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Evolution of the Etiologies of Purulent Meningitis in Children over a Period of 24 Months in Conflict-Affected Rural Areas of the Central African Republic after the Introduction of 2 New Vaccines in the Expanded Vaccination Program

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Abstract

Background and Objective: Purulent meningitis is a therapeutic emergency and remains a real public health problem in the world, particularly in limited resources countries. The study aimed to describe the epidemiological clinical, etiological and scalable features of purulent meningitis in children in Bria. **Methods:** A cross-sectional descriptive study was conducted from January 1, 2018 to December 31, 2019 (24 months). It included all suspected cases of purulent meningitis in children aged 0 to 15 years, confirmed by agglutination with Pastorex meningitis. A standard sheet was used to collect the data which was entered and analyzed on Epi Info 7 software. **Results:** A total of 37 cases of purulent meningitis were confirmed among 90 suspected cases. The female gender predominated (59.5%), with a sex ratio of 0.7. The age group from 0 to 11 months was majority (48.6%). Nearly 2 thirds of children were not vaccinated (64.8%). The most frequent functional signs were fever (83.8%), and convulsion (51.4%). The etiologies were *Streptococcus* (51.4%), *Neisseria*

meningitidis (35.1%) and *Haemophilus influenzae* (13.5%). Therapeutic success under 3rd generation cephalosporin treatment was obtained in 86.5% including 8.1% with sequelae; 13.5% of death was observed. *Streptococcus* was the most lethal bacterium at 21.1%. **Conclusion:** The results of these studies show that pediatric purulent meningitis is still common despite the availability of free vaccination. They require early therapeutic management to limit the occurrence of sequelae and death. Hence, it is important to strengthen prevention strategies.

Keywords

Purulent Meningitis, Children, Epidemiology, Etiologies, Bria, Central African Republic

1. Introduction

Worldwide, the number of new cases of purulent meningitis reaches one million each year, with a mortality rate of 10% [1]. In 2015, the World Health Organization (WHO) estimated the number of deaths from bacterial meningitis, all ages combined, at around 300,000; children are the most affected population [2]. Three pathogens dominate the etiologies of bacterial meningitis in children: *Streptococcus pneumonia*, *Haemophilus influenzae* and *Nesseria meningitidis* [3]. In France, each year out of 600 cases of meningitis is registered; the death rate is 10%. Otherwise, among the children who come out, 50% keep neurological sequelae [4], although the level of care is very high. Despite advances in prevention, the global burden of meningitis remains substantial. Meningitis still remains an infectious pathology for which significant efforts must be made, in order to limit the frequency of its occurrence and its consequences. The pathologies are largely preventable by vaccination witch to hope for a world without meningitis as provided for in the WHO in its global strategy: "overcoming meningitis by 2030" [5]. The epidemiology of bacterial meningitis in children is constantly changing. These changes are the result of several factors. The most important of these factors was the introduction of vaccines against *Haemophilus influenzae* serotype b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* in many countries [6]. On the African continent, particularly in the meningitis belt of Lapeyssonnie in 2018, 20,738 cases of meningitis were declared, particularly in children, and 1498 deaths, *i.e.* a lethality of 7.2%. This means that until now, despite significant advances in the management of these cases, children continue to pay a heavy price in terms of morbidity and mortality in relation to this condition [2]. Many studies have been devoted to bacterial meningitis in children around the world and particularly in Africa, given the importance of the subject. In Morocco in 2012, 1093 cases of meningitis were reported, *i.e.* a cumulative incidence of 3.3/100,000, including 142 deaths, *i.e.* a lethality of 12.9% [7]. In Cameroon, bacterial meningitis in 2001 was due to *Streptococcus pneumonia* (56.2%), *Haemophilus influen-*

zae (18.5%) and *Neisseria meningitidis* (13.4%), mainly affecting children (86.7%), with a higher proportion in children aged 6 to 15 years and in young people aged 16 to 25 years [8] [9].

In the Central African Republic, the bacteria responsible for meningitis in 2005 were mainly *Streptococcus pneumoniae* (48%), *Haemophilus influenzae* (35%), *Nesseria meningitidis* (6%) [10]. The same etiologies were found with the same proportions in adults [11]. After the introduction of anti-haemophilus vaccines in 2008 and anti-pneumococcal vaccines in 2011 in the routine Expanded Program of Immunisation (EPI) in CAR, a rural study in patients of all ages demonstrated in 2016 that *Streptococcus pneumoniae* was the majority etiology (51.8%), followed by *Neisseria meningitidis* (14.2%), *Haemophilus influenzae* (7.3%) [12]. These data from a study conducted in a single rural locality on all ages, do not reflect the reality of the CAR and even less those of children. Hence there is the need to conduct other studies in other localities, especially in children. It is in this context that we carried out this work, the aim of which was to describe the epidemiological, clinical, etiological and scalable features of purulent meningitis in children aged 0 to 15 tears at the Regional University Hospital (RUH) of Bria.

2. Methods

This was a descriptive cross-sectional study conducted over a period of 2 years from January 1, 2018 to December 31, 2019 at the RUH of Bria. The RUH of Bria is the reference hospital for the 5th Health Region (HR5) of the CAR. HR5 is the largest of all the 7 health regions, crossed in its upper part bordering Chad and Sudan by the meningitis belt of Lapeyssonnie. The climate is sub-equatorial with a dry season a little longer than the rainy season. Since 2012, despite the restoration of security in Bangui and other regions, HR5 has been an area of almost permanent insecurity. In this context, the HRU of Bria was supported by 2 Non-Governmental Organizations: Doctors without Borders (DWB France) and International Medical Corps (IMC). The support of these 2 partners specifically for the medical analysis laboratory has enabled the provision of laboratory inputs used for this study. The study population consisted of all the children received and hospitalized in the pediatric department of the RUH of Bria. Were included in the study all children from 0 to 15 years old, hospitalized at the RUH of Bria for suspicion of bacterial meningitis. Children whose meningitis diagnosis was not bacteriologically confirmed are finally excluded from the study. The sample size was set at 25 according to the Schwartz formula [13] and inclusion was systematic, subject to the informed consent of the child's parents.

In children, the diagnosis of meningitis is clinico-biological and meets the standard case epidemiological definition of bacterial meningitis according to the WHO [14] [15] from which the case definitions below are taken:

Presumed case: anyone presenting with a sudden fever (rectal temperature > 38.5˚C or axillary temperature 38.0˚C) and stiff neck or other meningeal sign

such as bulging fontanel in infants.

Probable case: any presumed case whose cerebrospinal fluid (CSF) appears cloudy or purulent on macroscopic examination; or in whom the white blood cell count is greater than 10 cells/mm^3; or in which bacteria were observed after Gram staining in the CSF.

Confirmed case: any suspected or probable case confirmed by culture or identification by polymerase chain reaction (PCR) amplification, agglutination test or immunochromatographic strip of *Nesseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* b in the CSF or in the blood.

After obtaining consent and confirming the definition of meningitis, data were collected using a standardized survey form that provided informations on epidemiological, clinical and bacteriological variables. Bacteriological confirmation was based on the detection, using an agglutination reaction of sensitized Latex particles, of soluble antigens of meningitis etiologies by Pastorex Meningitis (Bio-rad, Marnes-La-Coquette, France) [15]. The data was entered and then analyzed with Epi-Info version 7 software. The study was carried out in strict confidentiality with parental consent.

3. Results

During the study period, we identified a total of 90 suspected cases of meningitis out of 5795 hospitalizations, which represented a prevalence of 1.5% of admissions. All 90 CSFs were turbid, but the bacterial etiology was confirmed on 37 samples, *i.e.* a prevalence of 41.1%; the number of probable cases is 53 or 58.9%. The 37 confirmed cases consisted of 15 boys (40.5%), 22 girls (59.5%) with an M/F sex ratio of 0.7. The age group from 0 to 11 months (<1 month = 7, and 1 - 11 months = 11) was the most represented with 48.6%. The extremes ages were 1 day to 14 years. The vaccination status showed that 64.8% of the children were not vaccinated, particularly against Hib and *S. pneumoniae* (**Table 1**).

Purulent meningitis rages throughout the year with a peak observed in April 2018, May and November 2019. The first two peaks had the same amplitude of 10.8%; the last with the highest amplitude with a prevalence of 13.5% (**Figure 1**). The most common functional signs were fever (83.8%), followed by convulsion (51.4%). In infants, incessant crying was observed (24.3%), followed by refusal to suckle (13.5%).

From a physical point of view, neck stiffness was observed in almost half of the children (48.6%) followed by Kernig's and Brudzinski's signs as well as prostration with each having a frequency of 27.1% (**Table 2**).

Bacteria of the streptococcus genus dominated the etiologies with 51.4% including *Strpetococcus agalactiae* 27.0% and *Stresteptococcus pneumoniae* 24.3%. *Neisseria meningitidis* was the second etiology with 35.1% distributed as follows between the main serogroups: Serogroup Y/W135 (24.3%), serogroups A and C each had 5.7%. Bacteria belonging to the *Haemophilus influenzae* b species were the 3rd etiology with 13.5%.

Table 1. Epidemiological characteristics of confirmed cases of bacterial meningitis.

Characteristics	Number	Frequency (%)
Gender		
Female	22	59.5
Male	15	40.5
Total	37	100.0
Age group		
<1 month	7	18.9
1 - 11 months	11	29.7
12 - 23 months	3	8.1
24 - 35 months	2	5.4
3 - 5 years	3	8.1
6 - 15 years	11	29.7
Total	37	100.0
Vaccination status		
vaccinated	13	35.2
Not vaccinated	24	64.8
Total	37	100.0

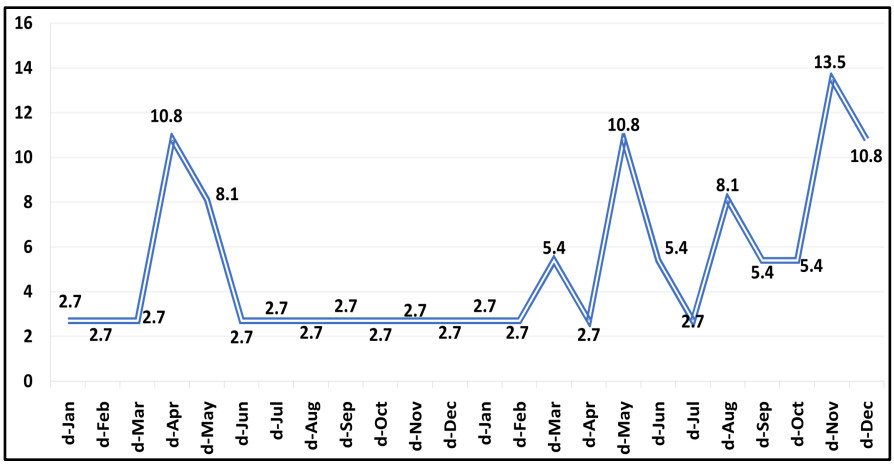

Figure 1. Evolution of the frequency of purulent meningitis over time.

All the children were treated with a 3rd generation cephalosporin, Ceftriaxone 81.1% and Cefotaxime associated with ampicillin 18.9%. The average duration of hospitalization of patients was 8.9 days with extremes ranging from 1 to 15 days. The therapeutic success rate was 78.4% without sequelae and 8.1% with sequelae in children aged 6 to 15 years. Five (5) deaths or 13.5% were recorded; most of these deaths were observed in children aged 6 to 15 (60%). Streptococcus was the most lethal bacterial group at 21.1% (Table 3).

Table 2. Clinical and etiological characteristics of meningitis cases.

Functional signs	Number (N = 37)	Frequency (%)
Fever	31	83.8
Convulsion	19	51.4
Vomiting	9	24.3
Incessant crying	9	24.3
Hustle	8	21.6
Headaches	6	16.2
Refusal to breastfeed	5	13.5
Diarrhea	2	5.4
Asthenia	2	5.4
neck pain	1	2.7
Physical signs	Number (N = 37)	Frequency (%)
Neck stiffness	18	48.6
Brudzinski + Kernig sign	10	27.1
Prostration	10	27.1
Bulging fontanel	7	18.9
Capped manhole	6	16.2
Focusing signs	5	13.5
Irritability	3	8.1
Hypotonia	1	2.7
Purpura	1	2.7
Drowsiness	1	2.7
Etiologies	Number (N = 37)	Frequency (%)
Haemophilus influenzae b	5	13.5
Neisseria meningitidis	13	35.1
Streptococcus	19	51.4
Total	37	100.0

Table 3. Distribution of 37 patients according to evolution and age group.

Age group	Recovered with sequelae	Recovered without sequelae	Deaths	Total
	Number (%)	Number (%)	Number (%)	Number (%)
<1 month	0	7 (18.9)	0	7 (18.9)
1 - 11 months	0	10 (27.0)	1 (9.1)	11 (29.7)
12 - 23 months	0	3 (8.1)	0	3 (8.1)
24 - 35 months	0	2 (5.4)	0	2 (5.4)
3 - 5 years	0	2 (5.4)	1 (2.7)	3 (8.1)
6 - 15 years	3 (8.1)	5 (13.5)	3 (8.1)	11 (29.7)
Total	3 (8.1)	29 (78.4)	5 (13.5)	37 (100.0)

4. Discussion

To describe the epidemiological clinical and etiological characteristics of purulent meningitis in children aged 0 to 15 years at the Regional University Hospital (HRU) of Bria, we conducted a cross-sectional study over a period of 2 years. The prevalence of purulent meningitis was 1.5%. Girls were more numerous (59.5%) with a sex ratio of 0.7. Almost half (48.6%) of the children were under 11 months old. Nearly 2 thirds (64.8%) were not vaccinated against *S. pneumoniae* and Hib. The evolution of the prevalence of meningitis over time showed 3 peaks in April 2018, May and December 2019. Fever (83.8%), followed by convulsion (51.4%) were the main complaints in all children followed by incessant crying (24.3%) and refusal to breastfeed (13.5%) in infants. Meningeal stiffness, prostration and Kernig's and Brudzinski's signs were the most noted physical signs with respective prevalences of 48.6% and 10%. After treatment mainly with 3rd generation cephalosporins, the cure rate was 86.5% including 8.1% with sequelae. The overall lethality was 13.5%, observed especially with *S. pneumoniae*.

Despite the introduction of vaccination against *S. pneumoniae* and Hib, purulent meningitis continues to be rampant in our country as in the others in the meningitis belt zone. The studies already carried out on the subject in the CAR did not concern the meningitis belt zone and even less did not include only children, the target population of the EPI [10] [12]. Our study is characterized by the fact that it took place in the meningitis belt area and included only children.

It made it possible to obtain a prevalence of purulent meningitis of 1.5%. This rate is higher than those of Maiga [16] in Mali (1.07%), Assande [17] in Cocody (Abidjan) in Ivory Cost (1.18%). On the other hand Bercion [10] in Bangui and Camara [18] in Dakar had found frequencies of 3.5% and 4.9% respectively. The military-political unrest that causes the displacement of populations and the distance between the villages of residence of the children and the health establishment could explain the low frequency obtained in our study. Dakar and Bangui are capitals with easy transport arrangements. These cases of meningitis occurred more frequently in newborns and infants aged 0 to 11 months. These accounted for 48.6% of meningitis cases. These results are similar to those of Daos [19] in Mali and Assande [17] in Ivory Cost who found frequencies of 47.7% and 52.3% respectively. However Barry [20] in Conakry (Guinea) found a frequency of 73.0%. The predominance of this condition in infants could be explained by an immaturity of the immune system, the susceptibility of children to respiratory infections, the respiratory tract being the gateway or even the habitat of non-pathogenic or potentially pathogenic strains of bacteria responsible for meningitis. In addition to newborns and infants under one year old, the female sex seems to be more affected in our study. Girls were predominant with a frequency of 59.5% against 40.5% for boys; the sex ratio (boys/girls) was 0.7. Our results were close to Mushagalusa [9] in the Democratic Republic of Congo and Dagnra [21] in Togo who found a sex ratio of 0.9. On the other hand, Tekpa [12] in the Cen-

tral African Republic, Maiga [16] in Mali and Camara [18] in Dakar had a male predominance in their studies with a sex ratio ranging from 1.2 to 1.5. This age and sex relative susceptibility to meningitis can be reduced or even eliminated by vaccination.

However, in our series, 64.6% of children are not vaccinated. This prevalence is higher than those of Coulibaly [22] in Mali (42.2%) and Barry [20] in Guinea (46.9%). The low rate of vaccination coverage frequently recorded in the country could be explained by the fact that our study took place in a rural environment, in a conflict zone where a large proportion of health infrastructure was vandalized and looted during the military and political crisis in the country beginning in 2013. In addition to the looting of health facilities, there is the displacement of the population linked to attacks by armed groups and above all the belief in traditional treatments, a factor which constitutes an obstacle to the acceptance of medical care within the community. All these factors influence the frequency of meningitis in our country. Thus, in unvaccinated children could frequently observe purulent meningitis recognized by the clinical signs of which fever is at the forefront.

Fever was the most constant sign at all ages; it is found in 83.8% of our patients, followed by convulsion (51.4%). Other signs such as incessant crying (24.3%), the bulging of the fontanel (18.9%), the capped gaze (16.2%) and the refusal to suckle (13.5%), in newborns and infants are important signs strongly suspecting meningitis. As for the meningeal syndrome, it became frank with age, thus making the diagnosis easy, as has been pointed out by several authors [7] [12] [20] [23] and must therefore require a lumbar puncture for laboratory investigation.

Bacteriologically, the diagnosis of purulent meningitis is generally easy to establish. However, the isolation and identification of the responsible bacteria sometimes pose a problem because of the weakness of the technical platform, unfavorable conditions, especially aggravated by military political conflicts that our country has known. All these factors did not allow us to carry out all the conventional bacteriological tests (fresh state, Gram stain, count of the blood elements, culture, identification of the bacteria and antibiogram) necessary for the diagnosis of meningitis. The exception is made in this context to the search for soluble antigens by agglutination with sensitized latex particles, which constitutes the only diagnostic test carried out in this present study. With agglutination to latex particles, 3 pathogens dominated the etiologies of purulent meningitis in our study: Streptococcus including *Streptococcus pneumoniae* and other species (51.4%), *N. meninigitis* (35.1%) and Hib (13.5%). The frequency of each etiology differs from one country to another, and depending on whether we are in an epidemic period or not. Our study took place in a rural environment in a conflict zone, outside the epidemic context where there was a lack of vaccination coverage within the framework of the EPI. This could explain the preponderance of *S. pneumoniae* compared to other bacteria [22]. Bercion in Bangui in CAR [10], Tekpa in Paoua in CAR [12], Ouédraogo in Burkina Faso [24], Daos [19]

and Maiga [16] in Mali, Assande [17] in Cocody, Ivory Coast, Fonkoua [8] in Cameroon, found in their studies in first position *S. pneumoniae* which corresponded to our results. However, Hib came second in their studies in some of these authors [8] [10] [16] [17] [19] against *N. meningitidis* in our series. Before the introduction of antihaemophilus vaccine in the EPI in CAR, Hib was the second causative agent of purulent meningitis in children. The introduction of anti-Hib vaccination in the EPI in 2008 against this bacterium has modified the bacterial epidemiology of purulent meningitis. In our study, over a period of 2 years, including the dry season corresponding to the epidemic period of meningitis due to *N. meninigitis*, there was a decrease in the number of cases of Hib (13.5%) occupied the 3rd place after *S. pneumoniae* (51.4%) and *N. meninigitis* (35.1%). The study carried out in Bangui by Bercion in 2004 at the Pediatric Complex of Bangui, before the introduction of the anti-Hib vaccine, showed that Hib (35%) came in 2nd position of etiologies [10]. These frequency variations influenced by vaccination suggest that with high vaccination coverage, the proportion of meningitis and bacteria targeted by these vaccines would decrease considerably. Vaccination, which modifies the bacterial epidemiology of meningitis, also modifies its lethality.

During our study we observed an overall lethality of 13.5%. Most of these deaths were observed in children aged 6 to 15 (60%). According to some studies, mortality during purulent meningitis under treatment can be up to 20% [25]. Our results are close to those of Mushagalusa 13% in the DRC [9], Thabet 13.7% in Tunisia [26]. However, in a study focusing on pneumococcal meningitis and carried out by Tekpa in Paoua in CAR, the lethality was 14.7% for all ages combined [12]. On the other hand Amrani and Merabet [7] [27] in Morocco found in their studies in children under 5 years of age a lethality of 11.8% and 19.2% respectively. At the Bangui Pediatric Complex, Bercion [10] found a lethality of 35% in 2008. Our results and those of Tekpa [12] are similar in that during this period our health facilities (RUH of Bria and District Hospital of Paoua) are supported by the same partner with the same protocol of treatment, which has improved the management of these serious diseases. This good care has reduced the frequency of sequelae which was 8.1% and a recovery rate without sequelae of 78.4% of cases. According to some authors, the sequelae can go up to 20% - 30% [25]. Our results are close to those of Tekpa [12] who found 12.0% a frequency of sequelae but differ from those of Thabet and Mushagalusa who found 21.7% and 34.5% respectively [9] [26].

5. Conclusion

The results of this study show that pediatric acute purulent meningitis whose etiologies were dominated by *S. pneumoniae*, remains to this day a worrying problem in the CAR where the lack of means and insufficient vaccination coverage induce sequelae and/or mortality. This study suggests the need to strengthen the preventive measures especially the increase in vaccination coverage. The development of appropriate technical platforms and the overall improve-

ment of sanitary conditions must remain a priority for resources limited countries.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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