Mini-Review

Dengue Virus in Nigeria: Current Status and Future Perspective

James Ayukepi Ayukekbong[1,2]

[1]*Department of Infectious Diseases/Section of Clinical Virology, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden;* [2]*Section for Clinical research, Redeem Biomedical System, Douala, Cameroon*

Abstract | Dengue is regarded globally as the most important mosquito-borne viral disease but there are currently no licensed vaccines or specific therapeutics. The virus and its vector are widely distributed throughout the tropics and subtropics regions of the world. Dengue and malaria are endemic in Nigeria. Two independent studies among febrile patients revealed dengue IgG seroprevalence of 73% and malaria prevalence of 80% in some areas of the country. The diagnosis of the disease is further complicated by the fact that, dengue fever mimics malaria fever and the prevalence of dengue-malaria co-infection is high. Differential diagnosis of fever is therefore necessary to initiate the appropriate clinical care. Despite the endemicity of dengue in Nigeria, the disease is not a reportable disease and routine diagnosis is neglected. Here I undertake an exhaustive assembly of known records of dengue prevalence in Nigeria and provide a focus for public health intervention.

Editor | Muhammad Munir, The Pirbright Institute, Compton Laboratory, UK
Received | October 17, 2014; **Accepted** | October 28, 2014; **Published** | November 10, 2014
***Correspondence** | Ayukekbong, J.A. University of Gothenburg, Sweden; **E-mail** | james.ayukekbong@microbio.gu.se
Citation | Ayukekbong, J.A., 2014. Dengue Virus in Nigeria: Current Status and Future Perspective. *British Journal of Virology,* 1(3): 106-111.

Epidemiology

Dengue is the most rapidly spreading mosquito-borne viral disease with an estimated incidence of 390 million cases per years (Simmons et al. 2012, Bhatt et al. 2013). It is regarded as the most important arboviral disease worldwide (Gubler 2011a) and it is estimated that every year between 2.5-3.6 billion people in over 125 endemic countries are at risk including 120 million travelers to these regions (Gubler 2002a, Guzman and Kouri 2002). About 2 million cases evolve to dengue hemorrhagic fever and about 20,000 may culminate to death (Gubler 2002a, Shepard et al. 2011). The first isolated case of dengue in Nigeria was in the 1960s (Carey et al. 1971, Amarasinghe et al. 2011), but dengue is not a reportable disease in this country with most cases often undiagnosed, misdiagnosed as malaria or referred to as fever of unknown cause. Dengue IgM seroprevalence of 30.8% was reported in Nigeria among febrile children (Faneye et al., 2013), while another study in the north of the same country among healthy children revealed a seroprevalence of 17.2% (Oladipo et al., 2014). The finding from the later study needs to be interpreted with caution as it's not clear from the study when samples were collected considering it is well established that dengue IgM antibody production may last for a couple of weeks after infection (Schwartz et al. 2000). Our recent survey of dengue IgG antibodies in Ibadan, Nigeria showed a seroprevalence of 73% among febrile patients age 4 – 82 years. A further investigation of samples for active dengue infection by non-structural 1 (NS1) antigen analysis revealed an NS1 seroprevalence of 35% (Oyero and Ayukekbong 2014). These data are consistent with the fact that dengue is an endemic and emerging cause of fever in Nigeria (Figure 1). However, the disease is neglected, under recognized and under reported in Nigeria due to lack of awareness by health care providers and lack of prioritization by the public health authorities.

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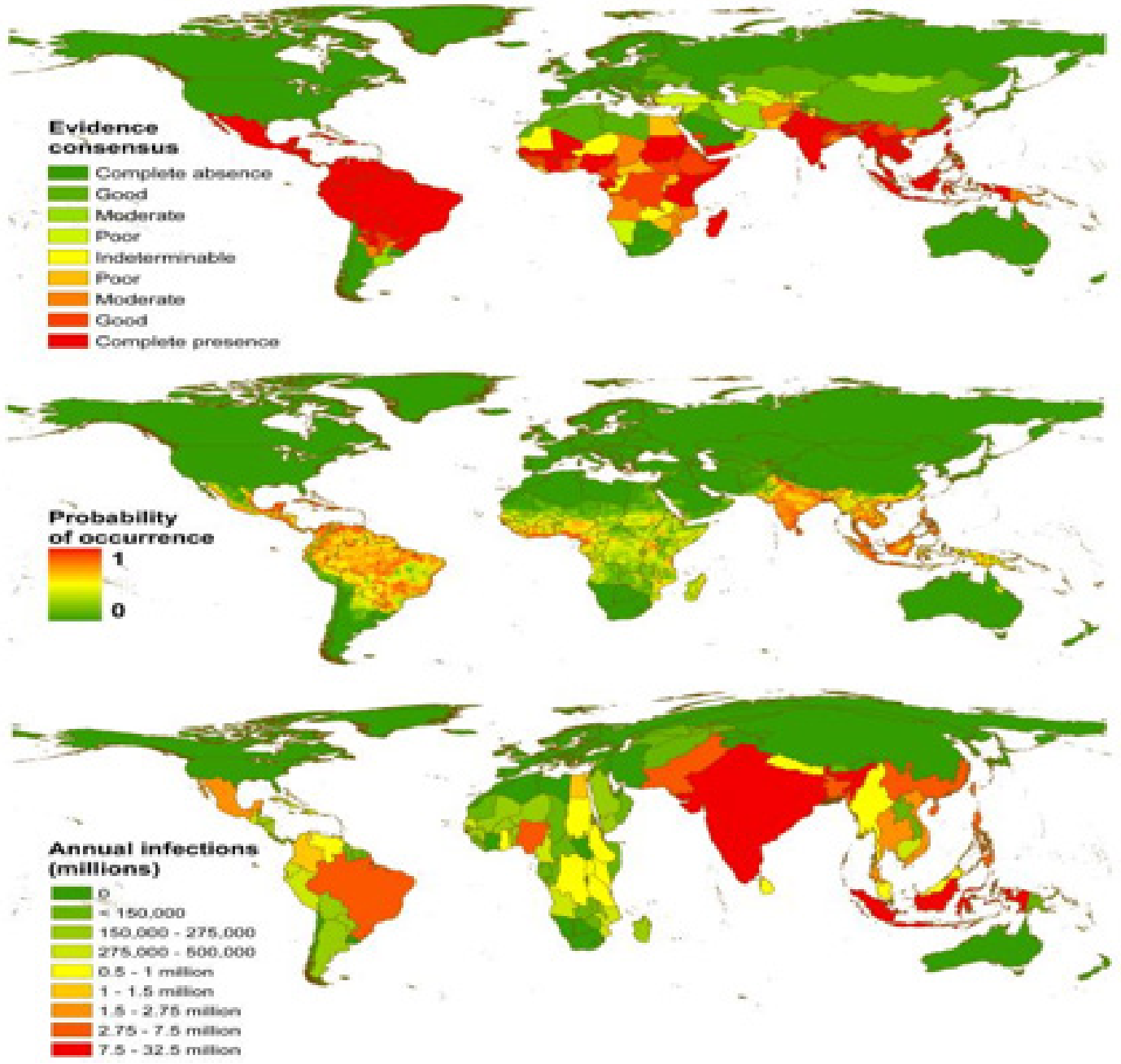

Figure 1. *top, shows National and subnational evidence consensus on complete absence (green) through to complete presence (red) of dengue. middle, shows the probability of dengue occurrence at 5km × 5km spatial resolution of the mean predicted map (area under the receiver operator curve of 0.81 (±0.02 SD, n = 336)) from 336 boosted regression tree models. Areas with a high probability of dengue occurrence are shown in red and areas with a low probability in green. bottom, shows a cartogram of the annual number of infections for all ages as a proportion of national or sub-national (China) geographical area. Figures are reused with permission from (Brady et al. 2012, Bhatt et al. 2013).*

Dengue virus and the disease

Dengue is an acute febrile disease caused by the mosquito-borne dengue viruses (DENVs). There are four distinct DENV serotypes (DENV 1 to 4) classified in the *flaviviridae* family and genus flavivirus (Westaway et al. 1985). The virus has a non-segmented, positive-strand RNA genome of about 10,700 nucleotides with a 5' cap structure and a non-polyadenylated 3' end (Back and Lundkvist 2013). The main arthropod vectors for the transmission of the DENVs is *Aedes aegypti* and *Aedes albopictus* which are now known to be extensively spread in both tropics and subtropics (McCall and Lenhart 2008). Infection may be asymptomatic or patients may present with dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS) (Gubler 2002b, Endy et al. 2011). The incubation period is between 3-15 days

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and symptomatic patients may present with headache, myalgia, arthralgia, retro-orbital pain, rash, and leucopenia (Henchal and Putnak 1990). Early symptoms of DF and DHF are indistinguishable, but DHF is associated with hemorrhagic manifestations, plasma leakage, and thrombocytopenia (Rigau-Perez et al. 1998). DSS on the other hand is distinguished from DHF by the presence cardiovascular compromise, which occurs when plasma leakage into the interstitial spaces results in shock. DSS is a fatal condition with mortality rates as high as 20% in developing countries with limited resources (Gubler 2002b). It is thought that infection with one serotype provides lifelong immunity against that serotype but confers only partial or transient protection against subsequent infection with any of the other three serotypes (Halstead 1988).

Dengue and other arbovirus co-infection in Nigeria

Arboviruses are widespread in Nigeria considering that the mosquito vectors responsible for the transmission of dengue, yellow fever, chikungunya (*Aedes spp*) and those responsible for malaria (*Plasmodium spp*) are well established in this country. Dengue co-infection with other arbovirus infections is therefore not uncommon and has been described in Nigeria (Baba et al 2012). These co-infections might provide an opportunity for exchange of genetic materials and mutations resulting in the emergence of strains with fitness and enhanced disease severity. Antibody cross reactivity by viruses of the *flaviviridae* family may also affects accurate serological diagnosis. Early signs and symptoms of dengue are indistinguishable from those of other tropical disease fever like malaria and typhoid. In Nigeria where malaria is highly endemic; most cases of febrile illnesses are likely to be treated as presumptive malaria (Amexo et al. 2004). We recently reported that 10% of malaria patients in Ibadan, Nigeria had active dengue infection. Further evaluation of dengue IgG seroprevalence among malaria patients revealed that all the malaria patients in the study were positive for dengue IgG antibodies suggestive of a past dengue infection and consistent with the endemicity of dengue virus in the region (Oyero and Ayukekbong 2014).

Potential risks to public health

The number of reported dengue cases has increased since the 1980s due to factors such as unplanned urbanization, lack of surveillance and vector control, poor public health, international travel and virus and vector evolution (Guzman and Kouri 2002, Gubler 2011b).

Understanding risk factors to infection is important for public health control programs. The evaluation of male-female difference in infection rates for instance has been difficult to discern. Three independent studies from dengue epidemics in Singapore and India found that the risk of infection in males was two times higher in females (Goh et al. 1987, Agarwal et al. 1999, Wali et al. 1999). A few studies in South America including out recent study in Nigeria reveal that both sexes are equally affected (Vasconcelos et al. 1993, Rigau-Perez et al. 2001, Oyero and Ayukekbong 2014). Taken together, a comprehensive evaluation of sex difference in infection rate requires well-designed studies that would take into consideration both biological and social factors that drive dengue transmission in the population.

The contribution of climate change to DENV transmission has been investigated previously and the incidence and, in particular epidemics of dengue has been common during the rainy season (Hales et al. 1996, Keating 2001). The availability of favorable breeding grounds for the mosquito vector enhances the spread of DENVs. Due to water requirements for breeding, mosquito densities speak during the wet season, resulting in an increase in the number of dengue cases during this period (Hales et al. 2002). The poor drainage system and inadequate waste disposal in most Nigeria cities results in the presence of stagnant water bodies and water collected in waste metal containers and vehicle tyres. These media serve as breeding sites for the mosquito vectors which are the agents of DENV transmission (Baba and Talle 2011). The increase in the number of susceptible individuals in these areas also enhances the risk of human to mosquito transmission and vice versa. Therefore, due to the nature of the route of infection, those at greatest risk of infection are those in regular exposure to the mosquito vector. A high IgG seroprevalence has be reported among adults >40 years of age compared to those younger than 40 years of age which is consistent with increased in vector exposure with age (Oyero and Ayukekbong 2014).

Laboratory diagnosis and dengue surveillance in Nigeria

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Dengue surveillance in Nigeria is affected by the lack of routine laboratory diagnosis. Laboratory diagnosis of dengue may include culture, polymerase chain reaction (PCR), and serological assays. There are, however, limitations with each test, and detection targets different virological markers, namely infectious virus in culture, viral RNA in PCR and DENV-specific antibodies (IgG/IgM) or antigens in the case of serology. DENV can be isolated from serum, plasma or washed buffy coat using specific cell lines. Autopsy tissues from fatal cases, especially liver, spleen, lymph nodes, and thymus may also be used. Culturing the virus requires an acute patient sample with sufficient viral load (Back and Lundkvist 2013). Therefore, the period when DENV can be successfully isolated in patient serum is short. Viraemia peaks before the onset of symptoms; hence virus levels might drop significantly once the patient seeks medical care. Furthermore, rising levels of antibody interfere with virus culture within a day or two after the subsidence of fever. Apart from sample collection limitations, other practical considerations limit the use of this method. Culture of the virus is both time and labor intensive requiring the need for improved laboratory safety capacity such as bio-safety level 3, consequently necessitating professional training of the personnel. These requirements limit the routine use of this diagnostic tool, especially in developing countries. Detection of viral RNA from serum, plasma, or cells by PCR is based on DENV-specific oligonucleotide primers (Back and Lundkvist 2013). This method is however financially prohibitive as most dengue prone or endemic countries lack the capacity for routine molecular diagnostics. A simple and inexpensive approach based on the presence of anti-DENV antibodies is commonly used. This method is based on screening of dengue IgG/IgM antibodies. The acute anti-DENV IgM antibody response lasts for a couple of weeks after infection and the IgG antibodies for several years (Schwartz et al. 2000, Rubens Costa Lima et al. 2012). Seroconversion following production of IgM has been suggested to occur 4-8 days after the onset of fever (Hunsperger et al. 2009). This method is limited due to considerable risk for false-positive results due to potential cross-reactivity with other flaviviruses, for example, vaccination against Yellow fever virus and also false negative due to an extended seroconversion period (Schwartz et al. 2000). Owing to the overwhelming drawback of these assays, the detection of the viral NS1 protein has emerged as a potential alternative to culture, PCR and serology (Wang and Sekaran 2010, Tang and Ooi 2012). The NS1 protein is produced during viral replication and can be detected shortly after dengue virus infection. That is from the first day of fever up to 9 days post-infection prior to IgM seroconversion (Kassim et al. 2011).

Prevention and control of dengue

Rapid, unplanned growth of urban centers in Nigeria combined with inadequate water supply and sewage systems have great influence on the transmission of DENV (McCall and Lenhart 2008). In the absence of a vaccine and specific antivirals, the main method to prevent DENV transmission is to reduce the vector population and to educate people in endemic areas on basic protection measures such as wearing protective clothing and the use of anti-insecticide sprays. This approach is attractive since the Aedes mosquitoes are active during the day, minimizing the use of bed nets. Anti-vector control programs include surveillance, spraying pesticides, minimizing potential breeding sites, genetically modified mosquitoes, and general improvement in the construction of houses.

Future perspectives

Due to poor disease surveillance and lack of reporting, the true incidence and impact of dengue in Nigeria is unknown. Thus data on the burden of the disease and associated economic impact is lacking. Also, due to the significant endemicity of malaria in Nigeria, the majority (>70%) of 'febrile illnesses', including dengue, are likely to be misdiagnosed and treated as malaria. Surveillance and reporting is therefore necessary for effective dengue prevention and control. Accurate quantification of the burden of dengue in Nigeria will allow public health prioritization of dengue control. Consequently, dengue NS1 antigen detection assays should be available at all health establishments so that routine diagnosis can be made. Misdiagnosis of dengue and other arboviral infection as malaria is likely to have tremendous consequences in the general management of febrile diseases in Nigeria.

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