

Action for child survival: elimination of *Haemophilus influenzae* type b meningitis in Uganda

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Objective To guide immunization policy, we determined the public health benefit of introducing *Haemophilus influenzae* type b (Hib) vaccine in Uganda and estimated the vaccine effectiveness.

Methods Surveillance data for acute bacterial meningitis among children aged 0–59 months were reviewed from three hospital sentinel sites, for July 2001 to June 2007, to determine the incidence of Hib meningitis, the effectiveness of Hib vaccine with a case-control design, and the number of vaccine-preventable cases and deaths of Hib disease in Uganda.

Findings Of the 13 978 children from 17 districts with suspected bacterial meningitis, 269 had confirmed Hib meningitis, declining from 69 patients in the prevaccine year (2001–2002) to three in 2006–2007. Hib meningitis incidence dropped from 88 cases per 100 000 children aged < 5 years in the year before vaccine introduction to 13 within 4 years, and to near zero in the fifth year. Vaccine effectiveness for 2 or more doses was 93% (95% confidence interval, CI: 69–99) against confirmed Hib meningitis and 53% (95% CI: 11–68) against purulent meningitis of unknown cause. In Uganda, Hib vaccine prevents an estimated 28 000 cases of pneumonia and meningitis, 5000 deaths and 1000 severe meningitis sequelae each year.

Conclusion Infant immunization with Hib vaccine has virtually eliminated Hib meningitis in Uganda within 5 years. Ensuring long-term benefits of Hib vaccine urgently requires sustainable vaccine financing, high-quality ongoing surveillance, and a health sector able to deliver a robust immunization programme.

Bulletin of the World Health Organization 2008;86:292–301.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Haemophilus influenzae type b (Hib) is a leading cause of bacterial meningitis and pneumonia in children worldwide, resulting in at least 3 million severe illnesses and 386 000 deaths each year.^{1,2} Immunization with Hib conjugate vaccine reduces the risk of invasive Hib disease in young children by more than 90%,^{3–5} and WHO recommends that Hib conjugate vaccines be included in all routine infant immunization programmes.¹ Uganda introduced Hib vaccine in 2002, and was to start vaccine cofinancing from its own resources by 2007.

Before the introduction of Hib vaccine, the estimated incidence of Hib meningitis found by rapid assessment in one hospital was 44–59 cases

per 100 000 children aged < 5 years,⁶ which is similar to prevaccine estimates from other African^{3–6} and industrialized countries.^{7–9} For every child with Hib meningitis in developing countries, there may be five to 10 others with pneumonia due to Hib.^{3,10,11} Robust estimates of disease burden and the public health benefit of vaccine use in Uganda are needed to guide immunization policy.

Surveillance for paediatric bacterial meningitis was established in Uganda 1 year before vaccine introduction, first in the national referral hospital in the capital city Kampala and later in two sites in northern and south-western Uganda.¹² We use 5 years of surveillance data to estimate the burden of Hib disease in Uganda and record the impact of the vaccination programme.

Methods

Population health and demographic indicators

In the 2002 Ugandan national census, the population was 24.4 million and the national growth rate was 3.3%.¹³ The projected population for 2007 is 28.4 million with 5.3 million children aged < 5 years (18.6% of the population).¹³ In Kawempe Division of Kampala, the location of the first paediatric bacterial meningitis surveillance site, the population was 312 475 in 2006 (municipal data). Mortality in infants and children aged < 5 years for Uganda was 88 and 152 deaths per 1000 live births respectively, in 2000/2001,¹⁴ and 76 and 137 in 2005/2006.¹⁵

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doi:10.2471/BLT.07.045336

(Submitted: 26 June 2007 – Revised version received: 3 January 2008 – Accepted: 9 January 2008 – Published online: 5 March 2008)

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Hib vaccine introduction and vaccination coverage

On 1 June 2002, the Uganda National Expanded Programme on Immunization (UNEPI) introduced Hib vaccine nationwide in a pentavalent formulation of liquid diphtheria–pertussis–tetanus–hepatitis B and lyophilized Hib conjugate vaccine (PRP-T from GlaxoSmithKline), procured through the United Nations Children's Fund (UNICEF) and funded by the GAVI Alliance.¹⁶ The routine immunization schedule offers this vaccine at ages 6, 10 and 14 weeks, replacing the diphtheria–pertussis–tetanus vaccine (DPT) previously used. Due to a global shortage, Hib vaccine was completely out of stock in Uganda from September to December 2003, during which time DPT was given. There was no catch-up programme for those not vaccinated before vaccine introduction or during September to December 2003.

Routine vaccination coverage for each district was obtained from national Health Management Information System data for 2001–2006.¹⁷ The coverage was the number of children receiving the third dose of DPT (DPT3) or DPT–hepatitis B–Hib (June 2002 to August 2003, and 2004 to 2006) divided by the number of surviving infants for the year.

Paediatric bacterial meningitis surveillance

On 12 July 2001, with support from WHO and the African paediatric bacterial meningitis surveillance network,¹² Uganda established sentinel surveillance for paediatric bacterial meningitis at Mulago Hospital, a national referral facility and the primary centre treating children from Kampala with acute bacterial meningitis. On 30 March 2003, Mbarara University Hospital in south-western Uganda and Lacor Hospital in Gulu District of north central Uganda initiated surveillance. These two hospitals receive an estimated 75% of children hospitalized with meningitis in their districts, and serve as regional referral centres for neighbouring districts. Complete data from all three sites were available up to and including August 2006. Hib case counts to June 2007 were also obtained.

All children aged < 5 years with suspected bacterial meningitis were

recorded in a surveillance register and, with informed consent of the parent or guardian, received a lumbar puncture as soon as feasible. Lumbar punctures were delayed or not done in patients with cardiac or respiratory failure, infection at the puncture site, history or signs of bleeding, coma or congenital dural defects.

The clinical case definition for suspected bacterial meningitis was a child aged 0–59 months with sudden onset of fever (> 38°C axillary or > 38.5°C rectal), and one or more clinical signs of meningitis: seizures (except simple febrile seizures with recovery within 1 hour), neck stiffness, bulging fontanel (in children aged < 12 months), poor sucking, altered consciousness, irritability, other meningeal signs, toxic appearance, or petechial or purpuric rash. A case of purulent meningitis was defined as a suspected case with turbid or cloudy cerebrospinal fluid (CSF) or CSF leucocytosis of ≥ 100 white blood cells per μl . Suspected or purulent meningitis was confirmed by identification of a pathological organism by culture or latex agglutination test of CSF.

Age in months, Hib vaccination status (vaccinated, unvaccinated or unknown, and the number of DPT–hepatitis B–Hib doses received), outcome (discharged alive, died, or unknown), district and village of residence, and prior use of antibiotics were recorded. Clinicians elicited a verbal vaccination history if immunization cards were unavailable.

Clinical and laboratory procedures

Upon lumbar puncture, 1 ml or 2 ml of CSF was collected in a sterile container and transported to the laboratory within 1 hour. The appearance was noted as clear, turbid, xanthochromic or blood-stained. Any CSF specimen not immediately processed was incubated at 37°C and analysed the following morning. Purulent CSF was tested for Hib, *Streptococcus pneumoniae*, *Escherichia coli* (K1), and *Neisseria meningitidis* (serogroups A, B, and C) by latex agglutination with commercial kits (Slidex, bio-Mérieux, Lyon, France), from January to June 2003 and from October 2004 to June 2006.

The CSF white blood cell count was determined with Fuchs-Rosenthal counting chamber and protein by Gallenkamp proteinometer. CSF was

centrifuged, prepared for Gram stain and plated for culture on a prewarmed chocolate agar plate containing trypticase soya agar and haemoglobin prepared from powder, supplemented with X and V factors (IsoVitaleX, Becton-Dickinson, Franklin Lakes, United States of America). Plates were prepared locally at all sites. Culture plates were placed in a carbon-dioxide incubator at 35–37°C for up to 72 hours, and checked for growth every 24 hours. The primary organisms of interest were identified by X and V factor tests (Hib), optochin disc (*S. pneumoniae*), and oxidase and carbohydrate utilization tests (*N. meningitidis*).

Antibiotic susceptibility of Hib was determined by the Kirby-Bauer method on chocolate agar plate based on standard guidelines.¹⁸ Laboratory quality control was ensured through internal protocols (filtering of Gram stains, inclusion of positive slides alongside the test specimen, culturing standard *H. influenzae* for testing potency of the media, incubating plates at 37°C before use to ensure sterility) and quarterly blind identification of enteric and meningitis-causing pathogens sent to Mulago and Lacor Hospitals from the National Institute for Communicable Diseases, South Africa.

From July 2004 onwards, serotyping of *H. influenzae* isolates was done at Kilifi Hospital, Kenya, when feasible, with a slide agglutination test with polyvalent and type-specific antisera.⁵ Because most serotyped isolates during the study period were type b, we assumed isolates were type b unless otherwise identified.

Disease burden and impact of vaccination

We estimated the incidence of Hib disease for each surveillance year (cases and deaths per 100 000 children aged < 5 years) from Mulago Hospital data, with the catchment area of Kawempe Division, one of five Kampala divisions. Mulago Hospital serves as primary, secondary and tertiary health-care institution for the area, the only hospital in the division to offer investigation and acute care for paediatric meningitis, accepting referrals from other health units. Incidence analysis was limited to children resident in Kawempe and recorded in the Mulago Hospital paediatric bacterial meningitis database.

Table 1. Cause of suspected acute bacterial meningitis, children aged 0–59 months, three sentinel sites, Uganda, 2001–2006

Time	No. of cases								
	Suspected bacterial meningitis	CSF collected	CSF purulent	Positive for any bacteria ^a	Hi	Sp	Nm	Sa	Other bacteria ^b
		(% of cases)	(% of CSF collected)						
Prevaccine year July 01–June 02	1 662	1 515 (91)	270 (18)	134	69 (51)	31 (23)	0	14 (10)	20 (15)
Hib vaccine year 1 July 02–June 03	2 780	2 651 (95)	301 (11)	216	85 (39)	70 (32)	3 (1)	35 (16)	23 (11)
Hib vaccine year 2 July 03–June 04	3 414	3 370 (99)	346 (10)	231	61 (26)	72 (31)	4 (2)	48 (21)	46 (20)
Hib vaccine year 3 July 04–June 05	3 085	3 046 (99)	289 (9)	203	35 (17)	88 (43)	2 (1)	50 (25)	28 (14)
Hib vaccine year 4 July 05–June 06	3 037	2 995 (99)	233 (8)	141	19 (13)	59 (42)	10 (7)	31 (22)	22 (16)
Total	13 978	13 577 (97)	1 439 (11)	925	269 (29)	320 (35)	19 (2)	178 (19)	139 (15)

CSF, cerebrospinal fluid; Hi, *Haemophilus influenzae*; Sp, *Streptococcus pneumoniae*; Nm, *Neisseria meningitidis*; Sa, *Salmonella* spp.

^a Among all purulent and non-purulent specimens.

^b Other organisms identified were coliforms, cryptococcus, *Escherichia coli*, *Enterobacter* sp, *Klebsiella* sp, *Moraxella catarrhalis*, *Proteus* sp, *Pseudomonas* sp, *Staphylococcus aureus*, non-pneumococcal *Streptococcus* sp.

^c For specific causes, the % refers to the proportion due to that organism of all CSF with a positive isolate.

Some Hib meningitis cases may not be identified on culture or latex agglutination. Thus, prevaccination hospitalized Hib meningitis incidence was calculated as follows: [incidence of confirmed *H. influenzae* meningitis for 1 year prevaccination] + [(the incidence of purulent meningitis with no identified cause pre-vaccination) × (vaccine effectiveness against this outcome)]. We used vaccine effectiveness from all three sites for the entire study period as the most robust estimate.

To account for access to care, the summary incidence was divided by 67% (the proportion of children with pneumonia taken to an appropriate health-care provider).¹⁹ In-hospital Hib meningitis mortality was estimated by multiplying the incidence by the prevaccine case-fatality ratio of 20%. We assumed that 90% of children with non-hospitalized Hib meningitis died² and that 34% of Hib meningitis survivors experienced neurological sequelae.²⁰ Hib pneumonia incidence was calculated at five times the value for meningitis.³ We assumed that 10% of hospitalized and 30% of non-hospitalized children with Hib pneumonia died.²¹ Finally, we estimated the total number of expected Hib meningitis and pneumonia cases and deaths among children aged < 5 years in Uganda in 2007.

Vaccine effectiveness

The effectiveness of Hib vaccine against different outcomes was assessed with a case-control design with the paediatric bacterial meningitis surveillance data. For confirmed *H. influenzae* meningitis, controls were children with pneumococcal meningitis. For patients with purulent meningitis or CSF with 20–99 white blood cells per µl with no identified pathogen, controls were children with CSF with fewer than 20 white blood cells per µl also of unknown cause. For each outcome, we estimated vaccine effectiveness for 1, 2, 3 and 2+ (two or more) vaccine doses for children with known vaccination dates for doses given at least 2 weeks before admission. For all calculations, the reference group was children who had received no vaccine doses. To estimate vaccine effectiveness for one or more vaccine doses, we included children with a verbal vaccination report. We excluded children aged 6 months or older when Hib vaccine was introduced, as they had no chance to be vaccinated. We assumed that children vaccinated during September to December 2003 did not receive Hib vaccine. We adjusted for age with logistic regression, and vaccine effectiveness was calculated as (1 – adjusted odds ratio).

To assess the indirect effect of Hib vaccine in the population (herd immunity), we determined *H. influenzae* meningitis cases among children 3 years and 4 years of age who did not receive Hib vaccine.

Results

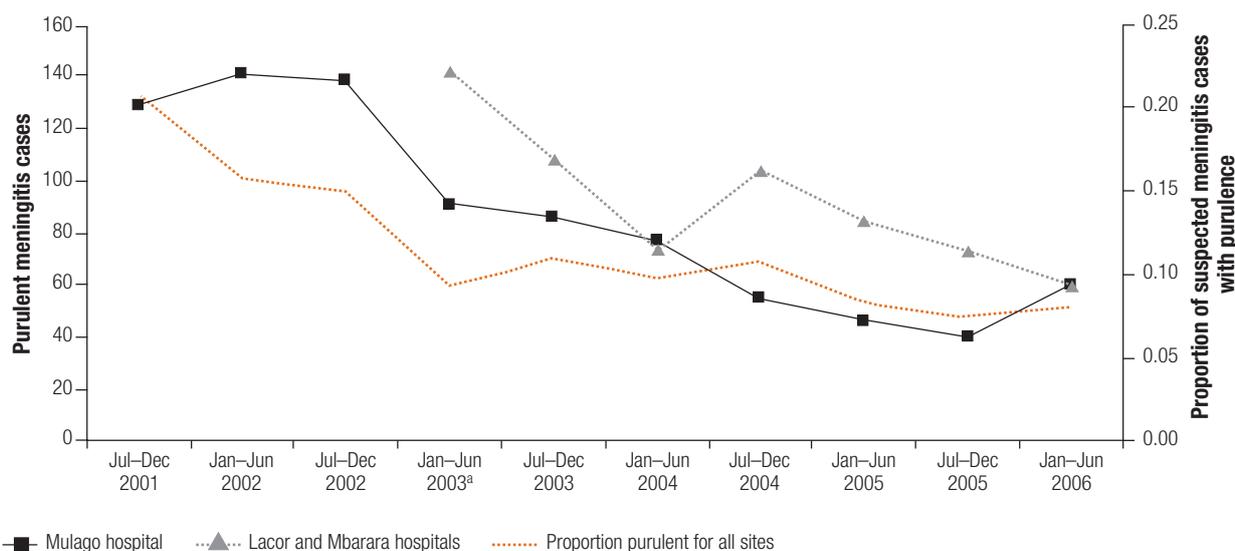
Immunization coverage

National infant immunization coverage for DPT3 rose yearly from 2001 to 2004 (61%, 72%, 81% and 87%, respectively), then declined (85% in 2005, 80% in 2006). Coverage for the third dose of Hib vaccine was 42% in 2002 (when vaccine was introduced mid-year), 63% in 2003 (due to the 4-month vaccine stockout), and the same as DPT3 thereafter.¹⁷ In districts with sentinel sites, vaccination coverage increased: Kampala 39% (2001) to 95% (2005), Gulu District 53% to 98%, and Mbarara District 53% to 88% (2003), dropping to 75% (2005).

Epidemiology of paediatric bacterial meningitis

Between 12 July 2001 and 30 June 2006, 13 978 children aged 0–59 months with suspected bacterial meningitis were identified by the three surveillance sites (Table 1). Of these, 6418 were girls (45.9%) and 9937 (71.1%)

Fig. 1. Purulent meningitis in children aged < 5 years with suspected bacterial meningitis, three sentinel sites, Uganda, 2001–2006



^a The data point for Jan-Jun 2003 for Lacor and Mbarara hospitals represents the purulent meningitis cases identified during Apr-Jun ($n = 71$), extrapolated to 6 months. All other data points are exact number of cases identified.

were below 2 years of age; 7843 (56.1%) were from Mulago, 1291 (9.2%) from Mbarara and 4844 (34.7%) from Lacor hospitals (45.8%, 11.4%, and 42.8% during 2003–2006 when three sites were operating); 13 577 (97.1%) had a lumbar puncture and CSF collected, of which 12 055 (86.2%) specimens were non-purulent, 1439 purulent (10.3%), and 484 (3.5%) had unknown CSF results. Of children with turbid or cloudy CSF, white blood cell counts were zero for 100 children (6.9%), 1–19 per μl for 31 (2.2%), 20–99 per μl for 177 (12.3%), 100–499 per μl for 561 (39%), 500 or greater per μl for 424 (29.5%), and missing for 146 (10.1%). Of specimens with fewer than 20 white blood cells per μl , only 0.1% had Hib identified.

The proportion of patients with purulent CSF dropped from 18% in 2001/02 to 8% in 2005/06, the fourth post-vaccine year (Fig. 1). During the same period the number of non-purulent cases generally remained constant in each hospital (data not shown).

There were 269 patients with confirmed Hib meningitis from 17 districts, 239 identified as Hib by culture (53 also positive for Hib by latex agglutination), 12 were positive by latex alone, and for 18, a non-specified positive test was recorded. The proportion of confirmed meningitis cases due to Hib fell from 51% in the prevaccine year to 13% in the fourth

vaccine year (Table 1). Of children with confirmed Hib, 119 (44%) were girls; 87 (32%) were aged < 6 months, 62 (23%) were 6–11 months, and 120 (45%) were 12–59 months of age. The proportion of patients aged < 1 year declined from 64% before vaccine introduction to 45% in the first vaccine year, rising again to 71% by the fourth year. Residence in the central region was reported for 189 (70%) cases from Kampala and five other districts, 46 (17%) were from Mbarara and five western districts, 22 (8.0%) from the north (Gulu, Apac and Masindi), 3 (1%) from the east and 9 of unknown residence.

Of the total 1439 patients with purulent CSF, 227 (16%) had *H. influenzae* identified. Of the 12 055 with non-purulent CSF, *H. influenzae* was identified in 41 (0.3%). Of the 268 *H. influenzae* cases for which data were available, 227 (85%) had purulent CSF.

In 2001 and 2002, 95% of Hib isolates were resistant to chloramphenicol, 76% to cotrimoxazole, 25% to ampicillin, compounds used as first-line therapy, and 7% to ceftriaxone. The case-fatality ratio for Hib meningitis in the first 3 months of surveillance at Mulago Hospital was 45%, when five of 11 patients died. After a change of antibiotic regimen to ceftriaxone, case

Table 2. Effectiveness of Hib conjugate vaccine against meningitis outcomes among children aged 0–59 months, Uganda, 2001–2006

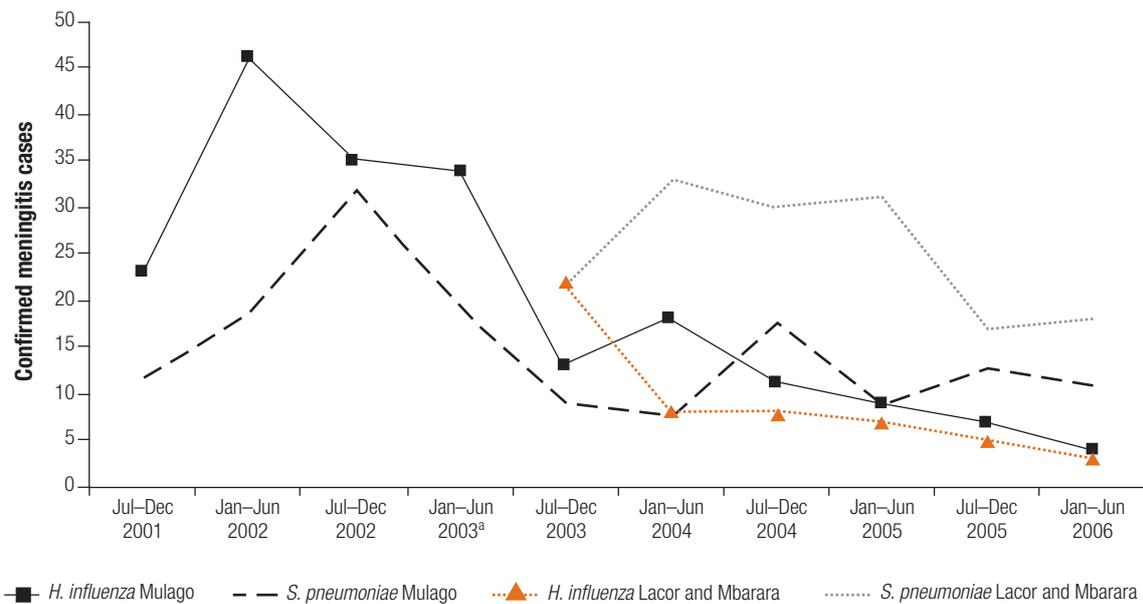
Vaccine doses ^a	Vaccine effectiveness against meningitis outcome ^b % (95% confidence interval)		
	Confirmed Hib	Purulent ^c CSF of unknown cause	CSF with 20–99 WBC/ μl of unknown cause
1	63 (0–86)	60 (21–80)	38 (–54–75)
2	93 (42–99)	36 (–10–63)	66 (–10–90)
3	94 (48–99)	68 (46–81)	15 (–51–52)
1 or more	65 (41–79)	38 (23–50)	31 (3–51)
2 or more	93 (69–99)	53 (11–68)	35 (–11–62)

CSF, cerebrospinal fluid; Hib, *Haemophilus influenzae* type b; WBC, white blood cells.

^a Values for 1, 2, 3 and 2+ vaccine doses were documented in immunization cards; values for 1+ doses also included a verbal report.

^b All vaccine effectiveness estimates adjusted for age.

^c CSF that was visually cloudy or had ≥ 100 white blood cells (WBC)/ μl .

Fig. 2. Confirmed *H. influenzae* and *S. pneumoniae* meningitis in children aged < 5 years, 3 sentinel sites, Uganda, 2001–2006

^a From April to June 2003, Lacor Hospital had 11 confirmed cases of *H. influenzae* and 14 of *S. pneumoniae*; Mbarara Hospital had 5 of each.

fatality decreased to 13%. In Lacor and Mbarara, case fatalities were 18% and 24% respectively during the study. There was no difference in case-fatality ratio by age group.

Vaccine effectiveness

The age-adjusted vaccine effectiveness against confirmed *H. influenzae* meningitis surpassed 90% for two or more and three doses (Table 2). Vaccine effectiveness against purulent meningitis of unknown cause was 36–68% according to number of doses.

As a measure of indirect immunity, for each year from 2001 through 2005, the number of *H. influenzae* meningitis cases among children aged 4 years was 4, 4, 2, 5, and 0, respectively. From 2001 to 2004, cases among 3 year-olds were 9, 9, 8, and 4.

Time trends in Hib disease with vaccine introduction

After Hib vaccine introduction, the number of confirmed Hib meningitis cases decreased to near zero in all three sites (Fig. 2) and all age groups (data not shown). At Mulago Hospital, cases declined from 69 in the prevaccine year to 11 in 2005–2006, and finally to three cases from July 2006 to June 2007. Cases of *S. pneumoniae* meningitis remained stable at Mulago (linear trend $P = 0.59$)

and Lacor ($P = 0.43$) hospitals, and declined at Mbarara hospital (linear trend $P = 0.049$). *S. pneumoniae* is now the most common cause of bacterial meningitis among children aged < 5 years (Table 1).

During the first year after vaccine introduction, 31 (94%) of 33 *H. influenzae* isolates identified by culture were confirmed as Hib by CSF latex agglutination, as were 22 (85%) of 26 culture-positive cases during the third and fourth years. Other isolates reported as Hib in Table 1 were identified only by culture. Of 23 serotyped isolates available from July 2004 onwards from CSF (14) or unrecorded source (9), 15 (65%) were type b, 5 (22%) were type a, and 3 (13%) were non-typable.

Estimated disease burden

Burden of disease estimates are presented in detail in Table 3. Yearly incidences of confirmed Hib meningitis and meningitis with no identified cause for Kawempe subdistrict were 33 and 62 per 100 000 children aged < 5 years respectively in the year before vaccine introduction. Estimated overall Hib meningitis yearly incidence during the prevaccine era was 88 cases per 100 000 children aged < 5 years, 66 and 22 per 100 000 for hospitalized and non-hospitalized patients respectively. Estimated yearly

Hib meningitis mortality was 33 deaths per 100 000 children aged < 5 years, 13 and 20 per 100 000 for hospitalized and non-hospitalized cases.

By the fourth year after vaccine introduction, yearly Hib meningitis incidence had declined by 85% from 88 to 13 cases per 100 000 children aged < 5 years and mortality to four deaths per 100 000. Estimated yearly incidence of neurological sequelae dropped from 19 to 3 cases per 100 000 children. Estimated Hib pneumonia incidence dropped from 351 to 52 hospitalized cases per 100 000 children aged < 5 years, and from 109 to 17 non-hospitalized cases per 100 000. Before Hib vaccine, about one in every 200 children had Hib meningitis or pneumonia, and mortality was almost one per 1000 per year.

In the absence of Hib vaccination, we estimated that in 2007, among children aged < 5 years in Uganda there would have been 4662 with Hib meningitis, 23 310 with Hib pneumonia, 5230 deaths, and 989 patients with severe neurological sequelae. In the fifth year after vaccine introduction, there were no confirmed Hib cases at Lacor and Mbarara Hospitals or in Kawempe Division, and just three cases were found from three different districts in the central region.

Table 3. Estimated burden of disease for *Haemophilus influenzae* type b (Hib) meningitis and pneumonia among children 0–59 months, before and 4 years after Hib conjugate vaccine introduction, Uganda, 2001–2006

	Pre-vaccine year	Fourth year of vaccination	Data source
MENINGITIS			
Hospitalized meningitis			
Confirmed hospitalized Hib incidence ^a	33	1.8	Study
Purulent meningitis of unknown cause			
Confirmed incidence ^a	62	16	Study
Vaccine effectiveness (% for 2+ doses)	53	53	Study
Estimated Hib incidence ^a among etiology-negative purulent cases (confirmed incidence x VE)	33	8.5	Calculated
Total hospitalized Hib incidence ^a (confirmed + estimated) ^a	66	10	Calculated
Case fatality ratio (%)	20	11	Study
Fatal <i>H. influenzae</i> meningitis incidence ^a (total hospitalized x CFR)	13	1.1	Calculated
Non-hospitalized meningitis			
Proportion of meningitis cases not presenting to hospital (%)	33	33	¹⁹
Estimated non-hospitalized Hib incidence ^a (total hospitalized x % not presenting to hospital)	22	3.4	Calculated
CFR (%)	90	90	Assumption
Fatal <i>H. influenzae</i> meningitis incidence ^a (total non-hospitalized x CFR)	20	3.1	Calculated
Neurologic sequelae among survivors			
Proportion (%)	34	34	²⁰
Incidence ^a of neurologic sequelae	19	3.2	Calculated
PNEUMONIA			
Ratio of Hib meningitis to Hib pneumonia	5	5	³
Hospitalized Hib pneumonia incidence ^a (hospitalized meningitis incidence x 5)	351	52	Calculated
Non-hospitalized Hib pneumonia incidence ^a (non-hospitalized meningitis incidence x 5)	109	17	Calculated
Hospitalized case fatality ratio (%)	10	10	²¹
Hospitalized fatal Hib pneumonia incidence ^a (hospitalized Hib pneumonia incidence x CFR)	33	5.2	Calculated
Non-hospitalized case fatality ratio (%)	30	30	²¹
Non-hospitalized fatal Hib pneumonia incidence ^a (non-hospitalized Hib pneumonia incidence x CFR)	33	5.1	Calculated
SUMMARY			
Total Hib pneumonia and meningitis incidence ^a	528	82	Calculated
Total fatal Hib pneumonia and meningitis incidence ^a	99	14	Calculated
BURDEN OF VACCINE-PREVENTABLE HIB DISEASE 2007			
	Without Hib vaccine^b		
Uganda population < 5 years of age in 2007	5 300 000		Calculated ¹³
Children with Hib meningitis, cases per year	4 662		Calculated
Children with Hib pneumonia, cases per year	23 310		Calculated
Child deaths due to Hib per year	5 230		Calculated
Children with severe Hib-related neurologic sequelae per year	989		Calculated

CFR, case-fatality ratio; Hib, *Haemophilus influenzae* type b; VE, vaccine effectiveness.

^a Incidence or fatal incidence: cases or deaths per 100 000 children < 5 years of age per year.

^b Pre-vaccine incidence applied to 2007 population.

Discussion

Vaccination has nearly eliminated paediatric meningitis due to Hib in Uganda and elsewhere in Africa.^{3-5,10} The incidence dropped by 85% within 4 years of vaccine introduction and to zero in the fifth year in Kawempe Division. Overall, we estimate that Hib vaccine in the Ugandan immunization programme now prevents almost 30 000 cases of severe Hib disease and more than 5000 deaths in children aged < 5 years annually, equivalent to the achievement of measles control efforts.^{22,23} These interventions make a substantial contribution towards achieving the Millennium Development Goal of reducing mortality in children aged < 5 years.²⁴

In this setting with limited resources and moderate vaccination coverage, vaccine effectiveness against confirmed Hib meningitis remained high at 93% for two or more doses, consistent with the 92–99% found in a rigorous case–control study in Uganda.²⁵ High effectiveness against Hib meningitis of two doses of conjugate vaccine has been observed elsewhere.^{3,4} However, whether two doses confer long-term immunity is unknown and once exposure to the pathogen declines, a fourth (booster) dose may be necessary to ensure continuing protection.^{26,27} We have also shown vaccine effectiveness against purulent meningitis of unknown cause in children, suggesting significant Hib disease not detected bacteriologically, similar to findings elsewhere.²¹

Hib vaccine and surveillance have changed the epidemiology of bacterial meningitis in Uganda. The incidence of confirmed Hib meningitis before Hib vaccine introduction was consistent with previous estimates.^{4,6} However, by also demonstrating vaccine effectiveness against meningitis without an identified pathogen, estimates of hospitalized Hib meningitis incidence doubled. Within months of starting surveillance, improved collaboration between clinicians and the laboratory resulted in fewer meningitis deaths. *S.*

pneumoniae and salmonella are now the most common causes of bacterial meningitis in children.²⁸ Surveillance also identified cases of invasive disease due to *H. influenzae* type a, as observed in Brazil.²⁹ Non-typable *H. influenzae* disease associated with HIV infection increased in South Africa after conjugate vaccine introduction.³⁰ In Uganda, HIV prevalence in children aged < 5 years is just 0.7%³¹ and not associated with Hib meningitis.²⁵ The appearance of type a and non-typable *H. influenzae* could be an artefact of surveillance or laboratory quality issues, or due to increased occurrence of these serotypes.³² Therefore, continuing high quality surveillance of paediatric bacterial meningitis is mandatory to monitor changes in epidemiology and vaccine effectiveness, to provide early warning of Hib re-emergence or serotype shift, to identify and investigate cases of vaccine failure and to monitor the antibiotic susceptibility of pathogens. Surveillance for pneumococcal disease in children is also essential in advance of introducing pneumococcal vaccine, now recommended by WHO and available for subsidized procurement through the GAVI Alliance.^{28,33}

Meningitis incidence was probably underestimated as some patients from Kawempe Division may have reported or been referred elsewhere. Nonetheless, as Mulago Hospital is the premier health facility and the only provider of tertiary paediatric care, our results are a reasonable minimum estimate of meningitis incidence for the area. Prior antibiotic treatment, limited laboratory facilities on nights and weekends and intermittent availability of latex agglutination will also have affected case detection. In this study, latex agglutination testing identified at least 5% of cases. Although these limitations remained fairly consistent, interpretation of trends was limited by lack of prevaccine data in two sites. Extrapolating burden of disease estimates nationally assumes that Hib meningitis incidence does not vary substantially.² Although proximity to a health facility in Kampala is high, in

urban areas, health-seeking behaviour better represents health service use.^{15,19} Should sparsely populated areas have lower incidence, mortality and sequelae may nonetheless be high because of limited geographical access to care. Finally, vaccine effectiveness may have been underestimated due to uncertain vaccination status, misclassification of controls due to undetected confounding^{25,34} or Hib infection, and herd immunity in later years. The small number of cases precluded estimation of vaccine effectiveness for each year.

This study confirms the public health benefit of Hib conjugate vaccine in Uganda and the high value of surveillance. Uganda now faces the challenge of maintaining vaccine availability and coverage.^{35,36} Although Hib vaccine is cost-effective in Africa,^{37,38} and Uganda is now cofinancing vaccine subsidized by the GAVI Alliance,¹⁶ national health budgets remain extremely constrained, with developing and donor countries falling far short of their respective commitments for health financing.³⁹ Current Hib vaccine prices remain unaffordable for many countries, jeopardizing the sustainability of immunization programmes. If we are to realize the tremendous benefits of immunization for children and achieve the Millennium Development Goals, it is urgent for all stakeholders to engage in constructive dialogue with the twin goals of meeting health financing targets and keeping new vaccine prices as low as possible. ■

Acknowledgements

The authors are grateful to Bekithemba Mhlanga and Eric Wobudeya for technical support for the surveillance network, Esther Nalumansi and Karl Herbinger for assistance with data management and analysis, and all the clinical and support staff of the surveillance site hospitals involved in patient care, microbiology laboratory work, and sustaining surveillance.

Competing interests: None declared.

Résumé

Action pour la survie des enfants : élimination de la méningite à *Haemophilus influenzae* type b en Ouganda

Objectif Pour guider la politique de vaccination, nous avons déterminé le bénéfice pour la santé publique de l'introduction en Ouganda du vaccin contre *Haemophilus influenzae* type b (Hib) et estimé l'efficacité de ce vaccin.

Méthodes Des données de surveillance concernant la méningite bactérienne aiguë chez les enfants de 0 à 59 mois, fournies par trois sites hospitaliers sentinelles entre juillet 2001 et juin 2007, ont été examinées pour déterminer l'incidence de la méningite à Hib, l'efficacité du vaccin anti-Hib par un contrôle cas-témoin et le nombre de cas et de décès dus à cette méningite évitables par la vaccination en Ouganda.

Résultats Parmi les 13978 enfants de 17 districts suspectés de méningite bactérienne, 269 cas de méningite à Hib ont été confirmés, le nombre de cas de cette maladie dans le groupe passant de 69 pendant l'année précédant l'introduction de la vaccination (2001-2002) à trois pour la période 2006-2007. L'incidence de

la méningite à Hib a chuté de 88 cas pour 100 000 enfants de moins de 5 ans l'année précédant l'introduction du vaccin à 13 en l'espace de 4 ans, puis à une valeur quasi nulle pour la cinquième année. L'efficacité de la vaccination en 2 doses ou plus était de 93 % (intervalle de confiance, IC, à 95 % = 69-99) contre la méningite à Hib confirmée et de 53 % (IC à 95 % = 11-68) contre la méningite purulente de cause inconnue. En Ouganda, on estime que le vaccin anti-Hib prévient chaque année 28 000 cas de pneumonie et de méningite, 5 000 décès et 1 000 cas de séquelles graves de méningite.

Conclusion En l'espace de 5 ans, la vaccination infantile anti-Hib a presque éliminé la méningite à Hib du territoire ougandais. Pour préserver à long terme les bénéfices de cette vaccination, on a besoin d'urgence d'un financement durable du vaccin, d'une surveillance continue et de qualité et d'une aptitude du secteur de la santé à délivrer un programme de vaccination énergique.

Resumen

Acción para la supervivencia infantil: eliminación de la meningitis por *Haemophilus influenzae* tipo b en Uganda

Objetivo A fin de racionalizar la política de inmunización, determinamos los beneficios para la salud pública reportados por la introducción de la vacuna contra *Haemophilus influenzae* tipo b (Hib) en Uganda y estimamos la eficacia de la vacuna.

Métodos Se examinaron los datos de vigilancia de la meningitis bacteriana aguda entre los niños de 0 a 59 meses en tres centros hospitalarios centinela entre julio de 2001 y junio de 2007, a fin de determinar la incidencia de meningitis por Hib, la eficacia de la vacuna contra Hib mediante un diseño de casos y controles, y el número de casos y muertes por Hib prevenibles mediante vacunación en Uganda.

Resultados De los 13 978 niños de 17 distritos con presunta meningitis bacteriana, se confirmó la meningitis por Hib en 269 casos, con una disminución desde 69 pacientes en el año anterior al comienzo de la vacunación (2001-2002) hasta tres casos en 2006-2007. La incidencia de meningitis por Hib disminuyó de 88

casos por 100 000 menores de cinco años en el año anterior a la introducción de la vacuna a 13 casos a los 4 años, y a casi cero en el quinto año. La eficacia de la vacuna en dos o más dosis fue del 93% (intervalo de confianza del 95%, IC95%: 69-99) para la meningitis confirmada por Hib y del 53% (IC95%: 11-68) para la meningitis purulenta de causa desconocida. Se estima que en Uganda la vacuna contra Hib previene unos 28 000 casos de neumonía y meningitis, 5000 defunciones y 1000 casos de secuelas meningíticas graves cada año.

Conclusión La inmunización infantil con la vacuna anti-Hib casi ha permitido eliminar la meningitis por ese agente en Uganda en un plazo de 5 años. Para garantizar los beneficios a largo plazo de la vacunación contra Hib se requieren urgentemente mecanismos de financiación sostenible de las vacunas, sistemas de vigilancia permanente de gran calidad y un sector de la salud capaz de sacar adelante un programa de vacunación robusto.

ملخص

العمل لإنقاذ الأطفال: التخلص من التهاب السحايا الناجم عن المستدميات النزلية من النمط بي في أوغندا

الموجودات: من بين 13 978 طفلاً يشبه بإصابتهم بالتهاب السحايا الجرثومي في 17 مقاطعة، تأكد إصابة 269 طفلاً منهم بالتهاب السحايا الناجم عن المستدميات النزلية من النمط بي، وقد انخفض العدد من 69 في السنة التي سبقت التلقيح (2001 - 2002) إلى 3 فقط في العام 2006 - 2007. كما انخفض معدل حدوث التهاب السحايا الناجم عن المستدميات النزلية من النمط بي من 88 حالة لكل 100 000 طفل ممن تقل أعمارهم عن 5 سنوات، في السنة التي سبقت إدخال اللقاح إلى 13 حالة في السنوات الأربع التالية لإدخال اللقاح، وإلى ما يقرب من الصفر في السنة الخامسة. وبلغت فعالية (نجاعة) اللقاح لجرعتين أو أكثر 93% (بفاصلة ثقة 95% وبقيم تتراوح بين 69 و 99) بالنسبة لالتهاب السحايا المؤكدة الناجمة عن المستدميات النزلية

الغرض: لتوجيه سياسات التمنيع، تعرف الباحثون على منافع إدخال اللقاح المضاد للمستدميات النزلية من النمط بي على صعيد الصحة العمومية في أوغندا وقدرها فعالية اللقاح.

الطريقة: استعرض الباحثون معطيات ترصد التهاب السحايا الجرثومي الحاد بين الأطفال الذين تتراوح أعمارهم بين 0 و 59 شهراً من ثلاثة مواقع خافرة في المستشفيات، في الفترة بين تموز/يوليو 2001 وحزيران/يونيو 2007، وذلك للتعرف على معدل حدوث التهاب السحايا الناجم عن المستدميات النزلية من النمط بي، وفعالية اللقاح، بدراسة الحالات والشواهد وعدد الحالات التي يمكن توقعها باللقاح وعدد الوفيات الناجمة عن المستدميات النزلية من النمط بي في أوغندا.

إلى التخلص شبه الكامل من التهاب السحايا الناجم عن المستدميات النزلية من النمط بي في أوغندا خلال فترة 5 سنوات. ويتطلب ضمان الحصول على منافع طويلة الأمد للقاح المضاد للمستدمية النزلية من النمط بي أن يبادر وبالحاح لتوفير التمويل المضمون الاستمرار للقاح، ومواصلة التصدُّد الرفيع الجودة، وتمكين القطاع الصحي من تقديم خدمات برنامج قوي للتمنيع.

من النمط بي و53% (بفاصلة ثقة 95% وبقيم تتراوح بين 11 و68) بالنسبة لالتهاب السحايا القبيحي الذي لا يعرف سببه. وهكذا أدى استخدام اللقاح المضاد للمستدميات النزلية من النمط بي إلى الوقاية من 28 000 وفاة ناجمة عن الالتهاب الرئوي والتهاب السحايا، ومن 5000 وفاة و1000 حالة لعواقب وخيمة لالتهاب السحايا كل عام في أوغندا.

الاستنتاج: لقد أدى استخدام اللقاح المضاد للمستدميات النزلية من النمط بي

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