TRENDS OF REPORTED CEREBROSPINAL MENINGITIS IN THE
UPPER WEST REGION THREE YEARS POST-INTRODUCTION OF THE
CONJUGATE VACCINE IN GHANA

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DECLARATION

I, Godfred Kundire Dogee, declare that except for other people’s investigations which have been duly acknowledged, this dissertation is the result of my own original thought and hypothesis, and that this thesis either in whole or in part has not been presented elsewhere for another degree.

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DEDICATION

I dedicate this piece of work to Prof. Felix Dapare Dakora for sowing this wonderful seed.
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I thank the almighty God for giving me the strength to carry out this all important assignment. I am also grateful to my supervisor Dr. Tony Danso-Appiah for his unflinching support offered me during this period. I will also say a big thank you to my head of department Dr. Patricia Akweongo for her encouragement any time the going got tougher. My heartfelt thanks also go to Mr. Mathias Dugu and His Lordship Justice Suuribaare for their materials and financial support throughout this work.
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ABSTRACT

Background: Cerebrospinal meningitis is a public health burden in Ghana and can cause mortality up to 10% annually. About 20% of those who survive cerebrospinal meningitis suffer permanent sequelae. The plain polysaccharide vaccine was therefore introduced to prevent the disease. Unfortunately, the vaccine lacked T-cell involvement and worked poorly in children and could not generate secondary response in adults. The licensure of the conjugate vaccine seemed to reduce cases of CSM across the meningitis belt. However, the rates and dynamics of carriage across the meningitis belt remains poorly understood unlike carriage in high-income countries. The General Objective of this study is to assess the trends of CSM before and after the introduction of the conjugate vaccine in the Upper West Region of Northern Ghana. The study also specifically seeks to determine any short term shift in age group distribution of CSM cases in the region and also to determine any short term change in strains of Neisseria meningitidis isolated in Northern Ghana.

Methodology: A pre-tested data abstraction form was used to abstract patients information from case-based records kept at the Upper West Regional Disease Control Unit three years pre-(2010-2012) and three years’ post(2013-2015) introduction of the conjugate vaccine in the region. Data were analyzed using STATA version 13 using the mid-year populations of the region as denominators.

Results: From 2010-2012, out of 688 reported cases of CSM, there were 226 confirmed cases. Among the confirmed cases, males comprised 112 and females 114. Out of the 688 reported cases, 49 of them died. Three years after the introduction of the conjugate vaccine, there was a decline in the number of reported cases. The total
number of cases for this period was 461 out of which 72 were confirmed cases. Among the reported cases there were 34 males and 38 females. Forty-nine patients died within the same period as result of the disease. Children below 5 years of age were most hit. The bacterium *Neisseria meningitidis* and its strains especially N.m W135 and N.m Y were responsible for most of the cases in the region. The study has shown a significant reduction of CSM cases in all age groups of over 50% after the introduction of the vaccine. Children below 5 years of age and adults 20 years and above were the most hit groups in both periods. It was also found out that the bacterium *Neisseria meningitides* and its associated strain N.m W135 were responsible for majority of the cases and caused death rates higher than the usual death rates in the region.

**CONCLUSION:** Although the introduction of the conjugate vaccine led to a decline in new cases of meningitis in Northern Ghana indicating possible effectiveness of the vaccine, the fact that there still were annual outbreaks of CSM cases in the North provides evidence that the vaccine is not 100% protective against meningitis.
LIST OF ABBREVIATIONS

CSM………………………………………………Cerebrospinal meningitis
IMD………………………………………………Invasive Meningococcal Disease
UWR………………………………………………Upper West Region
WHO……………………………………………World Health Organization
UWRHD……………………………………..Upper West Regional Health Directorate
MenAfriVacc……………………………………Meningococcal Africa Vaccine
PCR………………………………………………Polymerase Chain Reaction
OMP………………………………………………Outer Membrane Protein
OMV………………………………………………Outer membrane Vesicle
N.m………………………………………………Neisseria meningococcal
SBA………………………………………………Serum Bacteria Antibody
MVP………………………………………………Meningitis Vaccine Project
MCC………………………………………………Meningococcal conjugate
CHAPTER ONE

1.0 Introduction

Throughout the nineteenth and twentieth centuries, meningitis has been one of the most feared infectious diseases and it remains high both in public perception and public health priority (Pollard et al., 2009). Meningitis clinically is the inflammation of the meninges that surrounds the brain and the spinal cord and this has several causes including viruses, fungi, protozoa and bacteria (Gendelman et al., 2005). The most popular and common ones are those caused by the encapsulated bacteria: Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenza (Pollard et al., 2009).

Today, the annual number of invasive disease cases worldwide is estimated to be at least 1.2 million, with 135,000 deaths related to invasive meningococcal disease (IMD) (Jafri et al., 2013). In countries with high endemicity, the disease burden places an immense strain on the public health system. The risk of long-term disabling sequelae, including cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus, and loss of limbs due to tissue necrosis, are highest in low-income countries, where the burden of bacterial meningitis is greatest (Edmond et al., 2010).

The epidemiology of bacterial meningitis in the African ‘meningitis belt’ changes periodically (Collard et al., 2013). Neisseria meningitidis is responsible for frequent outbreaks of meningococcal meningitis in the African ‘meningitis belt’, a sub-Saharan zone which stretches from Ethiopia to Senegal. Epidemics show marked seasonality, peaking during the dry, hot season (Sultan et al., 2005) and they can cause many deaths (mortality around 10%) and residual disability. During major epidemics, attack rates can range from 100 to 800 per 100,000 population. Neisseria meningitidis serogroup A is the main cause of epidemics in Africa (Collard et al., 2013). However, serogroup C was
responsible for epidemics in Nigeria in the 1970s and in Upper Volta (now Burkina Faso) in the 1980s, serogroup W sequence type (ST)-11 caused severe epidemics in Burkina Faso in 2002 and 2003 (Zombre et al., 2007), and serogroup X caused an outbreak in Niger in 2006 (Boissier et al., 2007).

These bacteria normally cause diseases in children and young adults and if these diseases are not immediately rapidly and effectively treated, they can be fatal and those who survive develop permanent sequelae (Bamberger et al., 2010).

Antimicrobial agents are very effective for treating these diseases (Bamberger et al, 2010). A number of vaccines were available for treating these diseases but the development of the conjugate protein – polysaccharide vaccines brought an effective control of the disease (McIntyre et al., 2012). The *H. influenzae* vaccine was the first vaccine to be used (Schneerson et al., 1980, Murphy et al., 1993) followed by vaccine against serogroup C meningococci (MenC) (Beuvery et al., 1983), multivalent vaccines against pneumococci (Eskola et al., 2000, Jefferies et al, 2011) and vaccines for other serogroups like the MenAfriVac for serogroupA (Soriano-Gabarro et al., 2004). These vaccines are very safe and have high efficacy profile and work well in settings where high rates of immunization are attained. Ghana lies in the meningitis belt and has had several outbreaks which is more pronounced in the northern part of the country.

1.1 Problem statement

Cerebrospinal meningitis is a serious infectious disease with mortality rate around 10% annually and leaves up to 20% of those who survive the infection with permanent sequelae. The polysaccharide vaccines are T cell independent. The conjugation of polysaccharides to protein carriers (non-toxic diphtheria mutant toxin [CRM197] or
tetanus toxoid) alters the nature of the antipolysaccharide response to a T-dependent response. When B cells recognize the polysaccharide they process the conjugated carrier protein and present peptide epitopes to T-CD4+ cells. This antigenic complex induces the production of elevated antibody levels, including in young infants, higher antibody avidity and increases serum bactericidal activity (Balmer et al., 2002). They also induce the formation of long-lasting memory B lymphocyte populations, providing an excellent amnesic response (booster effect) on re-exposure. Furthermore, these vaccines have the capacity to reduce nasopharyngeal colonization, reducing the number of carriers among those vaccinated and so transmission of the disease within the population (herd immunity) (Aurélio et al., 2006). Hence the replacement of the polysaccharide vaccine with the conjugate vaccine.

The conjugate vaccine was expected to provide an improved immunity. The Upper West Regional Health Directorate report on the mass vaccination indicated that 88.5% of the targeted population (1-29 years) was vaccinated. However, recent reports indicate that CSM cases are recorded yearly with 2014 alone recording 192 new cases and 19 deaths. This study therefore seeks to document whether the expected outcome of the conjugate vaccine is being achieved.
The expected outcome of the conjugate vaccine was improved immunity and a drastic decrease or eradication of the disease in the UWR. However, the variables shown in the framework above could affect the desired outcome. CSM is associated with a number of pathogens and this can affect the outcome since the vaccine was manufactured for specific serogroups and therefore not effective against some serogroups. This is indicated in the findings of Brueggemann et al., 2007. High vaccination coverage has the potential to affect the effectiveness of vaccination since herd immunity could be achieved that is the protection of the unvaccinated as indicated in the findings of Barbour et al., 1995. Common bacteria associated with CSM in the Northern part of Ghana have other strains especially the bacterium Neisseria meningitides so the uncertainty in predicting which
strain will cause an outbreak in a particular geographical location or in a particular time is always very high.

Age is a determinant factor when considering outbreaks of meningococcal disease though people of all age groups can get the disease, there is highest incidence in children under 5 and especially among infants 3-12 months old this is evidence in the findings of Bilukha et al., 2005. The conjugate vaccine also targeted some particular age groups; children less than 5 years of age and young adults less than 30 years of age. It is thus possible that CSM incidence among persons aged above the targeted population may have added to the observed trends and this requires thorough investigations Salisbury, 2001. People in low settings and low socioeconomic status suffer more (Greenwood, 1999).

Beliefs and accessibility to healthcare are also important factors. This is particularly important in sub-Saharan Africa where most events are usually explained by religious beliefs rather than confirmed scientific evidences (Murguia et al., 2003). As regards seasonality, the trends of CSM are also affected by the typical hot dry conditions coupled with poor ventilation in the study area, (UWR) and this undoubtedly favors the occurrence of meningitis cases (Baffoe-Bonnie et al., 2006). CSM has also been reported to exhibit seasonality, with a larger number of cases during the dry season (Aurélio, Sáfadi, & Barros, 2006). Sex is also a determinant of trends as shown in the model. There is evidence that suggests that distribution of CSM by sex shows a slight predominance of the disease among male patients (Aurélio et al., 2006).

1.3 Justification

The introduction and large coverage of the conjugate vaccine in the UWR was seen as a key relief from the menace of CSM since herd immunity was expected. Recent reports on cases of CSM in the UWR are indications that the expected outcome has not been met and
this presents a gap. It is likely that figures about vaccination coverage were blown out of proportion, there may be a short term shift in age distribution of CSM cases since the vaccine targeted children and young adults as the most at risk groups or there may be an emerging strain/pathogen associated with the incidence of CSM cases in the UWR. This study determined the nexus between the above factors and the emerging trends. These key findings may be useful for public health policy interventions in Ghana.

1.4 Research questions

1. Has there been a change in the incidence of CSM since the introduction of the conjugate vaccine in the UWR?
2. Has there been any shift in age distribution of CSM?
3. Has there been any change in reported strains in Northern Ghana?

1.4.1 General objective

To assess the trends in the incidence of CSM before and after the introduction of the conjugate vaccine

1.4.2 Specific objectives

1. To compare the trends in the incidence of CSM before and after the introduction of the conjugate vaccine.
2. To determine any short term change in strains of *Neisseria meningitides* isolated in Northern Ghana.
3. To determine any short term shift in age distribution of CSM in the region.
CHAPTER TWO

LITERATURE REVIEW

2.0 An overview of cerebrospinal meningitis

The nineteenth and twentieth centuries have seen meningitis as one of the most feared infectious diseases, and it remains high both in public perception and as a public health priority (Maiden, 2013). Clinically, meningitis is an inflammation of the meninges, the membranes that surround the brain, which can have many causes including infection with bacteria, fungi, protozoa and viruses. In clinical research, meningitis means one of a number of invasive bacterial diseases, especially those caused by the encapsulated bacteria *Haemophilus influenzae*, *Neisseria meningitidis* (the meningococcus) and *Streptococcus pneumonia* (Maiden, 2013). These bacteria can cause severe, rapidly-progressing disease syndromes, usually in children and young adults, which may involve meningitis. The fearsome reputation of meningitis in this sense is because, in the absence of rapid and effective treatment, it is often fatal and disabling sequelae are common in those who survive (Kanchanaraksa, 2008).

Antimicrobial agents are very effective against these diseases and vaccines were available for much of the second half of the twentieth century, but it was the development of conjugate protein polysaccharide vaccines which has brought the prospect of effective disease control and the potential for an endgame. The first such vaccines to be used were the *H. influenzae* serotype b (Hib) vaccines, followed by vaccines against serogroup C meningococci (MenC), multivalent vaccines against pneumococci and vaccines against other meningococcal serogroups including the MenAfriVacserogroup A vaccine (Balmer, Borrow, & Miller, 2002).
2.1 Distribution in America and Europe

Cerebrospinal meningitis can be rapidly progressive with resulting significant morbidity and mortality, even with treatment. The vaccines available for the majority of serogroups that cause disease have proven effective in reducing the disease incidence in countries that have applied them at the population level. It is important to identify regions that have the highest disease incidence so that the global impact of these vaccines can be maximized in our attempts to curb the disease (Jafri et al., 2013).

Some studies of the incidence of bacterial meningitis performed in the United States during the 1950s, 1960s, and 1970s found significant attack rates for the common meningeal pathogens at that time (Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae), although these case-finding efforts were performed with relatively small populations (Brouwer, Tunkel, & van de Beek, 2010). Despite the retrospective design and relatively small populations in these studies, therapeutic and preventive strategies were targeted toward these microorganisms, given the high frequency of isolation of these specific pathogens (>70% of cases) (Brouwer et al., 2010). Today, the annual number of invasive disease cases worldwide is estimated to be at least 1.2 million, with 135,000 deaths related to invasive meningococcal disease (IMD) (Jafri et al., 2013).

In countries with high cases, the disease burden places a heavy strain on the public health system. The risk of suffering long-term disabilities like cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus, and loss of limbs due to tissue necrosis, are highest in low-income countries, where the burden of bacterial meningitis is highest (Edmond et al., 2010).

Apart from a few countries in the eastern part of the European Region, good surveillance data are available from most European countries. Serogroup B and C are the cause of most
disease, and implementation of a meningococcal immunization program with adequate vaccine coverage has helped to decrease endemic rates so that no country now falls in the high-endemicity group. Fifteen countries from this region are classified as moderate endemicity and 18 as low. Recent epidemiological surveillance indicates an increase of serogroup Y IMD in some parts of Europe, which is now the third most common serogroup after B and C (Annual Epidemiological Report, 2013).

2.2 Distribution in Africa
The epidemiology of bacterial meningitis in the African ‘meningitis belt’ changes periodically (Collard et al., 2013). Neisseria meningitidis is responsible for frequent outbreaks of meningococcal meningitis in the African ‘meningitis belt’, a sub-Saharan zone which stretches from Ethiopia to Senegal. Epidemics show marked seasonality, peaking during the dry, hot season (Sultan et al., 2005) and they can cause many deaths (mortality around 10%) and residual disability. During major epidemics, attack rates can range from 100 to 800 per 100 000 population. Neisseria meningitidis serogroup A is the main cause of epidemics in Africa (Collard et al., 2013). However, serogroup C was responsible for epidemics in Nigeria in the 1970s and in Upper Volta (now Burkina Faso) in the 1980s, serogroup W sequence type (ST)-11 caused severe epidemics in Burkina Faso in 2002 and 2003 (Zombre et al., 2007), and serogroup X caused an outbreak in Niger in 2006 (Boissier et al., 2007).

Twenty-five countries in the African region with an extremely high incidence of meningococcal disease constitute the meningitis belt (Jafri et al., 2013). To quickly detect the frequent epidemics, a strong watchdog system exists that monitors the number of cases on an ongoing basis for rapid response. This region has recently benefitted from huge
alliance of international health bodies that have made and are deploying an affordable and effective vaccine against serogroup A meningococcus, which is the major cause of majority of disease in this area, at population level (Bishai et al., 2011). Serogroup X, previously a rare cause of sporadic meningitis, became responsible for outbreaks between 2006 and 2010 in Kenya, Niger, Togo, Uganda, and Burkina Faso, the latter with at least 1,300 cases of serogroup X meningitis among the 6,732 reported annual cases (Xie et al., 2013). It is important to note that South Africa is among the moderate-endemicity group.

![Figure 2: Global distribution of Cerebrospinal Meningitis](image)

Sudan and Saudi Arabia have high endemic rates of serogroup A disease, and have also experienced outbreaks in recent years during the Hajj season with serogroup W-135. Other countries in this region do not have adequate data to permit a population-based estimate of true incidence, although outbreaks have been reported among returning travelers from Hajj (Jafri et al., 2013).
2.3 The case of CSM in Ghana

In Ghana, cases of cerebrospinal meningitis have been recorded in all ten regions, with Northern region recording the highest cases (Codjoe & Nabie, 2014). Studies into CSM cases in Ghana dates back to the 1900s when it was first discovered (Fogor, 2007). Initial studies mainly concentrated on mortality cases as a result of the disease. The first recorded outbreak of CSM was in Cape Coast in southern Ghana in 1900 among East African laborers who were brought to the Gold Coast to support the British campaign against the Ashanti of central Ghana. This outbreak died out rapidly without causing an epidemic in the local population. The next epidemic in the Gold Coast started in 1906 from the north-west and spread through the northern territory during the following dry season. Estimates show that the disease was responsible for the deaths of 20,000 people between 1906 and 1908 (Codjoe & Nabie, 2014). Since that period, epidemics were recorded every 8–12 years.

Thus, records have shown that the morbidity rate of the disease for a single year has ranged from a low of 8 cases near Bole in northern Ghana in 1944, to a high of 18,703 cases in the entire country in 1997. These deaths have occurred at the peak of the harmattan in the three northern regions of Ghana (Upper East, Upper West and Northern) with a marked decline by the end of April (Enos, 1997). A whole array of studies considers risk factors, survival and sequelae issues associated with meningitis in Ghana. Other studies have investigated different serogroups associated with the disease, and the emergence of a particular serogroup. i.e., W-135 linked with returned Hajj pilgrims.
2.4 Age distribution

Meningococcal disease affects individuals of all age groups, but the highest incidence is in children under 5, and especially among infants aged 3 to 12 months (Bilukha et al., 2005). During epidemics, a shift in the age distribution of meningococcal disease is observed, with increased numbers of cases among adolescents and young adults. The higher incidence of disease among infants, from 3 months of age, is related to a reduction in maternal antibody titers that had been passively acquired during pregnancy (Maiden, 2013). From 12 months on, children develop naturally acquired immunity, with increased protective antibody titers and, consequently, reduced incidence rates. A second peak in incidence can be observed, in some populations, among adolescents and young adults, probably as a result of increased risk of transmission of the disease, particularly in college students residing in dormitories (Maiden, 2013). It is important to point out that, in contrast with what is observed in the USA and certain European countries, in Brazil no increased incidence of the disease has been observed among adolescents and young adults. In the USA, incidence rates of meningococcal disease have remained steady over recent years (approximately 1 case per 100,000 inhabitants), with serogroup B being the primary cause of endemic disease and serogroup C related to outbreaks among adolescents and young adults. Increases in the proportion of cases due to serogroup Y have been observed during the last decade, mainly among adults and the elderly. In 2004 New Zealand embarked upon a mass vaccination program for children and adolescents under 19 with a vaccine using outer- membrane vesicle (OMV) proteins developed specifically to combat the epidemic strain in a partnership between the New Zealand government, the Norwegian Institute of Public Health and the Chiron laboratory. Characteristics peculiar to epidemics caused by meningococcus B are insidious onset and prolonged duration, sometimes as long as 10 years (Oster et al., 2005).
2.5 Types and causes of meningitis

There are many pathogens associated with CSM. These pathogens include bacteria, fungi, protozoa and viruses. Meningitis may also be caused by non-infectious factors such as physical injury, cancer or certain drugs (Ryan et al., 2004; MOH, 2010). Bacterial meningitis is the most common of all in sub-Saharan Africa. There are three types of bacterial meningitis: Neisseria meningitides, Haemophilus influenza and Streptococcus pneumonia. These three are encapsulated and can cause invasive bacterial diseases (Pollard et al., 2009). These bacteria can cause invasive diseases in any age group. They can be found in the pharynx of normal human beings and spread through saliva (spit), kissing, cigarettes and droplets from infected persons who sneeze or cough. Persons infected can immediately be treated using antibiotics. Meanwhile, there are vaccines that can be used to prevent this kind of meningitis (Ryan et al., 2004; Trotter et al., 2005; MOH, 2010). Neisseria meningitides alone has about thirteen different serotypes but the most common ones are A, B, C, Y and W (Manchanda et al., 2006).

2.6 Serotypes associated with CSM

Meningococci can be classified into 13 different serogroups based on the antigenic composition of the polysaccharide capsule: A, B, C, D, H, I, K, L, W135, X, Y, Z, 29E. Serogroups A, B, C, Y and W135 are responsible for virtually all cases of the disease, infecting humans only (Aurélio et al., 2006). Meningococci can be further classified into serotypes and serosubtypes, according to the antigenic composition of their outer membrane proteins (OMP) PorB and PorA, respectively.

Invasive infections by Neisseria meningitidis result in a wide range of clinical spectrum that includes meningitis and meningococcemia or both with meningitis being the most common one clinically. Against this background, the term meningococcal disease is
appropriate and has been adopted internationally (Aurélio et al., 2006). The distribution of patients by sex reveals a slight predominance of the disease among male patients. The disease also exhibits seasonality, with a larger number of cases during the winter.

Meningococcal disease occurs all over the world, although there are marked geographical differences in incidence and in the distribution of the different serogroups that cause disease. Historically, serogroup A is associated with epidemic disease in developing countries, especially in Sub-Saharan Africa, which is known as the meningitis belt (Kaaijk, Ende, Berbers, Dobbelsteen, & Rots, 2012). The annual incidence of disease during these epidemics can be as high as 1,200 cases per 100,000 inhabitants. Outbreaks of meningococcal disease caused by the W135 serogroup have been recently reported among nomadic Muslims in Saudi Arabia and also in countries in the African belt.

In developed regions, such as the USA and in Europe, the disease is mostly endemic. In Europe, more than 95% of cases are attributed to serogroups B and C. A high proportion of cases attributed to serogroup B are seen in Norway, Germany, Denmark and Holland, while in Spain, Greece, Slovakia, the Czech Republic, Ireland and the United Kingdom, a proportional increase in cases attributed to the C serogroup were observed from the end of the 1990s onwards.

New Zealand has been affected by an epidemic situation caused by meningococcus B (strain B:4:P1,7-2.4) since 1991, with a total of 5,300 cases of meningococcal disease and 215 deaths reported between 1991 and 2004 with incidence rates of up to 14 cases per 100,000 inhabitants in 2003. During that period around 80% of cases were attributed to the epidemic strain (Martin et al., 2005). During the 1970s Brazil suffered its largest recorded epidemic of meningococcal disease, with its epicenter in São Paulo and characterized by two overlapping epidemic waves, the first provoked by serogroup C meningococcus,
starting in April 1971, and the second by serogroup A meningococcus, beginning in April 1974, without the incidence of causes related to serogroup C meningococcus returning to endemic values by then (Macneil et al., 2014). The incidence rate, which had been 2.1 cases per 100 thousand inhabitants in 1970, reached a peak of 179 cases per 100,000 inhabitants in 1974. This epidemic provided the first major experience with polysaccharide A and C vaccines on a large scale, resulting in control of the epidemic from 1975 on (Lee et al., 2008).

During the 1980s there was a period of reduced disease incidence (1 case/100,000 inhabitants), with serogroup B becoming more prevalent than C and practically no cases of serogroup A reported. From 1987 onwards there was an increase in the number of cases, with epidemics attributed to serogroup B in several locations around the country. This growth reached its peak in 1996, with 7,104 cases recorded (4.5 cases/100,000 inhabitants), to a great extent resulting from outbreaks in large cities such as São Paulo and Rio de Janeiro. Nevertheless, from 2002 onwards an increase in the proportion of cases attributed to serogroup C was recorded, demonstrating an increasing trend in the proportion of this serogroup in some regions of the country, such as, the state of São Paulo, where it was responsible for 63% of identified cases of meningococcal disease in 2005, with serogroup B responding for 32% of cases and other serogroups for 5% (Aurélio et al., 2006).

2.7 Transmission, signs and symptoms of CSM

Dry weather, dusty winds, cold nights, and large populations living in overcrowded conditions leave people vulnerable to respiratory infections and are among some of the reasons behind the meningitis belt’s high burden of meningococcal disease. Symptoms of
the disease include stiff neck, high fever, rash, headache, vomiting, and confusion. Even with rapid diagnosis, 5-10% of patients typically die within 24-48 hours of symptom onset. Although sometimes fatal, CSM is most often treatable with antibiotics administered upon hospital admission. Studies have also shown that key early warning signs of meningitis and septicemia in children under 17 years old often include cold hands and feet, abnormal skin color (pale, bluish or mottled), and leg pains. These symptoms often occur hours before other classic symptoms, such as a rash and dislike of bright light. The rapid spread of the disease is due to the ease in which the bacteria are transmitted. Droplets of respiratory or throat secretions transmit the bacteria through methods such as kissing, sneezing and coughing.

2.8 The polysaccharide vaccines
The modern era of meningococcal vaccines began in the late 1960s, triggered by the evolution of resistance to available chemotherapies (Vipond et al., 2012). Meningococcal disease was first described at the beginning of the nineteenth century, with outbreaks reported globally over the succeeding 100 years (Maiden, 2013). The disease has been frequently reported in the military, especially in recruit camps, presumably because of increased transmission in the cramped conditions prevailing and the presence of rural recruits with low immunity to at least some meningococci (Broderick et al., 2012).

Outbreaks in the British Army in the First World War led to some of the earliest studies of meningococcal carriage and transmission and their relationship to disease outbreaks. It is now well established that most cases of invasive meningococcal disease occur shortly after an individual has acquired a novel meningococcus, presumably as a consequence of a dysfunctional or failed attempt by the bacterium to establish colonization. Attempts to interrupt transmission by changing factors such as the distance between beds in barracks
met with inconsistent success and during the Second World War the problem of meningococcal disease among recruits and in the populations of the combatant countries were severe (Broderick et al., 2012). In the military these problems were addressed by the prophylactic use of sulfonamide drugs, which had been developed in the 1930s, replacing serum therapy for meningococcal disease treatment. These antimicrobials were effective in eliminating meningococci from asymptomatic carriage, resulting in reduced transmission. In a setting such as a military recruit camp, where the at-risk group is easily defined in space and time, and compliant with treatment, this is a highly effective intervention and, in the post-war period, mass sulfadiazine prophylaxis successfully prevented meningococcal disease among recruits in the US Army.

There were two drawbacks to this intervention: first, while effective in closed and semi-closed communities, when the at-risk period is easily identified, widespread use of chemical prophylaxis is not an intervention that can be used routinely on a population scale. Prophylaxis in the wider community can be used when localized outbreaks have been identified, but defining the extent of the group to be treated can be difficult (Purcell et al., 2004). This intervention cannot be used in cases of hyper endemic meningococcal disease, where an outbreak remains in a community for many months or years, or when the outbreak is geographically dispersed. Further, where they clear carriage, widespread administration of antimicrobials can lead to the emergence of resistance. Not all antimicrobials affect carriage and the use of these agents does not lead to the emergence of resistant strains; for example, although penicillin are effective in disease treatment they do not affect carriage (Purcell et al., 2004), and reduced susceptibility to these antimicrobials is yet to become a therapeutic problem (Taha et al., 2007). Resistance to sulfonamides arises by a number of mechanisms and is now widespread in meningococci, and they have been replaced for treatment of both meningococcal carriage and disease. During the
Vietnam War, large outbreaks of sulfonamide-resistant meningococcal disease occurred among recruits in the US Army and Navy training camps in California, first caused by serogroup B organisms and subsequently by closely related serogroup C organisms. An influential set of investigations into the biology of meningococcal disease were undertaken in response to this emergency, which have become paradigms for the development of meningococcal vaccines in particular and encapsulated bacteria generally. In vitro assays demonstrated that most human adults have circulating antibodies capable of killing meningococci ('bactericidal antibodies'). The distribution of disease in the human population was inversely correlated with this bactericidal activity, with the age-group at most risk of disease, young children aged six months to 1 year, exhibiting the lowest levels, as a consequence of the waning of maternally acquired immunity before the development of adaptive immunity.

Tests with meningococci belonging to different serogroups showed that these antibodies were specific to particular capsules, and that the level of bactericidal effect corresponded to the degree of protection against disease. These studies led to the use of purified bacterial polysaccharide vaccines: the ‘plain’ polysaccharide vaccines, first against serogroup C meningococci and subsequently against serogroups A, W and Y (Maiden, 2013). These vaccines had an excellent safety profile and were effective in the military setting, their introduction preventing meningococcal disease caused by serogroup A, C, Y and W bacteria. Unfortunately, it was not possible to extend this success to serogroup B meningococci as this polysaccharide is poorly immunogenic, probably because of its structural similarity to host polysaccharides that decorate the neural cell adhesion molecule of human foetal tissues. A further concern with this polysaccharide is that effective vaccines may lead to autoimmune reactions, and the inclusion of this antigen in vaccine preparations remains controversial and unlikely in the foreseeable future. The
plain polysaccharide vaccines did not resolve the problem of meningococcal disease in the community. Bacterial polysaccharide capsules have evolved, at least in part, to evade the mammalian immune responses, and their repeating sugar structures are poorly recognized by the human immune system. Immune responses against these antigens do not invoke T-cell help and do not result in affinity maturation or the generation of immunological memory (Dellicour & Greenwood, 2007).

Consequently, plain polysaccharide vaccines elicit only primary immune responses comprising low-affinity IgM antibody and subsequent immunization does not generate a secondary response; indeed, repeated immunization can result in hypo responsiveness, as primary B cells with affinity to the polysaccharide are exhausted. The lack of T-cell involvement in the immune response therefore has a number of important consequences: (i) the vaccine works poorly or not at all in young children, a major at-risk group, and (ii) no memory response is generated in adults (Maiden, 2013). Plain polysaccharide vaccines are not suitable for use in infant immunization programmes for this reason and even in adults they have to be repeatedly administered. They are also ineffective against carriage, having at best a short-term effect (Dellicour & Greenwood, 2007), so, while effective in the short-term in a closed community setting, these vaccines are not suitable for population-scale interventions outside of epidemics or for infant immunization.

2.9 The conjugate vaccine

The conjugation of polysaccharides to protein carriers (non-toxic diphtheria mutant toxin [CRM197] or tetanus toxoid) alters the nature of the antipolysaccharide response to a T-dependent response. When B cells recognize the polysaccharide they process the conjugated carrier protein and present peptide epitopes to T-CD4+ cells. This antigenic
complex induces the production of elevated antibody levels, including in young infants, higher antibody avidity and increases serum bactericidal activity (Balmer et al., 2002). They also induce the formation of long-lasting memory B lymphocyte populations, providing an excellent amnesic response (booster effect) on re-exposure. Furthermore, these vaccines have the capacity to reduce nasopharyngeal colonization, reducing the number of carriers among those vaccinated and so transmission of the disease within the population (herd immunity) (Aurélio et al., 2006). The first conjugate vaccines, developed during the 1980s, contained meningococcal A and C capsular oligosaccharides conjugated to a mutant diphtheria toxin CRM197. Initial studies with these vaccines confirmed good immunogenicity, induction of immunologic memory and an acceptable safety profile.

Nevertheless, the low prevalence of meningococcal disease caused by serogroup A in developed countries directed the development of conjugate meningococcal vaccines towards controlling disease caused by serogroup C. Therefore monovalent conjugated meningococcal vaccines were developed from meningococcal serogroup C isolates containing O-acetyl groups (Oac(+)) in their polysaccharide capsule, conjugated to the mutant diphtheria toxin (MCC - CRM197 - Meningitec Wyeth Laboratories, and Menjugate Chiron Laboratories). These vaccines proved themselves immunogenic in infants, toddlers, older children, adolescents and adults.

Later, studies to characterize meningococcal antigens found that around 12% of meningococcal serogroup C isolates that cause disease do not have O-acetyl groups in their polysaccharide capsules (Oac(-)). This finding suggested the possibility that the immunoresponse, based fundamentally on group-specific antibodies, provoked by these vaccines using Oac (+) polysaccharides, could be ineffective against Oac (-) strains (Aurélio et al., 2006). A vaccine was then developed that utilized a de-O-acetylated capsular polysaccharide conjugated to a tetanus toxoid (MCC-TT- Neisvac-C Laboratory
Baxter). This Oac (-) vaccine elicits the production of antibodies aimed at epitopes present in meningococcal serogroup C isolates with and without O-acetyl groups, thus generating a wider-ranging response and higher serum bactericidal antibody titers (SBA).

The effect of MCC vaccines on carriage was not known at the time of introduction, although previous experience with the Hib conjugate vaccines suggested that the immunization with MCC vaccines would reduce carriage of group C meningococci (Macneil et al., 2014). For accidental pathogens, such as *H. influenzae* and the meningococcus, a vaccine that prevents disease, but has no impact on carriage, could have a very high level of efficacy, while being less useful per vaccinated person owing to the lack of herd immunity.

On the other hand, preventing carriage, while essential to herd immunity, potentially selects for both (i) capsule variants derived from strains expressing the targeted serogroups, as well as (ii) strains that compete with them but which are not targeted by the vaccine. The negative consequence of this, vaccine escape, is the evolution or spread of variants that are not affected by the vaccine-induced immunity, and are released from competition with those variants that are affected (Segal & Pollard, 2004). Both of these phenomena can be induced by vaccination campaigns. The level of population immunity generated by immunization will be a product of the efficacy of the vaccine against transmission and the vaccine coverage achieved. For infectious agents with no antigenic variation such as measles, or famously smallpox, high-levels of population immunity can lead to the removal of the infectious agent and disease eradication or extinction. However, where organisms have the capacity to vary their antigens, either by mutation, phase variation or lateral gene transfer, the selection pressures imposed by vaccine-induced immunity can lead to the emergence and/or spread of novel variants that escape vaccine
control (Trotter, Andrews, Kaczmarski, Miller, & Ramsay, 2004). Vaccine efficacy against carriage is therefore a two-edged sword, and whether it ultimately acts beneficially or harmfully depends on the biology of the agent being protected against and the mechanisms of immunity. Prior to the introduction of MCC vaccines, it was known that hyper-invasive meningococci could alter their capsules by lateral gene transfer of a single gene in the capsule locus, and that this had happened during the US Army outbreaks. This also involved ST-11 complex meningococci, although the change had been from serogroup B to serogroup C, a direction that had actually promoted the impact of vaccines on the epidemic.

The successful introduction of the MCC vaccines stimulated interest in vaccination against the greatest burden of meningococcal disease internationally: the periodic, large epidemics occurring in the ‘meningitis belt’ of sub-Saharan Africa (Maiden, 2013). These seasonal outbreaks, first reported in 1905 and systematically described by Lapeyssonnie in the mid-twentieth century, are typically caused by serogroup A meningococci and occur with a periodicity of 7–10 years. They frequently involve hundreds of thousands of cases and thousands of deaths. In addition to this large burden of morbidity and mortality, principally in children, the intensity of the outbreaks, which usually last a few weeks, increases their disruptive impact on health systems in low-income settings. Attempts to control these outbreaks with plain polysaccharide vaccines were only partially successful as the vaccines had to be administered once an outbreak had been detected, requiring the maintenance and mobilization of large stockpiles of vaccines at short notice. The Meningitis Vaccine Project (MVP), a partnership of the World Health Organization and the Programme for Appropriate Technology in Health, funded by the Bill and Melinda Gates Foundation was formed to address this problem by the development of an affordable serogroup A conjugate vaccine (Kaaijk et al., 2012). This was achieved with the
innovative formation of a ‘North–South’ partnership, with conjugate technology and vaccine components provided by North American and European partner’s and vaccine production by the Serum Institute of India. The resultant product, a tetanus-toxin (TT) polysaccharide conjugate vaccine (TT-PSA, MenAfriVac), was produced, tested prequalified and introduced during the first decade of the twenty-first century (Owusu et al., 2012). As little information was available on the carriage of meningococci in Africa at the time of vaccine introduction, it was decided to immunize all individuals up to the age of 29 to ensure the maximum effectiveness.

The vaccine was first introduced in Burkina Faso in 2010, with enhanced disease surveillance and simultaneous carriage studies to monitor the impact of the vaccine. As with the MCC vaccines, a rapid and dramatic effect was observed both on disease rates and on carriage of serogroupA meningococci although the carriage rates of these organisms were also very low even during epidemics (http://www.menafricar.org).

At the time of writing, the continued rollout of MenAfriVac across the meningitis belt has presented the prospect of the elimination of epidemic serogroupA meningococcal disease. For the maintenance of vaccine effectiveness, however, it is important to know the rates and dynamics of carriage across the meningitis belt, which remains poorly understood and which is unlike meningococcal carriage in high-income countries. The MenAfriCar consortium has worked to monitor the impact of vaccine introduction on the carriage of meningococci across the meningitis belt by means of pre- and post-vaccination carriage surveys and molecular characterization of the isolates obtained. Although serogroup C and A meningococcal disease are distinct in their geographical distribution, seasonality, attack rate and scale, both are caused by certain clonal complexes that are associated with a particular capsule, the expression of which appears to be important for transmission,
asymptomatic carriage and disease (http://www.menafricar.org). The continued success of vaccination against these organisms depends on the continued association of these characteristics. It is, unfortunately, not fully understood why these associations are so strongly maintained, even in the face of high levels of immunization and the potential for lateral gene transfer (Maiden, 2013). It is possible, and perhaps likely, that over time these particular meningococcal strains will be replaced in carrier populations with other hyper-invasive meningococci, perhaps associated with different serogroups, leading to renewed outbreaks of disease, and continued disease surveillance is required to assess this. In this respect, the lack of a comprehensive meningococcal vaccine remains a concern (Segal & Pollard, 2004).

In summary, the introduction of the meningococcal conjugate polysaccharide vaccines is a continuing success in combating invasive meningococcal disease as a consequence of their effectiveness in inducing herd immunity and not, at least up to the time of writing, leading to vaccine escape either by capsule switching (the acquisition of a novel capsule by the original pathogen strain) or replacement (the replacement of the original epidemic strain with a genetically and antigenically distinct strain) (Aurélio et al., 2006). This lack of escape from vaccine control appears to be the consequence of a number of factors, including the induction of long-lasting immunity effective against asymptomatic carriage and the association of the invasive meningococci with expression of a particular capsular polysaccharide. The extension of this paradigm to other meningococcal serogroups that are associated with disease (B, W, X, Y) would potentially result in the control and perhaps elimination of meningococcal disease (Balmer et al., 2002). This can likely be achieved for serogroups W, X and Y, and a number of such vaccines exist with others being developed, but there is little prospect of a polysaccharide vaccine against serogroup
B meningococci, and it is not clear at the time of writing whether ‘group B substitute’
vaccines, which mostly contain protein antigens, would have a similar effect.

The introduction of the conjugate vaccines and preventive treatment options for CSM has
had a major impact on the epidemiology and characteristics of CSM. However, these
successes are limited mainly to high- and median-income countries.

Worldwide, bacterial meningitis remains a disease with devastating attack rates and
growing drug resistance among causative bacteria, leading to treatment failures (Brouwer
et al., 2010). Empirical antibiotic therapy should be adjusted to local drug resistance
patterns and clinical subgroups. In a world of increasing resistance to antibiotics and
emerging pathogens, culture combined with susceptibility testing remains the gold
standard for diagnosis. Progression in prevention, diagnostic methods, and treatment has
benefited patients primarily in high-income countries, while the main burden of disease
lies in resource-poor countries. The worldwide availability of effective vaccines remains
the best option to curb this menace. A study of this nature as well as surveillance are thus
necessary to monitor the impact of these vaccines through direct immunity and herd
protection and allow for optimization of vaccination schedule.
CHAPTER THREE
METHODOLOGY

3.0 Introduction
This chapter gives an insight of the methods used in this study it also describes the study design, study area, the study population and the study variables. The chapter also explains the sampling techniques involved in carrying out the study, data collection techniques, data analysis and ethical considerations requirement for the study.

3.1 The study design
A retrospective review and analysis of all reported cases of CSM in case-based forms from all the available health facilities in the region at the Regional Disease Control Unit was carried out for the period 2010-2015 as stated in this study protocol. The data were collected in two main forms that is 2010-2012 three years before the introduction of the conjugate vaccine and 2013-2015, three years post introduction of the conjugate vaccine. In order to examine trends of CSM cases in the region, which was the general objective, the mid-year populations of the various years of the study period were used as denominators. Confirmed cases were based on number of patients with laboratory-based confirmation of CSM diagnosis, either through microscopy or PCR. Unconfirmed CSM cases were defined as patients who presented symptoms consistent with CSM in the absence of apparent or alternate cause.

3.2 The study area.
The Upper West Region has a boundary with the north by Burkina Faso, East by the Upper East Region, South by Northern Region and on the West by Cote d’Ivoire. The region has a land area of 18,478km$^2$ with a total population of 576,583. The Upper West
Region is one of the poorest regions in the country and has over 80% of its population engaged in agricultural activities (ghanadistricts.gov). These socioeconomic conditions have been proven to influence the incidence of CSM (Greenwood, 1999). The region also has two seasons - dry and wet seasons. The dry season is usually characterized by cold and hazy harmattan with mean annual temperatures ranging from 18.8\(^{0}\)C—35.5\(^{0}\)C. The wet season is characterized by rains with rainfall ranging from 78cm to 216cm a year and temperatures ranging from 15\(^{0}\)C—20\(^{0}\)C. Previous studies suggest that these conditions, especially the dry season, influence the seasonal variations in trends of CSM (Aurélio et al., 2006). The region has eleven districts of which the Wa Municipality is the regional head and the main business town. Most government agencies and facilities are clustered there. The Upper West Region has basically three main tribes; the Sissalas who are predominantly Muslims from Tumu, the Dagaabas who are predominantly Christians stretching from Nadowli to Nandom and the Waalas who are largely Muslims and found in the regional capital, Wa (ghanadistricts.gov). Such a diverse religious setting is also important as far as determinants of CSM trends are concerned (Murguia et al., 2003).

3.3 Variables
3.3.1 Dependent variable
Trends of reported cases of CSM before and after the introduction of the conjugate vaccine whether confirmed or unconfirmed.
3.3.2 Independent Variables

1. Demographic factors; Age and Sex; Continuous variables such as age was classified in years as 0-4, 5-9, 10-14, 15-19 and 20+. Sex being a categorical variable was classified as male and female.

2. Seasonality; which is also classified as a binary variable was classified as dry and wet seasons. The dry season stretches from November to April and the wet season May to October.

3. Types of strain of N.m; these were N.m A, N.m B, N.m C, N.m W135, and N.m Y. Since they were the four main common strains known to cause CSM in the region out of the 13 strains.

3.4 Study population

The study population comprises reported cases of CSM three years before (2010-2012) and after (2013-2015) the introduction of the conjugate vaccine.

3.5 Sampling

The Regional Disease Control Unit was chosen because of good record keeping and also the time the study was carried out, the required data were available.

3.6 Data collection procedures

Data were extracted using a pre-tested data extraction form to collect information on the following variables: patient age, sex, location, strains of Nm, survival, district of residence, the year and the epidemiological week case was reported. Any case base form that felt short of the above information was not used.
3.7 Statistical methods and analysis

Data collected were entered into Microsoft Excel and checked for errors and then converted to Stata version 13. Descriptive statistics were used to analyze patient characteristics that were collected from the case base forms (2010 to 2015). Line chart was used to demonstrate trends meningitis before and after the introduction of the conjugate vaccine for the period of the study.

3.8 Ethical Issues

The study got approval from the Ghana Health Service Ethics Review Committee (ETHICS APPROVAL-ID NO GHS-ERC: 42/12/15) and Upper West Regional Health Directorate. For issues of privacy and confidentiality, data that were extracted from the case base forms were locked up in a cabinet. Also, variables on which data were collected were given codes to enhance anonymity.
CHAPTER FOUR

RESULTS

4.0 Introduction

This chapter presents results of baseline characteristics on age and sex. It also describes the trends of CSM in the region and the various organisms associated with the disease especially the bacterium *Neisseria meningitidis*. The results are also presented in simple proportions and frequency tables to describe the trends of CSM cases before and after the conjugate vaccine.

In 2010, there were 405 reported cases of CSM in the region with most of the cases recorded within the 1st to the 13th weeks of the epidemiological year. Though there are 52 epidemiological weeks, most of the cases occurred within the first 3 months of the year. The number of cases recorded in 2011 was lower as compared to the previous year. Only 191 cases occurred within the 52 epidemiological weeks of the year. The number of cases recorded in 2012 was far less than cases in the previous years and all the cases came up in the first 9 weeks of the year totaling 92.

![Distribution of CSM cases in the Upper West Region for 2010-2012.](http://ugspace.ug.edu.gh)

Figure 3a: Distribution of CSM cases in the Upper West Region for 2010-2012.
The trend peaked between the 4th and the 10th epidemiological weeks and the trend begins to raise at the end of the year. From the figure above 2010 recorded the highest number of cases and the meningococcal disease persisted throughout the 52 epidemiological weeks though the numbers were small compared to the first three months of the year and the year ended with 405 cases recorded in the region. In 2011, cases were very high in the 1st week and declined into the 2nd week. Cases started to increase in the 3rd week until the 6th week when cases peaked and began to decline till the 13th weeks when cases occurred in small numbers throughout the year.

At the end of the year, the region had 191 cases in records.

In 2012, cases of the disease were very low in the 1st epidemiological week and continued with low numbers until the 8th and 9th weeks when higher number of cases were recorded and dropped drastically in the 10th week and the region recorded zero cases in the rest of the epidemiological weeks. In summary, 92 cases were recorded in the 52 epidemiological weeks of the year.

The conjugate vaccine was first used in the region in June 2012. In 2013 low cases were recorded as compared to the previous years though sparsely spread out in the entire year. The region had only 66 reported cases in 2013.

Figure 1b below shows the annual weekly distribution of CSM cases for 2013-2015.
Figure 3b: Distribution of CSM cases in the Upper West Region for 2013-2015

In figure 1b above it is observed that meningococcal disease incidence shot right from the first epidemiological week and declined in the 3rd week of 2014. The region had low cases at the 14th week and progressed in that trend throughout the rest of the weeks and finally 192 reported cases in the entire year.

A number of cases were recorded in the 1st and 2nd weeks of 2015. The number of cases dropped in the 4th week. In the 13th week alone 26 cases were reported been the week with the highest number of reported cases of CSM in that particular year. There were 203 reported cases in the year

Before the introduction of the conjugate vaccine (2010-2012), the total number of reported cases of CSM stood at 688 and out of this number there were 324 males and 364 females.

In 2013-2015, the region had 448 reported cases and among these cases, males comprised 224 and females also 224 (Table 1)
Table 1: Distribution of cases of CSM in the Upper West Region from 2010-2015 by sex

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Cases before Introduction of Conjugate Vaccine</th>
<th>Cases after Introduction of Conjugate Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2011</td>
</tr>
<tr>
<td>MALE</td>
<td>201(49.6%)</td>
<td>89(46.6%)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>204(50.4%)</td>
<td>102(53.4%)</td>
</tr>
</tbody>
</table>

Among the various age groups before the introduction of the conjugate vaccine, children less than 5 years of age as well as adults 20 years and above had higher number of reported cases than cases among other age groups. For instance, in 2010, cases among children less than 5 years were 81 and among adults 20 years above there were 168 reported cases. A similar trend was shown in 2011 and 2012 (Table 2)

Table 2: Age group distribution of CSM cases in the Upper West Region of Ghana

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Cases before Introduction of Conjugate Vaccine</th>
<th>Cases after Introduction of Conjugate Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2011</td>
</tr>
<tr>
<td>≤4 years</td>
<td>81(20.0%)</td>
<td>34(17.8%)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>53(13.1%)</td>
<td>32(16.8%)</td>
</tr>
<tr>
<td>10-14 years</td>
<td>39(9.6%)</td>
<td>34(17.8%)</td>
</tr>
<tr>
<td>15-19 years</td>
<td>64(15.8%)</td>
<td>21(11.0%)</td>
</tr>
<tr>
<td>≥20 years</td>
<td>168(41.5%)</td>
<td>70(36.6%)</td>
</tr>
</tbody>
</table>
Again from the above table, it is seen that the distribution of cases among the age groups 4 years and below as well as 20 years and above remained higher than cases among other age groups. In 2013 children 4 years and below experienced 24 cases and among adults 20 years and above, 20 cases were reported. The age group 10-14 years had the least number of reported cases in the year. A similar trend has been observed in 2014 and the trend shifted slightly in 2015.

The annual mortality as a result of CSM in the study showed higher cases among the age group 20 years and above as reported in 2010 compared to mortality among other age groups in the same year. Mortality among age groups in 2011 and 2012 were similar to the outcome in 2010 though reported deaths among adults 20 years and above reduced slightly(Figure 4a).

![Figure 4: Annual mortality due to CSM among age groups in the Upper West Region](image)

A year after the introduction of the conjugate vaccine, reported death cases went down especially in age group 20 years and above. In 2014, reported death cases among age group 4 years below shot up more than cases among other age groups. Finally in 2015, reported death cases were high among children 5-9 years old than the other age groups. This information is shown in figure 3b below.
Figure 5: Outcome of reported cases of CSM among age group 2013-15

Four main organisms were identified to be the cause of most reported cases of CSM in the region. Patients who showed signs symptoms of the disease upon reporting at the hospital and whose laboratory results did not indicate the presence of any organisms were labeled *No organism*.

Among the reported cases, the bacteria *Neisseria meningitides* and *Streptococcus pneumonia* caused more cases compared to their counterpart *Haemophilus influenzae* between the period 2010-2012 (Table 3).
Table 3: Organism causing Meningococcal disease in the Upper West Region

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Cases by Type of Organisms before Introduction of Conjugate Vaccine</th>
<th>Cases by Type of Organisms after Introduction of Conjugate Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2011</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>2(0.5%)</td>
<td>3(1.6%)</td>
</tr>
<tr>
<td>Neisseria meningistidis</td>
<td>49(12.1%)</td>
<td>28(14.7%)</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>29(7.2%)</td>
<td>68(35.6%)</td>
</tr>
<tr>
<td>No organism</td>
<td>325(80.2%)</td>
<td>92(48.2%)</td>
</tr>
</tbody>
</table>

From the above table it is observed that after the introduction of the conjugate vaccine the two main bacteria (*Neisseria meningitidis* and *Streptococcus pneumonia*) remained the main cause of Meningococcal disease in the region.

Thirteen serotypes of the bacterium *Neisseria meningitides* exist but four of them were identified to be involved in all the confirmed cases caused by the bacterium. These serotypes were N. m A, N. m B, N. m C, N. m W135 and N. m Y.

In the year 2010, the serotype N. m Y was responsible for most of the cases caused by the bacterium *Neisseria meningitides*. In 2011 the serotype N. m W135 caused most of the cases involved with the bacterium. Records of cases in 2012 showed a similar thing as in 2011. Below is figure 5a showing the various serotypes and their corresponding frequencies.
Figure 6: Serotypes of N. m and their corresponding frequencies in terms of number of cases the bacterium caused

From 2013 -2015 after the introduction of the conjugate vaccine, some of the strains did not cause any cases of Meningococcal disease. Figure 4b below shows the serotypes that were responsible for disease caused by the bacterium from 2013-2015.

Figure 7: Serotypes of N. m and their corresponding frequencies in terms of cases the bacterium caused 2013-2015

From the above figure the serotype N.Mw135 was responsible for most of the cases in 2013 and also in 2015
Reported deaths as a result of Meningococcal disease in 2010 was slightly higher than deaths in 2011. Also reported death cases were slightly lower in 2012 than in 2010 and 2011. The figure below shows the number of reported cases and deaths with their corresponding frequencies from 2010-2015.

![Bar graph showing reported cases and deaths from 2010 to 2015](image)

**Figure 8: Annual reported Meningitis cases and deaths from 2010-2015**

From the above figure reported cases of Meningococcal disease death reduced from 2013-2015 as compared to 2010 and 2011.
CHAPTER FIVE
DISCUSSION

This study determined the trends of reported cases of CSM in the Upper West Region of Ghana (2010-2015). The study showed that cases were recorded throughout the year with the highest numbers recorded from November to April. This is because of the hot climatic conditions and the dry harmmattan which creates cracks in the oro- and nasopharyngeal membranes. When this happens the bacteria can stray into the spinal fluid and the brain meninges and cause the disease. This agreed with the finding of (Sultan et al; 2005).

It was also observed that both the pre- and post- introduction of the vaccine periods displayed similar trends but it is quite glaring that more cases were reported during the time the vaccine was not introduce compared to the observed data after the introduction of the vaccine. This suggests that the vaccine might have protected both the vaccinated and the unvaccinated against the disease. This finding is similar to that of Mclyre et al., 2012.

In general, despite the inconsistent trends of reported cases, the Regional Disease Control data indicates a reducing trend before the introduction of the vaccine as 2010 had a total of 405 cases and this represented 57 per100, 000 populations, 191 reported cases in 2011 and this also represented 26 per 100,000 populations and 2012 had a total reported cases of 92 and this represented 12 per 100,000 populations in the region. The drastic reduction of reported cases in 2012 may be due to the vaccine since it was first administered in the region in June 2012 though low cases are always observed in that period of the year from previous studies.

Three years after the introduction of the vaccine, the trend indicated a reduction in confirmed cases of Meningococcal disease as can be seen from 2013-2015, the following confirmed cases 66 for 2013, 31 for 2014 and 29 for 2015. This suggested that the vaccine might be responsible for the reduction in cases. This is similar to the finding of Barbour et
al., 1999. However the resurgence of the Meningococcal disease in the Northern part of Ghana and especially the study area raises doubt about the long-lasting immunity of the vaccine. This is in consonance with a study carried out by Maiden, 2013.

The distribution of reported cases among males and females in the region indicated a slight increase in cases among females than males in the region and this is different from the finding of Aurelio et al., 2006.

Age is said to play a significant role in infectious diseases. The Meningococcal disease is an example as data from the region indicated high cases among those less than five years of age and those above twenty years. This is in line with the works of Maiden, 2013. Because most young adults are in colleges and secondary schools and the rate of transmission is high there and young children aged six months to one year as a result of waning maternal acquired immunity before the development of adaptive immunity.

It is also quite important to note that, in contrast with what is observed in the USA and certain European countries, in Brazil no increased incidence has been observed among adolescents and young adults.

On the other hand, after the introduction of the conjugate vaccine the trend changed slightly. In 2013, the region reported 35.8% of children less than 5 years with the disease. Those 21 years and above followed with 29.9% of total cases of the year. In 2014 the trend changed again and those 21 years and above recorded more cases representing 35.9% of total cases of the year. Meanwhile in 2015, this particular age group 21 years and above being recorded the least with a percentage of 3.9% of total cases recorded in the year. The nature of the trend of cases of CSM creates doubts regarding the long-lasting immunity of the vaccine in children and adults 21 years and above the most high risk age groups.
A similar study carried out in Gambia by Mackenzie et al., 2016 suggested a reduction of more than 50% in all age groups. Unlike my study, the Gambian study only looked at the pneumococcal conjugate vaccine.

Another study carried out by Safadi, M. A. P. and Barros, A. P. 2006 also indicated reduction in meningococcal disease but indicated that recent data shows waning efficacy among children who got immunised in their first of life and this raises doubts regarding the duration of protection of the vaccine suggesting that the vaccine might not be effective against the meningococcal disease as earlier expected.

Among the organisms associated with the reported cases of CSM, this study looked at the bacterium *Neisseria meningitidis* because it is established from WHO reports that the bacterium caused most of the outbreaks in the sub region. The reports also stated that the bacterium has a higher death rate than the usual. This may be as a result of the numerous serotypes of the bacterium of which four are known to cause outbreaks in the Meningitis belt. This study has revealed that most of the reported cases that the bacterium was responsible for were caused by the serotype N.m W135 in both the pre- and post-introduction of the vaccines periods. Even in 2015 this strain was responsible for all the reported cases as a result of the bacterium.

A case report carried by Siakwa et al., 2008 revealed that the strain N.m W135 was isolated the first time in Ghana in a three-year old boy, a native of Alhassan Akuraa from the Kintampo district in the Brong Ahafo Region.

A study conducted by Aurelio et al., 20013 also revealed that serogroups A, B, C, Y and W135 are responsible for almost all cases of the disease infecting humans only. This revelation is in line with this study findings since only these serogroups were found to have caused all the cases associated with the bacterium in the region. Meanwhile this study is
different from that of Kaaijk, Ende, Berbers, Dobblesteen and Rot, 2012 which stated that serogroup A was responsible for most epidemics.

Contrary to the findings of this study, in the USA and Europe the disease is mostly endemic and usually caused by serogroups B and C. Also while the vaccine has been able to eradicate or minimise cases caused by serogroup C in this study area, a study by (Aurelio et al., 2006) reported an increase in the number of cases attributed to serogroup C in other countries. For instance, in the state of Sao Paulo where the vaccine was responsible for 63% of the cases in 2005, with serogroup B representing 32% of the cases while the other serogroups contributed only 5%. These revelations are indications that some serotypes are likely to thrive well in some regions probably because of favourable geographical conditions.
CHAPTER SIX

CONCLUSION

Before the introduction of the conjugate vaccine, 2010-2012, there were higher proportions of CSM cases than the post intervention period; 2013-2015. Although the decline was significant, indicating the possible effectiveness of the vaccine, annual outbreaks of CSM cases in the North and other parts of the country tells that the vaccine is not an end game for meningitis.

6.1 Recommendation

Implication for Public health and policy

- Given that conjugate vaccine is not effective against some of the bacteria associated with the disease a tetravalent meningococcal conjugate vaccine may be effective against the bacteria than the current vaccine

- Surveillance system should be implemented within the window periods in the year where cases are very high.

Implication for research

Further research should be conducted on the epidemiology of the bacterium and its strains

Lastly, there is the need for effective surveillance system to determined the biology of the strain enable public health workers put up effective measures in case of an epidemic by the strain
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Appendix: Ethical approval Letter

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App/ Your Ref. No.

Godfred Kuundire Dogee
University of Ghana
School of Public Health
Legon, Accra

ETHICS APPROVAL - ID No: GHS-ERC: 42/12/15

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol titled:

“Trends of Reported Cerebrospinal Meningitis in the Upper West Region Three Years Post Introduction of the Conjugate Vaccine in Ghana”

This approval requires that you submit yearly review of the protocol to the Committee and a final full review to the Ethics Review Committee (ERC) on completion of the study. The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Please note that any modification without ERC approval is rendered invalid.

You are also required to report all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.

You are requested to submit a final report on the study to assure the ERC that the project was implemented as per approved protocol. You are also to inform the ERC and your sponsor before any publication of the research findings.

Please note that this approval is given for a period of 12 months, beginning 25th February, 2016 to 24th February, 2017. However, you are required to request for renewal of your study if it lasts for more than 12 months.

Please always quote the protocol identification number in all future correspondence in relation to this approved protocol.

SIGNED.............. PROFESSOR MOSES AIKINS
(GHS-ERC VICE-CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra