, 95% CI=0.81 to 7.42; p=0.080).

6.1.2.5 Anaemia

Data on anaemia as a risk factor for invasive *H influenzae* disease is scarce, however anaemia has been associated with *H influenzae* meningitis in a number of other studies. Anaemia was found in 35% (72 of 207) of children in this series. This is comparable with an earlier report from a Birmingham hospital of 31% of children admitted with *H influenzae* meningitis having anaemia.[304] It has been suggested that anaemia arises as a result of increased red cell haemolysis following invasive disease by the organism.[303] This study could not refute or confirm this hypothesis.

6.1.3 Family and community risk factors

6.1.3.1 Family size and structure

The results from the present study support the findings of other investigators, that the presence of siblings less than 5 years of age is a risk factor for invasive *H influenzae* disease.[154,295] Other researchers however, have reported contrasting results.[152,230] These studies have been conducted in different parts of the world and the lack of consistency may reflect differences in day-care arrangements or, .socioeconomic and cultural differences.

6.1.3.2 Lone parents

The data obtained in this study showed that overall 14% (32 of 234) of cases were from lone parent families. This variable has been reported as a risk factor for invasive *H influenzae* disease in case-control studies carried out in Switzerland and the United States.[151,152] Due to the sample size this could not be explored in this study, however 1991 population census data for the WMHR indicates that 10% of families are lone parent families.

6.1.3.3 Day-care

The proportion of children admitted to hospital with invasive disease who were attending daycare fell from 16% (32 of 199) in the two years prior to introduction of the conjugate vaccine to 12% (7 of 59) in the second period of the study. This occurred even though none of the children who attended daycare had received Hib conjugate vaccine, and they were also less likely to have siblings. The decrease may have occurred as a result of herd immunity. The study was not

able to accurately ascertain the impact of daycare as a risk factor because of the retrospective nature of case finding, lack of an accurate denominator regarding the number of children attending daycare, and inconsistent recording of daycare attendance in the medical notes. Hib conjugate vaccine however has been previously reported to decrease nasopharyngeal carriage in a number of European and North American studies and thereby reduce the risk of transmission.[289,463]

6.1.4 Environmental factors

6.1.4.1 Pre-Hib conjugate vaccine

Immunisation histories were documented for 167 of 199 (84%) children in the two years prior to introduction of Hib conjugate vaccine. Of this population 81% (136 of 167) were age-appropriately immunised. The figure obtained in this study is much lower than the average immunisation uptake for the WMHR in November 1991 of 92% for triple antigen at 12 months.[522] The present results are however comparable with data reported by Riley et al from Manchester. They found that only 75% of children admitted to an acute paediatric medical ward during a six month prospective study were fully immunised.[357]

Another feature of this study was that none of the children who were behind with their immunisations were opportunistically immunised before or at the time of discharge. Failure to opportunistically immunise has been reported in a number of studies with children admitted to hospital for a variety of diagnoses found not to be up to date with their immunisations.[357,358,360] Opportunistic immunisation is advocated at the primary care level,[359] however, it may be difficult to carry out due to certain policies, one of which may be that only doctors may give injections.[115]

Jefferson et al have argued that this type of policy contributes to missed immunisation opportunities.[363]

During the course of this study it was noted that several discharge letters from a number of hospitals requested the family's GP to arrange for the child to have Hib vaccine following discharge. It cannot be ruled out that verbal advice was also given to other parents to contact their GP's and to arrange for the vaccine to be given to their child. This suggests lack of ward-based immunisation policies and contributes to continued missed opportunities to immunise those most at risk. One possible way of improving the immunisation status of vulnerable children is to promote the use of parent-held child health records which have been shown to be acceptable by both parents and health professionals.[523]

In the present study, factors significantly associated with falling behind were being of SA origin and coming from a family with three or more siblings. Large families have previously been shown to be associated with failure to immunise in a number of studies.[106,108,348] Ethnic minority status has however not been reported in great detail with regard to immunisation in Britain, and at the time of writing there are no UK ethnic-specific data in the post-Hib conjugate vaccine period. The main ethnic minority group studied are children of 'Asian' origin and the reports are conflicting. Some studies point towards reduced immunisation uptake in this sub-group of the population.[114,163,353], while others report similar or better uptake compared with the indigenous population.[354,355]

In general, failure to immunise is recognised as an outcome of the interaction between parental attitudes, social circumstances of the child's family,

and the extent of the service arrangements for obtaining immunisation.[106,111,343,348,350,357]

6.1.4.2 Post-Hib conjugate vaccine

Immunisation histories documented in the hospital records were validated by checking district child health records of children resident in the WMHR. A highly significant level of agreement (p=0.0002) was obtained when comparing the two methods indicating that when present in hospital records, immunisation histories may be considered a good estimate of the child's actual immunisation status.

Not so encouraging was the finding that the majority of cases admitted in the post-conjugate vaccine era had not received Hib conjugate vaccine prior to admission, and were not opportunistically immunised while admitted. Furthermore, following discharge more than a third had not received the vaccine by the time the researcher obtained their data from the child health records. Of those who had received conjugate vaccine there had been an average wait of more than 3 months. These observations were quite surprising as 75% (33 of 44) of children admitted in the post-vaccine era were found to be up to date for all other primary immunisations. There are no comparable data for this finding and deprivation, family size and ethnic group were not associated with a failure to receive Hib conjugate vaccine.

In contrast to these findings a recent report of a case-control study from the United States carried out from 1991 to 1994, identified having a single mother (OR=7.0, 95% CI=1.2 to 40) and low income (OR=11.3, 95% CI=1.1 to 109) as

risk factors for delay in receiving Hib conjugate vaccine.[151] The wide confidence intervals reported are indicative of the small numbers available following introduction of Hib conjugate vaccines (57 cases *vs* 93 controls). Tokhani et al also conducted a case-control study examining uptake predictors for Hib vaccination in Northern Ireland in the first half of 1993.[524] They reported that children who had two or more younger siblings were less likely to have been immunised (OR=2.32, 95% CI=1.22 to 4.43) as were children whose mothers smoked (OR=2.82, 95% CI=1.41 to 5.62).

Other factors which may have contributed to the apparently poor uptake of Hib conjugate vaccine in the study group are the attitude and knowledge of parents and health professionals regarding Hib meningitis and Hib conjugate vaccine. Braun et al conducted research prior to the launch of Hib conjugate vaccine amongst a group of health visitors and parents.[525] They reported that only 6 of 52 (12%) health visitors named Hib as a cause of meningitis in young children, and only 16 (31%) would advise parents to immunise their child against Hib.

Anecdotal evidence gleaned from the hospital notes of some children included in this study may add support to these findings. One parent indicated that the GP had informed her that her child was "too young" for Hib vaccine when presenting for a scheduled immunisation appointment. Another parent had been told in similar circumstances that the child "did not need Hib vaccine". If these are an accurate record of what transpired then they indicate that GPs may have contributed to poor uptake by providing incorrect advice.

Prior to the launch of Hib conjugate vaccine in October 1992, McGuire carried out a study on parental attitudes to Hib conjugate vaccine for the Health

Education Authority in November 1991.[526] Her report indicated that parents had not heard of Hib meningitis and therefore perceived it as a less dangerous type of meningitis than other types of meningitis.

It is almost 10 years since the Peckham report indicated that parental attitude has a marked effect on vaccine uptake.[106] Experience with pertussis[527] and more recently MMR[528] vaccine has illustrated how adverse publicity resulting in parental concern can lead to reduced vaccine uptake. Fortunately immunisation uptake rates for Hib have been high resulting in a marked reduction in incidence of the disease.

Despite these high uptake rates, the finding of a negative relationship between deprivation and district immunisation uptake rates is in agreement with previous reports from the UK. The results from a national study by Jarman et al suggested that there were marked variations in immunisation uptake rates among health authorities and that those with the poorest social conditions had the lowest uptake rates.[163] Using a similar method to that of the HICARE study, Reading et al found that a greater proportion of children in the most deprived EDs of Northumberland were significantly more likely to be incompletely immunised against pertussis by 15 months of age.[529]

6.1.4.3 Vaccine failures

The definition of a vaccine failure used in this study was the same as that applied by the BPSU in their study.[476] Using this definition, 9 vaccine failures were identified from the HICARE register. Three of these were true vaccine failures, two occurring after three doses of vaccine. Although the number of

vaccine failures reported for the WMHR in this study are too small for detailed analysis the results are generally comparable to those reported by the BPSU.[476] Both the BPSU study and the HICARE study reported that following PRP-T immunisation one-third of vaccine failures were true vaccine failures. A study in Australia conducted from 1993 to 1994, one year after Hib vaccines became available, reported a similar proportion of true vaccine failures (9 of 33, 27%) among Hib cases classified as vaccine failures.[478] The study differed from the BPSU and HICARE studies as all four conjugate vaccines were in use in Australia. Of the recorded Australian vaccine failures, none were due to PRP-T.[478] A number of authors from the United States[460,477] and Canada[137] have also reported the occurrence of invasive *H influenzae* disease following vaccination with conjugate vaccines.

6.1.4.4 Deprivation in the post-Hib conjugate vaccine era

Following the introduction of Hib conjugate vaccine in October 1992, differences in disease experience between children living in the most deprived and the more affluent areas of the WMHR appear to have increased. Living in areas categorised as having low deprivation appeared to significantly reduce the risk of disease. This is in keeping with Blaxter's assertion that behavioural interventions such as immunisation have a much stronger influence on the health of the economically advantaged than on the health of the disadvantaged.[335]

Contrary to the results obtained in this study an ecological study in the North East Thames region which employed the ward as the unit of geographic analysis, found no evidence of an association between deprivation (using

Townsend deprivation tertiles) and increased risk of *H influenzae* meningitis.[19] It should be noted that the ward is a larger geographic unit than the ED, which was used in this study. It is therefore possible that the size of the unit used in the Thames study masked any possible differences as the aggregated groups would be more heterogenous than those aggregated using the smaller ED. Furthermore, the North East Thames study only provided incidence rates for 'white' children aged less than 5 years of age.[19] The results reported from North East Thames were similar to those found by Tarr and Peter in Rhode Island.[277] They examined *H influenzae* meningitis in census tracts where the populations were 99.2% white. They found that the occurrence of meningitis in these areas was not related to a number of socioeconomic variables including low family income and low adult educational level.[277]

Other studies which have examined proxies for deprivation such as low social class,[230] low family income[148,149,151,295,313] and low adult education level[149,154,277,295] have produced conflicting results. This may be due to confounding due to other socioeconomic and host factors.

Susser et al[530], and more recently Reading et al[352], have argued that improvements in the delivery of health services to the whole population may not only increase health inequalities but may actually widen them. The improved delivery of immunisation services, the introduction of Hib conjugate vaccine, together with the 'catch-up' programme and the subsequent high uptake of the vaccine is a good example of this type of improvement. This study suggests that despite an absolute reduction in disease experience among the study population

following the introduction of Hib conjugate vaccine, there has been a relative increase for the most deprived group of children.

6.1.4.5 Components of the Townsend score in the post-Hib conjugate vaccine era

Analysis of the four individual components of the Townsend material deprivation score showed a similar picture to that for the overall score. Differences in disease experience between the most deprived and the more affluent areas became apparent or more pronounced in the post-conjugate vaccine period.

Owner occupancy is broadly employed as a marker of long-term income and financial resources. The relationship between non-owner occupancy and invasive *H influenzae* disease has only been previously examined in a case-control study from the Republic of Ireland. Fogarty et al did not find a significant relationship between non-owner occupancy (defined as living in local authority accommodation) and increased risk of invasive *H influenzae* disease.[230] The significant association observed in the WMHR between living in areas of high non-owner occupancy and invasive *H influenzae* disease has been reported for meningococcal disease. In a case-control study which covered 8 districts in West England, Stanwell-Smith et al found that cases of childhood meningococcal disease were significantly less likely to have parents who were owner-occupiers than their control group.[47] In another case-control study, Stuart et al observed that cases living in council owned accommodation in South West England had a higher risk of meningococcal disease than their controls.[531] Case children also tended to live in houses which were damp and in poor structural condition. Previous reports

have shown that standards of housing and neighbourhood environment are generally better in more affluent areas,[21] and that poor housing has adverse effects on the health of children.[51,105]

In the WMHR, a general trend towards increased risk was seen with the other three components of the Townsend deprivation score, however none of these factors were significantly associated with invasive *H influenzae* disease.

The tendency towards a higher incidence of disease in areas with high unemployment has not been previously reported for invasive *H influenzae* disease. The observation is however supported by previously published studies. An ecological study by Maclure and Stewart on hospital admissions in Greater Glasgow found that children living in deprived areas were more likely to be admitted to hospital with infectious diseases than those from non-deprived areas.[93] They also reported that parental unemployment was one of the strongest predictors of admission for deprived children. Data from a smaller study suggests that these children are most susceptible around the time the parent becomes unemployed.[532] An ecological study at the district level in England reported that areas with high levels of unemployment had significantly lower immunisation uptake rates than areas with less unemployment. The nature of the study did not allow further exploration of this factor. However, individual level studies suggest that stressful family events affect the social environment of the child leading to increased susceptibility to illness.[45,532]

This study did not find a significant association between overcrowded households and increased risk of invasive disease. Using a variety of definitions of household crowding a number of studies from Britain,[19] Europe[152,230] and the

United States[155,277] have reported similar results. These findings are however, not universal, and contradictory results have been reported from the United States and Australia.[148,149,151,295,298]

Those studies which have reported a significant association between overcrowded households and invasive *H influenzae* disease have all been case-control studies. Two of the five studies reporting the lack of a significant association have been ecological studies. Failure to find an association in these studies, and the present study, may have been due to aggregated data not being sensitive enough to detect a relationship at the individual level.

Although the social meaning of car ownership may change with time and location, in this study it has been used as an indicator of material wealth, especially current income. This variable has not previously been examined as a risk factor for invasive *H influenzae* disease. However, a case-control study from South West England reported that fewer cases (71%) than controls (80%) had access to a car. Although a trend was seen suggestive of a relationship between areas with a high proportion of people without access to a car and invasive *H influenzae* disease in the WMHR, it was not statistically significant. Lack of access to a car has been associated with low immunisation uptake,[163] and this may contribute to an increased incidence of disease in these areas.

6.1.4.6 Socioeconomic factors in the post-Hib conjugate vaccine era

There was evidence in this study of an association between living in areas where the population was highly mobile and increasing incidence of invasive *H influenzae* disease. This risk factor has not been previously examined for invasive

H influenzae disease. A case-control study of meningococcal disease found that children who lived in families who had moved home in the 6 months prior to hospitalisation were significantly more likely to have meningococcal disease than controls.[47] This finding is consistent with previous reports which have associated this factor with low immunisation uptake rates and social disadvantage.[350,356,357] Migration may act by introducing carriers with different strains of the pathogenic organism to a group of susceptible children, or result from an influx of susceptible children. Another explanation is that changes in residence increase levels of stress, and this has been shown to have an association with infectious diseases in young children.[45,352] The finding of an increasing incidence of invasive *H influenzae* disease associated with areas of high migration also seems consistent with that reported for non-owner occupancy.

In this study low child population density of children less than 5 years of age was significantly associated with an increased incidence of invasive *H influenzae* disease in both the pre-conjugate and post-conjugate periods. To my knowledge there are no comparable data for this finding. Where population density has been studied in relation to invasive *H influenzae* disease, the whole population has been examined rather than just those less than 5 years of age. Only two reports were identified, both were from the United States and provided contradictory results. A study from Rhode Island of census tracts which contained populations that were 99.2% white did not find any relationship between *H influenzae* meningitis and population density.[277] However, the authors of this study failed to provide a definition for population density. Fraser et al defined population density as more than 100 people per square mile.[150] They found that in

Charleston County the incidence of *H influenzae* meningitis decreased with increasing population density in the white population, but could find no association with population density in the black population. These results are similar to those reported for the WMHR. One possible explanation for the finding in the present study are that children living in areas of low population density, are less likely to be exposed to the organism and therefore less likely to acquire natural immunity.

Lone parenthood has been reported as a significant risk factor for invasive *H influenzae* disease.[151,152] This study was unable to confirm such findings which have been observed in case-control studies carried out at the individual level.

6.1.4.7 Geographic distribution

The incidence of disease in the 'mainly rural' areas was consistently higher than that seen in the 'mainly urban' areas of the WMHR. This relationship has been previously reported[150,242] and may be linked to herd immunity or reduced susceptibility and earlier acquisition of natural immunity in the urban districts compared to rural districts due to children being in closer proximity. Other researchers have reported different findings. Floyd et al found that the incidence of *H influenzae* meningitis was significantly higher in urban areas than in rural areas.[132] Other reports from the United States[313] and Denmark[272] were unable to demonstrate any difference between urban and rural areas. The results reported for urban and rural areas in this study are consistent with those reported for areas of high and low population density in the WMHR (see section 6.1.4.6).

6.1.4.8 Seasonal variation

The bimodal pattern of disease seen in this study has been previously described by others.[126,231] The explosive increase in cases seen during October and November in the pre-conjugate vaccine era may be due to recent day-care or school attendees. These children either succumb to infection or introduce the organism into the household and siblings may then be affected.

The mean age at admission during the summer months was also significantly less than that seen during other seasons of the year. This may have resulted from a reduction in the number of susceptible children in the population as a result of acquired immunity. This finding may also be related to reduced interaction between young children, resulting in reduced risk of transmission of the organism.

A significant association was also observed between seasonality and ethnic group. Children of SA origin were less likely to present during the autumn compared to other seasons of the year. The reasons for this are not clear, however similar seasonal ethnic variations have been described in Israel. It was found that seasonal fluctuation in the occurrence of invasive *H influenzae* disease in the Jewish population was related to respiratory disease, whereas in the Bedouin population, it was related to seasonal epidemics of gastrointestinal disease.[292]

6.1.5 Clinical features

In the present study the clinical spectrum of disease were similar in both study periods. This contrasts with that reported by the PHLS six region study where an increase in the proportion of cases of epiglottitis was observed in the post-Hib conjugate vaccine period.[140]

6.1.5.1 Meningitis

In the WMHR 46% (62 of 136) of meningitis cases occurred in children less than 12 months of age in the pre-conjugate vaccine period. This is comparable with that reported from the Oxford region (49%),[139] Gwynedd (43%),[142] and Glasgow (42%)[141] during the same period. It is also congruent with the proportions of meningitis (37% - 46%)[126,270,271] seen in the populations of Western Europe.

The incidence of *H influenzae* meningitis fell by 92% between 1990/91 and 1993/94. This is similar to the reduction seen in the North East Thames region,[267] other parts of England and Wales,[140] and elsewhere in the world.[134,135,137,454]

It was disappointing to note that a smaller proportion of children with meningitis received pre-admission antibiotics in the post-conjugate era (29%) compared to the pre-conjugate era (39%). Overall, the results from this study indicate that 37% (62 of 168) children received pre-admission antibiotics, and that these children were older than those who did not. The age distribution may be related to the more overt signs of meningitis in older children. However, receiving antibiotics in the week prior to admission meant that these children were brought to hospital later than children with other diagnoses. Although the proportion who received pre-admission antibiotics is falling in the WMHR, it is still higher than

the 17% (53 of 305) reported by the British Society for the Study of Infection (BSSI) following a national survey of its members in 1989.[205] The study included 61 (20%) cases of *H influenzae* meningitis, however it was not possible to determine how many of these had received pre-admission antibiotics.

6.1.5.2 Epiglottitis

As with other reports of invasive *H influenzae* disease from Britain and Western Europe, epiglottitis was the second most common disease manifestation in the WMHR. British studies which have examined epiglottitis in detail are scarce, and comparisons have to be made by extrapolating data from the few available studies which have examined the epidemiology of invasive *H influenzae* disease. The annual incidence rate found in the pre-conjugate vaccine era in the WMHR (3.1 per 100 000 children less than 5 years of age) was similar to that seen in the Oxford region (3.7)[139] as well as France (2.0),[126] Israel (2.0)[234] and the Republic of Ireland (3.8).[230]

Incidence rates for epiglottitis in the WMHR in the first period of the study were lower than the 24.6 per 100 000 cases in children less than 5 years of age reported from Sweden[228] and the 20.4 per 100 000 observed in Australia.[232] In both of these studies cases of epiglottitis were clinically defined but did not need to be blood culture proven. The reduced incidence of this disease in the post-conjugate vaccine period in the WMHR is in keeping with data from the United States.[135,226,237]

Classically epiglottitis has been reported in older children. Comparing data in the present study with that previously reported indicates a shift towards a

younger age group. In the present study 41% (13 of 32) cases were aged less than 24 months. These findings are different from the 26%[141] and 32%[121] reported in recent British studies. They do however more closely resemble a recent report of 36% from the United States.[236] These findings may have implications for clinical practice as laryngotracheobronchitis commonly presents at less than 3 years of age.[225]

Previous reports have indicated a male predominance, with male:female ratios of between 1.4:1 and 2.1:1.[209,226,231,232] The present study reported a ratio of 2.6:1. The reasons for this difference, which was statistically significant, are not clear.

Extra-epiglottic complications are unusual, and pneumonia, observed in 16% (6 of 32) of epiglottitis cases, was the only complication. This figure is similar to the 10% reported by Broughton and Warren from Cambridge.[122] A number of studies have reported deaths from epiglottitis,[139,209,229] In this series there were no deaths from epiglottitis and this finding is similar to previous reports.[231,241]

6.1.5.3 Pneumonia

The incidence rate for *H influenzae* pneumonia in the WMHR in the pre-conjugate vaccine period (1.4 per 100 000 children less than 5 years of age) was comparable with that reported by Tudor-Williams et al from Oxford (1.2),[121] and Quigley et al from the North West (1.7).[233] In both of these studies only culture proven type b cases were included.

Prior to the introduction of Hib conjugate vaccine the infectious disease literature was not clear as to whether pneumonia was more likely to be caused by

serotypes other than type b *H influenzae*, and therefore less likely to be prevented by Hib vaccine.[244] In the present study the incidence of *Haemophilus* pneumonia fell by 71% when the two study periods were compared. This is in contrast to findings reported by Broadhurst et al in the USA,[135] where there was no change in incidence following the introduction of Hib conjugate vaccine. Results corresponding to those obtained in the WMHR have been reported recently following trials of PRP-T in 'developing' countries. Lagos et al reporting from Chile,[438] and Mulholland et al reporting from The Gambia,[439] both found reductions in the incidence of Hib pneumonia following immunisation with the conjugate vaccine.

The paucity of serotyping results for children with pneumonia in the WMHR emphasises the need for blood cultures to be taken and serotyped in order to confirm these findings in other populations.

6.1.5.4 Other invasive *H influenzae* diseases

The incidence of non-meningitic diseases other than epiglottitis experienced in the West Midlands (4.0 per 100 000 children aged less than 5 years) was in keeping with previous reports from Britain and Europe (range 5.1 - 7.0).[121,126,139,233]

6.1.5.5 Morbidity

The median length of hospital stay in both periods of the study were the same, and this suggests that the virulence of invasive *H influenzae* disease has not been altered by the vaccine.

All sequelae reported in this study were as a result of *H influenzae* meningitis, and are considered to be an underestimate. Insufficient detail was available in the medical notes and the presence of more subtle complications such as learning difficulties, motor abnormalities and behavioural problems may have been missed.

The occurrence of SNHL in 10% (10 of 102) cases tested is consistent with reports of SNHL ranging between 6% to 16% of survivors of *H influenzae* meningitis.[121,141,122,156,209] The estimate of children with SNHL in this study is conservative as only hospital case notes were used, and long-term follow-up was not part of the protocol. Furthermore, only 65% of *H influenzae* meningitis survivors in the WMHR had at least one hearing test following discharge. This is similar to the 69% of cases determined in a retrospective audit of case notes in a British hospital by Riordan et al.[217]

In the present study SNHL was significantly associated with symptoms of 48 hours duration or longer. This is in keeping with a previous report from the United States by Nadol,[533] but differs from the findings of a number of other studies. In these studies duration of illness was not associated with hearing loss.[207,534-536] The latter were prospective studies, whereas this report and that of Nadol were both retrospective in nature.

Antibiotics in the week prior to admission were received by 7 of 10 children with SNHL. Kaplan et al employed a similar methodology in an earlier prospective study carried out in two centres in the United States with a total of 281 children.[207] They found that 14 of 15 children who received antibiotics in the week prior to admission had SNHL following an episode of *H influenzae* meningitis.

Raivio and Koskiniemi used occupational class to classify a cohort of children followed-up for 1 to 15 years following an episode of *H influenzae* meningitis in Finland.[538] They found a higher proportion of hearing disorders in the lower social group compared to the highest. A Canadian study reported that children with sequelae of *H influenzae* meningitis were more likely to have lower socioeconomic status.[156]

This study also found that children from deprived areas (7 of 35) were significantly more likely to suffer post-meningitic SNHL compared to children from the most affluent areas (0 of 24, p=0.035). In this study deprived children were found to have generally poorer nutritional status than their peers from more affluent areas and this may be one factor which influenced the risk and severity of sequelae. Other risk factors at the individual level may also exert an effect on the severity of the disease.

6.1.5.6 Mortality

The overall case fatality rate of 3% amongst children with invasive *H influenzae* disease in the WMHR is comparable with that in a number of other reports from Britain,[142,141] Australia,[291] Switzerland,[209] France,[126] and the United States[279,280]. All have mortality rates which do not exceed 5%.

Most of the deaths in this series occurred prior to admission, and neonates and low birthweight babies were found to be at increased risk of death. This is concordant with data from a number of other studies.[260,301]

As with SNHL, children from the most deprived areas (6 of 109) were at greater risk of mortality than their more affluent counterparts (0 of 56, p=0.097). Again this may be due to factors operating at the individual level.

A trend towards increased mortality was noted in the second period of the study that almost reached statistical significance (p=0.078). This gives cause for concern especially as it did not appear to be related to antibiotic resistance. Although ampicillin resistance increased in the second period of the study, few children were actually given this antibiotic. The results add support to the suggestion that the virulence of the organism has not been diminished.[137]

6.1.5.7 Antibiotic regimens

Cephalosporins have been recommended as empirical therapy for suspected *H influenzae* meningitis because of increasing ampicillin resistance, the emergence of chloramphenicol resistance and multiple-drug resistant strains.[377] In this study the significantly increased use of cepahlosporins in the post-Hib vaccine period may reflect these recommendations. The pre-conjugate vaccine findings are generally similar to reports by the BSSI[205] and Quigley et al.[233] To my knowledge there are no data relating to prescribing in the post-conjugate vaccine era for invasive *H influenzae* diseases. Despite the changes in prescribing practice there has not been a reduction in the mortality associated with *H influenzae* meningitis in the post-conjugate vaccine period.

6.1.5.8 Dexamethasone

The Meningitis Working Party of the British Paediatric Immunology and Infectious Disease's Group reviewed the evidence regarding the use of dexamethasone in the treatment of meningitis.[129] They decided that there was insufficient evidence to recommend its use for *H influenzae* meningitis in particular, or other forms of bacterial meningitis in general in Britain.

Despite the report of the Working Party, parenteral dexamethasone was found to be administered in the WMHR with increasing frequency when the two study periods were examined (55% and 65% in the pre-conjugate and post-conjugate vaccine periods respectively).

This study did not find any evidence that dexamethasone reduced mortality, SNHL or neurological complications in children with *H influenzae* meningitis as reported by researchers in the United States and Switzerland.[219-221] The data are however in keeping with the results of two meta-analyses which examined published randomised controlled trials where dexamethasone had been used together with antibiotics to treat bacterial meningitis.[393,394] Both reported that the available evidence did not support the routine use of dexamethasone.

Unfortunately the present study is a retrospective examination and does not permit any firm conclusions to be drawn as treatment regimens were not standardised. Perusal of the case notes also indicated that in some cases the timing, dosages and duration were not consistent with recommended practice.[396]

The use of dexamethasone with regard to its potential for reducing morbidity and mortality associated with *H influenzae* meningitis generated great

debate. This debate has now been rendered virtually academic since the advent of Hib conjugate vaccine.

6.1.5.9 Prophylaxis

Rifampicin has been shown to be effective in eradicating carriage of Hib from the nasopharynx and is recommended for the index case prior to discharge and for close contacts, especially in households with unimmunised children under 4 years of age.[403]

In this study there was confusion amongst paediatricians as to who should receive prophylaxis, with only approximately 30% of cases with siblings aged less than 4 years receiving chemoprophylaxis. A recent Australian study found similarly poor compliance levels among medical staff regarding recommendations for rifampicin prophylaxis.[537]

There were also significant disease, ethnic, gender and seasonal differences amongst cases and contacts who received prophylaxis. The reasons for the gender and ethnic differences are not clear and have not previously been reported. Index cases of *H influenzae* meningitis and their contacts were more likely to receive prophylaxis than cases with non-meningitic disease and their contacts. Given that meningitis attracts more publicity and causes more anxiety than non-meningitic invasive *H influenzae* diseases, then this would be expected. However, the recommendation is that all appropriate contacts and all cases of invasive Hib disease be given prophylaxis.[403] It is not known whether the differences arose because of inadequate knowledge or misinterpretation of the guidelines. The

results obtained in this study confirm the assertion by Gilbert at al that poor medical compliance reduces the already limited value of prophylaxis.[537]

Fewer cases in the WMHR received chemoprophylaxis in the autumn and this may have been as a result of inappropriate knowledge regarding chemoprophylaxis on the part of newly appointed junior doctors or inadequate knowledge on the part of health professionals regarding Hib conjugate vaccines ineffectiveness in preventing acquisition and carriage of Hib. Support for these were found in the case notes where the dosage and duration of rifampicin for *H influenzae* (20mg/kg/day, upto a maximum of 600mg daily)was confused with that for meningococcal disease (10mg/kg twice daily for two days in children).[201]

6.1.6 Bacterial epidemiology

6.1.6.1 Diagnostic tests

The incidence of non-meningitic diseases may be higher than that reported in this study especially in cases where observed clinical features did not lead to confirmation by CSF or blood culture. This underlines the need for blood cultures to be taken in all cases, especially in the post-vaccine era to confirm serotypes and antibacterial sensitivity.

6.1.6.2 Serotypes

Of the 154 isolates typed in this study 152 (99%) were serotype b, the other two isolates were non-capsulate strains. This confirms the assumption that the incidence of invasive *H influenzae* disease is congruent with invasive type b disease, and falls within the range of 81% to 100% seen worldwide.[121,126,232,233,273,280]

There was also increased serotyping of isolates in the post-vaccine period which may be due to the continuing national surveillance carried out by the BPSU for vaccine failures.

There was some concern that the success of the vaccine would lead to an increase in other types of *H influenzae* as potential pathogens.[166] Serotyping provides an epidemiologic marker which can be used to determine whether changes in the pattern of *H influenzae* disease occur in the post-conjugate vaccine era. Hargreaves et al reported a progressive increase in the number of infections due to non-typeable *H influenzae* in England and Wales.[140] These pathogens rose slowly from 45 cases in 1990/91 to 67 cases in 1993/94. The authors acknowledged that their results may have been influenced by improved surveillance and awareness following the introduction of Hib conjugate vaccine.

Data from the USA has provided contrasting results. Anderson et al used national laboratory-based surveillance data to determine the impact of Hib conjugate vaccine on all cases of *H influenzae* disease.[459] They found that incidence rates had fallen substantially for both *H influenzae* type b disease and non-type b among children aged less than 5 years.

6.1.6.3 Antibiotic resistance

Antibiotic resistance to ampicillin was found in 19% of strains isolated from patients in the WMHR in the pre-conjugate vaccine period. This is in keeping with reports from other parts of Britain during the same time period. Anderson et al reported that 15% of isolates were resistant to ampicillin in the PHLS six region study[249] Similarly, Howard found ampicillin resistant strains in

12% of isolates in Wales.[142] Comparable data has also been reported from Australia (16%)[256] and the Republic of Ireland (16%).[230] Sweden appears to have a much lower antibiotic resistance rate (6%).[271,273] Several countries in Western Europe, such as Spain (60%)[127] France (55%)[126] and Switzerland (21%)[209] have much higher rates which approach or exceed those seen in 'developing' countries such as Barbados (40%),[539] Hong Kong (26%),[239] Thailand (24%),[243] and Nigeria (11%).[124] Strains resistant to chloramphenicol or cephalosporins were not identified in the WMHR although there have been reports of chloramphenicol resistance in upto 2% of isolates in Britain.[197,249] A number of British studies have also reported that up to 2% of isolates may be resistant to both chloramphenicol and ampicillin.[142,249] Both the Republic of Ireland (2%)[230] and France (3%)[126] have reported strains resistant to both ampicillin and chloramphenicol. However, Campos et al reported that 57% of isolates in Spain were resistant to both antibiotics.[127] The observed differences in antibiotic resistance may be as a result of differences in prescribing patterns, different methods of collecting and testing specimens or due to different strains of the organism.

Resistance changed over the course of this study with ampicillin resistance increasing in the post-conjugate vaccine period to 19% from 14% in the pre-conjugate vaccine era. This observation has also been reported by the PHLS six region study where ampicillin resistant Hib isolates increased from 15% in the pre-conjugate period to 22% in the post-conjugate vaccine period.[140]

A significant association ($p=0.045$) was noted between ampicillin resistant *H influenzae* isolates and subsequent SNHL in the WMHR. To my knowledge this has not been previously reported. This finding has important clinical implications

as children whose isolates exhibit ampicillin resistance may require more careful follow-up and evaluation for SNHL.

The spread of multiply resistant strains and the increasing frequency of antibacterial resistance are of some concern. In addition, the problems noted with the monitoring of chloramphenicol levels in this and other studies has led to the promotion of cephalosporins as alternative first-line antibiotics in the treatment of *H influenzae* meningitis.

6.2 METHODOLOGICAL ISSUES

6.2.1 Study limitations

The present study has several potential limitations which need to be addressed. The design of the study presented in this thesis was an ecological one which focused on the relationship between invasive *H influenzae*, deprivation and other markers of socioeconomic disadvantage. Ecological studies risk the 'ecological fallacy' thereby making it difficult to attribute area socioeconomic data to the individual.

The analysis of multiple variables is more likely to produce statistically significant associations by chance. However, in this study many highly significant probability (p) values as well as narrow confidence intervals were obtained. These reduce the likelihood that the results were obtained by chance.

The small numbers of cases limits the conclusions which may be drawn from the study and their generalisability. Multivariate analysis was not used in this

study as the numbers in each category or sub-category would have been small, especially in the post-conjugate vaccine era.

In a retrospective study, it is difficult to draw conclusions regarding the absence of a factor since the fact that it has not been documented is not a reliable indicator of whether it had been present or not at that particular time. Retrospective studies are therefore limited in the amount and quality of data collected at the individual level. This study was therefore unable to consider other potential risk factors suggested by the literature at the individual level, such as smoking and breast-feeding. Much of the data on these factors were either poor or entirely absent from the case notes and reflect poorly on the quality of paediatric medical notes.

Efforts were made to ensure that case ascertainment was as complete as possible. However, analyses of sub-groups resulted in small numbers in some instances, and this manifested as wide confidence intervals. It is possible that some cases were missed for a variety of reasons. One assumption made was that all children with invasive *H influenzae* disease were hospitalised and had their diagnoses confirmed microbiologically. Some children hospitalised outside the region, or those who had received pre-admission antibiotics resulting in negative cultures may have been missed. Similarly, different clinical practices for obtaining cultures may have affected ascertainment, particularly for non-meningitic cases.

As the study was not restricted to Hib cases it is possible that a number of other serotypes or non-typable invasive *H influenzae* cases which are not vaccine preventable would have been included. This approach however, was justified as

the results demonstrated that although only 60% of cases had specimens serotyped 99% of these were serotype b.

Death certificates, and discharge diagnoses using the International Classification of Disease (ICD) codes for the various manifestations of invasive *H influenzae* were not used to identify cases. Previous research using these methods has indicated that the reliability of these sources is questionable, especially with regard to quality and completeness. Furthermore, mortality in this study was equivalent to that seen in studies where identification of deaths were actively sought.

One of the criteria for inclusion in the study was the location of case notes. However, the reliance on historical data collected by different people using different interviewing techniques, illegible handwriting and incomplete social and clinical information, may have contributed to incomplete data sets. Failure to locate case notes resulted in a number of children being excluded from the study. Although this may have led to an underestimate of the incidence of disease the rates were still comparable with those reported from other parts of Britain.

Data extraction from the medical records of each patient was carried out by the researcher. This may have led to researcher bias as there would have been more incentive to search for as much information as possible for the study. However, there would have been less likelihood of interobserver variation. In order to minimise intraobserver variation, a standard proforma was used to abstract data.

Ethnic origin was obtained by dividing cases into two groups, children of South Asian and non-South Asian origin. It is recognised that neither group is

homogenous and that children of African-Caribbean origin were not identified separately. The criteria for dividing children according to ethnic origin were the last names and first names. In most cases African-Caribbean children have names which are similar to Caucasian names, it was therefore not possible to distinguish them. Even if this had been possible, their anticipated numbers would have been small as they constitute only a small proportion of the population in the West Midlands.

The geographic classification of districts into 'mainly rural' and 'mainly urban' meant that a number of urban areas were classified within the 'mainly rural' category and vice versa. More discriminatory operational criteria may have produced different results but would have resulted in the use of much smaller numbers.

Accurate population data were available only at one point in time during the period of this study. Changes outside the 1991 census year have not been taken into account and may have led to an underestimate in the population at risk.

6.2.2 Study strengths

This study has a number of strengths which lend support to the plausibility of its findings. Strong associations were observed in relation to the main objectives of the study. The results reported in this study were also consistent with those previously published by a number of different researchers using different methodologies over the last two to three decades. The results are also biologically plausible in that children living in the most deprived areas are at greater risk of lower immunisation uptake rates, have poorer nutrition and social environments

and are therefore at greater risk of disease. In the post-Hib conjugate vaccine era this has manifested itself as an increased risk of disease in these children relative to their more affluent peers.

Hospital or laboratory-based studies may be affected by different types of bias, particularly selection bias. This study was population-based and therefore attempted to avoid selection bias. The denominator consisted of a defined susceptible population, that is children aged less than 5 years of age.

Multiple sources of case ascertainment were used in this study because of inherent limitations in each of the individual systems. The systems are however linked to each other and taken together provide a comprehensive picture of the incidence of invasive *H influenzae* disease in both periods of the study. The period of surveillance involved varying amounts of prospective and retrospective data collection from each surveillance system. Nevertheless, complete case ascertainment was attempted throughout for each surveillance system, and the database is considered to be comprehensive.

The research was carried out in the WMHR using a defined geographic population which has a similar ethnic distribution to that of England and Wales. The study straddled the 1991 UK census, and this allowed accurate determination of both numerator and denominator.

The WMHR was not included in the PHLS six region study. It is therefore unlikely that contributors to the HICARE study would have assumed that reports to the PHLS would be provided to HICARE.

A clear case definition was used for this study which was limited to culture proven cases. This definition was employed in order to increase the precision of

the study. This seems justified as a number of cases which might have been included with inappropriate diagnoses were excluded.

The risk factors chosen for the socioeconomic analysis were selected *a priori*. They were all previously defined markers for either deprivation, poor immunisation uptake, or both. The Townsend material deprivation score was used for this study, and it has been demonstrated to be one of the best indicators of material deprivation.

The geographic unit of analysis chosen for this study was the ED. This is the smallest area unit available for ecological analysis. Diggle and Elliott have indicated that the use of larger geographic units such as wards, may mask differences in deprivation experience amongst the population due to the aggregation of data. They recommend the use of enumeration districts as area characteristics at this level are said to be more applicable to the individual.

CHAPTER 7

CONCLUSION AND RECOMMENDATIONS

CONCLUSION AND RECOMMENDATIONS

Various aspects of the health literature have been reviewed and the data obtained from HICARE analysed. The emphasis has been on the effect of Hib conjugate vaccine on the epidemiology and ecology of invasive *Haemophilus influenzae* disease following its introduction into the UK immunisation schedule. This, the final chapter attempts to draw together the threads of the previous chapters and to provide recommendations and pointers to areas requiring more information.

7.1 CONCLUSION

This four year study has described the epidemiology of invasive *H influenzae* disease and explored its relationship with deprivation in the WMHR both prior to and following the introduction of Hib conjugate vaccine using an ecological approach. To my knowledge this study provides the first detailed account of the relationship between deprivation and other socioeconomic risk factors and invasive *H influenzae* disease in the UK. The study is also the first to describe in detail the epidemiological changes brought about by the introduction of Hib conjugate vaccine in an ethnically and socioeconomically diverse population.

This study has indicated that the age-group of those most at risk has shifted to an older age group. Significant ethnic differences in age distribution were observed,

as well as different ethnic disease experiences in relation to gender, disease distribution and immunisation uptake.

Almost everyone is aware of the maxim 'prevention is better than cure', but rarely practice it. The sense of security surrounding the success of Hib conjugate vaccine and its efficacy should be tempered by the numerous missed vaccination opportunities. The clinical spectrum and virulence of the disease has not changed and invasive *H influenzae* disease still results in mortality and significant neurological sequelae. Despite new and more powerful antibiotics *H influenzae* meningitis remains potentially fatal and a potential cause of disability. Although a reduction in the proportion of children with neurological sequelae were noted in the post-conjugate vaccine period, case-fatality increased. The continued prevention of invasive Hib infections appears to be the measure which will continue to have the greatest impact.

With regard to socioeconomic analyses, disease gradients were demonstrated in relation to almost all the socioeconomic census variables examined. A number of these were statistically significant in the second half of the study. This thesis has therefore provided an original contribution to the continuing debate on inequalities in health by pointing out that although Hib vaccine has greatly reduced the incidence of disease, children from deprived areas remain at relatively greater risk than their peers who live in more affluent areas.

The inherent limitations of this type of study are also acknowledged. It is recognised that ecological studies are useful in identifying possible risk factors and generating ideas for further research.

It has been said that "infectious diseases are now under control". Hib conjugate vaccine appears to have tamed invasive *Haemophilus influenzae* disease, but recent experience with pertussis in England indicates that when a significant decrease in vaccine uptake occurs a marked increase in incidence will follow. There are also lessons to be learnt from the re-emergence of tuberculosis and other diseases previously thought to be under control. It is therefore important to maintain, expand and improve immunisation uptake and surveillance. This can be achieved by targeting individuals as well as areas in order to prevent Hib related morbidity and mortality reemerging as major public health problems.

7.2 RECOMMENDATIONS

The success of Hib conjugate vaccine in the WMHR has resulted in an improvement in the overall health of the child population. Unfortunately the health of the poorest or most deprived children has not improved relative to that of children from more affluent areas. However, it remains unclear as to whether this has occurred as a result of economic, social, cultural, behavioural or environmental factors.

History has demonstrated that health and poverty are intertwined, and that consequent to reductions in poverty there were improvements in health. If it is not possible to eradicate poverty, then there must be policies across all government departments which improve the overall socioeconomic conditions of deprived people. The following recommendations are therefore made from the results of this study:

7.2.1 Incidence of disease

1 Educate health professionals who contribute to the surveillance of *H influenzae* disease of the need to continue notifying and reporting Hib disease. The organism is still capable of causing considerable morbidity and mortality and they should not become complacent as a consequence of the success of the vaccine.

2 The extent of underreporting detected in this study indicates that the quality of the data available should be assessed before it is used for the formulation and implementation of health policies.

3 Improve the efficiency of locating medical records, especially those of children from ethnic minorities who may have similar names. Use of a single unique number, possibly the NHS number may be appropriate.

4 The recording of information in case notes should be improved, particularly for the collection of socioeconomic data and the child's immunisation history. A short standardised proforma could be employed.

5 There should be some mechanism for the storage and retrieval of the case notes of children who have died.

6 Disease registers for other infectious diseases may be organised using the HICARE register as a template. This will provide high quality data in anticipation of the introduction of new vaccines, and prevent the type of underreporting seen with invasive *H influenzae* disease.

7.2.2 Individual risk factors

1 Children of SA origin with *H influenzae* meningitis were hospitalised later than their NSA peers. This may indicate lack of awareness of SA parents as to the type and severity of the symptoms. Meningitis campaigns should therefore contain material targeted at this population.

2 The pattern of immunisation uptake in children of SA origin suggests that this population should be targeted for health education and health promotion. Similar provisions should be made for other disadvantaged groups.

3 The increased proportion of children who were underweight for age in the second period of the study suggests that there may be a need for improved nutrition among children in the WMHR in order to promote protection from disease.

7.2.3 Family and community risk factors

1 Ensure that daycare facilities maintain registers of communicable illnesses in attendees.

2 Daycare facilities should keep a register of the immunisation status of new admissions and encourage parents to immunise their child if he or she is found to be incompletely immunised.

3 Health personnel should be more aware of the preventive aspects of medicine, and the importance of public health should be strongly emphasised in the medical and nursing school curricula.

7.2.4 Environmental risk factors

1 Education regarding immunisation and its importance for parents and all health professionals. The benefits of personal immunity rather than community immunity should be emphasised.

2 The use of parent-held child records may improve immunisation uptake, especially if parents are asked to bring them along whenever their child is admitted to hospital.

3 This study has shown that GIS is a useful tool in the analysis of health data in relation to socioeconomic circumstances. GIS has been used to

identify where the areas of highest deprivation are, and it is within these areas that improved immunisation services which target disadvantaged families may help to reduce inequalities and reverse the 'inverse care law'.

3 Deprived areas and individual families should be targeted in order to improve immunisation uptake rates and reduce inequalities. This may require making vaccination more accessible and visiting families in their homes to bring children up-to-date with their immunisations.

4 Computer generated appointments for those children living in deprived areas should be flagged, and health professionals informed that the child is at risk of not completing the primary immunisation schedule.

5 Parental poverty and deprivatien impinge on the health of children, and the issue of deprivation needs to be addressed. One way to alleviate the social and economic disadvantage of deprived families is by educating them about social security benefits available to them, improving housing stock and employment opportunities. Therefore, multidisciplinary and cross-agency working to provide co-ordinated and comprehensive social, educational and health care for the child and family should be encouraged.

7.2.5 Clinical features

1 Education for parents and health professionals regarding the features of meningitis as many children were brought to hospital late. This may be undertaken in a structured manner in primary and secondary care settings. It should also be undertaken opportunistically during child health checks.

2 Education for health professionals regarding chemoprophylaxis for *H influenzae*, and how it differs from that for meningococcal disease. Alternatively, this chemoprophylaxis may be left to the hospital pharmacist or CCDC.

3 The use of dexamethasone for *H influenzae* meningitis is still not resolved and may need further study. However, given the success of the vaccine this is unlikely as there would be insufficient numbers. Physicians should therefore be educated on the appropriate usage of the drug.

4 If chloramphenicol is given then appropriate monitoring of blood levels should be conducted.

5 In the light of the increase in ampicillin resistance and the problems with chloramphenicol, this study supports the recommendation that cepahalosporins be used for the treatment of invasive *H influenzae* diseases. They are equally as effective as ampicillin and chloramphenicol, can be administered less often and do not require regular serum assays.

6 Parents should be made aware of the necessity to attend follow-up appointments, especially in cases where the child had meningitis. This may require co-operation at the primary care level.

7 Appropriate hearing tests should be carried out for all children following an episode of meningitis and hospital physicians should make the referrals directly rather than asking the family GP to do so.

8 Discharge letters should be written for all children following invasive *H influenzae* disease not just those with meningitis. This would be especially relevant for those attending daycare, childminders or school.

7.2.6 Laboratory investigations

1 Appropriate specimens and cultures should be taken and sent to the laboratory for typing and antibacterial sensitivity.

2 Continued surveillance is required regarding antibiotic resistance. This study has shown that ampicillin resistant *H influenzae* have increased in recent years.

3 Blood specimens of young children with pneumonia should be accompanied with requests for serotyping of any *H influenzae* strains identified. This will assist in determining the effect of Hib conjugate vaccine on the epidemiology of *H influenzae* pneumonia.

4 The current reliance on clinical suspicion as a basis for the notification of disease is inadequate. Laboratory reports give a more accurate picture and should be incorporated into the statutory system.

7.3 FURTHER RESEARCH

This study has identified factors associated with increased incidence of invasive *H influenzae* disease in children from deprived areas relative to children in affluent areas following a public health intervention. As a result of the study design only tentative findings can be reported. An analytical study design would be required before firm conclusions could be drawn. Although Hib conjugate vaccine has been a success there are still areas where more knowledge is required.

1 Continued surveillance of invasive *H influenzae* disease to determine any changes in serotypes causing disease and define populations at risk.

2 Immunogenicity of the vaccine in ethnic minorities is yet to be ascertained in the UK.

3 Determination of ethnic-specific rates in other areas for comparison with the data reported in this study would be valuable.

4 The exact role of reduced oropharyngeal carriage in herd immunity is yet to be determined. If the effect is real, then incidence rates in those above 5 years should also fall.

5 A post-Hib conjugate vaccine survey of immunisation uptake and attitude to immunisation by ethnic group.

6 A further study looking at deprivation and invasive *H influenzae* disease in a different health region or nationally, but with more differentiation between ethnic groups.

7 The epidemiology of *H influenzae* pneumonia needs to be ascertained in the post-conjugate vaccine era to determine the effect, if any, of Hib conjugate vaccine on the incidence *H influenzae* pneumonia.

8 Evaluation of the knowledge, attitude and practice of doctors, especially junior doctors, towards chemoprophylaxis.

9 Determination of paediatric ward policies with regard to opportunistic immunisation.

10 Continued monitoring of antibiotic resistance to inform treatment for invasive *H influenzae* disease.

11 Determination of environmental risk factors, if any associated with Hib conjugate vaccine failure.

12 The apparent increase in mortality since the introduction of the vaccine warrants further investigation.

13 Research is required into the apparent association between SNHL and deprivation, and SNHL and increased ampicillin resistance, and whether there is a similar relationship with other causes of meningitis.

14 An update of the Peckham report to determine the current knowledge and attitude of parents and health professionals towards immunisation. This is especially relevant in the light of the increasing number of vaccines becoming available and the recent debate surrounding adverse events associated with vaccines.

15 An economic evaluation of the impact of the reduced Hib caseload on hospital bed utilisation and community resources.

7.4 LONG-TERM PLANS

The experience gained from this study has already been utilised in constructing and maintaining a regionwide meningococcal disease register. The HICARE register has already provided a sampling frame for further research and can be used to follow-up these children, especially for the detection of sequelae following meningitis.

7.4.1 Dissemination of results

It is intended that the results of this study are disseminated widely. Presentations have already been made at the local, national and international level at child health and public health conferences (see appendix 3). Manuscripts are being prepared or have been submitted to peer-reviewed journals.

7.4.2 Data storage

It is intended that paper copies of correspondence, laboratory records, reports, data recording forms and other manual items used during the study will be stored for several years at the University of Warwick, after identifiers have been removed.

Data on computer will be downloaded onto disks and stored securely and separately from the paper records.

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APPENDIX 1

Research Proforma

IN STRICT MEDICAL CONFIDENCE

CONSULTANT PAEDIATRICIAN'S NAME

HOSPITAL No.

LABORATORY No.

SECTION I: PERSONAL DETAILS

1 NAME:

First name:

Last name:

2 DATE OF BIRTH: 19

3 SEX: M 1 F 2

4 INDEX ADDRESS:

POSTCODE

5 PARENT/MAIN CARER

6 FAMILY HISTORY

7 NAME & ADDRESS OF FAMILY GP

POSTCODE

8 SEEN BY GP IN WEEK PRIOR TO ADMISSION Yes 1 No 2

9 INITIAL GP DIAGNOSIS

IN STRICT MEDICAL CONFIDENCE

SECTION II: CLINICAL DATA

1 DATE OF ADMISSION: ☐☐ ☐☐ 19☐☐

2. MODE OF ADMISSION Self ☐ 1 GP ☐ 2 Other ☐ 3

3 TIME OF ADMISSION: ☐☐ hours ☐☐ minutes AM/PM

4. DURATION OF ILLNESS BEFORE ADMISSION (TICK ONE):
Less than 24 hours ☐ 1 24-48 hours ☐ 2 More than 48 hours ☐ 3 Unknown ☐ 9

5. ANTIBIOTIC TREATMENT IN 48 HOURS BEFORE ADMISSION:
Yes ☐ 1 No ☐ 2

IF YES, please indicate :

ANTIBIOTIC	DOSE	ROUTE	FREQUENCY	DATE STARTED	DATE STOPPED	RECEIVED
1						
2						

6. WEIGHT ON ADMISSION: ☐☐•☐☐ kg

7. TEMPERATURE ON ADMISSION: ☐☐•☐ °C

8. SIGNS & SYMPTOMS PRESENT ON ADMISSION:

Bulging/full ant. Fontanelle	☐ 1	Neck stiffness	☐ 13
Convulsions	☐ 2	Otitis media	☐ 14
Diarrhoea	☐ 3	Pallor	☐ 15
Drooling	☐ 4	Peripheral shutdown	☐ 16
Dysphagia	☐ 5	Photophobia	☐ 17
Fever	☐ 6	Poor feeding	☐ 18
Headache	☐ 7	Rash (specify state)	☐ 19
Irritability	☐ 8	_____	
Jaundice	☐ 9	Respiratory symptoms	☐ 20
Lethargy	☐ 10	Soft tissue swelling (specify state)	☐ 21
Limb/joint pain (specify site)	☐ 11	_____	
_____		Sore throat	☐ 22
Limb/joint swelling (specify site)	☐ 12	Vomiting	☐ 23
_____		Other (specify)	☐ 24
		_____	
		_____	

9. COMMENTS:

_____ _____
_____ _____
_____ _____

IN STRICT MEDICAL CONFIDENCE

10. STATE OF CONSCIOUSNESS ON ADMISSION:

Awake/fully conscious	☐	1
Drowsy	☐	2
Semi-conscious	☐	3
Unconscious	☐	4
Not documented	☐	5

OR DESCRIBE

_____

_____

_____

_____

11. DIAGNOSIS ON ADMISSION

Meningitis	☐	1	Septic arthritis	☐	6
Epiglottis	☐	2	Osteomyelitis	☐	7
Bacteraemia/Septicaemia	☐	3	Other diagnosis (specify)	☐	8
Cellulitis	☐	4			
Pneumonia	☐	5			

_____

_____

12. SEIZURE ACTIVITY DURING ADMISSION

None	☐	1
Yes, within 24 hours of admission	☐	2
Yes, between 24-48 hours after admission	☐	3
Yes, more than 48 hours but less than 72 hours after admission	☐	4
Yes, more than 72 hours after admission	☐	5

13. Other complications during admission? Yes ☐ 1 No ☐ 2

IF YES, specify: _____

14. THERAPEUTIC REGIME:

	DRUG	DOSE	ROUTE	FREQUENCY	DATE STARTED	DATE STOPPED	RECEIVED
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							

15. Was dexamethasone given?

No not given	☐	1
Yes, before antibiotics	☐	2
Yes at the same time as antibiotics	☐	3
Yes, but after antibiotics (specify how long after):_____	☐	4
Other (specify): _____	☐	5

16. Time first antibiotics given:

☐☐ hours ☐☐ minutes AM/PM

IN STRICT MEDICAL CONFIDENCE

17. Was child admitted to ITU or equivalent? Yes ☐ 1 No ☐ 2

IF YES, date of admission to ITU: ☐☐ ☐☐ 19

18. Date of discharge from ITU: ☐☐ ☐☐ 19

19. COMMENTS DURING ADMISSION:

20. PROCEDURES:

21. OUTCOME:
- Survived, no complications detected on discharge ☐ 1
- Survived, complications on discharge ☐ 2
- Died ☐ 3

22. DATE OF DISCHARGE: ☐☐ ☐☐ 19

23. FINAL DIAGNOSIS:
- Meningitis ☐ 1
- Epiglottitis ☐ 2
- Bacteraemia/Septicaemia ☐ 3
- Cellultitis ☐ 4
- Septic arthritis ☐ 5
- Osteomyelitis ☐ 6
- Other diagnosis (specify) ☐ 7

24. DISCHARGED TO:
- Home ☐ 1
- Died ☐ 2
- Other place (specify and give reason) ☐ 3

25. COMPLICATIONS

	ON DISCHARGE	AT FOLLOW-UP	AFTER 3 MONTHS	AFTER 6 MONTHS
None	☐ 1	☐ 1	☐ 1	☐ 1
Ataxia	☐ 2	☐ 2	☐ 2	☐ 2
Behaviour problems	☐ 3	☐ 3	☐ 3	☐ 3
Convulsions	☐ 4	☐ 4	☐ 4	☐ 4
Facial palsy	☐ 5	☐ 5	☐ 5	☐ 5
Hearing loss	☐ 6	☐ 6	☐ 6	☐ 6
Hemiparesis	☐ 7	☐ 7	☐ 7	☐ 7
Hydrocephalus	☐ 8	☐ 8	☐ 8	☐ 8
Impaired vision	☐ 9	☐ 9	☐ 9	☐ 9
Language problems	☐ 10	☐ 10	☐ 10	☐ 10
Quadriparesis	☐ 11	☐ 11	☐ 11	☐ 11
Recurrent meningitis	☐ 12	☐ 12	☐ 12	☐ 12
Strabismus	☐ 13	☐ 13	☐ 13	☐ 13
Others (specify)	☐ 14	☐ 14	☐ 14	☐ 14

IN STRICT MEDICAL CONFIDENCE

28. COMMENTS ON DISCHARGE:

29. CCDC/PUBLIC HEALTH CONSULTANT NOTIFIED?
Yes ☐ 1 No ☐ 2

30. BPSU NOTIFIED: Yes ☐ 1 No ☐ 2 Not appropriate ☐ 9

SECTION III: PAST MEDICAL HISTORY

1. BIRTH WEIGHT: lb | oz OR | • | kg

2. GESTATION: | weeks

3. PREVIOUS ADMISSIONS FOR MORE THAN 24 HOURS IN THE LAST 6 MONTHS?:
Yes ☐ 1 No ☐ 2

IF YES, indicate below:

	DATE OF ADMISSION	DATE OF DISCHARGE	DIAGNOSIS	COMMENTS
1				
2				
3				

4. HISTORY OF TREATMENT FOR A CHRONIC ILLNESS: Yes ☐ 1 No ☐ 2

IF YES, indicate the chronic illness and date of diagnosis (if date unknown, put in unknown):

	CHRONIC ILLNESS	DATE DIAGNOSED		
1				19
2				19
3				19

5. Recent illnesses:

6. IMMUNISATION STATUS PRIOR TO ADMISSION (not including Hib vaccine status)

Appropriate for age	☐ 1
Incomplete	☐ 2
None	☐ 3
Not recorded	☐ 4

Children should have received the following vaccines by:
6 months: *3 doses of DTP + polio (Hib after Oct.1992)*
15 months: *Measles/MMR*

7. Comment on Hib immunisation record:

Yes, received Hib vaccine during/after Oct. 1992	☐ 1
No, did not receive Hib vaccine during/after Oct. 1992	☐ 2
Not appropriate, case occurred before Oct. 1992	☐ 3
Not recorded	☐ 9

IN STRICT MEDICAL CONFIDENCE

If Hib immunisation received, record dates below:

DOSE			DATE RECEIVED		
First dose		1			19
Second dose		2			19
Third dose		3			19

8. Were any missed immunisations given prior to discharge? Yes ☐ 1 No ☐ 2

SECTION IV: PROPHYLAXIS/TAKE HOME MEDICATION

1. Prophylaxis to index child: Yes ☐ 1 No ☐ 2

2. Prophylaxis to contacts: Yes ☐ 1 No ☐ 2

IF YES, indicate below

RELATIONSHIP	AGE	DRUG	DOSE	ROUTE	FREQUENCY	DURATION
1. Index child						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						

3. Take home antibiotics for index child: Yes ☐ 1 No ☐ 2

IF YES, indicate below

DRUG	DOSE	ROUTE	FREQUENCY	DURATION

SECTION V: FOLLOW UP

1. Follow up date: Yes, see below ☐ 1 No, not given ☐ 2

Follow up date: ☐☐☐ 19

2. Was child brought for follow up? Yes ☐ 1 No ☐ 2

3. COMMENTS:

IN STRICT MEDICAL CONFIDENCE

4. Discharge letter to GP from unit? Yes ☐ 1 No ☐ 2

IF YES, date of letter: ☐☐ ☐☐ 19☐☐

5. Did GP request information re: immunisation/other following discharge?

Yes ☐ 1 No ☐ 2

6. COMMENTS:

_____

_____

_____

_____

7. Was hearing test requested? Yes ☐ 1 No ☐ 2 Not appropriate ☐ 3

8. Record dates of all tests (including hearing tests) requested:

	TEST	DATE REQUESTED	DATE CONDUCTED	OUTCOME/COMMENTS
1				
2				
3				
4				
5				
6				

IN STRICT MEDICAL CONFIDENCE

SECTION VI: INVESTIGATIONS DURING ADMISSION

Microscopy, culture and sensitivity

1. LUMBAR PUNCTURE PERFORMED:

Within 24 hours of admission 1
Between 24-48 hours after admission 2
More than 48 hours but less than 72 hours after admission 3
More than 72 hours after admission 4
No 5

2. DATES AND RESULTS OF REQUESTS FOR CSF INVESTIGATIONS:

	INVESTIGATION	DATE 1	DATE 2	DATE 3	DATE 4
1	Appearance				
2	Gram stain (POS/NEG)				
3	Culture (POS/NEG)				
4	Glucose (mmol/L)				
5	Protein (g/L)				
6	WBC - total ($x10^6$/l)				
7	WBC - PMN (total)				
8	WBC - PMN (%)				
9	WBC - Lymphocytes				
10	Red cells ($x10^6$/l)				
11	Antibiotics (RES/SEN)				
12	**Serotype**				
13	Biotype				
14	β-lactamase				
15	Other test 1				
16	Other test 2				

3. BLOOD CULTURE PERFORMED:

Within 24 hours of admission 1
Between 24-48 hours after admission 2
More than 48 hours but less than 72 hours after admission 3
More than 72 hours after admission 4
No 5

IN STRICT MEDICAL CONFIDENCE

4. DATES AND RESULTS OF REQUESTS FOR BLOOD CULTURE:

	INVESTIGATION	DATE 1	DATE 2	DATE 3
1	Culture (POS/NEG)			
2	Antibiotics (RES/SEN)			

5. OTHER CULTURES: Yes ☐ 1 No ☐ 2

	INVESTIGATION			
1	Microscopy			
2	Culture (POS/NEG)			
3	Antibiotics (RES/SEN)			

	INVESTIGATION			
1	Microscopy			
2	Culture (POS/NEG)			
3	Antibiotics (RES/SEN)			

Haematology

6. FBC - DATES AND RESULTS OF REQUESTS:

	INVESTIGATION			
1	Hb (g/dl)			
2	Glucose (mmol/L)			
3	Protein (g/L)			
4	WBC - total ($x10^9/l$)			
5	WBC - neutrophils			
6	WBC - lymphocytes			
7	WBC - monocytes			
8	WBC - eosinophils			
9	WBC - basophils			
10	WBC - other			
11	Platelets ($x10^9/1$)			
12	RBCs ($10^{12}/1$)			
13	Film (comments)			
14	Other 1 (specify)			

IN STRICT MEDICAL CONFIDENCE

7. SERUM ELECTROLYTES, UREA & CREATININE Yes ☐ 1 No ☐ 2

	INVESTIGATION	DATE 1	DATE 2	DATE 3
1	Sodium			
2	Potassium			
3	Urea			
4	Creatinine			
5	Other 1 (specify)			
6	Other 2 (specify)			
7	Other 3 (specify)			

8. OTHER HAEMATOLOGY INVESTIGATIONS Yes ☐ 1 No ☐ 2

INVESTIGATION	DATE 1	DATE 2	DATE 3

Radiology

9. RADIOLOGICAL INVESTIGATIONS Yes ☐ 1 No ☐ 2

	INVESTIGATION	DATE 1	DATE 2	DATE 3
1	CXR			
2	SXR			
3	CT SCAN			
4	Ultrasound			
5	Other 1 (specify)			
6	Other 2 (specify)			

Other investigations

10. OTHER INVESTIGATIONS Yes ☐ 1 No ☐ 2

INVESTIGATION	DATE 1	DATE 2	DATE 3

IN STRICT MEDICAL CONFIDENCE

SECTION VII: MATERNAL & BIRTH HISTORY - ONLY COMPLETE THIS SECTION IF THIS IS A NEONATAL CASE

IF THIS CASE IS A NEONATE, COMPLETE THIS BOX AND REST OF SECTION

MOTHER'S NAME:

LAST NAME FORENAME(S)

HOSPITAL No: LABORATORY No.

1. MATERNAL DATE OF BIRTH: | | | 19 |

2. PREVIOUS OBSTETRIC HISTORY:

DATE	MATURITY	TYPE OF DELIVERY	COMPLICATIONS	SEX	BIRTHWEIGHT	PRESENT HEALTH
1						
2						
3						
4						
5						
6						

3. PLACE OF DELIVERY:

Home 1
Hospital 2
Other (specify) 3
Not recorded 4

4. ATTENDED ANTENATAL CLINIC

Yes ☐ 1 No ☐ 2 Not recorded ☐ 9

5. DATE OF LMP: | | | 19 |

6. ESTIMATED DATE OF DELIVERY: | | | 19 |

7. ACTUAL DATE OF DELIVERY: | | | 19 |

8. MATURITY FROM DATES: | | weeks

9. ASSESSED MATURITY: | | weeks

10. TIME OF DELIVERY: | | hours | | minutes AM/PM

IN STRICT MEDICAL CONFIDENCE

11. METHOD OF DELIVERY:
Normal vertex 1
Elective CS 2
Breech 3
Forceps 4
Vacuum/Venthouse 5
Emergency CS 6
Other (specify): _____ 7

12. IF ASSISTED DELIVERY, REASON(S) _____

13. LENGTH OF LABOUR: [ ][ ] hours [ ][ ] minutes

12. INFANT WAS:
Preterm 1
Term 2
Post-term 3

15. BIRTHWEIGHT: [ ].[ ][ ] kg

16. APGAR SCORE AFTER 1 MINUTE: [ ]

17. APGAR SCORE AFTER 5 MINUTES: [ ]

18. CLINICAL FINDINGS IN NEONATE AT BIRTH:

1 _____ 4 _____
2 _____ 5 _____
3 _____ 6 _____

19. RESUSCITATION GIVEN:

_____ _____
_____ _____
_____ _____
_____ _____

20. CORD BLOOD pH: [ ]

21. DATE AND TIME OF ADMISSION TO SCBU: [ ][ ]19 TIME: _____

22. DATE OF DISCHARGE [ ][ ]19

23. WEIGHT ON DISCHARGE: [ ].[ ][ ] kg

24. OUTCOME:
Survived, no complications on discharge 1
Survived, complications on discharge 2
Died 3

IN STRICT MEDICAL CONFIDENCE

25. OBSTETRIC COMPLICATIONS AT TIME OF DELIVERY:

Preterm labour	☐	1
Maternal fever	☐	2
Pyrexia	☐	3
Rupture of membranes (specify date & time)	☐	4 _____
Vaginal discharge	☐	5
Other (Specify)	☐	6

_____

_____

26. Haemophilus influenzae isolated from:

NN blood	☐ 1	Other (specify)	☐ 5
Maternal blood	☐ 2	_____	
Placenta	☐ 3	_____	
Vagina	☐ 4	_____	

27. Method of contraception used:

Pill	☐ 1	Not recorded	☐ 4
IUD	☐ 2		
Other (specify)	☐ 3		

_____

_____

28. MOTHERS MEDICAL HISTORY THIS PREGNANCY:

_____ _____

_____ _____

_____ _____

29. MOTHER'S ADMISSION DATE: ☐☐☐ 19

30. MOTHER'S DISCHARGE DATE: ☐☐☐ 19

31. MATERNAL INVESTIGATIONS THIS PREGNANCY

INVESTIGATION	DATE 1	DATE 2	DATE 3
	☐☐☐	☐☐☐	☐☐☐

32. MOTHER'S THERAPEUTIC REGIME:

DRUG	DOSE	ROUTE	FREQUENCY	DATE STARTED	DATE STOPPED
1					
2					
3					
4					
5					

IN STRICT MEDICAL CONFIDENCE

33. COMMENTS

SECTION VIII: UNIT GUIDELINES FOR TREATMENT & PROPHYLAXIS

1. TREATMENT

2. FOLLOW UP

3. PROPHYLAXIS

SECTION IX: CASE IDENTIFICATION

SOURCES FROM WHICH THIS CASE HAS BEEN IDENTIFIED:							
1	Laboratory notifications to PHLS	Yes		1	No		2
2	Statutory notifications to CCDC	Yes		1	No		2
3	Search of laboratory records	Yes		1	No		2
4	Other source 1 (specify) _____	Yes		1	No		2
5	Other source 2 (specify) _____	Yes		1	No		2
6	Other source 3 (specify) _____	Yes		1	No		2

IDENTIFYING HOSPITAL: _____

DATE OF DATA COLLECTION: | | | 19 |

APPENDIX 2

Data tables

Data tables for results in chapter 5 section 4.2

tertile		population	all cases	inc rate all	95%LL all	95%UL all	95%LCI all	95%UCI all
townsend score 1 (low)		98825	56	14.17	42.3	72.72	10.70	18.40
2 (medium)		101012	78	19.30	61.66	97.35	15.26	24.09
3 (high)		151162	110	18.19	90.41	132.58	14.95	21.93
		350999	244	17.38	210.59	272.36	15.00	19.40
unemployed 1		97216	60	15.43	45.79	77.23	11.78	19.86
	2	104907	72	17.16	56.34	90.67	13.43	21.61
	3	148876	112	18.81	92.22	134.77	15.49	22.63
		350999	244	17.38	210.59	272.36	15.00	19.40
overcrowded 1		90939	71	19.52	55.45	89.56	15.24	24.62
	2	106395	66	15.51	51.04	83.97	11.99	19.73
	3	153665	107	17.41	87.69	129.3	14.27	21.04
		350999	244	17.38	210.59	272.36	15.00	19.40
no car 1		97652	55	14.08	41.43	71.59	10.61	18.33
	2	112604	89	19.76	71.47	109.52	15.87	24.32
	3	140743	100	17.76	81.36	121.63	14.45	21.60
		350999	244	17.38	210.59	272.36	15.00	19.40
not owner-occupied 1		114636	76	16.57	59.88	95.13	13.06	20.75
	2	101321	60	14.80	45.79	77.23	11.30	19.06
	3	135042	108	19.99	88.59	130.39	16.40	24.14
		350999	244	17.38	210.59	272.36	15.00	19.40
all movers 1		103880	64	15.40	49.29	81.73	11.86	19.67
	2	122312	72	14.72	56.34	90.67	11.52	18.53
	3	124845	108	21.63	88.59	130.39	17.74	26.11
		351037	244	17.38	210.59	272.36	15.00	19.40
local movers 1		112148	70	15.60	54.57	88.44	12.16	19.72
	2	125883	90	17.87	72.37	110.63	14.37	21.97
	3	113006	84	18.58	67	104	14.82	23.01
		351037	244	17.38	210.59	272.36	15.00	19.40
child density 1		69195	66	23.85	51.04	83.97	18.44	30.34
	2	109690	78	17.78	61.66	97.35	14.05	22.19
	3	172122	100	14.52	81.36	121.63	11.82	17.67
		351007	244	17.38	210.59	272.36	15.00	19.40
lone parents 1		82139	59	17.96	44.91	76.11	13.67	23.17
	2	110553	75	16.96	58.99	94.01	13.34	21.26
	3	158345	110	17.37	90.41	132.58	14.27	20.93
		351037	244	17.38	210.59	272.36	15.00	19.40
% of children <5 years 1		59059	48	20.32	35.39	63.64	14.98	26.94
	2	108312	71	16.39	55.45	89.56	12.80	20.67
	3	183636	125	17.02	104.05	148.93	14.17	20.28
		351007	244	17.38	210.59	272.36	15.00	19.40

KEY

inc rate all = incidence rate 1990-1994
95%LL = 95% lower limit
95%UL = 95% upper limit
95%LCI = 95% lower confidence interval
95%UCI = 95% upper confidence interval

Data tables for results in chapter 5 section 4.2

tertile		population	pre-hib	inc rat pre	95%LL	95%UL	95%LCI	95%UCI
townsend score 1 (low)		98825	46	23.27	33.68	61.36	17.04	31.04
2 (medium)		101012	62	30.69	47.54	79.48	23.53	39.34
3 (high)		151162	82	27.12	65.22	101.78	21.57	33.67
		350999	190	27.07	163.94	219.02	23.35	31.20
unemployed 1		97216	49	25.20	36.25	64.78	18.64	33.32
	2	104907	57	27.17	43.17	73.85	20.58	35.20
	3	148876	84	28.21	67	104	22.50	34.93
		350999	190	27.07	163.94	219.02	23.35	31.20
overcrowded 1		90939	57	31.34	43.17	73.85	23.74	40.60
	2	106395	50	23.50	37.11	65.92	17.44	30.98
	3	153665	83	27.01	66.11	102.89	21.51	33.48
		350999	190	27.07	163.94	219.02	23.35	31.20
no car 1		97652	45	23.04	32.82	60.21	16.80	30.83
	2	112604	70	31.08	54.57	88.44	24.23	39.27
	3	140743	75	26.64	58.99	94.01	20.96	33.40
		350999	190	27.07	163.94	219.02	23.35	31.20
not owner-occupied 1		114636	65	28.35	50.17	82.85	21.88	36.14
	2	101321	45	22.21	32.82	60.21	16.20	29.71
	3	135042	80	29.62	63.44	99.57	23.49	36.87
		350999	190	27.07	163.94	219.02	23.35	31.20
all movers 1		103880	54	25.99	40.57	70.46	19.53	33.91
	2	122312	56	22.89	42.3	72.72	17.29	29.73
	3	124845	80	32.04	63.44	99.57	25.41	39.88
		351037	190	27.06	163.94	219.02	23.35	31.20
local movers 1		112148	57	25.41	43.17	73.85	19.25	32.93
	2	125883	70	27.80	54.57	88.44	21.67	35.13
	3	113006	63	27.87	48.41	80.6	21.42	35.66
		351037	190	27.06	163.94	219.02	23.35	31.20
child density 1		69195	50	36.13	37.11	65.92	26.82	47.63
	2	109690	60	27.35	45.79	77.23	20.87	35.20
	3	172122	80	23.24	63.44	99.57	18.43	28.92
		351007	190	27.06	163.94	219.02	23.35	31.20
lone parents 1		82139	50	30.44	37.11	65.92	22.59	40.13
	2	110553	55	24.87	41.43	71.59	18.74	32.38
	3	158345	85	26.84	67.9	105.1	21.44	33.19
		351037	190	27.06	163.94	219.02	23.35	31.20
% of children <5 years 1		59059	36	30.48	25.21	49.94	21.34	42.28
	2	108312	60	27.70	45.79	77.23	21.14	35.65
	3	183636	94	25.59	75.96	115.03	20.68	31.32
		351007	190	27.06	163.94	219.02	23.35	31.20

KEY

inc rate pre = incidence rate 1990-1992
95%LL = 95% lower limit
95%UL = 95% upper limit
95%LCI = 95% lower confidence interval
95%UCI = 95% upper confidence interval

Data tables for results in chapter 5 section 4.2

	tertile	population	post-hib	inc rat post	95%LL	95%UL	95%LCI	95%UCI
townsend score 1 (low)		98825	10	**5.06**	4.8	18.39	**2.43**	**9.30**
2 (medium)		101012	16	**7.92**	9.15	25.98	**4.53**	**12.86**
3 (high)		151162	28	**9.26**	18.61	40.47	**6.16**	**13.39**
		350999	54	**7.69**	40.57	70.46	**5.78**	**10.04**
unemployed 1		97216	11	**5.66**	5.49	19.68	**2.82**	**10.12**
	2	104907	15	**7.15**	8.4	24.74	**4.00**	**11.79**
	3	148876	28	**9.40**	18.61	40.47	**6.25**	**13.59**
		350999	54	**7.69**	40.57	70.46	**5.78**	**10.04**
overcrowded 1		90939	14	**7.70**	7.65	23.49	**4.21**	**12.92**
	2	106395	16	**7.52**	9.15	25.98	**4.30**	**12.21**
	3	153665	24	**7.81**	15.38	35.71	**5.00**	**11.62**
		350999	54	**7.69**	40.57	70.46	**5.78**	**10.04**
no car 1		97652	10	**5.12**	4.8	18.39	**2.46**	**9.42**
	2	112604	19	**8.44**	11.44	29.67	**5.08**	**13.17**
	3	140743	25	**8.88**	16.18	36.91	**5.75**	**13.11**
		350999	54	**7.69**	40.57	70.46	**5.78**	**10.04**
not owner-occupied 1		114636	11	**4.80**	5.49	19.68	**2.39**	**8.58**
	2	101321	15	**7.40**	8.4	24.74	**4.15**	**12.21**
	3	135042	28	**10.37**	18.61	40.47	**6.89**	**14.98**
		350999	54	**7.69**	40.57	70.46	**5.78**	**10.04**
all movers 1		103880	10	**4.81**	4.8	18.39	**2.31**	**8.85**
	2	122312	16	**6.54**	9.15	25.98	**3.74**	**10.62**
	3	124845	28	**11.21**	18.61	40.47	**7.45**	**16.21**
		351037	54	**7.69**	40.57	70.46	**5.78**	**10.04**
local movers 1		112148	13	**5.80**	6.92	22.23	**3.09**	**9.91**
	2	125883	20	**7.94**	12.22	30.89	**4.85**	**12.27**
	3	113006	21	**9.29**	13	32.1	**5.75**	**14.20**
		351037	54	**7.69**	40.57	70.46	**5.78**	**10.04**
child density 1		69195	16	**11.56**	9.15	25.98	**6.61**	**18.77**
	2	109690	18	**8.20**	10.67	28.45	**4.86**	**12.97**
	3	172122	20	**5.81**	12.22	30.89	**3.55**	**8.97**
		351007	54	**7.69**	40.57	70.46	**5.78**	**10.04**
lone parents 1		82139	9	**5.48**	4.12	17.09	**2.51**	**10.40**
	2	110553	20	**9.05**	12.22	30.89	**5.53**	**13.97**
	3	158345	25	**7.89**	16.18	36.91	**5.11**	**11.65**
		351037	54	**7.69**	40.57	70.46	**5.78**	**10.04**
% of children <5 years 1		59059	12	**10.16**	6.2	20.96	**5.25**	**17.74**
	2	108312	11	**5.08**	5.49	19.68	**2.53**	**9.08**
	3	183636	31	**8.44**	21.06	44	**5.73**	**11.98**
		351007	54	**7.69**	40.57	70.46	**5.78**	**10.04**

KEY

inc rate post = incidence rate 1992-1994
95%LL = 95% lower limit
95%UL = 95% upper limit
95%LCI = 95% lower confidence interval
95%UCI = 95% upper confidence interval

APPENDIX 3

Publications

INTERNATIONALER KONGRESS
„PUBLIC HEALTH - ENTWICKLUNGEN UND POTENTIALE'
vom 6. bis 8. Oktober 1999 in Freiburg i. Br.

Kongress-Sekretariat:
Deutsche Koordinierungsstelle
für Gesundheitswissenschaften
an der A.-L.-Universität Freiburg
Hebelstraße 29 - D 79104 Freiburg
Tel. 0761/203-5521 - Fax 0761/203-5516
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Dr. Babakunde Olowokure
CDSC West Midlands
2nd Floor, Lincoln House
Heartlands Hospital
GB B95SS Birmingham

08.06.99

Int. Kongress „Public Health – Entwicklung und Potentiale"
vom 6. Bis 8. Oktober 1999 in Freiburg i. Br.

Sehr geehrte Frau Dr. Olowokure,

wir freuen uns, Ihnen mitteilen zu können, daß Ihr Abstract als Vortrag angenommen wurde.
Es ist vorgesehen, daß Ihr Vortrag

Olowokure, B.; Blair, I.; Spencer, N.; Hawker, J.: Surveillance of Haemophilus influenzae disease: comparision of surveillance systems and reporting patterns in the pre-Hib and post-Hib conjugate vaccine periods

im Rahmen der 7. Jahrestagung der DAE - Deutsche Arbeitsgemeinschaft für Epidemiologie - in der Veranstaltung

DAE - Infektionsepidemiologie
(Mod. : A. Ammon, A. Krämer)

gehalten wird, die am Freitag in dem Zeitblock von 13.30 bis 15.30 stattfinden wird.

In diesem Zusammenhang möchten wir Sie noch darauf hinweisen, daß die verbindliche schriftliche Anmeldung sowie der Eingang der Teilnehmergebühr bis zum 12. Juli 1999 vom Organisationskomitee als notwendige Voraussetzung dafür festgelegt wurde, daß Ihr Abstract wie vorgesehen in der Zeitschrift „Das Gesundheitswesen" abgedruckt werden kann.

Mit freundlichen Grüßen
Ihr

Prof. Dr. med. J. v. Troschke

Title: Surveillance of *Haemophilus influenzae* disease: comparison of surveillance systems and reporting patterns in the pre-Hib and post-Hib conjugate vaccine periods

Authors: Babatunde Olowokure, Iain Blair, Nick Spencer, Jeremy Hawker

Address: Dr B Olowokure, CDSC West Midlands, 2nd Floor, Lincoln House, Heartlands Hospital, Birmingham B9 5SS, England

Aim: Vaccination programmes require surveillance systems to evaluate the effect of the vaccine on disease incidence. In England and Wales surveillance systems for communicable diseases are primarily passive, and underreporting of cases is known to occur. The aim of this study was to establish the incidence of *Haemophilus influenzae* disease in the two years before and immediately following the introduction of Hib conjugate vaccine in the West Midlands region of England using two different surveillance systems, one active and the other passive.

Method: The study period was from October 1990 to September 1992 (pre-Hib conjugate vaccine) and from October 1992 to September 1994 (post-Hib conjugate vaccine). The data from voluntary laboratory reports sent to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) were compared with an active laboratory-based system which used data from several sources. The active system aimed to identify all cases of laboratory confirmed invasive *H influenzae* disease in children <5 years of age resident in the West Midlands region, and admitted to hospital in the region, during the study period.

Results: A comparison of cases reported to the active and passive surveillance systems over the four year period showed that a total of 258 cases were identified by the active system compared to 208 cases reported to the passive system.

Underreporting was seen to vary with time and other parameters. Fifteen per cent of cases identified by the active surveillance system were not reported to the CDSC in the period prior to the introduction of the vaccine. This proportion more than doubled in the two years following introduction of the vaccine to 36%. There was also apparent variation in the reporting of cases according to age. It was found that in children aged <2 years, approximately 24% of cases identified by the active surveillance system were not reported to the CDSC. This was almost four times more than the estimated 7% underreporting in children 2 years of age or older. There were no differences in reporting by sex or ethnic group.

Incidence rates for invasive *H influenzae* disease in the West Midlands based on reports to CDSC for the pre-Hib and post-Hib conjugate vaccine periods were found to be 24.2 (95% CI=20.7 to 28.1) per 10^5 children <5 years old and 5.4 (95%=CI 3.8 to 7.4) 10^5 respectively. The corresponding figures obtained utilising data from the active surveillance system were 28.3 (95% CI=24.5 to 32.6) 10^5 and 8.4 (95%=CI 6.4 to 10.8) 10^5 respectively.

Conclusion: The results obtained in this study provide further support for the importance of ensuring the quality of surveillance data prior to using it to evaluate an intervention, and confirm the value of using several sources of data to approach full case ascertainment. Given the publicity surrounding the launch of the vaccine and the national study of Hib vaccine failures, it was reasonable to assume that the introduction of Hib conjugate vaccine might improve the efficiency of reporting. However, in this study the introduction of Hib conjugate vaccine was associated with increased underreporting. To our knowledge this observation has not previously been reported and may have arisen due to a number of factors, including complacency on the part of physicians and microbiologists in reporting cases following the success of the vaccine in virtually eliminating Hib disease. These findings have implications for resource allocation and education of health care workers regarding the continued reporting of diseases following interventions such as immunisation.

Abstract book

European Public Health Association (EUPHA)

Annual Meeting 1998

on

New technology and public health

(including the 10th Health Services Research Conference)

Venue: Göteborg, Sweden
Svenska Mässan

10 – 12 December 1998

Annual EUPHA Meeting

ENVIRONMENTAL RISK FACTORS FOR INVASIVE *HAEMOPHILUS INFLUENZAE* DISEASE IDENTIFIED WITH GEOGRAPHIC INFORMATION SYSTEMS IN THE POST-HIB CONJUGATE VACCINE ERA

Babatunde Olowokure[1,2], Iain Blair[3], Nick Spencer[1]

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[2] Communicable Disease Surveillance Centre (CDSC), West Midlands, U K
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Introduction

Since the Black report, evidence has accumulated regarding the association between inequalities in health and deprivation. In Britain the nature of this problem associated with invasive *Haemophilus influenzae* (HI) disease has been poorly described. This study combines health data, geographic data, a geographic information system (GIS), and 1991 census data to identify environmental risk factors for invasive HI disease in the two years immediately following the introduction of HI type b (Hib) conjugate vaccine.

Methods

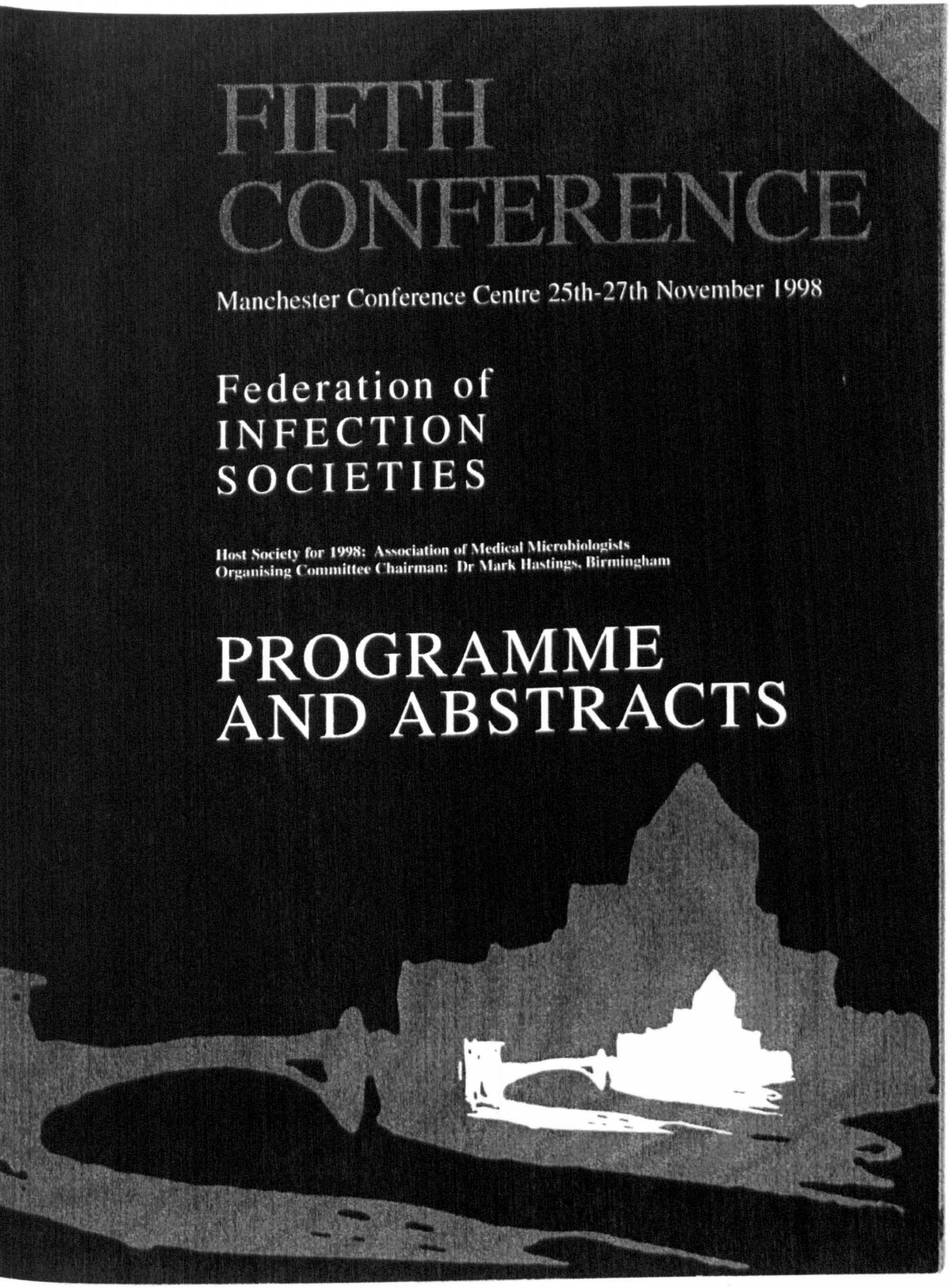
Several data sources, including laboratory reports and notifications, were used to obtain data on diseases caused by invasive HI in the West Midlands region of England in children under 5 years of age from October 1992 to September 1994. GIS was used to map the distribution of invasive HI cases using postcode of residence and to determine enumeration districts (EDs). Townsend deprivation scores (an area indicator of deprivation derived from 1991 census data) were then obtained for each of the EDs and grouped into three deprivation categories affluent, intermediate and deprived. The GIS was used to select a further 8 environmental variables for evaluation.

Results

Univariate analysis indicated that 4 variables were associated with invasive HI disease. Relative to children living in areas of high deprivation, there was a significantly reduced risk of invasive disease for children in more affluent areas (OR=0.73, 95% CI=0.54 to 0.99). Residence in areas with a high proportion of rented accommodation (p 0.0025), high population mobility (p = 0.001 3) and low child population density (p0.039) were associated with increased risk of invasive HI disease.

Conclusions

This analysis suggests that in the post-Hib conjugate vaccine era children living in socioeconomically deprived environments are at increased risk of disease. Furthermore, combining health and population data with GIS assists in identifying geographically referenced environmental risk factors for populations.


FIFTH
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Manchester Conference Centre 25th-27th November 1998
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INFECTION
SOCIETIES
Host Society for 1998: Association of Medical Microbiologists
Organising Committee Chairman: Dr Mark Hastings, Birmingham
PROGRAMME
AND ABSTRACTS

Proceedings of the Royal College of Paediatrics and Child Health Annual Meeting 1997; Vol 1:88

Thursday 17th April 1997

IMMUNOLOGY AND INFECTIOUS DISEASES — GROUP ABSTRACTS

G160 Pneumococcal meningitis: investigation using a brain ependymal ciliary model

Muhammad BJ*, Andrew P, Mitchell T, O'Callaghan C*.

Departments of Child Health* and Microbiology, University of Leicester

Densely ciliated ependymal cells line the aqueducts and the ventricular surface of the brain, forming a barrier between CSF and neuronal tissue. We have developed a unique ex-vivo method to assess ependymal ciliary function. Using this model to investigate pneumococcal meningitis we have shown the pneumococcal toxin 'pneumolysin' is extremely toxic to ependymal cilia.
Our study aims were to determine the effect on brain cilial function of:
(a) Wild type pneumococci and a mutant variety (without the penumolysin gene); (b) antibiotic induced lysis of pneumococci; (c) anti-pneumolysin antibody in preventing ciliary and ependymal cell damage.
Method: Ciliary beat frequency, from ependymal strips from Vistar rats, was measured using a high speed camera (1000 frames/sec) (Kodak Ektapro) attached to a microscope, at 37°C. Following base line readings ependymal strips were incubated with Wild type or Mutant pneumococci at colony counts of 10^8, 10^7, and 10^6. Experiments were repeated with penicillin lysed solutions of the same bacteria at similar colony counts, with or without the addition of anti-pneumolysin antibody. Seventy ependymal edges were studied in total.
Results: Ciliary beat frequency of control ependyma (n=12) was 39(2.3)Hz and did not change over a 4 hour period. Wild type pneumococci at 10^8 and 10^7 caused ciliary stasis within 30 minutes and 3.5 hours respectively. No effect was seen at a colony count 10^6. Pneumolysin negative pneumococci at 10^8 caused ciliary stasis after 60 minutes but no effect was seen at colony counts of 10^7. Penicillin lysed pneumococci caused rapid ciliary stasis (30 secs to 2 minutes) at 10^8 which was completely prevented by prior addition of anti-pneumolysin antibodies.
Conclusion: At higher colony counts pneumococcal bacteria affected the ciliary beat frequency. Penicillin lysis markedly accelerated this toxic process. The toxicity was completely blocked by anti-pneumolysin antibodies. Further work is underway to determine the therapeutic role of anti-pneumolysin antibodies in pneumococcal meningitis.

G162 Invasive *Haemophilus influenzae* disease and Hib conjugate vaccine: describing the changing epidemiology in the West Midlands

Olowokure B, Blair I, Spencer N.
Sections of Child Health, and Public Health, School of PGME, University of Warwick, England.

AIMS: To describe the epidemiology of invasive *Haemophilus influenzae* (HI) disease in a defined population in the period prior to (Oct. 1990-Sep. 1992), and immediately following (Oct. 1992-Sep.1994) the introduction of Hib conjugate vaccine. METHODS: 258 cases were identified from a retrospective register of invasive HI cases compiled using several sources. 199 cases were identified in the first period of the study, and 59 in the second. RESULTS: The age-specific incidence rate for invasive HI disease was $27.3/10^5$ in children <5 years of age in the 2 years prior to Hib conjugate vaccine, and $8.1/10^5$ in the immediate post-vaccine era. There were 104 cases (52.3%) in children aged 6-18 months of age in 1990-92, and 22 cases (37.2%) in 1992-94. Children aged 24-47 months accounted for 17.6% and 32.2% of cases in the pre- and post-vaccine periods respectively. HI meningitis was seen more in girls than boys both before (51.5%) and after (55.6%) the introduction of Hib vaccine. Three (5.1%) of the children identified in the post-vaccine era were too young to receive Hib vaccine, 18 (30.5%) had no documented vaccination history. Nine (15.3%) had received the vaccine, and at least 7 of these were vaccine failures.
CONCLUSIONS: This is an early report of the effect of Hib conjugate vaccine on the epidemiology of invasive HI disease. The data suggests that the vaccine has prevented many cases of invasive HI. However, there appears to be a shift to an older age group, and vaccine failures have been identified.

G161 Microbial growth inhibition in plasma during infection: effects of iron and zinc availability.

Golden B.E. & Clohessy P.A.
Dept of Child Health, University of Aberdeen

Calprotectin is an abundant calcium and zinc binding neutrophil protein which inhibits the growth of microorganisms in culture medium and abscess fluid by depriving them of zinc. We hypothesised that this also occurs in plasma because, during bacterial infection, plasma calprotectin rises from <1mg/l to up to 50mg/l, well above the MIC for many bacteria and fungi.

Therefore, we related the growth of Candida kefyr (24hr change in total viable count) to calprotectin (measured by ELISA) and zinc concentrations in plasma samples from 49 infected children and 20 age-matched controls. In the same samples, we also related Candida growth to plasma iron and transferrin saturation (TS). We then compared the effects of zinc and iron supplementation on Candida growth in the same plasma. Candida growth was lower ($p < 0.001$) in infected plasma than in control plasma and inversely related to calprotectin concentration ($r = -0.33$, $p < 0.005$). However, growth was not related to plasma zinc and was not affected by zinc supplementation of either infected or control plasma. In infected plasma, plasma iron and TS were low. Candida growth correlated positively with plasma iron ($p < 0.01$) as well as TS ($p < 0.001$); and iron supplementation of infected plasma returned Candida growth to that obtained in control plasma.

Thus, it appears that zinc availability, in contrast to iron availability, has no effect on Candida growth in plasma.

This work was supported by the Wellcome Trust.

Royal College of Paediatrics and Child Health

Proceedings of the 1st Annual Meeting University of York 15th - 18th April 1997

SCIENTIFIC PROGRAMME AND ABSTRACTS

Patron Her Royal Highness The Princess Royal
President Professor Sir Roy Meadow

P25

THE PERIODICITY OF IMPORTED VIVAX MALARIA IN BIRMINGHAM. M. Dedicoat, P. Venkatesan and C. Ellis, Department of Infection, Birmingham Heartlands Hospital, Birmingham, UK.

Objectives: The majority of patients admitted to our Infectious Disease Unit with vivax malaria present in the summer months. Most return from Northern Pakistan where malaria transmission peaks during the monsoon months of July to September. We reviewed cases to see whether time of presentation related to the time of travel or another factor.
Methods: Patients with Vivax malaria were identified, from notification slips between 1/1/88 and 31/12/97.
Results: 300 cases were identified with 176 returning from Northern Pakistan. The median time from arrival in the UK to development of symptoms was 105 days (range 0-1080 days). Of the latter 112 (64%) presented between June and September but only 65 (37%) returned to the UK in these months. Those returning in winter months were more likely to develop clinical malaria in our summer.
Conclusions: The time of presentation of vivax malaria in patients from Northern Pakistan returning to Birmingham does not relate purely to the timing of travel. The majority of cases in Birmingham occur during the months of peak transmission in Pakistan. Seasonal environmental factors may partly determine timing of clinical presentation.

P26

RISK FACTORS FOR INVASIVE *HAEMOPHILUS INFLUENZAE* (HI) DISEASE IN THE POST-CONJUGATE VACCINE ERA. B. Olowokure[1,2], I. Blair[3], J. Hawker[2], N. Spencer[1]. Section of Child Health, University of Warwick[1], Communicable Disease Surveillance Centre, West Midlands[2] and Department of Public Health, Sandwell Health Authority[3].

Introduction: This study combines health data and 1991 census data with a geographic information system (GIS) to identify environmental risk factors for invasive HI disease in the two years immediately following the introduction of HI type b (Hib) conjugate vaccine.
Methods: Several data sources, including laboratory reports, were used to identify diseases due to invasive HI in the West Midlands in children under 5 years of age from 1992 to 1994. Townsend deprivation scores were obtained for enumeration districts of residence. Three groups of deprivation were obtained, affluent, intermediate and deprived. **Results:** There was a significantly reduced risk of invasive disease for children in more affluent areas (OR=0.73, 95% CI=0.54-0.99). Residence in areas with a high proportion of rented accommodation ($p<0.01$), high population mobility ($p<0.01$) and low child population density ($p<0.05$) were associated with increased risk of invasive HI disease.
Conclusions: In the post-Hib conjugate vaccine era inequalities in the disease experience of children were associated with the introduction of Hib conjugate vaccine.

P27

AN AUDIT OF THE OUTCOME OF SCREENING NEW ARRIVALS TO THE UK FOR TUBERCULOSIS

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Department of Public Health and Strategy, Bedfordshire Health, Charter House, Alma Street, Luton LU1 2PL

Tuberculosis has been the subject of major concern in recent years with increasing incidence and changing epidemiology of the disease as a result of sociodemographic changes, which are intrinsically linked with immigration and asylum seekers. [1,2] Screening of new arrivals at port of entry has been ongoing for some years in the UK. However, no information was available in the published literature about the outcome of screening at the port of entry or in districts of their destination in the UK.
In addition, TB is more common in the first five years after arrival and screening at the port of entry does not detect these cases.[3]

We reviewed the outcome of screening of new arrivals in our district with a view to changing local practice to achieve maximum health gain.
Bedfordshire Health received a total of 883 port health forms in 1997. Of the immigrants and asylum seekers 275 were male, 247 female and 76 children under the age of 16 years.
A third of the patients were lost to follow up and 598 were seen at the local clinics. 483 had chest x-rays (CXR) taken locally although about half had been x-rayed at port health or the country of origin previously. Heaf testing and BCG were also offered locally. X-ray abnormalities were described in 4 cases, 3 were started on prophylactic chemotherapy. The screening had taken a considerable amount of time and resources duplicating procedures done elsewhere. The local programme is currently reviewed with the aim to rationalise the screening. Health advice provided to new arrivals in the district is being revised to include all primary care needs and immunisation, particularly rubella in young women. We recommend that the health need of all new arrivals is addressed more efficiently at the destination district and need for screening, including chest x-rays, decided locally.

1. Mangtani P, Jolley DJ, Watson JM, Rodrigues LC. Socioeconomic deprivation and notification rates for tuberculosis in London during 1982-91. *BMJ* 1995; 310:6985: 963-6.
2. Kumar D, Watson JM, Charlett A, Nicholas S, Darbyshire JH. Tuberculosis in England and Wales in 1993: results of a national survey Public Health Laboratory Service/British Thoracic Society/Department of Health Collaborative Group. *Thorax* 1997; 52:12: 1060-7.
3. McKenna MT, McCray E, Onorato I. The epidemiology of tuberculosis among foreign-born persons in the United States, 1986-1993. *N Engl J Med* 1995; 332:16: 1071-6.

P28*

CHRYSEOBACTERIUM MENINGOSEPTICUM OUTBREAK ASSOCIATED WITH COLONISATION OF WATER TAPS IN A NEONATAL INTENSIVE CARE UNIT.

Dr S.N. Hoque, Dr J. Graham, Professor S. Tabaqchali, Department of Medical Microbiology. St. Bartholomew's and The Royal London School of Medicine and Dentistry.

Chryseobacterium meningosepticum is a gram negative, ubiquitous organism that can exist in hospital water systems and can cause fatal meningitis in neonates.
From august 1994 to July 1996 a multi-resistant *C.meningosepticum* was isolated from eight ventilated babies (six from endotracheal secretions, one from a surface swab and one from blood culture, cerebrospinal fluid and endotracheal secretions).
Six babies had overlapping admissions and two babies became colonised six months later. Initial environmental screening was negative. Further screening included the inside of sink taps which yielded *C.meningosepticum* with identical antibiograms to the babies' isolates. The reference laboratory were unable to type the isolates.
Infection control involved, using sterile water for toileting and using alcohol hand rub after hand-washing. Whilst repair and chlorination of the water system, and changing the taps took place.
To date, further screening has been negative and there have been no further cases.