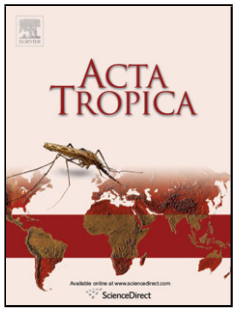

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PII: S0001-706X(16)30431-4
DOI: http://dx.doi.org/doi:10.1016/j.actatropica.2017.01.014
Reference: ACTROP 4185

To appear in: *Acta Tropica*

Received date: 24-6-2016
Revised date: 14-1-2017
Accepted date: 16-1-2017

Please cite this article as: Kwarteng, Alexander, Amuasi, John, Annan, Augustina, Ahuno, Samuel, Opare, David, Nagel, Michael, Vinnemeier, Christof, May, Jürgen, Owusu-Dabo, Ellis, Current meningitis outbreak in Ghana: Historical perspectives and the importance of diagnostics.Acta Tropica http://dx.doi.org/10.1016/j.actatropica.2017.01.014

Review

Current meningitis outbreak in Ghana: historical perspectives and the importance of diagnostics

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Abstract

Bacterial meningitis continues to be one of the most dreaded infections in sub-Saharan Africa and other countries that fall in the "meningitis belt" due to recurrent nature of the infection and the sequel of deliberating effects among survivors even after treatment. Ghana has had recurrent epidemics in the past but has been free from high mortality levels. Whereas reasons for the low reported number of deaths in the past are unclear, we hypothesize that it may be due to increased vaccination from expanded program on immunization (EPI) and consequent herd immunity of the general population. As at the end of February, 2016, 100 individuals were reported to have died out of 500 recorded cases. The infection may cause severe brain damage and kills at least 1 out of 10 individuals if quick interventions are not provided. The Ghana

Health Service (GHS) and the Ministry of Health (MoH), together with other local and international stakeholders are working intensely to control the spread of the infection in affected communities with treatment and other health management programmes. This review presents a quick overview of meningitis in Ghana with emphasis on *S. pneumoniae* (responsible for about 70% of cases in the recent epidemic) together with some recommendations aimed at ensuring a "meningitis-free Ghana".

Keywords: Meningitis; *Streptococcus pneumoniae;* Vaccine; Serotype; Antibiotics; Ghana

Introduction

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord (meninges). This inflammation could be as a result of viral, bacterial, or fungal infection of the fluid surrounding the brain and spinal cord. Although bacteria and viruses are most often implicated, meningitis caused by parasites and fungi, as well as non-infectious meningitis have also been reported [1].

Bacterial meningitis is mainly caused by *Streptococcus pneumoniae, Neisseria meningitidis* (commonly known as Meningococcal meningitis) and *Haemophilus influenzae* type B. The infection is reported to affect over 26 countries in sub-Saharan Africa which fall within what has become known as the 'meningitis belt' [2]. Outbreaks of meningitis in developing countries pose an enormous public health challenge to their already burdened healthcare delivery systems. In Ghana for example, between 1994 and 1996, about 17,000 persons were infected with bacterial meningitis, of which about 1,000 (5.8%) individuals were reported to have died [3].

In addition, like most other countries within the meningitis belt, Ghana experiences sporadic outbreaks of meningitis almost every year (Figure1); however, the current outbreak in Ghana has had significant impact and media attention since the last quarter of 2015. As at the end of January 2016, according to the Ghana Health Service (GHS), more than 400 suspected cases in Ghana had been reported, of which almost 90 individuals (22.5%) were reported dead, while a number of unconfirmed cases have been hospitalized [3]. The disease began in the Northern region of Ghana and spread to the Brong-Ahafo, Ashanti, and Eastern regions. At the time of drafting this paper, cases had just been reported in 9 out of the 10 regions of Ghana. Current figures indicate that the Brong-Ahafo is the worst hit, accounting for about 70% of all cases (Figure 2). Of the confirmed cases, *S. pneumoniae* has been identified as the leading causative organism, although *N. meningitidis* (strain NM W, which causes cerebrospinal meningitis (CSM) and *N. meningitidis* type C) have also been) isolated [3].

A number of factors are associated with the development of bacterial meningitis. First, low levels of complement-mediated killing via antibodies facilitate the progression of bloodstream infection; hence infants and young children are most susceptible after maternal antibodies have waned. Second, close contact with infected persons through activities such as kissing, sneezing, coughing, sharing of personal belongings (e.g. cutlery and fomites), as well as crowded living settings (a scenario commonly observed in many developing countries such as Ghana [4] facilitates spread of the causative organisms [4, 5]. Furthermore, smoking or exposure to second hand smoke has been linked with a high risk of pathogen carriage and transmission [6].

As with most infections, some exposed persons in the population remain asymptomatic, whereas others develop fulminant disease and may even die if not quickly treated. The dichotomy between frequent asymptomatic carriage and occasional devastating meningitis is in part attributable to the

variability of the biochemical composition of the capsular polysaccharide that characterizes serogroup [7]. For symptomatic individuals some of the overt manifestations include seizures, severe headache, stiff neck, cold extremities and confusion. Others also show signs of high fever, nausea and vomiting, photophobia and rashes [8].

Although bacterial meningitis in the sub-Saharan African belt occurs the entire year, most cases are recorded during the Harmattan season, characterized by low humidity, extreme temperature variations, as well as windy and dusty conditions [9]. The harsh weather conditions during the Harmattan easily causes damage to the mucous membranes of the oral cavity through dry air and strong dust winds, thereby creating propitious conditions for the easy transmission of the bacteria responsible for bacterial meningitis. Moreover, low absolute humidity and dust may enhance meningitis bacteria invasion by damaging the mucosal barrier directly or by inhibiting mucosal immune defenses [10]. While it is unclear why the number of cases in Ghana have increased this year, challenges associated with serotyping the specific *S. pneumoniae* involved in the current outbreak, harsh weather conditions, frequent movement of individuals from the affected areas to other parts of the country and as well, the emergence of a more virulent strain of the meningitis-causing bacteria, could account for the change observed in the epidemiology of the infection. Given the increased frequency of cases caused by *S. pneumoniae* in the ongoing outbreak in Ghana, this review focuses on pneumococcal meningitis.

Epidemiology of Meningitis in Ghana

Apparently, studies on Cerebrospinal Meningitis (CSM) could be traced back to the year 1900, the time in which the first major outbreak was recorded in Cape Coast, Ghana [11]. The subsequent meningitis outbreak was in 1906-1908 during the dry season in the northern part of Ghana which accounted for some 20,000 deaths [12]. The epidemics were recorded every 8-12 years ever since

[13]. A major landmark of the meningitis epidemics was the W-135 strain associated with the returnee Hajj pilgrims [14].

Epidemiological occurrence of *S. pneumoniae* meningitis in Ghana has strong resemblance to those associated with meningococcal meningitis outbreaks. Previous epidemiological studies in Northern Ghana reported 51 deaths (46%) out of 117 pneumococcal cases over the period of 1998-2003 [15]. The study reported a total of 76 pneumococcal isolates, from which fifty-eight (76%) belonged to serotype 1, forming the dominant strain. Non-serotype 1 isolates included 14, 3, 7F, 8, 12F, 6A, 10F, and 38 [15].

In addition, a recent study by Dayie and colleagues reported the prevalence of *S. pneumoniae* meningitis in two major cities in Ghana i.e., Accra and Tamale, as 34% and 31%, respectively [16]. The dominant serotypes reported by that study were 19F, 6B, 23F, and 6A. However, serotypes 19A and 6B emerged as the penicillin resistant isolates in the sample. In addition, 23% of the samples were non-typable in Accra, while 12% were non-typable in Tamale [16].

Current vaccines being used for the Ghanaian population are the pneumococcal conjugate vaccines (PCVs). PCV-13 covers close to half of the serotypes while PCV-23 covers 55% of the samples [16]. Several studies have investigated the impact of climate change on the epidemiology of meningitis [9, 10] as well as the seasonality of the meningitis epidemics. Such studies revealed that the epidemics stop with the onset of the raining season but resume in the dry season [15, 17]. Moreover, the disease has been linked with humidity [18], rainfall [19], dry harmattan winds and dusty conditions [10]. The above reports show that *S. pneumonia* meningitis epidemics is on the increase and appear to be overtaking that of meningococcal meningitis. This observation suggests that the control and management of bacterial meningitis in Ghana needs to be carefully evaluated.

Overview of *S. pneumoniae*

S. pneumoniae are Gram-positive cocci that are typically observed in pairs, but may also be found as individual bacteria or in short chains. *S. pneumoniae* infection is noted to cause a range of diseases such as meningitis, bacteremia, pneumonia, sinusitis, and otitis media [20]. Pneumococcal infection is relatively common at the extremes of age i.e. in children below the age of 2 years and adults aged over 65 years; 160 per 100,000 respectively, compared to 5 per 100,000 in adolescent and young adult years [21]. In children, *S. pneumoniae* has been shown to colonize the upper respiratory tract, causing mild respiratory tract infections [22].

The host-pathogen interaction with *S. pneumoniae* is remarkable, given the diversity of interactions that occur from asymptomatic nasopharyngeal colonization, through to focal infections of the meninges, joints, or eyes, to devastating meningococcal sepsis. In most affected communities, a high proportion of the population is colonized with *S. pneumoniae* at one time or another. However, why invasive disease occurs in a relatively very small percentage of individuals is unclear. While the production of endotoxin is one of the key pathogenic mechanisms, the presence of protective antibodies appears critical in the prevention of invasive disease [23].

Identification of *S. pneumoniae* infection

Rapid identification of the strain of *S. pneumoniae* is critical to controlling pneumococcal meningitis. Current diagnosis relies both on clinical assessment and laboratory investigations with varying degrees of sensitivities and specificities depending on the method and/or sample used [24]. Cerebrospinal Fluid (CSF) analysis via microscopy, culture, latex agglutination testing and clinical assessment remains fundamental for a timely diagnosis of *S. pneumoniae* [25]. Detection rates in

CSF may be as high as 90%, and the diagnostic yield of CSF microscopy can be improved by centrifugation [26], however, this decreases to about 50% in blood cultures.

Clinical laboratory investigations continue to advance, and more traditional approaches such as the Gram staining are being combined with rapid methods such as antigen testing and, more recently, molecular technologies such as Polymerase Chain Reaction (PCR) and microarray [27, 28]. The PCR method has provided a rapid and highly sensitive diagnostic technique for detecting several infections including pneumococcal infection [29]. Clinical samples, including CSF, blood and sputum have been extensively studied using PCR. In fact, PCR based testing of 96 samples of suspected *S. pneumoniae* showed a sensitivity of 100% (70 of 70) and specificity of 100% (26 of 26) [30].

Although these new technologies are creating more diagnostic options for pneumococcal meningitis infection, affordability and availability at the global level is constrained by socioeconomic disparities, with the most affected, poorest populations having the least access [31]. In response to the pneumococcal meningitis outbreak in Ghana, the World Health Organization (WHO) has supported the Ministry of Health (MoH) with rapid diagnostic test kits such as Pastorex, a family of rapid, latex agglutination test, and microscopy for detecting pneumococcal meningitis at the health facilities to ensure quicker treatment of infected persons [32].

However, these tests are limited, in that they fail to identify the serotype of *S. pneumoniae*, which is critical to initiating population-level interventions such as vaccination. In addition to these tests used at the health facilities, samples from infected persons are sent to the nearest reference laboratory for culture. But culturing requires a couple of days, and often results in delays in the appropriate antimicrobial treatment of pneumococcal meningitis patients.

Thus, given that molecular based assays such as PCR offers higher sensitivity and specificity compared to the current methods used at the lower hospitals (gram stain, microscopy and culture); samples from infected persons from the District Health Directorates could be further investigated at existing research institutions and referral hospitals equipped with molecular based-capacities. While the WHO continues to support the MoH by augmenting supplies of laboratory reagents, community and facility surveillance, sensitization and case management, there are serious gaps in the current *S. pneumoniae* serotyping efforts, particularly from remote areas where the number of cases are very high.

Vaccination

Mass vaccination is currently one of the best remedies for reducing the burden of meningitis in endemic regions [33]. Globally, there are two main types of pneumococcal vaccines. They are pneumococcal polysaccharide vaccine (PPV) and the pneumococcal conjugate vaccine (PCV). Polysaccharide vaccines have been used to control African meningitis epidemics for over three decades, unfortunately little or modest success has been chalked, largely because there were logistical problems hindering the success of reactive vaccination which have now been solved with the support of the WHO [34]. Currently, fifty-three developing countries have introduced PCV into their routine immunization programmes [35]. Recently, in The Gambia, a population- based surveillance in the 2-3 months age group resulted in an 82% reduction in invasive pneumococcal disease caused by PCV13 serotypes as well as a 55% reduction in all invasive pneumococcal disease [35]. According to the WHO, Ghana has made a huge progress over the years in immunization with a national coverage of 4% in 1985 to 90% in 2012. In 2012, the MoH concurrently introduced two vaccines, Rota and PCV in infants (beginning at age 6 weeks) into

the national expanded programme of immunization to accelerate improvement and child health survival [36]. Whether or not Ghana stands to benefit from mass immunization campaigns against *S. pneumoniae* is currently unclear given the fact that the specific *S. pneumococcus* strain remains to be serotyped in the various affected communities.

Treatment for Bacterial Meningitis

Meningitis treatment heavily relies on broad-spectrum antibiotics and vaccines. Upon suspicion of bacterial meningitis, ceftriaxone or cefotaxime in combination with vancomycin is administered [37]. Therefore, in response to *S. pneumoniae*, the key intervention is prompt identification of affected cases and treatment with full course of antibiotics according to national and WHO guidelines. Appropriate antibiotic treatment is started as soon as possible after the detection of *S. pneumoniae*. Interestingly, a recent study in a teaching hospital in Ghana reported that *S. pneumoniae* is highly susceptible to penicillin, chloramphenicol and ceftriaxone [38]. Thus the first choice for treating meningitis in accordance with hospital antibiotic policy in Ghana is penicillin and chloramphenicol, while ceftriaxone considered as alternative [39]. In the ongoing meningitis outbreak in Ghana, most of the affected areas have limited health infrastructure and resources. Since late diagnosis and management increases the risk of neurological sequelae in younger persons [40]; early diagnosis and management, especially among the younger population is highly recommended in endemic regions [41]. While providing appropriate medication for persons with *S. pneumoniae* meningitis in response to the outbreak in Ghana, there is also the need to address individuals who may have come in contact with the infected persons and are at risk of spreading the disease.

National-level Intervention

Public education on pneumococcal meningitis has been stepped-up country-wide as part of the intervention programme launched by the MoH and other stakeholders. Local media outlets (especially radio and TV), religious groups and schools continue to play a key role in the health education and communication efforts, as they usually serve as the primary sources of information to the public [42]. Current efforts aim at informing the general public on the mode of infection transmission, signs and symptoms and preventive measures individuals can take to prevent the spread of the disease. The MoH and GHS in consultation with private hospitals have intensified disease surveillance in all regions of the country. There has also been training of health personnel on case management and definitions. Early diagnosis and treatment saves lives, therefore individuals living in the affected communities have been encouraged to visit the nearest health centers immediately signs and symptoms of the disease are observed. As part of contributions to help bring the infection under control, an Accra-based pharmaceutical company has donated 2,520 vials of Nova Zone antibiotics (ceftriaxone) to the MoH for the treatment of meningitis in the affected regions. In addition, a number of health personnel have been dispatched to the affected areas [43]. Furthermore, the MoH has provided intravenous fluids, consumables and other logistics to support regional activities. While the donation of these logistics and the various intervention strategies outlined by the GHS are in the right direction, it appears insufficient, given the rate at which the infection is spreading across the country. The current situation has also seen technical partners such as the WHO and CDC playing supportive roles in mapping and control of the outbreak. Given the limited health infrastructure and financial resources, coupled with the gap in diagnostics, there is the need for greater collaborative effort in determining the serotype of the *S. pneumococcus*, which will feed into the development of specific vaccines to tackle the serotypes implicated in this outbreak.

Serotyping: existing capacity and current efforts

The polysaccharide capsule of *S. pneumoniae* is a major virulence factor and important for protecting the bacterial by the phagocytes of the host immune system. There are now over 90 different serotypes of *S. pneumoniae* with different virulence and epidemiological distribution [44]. The ability of the bacterial capsular polysaccharide to induce protective antibodies has been the underlying principle of the 23-valent polysaccharide and 7-valent conjugate vaccines that are licensed in over 70 countries in addition to the newly licensed 10- and 13-valent conjugate vaccines [45]. Although vaccinations are important in endemic regions, this has been associated with major shifts in circulating serotypes [46]. Elsewhere, vaccinations have triggered the emergence of non-vaccine, replacement serotypes [47] or possibly new serotypes by recombination of existing strains [45]. Serotyping is particularly important for epidemiological surveillance and long-term vaccine impact project [48]. However, this has remained a significant technical challenge [49] especially in developing countries. Despite the fact that majority of the ongoing outbreak in Ghana is associated with *S. pneumoniae*, little is known of the specific serotype implicated. Moreover, the constant modification of *S. pneumoniae* serotypes as implicated in most invasive pneumococcal outbreaks calls for the need to revise current vaccination programs [50]. Some studies have reported serotype 1 as the most implicated during endemic seasons in Ghana [15, 51]. A study by Dayie and colleagues [52] has indicated that of the 40% multi-resistant *S. pneumoniae* isolates from Accra and Tamale in Ghana were not included in PCV-13 vaccine. Current vaccines against the invasive pneumococcal are designed to provide a serotype-specific protection. There is therefore an urgent need to support existing research institutions with diagnostics capacities to

unravel the *S. pneumoniae* serotypes implicated in ongoing pneumococcal meningitis outbreak in Ghana.

Conclusion

We report on the outbreak of meningitis in Ghana and discuss the epidemiology, diagnostic techniques, therapy, antimicrobial resistance and vaccination against *S. pneumoniae* meningitis, as well as interventions put in place by the MoH, GHS and other partners. In comparison with other diseases including Ebola, our knowledge evolved as diagnostic techniques got more sophisticated, which informed the development of vaccines. Therefore, strengthening systems for rapid and accurate diagnosis of *S. pneumoniae* meningitis can go a long way in helping to control the fast spread of the infection and prevent future outbreaks. We further urge national-level stakeholders to be proactive; putting in place systems and appropriate resource allocation for research into recurrent and remerging infections.

Declarations

Competing interest

The authors have no conflict of interest.

Authors' contribution

AK, JA, AA, STA, DO, MN CDV, JM participated in its design and coordination and helped to draft the manuscript, edited and approved the final manuscript. EOD conceived of the study, edited and approved the final manuscript.

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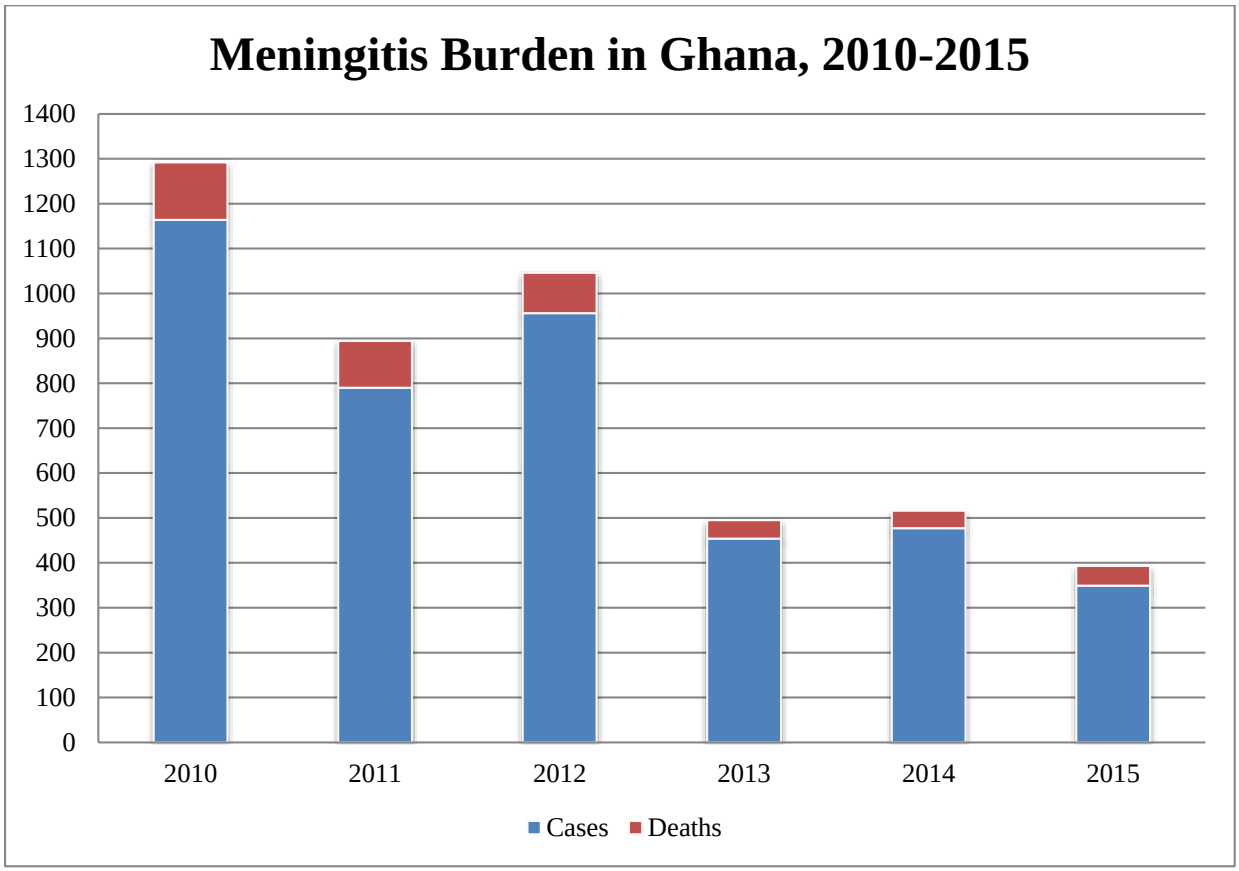

Figure 1: The burden of meningitis in Ghana from 2010-2015.

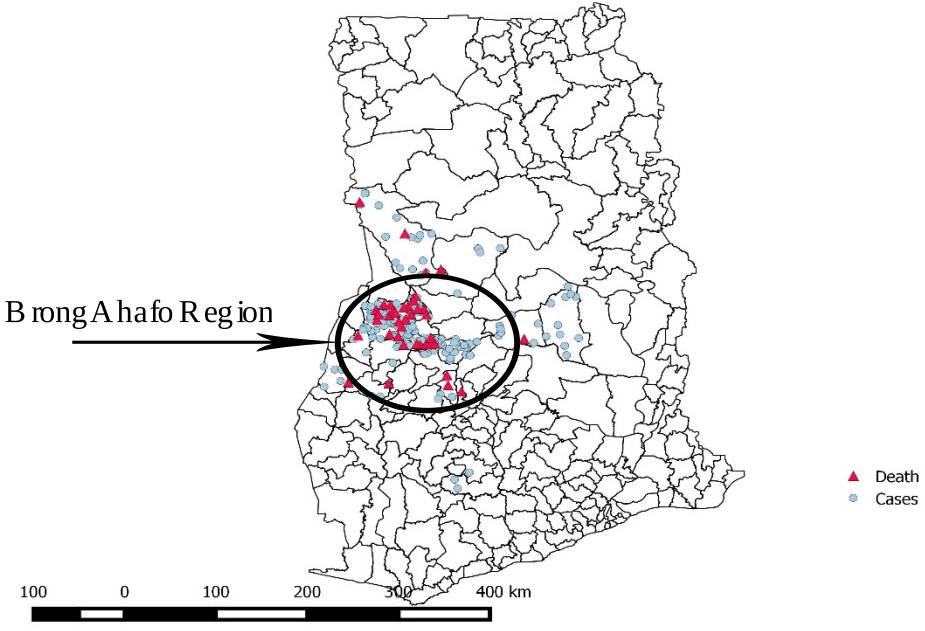
Brong Ahafo Region
Death
Cases
100 0 100 200 300 400 km

Figure 2: Distribution of Meningitis Cases, 26th January 2016