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SUPPLEMENT ARTICLE

Pneumococcal Meningitis Outbreaks in Africa, 2000–2018: Systematic Literature Review and Meningitis Surveillance Database Analyses

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Background. The meningitis belt of sub-Saharan Africa has traditionally experienced large outbreaks of meningitis mainly caused by *Neisseria meningitidis*. More recently, *Streptococcus pneumoniae* has been recognized as a cause of meningitis outbreaks in the region. Little is known about the natural history and epidemiology of these outbreaks, and, in contrast to meningococcal meningitis, there is no agreed definition for a pneumococcal meningitis epidemic. The aim of this analysis was to systematically review and understand pneumococcal meningitis outbreaks in Africa between 2000 and 2018.

Methods. Meningitis outbreaks were identified using a systematic literature review and analyses of meningitis surveillance databases. Potential outbreaks were included in the final analysis if they reported at least 10 laboratory-confirmed meningitis cases above baseline per week with ≥50% of cases confirmed as pneumococcus.

Results. A total of 10 potential pneumococcal meningitis outbreaks were identified in Africa between 2000 and 2018. Of these, 2 were classified as confirmed, 7 were classified as possible, and 1 was classified as unlikely. Three outbreaks spanned more than 1 year. In general, the outbreaks demonstrated lower peak attack rates than meningococcal meningitis outbreaks and had a predominance of serotype 1. Patients with pneumococcal meningitis tended to be older and had higher case fatality rates than meningococcal meningitis cases. An outbreak definition, which includes a weekly district-level incidence of at least 10 suspected cases per 100 000 population per week, with >10 cumulative confirmed cases of pneumococcus per year, would have identified all 10 potential outbreaks.

Conclusions. Given the frequency of and high case fatality from pneumococcal meningitis outbreaks, public health recommendations on vaccination strategies and the management of outbreaks are needed. Improved laboratory testing for *S. pneumoniae* is critical for early outbreak identification.

Keywords. Africa; meningitis; outbreak; pneumococcus; *Streptococcus pneumoniae*.

Acute bacterial meningitis is most commonly caused by 4 pathogens: *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib), and Group B Streptococcus (GBS). Although they have limited valency, effective vaccines are available against all but GBS and are commonly used within the countries in the meningitis belt of sub-Saharan Africa [1]. Large-scale meningitis outbreaks have traditionally been reported in this region, which runs from Ethiopia in the east to Senegal in the west, covering 26 countries [2]. The meningitis season in this region occurs during the dry months of December to June [3–5], when the endemic baseline weekly incidence is thought to be approximately 1 case per 100 000 population. During an outbreak, however, the weekly incidence can be as high as 800 cases per 100 000 population [6, 7].

Historically, the large-scale outbreaks of meningitis in the belt have been caused by *N. meningitidis* serogroup A. After the introduction of meningococcal serogroup A conjugate vaccine (MenAfriVac), the incidence of meningitis cases and localized outbreaks have drastically declined [6, 8–10]. With the decline of serogroup A meningococcus, non-serogroup A meningococcal meningitis (namely serogroups C, W, and X) and pneumococcus have become prominent causes of meningitis outbreaks. Before widespread use of pneumococcal conjugate vaccines, pneumococcus accounted for one quarter to one third of all laboratory-confirmed endemic meningitis cases in the belt [11, 12].

Streptococcus pneumoniae is a Gram-positive bacterium that causes both invasive disease (meningitis and septicemia) and noninvasive disease (pneumonia, sinusitis, and acute otitis media). Although community outbreaks of pneumococcal disease have been reported in high-income countries, little is known about the occurrence of these outbreaks in Africa [13].

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The natural history and epidemiology of community pneumococcal meningitis outbreaks in Africa is not fully understood, and consequently there is no agreed definition of what constitutes a pneumococcal outbreak [14–18]. Based on a review of meningitis surveillance data, the World Health Organization (WHO) proposed a provisional definition in 2016, stating that a pneumococcal meningitis outbreak should be considered in any district or subdistrict with a weekly incidence of ≥5 suspected meningitis cases/100 000 population, with at least 60% of confirmed meningitis cases due to *S. pneumoniae* and ≥10 confirmed cases of pneumococcal meningitis [19].

The objectives of this review are 2-fold: (1) to identify and describe pneumococcal meningitis outbreaks in Africa between 2000 and 2018 by systematic review of the literature and analysis of available meningitis surveillance databases; and (2) to use the findings to improve current understanding of pneumococcal outbreaks in Africa and thereby assess and inform the provisional pneumococcal outbreak definition. We did not consider literature or surveillance data before 2000 because of the poorer quality of data and lack of bacterial identification.

METHODS

We performed a systematic literature review and analysis of meningitis surveillance databases between January 1, 2000 and May 28, 2018. WHO recommendations and expert opinion were used to identify potential outbreak criteria (Supplementary Table 1). The potential criteria included peak weekly incidence, cumulative incidence, the number of confirmed cases, and the percentage of confirmed cases that were due to pneumococcus. The alert threshold for meningococcal meningitis outbreaks is used as an early warning system to trigger further investigation [20]. Alert and epidemic thresholds for pneumococcal meningitis outbreaks were provisionally defined as a weekly incidence of >5 and >10 suspected meningitis cases per 100 000 population, respectively. The duration of the outbreak was reported as the number of weeks that passed between a district crossing the alert threshold for the first time and final time in the season (Supplementary Table 2). Two different epidemic thresholds were considered. First, we used a cutoff of ≥10 suspected cases/100 000 per week, which was identified by Cooper et al [17] as having a sensitivity and negative predictive value of 100% and high positive predictive value and specificity for an outbreak. Second, the threshold of ≥5 suspected cases/100 000 population per week, which was chosen for the WHO provisional pneumococcal outbreak definition [19], was also assessed.

The current case definitions recommended by WHO for meningitis surveillance are listed in the following sentence [21]; however, case definitions differed between countries and over the period of study based on recommendations and type of surveillance used at the time [22]. A suspected meningitis case was defined as a patient admitted to hospital with sudden onset of fever (>38.5°C rectal or 38°C axillary) and 1 of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal signs; or any patient hospitalized with a clinical diagnosis of meningitis. A probable case met the criteria for a suspected case and had a cerebrospinal fluid (CSF) examination showing at least 1 of the following: turbid appearance, leukocytosis (>100 cells/mm^3), or leukocytosis (10–100 cells/mm^3) and either an elevated protein (>100 mg/dL) or decreased glucose concentration (<40 mg/dL). A confirmed case was defined as a suspected or probable case that is laboratory-confirmed by culture or identification of a bacterial pathogen (Hib, pneumococcus, or meningococcus) by antigen detection, latex agglutination, immunochromotography, or polymerase chain reaction (PCR) assays in the CSF or from the blood [23].

Systematic Literature Review

A systematic literature review was conducted of both published and unpublished literature from the years 2000–2018. Studies were included regardless of publication status and language. To ensure we did not miss potential outbreaks, studies were included for further review if they reported a minimum of 10 pneumococcal meningitis cases in 1 year and if the proportion of laboratory-confirmed meningitis cases that were identified as pneumococcus was ≥20%.

We conducted a search of electronic databases in May 2018 using Medline, Cochrane, and the African Journals Online (AJOL) database (https://www.ajol.info/). Searches were created to cover the terms "*Streptococcus pneumoniae*" or "pneumococcus," "meningitis," "outbreak," and "Africa." As given in the Supplementary Appendix, a combination of keywords and MeSH terms were used to cover both English and French, the 2 main publication languages in African countries; MeSH term searches were not possible in AJOL.

The search was supplemented by a reference list review of relevant articles and by a search of unpublished literature and conference presentations (namely, the International Symposium on Pneumococci and Pneumococcal Diseases). Studies describing the validation of laboratory tests and evaluating treatment regimens outside of outbreak settings were excluded because they did not provide information relevant to identifying outbreaks. The remaining documents were accessed and reviewed independently by 2 authors (K.F. and A.L.C.). Studies describing meningococcal outbreaks were individually reviewed to ensure that there was not a concurrent outbreak of pneumococcal meningitis. Articles that described outbreaks that met at least 3 criteria from Supplementary Table 1 were included. Authors of published articles were contacted to provide additional data when available and appropriate.

The quality of each study was assessed on the basis of completeness of weekly reporting, the number of suspected cases tested, and the percentage of tested cases with a positive

laboratory result. In accordance with current surveillance standards, Gram stain alone was considered less accurate than bacterial culture, PCR assay, or rapid diagnostic testing [21].

Meningitis Surveillance Data Analyses

Analyses of databases collecting surveillance data on meningitis in Africa were conducted to complement the systematic review. Databases were identified through WHO and collaborating organizations (Supplementary Table 3). In total, 3 major databases collecting surveillance information on meningitis cases in Africa were identified: the Enhanced Meningitis Surveillance Network (EMSN), the Global Invasive Bacterial Vaccine-Preventable Disease Surveillance Network (GISN), and MenAfriNet. The EMSN is a national, aggregate surveillance system across the African meningitis belt [8], GISN is a sentinel, case-based surveillance network in multiple African countries [24, 25], and MenAfriNet is a case-based surveillance network in 5 countries in the African meningitis belt [26].

The EMSN and MenAfriNet databases were both used to calculate suspected meningitis incidence per 100 000 population per district per week. The EMSN database was used for population estimates, except for the potential outbreak in Paoua, Central African Republic (CAR), where the population reported in the manuscript by Coldiron et al [27] was used. For the MenAfriNet data, population estimates provided by each country were used to calculate incidence estimates.

The data were analyzed using 3 different weekly and cumulative incidence thresholds for suspected meningitis: (1) ≥5 suspected meningitis cases/100 000 population per week (alert threshold); (2) ≥10 suspected meningitis cases/100 000 population per week (epidemic threshold); and (3) ≥5 suspected meningitis cases/100 000 population per week and ≥80 suspected meningitis cases/100 000 population per year.

The EMSN database did not contain case-based, linked laboratory confirmation. When possible, the results of each search were matched with national laboratory data and with the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control request database, which was used to rule out outbreaks where meningococcus was likely to be the predominant pathogen. As with the systematic literature review, districts were excluded if they did not meet at least 3 of the criteria outlined in Supplementary Table 1. Districts with a population of <30 000 were included if they had more than 5 suspect cases in a week or doubling of incidence in a 3-week period with more than 2 confirmed pneumococcal cases and >50% from the same serotype.

We analyzed the MenAfriNet surveillance data in Burkina Faso (2011–2016), Mali (2015–2017), Togo (2015–2017), Chad (2016–2017), and Niger (2015–2017). A separate analysis was conducted for the GISN database because sentinel site surveillance, without population-based denominators, cannot be used to calculate incidence. For this reason, monthly reports of pneumococcal meningitis cases between 2008 and 2018 were plotted by sentinel site hospital, and sentinel sites reporting pneumococcal meningitis above the average monthly number of baseline cases were compared with the corresponding district data in the EMSN database for the same time period, in an attempt to correlate the findings and identify outbreaks.

Combined Analysis

A list of all potential outbreaks was compiled from the systematic literature review and meningitis surveillance database analyses. The potential outbreaks were then classified as confirmed, possible, or unlikely. A confirmed outbreak was defined as an outbreak meeting all the criteria outlined in Table 1. A possible outbreak met at least 3 of the criteria. An unlikely outbreak either met fewer than 3 criteria, or the quality of the study, in combination with the features of the outbreak, made an outbreak of pneumococcal meningitis unlikely.

Ethics

Because this study included data from published literature or collected as part of routine surveillance, it was exempt from human subject review.

RESULTS

Systematic Literature Review

A total of 924 records were identified by the systematic literature review, and an additional 18 records were identified through other sources (Supplementary Figure 1). Duplicate records were removed, leaving a total of 838 unique articles, presentations, and manuscripts. Initial screening excluded 790 records that collected data from outside the specified timeframe, reported data from outside of Africa, reported on pathogens other than pneumococcus, or did not report on outbreaks. From the remaining 48 articles reviewed, 16 articles, presentations, and unpublished manuscripts were identified as reporting on 6 separate potential pneumococcal meningitis outbreaks.

Meningitis Surveillance Database Analyses

Enhanced Meningitis Surveillance Network

A total of 30 811 district-years was searched (Supplementary Figure 2). The threshold analyses identified between 612 and 1824 district-years with potential outbreaks. The limited amount of laboratory data available to link with the EMSN data meant that, although districts with potential outbreaks could be identified, there was insufficient data to identify the causative organism. Four outbreaks, additional to those identified in the literature search, met the criteria at each of the thresholds analyzed, for a total of 10 potential pneumococcal meningitis outbreaks identified from both the literature review and database analysis; 1 outbreak initially identified through the database analyses has been subsequently accepted for publication [28] (Tables 1 and 2).

Table 1. Potential Pneumococcal Outbreaks and Criteria for Outbreak Definition Met

	Criteria for Outbreak Definition						
Country/Region and Year of Potential Outbreak	Above Baseline for Previous Year	≥10 Suspect Cases/100K per Week	Cumulative Attack Rate ≥80 Suspect Cases/100K per Year	≥10 Confirmed Cases	Percentage of Confirmed Cases *Streptococcus pneumoniae* ≥50%	Predominant Serotype	Outbreak Confirmed?
1. Central African Republic (CAR), Paoua 2016–2017	Yes	Yes	Yes	Yes[a]	Yes	Yes[b]	Confirmed
2. Ghana, Brong Ahafo 2015–2016	Possibly[c]	Yes	Yes	Yes	Yes	Yes	Confirmed
3. Ghana, Northern 2015–2017	Yes	Yes (at district level)	NA	Yes (at district level)	50% Upper west, 32% Northern	Yes	Possible (at district level)[d]
4. Burkina Faso, Pama 2011	Yes	Yes	Yes	Yes	Yes	No	Possible
5. Burkina Faso, Karangasso Vigue 2011	Yes	Yes	No	Yes	Yes	Yes	Possible
6. Burkina Faso, Solenzo 2009	Yes	Yes	Yes	Yes	Yes	NA	Possible
7. Chad, Goundi 2009	Yes	Yes	Yes	Yes	Yes	NA	Possible
8. Burkina Faso, Bobo-Dioulasso 2002–2004	Yes (in 2004)	NA[e]	NA	Yes	41% 2003, 65% 2004	Yes	Possible
9. Ghana, Kassena-Nankana District 2001–2003	Yes	NA[e]	NA	Yes	38% 2001–2002, 52% 2002–2003	Yes	Possible
10. Chad, Goundi 2001	Yes	Yes	Yes	Yes	Unknown	NA	Unlikely

Abbreviations: NA, not applicable.

[a]Crosses epidemic threshold using suspected cases in Enhanced Meningitis Surveillance Network (EMSN) database.

[b]Ten cases tested, 6 serotype 1.

[c]Data not available in EMSN database to confirm. However, this occurrence is referred to in the literature on multiple occasions as an outbreak.

[d]There is currently insufficient data to analyze each district week by week.

[e]Only incidence of confirmed meningitis cases reported.

Global Invasive Bacterial Vaccine-Preventable Disease Surveillance Network

The analysis of the GISN database identified 3 sentinel site hospitals that reported confirmed pneumococcal cases above baseline. In the Abidjan region of Cote d'Ivoire, 41 of 74 suspected meningitis cases over a 3-month period were confirmed as pneumococcus. The Enugu region of Nigeria reported 70 suspected cases and 37 confirmed pneumococcal cases over 3 months. Finally, a hospital in Dakar, Senegal reported 64 suspected cases and 36 confirmed pneumococcal cases over 3 months. None of these periods correlated with increased incidence in EMSN, and incidence could not be calculated solely from GISN due to the sentinel site nature of reporting. Based on these factors, no additional outbreaks were identified through GISN.

MenAfriNet

In Burkina Faso, 18 districts reported between 5 and 7 confirmed pneumococcal meningitis cases in 1 week. Incidence in 2 districts in Burkina Faso exceeded the epidemic threshold of ≥10 suspected cases per 100 000: Pama and Karangasso Vigue, both in 2011. These 2 districts were also identified through EMSN. In Niger, the 5 districts in Niamey reported 5 pneumococcal cases in 1 week. However, this was during the 2015 meningococcal serogroup C epidemic. None of the districts covered by MedAfriNet in Mali, Togo, or Chad reported more than 3 pneumococcal cases in 1 week. Thus, no additional potential outbreaks were identified through MenAfriNet surveillance.

Description of Outbreaks

In total, 10 potential pneumococcal meningitis outbreaks were identified. These outbreaks occurred in 4 African countries, all of which are at least partially in the meningitis belt, although 3 of the outbreaks occurred in regions outside of the meningitis belt (Map). Burkina Faso had the most outbreaks identified (4), followed by Ghana (3), Chad (2), and CAR (1). Two outbreaks were considered confirmed, 7 possible, and 1 unlikely (Table 2). The outbreaks in Paoua, CAR (2016-2017) and Brong Ahafo, Ghana (2015-2016) were considered confirmed, having met each of the criteria, with good quality data from multiple sources. The potential outbreaks in Solenzo, Burkina Faso (2009) and Goundi, Chad (2009) were both deemed possible, meeting all of the criteria, except for having a predominant pneumococcal serotype. Goundi, Chad (2001) was deemed unlikely due to

Table 2. Country, Region, and Duration of Potential Outbreaks of *Streptococcus pneumoniae* Meningitis and Sources Used to Identify Them

Number	Country	Region	Epidemiological Week-Year	Source of Identification
1	Central African Republic	Paoua	47-2016 → 10-2017	Coldiron et al [27]
2	Ghana	Central (Brong Ahafo)	53-2015 → 9-2016	Cooper et al [17]; Kwambana-Adams et al [18]; unpublished data from same authors
3	Ghana	Northern	1-2016 → 11-2016	Asiedu-Bekoe et al [29]; Aku et al [16]; Domo et al [30]; Bozio et al [31]
4	Burkina Faso	Pama	8-2011 → 12-2011	EMSN database; MenAfriNet database
5	Burkina Faso	Karangasso Vigue	8-2011 → 9-2011	Soeters et al, [28]; EMSN database; MenAfriNet database
6	Burkina Faso	Solenzo	1-2009 → 10-2009	EMSN database
7	Chad	Goundi	1-2009 → 16-2009	EMSN database
8	Burkina Faso	Bobo-Dioulasso (included: Districts 15, 22 and Hounde)	August 2002 → April 2003 February 2004 → July 2004[a]	Traore et al [5]; Yaro et al [15]; EMSN database
9	Ghana	Kassena-Nankana District	August 2001 → September 2003[a]	Leimkugel et al [14]; EMSN database
10	Chad	Goundi	3-2001 → 18-2001	Bregani et al [32]

Abbreviations: EMSN, Enhanced Meningitis Surveillance Network.

[a]Epidemiologic week-year not available.

the use of Gram stain for case confirmation and conflicting results between Gram stain and the limited number of latex agglutination tests performed.

The number of suspected cases, the type of laboratory testing, and the number of cases confirmed by laboratory testing varied widely across outbreaks (Table 3). Seven of the 10 outbreaks

Table 3. Suspected, Tested, and Confirmed *Streptococcus pneumoniae* and *Neisseria meningitidis* Meningitis Cases by Outbreak With Method of Laboratory Confirmation

Confirmed and Potential Outbreaks	Suspected	Tested	Laboratory-Confirmed	*S. pneumoniae* Cases	*N. meningitidis* Cases	Predominant *S. pneumoniae* Serotype	Laboratory Technique (No. of Cases)
1. Central African Republic, Paoua 2016–2017	251	110 (44%)	65 (59%)	60 (92%)	1 (2%)	ST 1 6/10 (60%)	Latex agglutination (110); PCR (10)
2. Ghana, Central 2015–2016[a]	966	615 (64%)	208 (34%)	168 (81%)	40 (19%)	ST 1 38/49 (78%)	Gram stain 48/615 (8%); PCR 567/615 (92%); whole genome sequencing (9)
3. Ghana, Northern 2015–2017	1614	796 (49%)	409 (51%)	153 (37%)	236 (58%)	ST 1 85/137 (62%)	Gram stain + culture[b] (12); latex agglutination (769); PCR (249)
4. Burkina Faso, Pama 2011	90	NA	16	10 (63%)	4 (25%)	7 serotyped, no predominant ST (3 NT, 1 ST1, 1 ST12F/12A/12B/44/46, 1 ST 18C/18F/18B/18A)0	PCR, culture, or latex agglutination
5. Burkina Faso, Karangasso Vigue 2011	71	NA	42	34 (81%)	NA	ST 1 8/8 (100%)	PCR, culture, or latex agglutination
6. Burkina Faso, Solenzo 2009	307	NA	43	39 (91%)	4 (9%)	NA	NA
7. Chad, Goundi 2009	191	NA	110	66 (60%)	29 (26%)	NA	NA
8. Burkina Faso, Bobo-Dioulasso 2002–2004	1733	1686 (97%)	571 (34%)	249 (44%)	210 (37%)	ST 1 21/48 (44%)	Gram stain, culture 85/249 (34%)[c]; latex agglutination 193/249 (78%); PCR 182/249 (73%); multilocus sequence typing (3)
9. Ghana, Kassena-Nankana District 2001–2003	NA	NA	221	99 (45%)	122 (55%)	ST 1 58/76 (76%)	Gram stain culture/latex agglutination (221)[d]; Serotype Quellung (76)
10. Chad, Goundi 2001	595	388 (65%)[e]	185 (48%)	150 (81%)	29 (16%)	NA	Gram stain (388); latex agglutination (6)[f]

Abbreviations: NA, not applicable; PCR, polymerase chain reaction; ST, serotype.

[a]Data are combined from Cooper et al [17] and Kwambana-Adams et al [18]. Case numbers from Cooper et al [17] , serotype from Kwambana-Adams et al [18] (Cooper et al [17] reports 45% ST1).

[b]Completed but not used in case classification. Number of each test used is unclear in the published article [29].

[c]Testing method only reported for positive cases.

[d]Proportion of culture and latex agglutination not reported, article states all confirmed cases identified by 1 of the 2.

[e]Testing stopped mid outbreak due to high case numbers.

[f]Latex agglutination identified predominantly *N. meningitidis* serotype A cases, article states "a limited number of tests were used".

reported over 50% of confirmed cases due to pneumococcus. The Northern Ghana (2015–2017) possible outbreak reported regions or districts that had a predominance of pneumococcal or mixed pneumococcal and meningococcal outbreaks, with no single pathogen contributing more than 80% of the total disease burden. The Ghana Kassena Nankana district (KND) (2001–2003) possible outbreak reported 39% of confirmed cases as pneumococcus between 2001 and 2002 and 51% of confirmed cases as pneumococcus in 2002–2003. The Bobo-Dioulasso, Burkina Faso (2002–2004) outbreak reported 44% of cases as pneumococcus. However, pneumococcus was the predominant pathogen in this potential outbreak, with meningococcus being the next most frequently identified at 37%.

Pneumococcal serotype data were available for 4 of the potential outbreaks [14, 15, 18, 31]; 2 occurred before the introduction of pneumococcal conjugate vaccine (PCV) into the routine infant immunization program and 2 occurred after. The proportion of confirmed pneumococcal cases that were serotyped was small, ranging from 8% in Burkina Faso in 2002–2004 to 33% in both Northern Ghana (2015–2017) and Ghana, KND (2001–2003). Serotype 1 was the most frequently identified serotype, comprising more than 50% of tested cases in 3 of the 4 studies reporting serotype data (Supplementary Figure 3).

The age and case fatality data for each potential outbreak and PCV status of the country are summarized in Table 4. The outbreaks that occurred in pre-PCV settings tended to affect children under 5 years old more commonly, whereas the more recent outbreaks in Ghana, which occurred in the context of high routine infant immunization with PCV, affected older age groups [18]. This was further demonstrated in the outbreak in Paoua, CAR, where PCV is included in the national immunization program, but vaccine coverage is generally low [33].

Table 4. Age and Case Fatality Rate for Suspected and Confirmed Cases of *Streptococcus pneumoniae* and *Neisseria meningitidis* Meningitis

Country	Age of Confirmed Pneumococcal Cases		Case Fatality-Suspected	Case Fatality-Confirmed Pneumococcus	Case Fatality-Confirmed Meningococcus	Status of PCV Introduction and Vaccination Coverage[a]
1. Central African Republic, Paoua 2016–2017	0–59 mths[b] 5–29 yrs ≥30 yrs	27% 58% 15%	9/251 (4%)	6/60 (10%)	NA	Introduced 2011; 2016 estimated coverage 47%[c]
2. Ghana, Central 2015–2016	0–59 mths; 5–29 yrs; ≥30 yrs	3% 62% 35%	75–86/786–966 (9%-10%)	25–39/85–168[d] (23%-29%)	8–9/30–40 (23%–26%)	Introduced 2012; 2015–2016 estimated coverage 88%–93%
3. Ghana, Northern 2015–2017	0–59 mths[e] 5–29 yrs ≥30 yrs	12% 60% 28%	75/711[f] (11%)	28/98[g] (29%)	Aku reports 2/83 (2%)[g]	Introduced 2012; 2015–2016 estimated coverage 88%–93%
4. Burkina Faso, Pama 2011	0–59 mths 5–29 yrs ≥30 yrs	35% 30% 35%	6/90 (7%)	NA	NA	Introduced 2014; 2015–2016 estimated coverage 91%
5. Burkina Faso, Karangasso Vigue 2011	0–59 mths 5–29 yrs ≥30 yrs	18% 36% 45%	13/71 (18%)	NA	NA	Pre-PCV
6. Burkina Faso, Solenzo 2009	NA	NA	42/307 (14%)	NA	NA	Pre-PCV
7. Chad, Goundi 2009	NA	NA	37/NA	NA	NA	PCV not introduced as of 2018
8. Burkina Faso, Bobo-Dioulasso 2002–2004	0–59 mths 5–15 yrs ≥15 yrs	49% 19% 32%	NA	115/249 (46%)	42/306 (14%)	Pre-PCV
9. Ghana, Kassena-Nankana District 2001–2003	0–59 mths 5–29 yrs ≥30 yrs	40% 36% 24%	NA	51/117 (44%) (overall)	6/140 (4.3%)	Pre-PCV
10. Chad, Goundi 2001	0–59 mths 5–29 yrs ≥30 yrs	19% 67% 14%	52/595 (9%)	16/150[i] (11%)	NA	Pre-PCV

Abbreviations: mths, months; NA, not applicable; PCV, pneumococcal conjugate vaccine; yrs, years.

[a]Coverage estimates of a full course of PCV from World Health Organization (WHO), United Nations Children's Fund. Central African Republic: WHO and UNICEF estimates of immunization coverage: WHO Reports (see http://www.who.int/immunization/monitoring_surveillance/data/caf.pdf).

[b]Percentage within 0–59 months: in vaccinated areas, 17%; in nonvaccinated areas, 36%.

[c]A community-based catch-up multiantigen campaign was conducted in 2016, but it did not cover all areas of the district.

[d]19 cases unknown outcome, range of numbers reflects different time frame and reporting in available articles.

[e]Suspected cases, not pneumococcus.

[f]100 cases unknown outcome.

[g]55 cases unknown outcome.

[h]Number not available in Bregani et al [32].

[i]20 of the 52 total deaths had testing or a pathogen identified.

Before the outbreak, some areas of the district had community-based catch-up campaigns for PCV and other antigens. In the nonvaccinated areas, 36% (10 of 28) of cases were under 5 years of age. In the vaccinated areas, this was 17% (5 of 30).

The case fatality rate (CFR) of suspected cases ranged from 4% in Paoua, CAR to 18% in Karangasso Vigue, Burkina Faso (mean 8%) (Table 4). In contrast, the CFR of confirmed pneumococcal cases ranged from 10% in Paoua, CAR to 46% in Bobo-Dioulasso (mean 25%). Of 52 total reported fatalities in these outbreaks, 20 had a pathogen identified, 16 (80%) of which were pneumococcus.

Supplementary Tables 3 and 4 outline the duration of each of the potential outbreaks and the peak and cumulative incidences per 100 000 population. Three of the outbreaks recurred with peaks in more than 1 consecutive year. Pama, Burkina Faso had a 3-year period of increased incidence, although not all years had a predominance of pneumococcus. For the 8 outbreaks where weekly incidence could be calculated, 2 crossed the epidemic threshold of >10 suspected cases per 100 000 population for 1 week; Goundi, Chad (2001) spent the longest time above the epidemic threshold at 9 weeks. Jirapa, in Northern Ghana, also spent 9 weeks above the epidemic threshold; however, meningococcus was the predominant cause of this outbreak. Of the 8 outbreaks where the cumulative incidence could be calculated, all but the outbreaks in Pama, Burkina Faso and Karangasso Vigue, Burkina Faso (2011) exceeded a cumulative incidence of 100 suspected cases per 100 000 population. In the both the Brong-Ahafo and Northern Ghana (2015–2017) outbreaks, this threshold was met in 3 districts, but not overall.

DISCUSSION

The primary aim of this review was to identify and describe pneumococcal meningitis outbreaks in Africa over the past 18 years to inform prevention and response strategies. A systematic review of the literature and surveillance databases since 2000 revealed 10 potential pneumococcal meningitis outbreaks, including 2 that were confirmed and 7 that were considered probable. This is a minimum estimate, limited by the quality of the surveillance data. All outbreaks demonstrated seasonality and high CFRs. The duration of each identified outbreak varied, and the time spent above the epidemic threshold ranged from 1 to 9 weeks.

All outbreaks demonstrated a seasonal pattern, with an up to 10-fold increase in cases in the dry season. It has been previously reported that pneumococcal outbreaks peak 1 to 2 months earlier in the epidemic season than meningococcal outbreaks [19, 34]. These reports were partially based on the KND, Ghana outbreak described in this paper. In contrast, the data from Bobo-Dioulasso, Burkina Faso covering 4 years, did not support this.

The method of laboratory testing varied across studies. As expected, more recent outbreaks tended to use more advanced laboratory techniques, such as culture and PCR. However, even the most recent outbreaks in both central and northern Ghana identified a proportion of their cases via Gram stain alone, a method that is not considered adequate to confirm infection with *S. pneumoniae* [21]. If available, rapid diagnostic test (RDT) kits such as immunochromatography and latex agglutination testing can be used to identify pneumococcus; however, RDTs do not identify the serotype or serogroup. To further characterize a pneumococcal outbreak, serotyping should be performed to determine whether the majority of cases are from the same serotype and, if a response is considered, that the serotype is covered by PCV. The observed predominance of serotype 1 in identified pneumococcal meningitis outbreaks is important because it is a component of all currently available vacccines: the commonly used 10- and 13-valent PCVs and the recently WHO-prequalified 10-valent PCV [33]. This underscores the importance of ensuring high PCV coverage and suggests that vaccination could be used as a control or response strategy. The combination of findings that older age groups are affected more commonly in pneumococcal meningitis outbreaks and that the predominant serotypes are contained in PCV13 suggests that there may be a lack of indirect protection (ie, herd immunity) among older children and adults. A vaccine schedule with a booster dose may have the benefit of inducing higher antibody levels after infancy.

The choice of criteria used to define pneumococcal meningitis outbreaks has practical implications. The identification of an outbreak while it is happening allows a prompt public health response, whereas retrospective identification of an outbreak reveals the extent of the problem and highlights districts or regions with an increased incidence that could be targeted with immunization system strengthening efforts. At the district level, 8 of the 10 potential outbreaks described in this study would have fulfilled an operational definition of over 10 cases per 100 000 per week, with more than 10 confirmed pneumococcal cases at any time during the outbreak. Including the proportion of pneumococcal cases in the outbreak definition would have led to the exclusion of the 3 mixed outbreaks identified in this study.

Based on the data currently available, it seems unlikely that reactive vaccination campaigns would be of significant benefit in response to pneumococcal meningitis outbreaks. The 2 outbreaks with sufficient data to assess this are the Paoua outbreak in CAR and the central Ghana outbreak. The outbreak in Paoua was not recognized at the time to have crossed the epidemic threshold and was only retrospectively identified as doing so [27]. Therefore, a response would possibly not have been triggered nor been implemented in time to prevent much disease. A detailed modeling analysis of the number needed to vaccinate at different epidemic thresholds for the central Ghana outbreak has been published by Cooper et al [17]. They demonstrated that using a cutoff of 10 cases per 100 000 per week and assuming a 2-week lag period before the commencement of

the vaccination campaign, the vaccination of 5- to 29-year-olds would have prevented 36 cases.

A catch-up vaccination campaign targeting under-immunized children and unimmunized older children and adults may be a more effective option than a reactive vaccination campaign. This proposal is supported by the finding that 3 of the identified outbreaks occurred in consecutive years. A catch-up campaign in areas that met the criteria for a pneumococcal meningitis outbreak could target the older age groups more commonly affected that have not received PCV as part of the routine infant immunization program. This would have the advantage of quickly increasing the proportion of the population that is immune, rather than the slow increase that would occur if infant vaccination was the only strategy [17, 35].

The current study had a number of limitations. First, there was difficulty linking suspected cases identified through ESMN to laboratory confirmation data. It is likely that more districts met the criteria for pneumococcal meningitis outbreaks, with over 1000 districts that crossed the epidemic threshold having insufficient laboratory data. The study was limited by the quantity and quality of data reported in both databases and published articles. This included variations in the reporting of suspected and confirmed cases, incomplete laboratory data, and lack of serotype testing and age. Because laboratory and surveillance capacity both improved significantly over the search period, more recent studies were more likely to meet the quality standards and current case definitions. Outbreaks such as that in Goundi, Chad in 2001, although reported as a pneumococcal outbreak, was not assessed with the current standard of laboratory testing and was deemed unlikely to be a pneumococcal outbreak. Interpretation of both peak incidence and outbreak duration was challenging, given the mixture of pathogens reported in many outbreaks and the variation in incidence peaks between different pathogens. The possible outbreaks in northern Ghana (2015–2017), Goundi, Chad (2009), Bobo-Dioulasso, Burkina Faso (2002–2004), and KND, Ghana (2001–2003) may have been mixed outbreaks. Finally, although the laboratory capacity of the respective countries has improved over time, it was not possible to assess many districts, due to insufficient laboratory data.

To our knowledge, this is the first systematic review of pneumococcal meningitis outbreaks in community settings in Africa. It is important that countries be able to promptly identify the pathogens causing meningitis outbreaks, so that they can adequately direct the response. Based on the current data, it is not possible to make definitive recommendations about the ideal outbreak prevention or response approaches for pneumococcal meningitis outbreaks in the meningitis belt. It seems unlikely that reactive vaccination campaigns would have a meaningful impact, considering the difficulties with identifying an outbreak promptly and then implementing a campaign; however, the high CFR of pneumococcal meningitis and the pressure to respond to pneumococcal outbreaks like meningococcal outbreaks may influence decisions about reactive pneumococcal vaccination campaigns.

CONCLUSIONS

The WHO recommends that PCV should be introduced in all countries with or without a booster dose, although a booster dose may boost population immunity [36]. The fact that 3 of the outbreaks recurred over a 2-year period suggests that consideration of either catch-up preventative immunization campaigns in outbreak-prone regions or a booster dose of PCV could be beneficial in these settings. Because invasive pneumococcal disease can also present as pneumonia and sepsis in addition to meningitis, criteria for defining outbreaks may need to be expanded to consider the spectrum of clinical syndromes. Finally, given the changing epidemiology of meningitis in the African meningitis belt [10], countries in the region need strong surveillance and laboratory capacity for pneumococcus and other bacterial meningitis pathogens, including serotyping and serogrouping.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Table 1. Pneumococcal outbreak criteria, adapted from 2016 World Health Organization provisional definition [19].

Supplemental Table 2. Calculations used for epidemiological parameters.

Supplementary Table 3. Characteristics of databases accessed for search of *Streptococcus pneumoniae* meningitis cases.

Supplementary Table 4. Duration of outbreak and population used to calculate weekly incidence with number of weeks spent above alert and epidemic thresholds, and cumulative incidence per 100 000 people per year.

Supplementary Figure 1. PRISMA flowchart of articles identified and accessed as part of a systematic review of pneumococcal meningitis outbreaks in Africa.

Supplementary Figure 2. Results of the Enhanced Meningitis Surveillance Network database search: Number of district-years identified with each threshold analysis, reasons for exclusion by district-year and total district-years included.

Supplementary Figure 3. *Streptococcus pneumoniae* serotype data from 4 individual outbreaks with PCV introduction status.

Supplementary Appendix. Search terms used for systematic literature review and results per search.

Notes

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