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Review Article

The reemergence of Zika virus: a review on pathogenesis, clinical manifestations, diagnosis, treatment, and prevention

Running Title: Reemergence of Zika Virus

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Abstract

Zika virus (ZKV) is an arbovirus of the Flaviviridae family, which includes West Nile, Dengue Fever, Chikungunya Virus, Yellow Fever, and Japanese encephalitis virus. It is transmitted by the Aedes genus of mosquitoes. Prior to 2015, ZKV outbreaks occurred in areas of Africa, the Pacific Islands and Southeast Asia. The current large outbreak, which began in Brazil, has also emerged throughout a large part of South/Central America, a number of islands in the Caribbean, including Puerto Rico, the Virgin Islands, and Mexico. A sudden rise in the numbers of infants reported born with microcephaly in Brazil, and the detection of the single-stranded positive RNA virus in the amniotic fluid of affected newborns, has captured medical, mainstream media, and global political attention, causing considerable concern in a post-Ebola global community considerably more focused on the threat of internationally transmissible diseases. The goal of this article is to provide an overview of ZKV for clinicians, with the emphasis on pathogenesis, clinical manifestations, diagnosis, and treatment/preventive measures.

Introduction

On March 26, 2015, an outbreak of Zika Virus (ZKV) transmitted via *Aedes* mosquitoes was detected in the blood sample of 24 patients in the small town of Bahia, Brazil. Transmission of the virus has spread rapidly to become an emerging epidemic of global concern. (1). The epidemic in Brazil alone is estimated at 440 thousand to 1.3 million cases (2). The 2013-2014 ZKV outbreak in French Polynesia has been largest outbreak to date (3). Experts believe that the virus was introduced into Brazil during the World Cup soccer competition in 2014, during which four Pacific countries (New Caledonia, French Polynesia, Easter Island, and Cook Islands) in which ZKV circulated in 2014 had teams participating in this contest (3). With over 2.7 million arrivals from Brazil to USA (September, 2014 - August, 2015), Bogoch et al., listed high-risk international pathways for the dispersion of ZKV and other global destinations with appropriate mosquito populations to allow autochthonous transmission (2).

Furthermore, an abrupt rise of infants born with microcephaly and the detection of the single-stranded positive RNA virus in the amniotic fluid of affected newborns has produced significant global concern (4). The goal of this article is to provide an

overview of ZKV for clinicians, with the emphasis on pathogenesis, clinical manifestations, diagnosis, treatment, and preventive measures.

Pathogenesis

ZKV is a mosquito-borne flavivirus related to dengue virus, yellow fever virus, and West Nile virus. ZKV is a single-stranded positive RNA virus (10,794-nt genome), which is closely related to the Spondweni virus and is transmitted by several *Aedes* mosquitoes, including *Aedes. africanus*, *Aedes. hensilli*, *Aedes. luteocephalus*, *Aedes. Aegypti, etc.* ZKV was first recognized in rhesus monkeys in 1947 during the sylvatic yellow fever surveillance in Zika Forest of Uganda, and reported in humans in 1952 (**Figure 1**) (5, 6). Of the two known lineages of the ZKV (African and Asian), Phylogenetic studies indicate that the closest strain of ZKV to that which, emerged in Brazil, was isolated from samples taken in French Polynesia and spread among the Pacific Islands, and belongs to the Asian lineage (3).

Literature describes that the human epidermal keratinocytes, dermal fibroblasts, and immature dendritic cells are permissive to the most recent ZKV isolate, responsible for the French Polynesia epidemic (7). The virus next moves to the lymph nodes where autophagosomes may form causing enhanced viral replication and viremia (7). The notorious association of the virus and newborn microcephaly remains to be independently confirmed and verified.

To date, ZKV has been reported in human blood as soon as the day of the illness, while the viral nucleic acid has been detected until 11 days post onset. Ether, potassium permanganate, and temperatures >140°F (>60°C) have reportedly eliminated ZKV, whereas, 10% ethanol has failed to neutralize the virus (8).

Clinical Manifestations

Historically, ZKV presents as a mild or inapparent form of dengue-like disease with myalgia, arthralgia, fever, conjunctivitis, maculopapular rash, headache, and prostration (**Table 1**). Given the overlapping clinical manifestations of zika, chikungunya, and dengue virus, **Table 2** differentiates between the aforementioned viruses.

While severe disease requiring hospitalization from ZKV is uncommon, data from the French Polynesia epidemic documented a concurrent epidemic of 73 cases of Guillain–Barré syndrome and other neurologic conditions, which may represent complications of ZKV (9). The latest 20-fold increase in the Brazilian epidemic of microcephaly, from 2014 to 2015, has led public health officials to postulate that the cause may be ZKV infections in pregnant women. Reports of seeing calcifications in fetal brain and placenta have been documented using ultrasonography.

While no other virus of the *Flaviviridae* family is identified to have teratogenic effects, the microcephaly epidemic has yet to be linked to any other cause. Even with the lack of any definitive proof of a direct relationship, health officials recommend all expecting women take precautions in avoiding mosquito bites and even to delay pregnancy.

According to a preliminary analysis of research carried out by the Brazilian health ministry, the greatest risk of microcephaly and malformations appears to be associated with infection during the first trimester of pregnancy. Furthermore, these health authorities in conjunction with the Pan American Health Organization are conducting research to clarify the cause, risk factors, and consequences of microcephaly (9). Other sporadic literature has reported patients with hypertensive iridocyclitis and macular degeneration attributed to ZKV, as well as, the virus being sexually transmitted, with the latest report coming from Dallas, Texas (10-12).

Diagnosis

A preliminary diagnosis of ZKV revolves around the patient's clinical features (**Table 1 and 2)**, activities, places, and dates of travel. Though the transmission of the virus mostly occurs via mosquito vectors, reports of sexual transmission and blood transfusion have been recorded (10, 13). Furthermore, because ZKV is closely linked to dengue, the serologic samples may cross-react in tests for either virus. Gene-detection tests accomplished by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum to detect virus, viral nucleic acid, or virus-specific immunoglobulin M and neutralizing antibodies can reliably distinguish between infection with the dengue, zika, and the chikungunya viruses. The test is most accurate after day 7 of the disease.

Given the nationally notifiable condition of ZKV along with its laboratory diagnostic challenges, Center for Disease Control and Prevention (CDC) is facilitating diagnostic testing for all healthcare institutions by providing instructions using the "CDC Form 50.34" for submitting diagnostic specimens to its Division of Vector-Borne Diseases. **Appendix 1** describes the required amount and the type of specimen needed for submission. Upon appropriate submission of sufficient specimen, test results are available 4-14 days after receipt. Results may be delayed during summer when arbovirus activity increases.

Treatment

No specific treatment is available for ZKV. Supportive care includes rest, antipyretics, analgesics, and watching for coagulopathy or multi-organ failure are important goals of care. Antihistamines may be considered for cutaneous symptoms. Intravenous fluids, oxygen (as needed), and monitoring vital sign are further measures of care. Given the similarities in the symptoms and geographic distribution, suspected cases of ZKV should be assessed and managed for possible dengue or chikungunya virus infection. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin should be delayed until dengue can be ruled out to reduce the possibility of hemorrhagic complications.

Prevention

With no vaccine or antiviral therapy currently in the market, clinicians should focus on patient education and emphasize on preventive measures like repellent use, daytime avoidance of mosquito bites, air-conditioning, window/door screens, removal of household debris and water containers, which provide mosquito-breeding sites. Patients infected with zika, chikungunya, or dengue virus should be protected from further mosquito exposure, specially during the initial days of illness to prevent other mosquitoes from becoming infected and reduce the risk of local transmission.

Maternal-fetal transmission of ZKV has been documented throughout pregnancy (4, 14). As a result, the Center for Disease Control and Prevention (CDC) has released interim guidelines (**Figure 2**) for pregnant women considering travel to an area with ZKV transmission and recommendations for screening, testing, and management of pregnant returning travelers (15). Additionally, clinicians should remind non-pregnant women not to travel to plagued areas without obtaining pregnancy testing prior to travel and strongly consider cancelling or postponing travel to these areas if there is any risk of pregnancy.

The Royal College of Obstetricians and Gynecologists recommends that women testing negative should be referred for ultrasonography, which should be repeated every four weeks. While women who test positive should be referred for ultrasonography and to fetal medicine for follow-up (16). Male patients must also receive counseling prior to travel with emphasis on sexual abstinence or correct condom use with their pregnant or potentially pregnant female partners.

Conclusion

Historically, ZKV has caused major epidemics in pacific territories and is now emerging rapidly in various countries throughout the Americas including Brazil, where it has been suspected in the millions if not a few hundred thousand. In areas where potential vectors are present, preventive measures should be implemented to detect imported cases of ZKV, and laboratory capacity should be enhanced in detecting suspected ZKV infections.

Conflicts of interest: None

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Table 1: Basic Information on Zika Virus

Symptoms

Headache
Arthralgia
Myalgia
Conjunctivitis
Fever
Vomiting
Maculopapular Rash
Prostration
Edema of Extremities

Incubation Period

3-12 days

Treatment

Conservative Management (bedrest, fluids, acetaminophen)

Prevention

House Screens
Air Conditioning
Removal of Debris
Repellents
Avoid mosquito bite during 1st week of illness to avoid human → mosquitos →human transmission

Table 2: Clinical manifestations of chikungunya, zika, and dengue virus

Symptoms	Chikungunya	Zika	Dengue
Headache	*	*	***
Arthralgia	***	*	*/-
Myalgia	**	*	***
Conjunctivitis	**	***	-
Fever	**	*	***
Maculopapular Rash	**	***	*
Dyscrasia	*/-	-	**
Neutropenia	*	-	**
Lymphopenia	***	-	**
Thrombocytopenia	*/-	*/-	***
Shock Syndrome	*/-	-	***
Hepatomegaly	***	-	-
Edema of Extremities	-	**	-

*** High Intensity; ** Medium Intensity; * Low Intensity; (-) Absent

Figure 1: Timeline of major global ZKV outbreaks

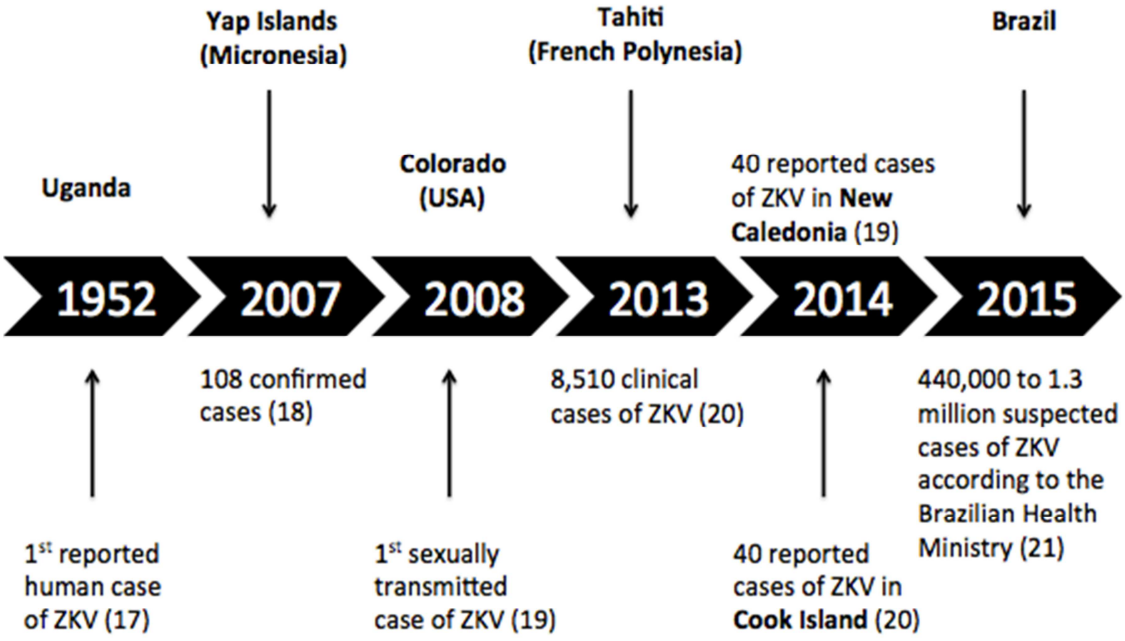
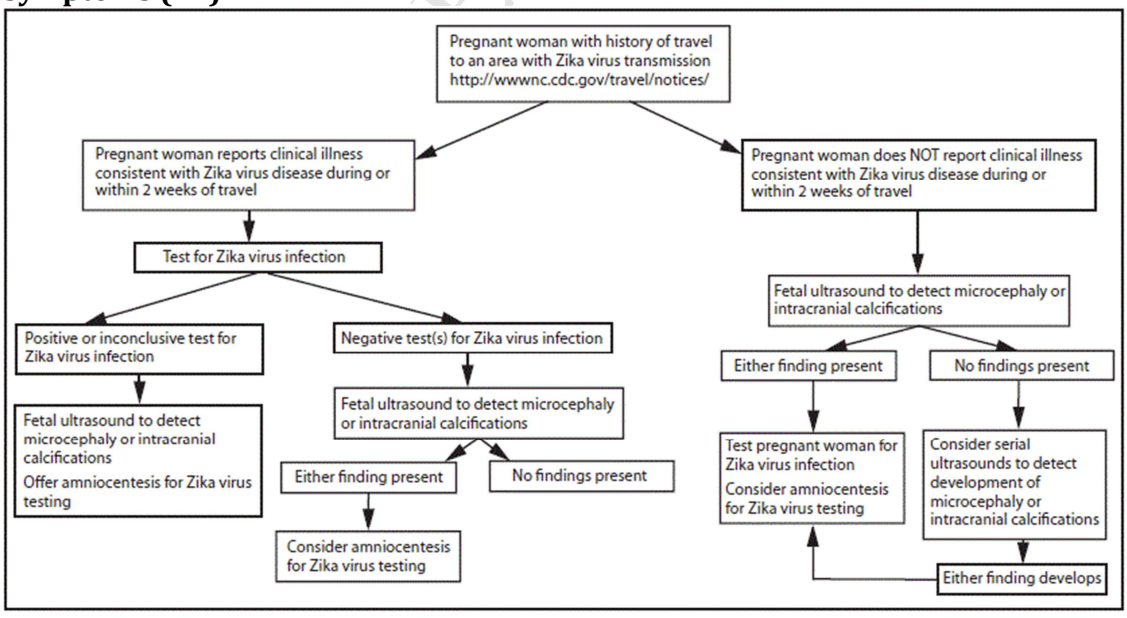


Figure 2: Interim guidance: testing algorithm for pregnant women with history of travel to an area with ZKV transmission, with/without clinical symptoms (14).



*Adopted from CDC Website

Appendix 1

Specimen Types and Amounts

a. Acute and convalescent specimens, if available, should be sent together.
b. Ideal timing of specimens for serology:

Specimen	Timing
Acute	3 to 10 days after onset of symptoms
Convalescent	2-3 weeks after acute sample

c. At least 0.5 mL of serum and/or 1.0 mL of CSF is required for serology testing. CSF specimens are routinely tested undiluted and therefore require larger amounts. Whole blood will not be accepted for serology testing. Please transfer serum or CSF to a plastic tube with screw cap measuring no more than 5 cm tall and approximately 13 mm in diameter (e.g. 1.8 mL cryotube or 2.0 mL microtube).
d. For serology testing, the specimen should be kept cold or frozen. The sample may be placed in an insulated container with blue ice packs. Additional blue ice packs should be used in the summer to ensure specimen integrity in hot weather.
e. For virus isolation and/or nucleic acid amplification testing, acceptable specimens are fresh frozen tissue, serum, or cerebrospinal fluid. Tissue specimens should be approximately 1 cm⊃3; frozen as soon as possible at -70ºC, and shipped on enough dry ice so that specimens remain frozen until received. Formalin-fixed specimens are not tested at DVBD and can be submitted to the Special Pathogens Laboratory in Atlanta, GA for immunohistochemistry:

   Infectious Disease Pathology Branch
   Centers for Disease Control and Prevention (MS-G32)
   1600 Clifton Rd, NE
   Atlanta, GA 30333

Clinical Significance

- The latest 20-fold increase in the Brazilian epidemic of microcephaly, from 2014 to 2015, has led public health officials to speculate that the cause may be ZKV infections in pregnant women.
- Health officials need to promote awareness in all traveling patients, and work with their respective state health officials in developing an understanding of our complex ecosystems in which sources of future pandemics are rapidly evolving.