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Ayomide Sokale 24 April 2019

The Epidemiology of Meningitis among Children in Nigeria in the Post-Vaccination Era

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The Epidemiology of Meningitis in Nigerian Children in the Post-Vaccination Era

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Abstract

The Epidemiology of Meningitis in Nigerian Children in the Post-Vaccination Era
By Ayomide Sokale

Background: Nigeria is one of twenty-six countries that lie in the meningitis belt of Sub-Saharan Africa which is an area that has the highest rate of meningitis in the world. Between the beginning of a national epidemic in December 2016 and the official end of the outbreak on June 23rd, 2017, Nigeria reported a total of 14,513 cases of meningitis with 1,166 deaths and a case fatality rate of 8%. Of the reported suspected cases only an approximate 7% of cases were laboratory tested, of which approximately 46.2% of these cases were confirmed positive for bacterial meningitis. The bacteria *Neisseria meningitides* serogroup C was the most dominant disease-causing strain, accounting for approximately 75.4% of positive cases.

Objective: To examine the epidemiology of meningitis in children (aged 0 to 18 years) in Nigeria, in the post-vaccination era, after MenAfriVac vaccination (2011) and the MenACWY conjugate vaccine (2017).

Methods: National Routine surveillance data for suspected cases of meningitis was collected for the years of 2017 and 2018 (n=13,585). All statistical analyses were performed using SAS version 9.4. Counts and proportions were given in place of an estimated prevalence or cumulative incidence.

Results: Out of the entire cohort of 13,585 children approximately 4174 children (30.7%) were within the age group of 5 to 9 years, and 4571 children (33.6%) were within the age group of 10 to 14 years. Of the total cases approximately 60% (n=7986) were male. Finally of the approximately 6% of cases for whom CSF samples were taken 61.5% (n=401) tested positive for *N.meningitidis* serotype C.

Conclusions/ Implications: Meningitis is more prevalent in children in Nigeria than in adults. Nigeria mostly experienced outbreaks of meningitis attributed to *N.meningitidis* serotype A. However the results of this research indicate that among the laboratory-tested cases within the study period, the majority of cases (61.5%) were caused by *N.meningitidis* serogroup C. The results of this study indicate that this emerging strain is more prevalent in children than in adults and may have implications for future vaccine research as well as future policies.

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Chapter I: Introduction

Introduction and Rationale

Nigeria is a country that sits within the Meningitis Belt of Sub-Saharan Africa, a region that has the highest rates of meningitis in the world [1]. This region of Africa spans from Senegal to Ethiopia, and includes twenty-six countries from east to west of the Sahel and Sub-Sahel regions [2, 3].

Prior to the beginning of a national epidemic in 2016, Nigeria had been implementing routine mass vaccination campaigns against *Neisseria meningitidis* serotype A, which had been deemed effective since the vaccine had been introduced into the country in 2011[4, 5]. However, meningitis attributed to *N.meningitidis* serotype C began to emerge as vaccination campaigns using MenAfriVac became effective, and vaccination against *N.meningitidis* serotype A began to approach herd immunity[6].

On February 20th, 2017 the World Health Organization was notified of an outbreak of meningitis in Nigeria[7]. The first reported case of the disease was reported in Zamfara state on December 12th, 2016[8]. Between the beginning of the outbreak in December 2016 and the official end of the outbreak on June 23rd, 2017, Nigeria reported a total of 14,513 cases of meningitis with 1,166 deaths and a case fatality rate of 8%[8, 9].

With the aid of organizations such as the World Health Organization (WHO) and the National Primary Health Care Development Agency (NPHCDA) the Nigeria Centre for Disease Control (NCDC) was able to establish an Emergency Operations Center (EOC) to address this outbreak. In response to this outbreak NCDC and WHO began mass vaccination campaigns in the states that were most affected [8-10]. They estimated that approximately 2 million individuals were vaccinated against meningitis, utilizing a variety of vaccines for meningitis. In the states that had the highest incidence of cases the polysaccharide serogroup A & C vaccine was given to people aged 1 to 29 years, the monosaccharide meningococcal conjugate C vaccine was given to people aged 1 to 20 years, and the polyvalent ACW conjugate vaccine was given to people aged 2 to 29 years[9]. These three age groups represented the most at risk population for disease, at that time.

This outbreak represented the largest outbreak ever attributed to *N.meningitides* serogroup C in Nigeria [8, 11]. Prior to this outbreak other studies attempted to describe the trends in meningitis throughout the country, however these studies only focused on *N.meningitides* Serotype A, as this was the strain of the bacteria that most often caused disease in Nigeria, and occasionally Serotype C was attributed to small localized outbreaks but seldom large-scale epidemics of disease[5, 12].

As this was the first outbreak attributed to *N.meningitides* serotype C, not much data exists on the true prevalence of the disease amongst individuals living in Nigeria and amongst the demographic that meningitis most affects, children[13, 14]. While the true cost, economic and otherwise of meningitis on the Nigerian government is unknown. Other countries within the meningitis belt have conducted research on the economic impact of vaccination with MenAfriVac and the subsequent decrease of disease on the economy. Two studies conducted in 2015 in Burkina Faso, found that in Burkina Faso which began vaccination in the year prior to Nigeria (2010) vaccination with MenAfriVac was a cost-saving strategy for the government, the healthcare system, and for individual families[15, 16]. They found that for every one United States dollar they invested in prevention they saved an additional 1.3 United States dollars, by opting for a preventive rather than reactive vaccine strategy[15].

Although, Nigeria and Burkina Faso have similar economic structures they do have differences. Burkina Faso is considered to be a low-income country with limited natural resources, while

Nigeria is a low-to-middle income country due to the fact that it is Africa's largest oil exporter, and has the largest source of natural gas on the continent [15, 17, 18]. Furthermore Nigeria has one of the largest populations of youth in the world[17]. While the recession in Nigeria has officially ended since 2017, the country still struggles with human capital development. This is exacerbated between the North-South divide that effects this country, and splits one large country into nearly two distinct countries. Culturally, ethnically, and religiously a divide exists between the Northern and Southern regions of the country. Generally, the cultural majority in Northern Nigeria are the Fulani and Hausa tribes, which are both religiously Muslim. Generally, the cultural majority in Southern Nigeria are the Igbo and Yoruba tribes, which are both religiously Christian. Given this divide in culture and religion, Northern and Southern Nigeria have very different economies[19, 20]. Finally Nigeria's estimated population is nearly 200 million citizens whereas Burkina Faso's population was estimated to be approximately 18.6 million citizens in 2016, a population that is approximately less than 10% of that of Nigeria[17].

Nigeria has continued to experience seasonal outbreaks of meningitis, since the end of the outbreak in 2017, the majority of which are caused by *N,meningitides* serotype C and not *N.meningitides* serotype A, as they had been historically[21, 22]. Given that this pathogen is fairly recent in outbreaks, Nigeria needs to have a current prevalence of meningitis due to *N.meningitidis* serotype C, in order to make recommendations for vaccine schedules and vaccine types.

Problem Statement

Meningitis, is an infectious disease that without attention and treatment can have devastating lifelong consequences, such as paralysis and hearing loss[23, 24]. Most of Northern Nigeria sits within the meningitis belt, where meningitis is endemic, however in the past three years Nigeria has experienced an emergence of meningitis due to serotype C [8]. The analysis of data collected from these outbreaks will aid in understanding emerging trends in the disease and inform vaccine policy and research.

Purpose Statement

This research will inform policy on vaccination against meningitis, and specifically *N.meningitides* serogroups A and C in Nigeria, by providing evidence for routine vaccination of children under 18 in areas where there is a high prevalence of disease.

Research Question and Hypotheses

Question: Has the epidemiology of Meningitis by *N.meningitidis* serotype A and C, changed in children (aged 0-18 years) living in Nigeria after the introduction of two vaccines against meningitis: MenAfriVac (2017) and all *N.meningitidis* serotype C containing vaccines such as the conjugate ACYW135 vaccine (2018)?

Furthermore the primary objective of this study is to have an accurate, as of the last time of data collection, prevalence and incidence of meningitis in children throughout Nigeria, as well as have an understanding of the pathogens that are causing disease, and to what degree they may cause disease throughout this population. To achieve this a secondary analysis of data collected during one large national epidemic and several smaller localized outbreaks will be conducted to gain an estimate of the prevalence and incidence of meningitis due to *Neisseria meningitides* serotypes A and C in Nigerian children.

Definition of Terms

Local Government Area (LGA): An LGA is the Nigerian-equivalent of a County in the United States.

Ward: A Ward is the Nigerian-equivalent of a city or town.

Cerebrospinal meningitis/ Meningitis: "[An] inflammation of the meninges caused by viral or bacterial infection and marked by intense headache and fever, sensitivity to light, and muscular rigidity, leading (in severe cases) to convulsions, delirium, and death.[25]"

Pastorex: A rapid slide agglutination test for the simultaneous detection of the fibrinogen affinity (clumping factor), protein A, and capsular polysaccharides of Staphylococcus aureus.

Culture: Refers to a cerebrospinal fluid culture

PCR: Polymerase Chain Reaction is a method used in molecular biology to make copies of a specific segment of DNA.

VACYW: VACYW refers to a vaccine against *N.meningitidis* serogroups A, C, Y, and W135

PCV: PCV refers to a pneumococcal vaccine

VNMA: VNMA refers to a vaccine against *N.meningitidis* serogroup A

VAC: VAC refers to a vaccine against *N.meningitidis* serogroup C

Chapter II: Literature Review

The History of *Neisseria Meningitides* and Meningitis

The first known incidence of an outbreak due to meningitis was described in Edinburgh by a Scottish physician by the name of Robert Whytt[26]. Whytt reported the first known case of tuberculosis meningitis, which he described as “inflammation of the meninges with a continual fever[26].” However, other outbreaks due to an, at that time unknown disease, meningitis, had been reported throughout various countries over centuries. Cases of meningitis had been identified by Viesseux in Geneva, Switzerland in 1806, by Danielson and Mann in Bedford, Massachusetts in 1806, and in what is now known as the Meningitis Belt in the early 1900s. However, it wasn’t until 1887, when Weichselbaum performed a lumbar puncture on a patient who presented with symptoms associated with meningitis, that the etiology of the disease was discovered, the meningococcus [25, 26]. What Weischelbaum defined as the meningococcus in 1887, we now know to be *Neisseria meningitides* the pathogen that causes meningitis in humans, and is responsible for outbreaks of the disease. In the late 19^{th} century, other organisms that cause meningitis such as *Streptococcus Pneumoniae*, and *Haemophilus influenzae* were identified, however *Neisseria meningitides* remains the most common cause of meningitis throughout the world[23, 27, 28].

Initially antibiotic treatment was used to treat meningitis, beginning with sulfonamides, which were used until antibiotic resistance to the treatment was observed in the 1960s[25]. This resistance led to the discovery and development of the first vaccines against the meningococcus.

The Microbiology and Pathobiology of *Neisseria Meningitides*

Neisseria meningitides is a gram-negative beta proteobacterium that is generally found in the nasopharynx of humans; however, if a human host has certain factors that promote the growth of the bacteria such as: host susceptibility, environmental conditions, and inadequate immune response the bacteria can replicate and invade the human host and cause meningitis, which will heretofore be referred to as meningitis [25, 29].

To infect the host, the bacterium enters the host's body through the nasopharyngeal mucosal epithelium, where it enters the blood, and if host conditions are appropriate it begins to begin the process of bacteremia. *N.meningitides* is capable of crossing the blood-brain-barrier and entering into the cerebrospinal fluid of the host to colonize the meninges[29].

N. meningititdis is a human-specific gram-negative beta proteobacterium, and is a member of the family *Neisseriaceae*, which several other pathogens are under as well. The bacterium can either be encapsulated or unencapsulated and is an aerobic diplococcus. The bacterium is naturally found in the environment and is commonly found in the human nasopharynx, one in ten individuals will have *Neisseria meningitides* colonization without infection in the nasopharynx [30, 31].

Thirteen meningococcal serogroups have been identified (A, B, C, D, 29E, H, I, K, L, Y, W-135, X, and Z), however the greater number of cases of the disease have been caused by five main capsule types. These types are: A, B, C, Y, and W-135. Other serotypes of meningitis exist that are independent of a serotype, however these serotypes rarely cause disease, and are considered hyper-invasive lineages [31-33].

Variation in the serogroups of meningitis that are attributed to outbreaks and epidemics exists. Within Europe and the Americas the serogroups that are mainly attributed with causing meningitis are serogroups B, C, and Y whereas in the continent of Africa, and in the eponymous Meningitis Belt meningitis is mainly attributed to serotypes A and C. Serogroup W-135 has also been attributed to outbreaks throughout the world[33].

Although, *Neisseria meningitides* can naturally be found in healthy individuals without infection, the pathogen often causes disease in infected and colonized individuals. This occurs when the pathogen penetrates the human body's first line immune defense: the mucosal barrier in the nasopharynx[31]. This is an effective barrier for the 10% of carriers throughout the world who have not progressed to infection. Once the bacterium penetrates the mucosal barrier it then moves to second line immune defenses, such as: epithelial and endothelial cells which are assisted by proteins and bacterial pili. If the bacterium is able to penetrate this level of defense it then enters the blood stream where it can cause meningitis, which is the case for approximately 75%-80% of infected individuals, of septicemia, which is the case for only 15%-20% of infected [13]individuals [29, 34].

The Epidemiology of Meningitis throughout the World

There are seven pathogens that are known to cause meningitis: *Escherichia coli, haemophilus influenzae, Neisseria meningitides, Streptococcus Pneumoniae, group B streptococcus agalactiae, staphylococcus aureus, and listeria monocytogenes* [13, 32, 35, 36]. Research has found that the two predominant infectious pathogens in cases of meningitis are *Neisseria meningitides* and *Streptococcus Pneumoniae*[22, 37]. A literature review of 56 research publications, from April 25th 2012 to April 25th 2017, five years, identified that *Streptococcus Pneumoniae* was mentioned as the causal pathogen in 25.1-41.2% of the publications that they found whereas *Neisseria meningitides* was identified as the causal pathogen in 9.1 – 36.2% of the publications that the found[38].

The incidence of meningitis varies throughout the world [32, 39]. Although the disease can be found through the world, there are several countries and geographical areas for which the prevalence of meningitis is endemically high. Furthermore, geographically the distribution of meningitis can be affected by several variables such as: the serogroup of the bacterium isolated, the climate and temperature, and the season, as well as other factors.

While meningitis occurs throughout the world, the majority of cases, approximately 90%, of all cases throughout the world of meningitis occur in an area of sub-Saharan Africa that has been eponymously named the Meningitis Belt [39-41].

The Epidemiology of Meningitis in Africa (The Meningitis Belt)

For over a century, a region of sub-Saharan Africa has been affected by large outbreaks and national epidemics of meningitis. This region is eponymously known as the meningitis belt. The meningitis belt spans from west to east Africa, from Senegal to Ethiopia [2].

These epidemics have created both economic and health strain on the countries that fall within the meningitis belt. The climate and temperature of this region makes sit particularly susceptible to outbreaks of meningitis, due to the nature of the pathogen replicating and spreading in hot, dry, and arid conditions [42]. Historically, over a century, outbreaks of meningitis in this region have been due to *Neisseria meningitides* serotype A, with few outbreaks being attributed to *Neisseria meningitides* serotypes W-135, X, and C[43].

Neisseria meningitides serotype W-135 has been attributed to causing outbreaks in Burkina Faso, Ghana, and Niger over the past two decades[44]. While *Neisseria meningitides* serotype A has been attributed to causing outbreaks in Chad, Niger, and Nigeria. However, outbreaks due to serotype W-135 tend to be on a much smaller scale than outbreaks attributed to *Neisseria meningitides* serotype A, on average these outbreaks were approximated to be 78% of the size of outbreaks attributed to *Neisseria meningitides* serotype A[45].

The twenty-six countries that are included in the meningitis belt are: Mauritania, Mali, Niger, Chad, and Sudan. Eritrea, Senegal, Burkina Faso, Nigeria, the Central African Republic, South Sudan, Ethiopia, Gambia, Guinea-Bissau, Guinea, Cote d' Ivoire. Ghana, Togo, Benin, Cameroon, the Democratic Republic of Congo, Kenya, Tanzania, Uganda, Rwanda, Burundi [2]. Although these countries are all included within the meningitis belt because they have high endemic rates of the disease, they have varying rates of disease. Some countries have a higher overall prevalence of meningitis than others.

The Epidemiology of Meningitis in Nigeria

The first major meningitis outbreak on the continent of Africa was described between 1905 and 1908, in both Nigeria and Ghana[25]. Since the first description of the disease in the country, Nigeria has experienced seasonal epidemics and outbreaks of meningitis for the past 100 years that seem to follow a pattern of occurring every five to twelve years [46, 47].

Historians believe that the first strain of *Neisseria meningitides* was introduced to West Africa from Sudan by pilgrims returning from Hajj, the Muslim pilgrimage to Mecca that takes place in the last month of the year [48, 49]. These outbreaks of the disease would continue to occur for over a century throughout various years and seasons.

The first severe epidemic of meningitis was described in Nigeria in 1996[46]. Prior to this Nigeria had experienced localized outbreaks of disease that were all under the pre-defined epidemic threshold that had been put into effect by the Ministry of Health. This epidemic resulted in 109,580 recorded cases, 11,717 deaths with an overall case fatality rate of 10.7% throughout the six-month epidemic. At the time this was the most severe epidemic of the disease that Nigeria had experienced and was the most severe recorded epidemic for the entire continent of Africa[40].

Although the outbreak was first recorded as beginning in January of 1996, surveillance reports from the ministry of health note that an increase in the amount of diagnoses of meningitis began from October 1995. The first state to reach the epidemic threshold (greater than or equal to (15 cases per 100,000 people in the population for two consecutive weeks) was Katsina state in November of 1995[46].

During this outbreak 467 cerebrospinal fluid samples were taken from patients within the age group of three months to thirty years in the six states with the highest prevalence of cases. These states were Bauchi, Kaduna, Kano, Katsina, Kebbi, and Yobe states[46]. The pathogen responsible for causing disease in more than half of these cases was identifies through latex agglutination to be *Neisseria meningitides* serogroup A, with Haemophilus influenzae being the second most common pathogen identified[46, 50].

This outbreak led to the first discovery of climatic and temperature risk factors and conditions that would contribute to the spread of the disease. By mid-April the epidemic had reached its summit[46]. This occurred at a time where the temperature was extremely dry and dusty, with an average temperature of 39 degrees Celsius, with a relative humidity of approximately 30%. Due to the nature of the pathogen it thrived and spread in these conditions compounded by the fact that most of the affected population lived in poorly ventilated and over-crowded areas [42, 43].

Once the epidemic threshold had been met in most states by the fourth week of the epidemic, it began to spread throughout the Northern region of the country, and within two weeks most states in the northern region had met the epidemic threshold for meningitis. The four most affected states in this epidemic were: Bauchi, Kano, Katsina, and Kebbi, accounting for approximately74% of all cases during the outbreak (81, 230 cases), all of these states fell within the meningitis belt, whereas states that fell outside of the meningitis belt experienced far fewer cases[46].

There were several demographic differences between cases during this outbreak. The male to female ratio for this outbreak was 1.2:1 indicating that in this epidemic in Nigeria the disease affecter men almost equally as it affected women. 72% of the cases in this epidemic were between the ages of less than one year and fifteen years of age [46, 51].

Information on vaccination campaigns indicated that in the states that had the highest prevalence of the disease, vaccination campaigns had not occurred within the two-year period before the onset of the epidemic. In states where some of the population was vaccinated (Borno, Yobe, Adamawa, Kaduna, Niger, and Sokoto) only 20% of the population under 30 had been immunized against any strain of *Neisseria meningitides* [52, 53].

Researchers who retrospectively studied this epidemic described it as the largest meningitis throughout the continent to date[54]. This occurred for several reasons. The primary reason that the pathogen was able to spread so quickly throughout the population and cause disease was due to the low herd immunity in the population in this region of Nigeria. Furthermore, the economic situation throughout the entire country was dire [53, 55, 56].

General Ibrahim Babangida became the president of Nigeria in August of 1985 with a promise of democracy and economic success. However, after gaining independence in 1960, Nigeria was still experiencing the economic strain that accompanies being a newly independent country, no longer under British rule. By 1995, when the epidemic began, Nigeria had already been experiencing an economic decline due to exploitation of oil that had been naturally found in the country [56, 57]. Due to the industrialization of oil in the country many middle-class and farmers in Nigeria found themselves facing economic ruin. It was these conditions that exacerbated the effect that the spread of the pathogen and the subsequent disease would have on people living throughout the country [58-60].

CHAPTER III:
Manuscript

The Epidemiology of Meningitis in Nigerian Children
In the Post-Vaccination Era

Ayomide Sokale, BA

Contribution of the Student

The work within this manuscript is the result of a secondary data analysis performed by the student. The student did not have a role in collection of the data through reporting of cases of meningitis in Nigeria, between 2017 and 2018. However, the student did perform all work after data collection independently, including the cleaning of the data, construction of age groups and any new variables, analysis of the data, summation of results in tables and figures, and all writing. Advisement during this process was provided by the student's thesis advisor.

Abstract

The Epidemiology of Meningitis in Children in Nigeria in the Post-Vaccination Era

By Ayomide Sokale

Background: Nigeria is one of twenty-six countries that lie in the meningitis belt of Sub-Saharan Africa which is an area that has the highest rate of meningitis in the world. This region spans from Senegal to Ethiopia. This region is associated with high endemic rates of meningitis. The most recent national epidemic of meningitis in Nigeria occurred in 2017. The first reported case of the disease was reported in Zamfara state on December 12th, 2016. Between the beginning of the outbreak in December 2016 and the official end of the outbreak on June 23rd, 2017, Nigeria reported a total of 14,513 cases of meningitis with 1,166 deaths and a case fatality rate of 8%. Of the reported suspected cases only an approximate 7% of cases were laboratory tested, of which approximately 46.2% of these cases were confirmed positive for bacterial meningitis. The bacteria *Neisseria meningitides* serogroup C was the most dominant disease-causing strain, accounting for approximately 75.4% of positive cases.

Objective: To examine the epidemiology of meningitis in children (aged 0 to 18 years) in Nigeria, in the post-vaccination era, after MenAfriVac vaccination (2011) and the MenACWY conjugate vaccine (2017).

Methods: National Routine surveillance data for suspected cases of meningitis was collected for the years of 2017 and 2018 (n=13,585). All statistical analyses were performed using SAS version 9.4 (Cary, NC). Counts and proportions were given in place of an estimated prevalence or cumulative incidence. Differences in disease characteristics between different demographic variables were calculated and compiled into a table. Finally, the counts of cases attributed to a specific geographic region or area was calculated and represented in a map.

Results: Out of the entire cohort of 13,585 children approximately 4174 children (30.7%) were within the age group of 5 to 9 years, and 4571 children (33.6%) were within the age group of 10 to 14 years. Of the total cases approximately 60% (n=7986) were male. Finally of the approximately 6% of cases for whom CSF samples were taken 61.5% (n=401) tested positive for *N.meningitidis* serotype C.

Conclusions/ Implications: Meningitis is more prevalent in children in Nigeria than in adults. Before the onset of a large national epidemic in 2016, Nigeria mostly experienced outbreaks of meningitis attributed to *N.meningitidis* serotype A. However the results of this research indicate that among the laboratory-tested cases within the study period, the majority of cases (61.5%) were caused by *N.meningitidis* serogroup C. The results of this study indicate that this emerging strain is more prevalent in children than in adults and may have implications for future vaccine research as well as future policies.

Introduction

Over 1.2 million cases of meningitis occur every year, throughout the globe[22, 33]. Meningitis is an inflammatory condition that manifests in inflammation of the brain and spinal cord[61, 62]. While meningitis can be caused by several pathogens, such as bacteria, mycobacteria, fungi, parasites, and viruses the majority of cases globally are caused by a bacteria called *Neisseria meningitides* [31, 33]. Although meningitis affects people of all ages, it is most prevalent in children, especially in children younger than one year of age and in adolescents aged sixteen to twenty-three years[13]. Though cases of meningitis are recorded in countries throughout the world, the highest incidence of meningitis is found in a region of Sub-Saharan Africa known as the African Meningitis Belt [1-3]. Public health surveillance in this area estimates that major epidemics or outbreaks of meningitis will occur in this region, every five to twelve years with average rates of disease that are up to 1,000 cases per every 100,000 people in the population [22, 47]. Thus, rates of disease are substantially higher in the meningitis belt than they are in other parts of the world[33].

Due to the high rates of meningitis in the African meningitis belt, scientists began to develop a vaccine specifically for this region to immunize individuals at risk for disease, to decrease the high rates of disease. In 2010, MenAfriVac, a vaccine against *Neisseria meningitides* serogroup A was developed and made available to the twenty-six countries within the meningitis belt[4]. Following the introduction of MenAfriVac, the incidence of reported meningitis cases in the African Meningitis belt decreased by 57% in countries that received the vaccine compared to countries without the vaccine six years after mass vaccination [63]. Furthermore, in the same study researchers found that in countries that were fully vaccine compliant, the incidence of laboratory-confirmed cases attributed to *Neisseria meningitides* serogroup A decreased by approximately 99%[63].

While the rates of disease caused by *Neisseria meningitides* serogroup A have decreased the rates of disease due to other serogroups, have been expected to increase. Researchers know that vaccination against infectious pathogens decreases morbidity and mortality associated with the diseases of interest[64, 65]. It is challenging to have a true prevalence of meningitis, and as of yet, the true prevalence of the disease is not known. However, given the well-established IDSR and meningitis reporting framework in Nigeria, the case count for previous outbreaks are known[66]. In addition, *N.meningitides* has been associated with past outbreaks, but the prevalence of the bacteria amongst the number of reported cases is still unknown [12]. Lastly, meningitis is a disease that is predominantly associated with children; still, this association has not been researched in Nigeria. The disease may affect children of other ages in Nigeria, and this may be different than what has previously been observed in other countries.

This secondary analysis of public health surveillance data collected by NCDC on suspected cases of meningitis, also known as cerebrospinal meningitis, from 2017 to 2018 aims to describe the current epidemiology of meningitis amongst Nigerian children (aged less than one year to eighteen years) and understand the association between immunization, and vaccine type, and the prevalence of suspected meningitis cases in the following year.

Background

Nigeria is one of twenty-six countries that lie in the meningitis belt of Sub-Saharan Africa which is an area that has the highest rate of meningitis in the world[1]. This region spans from Senegal to Ethiopia [2, 3]. This region is associated with high endemic rates of meningitis. Nigeria has continued to experience outbreaks of meningitis for over two decades, since experiencing its largest outbreak in 1996[12, 45, 67]. The most recent national epidemic of meningitis in Nigeria occurred in 2017[8].

Prior to the beginning of this epidemic in 2016, Nigeria had conducted several routine mass, and reactive vaccination campaigns against *Neisseria meningitides* serotype A, since 2011[4, 5]. These campaigns were thought of as successful as the rates of disease overall began to decrease throughout the years [6, 68].

The first reported case of the disease was reported in Zamfara state on December 12th, 2016[7]. Between the beginning of the outbreak in December 2016 and the official end of the outbreak on June 23rd, 2017, Nigeria reported a total of 14,513 cases of meningitis with 1,166 deaths and a case fatality rate of 8%. Of the reported suspected cases only an approximate 7% of cases were laboratory tested, of which approximately 46.2% of these cases were confirmed positive for bacterial meningitis [8]. The bacteria *Neisseria meningitides* serogroup C was the most dominant disease-causing strain, accounting for approximately 75.4% of positive cases[69].

With the aid of organizations such as the World Health Organization (WHO) and the National Primary Health Care Development Agency (NPHCDA), the Nigeria Centre for Disease Control (NCDC) was able to establish an Emergency Operations Center (EOC) to address this outbreak. In response to this outbreak NCDC and WHO began mass reactive vaccination campaigns in the states that were most affected [8, 10]. They estimated that approximately 2 million individuals were vaccinated against meningitis during this time[69].

This outbreak represented the largest national outbreak ever attributed to *N.meningitides* serogroup C in Nigeria [8, 11]. Prior to this outbreak other studies attempted to describe the trends in meningitis throughout the country, however these studies only focused on

N.meningitides Serotype A, as this was the strain of the bacteria that most often caused disease in Nigeria, and occasionally Serotype C was attributed to small localized outbreaks but seldom large-scale epidemics of disease[45].

Materials and Methods

The World Health Organization: Nigeria Country Office (WHO) in collaboration with the Nigeria Center for Disease Control (NCDC), conducted routine disease surveillance for meningitis and compiled the data collected into a national line list. As meningitis is a nationally notifiable disease in Nigeria, information on new and existing cases was collected by disease surveillance and notification officers (DSNO) from NCDC on a weekly basis. Cases were recorded in a national line list and data from December 2016, the entire year of 2017, and until June 11th, 2018 were used for this study.

Data Collection Area

Data were collected from individuals living throughout Nigeria, consisting of all thirty-six states including the Federal Capital Territory, Abuja. A case was defined as an individual who presented to a health facility with symptoms of meningitis.

Data Collection

Data were initially collected by NCDC and the WHO Nigeria Country Office, and are defined as data from routine national surveillance data, as such data collection was previously approved by the Federal Ministry of Health in Nigeria, the Nigeria Institute of Medical Research, and the National Health Research Ethics Committee of Nigeria. As this surveillance system was part of routine public health surveillance, ethical committee and institutional review board approval, as well as informed consent were not sought. Furthermore, as these data were collected as part of routine public health surveillance, ethical committee approval and informed consent were not required.

Informed consent and IRB approval were not required, by the United States Department of Health and Human Services (HHS) and the Office for Human Research Protections (OHRP), due to the nature of the data collected: public health surveillance. In accordance with 45 CFR part 46 public health surveillance activities are deemed not to be medical research, and as such do not require IRB approval. Finally, all personally identifying information (PII) were removed before analysis.

Emory IRB approval was not required, as public health surveillance is not considered to be human subject's research, and all PII were removed.

Using the case definition for cerebrospinal meningitis as outlined by NCDC and case identification, data were obtained from patients identified at health facilities within the thirty-seven states. DSNOs monitored weekly counts and rates of meningitis and notified NCDC and WHO when these counts were over the weekly threshold for a meningitis outbreak (10 reported cases within a population of 100,000)[10]. Information for all suspected cases was recorded at the time that the individual was admitted to the health facility; this information included: location, age, date of onset of symptoms, symptoms, and immunization status, amongst other information. Demographic information was collected, as well as data about disease risk factors, other medical histories, as well as a history of receipt of meningococcal vaccinations were obtained.

Population and Sample

As of April 2019, the estimated population of Nigeria is approximately 199, 810, 611 people, which is approximately 2.6% of the world's population[70, 71]. Since data were comprised of surveillance data collected for the entire country, this cohort of suspected cases of meningitis is a representative sample of the total population.

The total sample population was comprised of anyone who fit the case definition for a suspected, probable, or confirmed case of meningitis. To form the complete dataset for this study, data were compiled from the years of 2016, 2017, and 2018 (n= 18,022). These disease classifications were defined by the Integrated Disease Surveillance and Response (IDSR) guidelines for Nigeria [10, 72]. The case definitions are as follows:

A suspected case of meningitis[10].

- Any person with sudden onset of fever (>38.5ºC rectal or 38.0ºC axillary) and one of the following signs: neck stiffness, altered consciousness or other meningeal signs.
- Any person with a sudden onset of fever (>38.5˚C rectal or 38.0˚C axillary) and one of the following meningeal signs: neck stiffness, altered consciousness or other meningeal signs like Kerning's, Bruzinski, nuchal rigidity, raised intracranial pressure including bulging fontanelle in toddlers.

A probable case of meningitis[10].

- Any suspected case with cerebrospinal fluid (CSF) turbid, cloudy or purulent on visual inspection; or with a CSF leukocyte count >10 cells/mm3 on doing a cell count or with bacteria identified by Gram Stain of CSF.

A confirmed case of meningitis[10].

- A suspected case that is laboratory confirmed (positive IgM antibody, PCR or virus isolation) or epidemiologically linked to a laboratory-confirmed case.

Confirmed cases were then classified according to the pathogen that caused the disease using either culture, Pastorex, or PCR. For this analysis, the PCR result was used as the criterion for the final laboratory result, in accordance with the United States Centers for Disease Control guidelines[73]. For all further analyses, the suspected meningitis case definition was used, as inclusion criteria for the study. For any analyses, the exposure of interest was defined as the receipt of a vaccine for meningitis. Vaccines that were included in this study are as follows: any vaccine that contains *Neisseria meningitides* serogroup A, any vaccine that contains *Neisseria meningitides* serogroup C, any A, C, Y, W containing conjugate vaccine, a pneumococcal vaccine, and any other vaccine that solely immunizes against meningitis. Immunization status was either confirmed at the time that the case-patient was admitted to the health facility by a healthcare professional and the case patient's medical records or was self-reported at the time that the case-patient was admitted to the health facility. Immunization status was categorized and defined as follows:

Immunization Status = "Yes."

- The case patient either had written documentation showing receipt of a vaccine or provided an oral history that they received a vaccine, but cannot confirm this with a healthcare professional.

Immunization Status= “No”

- The patient had written documentation indicating that they did not receive a vaccine that could be confirmed by a healthcare professional or the patient provided an oral history of not having received the vaccine or having received the vaccine ten days before the onset of symptoms, or after presenting to a healthcare facility.

Immunization Status = “Unknown”

- The patient has no written documentation of having received a vaccine and cannot confirm with a healthcare professional whether they did or did not receive the vaccine, or the patient has provided oral history stating that they know their vaccine history to be unknown.

A sample from the original study population was taken that only consisted of children, aged less than one year to age eighteen. Age was recorded at the time that the patient was admitted to the health facility, for inclusion. Ages were then confirmed using the date of birth provided. The original study population consisted of 18,022 individuals who met the suspected case definition. Individuals were then excluded on the following criteria: an age was not recorded (n= 44), and they were defined as being an adult, an individual whose age was 19 years or older (n= 4392), and finally, the case occurred in 2016 (n=1). The final sample consisted of 13,585 cases which fit the primary investigator's definition of a child, and all other inclusion criteria.

Demographics and Definitions

Data were collected from 13,585 children, before analysis children were then placed into five age categories. The age categories are as follows: less than one year, one to four years, five to nine years, ten to fourteen years, and fifteen to eighteen years. All age categories are in four-year increments, exempting the age category of less than one year.

Study Design

From January 1st, 2017 through June 11th, 2018, routine national surveillance of suspected cases of meningitis was undertaken. Each suspected cases of meningitis was identified by a health care professional, at a healthcare facility in Nigeria, and diagnoses were based on the following criteria: any sign or symptom of meningitis (sudden onset of fever (>38.5ºC rectal or 38.0ºC axillary) and one of the following signs: neck stiffness, or altered consciousness) [10]). For each suspected cases, demographic data, signs and symptoms, prior history of immunization, and laboratory results were recorded on a standardized case report form.

Data Entry and Analysis

Data Entry forms were created by NCDC with input from WHO and other country partners, amongst these partners were the Nigerian Federal Ministry of Health (FMOH) and the Nigeria National Primary Health Care Development Agency (NPHCDA). Data were then compiled into an Excel workbook every week by each state's department of health and sent to NCDC and WHO who then jointly compiled all data into a national line list that was managed in a Microsoft Excel® workbook. Trained data entry staff in Nigeria from both NCDC and WHO entered all data into these excel workbooks, and conducted preliminary data cleaning. Final data cleaning was carried out by the primary investigator at the Emory University Rollins School of Public Health, before beginning analysis.

All data analysis was conducted by the author. The analysis was conducted in Microsoft Excel, SAS Version 9.4 (Cary, NC), and ArcGIS (Environmental Systems Research Institute (ESRI), 2018, ArcGIS Releases 10.6, Redlands, CA). For the data analysis, data were restricted to individuals who had an age under eighteen recorded.

Data Analysis

Data from 2017 and 2018 were analyzed separately by year and then were compiled into a more extensive dataset comprised of both years, and were analyzed as a cohort in a study period that spanned 1.5 years.

All statistical analyses were performed using SAS version 9.4 (Cary, NC). Cumulative incidence and prevalence could not be calculated as there was no reliable source for the estimate of the population of children in Nigeria However counts and proportions were given in place of an estimated prevalence or cumulative incidence. Differences in disease characteristics between different demographic variables were calculated and compiled into a table. Finally, the counts of cases attributed to a specific geographic region or area was calculated and represented in a map.

Analyses

The counts of meningitis per year at the end of each study period was calculated, defined as the number of the sample population with a suspected diagnosis of meningitis. The period prevalence for each year. The incidence of meningitis over the study period was calculated, defined as the number of new cases throughout the study period over the year. For each year, the case fatality rate, the proportion of deaths throughout the outbreak was calculated.

Maps representing the number of cases of suspected meningitis were created using ArcGIS (Environmental Systems Research Institute (ESRI), 2018, ArcGIS Releases 10.6, Redlands, CA).

Results

Characteristics of Suspected Meningitis Cases, 2017-2018

Throughout the surveillance period, 13,585 suspected cases were reported, of which 5,599 were female (41.2%). The remaining 7.986 cases were male (58.8%). Children aged ten to fourteen years accounted for the majority of cases, with 4,571 cases throughout the study period (33.6%). Following behind children aged ten to fourteen years, children aged five to nine years represented the second highest case count, accounting for 4,174 cases throughout the study period (30.7%). The age group for children less than one year of age had the lowest overall proportion of disease accounting for only 315 cases and approximately 2.3% of all suspected cases, the fact that this age group was not in a four-year increment as the other age groups were may explain the stark variation in the number of cases within this age group. Teenagers, within the age category of 15 to 18 years had the second lowest overall proportion of disease accounting for only approximately 16.6% of all suspected cases, while children within the age group of 1 to 4 years accounted for approximately16.8% of all suspected cases (**Table 1**).

The average age of a child with a suspected case of meningitis was approximately 9.3 years, indicating that for the outbreaks that occurred over these years, older children were more likely to have a suspected case of meningitis than younger children. The median age range of 10 also indicates that the age distribution for the outbreaks that occurred over the two years, were overall high, indicating that approximately 50% of the cases were within the age group of less than one year to ten years, whereas the other 50% of cases represented children within the age group of ten years to eighteen years (**Table 1**).

From 2017 to 2018, the majority of suspected cases of meningitis came from one state which accounted for approximately half of all suspected cases in children (44.34%). Zamfara state had a total number of 6,024 suspected cases of meningitis in children between January 1st, 2017 and June 11th, 2018. The state with the second highest case count was Sokoto state accounting for approximately 29% of suspected cases of meningitis, and 3,939 total cases during the study period (**Table 2**).

Immunization status was not always recorded with a case patient's medical history. There are several reasons why a patient would not have a record of their immunization history. One reason for this is that contrary to other countries where vaccines against meningitis are mandatory for school entry for groups at risk, meningococcal vaccines are not required for children in Nigeria. Furthermore, meningococcal vaccines are not a part of the Nigeria child immunization schedule and are therefore not routinely given to children (**Table** 1). Finally, despite areas of Nigeria having an endemically high prevalence of meningitis, Nigeria still has to request the vaccine during active outbreaks and does not have stocks of meningococcal vaccine.

Furthermore, Immunization status was recorded as three options: "Yes" the patient has a medical record of having received a vaccine for meningitis or has self-reported that they received the vaccine, "No" the patient does not have a medical record of having ever received a vaccine for meningitis or has self-reported that they did not receive a vaccine, and "Unknown", meaning that the patient's vaccine history is unknown.

For the total cohort, from 2017 to 2018, only 45 individuals had an immunization history that indicated that they received some vaccine against meningitis. Of these 45 individuals 14 of them, approximately 48.3% of them received a vaccine meningitis against *N.meningitidis* serotype A. This vaccine is most likely MenAfriVac, which was first introduced in Nigeria to lower the rates of disease. Of the 45 individuals overall, who received a vaccine only 14 of them reported receiving a vaccine that contained *N.meningitidis* serotype C and vaccinated against serotype C. Of these 10.3% reported receiving the conjugate vaccine (n=3), while 37.9% of them reported just receiving a vaccine that only contained *N.meningitidis* serotype C and no other serogroups (n=11) (**Table 1**).

Although only 45 individuals reported having received a vaccine, vaccine information was missing for 6092 of the children and reported as either "No" or "Unknown" for 1772 and 5676 children, respectively. These numbers represent 99.4 % of the sample population who had a recorded vaccine status, leaving only 0.6% of the sample population who received a vaccine.

Characteristics of Suspected Meningitis Cases, 2017

Of the 10,942 children who were recorded as having a suspected case of meningitis, 42.0% were female (n=4597), and 58.0% were male (n=6345), indicating that similar to the trends during the two year period, that meningitis is more common in male children than in female children. The mean age group for this cohort was the exact same as the mean age of 9.3 years for the entire sample population. Similarly, rates of disease were higher in older children and adolescents. Adolescents, ages 10 to 14 years accounted for the highest number of suspected cases during this year at 33.3% of suspected cases (n=3645) and children aged 5 to 9 years accounted for the second highest number of suspected cases, representing 30.4% of the total cases for this year (n=3329). This trend is similar to the trend that was observed for the cohort, where children less than one year of age had the lowest disease rates within the population (**Table 1**).

Again, as in the total cohort, the states with the highest rates of disease for the 2017 epidemic were Zamfara state accounting for 48.14% of all cases (n=5267) and Sokoto state accounting for 33.50% of all cases (n=3666). Katsina state followed behind, however, only accounting for 7.50% of cases during the 2017 epidemic (**Table 2, Figure 3**).

Information about immunization status was recorded in the same manner for the entire cohort, and the trends were the same. Only a fraction of cases reported ever having received a vaccine against meningitis, 0.3% (n=16), while the majority of cases were either missing vaccine information completely (n=4846) or had reported that their immunization status was either "No" or "Unknown." Finally, amongst the 16 children who reported having received a vaccine against meningitis, no vaccine-specific information or vaccine-type was reported (**Table 1**).

Characteristics of Suspected Meningitis Cases, 2018

Of the 2,643 children who were diagnosed as having a suspected case of meningitis in 2018, 37.9% were female (n=1002), and 62.1% were male (n=1641). Again, similarly to the 2017 sample and the entire study population men represented a higher number of cases than women, and one could interpret that as male children having a higher risk for disease than female children (**Table 1**).

However, the distribution of cases amongst states for the outbreaks that had occurred as of June 11th, 2018 were different from that of the past year. Contrary to the 2017 epidemic, Katsina state had the highest number of cases in 2018, accounting for almost half of all suspected cases, at a percentage of 43.59% (n=1152). Similar to the epidemic from 2017, Zamfara and Sokoto states represented the next highest number of suspected cases at 28.64% and 10.33% of cases respectively (**Table 3**).

The percentage for suspected cases that reported receiving some vaccine for meningitis was slightly higher in this cohort than in the entire sample population and the past year. In 2018, 2.1% of children were reported as having received a meningococcal vaccine (n=29). However, along with trends in the previous years' vaccine adherence rates were low. Amongst this cohort, approximately 97.9% of cases reported that they did not have a meningococcal vaccine or their vaccine status was unknown. Following the trend set by the past year (2017), vaccine information was missing for 1246 children.

Amongst the 29 children who received a vaccine against meningitis 14, 48.3%, reported that they received a vaccine for only *N.meningitidis* serotype A, this vaccine was most likely MenAfriVac. One child reported receiving a PCV pneumococcal vaccine. The remaining children all reported receiving a type C containing vaccine that was either the conjugate ACWY vaccine for just a type C containing vaccine (**Table 1**).

Meningococcal Epidemiology, 2017-2018

Among the entire sample population of 13,585 children, 789 cerebrospinal fluid samples were taken to be laboratory tested. Among these samples tested, 651 were positive for a disease-causing organism, by PCR. Of these cases only 401 were attributed to *N.meningitidis* serotype C, which was the most identified pathogen amongst this population. Furthermore, *N.meningitidis* serotype A accounted for the next highest amount of organism isolated, accounting for approximately 7.06% of cases. While *Streptococcus Pneumoniae* was the next highest disease-causing pathogen identified, being found in 4.91% of cases (**Table 3**). Some isolates were associated with multiple serogroups of *N.meningitidis*; however, most cases were only matched to one organism.

Prevalence of Meningitis

The primary investigator sought to determine an estimate of prevalence of meningitis in Nigerian children, from 2017-2018. However, data were collected differently during each year, and since the data collection methods were highly variable, there may be a limitation in the methodology used. These calculations represent the calculated prevalence given the data that were available and may not represent the true prevalence of the disease in Nigerian children, but will, however, serve as an estimate.

2017-2018

For the entire study population, the proportion of confirmed cases of the meningitis out of all cases that had cerebrospinal fluid tested for a disease-causing organism was approximately 49%, meaning that out of the 770 samples that were tested for a pathogen that caused meningitis, half of them were positive for a disease-causing pathogen. Further analysis of those 377 cases that tested positive by culture for an organism, the proportion of an *N.meningitidis* bacteria of any origin/serotype was approximately 79.6% indicating that the vast majority of confirmed cases of meningitis were caused by the bacterium *Neisseria meningitides*.

These proportions will give an estimate of the proportion of meningitis in the country, and an estimate of the organisms that may cause the disease. Amongst those who had a history of having received any vaccine against meningitis, the proportion of disease was approximately 45.5% indicating that the disease was present at the time that the case was recorded in almost half of the children who received a vaccine. Furthermore, when any uncertainty about immunization status is removed from the sample, by removing all cases who reported having an "Unknown" immunization status from the sample, the proportion of disease amongst those who have not received a vaccine is approximately 47% indicating that amongst those without vaccine disease was confirmed in almost half of the suspected cases, as well.

For 2017

For this subset of the original study population the proportion of confirmed cases of meningitis out of all cases that had cerebrospinal fluid tested was approximately 50.3% indicating that of the 515 cases that were tested for a disease-causing organism in 2017 approximately half of these cases tested positive for a pathogen that was known to cause meningitis or symptoms similar to that of meningitis. Of these cases that tested positive, the proportion of meningitis caused by *N.meningitidis* was approximately 79% of the cases were positive for any serotype of *N.meningitidis*. Vaccine information for 2017 is scarce as there were only 5 cases throughout the outbreak that tested positive for a disease-causing organism and reported having received a vaccine against meningitis.

For 2018

For this subset of the original study population, the proportion of confirmed cases of the meningitis out of all cases that had cerebrospinal fluid tested was approximately 46.3% indicating that similar to past years, amongst suspected cases of meningitis approximately half of those cases could be laboratory confirmed and linked to a disease-causing pathogen. Further analysis of the organism that caused the disease indicated that for this cohort of 118 children approximately 80.5% of the laboratory-confirmed cases were caused by the bacteria

N.meningitidis. Immunization history was also scarce for this population as only six children for this cohort had a self-reported history of having received a vaccine against meningitis.

Case fatality Rate

For the complete sample population, 1210 cases were recorded as dead. The case fatality rate for the total sample population was approximately 8.9%. For the 2017 cohort the case fatality rate was approximately 9.2% which was slightly higher than the case fatality rate for the outbreak, including adults, of 8%. Finally, for the 2018 cohort the case fatality rate was approximately 7.8%, lower than that of the previous year.

Discussion

The analysis of the surveillance data that was collected in Nigeria from 2017 to 2018 confirmed that both small localized outbreaks and larger scale national epidemics are being caused mainly by the same serogroup of bacteria, *N.meningitidis* serotype C, and that *N.meningitidis* is beginning to emerge in Nigeria [74]. This data seems to suggest that although these outbreaks are smaller in scale now, they could eventually develop into larger outbreaks or even national epidemics. Throughout the study period, *N.meningitidis* serotype C was the most common bacteria and serotype found, accounting for approximately 61.5% of all laboratory confirmed cases. This data seems to suggest that there is a difference in the epidemiology of the disease now, as compared to eight years ago, when MenAfriVac was first introduced in Nigeria. The results of these analyses seem to suggest that *N.meningitidis* serotype C is now the causative agent in outbreaks of meningitis and may continue to be, if, action is not taken.

Previous research has shown that trends in meningitis disease incidence are correlated with changes in the climate and temperature [43, 44]. The Sahel region is known for having a semiarid climate, characterized by heat, sun, dry, and wind. On the other hand, Sub-Saharan Africa is known to have a variety of climates and temperatures, and although all countries in Sub-Saharan Africa tend to experience a dry winter season and a wet summer season, as such, this area of the continent is often plagued by drought. The northern part of Nigeria is the area at the highest risk for meningitis. All of the states within this region fall within the African Meningitis Belt. These states are Sokoto, Kebbi, Zamfara, Kaduna, Kano, Katsina, Jigawa, Yobe, Borno, Gombe, Bauchi, Adamawa, Taraba, Niger, Kwara, Kogi, Benue, Nasarawa, Plateau, and the Federal Capital Territory, Abuja, all twenty states have a high endemic rate of meningitis disease and are at risk during the dry season, from December to July[12, 75, 76].

The introduction of MenAfriVac in the Meningitis Belt led to a stark decline in the incidence of meningitis across all countries in the belt, including Nigeria [63, 77]. The efficacy of the vaccine has been studied in all countries within the Meningitis Belt, and in the almost decade since it was introduced it has been shown to be the most effective prophylactic against meningitis in Africa [78, 79]. The strength and efficacy of MenAfriVac cannot be and is not being disputed with the results of this study.

However, this analysis does give credence to the hypothesis that widespread usage of the MenAfriVac vaccine in Nigeria may have an impact on the rates of meningitis attributed to other serogroups of the bacteria. This study gives evidence that the epidemiology of the disease is changing amongst children in Nigeria. However further research needs to be conducted into the association between vaccine usage and type and incidences of disease due to other serogroups of *N.meningitidis*.

The data were collected during the context of localized outbreaks in several states as well as national epidemics. Epidemiologic curves indicate where epidemics began in the three states with the highest number of cases, as well as when they officially ended (**Figure 3**). Statistical analyses indicate that the three states with the highest overall prevalence of disease were: Zamfara, Sokoto, and Katsina which also had the highest prevalence of disease per year for each year of data collection.

This may indicate that there is a regional/geographical effect of the disease and that geographical location or region may have an effect on the rates of disease [43, 44]. Many factors may influence this association. Research into the association between climate and meningitis has been conducted previously and continues to be conducted to ascertain a correlational relationship between climate changes and changes in meningitis incidence [80, 81]. Studies have shown that the bacteria causing meningitis are influenced by different aspects of climate change. Data also indicate that the ideal climate for transmission of the disease is the savannah dry, arid climate that can be found south of the Sahel, where precipitation is low[82]. These regions are usually arid but have warm winter seasons and abrupt onset of the rainy season. While research still needs to be conducted into the true association between dry, arid temperatures and meningitis preliminary research lends support for a hypothesis that there is an association between new cases of the disease in children and the current temperature in the area. It is expected that the states in the Northernmost region of the country would have a higher suspected disease count as the average temperature in those regions during the dry season is around 100 degrees Fahrenheit during the day and can drop to 54 degrees Fahrenheit during the night.

This study aimed to describe the changing epidemiology of meningitis in Nigeria in the post-vaccination era. Before the introduction of MenAfriVac in Nigeria in 2011, the incidence of new cases of meningitis continued to increase, according to data from 2005 to 2010[5, 63, 83]. In 2009, Nigeria experienced one of the largest outbreaks of meningitis to date, with approximately

56,128 cases [12]. After the introduction of the vaccine in 2011, however, the country was able to maintain an annual case count of fewer than 2,000 cases of disease per annum, until they experienced a large scale epidemic in 2016[16, 63].The results of the statistical analyses indicate that the epidemiology of meningitis has changed in Nigeria since the introduction of MenAfriVac in 2011 and again since 2017 after the introduction of the conjugate MenACWY vaccine in 2017[63, 75, 84-86]. The results show that the bacteria that is attributed to the largest outbreak since mass vaccination with MenAfriVac is *N.meningitidis* serotype C and that this disease is more common in older children and younger adolescents in Nigeria.

Limitations

A significant limitation of this study is the study design, as a secondary analysis of surveillance data, this data can only be used to describe meningitis and quantify various aspects of the disease. A potential limitation of the research methodology utilized was the classification of ages. Age groups were created using the classification of age as previous descriptive epidemiology studies focusing on meningitis. This is a potential limitation, because defined age categories may have been too large or too small to accurately describe the relationship between age and disease during the period. A limitation and potential source of misclassification bias was the use of cross-sectional data that had been collected within the context of either an outbreak or an epidemic of meningitis. Data were taken from IDSR-001 data, also known as line list data and then were cleaned and analyzed. However, given that these data represented cases of meningitis, necessary information pertaining to risk factors for the disease were not always collected in the forms that state DSNOs collected. Moreover, although children represent a high percentage of cases of meningitis, this study only involves children in Nigeria who presented to a health facility with symptoms of meningitis. This approach of creating a subset of the data limits the scope of the research to only those who could and did access a health facility and those younger than age 19.

Conclusion

In conclusion, this study is the first analysis of the prevalence of meningitis and its causes in Nigerian children since the significant epidemic of 2016 and 2017. While this study supports the hypothesis that the epidemiology of the disease amongst children in Nigeria is changing, it still has it is limitations and may be adversely affected by biases. As such, further research into the epidemiology of the disease in children in the country needs to be conducted to give conclusive evidence that the disease epidemiology is changing and this may be mediated by different vaccines against different strains of *N.meningitidis*.

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Tables and Figures

Table 1. Characteristics and Demographics of Suspected Meningitis Cases, 2017-2018

	n (%)		
	2017-2018 (n=13,585)	**2017 (n=10,942)**	**2018 (n=2643)**
Age (Years)			
Less than 1 year	315 (2.3)	226 (2.1)	89 (3.4)
1 to 4 years	2276 (16.8)	1838 (16.8)	438 (16.6)
5 to 9 years	4174 (30.7)	3329 (30.4)	845 (32.0)
10 to 14 years	4571 (33.6)	3645 (33.3)	926 (35.0)
15 to 18 years	2249 (16.6)	1904 (17.4)	345 (13.0)
Median Age (Interquartile Range)	10 (5-13)	10 (6-13)	9.0 (5-12)
Mean Age (SD)	9.3 (4.7)	9.3 (4.7)	8.9 (4.6)
Sex			
Female	5599 (41.2)	4597 (42.0)	1002 (37.9)
Male	7986 (58.8)	6345 (58.0)	1641 (62.1)
Immunization Status			
Yes	45 (0.6)	16 (0.3)	29 (2.1)
No	1772 (23.6)	814 (13.3)	958 (68.6)
Unknown	5676 (75.8)	5266 (86.4)	410 (29.3)
Missing	6092	4846	1246
Vaccine Administered			
VNMA	14 (48.3)	-	14 (48.3)
VAC	11 (37.9)	-	11 (37.9)
VACYW	3 (10.3)	-	3 (10.3)
PCV	1 (3.5)	-	1 (3.5)
Missing	16	16 (100.0)	0

Table 1. Characteristics and Demographics of Suspected Meningitis Cases from 2017-2018. For the Vaccine Administered variable: VNMA refers to a vaccine against *N.meningitidis* serogroup A, VAC refers to a vaccine against *N.meningitidis* serogroup C, VACYW refers to a vaccine against *N.meningitidis* serogroups A,C,Y, and W135, and PCV refers to a pneumococcal vaccine.

Table 2. Suspected Meningitis Case count by State

	n (%)		
	2017-2018 (n=13,585)	**2017 (n=10,942)**	**2018 (n=2643)**
State			
Adamawa	38 (0.28)	18 (0.16)	20 (0.76)
Bauchi	29 (0.21)	17 (0.16)	12 (0.45)
Borno	42 (0.31)	20 (0.18)	22 (0.83)
Cross River	77 (0.57)	65 (0.59)	12 (0.45)
Delta	16 (0.12)	16 (0.15)	-
Abuja	26 (0.19)	26 (0.24)	-
Gombe	3 (0.02)		3 (0.11)
Jigawa	188 (1.38)	55 (0.50)	133 (5.03)
Kaduna	67 (0.49)	67 (0.61)	-
Kano	312 (2.30)	228 (2.08)	84 (3.18)
Katsina	1973 (14.52)	821 (7.50)	1152 (43.59)
Kebbi	195 (1.44)	117 (1.07)	78 (2.95)
Nasarawa	9 (0.07)	9 (0.08)	-
Niger	150 (1.10)	103 (0.94)	47 (1.78)
Oyo	12 (0.09)	12 (0.11)	-
Plateau	37 (0.27)	36 (0.33)	1 (0.04)
Rivers	60 (0.44)	60 (0.55)	-
Sokoto	3939 (29.0)	3666 (33.50)	273 (10.33)
Yobe	388 (2.86)	339 (3.10)	49 (1.85)
Zamfara	6024 (44.34)	5267 (48.14)	757 (28.64)

Table 2. Suspected Meningitis Case count by State. Table 2 represents all of the states including the Federal Capital territory (FCT), Abuja, where suspected cases of meningitis in children were recorded, from 2017 to 2018. States that are missing case information are indicated by a dash (-).

Table 3. Laboratory Confirmation of Meningitis

Organism Isolated	n(%) 2017-2018 (n=651)	2017 (n=420)	2018 (n=231)
Diplococcus	1 (0.15)	-	1 (0.43)
Gram Negative Coccus	1 (0.15)	1 (0.24)	-
Gram Positive Bacillus	3 (0.46)	3 (0.71)	-
Gram Positive Coccus	3 (0.46)	3 (0.71)	-
Group B Streptococcus	1 (0.15)	-	1 (0.43)
Hib B	14 (2.15)	6 (1.43)	8 (3.46)
Inconclusive	1 (0.15)	1 (0.24)	-
N. Meningitidis Serotype A	46 (7.06)	22 (5.23)	24 (10.39)
N. Meningitidis Serotype B	1 (0.15)	1 (0.24)	-
N. Meningitidis Serotype C	401 (61.50)	258 (61.28)	143 (61.90)
N. Meningitidis Serotype Unspecified	13 (1.99)	10 (2.38)	3 (1.30)
N. Meningitidis Serotype W135	2 (0.31)	1 (0.24)	1 (0.43)
N. Meningitidis Serotype X	8 (1.23)	-	8 (3.46)
Streptococcus Pneumoniaee	32 (4.91)	16 (3.80)	16 (6.93)
Streptococcus Pyogenes	1 (0.15)	1 (0.24)	-
Missing	124 (19.02)	98 (23.28)	26 (11.26)

Table 3. Laboratory Confirmation of Meningitis. This table represents all cerebrospinal fluid samples that were taken from patients with a suspected case of meningitis and tested positive by PCR for a disease-causing pathogen. Missing values were missing report of any organism isolated and identified, and inconclusive tests were inconclusive for several reasons, including contamination. *N.meningitidis* unspecified refers to cases where *Neisseria Meningitidis* was reported as the organism identified, but neither a serotype nor serogroup accompanied the species name.

Figure 1. Meningitis cases by geographic region of Nigeria.

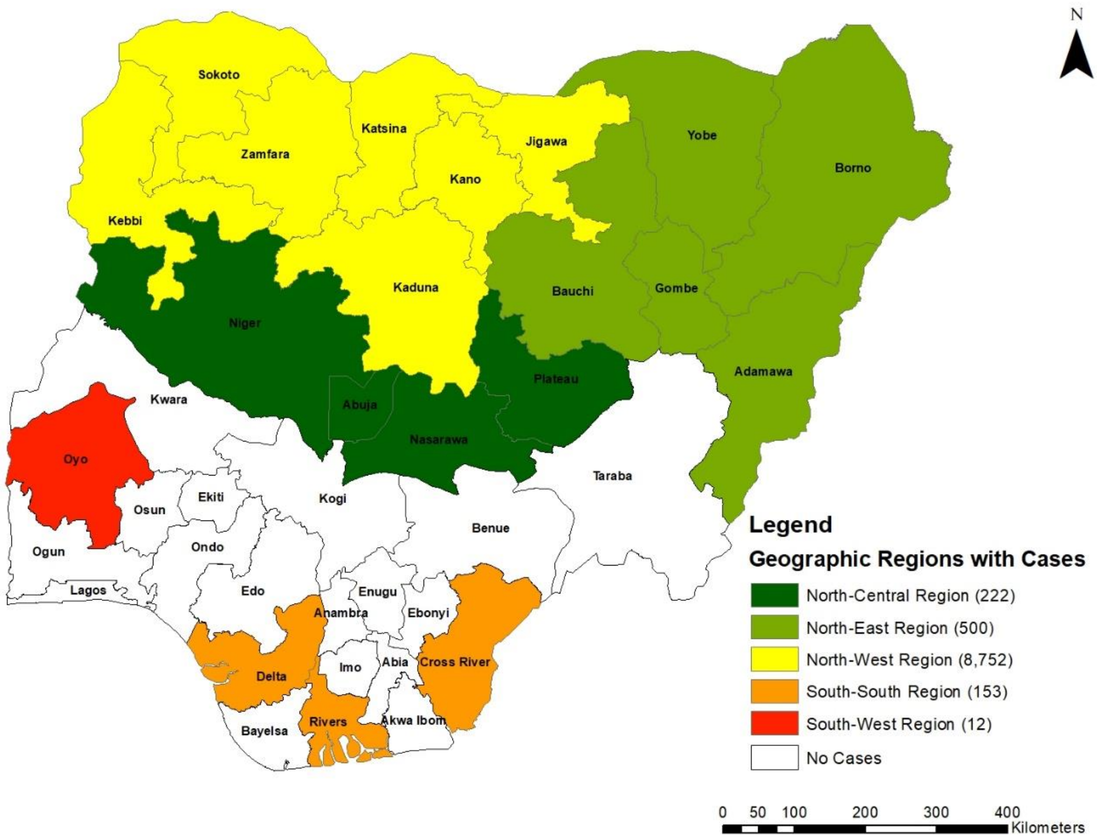

Figure 1. Meningitis cases by geographic region of Nigeria. The number of suspected cases identified during the study period for each region is shown in the legend in **boldface**. In total 13,585 children were identified as having a suspected case of meningitis throughout the country.

Figure 2. A comparison of all suspected meningitis cases by State and Local Government Area.

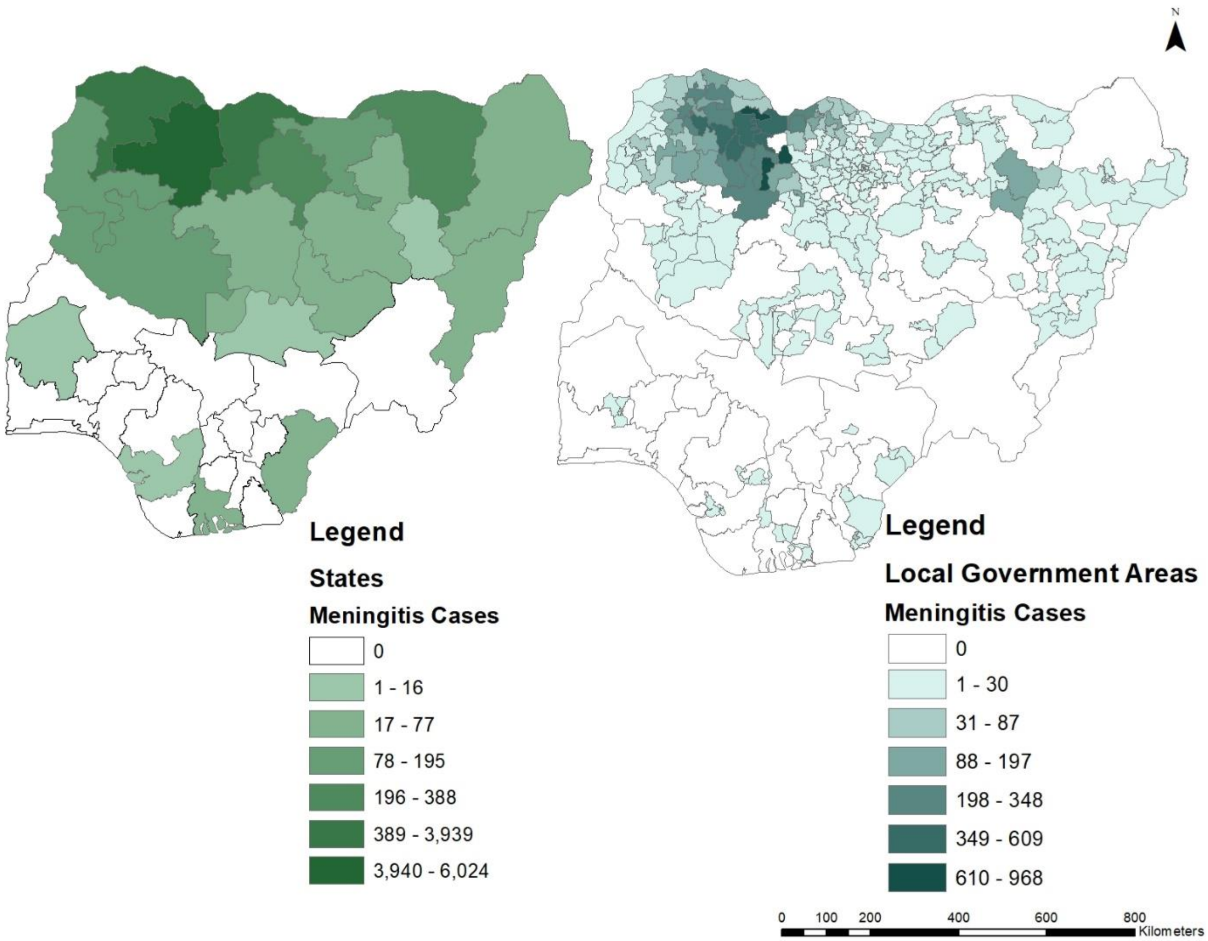

Figure 2. A comparison of all suspected meningitis cases by State and Local Government Area. Areas, both at the state and LGA (local government area) level where no cases were reported during the study period are indicated by white coloring. For both States and LGAs, areas with less suspected cases are indicated by a lighter shade, whereas areas with more suspected cases are indicated by a darker shade of green and blue, respectively.

Figure 3. Epidemiologic Curves for the States with the Highest Incidence of Cases

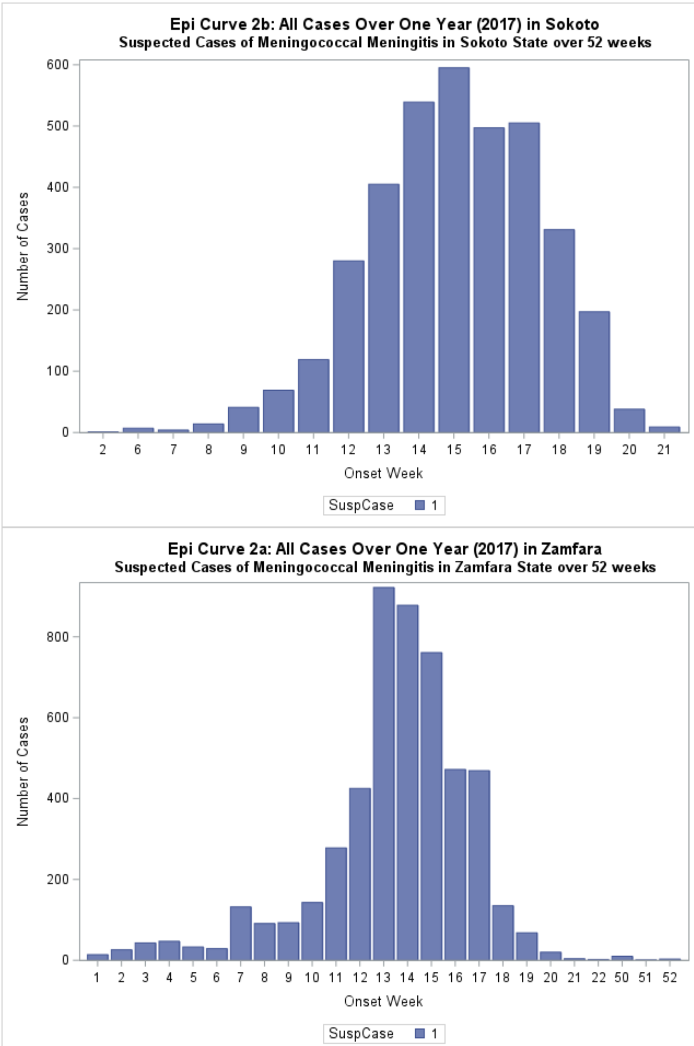

Figure 3. Epidemiologic Curves for the States with the Highest Incidence of Cases. Epidemiologic Curves for the 2017 National Epidemic in States with the highest incidence of meningitis, Sokoto and Zamfara.

Figure 4. Distribution of Cases by Ward Level

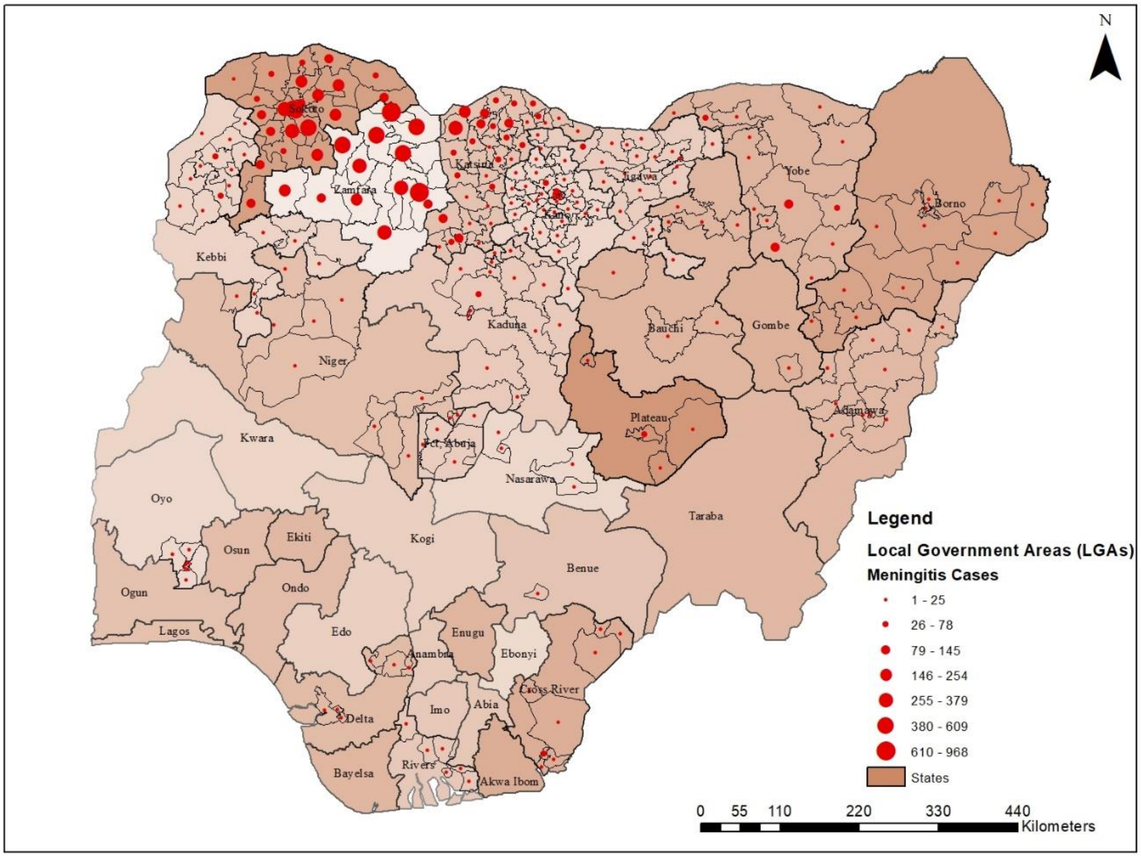

Figure 4. The distribution of all suspected cases in children by Ward. This map represents all suspected cases of meningitis by ward, represented by total cases counts for that ward. However, the geographical limits that are represented here are LGAs as Wards are too small to represent on a map, clearly.

Figure 5. The African Meningitis Belt

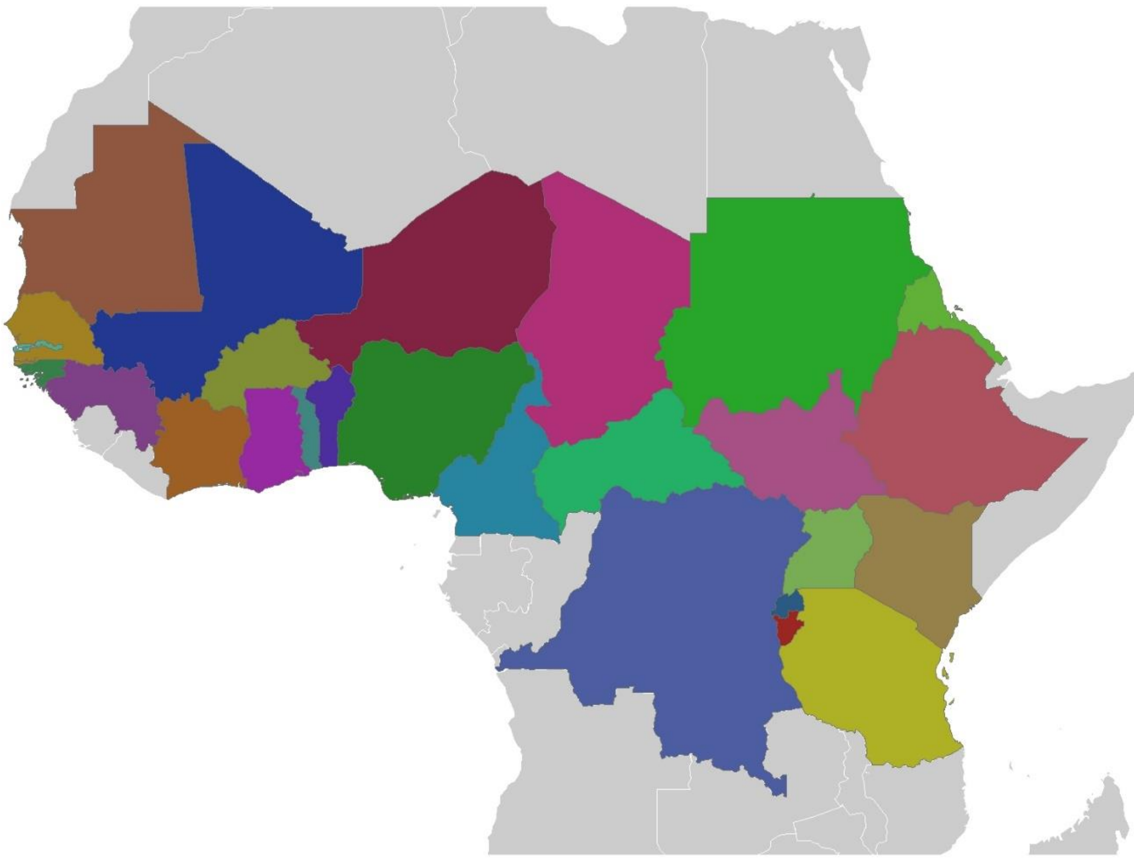

Figure 5. A Map of the African Meningitis Belt. This map represents the 20 countries (in color) that fall within the African Meningitis Belt. The countries are as follows: Mauritania, Mali, Niger, Chad, and Sudan. Eritrea, Senegal, Burkina Faso, Nigeria, the Central African Republic, South Sudan, Ethiopia, Gambia, Guinea-Bissau, Guinea, Cote d' Ivoire. Ghana, Togo, Benin, Cameroon, the Democratic Republic of Congo, Kenya, Tanzania, Uganda, Rwanda, Burundi [2]

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Chapter IV: Public Health Implications

This study represented a novel attempt to understand the distribution of meningitis due to *N.meningitidis* serotype C in Nigerian children, after the epidemic of 2017. This has several implications for both future research and future policies. The Meningitis Belt will continue to struggle with outbreaks of meningitis, especially amongst its most vulnerable population, children unless action is taken. The results from this study provide evidence that the epidemiology of meningitis as researchers have previously observed in Nigeria is changing. *N.meningitidis* serotype A is no longer the most prevalent serogroup of meningitis causing bacteria in Nigeria. Recently, scientists have begun to examine the association between meningitis caused by *N.meningitidis* serotype C and risk factors, for disease as well as immunization in an attempt to understand why the epidemiology of the disease is changing in this region.

This research gives evidence that the disease pathology has changed in Nigeria, the next question to answer is why. What are the other variables that need to be studied to understand why and how the disease epidemiology has changed? This research has generated several hypotheses to explain this phenomenon that need to be tested. Primarily, there may be an association between immunization and the type of vaccine received and the most prevalent serogroup of *N.meningitidis* during an outbreak or epidemic.

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