Review Article

Meningococcal Meningitis in Sub-Saharan Africa: A Review

ABSTRACT

The scourge of Meningococcal Meningitis in the Sub-Saharan African nations is well known. This review paper focuses on this very important topic and describes the symptoms, diagnoses, and available vaccines for the same. The review then focuses on the Meningitis Belt of Africa and elucidates on the introduction of MenAfriVac™ vaccine. The review ends with the success of this vaccine and the future of Meningococcal Meningitis in the context of overall global climate change.

Keywords: Meningococcal Meningitis, MenAfriVac™, Sub-Saharan Africa, Meningitis Belt, Climate Change

1. INTRODUCTION

This review paper focuses on the important topic of meningococcal meningitis in the meningitis belt of Sub-Saharan Africa. There are three forms of meningitis: bacterial, viral, and fungal, and meningococcal meningitis is the only bacterial form that can cause an epidemic (1). It is a very serious condition of the meninges, which is the thin lining surrounding the brain and spinal cord (2). Different bacteria can cause meningitis; however, throughout the world, *Nisseria meningitides* is the leading cause of bacterial meningitis (3). It is a Gram-negative coccus usually occurring in pairs. There are 12 serogroups associated with meningitis infections. The serogroups are based on the chemical structure and composition of the capsular polysaccharide (4, 5). The organisms from the serogroups A, B, C, X, Y, and W-135 account for majority of the infections in the world (3).

The transmission of meningitis is through person to person contact and there is no animal reservoir for this disease (6). Kissing, coughing, sneezing, living and sleeping in closed and crowded environments, sharing and eating from common utensils can also aid the transmission of meningococcal meningitis. The average incubation period is four days; however, this period can range from two to 10 days. At any given point of time, approximately 10 to 20% of the human population carries the *Nisseria Meningitidis* in their throat but it gets more activated during high epidemic periods.

The typical symptoms of this infection are stiff neck, high fever, visual impairment, seizures, motor deficits, confusion, headaches, vomiting, and phobia of the light (7). Patients succumb to this infection usually 24 to 48 hours of the onset of symptoms. Typically, 5-10% of the infected people die even after a timely diagnosis and early administration of medications. Also, in patients who survive the infection, the infection can cause serious brain damage resulting in cognitive impairment, permanent hearing loss, tissue necrosis resulting in limb loss (6). This infection can also cause *Meningococcal Septicaemia*, resulting in hemorrhagic rash and collapse of the circulation system resulting in a certain death (2).

The diagnosis of meningococcal meningitis is through clinical examination and usually involves a lumbar puncture of the spine. If the spinal fluid is purulent then it is indicative of an infection. Diagnosis is confirmed by growing the bacteria (acculturation) as it helps in the identification of the sero-group of the organism responsible for the infection and aids effective treatment. The drugs of choice that are used for the treatment of meningococcal meningitis are penicillin, ampicillin, chloramphenicol, and ceftriaxone. However, it is important to mention that penicillin in no longer effective in treating this infection in many parts of the world.

Vaccinations are available for meningitis and the following are the different types of vaccines presently available globally (2). These are as follows:

- Polysaccharide vaccines: Bivalent (Groups A & C), Trivalent (A, C, & W), and Tetravalent (A, C, Y, & W)
- M. conjugate vaccines for Group C
- Tetravalent A, C, Y & W conjugate vaccine
- MenA Conjugate vaccine for A (MenAfriVac)

It is difficult to prepare vaccine for the sero-group B due to antigen mimicry with polysaccharide in the neurological tissues.

2. THE MENINGITIS BELT

Albeit meningococcal meningitis is a major public health concern globally, certain nations in the Sub-Saharan part of the African continent bear the scourge of this deadly bacterial infection. The Meningitis belt, as defined by the French military physician Lapeyssonnie in 1963, encompasses nations from Senegal in West Africa to Ethiopia in the east (8). The ten countries that were initially part of this belt were Benin, Burkina Faso, Cameroon, the Central African Republic, Chad, Ghana, Niger, Nigeria, Sudan, and Togo. Five more countries were added to this belt in 1987 (9, 10). These were Ethiopia, The Gambia, Guinea, Mali, and Senegal. Figure 1 highlights the nations that comprise the Meningitis belt.

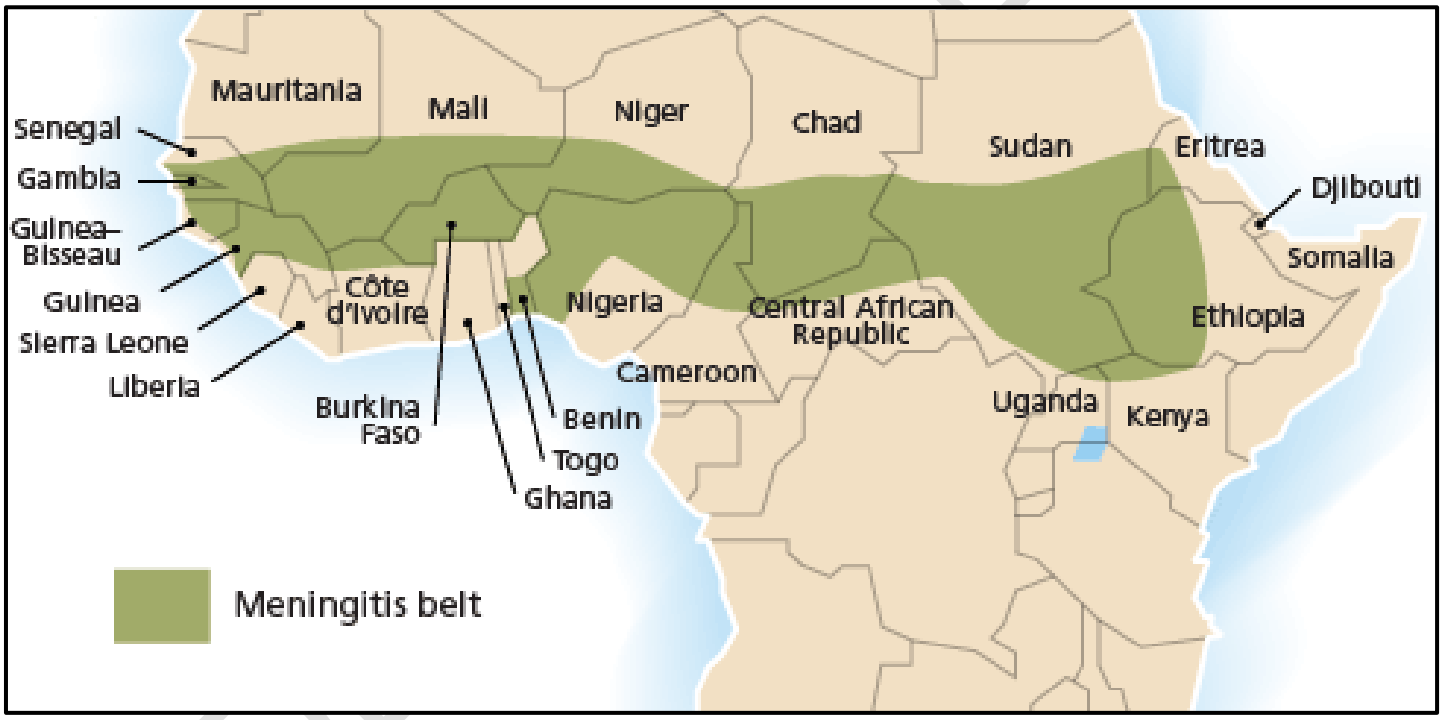

Figure 1: Meningitis Belt Countries in Sub-Saharan Africa

{**Source:** Control of Epidemic Meningococcal Disease, WHO practical guidelines, World Health Organization, 1998, 2nd edition, WHO/EMC/BAC/98.3, Accessed at http://www.meningvax.org/epidemics-africa.php, on April 12, 2016 [11]}

The meningitis belt is unique in that it encompasses the region that falls within the isohyets of 300 mm in the north and 1100 mm in the south (10). An isohyet is a line on the map that runs through areas that receive the same amount of rainfall. Some of the countries in this region are also known as the Sahelian nations of Africa and it stretches from Senegal, Mali, Burkina Faso, Niger, Nigeria, Chad, and Sudan (12). To the north of the Sahel is the Sahara Desert and to the south is the humid Savannah region. The climatic patterns of the Sahelian nations are typically semi-arid.

The meningitis belt has been experiencing meningitis epidemics usually at a five to 10- year interval throughout the 20th century (10). However, in the recent past the periodicity of the epidemic is becoming very irregular. Also, nations in this belt experience varying degrees and magnitudes of the epidemic. An epidemic threshold is crossed when a weekly attack rate of more than 15 cases per 100,000 people occurs (13). The attack rate during such epidemic is usually 400-

500/100,000 population (3) and the incidence can approach up to 1000 per 100,000 (14). 80- 85% of all the meningitis in this region could be attributed to Group A meningococcus (2). The decades of 80s and 90s in the previous century recorded high incidence rates in the meningitis Belt. There were approximately 704,000 cases reported between 1986 and 1997 and approximately 14% succumbed to their infection (15).

It is prudent to mention here that these statistics might not portray the actual ground realities. Many patients die before they even reach the health care center, and such cases almost always go unreported (15). This suggests that the actual burden of the disease is very likely underestimated. Meningococcal meningitis causes a huge financial strain on the public health systems of many low and middle-income countries in Sub-Saharan Africa. Conservative estimates suggest that approximately 430 million people are at risk of meningitis epidemic (11).

2.1 Weather Pattern Associated with Epidemics in the Meningitis Belt

The typical meningitis epidemic lasts during the dry season from December to June. The epidemic period peaks in February and dies out when the first rains lash the nations around June. There are many factors that contribute toward the meningitis epidemic. Low levels of absolute humidity (less than 10%), high day time temperatures, cold nights when the mercury drops below 50 ºF, and extremely windy conditions aggravate the conditions that are ripe for an epidemic. The dust laden *Harmatan* winds that blow from the Sahara Desert have the potential to irritate and damage the mucosal membranes thereby reducing the defense mechanisms of the body (5). Also, long drought spells can also aid the transmission of the Meningococci A (16). This results in a high exposure rate to the various meningococci groups. It has also been documented that the bacterial colonies are very high in air during the dry season (5, 17).

2.2 Socio-Economic Factors

Socio-economic factors in these low-income countries should also be accounted for while discussing this infection. During the cold wintry nights, family members tend to sleep indoors in crowded conditions. Also, this region experiences crowded conditions especially during the congregation of huge number of people at village markets. Tribal pilgrimages and movement of people within nations could contribute to epidemics (5). In addition, majority of the people in the Sahel nations profess the Islamic faith. The annual Hajj and Umrah pilgrimage results in hundreds of thousands of low-income people, who cannot afford expensive air fares, traversing the Sahelian nations to visit Mecca in Saudi Arabia via Sudan or Egypt (18, 5). In the past, various Sero-groups of meningitis were introduced by the pilgrims in their communities after their return from Mecca- a holy place which is visited by Muslims from almost all the nations of the world (18). Finally, the immunological susceptibility of the population in question also contributes toward the manifestation of epidemics (15). Figure 2 below shows the nations in Africa that are now at a high risk of meningitis epidemic. These nations are Democratic Republic of Congo, Kenya, Rwanda, Eritrea, Cote d'Ivoire, Uganda, Tanzania, and Burundi.

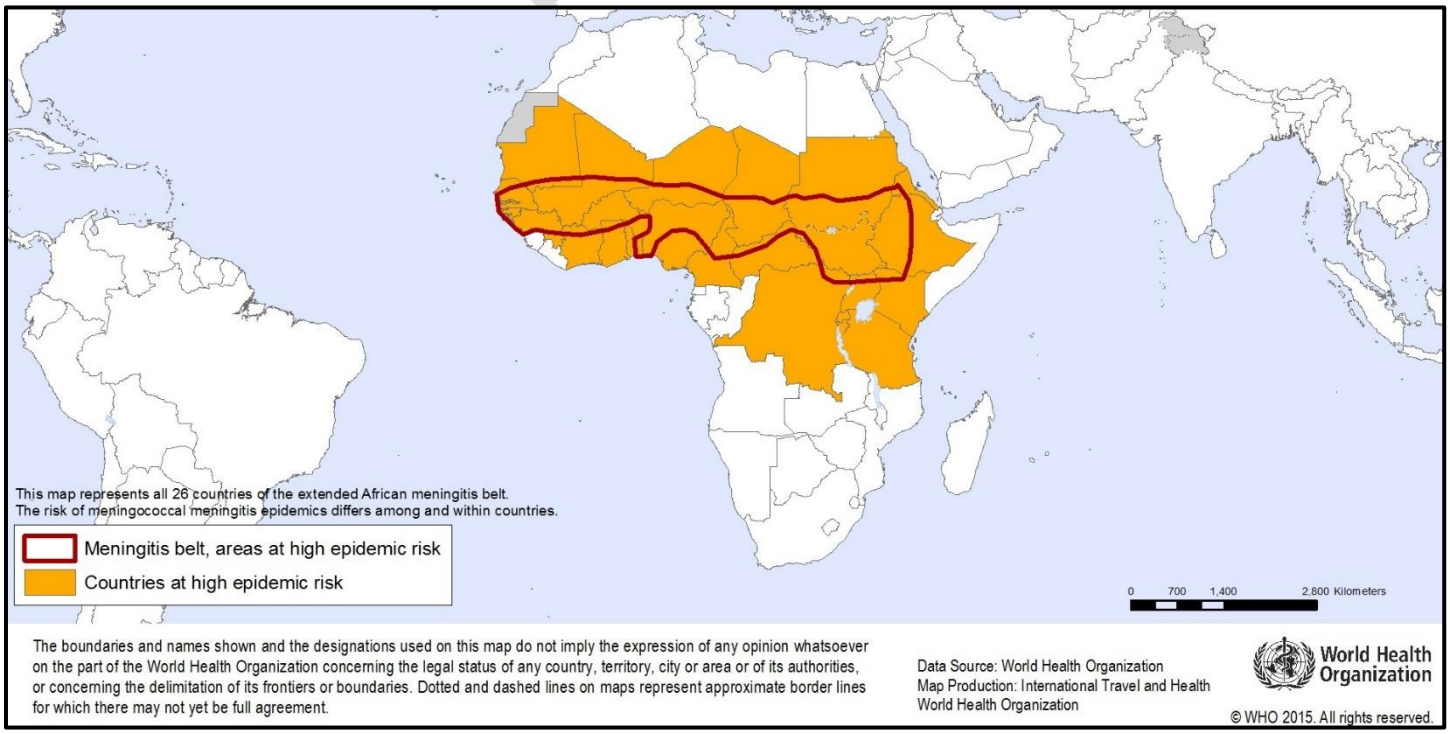

Figure 2: Twenty-six countries at high risk for Meningococcal Meningitis in 2014

Source: WHO, 2015, Accessed at http://www.who.int/csr/disease/meningococcal/en/ on April 12, 2016 [1]

Meningitis disability-adjusted life years (DALYs) as a percentage of total DALYs for the meningitis belt nations, as defined by researchers in the past (8, 9) are shown in Table 1(19). The DALYs correspond to both the sexes and all age groups for the year 2000, 2010, and 2010. The DALYs for meningitis as a percentage of total DALYs was the highest for Niger at 6.89 and lowest for Nigeria at 1.66 at Central African Republic for the 2000. The percentages were also high for Benin (3.69%) and Burkina Faso (3.61%). In contrast, the meningitis DALYs for all the nations of Sub-Saharan Africa was 2.41% and globally it was 1.1% in the year 2000. These findings suggest that the African meningitis belt nations shoulder a huge burden for meningitis with severe implications in terms of health and other economic factors. The DALYs have reduced considerably in 2010 and in 2019. The reasoning behind this is explained later in the manuscript.

Table 1: Meningitis DALYs as a percentage of total DALYs for the African Meningitis Belt Nations.
Source: vizhub.healthdata.org/gbd-compare, Accessed on March 20, 2022. [19]

Country/Region	**% of Total DALYs**		
Meningitis Belt Countries as per Lapeyssonnie, 1963	**2000**	**2010**	**2019**
Benin	3.69	3.34	2.27
Burkina Faso	3.61	3.86	2.77
Cameroon	1.8	1.97	1.41
Central African Republic	1.66	1.96	1.46
Chad	3.07	3.26	3.12
Ghana	2.5	2.15	1.62
Niger	6.89	5.37	4.09
Nigeria	3.28	3.46	3.04
South Sudan*	2.83	3.21	2.96
Togo	2.1	1.67	1.12
Additional Countries as per Greenwood et al. 1987			
Ethiopia	2.69	2.67	1.95
The Gambia	2.39	1.8	1.57
Guinea	3.07	3.26	3.3
Mali	3.94	4.02	3.22
Senegal	2.74	2.55	1.75
Sub-Saharan Africa	2.41	2.44	2.04
Global	1.1	0.94	0.64

Note: *South Sudan was partitioned from the nation of Sudan in 2011. Prior to her independence, almost all cases of meningococcal meningitis occurred in South Sudan which was then southern part of the erstwhile united Sudan. Hence DALYs for the year 2013 and 2019 are only reported here.

3. MENAFRIVAC™

MenAfriVac™, a monovalent serogroup A conjugate (PsA-TT) vaccine, was the fructification of the joint public/private partnership between various Africa Health Ministries, the World Health Organization, The Bill & Melinda Gates Foundation, Program for Appropriate Technology in Health (PATH), and the Serum Institute of India (SIIT) (20). The crippling and devastating epidemics of 1996-97, with approximately 200,000 cases and almost one tenth of them succumbing to the infection, spearheaded a movement led by the various African nations to finally develop a vaccine for this scourge. Plans to get the meningitis belt rid of the epidemics associated with the Neisseria Meningitis Serogroup A were thus conceived. Under the auspices of the 'Meningitis Vaccine Project', and a generous grant of $ 70 million from the Bill & Melinda Gates Foundation, project plans were conceived to develop, test, license, and introduce a conjugate Meningococcal A vaccine.

Right at the very onset it was obvious that pharmaceutical giants would not be interested in developing a vaccine from which the profits would be marginal or almost negligible (21). Also, it was crucial to develop a vaccine that would cost less than 50 cent each as anything expensive would not be affordable by the resource challenged African meningitis belt

nations, whose public health budgets were already overstretched fighting other epidemic infections such as malaria, TB, and HIV/AIDS.

3.1 Challenges Associated with the Development of MenAfriVac™

In addition, there were many challenges associated with the development of the vaccine (5). The idea of developing a polysaccharide vaccine was ruled out due to poor infrastructure and the non-accessibility of many rural areas that could be reached only by foot. Polysaccharide vaccines usually need to be stored under cold conditions and exposure to room temperature is limited to only three hours. This posed a major hindrance as many human settlements were spread across the length and breadth of any country. Also, polysaccharide vaccines were not effective in children under two years of age and it imparted immunity for two to three years resulting in the population being vulnerable to various other serogroups.

Therefore, it was decided instead to develop a conjugate vaccine. There are many advantages of conjugate vaccine compared to polysaccharide vaccine. First, conjugate vaccines reduce the carriage capacity of the bacteria in the throat. They also induce herd immunity in the community and induce high immunity (up to 20 times more than the polysaccharide vaccine). Finally, it also induces T-cell memory compared to polysaccharide vaccines (13).

3.2 Development of MenAfriVac™

The development of this vaccine was a glowing example of a synergistic relationship that was established between various stakeholders of both the developed and developing nations (20). These stakeholders came on a common platform to develop a vaccine for low-income nations of Sub-Saharan Africa. Vaccine grade meningococcal group A polysaccharide was sourced from SynCo - Bio Partners BV in Amsterdam, the Netherlands. Tetanus toxoid was sourced from the Serum Institute of India and the high efficiency conjugation technology was developed at the Laboratory of Bacterial Polysaccharides, Center for Biologics Evaluation & Research (CBER/FDA), in Bethesda, Maryland. The technology to develop the vaccine was transferred to the Serum Institute of India.

The clinical trials for the vaccine were conducted in India and Mali. In 2009, the vaccine was approved by the Drug Controller of India and in 2010, the WHO prequalified the vaccine (21). The greenlight from the WHO opened the door for the introduction of the vaccine. Burkina Faso was the first nation in the meningitis belt to introduce/administer the MenAfriVac™ vaccine. By the end of December 2010, approximately 11 million Burkinabe people were vaccinated. The efforts by the then President of Burkina Faso, Mr. Blaise Compaoré were laudable as he was instrumental in aggressively advocating the introduction of the vaccine to his countrymen. Apart from Burkina Faso, the vaccine was also introduced in certain areas of Mali and Niger (2).

3.3 Success of MenAfriVac™

The success of the vaccine has been corroborated both by many researchers (22, 23). A single dose of this vaccine is administered intramuscularly. The incidence rate for Serogroup A meningitis had dropped substantially after the introduction of the vaccine in Burkina Faso and no new cases for the Serogroup A were reported. These results are encouraging, and the various stakeholders are expecting the emulation of the Burkina Faso results across the nations in the meningitis belt. Till date, approximately 235 million people from ages one to 29 years in 16 African nations have been vaccinated with MenAfriVac™. By the end of the 2016-17 period, the remaining nations of the extended meningitis belt (Burundi, Central African Republic, Eritrea, Kenya, Rwanda, Uganda, and Tanzania) will also join the comity of nations that have introduced the vaccine successfully in their respective countries (24). Plans are also afoot to initiate the usage of the vaccine in the Expanded Programme on Immunization (EPI) in many nations of the Meningitis Belt (25). Till date, more than 300 million individuals have been vaccinated by MenAfriVac™(26).

Certain salient features of the MenAfriVac™ vaccine warrant attention here. It is a unique vaccine in that it was a vaccine that was tailor made for that part of the world where most of the people lived on less than $ 1- 2 a day. The vaccine was developed at one tenth the cost of a regular vaccine and was developed in a record number of time. Finally, it can last without ice storage for about four days, and this is, indeed, a boon for the hot Sub-Saharan African nations where commuting for health care professionals has always been a gargantuan effort (2).

Furthermore, success of the introduction of MenAfriVac™ is also obvious by looking at Figures 3 and 4. Meningitis percentage of total DALYs for 2019 clearly show a decrement when compared to 2000 and 2010 (See Table 1). In addition, Figure 4 is a great visual snapshot of the decreasing trend from 1990 to 2019. Albeit this figure involves all the various strains of Meningitis, it would be remiss not to mention the positive role played by MenAfriVac™ in achieving these decreasing trends in the last three decades in Sub-Saharan Africa.

4. CLIMATE CHANGE AND FUTURE MENINGOCOCCAL MENINGITIS EPIDEMICS

Climate change has become the reality of our lives. The fourth report of the Intergovernmental Panel on Climate Change (IPCC) reported that changing climatic patterns around the world would have a direct effect on the severity of many infectious

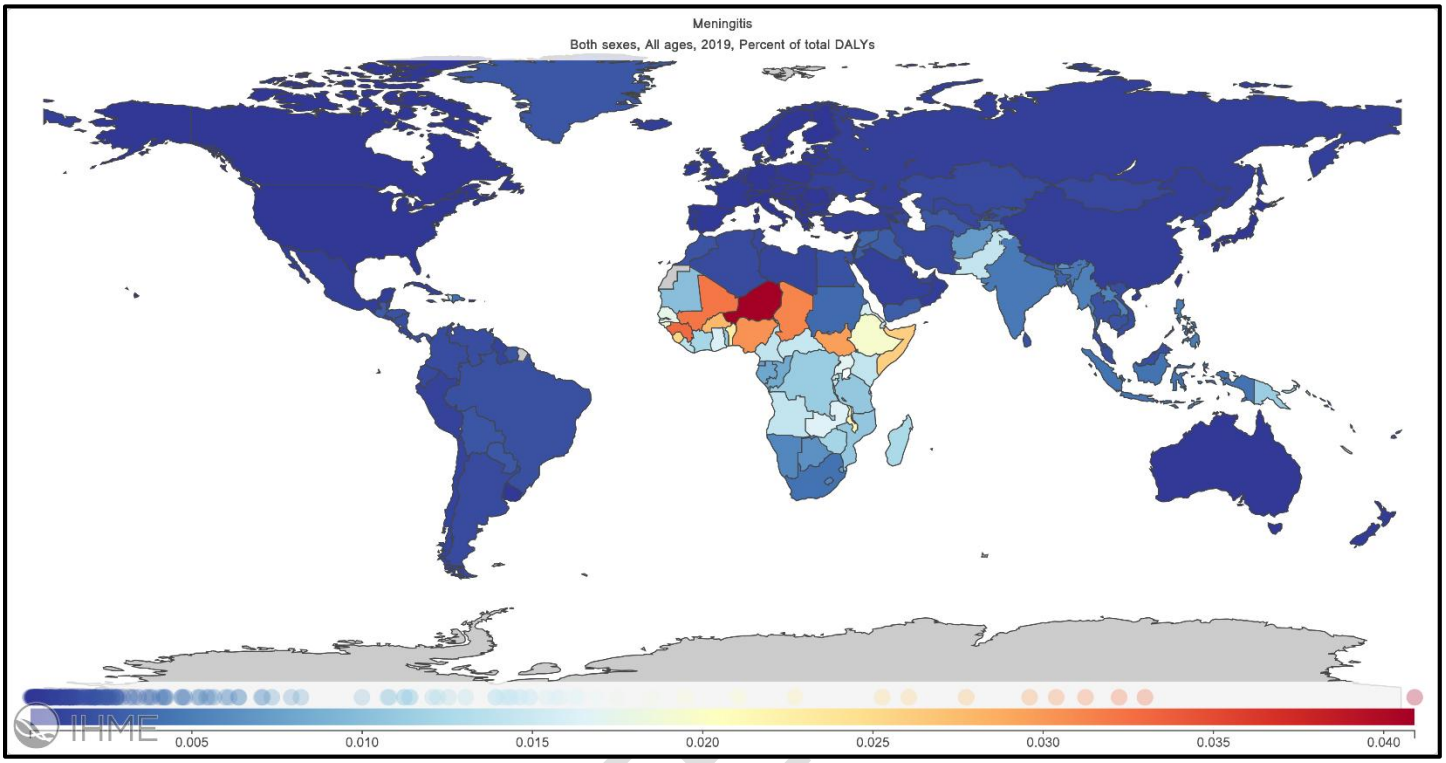

Figure 3: Meningitis percentage of total DALYs for all ages and all sexes for 2019
Data Source: IHME, University of Washington, Seattle, USA

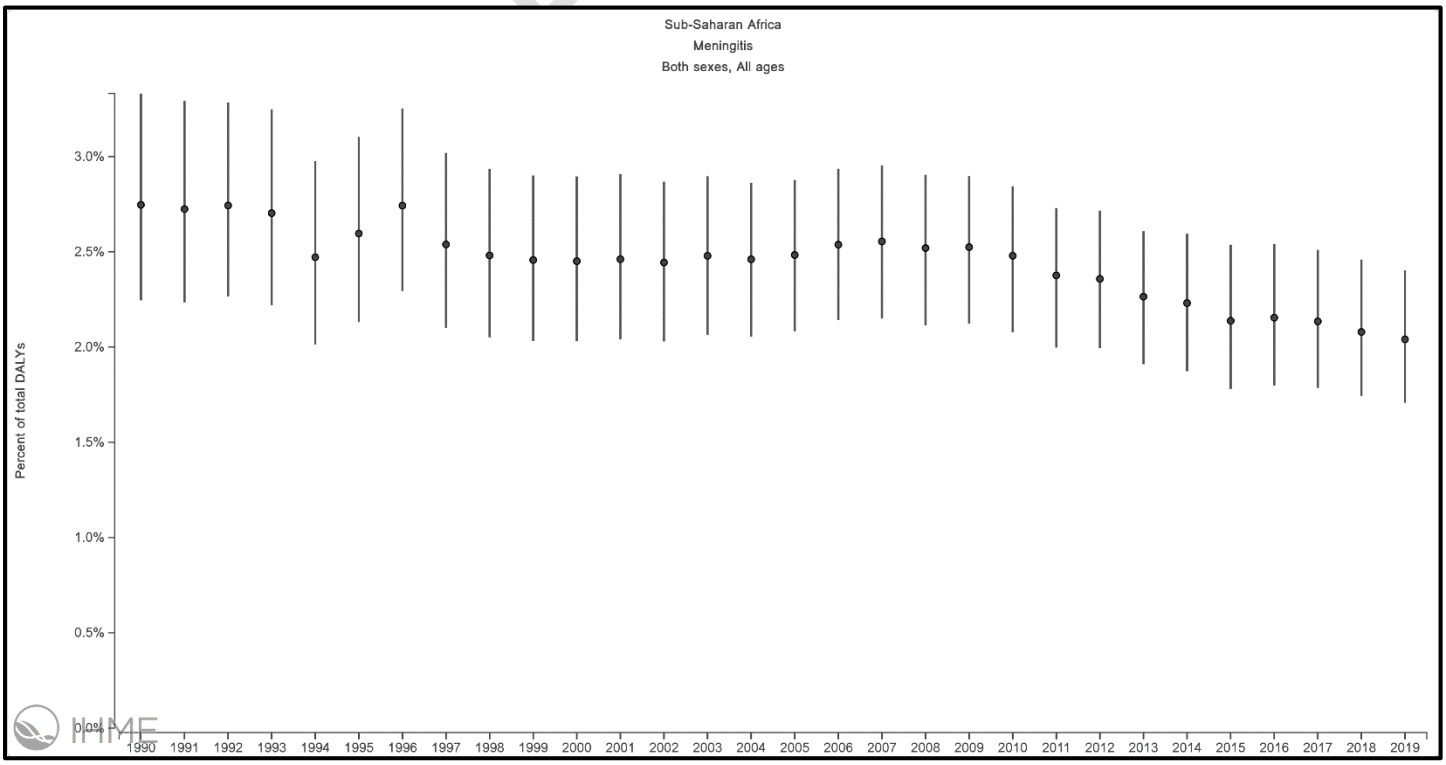

Figure 4: Percent of total DALYs for Meningitis for sub-Saharan Africa from year 1990 to 2019.
Data Source: IHME, University of Washington, Seattle, USA

diseases (27). Climate change, therefore, is a major cause of concern for infections such as meningococcal meningitis. Prolonged droughts, expansion of the Sahara Desert into the Sahelian nations, high temperatures, irregular or delayed rainfall may aggravate future epidemics in the meningitis belt nations (10). Climate change would also impact the land-cover patterns in this region. Dry Sahara Desert in the north, the semi-arid Sahelian steppes in the middle, and the tropical areas to the south of the Belt would all be impacted by the climatic variations. This may lead to the further expansion of the meningitis belt than its present limits, and onset of epidemics in areas that previously never experienced such events may now indeed become a possibility. The following two studies documented the probable implications of climate change on meningitis epidemics in this region.

Perez and colleagues (28) in their study quantified the relationship between meningitis infection rates and dust concentrations in Niger for the 20-year period from 1986 to 2006. Their modeling results demonstrated a direct correlation between high wind and dust episodes and higher incidence rates for meningitis. Another study conducted in Mali reported that the onset of Meningococcal Meningitis epidemic was in direct proportion to very high Harmattan wind indices for the study period from 1994 to 2002 (29). These findings suggest that effective and better surveillance and early warning systems for predicting windy weather conditions and onset of possible meningitis epidemics should be initiated in the meningitis belt nations. But these things are easier said than done due to the paucity of financial resources and technical expertise in these nations. It, therefore, becomes incumbent upon the United Nation agencies, and governments from developed countries to provide the technical know-how and the precious financial resources to help these meningitis belt countries fight the effects of climate change in relation to human health and adaptation.

5. INTERVENTION TO COUNTER FUTURE MENINGITIS EPIDEMICS

Emergency preparedness for a devastating and crippling epidemic is very important for the meningitis belt nations. To best use the limited public health resources during an epidemic such as meningitis, the International Coordinating Group (ICG) was established (5). The group comprises of members from Médecins San Frontières (Doctors Without Borders), International Federation of the Red Cross and Red Crescent Societies (IFRC), UNICEF, and WHO. In addition, representatives from the CDC are also part of the emergency preparedness group. The group's primary responsibilities are effective distribution of vaccines and other antibiotics during epidemics, sustainable stockpiling of vaccines, and coordinating relief efforts during epidemics. The group is also involved in helping the meningitis belt nations form a better surveillance for future epidemics (1).

In the future, surveillance improvements in these Sub-Saharan African nations is paramount to gauge the efficacy of mass vaccine campaigns and also optimizing the effective distribution of vaccines in regions impacted by epidemics. MenAfriVac™ vaccines are effective only against Meningococci Serogroup A. It is possible that changes in the molecular expressions of the capsular or subcapsular antigens, and variations in the serogroups and clonal characteristics may result in epidemics (18). Hence, the susceptibility of previously unaffected populations is a major cause of concern and more robust surveillance methodologies are necessary. Finally, new molecular epidemiology tools, as suggested by Jafri and colleagues (16), should be employed to determine the meningococcal disease burden in high endemic and epidemic nations.

6. CONCLUSIONS

In conclusion, it can be rightly said that in a globalized world, fighting infectious diseases such as meningococcal meningitis would require a holistic approach where various stakeholders work in tandem with each other to achieve the designated results. Nipping infectious diseases in the bud is important, more so in the coming decades, because of climate change and its corresponding environmental, social, economic, and political repercussions.

CONSENT

Not applicable

ETHICAL APPROVAL

Not Applicable

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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