Invasive Haemophilus influenzae Type b Disease in England and Wales: Who Is at Risk After 2 Decades of Routine Childhood Vaccination?

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Background. The introduction of the Haemophilus influenzae serotype b (Hib) conjugate vaccine into national immunization has led to rapid and sustained declines in invasive Hib disease incidence across all age groups. In industrialized countries with established Hib vaccination programs, however, little is known about individuals who develop invasive Hib disease. This study describes the epidemiology of invasive Hib disease in England and Wales during 2000–2012 and the clinical characteristics of laboratory-confirmed Hib cases diagnosed during 2009–2012.

Methods. Public Health England (PHE) conducts enhanced national surveillance of invasive Hib disease in England and Wales. Detailed clinical information was obtained for all laboratory-confirmed Hib cases diagnosed during 2009–2012.

Results. Invasive Hib disease in England and Wales has been declining since 2002, reaching its lowest incidence of 0.02 per 100,000 (14 cases) in 2012. In children aged <5 years of age, Hib incidence was 0.06 per 100,000 (2 cases), compared with 35.5 per 100,000 prior to routine Hib vaccination. Follow-up of all 106 case patients over the 4-year period revealed that most cases occurred in adults (73%) who often had preexisting medical conditions (77%) and presented with pneumonia (56%). The Hib-associated case fatality rate was 9.4% (10/106 cases).

Conclusions. Control of Hib disease in England and Wales is currently the best that has been achieved since the introduction of routine Hib vaccination in 1992. Invasive Hib disease is no longer a major cause of acute bacterial meningitis in children but, instead, cases are more likely to present as pneumonia in older adults with comorbidities, similar to the less virulent nonencapsulated H. influenzae.

Keywords. Haemophilus influenzae serotype b; epidemiology; pneumonia; epiglottitis; outcome.

Prior to routine vaccination, Haemophilus influenzae serotype b (Hib) was responsible for >80% of all invasive H. influenzae infections and was the most common cause of acute bacterial meningitis, particularly in young children [1–5]. Hib was also a major cause of septicemia, pneumonia, and epiglottitis as well as skin, soft tissue, bone, and joint infections [1–5]. In the United Kingdom, the estimated average annual incidence of invasive Hib disease in children aged <5 years in the Oxford region during 1985–1990 was 35.5 per 100,000 [6].

The Hib conjugate vaccine was introduced into the UK childhood immunization program in October 1992 at an accelerated 2-3-4 month schedule without a booster dose in the second year of life [7]. Instead, a 12-month catch-up campaign was implemented offering the vaccine to all children up to 4 years of age [7]. This program resulted in a rapid decline in invasive Hib disease across all age groups through direct and indirect (herd) protection [1, 7]. In children aged <5 years, Hib incidence fell to 0.65 per 100,000 by 1998, whereas in adults aged ≥15 years, Hib incidence fell from 0.17 to 0.03 per 100,000 [4]. The success of the Hib vaccination
program was similar to that reported in other European countries [8, 9]. In the United States, where a Hib polysaccharide vaccine was introduced in 1985 and replaced with Hib conjugate vaccines during 1987–1990, the overall incidence of invasive Hib disease decreased from 4.39 per 100,000 in 1989 to 1.55 per 100,000 in 2008 [8, 10].

After 1999, however, an increase in invasive Hib disease was observed, initially in toddlers but soon extending to all age groups, with incidence in adults exceeding that reported in the prevaccine period [11, 12]. Potential explanations for this increase include a greater than expected decline in Hib antibody concentrations after primary immunization with no booster dose in the second year of life, waning of herd protection after the initial catch-up campaign, and use of a less immunogenic Hib combination vaccine containing acellular pertussis (DTaP-Hib) in 2000–2001 [12, 13]. This resurgence led to the establishment of a number of control measures including reintroduction of a whole cell pertussis–containing Hib vaccine (DTwP-Hib) in 2002, a toddler Hib booster campaign in 2003, and a routine 12-month Hib booster in 2006, which together resulted in rapid control of Hib disease across all age groups [12]. In September 2004, although the recommended combination vaccine for infants was changed to a DTaP-Hib vaccine that also contained inactivated polio (Pediacel, Sanofi Pasteur MSD, Berkshire, UK), the acellular pertussis component was different to the one implicated in the increase in invasive Hib disease and was shown to have a satisfactory immune response to the Hib component. This vaccine is preferred to the DTwP combination because it is less reactogenic than whole cell pertussis and removes the risk of vaccine-associated paralytic poliomyelitis with oral polio vaccine [12]. By 2008, Hib incidence in England and Wales had fallen to 0.13 per 100,000 overall and 0.39 per 100,000 in children <5 years of age [14].

During 2009–2012, Public Health England, known as the Health Protection Agency (HPA) until April 2013, conducted enhanced national surveillance to collect detailed clinical data on all laboratory-confirmed invasive Hib cases in England and Wales to inform future strategies to prevent what has now become a rare but still potentially fatal bacterial infection.

METHODS

Public Health England provides a national serotyping service for all National Health Service hospital microbiology laboratories in England and Wales for invasive clinical H. influenzae isolates through its Haemophilus Reference Unit and conducts enhanced national surveillance through a combination of isolate submission, routine laboratory reporting, and clinical reporting schemes, as described previously [12, 15]. Invasive H. influenzae disease was defined as isolation of the organism from a normally sterile site. Localized infections such as epiglottitis or pneumonia were included if accompanied by a sterile site isolate. Isolates were confirmed as H. influenzae by their growth requirement for X and V factors [16] and ompP2-specific polymerase chain reaction (PCR) positivity [17]. Capsule status was determined by PCR by using bexA-specific primers [18]. Capsular type was confirmed by both capsule-specific primers for types a–f [19], and slide agglutination [16]. Laboratory-confirmed Hib infections diagnosed during 2009–2012 were followed up 2 months after the infection by sending a questionnaire (http://www.hpa.org.uk/topics/infectiousdiseases/infections/aZ/HaemophilusInfluenzaeTypeB/EnhancedSurveillance/HaemophilusInfluenzae) to the patient’s general practitioner. Reminder letters were sent 2 months later to all nonresponders. Additional follow-up was performed by telephone with the hospital clinician and/or consultant microbiologist. Cause of death was confirmed using Office for National Statistics (ONS) death registration data (www.statistics.gov.uk) and, for individuals who died, postmortem reports were requested when performed.

Data were analyzed using Stata software, version 11.0 (StataCorp, College Station, Texas). Categorical variables were expressed as proportions and compared using the χ² or Fisher exact test. Data that did not follow a normal distribution were presented as medians with interquartile ranges (IQRs). Annual population estimates were obtained from ONS. Poisson 95% confidence intervals were calculated for incidence rates. Univariate and multivariate logistic regression was used to investigate relationships between variables. The HPA has approval under PIA Section 60 of the Health and Social Care Act 2001 to process confidential patient information for public health purposes.

RESULTS

During 2009–2012, there were 7928 invasive H. influenzae cases diagnosed in England and Wales and, of the 5976 (75%) serotyped isolates, 1436 (24%) were subsequently identified as Hib, including 611 cases in children <5 years of age. In response to the various control measures implemented following the Hib resurgence after 1999, the incidence of invasive Hib disease has fallen year-on-year since 2002 across all age groups, with a more rapid decline among those aged 1–4 and 5–19 years (Figure 1). During 2009–2012, there were 2568 invasive H. influenzae cases and, of the 1906 H. influenzae isolates (74%) received by the HPA for serotyping, 6.5% (106 cases) were caused by Hib (Table 1). Clinical questionnaires were completed for all Hib case patients. Cases declined annually from 38 in 2009 (0.07/100 000; 95% confidence interval [CI], 0.05–1.10) to 14 in 2012 (0.02/100 000; 95% CI, 0.01–0.48), when only 2 cases in children aged <5 years (0.06/100 000; 95% CI, 0.01–0.21) were identified. The median age at disease onset was 49.4 years (IQR, 16.9–67.5 years), and half of patients were...
male (Table 1). Most patients were white (n = 97 [92%]) and the others were black Caribbean (n = 4), mixed or other ethnicity (n = 3), and South Asian (n = 2).

Vaccination Status
Of the 106 laboratory-confirmed Hib cases, 29 (27%) were born after 30 September 1988 and were therefore eligible for vaccination as part of the infant immunization program or the concurrent 12-month catch-up program for children up to 4 years of age. Of these, 3 cases occurred in infants who were too young for vaccination. Among the 26 patients who were at least two months old, 4 (15%) were unimmunized at the time of infection, including a 3-month-old who had not yet received primary immunizations, a 9-month-old who was unvaccinated against Hib but had received other vaccinations, a toddler whose parents had refused all vaccinations, and an adult who did not receive a catch-up dose during the 1992 vaccination campaign. A further 11 cases occurred in infants aged <1 year, of whom 7 were incompletely immunized with only 1 or 2 doses of vaccine prior to infection, whereas 4 had been age-appropriately vaccinated with 3 doses. The remaining 11 cases included 7 children born before September 2006 who had received the recommended 3 doses of vaccine in infancy and 4 born after September 2006, of whom 2 had received 3 of the 4 recommended doses and 2 had received all 4 doses. Vaccination status did not vary by sex or ethnicity (χ² = 1.43, P = .23 and P = .57, respectively).

Concurrent Conditions
One or more comorbidity was reported in 63 (59%) case patients (Table 1) and increased with age (adjusted odds ratio [OR] = 1.04; 95% CI, 1.02–1.05; P < .01), but was similar by sex (P = .21). The prevalence of multiple conditions also increased with age (Table 1). Chronic heart disease (n = 17; particularly among patients ≥65 years of age) and chronic lung disease (n = 17; mainly among those aged ≥45 years) were the most prevalent comorbidities, with a similar number of cases of malignancy/immunosuppression reported (n = 15); however, asplenia (n = 1) was rare.

Clinical Presentation
Clinical presentation varied by age, with meningitis (median age, 1.6 years; IQR, 0.3–14.3 years) being more common in young children and pneumonia (median age, 58.5 years; IQR, 45.4–71.9 years) in adults (Figure 2). Three-quarters of patients diagnosed with Hib meningitis were <5 years of age (n = 15/20) and the odds of presenting with meningitis decreased with age (OR = 0.95; 95% CI, 0.92–0.97; P < .01). In comparison, pneumonia developed mainly in adults (OR = 1.03; 95% CI, 1.02–1.05; P = .01). Of note, 68% (13/19) of culture-confirmed epiglottitis cases (median age, 49.2 years; IQR, 17.7–66.0 years) occurred in patients aged ≥45 years. Epiglottitis (63.2%; χ² = 4.90, P = .03) and meningitis (55.1%; χ² = 2.13, P = .14) were more common among those with no concurrent conditions, whereas pneumonia (73.3%; χ² = 6.27, P = .01) was more common among those with 1 or more concurrent conditions. However, when adjusted for age, only the findings for epiglottitis were significant (adjusted OR = 0.20; 95% CI, 0.06–0.68; P = .01), whereas those for meningitis (P = .46) and pneumonia (P = .45) were not significant.
Complications of Hib meningitis occurred in 35% of case patients (7/20) and included seizures (n = 4), cerebral abscesses (n = 2), subdural effusion (n = 1), and venous sinus thrombosis (n = 1). The latter child was also subsequently diagnosed with unilateral sensorineural deafness. By March 2013, 15 (14.2%) case patients had died. Five of these deaths, which all occurred among case patients aged ≥65 years with comorbidity, occurred >30 days after onset of infection and were not attributed to Hib postmortem and/or on the death certificate. Of the remaining 10 Hib-associated deaths, 9 were among those who were not eligible for vaccination, all had comorbidity, and 6 had >1 comorbidity. Only 1 death occurred in the vaccine-eligible cohort—a case of Hib meningitis in a partially vaccinated infant who was subsequently diagnosed with complement deficiency. The overall Hib-associated case-fatality ratio was, therefore, 9.4% (10/106 cases). The case-fatality ratio was higher for septicemia (3/16 [18.8%]) compared with meningitis (2/20 [10.0%]), pneumonia (4/44 [9.1%]), or epiglottitis (1/19 [5.3%]).

**DISCUSSION**

In England and Wales, Hib is currently better controlled than at any time since the Hib conjugate vaccine was introduced 2 decades ago. Following the introduction of the different Hib
immunization strategies over the past decade, cases in toddlers, older children, and adults have continued to decline rapidly and have now become extremely rare. The clinical and epidemiological characteristics of invasive Hib disease have changed significantly and now resemble those of invasive nonencapsulated *H. influenzae* disease, which has always been considered to be a condition caused by pathogen of low virulence afflicting vulnerable individuals [20].

In keeping with other European and North American countries with established Hib conjugate vaccination programs, Hib is no longer a major cause of acute bacterial meningitis in children [8, 9, 21]. Moreover, epiglottitis—once considered a life-threatening condition characteristically associated with Hib [22]—has become extremely rare in children, with only 4 cases reported in 4 years, and occurring mainly in older adults. As a consequence, the remaining invasive Hib cases now occur mainly in adults with comorbidities who usually develop respiratory tract infections, with most deaths also occurring in this vulnerable group. In patients who died more than a month after infection, particularly those with chronic respiratory diseases, invasive Hib disease could have exacerbated their preexisting medical conditions and, therefore, contributed to their death [23].

Overall, the Hib conjugate vaccine remains highly effective in preventing invasive disease in young children, with only 2 cases occurring after receipt of 4 vaccine doses in the past 4 years—1 in a child who was subsequently diagnosed with an immune deficiency [24, 25], and the other in a child who presented with epiglottitis and subsequently made a full recovery—and only 4 cases in infants after completion of their primary immunization schedule. Most cases in children occurred in those who were unvaccinated or partially vaccinated, emphasizing the importance of timely vaccination and completion of the recommended schedule. In our recent population-based sero-prevalence study, we reported high Hib antibody levels in children up to 10 years of age, most likely because of the various booster campaigns over the past decade as well as the addition of a routine 12-month Hib booster in 2006, which should provide more long-term protection against invasive disease in children [26]. In the sero-prevalence study, Hib antibody levels among 10- to 20-year-olds were significantly lower than in those aged <10 years but higher than in unvaccinated adults, suggesting that this age group may still have some protection after being immunized in infancy, as supported by the extremely low disease incidence in this age group [26]. Because young children are also the main carriers of Hib, the high antibody levels in those aged <10 years is also most likely protecting against carriage and, therefore, transmission to susceptible individuals, thus maintaining high levels of herd protection [4, 26].

This is particularly important at present because currently more than half the adults in the United Kingdom do not have sufficient Hib antibody levels to protect against invasive disease, probably because of lack of opportunities for natural boosting of immunity as Hib is no longer circulating in the population [26].

Despite the small number of cases, however, surveillance of invasive Hib disease across all age groups is going to be critical over the next few years. As the additional protection offered by the various childhood catch-up and booster campaigns wears off, it is possible that the current Hib immunization schedule may not be able to sustain very high antibody levels in toddlers and older children. This, in turn, could lead to increased Hib carriage and circulation in the community, thereby increasing the risk of transmission to susceptible individuals of all ages [12]. During 2000–2003, for example, the initial increase in Hib cases among toddlers was soon followed by an increase in adult cases. A sero-prevalence study subsequently showed a fall in Hib antibody concentrations among English adults following routine childhood Hib vaccination and proposed that this decline had resulted from reduced transmission of the organism and fewer opportunities for natural boosting of immunity by Hib colonization [11]. There is increasing evidence that the presence of circulating antibody at the time of exposure to Hib is critical for preventing invasive disease [27], and that immunological memory alone may not be sufficient to protect because the anamnestic response can take several days to develop [28]. Mathematical models developed to understand the increase in invasive Hib disease in the United...
Kingdom also cautioned against overreliance on immunological memory as a predictor of population protection or as a strategy for the control of invasive disease and, instead, emphasized the importance of high postimmunization antibody titers in age groups at highest risk of developing invasive disease [27].

The provision of a free national reference laboratory service for species confirmation and serotyping along with actively requesting submission of clinical isolates for all reported cases to the HPA and routine linkage of multiple national data sources should ensure that case ascertainment remains high. The experiences gained from the Hib conjugate vaccination program—the first conjugate vaccine to be introduced in the United Kingdom—and the success of the vaccine in controlling what was once a devastating infection in young children have already contributed to the successful implementation of other conjugate vaccination programs, namely, against invasive meningococcal capsular group C and pneumococcal disease. The 1992 catch-up campaign offering the Hib conjugate vaccine to children up to 4 years of age, for example, highlighted the importance of vaccinating age groups with the highest carriage rates to achieve high levels of herd protection through reduction in carriage, whereas the routine 12-month conjugate vaccine boosters introduced in 2006 should provide high antibody levels in toddlers and, therefore, maintain low carriage rates with longer duration of protection against invasive disease.

The observation that most Hib cases now occur in adults with comorbidities suggests that additional strategies may be required to protect this vulnerable group. Although Hib cases are currently very low, several of the comorbidities reported among older adult Hib cases are similar to those predisposing to invasive pneumococcal disease [29], suggesting that at least some of these risk groups might also benefit from the Hib conjugate vaccine, but this requires further evaluation. A recently licensed 10-valent pneumococcal conjugate vaccine that uses an antigenic H. influenzae surface protein D as its carrier protein for 8 of the 10 pneumococcal antigens has been shown to induce very high protein D antibody levels in vaccinated individuals. Although further evaluation is required, if these antibodies can be shown to protect against invasive H. influenzae disease, then this vaccine might have a role in protecting vulnerable individuals not only against invasive pneumococcal disease but also against H. influenzae, including Hib [20].

Notes

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