

## **Review Article**

# **A Review on Zika Fever**

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### **Abstract:**

Zika virus is a member of a family of viruses known as Flavi viruses. The defining characteristic of these viruses is that they are transmitted to humans via the bite of infected arthropods, most commonly mosquitoes and ticks. They are maintained in nature through a complex cycle in which they rotate between a vertebrate animal host and a blood-feeding vector that carries the virus from one host to another and spread the mild flu-like symptoms with fever, skin rash, red eyes and joint pain being the most common symptoms. As there is no such vaccines are developed, the people are suffering and dying mostly in developing country.

**Key Words:** Zika virus, Flavi, infected arthropods, joint pain.

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## **1. INTRODUCTION**

Zika virus, first identified in 1947 in Uganda, had been thought to produce a rare and mild disease until it suddenly emerged in Brazil in 2015 and spread explosively through South America, Central America, and the Caribbean. This large outbreak is associated with serious illnesses and continues to expand into even more countries. The virus is transmitted by mosquitoes and causes Zika virus disease. In most cases the disease is mild, but Zika virus is being linked to a rising number of cases of a birth defect known as microcephaly. It has also been associated with Guillain-Barre syndrome, a neurologic condition that can cause muscle weakness.<sup>1-3</sup>

### **Classification**

Zika virus is a member of a family of viruses known as Flaviviruses. This is the same family to which dengue virus, yellow fever virus, and West Nile virus belong. Flavi viruses are enveloped viruses that contain genomes which consist of non

segmented single-stranded positive-sense RNA. The viruses are transmitted to humans by infected mosquitoes.

Zika virus and the other flavi viruses are part of a larger group of viruses termed arboviruses (for **arthropod-borne**). The defining characteristic of these viruses is that they are transmitted to humans via the bite of infected arthropods, most commonly mosquitoes and ticks. They are maintained in nature through a complex cycle in which they rotate between a vertebrate animal host and a blood-feeding vector that carries the virus from one host to another. Another recently emergent arbovirus is chikungunya virus, which belongs to the Alphavirus family.<sup>4,6</sup>

## **2. WHAT'S ZIKA AND WHERE DID IT COME FROM?**

Zika is a virus that belongs in the same family of viruses as dengue and West Nile, called flavi viruses. It gets its name from the Zika forest in Uganda where it was first isolated in monkeys in

1947. The first human detection was in Uganda in 1952. Since then there are two distinct lineages that have been detected, an African lineage and an Asian lineage. According to health officials, the current outbreak is thought to be caused by the Asian lineage of the virus.

### **How and where is it spreading?**

Zika spreads through the bites of mosquitoes. The *Aedes* mosquitoes, which also transmit dengue and chikungunya are the major carriers of Zika. While the species *Aedes aegypti* is thought to be the primary carrier, knowledge is still limited. Once an infected mosquito bites an individual, he or she can carry the virus in the blood for up to a week after the infection. During this period mosquitoes that bite the person can get infected and then pass on the virus to others. There have been a few reports of transmission through sexual contact or via blood transfusion, but these are rare cases.

The bigger concern though is that the virus could be passed on from mother to child during pregnancy, and that is the cause of the increase in birth defects. Though experts suspect this to strongly be the case, a link has not been conclusively proven. "I think that the link between Zika virus infection and microcephaly has become reasonably strong with the detection of viral RNA in several fetuses diagnosed in Brazil," said Scott Weaver, an infectious diseases professor at the University of Texas Medical Branch in a comment to the Genetic Expert News Service (GENeS) which provides journalists with expert analysis on important issues in genetics and biotechnology. However, "an alternative cause cannot yet be ruled out until the maternal infection is linked directly to the onset of microcephaly in the absence of other viruses," he said

The most recent reports from the World Health Organization indicate that Zika outbreaks have been detected in 18 countries and territories in the Americas including Brazil. From the first reported outbreak in May 2015 in Brazil, over 1.5 million people are estimated to have been infected in

Brazil alone with thousands more in the other countries.

### **What can zika cause?**

According to the CDC, infection with Zika in most cases causes only mild flu-like symptoms with fever, skin rash, red eyes and joint pain being the most common symptoms. In other words, if you had Zika infection, a doctor would be hard pressed to suspect it was anything other than a mild flu – unless of course you lived in or visited any of the regions of the outbreak. What makes it harder to detect is that only 1 in 5 people even develop symptoms, which could be one of the reasons why it spread so fast. For the vast majority of people though, this will be the extent of their illness.

However, links between Zika outbreaks and Guillian-Barre Syndrome (GBS), an illness in which the body's own immune system attacks the nerves, have been reported in the past. In severe cases of GBS, the individual can be completely paralyzed. Outbreak related GBS illnesses have been minimal however, and similar reports have not appeared for the current outbreak.

More concerning however, has been the potential for Zika to cause birth defects, specifically microcephaly.

### **Is there a way to vaccinate against it?**

The short answer? No. "There are no licensed vaccines against the Zika virus anywhere in the world," said Lucey. The Brazilian government has recently announced that it will fund efforts to develop a vaccine in "record time," according to the Health Minister Marcelo Castro which is expected to take three to five years. According to Lucey, an effort led by the National Institutes of Health to develop a Zika vaccine has also only recently begun.

There is some good news. Nikos Vasilakis of the University of Texas Medical Branch said, "given the existence of highly successful and efficacious vaccines against yellow fever and Japanese encephalitis viruses, which are closely related to

Zika virus, development of a live attenuated or chimeric vaccine would be straightforward.” However, Lucey cautioned that expecting that a solution is around the corner might be too optimistic. “Assuming that the scientific and pharmaceutical industry challenges can be met as quickly as possible, based on past new vaccine development timelines, we are several years away from having an FDA-licensed Zika vaccine,”

### **Clinical features and sequelae**

The incubation period ranges between approximately three to 12 days after the bite of an infected mosquito.

Most of the infections remain asymptomatic (approximately 80%).

Disease symptoms are usually mild and the disease is usually characterised by a short-lasting self-limiting febrile illness of 4–7 days duration without severe complications, with no associated fatalities and a low hospitalisation rate.

The main symptoms are maculopapular rash, fever, arthralgia, fatigue, non-purulent conjunctivitis/conjunctival hyperaemia, myalgia and headache. The maculopapular rash often starts on the face and then spreads throughout the body. Less frequently, retro-orbital pain and gastrointestinal signs are present.

Congenital central nervous system malformations such as microcephaly in fetuses and newborns from mothers possibly exposed to Zika virus during pregnancy were notified during recent Zika disease outbreaks (French Polynesia and Brazil). Unusual increases of Guillain–Barré syndrome were reported in several countries in the Americas and French Polynesia coinciding with the Zika virus outbreak.

Further evidence is needed to establish a causal link between Zika virus infection and these neurological/neuro developmental impairments or auto-immune conditions.

## **3. TRANSMISSION & RISK**

### **How is Zika virus transmitted?**

#### **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 can then spread the virus to other people through bites.<sup>1-3</sup>

#### **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, but this is rare.
- A mother can pass Zika virus to her fetus during pregnancy. We are studying how Zika affects pregnancies.
- 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**

##### **What we know**

- Zika virus can be spread by a man to his sex partners.
- In known cases of likely sexual transmission, the men had Zika symptoms.
- In one case, the virus was spread a few days before symptoms developed.

- The virus is present in semen longer than in blood.

### **What we do not know**

- We do not know how long the virus is present in semen in men who have had Zika.
- We do not know if infected men who never develop symptoms can have Zika virus in their semen.
- We do not know if infected men who never develop symptoms can transmit Zika virus through sex.
- We do not know if a woman can transmit Zika virus to her sex partners.

### **Through blood transfusion**

- ❖ As of February, 1, 2016, there have not been any confirmed blood transfusion transmission cases in the United States.
- ❖ There have been multiple reports of blood transfusion transmission cases in Brazil. These reports are currently being investigated.
- ❖ During the French Polynesian outbreak, 2.8% of blood donors tested positive for Zika and in previous outbreaks, the virus has been found in blood donors.
- ❖ The maximum time for the virus to stay in the blood is unknown, but scientists think it is less than 28 days.

### **What is the difference between congenital and perinatal transmission of Zika virus?**

Congenital or intrauterine transmission of Zika virus occurs when a woman is infected with Zika virus during her pregnancy, but before delivery, and the virus passes to the fetus. Perinatal transmission of Zika virus occurs when a woman is infected with the Zika virus within 2 weeks of delivery, and the virus passes to the infant at or around the time of delivery. When an infant acquires Zika virus disease perinatally, the infant

may develop symptoms such as maculopapular rash, conjunctivitis, arthralgia, and fever.

### **If a mother had Zika virus infection during pregnancy or currently has Zika virus infection, should she breastfeed her infant?**

Zika virus RNA has been identified in breast milk, but attempts to culture the virus have been unsuccessful. No evidence of Zika virus infection associated with breastfeeding have been reported. Current evidence suggests that the benefits of breastfeeding outweigh the theoretical risks of Zika virus infection transmission through breast milk. CDC encourages mothers with Zika virus infection and mothers living in areas with ongoing Zika virus transmission to breastfeed their infants.

## **4. EPIDEMIOLOGY**

- Serological surveys in Africa and Asia indicate a most likely silent Zika virus circulation with detection of specific antibodies in various animal species (large mammals such as orangutans, zebra, elephants, water buffaloes) and rodents.
- The knowledge of geographical distribution of Zika virus is based on results of serosurveys and viral isolation in mosquitoes and humans, and with reports of travel-associated cases. Before 2007, the areas with reported Zika virus circulation included tropical Africa and Southeast Asia. Very few outbreaks were documented prior to 2007.
- An outbreak was reported on Yap Island, Federated States of Micronesia from April to July 2007 [3]. This was the first outbreak of Zika virus identified outside of Africa and Asia. Between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia. In 2015, Zika virus emerged in South America with further spread across the Americas.
- The very first known case of Zika fever was in a sentinel rhesus monkey stationed on a tree

platform in the Zika Forest in Uganda in 1947. Population surveys at the time in Uganda found a 6.1% prevalence. The first human cases were reported in Nigeria in 1954. A few outbreaks have been reported in tropical Africa and in some areas in Southeast Asia.

- The first major outbreak, with 185 confirmed cases, was reported in 2007 in the Yap Islands of the Federated States of Micronesia. A total of 108 cases were confirmed by PCR or serology and 72 additional cases were suspected. The most common symptoms were rash, fever, arthralgia and conjunctivitis, and no deaths were reported. The mosquito *Aedes hensilli*, which was the predominant species identified in Yap during the outbreak, was probably the main vector of transmission. While the way of introduction of the virus on Yap Island remains uncertain, it is likely to have happened through introduction of infected mosquitoes or a viraemic human with a strain related to those in Southeast Asia. This was also the first time Zika fever had been reported outside Africa and Asia.
- In 2013 another large outbreak was reported in French Polynesia that was thought to be from an independent introduction of the virus from Asia than the Yap Island outbreak.
- In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infections in Brazil. According to the Brazilian Health Ministry, as of November 2015 there was no official count of the number of people infected with the virus in Brazil, since the disease is not subject to compulsory notification. Even so, cases were reported in 14 states of the country. Mosquito-borne Zika virus is suspected to be the cause of 2,400 cases of microcephaly and 29 infant deaths in Brazil in 2015.
- The emergence of Zika virus in South America led to a rapid spread throughout South and Central America, reaching Mexico in November 2015. It has appeared

sporadically in travellers to the United States and Europe but has not established person to person spread in those areas. Because of the "growing evidence of a link between Zika and microcephaly" the CDC issued a travel alert on January 15, 2016 advising pregnant women to consider postponing travel to the following countries and territories: Brazil, Colombia, El Salvador, French Guiana, Guatemala, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Suriname, Venezuela, and the Commonwealth of Puerto Rico. The agency also suggested that women thinking about becoming pregnant should consult with their physicians before traveling.

### **Should pregnant women travel to places with Zika outbreaks?**

- Zika virus can be spread from a pregnant woman to her fetus. There have been reports of a serious birth defect of the brain called microcephaly in babies of mothers who had Zika virus while pregnant. Knowledge of the link between Zika and birth defects is evolving, but until more is known, CDC recommends special precautions for pregnant women. Pregnant women in any trimester should consider postponing travel to any area where Zika virus is spreading. If you must travel to one of these areas, talk to your healthcare provider first and strictly follow steps to prevent mosquito bites during your trip.

### **Should women trying to get pregnant travel to places with Zika outbreaks?**

- Until more is known, CDC recommends that women trying to get pregnant and their male partners talk to their healthcare provider before traveling to areas with Zika. Because sexual transmission is possible, both men and women should strictly follow steps to prevent mosquito bites during the trip.
- Areas where Zika is spreading will likely change over time. Check CDC's travel website often for a current list of areas with Zika. Specific areas where Zika virus is

spreading are often difficult to determine and are likely to change. As more information becomes available, travel notices will be updated. Please check back frequently for the most up-to-date recommendations.

## **5. ZIKA VIRUS INFECTION AND MICROCEPHALY**

### **What is the link between Zika virus in Brazil and the high numbers of infants born there with microcephaly?**

Zika virus infections have been confirmed in several infants with microcephaly from Brazil. The time frame and geographic location of reports of infants with microcephaly coincides with the outbreak of Zika virus infections in Brazil. The baseline prevalence of congenital microcephaly is difficult to determine because of underreporting and the inconsistency of clinical criteria used to define microcephaly. Although population-based estimates of congenital microcephaly in Brazil vary, the number of infants with microcephaly currently being reported in Brazil is greater than would be expected.

### **If a mother infected with Zika virus near the time of delivery passes the virus to her newborn at birth, can the baby develop microcephaly?**

We do not know if a newborn who gets Zika virus at birth will develop microcephaly after birth. Babies can develop microcephaly after birth if their head growth slows or fails to develop after birth. There have been no reports of Zika virus infection around the time of birth leading to microcephaly in infants.<sup>2-5</sup>

### **What birth defects have been reported in infants with confirmed congenital Zika virus infection?**

Brain abnormalities reported in infants with microcephaly and laboratory-confirmed congenital Zika infection include microcephaly and disrupted brain growth.

### **What birth defects have been reported in infants with suspected congenital Zika virus infection?**

A report of 35 infants with microcephaly who were born during an outbreak of Zika virus infection in Brazil in 2015 described the following brain abnormalities: intracranial calcifications, ventriculomegaly, and neuronal migration disorders (lissencephaly and pachygyria). Other anomalies included congenital contractures and clubfoot. Some infants with possible Zika virus infection have been found to have intracranial calcifications and abnormal eye findings. An important distinction is that neither these infants nor their mothers had laboratory-confirmed Zika virus; however, 75% of mothers reported symptoms consistent with Zika virus.

### **How is microcephaly diagnosed after birth?**

Microcephaly is diagnosed when an infant's head is smaller than expected as compared to infants of the same age (or gestational age) and sex. For the purpose of evaluating an infant for possible congenital Zika virus infection, microcephaly is defined as occipito-frontal circumference less than the third percentile, based on standard growth charts (e.g., Fenton, Olsen, CDC, or WHO growth curves) for sex, age, and gestational age at birth. For a diagnosis of microcephaly to be made, the occipito frontal circumference should be disproportionately small in comparison with the length of the infant and not explained by other etiologies (e.g., other congenital disorders).

### **What is the difference between occipito frontal circumference (OFC) and head circumference (HC)?**

Head circumference and occipitofrontal circumference are the same. These terms can be used interchangeably.

### **When should occipitofrontal circumference (OFC)/head circumference (HC) be measured?**

The shape of the head after delivery can affect the accuracy of the OFC/HC measurement as an estimate of brain volume due to molding of the head from the birth canal. The optimal time to measure HC is at 24-36 hours after birth when molding of the head has subsided.

### **How should occipito frontal circumference (OFC)/head circumference (HC) be measured?**

Head circumference measurements should be taken using a tape measure that cannot be stretched. The tape is securely wrapped around the widest possible circumference of the head, 1-2 finger widths above the eyebrow on the forehead and at the most prominent part of the back of the head. Ideally, the measurement should be taken 3 times and the largest measurement recorded to the nearest 0.1 cm. It may be helpful to have the parent or nurse hold the infant's arms. The OFC should be measured three times and the largest value should be used.

### **What are the potential sequelae of microcephaly?**

For infants diagnosed with microcephaly, head size correlates with underlying brain size. However, these measurements do not consistently predict long term sequelae. Neurologic sequelae may include seizures, vision or hearing problems, and developmental disabilities. Symptoms vary with the extent of brain disruption.

Additional information about microcephaly is available on CDC's Microcephaly webpage.

### **What causes congenital microcephaly?**

Causes of congenital microcephaly may include genetic conditions such as chromosomal abnormalities or maternal exposures (e.g., alcohol, mercury, or radiation) during pregnancy. Maternal infections that have been associated with microcephaly include cytomegalovirus (CMV), herpes simplex virus, rubella virus, lymphocytic choriomeningitis virus (LCMV), Treponema

pallidum (i.e., syphilis), and Toxoplasma gondii.

## **6. ZIKA VIRUS TESTING FOR INFANTS AND CHILDREN**

### **When should an infant with possible congenital infection be tested for Zika virus?**

For infants with possible congenital Zika virus infection who were born to mothers who traveled to or resided in areas affected by Zika virus, testing should be guided by (1) whether the infant has microcephaly or intracranial calcifications detected on prenatal or postnatal ultrasounds and (2) the mother's Zika virus testing results. Because information on the effects of congenital Zika virus infection is limited, healthcare providers should exercise clinical judgment in the assessment of newborns with abnormalities other than microcephaly or intracranial calcifications who were born to mothers who traveled to or resided in an area with active Zika virus transmission during pregnancy. For these infants, healthcare providers should consider testing the mother before testing the infant. Healthcare providers should notify their local, state or territorial health departments to arrange testing.

### **When should an infant or a child be tested for acute Zika virus disease?**

Acute Zika virus disease should be suspected in an infant or child aged <18 years who 1) traveled to or resided in an area with ongoing transmission of Zika virus within the past 2 weeks and 2) has 2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Because transmission of Zika virus from mother to infant during delivery is possible, acute Zika virus disease should also be suspected in an infant during the first 2 weeks of life 1) whose mother traveled to or resided in an affected area within 2 weeks of delivery and 2) who has 2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Healthcare providers should notify their local, state or territorial health departments to arrange testing. As an arboviral disease, Zika virus disease is a nationally notifiable condition.

**Arthralgia is a known symptom of Zika virus disease. How might arthralgia manifest in young children?**

Arthralgia can be difficult to detect in infants and young children and can manifest in irritability, walking with a limp (for ambulatory children), difficulty moving or refusing to move an extremity, pain on palpation, or pain with active or passive movement of the affected joint.

**When should an infant with microcephaly or intracranial calcifications be tested for Zika virus?**

For infants with microcephaly or intracranial calcifications and whose mothers have a history of travel to or who reside in areas with ongoing transmission of Zika virus, Zika virus testing is recommended within 48 hours of birth, if possible. Healthcare providers should work with their local, state or territorial health departments to arrange testing.

**When should an infant with possible congenital infection and no evidence of microcephaly or intracranial calcifications be tested for Zika virus?**

For infants without evidence of microcephaly or intracranial calcifications, Zika virus testing is recommended under the following circumstances: (1) if the mother tested positive (e.g. RT-PCR, IgM) for Zika virus, or (2) if the mother had inconclusive Zika virus test results. For infants without evidence of microcephaly or intracranial calcifications and whose mothers either tested negative for Zika virus or were not tested for Zika virus, testing is not recommended. The infant should receive routine care.

**How should infants born to mothers who traveled to or resided in an area with Zika virus transmission be evaluated if the mother was not tested for Zika virus infection during pregnancy?**

For infants born to mothers who were potentially exposed to Zika virus, the results of previous prenatal ultrasounds and maternal Zika virus

testing should be reviewed and a thorough newborn physical examination, with careful measurement of head (occipitofrontal) circumference, length, and weight, should be performed. Infants without evidence of microcephaly or intracranial calcifications whose mothers have negative Zika virus test results or who were not tested for Zika virus should receive routine care. Because information on the effects of congenital Zika virus infection is limited, healthcare providers should exercise clinical judgment in the assessment of newborns with abnormalities other than microcephaly or intracranial calcifications that were born to mothers who traveled to or resided in an area with active Zika virus transmission during pregnancy. For these infants, healthcare providers should consider testing the mother before testing the infant.

**How are infants diagnosed with possible congenital Zika virus infection?**

Zika virus infection can be diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) or through the detection of Zika virus-specific IgM and neutralizing antibodies. It has not been established which test is most reliable for a diagnosis of congenital infection in newborns. Therefore RT-PCR and IgM tests should both be performed. Plaque-reduction neutralization testing (PRNT) may also need to be performed to measure virus-specific neutralizing antibodies to differentiate Zika virus from infection with or vaccination for other flaviviruses. Histopathologic evaluation of the placenta and umbilical cord, immunohistochemical staining on fixed tissue, and Zika virus RT-PCR on fixed and frozen tissue can be performed.

**How is a possible acute Zika virus infection confirmed in infants and children?**

Zika virus infection can be confirmed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum within 7 days of symptoms onset. Serologic assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies 4 or more days after



symptoms onset. Evaluation of infants and children for acute Zika virus infection should include testing of serum and may include cerebrospinal fluid (CSF) testing for Zika viral RNA, if samples were obtained as part of routine care. A CSF sample collected for the sole purpose of Zika RT-PCR testing is not recommended.

**If Zika virus testing of an infant or a child is indicated, how is the test ordered?**

There are no commercially available tests for Zika virus. Zika virus testing is performed at the CDC Arbovirus Diagnostic Laboratory and at some state and territorial health departments. Healthcare providers should contact their local, state or territorial health department to facilitate testing. See the Diagnostic Testing webpage for information on how to obtain Zika testing.

**When is an infant or child considered to have laboratory evidence of Zika virus infection?**

Laboratory evidence of Zika virus infection in an infant or child would include, in any clinical specimen, detectable Zika virus in culture, Zika virus RNA (by RT-PCR) or antigen, or a clinical specimen positive for Zika virus IgM with confirmatory neutralizing antibody titers 4-fold higher than dengue virus neutralizing antibody titers. If Zika virus antibody titers are <4-fold higher than dengue virus antibody titers, test results for Zika virus would be considered inconclusive.

**What are the challenges in interpreting Zika virus testing in an infant or child?**

Zika virus testing in infants and children has several challenges. RT-PCR tests may not detect Zika virus RNA in an infant or child who had Zika virus infection in utero if the period of viremia has passed. Serologic tests for Zika virus can be falsely positive because of cross-reacting antibodies against related flaviviruses (e.g., dengue and yellow fever viruses). Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to Zika virus, but neutralizing antibodies may still yield cross-reactive results in

infants due to maternal antibodies that were transferred to the infant. It is important to work closely with local, state or territorial health departments to ensure the appropriate test is ordered and interpreted correctly.

**7. ZIKA AND PREGNANCY**

**Can mothers pass Zika on to their fetuses during pregnancy?**

Zika virus can be passed from a mother to her fetus during pregnancy. We are studying how Zika affects pregnancies.

**What should a pregnant woman do if she has previously traveled to a place with a Zika outbreak?**

Pregnant women who have recently traveled to an area with Zika should talk to a healthcare provider about their travel even if they don't feel sick. CDC has guidance to help doctors decide what tests are needed for pregnant women who may have been exposed to Zika. CDC recommends that all pregnant women who have traveled to an area with Zika talk to their doctors. It is especially important that pregnant women see a doctor if they develop a fever, rash, joint pain, or red eyes during their trip or within 2 weeks after traveling to a country where Zika has been reported. They should tell the doctor where they traveled.

**What should a pregnant woman do if she gets sick during or after travel to a place with a Zika outbreak?**

Pregnant women who are worried that they had Zika should talk to their healthcare provider and tell their provider about their recent travel. It is especially important for a pregnant woman to see a doctor if she develops a fever, rash, joint pain, or red eyes during her trip or within 2 weeks after traveling to an area with Zika. CDC has guidance to help doctors decide what tests are needed for pregnant women who may have been exposed to Zika. Information for healthcare providers can be found on the Zika virus Information for Health Care Providers webpage.<sup>3,4</sup>

## **Does Zika in pregnant women cause birth defects?**

Brazil has been having a significant outbreak of Zika virus since May 2015. Officials in Brazil have also noted an increase in the number of babies with congenital microcephaly (a birth defect in which the size of a baby's head is smaller than expected for age and sex) during that time. Congenital microcephaly is often a sign of the brain not developing normally during pregnancy. Health authorities in Brazil, with assistance from the Pan American Health Organization, CDC, and other agencies, have been investigating the association between Zika virus infection and microcephaly.

Additional studies are needed to determine the degree to which Zika is linked with microcephaly. More lab testing and other studies are planned to learn more about the risks of Zika virus infection during pregnancy.

Because of the association between Zika infection and microcephaly, pregnant women should take steps to prevent mosquito bites.

## **Are there reasons other than Zika (for example, pesticides) that might explain the increase in microcephaly cases in Brazil?**

Microcephaly can happen for many reasons, including genetics, maternal infections, and being close to or touching toxins during pregnancy. Results of recent epidemiologic and laboratory studies performed in Brazil strongly support, but don't yet prove, a link between Zika virus infection during pregnancy and microcephaly. For example, a report in the MMWR on February 10, 2016, presents findings from pathologic studies showing the presence of Zika virus in the brains of infants born with microcephaly and in placental tissues from early miscarriages.<sup>5</sup>

Several media reports in February 2016 suggested that a pesticide called pyriproxyfen might be linked with microcephaly. These media reports appear to be based on a February 3 publication authored by an Argentine physicians organization,

which claims that the use of pyriproxyfen in drinking water in Brazil is responsible for the country's increase in microcephaly cases.

The World Health Organization has approved the use of pyriproxyfen for the control of disease-carrying mosquitos. Pyriproxyfen is a registered pesticide in Brazil and other countries, it has been used for decades, and it has not been linked with microcephaly. In addition, exposure to pyriproxyfen would not explain recent study results showing the presence of Zika virus in the brains of infants born with microcephaly.

CDC is working closely with international partners to study infants with microcephaly to better understand what role various factors, including Zika virus, may play in this birth defect.

## **8. EFFECTS OF ZIKA ON FUTURE PREGNANCIES**

### **Can a previous Zika infection cause a woman who later gets pregnant to have a baby with microcephaly?**

Currently, there is no evidence to suggest that Zika virus, after it is cleared from the blood, poses a risk of birth defects for future pregnancies. Zika virus usually remains in the blood of an infected person for about a week.

### **Is it safe to get pregnant after traveling to a place with a Zika outbreak?**

Women thinking about getting pregnant who have recently traveled to an area with Zika should talk to their healthcare provider. Once a person becomes sick, Zika virus usually remains in the blood for about a week. Zika virus has been found in semen longer.

### **How are animals involved in outbreaks of Zika virus?**

At this time, animals do not appear to be involved in the spread of Zika virus. Zika virus was first discovered in a monkey with a mild fever in the Zika Forest of Uganda in the 1940s. However the prevalence of Zika virus in monkeys and other

nonhuman primates is currently unknown. At this time there have been no reports of other animals becoming sick with Zika or of being able to spread Zika to people or other animals.

Can animals spread Zika virus?

There is no evidence that Zika virus is spread to people from contact with animals. Zika virus is transmitted to people primarily through the bite of an infected *Aedes* species mosquito. These are the same mosquitoes that spread dengue and chikungunya viruses. More information on Zika virus transmission is available here.

What types of animals are known to get infected or sick with Zika?

Nonhuman primates, such as monkeys and apes, have shown the ability to become infected with Zika virus. Only a few naturally and experimentally infected monkeys and apes have had any signs of illness at all, and then it was only a mild, transient fever without any other symptoms.

Can pets or other animals other than non-human primates get infected or sick with Zika?

There have not been any reports of pets or other types of animals becoming sick with Zika virus. There is limited evidence from one study done in Indonesia in the late 1970s that horses, cows, carabaos (water buffaloes), goats, ducks, and bats could become infected with Zika, but there is no evidence that they develop disease or pose a risk for Zika virus transmission to humans.<sup>6,7</sup>

If a pregnant animal is infected with Zika virus, will her offspring have microcephaly?

Microcephaly has not been reported among populations of monkeys and apes in areas with previous or ongoing Zika virus transmission. This type of birth defect is not known to be associated with Zika virus infection in animals.

Are animals in the United States at risk of becoming sick with Zika?

Animals in the United States are not at risk of becoming sick with Zika virus. Only monkeys and apes have shown the ability to become infected with Zika virus. The risk of monkeys and apes in the United States becoming infected with Zika virus is low. All monkeys and apes imported into the United States undergo a mandatory 31-day quarantine period on arrival. The monkeys and apes are held indoors or in screened enclosures where the risk of mosquito contact is low. Any monkey or ape that may have entered quarantine with an active Zika virus infection would not be able to pass it to others without mosquitoes. Monkeys and apes develop antibodies to Zika virus within 14 days of infection; once antibodies develop a person or primate can no longer spread the virus. All imported monkeys and apes should be free of Zika virus by the end of the quarantine period and thus pose no risk of infecting local mosquito populations

What are the requirements for bringing pets or other animals into the United States?

Some animals, including monkeys and apes, are not allowed to be imported as pets under any circumstances. Each state and US territory has its own rules for pet ownership and importation, and these rules may be different from federal regulations. You can find more information about animal importation here.

## 9. ZIKA VIRUS EVALUATION AND POTENTIAL OUTCOMES

**What should healthcare providers do to evaluate infants with positive or inconclusive Zika virus test results?**

A thorough physical examination should be performed, including careful measurement of the head circumference, length, weight, and assessment of gestational age. Cranial ultrasound is recommended unless it was performed as part of prenatal screening in the third trimester and clearly showed no abnormalities of the brain. Ophthalmologic evaluation is recommended as well as newborn hearing screen. An evaluation for neurologic abnormalities, dysmorphic features,

splenomegaly, hepatomegaly, and rash or other skin lesions is also recommended. Full body photographs and any rash, skin lesions, or dysmorphic features should be documented. If an abnormality is noted, consultation with an appropriate specialist is recommended.

**What additional follow-up is recommended for children with microcephaly, intracranial calcifications or abnormal neurologic findings?**

Consultations are recommended with a clinical geneticist or dysmorphologist, a pediatric neurologist, and a pediatric infectious disease specialist. A complete blood count including platelet count, and tests for liver enzymes and function should also be conducted. Testing for other congenital infections is also recommended. If any additional congenital anomalies are identified through clinical examination and imaging studies, genetic and other teratogenic causes should be considered.

**If a mother had Zika virus infection during pregnancy but her newborn tests negative for Zika virus, what is recommended for additional follow-up?**

In the absence of abnormal findings on examination, the infant should receive routine pediatric care including measurement of growth and development, and appropriate evaluation and follow-up for any clinical findings that arise. If the newborn has abnormal findings on examination, diagnostic testing for other causes of the newborn's conditions should be performed including testing for other congenital viral infections if indicated.

**Is there any information on neurocognitive outcomes in neonates if they are exposed to Zika virus during labor and delivery or after birth?**

Perinatal transmission of Zika virus infection has been reported. However information is limited to two cases: one of these infants was asymptomatic and the other had thrombocytopenia and a diffuse rash. Evidence from other flaviviruses, such as West Nile virus and dengue virus, indicate that

transmission has resulted in findings in the neonate ranging from no symptoms to severe illness (including fever, thrombocytopenia, and hemorrhage). The spectrum of clinical features that might be observed in infants who acquire Zika virus during the perinatal period is currently unknown.

**What is the prognosis for a newborn with congenital Zika virus infection?**

The prognosis for infants with congenital Zika virus infection is not known.

**Are there concerns for long-term complications in older infants and children who are infected with Zika virus?**

Information on long-term outcomes among infants and children with acute Zika virus disease is limited. Thus, until more evidence is available to inform recommendations, routine pediatric care is advised for these infants and children. Most children infected with Zika virus are asymptomatic or have mild illness, similar to the findings seen in adults with Zika virus infection.

**Can Zika virus infection cause Guillain-Barre syndrome (GBS) or death in infants or children?**

In general, the risk for GBS from any cause appears to increase with increasing age. GBS has been reported following Zika virus infection, although a causal link has not been established. It is unclear how often GBS following Zika virus infection has occurred in children; one report from Brazil refers to 6 patients, aged 2–57 years, with neurologic syndromes (4 with GBS and 2 with acute disseminated encephalomyelitis) after laboratory-confirmed Zika virus infection; no further data are available. Deaths due to Zika virus infection appear to be very rare at all ages.

**Is there specific treatment for Zika virus infection in infants and children?**

Evidence indicates that Zika virus disease in children is usually mild, and treatment is supportive; this includes rest and fluids to prevent

dehydration. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be used until dengue is ruled out as a cause of illness and should be avoided in children aged < 6 months. Aspirin is not recommended for use with acute viral illnesses due to the risk of Reye's syndrome. For infants with congenital Zika virus infection, care is focused on diagnosing and managing conditions that are present, monitoring the child's development over time, and addressing problems as they arise.<sup>8</sup>

## 10. DIAGNOSTICS

Zika virus disease diagnostics is primarily based on detection of viral RNA from clinical specimens in acutely ill patients.

The viraemic period appears to be short, allowing for direct virus detection during the first 3–5 days after the onset of symptoms. Zika virus RNA has been detected in urine up to 10 days after onset of the disease.

From day five post onset of disease, serological investigations can be conducted by detection of Zika-specific IgM antibodies and confirmation by neutralisation, seroconversion or four-fold antibody titer increase of Zika specific antibodies in paired serum samples.

Serological results should be interpreted according to the vaccination status and previous exposure to other flaviviral infections.

### Case Management and Treatment

There is no vaccine or specific prophylactic treatment.

Differential clinical diagnostic should be considered as well as co-infection with other mosquito-borne diseases such as dengue fever, chikungunya and malaria.

The treatment is symptomatic and mainly based on pain relief, fever reduction and anti-histamines for pruritic rash.

Treatment with acetylsalicylic acid and non-steroidal anti-inflammatory drugs was

discouraged because of a potential increased risk of haemorrhagic syndrome reported with other flaviviruses as well as the risk of Reye's syndrome after viral infection in children and teenagers.

## 11. CONCLUSION

There appears to be little chance of Zika slowing down. The US aside, Brazil is expecting to host thousands, if not millions of travelers from around the world first for Carnival in February and then in the 2016 Summer Olympics. It could lead to the rapid spread of Zika to other parts of the world, said some experts, though local officials in Brazil suggest that by then the rainy season would be over, allowing the outbreak to subside. Summer is also when things might ramp up in the US, especially in the southern parts where conditions are more ideal for mosquitoes to breed. Better quality of resources and healthcare may prevent the virus from spreading as fast though.

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