



Review Article

Why Zika virus infection has become a public health concern?

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Abstract

Prior to 2015, Zika Virus (ZIKV) outbreaks had occurred in areas of Africa, Southeast Asia, and the Pacific Islands. Although a causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, such a connection has not yet been scientifically proven. In May 2015, the outbreak of ZIKV infection in Brazil led to reports of syndrome and pregnant women giving birth to babies with birth defects and poor pregnancy outcomes; the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed ZIKV infection in Brazil. Currently, ZIKV outbreaks are ongoing and it will be difficult to predict how the virus will spread over time. ZIKV is transmitted to humans primarily through the bite of infected mosquitos, *Aedes aegypti* and *Aedes albopictus*. These mosquitoes are the principle vectors of dengue, and ZIKV disease generally is reported to include symptoms associated with acute febrile illnesses that clinically resembles dengue fever. The laboratory diagnosis can be performed by using reverse-transcriptase polymerase chain reaction (RT-PCR) on serum, viral nucleic acid and virus-specific immunoglobulin M. 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. In February 2016, the Taiwan Centers for Disease Control (Taiwan CDC) activated ZIKV as a Category V Notifiable Infectious Disease similar to Ebola virus disease and MERS.

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1. 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 Subsequently, sporadic human infections were reported in Africa and Asia, and the first documented ZIKV outbreak was

reported from Yap State, Federated States of Micronesia in 2007.² The Asian lineage of the virus reappeared in French Polynesia in October 2013, and thereafter between November 2013 and February 2014, with an increased incidence of neurological complications, including 42 cases of Guillain-Barré syndrome; these complications were a unique and worrisome feature of the outbreak that warrants further study.³ 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.

2. Countries with current active Zika virus infection

As of February 4, 2016, the ZIKV epidemic has continued to spread in most of the countries where its presence was

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indicated, and evidence of local ZIKV infection cases has been reported from 31 countries within the past 2 months, and 36 countries in the past 9 months.⁴ Ultimately, ZIKV may be spread globally into additional environments where mosquitos can live and breed. The geographical range of ZIKV infection has increased in 2015 and 2016, with 26 countries and territories in the Americas now reporting autochthonous transmission of ZIKV.⁵

3. Mode of transmission

ZIKV is transmitted to humans primarily through the bite of infected mosquitos, namely: *Aedes aegypti* and *Aedes albopictus*), which are found throughout much of the Americas, including part of the United States. These mosquitoes are the principle vectors of dengue, chikungunya, Zika, and yellow fever.^{6,7} These vectors are aggressive day time biters that breed in domestic water holding containers, and feed primarily in the outdoors and indoors near dwellings. During the outbreaks, anthroponotic (human-to-vector-to-human) transmission can occur. Mosquitoes become infected when they bite a person already infected with the virus. Infected mosquitoes can then spread the virus to other people through bites. To date, infected ZIKV RNA has been detected in blood, urine, semen, saliva, cerebrospinal fluid, amniotic fluid, and breast milk. Regarding transmission of the virus through the mother and to her baby during pregnancy, blood transfusion and sexual contact have been reported; however, there is currently no evidence that the virus is transmitted to babies through breast feeding.^{7–10} However, the mechanism by which some mothers can pass the virus to their babies is still under study.

4. Clinical signs and symptoms

Signs and symptoms of ZIKV infection are relatively mild. Although the illness develops in only one in five persons, severe disease requiring hospitalization is uncommon and case fatality is very low.¹¹ The symptoms typically occur approximately 2 to 12 days after the mosquito bite, presenting most commonly with fever, maculopapular rash, conjunctivitis, and joint pain, and the clinical illness lasts for several days to a week. Other symptoms include muscle pain and headache, but abdominal pain, nausea, diarrhea, mucus membrane ulcerations, and pruritus are rarely observed.¹² There is a possible association between ZIKV and microcephaly in newborn babies with maternal ZIKV infection,^{4,13} and some infected adults with neurologic conditions like Guillain-Barré syndrome (GBS) were also reported.¹⁴ By the first week of February, 2016, 4783 suspected cases of microcephaly have been reported in Brazil; of these cases, 1132 (24%) were investigated and classified. It was found that 404/1132 (36%) cases had confirmed microcephaly and/or central nervous system malformations, and 17/404 (4%) were positive for ZIKV infection.⁴ In July 2015, Brazil reported 76 cases with ZIKV infection with neurologic syndromes in Bahia state, and 42 of those cases were confirmed to have GBS.⁵ In late

January 2016, 104, 2, 1, and 255 cases of GBS were reported from El Salvador, Martinique, New Zealand, and Venezuela, respectively. French Polynesia also reported one imported case of ZIKV with neurological symptoms in February 2016.⁴ Some countries, including Colombia and Suriname, reported ZIKV infection with deaths involving GBS or chronic medical illness.¹⁵

5. Diagnosis

The primary diagnosis of ZIKV infection is based on the patient's typical clinical features, places and dates of travel and activities. During the first week after onset of symptoms, laboratory diagnosis can be performed by using reverse-transcriptase polymerase chain reaction (RT-PCR) on serum or plasma to detect virus, viral nucleic acid,¹⁶ or virus-specific immunoglobulin M and neutralizing antibodies.^{17,18} During the acute illness period of ZIKV infection in patients, symptoms such as fever, rash, conjunctivitis, and serological testing can confirm the presence of ZIKV virus. However, there are no good laboratory tools with the capacity to confirm what occurs during the other months. Cross-reaction with some related flaviviruses, such as dengue 1,2,3, and 4, and with yellow fever and West Nile viruses is common, creating a circumstance where proper diagnosis of ZIKV may be difficult to achieve.¹⁹ Then, a plaque-reduction neutralization testing can be performed to measure virus-specific neutralizing antibodies and differentiate between cross-reacting antibodies in primary flavivirus infections.^{17,18} Due to a routine cross-reaction that is common in patients with dengue virus, patients with ZIKV infection should be evaluated for possible dengue virus infection. Dengue virus infection usually presents with high fever, severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash. Dengue fever usually occurs after an incubation period of 4–10 days after the bite of the infected mosquito, and symptoms usually last for 2–7 days.²⁰ Unlike ZIKV infection, dengue typically is not associated with conjunctivitis (Table 1).

6. 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.²¹ However, NSAIDs are not typically used during pregnancy.²²

7. Prevention of mosquito bite

During the first week of ZIKV infection, the infected patient 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.²³

8. Vaccine development

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.^{24,25} 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 2016.²⁶

9. 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.²⁷ 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.²⁸

10. 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.^{12,27}

11. Management and prevention of congenital Zika virus infections

To date, there is no vaccine and antiviral treatment available for ZIKV infection, and the only way to prevent congenital ZIKV infection is to prevent maternal infection. The CDC recommended that serologic testing be offered to asymptomatic pregnant women 2-12 weeks after returns from areas with ongoing ZIKV transmission. For asymptomatic pregnant women who are residing in areas with ongoing ZIKV transmission, Serological testing should be performed at the first prenatal care visit, and then followed-up in the mid-second trimester to prevent ongoing risk of transmission for women throughout their pregnancies. For symptomatic pregnant women, the CDC has recommended testing during the first week of illness.²⁸ Treatment of congenital ZIKV infection is supportive and should take into consideration specific medical and neurodevelopmental concerns for the infant's individual needs. No evidence has been found indicating that ZIKV infection can be transmitted through breast milk, and recommendations may even continue to suggest that women breastfeed infants even in areas with ZIKV found.²⁹

12. Zika virus infection and Congenital Microcephaly

Microcephaly is a condition where a baby's head is characteristically much smaller than expected compared to babies of the same gestational age and sex. Infants with microcephaly can have a range of problems such as neurological sequelae, seizure, problems with movement and balance, intellectual disability, vision or hearing problems, and developmental problems such as speech, delay milestones like sitting,

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

	Zika virus infection	Dengue fever
Vector	<i>Aedes aegypti</i> , <i>Aedes albopictus</i>	<i>Aedes aegypti</i> , <i>Aedes albopictus</i>
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 birth
Geographic distribution	Africa, Southeast Asia, and the Pacific Island; 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 Prevention	Supportive Environmental and Vector control, no vaccine, vaccine could take years	Supportive Environmental and Vector control, no vaccine, vaccine could be available in 2016.

standing, and walking. These problems can range from the mild to the severe, and may have lifetime consequences for infected patients.^{30,31} In early 2015, ZIKV infections were first confirmed in babies with microcephaly in Brazil, and the incidence of microcephaly in fetuses born to mothers with ZIKV infection continues to increase. This possible connection between ZIKV infection and microcephaly in babies represents a substantial public health concern. And apart from microcephaly, other brain abnormalities that disrupt brain growth³² such as intracranial calcifications, ventriculomegaly, and neuronal migration disorders (lissencephaly and pachygyria) may also be found to have some potential involvement in or vulnerability to ZIKV infection. Recently, Mlakar et al. reported on a case of severe fetal brain injury associated with ZIKV infection with vertical transmission. Pathological findings of the fetal brain showed complete agyria, hydrocephalus, multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. ZIKV was detected on RT-PCR assay from the fetal brain; however, neither ZIKV nor pathological changes were detected in any other fetal organs, which suggests a strong relationship between ZIKV and neurological damage.³³

In 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. However, there has been no significant increase in the number of microcephaly cases in Taiwan. In Taiwan, only one imported case of ZIKV infection was reported on January 10, 2016, and no other cases have been identified. Recently, China also has reported a case, a 39-year-old male who returned to China from Venezuela. The Taiwan CDC advised women who were pregnant or who planned to become pregnant to postpone travel to Zika-affected areas of ongoing local outbreaks.¹⁵ ZIKV infection has continued to spread worldwide, especially in Latin America and the Caribbean region, and Taiwan's CDC has issued travel notices and published guidelines for preventive measures, listing ZIKV infection as a Category V Notifiable Infectious diseases and closely monitored ZIKV importation, border quarantine and vector control in preparation for occurrence of local Zika outbreaks.³⁴

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