Haemophilus influenzae Type b Conjugate Vaccine Introduction in Mali: Impact on Disease Burden and Serologic Correlate of Protection

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Abstract. In Bamako, Mali, where surveillance revealed a high incidence of Haemophilus influenzae type b (Hib) invasive disease, Hib conjugate vaccine was introduced into the Expanded Program on Immunization and the impact assessed. Annual confirmed Hib hospitalizations for infants 0–11 months of age fell from 175/10⁵ to 44/10⁵ (P < 0.001); among infants 6–7 months of age Hib hospitalizations fell from 377/10⁵ to 69/10⁵, (82% decrease, P < 0.001). Invasive Streptococcus pneumoniae hospitalizations remained unchanged. In a baseline serosurvey, only 3/200 infants 6–7 months of age (1.5%) had protective anti-polysaccharidePRP PRP (PRP) titer ≥ 0.15 μg/mL and 1(0.5%) had ≥ 1.0 μg/mL. In serosurveys 18 and 30 months after vaccine introduction, 168/201 (84%) and 184/200 (92%) infants, respectively, had ≥ 0.15 μg/mL and 141/201 (70%) and 163/200 (82%) had ≥ 1.0 μg/mL. Introduction of Hib vaccine led to rises in anti-PRP seroprevalence, significant reductions in Hib disease, and all-cause hospitalizations, whereas S. pneumoniae disease remained unchanged.

INTRODUCTION

Mali, a land-locked Sahelian country in West Africa, falls among the world’s six least developed nations. Approximately 10% of Malians reside in the capital region, Bamako, where severely ill infants and young children requiring hospitalization are admitted to a government hospital, l’Hôpital Gabriel Touré (HGT). A survey in 2000 revealed that 71% of admissions to HGT among children < 16 years of age were for presumed infectious diseases and 21% of all admitted children died; however, no clinical microbiology laboratory existed to determine the agents causing these infections. In July 2002, after a clinical bacteriology laboratory was established, systematic surveillance for invasive bacterial infections began. Within 24 months it became evident that invasive Haemophilus influenzae type b (Hib) infections constituted a major cause of hospitalizations. The Hib incidence was low in infants < 4 months of age but rose precipitously to a peak of 370/10⁵ among infants 6–7 months of age; 18.2% of hospitalized infants 6–7 months of age had invasive Hib disease. Revelation of this enormous Hib disease burden led the Ministry of Health to apply to the Global Alliance for Vaccines and Immunization (GAVI) for support to introduce Hib vaccine into the Expanded Program on Immunization (EPI). A three-step introduction was planned, with Bamako (step 1, ~11% of the Malian infant cohort) scheduled for July 2005, other urban centers (step 2) for July 2006, and the remainder of the country (step 3) for July 2007. Ongoing systematic bacteriology laboratory-supported clinical surveillance allowed us to measure the impact of vaccine introduction on the Hib disease burden. Because serum IgG antibodies to Hib capsular polysaccharide, polysaccharideribitol phosphate (PRP), constitute a correlate of protection against invasive disease, in concert we monitored changes in the seroprevalence of protective levels of anti-PRP in infants 6–7 months of age before and after Hib vaccine introduction as an objective measure of vaccine coverage.

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MATERIALS AND METHODS

Systematic surveillance at HGT. Since July 2002, clinical staff of the Center pour le Développement des Vaccins du Mali (CVD-Mali) and HGT have been conducting systematic surveillance to detect invasive bacterial disease among hospitalized children < 16 years of age. Age-eligible children presenting to the emergency department with fever (≥ 39°C) or focal clinical findings suggestive of invasive bacterial infection (meningitis, septic arthritis, etc.) and requiring hospitalization are referred to CVD-Mali staff by the evaluating clinicians. For economic and logistical reasons, surveillance proceeded from 8 am until midnight (during which 90% of pediatric patients are admitted). A CVD-Mali physician obtains informed consent, records clinical and epidemiologic data, and obtains blood (and other relevant fluids) for culture in the HGT Clinical Bacteriology Laboratory. The child’s clinician is promptly notified when a culture yields a bacterial pathogen. The surveillance protocol and consent form were reviewed by the Ethics Committee of the Faculté de Médecine, Pharmacie et Odonto-Stomatologie, University of Bamako, and by the Institutional Review Board of the University of Maryland, Baltimore. This impact study focuses on children < 24 months of age.

Surveillance for hospitalized invasive Hib cases from July 1, 2002 through June 30, 2005, preceding the introduction of Hib conjugate vaccine into the EPI in Bamako for infants 6, 10, and 14 weeks of age, constitutes the baseline period. The 12-month transition period began when Hib vaccine was introduced into the Bamako EPI on July 1, 2005 and extended through June 30, 2006. July 1, 2006 through June 30, 2008 represents the first 24 months of the intervention period. During all three periods, parents of 94–97% of children gave permission for cultures to be obtained. The Malian National Directorate of Statistics and Informatics provided annual Bamako mid-year population data by age strata.

Serosurveys. Serosurveys were undertaken before the introduction of Hib vaccine (May 2005) and 18 and 30 months thereafter to measure the prevalence of protective levels of serum PRP antibody among random samples of 200 infants 6–7 months of age in three of the six communes of Bamako.
This age group was chosen because it represented when Hib disease incidence peaked and maternal IgG antibodies had for the most part disappeared. In each survey, sera were collected from 100 infants residing in Djikoroni and Sèbéninkoro quarters (Commune IV), 50 in Banconci quarter (Commune I), and 50 in Kalabankoro quarter (Commune VI). During the initial serosurvey, standard immunization survey methods randomly identified the first household, after which a prescribed route was followed to access additional households until the required number of infants was attained. In the last two serosurveys, infants in Djikoroni and Banconci were selected using a computer-generated random list of age-eligible children compiled from the demographic surveillance database that had been established in these quarters since the initial survey; infants in Sèbéninkoro and Kalabankoro were identified as during the initial survey. Informed parental consent was solicited to collect 2 mL of blood by venipuncture to measure IgG anti-PRP by enzyme-linked immunosorbent assay (ELISA) by a previously reported method, with slight modifications. Immulon II plates were coated with HbO-HA antigen (lot #17) at 1 μg/mL. Samples were run in serial dilutions, in duplicate wells. The HRP-labeled goat anti-human IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) was used as conjugate. Titers were calculated by interpolation of regression-corrected Absorbance values in the standard curve of the Center for Biologics Evaluation and Research (CBER) Food and Drug Administration (FDA) reference serum lot #1983 (70 μg/mL) and reported in μg/mL. During the two serosurveys conducted after the introduction of Hib vaccine, families of enrolled infants were asked to present their infant's immunization card. If a card was shown, the number of Hib vaccine doses received was recorded.

Estimates of vaccine effectiveness. Vaccine effectiveness (%VE) was estimated by the formula (1-RR [incidence rate ratio]) × 100 for children older than 4 months (i.e., those old enough to have received 2–3 doses of Hib vaccine). Incidence rate ratios for infants 4–11 months and children 4–23 months of age were calculated using the baseline period versus both years and versus the second year of the intervention period. Confidence interval (CI) estimation for %VE used a binomial transformation for the proportion of Hib cases occurring during the intervention period.

Statistical analysis. Data captured using Microsoft Access 2000 were stored in Microsoft SQL Server 2000 (Microsoft, Redwood, WA). Incidence rates during baseline and intervention periods were compared using a χ² statistic for Poisson rates. Proportions of seropositive 6–7 month olds during baseline and post-introduction serosurveys were compared by χ² or, for a numerator < 5, two-tailed Fisher exact test. Incidence by 6 month periods (July 1, 2002–June 30, 2008) was assessed by linear regression of Poisson incidence rates on time.

RESULTS

Incidence of invasive Hib. Table 1 shows the infant and toddler population of Bamako and the number of cases and incidence of confirmed, invasive Hib disease among hospitalized children during the 36-month baseline, the 12-month transition, and the two individual years of the intervention period. During baseline, the incidence of hospitalized cases of invasive Hib disease was 5-fold higher in infants than toddlers (Table 1); 94% (251/267) of infant cases occurred in the age range 4–11 months and the peak annual incidence, 377 cases/10⁵, was observed in 6–7 month of age.

Among infants 0–11 months of age, the incidence of invasive Hib disease fell progressively during each ensuing semester of the transition and intervention periods (P < 0.001, linear regression) (Figure 1). By the second year of the intervention period, the Hib incidence (30 cases/10⁵) had decreased by 83% from the mean annual incidence of the baseline period (175 cases/10⁵) (P < 0.001) (Table 1). The incidence began to fall during the second semester of the transition year (January 6–June 6, Figure 1) as vaccinated infants accumulated. By contrast, the incidence of invasive Hib disease among 12–23 month olds did not decrease until the intervention period (Table 1). In the high risk 6–7 month olds, the incidence dropped from 377 cases/10⁵ during baseline to 53 cases/10⁵ by the second year of the intervention period, a decrease of 86% (P < 0.001).

During the three baseline years, the annual number of fatalities among confirmed Hib cases 0–11 months of age admitted to HGT was 10, 7, and 14 (mean 10.3). Infant Hib deaths remained at 10 during the transition period but then dropped to 3 and 4 deaths, respectively, during years 1 and 2 of the intervention period.

Incidence of invasive pneumococcal infections. To verify that the fall in incidence of invasive Hib disease was specific to introduction of Hib conjugate vaccine and not to a secular trend or a broad change in pediatric ambulatory care, we analyzed the hospitalized cases of invasive disease resulting from Streptococcus pneumoniae in the 0–11 month old age group. Figure 1 compares the incidence of hospitalizations as a result of invasive pneumococcal versus Hib disease in infants 0–11 months of age calculated in 6-month blocks. The annual incidence of S. pneumoniae disease remained stable among

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<tr>
<td></td>
<td>Mean annual pop’n, Bamako</td>
<td>Mean annual Hib cases</td>
<td>Mean annual Hib inci/10⁵ children</td>
<td>Annual Hib inci/10⁵ children</td>
</tr>
<tr>
<td>0–11 months</td>
<td>50,885</td>
<td>89</td>
<td>175</td>
<td>53,782</td>
</tr>
<tr>
<td>12–23 months</td>
<td>44,525</td>
<td>15</td>
<td>34</td>
<td>47,059</td>
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<td>6–7 months</td>
<td>8,498</td>
<td>32</td>
<td>377</td>
<td>8,981</td>
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0–23 month olds during baseline (83/10^5) and intervention periods (77/10^5) (P = 0.5), whereas Hib incidence dropped by 74% from baseline (110/10^5) to intervention (28/10^5) (P < 0.001).

**Survey to estimate Hib immunization coverage and the prevalence of serum anti-PRP antibody.** The baseline serosurvey in 6–7 month olds before the introduction of Hib vaccine revealed that only 1.5% of 200 infants had serum concentrations of PRP antibody ≥ 0.15 μg/mL and just one infant had an antibody concentration ≥ 1.0 μg/mL (Table 2). By the third serosurvey, over 80% of 6–7-month-old infants at this peak age of susceptibility now had ≥ 1.0 μg/mL of serum PRP antibodies (P < 0.001) (Table 2). Moreover, the proportion of infants with PRP antibody ≥ 0.15 μg/mL or ≥ 1.0 μg/mL detected on the third serosurvey was slightly (~8–12%) but significantly greater than observed during the second survey (Table 2).

The proportions of families that produced the infant’s immunization record during the second and third serosurveys were 187 of 201 (93%) and 180 of 200 (90%). The percentage of infants with immunization records who received at least one dose of Hib conjugate and the proportion who got all three vaccine doses are summarized in Table 2. Prevalence and geometric mean concentration of serum PRP antibody rose progressively with the number of doses of Hib vaccine received (Figure 2).

**Estimates of vaccine effectiveness.** Comparing the incidence of invasive Hib disease among infants 4–11 months of age in the baseline period (259/10^5) versus both years of the intervention (65/10^5) (Table 3), vaccine effectiveness (VE) was 75% (95% CI, 66–82%); VE in year 2 of the intervention period (44/10^5) was 83% (95% CI, 72–90%). Among children 4–23 months of age, the Hib vaccine similarly showed 74% VE (95% CI, 66–81%) over both years of the intervention period and 81% VE (95% CI, 71–88%) in year 2.

**All-cause hospitalizations.** Because multiple culture-negative cases of invasive and pneumonic Hib disease are known to occur for each culture-positive case, we analyzed the incidence of all-cause hospitalizations before and after introduction of Hib vaccine among infants 4–11 months of age. We focused on this age group to assess direct protection (younger infants would be only indirectly protected), and because this age group contributed 80% of all cases among children < 24 months of age during baseline. The incidence of all-cause hospitalizations among infants 4–11 months of age dropped by 29.2% from the baseline to the intervention periods (P < 0.001) (Table 3).

**DISCUSSION**

Five factors led the Malian government to introduce Hib conjugate vaccine into the Malian EPI: 1) enormity of the Hib invasive disease burden revealed by systematic, laboratory-supported surveillance; 2) existence of a well-tolerated conjugate vaccine with an excellent effectiveness track record in industrialized and transitional countries; 3) potential to receive donated vaccine for the cohort of Malian infants for 5 years through the GAVI Fund; 4) advocacy and support for the introduction of Hib vaccine from the highest levels of the Malian government; and 5) availability of practical pentavalent vaccine formulations that allow Hib conjugate and hepatitis B vaccines to be given in combination with diphtheria, tetanus, pertussis (DPT) vaccine via a single injection.

The impact of Hib vaccine introduction on disease burden in Bamako was monitored by continuing surveillance for cases of invasive Hib disease admitted to HGT. An impressive decline was observed, with cases among infants falling by more than 80% by the second year of the 24-month intervention period. The decline in Hib incidence in toddlers (age 12–23 months) did not commence until 1 year later when the initial vaccinated infant cohort reached toddler age. By analogy, culture-confirmed hospitalized cases of Hib disease represent only the “eyes and ears of the hippopotamus,” as a much larger “submerged” Hib disease burden remains largely undetected. Indeed, vaccine probe studies have estimated that ~5 cases of non-bacteremic Hib pneumonia, and ~3–8 cases of culture-negative invasive Hib focal infection (e.g., purulent meningitis).

**Table 2**

<table>
<thead>
<tr>
<th>Survey</th>
<th>Total infants in random sample</th>
<th>No. (%) with immunization records</th>
<th>No. (%) who got at least 1 dose of Hib vaccine*</th>
<th>No. (%) who got 3 doses of Hib vaccine*</th>
<th>No. (%) with PRP antibody ≥ 0.15 μg/mL †</th>
<th>No. (%) with PRP antibody ≥ 1.0 μg/mL †</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>200</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3† (1.5)</td>
<td>1‖ (0.5)</td>
</tr>
<tr>
<td>18 months after</td>
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<tr>
<td>initiation of the Hib vaccine program</td>
<td>201</td>
<td>187 (93.0)</td>
<td>167 (89.0)</td>
<td>138 (73.8)</td>
<td>168§ (83.6)</td>
<td>141** (70.1)</td>
</tr>
<tr>
<td>30 months after</td>
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<td></td>
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<tr>
<td>initiation of the Hib vaccine program</td>
<td>200</td>
<td>180 (90.0)</td>
<td>175 (97.2)</td>
<td>146 (81.1)</td>
<td>184¶ (92.0)</td>
<td>163†† (81.5)</td>
</tr>
</tbody>
</table>

* Of the infants whose parents showed an immunization record.
† Of all infants in the survey.
‡ vs. § or ¶, P < 0.001; † vs. ** or ††, P < 0.001, compared by two-tailed Fisher exact test.
§ vs. †, P = 0.001 and ** vs. ††, P = 0.008, compared by χ² test.
Antibiotic usage is promiscuous in many venues, including culture-negative cases are anticipated in Bamako because concentrations consistent with short-term protection (≥ 0.15 μg/mL) or long-term protection (≥ 1.0 μg/mL), in relation to the number of Hib vaccine doses received (as recorded on infants’ vaccination cards). Shown are the results of surveys conducted in (A) 2007 and (B) 2008. The prevalence of antibody increased with the number of doses of Hib vaccine received. The geometric mean concentration (GMC) of PRP antibody also increased with the number of doses.

Figure 2. The percentage of randomly selected 6 to 7 month olds with serum IgG anticapsular polysaccharide (PRP) antibody concentrations consistent with short-term protection (≥ 0.15 μg/mL) or long-term protection (≥ 1.0 μg/mL), in relation to the number of Hib vaccine doses received (as recorded on infants’ vaccination cards). Shown are the results of surveys conducted in (A) 2007 and (B) 2008. The prevalence of antibody increased with the number of doses of Hib vaccine received. The geometric mean concentration (GMC) of PRP antibody also increased with the number of doses.

Table 3
A comparison of the incidence of hospitalizations from all causes, confirmed invasive Hib disease and confirmed invasive pneumococcal disease among infants 4–11 months of age before and after introduction of Hib conjugate vaccine into the Expanded Program on Immunization

<table>
<thead>
<tr>
<th>Incidence per 10⁵ infants age 4–11 months</th>
<th>Percent decrease (%)</th>
<th>P-value‡</th>
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<tbody>
<tr>
<td>All-cause hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline*</td>
<td>2041</td>
<td></td>
</tr>
<tr>
<td>Intervention†</td>
<td>1444</td>
<td></td>
</tr>
<tr>
<td>Confirmed Hib disease</td>
<td></td>
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<tr>
<td>Baseline*</td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>Intervention†</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Confirmed Streptococcus pneumoniae disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline*</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Intervention†</td>
<td>113</td>
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* Mean annual incidence in the period July 2002 to June 2005.
† Mean annual incidence in the period July 2006 to June 2008.
‡ Compared by χ² statistic.

Healers. Thus, in evaluating the impact of vaccine introduction, one would expect that many additional cases of disease were prevented beyond the enumerated culture-confirmed cases. Some support for this contention comes from the analysis of all-cause hospitalizations among infants 4–11 months of age, which fell by 29.2% between the baseline and intervention periods (Table 3). Before Hib vaccine introduction, 80% of all cases in children < 24 months of age occurred in this age range. Comparing the decrease in incidence of all-cause hospitalizations (596 fewer hospitalizations/10⁵) with confirmed Hib cases (195 fewer cases/10⁵) from baseline to intervention (Table 3), one estimates that approximately two culture-negative Hib cases (total 401 cases) were prevented for each culture-positive case (total 195 cases). Thus, the actual Hib disease hospitalizations averted may have been ~596/10⁵, not 194/10⁵, indicating that Hib vaccination in Mali had a broad impact. Moreover, the impact at the population level is surely even greater than assessed just by hospitalizations, because many children treated in ambulatory health centers and by traditional healers have invasive Hib disease but are not cultured and yet other children never access health care.

The incidence of invasive pneumococcal disease remained virtually unchanged in the same age groups where Hib disease plummeted (Table 3, Figure 2). Streptococcus pneumoniae is also transmitted by the respiratory route and induces identical clinical syndromes (meningitis, sepsis, septic arthritis, etc.) as Hib via a similar pathogenesis. Thus, the stable incidence of invasive pneumococcal disease indicates the vaccine-related specificity of the decline in invasive Hib disease and in all-cause hospitalizations.

Serum PRP antibodies are widely accepted as a correlate of protection and protective thresholds are recognized. Therefore, we used this serologic marker as an objective measurement of Hib immunization coverage and capacity of the Malian EPI to deliver the new vaccine. A PRP antibody level ≥ 0.15 μg/mL represents a protective level present when that serum specimen was obtained, whereas ≥ 1.0 μg/mL suggests long-term protection. In the baseline serosurvey before Hib vaccine introduction, only 3 of 200 infants age 6–7 months had protective levels of PRP antibody and only one had a titer ≥ 1.0 μg/mL. These serologic data document the immunologic susceptibility of infants at this age and explain their extremely high attack rates of invasive Hib disease. The seroprevalence data in unvaccinated Malian 6–7 month olds resemble seroprevalence data from unimmunized infants 9 months of age in neighboring Niger who served as controls in a Hib conjugate vaccine immunogenicity study in the 1990s; among these infants only 1/39 (2.6%) had a serum PRP antibody concentration ≥ 1.0 μg/mL (measured by Farr type radioimmunoassay). The two subsequent serosurveys conducted in Bamako during the intervention period (18 and 30 months after initiation of the Hib vaccine program) showed that 70.1% and 81.5% of infants 6–7 months of age now possessed serum PRP antibody at a concentration of ≥ 1.0 μg/mL (P < 0.001 versus baseline). These antibody prevalences correlate well with estimates of the immunization coverage for three doses of Hib vaccine (73.8% and 81.1%), as determined by inspection of infant immunization records during the surveys (Table 2) and with the reductions in disease incidence (Table 1). Higher immunization coverage for three Hib vaccine doses would likely have been observed if we surveyed slightly older infants, because many infants receive vaccinations several weeks later than
the target age. However, we deemed it important to ascertain coverage at the peak age (6–7 months) of susceptibility.

Our favorable experience in Bamako leads us to propose that this serosurvey method be explored further as a useful tool to document the susceptibility of infant populations to Hib and to monitor objectively the effectiveness of EPI services in delivering Hib vaccine to infants in different geographic areas and settings. This serosurvey tool nicely complements methods that measure Hib disease incidence before and after introduction of Hib vaccine, such as we used in Bamako and that have been previously used in The Gambia,14 South Africa,15 Kenya,20 and Malawi.21 Concern has been raised that administrative estimates of vaccine coverage (number of doses putatively given divided by the target population), even if subjected to data quality audits, do not correlate well with vaccine coverage estimates based on random sample-based immunization surveys.22 Accordingly, it has been proposed that serosurveys be performed in conjunction with immunization record surveys to document in an objective manner immunization coverage, population susceptibility, and quality of local immunization services.22,23 The impact of Hib vaccine introduction may be considered a composite of VE and vaccine coverage in the local population. The VE largely depends on the anti-PRP responses elicited by the vaccine; the same Hib conjugate can stimulate substantially different anti-PRP responses from one population to another.24,25 The Hib VE among children 2–59 months of age in Malawi was estimated by a case-control method to be 93% (95% CI, 67–98%) for recipients of three doses of vaccine.26 The VE among children <24 months of age in Kilifi, Kenya by 1-incidence RR method was 87% (95% CI, 66–96%).20 Using the RR method in Bamako, we calculated a VE of 81% among children 4–23 months of age during the second year of the intervention period.

The Malian Hib vaccine experience adds further data to the burgeoning evidence base confirming the public health importance of this vaccine for infants in sub-Saharan Africa. Introduction of Hib vaccine in nearby Gambia and demonstration of its impact followed a pioneering large-scale controlled field trial that assessed the efficacy of Hib conjugate vaccine against both invasive disease and pneumonia of likely bacterial etiology.13,19,26,27 Kenya was another early introducer of Hib vaccine but did so without quantifying the Hib burden beforehand.20 Cowgill and others10 note that, as a consequence, “there was little enthusiasm among Kenya’s public health community to maintain the program when GAVI support was due to expire.” Fortunately, the availability of Hib burden data in Kilifi District from ongoing hospital-based surveillance before and after Hib vaccine introduction ultimately provided the Kenyan health authorities with invaluable evidence of effectiveness. The Ugandan experience after Hib vaccine introduction,28 although confined to measurement of the impact on meningitis and with only 1 year of baseline, nevertheless shares many similarities to what was observed in Mali. Evidence of the impact of Hib vaccine introduction in Rwanda29 and Ghana,30 based mainly on changes in the occurrence of clinical meningitis, is more tenuous. The Malian Hib vaccine experience, a public health success, reinforces the collective African evidence base.

Received December 18, 2008. Accepted for publication February 11, 2009.

Acknowledgments: We thank Patrick Murray for invaluable early help in establishing the Clinical Bacteriology Laboratory at l’Hôpital Gabriel Touré, James D. Campbell for assistance in clinical activities, William C. Blackwelder for biostatistical assistance, and Mardi Reymann and Lilian Cuberos from the CVD Applied Immunology Section for technical assistance measuring Hib antibodies. During the period 2002–2008, the activities described in this report received enthusiastic support from the incumbent Ministers of Health (Fatoumata Nafo Traoré, Keita Rokiatou N’Diaye, Maiga Zeinab Mint Yuba, and Oumar Ibrahim Touré) and their respective Vice Ministers (Abdramane Tounkara, Mamadou Adama Kane, Daba Diawara, and Lanssden Konaté). We also acknowledge the staunch support for Hib vaccine introduction provided by His Excellency, Amadou Toumani Touré, President of the Republic of Mali.

Financial support: Grants from the Bill and Melinda Gates Foundation (#1187 and #32470) and a grant from the Rockefeller Foundation to M. M. Levine.

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