Antibody Concentration and Clinical Protection After Hib Conjugate Vaccination in the United Kingdom

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H. influenzae type b (Hib) is an important cause of meningitis, septicaemia, pneumonia, and epiglottitis in children worldwide. Many countries have introduced Hib conjugate vaccines into their routine childhood vaccine schedules and the impact on invasive Hib disease has been uniformly impressive. In general, the schedule chosen for vaccination against Hib has reflected that already in place for the established infant vaccines against diphtheria-tetanus-pertussis (DTP) and polio. With few exceptions, a booster dose of Hib vaccine has been included in the second year of life. One of the major reasons for this is that vaccine-induced antibody wanes as children get older, leading to the concern that this may be accompanied by an increase in susceptibility to disease. The relationship between antibody to polyribosylribitol phosphate (PRP, the capsular polysaccharide of Hib) and clinical protection is inferred from studies of natural immunity, passive immunization, and the plain unconjugated PRP vaccine. From such studies arose the figures of 0.15 µg/mL as a correlate of short-term protection and

Context The schedule for Haemophilus influenzae type b (Hib) vaccination of infants in the United Kingdom consists of 3 doses given at 2, 3, and 4 months of age. Many countries include a fourth dose (booster) of Hib vaccine in the second year of life on the basis of declining Hib antibody concentrations after the primary series. Few data are available to show that this fourth dose is actually necessary.

Objective To evaluate long-term clinical protection against Hib disease and Hib antibody concentrations following primary Hib vaccination without a booster dose.

Design, Setting, and Subjects Clinical protection study conducted between October 1992 and March 1999 in the United Kingdom, in which children developing invasive Hib disease despite vaccination in infancy with 3 doses of Hib conjugate vaccine were reported by pediatricians through an active, prospective, national survey. Separate antibody studies were conducted among 2 cohorts of children (n=153 and n=107) vaccinated at 2, 3, and 4 months of age with Hib conjugate vaccine and followed up to 43 and 72 months of age.

Main Outcome Measures Age-specific vaccine effectiveness, derived from the observed number of true vaccine failures after 3 Hib vaccine doses compared with the number of cases expected based on the age-specific rates of invasive Hib disease obtained prior to the introduction of Hib vaccines; and proportion of children in the 2 cohorts with Hib antibody concentrations of less than 0.15 and less than 1.0 µg/mL.

Results Ninety-six true vaccine failures occurring after 3 vaccine doses were detected. During the study period, an estimated 4368200 infants in the United Kingdom received 3 doses of vaccine; therefore, the vaccine failure rate was 2.2 per 100000 vaccinees (95% confidence interval, 1.8-2.7 per 100000). Although vaccine effectiveness declined significantly after the first year of life (P < .001), it remained high until the sixth year of life (99.4% in children aged 5-11 months vs 97.3% in those aged 12-71 months). The proportion of cohorts 1 and 2 with anti-PRP antibody levels of less than 0.15 µg/mL increased between 12 and 72 months of age (6% at 12 months, 8% at 43 months, and 32% at 72 months; χ² = 18.25; P < .001 for trend).

Conclusions Our results suggest that anti-PRP antibody levels and clinical protection against Hib disease wane over time after Hib vaccination at 2, 3, and 4 months of age without a booster dose at 2 years of age. The decline in clinical protection is minimal, however, suggesting that a booster dose of Hib vaccine following infant vaccination is not essential.

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1.0 µg/mL as a correlate of long-term protection against invasive Hib disease. 

Experience with the Hib conjugate vaccines has suggested that the serum anti-PRP antibody concentration may not be as robust a correlate as it was after PRP polysaccharide vaccination. The first Hib conjugate vaccine, PRP-D (PRP conjugated to diphtheria toxoid), serves as a good example of this. After 3 doses of this vaccine, typically only 40% of infants achieve antibody concentrations of 1.0 µg/mL and 70% achieve 0.15 µg/mL.5 Yet, most clinical trials as well as widespread implementation in several populations6,7 suggest clinical protection in more than 90% of vaccinees. The explanation appears to be that conjugation of PRP to a protein converts it from a T-cell–independent to a T-cell–dependent antigen with the capacity to induce immunological memory.8 In the presence of immunological memory, a rapid and protective increase in antibody concentration may be achieved in response to exposure to the organism, despite a low background antibody concentration.

In the United Kingdom, routine immunization with Hib conjugate vaccines was introduced in October 1992 at the primary infant DTP schedule of 2, 3, and 4 months of age. No booster dose of Hib vaccine was included in the schedule. There was catch-up vaccination for children up to 48 months of age that took place over the first year of the program: 3 doses of vaccine were given to infants younger than 1 year with a single dose to older children. A national, active, prospective survey of Hib vaccine failures was established simultaneously. The major objective of this survey was to assess the effectiveness of the Hib vaccine program in the absence of a routine booster dose. Surveillance was widened in 1995 to cover H influenzae disease in all children, regardless of vaccination status.

In this article we present the first 6 years of surveillance of vaccine failures as well as 3 years of surveillance of Hib disease in unvaccinated children. In addition, we present longitudinal anti-PRP antibody data from children who were vaccinated with 3 doses of PRP-T (PRP conjugated to tetanus toxoid) conjugate vaccine during preliminary immunogenicity studies in Oxford, England, and have now been followed up to school age. The major objective of these studies was to evaluate long-term clinical protection against Hib disease and antibody concentrations following primary Hib vaccination without a booster dose.

**METHODS**

**Surveillance for Hib Vaccine Failures**

This study was performed under the auspices of the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health. The BPSU has a program of active surveillance for selected rare pediatric conditions in the United Kingdom. Every month more than 90% of pediatricians routinely report to the BPSU.9

Pediatricians were asked to provide early notification by telephone of a case of *H influenzae* disease (b and non-b *H influenzae* disease were eligible). They were sent a questionnaire requesting clinical, demographic, and laboratory information. Microbiologists and consultants in communicable disease control (CCDCs) were informed about the study and encouraged to contribute to surveillance by notifying the BPSU about cases and sending isolates of *H influenzae* to the national reference laboratory.

For the first phase of the study (October 1, 1992-October 31, 1995), reports were requested of any child with invasive *H influenzae* disease who had received Hib conjugate vaccine. From November 1, 1995, the case definition was broadened to include all children with invasive *H influenzae* disease regardless of vaccination status. Invasive disease was defined as isolation of *H influenzae* from a normally sterile site or a positive Hib antigen test combined with a clinical picture compatible with invasive Hib disease.

The dates of all primary immunizations were obtained from the child's general practitioner or from the district child health immunization computer. The local microbiologist was asked to send the isolate to the Public Health Laboratory Service Haemophilus Reference Laboratory (Oxford) where the identity was verified by standard slide agglutination and polymerase chain reaction techniques.10

To maximize the reporting of cases, the study was widely publicized in the medical press prior to its commencement, and pediatricians, microbiologists, and CCDCs were then updated through quarterly BPSU bulletins, an annual BPSU report, and publications in the *Communicable Disease Report* (England and Wales) and the *Scottish Centre of Infection and Environmental Health Report*. Reports to other agencies of vaccine failures were checked against those reported to the study including the 2 pharmaceutical companies supplying the vaccines, the UK Department of Health Medicine Control Agency, the Public Health Laboratory Service Communicable Disease Surveillance Centre for England and Wales, and the Scottish Centre for Infection and Environmental Health.

**Hib Conjugate Vaccines**

The specific Hib conjugate vaccines and combinations administered to children changed over the period of the study. Between 1992 and 1996 the dominant vaccine was PRP-T (Aventis Pasteur, Berkshire, England) given as a separate injection, with HbOC (PRP conjugated to mutant diphtheria toxoid, CRM197 [Wyeth, Berkshire, England]) used for catch-up vaccination of children older than 1 year (1992-1994). From 1996 PRP-T (Aventis Pasteur) has been given as a combination vaccine (with DTP), and HbOC has also been available for primary vaccination. Since 1997, another PRP-T vaccine (SmithKline Beecham, Hertfordshire, England) has also been available for primary vaccination. Since 1997, another PRP-T vaccine (SmithKline Beecham, Hertfordshire, England) has also been available for primary vaccination (Debby Webb, Department of Health, London, England, written communication, August 1999). All children received whole cell pertussis–containing DTP vaccines. For the purposes of this analysis all of these...
conjugates have been considered equivalent.

**Vaccine Failures**

A *true vaccine failure* (TVF) was defined as invasive Hib disease occurring more than 2 weeks after a single dose of vaccine given to a child when older than 1 year, or more than 1 week after at least 2 doses of vaccine had been given to an infant aged 1 year or younger. Clinical effectiveness data are presented only for infants given 3 doses of vaccine. A case of Hib disease occurring after receipt of 1 or 2 doses of vaccine but before sufficient time had elapsed to be counted as a TVF was defined an *apparent vaccine failure*. If a strain of *H influenzae* was isolated from a vaccinated child but not sent to the reference laboratory for verification, it was defined as a *possible vaccine failure*.

**Immunogenicity Studies**

The recruitment methods have been described previously. The first cohort of children was enrolled in an immunogenicity and safety study of PRP-T vaccine. Briefly, parents of infants born at the John Radcliffe Hospital in Oxford were approached after the birth of their child and given information about the study. Written informed consent was obtained and infants received PRP-T vaccine as a separate injection from DTP at 2, 3, and 4 months of age. No further doses of Hib vaccine were given. A total of 107 infants were initially enrolled and serum samples were obtained from as many of these infants as possible at 2 months of age (90), 5 months of age (105), and 12 months of age (95); the results have been reported previously. A further sample was obtained at 6 years of age from 59 children (first cohort).

A separate group of 153 children born in 1991 and vaccinated with PRP-T vaccine at 2, 3, and 4 months of age had samples taken at 43 months of age (second cohort). These children were originally part of a large PRP-T implementation trial that took place in the Oxford Health Region in 1991-1992. The names of these children were obtained from the Oxford district child health immunization computer records and the parents were approached by letter. Those who agreed to participate were visited at home and written informed consent obtained.

Serum was stored at ~20°C until serological tests were performed. Anti-PRP IgG antibodies were quantified using an enzyme-linked immunosorbent assay technique.

**Statistical Analysis**

**Vaccine Effectiveness.** To derive estimates of vaccine effectiveness of Hib conjugate vaccine, the observed number of TVFs (after 3 doses) that accrued in infants born between August 1, 1992, and March 1, 1999, was divided into age bands and compared with the number of cases expected based on the age-specific rates of invasive Hib disease. These rates were obtained from a 6-year survey that took place between 1985 and 1990, prior to the introduction of the Hib vaccine in the Oxford Health Region. The population at risk in the Oxford Health Region survey was calculated using census data for mid 1988 (Office of National Statistics, London). The follow-up (exposure) time of vaccinated children began from 5 months of age, 1 week after the average time at which infants complete the primary course of immunization. The exposure times were then calculated using the national vaccine coverage figures for each year from 1992-1998 (COVER [Coverage of Vaccination Evaluated Rapidly] data, published quarterly in the Communicable Disease Report CDR Weekly) and the annual national birth and mortality rates (Office of National Statistics, London). The annual UK birth cohort varied from 717000 to 781000 over the period of the study.

Poisson regression models were used to estimate the relative incidence rate for each age year between the 2 samples. Vaccine effectiveness was calculated as 100 × (1 − relative incidence rate) and is quoted together with 95% confidence intervals (CIs). A comparison between the vaccine effectiveness in the first year of life with subsequent years was computed by including an interaction term in the model. All statistical analyses were performed using STATA statistical software. Estimates and CIs of the relative vaccine effectiveness comparing those vaccinated and unvaccinated were made using standard methods for comparing incidence rates.

**Anti-PRP Antibody Concentrations.** Anti-PRP antibody concentrations were determined at ages 2, 5, 12, and 72 months from the first cohort and at 43 months from the second cohort. Three sets of comparisons between antibody concentrations were made:

1. (to assess the response to vaccine; (2) between month 5 and month 12 (to assess the early decline following completion of the vaccine schedule); and (3) between months 12, 43, and 72 (to assess the long-term decline in antibody levels). Comparisons between anti-PRP antibody concentrations at ages 2, 5, 12, and 72 months were made accounting for the longitudinal nature of the data, whereas all comparisons involving the 43-month data treated the data from other time points as if they were from an independent group. Antibody concentrations are summarized using geometric mean concentrations (GMCs), and all statistical analyses were performed after log-transforming the data. Changes in GMCs between time points are reported as fold rises. Where antibody levels were undetectable (<0.15 µg/mL), the value 0.08 was substituted. The differences between the time points were tested using t tests, while the trends in antibody levels over several time points were assessed using linear regression. Changes in the proportion below the antibody thresholds of 0.15 and 1.0 µg/mL were analyzed using the χ² test for trend. Confidence intervals for proportions were calculated using the Binomial Exact method.

All studies were approved by the Central Oxford Research Ethics Committee.
RESULTS

Clinical Hib Disease

During the 6-year, 5-month period between October 1, 1992, and March 1, 1999, 112 TVFs and 58 apparent vaccine failures were reported to the study. There were 7 possible vaccine failures. In the 3-year, 4-month period between November 1, 1995, and March 1, 1999, 39 cases of invasive Hib disease were reported in unvaccinated children.

Vaccine Failures

Of 112 TVFs, there were 96 children who had previously received 3 doses of Hib vaccine, 9 who had received 2 doses, and 7 who had received 1 dose. There were 4 deaths among the TVFs, 3 occurring after 3 doses of vaccine (ages 5, 17, and 30 months), and 1 after 1 dose.

During the study period an estimated 436 820 0 infants in the United Kingdom received 3 doses of vaccine; the vaccine failure rate after 3 doses was therefore 2.2 per 100 000 vaccinees (95% CI, 1.8-2.7).

There were 7 possible vaccine failures. Of 112 TVFs, there were 96 children who had previously received 3 doses of Hib vaccine, 9 who had received 2 doses, and 7 who had received 1 dose. There were 4 deaths among the TVFs, 3 occurring after 3 doses of vaccine (ages 5, 17, and 30 months), and 1 after 1 dose.

During the study period an estimated 436 820 0 infants in the United Kingdom received 3 doses of vaccine; the vaccine failure rate after 3 doses was therefore 2.2 per 100 000 vaccinees (95% CI, 1.8-2.7).

Table 1 divides the TVFs that occurred after 3 doses of vaccine according to age at disease and compares the observed number of TVFs with the number of cases expected, based on the child years of exposure and the age-specific attack rate observed in prevaccination surveillance. Vaccine effectiveness at different ages is estimated. Inclusion of the 7 possible vaccine failures makes no significant difference to estimates of vaccine effectiveness.

The vaccine effectiveness declined after the first year (P<.001), although the decrease was small (99.4% in children aged 5-11 months compared with 97.3% in children between 12-71 months of age; relative disease incidence rate, 4.1 [95% CI, 2.3-7.2]).

Performing a sensitivity analysis where the assumption is made that surveillance for vaccine failures was considerably incomplete by doubling the number of TVFs actually notified to the study, the vaccine effectiveness estimates are only minimally affected (FIGURE). The overall vaccine effectiveness calculated by doubling the actual number of cases reported becomes 96.4% (95% CI, 95.7%-97.0%).

Subdividing TVF by age of a hypothetical booster dose (given at 12-15 months of age plus 1 week to develop a protective antibody response) reveals that 79 patients were 12.25 months of age or older and 71 patients were 15.25 months of age or older at the time of disease. Two of the 3 deaths after 3 doses were in children older than the age of a hypothetical booster dose.

Hib Disease in Unvaccinated Children

Thirty-nine cases of Hib disease occurred in unvaccinated children. There were 3 deaths. The median age at disease for all Hib patients was 8.7 months (range, 0-164 months). Timely Hib vaccination could have prevented 13 of these cases (including 1 death). The remaining 26 were either too young to have received a protective course of vaccination, too old to have been eligible for vaccination (born before 1988), were born outside the United Kingdom, or had underlying conditions and may not have responded to vaccination.

Hib Disease in All Children

For the period November 1, 1995, to March 1, 1999, all children younger

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than 16 years with invasive Hib disease, regardless of vaccination status, were eligible for notification to the study. The incidence of Hib disease in infants younger than 1 year and children younger than 5 years for the 3 full years of surveillance (1996, 1997, and 1998) are shown in Table 2 according to vaccination status (receipt of any number of doses of Hib vaccine). In 1996 the relative risk of a vaccinated child (any number of doses) having invasive Hib disease compared with an unvaccinated child was 0.03 (95% CI, 0.01-0.15); in 1997, 0.05 (95% CI, 0.01-0.16); and in 1998, 0.04 (95% CI, 0.01-0.20).

**Persistence of Anti-PRP Antibody**

The GMC of anti-PRP antibody and the proportions of children with an anti-PRP antibody concentration below 0.15 µg/mL and 1.0 µg/mL at different ages are shown in Table 3. A significant increase in GMC was found between months 2 and 5 (13-fold increase, \( P < .001 \)) and a significant decrease in the period between month 5 and month 12 (5-fold decline, \( P < .001 \)). However, the decline in GMC between month 12 and month 72 was small and nonsignificant, both when estimated by comparing paired serum samples from month 12 with month 72 (1.35-fold decline, \( P = .30 \)) and when considering the trend between months 12, 43, and 72 (1.09-fold decline per year; 95% CI, 0.98-1.20, \( P = .13 \)). The proportion with levels below 0.15 µg/mL significantly increased during this period (\( \chi^2 \) test for trend=18.25, \( P < .001 \)).

In the Figure, vaccine effectiveness is shown in different age groups comparing that estimated by clinical vaccine failure rates (after 3 doses) with that predicted by the proportions with anti-PRP antibody concentrations greater than 0.15 µg/mL and greater than 1.0 µg/mL (after 3 doses).

**COMMENT**

The introduction of routine Hib vaccination in the United Kingdom has resulted in a rapid, dramatic, and sustained decline in the incidence of Hib disease. The incidence in children younger than 5 years in 1998 was 0.6 per 100000. In contrast, prior to the introduction of vaccination, the incidence for England and Wales was 31 to 36 per 100000,\(^{11,12}\) a reduction of 98%. This incidence compares favorably with recent estimates in other countries. In the United States in 1996 and 1997, the incidence of Hib disease in those younger than 5 years identified through national surveillance ranged between 0 and 2.9 per 100000 in different states (excluding Alaska). The race-adjusted incidence derived from active laboratory-based surveillance in selected areas in 1997 was 0.4 per 100000 in children younger than 5 years and the decline in incidence between 1989 and 1997 was estimated at 99%.\(^{20} \)

Key factors in the success of the UK program are likely to include the high vaccine coverage achieved as well as a program that included all children to 48 months of age. The rationale for this strategy was that susceptibility to Hib disease continues to this age\(^1 \) and that pharyngeal carriage rates of Hib is relatively more common in older preschool children (summarized by Coen et al\(^{21} \)). Inclusion of this group may therefore have had an important effect on reducing the circulation of Hib in the population. As in other countries,\(^{22,23} \) pharyngeal carriage rates of Hib have declined in the United Kingdom since the introduction of Hib vaccination.\(^1 \) Recent experience in the Alaskan native population underscores the

**Table 2. Incidence of Invasive Haemophilus influenzae Type b (Hib) Disease in Unvaccinated, Vaccinated (Any Number of Doses), and All UK Children Younger Than 1 Year and Total Incidence in Children Younger Than 5 Years (per 100 000) by Year**

<table>
<thead>
<tr>
<th>Year</th>
<th>Age &lt;1 y and Unvaccinated: Incidence of Hib Disease (95% CI)</th>
<th>Age &lt;1 y and Vaccinated: Incidence of Hib Disease (95% CI)</th>
<th>Age &lt;1 y: Total Incidence of Hib Disease (95% CI)</th>
<th>Age &lt;5 y: Total Incidence of Hib Disease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>13.9 (5.1-30.3)</td>
<td>0.4 (0.1-1.3)</td>
<td>1.3 (0.6-2.4)</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>1997</td>
<td>15.3 (7.0-29.0)</td>
<td>0.7 (0.2-1.7)</td>
<td>1.9 (1.0-3.2)</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>1998</td>
<td>10.2 (3.7-22.2)</td>
<td>0.4 (0.1-1.3)</td>
<td>1.2 (0.6-2.3)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
</tbody>
</table>

**Table 3. Serum Anti-PRP (Polyribosylribitol Phosphate) Antibody Concentrations After 3 Doses of Haemophilus influenzae Type b Vaccine in Infancy**

<table>
<thead>
<tr>
<th>Age, mo (No.)</th>
<th>Anti-PRP Antibody: Geometric Mean Concentration, µg/mL (95% CI)</th>
<th>Concentration &lt;0.15 µg/mL, % (95% CI)</th>
<th>Concentration &lt;1.0 µg/mL, % (95% CI)</th>
<th>Fold Change in Anti-PRP Antibody Concentration, Geometric Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (prevaccination) (90)</td>
<td>0.37 (0.31-0.44)</td>
<td>10 (6-18)</td>
<td>89 (81-95)</td>
<td>...</td>
</tr>
<tr>
<td>5 (postvaccination) (105)</td>
<td>4.60 (3.51-6.03)</td>
<td>1 (0-5)</td>
<td>12 (7-20)</td>
<td>Fold change from month 2: 13.0 (9.0-18.6) ( P &lt; .001 )</td>
</tr>
<tr>
<td>12 (95)</td>
<td>0.88 (0.66-1.17)</td>
<td>6 (2-13)</td>
<td>57 (46-67)</td>
<td>Fold change from month 5: 0.20 (0.15-0.25) ( P &lt; .001 )</td>
</tr>
<tr>
<td>43 (153)</td>
<td>1.06 (0.81-1.38)</td>
<td>8 (4-13)</td>
<td>49 (41-57)</td>
<td>...</td>
</tr>
<tr>
<td>72 (59)</td>
<td>0.51 (0.31-0.84)</td>
<td>32 (21-46)</td>
<td>71 (58-82)</td>
<td>Fold change from month 12: 0.74 (0.44-1.27) ( P = .30 )</td>
</tr>
</tbody>
</table>

*Data at ages 2, 5, 12, and 72 months are from the same children (first cohort); data at 43 months are from a different cohort (second cohort). CI indicates confidence interval.
importance of reducing Hib transmission through vaccination. A resurgence of invasive Hib cases in children in 1996 and 1997 was attributed to continuing Hib carriage unmasked by a change in the vaccination regimen.

Similar to other investigators, we have shown a decline in anti-PRP antibody concentrations after primary immunization. In our cohort, the fall in antibody between 5 and 12 months of age was statistically significant and thereafter, although the decline in GMC was not statistically significant, the trend in proportions of children with anti-PRP concentrations below 0.15 µg/mL (a putative protective threshold) was also significant. This might suggest an increasing susceptibility to invasive Hib disease as children in the United Kingdom get older. Indeed, in the absence of surveillance data, it would seem prudent to recommend a second year booster dose to prevent this apparent decline in protection. However, we have had the unique opportunity to interpret these serological data in the light of clinical vaccine failure cases. Vaccine protection, as assessed through clinical failures, remains high until 6 years of age. Although there is a statistically significant decline after the first year of life, it is small in real terms with the absolute estimates of vaccine effectiveness and their 95% lower confidence limits remaining very high up to 4 years of age. Even if underreporting is assumed, the estimates of vaccine effectiveness remain high.

A comparison between predicted efficacy from immunogenicity data and estimated efficacy from surveillance data suggests that a threshold of 0.15 µg/mL correlates much better than a threshold of 1.0 µg/mL, although even a level of 0.15 µg/mL clearly underestimates effectiveness. Why do antibody concentrations after receipt of conjugate vaccines not correlate well with clinical protection? The antibody thresholds of 0.15 and 1.0 µg/mL were derived from unvaccinated populations and those who received passive immunization (0.15 µg/mL) and populations who received the PRP capsular polysaccharide vaccine (1.0 µg/mL). In contrast to this vaccine, the conjugate Hib vaccines are capable of inducing immunological memory in recipients; thus, even those individuals with low antibody concentrations may still be protected against disease. Immunological memory has been demonstrated using the UK schedule. Other laboratory markers of immunological memory, such as antibody avidity, may now prove more useful than specific antibody concentration measurement in the context of conjugate vaccines. This argument has recently been advanced to support the use of acellular pertussis/Hib conjugate vaccine combinations despite the lower Hib antibody concentrations frequently encountered with such combinations.

Conjugate vaccines also have an impact on carriage of Hib and thereby reduce Hib circulation and provide benefit through reduced transmission of Hib in the population (herd immunity). Thus, the unvaccinated, partially vaccinated, or vaccine failures may avoid coming in contact with Hib. This is demonstrated in this article by the 10-fold reduction in Hib disease seen in unvaccinated infants younger than 1 year when compared with their rate in the prevaccine era. Thus, both immunological memory and herd immunity are likely to be contributing to the successful impact of Hib conjugate vaccines in the United Kingdom.

If a booster dose of Hib vaccine were to be incorporated into the UK schedule, it might logically be given at the same time as the measles-mumps-rubella vaccine, ie, between 12 and 15 months of age. If such a program had been in place, with an uptake of 100% and vaccine effectiveness of 100%, then 71 to 79 Hib cases including 40 to 44 cases of meningitis and 2 deaths may have been avoided. However, approximately 4.2 million booster doses would need to have been administered in the United Kingdom to do so—equivalent to 100,000 doses for each case of Hib meningitis prevented. This further assumes that a booster dose would have been effective (25% were known to have had clinical risk factors and/or low immunoglobulin concentrations that may have impaired response to vaccination). A formal cost-benefit analysis is beyond the scope of this article, but would be of interest to countries that currently recommend a booster dose as they reevaluate their immunization schedules.

The overall impact of routine immunization in the United Kingdom with a 3-dose primary schedule without a fourth dose is similar or greater in magnitude to Iceland, the United States, Canada, the Netherlands, and Australia, which have routinely included a fourth dose. The impact of the UK program is also similar to that witnessed in those Scandinavian countries that also use only 3 doses of Hib vaccine but administer 2 doses in the first year and the third dose in the second year of life.

The demonstration that a booster dose in the second year of life is not essential has significant implications for countries yet to initiate routine Hib vaccination. In particular, in much of the developing world, Hib is an important pathogen, yet there are few developing countries that can afford the relatively expensive Hib conjugates. The decision to introduce this vaccine would be made easier if fewer doses were required. Hib conjugate vaccines have recently been introduced in Chile and The Gambia using 3-dose schedules, and the early experience in The Gambia is promising. Encouraging recent studies in Chile suggest further that 2 doses may suffice. Long-term follow-up of persons with Hib disease in nonindustrialized countries will be critical in extrapolating the need for a booster dose to all populations.

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