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REVIEW ARTICLE

A REVIEW ON THE STATE OF ZIKA VIRUS IN NIGERIA

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ABSTRACT

Background: Zika virus, a flavivirus primarily transmitted through bites of mosquito (*Aedes aegypti*), blood transfusion, sexual contact and mother-to-child was named after Zika forest in Uganda where it was first isolated from a sentinel monkey in 1947. It is a positively sensed single stranded RNA virus (+ssRNA) of approximately 11000Kb in length, encoding three (3) structural and seven (7) non-structural proteins. The virus has spread across several countries of the world between 1947 and today. Between March 2015 and November 2016, about 500,000 to 1.5 million people have been reported infected with Zika virus in Brazil alone, resulting in several cases of microcephaly, severe brain and ocular malformations, abortions, Guillain-Barre syndrome and even deaths. Cases of Zika virus infections have also been documented in some African countries with resulting isolation and sequencing of several strains. In Nigeria however, the first case of Zika virus was reported as far back as 1954 in the Eastern part of the country during a research on Yellow fever. Zika virus mutant strains might have evolved with corresponding effects on man due to continuous environmental changes and human factors worldwide.
Aim: This study was aimed at reviewing the state of Zika virus in Nigeria: past and present.
Methods: Original research articles and reviews were searched on the NCBI, Research gate, PubMed and Google scholar using queries such as; Zika, epidemiology of Zika, pathogenesis of Zika and molecular characterization of Zika.
Results: High points on virology, epidemiology, pathogenesis, diagnosis, prevention and management were pooled together and discussed.
Conclusion: The knowledge gained from this paper will help understand the current state of Zika virus in Nigeria.

Keywords: Nigeria, Zika, flavivirus, RNA, microcephaly, epidemiology, genomics.

All co-authors agreed to have their names listed as authors.

1.0 INTRODUCTION

Zika virus is coined after Zika forest in Uganda where the first case was first reported in 1947. It is an arthropod- borne virus that causes Zika viral infections and belongs to the flaviviridae family of viruses such as dengue, yellow fever, Japanese encephalitis [1] etc. The animal reservoir is not too clear yet as to whether it is sentinel rhesus monkey from which it was first isolated or mosquito. Zika virus is transmitted horizontally through the bite of mosquitoes; Aedes spp [2], mother-to-child, sexual contact [3] and blood transfusion [4]. In a horizontal relationship, Zika virus and spondweni virus form the spondweni serogroup. The disease caused by Zika virus is called Zika fever or Zika viral infection which is characterized by symptoms such as fever, arthralgia, headache, asthenia, swelling in lower limbs, pruritis, maculopapular rash etc. Zika virus is a positive-sensed single stranded virus (+ssRNA) with a genome length of approximately 11000 Kb encoding 3,419 amino acids [5] and two flanking non-coding regions (5' and 3' NCR) and a single long open reading frame (ORF) encoding 3 structural proteins: Precursor of membranes (prM), Envelope (E), Capsid (C) and seven (7) non-structural proteins: NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5 [6]. The 3' NCR of ZikV genome contains about 428 nucleotides including 27 folding patterns [5]. The functions of each of the components of the genome are summarized below.. Genetics studies of the nucleotide sequences derived from the NS5 gene shows that there are three ZikV lineages: Eastern African lineage, West African lineage and Asian lineage [7].

1.1 ZIKA VIRAL PROTEINS AND THEIR PROPERTIES/FUNCTIONS

Envelope (E)
- involves in various aspects of viral cycles
- Mediates binding and membrane fusion [8]
- It is approximately 53KDa in size [9]

Capsid (C)
- Virion maturation
- approximately 12 KDa in size [10]

Precursor membrane (prM)
- facilitates E-protein folding and trafficking
- Helps in virion maturation
- approximately 20KDa in size [11]

NS1
- It is approximately 50Kda in size [12]
- It interacts with the cellular membrane of the host
- It is essential for making new copies of the virus
- It subverts immune system of the host cell
- It is central to viral replication

NS2a
- It is approximately 25KDa in size [13]
- It helps in viral assembly
- It inhibits interferon response

NS3
- It is a multi-domain protein

NS4a
- It is approximately 16 KDa in size [14]
- It helps in viral replication

NS4b
- It is approximately 22KDa in size [15]
- It suppresses interferon activities
- It suppresses host RNAse
- It functions in viral replication

NS5
- It is approximately 103Kda in size [16]
- It is the largest viral protein
- Its C-terminal portion has RNA dependent RNA polymerase and the N-terminal is involved in RNA capping.

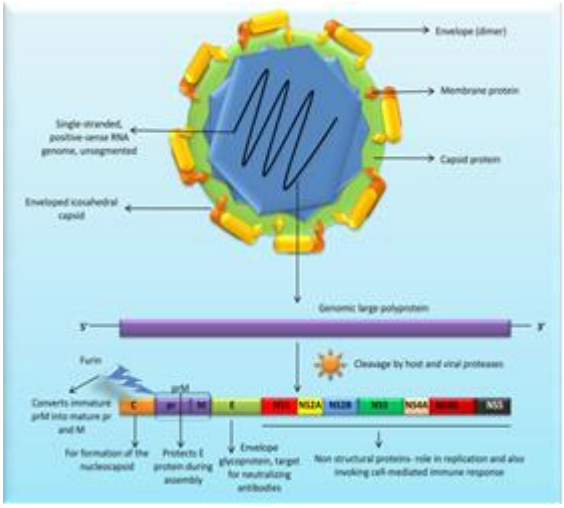

Figure 1. Structure of Zika virus genome [17]

2.0 EPIDEMIOLOGY OF ZIKA VIRUS.

Recent outbreaks of Zika virus infection since 2007 ranges from the outbreak in humans on the Pacific Island of Yap, Federal State of Micronesia; 2008 infection in Senegal; 2013-2014 outbreaks in French Polynesia, Eastern Island, The Cook Island and New Caledonia; and then the 2015-2016 outbreaks in Brazil and other South American countries calls for more attention towards this emerging human pathogenic flavivirus which if neglected could be a time bomb.
Despite the work that has already been done in other countries, Nigeria seems to remain in the dark towards the activities of Zika virus despite the fact that there is an evidence of Zika virus in Nigeria as reported by the work done McNamara, 1954 [18] and then Fagbami, 1979 [19].
Hence, there is a need for an aggressive research on Zika virus in Nigeria.

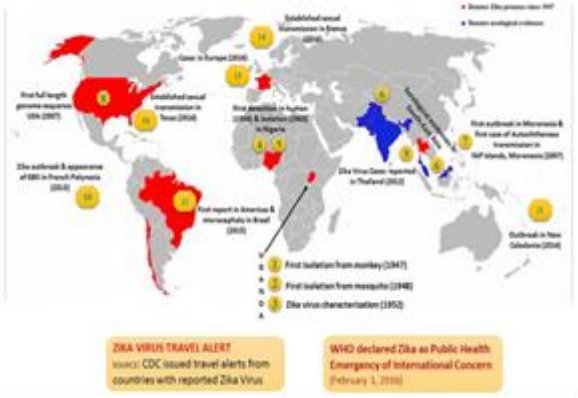

Figure 2: Endemic areas of Zika virus [17]

Below is the summary of the activities of Zika virus thus far:

1. 1947 & 1948- In Zika forest, Uganda, Zika virus was isolated from a sentinel rhesus monkey during a routine yellow fever surveillance and in 1948, from Aedes (stegomyia) africanus mosquito [20]

2. 1952 - The first human cases were detected in Uganda and Tanzania in a study demonstrating the presence of neutralizing antibodies to Zika virus in sera [21]

3. 1954 – In Nigeria, Zika virus was first isolated from a young girl in the Eastern region of Nigeria during a routine yellow fever surveillance, who was said to show symptoms of mild febrile illness [1]

4. 1964 – In Uganda, a researcher took ill from Zika virus infection with a pinky non-itchy rash lasting 5 days which covered the whole body, while working on strains isolated from mosquito [22].

5. 1960s-1980s – In Africa and Asia, more detections of Zika virus were carried out in mosquitoes and sentinel monkeys across African countries that stretch across the Equatorial belt [4]. Zika virus crosses to Asia where it is detected in mosquitoes. Sporadic human cases continue to be detected across Africa and Asia but no outbreaks [4].

6. 2007 - First large outbreak in humans with 185 cases of suspected Zika viral infections took place at Pacific Island of Yap, Federated States of Micronesia. An estimated 73% of Yap residents over 3 years of age were infected with Zika virus [4].

7. 2008 – In the United States of America,a an American scientist working in Senegal was said to have infected his wife with Zika virus on his return to the US. This is the first case of sexual transmission recorded [23]

8. 2013-2014- In French Polynesia; Eastern Island; The Cook Island; New Caledonia, several outbreaks in these regions [24,25] which lead to several researches that implicated Zika virus in congenital malformations and autoimmune complications [26]. A rise in the incidence of Guillain-Barre syndrome was also recorded [25].

9. 2015-2016 – First case of Zika virus in America was reported in Brazil in March, 2015 [4] after then, several confirmed cases were reported in several countries in America with rampant cases of microcephaly, Gullian Barre syndrome and other complications.

2.1 STATE OF ZIKA VIRUS IN NIGERIA.

MacNamara *et al.,*1954 [1] isolated Zika virus from a young girl in the Eastern Part of Nigeria during an epidemic of jaundice in a Yellow fever surveillance study in Eastern Nigeria. This was the first case of Zika virus reported in Nigeria though no details on isolation was given as Zika virus was not the primary target of study. However, between 1971 and 1975, Fagbami [19] did a study on Zika virus infections in Nigeria which yielded two Zika virus isolations from humans who were having a mild febrile illness [19]. He performed a haemagglutination inhibition test where 31% of the samples (189) tested positive for Zika virus, 50% for Yellow fever virus, 46% for West Nile virus, and 59% for Wesselsbron virus. He noted that 49 persons (38%) of those with positive haemagglutination-inhibition test have Zika N-antibodies in a neutralization test.

Moore *et al*., (1975) [27] in their research on arthropod-borne viral infections of man in Nigeria reported that Zika virus was one of the viruses that were recovered less frequently in his research. However, no isolation of Zika virus seemed to have been done then.
Carey *et al*., (1972) [28], in one of their studies carried out during a Yellow fever outbreak in Jos Plateau, employed Zika virus antigen as one of the viruses to identify. He reported that 20 out of 24 sera of his samples inhibited Zika virus antigen in a 1:80 serum dilution which indicates that about 83% of the samples were seropositive for Zika virus. Other researchers such as [29] reported that 56% of 267 samples showed prevalence of antibodies to individual Zika virus antigen in a research he carried out at Kainji Lake Basin in Nigeria.

Also, McNamara *et al*. (1959) [1] discovered that there were significant associations between Zika and dengue viruses, Zika and Uganda S viruses, Zika and Yellow fever viruses. This could be a pointer to a possible co-infection among these organisms.

In Benue state, Nigeria, Monath *et al*., (1970) [30] in a study on Yellow fever noted that N antibodies for Zika virus were found most frequently. They further stated that of all the viruses tested in his study, dengue and Zika viruses appeared to be most frequently responsible for infections prior to the yellow fever epidemic in Nigeria. They discovered that of 51 persons with prior immunity infected with fever, 78% had Zika antibodies.

In comparison to other African countries where Zika virus research is going on, only one strain (IBH 30656)

[31] of Zika virus has been identified in Nigeria. For instance: Senegal; 5 strains {(ArD41519, [31]), (ArD158084, ArD157995, ArD128000 and ArD7117, [32])}; Central African Republic; 4 strains { ArB 1362, ARB13565, ARB15076, ARB7701, **[33]**}; and Uganda; 4 strains {AY632535, LC002520, DQ859059, (MR766, [31])}.

A closer look at the review of the literatures on Zika virus in Nigeria, one could deduce that there is a high immunity to Zika virus infections among the samples studied. Contrariwise, this might not be true considering the population involved and also the fact that Zika virus was not the primary target in the studies. Following recent outbreaks of Zika virus in South Americas with several complications and clinical manifestations reported, there is a need to do a thorough research to ascertain the present status of Zika virus in Nigeria.

3.0 PATHOGENESIS

There is no clear pathogenesis of Zika virus in human yet. However, it is opined to be similar to the one as observed in other flaviviruses such as dengue, Japanese encephalitis, West Nile viruses etc. It starts with mosquito inoculation of the virus into humans, the virus enters skin cells through cellular channels and then moves to the lymph nodes and blood stream [3]. Zika virus replicates in the mosquito's mid-gut epithelial cells and then its salivary gland cells. After 5–10 days, the virus can be found in the mosquito's saliva. If the mosquito's saliva is inoculated into human skin, the virus can infect epidermal keratinocytes, skin fibroblasts in the skin and the Langerhans cells. The pathogenesis of the virus is hypothesized to continue with a spread to lymph nodes and the bloodstream [3] (Fig 3). Flaviviruses generally replicate in the cytoplasm, but Zika viral antigens have been found in infected cell nuclei [34].

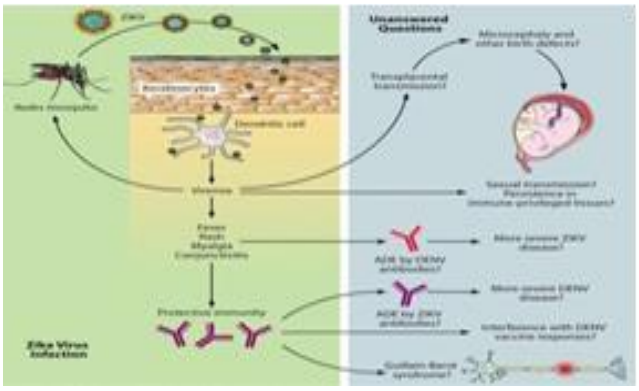

Fig 3: DENV – Dengue virus; ADE – Antibody-dependent enhancement.

4.0 CLINICAL MANIFESTATIONS/SYMPTOMS

After mosquito bite, the incubation period before manifestation of symptoms is approximately 5- 12 days. Most of the times, infections do not present tangible signs and symptoms [35] and where it presents, they are typically mild, self-limiting or non-specific. Symptoms are majorly similar to those of dengue and chikungunya viral infections. Other clinical manifestations identified are hearing loss, hypotension and genitourinary symptoms [**3**]. Severe cerebral malformation including microcephaly (Fig 4), Guillian-Barre syndrome, neonatal brainstem dysfunction, ocular malformation and other neurological disorders have been implicated. Death has rarely been recorded in Zika virus infected patients (Table 1).

Table 1: Cases of microcephaly and deaths associated with Zika viral infection in some American countries

SN	Year	Country	Number Of Cases Of Microcephaly Reported	Number Of Deaths	Reference
1	2015	Brazil	Not reported	4	**4**
2	2015	Brazil	2975	Not reported	
3	2016	Brazil	3893	49	
4	2016	Suriname	1107	Not reported	
5	2016	Cape Verde	7081	Not reported	

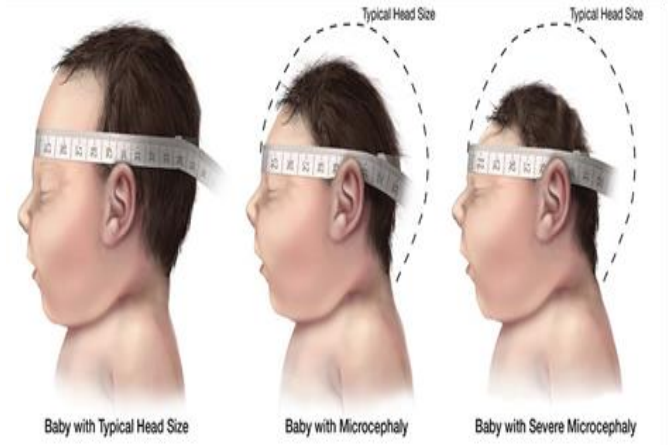

Figure 4: Effect of Zika viral infection (microcephaly) [37]

5.0 DIAGNOSIS

Zika viral infections can be detected in serum or plasma, urine, saliva of an infected person for the presence of the virus RNA [36] or by testing the semen of an infected man. During the first 5-12 days after onset of symptoms, Zika virus disease can be diagnosed by performing reverse transcription-Polymerase chain reaction (RT-PCR) in the blood of asymptomatic patients. Also, virus specific IgM and

neutralizing antibodies are usually present after the first week of illness and may be detectable in serum for up to 12 weeks. Detection of IgM antibodies shows the presence of acute or recent infection. The incubation period from mosquito bite to symptoms onset is approximately 3-12 days. Zika viral infection is likely asymptomatic in approximately 80% of cases [**35**]. Every age group of humans is susceptible to Zika viral infections.

6.0 PREVENTION

Since the major ways through which Zika virus is transmitted are: through mosquito bite and sexual contact, prevention could involve decreasing the population of the vector in areas where the infection occurs and proper use of condom [4]. It is also advisable that pregnant women should avoid areas with outbreaks of the infection [38]. There are presently no vaccines against Zika virus. However, researches are ongoing towards the development of inactivated vaccines and other non-live vaccines, which are safe to use in pregnant women and those of childbearing age [39].

7.0 CONCLUSION

Zika virus might have been underrated all these while; but the current range of outbreaks and its complications are signs that there is more to Zika virus than has been known especially in the face of consistent changes in the environment and the capability of the vector to change too in response to the changing ecosystem. Newer and more virulent strains of Zika virus may therefore soon emerge which could cause a pandemic beyond the range of HIV since the primary carrier is mosquito which is ever present with man.

In light of above, a more vigorous research approach is needed towards Zika virus in Nigeria in order for everyone to be aware and know what to do in case of an outbreak of a more virulent strain.

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