Surveillance for *Streptococcus pneumoniae* Meningitis in Children Aged <5 Years: Implications for Immunization in Uganda

Annet Kisakye,[1] Issa Makumbi,[1] Denis Nansera,[4] Rosamund Lewis,[2] Fiona Braka,[2] Eric Wobudeya,[3] Duku Chaplain,[3] Esther Nalumansi,[3] William Mbabazi,[2] and Bradford D. Gessner[5]

[1]Uganda National Expanded Programme on Immunization, Ministry of Health, [2]World Health Organization, Uganda Country Office, and [3]Mulago National Referral Hospital, Kampala, and [4]Mbarara University Teaching Hospital, Mbarara, Uganda; and [5]Agence de Médecine Préventive, Paris, France

Affordable pneumococcal conjugate vaccines will soon become available to developing countries through the Global Alliance for Vaccines and Immunization. Data on *Streptococcus pneumoniae* meningitis epidemiology in Uganda will assist decision makers in determining the best national vaccine policy. We reviewed acute bacterial meningitis surveillance data for children aged <5 years from 3 sentinel surveillance sites in 3 Ugandan districts collected from 2001 through 2006. Serotype and antibiotic-resistance testing were performed on pneumococcal isolates collected from 2005 through 2006 from the Kampala district in the tropical central region of Uganda. Minimum pneumococcal meningitis incidence estimates were calculated for a portion of the Kampala district and all of the Gulu district, where case ascertainment was more complete. At the 3 sites, 14,388 probable acute bacterial meningitis cases were observed. The most common cause identified was *S. pneumoniae* ($n = 331$; 35% of all confirmed cases), which had an overall case fatality ratio of 19%. Yearly pneumococcal meningitis incidence was 3–20 cases per 100,000 population in Kampala versus 28–42 cases per 100,000 population in Gulu. The most commonly identified serotypes were 6A/6B (40%); 43% of isolates were serotypes that are in the available 7-valent pneumococcal conjugate vaccine and 70% are in the proposed 13-valent pneumococcal vaccine. Twenty-five isolates (83%) had intermediate resistance to penicillin but none were fully resistant. Pneumococcal meningitis is common and severe in Uganda, indicating a role for the pneumococcal conjugate vaccine.

Streptococcus pneumoniae accounts for ~800,000 global childhood deaths every year, mostly among infants and toddlers in developing countries [1]. Various studies in Africa have found substantial pneumococcal disease rates that are up to 10-fold higher than that in industrialized countries [2–4]. In Ghana [5] and Burkina Faso [6], pneumococcal meningitis due to serotype 1 and, to a lesser degree, other serotypes may occur in an epidemic pattern indistinguishable from meningococcal disease. The 9-valent pneumococcal conjugate vaccine that includes serotype 1 has demonstrated significant protection against childhood meningitis and pneumonia in clinical trials conducted in The Gambia [7] and South Africa [8]. In The Gambia, this amounted to annual minimal vaccine-preventable pneumococcal pneumonia and meningitis or sepsis incidences of 1700 and 82 cases per 100,000 children aged <2 years, respectively [7]. The South African trial also confirmed that the pneumococcal conjugate vaccine is effective among children infected with HIV [8].

The GAVI alliance has provided support for the introduction of new vaccines to developing countries since 2001. In November 2006, the GAVI alliance board approved provision of financial support for the intro-

Reprints or correspondence: Dr. Annet Kisakye, National EPI Surveillance Officer, Uganda National Expanded Programme on Immunization, Ministry of Health, P. O. Box 7272, Kampala, Uganda (akisakye2@yahoo.com).

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duction of the pneumococcal conjugate vaccine to eligible countries [9] (http://www.gavialliance.org; accessed 8 May 2007). It is therefore important to document the disease epidemiology and serotype distribution of *S. pneumoniae* and to establish appropriate surveillance to monitor vaccine impact.

With support from the World Health Organization, Uganda established surveillance for pneumococcal disease in 2001 as part of the sub-Saharan Africa Paediatric Bacterial Meningitis Surveillance Network [10]. In 2003, additional support was provided by the Network for Surveillance of Pneumococcal Disease in the East African Region (netSPEAR) [11] and the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP). In this study, we aim to describe the disease epidemiology, serotypes, and antibiotic-resistance of *S. pneumoniae* among children aged <5 years in Uganda.

METHODS

Population health and demographic indicators. The Republic of Uganda had a population of 24,227,297 (4,966,596 aged <5 years) in 2002, with a national annual growth rate of 3.4% [12]. The total populations for the districts in which pediatric bacterial meningitis surveillance was in place in 2002 were 1,189,142 (243,774 aged <5 years) for Kampala, 298,527 (61,198 aged <5 years) for Gulu, and 361,477 (74,103 aged <5 years) for Mbarara. The Kampala district consists of the capital city and lies in the central part of the country, is primarily urban, and has a high population density (4581 persons per km^2). Mbarara is in the southern part of the country, is primarily rural, and has a moderate population density (138 persons per km^2). Gulu is in the northern part of the country, is rural, and has a low population density (41 persons per km^2).

In Uganda, the mortality rates for infants aged <1 year and children aged <5 years were 88 and 131 deaths per 1000 live births, respectively, in 1999 [13] and 79 and 136 deaths per 1000 live births, respectively, in 2005 [14]. Access to primary health care services is relatively low, with 67% of children aged <5 years having been taken to a health center [14]. Approximately 23% of children aged <5 years are moderately or severely underweight [14]. In 2005, the estimated prevalence of HIV among pregnant women aged 15–24 years in Kampala was 5.2% [14], which represented a decrease from 10% in 2001 at the start of our study. Widespread antiretroviral therapy programs were introduced in 2003. Uganda initiated routine, universal infant immunization with *Haemophilus influenzae* type b (Hib) conjugate vaccine in June 2002, with vaccination coverage increasing from 42% in 2002 (diphtheria and tetanus toxoids and pertussis vaccine 3-dose coverage was 72%) to 86% in 2005 and 80% in 2006 (Ugandan Health Management Information System data). In districts with the sentinel sites, vaccination coverage of diphtheria and tetanus toxoids and pertussis, hepatitis B, and Hib (third dose) vaccines varied from 39% to 98% during the study period: coverage in Kampala increased from 39% (2001) to 95% (2005); coverage in the Gulu district increased from 53% (2001) to 98% (2005); and coverage in the Mbarara district increased from 53% (2001) to 88% (2003), then decreased to 75% (2005).

Pediatric bacterial meningitis surveillance. On 12 July 2001, with support from the World Health Organization and as part of the African Paediatric Bacterial Meningitis Surveillance Network [10], Uganda established a pediatric bacterial meningitis sentinel surveillance site at Mulago National Referral Hospital in the Kampala district (central Uganda) for children aged <5 years. On 30 March 2003, Mbarara Regional Referral Hospital (Mbarara district, Southwestern Uganda) and St. Mary's Lacor Hospital (Gulu district, north central Uganda) also initiated pediatric bacterial meningitis surveillance. Data from all 3 sites were available through August 2006.

The clinical case definition for a probable case of pediatric bacterial meningitis at the sentinel sites included a child aged 0–59 months presenting with sudden onset of fever (temperature of >38°C axillary or >38.5°C rectally) and ⩾1 of the following clinical symptoms or signs of meningitis: seizures other than febrile seizures (the latter defined as full recovery within 1 h), neck stiffness, bulging fontanel (in children aged <12 months), poor sucking, altered consciousness, irritability, other meningeal signs, toxic appearance, or petechial or purpuric rash. All children who met the case definition were enrolled in the surveillance system. For each case, the Paediatric Bacterial Meningitis Surveillance Network protocol required collection of age in months; outcome (discharged alive, died, or unknown); district, subdistrict, and village of residence; and prior use of antibiotics. After providing informed consent, children underwent a lumbar puncture as soon as was feasible. Lumbar punctures were delayed or not performed in the case of cardiac or respiratory failure, infection at the puncture site, history or signs of bleeding, congenital dural defects, or coma. A case of purulent meningitis was defined as a probable case if there was turbid or cloudy CSF or CSF leukocytosis with a WBC count of ⩾100 cells/mm^3.

Laboratory procedures. Cause of infection was confirmed by CSF culture or latex agglutination test. After collection in a sterile container, 1–2 mL of CSF was transported to the laboratory within 1 h. The appearance was noted as clear, turbid, xanthochromic, or blood stained. If the specimen could not be immediately processed, the CSF was incubated (on transisolate medium, if available) at 37°C and analyzed the next morning. Latex agglutination kits (bioMérieux) were available for all of 2003 and from June 2004 through August 2006 and were used on purulent CSF for detection of Hib, *S. pneumoniae*, *Escherichia coli* (strain K1), and *Neisseria meningitidis* (serogroups A, B, and C).

On arrival in the laboratory, CSF was evaluated for WBC

count by microscopic observation of a well-mixed, uncentrifuged sample in a Fuchs-Rosenthal counting chamber and for protein content with use of a proteinometer. CSF was then centrifuged, prepared for Gram stain, and plated on prewarmed media for culture. Samples were plated on blood agar prepared from Mueller-Hinton agar plus 5% horse blood and on supplemented chocolate agar containing trypticase soy agar with oxoid and hemoglobin. Plates were prepared locally at all sites. IsovitaleX supplement (BD) containing X and V factors was used to supplement organism growth. Culture plates were placed in a carbon dioxide incubator at 35°C–39°C for 48 h and checked for growth at 24-h intervals. The primary organisms of interest were identified by oxidase, X and V factor tests *(H. influenzae),* Optochin and bile solubility *(S. pneumoniae),* and oxidase and carbohydrate utilization test *(N. meningitidis).* All samples with positive culture results were purified and inoculated into glycerol broth and stored at −35°C. HIV testing was performed occasionally as needed during the surveillance period as part of clinical care, and results were not generally available in the Paediatric Bacterial Meningitis Surveillance Network database.

From 2001 through 2004, no serotyping of isolates was performed. Beginning in 2005, pneumococcal isolates were transported quarterly in chocolate agar slants to the Kilifi reference laboratory in the Kilifi District Hospital in Kenya, where serotyping was performed based on the Quellung reaction [15]. This laboratory also performed antibiotic sensitivity testing for *S. pneumoniae* isolates with use of the Kirby-Bauer method on chocolate agar plates [16]. Only Mulago Hospital routinely succeeded in delivering viable specimens to the reference laboratory, and thus only isolates from this hospital were included in our analysis.

Internal quality control was performed routinely. We regularly filtered the Gram stain solutions and included both positive and negative control smears with every staining procedure. We checked the culture media for contamination by incubating at 37°C, and we tested its potency by culturing standard organisms. In addition, external quality control was performed by quarterly assessment of blind panels sent to the Mulago and Lacor hospitals from the National Institute for Communicable Diseases in South Africa.

Data analysis. For all sites, we evaluated trends over time in the proportion of probable meningitis cases that yielded purulent CSF and the proportion of collected CSF samples that yielded an infectious etiology. The surveillance system was not designed to be population based, which precluded incidence calculations for any site. Nevertheless, we calculated minimum and maximum incidence estimates of documented meningitis for August 2001–August 2006 for the Kawempe division in the Kampala district and for all of the Gulu district, because most children with bacterial meningitis in these areas should have presented to Mulago Hospital and Lacor Hospital, respectively. First, the number of potential additional cases of meningitis due to *S. pneumoniae* was calculated by multiplying the percentage of cases with known bacterial etiology that were due to *S. pneumoniae* by the number of cases without a known etiology but with purulent CSF. This number of potential additional cases of meningitis due to *S. pneumoniae* was added to the number of confirmed cases due to *S. pneumoniae* and divided by the population for each year, to determine a new incidence estimate for each year of the study.

However, we are aware that a case of meningitis with purulent CSF may not necessarily be confirmed to be bacterial (even though most nonbacterial meningitis patients have low WBC counts in CSF, whereas others may have higher values). Therefore, this method of calculation is likely to overestimate the incidence of meningitis due to *S. pneumoniae.*

Ethical considerations. Parents and guardians of patients provided informed consent before the performance of lumbar punctures. As part of routine national public health surveillance, no institutional review board approval was sought or obtained for pediatric bacterial meningitis surveillance. When the decision was made to publish the results of the surveillance, approval was obtained from the Ugandan Ministry of Health.

RESULTS

Probable pediatric bacterial meningitis cases. From August 2001 through August 2006, 14,388 patients with probable bacterial meningitis aged 0–59 months were seen at the 3 surveillance sites; 13,980 (97%) underwent a lumbar puncture (table 1). Of the 13,980 CSF samples obtained, an etiologic agent was identified for 944 (7%) by either culture or latex agglutination test. An etiologic agent was identified for 699 (48%) of 1463 CSF samples that were purulent, 56 (11%) of 509 CSF samples that were nonturbid and yielded a WBC count of 10–99 cells/mm^3, and 52 (1%) of 9604 CSF samples that were nonturbid and yielded a WBC count of <10 cells/mm^3. Among the 314 visually turbid CSF specimens with a WBC count <100 cells/mm^3, 108 (34%) had an etiologic agent identified (including 48 pneumococcus). Meningitis due to *Salmonella* species was noted to be common and affected mostly young children with a mean age of 10 months and a median age of 7 months.

S. pneumoniae was the causative agent identified for 331 (35%) of all confirmed bacterial meningitis cases, making it the most commonly identified cause. It accounted for 51% of confirmed isolates in the Gulu district, compared with 28% and 32% in the Kampala and Mbarara districts, respectively. Of the 331 *S. pneumoniae* isolates, 275 (83%) were isolated from purulent CSF specimens. Among all 331 pneumococcal cases, culture alone was performed for 222 (67%), whereas culture and latex agglutination test were performed for 109

Table 1. Probable acute bacterial meningitis cases among children aged <5 years, by surveillance site in Uganda, 2001–2006.

District and period[a]	No. of cases	Lumbar puncture performed (% of cases)	Purulent CSF (% of specimens)	Confirmed causes (% of all confirmed causes)					
				Streptococcus pneumoniae	*Haemophilus influenzae*	*Neisseria meningitidis*	*Salmonella* species	Contaminants	Others[b]
Kampala, central Uganda (urban)									
August–December 2001	678	622 (92)	129 (21)	12 (24)	23 (47)	0 (0)	6 (12)	0 (0)	8 (16)
January–December 2002	1979	1819 (92)	280 (15)	51 (29)	81 (47)	0 (0)	19 (11)	2 (1)	20 (12)
January–December 2003	1948	1883 (97)	177 (9)	28 (20)	47 (34)	4 (3)	24 (17)	12 (9)	25 (18)
January–December 2004	1410	1381 (98)	132 (10)	26 (30)	29 (34)	0 (0)	11 (13)	3 (3)	17 (20)
January–December 2005	1210	1175 (97)	86 (7)	22 (35)	16 (25)	1 (2)	15 (24)	1 (2)	8 (13)
January–August 2006	837	817 (98)	78 (10)	16 (44)	4 (11)	1 (3)	9 (25)	0 (0)	6 (17)
Total	8062	7697 (95)	882 (11)	155 (28)	200 (37)	6 (1)	84 (15)	18 (3)	84 (15)
Gulu, northern Uganda (rural)									
April–December 2003	1200	1200 (100)	104 (9)	23 (38)	13 (21)	0 (0)	25 (41)	0 (0)	0 (0)
January–December 2004	1354	1352 (100)	131 (10)	47 (57)	6 (7)	1 (1)	28 (34)	0 (0)	0 (0)
January–December 2005	1577	1567 (99)	114 (7)	40 (51)	2 (3)	1 (1)	28 (35)	0 (0)	8 (10)
January–August 2006	853	851 (100)	46 (5)	22 (59)	1 (3)	7 (19)	4 (11)	0 (0)	3 (8)
Total	4984	4970 (99)	395 (10)	132 (51)	22 (8)	9 (3)	85 (33)	0 (0)	11 (4)
Mbarara, southern Uganda (rural)									
April–December 2003	474	445 (94)	77 (17)	18 (32)	25 (45)	2 (4)	4 (7)	1 (2)	6 (11)
January–December 2004	317	317 (100)	47 (15)	16 (44)	10 (28)	0 (0)	2 (6)	1 (3)	7 (19)
January–December 2005	337	337 (100)	43 (13)	8 (24)	10 (29)	2 (6)	5 (15)	3 (9)	6 (18)
January–August 2006	214	214 (100)	19 (9)	2 (17)	2 (17)	2 (17)	3 (25)	0 (0)	3 (25)
Total	1342	1313 (98)	186 (14)	44 (32)	47 (34)	6 (4)	14 (10)	5 (4)	22 (16)
Overall total	14,388	13,980 (97)	1463 (10)	331 (35)	269 (28)	21 (2)	183 (19)	23 (2)	117 (12)

[a] The Gulu site was St. Mary's Hospital in Lacor, the Mbarara site was Mbarara Regional Referral Hospital, and the Kampala site was Mulago National Referral Hospital in Kampala.

[b] Others included coliforms, *Cryptococcus, Escherichia coli, Enterobacter* species, *Klebsiella* species, *Moraxella catarrhalis, Proteus* species, *Pseudomonas* species, *Staphylococcus aureus,* and nonpneumococcal *Streptococcus* species.

(33%). Among the latter cases, 5 (5%) were positive by culture alone, 34 (31%) by latex agglutination test alone, and 70 (64%) by both tests.

Sex, age, and case fatality ratios of pneumococcus meningitis. Boys were involved in 172 pneumococcal meningitis cases (52%). Children aged ≤6 months were involved in 43% of cases, with 16%, 19%, and 23% of cases occurring in those aged 7–11 months, 12–23 months, and 2–4 years, respectively. The case fatality ratios of all cases and the purulent pneumococcal meningitis cases were 19% and 20% (64 of 331 and 56 of 275 cases), respectively. The age-specific case fatality ratios were 18% (25 of 141 cases) for those aged ≤6 months, 13% (7 of 53 cases) for those aged 7–11 months, 31% (19 of 62 cases) for those aged 12–23 months, and 17% (13 of 75 cases) for those aged 2–4 years.

Serotypes. Serotyping was not begun until 2005, and isolates were only available from Mulago National Referral Hospital in Kampala. Serotyping was determined for 30 (75%) of the 40 *S. pneumoniae* isolates collected from January 2005 through August 2006 at this site. Serotypes 6A and 6B (40%) were most commonly identified. After these serotypes, 22A and 23F were the most common (figure 1). Seven (64%) of 11 serotype 6A/6B and 7 (44%) of 16 other serotypes occurred among children aged <12 months. Age was not documented for 3 children.

Of the 30 serotyped *S. pneumoniae* isolates, 13 (43%) were included in the currently licensed 7-valent pneumococcal conjugate vaccine (which includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). Fourteen (46%) were included in the proposed 10-valent vaccine (which includes those in the 7-valent vaccine plus serotypes 1, 5, and 7F), and 21 (70%) were included in the upcoming 13-valent vaccine (which includes those in the 7-valent vaccine plus serotypes 1, 3, 5, 6A, 7F, and 19A). Including the cross-reactive serotype 6A, 18 (60%) and 19 (63%) of the identified serotypes are included in the 7-valent and 10-valent vaccine, respectively.

Antibiotic resistance. Antibiotic resistance testing by E-test showed that all 30 serotyped isolates were susceptible to cefotaxime (MIC range, 0.012–0.5 μg/mL; mean, 0.107 μg/mL; median, 0.094 μg/mL; mode, 0.094 μg/mL). None of the isolates were fully resistant to benzylpenicillin, amoxicillin, or chloramphenicol except 1 serotype 6A isolate and 1 serotype 6B isolate that were fully resistant to chloramphenicol. Intermediate resistance to benzylpenicillin was observed for 25 isolates (including serotypes 14, 38, 6A, 6B, 9V, 10A, 19A, 22A, and 23F) and to amoxicillin for 9 isolates (including serotypes 14, 22A, 6A, and 38), whereas no isolates had intermediate resistance to chloramphenicol. Of 7 serotype 6B isolates, all were intermediately resistant to penicillin, whereas 1 was fully resistant to chloramphenicol.

Incidence and seasonality. The calculated minimum annual incidence of invasive pneumococcal meningitis varied during the study period, with 3–20 cases per 100,000 children aged <5 years in the Kawempe division of the Kampala district and 28–42 cases per 100,000 children aged <5 years in the Gulu district (figure 2). An upper limit for the incidence of patients hospitalized with meningitis can be determined by assuming that the distribution of pneumococcus among patients with confirmed bacterial meningitis is the same as that for patients with purulent meningitis with no bacterial cause identified and by defining purulence as visual turbulence or CSF with a WBC cell of ≥100 cells/mm^3. In the Kawempe division, 33% of all confirmed bacterial meningitis cases were due to *S. pneumoniae*; 91 cases of meningitis with no etiology determined were identified, suggesting that 30 (33%) of these cases were potentially due to pneumococcus. During the years of the study, upper bounds on the incidence estimate for patients hospitalized with meningitis were 5–36 cases per 100,000 children aged <5 years. Similarly, for the Gulu district, 53% of confirmed cases were due to *S. pneumoniae*, 147 cases of purulent meningitis with no etiology determined were identified, and during the study years, the upper bounds on the incidence estimate for patients

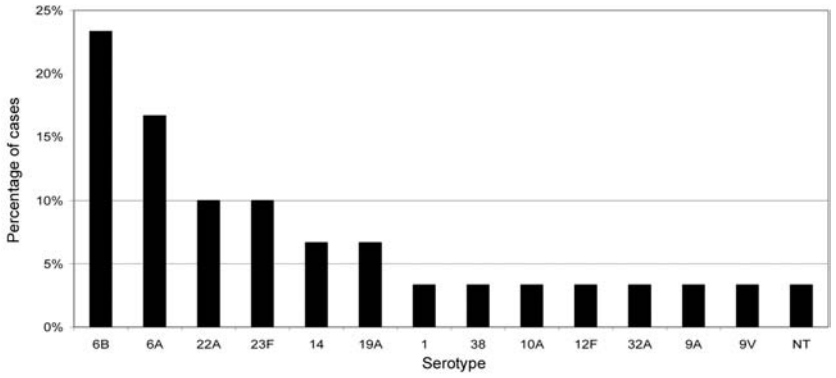

Figure 1. Proportions of serotypes from children aged <5 years with meningitis due to *Streptococcus pneumonia* in Uganda from 2005 through August 2006 ($n = 30$).

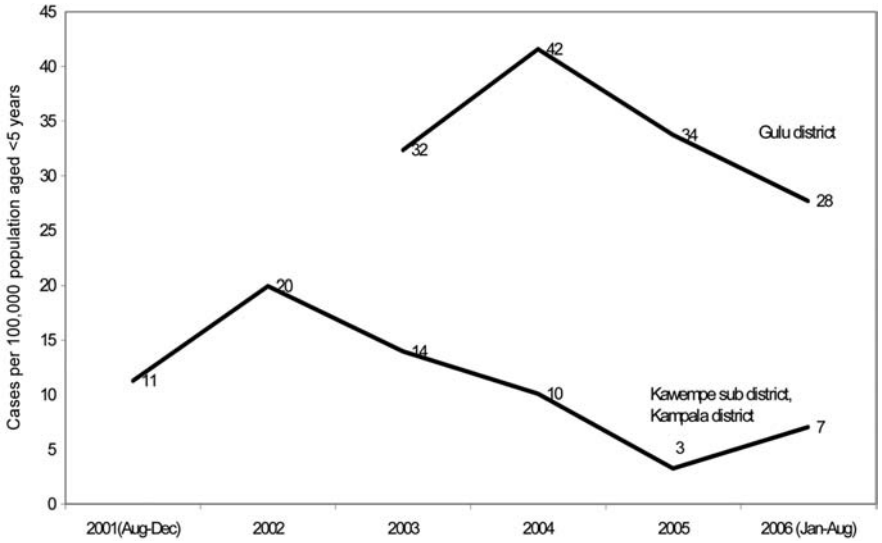

Figure 2. Annual minimal invasive pneumococcal meningitis incidence rate among children aged <5 years, by year of diagnosis for the Gulu district and the Kawempe subdistrict in the Kampala district of Uganda, August 2001 through August 2006. These are minimal incidences with an assumption that all cases in a district presented to the Paediatric Bacterial Meningitis Surveillance Network site hospital in that district and that all true cases had a cause identified.

hospitalized with meningitis were 42–69 cases per 100,000 children aged <5 years.

The rate of isolation of *S. pneumoniae* was modestly seasonal with peaks during the rainy seasons of March–May and September–November (figure 3), with a mean of 6 isolates per month during those months, compared with 4 isolates per month during other months. This seasonality did not vary by serotype grouping (1, 6A/B, and other serotypes).

DISCUSSION

After the introduction of Hib conjugate vaccine in Uganda in 2002, an 85% decrease in the incidence of meningitis due to *H. influenzae* was observed by 2006 [17]. Subsequently, pneumococcus has become the most common cause of pediatric bacterial meningitis in Uganda. The minimum incidence of invasive pneumococcal meningitis was as high as 20 cases per 100,000 population per year in the national capital and even higher in the Gulu district, a rural setting. Upper bounds on the incidence of hospitalized patients with meningitis were 36 in Kampala and 69 in Gulu. The higher incidences reported from Gulu may reflect its location on the border of the African meningitis belt, which is known to have high *S. pneumoniae* meningitis incidences [5, 6], compared with the tropical locations of the other included areas. Considering that, in Uganda, an unknown but likely substantial number of children with meningitis do not present to a hospital, our incidence figures are likely to underestimate overall incidence. On the basis of the available data, pneumococcal meningitis currently may be as common as Hib meningitis was in African countries in the era before the Hib vaccine [18]. Moreover, pneumococcal meningitis is associated with a high case-fatality ratio in Uganda and elsewhere in Africa [6] and is a common cause of bacterial pneumonia, as shown in 2 recent vaccine-probe studies [7, 8].

We found that a limited number of serotypes were responsible for the meningitis cases we evaluated (only 13 of the 90 possible serotypes were observed), as has been reported from elsewhere in Africa [19]. Several recent articles from the African meningitis belt demonstrated the occurrence of outbreaks of meningitis due to *S. pneumoniae* serotype 1 among older children and adults [5, 6]. Among our population of younger children from a more tropical site, we found only 1 serotype 1 isolate. It is possible that older children and adults, particularly those from the North, may have substantially more disease due to this serotype. More generally, only limited data exist on pneumococcal serotype distribution in Africa, particularly for meningitis belt areas such as Northern Uganda, and several studies indicate that serotype distribution may change substantially in just a single year [6, 19]. Although we did not determine pneumococcal serotypes from cases of bacteremic or nonbacteremic pneumonia, clinical presentation by serotype generally does not differ notably [20].

Serotype distribution and change over time are the key considerations in designing pnuemococcal vaccine strategies, because the antigenic component of current vaccines is based on the polysaccharide capsule. In addition, serotype may predict virulence and antibiotic resistance [20]. The available data suggest that the proposed 7-valent, 10-valent, and 13-valent pneumococcal vaccines may prevent a substantial proportion of

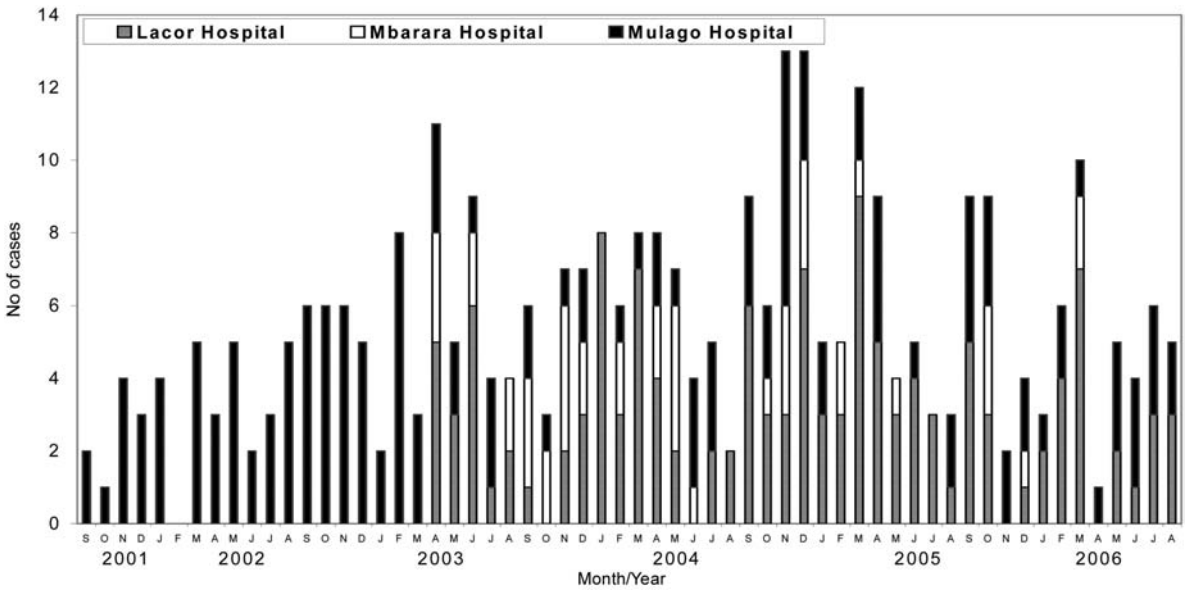

Figure 3. Distribution of cases of *Streptococcus pneumoniae* meningitis among children aged <5 years by site, month and year, and sentinel hospital, Uganda, September 2001 through August 2006.

pneumococcal meningitis cases. Two studies from opposite ends of the African continent have demonstrated the utility of the 9-valent pneumococcal conjugate vaccine in preventing both meningitis and nonbacteremic pneumonia [7, 8]. Thus, it is likely that such vaccines will be appropriate for Uganda as well. However, we have limited information on serotype distribution from the current study or from Africa in general and few data worldwide on the effect of vaccine on serotype replacement. Consequently, although vaccine introduction is an urgent public health priority, introduction should be accompanied by expanded surveillance to document the effect of the vaccine on a range of African populations.

HIV seroprevalence may substantially alter pneumococcal disease epidemiology [21]. In some areas with high HIV prevalence, most pneumococcal cases may occur in association with HIV infection, because of an increased risk of colonization [22] and an increased risk of invasive disease once colonized. In Kampala, Uganda, HIV seroprevalence among young pregnant women decreased by one-half during our study. This occurrence may have contributed to an apparent modest decrease in pneumococcal meningitis incidence that was observed among children in our evaluation, a decrease that occurred in the absence of pneumococcal vaccine use. Surveillance will be necessary to document long-term effects of pneumococcal conjugate vaccine use in African populations with high HIV prevalence, particularly considering the decreasing immunogenicity [23] and increasing carriage [22] over time reported among HIV-infected children.

Development of antibiotic resistance has increased the urgency for vaccine introduction in much of the world, including Uganda. Pretreatment with antibiotics, especially penicillins obtained from street pharmacies, commonly occurs in Uganda, which possibly explains the frequent occurrence of strains that demonstrate intermediate resistance to penicillin. By contrast, pneumococcal isolates remained susceptible to cefotaxime, a more expensive and less readily available antibiotic. Most intermediate resistance to penicillin was identified among vaccine serotypes, suggesting that vaccine introduction might substantially reduce the developing problem of pneumococcal antibiotic resistance.

The main limitation of the current study was the difficulty in obtaining serotype information. Uganda does not have a reference laboratory with skills in serotyping, and at the beginning of surveillance, no agreement existed with an external laboratory. This resulted in a relatively short period of 20 months during which serotyping was performed. Isolates from Lacor were contaminated during the process of preparing the chocolate agar for transportation to the Kilifi reference laboratory and could not be included in the analysis, and a proportion of isolates from Mulago arrived at the Kilifi reference laboratory in a contaminated state. We likely underestimated incidence of meningitis due to *S. pneumoniae* for several reasons. We assumed that a representative population was observed at 2 sites, but some children residing in these areas may have presented for care elsewhere. We included only hospitalized patients, and an unknown number of children with meningitis do not present or may not be referred to a hospital for care. Lastly, a bacterial etiologic agent was identified for only 7% of cases that met a sensitive clinical case definition for surveillance. Effectiveness of Hib vaccine against purulent men-

ingitis without a confirmed bacterial etiology has recently been demonstrated [17]. This suggests that true cases of bacterial meningitis remain unconfirmed, perhaps because pneumococci are fastidious organisms. However, many other patients who met the surveillance case definition were ultimately diagnosed as having cerebral malaria, viral or cryptococcal meningitis, or other conditions. These issues highlight the difficulty of sustaining high-quality pneumococcal disease diagnosis and surveillance in resource-poor settings.

Our data suggest that Uganda would benefit from including pneumococcal conjugate vaccine in the infant immunization program. Similar to the Hib vaccine, the great challenge will be to develop sustainable financing mechanisms. GAVI has recently made pneumococcal conjugate vaccine available for use in routine infant immunization programs at a subsidized vaccine price of as little as US$0.15 per dose for eligible countries. A new financing mechanism, the Advance Market Commitment, is also designed to create incentives for vaccine manufacturers to produce pneumococcal vaccine through guaranteeing, in the initial period, a higher market price to manufacturers than that paid by eligible countries [24]. The challenge for the future will be to sustain financing indefinitely until Uganda's economic development allows for complete self-sufficiency. Ensuring a robust immunization program capable of introducing new vaccine products will also be critical. Future vaccine introduction should be accompanied by continued high-quality pneumococcal disease surveillance to monitor impact on disease caused by specific serotypes and the possibility of serotype replacement, especially in early adopter countries. Countries such as Uganda will require continued support for this resource-intensive but necessary activity.

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