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Effects of MenAfriVac® Introduction in the African Meningitis Belt, 2010-2017

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2018

Abstract

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by

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MD, University of Yaounde 1, 1999

MPH, Walden University, 2015

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Walden University

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Abstract

Meningococcal meningitis is a burden in the African meningitis belt. Before 2010, *Neisseria meningitidis* serogroup A (*N. meningitidis* A) was the predominant pathogen causing deathly epidemics. MenAfriVac® vaccine protects against *N. meningitidis* A. It was introduced in 2010 into highest meningitis risk health districts. There was limited data on the effects of MenAfriVac®, mainly on the degree of relationship between *N. meningitidis* A and the MenAfriVac® immunization. The social ecological model was used as a theoretical framework for this study. The purpose of this quantitative study was to assess the effectiveness of MenAfriVac® from 2010 to 2017 in 21 out of 26 countries of the African meningitis belt. The four research questions contributed to establishing the effects of MenAfriVac®. An interrupted time series design and nonprobability sampling were used. Secondary data were retrieved from World Health Organization database. The binomial negative regression and Pearson's Chi-Square tests were used. The study found that after the MenAfriVac® introduction there were 39% decline of incidence rate of the meningitis suspected cases (IRR 0.61, 95% CI 0.48 – 0.79, $p < .001$), a high degree of relationship between *N. meningitidis* A and MenAfriVac® immunization (χ^2 (1) = 11039.49, p = 0.000, Phi = 0.657, P=0.000), 99% decline of the risk of *N. meningitidis* A (RR 0.01, 95% CI 0.08-0.013), and 99.6% decline of risk of epidemic due to *N. meningitidis* A (RR 0.004, 95% CI 0.001-0.016). The study demonstrated that high MenAfriVac® coverage and enhanced surveillance are pivotal to reduce the meningitis burden. Results will be used to inform policy and public health practice to reduce the meningitis cases and improve quality of live in the community.

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Dedication

I dedicate my dissertation research to my wife, Gertrude. Gertrude inspired and encouraged me to pursue my doctoral degree in public health concentration in epidemiology. I am so proud and grateful to her; she is the most lovely and amazing wife of the earth. I love you for being funny supportive, tolerant, and for the most part patient. This doctoral study is also dedicated to my children, Lynda, Sylvia, Solange, Manuel, Andrea, and Maria, and my parents Sylvia and Pierre. They were supportive, patient, and too kind.

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Introduction

Meningococcal meningitis is a major public health problem in 26 countries that have the highest rates of the disease in the African meningitis belt, stretching from Senegal in the west to Ethiopia in the east (World Health Organization [WHO], 2015a). The meningococcal meningitis is a bacterial form of meningitis, a serious infection of the meninges, thin fibrous tissue that covers the brain and spinal cord. It can cause severe brain damage and is fatal in 50% of cases if left untreated (WHO, 2015a, WHO, 2015b, Kiefer, 2016). Before 2010, *Neisseria meningitidis* serogroup A (*N. meningitidis* A) was the predominant cause of meningitis epidemics, and it accounts for almost 80%-85% of meningitis outbreaks. The meningococcal conjugate A vaccine called MenAfriVac® prequalified by WHO was developed by Serum Institute of India. This new vaccine is being introduced in countries of the meningitis belt to eliminate meningococcal meningitis caused by *N. meningitidis* A (WHO, 2015a; Tiffay, Jodar, Kieny, Socquet, & Laforce, 2015).

Few studies showed the early effects of the introduction of MenAfriVac® in 15 countries using the carriage, surveillance, and determination of antibodies provided by the new vaccine. In this study, I considered 21 out of 26 of meningitis belt countries. Meningitis enhanced surveillance has been enhanced since 2002 in the meningitis belt. In preparation for the introduction of MenAfriVac®, an enhanced meningitis surveillance network was established by WHO. Meningitis enhanced surveillance aims to assess the effects of the introduction of new vaccines, to detect and confirm epidemics and launch

appropriate response strategies, to assess case burden and incidence trends, to monitor the antibiotic resistance profile of *N. meningitidis,* including *N. meningitidis* A or other pathogens, and to monitor the circulation, distribution, and evolution of *N. meningitidis* serogroups and other pathogens (WHO, 2014a). I used enhanced surveillance as an instrument of measurement in this study. For this study, I considered the longest period and more countries than the study conducted previously. The estimation of MenAfriVac® protection is ten years. Therefore, studying effects including protection more years after the first introduction is relevant. This study also aimed to show that meningococcal meningitis caused by other serogroups than *N. meningitidis* A remains a burden in the African meningitis belt. The use of meningitis enhanced surveillance is relevant because it helps not only to detect epidemics earlier but also to control the elimination of disease within all health areas at high risk of *N. meningitidis* A. The reasons to conduct this study can be explained by the needs of use of another measurement method such as enhanced surveillance that is feasible in all health areas as a routine activity with low cost. The number of countries concerned in this study is higher than in previous studies, and therefore the generalizability of findings is greater. Findings on crude fatality rate (CFR) and the degree of relationship between *N. meningtitidis* A and MenAfriVac® are insufficient in the literature. For the reasons stated above, this study contributed to reducing the gap in the literature on the effects of the introduction of MenAfriVac® in the African meningitis belt.

The potential positive social change is the reinforcement of public health policies, especially on surveillance and immunization, to achieve the elimination of vaccine-

preventable diseases. The high level of MenAfriVac® coverage and the quality of meningitis enhanced surveillance might be two relevant factors in achieving the elimination of *N. meningitidis* A. In addressing and emphasizing these factors; sought in this study to create a positive social change with the strengthening of immunization and surveillance policies.

This chapter presents the background of the study, problem statement, purpose of the study, and research questions. This chapter also includes the theoretical framework, the nature of the study, definition of terms, and assumptions, scope, limitations, and significance of the study.

Background of the Study

Meningococcal disease is a leading cause of bacterial meningitis and sepsis, and a major cause of epidemics. It is a very serious disease with a fatality rate of 50% if left untreated. The common risk factors are age between 1 to 29 years old, community setting, environment, and travel. The findings showed that meningococcal meningitis has the greatest incidence with large epidemics in Africa in the dry season (Centers for Disease Control and Prevention [CDC], 2014; Greenwood, 1999; Lapeyssonnie, 1963; Molesworth, Cuevas, Connor, Morse, & Thomson, 2003;). *N. meningitidis* is transmitted from person-to-person through droplets of respiratory or throat secretions from carriers. Ten percent to 20% of the population carries *N. meningitidis* in their throat at any given time (WHO, 2014b, WHO, 2015b).

By far the highest incidence of meningococcal disease occurs in the meningitis belt of sub-Saharan Africa. During epidemics, the incidence can approach 1,000 per

100,000, or 1% of the population (CDC, 2014; CDC, 2015a; Harrison et al., 2009; Kiefer, 2016; National Institute of Health. [NIH], 2016; WHO, 2015a, WHO, 2015b). Of the 12 serogroups of *N. meningitidis* identified, four serogroups, A, B, C, and W135, are recognized to be the main causes of epidemics. Meningococcal meningitis cases occur throughout the world. Before the introduction of MenAfriVac® in 2010, *N. meningitidis* A accounted for an estimated 80%–85% of all cases in the African meningitis belt, with epidemics occurring at intervals of 7–14 years. The African meningitis belt stretches from Senegal in the west to Ethiopia in the east and includes 26 countries where an estimated 450 million people are living (CDC, 2015a; Nicolas, 2012; Programme for Appropriate Technology Health [PATH], 2016a; WHO, 2015a; WHO 2015b; WHO, 2017, March 13).

The largest meningococcal meningitis epidemic was reported in 1996 and 1997, where more than 25,000 people died and more than 250,000 were affected. Following this devastating epidemic, African leaders called for the development of an affordable vaccine that would eliminate *N. meningitidis* A epidemics in Africa (Aguado et al., 2015; Nicolas, 2012; PATH, 2016a; PATH, 2016b; Vergnano & Health, 2003). An affordable monovalent MenA polysaccharide-tetanus toxoid conjugate vaccine called MenAfriVac® was developed and prequalified in 2009 by WHO. MenAfriVac® has been introduced in African meningitis belt countries since 2010 (Frasch, Preziosi, & LaForce, 2012; Idoko et al., 2014)**.** Only the health districts that are at highest risk were selected to introduce MenAfriVac®. The selection was made through the risk assessment using the district prioritization tool developed by WHO (Cibrelus, Lingani, Fernandez, Perea, & Hugonnet,

2015). MenAfriVac® vaccine can provide herd and individual protection when a health district has reached at least 90% of administrative coverage or 70% of immunization coverage during a mass vaccination campaign. Between 2010 and 2017, 21 countries have introduced MenAfriVac® with over 260 million people vaccinated aged 9 months to 29 years through mass vaccination campaigns and routine vaccination programmes (Djingarey et al., 2012; Djingarey et al., 2015; WHO, 2017, March 13).

The early effects are being found by some authors. The global reduction of the incidence and occurrence of meningitis epidemics caused by *N. meningitidis* A in the meningitis belt were shown by PATH (2016d), PATH and WHO (2016), and WHO (2014d, 2015b, 2016b, 2017),. Specifficly, Novak et al. (2012) showed 71% decline in risk of meningitis (suspected cases) and >99% decline in risk of *N. meningitidis* A (confirmed cases) in Burkina Faso 1 year after the introduction of MenAfriVac®. Daugla et al. (2013) found a 94% reduction in the incidence of meningitis in a vaccinated population and 98% decrease in *N. meningitidis* A carriage prevalence within 4–6 months after MenAfriVac® mass vaccination campaign. A study by Trotter et al. (2017) in nine countries (Benin, Burkina Faso, Chad, Côte d'Ivoire, Ghana, Mali, Niger, Nigeria, Togo) showed a 58% decline in incidence of meningitis (suspected cases), > 99% decline in incidence of *N. meningitidis* A (confirmed cases), and 60% decline in epidemics risk of a district reaching the epidemic threshold. Kristiansen et al. (2013) found the effectiveness of MenAfriVac® on the carriage of *N. meningitidis* A among persons vaccinated in Burkina Faso 2 years after a MenAfriVac® mass vaccination campaign. The study was needed to fill the gap of the literature, especially on the relationship between

MenAfriVac® introduction and the CFR and the level of relationship between *N. meningitidis* A and MenAfriVac® immunization. This study was also needed to fill the gap on the effects of MenAfriVac® several years after its introduction and in considering many countries for relevant generalizability.

Problem Statement

Meningococcal meningitis remains a public health problem in the 26 high-risk countries situated in the African meningitis belt. Before 2010, *N. meningitidis* A represented between 80% and 85% of meningitis infections. Following the deadliest meningitis epidemics in 1996-97, MenAfriVac® was developed. MenAfriVac® provided people who were vaccinated individual protection and reduced the carriage of *N. meningitidis* A and, therefore, increased the herd immunity (WHO, 2015a). According to WHO (2017, March 13), by 2016, 260.6 million people aged 1-29 years old were vaccinated with MenAfriVac® through preventive campaigns in 19 countries: Benin, Burkina Faso, Cameroon, Chad, Cote d'Ivoire, Democratic Republic of Congo, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Mauritania, Niger, Nigeria, Senegal, South Sudan, Sudan, and Togo.

The objective of this study was to assess the effects of the introduction of MenAfriVac® in the 21 out of 26 countries of the African meningitis belt. Few studies conducted previously evaluated the early effects of MenAfriVac®. These studies showed a decrease in the incidence of meningococcal meningitis after the introduction of MenAfriVac® (Djingarey et al., 2012; Kristiansen, 2013; Novak et al., 2012; Diomandé et al., 2015). However, the gap in the literature was significant, especially regarding the

relationship between MenAfriVac® introduction and the CFR and the level of relationship between *N. meningitidis* A and MenAfriVac® immunization. This study evaluated the effectiveness of the introduction of MenAfriVac® in 21 countries using meningitis enhanced surveillance data from 2004 to 2017. This multi-country study involved 21 countries with the population living in the 1,713 meningitis highest risk health districts. It helped to assess more years protection provided by MenAfriVac® and showed the risk of the occurrence of meningococcal meningitis due to serogroups other than *N. meningitidis* A. The generalizability of the results of this study was relevant. The study also assessed the risk of meningitis due to other meningococcal serogroups through analyses of occurrence of epidemics, incidence, and mortality of meningococcal meningitis before and after 2010.

Purpose Statement

The research purpose of this quasi-experimental and quantitative study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called "MenAfriVac®" in 21 countries of the meningitis belt from 2010 to 2017. I retrieved secondary data from meningitis surveillance between 2004 and 2017 and MenAfriVac® immunization between 2010 and 2017 to complete the study. This study compared the risk of meningitis disease, deaths, and occurrence of epidemics before and after MenAfriVac® introduction. Incident rate ratio (IRR) of meningitis suspected and fatal meningitis was calculated using the negative binomial regression. I calculated Pearson's Chi-Square test to estimate the relative risk of CFR, *N. meningitidis* A confirmed cases (*N. meningitidis* A and non-*N. meningitidis* A), and I estimated the

frequency of epidemics due to *N. meningitidis* A in MenAfriVac® vaccinated and unvaccinated populations. The dependent variables selected were occurrence of *N. meningitidis* A or not (another pathogen than *N. meningitidis* A, negative cerebrospinal fluid [CSF] sample), meningitis suspected cases, deaths, and the occurrence of meningitis epidemics. The independent variable was MenAfriVac® vaccination status of health district (vaccinated after the introduction of MenAfriVac®; vaccinated with any other polysaccharide vaccine that includes antigen A; unvaccinated before the introduction of MenAfriVac®). Pathogens were isolated from CSF samples by culture or detected by latex agglutination test or polymerase chain reaction (PCR). CSF samples were transported from healthcare facilities to the district or national reference laboratories that conduct laboratory testing.

Research Questions and Hypotheses

The four research questions (RQ) were developed to assess the effects of MenAfriVac® introduction in the 21 out of 26 African meningitis countries between 2010 and 2017. The null hypotheses (H_0) and alternatives hypotheses (H_a) defined below related to each RQ. These hypotheses were tested using inferential statistics to assess the effects of MenAfriVac® by establishing the strength of the relationship between immunization with MenAfriVac® of people living in high-risk meningitis districts and the reduction of occurrence of meningitis suspected cases, deaths, and health districts in epidemic due to *N. meningitidis* A. The RQs and hypotheses were as follows:

RQ1: What is the difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$1: There is no difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a1: There is a difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ2: What is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$2: There is no difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a2: There is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ3: What is the degree of relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$3: There is no relationship between the incidence of *Neisseria meningitidis* group A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a3: There is a relationship between the incidence of *Neisseria meningitidis* A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ4: What is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt?

$H_0$4: There is no difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

H_a4: There is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

Theoretical Framework

The social ecological model (SEM) was a theoretical framework for prevention used in this research dissertation. According to CDC (2015b), the SEM is a theory-based framework that can be used to better understand the effect of potential prevention strategies such as immunization because it is a framework for prevention. SEM comprises multiple-level approaches that are individual, relationship, community, organizational, and policy levels. All these approaches fit with the risk factors of

meningococcal meningitis and the public health interventions that are being implemented. Prevention using immunization and public health policies were built by countries to provide individual protection and herd immunity against *N .meningitidis* A.

The SEM is based on evidence that no single factor can explain why some people or groups are at higher risk for meningococcal meningitis while others are more protected from it. This framework views protection with MenAfriVac® as the outcome of interaction among many factors. These factors are the individual, the relationship, the community, and the societal levels. Therefore this framework was related to the research questions that sought to show the effectiveness of the protection provided by MenAfriVac® to individual and community. Concerning especially the societal level, it is characterized by the quality of the public health policy used to organize immunization campaigns and routine programs with the involvement of the health institutions and researchers to contribute to the achievement of the elimination of meningococcal meningitis due to *N. meningitidis* A.

Nature of the Study

The study was quasi-experimental research, and an interrupted time series quantitative research design. I used the interrupted times series design to assess the effect of the introduction of the MenAfriVac® in 21 countries selected for this study between 2010 and 2017. Secondary data from meningitis enhanced surveillance and MenAfriVac® immunization coverage were used for the period between 2004 and 2017. The variables selected in this study helped to provide descriptives and inferential statistics. I chose the negative binomial regression model and Pearson's Chi-Square tests to assess the effects

of MenAfriVac® introduction, especially the relationship between vaccination with MenAfriVac® and the occurrence of meningitis suspected cases, *N. meningitidis* A cases, deaths, and epidemics.

The dependent variables selected were occurrence of *N. meningitidis* A or not (another pathogen than *N. meningitidis* A, negative CSF sample), incidence rate of meningitis suspected cases, deaths, and the occurrence of meningitis epidemics. The independent variable was MenAfriVac® vaccination status of health district (vaccinated after the introduction of MenAfriVac®; vaccinated with any other polysaccharide vaccine that includes antigen *N. meningitidis* A; unvaccinated before the introduction of MenAfriVac®). I chose the period between 2004 and 2017.

Definition of Terms

Some terms were used in the study to assess the effects of MenAfriVac® in meningitis belt below:

Alert threshold: A level of incidence that triggers action to prepare for an epidemic, including strengthening surveillance, confirming cases, distributing treatment protocols and informing the authorities (WHO, 2014c; WHO, 2015b).

Case definition of meningitis disease: Any person with sudden onset of fever (>38.5 °C rectal or 38.0 °C axillary) and neck stiffness or another meningeal sign including bulging fontanel in toddlers (WHO, 2015b).

Case fatality rate (CFR): The proportion of persons with a disease in a specified period that dies from the disease (Johns Hopkins, International Federation of Red Cross, & Red Crescent Societies, 2008).

Confirmed meningitis case: Any suspected or probable case that is laboratory confirmed by culturing or identifying (i.e., by PCR, immunochromatographic dipstick, or latex agglutination) of *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenza* type b in the CSF or blood (WHO, 2015b).

Effectiveness: The ability of an intervention or program to produce the intended or expected results in the field

Epidemic threshold: A higher level of incidence that triggers an epidemic response, including mass vaccination, antibiotic distribution, and raising public awareness (WHO, 2014c; WHO, 2015b).

Epidemic: An increase, often sudden, in the number of cases of disease above what is generally expected in that population in that area (CDC, 2012c).

Incidence rate ratio (IRR): A measure of the frequency with which new cases of illness, injury, or other health conditions occur, expressed explicitly per a time frame.

Incidence: A measure of the frequency with which new cases of illness, injury, or other health conditions occur among a population during a specified period (CDC, 2012c).

Cumulative incidence: The ratio of the number of new cases of disease to the total number of participants who are at risk (Sullivan, 2012).

MenAfriVac® (PsA-TT, MenA, MACV)*:* The meningococcal A conjugate vaccine, a lyophilized vaccine of purified meningococcal serogroup A polysaccharide (PsA) covalently bound to tetanus toxoid (TT) that acts as a carrier protein (Frasch et al., 2012; Sambo et al., 2015; WHO, 2017a).

Meningococcal meningitis: A bacterial disease caused by *N. meningitidis*. A serious infection of the thin lining that surrounds the brain and spinal cord. It can cause severe brain damage and is fatal in 50% of cases if untreated (WHO, 2015a, WHO, 2015b, WHO, 2017, March 13).

Mortality rate: A measure of the frequency of occurrence of death among a defined population during a specified time interval (CDC, 2012c).

Operational threshold: Criteria that trigger specific actions to prepare for an epidemic (the alert threshold) or respond to an epidemic (the epidemic threshold) in health districts, subdistricts, or populations at risk (WHO, 2014c).

Relative risk (RR): The ratio of prevalence or incidence in the exposed group to the prevalence or incidence in the unexposed group. (Sullivan, 2012).

Surveillance: The ongoing systematic collection, analysis, and interpretation of health data (WHO, 2010).

Suspected case (of meningitis): Any person with sudden onset of fever (> 38.5^{o} C rectal or > 38.0^{o} C axillary) and one of the following signs: neck stiffness, flaccid neck, bulging fontanelle, convulsion, or other meningeal signs (WHO, 2014c).

The key pillars strategy or the control of epidemic meningitis: Surveillance, treatment and care, and vaccination (WHO, 2015b).

The African meningitis belt: Stretches from Senegal in the west to Ethiopia in the east. It is constituted by 26 countries: Benin, Burkina Faso, Burundi, Cameroon, Chad, Centre African Republic, Cote d'Ivoire, Democratic Republic of Congo, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Mauritania, Niger,

Nigeria, Rwanda, Senegal, South Sudan, Sudan, Tanzania, Togo, and Uganda (WHO, 2015a).

Vaccine effectiveness: The ability of the vaccine to prevent outcomes of interest (McNeil, 2006).

Assumptions

Four assumptions were retained for this dissertation research. These assumptions focused on the relevance of the surveillance, the accuracy of data retrieved from WHO databases. The fourth assumption focused also on the fact that meningococcal meningitis remains a public health problem despite the introduction of MenAfriVac®. What follows are the four assumptions explained.

The first assumption was that surveillance is a relevant instrument measure to evaluate the effects of the introduction of a new vaccine such as MenAfriVac®. The goals of meningococcal surveillance are: to detect outbreaks of meningococcal disease so that appropriate control measures can be promptly instituted. Secondly, to assess changes in the epidemiology of meningococcal disease over time to permit the most efficient allocation of resources and formulation of the most effective disease control and prevention policies. Meningococcal serogroup surveillance data are essential to monitor and assess the impact of new vaccines. African meningitis belt countries have national plans for integrated disease surveillance and response, which include meningitis. WHO support countries to strengthen their disease surveillance especially meningitis. The purpose of meningitis enhanced surveillance is to detect changing epidemiological patterns of meningitis epidemics promptly. Also to provide evidence to guide case

management and prompt epidemic response (MacNeil, & Cohn, 2013; WHO, 2009a, WHO & CDC, 2010; WHO, 2015; Mueller, 2013; Harrison et al., 2009; Djingarey et al., 2008).

WHO recommended three instrument measures to assess the effectiveness of a new vaccine. These instrument measures are a study of the carriage, a calculation of antibodies provided by immunization, and enhanced surveillance. Enhanced surveillance is used at all the levels of health, and the cost is affordable. It is a routine activity carried out by training health personnel that are often engaged in immunization activities especially in the filed thus health district. Therefore, showing that surveillance is relevant because of its reliability and its validity are valuable for a routine and affordable activity.

The second assumption was that the two databases of WHO IST WA are relevant to gather secondary data respectively from meningitis surveillance and MenAfriVac® vaccination coverage between January 2004 and December 2017. Therefore, it can be used for the dissertation research to assess the effects of the introduction of MenAfriVac® in 21 countries of meningitis belt. Data for meningitis surveillance as well as for MenAfriVac® immunization activities found in the WHO Inter-country Support Team for West Africa (WHO IST WA) databases are aggregated data sent by countries regularly on a weekly basis. These data were gathered, treated, consolidated and validated at the country level before sending to WHO ISTWA with the technical support of partners such as CDC and WHO country staffs. It was essential to show their accuracy and then their usefulness such as measuring the effects of the introduction of a new vaccine to reduce the burden of disease such as meningitis due to *N. meningitidis* A.

The third assumption was that the introduction of MenAfriVac® in Africa using appropriate public health intervention and organization with health agencies and human resources reduced the burden of meningococcal meningitis especially due to *N. meningitidis* A. The success of any public health intervention such as immunization or surveillance requires effective preparedness, activities, strategies planned and appropriate resources mobilized. That seems to be the case of introduction of MenAfriVac® in Africa that could be benchmarked in other diseases to challenging in Africa.

The fourth assumption was that meningitis disease remains a public health problem in the African meningitis belt due to other pathogens than *N. meningitidis* A. This study showed also the incidence of meningitis disease and meningitis epidemics recorded in African meningitis belt.

The Scope of the Study

The previous studies on evaluation of early effects of MenAfriVac® were limited in 15 countries out of 21 that introduced from 2010 to January 2017. The meningitis belt comprises almost 450 million persons at risk (Frash et al., 2012). The time of the study concerned the period from January 2004 to June 2017, seven years before and after the beginning of the introduction of MenAfriVac® in 2010. This period was chosen to measure the incidence and the occurrence of meningitis epidemic before and after the introduction of MenAfriVac® in the 21 countries selected. Also, the health district of the 21 countries that introduced or not MenAfriVac® were considered. The pathogens reported were considered. This rsult contributed to measuring the updated predominance of the cause of meningitis epidemics. According to WHO (2009a), three methods of

measurement can be used as measurement methods to demonstrate the effectiveness of MenAfriVac® that are meningitis surveillance, find the immunity by the determination of *N. meningitidis* A antibodies, and the meningococcal carriage study. In this study, the measurement method used was meningitis enhanced surveillance. The size of the sample used was extensive with 21 out of 26 countries of the meningitis belt selected for the study given relevant generalizability of findings.

Limitations

For this study, the use of secondary data was one of the limitations because of the lack of control over data. However, secondary data used in this study were gathered, curated, and validated by the government with the technical support of WHO. These procedures were to ensure the accuracy of surveillance data and therefore raise internal validity and specificity. The use of negative binomial regression model as statistical analysis test in this research will contribute to reducing confounding. Countries and WHO monitor the high quality by using meningitis case definition, deaths related to meningitis, and the CSF samples laboratory testing to reduce selection bias. Few selection biases might be found in some health districts (health facilities and laboratories). It would have been valuable to determine the relationship between the effects of MenAfriVac® and the other risk factors such as gender and age. Sequelae would have also been valuable to found before and after MenAfriVac® introduction. Unfortunately, gender, age, and sequelae were removed as variables because they were not gathered by meningitis enhanced surveillance WHO IST WA database.

Significance

This research filled the gap in the literature on the effectiveness of the introduction of MenAfriVac® in the African meningitis belt, taking in consideration more countries and period than the previous studies have done. Only one multi-country study to estimate the effects of MenAfriVac® was conducted by Trotter et al. (2017) in nine countries between 2010 and 2015. This multi-country study chose 21 countries and seven years after since the introduction of MenAfriVac®. Few studies were conducted using either carriage method or antibodies determination. These studies showed the early effects of MenAfriVac® (Kristiansen, 2013; Novak et al., 2012; Diomandé et al., 2015; Lingani et al., 2015; Collard et al., 2013; Djingarey et al., 2012, Djingarey et al., 2015). The use of the surveillance is valuable because is a routine intervention that is conducted in all countries, and it is useful and cost-effectiveness to monitor the trends of diseases concerned, to detect epidemics, to evaluate the effectiveness of epidemic response, case management, and effects of vaccination. The previous studies provided early effects in few countries, and it was useful to conduct a research that included more countries and many years after the beginning of the introduction of MenAfriVac®. This study could also create positive social change in practice by fostering the countries to reinforce public health policies in surveillance and immunization because of achievements obtained with high MenAfriVac® immunization coverage and high quality of meningitis enhanced surveillance.

Summary

Meningococcal meningitis is a public health problem in Sub-Saharan Africa. Out of the 12 meningococcal serogroups, *N. meningitidis* A represented for an estimated 80–85% of meningitis disease before the introduction of MenAfriVac® in 2010 and since 2013, findings from the literature are showing that its proportion is being reduced. To reduce the burden of Meningococcal meningitis caused by *N. meningitidis* A, a new meningococcal conjugate A vaccine called MenAfriVac® was introduced in African meningitis belt. The early effects of the introduction of MenAfriVac® in some countries of meningitis belt showed the reduction of the incidence of *N. meningitidis* A. The research purpose of this study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called "MenAfriVac®" in 21 countries of the meningitis belt from 2010 to 2017, using the data of meningitis surveillance from 2004 to 2017 as a method of measurement. The socio ecological model was used to respond to the research questions. The study was quasi-experimental research, interrupted time series quantitative research design. This research filled the gap in the literature on the effectiveness of the introduction of MenAfriVac® in the African meningitis belt, taking in consideration more countries and period than the previous studies have done.

Chapter 1 provides a brief overview of the study's purpose in the examination of the effects of MenAfriVac® introduction in the African meningitis belt, 2010-2017. Chapter 2 reviewed the literature delineating the effects introduction of MenAfriVac® in African meningitis belt. Chapter 3 shows the details of the research methodology used in the study.

Chapter 2: Literature Review

Introduction

Meningitis disease remains a public health problem in the 26 high-risk countries situated in the African meningitis belt. Before 2010, *N. meningitidis* A represented the predominant meningitis pathogen and for an estimated 80% to 85% of meningitis epidemics in Africa. Following the deadliest meningitis epidemics in 1996-97, MenAfriVac® was developed. MenAfriVac® provided people who were vaccinated individual protection and reduced the carriage of *N. meningitidis* A and, therefore, increased the herd immunity (WHO, 2015a). According to WHO (2017, March 13), by 2016, 260.6 million people aged 1-29 years old were vaccinated with MenAfriVac® through preventive campaigns in 19 countries. The 19 countries concerned were Benin, Burkina Faso, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of Congo, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Mauritania, Niger, Nigeria, Senegal, South Sudan, Sudan, and Togo. The research purpose of this quasi-experimental and quantitative study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called MenAfriVac® in 21 out of 26 countries of the meningitis belt from 2010 to 2017.

The major preview sections of this chapter are search literature strategy, theoretical framework, a literature review related to key variables and concepts, summary, and conclusion.

Literature Search Strategy

There are 109 references found in following library database and search engines: Walden University library, National Center Biotechnology Information, U.S. National Library of Medicine–National Institute of Health (PubMed), Elsevier, WHO Library Cataloguing, Programme for Appropriate Technology Health (PATH) Vaccine Resources Library, Oxford University Press, University of Oslo Library, Princeton University, John Libbey Eurotext, Google Scholar, Medline Plus, Medline, Semantic Scholar, and Scientific Research Publishing, Inc., WHO websites, CDC Website, and PATH website.

Key search terms and combinations of search terms were *meningitis, Africa, carriage, Burkina Faso, Mali, Niger, MenAfriVac®, meningococcal meningitis, meningitis belt, Neisseria meningitidis, Neisseria meningitidis serogroup A, PsA-TT, Rollout of the group A meningococcal vaccine, new meningococcal vaccine, meningitis epidemic, impact, conjugate vaccine, meningococcal A conjugate vaccine, surveillance, serogroup A meningococci,* and *cerebrospinal meningitis.* As stated above, there were 107 references found including 71 periodical peer-reviewed articles in 31 periodical peer-reviewed journals, ten periodical newspaper articles, 17 articles in health agency websites, 16 books, two meeting/conference and conference reports, and one meeting press release. These references were published between 1963 and 2018, mainly in the 26 countries of African meningitis belt. Fifty-nine references were published within five years from 2014 to 2018.

Currently, few studies have been conducted to determine the level and the duration of immunogenicity of MenAfriVac®. The main purpose of these studies was to

assess the duration of the persistence of antibodies against *N. meningitidis* A at a high level among people vaccinated to provide effective protection. These studies were conducted by WHO, CDC, AMP, PATH, and the National Institute of Public Health of Oslo.

Theoretical Foundation

I used the SEM as a theoretical framework. Prevention refers to the efforts of society to promote, protect, and sustain the health of the population. Vaccination is one of the methods of prevention against vaccine-preventable diseases such as meningitis, poliomyelitis, measles, rubella, and so forth. Vaccination aims to limit the incidence of disease by protecting the population from attack before being affected. The SEM is a theoretical framework for prevention. Therefore, SEM can be used to better understand the effect of potential prevention strategies such as vaccination. Since 1979, the ecological model and Bronfenbrenner's ecological systems theory were developed by few researchers. Following this, McLeroy, Bibeau, Steckler, and Glanz (1988) developed the SEM of health promotion (CDC, 2015b; Glanz, Rimer, & Viswanath, 2008; Nyambe, Van Hal, & Kampen, 2016).

According to McLeroy et al. (1988), SEM addresses the importance of interventions directed at changing the individual, interpersonal, organizational, community, and public policy factors that support and maintain unhealthy behaviors. The model assumes that appropriate changes in the social environment will produce changes in individuals and that the support of individuals in the population is essential for implementing environmental changes. (CDC, 2015b; Elder et al., 1999; Glanz et al.,

2008; McLeroy et al., 1988; Nyambe et al. 2016). The use of SEM helped to respond to the four RQs selected. The four questions took into consideration the five approaches of SEM to assess the effects of MenAfriVac®introduction in African maningitis belt countries.

At the individual level, biological and personal history factors that increase the likelihood of becoming affected by meningococcal meningitis serogroup A were identified. The purpose was to increase the individual's knowledge and influence attitudes, behavior change, and beliefs. At the second level, the interpersonal, close relationships that may increase the risk of becoming affected by meningococcal meningitis serogroup A were examined. This level was intended to facilitate individual behavior change through a social network or social support systems by affecting social and cultural norms and overcoming individual-level barriers. The third level of the SEM was the community. In this research I explored the settings of overcrowding that is one of the risk factors of meningococcal meningitis serogroup A. These settings might be schools, markets, workplaces, households, and neighborhoods. Activities might be developed and implemented to provide individual and community behavior changes. The involvement and the participation of individuals, communities, and institutions could contribute to promoting elimination of meningococcal meningitis serogroup A in Africa. The fourth level was organizational. It represented prevention activities implemented at the organization level. These activities were intended to facilitate individual behavior change by influencing organizational systems. The fifth level was societal or policy level.

In this level, activities involved interpreting and implementing existing policy that might promote healthy behavior that contributed to eradicating meningococcal meningitis A.

The SEM Has been applied to vaccination and the assessment of new vaccines. For example, Kumar et al., (2012) conducted a study that examined influenza vaccine uptake during the 2009 H1N1 pandemic in the United States. The use of SEM was largely focused on individual determinants (perceived risk, past vaccine acceptance, perceived vaccine safety) and physician recommendation. Nyambe et al. (2016) found that SEM as the multilevel model was effective for vaccination for controlling the spread of a vast number of diseases and conditions. The United Nations Children's Fund (UNICEF) has used SEM in this manner to support countries in improving their public health policies that require childhood immunizations (CDC, 2015b).

I chose this theory because all five approaches fit with the topic of the dissertation. SEM is based on evidence that no single factor can explain why some people or groups are at higher risk for meningococcal meningitis while others are more protected from it. This framework viewed protection with MenAfriVac® as the outcome of interaction among many factors. These factors were the individual, the interpersonal, the community, organizational, and the societal levels. The societal level was characterized by the quality of the public health policy used to organize immunization campaigns and routine programs with the involvement of the health institution and researchers to contribute to eliminating meningococcal meningitis due to *N .meningitidis A.*

Literature Review

Meningococcal Meningitis: Overview

Definition and pathogens. Meningitis is an infection of the membranes covering the brain and spinal cord. Meningococcal meningitis is the common form of meningitis infection. It can be defined as a bacterial form of meningitis caused by *N. meningitidis.* It is an infection of the thin lining that surrounds the brain and spinal cord that can cause severe brain damage. It is very serious and can be deadly: it is fatal in 50% of cases if untreated, and almost 20% of survivors suffer serious sequelae such as deafness and mental retardation (CDC, 2014; WHO, 2015a, WHO, 2015b, National Institute of Health, 2016; Agauado et al. (2015); Kiefer, 2016). Of the 13 serogroups of *N. meningitidis* identified, four (*N. meningitidis.* A, B, C, and W135) are recognized to be the main causes of epidemics, while occasional outbreaks are also caused by *N. meningitidis* X and Y. Meningococcal meningitis cases occur throughout the world. Large, recurring epidemics affect the meningitis belt. Before 2010, *N. meningitidis* A was responsible for the large majority of epidemics in this area. In this area, outbreaks occur during the dry season, usually covering a period between January and June (WHO, 2015a; WHO 2015b; WHO, 2017 March 13).

Risk factors. The common risk factors are being 1 to 29 years old, community setting, and travel. Travelers may be at increased risk particularly during the dry season (December to June) and in Mecca during the annual Hajj and Umrah pilgrimage. A relationship between the environment and the location of meningococcal meningitis epidemics has been found. The findings show that meningococcal meningitis has the

greatest incidence for large epidemics in Africa in the dry season. The dry season coincides with periods of very low humidity and dusty conditions and disappears with the onset of the rains, suggesting that these environmental factors may also play an important role in the occurrence (CDC, 2014; Greenwood, 1999; Lapeyssonnie, 1963; Molesworth et al., 2003)

Transmission, symptoms, and complications. *N. meningitidis* is transmitted from person-to-person through droplets of respiratory or throat secretions from carriers. Ten percent to 20% of the population carries *N. meningitidis* in their throat at any given time, and this carriage rate may be higher in epidemic situations. The average incubation period is 4 days but can range between 2 and 10 days. *N. meningitidis* only infects humans (WHO, 2014b, WHO, 2015b). The most common symptoms of meningitis disease are a headache, stiff neck, confusion, vomiting, sensitivity to light, high fever, skin rash, and convulsions. The common complications are septicemia, endocarditis, arthritis, and sequelae such as partial or total hearing loss, memory and concentration problems, partial or total vision loss, insomnia, speech problems, migraine, and epilepsy (Kiefer, 2016; WHO, 2014b; WHO, 2015b).

Diagnosis. The diagnosis of meningococcal meningitis can be made by clinical examination followed by a lumbar puncture showing a purulent spinal fluid. The bacteria can sometimes be seen in microscopic examinations of the spinal fluid. The diagnosis is supported or confirmed by growing the bacteria from specimens of spinal fluid or blood, by agglutination tests or by PCR. The identification of the serogroups and susceptibility

testing to antibiotics are important to define control measures (WHO, 2009a; WHO, 2009b; WHO, 2014c; WHO, 2015a)

Pillar strategies for elimination of meningitis in Africa. The three pillar strategies for elimination of meningitis in Africa are as follows: surveillance, treatment and care, and vaccination (WHO, 2015b, WHO, 2015, February 20; WHO, 2015, November 20). Enhanced meningitis surveillance has been implemented since 2002 in countries of the African meningitis belt. The main objectives are to rapidly collect, disseminate, and use weekly district data on meningitis incidence. Standard operating procedures for meningitis enhanced surveillance were developed to guide countries. Concerning treatment and care, even when the meningitis is diagnosed early and adequate treatment is started, 5%-10% of patients die, often 24 to 48 hours after the onset of symptoms. Few antibiotics can treat meningitis infection. Ceftriaxone by injection is recommended as the first treatment for a minimum of 5 days (WHO, 2014b; WHO, 2014c; WHO, 2015b). Concerning the vaccination pillar strategy, it contributes to reduce the incidence of meningitis disease (preventive vaccination) and to limit the magnitude of the epidemic (reactive vaccination). There are polysaccharide and conjugate monovalent and polyvalent vaccines available that are used both for preventive and reactive immunization, vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* as well (WHO, 2011 November; WHO, 2014b; WHO, 2014c; WHO, 2015a; WHO, 2015b; WHO, 2017 March 13). The main objectives of surveillance are to evaluate the impact of vaccination, to detect and investigate epidemics and to provide material for

research (Djingarey et al., 2008; Harrison et al., 2009; Lingani et al., 2015; Mueller, 2013; WHO, 2015; WHO & CDC, 2010).

Epidemiology of Meningococcal Meningitis

Meningococcal disease is a leading cause of bacterial meningitis and sepsis, and a major cause of epidemics in sub-Saharan Africa. The causative organism is *Neisseria meningitidis.* Meningococcal meningitis is a major public health problem and burden worldwide especially in the extended meningitis belt of sub-Saharan Africa. The extended meningitis belt stretching from Senegal in the west to Ethiopia in the east where an estimated 450 million people are at risk from meningitis epidemics are living. 26 countries at highest rates of the disease are in meningitis belt (WHO, 2015a; CDC, 2015a; PATH, 2016a; Nicolas, 2012). Before 2010 and the mass preventive immunization campaigns, *N. meningitidis* A accounted for an estimated 80–85% of all cases in the meningitis belt, with epidemics occurring at intervals of 7–14 years. Manigart et al. (2016) showed that before vaccination with the serogroup A meningococcal conjugate vaccine, meningococcal serogroup A IgG antibody concentrations were high across the African meningitis belt and yet the region remained susceptible to epidemics. The human and socioeconomic toll of these epidemics is devastating. By far the highest incidence of meningococcal disease occurs in the meningitis belt of sub-Saharan Africa. During epidemics, the incidence can approach 1000 per 100,000, or 1% of the population (CDC, 2015a; Harrison et al., 2009).

Some countries of meningitis belt reported deadly epidemics due to *N. meningitidis* A. The largest meningococcal meningitis. An epidemic was reported in 1996

and 1997 with more than 25,000 people died and more than 250,000 were sickened. In 2009 more than 88,000 people in Africa were stricken by meningitis (Nicolas, 2012; PATH, 2016a; Vergnano & Health, 2003). Caugant et al. (2012) found that in the seven years preceding the introduction of a new serogroup A conjugate vaccine, serogroup A of the ST-5 clonal complex was identified as the predominant disease-causing strain. Sow et al. (2011) stated that *N. meningitidis* A was the source of major epidemics of meningitis in Africa. An affordable, highly immunogenic meningococcal A conjugate vaccine was needed. Thus, since 2010, some authors found that the proportion of *N. meningitidis* A has declined significantly. The bacterial profile has changed with the predominance of, *N. meningitidis* W135, *N. meningitidis* C, *N. meningitis* X, *S. pneumoniae* (Collard et al., 2013; Trotter et al., 2017; Retchless et al., 2016; Carod, 2015; WHO, 2017, March 13).

MenAfriVac® Vaccine

Public health initiative and Meningitis Vaccine Project (MVP). Following the devastating epidemic of 1996–97 African leaders called for the development of an affordable vaccine less than US$ 0.50 that would eliminate, once and for all, group A meningitis epidemics in Africa (PATH, 2016b; Aguado et al., 2015; Tiffany et al., 2015). WHO accepted the challenge and created a project called Epidemic Meningitis Vaccines for Africa (EVA) that served as an organizational framework for external consultants, PATH, CDC and Bill and Melinda Gates Foundation (BMGF) (WHO 2011; WHO 2014b; Aguado et al., 2015). In June 2001, BMGF awarded a grant of US$ 70 million to create the MVP as a partnership between PATH and WHO. The specific goal of MVP was the development, licensure, and the introduction of MenAfriVac® in meningitis belt

countries to eliminate meningitis A epidemics in Africa (Okwo-Bele et al., 2015; PATH, 2016b; Aguado et al., 2015; Idoko et al., 2014 ; Frasch et al., 2012; WHO, 2010, December 6).

Development of PsA-TT (MenAfriVac®) and ethical challenges. WHO (2015, February 20), Frasch et al. (2012), and Idoko et al. (2014) showed that an affordable monovalent MenA polysaccharide-tetanus toxoid conjugate vaccine (MACV/ PsA-TT) so-called MenAfriVac® was developed. This vaccine is against meningococcal meningitis caused by *N. meningitidis* A. This vaccine was developed by scientists working with MVP. A high-efficiency conjugation method was developed in the laboratory of bacterial polysaccharides in the center for biologics evaluation and research and transferred to the Serum Institute of India, Ltd (SILL). Then after, SILL developed methods of purification of group A polysaccharide and used tetanus toxoid as the carrier protein to produce the new licensed, highly effective MenAfriVac® conjugate vaccine. The PsA-TT conjugate vaccine is a lyophilized preparation that is reconstituted before injection. The vaccine is administrated intramuscularly (Frasch et al., 2012). A 5µg formulation was prequalified by WHO for routine immunization while 10µg formulation was prequalified for vaccination mass campaign.

Ethical issues encountered during clinical trials of PsA-TT and they have been rose and were well-taken in consideration. Martellet et al. (2015) showed that groups that conducted the clinical trials successfully resolved ethical issues that arose. The key factors of the success in all the sites of clinical trials were the constant dialogue between partners to explore and answer all ethical questions. Also, the alertness and preparedness

for emerging ethical questions during the research and the context of evolving international ethics standards were followed. The care to assure that approaches were acceptable in the diverse community contexts was effective.

Idoko et al. (2015) and Berlier et al. (2015) emphasized the relevant role played by the communications strategy that engaged stakeholders, potential supporters, and communities concerned during the development of PsA-TT. Moreover, Idoko et al. (2015) stated that the understanding and integration of sociocultural realities of communities were major assets in the conduct and acceptance of these trials in Gambia, Ghana, and Senegal. Communication, rumor management, recruitment, sharing results with communities involved and the consent were relevant and well-prepared and well-conducted. Therefore MVP succeeded in these sites and provided a sound example for future clinical studies in Africa. Okwo-Bele et al. (2015) and PATH (2016c) emphasized the successful partnership between WHO and PATH, an international nonprofit organization during the development, and licensure of PsA-TT. The development, licensure of MenAfriVac® a safe, effective and affordable vaccine to face a dramatic public health problem in Africa was a relevant public-private partnership. Therefore, it had shown the possibility and challenge to develop other vaccines especially targeting populations in developing countries (Tiffany et al., 2015; Okwo-Bele et al. (2015); PATH, 2016c, Bishai et al., 2011, Jódar et al., 2003).

Immunogenicity, safety, licensure, prequalification, and registration of MenAfriVac®. Sow et al. (2011), Frasch et al. (2015), Tapia et al. (2015), WHO (2015, February 20), and Idoko et al. (2014) demonstrated that PsA-TT 10 µg and 5 µg when

tested in Africans between 1 and 29 years of age had a safety profile, well-tolerated, and more persistent response from functional antibodies against *N. meningitidis* A. They also found that PsA-TT could induce immunologic memory and induced herd immunity. All participants had a significant response to antibody titers especially after receiving PsA-TT. Therefore, the introduction of PsA-TT could potentially decrease epidemics caused by *N. meningitidis* A in the African meningitis belt. In another hand, WHO (2014b), WHO (2014d), and Karachialou et al. (2015) showed that MenAfriVac® introduction trough vaccination mass campaigns must be completed by the introduction in routine immunization program for children between 9 to 18 months. That will contribute to a sustainable elimination of meningococcal meningitis A. an additional benefit of immunizing with PsA-TT is the carrier protein tetanus toxoid (TT) itself. PsA-TT has been shown to generate effective tetanus protection (Borrow et al., 2015).

Concerning the pharmacovigilance activities during the development of PsA-TT and the implementation of vaccination mass campaigns, Diomandé, Yaméogo,Vannice et al. (2015), Wak et al. (2015), and Vannice et al. (2015) enlighted the relevance of monitoring and review serious adverse events following immunization (AEFIs) in all countries. These activities are being conducted by the national expert advisory groups in all countries that introduced MenAfriVac®. As during the clinical trials, AEFIs reported were not significant during the vaccination mass campaigns showing that MenAfriVac® is safe for people vaccinated including pregnant women (WHO, 2006; Diomandé, Yaméogo, Vannice, et al., 2015; Wak et al., 2015; Vannice et al., 2015). The vaccine was successfully tested in Phase I, II and II/III clinical trials in India and African countries of

the meningitis belt that are Mali, The Gambia, and Senegal. In December 2009, MenAfriVac® 10µg was licensed in India for vaccination of individuals 1-29 years old in Africa. It was prequalified by WHO in June 2010 for vaccination mass campaigns. In October 2014, MenAfriVac® 5µg was prequalified by WHO for children aged 3-23 months. All the 21 countries that introduced MenAfriVac between 2010 and 2017 registered at national level the PsA-TT prior the vaccination mass campaign and introduction into routine vaccination programme (WHO, 2011; PATH, 2014; WHO, 2014b; WHO, 2014d; WHO, 2015 January 9, Frasch et al., 2012; Novak et al., 2012).

MenAfriVac® is affordable costing less than US$ 0.50 per dose (Sambo et al., 2015). Laforce et al. (2011) found that MenAfriVac® is expected to be cost-saving when compared to expenditures epidemics caused by *N. meningitidis* A. On the same line, Colombini et al. (2011) stated that MenAfriVac® should contribute to the more efficient use of funds dedicated to meningitis epidemics and limit the disruption of routine health services. Socioeconomic impact study estimated the expected health outcomes, treatment costs, vaccination costs, and cost-effectiveness of vaccination in the hyper endemic countries over a six-year-period (PATH, 2016d)

MenAfriVac® Rollout in Africa

Only the health districts that are at highest risk are selected to introduce MenAfriVac®. The selection is made through the risk assessment using the district prioritization tool developed by WHO (Cibrelus et al., 2015). After the selection of health districts in each country, the next step is to apply to GAVI alliance for a grant that will help to finance vaccine costs and operational costs for the preparation, implementation,

monitoring, and evaluation of the vaccination mass campaign. All the 21 countries selected for this study have followed all the steps of the process shown above. The herd protection and individual protection become while health district has obtained at least 90% of administrative coverage or 70% of immunization coverage from the independent coverage survey. Therefore, one of the objectives of the vaccination mass campaign is for each health district to reach at least 90% of administrative coverage. The findings in the literature show that the preparation, implementation, monitoring, and evaluation have been well-done in the 21 countries involved in this research. Some authors found that the majority of communities living in highest risk health districts were engaged and participated effectively in preparation, implementation, and evaluation of vaccination mass campaigns, public health professionals, researchers, community and political leaders as well. Djingarey et al. (2012) showed that African national immunization programs are capable of achieving very high coverage for a vaccine desired by the public, introduced in a well-organized campaign, and supported at the highest political level. In Burkina Faso, the ensuing 10-day national campaign was hugely successful, and 100% of target population aged between 1 and 29 years were vaccinated. In the same line, Djingarey et al. (2015) found that between 2010 and 2014 the preparation and implementation of vaccination mass campaigns were relevant and the participation of communities concerned exemplary. Few studies conducted by PATH (2016a), Idoko et al. (2015), Martellet et al. (2015), Belier et al. (2015), and Okwo - Bele et al. (2015) provided information on the contribution of social values while introducing MenAfriVac®. These social values were the community engagement, the government

commitment, and the accountability of public health agencies and researchers reported to achieve the goal of the elimination of meningitis disease due to *N. meningitidis* A in Africa.

Djingarey et al. (2015) found that from 2010 to 2014, 217 million persons aged 1-29 years were vaccinated in 15 out of 26 countries of meningitis belt with the country coverage rates ranging from 85% to 95%. WHO (2017, March 13) showed that from 2010 to 2016, 260.6 million persons in 19 countries aged from nine months to 29 years old were vaccinated with MenAfriVac®. In 2017, two additional countries Uganda and Central African Republic (CAR) have introduced MenAfriVac® respectively in January and March-May.

Early Effects of the Introduction of MenAfriVac®

Since 2010, the serogroup A conjugate vaccine (MenAfriVac®) is being introduced through mass campaigns and routine immunization to countries of the meningitis belt. Between 2010 and 2016, 260.6 million persons aged between nine months to 29 years were vaccinated in 19 countries (WHO, 2017 March 13). The age group concerned by vaccination mass campaigns is 1 -29 years with MenAfriVac® 10µg. Whereas the age group concerned by routine immunization program varies between nine to 18 months with MenAfriVac® 5µg (WHO, 2014d; WHO, 2017a; WHO, 2011 November; who, 2015 February 2). According to WHO (2014d) and WHO (2015, February 20), both immunization through the mass campaign and routine program are critical for a sustainable elimination of *N. meningitidis* A. Obaro and Habib (2016) stated that after the widespread vaccination with serogroup A conjugate vaccine of people aged

1–29 years from 2011 to 2014, the susceptible pool of unvaccinated people has increased because routine vaccination has not been introduced.

The early effects are being found by some authors. The global reduction of the incidence and occurrence of meningitis epidemics caused by *N. meningitidis* A in the meningitis belt were shown by WHO (2014d), WHO (2015b), WHO (2016b), WHO (2017), PATH (2016d), PATH and WHO (2016), WHO (2017, October 13), and Dakar discussion group on priorities for research on epidemic meningococcal disease in Africa et al. (2013). Some authors assessed the effects of MenAfriVac® within one or few countries between 2012 and 2016 using as measurement instrument carriage study or antibodies determination or surveillance. Surveillance is used in this study to assess the effects of MenAfriVac®. The other authors who found the effective impact of MenAfriVac®, using surveillance are Novak et al. (2012) and Diallo et al. (2017) in Burkina Faso. Maïnassara et al. (2015) found the predominance of *N. meningitidis* C epidemics after the introduction of MenAfriVac® in 2010 in Niger. Lingani et al. (2015) found that confirmed a dramatic fall in *N. meningitidis* A incidence after the introduction of MenAfriVac® between 2004 and 2013 within ten countries (Benin, Burkina Faso, Chad, Democratic Republic of Congo, Ghana, Côte d'Ivoire, Mali, Niger, Nigeria, and Togo). Trotter et al. (2017) found in nine countries (nine countries- Benin, Burkina Faso, Chad, Côte d'Ivoire, Ghana, Mali, Niger, Nigeria, and Togo) the reduction of the incidence and epidemics in epidemics due to *N. meningitidis* A after the introduction of MenAfriVac®. Diallo et al. (2016) reported the first documented MenAfriVac® vaccine failure in Burkina Faso in 2015.

Kristiansen (2012) and Kristiansen et al. (2013) found the effectiveness of MenAfriVac® on the carriage of *N. meningitidis* A among persons vaccinated in Burkina Faso. The similar result with the carriage measurement was found by Daugla et al. (2013) in Chad. Using the culture, seroagglutination and speciation PCR, followed by genogrouping PCR for *N. meningitidis*, Collard et al. (2013) found the reduction of incidence of *N. meningitidis* A and the predominance of *N. meningitidis* W135 in Niger from 2008 to 2011. The similar findings were showed by Retchless et al. (2016) in Burkina Faso and Mali. Carod (2015) found that the predominant of non-*N. Meningitidis* A after the introduction of MenAfriVac® in African meningitis belt.

The population-level persistence of immunity few years after the MenAfriVac® mass vaccination campaigns in few countries have been found. Basta et al. (2015) found in Mali the persistence of immunity two years after the campaign. Diomandé, Djingarey, Daugla, et al. (2015) found the persistence of immunity four years after the campaigns in Burkina Faso and Chad. MenAfriCar consortium (2016) found that Meningococcal serogroup A IgG antibodies by country and by sub-group were high in the populations of six countries (Ethiopia, Senegal, Mali, Ghana, Mali, Nigeria) investigated.

Kristiansen et al. (2015), found that the administration in mass vaccination campaigns of a single dose of MenAfriVac®, to the target (1-29 years old) population of sub-Saharan Africa has prevented epidemics of meningitis caused by serogroup A Neisseria meningitidis. This strategy has also been shown to provide herd protection of the non-vaccinated population. Moreover, WHO and PATH (2016, February) declared during the closure MVP meeting that meningitis A is nearly eliminated in Africa through

vaccination. In the same line, Sambo et al. (2015) stated that MenAfriVac® met its promise and the success in controlling epidemic meningococcal meningitis in Sub-Saharan Africa is noted.

Summary and Conclusions

The literature review shows that meningococcal meningitis remains a major public health problem worldwide and Africa the most affected. *N. meningitidis* A before the introduction of MenAfriVac® accounted for 80-85% of meningitis cases and epidemics. Following the devastating epidemic of 1996–97 African leaders called for the development of an affordable vaccine that would eliminate, once and for all, *N. meningitidis* A meningitis epidemics in Africa. The collaboration of WHO, PATH, and SIIL contributed to developing and to licensure MenAfriVac® with a grant provided by BMGF. MenAfriVac® has effective immunogenicity. This vaccine is safe and was prequalified by WHO in 2009 for vaccination mass campaigns among people aged 1-29 years and in 2014 among children aged 9-18 months old. MVP with the partnership of public health professionals, communities, and governments support the preparation and implementation of vaccination mass campaigns with MenAfriVac® and its introduction into routine immunization programs in the meningitis belt. Almost 280 million people have been vaccinated in 21 out of 26 countries of meningitis belt from 2010 to June 2017. The early effects of the introduction of MenAfriVac® show the reduction of incidence of *N. meningitidis* A and the occurrence of epidemics due to *N. meningitidis* A.

The purpose of this study was to fill the gap in the literature by assessing the effects of MenAfriVac® in more countries and several years after the introduction in

2010 than the previous studies. This study also helped to provide more information on the relationship between MenAfriVac® introduction and the CFR, and the strength of the relationship between MenAfriVac® introduction and *N. meningitidis* A. Another gap to fill was to establish the relationship between the introduction of MenAfriVac® and the occurrence of epidemics caused by *N. meningitidis* A. while showing in this study the advantage of having high MenAfriVac® immunization coverage and performant meningitis surveillance, it will create a positive social change fostering the improvement of public health policies.

The background showed the definition of meningococcal meningitis, the pathogens, risk factors, symptoms, complications, and diagnosis. The second part of the literature was marked by how the initiative to eliminate meningitis An epidemic as a public health problem in Africa, the development, immunogenicity, licensure, safety, and prequalification of MenAfriVac®. Then, the third part showed the MenAfriVac® roll-out and, the last part provided the early effects of MenAfriVac®. The next chapter presents the research design and rationale and the methodology. The methodology presents the population, sampling and sampling procedures, procedures for recruitment participants, and data collection, instrumentation and operationalization of instruments, research questions, variables, the operationalization of data analysis plan, threats of validity, and ethical procedures.

Chapter 3: Research Method

Introduction

The research purpose of this study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called MenAfriVac® in 21 out of 26 countries of the meningitis belt in Africa from 2010 to 2017. The major sections of this chapter are the introduction, research design and rationale, and methodology (population, sampling and sampling procedures, procedures for recruitment participants, data collection, instrumentation and operationalization of instruments, research questions, variables, and the operationalization of data analysis plan), threats of validity, and ethical procedures.

Research Design and Rationale

I chose four dependent variables and one independent variable to achieve the purpose of this study. The dependent variables selected were the occurrence of *N. meningitidis* A or not (another pathogen than *N. meningitidis* A, negative CSF sample), incidence rate of meningitis suspected cases, CFR, deaths, and occurrence of meningitis epidemics. The independent variable was MenAfriVac® vaccination status of the health district (vaccinated after the introduction of MenAfriVac®; vaccinated with any another polysaccharide vaccine that includes antigen A; unvaccinated before the introduction of MenAfriVac®). Pathogens were isolated from CSF samples by culture or detected by latex agglutination test or PCR.

The study was quasi-experimental, retrospective, and quantitative. It was also consistent with the research design chosen. The research design was an interrupted time series. Secondary data retrieved from WHO IST WA database concerned meningitis suspected cases, CFR, deaths, *N. meningitidis* A confirmed cases, and occurrence of epidemics due to *N. meningitidis* A before and after 2010. Secondary data from meningitis enhanced surveillance and MenAfriVac® coverage concerned the period from 2004 to 2017. No time and resource constraints were found.

Methodology

Population

The population of this study was characterized by people living in 1,713 out of 3,817 health districts at highest risk for meningitis in 21 countries of the African meningitis belt. Health districts at highest risk for meningitis were selected to introduce MenAfriVac®. The selection was made through risk assessment using the district prioritization tool developed by WHO (Cibrelus et al., 2015). The 21 countries that were participants of this study were Mali, Burkina Faso, Cameroon, Central Africa Republic, Chad, Benin, Cote d'Ivoire, Togo, Mauritania, Niger, Nigeria, Ghana, Gambia, Guinea, Guinea Bissau, Ethiopia, Sudan, South Sudan, Senegal, and Uganda. The total estimated population was 407,958,506 persons. People who were vaccinated with MenAfriVac® were aged 1-29 years old because they were the highest risk of meningitis infection caused by *N. meningitidis* A. The age group 1-29 years old represented almost 70% of the total population. The estimated target population for MenAfriVac® vaccination was 285,570,957 people. Figure 1 and Table 1 show that between 2010 and 2017,

286,995,073 were immunized with MenAfriVac®, thus there was 100% administrative coverage in the 21 countries of the study. The target population of this study was large and representative. The findings can be generalized.

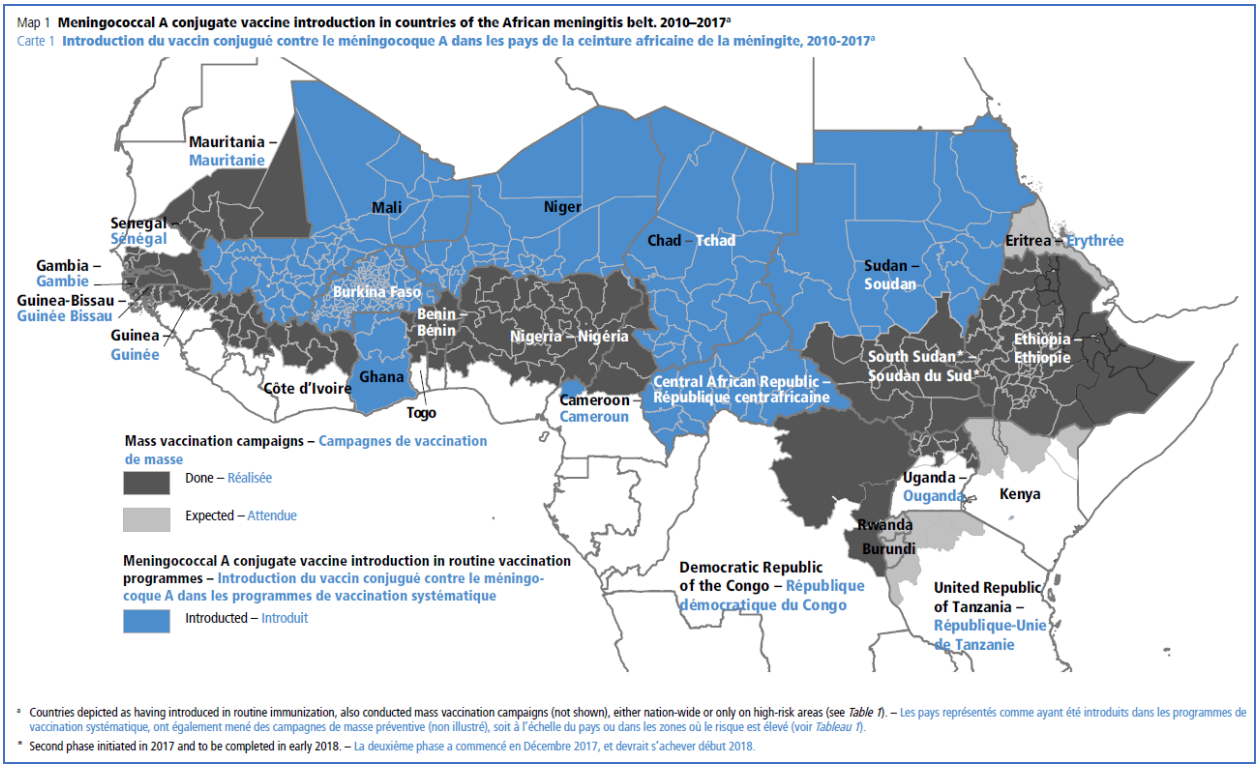

Figure 1. African Meningitis Belt and MenAfriVac® Roll-out 2010-17. (Source WHO).

Table 1

People Vaccinated With MenAfriVac® 2010-17

Countries	Total population 2017 at meningitis risk	Health districts at high risk covered By MenAfriVac vaccination campaign	Years of introduction	The target population for MenAfriVac vaccination campaigns	Persons vaccinated	Administrative coverage
Benin	3708077	33	2013	2595654	2718459	105%
Burkina Faso	21557784	63	2010, 2016	15090449	15295276	101.35%
Cameroon	8751220	70	2011-12	6125854	6510729	112.80%
Central African Republic	5226069	30	2017	3658248	3220358	88.24%
Chad	13177019	99	2011-12	9223913	8732151	95
Cote d'Ivoire	3244287	42	2014	2271001	2764839	100.40%
Democratic Republic of Congo	26008263	149	2016	18205784	18058535	99.20%
Ethiopia	88330603	102	2013-15	61831422	60996186	98.64%
Gambia	1682750	7	2013	1177925	1228419	104%
Ghana	5395356	49	2012, 2016	3776749	3705081	98.10%
Guinea	3657747	15	2015	2560423	2442566	95.40%
Guinea Bissau	1821931	11	2016	1275352	1150136	90.10%
Mali	20260730	60	2010, 2011 2016	14182511	14593475	102.89%
Mauritania	2300747	33	2014	1610523	1561720	97%
Niger	15529739	42	2010	10870817	10575365	95.70%
Nigeria	118680713	571	2011-14	83076499	87062324	104.79%
Senegal	6261793	35	2012	4383255	4216691	96.20%
South Sudan	6246709	47	2016	4372696	4023659	92%
Sudan	42176594	188	2012-13	29523616	28232735	95.62%
Togo	3934556	28	2014	2754189	2764839	102.20%
Uganda	10005820	39	2017	7004074	7141530	102%
Total	407958506	1713	2010-17	285570954	286995073	100.49%

Note. Source WHO.

Sampling and Sampling Procedures

Nonprobability sampling was chosen because all countries that introduced MenAfriVac® between 2010 and 2017 were participants. I intended this choice to have more evidence of the effects of MenAfriVac® that can be generalized. The countries included in this study are located in the African meningitis belt, and they introduced

MenAfriVac® between 2010 and June 2017. The other African countries are excluded. This study took into consideration all CSF samples tested in the laboratory with either culture, latex agglutination test, or PCR. CSF samples were transported from healthcare facilities to the district or national reference laboratories, which conducted laboratory testing. Cytology and gram staining found for probable meningitis were excluded in this study. WHO recommended that any reported *N. meningitidis* A case after MenAfriVac® introduction should be investigated.

I used the non-probably sampling method instead of random sampling to have more evidence that could provide greater validity with generalization. The minimum sample size was 144 calculated using G*Power 3.1.9.2. I used the following estimated parameters to calculate the minimum sample size: confidence interval chosen was 95% with Z =1.96, alpha = .05, type II error =20%, power = 80% with two tails. For this study, the estimate sample size of CSF samples was over 100,000. The estimate of incidence rate of meningitis suspected cases and deaths was over 400,000. Moreover, the number of health districts that reported epidemics caused by *N. meningitidis* A from 2004 to June 2017 was over 200. With the large sample size, the results could be generalized with appropriate size effect.

To measure effects of MenAfriVac® introduction in the African meningitis belt, I retrieved data from meningitis enhanced surveillance between 2004 and 2017 and MenAfriVac® immunization coverage from WHO ISTWA database. I found other relevant information on meningitis enhanced surveillance and polysaccharides vaccines immunization coverage in archives and meningitis bulletins posted in public WHO

websites. A data use agreement to retrieve the data for this study was given by WHO regional director of Africa in December 2017 following the request in December 2016. The secondary data from meningitis enhanced surveillance concerned meningitis suspected cases that fit the case definition, CFR, CSF samples tested in laboratories, and the meningitis epidemics reported using meningitis epidemic threshold. Concerning MenAfriVac® coverage provided by mass vaccination campaigns and routine immunization programmes, they were retrieved from WHO ISTWA database. I also found data from meningitis surveillance and MenAfriVac® coverage in the WHO IST WA databases. These are aggregated data sent by countries on a weekly basis concerning meningitis surveillance and monthly about routine immunization or by one month following mass vaccination campaigns. These data were collected, treated, consolidated, harmonized, and validated at the country level before they are sent to WHO ISTWA. WHO and other partners such as CDC provide technical support to have accurate data at each level of the health system. WHO and CDC have developed together reference documents on standard operating procedures for meningitis surveillance; they also have supported training in the African meningitis belt since 2002. Data quality audits and supervision are being done to improve the quality of surveillance data from health facilities directly to the central level (WHO, 2014c; WHO & CDC, 2010). These procedures were developed to assure their accuracy. Data quality audits are being doing at all levels by ministries of health with WHO to ensure the accuracy of data shared in the health information system.

Instrumentation and Operationalization of Constructs

The measuring instrument that I used in this study was enhanced surveillance. Enhanced surveillance is the continuous, systematic collection, analysis, and interpretation of health data linked with giving feedback to people at all levels of the data collection chain. Enhanced surveillance serves as an early warning system for impending public health emergencies. Surveillance also serves to evaluate and to document coverage and effectiveness of programme interventions such as the introduction of new vaccines. It also contributes to track progress towards specified goals and monitor the epidemiology of health problems. Meningitis enhanced surveillance was developed in 2002 by WHO and CDC to reinforce the meningitis surveillance (Johns Hopkins et al., 2008; MacNeil, & Cohn, 2013; WHO, 2009a; WHO, 2014b; WHO, 2017b; WHO & CDC, 2010).

Enhanced surveillance is a relevant measure to evaluate the effects of the introduction of a new vaccine such as MenAfriVac®. The goals of meningococcal enhanced surveillance are: to detect outbreaks of meningococcal disease so that appropriate control measures can be promptly instituted and to assess changes in the epidemiology of meningococcal disease over time to permit the most efficient allocation of resources and formulation of the most effective disease control and prevention policies. Meningococcal serogroup surveillance data are important to monitor and assess the impact of new vaccines. The African meningitis belt countries have national plans for integrated disease surveillance and response, which include meningitis. WHO supports those countries to strengthen their disease surveillance, especially meningitis surveillance

(Djingarey et al., 2008; Harrison et al., 2009; MacNeil, & Cohn, 2013; Mueller, 2013; WHO, 2009a, WHO, 2014a; WHO, 2015; WHO & CDC, 2010).

The two key concepts that determine the high quality of enhanced surveillance are reliability and validity. The appropriateness or quality of surveillance information depends on the accuracy of that information (Teutsch & Churchill, 2000). Enhanced surveillance is relevant because it provides high validity and reliability. Data provided must be accurate. Based on its reliability and validity, WHO recommends surveillance to assess effects of the new vaccines. The purpose of meningococcal surveillance is to detect epidemics of meningococcal disease, to assess changes in the epidemiology of meningococcal disease over time, to build efficient prevention policies, and to monitor and evaluate the impact of meningococcal vaccine (Djingarey et al., 2008; Harrison et al., 2009; MacNeil, & Cohn, 2013; Mueller, 2013; WHO, 2009a, WHO, 2014a; WHO, 2015; WHO & CDC, 2010;). Studies conducted by Diallo et al. (2017), Djingarey et al. (2015), Lingani et al. (2015), Novak et al. (2012), and Totter et al. (2017) showed effects of MenAfriVac® using meningitis enhanced surveillance as measure instrument.

Data and information found in WHO IST WA databases were accurate based on the procedures followed within countries with the technical support of WHO country staffs that help to collect and to curate data before sending. The data from surveillance were treated, harmonized, validated with the stakeholders of the surveillance system with the technical support of partners such as WHO and CDC to assure their reliability and validity. Meningitis surveillance implements within countries supported by WHO presents timeliness, representation, sensitivity, and specificity. Meningitis surveillance is

being strengthened with the technical support of WHO and CDC since 2002. Many authors used surveillance as a measure of the instrument to evaluate the effectiveness of vaccines. Novak (2012), Lingani et al. (2015), Djingarey et al. (2014), Diallo et al. (2017), and Trotter et al. (2017) used meningitis surveillance to assess the early effects of MenAfriVac® in Africa.

Meningitis enhanced surveillance helped to respond to the four research questions of this study by providing incidence of meningitis suspected case definition, CFR, and occurrence of meningitis epidemics between 2004 and June 2017. The definition and characteristics of these key elements are as follows:

Case definition of meningitis disease: Any person with sudden onset of fever (>38.5 °C rectal or 38.0 °C axillary) and neck stiffness or another meningeal sign including bulging fontanel in toddlers (WHO, 2015b).

Suspected case (of meningitis): Any person with sudden onset of fever (>38.5^{o}C rectal or >38.0^{o}C axillary) and one of the following signs: neck stiffness, flaccid neck, bulging fontanelle, convulsion or other meningeal signs (WHO, 2014c).

Confirmed meningitis case: Any suspected or probable case that is laboratory confirmed by culturing or identifying. Identification can be done either by PCR or immunochromatographic dipstick or latex agglutination of pathogens in the CSF or blood (WHO, 2015b).

Alert threshold: A level of incidence that triggers action to prepare for an epidemic, including strengthening surveillance, confirming cases, distributing treatment

protocols and informing the authorities (WHO, 2014c; WHO, 2015b). For meningococcal meningitis, the alert threshold is as follows:

- For population 30,000–100,000: three suspected cases per 100 000 inhabitants a week (minimum of 2 cases in one week).
- For population under 30,000: two suspected cases in one week *or* increased incidence compared to previous non epidemic years.

Epidemic threshold: A higher level of incidence that triggers an epidemic response, including mass vaccination, antibiotic distribution and raising public awareness (WHO, 2014c). For meningococcal meningitis, the epidemic threshold is as follows:

- For population 30,000–100,000: 10 suspected cases per 100 000 inhabitants a week.
- For population under 30,000: suspected cases in 1 week *or* doubling of the number of cases in a 3-week period (e.g., week 1: 1 case, week 2: 2 cases, week 3: 4 cases).

Incidence: A measure of the frequency with which new cases of illness, injury, or other health condition occurs among a population during a specified period (CDC, 2012c).

Incidence rate ratio (IRR): It is a measure of the frequency with which new cases of illness, injury, or other health condition occur, expressed explicitly per a time frame.

Relative risk (RR): It is a useful measure to compare the prevalence or incidence of disease between two groups. It is the ratio of prevalence or incidence in the exposed group to the prevalence or incidence in the unexposed group (Sullivan, 2012).

The confirmation of pathogens in meningitis surveillance is done by national or WHO reference laboratories by investigating CSF samples. The confirmation is done through culture or identification of pathogen. Identification can be done either by PCR or immunochromatographic dipstick or latex agglutination of pathogens in the CSF or blood (WHO; 2009a; WHO, 2009b; WHO, 2015b).

Data Analysis Plan

The inferential statistics were used to respond to the four research questions. The first research question contributed to find the difference of meningitis suspected cased before and after the introduction of MenAfriVac®. For that, IRRs of meningitis suspected cases in vaccinated and unvaccinated populations were estimated using a negative binomial regression model. The second research question helped to find the difference of CFR of meningitis before and after the introduction of MenAfriVac®, for that the Pearson's chi-square was used to determine whether or not they were the difference between CFR (> =10% or <10%). Additional IRR of deaths (fatal meningitis) was calculated using negative binomial regression. The third research question contributed to establish the degree of relationship between *N. meningitidis* A confirmed and the MenAfriVac® immunization. The Pearson's chi-square was used to determine the degree of the relationship between *N. meningitidis* A confirmed and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. The fourth research question contributed to establish the difference of meningitis epidemics caused by *N. meningitidis* A before and after the

introduction of MenAfriVac®. The Pearson's chi-square was used to estimate the relative risk of districts to be in epidemic after the introduction of MenAfriVac®.

Descriptive and inferential statistics were conducted in this study using SPSS 21 version and Microsoft Excel 2013. Before conducting inferential statistics, cleaning data was done for all research questions. A codebook created contain variable names, variable labels, value labels, and a list of any changes.

The four RQs and hypotheses developed to assess the effects of MenAfriVac® introduction in the 21 out of 26 African meningitis countries between 2010 and 2017 were as follows:

RQ1: What is the difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$1: There is no difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a1: There is a difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ2: What is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$2: There is no difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a2: There is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ3: What is the degree of relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$3: There is no relationship between the incidence of *Neisseria meningitidis* group A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a3: There is a relationship between the incidence of *Neisseria meningitidis* A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ4: What is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt?

$H_0$4: There is no difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

H_a4: There is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

Statistical Tests

To test the four hypotheses, descriptive and inferential statistics were chosen. This study compared the risk of meningitis disease, CFR and deaths, *N. meningitidis* A confirmed, and the occurrence of epidemics before and after MenAfriVac® introduction. Negative binomial regression was used to calculate the IRR of meningitis suspected cases and the deaths in MenAfriVac® vaccinated and unvaccinated populations. The relative risk was calculated using Pearson's chi-square to determine the degree of relationship between the incidence of *N. meningitidis* A confirmed and the MenAfriVac® immunization coverage, and the occurrence of health districts that reported epidemic due to N. meningitidis A before and after the introduction of MenAfriVac®.

The dependent variables selected were the occurrence of *N. meningitidis* A or not (another pathogen than *N. meningitidis* A, negative CSF sample), meningitis suspected cases, deaths, and occurrence of meningitis epidemics. The independent variable was MenAfriVac® vaccination status of health district (vaccinated after the introduction of MenAfriVac®; vaccinated with any other polysaccharide vaccine that includes antigen A; unvaccinated before the introduction of MenAfriVac®). Pathogens are being isolated from CSF samples by culture or detected by latex agglutination test or PCR. The period used for comparison was between 2004 and 2017. The following key parameter estimates

were chosen: confidence interval chosen is 95% with Z =1.96, alpha = .05, type II error =20%, power 0 80% with two tails.

Threats to Validity

The external validity requires a sound definition of the sample group and its environment that include demographic data from surveillance. The generalizability was feasible due to the large sample size, the sample was well-defined, and the instrumentation related to the CSF sample testing was appropriate and followed by laboratories involved in meningitis surveillance.

Countries selected for this study are being taken in consideration different biases in the whole national surveillance systems including meningitis surveillance with the main support of WHO. Routine testing of internal validity is implemented. Thus, selection bias, information bias, and confounding bias were looked and identified. The accuracy of surveillance information and completeness of information at all levels contribute to reduce information bias. The meningitis case definition, deaths related, and laboratory confirmation of CSF samples are being monitored by public health professionals and WHO. It contributes to reduce selection bias (WHO, 2014c). Concerning confounding bias, information given at health district level are verified to be sure that the vaccination status of populations with another vaccine with antigen *N. meningitidis* A is accurate.

The high quality of surveillance information depends on validity. Globally African meningitis countries involved in this study are being used appropriately case definition of meningitis and standards operating and procedures to testing CSF samples.

The adequate use of standards operating and procedures for meningitis surveillance including testing CSF samples contributed to provide validity of meningitis surveillance. Meningitis surveillance that is being implemented by countries presents timeliness, representation, sensitivity, and specificity.

Ethical Procedures

Two databases from WHO Inter-country Support Team of WEST Africa (IST WA) websites were used. The request for the use of secondary data from these databases was done in December 2016 to the regional director of WHO in Africa, and the approval was given on December 19, 2017. The secondary data used for this study both are anonymous, confidential, and will be secured hard and soft copies (password for folders). Walden University gave IRB approval on February 7, 2018 (02-07-18-0409702). There was no conflict of interest and, no incentive was taken for this study.

Summary and Conclusions

The research purpose of this study was to assess the effectiveness of the introduction MenAfriVac® in 21 out of 26 countries of the meningitis belt from 2010 to 2017. Dependent variables selected were the occurrence of *N. meningitidis* A or not (another pathogen than *N. meningitidis* A, negative CSF sample), meningitis suspected cases, deaths, and occurrence of meningitis epidemics. The independent variable was MenAfriVac® vaccination status of health district (vaccinated after the introduction of MenAfriVac®; vaccinated with any other polysaccharide vaccine that includes antigen A; unvaccinated before the introduction of MenAfriVac®). Pathogens are being isolated from CSF samples by culture or detected by latex agglutination test or PCR. Secondary

data were gathered from surveillance and MenAfriVac® coverage databases of WHO ISTWA. To test the four hypotheses, descriptive and inferential statistics were chosen. This study will compare the risk of meningitis disease, CFR and deaths, *N. meningitidis* A confirmed, and the occurrence of epidemics before and after MenAfriVac® introduction. Negative binomial regression was used to calculate the IRR of meningitis suspected cases and deaths in MenAfriVac® vaccinated and unvaccinated populations. The relative risk was calculated using Pearson's chi-square to determine the degree of relationship between the incidence of *N. meningitidis* A confirmed and the MenAfriVac® immunization coverage, and the occurrence of health districts that reported epidemic due to *N. meningitidis* A before and after the introduction of MenAfriVac®. The following parameters estimated are chosen: confidence interval chosen is 95% with Z =1.96, alpha = .05, type II error =20%, power = 80% with two tails.

The 21 African meningitis countries involved in this study used the appropriate case definition of meningitis and the standards operating and procedures for testing CSF samples (Djingarey et al., 2015; Lingani et al., 2015). The adequate use of standards operating and procedures for meningitis surveillance including testing CSF samples contributed to provide and therefore guarantee the validity of meningitis surveillance. Meningitis surveillance that is being implemented by countries presents timeliness, representation, sensitivity, and specificity. Ethics was taken into consideration. Agreement for data collection of this study was given by WHO on December 19, 2017. The IRB approval was received on February 7, 2018. The secondary data used for this study were anonymous, confidential, and secured.

The next chapter is titled results. This chapter comprises the following sections: the introduction, the data collection, the descriptive and demographic characteristics, the results (questions 1, 2, 3, and 4), and the summary.

Chapter 4: Results

Introduction

The purpose of this study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called MenAfriVac® in 21 of the 26 countries of the African meningitis belt between 2010 and 2017. I developed four RQs and respective null and alternative hypotheses. They were as follows:

RQ1: What is the difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis bel between 2010 and 2017?

$H_0$1: There is no difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a1: There is a difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ2: What is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$2: There is no difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a2: There is the difference in the CFR of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ3: What is the degree of relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

$H_0$3: There is no relationship between the incidence of *Neisseria meningitidis* group A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

H_a3: There is a relationship between the incidence of *Neisseria meningitidis* A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

RQ4: What is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* serogroup A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt?

$H_0$4: There is no difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

H_a4: There is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt.

This chapter includes a description of time frame, data collection, any discrepancies in data, descriptive and demographic characteristics, results of the study, and findings.

Data Collection

I retrieved the data for this study between February 10 and February 28, 2018, from WHO ISTWA databases and WHO websites. The secondary data retrieved concerned meningitis surveillance between 2004 and 2017 and MenAfriVac® vaccine introduction from 2010 to 2017. The secondary data from meningitis surveillance concerned especially meningitis suspected cases that fit the case definition, CFR, CSF samples tested in laboratories, and the meningitis epidemics due to *N. meningitidis* A reported by health districts using meningitis epidemic threshold. Concerning the MenAfriVac® introduction, information gathered mainly concerned vaccination coverage, the quality of implementation and evaluation of mass vaccination campaigns, and routine immunization programmes. The data retrieved were aggregated and sent by countries on a regular basis. Data were sent on a weekly basis concerning meningitis surveillance, and monthly regarding MenAfriVac® immunization activities. The data collected were prior treated, consolidated, harmonized, and validated at the country level before sending to WHO ISTWA. To improve the quality of data, WHO, CDC, and UNICEF provided technical support. Reference documents on standards were operating, and procedures for meningitis surveillance and MenAfriVac® introduction activities were developed. Between 2002 and 2017, training on data management and enhanced surveillance were regularly done in the countries of the African meningitis belt. Data

quality audit and supervision were done to improve the quality of surveillance and vaccination data from health facilities directly to the central level (WHO, 2014c; WHO & CDC, 2010). The procedures stated above aimed to assure the accuracy of data. I exported the data to SPSS (Version 21) for analysis. I created the new dataset of the study called MenA_dataset. They were no discrepancies in data collection. Almost 2.5 % of data were missing because few countries didn't share the data with WHO IST WA.

The dependent variables selected were the occurrence of *N. meningitidis* A, laboratory-confirmed or not, meningitis suspected cases, CFR, deaths, and occurrence of meningitis epidemics due to *N. meningitidis* A as reported by health districts. The independent variable was MenAfriVac® vaccination status of people living in health districts (vaccinated after the introduction of MenAfriVac®; vaccinated with any other polysaccharide vaccine that includes antigen A; unvaccinated before the introduction of MenAfriVac®). The statistical assumptions for negative binomial regression were met. The conditional means were not equal to the conditional variances, and the outcome variables were over-dispersed. The distribution was a Poisson distribution, where the mean and variance differ from one another. In this study, observations were independent variables. The statistical assumptions for Pearson's Chi-Square were met because the observations for the two-way contingency table analysis were independent of each other, and all the expected occurrences of the crosstab were greater than five.

Descriptive and Demographic Characteristics

The population of this study was characterized by people living in 1,713 meningitis highest risk health districts of 21 countries of the African meningitis belt. The

21 countries had 3,817 health districts. Meningitis highest risk health districts were selected to introduce MenAfriVac®. The selection was made through the risk assessment using the district prioritization tool developed by WHO (Cibrelus et al., 2015). The 21 countries that were participants of this study were Mali, Burkina Faso, Cameroon, Central Africa Republic, Chad, Benin, Cote d'Ivoire, Togo, Mauritania, Niger, Nigeria, Ghana, Gambia, Guinea, Guinea Bissau, Ethiopia, Sudan, South Sudan, Senegal, and Uganda. The total estimated population was 407,958,506 persons. People who were vaccinated with MenAfriVac® were aged 1-29 years old because they were the highest risk for meningitis infection caused by *N. meningitidis* A. The age group 1-29 years old represented almost 70% of the total population. The estimated target population for MenAfriVac® vaccination was 285,570,957 people. Between 2010 and 2017, 286,995,073 were immunized with MenAfriVac® thus there was 100% administrative coverage (see Table 1). The target population of this study was large and representative. The findings can be generalized over the African meningitis belt countries.

Before MenAfriVac®, people were immunized with other multivalent polysaccharide vaccines (AC, ACW, ACW) that included antigen A against *N. meningitidis* A. These polysaccharides vaccines were mainly administrated to populations to respond to meningitis epidemics and during the pilgrimage to Mecca. People are being vaccinated mostly within meningococcal meningitis epidemics. These vaccines protect for three years with no properties on the carriage, whereas MenAfriVac® protects both the individual and the community. It reduces the carriage of *N. meningitidis* A, and so increases the herd immunity (WHO, 2015a). Table 2 shows that an estimated

304,155,728 persons were vaccinated against *N. meningitidis* A with polysaccharide vaccines. Between 2008 and 2017, 286,995,073 people (94.4%) were immunized with MenAfriVac®, whereas 17,160,655 (5.6%) were protected with the other polysaccharides vaccines (AC, ACW, ACW).

Table 2

People Vaccinated With Vaccines That Include Antigen A 2008-2017

Countries	People vaccinated with MenAfriVac 2010-2017		Estimated people vaccinated with other multivalent vaccines that include antigen A 2008-2017		Total	
	Number	%	Number	%	Number	%
Benin	2718459	83.7	527631	16.3	3246090	100.0
Burkina Faso	15295276	87.3	2220000	12.7	17515276	100.0
Cameroon	6510729	99.9	7200	0.1	6517929	100.0
Central African Republic	3220358	98.8	40000	1.2	3260358	100.0
Chad	8732151	79.8	2215200	20.2	10947351	100.0
Cote d'Ivoire	2764839	94.4	163000	5.6	2927839	100.0
Democratic Republic of Congo	18058535	100.0	0	0.0	18058535	100.0
Ethiopia	60996186	99.8	120560	0.2	61116746	100.0
Gambia	1228419	100.0	0	0.0	1228419	100.0
Ghana	3705081	91.2	356540	8.8	4061621	100.0
Guinea	2442566	97.5	63075	2.5	2505641	100.0
Guinea Bissau	1150136	100.0	0	0.0	1150136	100.0
Mali	14593475	99.8	34348	0.2	14627823	100.0
Mauritania	1561720	100.0	0	0.0	1561720	100.0
Niger	10575365	70.9	4349540	29.1	14924905	100.0
Nigeria	87062324	95.9	3703340	4.1	90765664	100.0
Senegal	4216691	100.0	0	0.0	4216691	100.0
South Sudan	4023659	100.0	0	0.0	4023659	100.0
Sudan	28232735	92.8	2176353	7.2	30409088	100.0
Togo	2764839	77.9	782918	22.1	3547757	100.0
Uganda	7141530	94.7	400950	5.3	7542480	100.0
Total	286995073	94.4	17160655	5.6	304155728	100.0

Note. Source WHO

Table 3 shows the descriptive analyses for meningitis suspected cases, deaths, *N. meningitidis* A laboratory-confirmed, and health districts that reported *N. meningitidis* A epidemics from 2004 to 2017.

Table 3

Meningitis Incidence, N. Meningitidis *A Confirmed, Deaths, CFR, Epidemics*

Items	Countries	N	Missing data	Median	Minimum	Maximum
Meningitis Suspected cases	Country	485664	12	416	0	56128
	All			28343	18938	90996
Deaths due to meningitis disease	Country	42004	16	46	0	2488
	All			2547	1418	5507
N. meningitidis A Confirmed cases	Country	6659	0	0	0	1460
	All			210	3	2066
Crude Fatality Rate (CFR)	Country	NA	16	8.84	0.00	76.27
	All			8.60	6.05	13.82
Health districts reported N. meningitidis A epidemics	Country	516	0	0	0	175
	All			18	0	207

Meningitis Suspected Cases

Table 3 shows that 485,664 cumulative suspected meningitis cases had been reported between 2004 and 2017 in the 21 countries selected for this study (out of the 26 of the African meningitis belt). Table 3 also shows that the median for each country was 416, and the range was 0–56,128. For all the 21 countries the median of meningitis suspected cases was 28,343, and the range was 18,936–90,996. The higher number of suspected meningitis cases was 90,996 reported in 2009 and the lowest number of suspected meningitis cases was18,939 reported in 2016. Figure 2 shows a decline of meningitis suspected cases after 2010 in the 21 countries selected for the study (out of the

26 of the African meningitis belt). Meningitis suspected cases remained high and therefore a public health problem after 2010. Between 2010 and 2017, the highest number of meningitis suspected cases reported was 29,335 in 2012, and the range was 18,938–29,335.

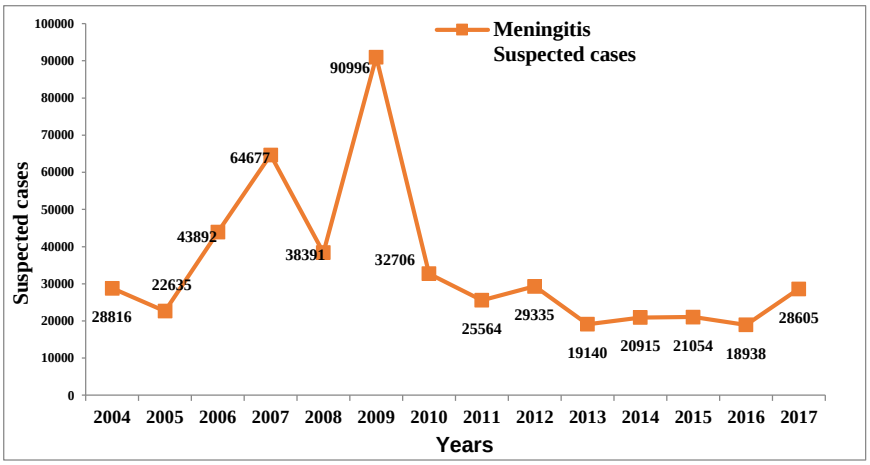

Figure 2. Meningitis suspected cases 2004-2017.

Deaths and Crude Fatality Rate

Table 3 shows that 42,004 deaths caused by meningitis disease (fatal meningitis) have been reported between 2004 and 2017 in the 21 countries selected for this study. Table 3 shows that the median number of deaths caused by meningitis disease for each country was 46, and the range was 0–2,488). Whereas for all the 21 countries selected for this study, the median of deaths was 2,547, and the range (1,418–5,507). Table 3 shows

that the median of CFR for each country was 8.84, and the range (0–76.27). Whereas for all countries, the median of CFR was 8.6, and the range (6.05-13.82).Figure 2 shows that the highest number of deaths caused by meningitis disease was 5,507 reported in 2009. The lowest number of deaths was 1,418 reported in 2016. The number of meningitis deaths was higher before 2010. The highest number of meningitis deaths was 5,507 reported in 2004. Figure 3 shows a decline of meningitis deaths and CFR after 2010. The CFR was higher before 2010; most were over 10%. The highest CFR was 14% reported in 2004, and the lowest CFR was 6% reported in 2017.

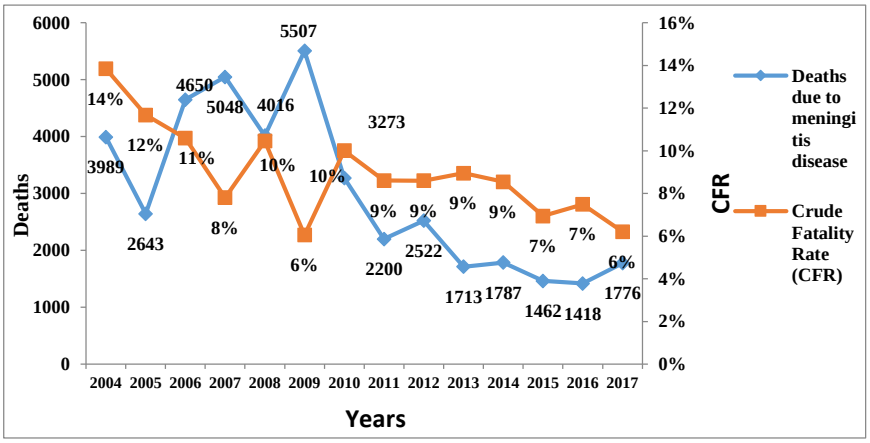

Figure 3. Incidence of meningitis deaths and crude fatality rate 2004-2017.

N. Meningitidis A Confirmed Cases

The Table 3 shows that 6,776 *N. meningitidis* A laboratory-confirmed cases have been reported between 2004 and 2017 in the 21 countries selected for this study out of the

26 of the African meningitis belt. Figure 3 shows that the incidence of *N. meningitidis* A confirmed case was higher before 2010. The highest *N. meningitidis* A was 2066 reported in 2009. Whereas the lowest incidence of meningitis deaths was three, reported in 2017. The median of *N. meningitidis* A laboratory-confirmed cases for each country was 0, and the range (0-1,460). Whereas for all the 21 countries selected for the study the median of *N. meningitidis* A laboratory-confirmed case was 210, and the range (3 - 2,066). Figure 4 shows N. meningitidis A reported decline significantly after 2010 with the introduction of MenAfriVac®.

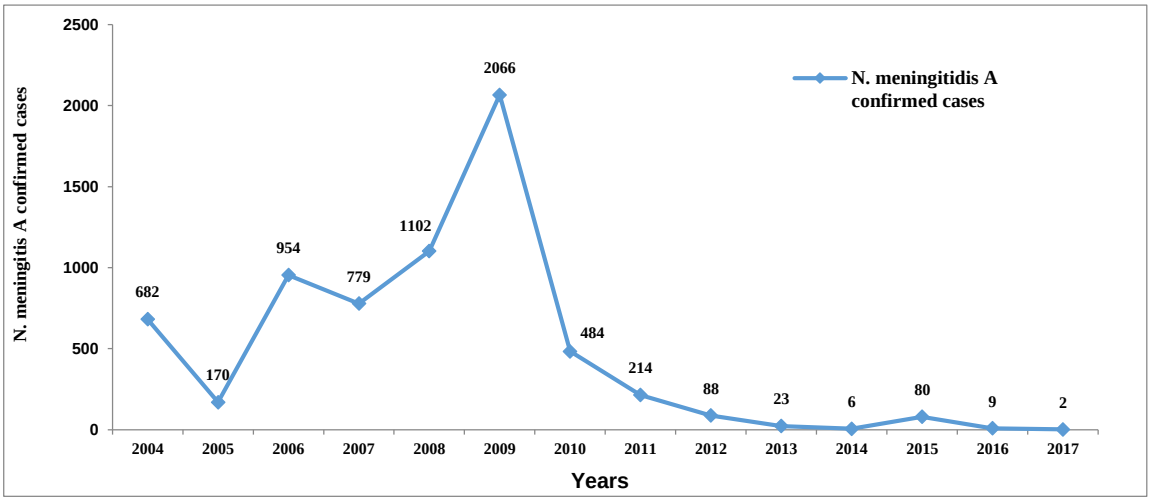

Figure 4. N. meningitidis A confirmed 2004-2017.

Figure 5 shows the decline of *N. meningitidis* A since 2010 and the predominance of other pathogens as follows *S. Pneumoniae*, *N. meningitidis* W135, and *N. meningitidis* C. Table 4 shows that meningococcal disease remains predominant and a public health problem. 15,885 (62.06%) out of 25,596 meningitis pathogens were confirmed between 2010 and 2017.

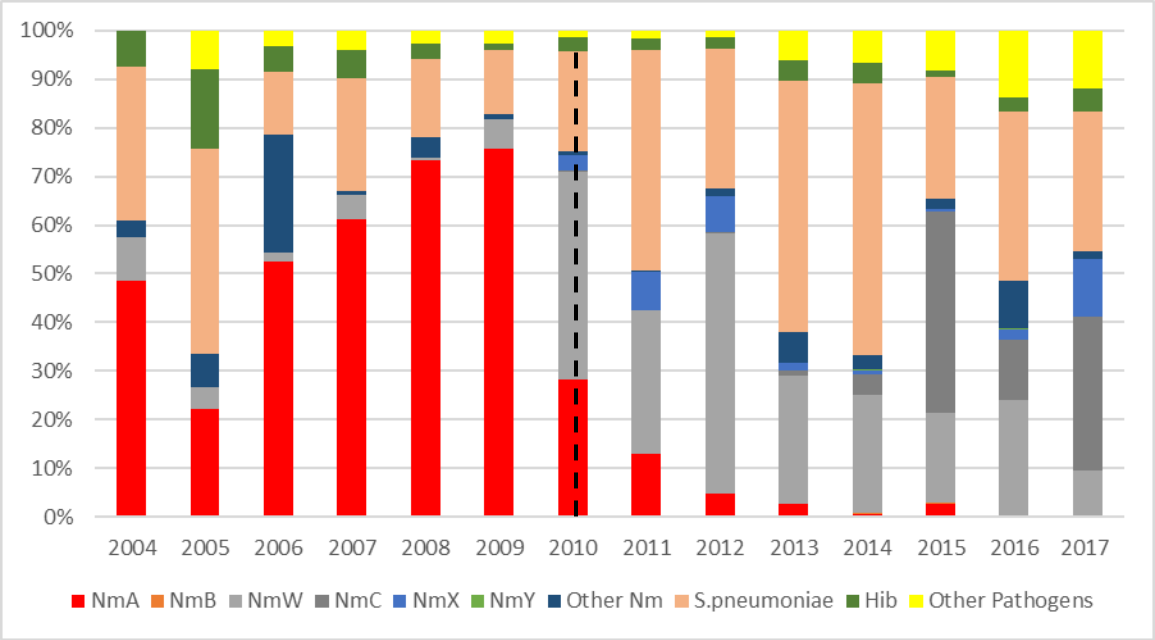

Figure 5. Meningitis pathogens laboratory confirmed 2004-2017.

Table 4

Meningitis Pathogens Profile

Countries Years	N.meningitidis A	*N. meningitidis* B	*N. meningitidis* W135	*N. meningitidis* C	*N. meningitidis* X	*N. meningitidis Y*	Other *N. meningitidis*	S.pneumoniae	Haemophilus influenza b	Other Pathogens	Total
2004	682	0	125	0	0	0	48	447	104	0	1406
2005	170	0	33	0	0	0	53	323	125	61	765
2006	954	0	34	0	0	0	441	234	95	60	1818
2007	779	0	62	0	0	0	9	297	74	50	1271
2008	1102	0	7	0	0	0	65	243	48	39	1504
2009	2066	0	167	0	0	0	29	355	37	74	2728
2010	484	0	727	4	55	0	14	351	47	25	1707
2011	214	0	487	0	128	0	4	748	40	27	1648
2012	88	1	1009	4	138	1	31	539	45	25	1881
2013	23	2	237	10	15	0	57	466	38	55	903
2014	6	2	286	48	11	1	34	656	50	76	1170
2015	80	2	545	1224	20	0	62	734	40	243	2950
2016	9	1	719	375	68	6	296	1062	87	416	3039
2017	2	0	263	891	333	2	40	809	136	330	2806
Total	6659	8	4701	2556	768	10	1183	7264	966	1481	25596

Health Districts Reported N. Meningitidis A Epidemics

The Table 3 shows that 515 health districts reported *N. meningitidis* A epidemics between 2004 and 2017 in 21 countries selected for this study out of the 26 of the African meningitis belt. The figure 4 shows that the highest number of health districts that reported *N. meningitidis* A was 207 reported on 2009. Whereas, the lowest number of health districts that reported N. meningitidis A was 0 reported between 2015 and 2017.The median of *N. meningitidis* A for each country was 0, and the range (0-175). Whereas, for all the 21 countries selected for this study the median of health districts that reported *N. meningitidis* A epidemic was 18, and the range (0-207). The figure 6 shows the decline of meningitis epidemics due to *N. meningitis* A reported since 2010. Since 2015 any health district reported *N. meningitis* A epidemic.

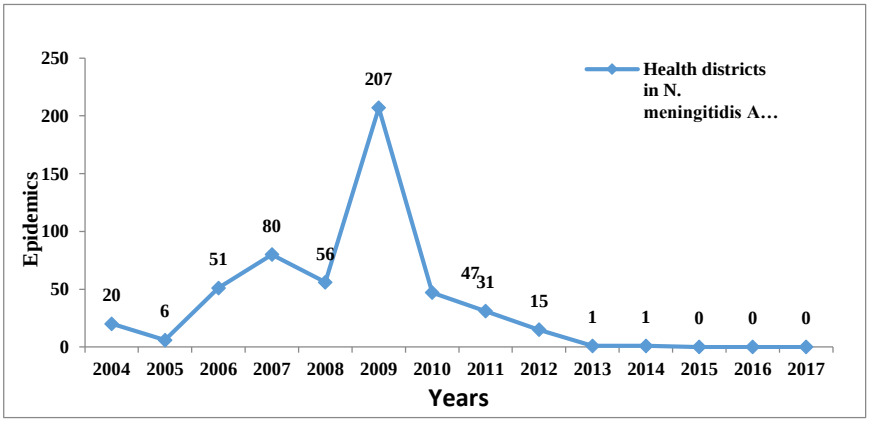

Figure 6. Health districts that reported *N. meningitidis* A epidemics 2004-2017.

Results

Descriptive and inferential statistics were done using SPSS statistics 21. The negative binomial regression was used to calculate IRR to calculate the difference of meningitis suspected cases and deaths before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. IRR was also calculated to determine whether or not they were a reduction of meningitis suspected cases and deaths. The Pearson's chi-square was used to determine whether or not they were the difference between CFR and districts that reported epidemics due to *N. meningitidis* A before and after the introduction of MenAfriVac. The Pearson's chi-square was also used to determine the degree of the relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017.

Research Question 1

RQ1: What is the difference of incidence rate of suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

Table 5 shows that after the introduction of the MenAfriVac®, there was a 39% decline of incidence rate of meningitis suspected cases (IRR 0.61, 95% CI 0.48 – 0.79, $p < .001$), with heterogeneity observed by country. The null hypothesis was rejected because it was less than .05. Therefore, there is a difference in incidence rate of the suspected cases of meningitis disease before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. The difference

of incidence rate of the meningitis suspected cases was significant ($p < .05$) in Burkina Faso, Nigeria, South Sudan, and Sudan.

Table 5

Incidence Rate Ratio for Meningitis Suspected Cases 2004-2017

	IRR	95%CI	p
All	0.61	0.48 - 0.79	**.000**
Benin	1.78	0.60 - 5.32	0.301
Burkina Faso	0.33	0.12 - 0.96	**.000**
Cameroon	1.99	0.69 - 5.69	0.197
Central African republic	2.88	0.38 - 22.06	0.308
Chad	0.19	0.02 - 1.45	0.11
Democratic republic of Congo	0.34	0.08 - 1.52	0.157
Ethiopia	11.17	3.50 - 35.68	0.014
Gambia	0.87	0.29 - 2.64	0.881
Ghana	1.45	0.50 - 4.20	0.488
Guinea	0.61	0.17 - 2.26	0.461
Guinea- Bissau	7.31	1.59 - 33.6	**0.011**
Ivory coast	0.5	0.16 - 1.60	0.244
Mali	0.51	0.18 - 1.48	0.217
Mauritania	0.35	0.09 - 1.33	0.125
Niger	0.49	0.17 - 1.42	0.188
Nigeria	0.25	0.09 - 0.70	**.000**
Senegal	3.28	1.14 - 9.49	**0.028**
South Sudan	0.02	0.005 - 0.10	**.000**
Sudan	0.11	0.04 - 0.35	**0.033**
Togo	1.75	0.55 - 5.60	0.343
Uganda	0.25	0.03 - 1.97	0.187

Note. IRR = Incidence Rate Ratio. CI = Confident Interval. NA = Not Applicable. p = p-value.

Research Question 2

RQ2: What is the difference in the CFR of meningitis before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

Table 7 shows that X^2 (1) = 14.18, p = .000. The null hypothesis was rejected because p was less than .05. Therefore, there was a difference in the meningitis CFR before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt. The table 8 shows that there was 46% decline of risk to report high *CFR* (>=10%) after the MenAfriVac® immunization (RR 0.547, 95% CI 0.40 – 0.74). Table 9 shows that after the introduction of the MenAfriVac® vaccine, there was a 49% decline of meningitis deaths (IRR 0.51, 95% CI 0.40 – 0.66, p < .001), with heterogeneity observed by country. The null hypothesis was rejected because p was less than .05. Therefore, there was a difference in fatal meningitis before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt. The difference in the fatal meningitis was significant (p < .05) in Ivory Coast, Mali, Mauritania, Nigeria, South Sudan, and Sudan.

Table 6

MenAfriVac Introduction and CFR Cross Tabulation

			CFR		Total
			>=10%	<10%	
Factor (MenAfriVac introduction)	After MenAfriVac introduction	Count	101_a	40_b	141
		% within Factor	71.6%	28.4%	100.0%
		% within CFR	61.2%	36.7%	51.5%
		% of total	36.9%	14.6%	51.5%
	Before MenAfriVac introduction	Count	64_a	69_b	133
		% within Factor	48.1%	51.9%	100.0%
		% within CFR	38.8%	63.3%	48.5%
		% of total	23.4%	25.2%	48.5%
Total		Count	165	109	274
		% within Factor	60.2%	39.8%	100.0%
		% within CFR	100.0%	100.0%	100.0%
		% of total	60.2%	39.8%	100.0%

Table 7

Chi-Square Tests for CFR and MenAfriVac® Introduction

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	15.792[a]	1	.000		
Continuity Correction[b]	14.826	1	.000		
Likelihood Ratio	15.944	1	.000		
Fisher's Exact Tests				.000	.000
N of Valid Cases	274				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 39.12.
b. Computed only for a 2x2 table.

Table 8

Risk Estimate of CFR and MenAfriVac® Introduction

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Factor (After MenAfriVac introduction / Before MenAfriVac introduction)	2.722	1.652	4.487
For cohort *CFR* = No	1.489	1.213	1.827
For cohort *CFR* = Yes	.547	.401	.745
N of Valid Cases	274		

Table 9

Incidence Risk Ratio of Meningitis Deaths 2004-2017

	IRR	95%CI	p
All	0.51	0.40 - 0.66	**.000**
Benin	1.13	0.38 - 3.38	0.301
Burkina Faso	0.38	0.13 - 1.10	0.073
Cameroon	1	0.34 - 2.87	0.99
Central African republic	1.72	0.22 - 13.27	0.308
Chad	0.16	0.02 - 1.27	0.11
Democratic republic of Congo	0.27	0.06 - 1.19	0.157
Ethiopia	0.74	0.23 - 2.42	0.620
Gambia	2.48	0.69 - 8.80	0.162
Ghana	0.91	0.31 - 2.64	0.488
Guinea	0.39	0.10 - 1.49	0.461
Guinea-Bissau	NA		
Ivory coast	0.27	0.08 - 0.89	**0.032**
Mali	0.29	0.10 - 0.86	**0.026**
Mauritania	0	0.00 - 0.00	**.000**
Niger	0.61	0.21 - 1.77	0.188
Nigeria	0.24	0.08 - 0.69	**0.009**
Senegal	1.61	0.53 - 4.92	0.400
South Sudan	0.012	0.002 - 0.08	**.000**
Sudan	0.08	0.02 - 0.26	**.000**
Togo	0.95	0.29 - 3.06	0.343
Uganda	0.59	0.07 - 5.25	0.638

Note. IRR = Incidence Rate Ratio. CI = Confident Interval. NA = Not Applicable. p = p-value.

Research Question 3

RQ3: What is the degree of relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017?

Table 11 shows that χ^2 (1) = 11039.49, p = 0.000. The null hypothesis was rejected because p was less than .05. Therefore, there was a relationship between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. Table 12 shows that

Phi = 0.657, P=0.000 that means the strength of the relationship is high between the incidence of *Neisseria meningitidis* serogroup A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. Table 13 shows 99% decline of risk to report *N. meningitidis* A after the introduction of MenAfriVac® (RR 0.01, 95% CI 0.08-0.013).

Table 10

MenAfriVac® Introduction and N. Meningitidis A Cross Tabulation

			N. meningitidis A		Total
			No	Yes	
Factor (MenAfriVac® introduction)	After MenAfriVac® introduction	Count	14310	87	14397
		Expected Count	10651.5	3745.5	14397.0
		% within Factor	99.4%	0.6%	100.0%
		% within *N. meningitidis* A	75.6%	1.3%	56.2%
		% of total	55.9%	0.3%	56.2%
		Standard Residual	35.4	-59.8	
	Before MenAfriVac® introduction	Count	4627	6572	11199
		Expected Count	8285.5	2913.5	11199.0
		% within Factor	41.3%	58.7%	100.0%
		% within *N. meningitidis* A	24.4%	98.7%	43.8%
		% of total	18.1%	25.7%	43.8%
		Standard Residual	-40.2	67.8	
Total		Count	18937	18937	6659
		Expected Count	18937.0	18937.0	6659.0
		% within Factor	73.6%	74.0%	26.0%
		% within *N. meningitidis* A	100.0%	100.0%	100.0%
		% of total	73.6%	74.0%	26.0%

Table 11

Chi-Square Tests for MenAfriVac® Introduction and N. Meningitidis A

	Valuedf	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	11039.494a1	.000		
Continuity Correctionb	11036.4771	.000		
Likelihood Ratio	13096.3701	.000		
Fisher's Exact Tests			.000	.000
N of Valid Cases	25596			

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 2501.37.
b. Computed only for a 2x2 table

Table 12

Symmetry Measures for MenAfriVac® Introduction and N. Meningitidis A

		Value	Approx. Sig
Nominal by Nominal	Phi	.657	.000
	Cramer's V	.657	.000
	Contingency Coefficient	.549	.000
N of Valid Cases		25596	25596

Table 13

Risk Estimate for MenAfriVac® Introduction and N. Meningitidis A

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Factor (After MenAfriVac® introduction / Before MenAfriVac® introduction)	233.625	188.598	289.401
For cohort *N. meningitidis* A = No	2.406	2.353	2.460
For cohort *N. meningitidis* A = Yes	.010	.008	.013
N of Valid Cases	25596		

Research Question 4

RQ4: What is the difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt?

Table 15 shows that χ^2 (1) = 595.351, p = 0.000. The null hypothesis was rejected because p was less than .05. Therefore, there was a difference in the frequency of meningitis epidemics caused by *Neisseria meningitidis* A before and after the MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt. Table 16 shows 99.6% decline of risk for a health district to be in epidemic due to *N. meningitidis* A after the introduction of MenAfriVac® (RR 0.004, 95% CI 0.001-0.016).

Table 14

MenAfriVac® Introduction and District in N. Meningitis A Epidemics

			District in *N. meningitis A* Epidemics		Total
			No	Yes	
Factor (MenAfriVac® introduction)	After MenAfriVac® introduction	Count	1711	2	1713
		Expected Count	1456.0	257.0	1713.0
		% within Factor	99.9%	0.1%	100.0%
		% within District in *N. meningitis A* Epidemics	58.8%	0.4%	50.0%
		% of total	49.9%	0.1%	50.0%
		Standard Residual	6.7	-15.9	
	Before MenAfriVac® introduction	Count	1201	512	1713
		Expected Count	1456.0	257.0	1713.0
		% within Factor	70.1%	29.9%	100.0%
		% within District in *N. meningitis A* Epidemics	41.2%	99.6%	50.0%
		% of total	35.1%	14.9%	50.0%
		Standard Residual	-6.7	15.9	
Total		Count	2912	514	3426
		Expected Count	2912.0	514.0	3426.0
		% within Factor	85.0%	15.0%	100.0%
		% within district in *N. meningitis* A Epidemics	100.0%	100.0%	100.0%
		% of total	85.0%	15.0%	100.0%

Table 15

Chi-Square Tests for MenAfriVac® Introduction and District in N. Meningitis A Epidemics

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	595.351a	1	.000		
Continuity Correctionb	593.019	1	.000		
Likelihood Ratio	776.149	1	.000		
Fisher's Exact Tests				.000	.000
N of Valid Cases	3426				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 257.50. b. Computed only for a 2x2 table

Table 16

Risk Estimate for MenAfriVac® Introduction and District in N. Meningitis A Epidemics

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Factor (After MenAfriVac® introduction / Before MenAfriVac® introduction)	364.709	90.789	1465.084
For cohort district in *N. meningitis* A Epidemics = No	1.425	1.381	1.469
For cohort district in *N. meningitis* A Epidemics = Yes	.004	.001	.016
N of Valid Cases	3426		

Summary

In this chapter, descriptive and inferential statistics were presented above on the line of the four research questions. The statistical assumptions for negative binomial regression and Pearson's Chi-square were met. They were no data discrepancies. After 2010, the descriptive analyses showed into meningitis belt decline of incidence rate of the meningitis suspected cases, fatal meningitis, *N. meningitidis* A confirmed cases, and epidemics due to *N. meningitidis* A. The trends found might be related to the introduction of MenAfriVac in the 21 out of 26 countries of the African meningitis belt. Before 2010,

N. meningitidis A was predominant after 2010, *N. meningitidis* A declined and the predominant meningitis pathogens found were *S. Pneumoniae*, *N. meningitidis* W135, and *N. meningitidis* C *N. meningitidis* represent almost 55% out of all meningitis pathogens laboratory-confirmed between 2010 and 2017.

The inferential analyses showed that after the introduction of the MenAfriVac® vaccine:

1. There was a 39% decline of incidence rate of meningitis suspected cases (IRR 0.61, 95% CI 0.48 – 0.79, $p < .001$), with heterogeneity observed by country.
2. There was a difference in the meningitis CFR before and after MenAfriVac® introduction in 21 out of the 26 countries of African meningitis belt. After the introduction of MenAfriVac., there was a 46% decline in risk to report high *CFR* (>10%) after the MenAfriVac® immunization (RR 0.547, 95% CI 0.40 – 0.74).
3. There was a 49% decline of fatal meningitis (IRR 0.51, 95% CI 0.41 – 0.68, $p < .001$), with heterogeneity observed by country.

4. There was a high degree of relationship between the incidence of *N. meningitidis* A and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017, (χ^2 (1) = 11039.49, p = 0.000, Phi = 0.657, P=0.000).
5. After the introduction of MenAfriVac®, there was 99% decline in the risk of *N. meningitidis* A (RR 0.01, 95% CI 0.08-0.013).

6. After the introduction of MenAfriVac® in the meningitis belt, there was 99.6% decline of risk for a health district to report epidemic caused by *N. meningitidis* A (RR 0.004, 95% CI 0.001-0.016).

In summary, the introduction of MenAfriVac in African meningitis belt reduced significantly the incidence rate of meningitis suspected cases, meningitis CFR, deaths due to meningitis disease, and epidemics caused by *N. Meningitidis* A.

The next chapter presents discussion, recommendations, and conclusions of the study.

Chapter 5: Discussion, Recommendations, and Conclusions

Introduction

The purpose of this study was to assess the effectiveness of the introduction of a new meningococcal conjugate A vaccine called MenAfriVac® in 21 out of 26 countries of the African meningitis belt between 2010 and 2017. The study was quasi-experimental research with an interrupted time series quantitative research design. The interrupted times series design was used to assess the effect of the introduction of the MenAfriVac® between 2010 and 2017 in 21 countries selected for this study using data from meningitis surveillance and *N. meningitidis* A coverage from 2004 to 2017. The major preview sections of this chapter are the introduction, key findings of the study, interpretation of findings, limitations of the study, recommendations for future research, social change implications, and the conclusion.

Key Findings of the Study

With the introduction of MenAfriVac® between 2010 and 2017 in the 21 countries selected out of the 26 of the African meningitis belt, the study showed:

1. a 39% decline of incidence rate of the meningitis suspected cases (IRR 0.61, 95% CI 0.48 – 0.79, $p < .001$), with heterogeneity observed by country;
2. a 46% decline of risk to report high *CFR* (> = 10%) after the MenAfriVac® immunization (RR 0.547, 95% CI 0.40 – 0.74);
3. a 49% decline of fatal meningitis (IRR 0.51, 95% CI 0.41 – 0.68, $p < .001$), with heterogeneity observed by country;

4. a high degree of relationship between *N. meningitidis* A reported and the MenAfriVac® immunization between 2010 and 2017 in 21 out of the 26 countries of African meningitis belt, (χ^2 (1) = 11039.49, p = 0.000, Phi = 0.657, P=0.000);
5. a 99% decline in the risk of *N. meningitidis* A after the introduction of MenAfriVac® (RR 0.01, 95% CI 0.08-0.013); and
6. a 99.6% decline of risk for a health district to report epidemic caused by *N. meningitidis* A after the introduction of MenAfriVac, (RR 0.004, 95% CI 0.001-0.016).

In summary, the study found that the introduction of MenAfriVac® in African meningitis belt reduced significantly the incidence rate of the meningitis suspected cases, meningitis CFR, deaths due to meningitis disease, and epidemics caused by *N. Meningitidis* A. Before 2010, *N. meningitidis* A was predominant. The study also showed that after the introduction of MenAfriVac® in 2010 and until 2017, the predominant meningitis pathogens were *S. Pneumoniae*, *N. meningitidis* W135, and *N. meningitidis* C. *N. meningitidis* represented almost 62.06% out of all meningitis pathogens laboratory-confirmed between 2010 and 2017.

Interpretation of Findings

I defined four RQs to assess the effects of the introduction of MenAfriVac® in 21 out of 26 countries of the African meningitis belt before and after 2010. All the null hypotheses were rejected. In the following sections, I present the key findings compared with those found in literature review in four areas related to the research questions.

Key Findings

Meningitis suspected cases reported before and after MenAfriVac® introduction. The study found 39% decline of incidence rate of meningitis suspected cases (IRR 0.61, 95% CI 0.48 – 0.79, $p < .001$) after the introduction of MenAfriVac®, with heterogeneity observed by country. These results confirm the same trend of reduction of meningitis suspected cases found in the literature review (Carod, 2015; Daugla et al., 2013; Diallo et al., 2017; Diomandé et al., 2015; Novak et al., 2012; PATH, 2013; Trotter et al., 2017; WHO, 2013 March 12; WHO, 2016a). However, Trotter et al. (2017) found a 57% decline of meningitis suspected cases in nine countries (Benin, Burkina Faso, Chad, Ivory Coast, Ghana, Mali, Niger, Nigeria, and Togo) 5 years after introduction of MenAfriVac® (IRR 0.43, 95% CI 0.41-0.45, $p < .001$). In Burkina Faso, Novak et al. (2012) found 71% decline of meningitis suspected cases one year after the introduction of MenAfriVac® (hazard ratio 0.29, 95% CI 0.28-0.30) and Trotter et al. (2017) found a decline of 70% 5 years after the introduction of MenAfriVac® (IRR 0.30, 95%CI 0.29-0.31). This study found a 77% decline 7 years after the introduction of MenAfriVac® in Burkina Faso (IRR 0.33, 95% CI 0.12-0.96, $p < .001$). Conversely, Trotter et al. (2017) and Daugla et al. (2013) found respectively 91% (IRR 0.086, 95%CI 0.077-0.097) and 94% ($p < 0.0001$) of reduction of meningitis deaths in Chad. This study also found that the decrease of meningitis deaths before and after the introduction of MenAfriVac® was significant (IRR 0.19, 95% CI 0.02-1.45).

Meningitis CFR and deaths reported before and after MenAfriVac® introduction. The study found a 46% decline of risk to report high *CFR* (>= 10%) after

the MenAfriVac® immunization (RR 0.547, 95% CI 0.40 – 0.74) and 49% decline of fatal meningitis (IRR 0.51, 95% CI 0.41 – 0.68, $p < .001$), with heterogeneity observed by country. The results confirm the findings of the literature (Diallo et al., 2017; Novak et al., 2012; WHO, 2016a). The decline of high CFR can be explained by the modification of treatment protocol that was included since 2014 ceftriaxone. Diallo et al. (2017) found between 2011 and 2015 in Burkina Faso that CFR was 8%. WHO (2016a) found between 1995 and 2014 in meningitis belt countries CFR = 10%. Conversely, Collard et al. (2013) found in Niger an increase of CFR from 6.7% in 2008 to 12.2% in 2011. Concerning meningitis deaths, this study found that in Niger there was no significant difference of fatal meningitis before and after the introduction of MenAfriVac® (IRR 0.61, 95% CI 0.21 – 1.77, p = 0.188) probably because of the high number of meningitis deaths during meningitis epidemics from 2015 to 2017. Novak et al. (2012) found in Burkina Faso 1 year after the introduction of MenAfriVac® a 64% decline in risk of fatal meningitis. However, this study found that 7 years after the introduction of MenAfriVac®, there was a significant difference of reduction of fatal meningitis (IRR 0.38, 95% CI 0.13 – 1.77).

The relationship between the *N. meningitidis* A reported and the MenAfriVac® immunization in 21 out of the 26 countries of the African meningitis belt. This study found a high degree of relationship between *N. meningitidis* A reported and the MenAfriVac® immunization between 2010 and 2017 in 21 out of the 26 countries of the African meningitis belt, (χ^2 (1) = 11039.49, p = 0.000, Phi = 0.657, P=0.000). The study also found 99% decline in the risk of *N. meningitidis* A after the introduction of MenAfriVac® (RR 0.01, 95% CI 0.08-0.013). These results globally confirmed the

findings of the literature. The findings showed the relationship between the reduction of *N. meningitidis* A reported and the MenAfriVac® immunization in African meningitis belt countries (Carod, 2015; Collard et al., 2013; Daugla et al., 2013; Diallo et al., 2017; Diomandé et al., 2015; GAVI, 2016; LaForce et al., 2017; Lingani et al., 2015; Meyer, 2017; Novak et al., 2012; PATH and WHO, 2016; Retchless et al., 2016; Sambo et al., 2015; Stuart, 2018; Trotter et al., 2017; WHO, 2015a). The findings in the literature did not assess the strength of the relationship between *N. meningitidis* A reported and the MenAfriVac® immunization in African meningitis belt. The extended finding of this study was the high degree of relationship between the reduction of *N. meningitidis* A reported and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt (Phi = 0.657, P=0.000). Stuart (2018) and Trotter et al. (2017) also found a 99% decline of *N. meningitidis* A in MenAfriVac® vaccinated countries. As with this study, some authors found that after the introduction of MenAfriVac®, there was predominance of other meningitis pathogens (*N. meningitidis* W135, *N. meningitidis* C, *N. meningitidis* X, and Streptococcus pneumoniae) with the near disappearance of *N. meningitidis* A in African meningitis belt countries (Diallo et al., 2017; LaForce et al., 2017; PATH and WHO, 2016; Trotter et al., 2017).

***N. meningitidis* A epidemics reported by health districts before and after MenAfriVac® introduction.** The study found 99.6% decline of risk for a health district to be in epidemic due to *N. meningitidis* A after the introduction of MenAfriVac®, (RR 0.004, 95% CI 0.001-0.016). This result confirmed findings of the literature characterized by a disappearance of *N. meningitidis* A epidemics in MenAfriVac®

vaccinated health districts (Diallo et al., 2017; Diomandé et al., 2015; GAVI, 2016; Kristiansen et al., 2015; Meyer, 2017; Novak et al., 2012; Obaro et al., 2016; PATH and WHO, 2016; Retchless et al., 2016; Sambo et al., 2015; Stuart, 2018; Trotter et al., 2017, WHO, 2015a). However, the risk for a health district to report *N. meningitidis* A epidemic after the introduction of MenAfriVac® was not found in the literature. Trotter et al. (2017) observed a 59% decline globally in risk of a health district reaching meningitis epidemic threshold. Stuart (2018) found that the number of all meningitis epidemics at health district level has fallen by 60% following MenAfriVac® vaccination; meningitis is caused by other meningococcal serogroups than A.

The results of the study confirmed those found in the literature. The multiple-level approaches that are individual, relationship, community, organizational, and policy levels of SEM as a theory-based framework fit with the findings of the study. MenAfriVac® immunization campaigns implemented in 21 out of 26 African meningitis belt countries to protect individuals and communities have achieved one of the main objectives of the meningitis control program, to eliminate meningitis epidemics caused by *N. meningitidis* A. The results of this study show near elimination of *N. meningitidis* A epidemic with a 99.6% decline of risk for a health district to report *N. meningitidis* A epidemic. MenAfriVac® unvaccinated individuals and communities living in high-risk areas of *N. meningitidis* A epidemic are vulnerable. Therefore, prevention using MenAfriVac® immunization was relevant to provide individual protection and herd immunity against *N. meningitidis* A.

Limitations of the Study

To measure the effects of a new vaccine, surveillance was relevant because it provided high validity and reliability. Data and information used in this study were accurate. This study retrieved accurate data from meningitis surveillance and immunization from WHO IST WA database. The 21 African meningitis countries involved in this study have used appropriately the case definition of meningitis and the standard operating procedures for testing CSF samples. The adequate use of standard operating procedures for meningitis surveillance including testing CSF samples contributes to the validity of meningitis surveillance. Meningitis surveillance implemented by most of the countries in the African meningitis belt demonstrate timeliness, representation, sensitivity, and specificity. However, for a few countries, there were missing data. Fortunately, the missing data from countries were not significant at slightly under 2.5%. External validity requires a sound definition of the sample group and its environment that include demographic data from surveillance. This study met this condition.

The generalizability of this study is feasible due to the large sample size from the 21 countries chosen for this study out of 26 countries of the African meningitis belt. The total estimated population of the 21 African meningitis belt countries was 407,958,506 persons at highest risk of meningitis. Between 2010 and 2017,286,995, 073 persons aged 1-29 years old living in 1,713 health districts were immunized with MenAfriVac® with 100% administrative coverage achieved. The target population of this study was large and representative because a nonprobability sampling method was used and the minimum

sample size was 144 calculated using G*Power 3.1.9.2. Therefore, the findings of this study can be generalized.

Recommendations for Future Research and Practice

The purpose of this study was to fill the gaps in the literature by assessing the effects of MenAfriVac® in more countries and several years after the introduction in 2010 than the previous studies. This study provided more information on the relationship between MenAfriVac® introduction and the CFR, the strength of the relationship between MenAfriVac® introduction and *N. meningitidis* A, and also established the relationship between the introduction of MenAfriVac® and the occurrence of epidemics caused by N. meningitidis A. To evaluate the effectiveness of the introduction of MenAfriVac®, the study used meningitis enhanced surveillance data from 2004 to 2017, and immunization coverage between 2010 and 2017. This multi-country study involved 21 out of the 26 countries of African meningitis belt that introduced MenAfriVac®. People living into the 1,713 meningitis highest risk health districts were involved. The study also helped to assess more year's protection provided by MenAfriVac® and showed the risk of the occurrence of meningococcal meningitis due to other serogroups than *N. meningitidis* A.

The study found that the introduction of MenAfriVac® in African meningitis belt reduced significantly the incidence rate of the meningitis suspected cases, the meningitis CFR, deaths due to meningitis disease, and epidemics caused by *N. Meningitidis* A. Before 2010, *N. meningitidis* A was predominant. The study also showed that after the introduction of MenAfriVac® since 2010 until 2017, the predominant meningitis pathogens were *S. Pneumoniae*, *N. meningitidis* W135, and *N. meningitidis* C. *N.*

meningitidis represent almost 62.06% out of all meningitis pathogens laboratory-confirmed between 2010 and 2017. Based on the existent gaps in the literature, pertinent findings statistically significant provided by the study, and the limitations of this study, few relevant recommendations on practice and future studies were developed.

Concerning research, the first recommendation is to conduct in future a longitudinal study that permits long-term follow-up of people vaccinated with MenAfriVac®. This study was a quantitative retrospective study such as those conducted using enhanced surveillance on the same topic (Lingani et al.,2015; Djingarey et al.,201; Diomandé et al., 2015; Novak et al., 2012; Diallo et al., 2017; Trotter et al., 2017). Few longitudinal studies using antibodies determination and carriage were done showing early effects of MenAfriVac® (Kristiansen, 2012; Kristiansen et al., 2013; Collard et al., 2013; Daugla et al., 2013). One of the limitations of this study and the others that used retrospective data cited above is the lack of control over data. A longitudinal study, for example, a cohort study will involve people living in high-risk districts vaccinated with, and the occurrence of meningitis and deaths caused by *N. meningitidis* A among them. The control of data by an investigator will be better and missing data will be probably reduced.

The second recommendation is to conduct more studies on the relationship between the effects of the introduction of MenAfriVac® and the meningitis mortality and CFR. CFR is pertinent because it might demonstrate the gravity of disease, the effects of the case management, the awareness of the population on the disease, and the health care system and policies to respond to the disease. The high level of CFR may contribute to

improve or adjust public health policies to inverse the situation. The study showed 46% of reduction of CFR after the introduction of MenAfriVac®. The majority of the studies conducted provided results on meningitis deaths. Few studies conducted by Novak et al. (2012), Diallo et al. (2017), and WHO (2016) showed the relationship between MenAfriVac® and the meningitis mortality and CFR.

The third recommendation concerns the research and development of an affordable multivalent polysaccharide conjugate vaccine against *N. meningitis* (A, C, W135, X, Y). The findings of this study as the literature showed the predominance of other pathogens than *N. meningitis* A, after the introduction of MenAfriVac®. These pathogens are *N. meningitidis* W135, *N. meningitidis* C, *N. meningitidis* X, *and* Streptococcus pneumoniae (PATH and WHO, 2016; Diallo et al., 2017; Trotter et al., 2017; LaForce et al., 2017). The existent multivalent polysaccharides are not affordable for African countries, and the vaccine against *N. meningitidis* X is not yet developed. Therefore, the research and development of an affordable multivalent polysaccharide conjugate vaccine against *N. meningitis* (A, C, W135, X, Y) are pertinent because it will help to eliminate meningococcal disease representing 55% of meningitis disease in Africa.

Concerning the practice, the fourth recommendation is to update the risk assessment of the meningitis status after the introduction of MenAfriVac® in all the 26 countries of meningitis belt. The risk assessment conducted on N. meningitis A showed that people were living in 1,713 meningitis highest risk health districts out of 3,817 of the 26 countries of African meningitis belt. Lapeyssonnie (1963) described for the first time

African meningitis with 22 high-risk countries. With findings of Greenwood (1999) establishing endemicity, four new countries were added in 1987. Following the introduction of MenAfriVac®, the meningitis bacterial profile and level of risk due to meningitis disease might change. The changes can be explained by the current distribution and profile of the predominant pathogens found that are N. *meningitidis* W135, *N. meningitidis* C, *N. meningitidis* X, and *Streptococcus pneumoniae*, and the reduction of N. meningitidis A (PATH and WHO, 2016; Diallo et al., 2017; Trotter et al., 2017; LaForce et al., 2017). The results of the future risk assessment will help to improve public health policies, and review strategies to eliminate meningitis as a burden in Africa.

The fifth recommendation is to continue to improve meningitis enhanced surveillance to avoid missing data. Even though technical partners as WHO and CDC support countries to provide complete and accurate data, there are few countries that should improve meningitis enhanced surveillance. Especially reinforce the completeness rate. This study retrieved accurate secondary data from WHO data base with almost 2.5% missing data. This situation would have been less or null if the enhanced surveillance was improved especially the completeness in following Guinea Bissau, Guinea, Mauritania, South Sudan, and Uganda.

The sixth recommendation is to improve public health policies on immunization and enhanced surveillance to ensure sustainable high immunization coverage and high quality of enhanced surveillance. WHO. The MenAfriVac® herd protection and individual protection become while health district obtains at least 90% of administrative

coverage or 70% of immunization coverage from the independent coverage survey. Therefore, one of the objectives of the vaccination mass campaign is for each health district to reach at least 90% of administrative coverage. CAR obtained 88% MenAfriVac® coverage, the other 20 countries selected for this study achieved 90% and more of MenAfriVac® coverage. The data provided by meningitis enhanced surveillance and used in this study showed a significant reduction of risk of reporting N. meningitis A in all the 21 countries. The MenAfriVac® high coverage was explained by the relevant organization of vaccination mass campaigns in the countries that introduced MenAfriVac® (Djingarey et al., 2012; Djingarey et al., 2015; WHO, 2017 March 13). Therefore, it is pertinent to reinforce public health policies on immunization and enhanced surveillance to ensure sustainable high immunization coverage and high quality of enhanced surveillance.

Social Change Implications

The positive social change demonstrated in the study was firstly the high quality of organization and implementation of MenAfriVac® immunization that provided high immunization coverage. The high immunization coverage was adequate for individual and herd protection in health districts that introduced MenAfriVac®. The second positive social change demonstrated by the study was the use of high-quality meningitis surveillance as a public health intervention to assess the effectiveness of MenAfriVac® into the meningitis belt. These positive social changes fit the SEM because they take into consideration the protection through prevention with the multiple-level approaches that are individual, relationship, community, organizational, and policy levels.

It is valuable to build strong health policies based on evidence that will contribute to achieve public health problems as vaccine-preventable disease including meningitis. The findings of this study will create a positive social change fostering countries to improve immunization and meningitis surveillance policies to maximize MenAfriVac® coverage and the performances of meningitis surveillance respectively. The improvement of meningitis surveillance will help to detect earlier meningitis epidemics and master distribution and profile of pathogens.

The high MenAfriVac® coverage and the performant meningitis surveillance are the main factors that determined achievement of near elimination of *N. meningitidis* A. The study demonstrated that high MenAfriVac® coverage and enhanced surveillance are pivotal to reduce the meningitis burden. Results will be used to inform policy and public health practice to reduce the meningitis cases and improve quality of live in the community..

Conclusions

Meningitis disease including meningococcal infection remains a burden in the 26 African meningitis belt countries (WHO, 2015a). The purpose of the study was to assess the effects of the introduction of MenAfriVac® in African meningitis belt countries. For this study 21 out of the 26 African meningitis belt countries were chosen. The period of assessment was between 2004 and 2017 including the introduction of MenAfriVac® from 2010 to 2017. The study contributed to answering all the four questions selected. The results of the study confirmed the finding of the literature with few non-significant difference. The study provided additional research evidence. Firstly, on the difference of

CFR before and after the introduction of MenAfriVac®. Secondly, the study provided other research evidence of literature was the high strength of the relationship between the *N. meningitidis* A reported and the MenAfriVac® immunization coverage. Thirdly, the study also showed the effects of the introduction of MenAfriVac® within the longest period in all the 21 countries that introduced MenAfriVac® between 2010 and 2017.

The study showed the effectiveness of introduction of MenAfriVac® in African meningitis belt. The key findings of the study indicated that meningitis disease is reducing since the introduction of MenAfriVac®, meningitis deaths as well. The severity of meningitis disease is also decreasing after the introduction of MenAfriVac®. The high CFR 10% and over with 46% decline after the introduction of MenAfriVac® that can be explained by the improvement of interventions against meningitis disease and the change of treatment protocol with ceftriaxone that is used since 2014. The study also found a high degree of relationship between N. *meningitidis* A reported and the MenAfriVac® immunization in 21 out of the 26 countries of African meningitis belt between 2010 and 2017. The cases and epidemics of *N. meningitidis* A in African meningitis belt countries that vaccinated have declined significantly following the extensive roll-out of MenAfriVac®. The findings showed that *N. meningitidis* A is being eliminated. Despite the fact that the cases significantly decreased, it still a threat, and the bacterial profile changed with the predominance of *N. meningitidis* (C, W135, X, Y) and *S. pneumoniae* that have continued to cause epidemics.

The vaccination coverage obtained during campaigns were high and contributed to reducing *N. meningitidis* A cases and epidemics. The multiple-level approaches of

SEM that are individual, relationship, community, organizational and policy levels fit with the findings of the study. This study showed that the achievement of high MenAfriVac® immunization coverage reduced *N. meningitidis* A cases and epidemics. The study demonstrated that high MenAfriVac® coverage and enhanced surveillance are pivotal to reduce the meningitis burden. Results will be used to inform policy and public health practice to reduce the meningitis cases and improve quality of live in the community.

Considering the existent literature, findings on the effects of the introduction of MenAfriVac® in the meningitis belt, and the limitations of this study, few researches should be done in future. These studies should be conducted on: the long-term follow-up of people vaccinated with MenAfriVac®, update of the risk assessment on the meningitis status after introduction of MenAfriVac® in all the 26 countries of meningitis belt, the factors to improve meningitis enhanced surveillance, the effects of the introduction of MenAfriVac® and the meningitis mortality and CFR, the development of affordable multivalent polysaccharide conjugate vaccine against *N. meningitis* (A, C, W135, X, Y), and on how to improve public health policies on immunization and enhanced surveillance to ensure sustainable high immunization coverage and high quality of enhanced surveillance.

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Appendix A: Data use Agreement

DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of December 19, 2017 is entered into by and between **ANDRE ARSENE BITA FOUDA** "Data Recipient" and **WORLD HEALTH ORGANIZATION** "Data Provider". The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research in accord with the HIPAA and FERPA Regulations.

1. Definitions. Unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the "HIPAA Regulations" codified at Title 45 parts 160 through 164 of the United States Code of Federal Regulations, as amended from time to time.

2. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable HIPAA or FERPA Regulations

Data Fields in the LDS. **No direct identifiers such as names may be included in the Limited Data Set (LDS).** The researcher will also not name the organization in the doctoral project report that is published in Proquest. In preparing the LDS, Data Provider or designee shall include the **data fields specified as follows**, which are the minimum necessary to accomplish the research:

- ***Meningitis disease data in Africa January 2004 - December 2017***
  - Incidence (suspected cases, epidemics)
  - Deaths
  - Crude fatality rate
  - Alert and epidemic thresholds
  - Case confirmation from laboratories
  - Meningitis bacterial profile
  - Epidemic investigation reports
  - Meningitis control program reports
- ***MenAfriVac introduction in countries of meningitis belt January 2010 – December 2017***
  - Coverage (administrative and surveys: all levels: national, regional, peripheral)
  - Information on preparation, implementation, monitoring and evaluation
  - Adverse events following immunization and case management

Responsibilities of Data Recipient. Data Recipient agrees to:

a. Use or disclose the LDS only as permitted by this Agreement or as required by law;

b. Use appropriate safeguards to prevent use or disclosure of the LDS other than as permitted by this Agreement or required by law;

c. Report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or required by law;

d. Require any of its subcontractors or agents that receive or have access to the LDS to agree to the same restrictions and conditions on the use and/or disclosure of the LDS that apply to Data Recipient under this Agreement; and

e. Not use the information in the LDS to identify or contact the individuals who are data subjects.

3. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS for its research activities only.

4. Term and Termination.

a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

b. Termination by Data Recipient. Data Recipient may terminate this agreement at any time by notifying the Data Provider and returning or destroying the LDS.

c. Termination by Data Provider. Data Provider may terminate this agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

e. Effect of Termination. Sections 1, 4, 5, 6(e) and 7 of this Agreement shall survive any termination of this Agreement under subsections c or d.

5. Miscellaneous.

a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in section 6.

b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. Headings. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

DATA PROVIDER	**DATA RECIPIENT**
Signed: _____	Signed: _____
Print Name: RICHARD MIHGO FOUDA	Print Name: ANDRE ARSENE BITA
Print Title: IVD PROGRAMME COORDINATOR.	Print Title: Researcher: PhD student Public Health concentration in Epidemiology