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RESEARCH NOTE

REVISED **Seasonal upsurge of pneumococcal meningitis in the Central African Republic** [version 2; peer review: 3 approved]

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Abstract

A high incidence of bacterial meningitis was observed in the Central African Republic (CAR) from December 2015 to May 2017 in three hospitals in the northwest of the country that are within the African meningitis belt. The majority of cases were caused by *Streptococcus pneumoniae* (249/328; 75.9%), which occurred disproportionately during the dry season (November-April) with a high case-fatality ratio of 41.6% (95% confidence interval [CI] 33.0, 50.8%). High rates of bacterial meningitis during the dry season in the meningitis belt have typically been caused by *Neisseria meningitidis* (meningococcal meningitis), and our observations suggest that the risk of contracting *S. pneumoniae* (pneumococcal) meningitis is increased by the same environmental factors. Cases of meningococcal meningitis (67/328; 20.4%) observed over the same period were predominantly group W and had a lower case fatality rate of 9.6% (95% CI 3.6, 21.8%). Due to conflict and difficulties in accessing medical facilities, it is likely that the reported cases represented only a small proportion of the overall burden. Nationwide vaccination campaigns in the CAR against meningitis have been limited to the use of MenAfriVac, which targets only meningococcal meningitis group A. We therefore highlight the need for expanded vaccine coverage to prevent additional causes of seasonal outbreaks.

Keywords

Central African Republic, pneumococcal meningitis, Streptococcus pneumoniae, Neisseria meningitidis, meningococcal meningitis, African meningitis belt

This article is included in the Mahidol Oxford Tropical Medicine Research Unit (MORU) gateway.

Open Peer Review

Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
	1	**2**	**3**
REVISED **version 2** published 29 Mar 2019	✓ report	✓ report	✓ report
	↑	↑	↑
version 1 published 19 Oct 2018	? report	? report	? report

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Crellen T: Conceptualization, Data Curation, Formal Analysis, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Rao VB**: Investigation, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Piening T**: Resources, Supervision, Writing – Review & Editing; **Zeydner J**: Resources, Supervision; **Siddiqui MR**: Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Crellen T, Rao VB, Piening T *et al.* **Seasonal upsurge of pneumococcal meningitis in the Central African Republic [version 2; peer review: 3 approved]** Wellcome Open Research 2019, **3**:134 (https://doi.org/10.12688/wellcomeopenres.14868.2)

First published: 19 Oct 2018, **3**:134 (https://doi.org/10.12688/wellcomeopenres.14868.1)

Introduction

The northern districts of the Central African Republic (CAR) form part of the meningitis belt, a broad swathe of sub-Saharan Africa where the incidence of bacterial meningitis typically peaks during the dry season[1]. The mechanism for the increase in cases of bacterial meningitis has been postulated to be a result of damage to host mucosal defenses by the extreme environmental conditions of the dry season in this region, resulting in an increased rate of conversion from asymptomatic carriage to invasive disease[2]. The CAR is among the world's least developed nations and large areas of the country remain unstable following conflict between ethnic groups in 2013 and 2014. Consequently reliable medical data is scarce.

While outbreaks in the meningitis belt, including the CAR, have historically been caused by meningococcus group A[3,4], national vaccination campaigns with MenAfriVac, which targets exclusively this group, has resulted in a shift in the epidemiology of bacterial meningitis. A surveillance study in ten African countries found that since MenAfriVac was introduced in certain countries in 2010, the proportion of confirmed cases due to meningococcus group A dropped substantially, while the proportion attributable to meningococcus group W and pneumococcus increased over the same period[5]. The CAR began nationwide vaccination with MenAfriVac in 2016, though coverage levels have not been assessed.

Here we report on findings from routinely collected data on meningitis patients in health facilities supported by the medical organisation Médecins Sans Frontières (MSF) in Bossangoa, Ouham Prefecture from 1st December 2015 to 31st May 2017, along with additional data from MSF supported hospitals in Batangafo, Ouham Prefecture and Paoua, Ouham-Pendé Prefecture within the same period. These towns are all located in the northwest of CAR close to the Chadian border and are separated by linear distances of 130–200km (see map, Figure 1).

Methods

Patients

Data were collected prospectively from three reporting hospitals (shown in Figure 1) from December 2015 to May 2017 as part of routine communicable disease surveillance. Our confirmed case criteria and clinical management of patients followed the guidelines from the World Health Organization[6]. Our analysis included all confirmed cases with bacterial meningitis in the three hospitals over the observed periods. Data on suspected and negative cases were collected in Paoua using established definitions[5]. Patient outcomes were recorded in Bossangoa and Batangafo along with socio-demographic characteristics (age, sex, residence) in all regions. Patient outcomes and incidence rates have previously been reported from Paoua Hospital over a subset of our observation period[7].

Figure 1. Map showing the location of the three reporting hospitals in the Central African Republic: Bossangoa, Batangafo and Paoua in relation to one another and to the capital Bangui. The country is shown divided by prefecture (highest administrative level), Bossangoa and Batangafo are located in Ouham prefecture and Paoua is located in Ouham-Pendé prefecture.

Laboratory Testing

Bacterial meningitis cases were confirmed by a latex agglutination test (Pastorex, Bio-Rad; cat. No. 61607) on cerebrospinal fluid (CSF), following the guidelines of the CAR Ministry of Health (MoH). The causative agent was confirmed by PCR of CSF samples at the Pasteur Institute in Bangui for around 5% of patients. PCR conditions were identical to those given by Corless *et al.*[8].

Statistical analysis

Patient data were recorded using Microsoft Excel and statistical analysis was performed in R (version 3.5.1). Logistic regression and a chi-squared test for counts were performed. Statistical significance was defined as $p<0.05$ or non-overlapping 95% confidence intervals.

Ethical Statement

Médecins Sans Frontières (MSF) is able to operate in countries such as the Central African Republic only with the support of national and local authorities and through continued dialogue with the beneficiary communities.

The high incidence of meningitis cases during this period was known to the communities and MSF gave health advice and provided medical services during the outbreak. Communities in the CAR were made aware that MSF collects data as part of its medical operations, including for research purposes. This research fulfilled the exemption criteria set by the MSF Ethical Review Board (ERB) for *a posteriori* analyses of routinely collected clinical data and thus did not require MSF ERB review. Data collected from patients was anonymized, though patient consent was not sought retrospectively. This study was conducted with permission from the Medical Director Sidney Wong (MSF-Operational Centre Amsterdam).

Results

Overview of cases

In Bossangoa Hospital, 139 cases of confirmed bacterial meningitis were reported over 18 months (Dec 2015 – end May 2017). The median case age was 16 years (Interquartile range [IQR] 7, 32) and 52.2% of patients were male. The majority of confirmed cases were caused by *Streptococcus pneumoniae* (pneumococcal meningitis); 114/139 (82.0%), rather by than *Neisseria meningitidis* (meningococcal meningitis) and this was also observed in the majority of confirmed meningitis cases in Paoua Hospital over 17 months (93/106, 87.7%) and Batangafo Hospital over 12 months (42/83, 50.6%), see Table 1 and Figure 2 for cases of pneumococcal meningitis by reporting Hospital. Across all sites, the majority of confirmed cases of bacterial meningitis were caused by *S. pneumoniae* (249/328; 75.9%) followed by *N. meningitidis* (67/328; 20.4%) and *Haemophilus influenzae* (12/328; 3.7%); see Figure 3 for cases by causative agent over time.

There were 42 suspected cases of bacterial meningitis in Paoua Hospital over 17 months and 409 individuals that tested negative. The proportion of suspected cases relative to the total number of suspected, negative and confirmed cases (42/557; 7.5%) is low compared to other outbreaks of pneumococcal meningitis[9], suggesting that the majority of patients arriving with a clinical suspicion of bacterial meningitis were laboratory tested. The proportion of patients testing positive from latex agglutination test of cerebrospinal fluid (106/515; 20.6%) is comparable to a contemporaneous outbreak of pneumococcal meningitis in Ghana (23.8%)[9].

The temporal distribution of cases over the observed period was non-random, with the majority occurring in the dry season of November-April. Of all cases of bacterial meningitis, 175/221

Table 1. Summary of the patients diagnosed as positive for bacterial meningitis from three hospitals in the northwest Central African Republic. The number of patients with reported sex and case fatality ratios may be lower than the total numbers due to missing data. IQR, interquartile range; CFR, case fatality ratios; CI, confidence interval; pneumococcal, pneumococcal meningitis; meningococcal, meningococcal meningitis.

|	Bossangoa Hospital	Batangafo Hospital	Paoua Hospital	Total
Prefecture	Ouham	Ouham	Ouham-Pendé	
Reporting Period	Dec 2015 - May 2017 (18 months)	Dec 2015 - Dec 2016 (12 months)	Jan 2016 - May 2017 (17 months)	
Total Confirmed Cases (Confirmed Pneumococcal Cases)	139 (114; 82.0%)	83 (42; 50.6%)	106 (93; 87.7%)	328 (249; 75.9%)
Median Age of Confirmed Cases (IQR)	16 years (7, 32)	10 years (5, 20)	7 years (1, 13)	11 years (4, 25)
Male Confirmed Cases (%)	72/138 (52.2%)	46/83 (55.4%)	57/105 (54.3%)	175/326 (53.7%)
Pneumococcal CFR (95% CI)	41/88 (46.6%) (36.0, 57.5%)	11/37 (29.7%) (16.4, 47.2%)	Data Unavailable	52/125 (41.6%) (33.0, 50.8%)
Meningococcal CFR (95% CI)	1/15 (6.7%) (0.3, 40.0%)	4/37 (10.8%) (3.5, 40.0%)	Data Unavailable	5/52 (9.6%) (3.6, 21.8%)
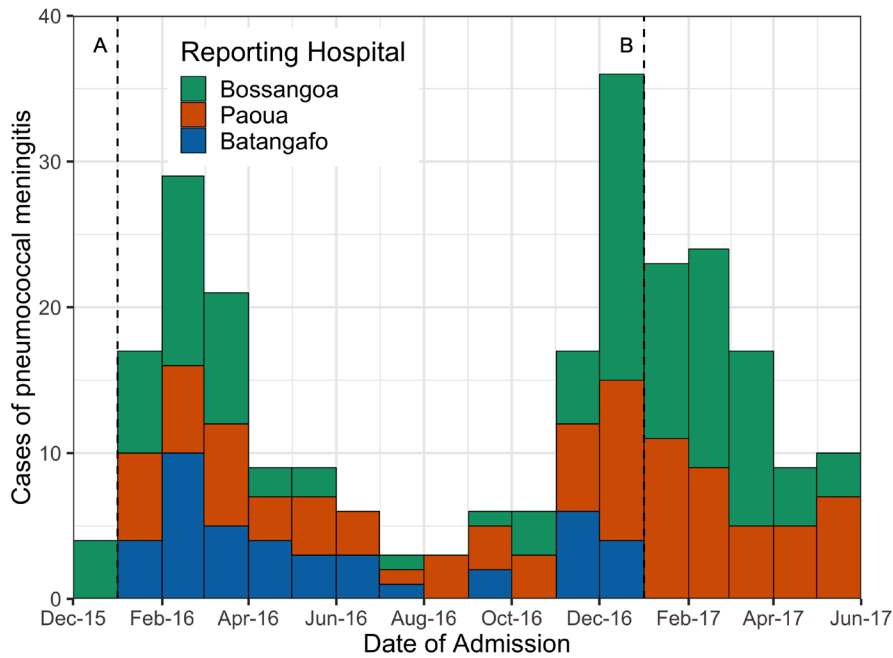
Figure 2. Cases of confirmed pneumococcal meningitis from three hospitals in the Central African Republic from 1st December 2015 to 31st May 2017. The plot shows a histogram where cases are collected into bins of one month. Cases are more numerous during the dry season (November to April), suggesting a seasonal trend. The dashed line A denotes the start of the reporting period for the health facilities in Batangafo and Paoua and B denotes the end of the reporting period for Batangafo. Bins are coloured by hospital.
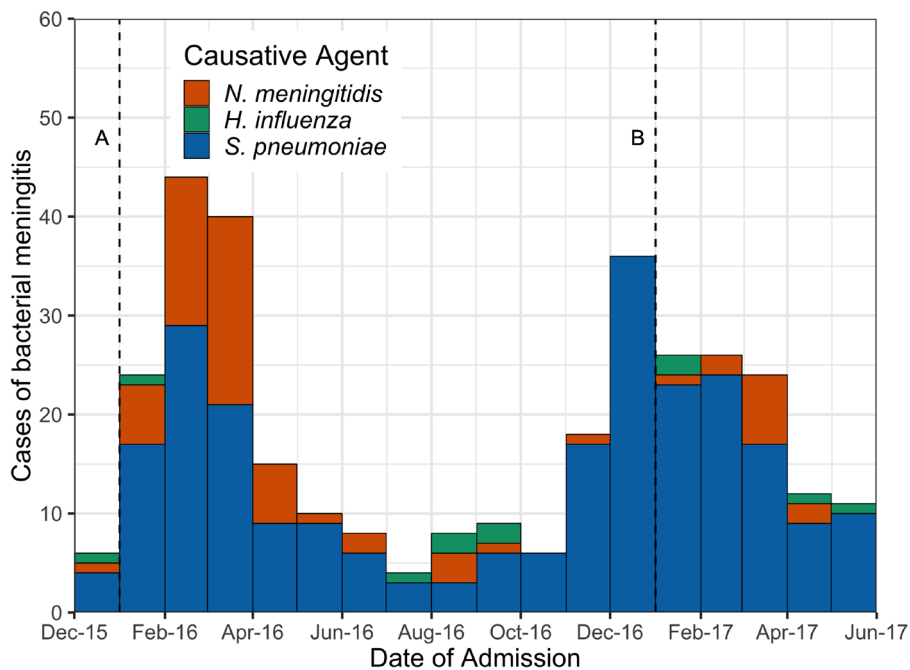

Figure 3. Cases of confirmed bacterial meningitis from three hospitals in the Central African Republic from 1st December 2015 to 31st May 2017. The plot shows a histogram where cases are collected into bins of one month. Cases are more numerous during the dry season (November to April), suggesting a seasonal trend. The dashed line A denotes the start of the reporting period for the health facilities in Batangafo and Paoua and B denotes the end of the reporting period for Batangafo. Bins are coloured by causative agent (*Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae*).

(79.2%) were in the dry season months in 2016, and 128/161 (79.5%) of pneumococcal meningitis cases (Figure 2 and Figure 3). A chi-squared (χ^2) test for count data showed the difference between the number of cases in dry and wet season months to differ significantly for all cases of bacterial meningitis by any causative agent ($\chi^2 = 75$, $p = 2.2 \times 10^{-16}$, degrees of freedom [df] = 1), and for cases of pneumococcal meningitis ($\chi^2 = 56$, $p = 7.0 \times 10^{-14}$, $df = 1$). Species confirmation by PCR was consistent with the latex agglutination test for the subset of confirmed cases. Six isolates of *S. pneumoniae* from Paoua Hospital were confirmed by PCR as serotype 1, however the majority of isolates were not serotyped.

Patient outcomes

Medical staff in MSF-supported facilities reported that patients typically presented with advanced symptoms (Glasgow Coma Scale 1-4) and that they had often sought the advice of traditional healers beforehand, though data on clinical symptoms and previous treatment at admission were not systematically recorded. Patient outcomes were recorded in Bossangoa and Batangafo (Table 1); case fatality ratio (CFR) estimates were high for patients with *S. pneumoniae* in Bossangoa, 46.6% (95% confidence interval [CI] 36.0%, 57.5%) and Batangafo, 29.7% (95% CI 16.4%, 47.2%), though these values are within the range of CFR estimates for pneumococcal meningitis from other African countries in the meningitis belt (36-66%)[10]. In Bossangoa and Batangafo the median age of pneumococcal meningitis patients was 6 years (IQR 6, 27) and 53.8% were male. In a logistic regression model where the outcome variable was death or survival, children (<16 years) admitted with pneumococcal meningitis were found to have a lower CFR (24.6% [95% CI 12.7%, 39.7%], odds ratio [OR] = 0.33, $p = 0.0035$) compared to adults, (CFR 49.2% [95% CI 33.9%, 64.6%]). A higher CFR was also found in adults with pneumococcal meningitis in Burkina Faso from 2002–05[11], though age did not predict mortality in Northern Nigeria from 1971–76[12]. This may reflect statistical control for clinical severity in 8, and the variation in mortality we observe may be confounded by differences in healthcare-seeking behaviour between children and adults, whereby adults present later to healthcare facilities when their symptoms are more advanced[13]. The effect of sex on the odds of mortality was not significant (OR for males = 1.39, $p = 0.39$).

Incidence rates

The World Health Organization lacks a formal definition for outbreaks of pneumococcal meningitis[14]; however, the 'alert threshold' is defined by the CAR MoH as 3 cases per 100,000 per week and 'epidemic threshold' as 10 cases per 100,000 per week. Bossangoa reported 11 cases of pneumococcal meningitis in the 9th epidemiological week of 2017; given an estimated target population of 350,000 this meets the alert threshold (3.1 cases per 100,000 per week; population estimate based on 2003 census).

Meningococcal meningitis

Amongst the cases of meningococcal meningitis (67, 19.5% of total confirmed cases) the CFR estimates were significantly lower in both Bossangoa, 6.67% (95% CI 0.3, 40.0%) and Batangafo, 10.8% (95% CI 3.5, 40.0%) than those reported for pneumococcal meningitis (see Table 1). The median age of patients with meningococcal meningitis was 7 years (IQR 3, 19) and 56.1% of patients were male. Nearly all cases were group Y/ W (96.9%) with the latex agglutination test, and a subset of these were confirmed as group W by PCR at the Institute Pasteur in Bangui. This is most likely to be the strain of *N. meningitidis* as W is known to be present in Africa whereas strain Y is confined to North America[15]. Recent work has shown that between 2015 and 2016 100% (66/66) of meningococcal samples isolated from patients nationwide in the CAR were of group W and that the majority of subtyped isolates belonged to the ST11 complex[16].

Vaccination campaigns

A recent nationwide vaccination campaign by the CAR MoH commencing in 2016 used MenAfriVac, which is only active against meningococcal meningitis group A. While group W is considered less infectious than group A, outbreaks with W have been reported from the meningitis belt, for instance in Burkina Faso in 2002[17]. Vaccinations against pneumococcal meningitis have been given routinely to infants in MSF supported health facilities since 2012, and in addition MSF conducted a multi-antigen vaccination catch up campaign in the Paoua sub-prefecture for children less than 5 years from 2015 to mid-2016. This included two rounds of vaccination with pneumococcal conjugate vaccine (PCV13), which is effective against thirteen serotypes of *S. pneumoniae*. In the first round 70% of the population were targeted with 95% coverage. Separate attempts have been made to improve vaccine coverage in Mambéré-Kadéï prefecture in western CAR following disruption due to acute conflict[18]. However, the coverage of PCV13 nationwide is unknown.

Discussion and conclusion

In this study we have observed high rates of meningitis in the northern regions of the CAR from December 2015 to May 2017, predominantly caused by pneumococcus and occurring disproportionately in the dry season. A heightened incidence of bacterial meningitis during the dry season in the African meningitis belt has historically been associated with *Neisseria meningitidis*, though occasional seasonal outbreaks of *S. pneumoniae* have previously been observed[11,19].

During our observation period from December 2015 to April 2016 a large outbreak of predominantly serotype 1 pneumococcal meningitis occurred in the Brong-Ahafo region of Ghana (886 suspected cases). The epidemiological features of this contemporaneous outbreak, including the age distribution of cases, the case fatality ratio, the proportion of aetiological agents, and the ratio of negative to positive cases, were broadly comparable to the setting we observed[9]. Notably, this outbreak occurred despite a recent nationwide PCV13 vaccination campaign.

A subset of six pneumococcal samples were all classified as serotype 1 by PCR. While this number is small relative to the total number of samples, it confirms a previous result from the CAR which found that serotype 1 was the predominant *S. pneumoniae* serotype (44% of typed CSF samples) in a Bangui hospital from 2004-5[20]. Serotype 1 is among the serotypes targeted by

PCV10 and PCV13. Establishing the serotype of pneumococcal meningitis during an outbreak is crucial for establishing an appropriate control strategy, such as reactive vaccination[21,22].

Reliable estimates of the underlying population in the CAR are lacking which makes it challenging to calculate per-capita incidence rates. It has been estimated that one-fifth of the population of the CAR has been displaced internally or in neighbouring countries following civil conflict in 2014[23]. Therefore our estimates of the per-capita incidence should be treated cautiously as they likely underestimate the true rate. Improved reporting of suspected cases from Batangafo and Bossangoa would enhance epidemiological surveillance, as a threshold of 10 suspected cases per 100,000 per week has been suggested as an appropriate "epidemic threshold" and outbreak definitions using suspected cases is also employed for meningococcal meningitis[5,22].

Further uncertainty surrounds the proportion of true cases that report to our medical facilities given the ongoing instability and the difficulties faced by patients from remote rural areas in accessing care. In February 2016 MSF medical staff made an exploratory visit to the community of Kouki in Ouham Prefecture (population 600) as a response to a rise in pneumococcal cases in Bossangoa Hospital. Community health workers reported 17 deaths with symptoms suggestive of bacterial meningitis over the previous 2 months. None of these fatal cases had reported to a healthcare facility, raising the possibility that the cases we observed represent only the 'tip of the iceberg' during the seasonal peak. Given the relatively low attack rate of *S. pneumoniae*, whereby bacteria in carriage become invasive and cause disease, it is likely that there is high underlying prevalence of *S. pneumoniae* carriage in the community[24].

In conclusion it appears that the northern region of the Central African Republic experienced an outbreak of pneumococcal meningitis, most likely serotype 1, over the observed period, with a similar seasonal pattern to meningococcal meningitis. A comprehensive follow-up of cases in the community was not possible due to security constraints. Despite a MenAfriVac campaign conducted in 2017 meningococcal meningitis is still present although with predominantly non-A groups circulating, namely W. Our analysis is limited by incomplete PCR confirmation and serotyping for *S. pneumoniae*, however our findings suggest that increasing PCV13 coverage in routine vaccination programmes would be beneficial in preventing future seasonal outbreaks of pneumococcal meningitis.

Data availability

Raw, de-identified data taken from the present study are available on figshare, DOI: https://dx.doi.org/10.6084/m9.figshare.7210367[25].

Data are available under the terms of the https://creativecommons.org/licenses/by/4.0/ (CC-BY 4.0).

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http://www.doi.org/10. 6084/m9.figshare.7210367

Open Peer Review

Current Peer Review Status: ✓ ✓ ✓

Version 2

Reviewer Report 15 May 2019

https://doi.org/10.21956/wellcomeopenres.16584.r35167

✓   **Caroline Trotter** (iD)
Department of Veterinary Medicine, University of Cambridge, Cambridge, UK

Thank you for addressing my previous comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 May 2019

https://doi.org/10.21956/wellcomeopenres.16584.r35166

✓   **Hélène Broutin** (iD)
Department of Parasitology, Faculty of Medicine, Cheikh Anta Diop University (UCAD), Dakar, Senegal

I think that authors replied and amended the paper accordingly to my first comments. I would accept this new version for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ecology of infectious diseases, Meningitis ecology and dynamics, Epidemiology.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 April 2019

https://doi.org/10.21956/wellcomeopenres.16584.r35168

Alexandre Manirakiza
Epidemiological Service, Pasteur Institute of Bangui, Bangui, Central African Republic

I feel the authors provided satisfactory information to my previous comments. So, I have no further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 1

Reviewer Report 11 February 2019

https://doi.org/10.21956/wellcomeopenres.16204.r34726

Alexandre Manirakiza
Epidemiological Service, Pasteur Institute of Bangui, Bangui, Central African Republic

This article reports very important information for understanding the epidemiology of meningitis in the Central African Republic.

However, some additional information can be brought to the article for the reader.
1. Introduction: The introduction could be more informative about the context of this work if the authors add some bibliographical references, such as the existing and published data on bacterial meningitis in the Central African Republic[1-3].

2. Methods/Patients: How many patients where excluded? Why were suspected cases excluded? These cases were excluded because they had a negative result or because cerebrospinal fluid analysis could not be performed? Details about this, should be provided at the beginning of the Result section.

3. Statistical analysis: Authors stated that "Patient data were recorded using Microsoft Excel". They should provide these data in their Excel format. Visibly, this is not the case at this link: https://dx.doi.org/10.6084/m9.figshare.7210367.

4. Results/Discussion: It seems to me more interesting to separate these two parts.

5. Conclusion: The limitations of this study ("A comprehensive follow-up of cases in the community….. Our analysis is limited by incomplete PCR confirmation and a lack of serotyping……"could be moved at the end of the discussion.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Mar 2019

Tom C, Médecins Sans Frontières Holland, Bangui, Central African Republic

We thank Dr. Manirakiza for his helpful comments.

To address the specific issues he raises:

1. Introduction: We have expanded the introduction and the discussion/ conclusion to place the current study in a broader context, including incorporating the recommended references.

2. Methods/Patients: Data on patients that tested negative and suspected cases were collected only in Paoua Hospital. We have added a paragraph describing the suspected and negative cases in the methods section. We are aware of this limitation in our data from Batangafo and Bossangoa and encourage more thorough reporting of suspected and negative cases in the future.

3. Statistical analysis: The data we provide at https://dx.doi.org/10.6084/m9.figshare.7210367 is a .txt file which is readable by Excel. It can be imported by (File -> Import -> Text file).

4. Results/Discussion: We have added a discussion section where we discuss the study in a broader context. We retain some discussion elements in results sections as we feel that this contributes better to reader flow and prevents the discussion / conclusion section from being overly repetitive.

5. Conclusion: We have added a discussion section as mentioned above.

In addition to these points we have added information regarding serotyping of pneumococcus and added details of other outbreaks of pneumococcal meningitis that occurred at a similar time.

Overall we consider the quality and usefulness of our article to be substantially improved in light of the comments by Dr. Manirakiza and the other reviewers.

Competing Interests: None

Reviewer Report 31 January 2019

https://doi.org/10.21956/wellcomeopenres.16204.r34638

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Hélène Broutin iD

Department of Parasitology, Faculty of Medicine, Cheikh Anta Diop University (UCAD), Dakar, Senegal

This study represents an important contribution to understand the current epidemiology situation of bacterial meningitis in the African Belt in the context of One serogroup targeted vaccine. Pneumococcal meningitis continues to kill people and this contribution could help in designing potential new vaccination strategies for meningitis control.

The limit of this study consists in the lack of information about the serotypes of Streptococcus pneumonia. Indeed, authors conclude from their results that PCV vaccines can help to control pneumo meningitis control but they did not provide serotypes information for cases in comparison to serotypes included in PCV vaccine. The study deserves to be published without this information about serotypes but authors should discuss this lack of serotype information as a limitation and explain that it should be a next step of the study to be able to inform the potential role of PCV vaccination in the meningitis control.

The paper is simply and clearly written. Introduction could be more developed to provide readers with a brief overview of what is known about pneumo meningitis in the African belt. The point is that this information is lacking so far and that makes this study highly relevant and informative.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ecology of infectious diseases, Meningitis ecology and dynamics, Epidemiology,

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Mar 2019

Tom C, Médecins Sans Frontières Holland, Bangui, Central African Republic

We thank Dr Broutin for her helpful remarks.

We have added details on serotyping. Six pneumococcal CSF isolates have been typed as serotype 1 by PCR. While this represents a small proportion of the total isolates, it confirms previous research in the Central African Republic that found serotype 1 to be the dominant strain in *S. pneumoniae* meningitis cases in Bangui. An outbreak that occurred contemporaneously in Ghana in 2015/6 was also predominantly pneumococcus serotype 1. This suggests that PCV10/13 would be effective against the outbreak strains of *S. pneumoniae* in CAR.

We have also expanded the introduction and discussion to place the CAR outbreak in a broader context and included more references.

Overall we consider the article to be substantially improved and more informative after the comments from Dr Broutin and other reviewers.

Competing Interests: None

Reviewer Report 15 November 2018

https://doi.org/10.21956/wellcomeopenres.16204.r34111

? **Caroline Trotter** iD

Department of Veterinary Medicine, University of Cambridge, Cambridge, UK

This is an interesting paper describing the epidemiology of bacterial meningitis in CAR. While this is clearly presented, I have two major comments about suspect vs confirmed cases and references to the current literature.

1. The analysis concentrates on laboratory confirmed cases, which contains the richest information. Suspect cases were excluded. However, many more suspect cases than laboratory confirmed cases are identified in enhanced meningitis surveillance, which are collated and reported weekly by WHO-IST (see amongst others Lingani *et al.* [1]. It would therefore be very useful to also report the patterns of suspected cases. What proportion of suspect cases were laboratory confirmed? What proportion of CSFs tested were negative? What was the CFR of the suspect cases? (high CFR might imply they were also likely to be due to Spn). Does the incidence of suspected cases exceed alert and epidemic thresholds? I think this would provide important context for the more detailed description of lab confirmed cases presented currently.

2. An outbreak of Spn meningitis occurred in Ghana in 2016 - see Kwambana-Adams *et al.*[2] - and this paper should be considered and referenced. For example, this outbreak occurred in the context of high uptake with infant PCV. Further published work has also examined the need for alternative routine and reactive vaccination programmes in the context of Spn outbreaks[3-4].

Other minor points:

- Please use meningococcal meningitis group A (not type A)
- In the abstract there is speculation about Spn carriage. It is indeed likely high, but this will be true in many sub-Saharan African settings. Probably more important than prevalence is distribution of serotypes, and in the absence of serotype information on cases, I don't feel that this comment on carriage adds much. It is more important to highlight the information on <u>disease burden</u> outside of the reporting hospitals.
- Did you refer to the 2014 WHO epidemic meningitis guidelines?

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Mar 2019

Tom C, Médecins Sans Frontières Holland, Bangui, Central African Republic

In response to the helpful comments by Prof. Trotter we have included information on suspected and negative cases (this was possible in only one of the reporting hospitals), and we have expanded the introduction and discussion section to place the outbreak in CAR into a broader context. We include all of the suggested references. We discuss the contemporaneous outbreak of pneumococcal meningitis in Ghana in the discussion. We also include brief information on serotype (six pneumococcus isolates were typed by PCR as serotype 1). Overall we consider the quality and usefulness of the article has improved substantially as a result of the comments by Prof Trotter and the other reviewers.

Competing Interests: None