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Etiological Agents of Meningitis in Northern Cameroun: a Retrospective Study from Patients Suspected of Meningitis Enrolled in Case by Case Based Surveillance after MenAfriVac

Agents étiologiques de la méningite dans le Septentrion du Cameroun : une étude rétrospective de patients suspectés de méningite enrôlés dans la surveillance au cas par cas après MenAfriVac

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ABSTRACT

Introduction. Bacterial meningitis is among most severe infectious diseases with a high rate of morbidity and mortality in developing countries. The heaviest burden is reported in Africa, in particular in the "african meningitis belt" which include the northern regions of Cameroon. This study aims to provide information on the profile of bacterial agents of meningitis in Cameroon's northern regions after MenAfriVac. **Methods.** We retrospectively reviewed the biological monitoring data from 1st January, 2013 to 20 September 2015, of case by case-based surveillance for meningitis, obtained at the National Reference Laboratory. Data were retrieved from Excel linelists of cases and analyzed using SPSS 20.0. **Results.** In this study, we considered 742 cerebrospinal fluid samples analysis. The mean patients age was 9.6 years [2 days–77 years] with male sex ratio dominance (1.3). Seventy-one (9.57%) cases were positive. Confirmed meningitis cases were made up of 28 culture positive bacteria, 11 Rt-PCR positive bacteria, and 64 soluble antigen positive tests. Among 67 bacterial isolates, *Streptococcus pneumoniae* was the predominant organism across all age group, 45 (63.38%), followed by *Neisseria meningitidis*, 18 (25.34%), predominating in patients aged 12-59 months, *Salmonella sp* 3 (4.22%), and *Streptococcus agalactiae*, 1 (1.4%). *Cryptococcus neoformans* was the only fungus isolated in 4 (5.63%) cases. **Conclusion.** *S. pneumoniae* is the predominant bacterial agent of meningitis in the northern regions of Cameroon, followed by Serogroup W of *N. meningitidis*. The pneumococcal vaccine could be widely implemented for the management of meningitis. Other bacterial and fungal pathogens should be considered in meningitis patients.

RÉSUMÉ

Introduction. La méningite bactérienne est l'une des infections les plus graves avec un taux élevé de morbidité et de mortalité dans les pays en développement. Un lourd fardeau est reporté en Afrique, particulièrement dans la « ceinture africaine de la méningite » qui inclus les régions septentrionales du Cameroun. Cette étude vise à déterminer le profil des agents bactériens de la méningite dans les régions septentrionales du Cameroun après le MenAfriVac. **Méthodes**. Nous avons examiné rétrospectivement les données biologiques du 1er Janvier 2013 au 20 Septembre 2015 de la surveillance cas-par-cas de la méningite obtenues auprès du laboratoire national de référence. Les données ont été analysées avec le logiciel SPSS 20.0. **Résultats**. Au total 742 analyses de liquide céphalo-rachidien ont été considérés. L'âge moyen des patients était de 9,6 ans, avec un sex-ratio de 1,3. Soixante-onze (9,57%) cas étaient positifs, isolats obtenus soit par culture (28), RT-PCR (11) ou par antigènes solubles (64). Les cas positifs étaient constitués de 67 bactéries avec 45 (63,38%) cas de *Streptococcus pneumoniae*, 18 (25,34%) cas de *Neisseria meningitidis*, 3 (4,22%) cas de *Salmonella sp*, et 1 (1,4%) cas de *Streptococcus agalactiae* ; et un champignon, le *Cryptococcus neoformans* isolé dans 4 (5,63 %) cas. **Conclusion**. *S. pneumoniae* est l'agent bactérien prédominant de la méningite dans les régions septentrionales du Cameroun, suivi du sérogroupe W de *N. meningitidis*. Le vaccin antipneumococcique devrait être largement mis en œuvre pour la prévention de la méningite. D'autres agents bactériens et fongiques doivent être pris en compte chez les patients atteints de méningite.

HIGHLIGHTS OF THE STUDY

What is already known on this topic

The impact of MenAfriVac on *Neisseria meningitidis* serogroup A has been demonstrated in several studies. Little is known about remaining circulating germs in the targeted populations of the northern regions of Cameroon.

What question this study addressed

Profile of bacterial agents of meningitis in Cameroun's northern regions after MenAfriVac.

What this study adds to our knowledge

S. pneumoniae is the dominant bacterial agent of meningitis, followed by serogroup W of *N. meningitidis*. Serogroup A of *N. meningitidis* is no longer found.

How is this relevant to practice, policy or future research.

The study suggests that prevention policies with the pneumococcal vaccine be enhanced. Conjugate vaccines taking into account *Neisseria meningitidis* serogroup W are another adequate option for prevention.

INTRODUCTION

Bacterial meningitis (BM) is an inflammatory response to pyogenic bacterial invasion of the meninges surrounding the central nervous system [1]. It is one of the most severe infectious diseases with a high morbidity and mortality rate in developing countries [2, 3]. In 2019, worldwide meningitis mortality was more than 236,000, with approximately 2.5 million new cases [2], it is a serious infection which can develop rapidly into a life-threatening disease even in previously healthy children or adults [1]. Rates of BM vary from region to region, as do the pathogens associated with this syndrome. The burden of BM is higher in Africa [3], in a particular climate zone called "african meningitis belt" where the heaviest burden is reported [4].

Cameroon belongs to the meningitis belt, thus is not spared by BM. Cerebrospinal meningitis epidemics mainly affected the northern regions of Cameroon: in 1992 in the Far-North region with 8046 cases and 968 deaths. In the North region, epidemics occurred in 1993 with 1190 cases and 136 deaths; and in 1998 with 2054 cases and 225 deaths [5]. In 2010, the Adamawa region recorded 126 cases. The etiological agent identified in most cases was serogroup A of *N. meningitidis* [6, 7]. Other regions of Cameroon are also affected [8 - 14]. BMs are of greater importance than other etiologies, because of gravity and live-threating potential. It is a therapeutic emergency.

In addition to *N. meningitidis*, other etiological agents are identified: *S. pneumoniae*, *Haemophilus. influenzae*, *L. monocytogenes*, *S. aureus*, *S. agalactiae*, *E. coli* with substantial variations in prevalence [15 - 17]. This changing challenge must be followed to maintain an actualized profile of etiological agents for the appropriate management of cases. The northern regions of Cameroon have been marked by important public health interventions in the fight against meningitis through immunization interventions to prevent BM: The *H. influenzae* type b conjugate vaccine was introduced in 2009 and since then the coverage has remained >80% [13], the pneumococcal conjugate vaccine (PCV13) was introduced in 2011, with the Expanded Programme of Immunization. Although the estimated coverage of children immunized with PCV13 was low (23%), it then reached 85% in subsequent years. We note in the same vein the introduction of MenAfriVac (meningococcal A conjugate vaccine) in 2011 in the Far-north, North, and Adamawa regions targeting 1 to 29 years old. The efficacy of PCV13, Hib vaccine, and MenAfriVac in reducing the burden of disease is well documented over the world [16, 18]. In Yaoundé, the capital city of the Center Region of Cameroon, belonging to the southern part of the country, and which is outside the meningitis belt, the etiologies of BM has been studied by some authors [11, 12, 14]. However, in northern Cameroon regions, little is known about the bacterial agents of meningitis after vaccination campaigns. This study aims to provide the profile of bacterial agents of meningitis in the northern regions of Cameroon.

MATERIALS AND METHODS

We retrospectively reviewed line lists of case-based biological surveillance of meningitis from January 1, 2013 to September 20, 2015, where 730 suspected cerebrospinal fluid (CSF) were sent to Garoua Center Pasteur of Cameroon (CPC) of Garoua for analysis in the setting of the case based biological surveillance of meningitis.

Study population

The study population was that of the three northern regions of Cameroon (North, Far North, and Adamawa), which was about 7.5 million (7,539,655) inhabitants, spread over an area of 163 500 km^2. The target population is that of patients suspected of having meningitis who have undergone lumbar puncture in the health facilities in the regions concerned and the CSF was sent to the CPC for analysis.

Setting of survey

Spinal tap was performed on patients suspected of having meningitis in health settings in the concerned regions. CSFs were analyzed in health facilities for preliminary tests and then confirmed at the national reference laboratories (CPC Annex of Garoua).

Methods

CSFs were analyzed using classical bacteriological methods: Gram staining, soluble antigen test by Pastorex Meningitis® method, culture on blood agar supplemented with polyvitex incubated in an atmosphere enriched with 5% CO_2. The polymerase chain reaction (PCR) was used to confirm the cases.

Sources of data collection

Data were obtained from the line-listing of meningitis case line list, CSF analysis sheets, and the biological meningitis surveillance registers. The variables of our study were: age, sex, date of sampling, region, treatment received before sampling, and bacteriological diagnosis (by test strip, soluble antigen test, culture, or PCR).

Data Analysis

Data analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20 and graphs were set up using Excel. The Chi-square test was performed to identify the association between meningitis cases and the age groups and sex of the patients, if any relationship between the variables could be identified. A P value less than 0.05 was considered significant.

Legal and ethical considerations of the study

The study was carried out within a national program of meningitis surveillance on a case-by-case basis, under the direction of the Ministry of Health, and the CPC laboratories were the National Reference Laboratories. Ethical approval was not required for the routine surveillance of meningitis.

RESULTS

Demographic characterization of enrolled cases

Between January 1, 2013, and September 21, 2015, a total of 742 CSF analyzes were recorded at the Centre Pasteur annex of Garoua from the three northern regions of Cameroon (North, Far North and Adamawa). Of these CSFs, 71 were positive, 40 cases from the North region, 25 from the Far North, and 6 from Adamawa. The age of patients suspected of meningitis recorded in this study ranged from 2 days to 77 years with an average of 9.6 years. There is a male predominance in this study, 417/730 (57.12%) male, and 313/730 (42.87%) female (sex ratio 1.3). The distribution of patients by age group and sex is presented in Figure 1, with ages under 15 years predominating.

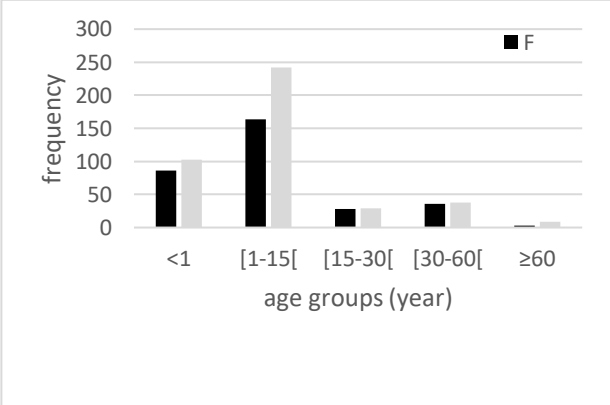

Figure 1: number of patients suspected of meningitis by age and sex

CSF Characteristics and Bacterial Isolation Rate. The macroscopic characteristics of the 742 CSF analyzes showed 67.38% (500) clear, 23.72% (176) turbid, and 8.89% (66) hematic; with respective isolation rates of 2.20%, 33.95% and 3.03%, as summarized in Table I.

Tableau I: Appearance of CSF sample and positive diagnosis

	Total CSF samples (N=742)		Positive diagnostics (N=71)		
Appearance of CSF	**n**	**%**	**n**	**%**	
Clear	500	67.38	11	2.20	
Turbid	176	23.72	58	33.95	9.57
Bloody	66	8.89	2	3.03	

Of the 742 CSFs, 71 revealed a bacterial or fungal agent, the isolation rate was 9.57%. The isolation rate varied by age and gender. Of the 728 patients whose age was recorded, most were under the age of 15, with 401 cases between the ages of 1 and 14 and 189 being under one year old. Isolation rates by age group are summarized in Table 2. By gender, 39 pathogens were isolated from males and 32 from females. Chi-square analysis did not show statistically significant association with age group (p=0.88) and sex (p=0.88) (Table II).

Tableau II: Association of positive diagnosis of meningitis with age group and sex

			Patients with isolated pathogen		Patients without pathogen	
			n	**%**	**n**	
Age groups	<1	9	4,76	180	189	x^2 = 9,575 df=5 p=0,88 NS
	1-14	42	10,47	359	401	
	15-30	9	16,98	44	53	
	31-60	9	12,32	64	73	
	>60	2	16,66	10	12	
	Total	71	9,75	657	728	
Sex	Male	39	9,35	378	417	x^2 = 0,237 df=2 p=0,88 NS
	Female	32	10,22	281	313	
	Total	71	9,72	659	730	

This detection was made by culture (28), latex agglutination test for soluble antigens (64), PCR (11), or Indian ink examination (4) as reported in Table III.

Tableau III: Pathogens identified and testing techniques used

	Agglutination test		Culture		Rt-PCR for *N. meningitis*		Rt-PCR *S. pneumoniae*		Indian ink	
Organisms	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Neisseria meningitidis	18		4		2					
Streptococcus pneumoniae	44		21				9			
Streptococcus agalactiae	1		0							
Salmonella sp	1		3							
Cryptococcus neoformans	0		0						4	

Distribution of isolated microorganisms and prevalence

In this study, 71 pathogens were isolated, including 67 bacteria (94.36%) and 4 fungi (5.63%). Of the 57 bacteria isolated, *S. pneumoniae* is the most predominant with 45 cases (63.38%), followed by *N. meningitidis*, with 18 cases (25.34%), 3 cases of *Salmonella sp* (4.22%) and 1 case of *S. agalactiae* (1.40%). The only isolated fungus was *C. neoformans* with 4 cases. Regarding the isolated meningococci, 17 strains belong to serogroup W and one strain to serogroup A.

The prevalence of pathogens identified in 742 patients shows a clear predominance of *S. pneumoniae* with 6.06%, followed by *N. meningitidis* with 2.43%. *S. agalactiae*, *Salmonella sp*, and *C. neoformans* have respective prevalences of 0.13%, 0.40%, and 0.54% in the patients studied as summarized in Table 4.

Frequency of distribution of pathogens isolated by age group

To study the distribution of bacteria responsible for meningitis according to age, patients were distributed as follows: 1 month, 1 to 11 months, 12 to 59 months, 5 to 14 years, 15 to 29 years, 30 to 59 years and 60 years. The most affected age group is that of 5 to 14 years with 39.4% of isolated pathogens, followed by 12 to 59 months with 19.70% as summarized in Table 4.

Among isolated germs: *S. pneumoniae* globally predominated almost all age groups, with rates ranging from 27 to 100%, except for the 12-to-59-month group which is dominated by *N. meningitidis* at 53%.

Tableau IV: Laboratory confirmed cases of meningitis, etiology, and prevalence of isolated organisms

Type	Etiologic agent	Number of strains (N=71)	%	Prevalence % (N=742)
Bacterial	*Neisseria meningitidis*	18	25.34	2.43
	Serogroup A	01		
	Serogroup W	17		
	Streptococcus pneumoniae	45	63.38	6.06
	Streptococcus agalactiae	1	1.40	0.13
	Salmonella OMA	3	4.22	0.40
Fungal	*Cryptococcus neoformans*	4	5.63	0.54

OMA= one of serogroups A, B, D, E or L of Salmonella

The prevalence of the different germs isolated by age group is summarized in Table V.

Tableau V: Age distribution of bacterial agents causing meningitis by age group in the northern Cameroon regions after MenAfriVac from 2013 to 2015

Bacterial agents	Age of patients							Total
	≤1 m	2-11 m	12 -59 m	5-14 y	15-29 y	30-59 y	≥60 y	
Total CSF	22	167	242	164	57	74	12	738
Turbid CSF	6	31	36	54	19	26	4	176
Bloody CSF	3	19	21	8	6	8	1	66
S. pneumoniae	1	5	4	23	6	4	2	45
	(33%)	(83%)	(27%)	(82%)	(66%)	(44%)	(100%)	(63.4%)
N. meningitidis	1	0	8	5	3	1	0	18
	(33%)		(53%)	(18%)	(33%)	(11%)		(25.4%)
Salmonella sp	0	1	2	0	0	0	0	3
		(16%)	(13%)					(4.2%)
S. agalactiae	1	0	0	0	0	0	0	1
	(33%)							(1.4%)
C. neoformans	0	0	0	0	0	4	0	4
						(44%)		(5.6%)

m = month;
y = year;
CSF=Cerebrospinal Fluid

DISCUSSION

BM is a life-threatening disease. Its etiological profile has to be maintained up to date periodically for better management of cases, as the epidemic pattern varies over time, geographic area, and patient age. It is also necessary for appropriated vaccine measures. This study aimed to provide the profile of bacterial agents of meningitis in northern regions of Cameroon after vaccination with MenAfriVac. This study is the first to provide that information for the northern regions (North, Far North, and Admawa) of Cameroon, which belong to the African meningitis belt, after MenAfriVac.

The overall isolation rate in this study was 9.57% (71/742). Our isolation rate compared to other studies appears closer to that of Britz et al. [19] in South Africa (10.75%) and in Kenya (11.20%)[20], it is lower than that of Massenet's [21] in a previous years (2007-2010) in the same study area (20.4%). A higher isolation rate is observed in Qatar with (53.60%)[22]. Indeed, the isolation is higher in Qatar because patients studied were enrolled in a specialized infectiology service where the definition of cases is more specific. The isolation rate varies notably with study and period. This may be due to differences in characteristics and geographical distribution of the study population, sample size, diagnostic techniques, and differences in infection control policies [23]. In the same vein, the fastidious nature of germs and / or antibiotic intake before presentation for treatment at the hospital or before spinal tap may also explain this variability [24].

This rate seems low for northern regions belonging to the "meningitis belt". A rate of 20.4% was reported in the same study area by Massenet et al. in previous years [21]. This difference can be explained by the techniques used; he implemented PCR for all cases. In our study, we used agglutination test, culture, PCR for confirmation of a few cases, and Indian ink. Rate of isolation is linked to the diagnostic techniques used. There are 66.05% of turbid

CSFs without pathogens isolated. In our study, 469 cases were under antibiotic treatment prior to spinal tap, and 122 turbid samples were among these. There was concordance between the results of the agglutination test performed and the few confirmation PCR tests performed. Pastorex Latex agglutination test is a valuable technic in the diagnostic of BM [25]. The trend in etiological agents identified in our study was in accordance with the epidemiology of meningitis according to WHO [26]. Variation in isolation rate is also known to vary over time and with immunization interventions. This study occurred after the implementation of MenAfriVac (2011-2012) in the northern Cameroon regions where serogroup A of *N. meningitidis* dominated the epidemiology of meningitis. Massenet et al. reported 58.5% cases of serogroup A among meningococcal meningitis cases [7], and Gake et al. in the same vein reported 88.73% (126/142) of serogroup A meningococcal meningitis in 2011-2012 [18]; after this period, the overall number of suspected meningitis cases also decreased gradually.

This study demonstrated not any statistically significant association between meningitis and age group (p=0.88) and sex (0.88). However, we found a male dominance in meningitis patients in our study like some studies [23], [27]. The age group most represented among subjects suspected of meningitis is between 1-14 years old, with 401 cases, and it is also the one with highest number of positive cases (42). This is also found in many studies [8], [28], [20]. This may be due to immunological immaturity for less than 5 years and the fact that people aged between 5 and 15 years have the highest carriage rate in the rhinopharynx of bacterial agents that cause meningitis [29], [30]. They mix with other people in schools, where close contact with each other favors the transmission of respiratory microorganisms throughout saliva and flüdgge droplet [29].

This study showed that *S. pneumoniae* and *N. meningitidis* were the leading causes of meningitis in the northern Cameroon regions after MenAfriVac with up to 88.7% (63/71). *S. pneumoniae* remains an important cause of BM due to its high isolation rate. This is in agreement with many studies both inside and outside of the meningitis belt. Tigabu et al. in Ethiopia [23], Boni-Cissé et al. in Ivory Coast [31], Fonkoua et al. and Chiabi et al. in Yaounde [8], [14], Owusu et al. in Ghana [32], Gituro et al. in Kenya [20] and Khan et al. in community acquired meningitis in Qatar [22]. The high burden of pneumococcal meningitis is seen in all age groups. This may be due to the low coverage of pneumococcal vaccine as reported by Massenet [21] and the natural pathogenicity of this microorganism. We also note that it is a normal inhabitant of the human higher respiratory tract flora [33], [34], easily transmitted during close contact with carriers and capable to resist in environment [35]. The second most prevalent etiological agent was *N. meningitidis* with 18 (25.34%) cases, of which 17 strains belong to serogroup W, and one to serogroup A. The serogroup A of *N. meningitidis* was the leading cause cerebrospinal meningitis in Africa before 2010, accounting for at least 80% of meningitis causes [36]. This organism is among the most prevalent bacterial agents of meningitis in the African meningitis belt that extends from Senegal to Ethiopia including the northern regions of Cameroon [37], [38]. the low rate of serogroup A reported here is in accordance with the tendency in African meningitis belt after the introduction of MenAfriVac vaccination witch drastically decreased the prevalence of serogroup A meningococcus [39]–[43].

The absence of *H. influenzae* in our study was also reported in previous studies in Cameroon, where this organism disappeared 20 months after the introduction of the type b *H. influenzae* vaccine [44], [45]. This may be the consequence of vaccine coverage of *H. Influenzae* type b vaccine was introduced in 2009 and since then remained >80% [13]. However, in other countries, following the introduction of the *H. influenza* type b, cases of *H. influenzae* meningitis, but their rate seems to be increasingly low due to the effect of vaccination, and other serotypes are reported[34],[48],[33].

Among the other germs isolated, *Salmonella sp* isolated in children aged 1 to 59 months, and *S. agalactiae* in a child aged 01 months. These germs have also been reported by other authors [23], [32] [47], cases mainly observed in newborns. The only fungus isolated was *C. neoformans* with 4 isolates (5.63%). It mostly causes meningitis in immunocompromised patients in populations affected by HIV/AIDS [19], [48]. In the present study, HIV status was not investigated.

CONCLUSION

At the end of this study, the aim was to provide a new etiological profile of bacterial agents of meningitis in the northern regions of Cameroon after MenAfriVac. The results showed that *S. pneumoniae* is the most prevalent etiology of meningitis. As the vaccine exists, it is necessary to reinforce vaccination. For meningococci, we find that serogroup W, which was already circulating, is increasingly isolated; hence the need to implement vaccination with multivalent conjugate vaccines including serogroup W. *C. neoformans* has also been isolated and, as it is an opportunistic germ that affects people living with HIV/AIDS, it is necessary to consider isolating it in case of suspicion of meninge syndrome in these patients. *Salmonella sp* and *S. agalactiae* germs have been isolated in babies, hence the need to think about these germs in babies with meningeal syndrome.

Data Availability

Our data may be available upon request.

Conflict of Interest

The authors declare that they have no conflict of interest.

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