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REVIEW

Emergence and control of epidemic meningococcal meningitis in sub-Saharan Africa

Idris Mohammed[a], Garba Iliyasu[b] and Abdulrazaq Garba Habib[b]

[a]Federal Teaching Hospital Gombe, Gombe, Nigeria; [b]Infectious Disease Unit, Department of Medicine, College of Health Science, Bayero University Kano, Kano, Nigeria

ABSTRACT

For more than a century, meningitis epidemics have regularly recurred across sub-Saharan Africa, involving 19 contiguous countries that constitute a 'meningitis belt' where historically the causative agent has been serogroup A meningococcus. Attempts to control epidemic meningococcal meningitis in Africa by vaccination with meningococcal polysaccharide (PS) vaccines have not been successful. This is largely because PS vaccines are poorly immunogenic in young children, do not induce immunological memory, and have little or no effect on the pharyngeal carriage. Meningococcal PS–protein conjugate vaccines overcome these deficiencies. Conjugate meningococcal vaccine against serotype A (MenAfriVac) was developed between 2001 and 2009 and deployed in 2010. So far, 262 million individuals have been immunized across the meningitis belt. The public health benefits of MenAfriVac have already been demonstrated by a sharp decline in reported cases of meningococcal disease in the countries where it has been introduced. 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 the African. For an effective control of meningococcal meningitis in the African meningitis belt, there is a need for an effective surveillance system, provision of rapid antigen detection kits as well as affordable vaccine that provides protection against the main serogroups causing meningitis in the sub-region.

KEYWORDS

Meningococcal meningitis; control; meningitis belt; Africa; serogroup dynamics

Introduction

An illness resembling meningococcal disease was described as far back as the sixteenth century; however, it was not until 1805 when the meningococcal disease was first described by Vieusseux during an outbreak with 33 deaths in the vicinity of Geneva, Switzerland [1]. In 1884 an oval micrococcus was described by an Italian pathologist in a sample of cerebrospinal fluid (CSF) [2], while, in 1887 Anton Weichselbaum first identified bacterium causing meningococcal disease in the CSF of patients with bacterial meningitis and the bacterium was named *Diplococcus intracellularis meningitis* [3]. There are 12 serogroups of *N. meningitidis* characterized by different capsular polysaccharides; only 6 of them (A, B, C, W, X, and Y) cause most life-threatening invasive disease.

For more than a century, meningitis epidemics have regularly recurred across large sections of sub-Saharan Africa, involving twenty-six contiguous countries that constitute a 'meningitis belt' stretching from Senegal in the west to Ethiopia in the east, largely caused by the serogroup A meningococcus [4]. About 240 million people live in the seven countries with the highest risk: Burkina Faso, Mali, Niger, Chad, northern Nigeria, Sudan, and Ethiopia.

Meningococcus could have been introduced into Africa through the Sudan by pilgrims returning from the Hajj around the turn of the century and subsequently appeared in the northern savanna of Africa in the 1880s. Since 1905 major epidemics of meningococcal meningitis have occurred in countries of the Sahel and sub-Sahel every few years, culminating in a massive epidemic in which nearly 200,000 cases were reported in 1996 [5]. Attempts to control epidemic meningococcal meningitis in Africa by vaccination with meningococcal polysaccharide(PS) vaccines have met with only modest success because epidemics can progress with great rapidity and vaccination is often started too late. However, in the medium term, the best prospect for the control of meningococcal meningitis in Africa lies in recent development of polysaccharide-protein conjugate vaccines which, unlike polysaccharide (PS) vaccines, are immunogenic in the very young, induce immunological memory, likely to reduce carriage and give long-lasting protection.

Major African epidemics

Epidemics in Africa occur in the dry season, and an epidemic wave can last two to three years, dying out during

CONTACT Garba Iliyasu ilyasug@yahoo.com

Table 1. Major epidemics in sub-Saharan Africa over the past 40 years.

Country	Year	Number of cases	CFR	Serotype
Before MenAfriVac Campaign				
Nigeria[15]	1977	1257	8.3	A
Rwanda[16]	1978	1182	4.8	A
Burkina Faso[17]	1979	538	10.2	C
Côte d'Ivoire[18]	1983	414	NA	A
	1985	251	8.5	A
	1985	367	8.5	A
Chad[19]	1988	4542	9.5	A
Sudan[20]	1988	32,016	NA	A
Ethiopia[21,22]	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
Burkina Faso[26]	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
Niger[27,28]	1995	41,930	8.7	A
	1996	16,145	9.9	A
Nigeria[29]	1996	109,580	11.2	A
Burkina Faso[30]	2002	13,000	8.7	W
Nigeria[31]	2009	55,626	4.1	A
Niger[31]	2009	12,604	4.0	A
After MenAfriVac Campaign				
Burkina Faso[32]	2012	2825	16.9	W
Chad[32]	2012	5808	4.4	A
Nigeria[33]	2015	6394	5.0	C
Niger[34]	2015	8500	6.7	C

the intervening rainy seasons. The size of these epidemics can be enormous and place an immediate and great burden on the health systems. In major African epidemics, the attack rate ranges from 100 to 800 per 100,000 populations, but individual communities have reported rates as high as 1/100 [6]. The true disease burden is likely to be higher than statistics suggest because routine reporting systems break down during epidemics. In addition, many people die before reaching a health center and thus remain unrecorded in official statistics [7].

Since the 1940s, epidemic cycles have been detected every 8 to 12 years, but two troubling phenomena have been observed since the early 1980s: the intervals between epidemics have become shorter and more irregular, and the meningitis belt seems to be extending further south, touching regions that had been spared until now, such as Angola, Burundi, the Democratic Republic of the Congo, Rwanda (Great Lakes region), and Zambia. Climatic changes have been suggested as a reason for the expansion of the meningitis belt. However, it is not certain whether these changes are also due to enhanced disease surveillance. The most recent large-scale meningitis epidemic in the African meningitis belt occurred in 2009, with a total of 88,199 suspected cases and case fatality rate of about 6.1% [8,9]. More than 85% of the cases occurred in Northern Nigeria and Niger and are characterized by the predominance of *Neisseria meningitidis* (Nm) serogroup A. In 2012 another epidemic occurred in the African meningitis belt involving 10 countries with a majority of cases reported in Burkina Faso and Chad. The outbreaks were mainly caused by the W serogroup of *Neisseria meningitidis* (Nm) [10]. An outbreak occurred recently starting from late 2013 to 2015 mostly affecting Niger and Nigeria with a predominance of serogroup C [11]. Molecular epidemiologic studies suggest the organism originated in northwestern Nigeria though the last time serogroup C caused disease in Nigeria was 40 years ago in 1975 [12,13].

Risk factors for invasive disease and for outbreaks are not completely understood. Combinations of conditions (environment, host, and organism) are necessary for an epidemic to occur. These include the immunological susceptibility of the population (perhaps due to loss of herd immunity to the prevalent strain), special climatic conditions (dry season, dust storm), low socioeconomic status, pharyngeal carriage in the community and transmission of a virulent strain. Acute respiratory tract infections may also contribute to the development of meningococcal disease epidemics [14].

Electronic databases (Google Scholar, Medline, Embase, PubMed, AJOL, and Scopus) were searched for literatures in English or French. WHO Weekly Epidemiological Record was also searched. Cross references were also checked for other potentially relevant studies. Keywords used in the search include: Meningococcal meningitis, Epidemic, Outbreak, Africa, sub-Saharan Africa, Meningitis belt, Meningococcal vaccine, Meningococcal polysaccharide vaccine, meningococcal conjugate vaccine (see Table 1).

Control effort

Before the 1970s epidemic meningococcal meningitis used to be controlled mainly by mass chemoprophylaxis with sulpha-based drugs [35], this lead to the occurrence of regular epidemics. The control effort was also confounded by the emergence of resistance to sulpha drugs among Neisseria meningitidis isolates [36]. Vaccination was then given serious consideration when it was proven to prevent meningococcal meningitis [37–41]. Hence for many years an anti-meningococcal A/C PS vaccine has been used to control epidemics in the African meningitis belt, using reactive immunization strategy because the vaccine was expensive and not available in sufficient quantities for mass vaccination campaigns in the resource limited countries constituting the meningitis belt [42]. (Table 2) Over the years vaccination campaigns has produced sufficient evidence that PS vaccines groups A+C were effective in preventing many cases [43], and has mitigated the extent of meningitis outbreaks, but it has not prevented the continuing occurrence of large outbreaks of the disease, because PS vaccines are poorly immunogenic in young children, do not induce immunological memory, and have little or no effect on pharyngeal carriage. Meningococcal PS–protein conjugate vaccines overcome these deficiencies and can prevent carriage [44]. The usefulness of meningococcal

Table 2. Massive polysaccharide vaccination campaign in the meningococcal meningitis belt of Africa.

Country	Year	Population (estimated)	Number of cases	Percentage vaccinated	Number of persons vaccinated	Type of vaccine
Egypt[40]	1973	–	–	–	62,295	A
Egypt[41]	1977	–	–	–	88,263	A
Rwanda[16]	1978	35,644	9290	38.5%	13,735	A+C
Nigeria[52]	1978–1981	14,500,548	7471	52.0%	7,535,350	A+C
Mali[53]	1982	671,000	837	59.6%	400,000	A+C
Chad(N'Djamena)[19]	1988	550,000	4542	48.5%	266,738	A+C
Niger[54]	1991	3,070,160	4052	–	216,218	A+C
Zaire(Kibumba)[55]	1995	180,000	162	76%	121,588	A+C
Zaire (Katale)[55]	1995	11,000	137	–	112,354	A+C
Mali[56]	1996	–	2347		865,903	A+C
Central African Republic[57]	1996	200,000	1500	57.5%	115,000	A+C
Togo [58]	1997	500,000	2992	67.3%	346,469	A+C
Ghana[59]	1997	1,700,000	18,703	73%		A+C
Chad[60]	1997	–	2835	–	1,650,000	A+C
Sudan(Northern Dafur)[61]	1998–1999	644,906	896	14.0%	90,153	A+C
Nigeria[62]	2014	–	75,000		28,997,903	A+C+W & A+C
Niger[63]	2015	–	8500	68%	960,000	A+C+W/A+C+Y+W

conjugate vaccine was shown by the almost complete elimination of the serogroup C disease from countries in Europe which introduced the serogroup C meningococcal vaccine [45]. Because conjugate vaccines developed for use in industrialized countries are not affordable for sub-Saharan African, countries within the meningitis belt of Africa have continued to use PS vaccine until 2010 when meningococcal serogroup A PS–tetanus toxoid conjugate vaccine (PsA–TT, MenAfriVac), produced by the Serum Institute of India was introduced through the Meningitis Vaccine Project [46].

From 2010 to 2014, MenAfricVac was introduced in 26 countries of the African meningitis belt and projected to continue in to 2017. During the 5-year period, up to 235 million Africans were vaccinated [47,48]. Results from rigorous coverage surveys conducted during the first 3 years of the introduction and for the most part confirmed that coverage in the correct age group (1 to 29 years) was >90%. The public health benefits of MenAfriVac have already been demonstrated by a sharp decline in reported cases of meningococcal disease in the countries where it has been introduced [49–51].

Polysaccharides vaccine and Men Afric vaccine including efficacy of these vaccines

The first vaccines against meningococcal disease were polysaccharide vaccines, used since the 1970s [64]. Even though previous studies in the African meningitis belt have shown some reasonable efficacy of meningococcal polysaccharide vaccine [51,65,66], its failure to effectively prevent major epidemics has been observed [67–71]. As a response to the devastating meningococcal epidemics in the meningitis belt in 1996 and 1997 [29,72], a public–private partnership between the WHO and Program for Appropriate Technology in Health (PATH) was established in 2000; the Meningitis Vaccine Project (MVP), aimed at eradicating meningococcal epidemics from the meningitis belt by developing, testing and implementing a safe, immunogenic and affordable NmA conjugate vaccine [73]. This untraditional vaccine development model leads to the emergence of MenAfriVac, manufactured by the Serum Institute of India. Clinical trials conducted among approximately 10,000 persons aged 1–29 years, in India and in Africa, confirmed a vaccine safety profile similar to that of licensed PS vaccines, as well as a stronger and more persistent immunological response against group A meningococcus (MenA) [74,75]. In June 2010 world health organization (WHO) allowed its use in the meningitis belt of Africa at an affordable cost of US$ 0.4 per dose [73].

The deployment of MenAfriVac vaccine has signaled a major decline in the incidence of meningococcal disease outbreaks in the sub-region. Initial evaluation of the vaccine's effectiveness and its safety profile during the first introduction showed that the vaccine is safe, significantly reduced meningococcal carriage, and dramatically reduced disease incidence [49,50,76].

Meningococcal serogroup dynamics

In the African meningitis belt, most meningitis outbreaks have been caused by *N. meningitidis* serogroup A [77–79], with smaller and less frequent outbreaks due to N. meningitides serogroup C [80]. Following the introduction of MenAfriVac, the number of meningitis A cases has decreased dramatically, with no outbreaks caused by this serogroup occurring in vaccinated areas [81]. Reports from Niger and Burkina Faso have indicated a significant increase in serogroup W prevalence in the years following campaigns with MenAfriVac around 2010 [82,83]. Also following a mass vaccination with MenAfriVac in Chad in 2011–2012, serogroup A carriage decreased from 0.7 to 0.02%, while carriage of 'other' serogroups (i.e. not A, W, X) increased from 0.4 to 0.7% [84]. In 2015 an epidemic with a novel strain of serogroup C was recorded

in Niger and Nigeria for the first time since 1975 [12,13]. However, even before the MenAfriVac campaigns there have been an increasing number of outbreaks caused by *N. meningitidis* serogroups W and X [85–89]. Therefore, the recent emergence of other non-A serogroups as an important cause of invasive disease, could be as result of these serogroups expanding to fill the niche left by serogroup A, as capsule switching has not been documented.

Conclusion

The introduction of MenAfriVac which is affordable, effective, long-lasting conjugate vaccine against Group A meningococcus offers extraordinary hope for wiping out epidemics of group A meningococcal meningitis in sub-Saharan Africa. However, the emergence of new serogroups coupled with the increasing number of population at risk as a result of lack of routine vaccination has posed a serious challenge toward achieving this goal. As long as pathogenic serogroup freely circulate in unprotected Sub-Saharan Africans the potential for major meningitis epidemics is always present. This underlines the need for an effective surveillance system including community-based surveillance and also the provision of validated rapid antigen detection kits as well as an affordable vaccine that provides protection against the main serogroups causing meningitis in Africa and potentially against serogroups that may emerge in the region in the future. The success of MenAfriVac, in virtually eliminating group A meningococcal disease and carriage in large regions of sub-Saharan Africa, has highlighted the need for a polyvalent vaccine to achieve the same for groups C, W, X, and Y. The current effort to develop an affordable, heat-stable, pentavalent conjugate meningococcal vaccine targeting all meningitis strains in Africa is hope to eventually put meningitis-free Africa within reach.

Robust surveillance has been poor in Nigeria due both to the failure of Nigeria (or its health systems, practitioners, etc) and the international community perhaps due to insecurity. Being the most populous of the meningitis belt countries this may compromise control efforts. The emergence of serotype C in Nigeria which spread to Niger is a case in point. Unless the Nigerian region is fully embedded in control efforts large gaps may be left with disastrous consequences.

Disclosure statement

All the authors declared no conflict of interest.

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