EPIDEMIOLOGIC REVIEW OF ZIKA VIRUS DISEASE

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SUMMARY

Zika virus disease has resonated great concern globally. The World Health Organization declared it "a public health emergency of International concern" on 1st February, 2016. The recent outbreaks have become a major challenge due to a drift from its earlier known benign exanthematous spectrum to a causal link to microcephaly. Historically, the name Zika virus comes from the Zika Forest of Uganda. It was first identified in 1947 among Rhesus Macaque sub-population. Two genetically distinct isolates have been well characterized; the Asian and African strains. This virus is spread by bites of day-time-active Aedes mosquitoes; the Aedes aegypti and Aedes albopictus. Zika Virus appears to spread along a narrow equatorial belt of Africa to Asia through the Pacific Ocean to French Polynesia, New Caledonia (southwest Pacific Ocean), the Cook Islands (south Pacific), and Easter Island (a Chilean territory in Polynesia), and most recently to Mexico, Central America, the Caribbean, and South America, where today has assumed a pandemic proportion.

Up to eighty percent of infections are asymptomatic. Symptomatic infections are characterized by a self-limiting febrile illness and maculopapular rash, arthralgia, conjunctivitis, back pain and mild headaches. Maternal Zika viral load is thought to be a significant risk factor to fetal infection leading to invasion of either trophoblasts or placental cells or both through maternal decidua. Zika viral RNA proteins and associated extensive selective tissue injuries have been demonstrated in the brains and spinal cords of abortuses. Diagnosis of Zika virus is essentially based on viral RNA detection from clinical specimens. Currently, licensed preventive medicines or vaccines are unavailable. With the wide spate of recent outbreaks and consequent neurologic morbidity and mortality, there is need for deployment of point-of-care equipment for screening of pregnant women in our environment. This is an ambitious call for advocacy by all relevant health care providers.

Key words: Zika Virus, disease outbreaks, microcephaly, Aedes mosquitoes.

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INTRODUCTION

Zika virus fever is anarthropod-borne viral infection caused by Zika virus.[1] It is a Flavirus from Flavivirdae family. Historically, its name comes from the Zika Forest of Uganda in East Africa where it was first identified in 1947, among the Rhesus Macaque sub-population.[2] Two genetically distinct isolates have been characterized; the Asian and African strains.[2-4]

The Zika virus is spread by bites from daytime-active *Aedes* mosquitoes; *A. aegypti* and *A. albopictus*.[5] From the nineteen-fifties, this virus has been known to spread characteristically eastward and appears to do so within a narrow equatorial belt from Africa to Asia through the Pacific Ocean to French Polynesia, New Caledonia (southwest Pacific Ocean), the Cook Islands (south Pacific), and Easter Island (a Chilean territory in Polynesia), and most recently to Mexico, Central America, the Caribbean, and South America, where today has assumed a pandemic proportions.[6]

A population based-survey in 1947 in Uganda found a prevalence of 6.1%.[7] Another sero-prevalence survey among healthy population in sub-urban community in Indian found substantial antibodies to Zika virus, suggesting a prior exposure.[8] The first reported human case of Zika virus infection in Nigeria was in 1954.[9] In a population based study which included 60% pregnant women in north-central Nigeria,

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(2018), Phillip *et al* found an anti-ZIKV positive rate of 6% for IgM and 4% for IgG. Pregnant women showed antiZIKV positive rates of 4% for IgM and 3% for IgG. A significant association with male sex was found for anti-ZIKV IgG ELISA positivity (prevalence ratio 3.49; 95% CI: 1.48–8.25; p=.004). In the same study, ZIKV neutralizing antibodies were detected in 17/18 (94%) anti-ZIKV NS1 positive/borderline samples and in one sample without detectable ZIKV NS1 antibodies. Partial ZIKV E gene sequence was retrieved in one sample without ZIKV antibodies, which clustered within the West African ZIKV lineage.[10]

The virus may be transmitted vertically from an infected pregnant mother to her unborn baby. This intra-uterine infection has recently been causally associated with microcephaly. Infection in adult sub-population may also result in Guillain-Barre syndrome. [11]Currently, prevention medicines and vaccines against Zika virus fever does not exist.[12]

With increased global travels for economic, medical and social tourisms, no country of the world is immune to this infectious virus. While there are plethora of literature and ongoing research efforts on the Zika virus infection in some parts of the world, same cannot be said in our setting. The aim of this article therefore, is to provide an epidemiological review of Zika Virus Disease and to highlight relevant lessons that could be learnt from previous Zika virus outbreaks in regard to epidemic preparedness.

Documented outbreaks

The discovery of Zika virus was rather an incidental finding. In April, 1947, a team of scientists of the Yellow Fever Research Institute first isolated a filterable transmissible infectious particle from serum of a febrile rhesus macaque monkey which had been placed in a cage in the Zika Forest of Uganda near Lake Victoria.[13] This team of researchers at the time was working on Yellow Fever Virus project.[13]A second viral isolation was subsequently made in January, 1948 from *Aedes africanus* among the same sub-populations of febrile monkeys. [14,15]

The first evidence suggestive of human Zika virus infection

Historically, Zika virus has been known to infect human subjects from previous serological surveys in Uganda and Nigeria: Fifty of 84 cohort screened for Zika virus were seropositive and all of who were over 40 years of age.[14] A similar survey amongst Indian natives demonstrated strong immunogenicity. Both studies cited above suggests widespread Zika virus infection in human population.[16]

In 1952, a team of scientists was investigating a suspected Yellow Fever outbreak in a 10-year old Nigerian female who had fever, headaches, joint pain but no jaundice and had recovered spontaneously from her illness within few days. Her blood was injected into the brain of a laboratory mice. The virus isolates from the mouse brain was then tested for neutralizing specific antibodies to Zika virus using rhesus monkey sera. Curiously, no virus was isolated from the blood of two infected adults with fever, jaundice, cough, diffuse joint pains in one of the adults and fever, headaches, and arthralgia. Zika virus infection was then isolated in human for the first time. In 1954, the finding was published.[17]

Zika virus spread in Equatorial Africa and Asia, 1952 to 1983

Between 1951 and 1983, clinical and laboratory evidence of human Zika virus were subsequently reported from other African countries like the Central African Republic, Egypt, Gabon, Sierra Leon, Tanzania and Uganda. Similar reports were documented in other parts of Asia such as India, Malaysia, the Pakistan, Philippines,

Vietnam and Thailand. [18,19] As at 2007, fourteen countries had confirmed human cases of Zika fever from continents of Africa and South-East Asia. [20]

ZVD Outbreak in Micronesia, 2007

The first and major reported outbreak of zika fever outside the continents of Africa and Asia was in April, 2007 on the Yap Island Federation, Micronesia. The commonest clinical manifestations were fever, skin rash, arthralgia and conjunctivitis. [21]These symptomatology was previously considered to be dengue, Chikungunya or the Ross River disease. However, during the acute phase of the disease, 108 Zika RNA seropositiveby PCR or serology and 72 additional suspect cases. No morbidity or mortality from ZVD was recorded. [22]

The predominant mosquito vector spp. identified was *Aedes hensilli*. While the mode of introduction of the Zika fever had remained elusive, it was thought to have happened through infected mosquitoes or a human infected with related strains from the Southeast Asia.[23]

Oceania ZVD outbreak of 2013 to 2014

Between 2013 and 2014, pockets of Zika fever outbreaks were reported. Among those were in the French Polynesia, Easter Island, New Caledonia and the Cook Islands. The virus source of this outbreak was not immediately clear. It was however, thought to be an independent introduction from those of the Southeast Asia which was linked to the Yap Island outbreak described above. [24]

The Americas: Zika virus Outbreak from 2015 to date

In February 2014, Zika virus outbreak was reported throughout South and Central America, and by November of 2015, it had reached Mexico.[25]Ten confirmed cases of Zika travel-related infections were reported in Dallas and Texas, United States of America and Europe without identifiable mosquito vectors.[26] Sexual transmission of Zika virus was reported almost for the first time in Texas in February 2016.[25,27].

Brazilian health authorities reported its first 16 cases of Zika fever in 14 states of the country as at May, 2015.[28] By December 12, 2015, the Brazilian Ministry of Health reported about 2,400 suspected cases of microcephaly in the country, of which 29 cases resulted in mortality.[29-31] In the State of Pernambuco alone, cases of microcephaly had exponentially rose from 150 to 200 per year the preceding 5 years. [32] A mathematical model estimated the risk of microcephalyto 1% of all infants born to Zika virus seropositive mothers in the first trimester of pregnancy. [33]

On January 2016 WHO issued a public health warning of possible Zika virus spread to contiguous countries of the Americas because of the bionomics of the *Aedes* mosquito vector. [34] By February, 2016, it declared Zika virus a Public Health Emergency of International Concern because of compelling evidence of pregnancy loss, birth defects and other neurological deficits.[35] In April 2016, there was an expert consensus on Zika related microcephaly and Guillain-Barre syndrome in human adult. [36,37]

Aetiology of ZVD

Zika fever is caused by Zika virus. It is an envelope, icosahedral, non-segmented single- stranded, positive-sense RNA virus, aFlavirus from the Flaviviridae family. Viral particles are 40nm in diameter with an outer envelope and a dense inner core[38,39,40]Thus, it is related to dengue, yellow fever, Japanese encephalitis and West Nile virus.

Transmission

Zika virus disease is predominantly spread through the bite of infected female *Aedes* mosquito.[41] An infected male can transmit the virus to his sex partner. Sexual transmission has been reported in 6 countries: Argentina, Chile, France, Italy, New Zealand and the

United States of America in 2015[11] Zika virus transmission via blood and blood products transfusions have also been documented.[42] In April, 2016, 2 cases were reported both from Brazil. [43]Transplacental spread from an infected pregnant mother to her unborn baby or at delivery (birth canal) have been recognized [11,44]

The *Aedes* mosquito vector is very active during day time. It breeds around stagnant water, abandon automobile parts, flower vases, uncovered buckets and wet shower flows. Only the female bites for blood, required to mature her eggs. Characteristically, she bites 4 to 5 times a day in the afternoon and early in the evenings. There are two types: the *Aedes egypti* and *Aedes albopictus*.[45]

Pathogenesis

Zika virus replicates in the epithelial lining of the mid-gut and the salivary cells of mosquito vector. After a variable period of about 5 days, it appears in the mosquito saliva which subsequently becomes infectious. During blood meal, the vector inoculates its human host skin. The virus may then infect the epidermal keratinocytes, the fibroblast and the Langerhans cells. It is thought that, the Zika virus spreads to the lymphatic and haematogenously.[3,8,46] In stark contrast to other Flaviruses, its antigen has been demonstrated in host cell nucleic.[46]

Clinical features

Up to eighty per cent of infections are asymptomatic.[48]Symptomatic (viraemic stages)of infections are characterized by a self-limiting febrile illness of 4–7 days duration associated by maculopapular rash, arthralgia, conjunctivitis, back pain and mild headaches.Within 2 days, skin rash begin to fade spontaneously and within 3 days, fever starts to resolve and only few rash persists.[49]

Maternal Zika viral load is thought to be a significant risk factor to fetal infection. The mechanism for intra-uterine infection is not completely clear. It is thought that, maternal Zika viraemia is critical to invasion of either trophoblasts or placental cells or both through maternal decidua. Zika virion then binds to maternal intervillous spaces by a process of transcytosis to yet unidentified receptors. It said to now replicates more efficiently in FcyR in myeloid cells. Zika viral RNA proteins and associated extensive selective tissue injuries have been demonstrated in the brains and spinal cords of abortuses.[50]

Gullain-Barre syndrome is thought to be due to immunopathology resulting from antigenic mimicry of a host protein. Zika virus appears to have selective tropism to neurons/glial cells causing demyelination of affected neurons. Frequently reported clinical manifestations include: muscle weakness, tingling sensations on the arms and legs and parasthesias. Recently, a positive association has been observed with prior or concurrent Dengue virus infections.[45]

Some yet unanswered pathogenetic questions about Zika virus disease; are there sanctuary sites for Zika virus in human host? What is the nature of pathologic lesions of the virus and why only certain individual human hosts manifest the disease? Detailed longitudinal studies are needed to answer such questions. [51]

Ultrasonographic findings at 18 to 19 week's gestation suggestive of Zika virus infection includecerebral hemispheres were markedly asymmetric (severe unilateral ventriculomegaly) - almost complete disappearance or failure to develop the thalami - thin pons and brainstem Mother.[50] By the 29 weeks intra-uterine life, observed changes become evident such as microcephaly, brain atrophy with coarse calcifications involving the white matter of the frontal lobes, the caudate nucleus, lentostriatal vessels and the cerebellum. Other notable sonographic anomalies are

dysgenesis of the vermis and corpus callosumand enlargement of the cisterna magna.[51]

Laboratory Diagnosis

Diagnosis of Zika virus is essentially based on viral RNA detection from clinical specimens. Direct virus detection is only during the first 3 to 5 days after onset of symptoms[1, 52, 53]Specific assays targeting the Asian and African Zika virus isolates of the envelope gene or NS5 region [1,52]Pan-flavivirus assays and sequencing analysis can be used as a surrogate for possible Zika virus infection[53,54]

Saliva and urine specimens for viral genome detection by RT-PCR might be diagnostic. ZIKV-specific IgM/IgG antibodies can be detected by ELISA and immunofluorescence assays in serum specimens, usually from day five or six of symptomatic illness.

False positive test results may be with dengue and other Flavivirus infections. A positive result for dengue IgM antibodies without detection of dengue IgG in paired sera among travellers returning from areas affected by ZIKV should prompt a possible investigation for another flavivirus aetiology. Positive results should be confirmed by neutralization test.

Treatment

At the moment, no preventive medicines or vaccines are available. However, Zika virus disease symptoms may be controlled with bed rest, intravenous fluids and acetaminophen [55]

Vaccine development

As at January 2016, the NIH Vaccine Research Center started some work toward s development of effective vaccine for Zika.[56] In February, 2016, Bharat Biotech International announced it was developing 2 candidate vaccines; recombinant and inactivated Zika vaccines, both of which are at preclinical stages of development. [57] eighteen international companies as at March, 2016 have been working very hard to produce vaccines against Zika virus, but known had reached clinical trials [58]

CONCLUSION

With wide distribution of competent *Aedes aegypti* and *Aedes albopictus* mosquito vectors in the Americas, some European countries, sub-saharan Africa including Nigeria, the unfortunate absence of available vaccines globally, ZIKV Disease spread is likely to continue for some time. These possibilities are significantly made even easier by increased global travels for both economic and tourism purposes. The causal link of ZIKV infection to abortion, microcephaly and other Central Nervous System anomalies has further made it even urgent for coordinated effort by health authorizes of other seeming Zika-free countries to set up surveillance and containment strategies in countries where the *Aedes* mosquito vectors are equally abundant. In addition, deployment of point-of-care equipment for screening of pregnant women in antenatal clinics may be helpful in our environment. This, is an ambitious call for advocacy by all relevant health care providers.

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