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Hospital-based Sentinel Surveillance of *Haemophilus influenzae* Type b among Children in Burkina Faso, 2004-2012: Impact of Vaccine Introduction

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Abstract

Background: *Haemophilus influenzae* type b (Hib) is a leading cause of childhood bacterial meningitis in Africa. This study assessed the impact of Hib conjugate vaccine introduced in 2006 into the Expanded Program on Immunization (EPI) in Burkina Faso.

Methods: From 2004-2012, we conducted hospital-based surveillance for invasive Hib disease among children <5 years of age with suspected bacterial meningitis. All cerebrospinal fluid (CSF) samples were tested using culture methods and/or PCR. Incidences calculated using population denominators were compared between pre-vaccine (2004-2005) and post- vaccine (2007-2012) periods.

Results: 3928 cases of suspected meningitis were identified from the pediatric service, 231(5.9%) of whom had a bacterial pathogen confirmed. Hib was found in 80 (34.6%) of confirmed cases, followed by *Streptococcus pneumoniae* in 76 (32.90%) and *Neisseria meningitidis* in 54 (23.38%). The average annual incidence (per 100 000 children) of Hib meningitis was 4.11; the annual incidence of Hib meningitis declined by 94.13% from 16 per 100 000 in pre-vaccine (2004-2005) to 0.94 per 100 000 in post-vaccine (2007-2012) periods. None of the 80 Hib confirmed cases was immunized and no death was notified after the introduction of the vaccine.

Conclusion: Admissions for Hib meningitis in the department of pediatrics at University Hospital, CHU-Yalgado Ouédraogo have practically disappeared two years after the introduction of the Hib vaccine into Burkina Faso's Expanded Program on Immunization.

Keywords: Bacterial meningitis; *Haemophilus influenzae* b; Vaccine; Burkina Faso

Introduction

Acute Bacterial Meningitis (ABM) remains a major cause of mortality among children in Africa [1,2]. Beyond the newborn period, the most common causes of bacterial meningitis are *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae.* WHO estimated that Hib causes about 3 million cases of serious disease and 386 000 child deaths every year [3]. The introduction of vaccines to prevent invasive disease by Hib in developed countries in 1987-1991 has had a profound impact on morbidity and mortality from this infection in young infants [4]. In view of these results, WHO has recommended the inclusion of Hib conjugate vaccine in all infant immunization programmes and further recommended the putting in place surveillance programs to help in the monitoring of Hib strains and the determination of vaccine effectiveness [3].

Data on Hib conjugate vaccine impact in African countries are limited and Burkina Faso, located in the middle of West Africa, the heart of African meningitis belt of Lapeyssonnie is one of the countries in sub-saharan Africa in which meningitis is a public health issue. Hib meningitis incidence in the country was reported as 34 per 100 000 in children aged <5 years between 2002-2005, before vaccine introduction [5]. In anticipation to Hib conjugate vaccine introduction, a sentinel site hospital surveillance system for Hib in Burkina Faso was introduced in January 2004 at the University Hospital, CHU-Yalgado Ouédraogo (CHU-YO). Furthermore, from January 2006, Hib conjugate vaccine in combination with diphtheria, pertussis, tetanus and hepatitis B was also introduced into the Expanded Program on Immunization (EPI) in Burkina Faso. A previous report in Bobo Dioulasso, on the western part of Burkina Faso, has observed a marked impact of Hib conjugate vaccine introduction in the region [6].

This study assesses, for the first time, the impact of Hib conjugate vaccine among children with suspected bacterial meningitis at the University Hospital CHU-YO in Ouagadougou, the capital city located in the centre of Burkina Faso.

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Materials and Methods

Study design and patients

This study was conducted at the University Hospital, CHU-YO in the capital city of Ouagadougou, Burkina Faso. CHU-YO is the site of sentinel surveillance of Hib in Burkina Faso and its pediatric ward has a capacity of 180 beds and admits over 6000 children each year.

This study included 3928 children under the age of 5 years, admitted in the pediatric service for suspected meningitis from January 1, 2004 to December 31, 2012. Demographic information, clinical symptoms and vaccination history were recorded for each child using a questionnaire.

Laboratory methods

A lumbar puncture was performed in each child, and cerebrospinal fluids (CSF) were analyzed in the bacteriology laboratory of the sentinel site according to the standard protocol. Briefly, a microscopic examination of the CSF performed using Gram staining technique. CSF was further cultured on blood agar plate supplemented with polyvitex incubated for 24-72 hours at 37°C with ~5% CO_2. Bacterial isolates were identified by colony morphologic analysis, growth requirements and biochemical and antigenic characteristics. From 2010, to enhance meningitis bacteria detection, CSF was subjected to a real time polymerase chain reaction (PCR) based on *bex*A gene, as described previously [7]. For quality control, a sample of isolated strains and CSF specimens with either positive or negative results from University Hospital CHU-YO was sent to Centers for Disease Control (Atlanta, USA).

Data management and statistical analysis

We based our estimates of Hib meningitis incidence on data collected from January 1, 2004 to December 31, 2005 as the pre-vaccine period and January 1, 2007 to December 31, 2012 as the post-vaccine introduction period. The year of Hib conjugate vaccine introduction (2006) was not included in the comparative analysis of 2 pre-/post introduction periods.

The chi-square test or Fisher's exact test of OPENEPI version 2.3.1 was used to determine the statistical significance of the data. A value of $p<0.05$ indicated statistical significance.

Results

Bacterial causes

From January 1, 2004 to December 31, 2012, a total of 3928 cases of suspected meningitis were identified from the pediatric service, 231(5.9%) of whom had a bacterial pathogen confirmed by the laboratory diagnosis. Of the confirmed cases, 210 (90.91%) represented the three major etiologies of bacterial meningitis (*N. meningitidis, S. pneumoniae* and Hib) and 21 (9.09%) for other pathogens (Table 1).

Hib were found in 34.63% of the cases, followed by *N. meningitidis* (32.90%) and *S. pneumoniae* (23.38%).

Hib prevalence declined to 16.2% behind *S. pneumoniae* and *N.meningitidis* (39.23% each) after Hib conjugate vaccine introduction. Among 21 other pathogens isolated, six were *Salmonella* Paratyphi B, four were *Cryptococcus neoformans*, three were *Escherichia coli* and *Staphylococcus aureus*, two were *S. agalactiae* and *Listeria monocytogenes, Klebsiella pneumonia* and *Pseudomonas aeruginosa* (in 1 patient each) (Table 1).

Cases and incidence of Hib

Of the 80 cases of Hib disease, 59 occurred in the pre-vaccine period (2004-2005), and 13 cases occurred in the post-vaccine period (2007-2012) ($P<0.001$). Eight cases occurred during Hib conjugated vaccine introduction (2006). In the pre-vaccine period, of the 59 children with Hib, 83.05% were aged 3-36 months, 10.17% were aged <3 months and 6.78% were aged >36 months.

In the post-vaccine period, of the 13 children with Hib, 84.62% were aged 3-36 months, 9.72% were aged <3 months and 6.94% were aged >36 months (Table 2).

The average annual incidence (per 100 000 children) of Hib meningitis was 4.11; the annual incidence of Hib meningitis declined by 94.13% from 16 per 100 000 in pre-vaccine (2004-2005) to 0.94 per 100 000 in post-vaccine (2007-2012) periods.

Hospital outcome

The parents of all 80 confirmed cases of Hib meningitis certified that their children were not immunized with Hib conjugate vaccine. However, 14 (17.5%) of them had received the meningococcal A conjugate vaccine. All the 21 cases identified after the Hib vaccine introduction have recovered, while from 2004 to 2005 before Hib vaccine introduction one girl and one boy (14 and 19 months old respectively) had died.

Discussion

This study documents the impact of Hib conjugate vaccine during

Table I: Number of bacterial meningitis cases University Hospital, CHU-YO in 2004-2012, by year and etiologic agent.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total (%)
influenzae b	24	35	8	4	4	2	1	1	1	80 (34.63%)
S. pneumoniae	9	16	8	14	12	7	3	4	3	76 (32.90%)
N. meningitidis	1	2	8	14	12	7	3	4	3	54 (23.38%)
Others	6	8	1	2	1	0	2	0	1	21 (9.09%)
Total	40	61	25	34	29	16	9	9	8	231 (100%)

Others: *S. aureus*=3 ; *Streptococcus agalactiae=2* ; *Listeria =1 ; Salmonella Paratyphi B*=6, *E. coli*=3, *Klebsiella pneumoniae*=1 ; *Pseudomonas*= 1 ; *Cryptococcus neoformans*=4

Table II: Proportion of Hib cases by age groups in pre- and post Hib conjugate vaccine introduction University Hospital, CHU-YO.

	<3 months	3-36 months	>36 months mois	Total
Pre-vacine period (2004-2005)	6 (10.17%)	49 (83.05%)	4 (6.78%)	59 (100%)
Post-vaccine period (2007-2012)	1 (7.69%)	11 (84.62%)	1 (7.69%)	13 (100%)
Total	7 (9.72%)	60 (83.33%)	5 (6.94%)	72 (100%)

2004-2012, representing the longest-term study for Hib surveillance in Burkina Faso. We observed that Hib was the most common bacteria that caused childhood meningitis before vaccine introduction, which dropped sharply behind *S. pneumoniae and N. meningitidis* in the post vaccine period. These results are supported by the well-documented information on Hib vaccine impact on the disease in both developed and developing countries [8-11]. In addition to reducing hospitalizations and deaths, Hib vaccine will substantially reduce the frequent sequelae such as deafness that occur following Hib meningitis [12]. As observed by others researchers, pneumococcal meningitis is known to be associated with higher case fatality ratios throughout Western Africa [5,13]. Luckily, Burkina Faso with support of GAVI has introduced pneumococcal vaccine (PCV-13) into the EPI in October 31, 2013 which will be of substantial benefit for the country.

Our results from the sentinel site hospital surveillance for invasive Hib disease demonstrated that Hib has practically disappeared (<1 case per 100 000) after the introduction of the vaccine into the routine child immunization schedule. Similar results have also been reported in eastern and western Africa, e.g. in Uganda and Senegal [9,14]. These observations are also consistent with other studies in countries of Latin America and the Caribbean [15]. We further observed that annual incidences before Hib vaccine introduction were lower than in previous report [6] in Burkina Faso (16 cases vs. 34 cases per 100 000 persons). However, that study was conducted only in 3 districts of another region (western part) during 2002 to 2005, which may explain the differences.

The high frequencies of Hib in children from 3-36 months of age were expected, since Hib infection is common in this age group as observed elsewhere [1]. Our results show also that all cases identified in post-vaccine period were not vaccinated. Most of these cases occurred during three years following the vaccine introduction showing the difficult to reach 100% coverage during the first years of vaccine introduction. The existence of no vaccinated cases may also be explained by the advanced age of patients at the time the vaccine was introduced because the target EPI population is three months to one year old. All the cases identified in post-vaccine introduction have recovered unlikely two cases fatality were observed in pre-vaccine period. Indeed, the access to care, reference structure for meningitis, referral practices, and associated treatment practice after vaccine introduction by the ministry of health may explain this situation. This may be also one of the reasons to explain the reduction of uncommon meningitis bacteria (14 vs. 6) observed in our study (*Salmonella* Paratyphi B*, K. pneumoniae*, *E. coli*, *C. neoformans*, *S. aureus*, *S. agalactiae*, *L. monocytogenes,* and *P. aeruginosa*) in post-vaccine periods. Uncommon meningitis due to Gram negative enteric bacilli infections are the second most common pathogens in neonatal infections. They are mostly acquired by vertical transmission, but nosocomial transmission is also important in patients who require long-term intensive care [1]. Other bacteria such as *S. aureus*, *S. agalactiae* , *L. monocytogenes,* and *P. aeruginosa* can also cause meningitis [16].

To conclude, this study has observed a marked impact of Hib conjugate vaccine in Burkina Faso. It shows also how Hib conjugate vaccine can help reduce child morbidity and mortality in low-income settings. Continuation of the surveillance system established at the University Hospital, CHU-YO will be useful for Hib impact vaccine in the future as well as the bacteria trends in childhood meningitis.

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