

# Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccine Introduction Into Routine Childhood Immunization in Kenya

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**H**AEMOPHILUS INFLUENZAE TYPE b (Hib) causes 3 million episodes of serious disease among children each year, leading to half a million deaths.<sup>1</sup> In Kilifi, Kenya, invasive *H influenzae* disease is responsible for 5% of inpatient deaths among young children; *Streptococcus pneumoniae* and malaria, by comparison, are responsible for 9% and 22% of inpatient deaths, respectively.<sup>2</sup> The efficacy of conjugate Hib vaccines was established in European and American children in 1987-1991.<sup>3,4</sup> The vaccines were licensed in the United States in 1991 and were rapidly introduced into wealthy countries from which Hib disease has now almost disappeared.<sup>5,6</sup> In 1997, in The Gambia, the efficacy of conjugate vaccine against invasive Hib disease was 95%,<sup>7</sup> but the vaccine was not introduced into any other developing coun-

**Context** *Haemophilus influenzae* type b (Hib) conjugate vaccine is not perceived as a public health priority in Africa because data on Hib disease burden and vaccine effectiveness are scarce. Hib immunization was introduced in Kenyan infants in 2001.

**Objective** To define invasive Hib disease incidence and Hib vaccine program effectiveness in Kenya.

**Design, Setting, and Patients** Culture-based surveillance for invasive Hib disease at Kilifi District Hospital from 2000 through 2005 was linked to demographic surveillance of 38 000 children younger than 5 years in Kilifi District, Kenya. Human immunodeficiency virus (HIV) infection and Hib vaccination status were determined for children with Hib disease admitted 2002-2005.

**Interventions** Introduction of conjugate Hib vaccine within the routine childhood immunization program at ages 6, 10, and 14 weeks beginning November 2001.

**Main Outcome Measures** Incidence of culture-proven Hib invasive disease before and after vaccine introduction and vaccine program effectiveness.

**Results** Prior to vaccine introduction, the median age of children with Hib was 8 months; case fatality was 23%. Among children younger than 5 years, the annual incidence of invasive Hib disease 1 year before and 1 and 3 years after vaccine introduction was 66, 47, and 7.6 per 100 000, respectively. For children younger than 2 years, incidence was 119, 82, and 16 per 100 000, respectively. In 2004-2005, vaccine effectiveness was 88% (95% confidence interval, 73%-96%) among children younger than 5 years and 87% (95% confidence interval, 66%-96%) among children younger than 2 years. Of 53 children with Hib admitted during 2002-2005, 29 (55%) were age-ineligible to have received vaccine, 12 (23%) had not been vaccinated despite being eligible, and 12 (23%) had received 2 or more doses of vaccine (2 were HIV positive).

**Conclusions** In Kenya, introduction of Hib vaccine into the routine childhood immunization program reduced Hib disease incidence among children younger than 5 years to 12% of its baseline level. This impact was not observed until the third year after vaccine introduction.

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try in Africa. By 2000, only 2% of the global Hib disease burden was being prevented by vaccination.<sup>1</sup>

In 2001, the Global Alliance for Vaccines and Immunization (GAVI) offered financial support to countries with a per capita gross domestic product less than \$1000 to introduce Hib conjugate vaccine into routine childhood immunization over 5 years. Kenya was among the first 5 African countries to introduce Hib vaccine with this support, although its burden of Hib disease was unknown and there was no national surveillance in place for culture-proven Hib disease. GAVI now supports Hib vaccine in 11 African countries, but, with the exception of The Gambia, none have examined vaccine effectiveness.

Most cases of radiologically confirmed pneumonia and clinical meningitis are not caused by Hib,<sup>7,8</sup> so the effect of vaccination would be difficult to establish without microbiological confirmation. As there was no culture-based evidence to make *H influenzae* visible in East Africa, Hib vaccine was not perceived as a priority, and, given the substantial cost of vaccine, there was little enthusiasm among Kenya's public health community to maintain the program when GAVI support was due to expire. Among 6 neighboring countries in East Africa, only half have subsequently introduced Hib vaccine with GAVI support.

A clinical research center was established in Kilifi in 1989 through a collaboration between the Kenya Medical Research Institute and the Wellcome Trust and was linked to a defined population from 2000. We used the clinical, microbiological, and epidemiologic surveillance mechanisms of this center to evaluate the effectiveness of Hib vaccine introduction.

## METHODS

Kilifi District, Kenya, is located on the Indian Ocean Coast and is predominantly rural, with 1 small urban center. Within a defined geographical area in Kilifi District, we compared the incidence of invasive Hib disease in hospitalized children in the 2 years before

and the 4 years after introduction of Hib vaccine into the childhood immunization schedule and calculated vaccine effectiveness. Because the effectiveness of the program in the first few years would be strongly influenced by the age distribution of children with invasive Hib disease, we defined the age frequency curve for invasive Hib disease as precisely as possible by using data from children hospitalized during the 8 years preceding vaccine introduction.

The definition of the denominator population was adapted from the study area of the Kilifi Demographic Surveillance Study (DSS). At its inception, the boundaries of the DSS were chosen to represent the smallest area that would include the residence of 80% of children admitted to Kilifi District Hospital (KDH). This comprised 14 administrative locations and half of a 15th location, a total area of 891 km<sup>2</sup>. The Hib vaccine effectiveness study area was confined to the 14 locations covered completely (869 km<sup>2</sup>). In 2000, the area was mapped by fieldworkers on motorcycles and on foot, and every building structure was registered by its global positioning system coordinates and categorized into residential household units. A census in September 2000–October 2001 defined the resident population, and all subsequent births, deaths, and migration events were monitored by fieldworker visits to every participating household on 8 subsequent occasions at approximately 6-month intervals. At each re-enumeration round the housing register was also updated by remapping. Participation rates were high. For example, of 23 389 households identified in the Hib vaccine study area in the last re-enumeration round, only 19 declined to participate. At the midpoint of the study (January 1, 2003), the population of children younger than 5 years under surveillance in this area was 37 614.

There are 10 government-funded health centers within the study area and a similar number of private clinics; none of these has inpatient facilities. Sick children are normally referred to KDH for admission. Since 1994, all admissions

to the 42-bed pediatric ward have been recorded and investigated in a standardized manner. Approximately 5000 children are admitted annually from 20 000 outpatient visits. Since July 1998, all children, except nonemergency patients, have been investigated with blood cultures on admission.<sup>2</sup> From August 1998 forward, the clinical indications for lumbar puncture were impaired consciousness or meningism in children younger than 5 years, prostration in children younger than 3 years, seizures (other than febrile seizures) in children younger than 2 years, and suspicion of sepsis in children younger than 60 days. In March 2004, the criterion of prostration (inability to sit or drink/suck) was replaced by coma (inability to localize a painful stimulus). Sensitivity of the new lumbar puncture criteria for bacterial meningitis was 79%.<sup>9</sup>

Tetanus toxoid–conjugated Hib vaccine was introduced into the Kenya Expanded Programme on Immunisation as part of a pentavalent formulation in which lyophilized Hib vaccine (Hiberix; GlaxoSmithKline, Uxbridge, England) was resuspended in diphtheria/tetanus/whole-cell pertussis/hepatitis B virus vaccine (Tritanrix, GlaxoSmithKline). Pentavalent vaccine was distributed from KDH to 10 government clinics throughout the study area during October 2001, and all stocks of trivalent diphtheria-tetanus-pertussis vaccine were withdrawn by November 1, 2001.

Pentavalent vaccine was targeted at children aged 6, 10, and 14 weeks. The first children eligible to receive a 6-week dose of pentavalent vaccine on November 1, 2001, were born on September 20, 2001, and would have received their third dose at the end of December 2001. For population-based analyses we designated January 1, 2000, through December 31, 2001, as the prevaccine period and January 1, 2002, through December 31, 2005, as the postintroduction period. To analyze the change in vaccine effectiveness over time, we split the postintroduction period into 2 observation periods of 2 years each.

To describe the age distribution of invasive Hib disease prior to vaccine introduction, we analyzed all cases of invasive Hib disease admitted to KDH between January 1994 and December 2001, irrespective of their geographical residence.

### Laboratory Studies

Throughout the study, blood was cultured in BACTEC Peds-Plus medium (Becton, Dickinson & Co, Franklin Lakes, NJ) in a BACTEC 9050 instrument for 4 days. Samples testing positive were subcultured on 7% horse blood and chocolate agar and incubated overnight in 5% CO<sub>2</sub>. Cerebrospinal fluid (CSF) was cultured on horse blood and chocolate agar. *Haemophilus* species were identified by colony morphology, Gram stain, X and V factor dependence, and serotyping. External quality control for microbiological laboratory standards was provided by the UK National External Quality Assessment Service (<http://www.ukneqas.org>). Serotype results for invasive *H influenzae* isolates were confirmed in England by polymerase chain reaction–based capsular genotyping using primers designed to amplify the type-specific regions of the *cap* loci in each of the 6 (a-f) capsular types.<sup>10</sup>

Between 1994 and 2000, latex agglutination tests for Hib antigen were performed on CSF specimens having a white cell count greater than  $10 \times 10^6$  cells/L or a ratio of CSF glucose to plasma glucose less than 0.67. In January 2001, the year that Hib vaccine was introduced, the CSF criteria for latex agglutination testing were changed. Therefore, Hib antigen results were not included in the case definition evaluating vaccine effectiveness but were used to describe the age distribution of children with Hib prior to vaccine introduction.

Human immunodeficiency virus (HIV) antibodies were assayed by enzyme-linked immunosorbent assay (Vironostica; BioMerieux, Marcy l'Etoile, France) and rapid test (Determine; Abbott Laboratories, Abbott Park, Ill). Samples testing positive from children younger than 18 months and dis-

cordant samples were assayed by polymerase chain reaction for proviral DNA. After July 2003, HIV testing was offered as part of standard clinical care. For children admitted before July 2003, we invited the families of surviving children to voluntary counseling and testing; for children who had died we tested stored serum samples, if available.

### Statistical Analysis

Data were analyzed using STATA version 8.2 (StataCorp, College Station, Tex). The incidence of invasive Hib disease was calculated as the number of culture-confirmed cases of Hib disease admitted to KDH among residents of the study area divided by the resident population at the midpoint of each observation period. The resident population at the midpoint of each observation period was estimated from a linear regression line of the log-transformed population counts at the original census and at each of the 8 re-enumeration rounds.<sup>11</sup> Each population count was considered to have taken place on the median enumeration date for the entire round, and ages were calculated for the day each individual was enumerated. Vaccine effectiveness was calculated as 1 – rate ratio (RR), expressed as a percentage. Incidence RRs were calculated for each of the 2 postintroduction periods compared with the prevaccine period.

To assess the effect of secular trends in the presentation and investigation of invasive bacterial disease at KDH throughout the study period, we evaluated the incidence of a control condition, invasive pneumococcal disease. No pneumococcal vaccine was used in this population during 2000–2004, and in 2005 the number receiving conjugate pneumococcal vaccine was less than 100 throughout the whole study area.

When the indications for undertaking a lumbar puncture changed in March 2004, the number of children being investigated with CSF cultures was reduced by approximately one third. Therefore we were unable to compare the incidence rates of culture-confirmed meningitis before and after vaccine introduction to evaluate vaccine efficacy against

Hib meningitis. Because Hib meningitis is clinically indistinguishable from other causes of bacterial meningitis, we assumed that the change in clinical indications would affect our detection of all bacterial meningitis cases equally. Under this assumption the odds of Hib culture in cases of probable bacterial meningitis would remain constant in the absence of vaccine use, and the odds ratio in the preintroduction and postintroduction periods would approximate the incidence RR for Hib meningitis in the presence of vaccine. For this analysis, probable bacterial meningitis was defined by a CSF white cell count of  $50 \times 10^6$  cells/L or greater or a ratio of CSF glucose to plasma glucose less than 0.1,<sup>12</sup> and the effectiveness of the vaccine program against Hib meningitis was calculated as 1 – odds ratio, expressed as a percentage.

Because the observed incidence of invasive Hib disease did not decline perceptibly in the 2 years following vaccine introduction, we investigated whether this was caused by poor vaccine coverage or by failure of the vaccine to protect children because they were HIV infected. We estimated the immunization coverage for pentavalent vaccine doses 1 through 3 using vaccine cards and mothers' histories in 204 children selected at random from the DSS register in March 2004.<sup>13</sup> We also investigated the vaccination and HIV infection status of children who presented to hospital with invasive Hib disease in the postintroduction period. Again, vaccination status was determined by vaccine card or mother's history. An effective dose of vaccine was defined as an immunization given 14 or more days before hospital admission for dose 1, or 7 or more days before admission for doses 2 and 3. Evidence from several studies suggest that 2 effective doses are protective, and we categorized patients at this threshold.<sup>14–16</sup>

The surveillance evaluation was approved by the Kenya Medical Research Institute national ethical review committee and the institutional review board of the US Centers for Disease Control and Prevention. Informed consent was not required.

**RESULTS**

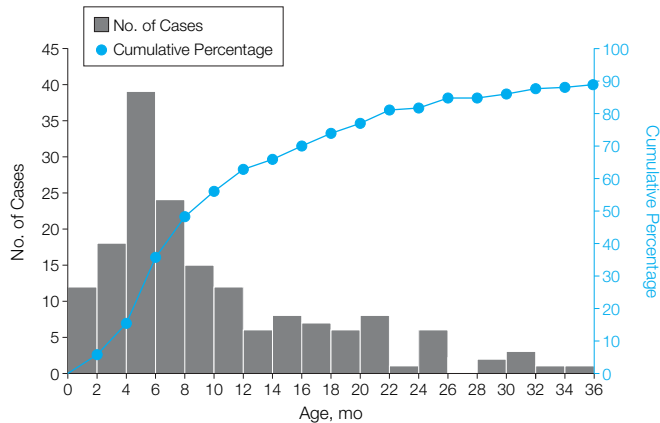
The age distribution of Hib disease prior to introduction of the Hib vaccine is described in 190 patients with laboratory-confirmed invasive Hib disease admitted to KDH between 1994 and 2001, comprising 86% (190/221) of invasive

*H influenzae* infections of all serotypes during this period (FIGURE 1). Eight episodes were diagnosed by Hib antigen CSF latex agglutination tests alone. Hib was cultured in blood from 152 patients, including 70 who had positive CSF cultures, in CSF alone in 29 pa-

tients, and in pleural fluid alone in 1. Ninety-seven patients (51%) were boys. The median age was 8 months; 27 patients (14%) were younger than 14 weeks, 120 (63%) were younger than 1 year, 156 (82%) were younger than 2 years, and 11 (6%) were 5 years or older.

The characteristics of invasive *H influenzae* disease among children younger than 5 years admitted to KDH during the period for which population counts were available (2000-2005) are shown in TABLE 1. Although the number of Hib cases declined after the vaccine was introduced, the site of culture, age, sex, mortality, and geographical distribution of cases did not change significantly (Table 1). The subset of 88 patients who were resident in the study area was used to calculate incidence rates. The diagnoses were made by cultures of pleural aspirate, CSF, or blood alone in 1, 3, and 44 patients, respectively; 37 had positive blood and CSF cultures, and 3 had positive blood and pleural aspirate cultures. Among children diagnosed only by CSF culture, 2 were identified in 2001 and 1 in 2003.

**Figure 1.** Age Frequency of 190 Children With Invasive *Haemophilus influenzae* Type b (Hib) Disease Admitted to Kilifi District Hospital Before Hib Vaccine Introduction (1994-2001), and Cumulative Percentage of Cases With Increasing Age



Hib was diagnosed by latex agglutination tests for Hib antigen in cerebrospinal fluid (CSF) or by culture of CSF, pleural fluid, or blood. Twenty-one (11%) of 190 cases were aged 36 months or older (not illustrated). The oldest child was 8 years old.

**Table 1.** Children Younger Than 5 Years Admitted to the Kilifi District Hospital With Culture-Confirmed *Haemophilus influenzae* Disease, by Year

	No. (%)						P Value*
	Before Hib Vaccine		After Hib Vaccine				
	2000	2001	2002	2003	2004	2005	
<b>All Admissions</b>							
No. of patients	4516	4468	4236	4824	4449	3957	
With blood culture	4462 (99)	4383 (98)	4130 (97)	4720 (98)	4295 (97)	3786 (96)	<.001
With lumbar puncture	1145 (25)	1093 (24)	1204 (28)	1025 (21)	606 (14)	873 (22)	<.001
With probable bacterial meningitis	46 (1)	62 (1)	74 (2)	68 (1)	42 (0.9)	51 (1)	<.001
<b>Culture-Confirmed <i>H influenzae</i> Disease</b>							
No. with all types	31	44	30	35	7	8	
Types a, c, d, e, f	2 (6)	1 (2)	1 (3)	4 (11)	2 (29)	2 (25)	.02
Noncapsular	4 (13)	2 (5)	4 (13)	8 (23)	1 (14)	2 (25)	
Type b	25 (81)	41 (93)	25 (83)	23 (66)	4 (57)	4 (50)	
<b>Culture-Confirmed Hib Disease†</b>							
Hib cultured in CSF	9 (36)	22 (54)	14 (56)	13 (57)	3 (75)	2 (50)	.34
Age <24 mo	22 (88)	32 (78)	14 (56)	20 (87)	3 (75)	3 (75)	.98
Boys	11 (44)	22 (54)	10 (40)	14 (61)	4 (100)	1 (25)	.36
Died during this episode	5 (20)	10 (24)	10 (40)	8 (35)	0	1 (25)	.84
Resident of the DSS area	19 (76)	28 (68)	17 (68)	18 (78)	3 (75)	3 (75)	.36

Abbreviations: CSF, cerebrospinal fluid; DSS, Kilifi Demographic Surveillance Study; Hib, *H influenzae* type b.  
 \*From  $\chi^2$  tests of the distributions in 2 time strata, before and after Hib vaccine introduction.  
 †Denominators for calculation of percentages are the numbers of all culture-confirmed Hib disease given in "type b" row above.

The incidence of culture-proven invasive Hib disease for 2 years before and 4 years after Hib vaccine introduction is shown in FIGURE 2. There was no significant change in Hib disease incidence in the first 2 years following vaccine introduction. Vaccine effectiveness was therefore evaluated by comparing the 2-year periods 2002-2003 and 2004-2005 with the baseline prevaccine years 2000-2001. The population estimates for children younger than 5 years on the first of January in 2001, 2003, and 2005 in the Hib vaccine study area were 35 809, 37 614, and 39 513, respectively; for children younger than 2 years these estimates were 14 689, 15 273, and 15 881, respectively. The annual incidence of invasive Hib disease per 100 000 children younger than 5 years in 2000-2001 was 66 (95% confidence interval [CI], 48 to 87). In 2002-2003, it was 47 (95% CI, 32 to 65); in 2004-2005, it was 7.6 (95% CI, 2.8 to 17.0). In 2004-2005, the incidence rate difference per 100 000 compared with baseline was -58 (95% CI, -38 to -78) and the RR was 0.12 (95% CI, 0.04 to 0.27), with a corresponding vaccine effectiveness of 88% (95% CI, 73% to 96%).

The annual incidence of invasive Hib disease per 100 000 children younger than 2 years in 2000-2001 was 119 (95% CI, 83 to 166). In 2002-2003, it was 82 (95% CI, 53 to 121); in 2004-2005, it was 16 (95% CI, 5 to 37). In 2004-2005, the incidence rate difference per 100 000 compared with baseline was -103 (95% CI, -62 to -145) and the RR was 0.13 (95% CI, 0.04 to 0.34), with a corresponding vaccine effectiveness of 87% (95% CI, 66% to 96%).

In the prevaccine period the case fatality of invasive Hib disease was 23%, and this did not change significantly with the introduction of vaccine (Table 1). From the DSS area there were 11 in-hospital deaths among Hib cases during the baseline period and 1 in 2004-2005; the incidence rate difference per 100 000 per year was -14.1 (95% CI, -4.7 to -23.5), the RR was 0.08 (95% CI, 0.002 to 0.57), and the

vaccine effectiveness in preventing deaths attributable to invasive Hib disease was 92% (95% CI, 43% to 100%).

During the baseline period the incidence per 100 000 of CSF culture-proven Hib meningitis among children younger than 5 years was 28 (95% CI, 17 to 43). TABLE 2 shows a significant downward trend in the odds of Hib culture in the CSF of children with probable bacterial meningitis after the introduction of Hib vaccine ( $\chi^2$  for trend,  $P < .001$ ); the corresponding vaccine effectiveness against Hib meningitis in 2004-2005 was 89% (95% CI, 21% to 96%).

The incidence of culture-positive pneumococcal disease (Figure 2) in children younger than 5 years or younger than 2 years did not differ significantly in 2002-2003 or 2004-2005 compared with the baseline period. The incidence RRs for invasive pneumococcal disease in children younger than 5 years in 2002-2003 and 2004-2005 compared with the baseline were 1.04 (95% CI, 0.78 to 1.39) and 0.80 (95% CI, 0.59 to 1.09), respectively.

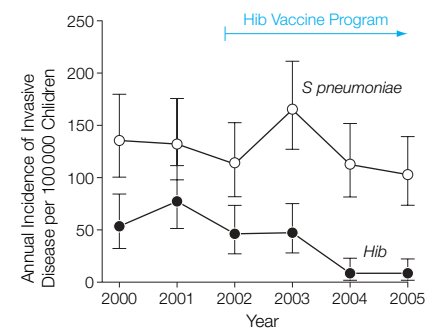
The results of the immunization coverage survey conducted in the DSS area are presented in detail elsewhere.<sup>13</sup> By 12 months of age, 93%, 91%, and 87% of children had received 1, 2, and 3 doses of pentavalent vaccine, respectively. The median age for receiving the second dose of pentavalent vaccine was 13 weeks.

Among 56 children younger than 5 years admitted to KDH with invasive Hib disease between January 2002 and December 2005, immunization data were obtainable from vaccine cards in 31 cases

and from the mothers' recall in 22 cases (TABLE 3). Twelve (23%) of the children developed disease despite receiving 2 or more effective doses of Hib vaccine and were therefore true vaccine failures; 9 had received 3 effective doses. Twelve (23%) of the children were eligible to have received 2 or more effective doses but had not done so prior to admission and were therefore considered failures of vaccine coverage. Twenty-nine children (55%) were not eligible to have received 2 effective doses of Hib vaccine, either because they were too young when they were admitted with invasive Hib disease (n=7) or because they were immunized with diphtheria-tetanus-pertussis before the Hib vaccine program began (n=22).

HIV status was determined for 54 of the 56 children with invasive Hib disease in the postintroduction period; 8 (15%) were positive. Among 12 pa-

**Figure 2.** Incidence of Invasive Disease Caused by *Haemophilus influenzae* Type b (Hib) and *Streptococcus pneumoniae* Among Children Younger Than 5 Years in the Kilifi Demographic Surveillance Study Area in Each Year of the Study



Error bars indicate 95% confidence intervals.

**Table 2.** Cases With and Without Culture Evidence of *Haemophilus influenzae* Type b (Hib) and Odds of Hib Isolation Among Children Younger Than 5 Years Admitted to Kilifi District Hospital with Probable Bacterial Meningitis Before (2000-2001) and After (2002-2005) Introduction of Hib Conjugate Vaccine\*

Year	Hib Culture		Odds of Hib Isolation	OR (95% CI)
	Positive	Negative		
2000-2001	31	77	0.40	1.00
2002-2003	25	117	0.21	0.53 (0.29-0.97)
2004-2005	4	89	0.04	0.11 (0.04-0.35)

Abbreviations: CI, confidence interval; OR, odds ratio.

\* $P < .001$  by  $\chi^2$  test for trend. Hib was cultured from 3 cerebrospinal fluid specimens in which it was not possible to analyze the criteria of probable bacterial meningitis (glucose ratio or white cell count). These are not included in this table.

**Table 3.** Cases of Invasive *Haemophilus Influenzae* Type b (Hib) Disease Admitted to Kilifi District Hospital After Introduction of Hib Conjugate Vaccine (2002-2005), According to Immunization Data Derived From Vaccine Records (n = 31) or Mothers' Reports (n = 22)

Effective Doses, No.	Eligible to Receive $\geq 2$ Effective Doses	Category	Patients With Hib				Total, No. (%)
			No.				
			2002	2003	2004	2005	
<2	No	Age ineligible	17	11	1	0	29 (55)
	Yes	Coverage failure	2	8	2	0	12 (23)
$\geq 2$	Yes	Vaccine failure	6	2	1	3	12 (23)
Total			25	21	4	3	53 (100)

tients in whom Hib vaccine failed, 2 (17%) were HIV positive; among 39 patients in whom vaccine did not fail, 5 (13%) were HIV positive ( $P = .66$ ). For comparison, HIV prevalence among women aged 15 to 49 years in coastal Kenya in 2003 was 6.6%<sup>17</sup>; among 1044 children admitted to KDH with bacteremia in 1998-2002, it was 18%.<sup>2</sup>

## COMMENT

The baseline incidence for invasive Hib disease in Kilifi in children younger than 5 years (66/100 000) is similar to the baseline incidence of invasive Hib disease in South Africa (47/100 000) and Mali (45/100 000), and of Hib meningitis in Niger (52/100 000) and The Gambia (60/100 000).<sup>18-21</sup> The effectiveness of Hib conjugate vaccine against invasive disease in Kilifi (88%) in 2004-2005 is similar to that against Hib meningitis or invasive Hib disease in The Gambia (75%-100%), Chile (90%), the United States (85%-92%), and the United Kingdom (87%).<sup>16,22-25</sup> Three years after starting the Hib conjugate vaccine program the incidence of invasive Hib disease in children in Kilifi had decreased to 12% of its baseline level. Extrapolating the incidence difference observed in Kilifi in 2004-2005 to the 5.81 million children younger than 5 years living in Kenya in 2005<sup>26</sup> suggests that the vaccine prevented 3370 hospitalizations with culture-proven invasive Hib disease in that year.

Vaccine is not the only factor that may have affected Hib disease incidence in 2000-2005, but several arguments suggest that the contribution of secular changes in other pertinent epidemiologic variables was limited: (1) The num-

ber of patients admitted to KDH varied little from year to year, with no discernible trend over time. (2) The clinical and laboratory handling of blood cultures throughout the study period was stable and standardized. The proportion of admitted children who underwent blood cultures varied only from 96% to 99% each year during the study period. Laboratory protocols for blood culture did not vary throughout the 6 years, and the laboratory performed consistently well in an international external quality assurance scheme. There were significant changes in the number of lumbar punctures performed each year and also in the use of Hib antigen detection in CSF. However, only 3 of 88 cases contributing to the vaccine effectiveness analysis were detected by CSF cultures alone, and antigen test results were excluded from these analyses. (3) The magnitude of the change in Hib disease incidence was very large. Few secular trends are capable of producing an 88% reduction in disease incidence. (4) The changes took place over a period that was consistent with vaccine introduction. It is conceivable that changes in socioeconomic status or use of private medical services might reduce the numbers of patients with Hib who present to KDH over time, but such changes are likely to be detectable over decades rather than the 4 years of primary comparison in this study. (5) To estimate effectiveness against Hib meningitis, we restricted our analysis to patients who had been admitted to KDH and investigated with CSF cultures, so secular changes in these 2 factors over time would not affect the outcome. Vaccine effectiveness by this methodology was

almost identical to that observed in the primary analysis against invasive disease (89% vs 88%, respectively). (6) We used detection of invasive pneumococcal disease as a control indicator for secular trends in prior treatment, hospital presentation patterns, investigation practices, and laboratory methods. In the 4 years following Hib vaccine introduction there was no significant change in the incidence of invasive pneumococcal disease.

The primary limitation of the study is that the surveillance methods are unlikely to have captured most cases of invasive bacterial disease occurring in the surveillance area, both because children with serious illnesses do not all present to KDH and because, when they do, culture is an insensitive diagnostic tool. For example, in 2003-2004, among children aged 1 to 59 months, only 32% (207/652) of deaths recorded in the DSS occurred at the hospital. In Kilifi, children who have a short severe illness or who live further from public transport are less likely to seek care at the hospital during a fatal illness.<sup>27</sup> The sensitivity of blood culture is limited by contamination in 14% of children, by bloodstream antibiotics in 9% to 11%,<sup>2</sup> and by the fact that not all serious Hib disease is bacteremic. The ratio of Hib pneumonia to meningitis is normally estimated at 5:1,<sup>28</sup> yet Hib was cultured in CSF in half the cases in this study, suggesting that most patients presenting to KDH with Hib pneumonia went undetected. However, the insensitivity of the hospital surveillance applies equally to both the prevaccine and the postintroduction periods, so it is unlikely to

influence the estimate of vaccine effectiveness. Nonetheless, the absolute benefits of the vaccine program are likely to have been substantially underestimated, and this should be considered when evaluating the cost-effectiveness of the program. In addition, the calculation of vaccine effectiveness is a programmatic estimate, independent of vaccine coverage.

The lag between vaccine introduction and an observable decline in incidence of Hib disease has several potential explanations, including annual fluctuations in disease incidence, vaccine failure among HIV-infected children, inadequate immunization coverage under the Expanded Programme on Immunisation, a broad age-frequency curve, or slow development of herd immunity. Hib disease fluctuates yearly, as does pneumococcal disease, and a waxing of incidence in the first 2 years after vaccine introduction might possibly have obscured a moderate vaccine impact. Infection with HIV is associated with a 29-fold increased risk of invasive Hib disease among South African children who have received Hib vaccine.<sup>29</sup> In a population with high HIV prevalence this may retard and ultimately limit the impact of a Hib vaccine program. In Kilifi, however, HIV seroprevalence is not high, and HIV-infected children accounted for only 2 of 12 vaccine failures. Inadequate immunization coverage was discounted by our own coverage survey, and only one quarter of Hib cases presenting in 2002-2005 were attributable to failure to immunize. Invasive Hib disease in Kilifi was concentrated in the first 18 to 24 months of life; 82% of cases occurred in children younger than 2 years, and the fact that disease incidence declined significantly only after a 2-year cohort had passed through the routine Hib immunization program suggests that this factor was the most likely determinant of the timing of the program's impact.

Hib conjugate vaccine reduces the prevalence of Hib nasopharyngeal colonization in vaccinated children, which means that unvaccinated individuals are

less frequently exposed to Hib and less likely to develop disease.<sup>30</sup> In The Gambia, for example, 100% reduction in Hib meningitis incidence was achieved by a vaccine program that could be predicted, on the basis of the timing of immunization and the age-incidence curve, to provide direct protection to only 41% of cases.<sup>16</sup> The residual indirect effect, herd protection,<sup>31</sup> could be established more rapidly in Hib vaccine programs if vaccine introduction was accompanied by a catch-up campaign targeting the carrier population, ie, children younger than 5 years. In regions that are skeptical about the importance of vaccination against Hib disease, more rapid evidence of declining incidence might generate critical early momentum to sustain a vaccine program.

This study has made visible the incidence of invasive Hib disease and the effectiveness of the Hib vaccine program in Kenya. It also illustrates the difficulties of program evaluation within a 5-year introduction schedule. In countries that have not yet introduced Hib vaccine, it would be highly desirable to establish surveillance before introduction and vaccinate a sufficiently high proportion of young children to provide evidence of effectiveness within the period of program evaluation. In Kilifi, where 82% of Hib disease occurs in children younger than 2 years, we did not see a discernible decrease in Hib disease incidence until the third year after vaccine introduction.

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**Study concept and design:** Cowgill, English, Newton, Feikin, Scott.

**Acquisition of data:** Cowgill, Ndiritu, Nyiro, Slack, Chiphatsi, Ismail, Kamau, Mwangi, Scott.

**Analysis and interpretation of data:** Cowgill, Ndiritu, Slack, Newton, Feikin, Scott.

**Drafting of the manuscript:** Cowgill, Newton, Feikin, Scott.

**Critical revision of the manuscript for important intellectual content:** Cowgill, Ndiritu, Nyiro, Slack, Chiphatsi, Ismail, Kamau, Mwangi, English, Newton.

**Statistical analysis:** Cowgill, Newton, Scott.

**Obtained funding:** Feikin, Scott.

**Administrative, technical, or material support:** Ndiritu, Nyiro, Slack, Chiphatsi, Ismail, Kamau, Mwangi, English, Scott.

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For a novelist, a given historic situation is an *anthropologic laboratory* in which he explores his basic question: *What is human existence?*

—Milan Kundera (1929- )