

Emergence of Zika Virus Infection: Present and Future Outlook

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ABSTRACT

Zika virus infections have been known in Africa and Asia since the 1940s, but the virus's geographic range has expanded dramatically since 2007. Between January 1, 2007, and March 1, 2016, local transmission was reported in an additional 52 countries and territories, mainly in the Americas and the western Pacific, but also in Africa and southeast Asia. There is scientific consensus that Zika virus is a cause of microcephaly and Guillain-Barré syndrome. Links to other neurological complications are also being investigated. In January 2016, the United States Centers for Disease Control and Prevention (CDC) issued travel guidance on affected countries, including the use of enhanced precautions, and guidelines for pregnant women including considering postponing travel. This review describes the current understanding of the epidemiology transmission, clinical characteristics, and diagnosis of Zika virus infection, as well as the future outlook with regard to this disease.

Key words: Zika Virus, Epidemiology, Transmission, Clinical Manifestation, Diagnosis, Treatment.

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INTRODUCTION

Zika virus (ZIKV) is a single-stranded RNA virus, an arthropod-borne flavivirus distributed throughout much of Africa and Asia. Other mosquito-borne flaviviruses previously determined to be of public health importance include yellow fever, dengue, St. Louis encephalitis, West Nile and Japanese encephalitis viruses. ZIKV is transmitted to humans primarily through the bite of an infected *Aedes* mosquito species, first isolated from a monkey in the Zika forest of Uganda in 1947.¹ ZIKV disease is generally reported with characteristics of acute febrile illnesses that clinically resembles dengue fever. The most common symptoms are fever, joint pain, rashes, and conjunctivitis, with symptoms lasting from several days to a week. To determine whether Zika virus infection during pregnancy causes these adverse outcomes, we evaluated available data using criteria that have been proposed for the assessment of potential teratogens. On the basis of this review, we conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies. Evidence that was used to support this causal relationship included Zika virus infection at times during prenatal development that were consistent with the defects observed; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with presumed or confirmed congenital Zika virus infection; and data that strongly support biologic plausibility, including the identification of Zika virus in the brain tissue of affected fetuses and infants.²⁻⁴ There is currently no vaccine and antiviral treatment available for ZIKV infection, and the only way to prevent congenital ZIKV infection is to prevent maternal infection.

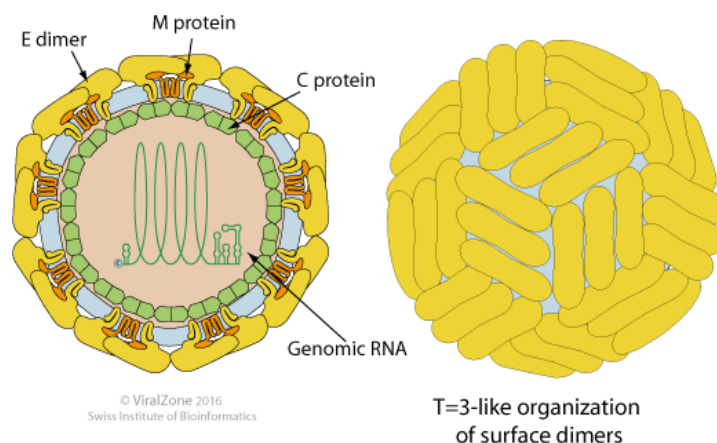


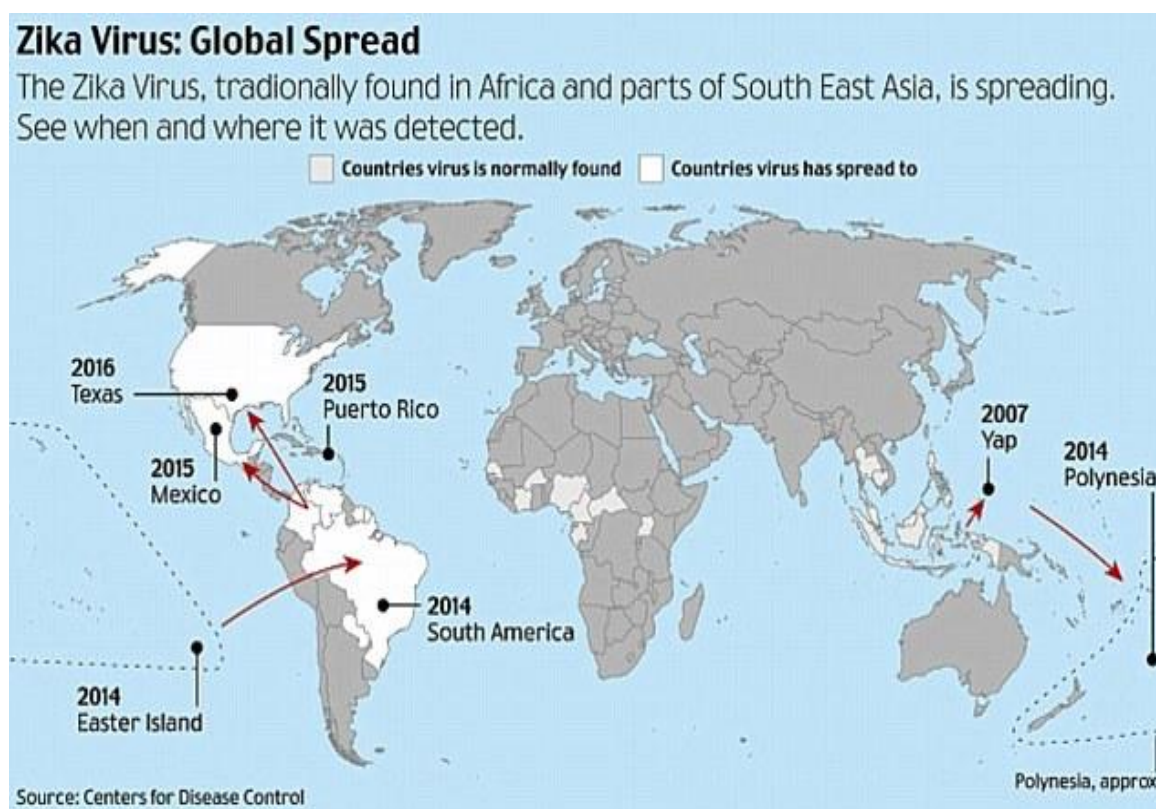
Fig 1: Zika Virus

HISTORY AND EPIDEMIOLOGY OF ZIKV

ZIKV was isolated in Uganda in 1947 from rhesus monkeys and from the mosquito *Aedes africanus* in 1948

⁵The first human ZIKV infection was reported in 1954 in Nigeria⁶. ZIKV antibodies were detected in

serosurvey studies conducted in all parts of Africa⁷⁻¹⁰, India¹¹ and Asia¹². ZIKV antibodies were also detected from animal species, especially non-human primates¹³. ZIKV was isolated from several mosquitoes species in Africa and Asia including arboreal mosquitoes as *Aedes africanus* or mosquitoes with a large tropical and subtropical distribution as *Aedes aegypti* and *Aedes albopictus*] ince last update (February 24, 2016), no additional countries/territories have reported autochthonous (locally acquired) confirmed cases of Zika virus (ZIKV) infection. Thirty-one countries / territories in the Americas have autochthonous confirmed cases of ZIKV infection. Since last update (February 24, 2016), no additional countries/territories have reported autochthonous (locally acquired) confirmed cases of Zika virus (ZIKV) infection. Thirty-one countries / territories in the Americas have autochthonous confirmed cases of ZIKV infection.



TRANSMISSION

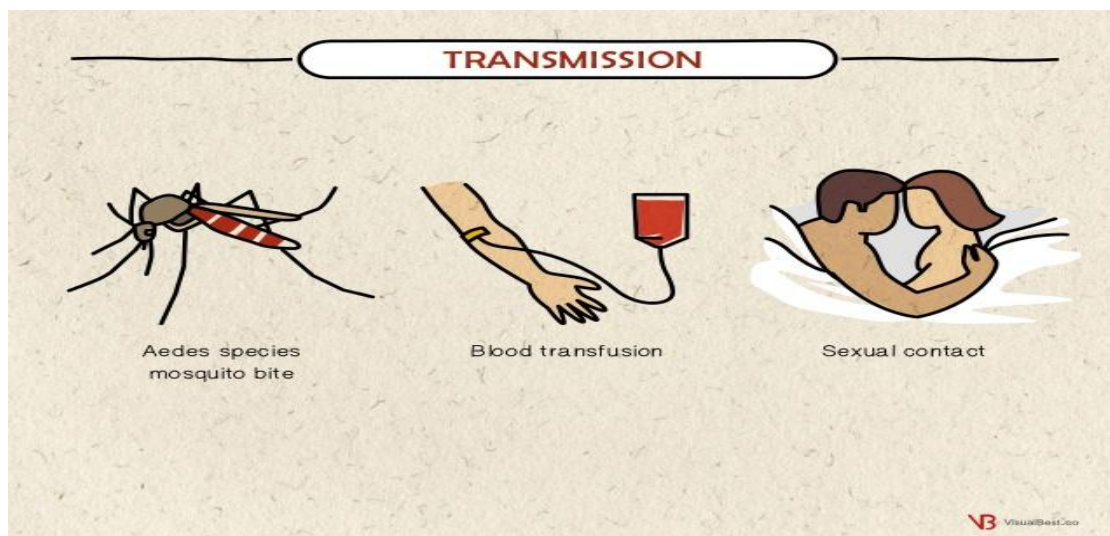


Fig 2: Transmission of Zika Virus

Zika virus is primarily transmitted to humans through bites from *Aedes* mosquitos, which often live around buildings in urban areas and are usually active during daylight hours (peak biting activity occurs in early mornings and late afternoons).

Some evidence suggests Zika virus can also be transmitted to humans through blood transfusion, perinatal transmission and sexual transmission. However, these modes are very rare.¹⁴⁻¹⁵

The incubation period is typically between 2 and 7 days.

Sexual Transmission of ZIKV

During the past week, ZIKV cases of sexual transmission were reported in the United States of America, France, and Italy.

Argentina has reported a case of ZIKV infection in a woman with no travel history whose sexual partner had travelled to Colombia. The partner was symptomatic, upon return from travel, with fever, rash, headache, and joint pain.

SIGNS AND SYMPTOMS

Zika virus infection is characterized by low grade fever (less than 38.5°C) frequently accompanied by a maculopapular rash. Other common symptoms include muscle pain, joint pain with possible swelling (notably of the small joints of the hands and feet), headache, pain behind the eyes and conjunctivitis. As symptoms are

often mild, infection may go unrecognized or be misdiagnosed as dengue. A high rate of asymptomatic infection with Zika virus is expected, similar to other flaviviruses, such as dengue virus and West Nile virus. Most people fully recover without severe complications, and hospitalization rates are low. To date, there have been no reported deaths associated with Zika virus¹⁶⁻¹⁷

Management and Prevention of Zika virus infection

There is presently no vaccine and no specific antiviral treatment for ZIKV infection. Treatment is often supportive, and symptoms can be generally treated with fluids, rest and oral analgesics and antipyretics (e.g., acetaminophen) for fever and pain relief, while aspirin and others nonsteroidal anti-inflammatory drugs (NSAIDs) should be used only when dengue has been ruled out because of the risk of bleeding.⁴⁶ However, NSAIDs are not typically used during pregnancy⁴⁷

For travelers

Travelers visiting countries where the ZIKV virus is active should use individual protective measures to avoid mosquito bites. Such protective measures include using repellent, wearing long-sleeved shirts and long trousers, and utilizing mosquito nets when sleeping even during daytime hours. There is evidence that the ZIKV can be sexually transmitted from a man to his sexual partners. Therefore, men who reside in or have traveled to an area of active ZIKV transmission should abstain from sexual activity, or consistently and correctly use condoms when having sex within 2 weeks after he returns, and postpone giving blood for at least 28 days to prevent ZIKV transmission.⁴⁸ Due to potential risks of ZIKV infection by sexual transmission in women of reproductive age (15-44 years), the CDC has recommended that health care providers should discuss and provide counseling about reproductive screening, testing and pregnancy planning in those women residing in areas with ongoing ZIKV infection.⁴⁹

For pregnant women

The Centers for Disease Control and Prevention (CDC) has recommended that women who are pregnant or plan to become pregnant in the near term consider delaying travel to areas with active Zika virus. Pregnant women residing in or traveling to areas of active ZIKV transmission should take steps to prevent ZIKV infection through prevention of mosquito bites, including use of insect repellent. For those pregnant women who have recently traveled to Zika-infected areas,

they should consult with their healthcare provider even if they don't feel any symptoms of the disease.^{50,51}

Table 1: Differential diagnosis of Zika virus infection vs Dengue fever.

Zika virus infection		Dengue fever
Vector		Aedes aegypti, Aedes albopictus
Signs and symptoms	Mild fever, conjunctivitis, rash, muscle and joint pain	High fever, severe muscle and joint pain, severe headache, retro-orbital pain, rash, mild bleeding
Maternal-fetus transmission	Fetal microcephaly, intracranial calcification	Still birth, low birth weight, and premature
Geographic distribution	Africa, Southeast Asia, and the Pacific Islands; currently outbreak Americas	Tropics and subtropics, endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean
Onset time	2 to 12 days	3 to 8 days (14 days longer)
Management		
Supportive	Supportive Environmental and Vector control, no vaccine, vaccine could take years	Environmental and Vector control, no vaccine, vaccine could be available in 2016.

CLINICAL ASPECTS

In the majority of cases, Zika fever is a self-limited disease. The most frequent reported symptoms (over 60% during the French Polynesia outbreak) are mild fever, fatigue, cutaneous rash, arthralgia-myalgia and conjunctivitis^{36, 37}. Other reported symptoms are headache, malaise, dizziness, oedema of the extremities, retro orbital pain, anorexia, photophobia, gastro intestinal disorders, sore throat, cough, aphthous ulcers, back pain, sweating and lymphadenopathies. None of these symptoms are specific and Zika fever can be misdiagnosed with other bacterial and viral infections, especially with other arboviruses in endemic areas.

1. Zika Virus Associated with Microcephaly

Microcephaly is a clinical finding of a small head size for gestational age and sex and is indicative of an underlying problem with the growth of the brain¹⁸. Microcephaly can occur as a result of fetal brain disruption sequence, a process in which, after relatively normal brain development in early pregnancy, collapse of the fetal skull follows the destruction of fetal brain tissue¹⁹⁻²¹.

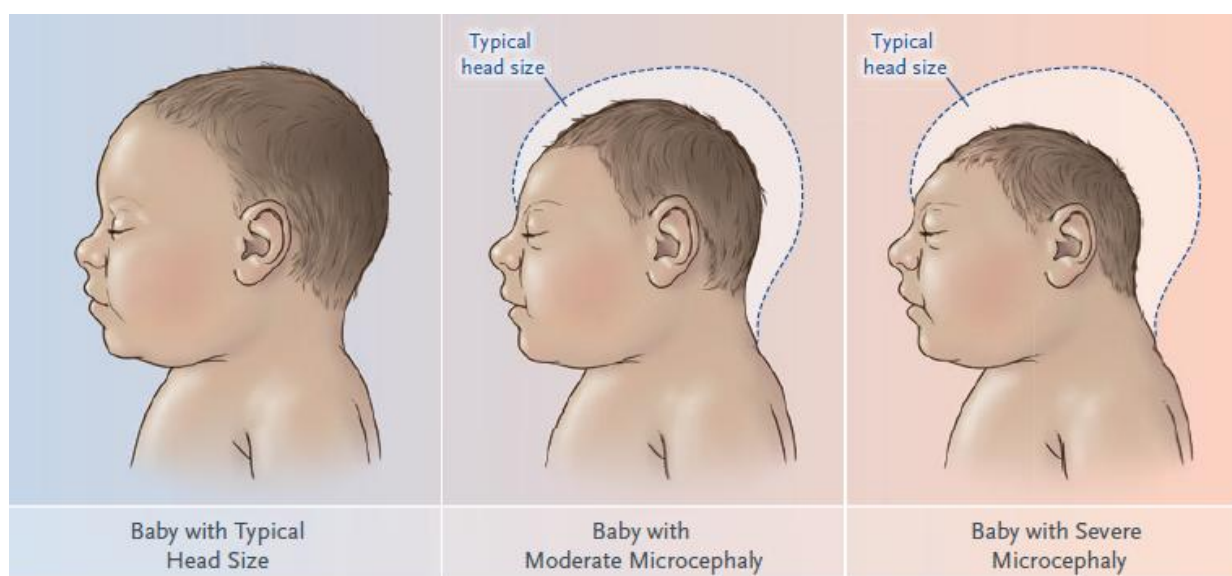


Fig 3: Microcephaly

The findings of Zika virus RNA in the amniotic fluid of fetuses with microcephaly^{22,23,24} and in the brain tissue of fetuses and infants with microcephaly^{25,26,27} as well as the high rates of microcephaly among infants born to mothers with proven antecedent acute Zika virus infection,²⁸ provide strong evidence linking microcephaly to maternal Zika virus infection.

Although microcephaly and other fetal abnormalities may be detected as early as 18 to 20 weeks of gestation,^{38,39,40,41} they are often not detected until later in pregnancy, in part because some cases do not occur earlier in pregnancy.⁴² Furthermore, the use of ultrasonography to detect microcephaly is dependent on clinical and technical factors,⁴³ and ultrasonography is not a highly sensitive means of detecting microcephaly.⁴⁴ Findings associated with Zika virus infection that have been noted on ultrasound have included, in addition to microcephaly, an absent corpus callosum, hydranencephaly, cerebral calcifications, ventricular dilatation, brain atrophy, abnormal gyration, hydrops fetalis, anhydramnios, and intrauterine growth retardation.

The localization of immunofluorescence signal and the morphologic appearance of the calcifications, which resembled destroyed neuronal structures, indicate a possible location of the

Virus in neurons. The consequent damage might cause arrested development of the cerebral cortex at the embryonic age of approximately 20 weeks.⁵⁷ The mechanism involved in the neurotropism of ZIKV is currently not clear. The association between ZIKV infection and fetal brain anomalies was also noted by findings on electron microscopy that were consistent with ZIKV detection in the fetal brain. Dense particles consistent with ZIKV were seen in damaged endoplasmic reticulum. Groups of enveloped structures with a bright interior resembling the remains of replication complexes that are characteristic of flaviviruses^{58,59} indicate viral replication in the brain. The findings on electron microscopy suggest a possible persistence of ZIKV in the fetal brain, possibly because of the immunologically secure milieu for the virus. The number of viral copies that were detected in the fetal brain were substantially higher than those reported in the serum obtained from adult ZIKV-infected patients¹⁷ but similar to those reported in semen samples⁶⁰.

2. Zika Virus Associated with Meningoencephalitis

Zika virus (ZIKV) is currently spreading widely, while its clinical spectrum remains a matter of investigation. Evidence of a relationship between ZIKV infection and cerebral birth abnormalities^{29,30} is growing³¹. ZIKV that was associated with meningoencephalitis and incidence of some peripheral nervous syndromes in adult.

Zika Virus as a Cause of Neurologic Disorders

The virus was found to be neurotropic in animals in experiments conducted in the 1950s, and recent experiments have shown how it can cause neural-cell death. A rise in the incidence of Guillain–Barré syndrome, an immunemediated flaccid paralysis often triggered by infection, was first reported in 2013 during

a Zika outbreak in French Polynesia. An increase in the incidence of microcephaly, a clinical sign that can be caused by underdevelopment of the fetal brain, was first reported in northeastern Brazil in 2015, after Zika virus transmission had been confirmed there. These reports of excess cases of Guillain–Barré syndrome and microcephaly led the World Health Organization (WHO) to declare a Public Health Emergency of International Concern on February 1, 2016, and to recommend accelerated research into possible causal links between Zika virus and neurologic disorders.⁴⁵

PREVENTION

During the first week of ZIKV infection, the infected patients should avoid further mosquito bite because the ZIKV can be found in the blood and pass from an infected person to a mosquito. Consequently, an infected mosquito can then spread the virus to another person. Preventing further mosquito bite can be accomplished by using insect repellent, wearing long-sleeved shirts and long pants, and treating clothing with permethrin. However, insect repellent should not be used on babies younger than 2 months of age. An infected female mosquito lays several hundred eggs on the wall of the water-filled containers. Therefore, it is important to eliminate standing water in and outside of the home by emptying, washing and scrubbing thoroughly, and then tightly covering water storage containers (buckets, cisterns, rain barrels) once a week so that mosquitoes cannot get inside to lay eggs.

Laboratory diagnosis

Serological diagnosis is limited due to cross-reactions within the Flavivirus genus. Serological diagnosis is limited due to cross-reactions within the Flavivirus genus⁵², especially with dengue, then caution should be observed if diagnosis relies only on serological results, even when using neutralization test⁵³ which is the more specific method for Flavivirus serology. ZIKV can be isolated from cell culture⁵⁴ but the protocol is reserved to specialized laboratories. Zika fever diagnosis relies in routine on the detection of ZIKV RNA by molecular tools. Detection of ZIKV RNA is possible on blood and saliva collected at the acute phase of the disease⁵⁵. The use of saliva sample is of particular interest when blood samples are difficult to collect⁵⁵. Detection of ZIKV RNA after the first week after symptoms onset can be performed in urines⁵⁶. Molecular diagnosis of Zika fever is reserved to reference laboratory because there is no commercial test available.

TREATMENT AND VACCINE DEVELOPMENT

There is no specific treatment and no vaccine against Zika fever. Acetylsalicylic acid and non-steroidal anti-inflammatory drugs are not recommended due to the increased risk of hemorrhagic syndrome described with other arboviruses as DENV³⁶. Symptomatic treatment is based on acetaminophen and antihistaminic for pruritic rash. Effective vaccines exist for several flaviviruses, such as yellow fever virus, Japanese encephalitis, and tick-borne encephalitis. These vaccines were introduced in the 1930s, while the vaccine for dengue fever only became available for use in the mid-2010s.^{33,34} Recently, the Indian Bharat Biotech International company reported that it has two ZIKV vaccine candidates that will be entering pre-clinical trials in animal and commenced in late February 2016.³⁵

CONCLUSION

There appears to be significant evidence suggesting that Zika is the cause of microcephaly which can lead to severe neurological sequelae in babies. The WHO declared ZIKV infection to be an international public health emergency in early February 2016. The WHO recommends applying key interventions such as intensive mosquito control; personal protection against mosquito bites; provision of appropriate clinical care for all patients with Guillain–Barre syndrome and for women before, during, and after pregnancy; and prevention of Zika virus transmission through sexual contact or blood transfusion. Most of these are not new interventions, but they do need strengthening. Populations must be informed of the potential current and future risks of neurologic disorders, wherever the virus is being or could be locally transmitted and in other regions inhabited by the mosquito vectors. As the putative link between Zika virus and neurologic disorders is reinforced, refined, or even refuted, public health measures will be adjusted accordingly.

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