EDITORIAL

Invasive *Haemophilus influenzae* disease: the impact of Hib immunisation

On 1st October 1992, immunisation of children < 4 years old with *Haemophilus influenzae* type b (Hib) conjugate vaccine became part of the routine immunisation schedule in the United Kingdom and the Republic of Ireland. Hib vaccine has been well received and vaccination uptake is high. There is already good evidence of the impact of Hib immunisation in England and Wales from the laboratory notifications to the PHLS Communicable Disease Surveillance Centre of *H. influenzae* meningitis and bacteraemia. In the first 9 m of 1994 there were 32 cases of *H. influenzae* meningitis and bacteraemia (7 reported as Hib), and in 1993 66 cases (38 Hib); this compared with 343 reports (229 Hib) for 1992 and 374 cases (242 Hib) in 1992. In 1993 there was an 85% reduction in invasive Hib disease in children aged < 5 years in the Oxford region.¹ It is now opportune to consider the likely role of *H. influenzae* as a significant pathogen when the Hib vaccine programme has been fully implemented.

H. influenzae has long been recognised as a major cause of serious infections in infants and young children. Hib is the most invasive type of haemophilus, being responsible for > 90% of systemic haemophilus infections in previously healthy children in industrial societies.^{2,3} Before the introduction of Hib immunisation in the UK, the risk of a child suffering an invasive haemophilus infection was 1:600 by 5 years of age.² As meningitis accounts for c. 70% of invasive disease, 1:800 children would be expected to suffer from haemophilus meningitis by 5 years of age. Hib is also a major cause of epiglottitis, pneumonia, septic arthritis and cellulitis in this age group. It must be remembered that the other serotypes (a, c, d, e, f) and non-serotypable (NST) strains may also cause invasive disease. Since September 1990, the Public Health Laboratory Service (PHLS) has been monitoring all cases of invasive haemophilus infection in six regions of England and Wales. Before the introduction of Hib vaccine, c. 10% of invasive haemophilus disease was caused by NST strains and 1.7% by serotypes other than b.⁴ This is even more striking in developing countries where, in the absence of Hib vaccination, serotypes other than b (notably a) and NST strains are a significant cause of invasive disease.^{5,6} Hib vaccine offers no protection against such strains. NST *H. influenzae* are also responsible for respiratory tract infections, including otitis media, sinusitis and pneumonia, and are the commonest cause of acute exacerbations in chronic obstructive airways disease.⁷ These infections will not be prevented by the Hib vaccine.

We tend to think of Hib infections as occurring

almost exclusively in children < 5 years old, but Hib also causes invasive disease in older children and adults. In the PHLS Regional Survey of *H. influenzae* infections, before the introduction of Hib vaccine, 8.1% of invasive Hib infection occurred in adults.⁴ We may well see an upward shift in the age distribution of Hib disease in the UK as Hib vaccination reduces the incidence of disease in children. In Atlanta, Georgia there has been a dramatic fall in the incidence of Hib disease in children between the introduction of Hib conjugate vaccine in 1988, and 1991.⁸ However, there has been no decline in the number of adult cases and 35% of invasive *H. influenzae* disease (both type b and NST) occurred in adults.

Data from the USA and Finland show that within a short space of time the introduction of Hib immunisation results in a dramatic decline in the incidence of invasive Hib disease in children.^{9,10} Indeed, in Finland, Hib disease has been virtually eradicated following Hib vaccine implementation.¹⁰ However, it cannot be assumed that similar results will be obtained in the UK and the Republic of Ireland, because primary immunisation is completed at a younger age (4 months in the UK, 6 months in the Republic of Ireland) and no booster dose is offered in the second year of life. Also, different ethnic groups may respond differently to Hib vaccine. The Hib vaccine PRP-D (polyribosyl-ribitolphosphate conjugated to diphtheria toxoid) was highly effective in Finland but poorly protective in Alaskan eskimos.¹¹ In the UK, two vaccines are used—PRP-T, a conjugate of tetanus toxoid with PRP, and HbOC, a conjugate of an oligosaccharide derived from PRP directly bound to a mutant non-toxic diphtheria toxin.

Invasive *H. influenzae* infection that occurs after Hib immunisation has been incorporated into the British Paediatric Surveillance Unit Scheme in the UK and Republic of Ireland. Since October 1992 there have been 23 cases of “true” vaccine failure (i.e., disease occurring at least 1 week after at least two doses of the conjugate vaccine given in the first year of life, or at least 3 weeks after a single dose of Hib conjugate vaccine given to children older than 12 months). Meningitis was the diagnosis in 13, there were six cases of epiglottitis, two cases of pneumonia and one each of bacteraemia and peri-orbital cellulitis. All of these strains have been confirmed as Hib by polymerase chain reaction (PCR)-based capsular typing. There have also been 50 “apparent” vaccine failures when disease developed after Hib vaccine was given but before protective immunity could have

developed. Non-vaccine-preventable invasive disease caused by NST strains and *H. influenzae* serotypes other than b occurred in 18 and six children respectively. This important surveillance is continuing.

The widespread use of conjugate Hib vaccine will reduce or delay Hib colonisation rates in infants, and may induce herd immunity that would result in greater than expected reductions in disease incidence.^{12,13} Nasopharyngeal carriage is crucial in the transmission and pathogenesis of invasive Hib disease.¹⁴ It is likely that diminished carriage rates of Hib *per se* will alter the epidemiology of invasive Hib disease. Whether reduced carriage rates in children will lead to a fall in the number of adult cases of invasive Hib disease is as yet uncertain. There is some evidence that the reduction in Hib carriage rates may wane with time.¹⁵ Another factor to be considered is the role of nasopharyngeal Hib carriage in the development and persistence of protective antibodies. A fall in the prevalence of Hib carriage in the community may prevent the development of natural immunity in unvaccinated children and the boosting of immunity in vaccinated children. This could conceivably result in a shift towards invasive Hib disease in older age groups and an increased susceptibility within the unvaccinated population to any strains of Hib that they encounter, e.g., strains carried by children from areas of the world where Hib vaccination is not performed. Clearly this is an area that warrants continuing study.

For these reasons it is imperative that we continue careful surveillance of *H. influenzae* infections in this country. Recent years have seen a marked improvement in our ability to characterise *H. influenzae* isolates fully. Traditionally, strains of *H. influenzae* are serotyped with type-specific antisera. However, this method may be unreliable.¹⁶ Cross-reactions can occur and serotyping cannot distinguish between capsule-deficient mutants and non-capsulate strains. *H. influenzae* type b spontaneously loses the capacity to express capsule formation at a frequency of 0.1–0.3% both *in vivo* and *in vitro*.¹⁷ These strains have a partial deletion of the *cap b* locus¹⁸ and lack a functional copy of a gene (*Bex A*) which is essential for polysaccharide export.¹⁹ These capsule-deficient strains (*b*⁻ strains) are non-serotypable but still produce PRP as detected by antigen assays²⁰ and immunofluorescence.²¹ It is conceivable that otherwise virulent (invasive) *b*⁻ strains that can evade the immune response initiated

by the capsule-directed vaccine may assume increasing importance, and laboratory identification of such strains is, therefore, essential. PCR-based techniques have been developed that can identify capsule type-specific DNA sequences and also capsule-deficient type b (*b*⁻) mutants.²² Thus it is now possible to determine unequivocally the capsular type and fundamental structure of *H. influenzae cap* loci. The use of such techniques will be invaluable in studying strains isolated from recipients of Hib vaccine to see if there is any subtle change in the *cap* genes of *H. influenzae* under the pressure of Hib vaccine.

The ability to characterise bacterial strains is a prerequisite for epidemiological studies. Many subtyping techniques have been applied to *H. influenzae*, including biotyping,²³ antibiotic resistance patterns, SDS-PAGE of outer-membrane proteins (OMPs),²⁴ lipopolysaccharide (LPS) analysis,²⁵ whole-cell polypeptide analysis,²⁶ multilocus enzyme electrophoresis²⁷ and ribosomal RNA gene restriction patterns.²⁸ These studies have all been frustrated by the tight clonal population genetic structure of Hib²⁷ in which at least 60% of clinical isolates from meningitis in Europe belong to a single OMP subtype. It is far more rewarding to apply these techniques to non-capsulate *H. influenzae* because their population genetic structure is extremely heterogeneous with many detectable clones. For example, putative outbreaks of infection with non-serotypable *H. influenzae* on chest diseases wards have been studied successfully by SDS-PAGE of OMPs, ribosomal RNA gene restriction patterns and a PCR-based technique with randomly amplified polymorphic DNA (RAPD) fingerprints.²⁹ Ribotyping can also be used to characterise the overall population genetic structure of *H. influenzae*.²⁸ The selection of a highly resistant or virulent clone could be detected by these techniques.

The introduction of Hib vaccine into the UK will profoundly alter the pattern of serious haemophilus infection. There is still a clear need for careful monitoring and surveillance of invasive haemophilus infection in this country. In particular, the role of *H. influenzae* type b in causing invasive disease in adults and serious disease caused by other serotypes and non-capsulate strains must be monitored.

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