Epidemiology of paediatric meningitis in central Côte d'Ivoire after the implementation of *Haemophilus influenzae* type b vaccination

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SUMMARY

Infectious meningitis accounts for enormous morbidity worldwide, but there is a paucity of data on its regional epidemiology in resource-constrained settings of sub-Saharan Africa. Here, we present a study on the aetiology of paediatric meningitis in central Côte d'Ivoire. Between June 2012 and December 2013, all cerebrospinal fluid (CSF) samples drawn at the University Teaching Hospital Bouaké were examined for the presence of bacterial and fungal pathogens. A causative agent was detected in 31 out of 833 CSF specimens (3.7%), with the most prevalent pathogens being *Streptococcus pneumoniae* (n=15) and *Neisseria meningitidis* (n=5). With the exception of neonates, these two bacteria were the most common agents in all age groups. Of note, only a single case of *Haemophilus influenzae* meningitis was detected. Hence, this study reports a considerable shift in the epidemiology of paediatric meningitis in central Côte d'Ivoire. Following the implementation of a nation-wide childhood vaccination programme against *H. influenzae* type b, this pathogen was much less frequently reported than in previous studies. The integration of specific vaccines against *S. pneumoniae* and *N. meningitidis* into the childhood vaccination programme in Côte d'Ivoire holds promise to further reduce the burden due to infectious meningitis.

INTRODUCTION

Infectious meningitis is a severe infectious disorder of the central nervous system (CNS) that may be caused by bacterial, viral, fungal and parasitic pathogens (John *et al.*, 2015; McGill *et al.*, 2016). While typical clinical signs and symptoms can suggest the diagnosis of infectious meningitis, lumbar puncture is usually performed to obtain a sample of cerebrospinal fluid (CSF) for microbiological and cytological diagnostics. A distinction between the aetiological agents cannot always be done on clinical grounds alone, but some frequent causes of viral meningitis (e.g. enteroviruses) have a benign course and may resolve spontaneously (Jarrin *et al.*, 2016). In contrast, CNS infections caused by fungal (e.g. *Cryptococcus neoformans*) (Gottfredsson and Perfect, 2000) and parasitic pathogens (e.g. due to the amoeba *Balamuthia mandrillaris* or the helminth *Angiostrongylus cantonensis*) (Utzinger *et al.*, 2012; Thanaviratananich and Ngamjarus,

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2015) are rare and can often be linked to an underlying immunosuppressive condition (such as infection with the human immunodeficiency virus (HIV)). Bacterial meningitis is frequently seen in both immunocompetent and immunocompromised individuals, and it accounts for considerable morbidity and mortality worldwide. Bacterial meningitis occurs either as community-associated or healthcare-associated entity (e.g. post-neurosurgical). The significant disease burden caused by this condition can be alleviated through targeted treatment of the causative pathogens and through preventive measures such as vaccination programmes targeting age groups at highest risk (i.e. children). Indeed, the widespread use of highly effective vaccines against the three most common aetiological agents, i.e. *Streptococcus pneumoniae, Haemophilus influenzae* type b and *Neisseria meningitidis*, has led to a dramatic decline in the incidence of bacterial meningitis in many high-income countries (Thigpen *et al.*, 2011). Likewise, in such settings, adults are now more commonly affected by infectious meningitis than infants and children (Nudelman and Tunkel, 2009). In contrast, many individuals living in poor areas of low- and middle-income countries continue to suffer from an inadequate access to healthcare, and vaccine-preventable pathogens still prevail in these populations (Peltola, 2001).
The costs for the clinical care of patients with bacterial meningitis are high (Portnoy *et al.*, 2015), and many

emerging countries are now implementing interventions such as childhood vaccination programmes to tackle the unacceptable burden caused by bacterial CNS infections (Sambo *et al.*, 2015). Before such an intervention is implemented in a given area, it is of utmost importance to accurately assess the setting-specific epidemiology of meningitis in order to develop the most cost-effective interventions. Côte d'Ivoire is one of the fastest growing countries in West Africa, but few epidemiological data are available pertaining to the epidemiology of bacterial meningitis. Indeed, the country has suffered from more than a decade of civil unrest (1999-2011) during which most public health activities and disease surveillance systems had been interrupted (Bonfoh *et al.*, 2011; Akoua-Koffi *et al.*, 2015). In 2009, country-wide routine vaccination of all children aged ≥6 weeks against *H. influenzae* type b was included in the national vaccination plan in Côte d'Ivoire, but no epidemiological studies on the aetiology of bacterial meningitis have been published since then; hence, it remains to be elucidated whether this intervention has led to a decrease in meningitis cases caused by *H. influenzae*.

The goal of the current study was to identify the major causative agents giving rise to community-acquired bacterial meningitis in Bouaké, central Côte d'Ivoire, and to describe their epidemiology and antimicrobial susceptibility patterns. Furthermore, we wanted to assess the potential impact of the nation-wide childhood vaccination programme against *H. influenzae* type b in Côte d'Ivoire.

MATERIAL AND METHODS

Study population

The study population comprised all patients with suspected bacterial meningitis who had a CSF sample taken at the University Teaching Hospital in Bouaké (UTHB), central Côte d'Ivoire, between June 2012 and December 2013. Most samples were drawn at the UHTB's Department of Paediatrics.

Microbiological diagnostic techniques

All specimens were sent to the Department of Microbiology at the UTHB and were immediately processed. Upon macroscopic visualisation, the CSF samples were categorised as clear, turbid or haematic/bloody/reddish. Gram staining was performed to document the presence of leukocytes and of pathogens. The staining characteristics (i.e. Gram-positive and Gram-negative) and morphology of bacteria (i.e. rods and cocci) were documented.

CSF agar culture was performed utilising three different culture media, i.e.

1. brain-heart infusion bouillon;
2. 5% blood agar plates;
3. chocolate agar plates.

All media were incubated for 48 hours at 37°C in CO_2-enriched atmosphere. Identification of bacteria to the species level was performed based on colony morphology and biochemical reactions. Antimicrobial susceptibility testing was introduced during the study period and was carried out for strains of *S. pneumoniae* and *N. meningitidis*, according to recommendations of the French Society of Microbiology.

In addition to microscopy and culture techniques, additional techniques were employed on all turbid samples with a number of ≥10 leucocytes/mm³ and all haematic

specimens. First, a rapid antigen detection test utilising latex agglutination (Pastorex™ Meningitis, Bio-Rad; Hercules, CA, USA) was used to assist in the diagnosis of *N. meningitidis* serogroup A, B, C, Y and W135, *Escherichia* coli K1, *H. influenzae* b, *S. pneumoniae* and group B streptococci (e.g. *Streptococcus agalactiae*). Second, pathogen-specific polymerase chain reaction (PCR) examinations for *N. meningitidis*, *S. pneumoniae* and *H. influenzae* were subsequently performed at the national reference centre for bacteriological diagnostics (Institut Pasteur de Côte d'Ivoire; Abidjan, Côte d'Ivoire).

Statistical analysis

All data were double-entered, cross-checked and analysed using the public domain statistical software Epi Info (Atlanta, GA, USA).

RESULTS

During the 19-month study period, 833 CSF samples were submitted to the laboratory in Bouaké. The study population comprised paediatric patients aged between 1 day and 15 years (median age: 30 months; mean age: 37.97 months). 44.7% of all samples (n=373) stemmed from female patients. Following visual inspection, 756 specimens were macroscopically clear and colourless (90.7%), while 77 CSF samples were reported as abnormal (9.3%), either being turbid (n=41) or bloody/reddish (n=36). Microbiological diagnostic work-up identified a pathogen in 31 samples, owing to a total positivity rate of 3.7% of the 833 examined CSF samples. Of note, 76% (31/41) of the macroscopically turbid samples were positive for a pathogen, while none of the bloody CSF specimens was found to be positive by any of the diagnostic techniques.

The majority of meningitis cases with an identified aetiology were of bacterial origin (n=29; 94%), while two fungal CNS infections caused by *Cryptococcus* spp. were detected. In three meningitis cases, bacteria were visualised upon microscopy of Gram-stained slides, but no specific pathogen could be detected using culture and PCR. In contrast, the causative agents could be identified in the remaining 26 cases. Two third of all bacterial aetiologies were caused by two pathogens, namely *S. pneumoniae* (15/26) and *N. meningitidis* serogroup A and W135 (5/26). In contrast, only one single case of *H. influenzae* infection was observed. *S. aureus*, *Streptococcus agalactiae* and *Enterobacteriaceae* were further rare causes of bacterial meningitis. Details on the distribution of pathogens in relation to the employed diagnostic techniques are given in *Table 1*. Of note, cultures were positive in only 68.9% (20/29) of patients with a bacterial pathogen.

With regard to the age-specific pathogen distribution, *S. pneumoniae* and *N. meningitidis* were the predominant causes of bacterial meningitis in all patients aged >28 days, while *E. coli* K1 and *S. agalactiae* were the only pathogens detected in neonates (*Figure 1*).

Antimicrobial susceptibility testing could be performed on eight culture-grown strains of *S. pneumoniae* and three strains of *N. meningitidis*. The resistance patterns of *S. pneumoniae* are displayed in *Table 2*. Of note, one strain exhibited a reduced susceptibility to penicillin with a minimal inhibitory concentration (MICs) of 0.09 mg/l. All strains were fully susceptible to vancomycin and rifampicin, but resistance to the frequently utilised antibiotic cotrimoxazole was common.

Table 1 - *Aetiology of community-acquired meningitis in Bouaké, Côte d'Ivoire, 2012-2013, stratified by employed diagnostic techniques, i.e. 1) microscopy of Gram-stained slides; 2) microbiological culture; 3) antigen detection test; and 4) polymerase chain reaction (PCR) assay.*

Pathogen	Total (n=31)		Diagnostic technique			
	n	%	Microscopy[a]	Culture	Antigen detection	PCR
Bacteria						
Streptococcus pneumoniae	15	48.4	15	13	11	5
Neisseria meningitidis	5	16.1	5	3	5	1
Streptococcus agalactiae	2	6.5	1	1	2	0
Escherichia coli K1	1	3.2	1	1	1	0
Haemophilus influenzae	1	3.2	1	0	1	0
Salmonella enterica	1	3.2	1	1	0	0
Staphylococcus aureus	1	3.2	1	1	0	0
Not identified	3	9.7	Gram-positive cocci, n=1; gram-negative cocci, n=1; gram-negative rods, n=1			
Fungi						
Cryptococcus spp.	2	6.5	2[b]			

[a]Microscopy of Gram-stained slides.
[b]Cryptococcosis was microscopically diagnosed using India ink staining.
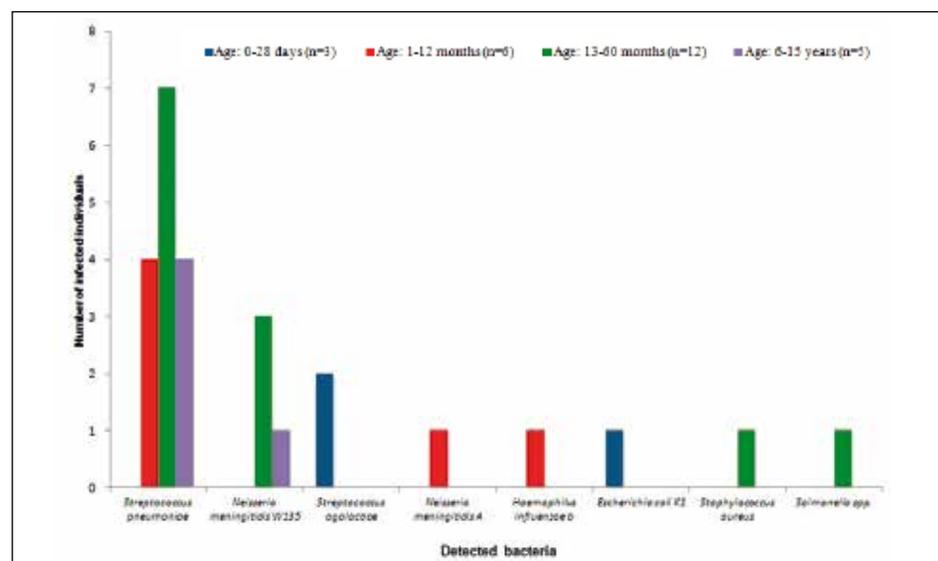

Figure 1 - *Age group-specific distribution of pathogens detected in children with community-acquired bacterial meningitis in Bouaké, central Côte d'Ivoire, 2012-2013.*

Table 2 - *Antimicrobial susceptibility testing of S. pneumoniae strains isolated from cerebrospinal fluid of patients with community-acquired meningitis in Bouaké, Côte d'Ivoire, 2012-2013.*

Antibiotic	Number of tested strains	Sensitive	Resistant
Penicillin G	8	7	1
Amoxicillin/clavulanic acid	8	8	0
Ceftriaxone	8	7	1
Gentamicin	8	8	0
Erythromycin	8	7	1
Lincomycin	8	8	0
Chloramphenicol	8	7	1
Tetracycline	7	4	3
Cotrimoxazole	8	4	4
Vancomycin	8	8	0
Rifampicin	8	8	0
Fosfomycin	8	8	0

DISCUSSION

Infectious meningitis is an important medical condition that remains insufficiently addressed in many low- and middle-income countries. In the current study from central Côte d'Ivoire pertaining to the aetiology of meningitis in a paediatric population, bacteria were the most frequently detected causative agents, with the two pathogens *S. pneumoniae* and *N. meningitidis* accounting for the majority of all cases. Interestingly, *H. influenzae* - globally one of the three most common agents of bacterial CNS infections - was found in less than 5% of the patients.

The aetiological spectrum of meningitis varies considerably from one setting to another. However, the three bacterial species *H. influenzae*, *N. meningitidis* and *S. pneumoniae* cause the vast majority of purulent meningitis cases in children throughout most regions of sub-Saharan Africa (Peltola, 2001). Indeed, *S. pneumoniae* was the most prevalent pathogen in our study, which confirms previous studies from south and central Côte d'Ivoire and the Cen-

tral African Republic, where *S. pneumoniae* accounted for 42-48% of all meningitis cases (Assé *et al.*, 2001). Of note, only a single strain with reduced susceptibility to penicillin was documented in the current study. Indeed, it has recently been shown that the rates of penicillin resistance in *S. pneumoniae* isolates seem to be lower in West Africa than in Central and East Africa (Kacou-Ndouba *et al.*, 2016). In future studies, it would be helpful to characterise the serotypes of circulating *S. pneumoniae* strains in order to decide on the potentially most effective vaccine strategy, as there are different polyvalent conjugate vaccines commercially available (Wu *et al.*, 2015). In Côte d'Ivoire, a 13-valent conjugate vaccine directed against *S. pneumoniae* has been included in the routine vaccination programme for all children aged ≥2 years in late 2014, after the current study had been carried out. Hence, it will be very important to monitor the changing epidemiology of bacterial meningitis in Côte d'Ivoire over the next years, so that potential benefits caused by the introduction of the vaccine are adequately assessed.

N. meningitidis, the second most prevalent pathogen in the current study, was the most frequently reported causative agent in similar studies from Burkina Faso (Ouedraogo *et al.*, 2011) and Sudan (Youssef *et al.*, 2004). In our setting in central Côte d'Ivoire, 4 out of 5 isolates belonged to the serogroup W135. Of note, this serogroup seems to have been recently introduced into the area of Bouaké, because it had been absent in a previous study conducted by Assé and colleagues in 2001 (Assé *et al.*, 2001). Two hypotheses could explain this emergence; first, an increased in-country migration from the northern areas of the 'meninigitis belt' into the Bouaké area may have occurred during the political crisis after 2002. Second, the growing importance of serogroup W135 could be explained by the sharp decline of infections related to serogroup A after the introduction of the anti-A MenAfriVac vaccine in areas around the African 'meningitis belt' (Ouangraoua *et al.*, 2014). Our finding of the predominance of W135 calls for further molecular characterisation of the circulating *N. meningitidis* strains in central Côte d'Ivoire.

With regard to *H. influenzae*, our observed prevalence of 3.2% in Côte d'Ivoire was lower than previously reported from other African settings in Egypt (39.0%) (Farag *et al.*, 2005), Mozambique (32.6%) (Roca *et al.*, 2009), Nigeria (55.1%) (Lagunju *et al.*, 2008) and Tunisia (66.4%) (Maalej *et al.*, 2006). Earlier studies from Côte d'Ivoire had also reported considerably higher rates of invasive *H. influenzae* infections (Edoh *et al.*, 2001; Faye-Ketté *et al.*, 2003). Hence, it is likely that the decline of *H. influenzae* can be explained by the implementation of the *H. influenzae* type b (Hib) vaccine as part of the routine childhood vaccination programme in all parts of Côte d'Ivoire. Indeed, in 2009, the Hib vaccine has been made available free of charge for all children aged above 6 weeks (3 individual doses given one month apart, followed by another injection at 18 months and then every 5 years) and has reached coverage rates of 87-100% between 2012 and 2014 (Blau *et al.*, 2012). There is compelling evidence from high-income countries that the implementation of the Hib vaccine can lead to a rapid decline of invasive infections due to *H. influenzae* (Peltola *et al.*, 1992), and similar reductions have recently also been reported from a number of low- and middle-income countries such as Angola (Peltola *et al.*, 2014), Burkina Faso (Kaboré *et al.*, 2012), The Gambia (Howie *et al.*, 2013), Malawi (McCormick and

Molyneux, 2011; Wall *et al.*, 2014) and Morocco (Braikat *et al.*, 2012). *H. influenzae* type b is of particular importance in the setting of bacterial meningitis because it is known to cause residual sequelae in a high percentage of successfully treated patients (Wee *et al.*, 2016). Hence, it has been recommended to further the implementation of this beneficial and highly cost-effective vaccine across Africa (Bröker, 2008; Griffiths *et al.*, 2013), and the data from our study provide additional evidence to underscore such recommendations (McIntyre *et al.*, 2012). Likewise, a dramatic >10-fold decline had previously been observed for meningitis due to *N. meningitidis* group A in countries of the African meningitis belt after the implementation of a specific group A meningococcal conjugate vaccine (Lingani *et al.*, 2015). Furthermore, a systematic review of hitherto published data concluded that up to three quarters of meningitis deaths might be preventable trough widespread use of vaccines against *H. influenzae* and *S. pneumoniae* (Davis *et al.*, 2013).

The study reported here has several limitations. First, the number of analysed CSF specimens (n=833) is relatively low and all samples were drawn at a single centre. Yet, the study is the first to report on the changing epidemiology of bacterial meningitis in Côte d'Ivoire after the introduction of the Hib vaccine, and therefore provides relevant additional evidence. Second, CSF samples could only be examined for a limited number of pathogens, e.g. no detection methods for viruses were available during the conduct of the study. This may explain the relatively low pathogen detection rate of 3.4%. Second, the broader application of more sensitive diagnostic tools such as multiplex PCR for the major bacterial agents of community-acquired meningitis might have further improved the detection rate. While this could have led to a higher positivity rate, it is nevertheless unlikely that such an approach would have led to a significantly different distribution of the main bacterial pathogens. Third, antimicrobial susceptibility testing could not be uniformly performed on all specimens due to the unavailability of reagents at the start of the study. However, such a lack of equipment and laboratory medicine is common in many parts of sub-Saharan Africa, and needs to be tackled by public health authorities to provide improved health care (Petti *et al.*, 2006). Fourth, this retrospective, laboratory-based study did not allow for accurate documentation of clinical data, which would have been interesting to assess the pathogen-specific clinical outcome of patients with meningitis and to infer recommendations for an improved medical treatment and clinical management.

CONCLUSIONS

In this study, the vaccine-preventable pathogens *S. pneumoniae* and *N. meningitidis* were the most commonly detected causative agents of paediatric meningitis in central Côte d'Ivoire. By contrast, infections due to *H. influenzae* were rarely observed (<5%) and were less prevalent than in studies conducted before 2009, when the Hib vaccine was implemented as part of the free nation-wide childhood vaccination programme in Côte d'Ivoire. During the study period, vaccination against *N. meningitidis* or *S. pneumoniae* was not routinely available in the country and these vaccines had to be paid for by the parents or caregivers of the affected children. The decline of invasive *H. influenzae* infections can likely be attributed to the previously im-

plemented vaccination programme, and future research should thus be conducted to document whether similar effects will be seen for *S. pneumoniae* after the country-wide implementation of a 13-valent conjugate vaccine in 2014.

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