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DENGUE FEVER IN NIGERIA: A MINI REVIEW

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Abstract

Dengue is a disease caused by dengue virus. It is a major mosquito-borne viral disease of humans that is endemic in areas of tropical and subtropical regions, which are environmentally suitable for vector propagation. The disease poses a major threat to the overwhelmed and weak public healthcare delivery system in the developing world, especially in Africa where febrile illnesses are common. The disease undermines the fight against febrile illnesses as infection with dengue often remains undetected or misdiagnosed as malaria or other febrile diseases. This review article highlights dengue epidemiology in Nigeria, dengue transmission dynamics, pathogenesis, diagnosis and current interventions strategies, challenges in addressing dengue infection and future prospects towards dengue elimination. The literature search for publications on dengue virus infection in Nigeria was performed using Google Scholar, PubMed, Web of Science, African Journals Online and other scholarly online databases. Dengue remains a threat to Nigeria and other African countries. In Nigeria, the occurrence of this infection remains a low priority in the public health sector even though it has been reported in about 17 states across the country. The reports of dengue infection in all the geo-political zones suggests active transmission of dengue, hence the need to consider other etiologies of febrile illnesses and engage the public to sustain local involvement as local risk to dengue outbreaks is linked to the population's knowledge, attitude and behavioral practices that encourage vector breeding.

Keywords: dengue, fever, transmission, diagnosis, pathophysiology, intervention, challenges, strategy, vector, occurrence.

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1. Introduction

Dengue fever is a disease caused by dengue virus. It is a major arthropod-borne viral disease of humans characterized by prolonged elevated body temperature (>38 °C), headache, nausea and vomiting, muscular and joint pains, tiredness, rash, eyes and nose bleeding etc. The disease is primarily transmitted through the bite of an infected Aedes aegypti mosquito during a blood meal. Dengue can be grouped as either asymptomatic/symptomatic or severe dengue. The dengue virus is a positive-sense single-stranded RNA virus with a genome size of approximately 11 kb. The virus belongs to the genus Flavivirus and family Flaviviridae. Four serotypes of dengue virus (DENV1-DENV4) are reported to be in circulation across the tropics and subtropical regions. These serotypes each have distinct interaction to immune response but share approximately 65 % genome similarity. The serotypes are further divided in genotypes due to the viral RNA sequence variation. Primary infection with any of the serotypes provides a lifelong immunity against the same serotype and partial immunity against other serotypes. In areas where the serotypes co-exist, secondary infection with other serotypes usually results in symptomatic and severe forms of dengue. Currently, dengue control measures heavily rely on effective vector control measures. For the past decades, commitments have been made to focus on three ground-lying areas: surveillance for

planning and response, reducing the disease burden and consciously changing behavior patterns to improve vector control [1]. Data on dengue epidemiology remains critical for effective control, management and potential outbreaks preparedness [2]. Dengue has emerged to be the most important mosquito-borne viral disease of humans. This review article highlight the current state of dengue distribution in Nigeria.

2. Methodology

The search for scientific literature on dengue in Nigeria was performed using the established relevant database such as PubMed Central, Scopus, Google Scholar, Web of Science, Directory of Open Access, Science Direct, ResearchGate and African Journals Online. The search was narrow down to "Dengue in Nigeria".

Dengue Transmission. In areas with environmental suitability where dengue vectors are established, local risk of transmission is usually high. In the tropics, dengue infection and infection with other flaviviruses is a major cause of febrile illness second to only malaria. *Aedes aegypti*, *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes niveus* are reported to be responsible for dengue transmission with the former considered a principal vector. The vector species now have a widespread distribution in the tropics due to rapid and unplanned urbanization, increased human population, intensive agricultural practices, traveling and climate change [3]. Dengue transmission primarily depends on the availability of susceptible human hosts and vector density. Climate and behavioral practices are crucial factors that encourage the breeding and distribution of dengue vectors in endemic areas [2].

The availability of transportation systems have facilitated the movement of people across towns and states leading to increased distribution of vectors and viruses. This results in geographical expansion and epidemic risk. The virus maintains the traditional human-vector transmission cycle with little report on human-human transmission. When a vector feeds on an infected individual, the vector remains infected for the rest of its life and has the capacity to transmit the disease to as many people as possible within its lifespan.

In Nigeria, febrile illness has been largely limited to malaria or misdiagnosed as malaria with little emphasis on other possible causative agents. The threat of dengue outbreaks in Nigeria has increased in recent times with the locally reported cases in different states across the nation. There have been cases of dengue outbreaks in some Nigerian states that have been under-reported due to lack of awareness and this may have a significant impact in the overall management of febrile illnesses [2].

Data on dengue occurrence and prevalence remains critical to dengue control and creation of awareness to sensitize and educate the public so as to discourage practices that encourage vector breeding. This is important as the knowledge of the populace and attitude towards dengue control has a significant risk to dengue outbreaks. A recent dengue serological and molecular survey conducted in Adamawa State, North-eastern Nigeria reported a significant association between dengue infection and behavior patterns [2].

There are four known serotypes of dengue virus (DENV1-DENV4) that are antigenically distinct and circulating in endemic areas. Infection with any serotype provides life-long homotypic immunity. Severe cases of dengue may be seen when an individual is exposed to secondary infection with heterotypic serotype although few reports indicate dengue outbreaks due to primary infection [4]. When an infected vector feeds on a host, the incubation period usually lasts from 4–7 days. According to WHO report, dengue infection has been classified as dengue with or without warning signs/symptoms and severe forms of dengue [5].

Annually, 24,000 deaths have been reported due to severe secondary infection with dengue virus serotypes across the world [6]. Despite the growing efforts made towards understanding dengue infection, the pathogenesis remains to be fully understood, largely due to complexity of underlying mechanism of infection and lack of animal models. Certain factors have been emphasized as risk factors to severe forms of dengue infection. These factors include viral serotypes, primary exposure, age, genetics, secondary infection and hyperendemicity of the viral strain. DENV2>DENV3>DENV4>DENV1 serotypes have been arranged in order of severity [7].

When an infected vector feeds on a susceptible host, the mosquito vector injects the virus into the bloodstream. Following viral infection, dengue virus pathophysiology is a complex interplay between the virus and the host immune response. Host and genetic factors play central roles to the disease susceptibility. The antibody-dependent enhancement (ADE), memory *T* cells and autoimmunity are some of the reported major determinants of disease progression. The presence of nonstructural protein 1 (NS1) and their corresponding antibodies were reported to have initiated severe forms of dengue pathogenesis. The autoimmune response of CD4+T cells gets disoriented with secondary infection with heterotypic serotype, resulting in subsequent activation of pro-inflammatory immune responses with catastrophic effects. *Fc*γ receptor-mediated antibody-dependent enhancement (ADE) further releases cytokines from host factors resulting in dysfunctional vascular endothelial cells and advanced stage of inflammation. The viral factors such as genomic variation across serotypes and genotypes of dengue virus and subgenomic flavivirus RNA (sfRNA) that undermine the host cytokines determine disease severity. The presence of NS1, pre-membrane proteins (prM) and envelope proteins (E) in the event of dengue infection generates autoimmune responses which may lead to cross-reactivity with plasminogen, integrin, and platelet cells [8].

Dengue diagnosis. The gold standard employed in the diagnosis of dengue disease is through identification of the virus using fluorescent antibodies following viral isolation in cell culture. Notwithstanding, this approach is not a clinical routine. The diagnosis of acute dengue infection is based on the detection of viral antigens, viral RNA or dengue specific antibodies in the bloodstream. The detection of antibodies IgM and IgG with Enzyme-linked Immunosorbent assay (ELISA) is the most frequent approach for dengue diagnosis obviously due to its high sensitivity, specificity and ease of use [9]. In primary infection, the immunoglobulin M (IgM) is the first to be produced and it usually presents a higher titer. IgM antibodies can be detected in the serum of infected individuals from day 5 following the onset of symptoms, with high sensitivity and specificity. IgG antibodies, on the other hand, are synthesized with low titers at the onset of symptoms and gradually increase. Detection of IgM and IgG antibodies in recent infection in serum samples can be useful in serological analysis. On the contrary, in secondary infection, IgG is shown to be in higher titers within the first two weeks of infection. The mechanism of the reaction of IgM may vary, appearing later during the febrile disease and preceded by IgG. In some cases, however, IgM is not detectable in secondary infections [10].

The use of dengue non-structural protein 1 antigen (NS1) is another direct and specific method in the diagnosis of dengue virus infection at the early phase of infection. When humans are infected with dengue virus, usually at the acute phase of the infection, they secrete a glycoprotein (NS1) antigen synthesized by all flaviviruses. Even though the NS1 approach is effective and specific in the dengue detection test so far, the test alone is not serotype specific; hence it's mainly a detection test [11].

Reverse transcriptase-polymerase chain reaction (RT-PCR) is a simple, sensitive, rapid and reproducible technique for serotype-specific identification of dengue virus infection. RT-PCR has become a primary approach in the diagnosis and identification of viral RNA at the early stage of the infection with 80–90 % sensitivity and 95 % specificity [12].

3. Results and Discussion

In Nigeria, reports of dengue virus isolation and identification, dates as far back as 1964. This stems from a study conducted by the arbovirus programme at the University of Ibadan, Faculty of Medicine, where investigations of arthropod-borne virus infections in Nigeria and adjacent areas of West Africa were conducted. The study confirmed by virus isolation, the occurrence of dengue type 1 and type 2 [13]. Other studies were also conducted after the first isolation of the dengue virus, notable were the reports of serological and virological evidence of dengue endemicity in the country [14, 15] and the epidemic confirmation study where serological survey was conducted to determine the prevalence of infection in human and non-human primates [16, 17].

The presence of the vector (mosquitoes) of the virus in the country predisposes the country to a widespread distribution of the virus. Mosquitoes are found in almost every region of the country, and several reports showed cases of dengue virus isolated from serological studies on the host. The dengue burden within the country is greatly under-reported with the country being hy-

per-endemic where all four known serotypes have been isolated and reported. A systematic review of the prevalence study conducted on reports ranging from 2009 to 2020 showed a prevalence of 3.9 % to 77.1 % across the country [18]. The study analyzed 21 studies with a total of 6,210 (1,752 in North-central, 1,422 in North-west, 1,171 in South-west, 1,015 in North-east, 754 in South-south and 96 in South-east) participants across the country. Based on spatial distribution of dengue virus infection across geographical zones of the country, seroprevalence of dengue virus IgG was greatest in South-east Nigeria (77.1 %), North-west (37.6 %), South-west (34.3 %), North-central (23.5 %) and least in South-south (3.9 %) of the country.

In the North Eastern region of the country, a serological study attempted to identify and isolate dengue virus type 3 among febrile patients in Maiduguri, Borno State. The study identified 10.1 % seroprevalence from 256 samples [19]. A similar study in the same region (Maiduguri) used 200 serum samples collected in 2018. The study tested for flaviviral RNA where 26 samples were positive for the flavivirus [20]. In a study carried out in Adamawa State, an overall 19.4 % sero-positive dengue virus in a study of 424 febrile patients across three local government areas of the state was reported. The study identified dengue serotype 1 in circulation in all three local government areas studied [2].

In the North-Central geopolitical region of the country, investigations on the prevalence of the dengue virus and its vectors were conducted by independent researchers. Serological evidence of acute dengue virus infection was reported in Plateau State. The study employed 182 sera of patients presenting febrile symptoms and 2.2 % were identified to be positive for the NS1 antigen [21]. A study in Ilorin Metropolis of Kwara State, of concurrent infection of dengue virus and malaria was conducted. The study recruited 176 participants and confirmed 11 seropositive samples out of which 5 were identified as belonging to dengue serotype 2 while suggesting possible circulation of serotypes 3 and 4 which were equally identified within the sample [22]. A facility-based cross-sectional study at the University Teaching Hospital, Abuja was conducted to investigate dengue occurrence and prevalence. Out of 171 participants employed, 8.8 % and 43.3 % seropositivity were confirmed using Non-structural protein 1 (NS1) antigenemia and IgG respectively [23].

In the South-Western region, a sero-survey study conducted in Ibadan involving 188 patients, where they discovered that 43 % of patients admitted for malaria treatment within the study population, had acute dengue infection (NS1 determination) while the rest were IgG seropositive for the dengue virus [24]. In another separate study in the same region, incidence of dengue infection in Ile-Ife, where an incidence of 25.7 % dengue virus positive of 179 samples studied were identified [25]. In Lagos State, a molecular survey to determine dengue serotypes in circulation identified dengue serotypes 1 and 3 actively circulating within the state. The study employed 130 febrile patients from which 8.5 % were identified as dengue virus positive [26].

On the contribution of climate change to the spread of the virus, several studies noted a great influence of climate change on the prevalence of the dengue virus and its vector. An investigation on 973 samples within Maiduguri during the wet season, harmattan and dry season of the year to determine the influence of climate on dengue prevalence. The study was designed to determine the seasonal distribution of dengue virus infections among febrile patients in the semi-arid region of the country. The study reported a significantly higher dengue virus antibody of 1.3 % in the wet season than the harmattan season with 0.3 %. Within the study area, no antibody activity was detected within the samples analyzed during the dry season [27].

On vector distribution, a review on dengue vectors in Africa, reported vector distribution within the continent. In the urban cycle, *Aedes aegypti*, associated with the dengue virus, has been collected in Nigeria [28]. Several entomological studies showed the presence of both *Ae. Aegypti* and *Ae. albopictus*, but only *Ae. Aegypti* was found infected with all dengue virus serotypes in the field [28]. In the sylvatic/rural cycle, *Aedes (Stegomyia) luteocephalus*, has been reported in Nigeria in 1969 in Jos, Plateau State of Nigeria and *Aedes (Stegomyia) africanus* and *Ma. (Mansonoides) africana* was collected in 1977 in the Eastern River reserves of the country. In 2015, *Ma. africana* was collected in the locality of Ikarama, Bayelsa state of Nigeria. Very little is available on the vector control strategies, but the most commonly employed controls are limited to insecticides spraying and the use of mosquito nets in the locality. **Fig. 1** presents a map of Nigeria showing States with reported cases of dengue infection.

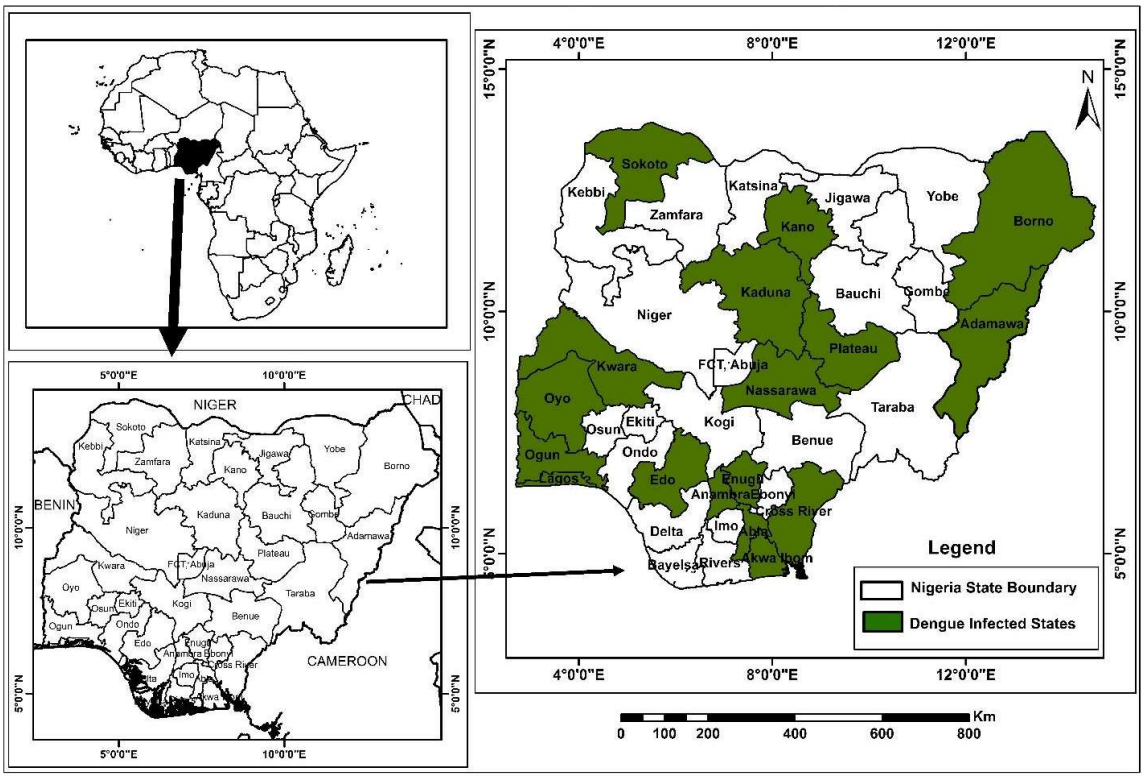

Fig. 1. Spatial distribution of dengue infection in Nigeria

Current Strategies in Dengue Intervention. Human activities and selective advantage are some of the major determinants of the dengue virus transmission dynamic. Dengue virus, unlike other flaviviruses, has evolved to maintain its endemicity without the need for a reservoir; hence the absence of effective and efficient control measures poses a challenge of increased morbidity and mortality [29].

The global strategy suggested by the World Health Organization [30] provides technical elements and enabling factors whose implementations are necessary to reverse the growing trend in the number of dengue cases. This strategy suggested the application of existing knowledge for dengue prevention and control through collaboration among partners, organizations and countries, leadership by WHO and increased funding. To reduce mortality due to dengue, the strategy suggests implementation of early case detection and referral systems for patients for ease of management of severe cases with appropriate treatment; reorientation of health services to cope with dengue outbreaks; and training of health personnel at all levels of the health system. For morbidity due to dengue, this can be reduced through the implementation of improved outbreak prediction and detection systems by using coordinated epidemiological and entomological surveillance; promotion of the principles of integrated vector management; deployment of locally-adapted vector control measures, including effective urban and household water management; and through improvement in communication to achieve behavioral outcomes in prevention programmes.

Dengue infection can cause a spectrum of disease manifestation, and due to this, there is a need for accurate estimation of its true burden which can help to assess the progress and success of implementation of preventive measures. Although this is a much better option, this enhanced surveillance systems and dedicated studies/research may require a lot of funding and investment and as such, its implementation can be challenging to endemic countries. Therefore, additional investment from both domestic and international aid is paramount to the success of implementation of this strategy as research for most neglected tropical diseases including dengue research has received relatively little support.

The long-term trend of dengue in Nigeria is one of increasing prevalence. This is likely due to a combination of factors, such as vector populations, climate change, and poor vector control

measures. In addition, poverty and lack of access to healthcare can increase the risk of dengue, as people living in poverty are more likely to be exposed to mosquitoes and lack the resources to access treatments. To reduce the incidence of dengue in Nigeria, the government and other organizations must work to improve vector control measures and public health campaigns. These measures should help reduce the prevalence of dengue in the future, and help to ensure that people have access to treatments and preventive measures. Additionally, research into potential vaccines and treatments for dengue are ongoing, and it is hoped that these will result in improved treatments and prevention in the future.

Currently, there is no specific, effective and efficient antiviral therapy for patients infected with dengue and management of dengue patients depends on the phase of illness. To save febrile infected individuals from dehydration due to vomiting or loss of fluid intake, patients with dengue virus infection are encouraged to drink rehydration fluids such as water and fruit juices. Patients are encouraged to take analgesic and antipyretic drugs to get relief from ache and fever. Patients of conventional dengue fever and dengue hemorrhagic fever are encouraged to avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs). Intravenous fluid replacement therapy may be recommended to patients with dengue shock syndrome or dengue hemorrhagic fever [12].

Challenges in Dengue Elimination. Dengue is a global public health burden occurring in over 120 countries. Globally, efforts towards curtailing and controlling the spread of dengue have been on the increase, awareness of the dangers and risks posed by the disease has greatly increased among both rural and urban dwellers. Currently, with the availability of global networking through the internet, vast information regarding the disease and vector is widely available. But challenges are still being experienced in effectively controlling or eliminating the disease and its vector. One key contributing factor to the resurgence of dengue is the rise in the number and size of densely populated urban cities, which encourage the spread of the disease by providing a conducive environment for the proliferation of the dengue vectors. A second contributing factor is the increase in the ease of inter- and intra-continental travel. This has encouraged the spread of different variants and a contamination of the balanced genotypes/serotypes. A third contributory factor is funding and the financial implication of implementation of management and control strategies. Although for a short-term control strategy, the financial cost can be manageable, prevention and control management implementation is not a one-off step but a continuous process for over a long period of time which can be too much for endemic regions to sustain these expenses.

Future prospects in dengue elimination. For effective management of dengue, preparedness and response are key. A report in 2017 on challenges and control options in dengue control and prevention opined preparedness to include stringent viral and vector surveillance, institution of warning systems, supply and provision of diagnostic kits as well as development of locally adapted integrated vector control measures and community awareness [31]. Traditional approaches to prevention relies on targeted vector elimination. This approach relies on the use of chemicals to reduce vector burden. Although this strategy is effective, it poses more danger due to its indiscriminate action on non-target vectors. A future target for elimination of dengue is the development and use of dengue vaccines. Development of the dengue vaccine has been challenging, because of the need to provide protection against all four dengue serotypes to avoid potentially causing antibody-dependent enhancement in further infections [32]. Despite these challenges, Vaccines are currently under review and development with some being approved for use. Dengvaxia®(CYD-TDV) developed by Sanofi Pasteur is one of such approved vaccines. Since the most effective method for elimination of dengue is through source reduction, a shift in behavior of communities towards vector and management is vital. Vaccines if and when available would only be half of the solution as without vector control, all efforts would be wasted. Increase in surveillance programmes and awareness should be part of strategy for dengue elimination, this requires the participation of all key players (government, non-government and the community).

This article is limited to available data online.

It is interesting to note that despite the occurrence of dengue in Nigeria, severe forms of dengue appear not to be common and this may likely be the reason why most public healthcare professionals dismiss the possibility of dengue infection. Why Nigerians rarely develop severe forms

of dengue is yet to be fully understood. But the occurrence of the severe forms cannot be ruled out, due to poor surveillance, awareness by health workers and absence of appropriate diagnostic tools among others. We therefore encourage further research to delineate possible reasons why severe forms of dengue are not common despite its occurrence across the country.

4. Conclusions

Dengue may be one of the major causes of febrile illness in Nigeria second to only malaria. Some studies have reported dengue and malaria co-infection, suggesting the possibility of misdiagnosis and negating the possibility of dengue infection especially in healthcare facilities, where standard laboratory procedures for dengue diagnosis are not available and the possibility of other febrile agents have been overruled. The occurrence of dengue has been established in all the geo-political zones; this indicates active transmission of dengue at an alarming rate. This calls for a public awareness campaign against flaviviruses to deliberately change behavioral practices such as open gutter/drainage system, open water containers and bodies in or around residential buildings, dumped tires, aesthetic exterior containers, etc. that encourage vector breeding.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Manuscript has no associated data.

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