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Nedghie Adrien Date: 4/21/2014

Evaluation of the Effectiveness of the PsA-TT conjugate vaccine MenAfriVac ™ against Probable Meningococcal Meningitis in 1-29 year olds in Burkina Faso, 2011-2013

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B.A., Tufts University, 2011

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An abstract of a thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

In partial fulfillment of the requirements for the degree of Master of Public Health in Global Epidemiology

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Abstract

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By Nedghie J. Adrien

Background: Explosive outbreaks of meningitis are an important public health threat to a region of Africa known as the "Meningitis Belt" [1, 2]. In order to address the specific needs of the African continent, eliminate epidemics and reduce the burden of disease, an affordable conjugate vaccine MenAfriVac™ was developed and introduced to Burkina Faso in 2010.

Methods: Using a case-control design (n = 1,736), this analysis assessed the vaccine effectiveness (VE) against probable meningococcal disease to determine potential indirect protection. Analyses were conducted using conditional logistic regression.

Results: There were 778 cases enrolled and matched by age and districts to 958 controls. Of those 778, 111 were classified as probable meningococcal cases. Following adjustments for independent risk factors, estimated VE was 38% (95%CI -41.0-73, p =0.25) for reported vaccination (including verified) and 57.0% (95%CI -5-82.3, p=0.06) for verified vaccination, excluding reported status.

Conclusions: Results from this analysis provide unpersuasive support for the current belief that the progressive introduction of the vaccine corresponds with the decrease in the number of reported meningitis cases [3]. Larger future studies are needed to provide a stronger argument on cross-protection from MenAfriVac™ against other serogroups of meningitis.

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Background

Epidemiology of bacterial meningitis

Meningitis is the inflammation of the membranes (meninges) and/or, of the cerebrospinal fluid (CSF) that surround the brain and spinal cord [4, 5]. Left untreated, the case-fatality rate can be as high as 70%. The incidence and case-fatality vary by region and patient demographics [4, 5]. There are several causes of meningitis, both infectious and non-infectious. The most common causes of bacterial meningitis beyond the newborn period are *Streptococcus pneumonia, Haemophilus influenza* type b (Hib), *and Neisseria meningitidis* [4, 5]. They account for 75% of all cases of bacterial meningitis in most studies, and 90% of bacterial meningitis in children [6]. In industrialized countries, meningitis due to Hib, formerly the most common cause of meningococcal disease, has been largely eliminated through immunization programs [6].

These respiratory pathogens spread person to person through contact with respiratory secretions. Close and prolonged intimate contact with an infected person, such as kissing or living in close quarters, facilitates the spread of disease. Following infection, the species colonize the mucosa of the nasopharynx and oropharynx, which is referred to as nasopharyngeal carriage. The colonized pathogens enter the blood and reach the meninges, causing meningitis. The incubation period ranges from 2 to 10 days. It is estimated that there are over 1.2 million cases of bacterial meningitis worldwide [4].

Neisseria meningitidis

Of the three most common pathogens responsible for bacterial meningitis, *Neisseria meningitidis* is the bacteria with the potential to cause large epidemics. The meningococcus is a Gram-negative, aerobic diplococcus [6]. *N. Meningitidis* organisms are surrounded by a polysaccharide capsule, which is used to classify the organism in 12 serogroups [4]. Half of those 12 serogroups cause the majority of infections: serogroups A, B, C, W135, X, and Y. The incidence rate of *N. meningitis* is historically highest in children under 5 years of age and adolescents. There is a large variety in the distribution of serogroup of *N. meningitidis* around with the world, with serogroups B and C being more common in the Americas and Europe, while

serogroup A is responsible for the majority of disease in Africa and Asia [5]. The emergence of other serogroups has been documented, such as the outbreak caused by serogroup W135 in 2002 in Burkina Faso [7].

Clinical presentation of disease and laboratory testing

Meningitis symptoms include fever and chills altered consciousness, nausea and vomiting, photophobia (sensitivity to light), severe headaches and neck stiffness [8]. Other symptoms may include bulging fontanels in infants, poor feeding or irritability and rapid breathing. Even with early diagnosis and proper treatment, the disease is fatal for 5-10% of patients in the first 24-48 hours following the onset of symptoms [6, 9]. In 10-20% of survivors, bacterial meningitis results in brain damage, hearing loss or a learning disability. Humans are the only known reservoirs of disease and about 5-10% of adults are asymptomatic meningococcal carriers [10]. The period of communicability lasts until there are no longer any live meningococci in discharges from the nose or mouth, which occurs within 24 hours of the establishment of an antimicrobial treatment to which the organisms are sensitive [6]. Susceptibility of disease decreases with age, which induces a high ratio of carriers to cases [6].

Laboratory-based meningococcal disease surveillance is the gold standard to assess the local epidemiology and disease burden [11]. In order to confirm the diagnosis of meningitis and identify the meningococcus, a lumbar puncture must be done following the clinical assessment, since most laboratory-based surveillance systems rely on cultures from cerebrospinal fluid [11]. In a potential case, the cerebrospinal fluid is usually turbid or purulent, but may be clear or bloody. Basic laboratory tests to determine the meningococcus, and exclude other causative pathogens such as pneumococcus, include [4, 12]:

1) High white blood cell count, typically greater than 1,000 cells/mm^3 (<3 in normal CSF), with greater than 60% polymorphonuclears;

2) Measurement of protein level: greater than 0.80 g/L. Protein levels should be less than 0.60 g/L in a normal CSF

3) Gram stain, showing negative Gram-stain diplococci.

Cases of *N. meningitidis* are further classified according to serogroup using three confirmatory tests: latex agglutination, Polymerase Chain Reaction (PCR) or after culture, by agglutination on colonies [4].

Meningitis in Sub-Saharan Africa

In 1963, Lapeysonnie described the African "meningitis belt" as an area stretching from Senegal to Ethiopia, where meningococcal epidemics constituted a public health problem [2]. However, during recent years, outbreaks of meningococcal disease have been reported in areas adjacent to the African "meningitis belt", as well as in eastern and southern Africa [13]. Lapeysonnie's findings detailed the striking seasonality of these outbreaks. The outbreaks began at the start of the dry season in December, peaked towards the end of the dry season and abated at the beginning of the rainy season in May-June [13-15]. Most countries in the African "meningitis belt" experience annual cycles of disease, with large outbreaks occurring every 8-12 years. The incidence rate of meningococcal disease in Africa is several folds higher than rates observed in developed countries. During explosive outbreaks, rates of disease can be as high as 1,000 cases per 100,000 can be observed, or 1% of the population [11]. During the 1996 epidemic season, there were approximately 25,000-recorded deaths and 250,000 cases, a case-fatality ratio of 10% [14, 16, 17]. Since then, two large epidemics resulting in 5,600 deaths were reported between 2003 and 2005 [17].

Outbreaks in this region are usually caused by *Neisseria meningitis* serogroup A, although outbreaks caused by serogroup C and more recently W135 have been documented [4, 6, 11, 18, 19]. In 2000, an epidemic of NmW135 meningococcal disease was associated with the Hajj pilgrimage to Mecca. In 2001, Burkina Faso and Niger were affected by a significant number of W135 cases and in 2002, a laboratory-based investigation documented the first large epidemic caused by W135 in Burkina Faso [20]. An analysis of cerebrospinal fluid samples collected in Niger from 2003 to 2006, found that approximately 67% of meningococcal meningitis cases were due to serogroup NmA, followed by NmX (26.2%), NmW135 (4.7%), NmY (0.4%) and NmC (0.1%), while no serogroup could be predicted in 1.9% of cases [21]. In 2006, more than 4000 cases of meningitis were reported in Niger and in an unprecedented occurrence, NmX accounted for 51% of the 1139

confirmed cases [22]. These numbers highlight that while serogroup A *Neisseria meningitidis* is responsible for the highest burden of disease, there is a documented rise in other serogroups across the Meningitis Belt.

Figure 1. The African Meningitis Belt

Prior control measures

Prior to the introduction of a new meningococcal A conjugate vaccine; there were three types of vaccines available for prevention of bacterial meningitis: bivalent (groups A and C), trivalent (A, C, W) or tetravalent (A, C, Y, W135) polysaccharide vaccines, outer membrane protein (OMP) and strain-specific group B vaccines, and meningococcal C conjugate vaccines. The tetravalent polysaccharide vaccines have only been used in the United States of America, Canada and Europe [8, 9]. The meningococcal conjugate vaccines against serogroups A, C, Y and W135 are marketed in industrialized countries, but are not affordable for most African countries [18].

In the African meningitis belt, the traditional control measures were mass vaccination campaigns with meningococcal purified polysaccharide vaccine implemented when an affected area reached a World Health Organization (WHO) recognized epidemic threshold [23]. This reactive vaccination approach, implemented since the late 1970s, can be effective in reducing mortality and morbidity when initiated early. However, despite the administration of millions of doses of polysaccharides vaccines, reactive vaccination has not reduced the frequency of epidemics [18, 24]. Meningococcal polysaccharide vaccines induce a short lasting immunity, do not induce immunological immunity and have very little effect on pharyngeal carriage, thus making them unable to reduce to transmission [25]. These limitations are overcome by conjugate vaccines and indicated a need for a conjugate vaccine specific to the needs of the African meningitis belt.

MenAfriVac ™

In order to respond to the specific needs of the African meningitis belt, the Meningitis Vaccine Project (MVP) was founded in 2001 with the mission to eliminate meningitis as a public health problem in Sub-Saharan Africa through the development, testing and widespread introduction of conjugate meningococcal vaccines. The Bill and Melinda Gates funded public-private collaboration between WHO and the Program for Appropriate Technology in Health (PATH) resulted in a monovalent serogroup A polysaccharide/tetanus toxoid conjugate vaccine (PsA-TT) [19]. The vaccine was manufactured by the Serum Institute of India and was

prequalified for use by the WHO in 2010 upon meeting the non-inferiority criteria to a reference polysaccharide vaccine, and based on its safety and immunogenicity [10, 26].

Following pre-qualification, the vaccine was pilot tested in the health district of Kaya, in Burkina Faso in September 2010. In December 2010, a nationwide campaign was launched and over 11 million people were vaccinated in 10 days [16]. Mass vaccination campaigns were also launched in Mali and Niger and a rollout plan has been implemented to progressively achieve mass vaccination coverage across the meningitis belt in the next 4 years [24, 27]. Initial reports following the introduction of PsA-TT in Burkina Faso suggest that the vaccine is highly effective at preventing invasive disease, reducing the incidence of serogroup A meningococcal disease by almost 100% [16] and a reduction in carriage [18]. There have been no reported cases of serogroup A meningococcal disease in vaccinated patients in the years following the introduction of the vaccine [24]. These preliminary results suggest that high vaccination coverage could greatly attenuate the burden of serogroup A meningococcal disease in the meningitis belt, although it should be noted that the vaccine was introduced during a season of low natural transmission [24, 27]. The initial success of the vaccine highlights important remaining challenges and gaps of knowledge in the control of epidemic meningitis in Africa. The primary objective of the research to fill these gaps of knowledge is to estimate field effectiveness of the vaccine against NmA. A secondary objective is determining if the vaccine is effective against all meningococcal disease, including other, non-NmA serogroups (cross-protection) [24]. Recently, the vaccine was approved for use in a controlled temperature chain (CTC), at temperatures up to 40°C for no more than 4 days after a campaign in Benin [28]. These findings expand the possibilities for new immunization strategies and highlight the need for field effectiveness estimates.

Introduction

For over 100 years, an area in the Sahel and sub-Sahel region of Africa, stretching from Senegal to Ethiopia, known as the "Meningitis Belt", has experienced large epidemics of bacterial meningitis [2]. Contrary to Europe or the United States, where only sporadic cases are observed, the large scale of these epidemics presents a serious public health problem. Approximately 430 million people are at risk to seasonal outbreaks, while explosive epidemics occur every 5-12 years [16]. From 1996-2010, over 800,000 cases were reported. Of those, 10% resulted in deaths and another 20% resulted in neurological sequelae [8].

Located within the aforementioned African "Meningitis Belt", Burkina Faso is a landlocked West African country with a population of about 17.8 million and is one of the few countries located entirely within the belt and has hyper endemic rates of disease. The country experiences annual outbreaks during the dry season and the ministry of health spends 2% of its annual health budget on response measures to the meningitis epidemics [7, 16, 29]. During the 2010 epidemic season, there were 22,831 cases reported, including 2,415 deaths, a case fatality ratio of 10.6%. Burkina Faso reported the greatest number of cases (6,145 including 863 deaths), followed by Nigeria and Chad. During the 2013 surveillance period, 18 of the 19 countries under active surveillance reported 9,249 suspected cases and 857 deaths, a case fatality ratio of 9.3% [8].

In the meningitis belt, *Neisseria meningiditis* serogroup A (NmA) has been responsible for most of the major epidemics, but outbreaks caused by serogroups W135 (NmW135) and X (NmX) have also been reported [18, 19]. In 2001, Burkina Faso and Niger were affected by an epidemic where NmW135 accounted for a significant number of the cases. In 2002, Burkina Faso reported the first large epidemic caused by W135 [20]. And although there has not been any evidence of serogroup replacement in Europe following the deployment of serogroup C meningococcal conjugate vaccines, the same cannot be assumed following the introduction of the serogroup A meningococcal conjugate vaccine, due to the vastly different environment in the African meningitis belt [24]. Across the meningitis belt, outbreaks caused by meningococci belonging to non-A serogroups meningococci continue to occur. The growing diversity of serogroups of meningococcal disease in Burkina Faso, and across the meningitis Belt, emphasize the complex nature of the disease burden in Africa and

the need to assess the effect of vaccines on the prevalence of different serogroups as well as all-cause meningococcal disease.

Since the late 1970s, traditional control measures have relied on reactive mass vaccination campaigns with meningococcal polysaccharide vaccine when incidence of cases reached WHO defined epidemic threshold [19, 24, 30]. When reactive polysaccharide vaccination campaigns have been deployed early in the course of an epidemic, they have proven effective at reducing mortality and mortality, but have not reduced the frequency of epidemics. Similar to other polysaccharide vaccines, the limited duration of immunity of the meningitis polysaccharide vaccines do not result in immunological memory, especially in children and small infants, nor affect nasopharyngeal carriage of meningococci and are thus unable to prevent transmission [7, 19, 24, 31]. Conjugate vaccines are likely to be a more appropriate tool for the effective prevention of epidemics because they induce immunological memory [19].

In 2010, MVP developed a meningococcal serogroup A polysaccharide/tetanus toxoid conjugate vaccine (PsA-TT) (MenAfriVac™) [16, 24]. The vaccine was manufactured by the Serum Institute of India and priced at $0.40 per dose. Results from clinical trials suggested that the vaccine is highly immunogenic in targeted age groups [32, 33]. A randomized clinical trial conducted in India (n=74) found an increase in SBA titters in males vaccinated with PsA-TT vaccine compared to comparison groups [32]. A Phase-II, observer-blind, randomized study found that the antibody persistence and the boost responses elicited by the vaccine were in accordance with features of conjugate vaccines, with no serious adverse events related to the study vaccine [26]. Like other polysaccharide-protein conjugate vaccines, MenAfriVac is expected to generate longer-lasting immunity, prime for immunologic memory, protect young children, and reduce carriage and disease in unvaccinated populations (herd immunity).

Fully licensed and implemented in December 2010, the vaccine has the potential to eliminate meningococcal disease epidemics as a public health problem in the African meningitis belt. The first mass vaccination campaign occurred in December 2010 in Burkina Faso, in persons aged 1-29 years following a pilot campaign in the health district of Kaya. Vaccine introduction has been followed by several studies designed to

establish the performance of the vaccine [33]. These studies include comparing pre- and post-introduction disease rates through population-based surveillance, surveys to compare pre- and post-introduction carriage and seroprevalence to demonstrate protection against transmission and acquisition of carriage, prevention effectiveness studies to assess the effect of the new vaccine on health costs and outcomes, and estimates of field effectiveness of the vaccine using a case-control design.

A national survey conducted in Burkina Faso estimated national coverage at 95.9%, with coverage documented by vaccination card estimated at 74.3% and by recall only at 21.6 %. The estimated coverage in all regions was estimated at >90% [34]. Initial surveillance results suggest that MenAfriVac™ has been highly effective at preventing serogroup A meningococcal disease [16, 24]. The incidence of suspected cases in Burkina Faso was reduced in all age groups, including those outside of the vaccination age range [24]. Following the introduction of the vaccine, there was a 71% decline in risk of meningitis and a 64% in risk of fatal disease. There was a 99.8% reduction in risk of meningococcal A meningitis [16]. No cases of serogroup A disease have been observed in the vaccinated population since vaccine introduction. High PsA-TT vaccination coverage rates in Burkina Faso have provided context for the observed reduction in meningitis serogroup A disease rates [16].

As MenAfriVac™ continues to be rolled out, further evaluation of its impact on carriage and field effectiveness are essential before it is proven to prevent epidemics of meningococcal disease in the African meningitis belt [35]. However, the almost-100% reduction in risk of meningococcal A meningitis [16] and NmA carriage [18] have made it difficult to assess the impact of MenAfriVac™ on nasopharyngeal carriage and its ability to induce herd immunity. In addition, MenAfriVac™ was licensed on the basis of immunogenicity and meeting the non-inferiority criteria to other *N. meningitidis* serogroup A conjugate vaccines, without randomized trials for vaccine efficacy [35]. And while there has been research analyzing national surveillance data to investigate the initial impact of the mass vaccination campaigns on the incidence of meningitis, there is little to no literature available on estimates of the field effectiveness of the vaccine. Because

vaccine licensures studies rely on short-term immunogenicity outcomes, disease surveillance and post licensure evaluations are necessary to inform immunization strategies [36].

Due to the inability to estimate the field effectiveness of this vaccine at reducing the risk of serogroup A meningococcal disease, this investigation will focus on estimating the field effectiveness of this novel conjugate vaccine against probable meningococcal meningitis disease, as defined by the WHO case classification criteria. Results from this investigation will contribute to determining the potential impact of the vaccine on all meningococcal disease in Burkina Faso and whether the vaccine may potentially offer indirect protection to vaccinated persons.

Methods

Data Collection

Original data collection was performed by the *Meningitis and Vaccine Preventable Diseases Branch* (MVPDB) of the *U.S Centers for Disease Control and Prevention* (CDC), and approved by the CDC Institutional Review Board (IRB). Informed consent was obtained from case patients > 18 years old and from parents/guardians for case patients < 18 years old. This study was done using de-identified data and was not required to obtain additional IRB approval.

Using a case-control design, data was obtained from case patients identified at health facilities in the surveillance areas. Surveillance officers monitored weekly counts and rates of meningococcal disease. Personnel traveled to districts where potential clusters were identified and attempted to enroll all suspected cases (as described below). Investigators presented potential case-patients with an introductory letter and consent form, which were read in French or the appropriate local language. Consent was requested from case patients (≥ 18 years of age) or parents/guardians (for case-patients < 18 years of age). Consent was obtained from the next-of-kin for deceased case-patients at least 18 years of age. The investigators obtained oral consent before proceeding with evaluation. Written consent from the participant's physician or the local IRB was required to review medical records.

Once consent was given, investigators administered a standardized questionnaire to either the case-patient (if aged ≥ 18 years old) or to a parent or guardian. The investigators obtained information on socio-demographics including household size/crowding, disease risk factors such as smoking, type of fuel used, preceding respiratory infection or recent contact with persons with meningitis, as well as history of receipt of meningococcal vaccinations, both the older polysaccharide and the newer conjugate A (MenAfriVac™) vaccines. In addition to administering questionnaires, evaluation personnel requested to review case-patients' vaccination card for evidence of meningococcal vaccination.

A case was defined as persons aged 1 to 29 years, residing in the surveillance area, with onset of illness between January 1 and June 30, 2011. Residence in the surveillance area was defined as living in the same area

(village/town) for at least three months before the onset of illness. Meningococcal cases were defined using the following WHO case definitions [4]:

Suspected meningitis case**:**

- Any person with sudden onset of fever (>38.5 C rectal or 38.0 C axillary) and one of the following signs: neck stiffness, altered consciousness or other meningeal signs.
- Any toddler with sudden onset of fever (>38.5 C rectal or 38.0 C axillary) and one of the following signs: neck stiffness, or flaccid neck, bulging fontanel, convulsion or other meningeal signs.

Probable meningitis case:

- Any suspected case with macroscopic aspect of its cerebrospinal fluid turbid, cloudy or purulent; or with microscopic test showing Gram negative diplococcus, Gram positive diplococcus, Gram negative coccobacillus: or with leucocytes counts more than 10 cells/mm^3

Probable meningococcal meningitis case:

- **Any suspected case with microscopic test showing Gram negative diplococcus**

Confirmed meningococcal meningitis case:

- Isolation of the causal pathogen *Neisseria meningitidis* from the cerebrospinal fluid sample of a suspected/probable case by Culture, Latex agglutination or PCR.

Confirmed cases were then further classified according to serogroup (A, W135, X, Y etc…) using slide agglutination, latex agglutination or PCR with a specific target. For the purposes of this analysis, only the probable meningococcal meningitis case definition was used. Controls were frequency matched to cases by age and district. Control enrollment took place after sufficient case ascertainment, to streamline the frequency matching process. The age distribution of cases (within fixed age groups) was summarized and controls were recruited to match the age group distribution of the cases (1-4; 5-14; 15-29). Exposure of interest was defined as the receipt of the meningococcal serogroup A conjugate vaccine, MenAfriVac™. Vaccination status was categorized and defined as follows:

Confirmed vaccinated

- The participant had written documentation showing the receipt of MenAfriVac™ during the 2010 vaccination campaign (i.e. vaccination card)

Reported vaccinated

- The participant provided verbal history but is unable to present written documentation showing receipt of MenAfriVac™ during the 2010 vaccination campaign

Unvaccinated

- The participant reports not receiving the vaccine or receiving the vaccine less than 10 days before the onset of illness.

Statistical Analyses

Crude vaccine effectiveness was calculated using conditional logistic regression with the SAS logistic procedure (version 9.3, SAS Institute, Cary, NC). Vaccine effectiveness was calculated as (1- OR)*100% [37]. The adjusted vaccine effectiveness (aVE) and 95% confidence intervals were obtained after assessing the effect of potential confounding risk factors by multivariate conditional logistic regression analyses. Based on current literature and current data available on effectiveness studies of similar vaccines, lack of education, previous respiratory illness, household crowding (assessed as sharing a room in this analysis), and contact with a known meningitis case were assessed as potential confounders. Other variables such as sex and occupation were also assessed as potential confounders. A backwards elimination variable selection process was used to derive the most descriptive multivariable model. The model was stratified on age categories and district to account for the matching during the study implementation and data collection. A *p*-value of 0.05 was used to evaluate statistical significance.

VE analyses were limited to examining vaccine effectiveness for cases classified as suspected and probable meningococcal meningitis cases. Analyses were performed using two different scenarios to assess vaccination status: (1) classifying those with vaccination cards as truly vaccinated and excluding those who reported vaccination but had no vaccination cards; (2) accepting the reported vaccinated status and only classifying as unvaccinated those who were truly unvaccinated.

Results

During the study period from 2011-2013, 778 cases and 958 matched controls were enrolled. Since the vaccine was indicated for persons 1-29, cases and controls that were younger than 1 year of age or older than 30 were removed from the analysis. Of those 778 cases, 394 cases were classified as suspected cases, 301 probable bacterial meningitis cases, and 136 probable meningococcal cases, using WHO case definitions [Table 1,2]. The median age of the suspected cases was 9 years, 55% were male, 70% had no formal education, 87% were skilled laborers and 85% either reported or had verified receipt of MenAfriVac™. Very few reported having received the older meningococcal polysaccharide vaccine (16.7%). Among the probable meningococcal cases, 59% were male, 70% had no formal education, 87% were skilled laborers and 88% either reported or had verified receipt of MenAfriVac™. Their median age was 8 years old and similarly to the suspected cases, few reported previous meningitis vaccination (16.2%). The controls (n=945) were and they were less likely to be male (49%), about slightly less likely to be a skilled laborer (84%) and more likely to have a formal education. About 61% of the controls reported no formal education compared to 70% among both suspected and probable cases. There was also high reported vaccination coverage among the controls, about 90% when including both reported or verified receipt of the vaccine [Table 1].

Preliminary laboratory results from the CSF samples indicated that there were 58 *Streptococcus pneumoniae*, 2 Hib and 111 *Neisseria meningitidis* pathogens [Table 2,3]. The *N. meningitidis* pathogens were predominantly NmW135 (78.4%), with 23 NmX (20.7%) samples and 1 (0.9%) non-determined serogroup [Table 3]. As expected there were no NmA confirmed cases. The overall proportion of all confirmed meningitis cases was 22% (171 of 778). Confirmed *N. meningitidis cases* represented 65% of all confirmed meningitis cases, and 14% of all enrolled cases subjects (111 of 778). Due to a high proportion of "missing" or "in process" PCR results these data were not analyzed.

Vaccine effectiveness was estimated by univariate and conditional logistic regression analysis using the two scenarios indicated above to define vaccination status. The data from probable meningococcal cases were the only data analyzed. Univariate VE against probable meningococcal meningitis disease was 59.0% (95% CI

11-81, p =0.02) for persons with verified vaccination status (scenario 1) and 51.0% (95% CI 3-75, p =0.04) for persons with both verified and reported vaccination status (scenario 2) [Table 4].

Following adjustment for risk factors, the estimated VE against probable cases was 38% (95%CI -41-73, p =0.25) for reported vaccination (including verified) [Table 5] and 57.0% (95%CI -5-82.3, p=0.06) for verified vaccination, excluding reported status [Table 6]. The estimated VE for the probable cases was not statistically significant at α=0.05. Sex, lack of education, sharing a room with more than 4 persons and prior contact with a meningitis case were statistically significant independent risk factors.

Discussion

There was no statistically significant reduction in risk of probable meningococcal disease at $\alpha = 0.05$. Adjusted VE estimates for the verified vaccinated group was 57.0%% (95%CI: -5-82.3) and 38% (95% CI: -41-73) for all vaccinated (reported and verified persons). A near 60% reduction in disease for the verified vaccinated group is clinically significant and may provide timid, albeit unpersuasive, support for the current belief that the progressive introduction of the vaccine corresponds with the decrease in the number of reported non serogroup A meningococcal meningitis cases [3]. However, the progressive introduction of MenAfriVac™ has corresponded to the elimination of serogroup A among the 152 million individuals that have received this vaccine in 12 countries to date [16, 41].

Previous studies evaluations have determined that the vaccine has almost completely reduced the risk of serogroup A disease [16] and significantly reduced carriage of NmA [38]. Results from this analysis support previous research on the disappearance of NmA cases since vaccine introduction. Of the 111 confirmed *Neisseria meningitidis* samples, none (0) were classified as NmA. The vast majority were NmW135 (78.4%) pathogens, highlighting the need to investigate possible serogroup replacement [24].

To our knowledge, this is the first vaccine effectiveness study examining the potential of indirect protection by MenAfriVac™ against all meningococcal disease. The primary objective of vaccine effectiveness studies is to obtain field estimates of the effect of the vaccine on the targeted disease. Due to the absence of serogroup A case, the analysis was unable to address this objective since vaccine effectiveness cannot be assessed with low or zero prevalence of the disease of interest. Therefore these analyses focused on attempting to estimate vaccine effectiveness in reducing the risk of all meningococcal meningitis disease; and determine whether the vaccine potentially offers indirect protection for other causes of bacterial meningitis or other serogroups (non NmA).

At the time of this analysis, PCR results for several cases were still pending which limited the ability to examine vaccine effectiveness for confirmed *Neisseria meningitidis* cases. This delay in obtaining final results from confirmatory laboratory tests limited the ability to estimate indirect protection against confirmed

meningococcal cases. However, it is expected that results of a VE study against confirmed meningococcal cases would produce similar results. A full model- adjusting for sex, education level, occupation, prior contact to a case, previous disease and household crowding- preliminary analysis of confirmed pathogens available at the time of this study resulted in a VE of 50.6% (95% CI -25.9-80.6, $p = 0.14$) [analysis not shown]. Again results from the analysis were not statistically significant at $\alpha = 0.05$, but hint at the clinical significance of the vaccine in the overall reduction of disease.

Furthermore, field estimates can be realistically assessed through epidemiological means, without laboratory support. Assessment without laboratory support proves useful when the vaccine coverage is high and there will be more cases occurring in vaccinated persons, despite high vaccine efficacy [39]. Due to the high vaccination coverage in Burkina Faso, this epidemiological assessment without laboratory support is appropriate [34].

Another potential limitation of this analysis is the relatively low incidence of disease and low sample size. Due to the cyclical nature of the outbreaks, these data were collected during a low disease season. Vaccine effectiveness should be measured when both vaccinated and non-vaccinated have an equal chance of exposure to the disease. This is most likely to occur during periods of high disease rates [39]. Since outbreaks occur every 8-12 years, data collection should continue and this analysis should be repeated [11, 38].

Successful epidemiological assessment of vaccine effectiveness requires a uniform and specific case definition. While the case definition used for this analysis was more sensitive, it is consistent with WHO guidelines and is often used in the African “meningitis belt” due to low PCR capabilities and high meningitis burden. Strengths of this study include matching and stratification by possible confounding variables, age and location [40]. The risk factors identified were consistent with previous vaccine effectiveness studies’ findings [23].

MenAfriVac™ is providing a new solution to meningitis as a public health problem in Africa. It has the potential to eliminate epidemics of meningitis in the region. Less than 5 years after introduction of the vaccine,

serogroup A disease has virtually disappeared from the population. The overwhelming success of the vaccine has also limited the ability to assess its effectiveness against NmA meningitis. Due to the lack of NmA disease, this analysis investigated whether the vaccine may have a potential impact on all meningococcal disease. These results suggest that the introduction of the vaccine may have reduced the prevalence of overall meningococcal disease but were unable to provide a persuasive argument due to sample size restrictions. These results also supported the disappearance of NmA cases. This analysis should be repeated with laboratory confirmed cases and during a period of high disease incidence. These preliminary results support the beneficial impact of MenAfriVac™ on all meningococcal disease. These results also support the mass vaccination campaigns as a control measure for meningitis and reinforce the need to incorporate MenAfriVac™ in routine immunization.

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Table 1. Baseline characteristics of cases and controls, Burkina Faso, 2011-2013 (n = 1,736),

	n (%)		
	Suspected Cases (n=394)	**Probable cases[a] (n=136)**	**Controls (n=945)**
Age, years			
1-4	50 (12.7)	20 (14.7)	247 (26.1)
5-14	263 (66.8)	98 (72.1)	603 (63.8)
15-29	81 (20.6)	18 (13.2)	95 (10.1)
Median age in years (interquartile range)	9 (6-13)	8 (5-12)	7 (4-12)
Sex			
Female	176 (44.7)	55 (40.4)	477 (50.9)
Male	218 (55.3)	81 (59.6)	460 (49.1)
District			
Banfora	49 (12.4)	17 (12.5)	122 (12.9)
Sindou	41 (10.4)	21 (15.4)	185 (19.6)
Koupéla	26 (6.6)	9 (6.6)	97 (10.3)
Sapouy	16 (4.1)	11 (8.1)	10 (1.1)
Tenkodogo	33 (8.4)	3 (2.2)	79 (8.4)
Kaya	22 (5.6)	11 (8.1)	35 (3.7)
Kongoussi	22 (5.6)	5 (3.7)	70 (7.4)
Koudougou	36 (9..1)	2 (1.5)	48 (5.1)
Dafra	97 (24.6)	35 (25.7)	190 (20.1)
Dô	52 (13.2)	22 (16.2)	109 (11.5)
Education			
None	275 (70.0)	95 (70.4)	578 (61.4)
Primary	78 (19.9)	24 (17.8)	243 (25.8)
Secondary	37 (9.4)	16 (11.9)	110 (11.7)
University	3 (0.8)	0	10 (1.1)
Occupation			
Student	4 (1.0)	0	2 (0.2)
Professional	24 (6.2)	6 (5.5)	64 (6.9)
Skilled Labor/Non Professional	333 (86.5)	95 (87.2)	782 (83.8)
Unemployed	24 (6.2)	8 (7.3)	85 (9.1)
Vaccination Status			
Previous meningitis vaccination	49 (16.7)	17 (16.2)	81 (9.9)
MenAfrivac[b]	298 (85.4)	108 (87.8)	804 (90.3)
Reported MenAfriVac[c]	167 (50.0)	63 (52.5)	355 (40.5)
Verified MenAfrivac[d]	117 (34.9)	42 (35.0)	436 (49.7)
Unvaccinated	51 (15.2)	15 (12.5)	86 (9.8)

[a] Probable meningococcal meningitis cases
[b] Includes verified and reported MenAfriVac vaccination status
[c] Reported vaccination included persons who recalled receiving vaccine but had no proof of vaccination
[d] Verified vaccination included persons who recalled receiving the MenAfriVac vaccine and had proof of vaccination

Table 2. Classification of meningitis disease cases; Burkina Faso 2011-2013

Case classification	n (%)
Cases[a]	778 (44.8)
Controls	958 (56.2)
Suspected cases†	399 (51.3)
Probable meningitis cases†	301 (38.7)
Probable meningococcal meningitis cases†	136 (17.5)
Confirmed *Neisseria meningitidis* cases †	111 (14.3)

[a] Persons identified as potential cases during original surveillance and case ascertainment
† Percentage of cases from total cases (n=778)

Table 3. Laboratory classification of identified pathogens ; Burkina Faso 2011-2013

Lab classification	n (%)
S. pneumoniae [a]	58 (26.6)
Hib [a]	2 (0.9)
Neisseria meningitidis[a]	111 (50.9)
NmA	0
NmC	0
NmW135[b]	87 (78.4)
NmX[b]	23 (20.7)
NmY	0
Nm nongrouped[b]	1 (0.9)

[a] Percentage of identified pathogens from laboratory testing (n = 218)

[b] Percentage of *Neisseria meningitidis*

Table 4. Univariate associations of independent disease risk factors and disease status in probable meningococcal meningitis disease cases; stratified on categorized age* and districts, Burkina Faso 2011-2013 (n=136)

Variable	Odds Ratio	95% CI		*p*
Male	1.53	1.05	2.22	0.03
Education[a]	0.53	0.35	0.81	<0.01
Occupation[b]	1.17	0.60	2.31	0.65
Previous respiratory illness[c]	1.15	0.75	1.78	0.52
Flu-like symptoms[c]	1.31	0.89	1.92	0.17
Prior meningitis disease[c]	3.11	0.95	10.23	0.06
Contact with ill person in month before illness	5.48	2.26	13.31	0.0002
Sharing a room[d]	1.72	1.17	2.52	<0.01
All MenAfriVac vaccination[e]	0.49	0.25	0.97	0.04
Verified MenAfrivac[f]	0.41	0.19	0.89	0.02

*Age categories (1-4, 5-14, 15-29, 30+)

[a]No education was treated as the reference group. The comparison is between any education or none

[b]Comparison between employed (professional, non-professional) and unemployed (including students) (reference)

[c]No previous illness was treated as the reference group

[d]Sharing a room with less than 4 persons was treated as the reference

[e]Includes verified and reported MenAfrivac vaccination status

[f]Reported vaccinated considered missing

Table 5. Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI) of MenAfriVac against probable meningococcal meningitis disease, in a case-control from multivariate analysis, Burkina Faso 2011-2013

Variables	Unadjusted Model	Full Model	Final Model [a]
Main Exposure			
All MenAfriVac	0.49 (0.25-0.97) *	0.62 (0.27-1.41)	0.62 (0.27-1.41)
Demographic Variables			
Sex			
Female	---	---	---
Male		1.57 (0.98-2.50)	1.57 (0.98-2.50)
Education			
None	---	---	---
Any		0.73 (0.44-1.20)	0.73 (0.44-1.20)
Occupation			
Employed		1.88 (0.71-4.93)	1.88 (0.71-4.93)
Unemployed	---	---	---
Health			
Previous meningitis disease		2.38 (0.57-10.02)	2.38 (0.57-10.02)
Contact with sick person		8.83 (2.98-26.20) ***	8.83 (2.98-26.20) ***
Household crowding		2.03 (1.26-3.27) **	2.03 (1.26-3.27) **

* *p <0.05*

** *p <0.001*
*** *p <0.0001*
[a] The final model was the full model and included vaccination status, sex, education, occupation, prior disease, contact with a known case and household crowding

Table 6. Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI) of Verified receipt MenAfriVac against probable meningococcal meningitis disease, in a case-control from multivariate analysis, Burkina Faso 2011-2013

Variables	Unadjusted Model	Full Model	Final Model [a]
Main Exposure			
Verified MenAfriVac	0.41 (0.18-0.93)*	0.52 (0.20-1.37)	0.43 (0.18-1.05)
Demographic Variables			
Sex			
Female		---	---
Male		0.58 (0.29-1.18)	0.54 (0.27-1.09)
Education			
None		---	---
Any		0.73 (0.33-1.61)	0.69 (0.31-1.50)
Occupation			
Employed		3.57 (0.45-28.68)	1.74 (0.37-8.22)
Unemployed		---	---
Health			
Previous meningitis disease		<0.001	
Contact with sick person		5.75 (1.40-23.61)*	4.47 (1.19-16.85)*
Household crowding		2.03 (0.99-4.17)	1.82 (0.91-3.64)

* *p <0.05*

** *p <0.001*

*** *p <0.0001*

[a] Final model adjusted for vaccination status, sex, education, occupation, previous contact with a sick person and household crowding.

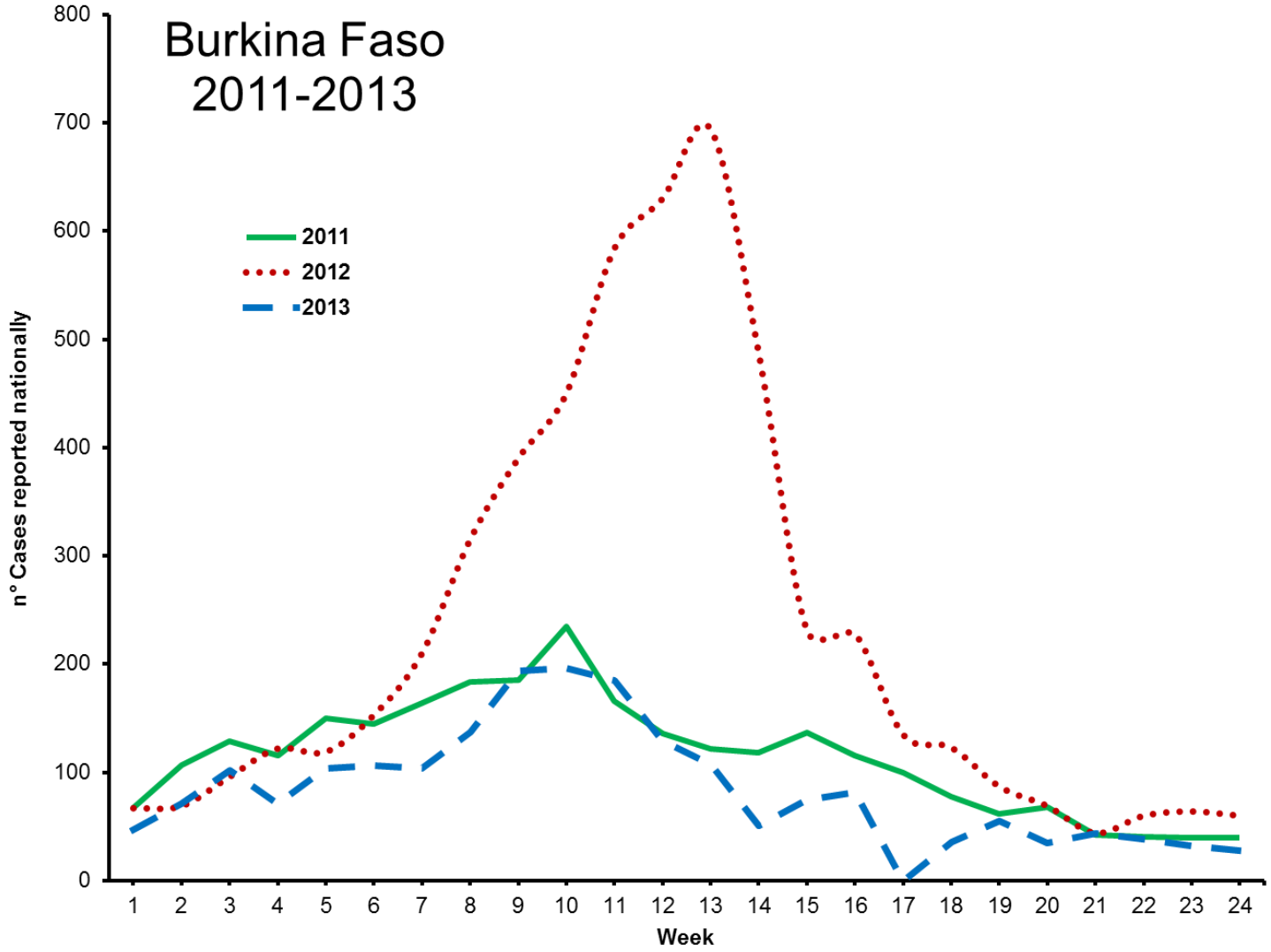

Figure 2. Weekly incidence (week 1-24) of meningitis in Burkina Faso reported to WHO *Meningitis Weekly Bulletin*, 2011-2013