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R E V I E W A R T I C L E

A Review on Zika Virus Diagnosis

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A B S T R A C T

Zika virus is a mosquito borne flavivirus that is the focus of an ongoing pandemic and public health emergency. It was first isolated in 1947. Since then, multiple outbreaks of ZIKV have been reported in different countries. It is transmitted mostly by Aedes mosquitoes, and the symptoms of fever, joint pain, red eyes, headache, and maculopapular rash closely resemble chikungunya and dengue. The most severe complications of ZIKV infection include the risk of microcephaly and other congenital brain anomalies in infected pregnant women. This review is based on literature search in PubMed/Medline, Google Scholar and the WHO, http://www.who.int. This include all relevant articles written in English published through June 2018, with subject heading and keywords such as Zika, ZIKV, Zika pathogenesis, diagnosis of Zika, Zika Nigeria, Zika Africa and Zika resource-limited settings. Following ZIKV infection, viraemia ensues targeting primarily the monocytes for both the Asian and African strains. There is no routine laboratory diagnosis of ZIKV infection in resource-constrained countries. Serologic tests should be interpreted with caution since there can be cross-reactivity with other flaviviruses, especially in Africa where the burden of infection with flaviviruses is comparatively high.

Keywords: Zika virus, Mosquitoes, Flavivirus, Chikungunya, Dengue, Diagnosis

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1. Introduction

Zika virus is a flavivirus that was first isolated in 1947 from a febrile rhesus macaque monkey in the Zika Forest of Uganda and later identified in Aedes africanus mosquitoes from the same forest. In 1954, the first 3 cases of human infection were reported in Nigeria. Serosurveillance studies in humans suggest that Zika virus is widespread throughout Africa, Asia, and Oceania. However, these studies may overestimate the virus's true prevalence, given serologic

overlap between Zika virus and related flaviviruses, such as dengue virus (DENV) and West Nile virus (WNV)[1]. Zika virus is a growing concern – it is endemic in parts of Africa, has been reported in South East Asia and is becoming established in the Americas and Caribbean. Since its detection in Brazil in 2015, it has emerged as a major public health challenge in the Americas. As of 16 June 20161, 60 countries and territories report continuing mosquito-borne transmission of which:46 countries are experiencing a first outbreak of Zika virus since 2015, with no previous evidence of circulation, and with ongoing transmission by mosquitos. 14 countries have reported evidence of Zika virus transmission between 2007 and 2014, with ongoing transmission. While the virus is known to cause mild illness (characterized by conjunctivitis, fever, rash and joint pain) many of the countries affected by Zika virus are also reporting potential neurological and auto-immune complications related to Zika virus infection with increased reports of Guillain-Barré syndrome, and birth defects including microcephaly[2].

Virology and Pathogenesis

Zika virus is a positive-sense single-stranded RNA virus in the family Flaviviridae, which includes several other mosquitoborne viruses of clinical importance (e.g., DENV, WNV, and yellow fever virus [YFV]). Its closest relative is Spondweni virus, the only other member of its clade. The Zika virus genome contains 10,794 nt encoding 3,419 aa. Like other flaviviruses, Zika virus is composed of 2 noncoding regions that flank an open reading frame, which encodes a polyproteincleaved into the capsid, precursor of membrane, envelope, and 7 nonstructural proteins. Phylogenetic analysis shows that Zika virus can be classified into distinct African and Asian lineages; both emerged from East Africa during the late 1800s or early 1900s. The Asian lineage originated during the virus's migration from Africa to Southeast Asia, where it was first detected in Malaysia[3]. From there, Zika virus spread to the Pacific Islands, separately to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas

2. Transmission of Zika virus

Through mosquito bites:

Zika virus is transmitted to people primarily through the bite of an infected Aedes species mosquito. These mosquitoes typically lay eggs in and near standing water in things like buckets, bowls, animal dishes, flower pots and vases. They prefer to bite people, and live indoors and outdoors near people. Mosquitoes that spread chikungunya, dengue, and Zika are aggressive daytime biters. They can also bite at night. Mosquitoes become infected when they feed on a person already infected with the virus. Infected mosquitoes canthen spread the virus to other people through bites[4].

From mother to child:

A mother already infected with Zika virus near the time of delivery can pass on the virus to her newborn around the time of birth.It is possible that Zika virus could be passed from a mother to her baby during pregnancy.To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

Through sexual contact:

Zika virus is transmitted to the people through sexual activity. Dallas County Health and Human Services (DCHHS) has received confirmation from the Centers for Disease Control and Prevention (CDC) of the first Zika virus case acquired through sexual transmission in Dallas County in 2016. The patient was infected with the virus after having sexual contact with an ill individual who returned from Venezuela,a country where Zika virus is present.

Transfusion:

The potential for Zika virus transfusion transmitted infection was suspected in French Polynesia after viral RNA was detected in 2·8% of asymptomatic blood donors in 2014,2 and further confirmed in Puerto Rico in 2016 with 1·1% of blood donors identified as viraemic. In 2017, Zika virus RNA- positive asymptomatic blood donors were detected in Florida and Texas. Transfusion transmitted infection was confirmed in Brazil in 2016. As with sexual transmission, transfusion transmitted infection is difficult to prove in endemic areas. With the poor availability of molecular biology based assays and the challenges associated with interpretation of serology data, the number of documented cases of transfusion transmitted infection is probably underestimated[5].

Zika virus is a new challenge for the blood supply. WHO, the US Food and Drug Administration (FDA), and the American Association for Blood Banks have issued recommendations to prevent transfusion transmitted infections. As most infections are asymptomatic, the most effective mitigation strategies to prevent transfusiontransmitted infection are nucleic acid testing of blood donations or pathogen inactivation. A commercially available licensed pathogen inactivation system has been shown to inactivate a wide range of pathogens, including Zika virus, after photochemical treatment of plasma and platelets. Robust inactivation of Zika virus has also been shown with a pathogeninactivation system under development for the chemical treatment of red blood cells[6].

Clinical manifestations

About 80% of ZIKV infection is asymptomatic. Symptomatic infections are characterised by a self-limiting febrile illness which usually lasts 4–7 days and is associated with maculopapular rash, arthralgia, especially affecting the small joints of the hands and feet, conjunctivitis, back pain and mild headaches. Within 2 days, the skin rash begins to fade spontaneously and within 3 days, fever starts to resolve and only few rash persists. Other less common clinical features include nausea, diarrhoea, abdominal pain, ulcerations of mucous membranes, uveitis and palatal petechiae. Severe ZVD may be seen following in utero infection leading to neurological complications, notably microcephaly and Gullian-Barre syndrome (GBS). Meta-analysis showed that prevalence of ZIKV-associated GBS and microcephaly among all pregnancies were 1.23% (95% confidence interval [CI] = 1.17%–1.29%) and 2.3% (95%

CI = 1.0%–5.3%), respectively[7,8]. Other neurological manifestation seen include craniofacial disproportion, spasticity, seizures, irritability and brainstem dysfunction, feeding difficulties and ocular abnormalities. Neonates with ZVD usually have intrauterine growth restriction; other features may include a transient diffuse rash, conjunctivitis and conjunctival injection. Ocular abnormalities such as focal pigment mottling, chorioretinal macular atrophy, optic nerve abnormalities, cataract, intra-ocular calcifications, microphthalmia, conjunctival injections, optic disc cupping, lens subluxation in addition to bilateral iris coloboma, foveal reflex loss, macular hypoplasia and scarring. Several foetal neuronal abnormalities have been demonstrated when ultrasound was done at 29 weeks gestation; this include brain atrophy, large cysterna magna, severe unilateral ventricular enlargement, corpus callosum and vermian dysgenesis, absence or redumentary thalamus, thin brainstem and pons calcifications involving frontal lobes white matter, caudate, lenticulostriatal vesssels and cerebellum. Neuroimaging (computed tomography and magnetic reasoning imaging) features commonly reported in newborns include enlarged cisterna magna, hypogenesis of corpus callosum, ventriculomegaly, delayed myelination, cerebellar and brainstem hypoplasia, calcifications in the junction between cortical and subcortical white matter and cortical malformations like polymicrogyria in the frontal lobes. Interestingly, abnormality of frontal lobe has not been reported in other congenital infections.

Congenital Zika syndrome (CZS) refers to the range of abnormalities seen in neonates following Zika infection in pregnancy. This includes visual, hearing and other neurological abnormalities (including neuroimaging findings). Complete cranial growth may be attained at 30 weeks, Therefore, ZIKV infection in late pregnancy may not affect head size. The sensitivity of microcephaly in detecting probable or definite ZIKV infection is 83% (95% CI = 79–86). It has thus been suggested that microcephaly should not be a necessary criterion for diagnosis of CZS. The Centres for Disease Control and prevention, the USA has described five features to define CZS which include: severe microcephaly with partially collapsed skull; specific pattern of brain damage including subcortical calcifications and decreased brain tissue; damage to the back of the eye, including macular scarring and focal pigmentary mottling of the retina; congenital contractures such as club foot or arthrogryposis and hypotonia which restricts foetal body movement soon after birth. Routinely characterising this syndrome may be a challenge in resource constraint settings, with paucity of high cadre health workforce. Therefore, it is needful to develop a simple algorithm that low cadre health worker can readily identify. This is further compounded by challenge of confirming maternal Zika infection. Birth defects surveillance program in Atlanta for 2014 and North Carolina and Massachusetts in 2013–2014 found 2.86/1000 live births with one or more defects that met the 2016 CDC case definition for Zika surveillance. 52% of the birth defects were brain defects or microcephaly, other defects include neural tube defects and other early brain abnormalities (31%); eye defects (11%); sequelae of CNS dysfunction (0.6%). There were 48% pregnancy losses and 66% preterm delivery (<37 weeks' gestation). Between 2015 and 2018, in Brazil, there were 2952 CZS in a population of Population of 209,553,000. This gives a CZS population prevalence of 0.001. On the African continent data are scarce regarding CZS. However, the scarce data does not definitively proof the absence of CZS[9-13].

General Laboratory Findings

Information on laboratory findings for Zika virus infection is limited. Complete blood count is often normal; even if blood count is abnormal, changes may be nonspecific (e.g., mild lymphopenia, mild neutropenia, mild-to-moderate thrombocytopenia). Mild elevations in inflammatory markers (C-reactive protein, fibrinogen, and ferritin), serum lactate dehydrogenase, or liver enzymes have been described. These findings are observed in many other viral infections, including the co-circulating viruses DENV and CHIKV, so none of these laboratory alterations reliably distinguish among these infections[14].

Laboratory Diagnosis

The largely asymptomatic or mildly symptomatic nature of ZIKV infection makes laboratory testing important for diagnosis. Serologic test results should be interpreted with caution since there can be cross-reactivity with other flaviviruses, including in individuals who have been vaccinated against yellow fever or Japanese encephalitis. Infections with flaviviruses such as Yellow fever and Dengue fever are common in Africa as well as vaccination against yellow fever which makes cross-reactivity a critical challenge in the interpretation of test results in these settings. Current algorithms proposes a combination of IgM tests followed by plaque-reduction neutralisation tests (PRNTs) in cases of positive or equivocal results for definite diagnosis. If ZIKV IgM tests results are positive, equivocal or inconclusive, testing for neutralisation antibodies using PRNT should be performed to determine whether the ZIKV IgM reflects recent ZIKVinfection or a false-positive result[15].

A PRNT titre >10 should be interpreted as evidence of recent infection with ZIKV when the PRNT to the other flaviviruses tested is <10. The gold standard of ZIKV infection diagnosis is based on viral RNA detection from clinical specimens. Direct virus detection is only possible during the first 3–5 days after onset of symptoms. Saliva and urine specimens for viral genome detection by RT-PCR might be the best diagnostic specimen. Bingham et al. found that only 56% of Zika antigens were isolated from serum samples within 5 days of the onset of symptoms compared to 95% of urine samples collected on the same day. It is important to use PCR assays that target both the Asian and African ZIKV lineages which target the conserved regions of the envelope gene or NS5 region. This is to avoid false-negative results[16]. It is also important to note that real-time reverse transcriptase polymerase chain reaction (rRT-PCR) negative results does not rule out Zika infection due to decay in viraemia over time and inaccuracy in reporting onset of Zika symptoms. This challenge of clearly determining onset of Zika symptoms is particularly

challenging in Nigeria and other settings that are resource constrained, where several tropical diseases may present with fever. It has been proposed that pan-flavivirus assays and sequencing analysis can be used as a surrogate for possible ZIKV infection. However, in settings with high flaviviral infections like Nigeria; this may be fraught with high false-positive making its clinical utility suboptimal. This is because ZIKV IgM enzyme-linked immunosorbent assay can provide false-positive results because of cross-reacting IgM antibodies against related flaviviruses or non-specific reactivity.

Dengue infection serology in some parts of Nigeria is between 2.3% and 44.4%. In 1986, there were 9800 cases of yellow fever with 5600 deaths in Oju, Benue state, Nigeria. Moreover recently, between 12 September 2017 and 21 February 2018, there were 87 confirmed yellow fever cases in seven States of Nigeria (Kwara, Kogi, Kano, Zamfara, Kebbi, Nasarawa and Niger). There is no routine laboratory diagnosis of Zika in Nigeria like in other resource constraint countries[17,18]. In these countries, health systems are weak because of inadequate funding. There is a paucity of well-equipped laboratories for comprehensive ZIKV diagnosis. In addition, the out of pocket payments for health services in developing countries such as Nigeria is high, making health workers to prioritise treatment over testing. It is imperative to strengthen the health systems, improve health workforce and diagnostic capacity of such settings.

3. Management and Prevention

No specific treatment or vaccine is available for Zika virus infection. Management is supportive and includes rest, fluids, antipyretics, and analgesics. Aspirin and other nonsteroidal antiinflammatory drugs should be avoided until dengue is excluded because of the risk for hemorrhage among dengue patients. Other general measures focus on prevention of mosquito bites, including individual protection (e.g., long pants, light-colored clothing, insect repellants, bed nets), particularly during known Ae. aegypti peak biting times (early morning and late afternoon). Community-level strategies target mosquito breeding through elimination of potential egg-laying sites (e.g., potted plant saucers, water storage units, used tires) by drying wet environments or using insecticide treatment[19].

Pregnant women residing in countries that are not Zika virus–endemic are advised against travel to affected countries (online Technical Appendix reference. Testing should be offered to all pregnant women who have traveled to areas with ongoing Zika virus transmission. Serial fetal ultrasounds should be considered to monitor fetal anatomy and growth every 3–4 weeks in pregnant women with positive or inconclusive Zika virus test results, and the infant should be tested at birth. Men who reside in or have traveled to an area of active Zika virus transmission and who have a pregnant partner should abstain from sexual activity or use condoms during sex; similar guidelines apply for men with a nonpregnant female sex partner who is concerned about sexual transmission of Zika virus[20].

4. Vaccines and drugs against Zika virus

Vaccine development has been well supported by international funding agencies. A DNA vaccine has entered phase 1 clinical trials and there are more than 40 vaccine candidates in the pipeline, some of which are being fast tracked for licensure. Nevertheless, a vaccine will probably not be available for at least 2 years. It is also not known if Zika virus infections lead to lifelong immunity. Using large screening strategies, several compounds have been found to have in- vitro activity against Zika virus, but there are no antiviral drugs that have shown activity against the virus in vivo[21].

5. Conclusion

ZIKV has caused global concern, especially because of its associated congenital malformations and neurological sequelae. It is pertinent to fully understand the pathogenesis of Zika including the African strain. The largely asymptomatic nature of the infection and lack of routine viral diagnostic facilities makes the establishment of true extent of infection a challenge while its largely asymptomatic course also means testing may not be a priority for health-care providers.Given reports of possible transfusion-transmitted Zika virus, the pandemic also has implications for the blood supply within Zika virus–endemic and nonendemic regions. The US Food and Drug Administration recommends 28day deferral for blood donors with confirmed or suspected Zika virus infection.The current knowledge of Zika virus infection is based only on a short period of 10 years, with most efforts deployed over the last year, and the consequences of long- term congenital Zika- associated syndrome are unknown and should become clearer over the next decade.

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