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Recurring Epidemics of Meningococcal Meningitis in African Meningitis Belt: A Review of Challenges and Prospects

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Authors' contributions

This work was carried out in collaboration between all authors. Author DJO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors BAO and Author CKO managed the analyses of the study. Authors DJO and CKO managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The African meningitis belt (AMB) is made up of 26 contiguous countries from Senegal in the West to Ethiopia in the East. Recurring epidemics of meningococcal meningitis have afflicted this region for more than a century. Epidemics are seasonal, occurring during the dry hot season and they can cause many deaths, and residual disability.

This review presents a quick overview of the past and current trends of epidemic meningococcal meningitis in African meningitis belt, together with some recommendations aimed at ensuring "epidemic meningitis - free Africa". Data was collected through the analysis of peer-reviewed studies and surveillance data on national, sub-national, and regional levels. This was performed using various search engines such as Pub Med, Google scholar, regional WHO homepages, and department of health websites.

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Despite much progress in surveillance and biological research, the pattern of epidemic meningitis in the African meningitis belt is still poorly understood, making it difficult to model and predict the epidemics. Other major challenges in controlling the menace of epidemic meningococcal meningitis in this area include inadequate surveillance during epidemics, and non availability of effective vaccines. For an effective control of meningococcal meningitis in the African meningitis belt, there is a need for an effective surveillance system and accelerated development of a polyvalent conjugate vaccine that will be affordable to Sub-Saharan African countries.

Keywords: Meningococcal meningitis; Neisseria meningitidis; epidemics; meningitis belt; Meningococcal A conjugate vaccine.

1. INTRODUCTION

Every year, West African countries within the Sahelo-Sudanian band are afflicted by major meningococcal meningitis (MCM) outbreaks. The timing of the epidemic year, which starts in December and ends in late May, and the spatial distribution of disease cases throughout the African meningitis belt strongly indicate a close linkage between the activity of the causative agent of MCM and climate variability. However, mechanisms responsible for the observed patterns are still not clearly identified [1,2]. An effective vaccine has been in existence for more than 30 years, but despite this, the control of epidemics has failed. Moreover, the geographical distribution of *Neisseria meningitidis* seems to be increasing, perhaps because of climate change but also because of the economic crisis which prevails throughout much of Africa leading to population movements and the breakdown of essential services [3].

This review article will highlight the trends of these epidemics, elucidate the factors responsible for the unending recurrence of the epidemics, and proffer some recommendations targeted at controlling this menace.

2. METHODS

Data was collected through the analysis of peer-reviewed studies and surveillance data on national, sub-national, and regional levels performed using various search engines such as PubMed, Google scholar, regional WHO homepages, and department of health websites. We searched the published medical literature up to April, 2017 for eligible articles written in English, using the search terms ‘‘meningococcal meningitis,’’ ‘‘African meningitis belt,’’ ‘‘epidemics,’’ and ‘‘meningococcal vaccine. ’’ All abstracts found were screened by two reviewers independently. Those potentially eligible for inclusion were read in full text by the same two reviewers independently and subsequently discussed during a consensus meeting. Reference lists of each of the selected publications were checked to retrieve relevant publications which had not been identified by the computerized search. The exclusion criterion was non-English articles.

2.1 Historical Perspectives

Meningitis outbreak was first recorded in Geneva in 1805. Gaspard Vieusseux (1746-1814) and Andre Matthey (1778-1842) in Geneva, and Elisa North (1771-1843) in Massachusetts, described epidemic (meningococcal) meningitis [4]. In Africa, the first outbreak was described in 1840. African epidemics became much more common in the 20th century. The first major one was reported in Nigeria and Ghana in 1905–1908. The first evidence that linked bacterial infection as a cause of meningitis was documented by Austrian bacteriologist Anton Vaykselbaum who described meningococcal bacterium in 1887 [5].

A particularly severe epidemic of meningococcal meningitis occurred in Nigeria between January and June 1996. 109,580 cases were recorded and 11,717 of affected individuals died, giving a case fatality rate of 10.7% overall. This remains the most serious epidemic of cerebrospinal meningitis ever recorded in Nigeria, and may be the largest in Africa this century [6].

2.2 Epidemiology

Throughout the AMB (Fig. 1), epidemics of meningococcal disease have been reported since it was first described in early 20th century. Meningococcal meningitis is a major public health problem in the AMB. Despite the obvious seasonality of epidemics, the factors driving them are still poorly understood [7,8]. Meningococcal disease is common among persons with low socioeconomic status, and household crowding. Active and passive smoking is also a risk factor

[5]. An epidemic was defined as a cumulative district attack rate of at least 100 cases per 100,000 population during the period of epidemic risk which extends from December through May. Overall, the sensitivity of the threshold rate for predicting epidemics was 97%, the specificity was 95%, and the positive predictive value was 93% [9].

In major African epidemics, the attack rate ranges from 100 to 800 cases per 100,000 populations (Fig. 2), but individual communities have reported rates as high as 1% [10]. The true disease burden is likely to be higher than statistics suggest because routine reporting systems usually break down during epidemics. In addition; many people die before reaching a health center and thus remain unrecorded in official statistics [11,12].

Whereas, the majority of the cases in the AMB are caused by serogroup A meningococci. Historically, Serogroup C meningococci were responsible for outbreaks in the AMB in the 1980s, while serogroup W (formerly W-135) has emerged as a cause of epidemic meningitis since 2000 [13]. (Table 1).The analysis of surveillance data from Togo and Burkina Faso during 2006–2010 confirms that serogroup X meningococci not only causes small outbreaks and sporadic meningitis cases during seasonal hyper- endemicity, but has epidemic potential [14].

Generally, *N. meningitides* account for about half (50.5%) of all bacterial meningitis cases [15]. Other important causes of bacterial meningitis are *H. influenzae type b* (10.2%), *S. pneumonia* (7.5%), and the unspecified group (29.6%). The unspecified group consists of *group B Streptococcus, Salmonella spp, Streptococcus spp, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus spp, Brucella melitensis, Klebsiella pneumoniae, Acinetobacter anitratus, Enterobacter cloaca, Mycoplasma pneumoniae, Proteus spp, Rickettsiae spp.* They all constitute possible differential diagnoses to meningococcal meningitis.

Fig. 1. Meningitis Belt in West Africa
(https://microbewiki.kenyon.edu/index.php/Meningitis_In_West_Africa)

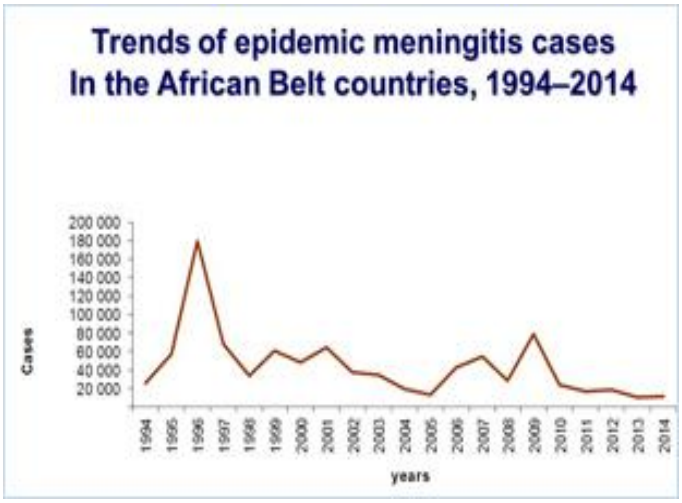

Fig. 2. Trends of epidemic meningitis cases in the African Meningitis Belt
(http://www.who.int/gho/epidemic_diseases/meningitis/Meningitis_001.jpg?ua=1)

Table 1. Major epidemics and implicated serotypes before and after introduction of conjugate meningococcal vaccine against serotype A

Country	Year	Number of cases	CFR	Serotype
Before the introduction of meningococcal A conjugate vaccine				
Nigeria [16]	1977	1257	8.3	A
Rwanda [17]	1978	1182	4.8	A
Burkina Faso [18]	1979	538	10.2	C
Côte d'Ivoire [19]	1983	414	NA	A
	1985	367	8.5	A
Chad [20]	1988	4542	9.5	A
Sudan [21]	1988	32,016	NA	A
Ethiopia [22]	1981	50,000	2.0	A
	1989	41,139	3.9	A
Kenya [23]	1989	3800	9.4	A
Burundi [24,25]	1992	1615	8.0	A
Niger [26,27]	1995	41,930	8.7	A
	1996	16,145	9.9	A
Burkina Faso [28]	1996	42,129	10.0	A
	1997	22,305	11.3	A
Mali [25]	1996	7254	11.5	A
	1997	11,228	10.1	A
Nigeria [6]	1996	109,580	11.2	A
Burkina Faso [29]	2002	13,000	8.7	W
Nigeria [30]	2009	55,626	4.1	A
Niger [30]	2009	12,604	4.0	A
After the introduction of meningococcal A conjugate vaccine				
Burkina Faso [31]	2012	2825	16.9	W
Chad [31]	2012	5808	4.4	A
Nigeria [32]	2015	6394	5.0	C
DR Congo [33]	2016	5675	10.3	W
Ghana [33]	2016	2406	10.8	w
Nigeria [34]	2017	5,595	10.9	C

Key: CFR = Case Fatality Rate; [16-34]

Source: Modified with permission from Mohammed I, Iliyasu G, Habib AG. Emergence and control of epidemic meningococcal meningitis in sub-Saharan Africa. Pathog Glob Health [Internet]. 2017;111(1):1–6

3. PATHOGENESIS

Meningococcal meningitis is a bacterial disease caused by *Neisseria meningitidis*. The mode of transmission of *N. meningitidis* is by droplet aerosol or secretions from the nasopharynx of colonized persons. The bacteria colonize and multiply on nasopharyngeal mucosa. In a few percentages of persons with nasopharyngeal colonization, the organism penetrates the mucosal cells to gain access to the bloodstream. It is possible that the ability of the organism to penetrate the mucosa is enhanced in persons with preceding upper respiratory tract infection. The organism crosses the blood–brain barrier in about 50% of bacteremic individuals to cause purulent meningitis [5].

Of the 13 subtypes or serogroups of *N. meningitidis* identified, serogroups A, B, C and W are recognized to be the main causes of epidemics, while occasional outbreaks are also caused by serogroups X and Y. [33] *N. meningitidis* is a fastidious, encapsulated, aerobic gram-negative diplococcus. Colonies are positive by the oxidase test and most strains utilize maltose. The phenotypic classification of meningococci, based on structural differences in capsular polysaccharide, lipooligosaccharide (LOS) and outer membrane proteins, is now complemented by genome sequence typing (ST).

The virulence of *N. meningitidis* is influenced by multiple factors: capsule polysaccharide expression, expression of surface adhesive proteins (outer membrane proteins including pili, porins: Por A and B, adhesion molecules: Opa and Opc), iron sequestration mechanisms, and endotoxin (LOS). *N. meningitidis* also has evolved genetic mechanisms resulting in a horizontal genetic exchange, high frequency phase, antigenic variation, and molecular mimicry, allowing the organism to successfully adapt at mucosal surfaces and invade the host [35].

Complement C5 deficiency (C5D) is a rare primary immunodeficiency associated with recurrent infections, particularly meningitis, by *Neisseria* species. The recently described C5 p.A252T mutation is reported to be associated with approximately 7% of meningococcal disease cases in South Africa. Data from genomic variation databases, indicate a 0·5-2% prevalence of the C5 p.A252T mutation in heterozygosity in Sub-Saharan Africa. Therefore, this mutation may have a relevant role in meningococcal disease susceptibility in this geographical area [36]. Also, persons with asplenia and chronic diseases are at increased risk of developing meningococcal meningitis.

4. DIAGNOSIS AND MANAGEMENT

The presentation of meningococcal meningitis is similar to every other form of purulent meningitis and includes fever, neck stiffness, photophobia, altered mental status, headache, and vomiting. There may be history of contact or ongoing epidemics. The incubation period of meningococcal disease is 3 to 4 days, with a range of 2 to 10 days [5].

The presentation can be much more severe in bacteremic patients (5 -20%) who may present with characteristic skin manifestations, such as petechiae and palpable purpura, adrenal infarction leading to adrenal insufficiency (Waterhouse-Friderichsen syndrome), purpura fulminans, and disseminated intravascular coagulation leading to rapid circulatory collapse. Less common presentations of meningococcal disease include pneumonia (5% to 15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%) [5,37].

Definitive diagnosis is by isolation of meningococci from cerebrospinal fluid (CSF) or blood. Meningococci can be isolated from the blood in up to 75% of persons with meningitis. Detection of meningococcal DNA in clinical specimen by polymerase chain reaction (PCR) is also helpful [5].

Treatment consists of hospital care and prompt intravenous antibiotic therapy. Antibiotics recommended by WHO include intravenous penicillin, ampicillin, chloramphenicol or ceftriaxone. In cases of epidemics where resources are limited, a single dose of intravenous ceftriaxone or intramuscular, long-acting (oily) chloramphenicol has been shown to be effective [38].

Rifampin, ciprofloxacin, and ceftriaxone are 90%–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis in close contacts (household members, child care center contacts, and anyone directly exposed to the patient's oral secretions) [5].

Meningococci strains resistant to chloramphenicol, rifampin, fluoroquinolones, and

penicillin have been isolated in small proportions in many parts of the world. However, there is limited data on the current chemo-resistant pattern of meningococci in the Sub-Saharan Africa. In a review of *N. meningitidis* isolates from Sub-Saharan Africa published in 2009, all *N. meningitides* isolates were susceptible to ceftriaxone, chloramphenicol and ciprofloxacin. No isolate produced b-lactamase, and only three isolates (2%) displayed reduced susceptibility to penicillin G. One percent of isolates displayed reduced susceptibility to rifampin, while 52% of the isolates were resistant to tetracycline, 74% were resistant to erythromycin, and 94% were resistant to sulfadiazine [37,39].

The case-fatality ratio of meningococcal disease is 10% to 15%, even with appropriate antibiotic therapy. The case fatality ratio of meningococcemia is up to 40%. As many as 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb [5].

5. VACCINATION

The field introduction of a new group A meningococcal conjugate vaccine, has been a stunning success, with the virtual disappearance of group A meningococcal meningitis in Sub-Saharan Africa. In 2001, the Bill & Melinda Gates Foundation awarded a grant of US$ 70 million to create the Meningitis Vaccine Project as a partnership between Program for Appropriate Technology in Health (PATH) and World Health Organization (WHO), with the single goal of developing, licensing, and introducing at public health scale a group A meningococcal conjugate vaccine for Sub-Saharan Africa, manufactured at the Serum Institute of India, Ltd. With study results showing safety and strong immunogenicity of a single dose at the age of 9 months and following the WHO Strategic Advisory Group of Experts on Immunization recommendations of October 2014, the vaccine is now gradually introduced as a new Expanded Program on Immunization (EPI) antigen in meningitis belt countries. The 2011 epidemic season ended with no reported case of group A meningitis in vaccinated individuals [40,41,42,43]. Conjugate meningococcal vaccine against serotype A was deployed in 2010. So far, 262 million individuals have been immunized across the meningitis belt [11].

Prior to the development of the meningococcal A conjugate vaccine, capsular polysaccharide vaccines were in use. However, the polysaccharide antigen is T-cell independent and stimulates antibody production in mature B-lymphocytes. Without a T-cell mediated response, there is no class switching, affinity maturation, or development of memory cells. Polysaccharide vaccines are not as effective in infants because infants lack the mature lymphocytes required for a robust immune response. Infants vaccinated between 7 and 12 months of age have a serum bactericidal activity concentration indistinguishable from unimmunized children by 24 months of age [44,45]. The immunity developed following vaccination in adolescents also drops off drastically after one year, requiring re-vaccination during each outbreak. Finally, polysaccharide vaccines do not completely protect from acquisition of nasopharyngeal carriage and therefore they do not provide long-term herd immunity [44,46].

The conjugate vaccine boosts immunogenicity by transforming the vaccine from T-cell independent to T-cell dependent, thus allowing for priming of immunological memory and increasing immunogenicity in infants. One year following introduction of these vaccines, a 66% decrease in the prevalence of nasopharyngeal carriage of serogroup A meningococci in adolescents and 67% reduction in the attack rate in the unvaccinated adolescent population were noted, conferring a high level of herd immunity. This success opens the door for the development of polyvalent conjugate vaccines against other serotypes [47,48,49]. Those vaccinated with conjugate meningococcal vaccines will require booster doses every 5 years [5].

6. CHALLENGES

The control strategy of meningitis epidemics in Sub-Saharan countries, although re-examined regularly, is based on epidemiological, immunological and logistical considerations put forward at the end of the 1970s. Despite much progress in surveillance and biological research, no explanation exists to date for the epidemic pattern of meningitis in the African meningitis belt, which is required to mathematically model the impact of vaccine strategies or to predict epidemics [50,51].

The effectiveness of mass vaccination as a strategy for the control of meningitis epidemics has been questioned. The sporadic nature of the outbreaks and the optimal use of vaccines to

control both short-term epidemic and endemic meningococcal disease has been the subject of much debate. In particular, the results of several studies in Africa have shown that vaccination during outbreak situations is suboptimal, mainly because populations in resource-poor areas cannot be immunized rapidly enough. In addition, although rapid laboratory diagnosis is an essential component in the surveillance of meningococcal epidemics, as it allows decision-makers to select the most appropriate vaccine for mass vaccination .The resource-poor countries most affected by such epidemics struggle to achieve such diagnosis [7].

Recent findings confirm that the areas affected by smaller epidemics are still expanding to new districts, with the southwards extension in the Sahelian region (in Cote d'Ivoire, Togo, the Central African Republic, and Cameroon) particularly apparent. The authors believe this is consistent with increased human activity in this area such as deforestation and desertification that may have caused the Sahelian areas to expand southwards.

The public health benefits of Meningococcal A conjugate vaccine have already been demonstrated by a sharp decline in reported cases of meningococcal serogroup A disease in the countries where it has been introduced [11]. However, serogroup replacement following mass meningitis vaccination has been noted, and in 2015 an epidemic with a novel strain of serogroup C was recorded in Niger and Nigeria for the first time since 1975. This has posed a serious challenge toward elimination of meningococcal meningitis epidemics in Africa [11].

In addition, no consistent annual spatio-temporal pattern for cluster emergence and epidemic spread could be observed, thus precluding the capacity to predict where the next epidemic would break out, and what geographical direction it would follow [52].

Surveillance of meningitis in Africa has been hampered by a lack of laboratory facilities—particularly in outlying areas, which may have substantially different patterns of disease than those seen in urban centers. The cost of PCR may also prove to be a substantial barrier to more-widespread use [53].

7. RECOMMENDATIONS

For an effective control of meningococcal meningitis in the AMB, there is a need for an effective surveillance system, provision of rapid antigen detection kits, as well as development of affordable polyvalent conjugate vaccine that provides protection against the main serogroups causing meningitis in the sub-region [11]. In order to eliminate meningococcal outbreaks, accelerated development of an affordable polyvalent conjugate vaccine should be a high priority for WHO and partners.[33] African national immunization programs are capable of achieving very high coverage for a vaccine desired by the public, introduced in a well-organized campaign, and supported at the highest political level. The Burkina Faso success augurs well for further rollout of the Meningococcal A conjugate vaccine in meningitis belt countries [54].

Present studies indicate that PCR technology can be used in African settings to overcome some of these limitations [55]. PCR has a high sensitivity and specificity [56] and the lower limit of bacterial concentrations necessary for detection are such that false-positive results caused by transient contamination (e.g. nasopharyngeal carriage) are unlikely to occur [57]. PCR technology is also rapid. Thus, PCR could be used as the basis for implementing etiology-specific treatment guidelines and for determining the appropriate vaccines for use in the response to and prevention of epidemics [53].

The results of the first large-scale study of meningococcal meningitis dynamics highlight the strong interest and the necessity of a global survey of meningococcal meningitis in order to be able to predict and prevent large epidemics by adapted vaccination strategy. International cooperation in Public Health and cross-disciplines studies are highly recommended in controlling this infectious disease [58]. Further studies are equally needed to enhance our understanding of the complex relationship between meningitis epidemics and the environment [59].

8. CONCLUSION

Recurring epidemics of meningococcal meningitis remain a major public health issue in Sub-Saharan Africa. The challenges are numerous, ranging from dearth of efficient and affordable polyvalent conjugate vaccine, serogroup replacement following mass meningitis vaccination, poor surveillance during epidemics, to harsh environmental changes and

poor political will. The success story of Meningococcal A conjugate vaccine needs to be replicated to include other serogroups and to reach every nook and cranny of this region. This will be achieved through international collaboration among all stakeholders.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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