

# ZIKA VIRAL INFECTION

Revised 2/13/2016

## Contents

|  |    |
|--|----|
| ZIKA VIRAL INFECTION .....                           | 1  |
| Virology.....  | 2  |
| History .....  | 2  |
| Epidemiology .....                                   | 3  |
| Transmission /Vector .....                           | 3  |
| <i>Aedes aegypti</i> .....                           | 3  |
| <i>Aedes albopictus</i> .....                        | 4  |
| Viremia.....   | 4  |
| Geographical Distribution .....                      | 5  |
| Sexual Transmission.....                             | 6  |
| Transfusion.....                                     | 6  |
| Symptoms .....                                       | 6  |
| Diagnostic.....                                      | 6  |
| Laboratory Tests.....                                | 7  |
| RT-PCR .....   | 7  |
| Virus-specific IgM and Neutralizing Antibodies ..... | 7  |
| Complications.....                                   | 7  |
| Microcephaly.....                                    | 7  |
| Recommendation for Infants .....                     | 9  |
| Guillain–Barré Syndrome.....                         | 10 |
| Blood Transfusions.....                              | 10 |
| Treatment.....                                       | 11 |

## Virology

The Zika virus (ZIKV) is a member of the virus family *Flaviviridae* and the genus *Flavivirus*. It is transmitted by daytime-active *Aedes* mosquitoes, such as *A. aegypti* and *A. albopictus*. Its name comes from the Zika Forest of Uganda, where the virus was first isolated in 1947. Zika virus is related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses.

Like other flaviviruses, Zika virus is **enveloped** and icosahedral and has a non-segmented, single-stranded, positive-sense RNA genome. There are two lineages of the Zika virus: the African lineage, and the **Asian lineage**. Phylogenetic studies indicate that the virus spreading in the Americas is most closely related to the Asian strain, which circulated in French Polynesia during the 2013 outbreak.

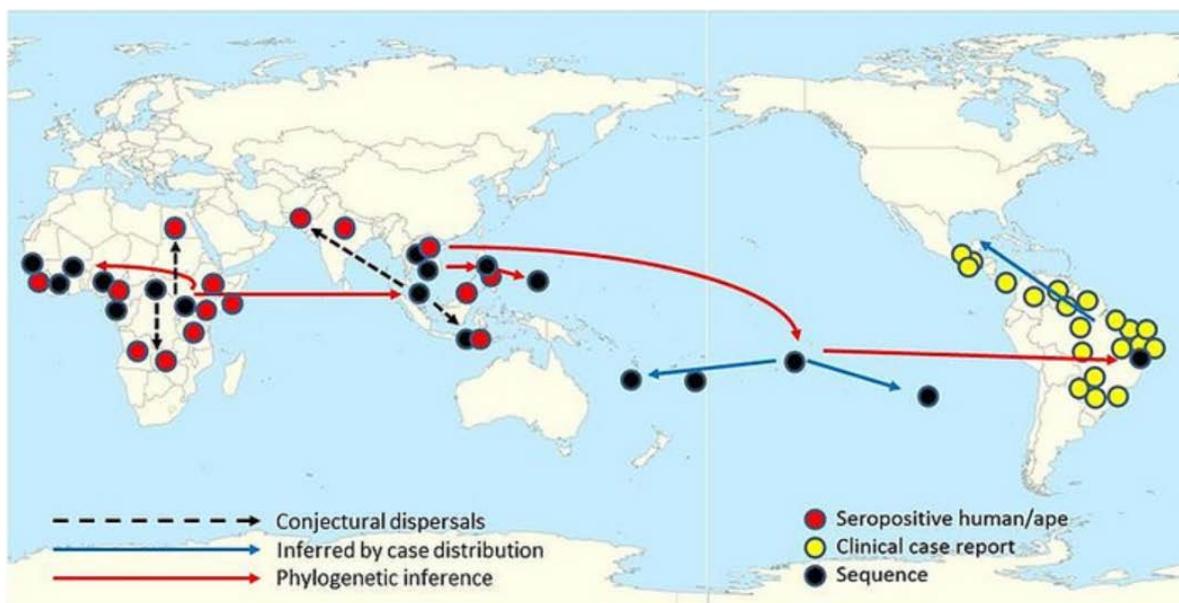
## History

The virus was first isolated in April 1947 from a rhesus macaque monkey that had been placed in a cage in the Zika Forest of Uganda, near Lake Victoria, by the scientists of the Yellow Fever Research Institute. A second isolation from the mosquito *A. africanus* followed at the same site in January 1948. When the monkey developed a fever, researchers isolated from its serum a "filterable transmissible agent" that was named Zika virus in 1948.

In 1952 there was an outbreak investigation of jaundice that was suspected to be yellow fever. Zika was found in the blood of a 10-year-old Nigerian female with low grade fever, headache, and evidence of malaria, but no jaundice, who recovered within three days. Blood from this child was injected into the brain of laboratory mice, followed by up to 15 mice passages. The virus from mouse brains was then used in neutralization tests using rhesus monkey sera specifically immune to Zika virus. Infection was proven by a rise in Zika virus specific serum antibodies.

A 1952 research study conducted in India had shown a "significant number" of Indians tested for Zika had exhibited an immune response to the virus, suggesting it had long been widespread within human populations.<sup>1</sup>

From 1951 through 1981, evidence of human infection with Zika virus was reported from other African countries, such as the Central African Republic, Egypt, Gabon, Sierra Leone, Tanzania, and Uganda, as well as in parts of Asia including India, Indonesia, Malaysia, the Philippines, Thailand, and Vietnam. From its discovery until 2007, there were only 14 confirmed human cases of Zika virus infection from Africa and Southeast Asia.



## Epidemiology

The vertebrate hosts of the virus were primarily monkeys in a so-called enzootic mosquito-monkey-mosquito cycle, with only occasional transmission to humans. Before the current pandemic began in 2007, Zika virus "rarely caused recognized 'spillover' infections in humans, even in highly enzootic areas."

Infrequently, other arboviruses have become established as human diseases, and spread in a mosquito-human-mosquito cycle, as with the yellow fever virus and the dengue fever virus (both flaviruses), and the chikungunya virus (a togavirus).

## Transmission /Vector

### *Aedes aegypti*

The Zika virus is transmitted by daytime-active mosquitoes as its vector. It is primarily transmitted by the female *Aedes aegypti* in order to lay eggs. These mosquitoes can also transmit dengue and chikungunya viruses. Zika has been isolated from a number of arboreal mosquito species in the *Aedes* genus, but the role of these other mosquitoes in the transmission is assumed to be minimal.

- *Aedes aegypti* is a small, dark, mosquito with white lyre-shaped markings and banded legs.
- They prefer to bite indoors and primarily bite humans.
- These mosquitoes can use natural locations or habitats (for example tree-holes and plant axils) and artificial containers with water to lay their eggs. They lay eggs during the day in water containing organic material (e.g., decaying leaves, algae, etc.) in containers with wide openings and prefer dark-colored containers located in the shade.
- About three days after feeding on blood, the mosquito lays her eggs inside a container just above the water line. Eggs are laid over a period of several days, are resistant to desiccation and can survive for periods of six or more months. When rain floods the eggs with water, the larvae hatch.
- Generally larvae feed upon small aquatic organisms, algae and particles of plant and animal material in water-filled containers.
- The entire immature or aquatic cycle (i.e., from egg to adult) can occur in as little as seven to eight days. The life span for adult mosquitoes is around three weeks.
- Egg production sites are within, or in close proximity to households.
- *Aedes aegypti* do not remain alive through the winter in the egg stage in colder climates.

Although *Aedes aegypti* mosquitoes most commonly feed at dusk and dawn, indoors, in shady areas, or when the weather is cloudy, they can bite and spread infection all year long and at any time of day.

The mosquitoes prefer to breed in areas of stagnant water, such as flower vases, uncovered barrels, buckets, and discarded tires, but the most dangerous areas are wet shower floors and toilet tanks, as they allow the mosquitos to breed within a residence. Research has shown that certain chemicals emanating from bacteria in water containers stimulate the female mosquitoes to lay their eggs. They are particularly motivated to lay eggs in water containers that have the correct amounts of specific fatty acids associated with bacteria involved in the degradation of leaves and other organic matter in water. The chemicals associated with the microbial stew are far more stimulating to discerning female mosquitoes than plain or filtered water in which the bacteria once lived. It is recommended that once a week, eggs sticking to wet containers should be scrubbed off and the containers, sealed and/or discarded.

The **extrinsic incubation period** (EIP) is the viral **incubation period** between the time when a mosquito takes a viremic blood meal and the time when that mosquito becomes infectious. The **intrinsic incubation period** (IIP) is the time between a human being infected and the onset of symptoms due to the infection. Boorman and Porterfield subsequently demonstrated transmission of ZIKV to mice and monkeys by *Ae. aegypti* in a laboratory. Virus content in the mosquitoes was high on the day of artificial feeding, dropped to undetectable levels through day 10 after feeding, had increased by day 15,

and remained high from days 20 through 60. Their study suggests that the extrinsic incubation period for ZIKV in mosquitoes is  $\approx 10$  days.

### *Aedes albopictus*

- *Aedes albopictus* is a small, dark, mosquito with a white dorsal stripe and banded legs.
- They are strongly attracted to bite humans, but will feed on cats, dogs, squirrels, deer and other mammals, as well as birds. They will bite any exposed skin surface. They bite outdoors and indoors, but are usually found outside.
- These mosquitoes can use natural locations or habitats (for example treeholes and plants) and artificial containers with water to lay their eggs.
- About four or five days after feeding on blood, the female mosquito lays her eggs just above the surface of the water. When rain covers the eggs with water, the larvae hatch. Generally, larvae feed upon small aquatic organisms, algae and particles of plant and animal material in water-filled containers.
- The entire immature or aquatic cycle (i.e., from egg to adult) can occur in as little as seven to nine days. The life span for adult mosquitoes is around three weeks.
- They have a short flight range (less than 200 m), so egg production sites are likely to be close to where this mosquito is found. *Aedes albopictus* mosquitoes remain alive through the winter in the egg stage in temperate climates (areas with four seasons), but are active throughout the year in tropical and subtropical locations.

Transmission by *A. albopictus*, the Asian tiger mosquito, was reported from a 2007 urban outbreak in Gabon where it had newly invaded the country and become the primary vector for the concomitant chikungunya and dengue virus outbreaks. It is originally indigenous to Southeast Asia, islands of the Western Pacific and Indian Ocean. It has spread during recent decades to Africa, the mid-east, Europe and the Americas (north and south) after extending its range eastwards across Pacific islands during the early 20th century. The majority of introductions are apparently due to transportation of dormant eggs in tires.

Among public health authorities in the newly infested countries and those threatened with the introduction, there has been much concern that *Ae. albopictus* would lead to serious outbreaks of arbovirus diseases (*Ae. albopictus* is a competent vector for at least 22 arboviruses), notably dengue (all four serotypes) more commonly transmitted by *Aedes aegypti* (L.). Results of many laboratory studies have shown that many arboviruses are readily transmitted by *Ae. albopictus* to laboratory animals and birds, and have frequently been isolated from wild-caught mosquitoes of this species, particularly in the Americas.

*Ae. albopictus* continues to spread, displacing *Ae. aegypti* in some areas, and is **anthropophilic** throughout its range. Examination of the extensive literature indicates that *Ae. albopictus* probably serves as a maintenance vector of dengue in rural areas of dengue-endemic countries of Southeast Asia and Pacific islands. Also *Ae. albopictus* transmits dog heartworm *Dirofilaria immitis* in Southeast Asia, south-eastern United States and both *D. immitis* and *Dirofilaria repens* in Italy. Despite the frequent isolation of dengue viruses from wild-caught mosquitoes, there is no evidence that *Ae. albopictus* is an important urban vector of dengue, except in a limited number of countries where *Ae. aegypti* is absent, i.e. parts of China, the Seychelles, historically in Japan and most recently in Hawaii. Surveillance must be maintained on the vectorial role of *Ae. albopictus* in countries endemic for dengue and other arboviruses (e.g. chikungunya, EEE, Ross River, WNV, LaCrosse and other California group viruses), for which it would be competent and ecologically suited to serve as a bridge vector.

### **Viremia**

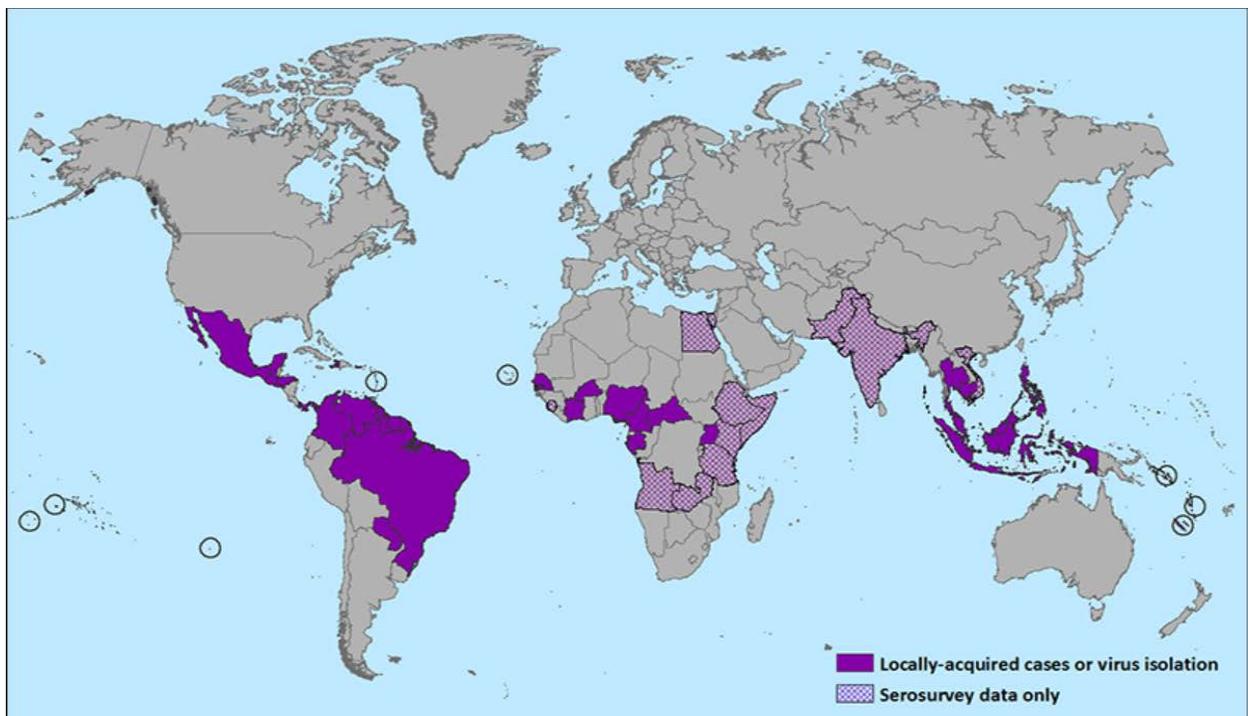
To date, infectious ZIKV has been detected in human blood as early as the day of illness onset; viral nucleic acid has been detected as late as 11 days after onset.

|  |
|--|
| <b>Viremia = Three (3) to Twelve (12) Days</b> |
|--|

## Geographical Distribution

- Since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia.
- In April 2007, the first outbreak outside of Africa and Asia occurred on the island of Yap in the Federated States of Micronesia, characterized by rash, conjunctivitis, and arthralgia, which was initially thought to be dengue, chikungunya, or Ross River disease. Serum samples from patients in the acute phase of illness contained RNA of Zika virus. There were 49 confirmed cases, 59 unconfirmed cases, no hospitalizations, and no deaths. Seroprevalence survey determined that less than or equal to 70% of the population had been infected
- In 2014, the virus spread eastward across the Pacific Ocean to French Polynesia, then to Easter Island and in 2015 to Brazil, then to Mexico, Central America, the Caribbean, and South America
- A large ZIKV outbreak occurred in French Polynesia during 2013-2014. The outbreak spread to other Pacific Islands: New Caledonia, Cook Islands, Easter Island, Vanuatu, and Solomon Islands. The origin of introduction of ZIKV to French Polynesia remains unknown; introduction of ZIKV in other south Pacific islands was by imported cases from French Polynesia
- In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infections in Brazil. Phylogenetic studies showed that the closest strain to the one that emerged in Brazil was isolated from samples from case-patients in French Polynesia and spread among the Pacific Islands. Both strains belong to the Asian lineage
- In May 2015, reported in South America: Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Suriname, Venezuela
- In October 2015, reported in Cape Verde.
- In November 2015, reported in Mexico, and in Central America: Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama; also reported in more Pacific islands: American Samoa, Samoa, Tonga
- In December 2015, reported in the Caribbeans: Barbados; Curaçao; Dominican Republic; Guadeloupe; Haiti; Jamaica; Martinique; the Commonwealth of Puerto Rico; Saint Martin; U.S. Virgin Islands

Zika virus will continue to spread and it will be difficult to determine how and where the virus will spread over time.



## Sexual Transmission

As of February 2016, three reported cases indicate that Zika virus could possibly be sexually transmitted. In 2014, Zika virus capable of reproducing itself was found in the semen of a man at least two weeks (and possibly up to 10 weeks) after he fell ill with Zika fever. The second report is of a United States biologist who had been bitten many times while studying mosquitoes in Senegal. Six days after returning home in August 2008, he fell ill with symptoms of Zika fever but not before having unprotected intercourse with his wife, who had not been outside the US since 2008. She subsequently developed symptoms of Zika fever, and Zika antibodies in both the biologist's and his wife's blood confirmed the diagnosis. In the third case, in early February 2016 the Dallas County Health and Human Services department reported that a person contracted Zika fever after sexual contact with an ill person who had recently returned from a high risk country.

It is unknown whether women can transmit Zika virus to their sexual partners. As of February 2016, the Centers for Disease Control and Prevention (CDC) recommends that men "who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy." Men who reside in or have traveled to an area of active Zika virus transmission and their non-pregnant sex partners "might consider" abstinence or condom use. The CDC did not specify how long these practices should be followed with non-pregnant partners because the "incidence and duration of shedding in the male genitourinary tract is limited to one case report" and that "**testing of men for the purpose of assessing risk for sexual transmission is not recommended.**"

## Transfusion

A potential risk is suspected, based on a study conducted between November 2013 and February 2014 during the Zika outbreak in French Polynesia in which 2.8% of blood donors tested positive for the Zika virus RNA and were asymptomatic at the time of blood donation. Eleven of those positive donors reported symptoms of Zika fever after their donation; only three of 34 samples grew in culture. Since January 2014, nucleic acid testing of blood donors was implemented in French Polynesia to prevent unintended transmission.

## Symptoms

Common symptoms of infection with the virus include:

- Mild headaches, particularly retro-orbital
- Maculopapular rash, which fades in a few days
- Fever, (37.8°C - 38.5°C)
- Malaise
- Conjunctivitis
- Joint pains, notably of small joints of hands and feet, myalgia, possibly back pain

In more than 60 years of observation, Zika has not been noted to cause hemorrhagic fever or death. There is in vitro evidence that Zika virus mediates antibody-dependent enhancement of infection, a phenomenon observed.

Zika fever has been a relatively mild disease of limited scope, with only one in five persons developing symptoms, with no fatalities,

## Diagnostic

In a "pure" Zika epidemic, a diagnosis can be made reliably on clinical grounds. Unfortunately, the fact that dengue and chikungunya, which result in similar clinical pictures, have both been epidemic in the

Americas confounds clinical diagnoses. Specific tests for dengue and chikungunya are not always available, and commercial tests for Zika have not yet been developed. Moreover, because Zika is closely related to dengue, serologic samples may cross-react in tests for either virus. Gene-detection tests such as the polymerase-chain-reaction assay can reliably distinguish the three viruses, but Zika-specific tests are not yet widely available.

## **Laboratory Tests**

### RT-PCR

During the first week after onset of symptoms, Zika virus disease can often be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum.

In a study performed in New Caledonia, urine samples from two patients were also positive for ZIKV; the samples showed a higher viral load than corresponding serum samples and were positive for less than or equal to seven days and probably greater than 20 days for one patient after viremia reached an undetectable level. Urine samples from six healthy patients were also assessed and showed negative results. For ZIKV infection, date of onset of illness is difficult to establish because of sporadic and frequently mild fever. Although rash has been reported three to five days after the febrile phase, the six patients in this study had light asthenia and mild fever two to three days before the rash was observed; these symptoms were considered indicative of disease onset. Therefore, at the time the rash was observed, viremia was probably decreasing, which makes detection of virus in serum samples extremely challenging. Urine samples showed strongly positive results; estimated maximum viral load was 0.7 to 220.106 copies/mL.

### Virus-specific IgM and Neutralizing Antibodies

These antibodies typically develop toward the end of the first week of illness; cross-reaction with related flaviviruses (e.g., dengue and yellow fever viruses) is common and may be difficult to discern. Although data on the performance of IgM serologic testing in asymptomatic persons is limited, on the basis of experience with other flaviviruses, when performed from two to 12 weeks after travel to areas of ongoing Zika virus transmission, a negative (IgM) result suggests that infection did not occur and could obviate the need for serial ultrasounds.

|   |
|---|
| <b>Antibodies Detected in Serum from Two (2) to Twelve (12) Weeks</b> |
|---|

Plaque-reduction neutralization testing can be performed to measure virus-specific neutralizing antibodies and discriminate between cross-reacting antibodies in primary flavivirus infections.

There are no commercially available diagnostic tests for Zika virus disease. Zika virus testing is performed at the CDC Arbovirus Diagnostic Laboratory. The Office of Public Health (OPH) laboratory can now perform RT-PCR testing.

## **Complications**

### Microcephaly

Although no other flavivirus is known to have teratogenic effects, it appears that the Zika virus may affect the fetus. By September 2015, reports of an increase in the number of infants born with microcephaly in Zika virus-affected areas began to emerge, and Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had been found to have microcephaly by prenatal ultrasound. The Brazil Ministry of Health (MoH) established a task force to investigate the possible association of microcephaly with Zika virus infection during pregnancy and a registry for incident microcephaly cases (head circumference  $\geq$  two standard deviations [SD] below the mean for sex and gestational age at birth) and pregnancy outcomes among women suspected to have had Zika virus infection during pregnancy. Among a cohort of 35 infants with microcephaly born during August-October 2015 in eight of Brazil's 26

states and reported to the registry, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy, 25 (71%) infants had severe microcephaly (head circumference > three SD below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities.

In October, the Medical Officer of Health (MoH) confirmed an increase in birth prevalence of microcephaly in northeast Brazil, compared with previously reported estimates (approximately 0.5 per 10,000 live births), which are based on review of birth certificates and include descriptions of major congenital anomalies. The expected estimate for microencephaly is one to two cases per 10,000 live births.

In December, the Pan American Health Organization (PAHO) reported the identification of Zika virus RNA by reverse transcription-polymerase chain reaction (RT-PCR) in amniotic fluid samples from two pregnant women whose fetuses were found to have microcephaly by prenatal ultrasound, and the identification of Zika virus RNA from multiple body tissues, including the brain, of an infant with microcephaly who died in the immediate neonatal period.

The CDC recently tested samples from two pregnancies that ended in miscarriage and from two infants with microcephaly who died shortly after birth. All four cases were from Brazil and were positive for Zika virus infection, indicating that the infants had become infected during pregnancy. Zika virus was present in the brain of the full term infants, and genetic sequence analyses show that the virus in all four cases was the same as the Zika virus strain currently circulating in Brazil. All four mothers reported having experienced a febrile rash illness during their pregnancies. This report describes evidence of a link between Zika virus infection and microcephaly and fetal demise through detection of viral RNA and antigens in brain tissues from infants with microcephaly and placental tissues from early miscarriages. Histopathologic findings indicate the presence of Zika virus in fetal tissues

Microcephaly usually results from abnormal brain development. The long-term consequences of microcephaly depend on underlying brain anomalies and can range from mild developmental delays to severe motor and intellectual deficits, like cerebral palsy. In addition to congenital infections, microcephaly can result from chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull (craniosynostosis); and certain metabolic disorders. The sudden increase in the number of infants born with microcephaly associated with cerebral damage characteristically seen in congenital infections in a region where an outbreak of a newly circulating virus has recently occurred is suggestive of a possible relationship. The association between maternal infections and congenital anomalies has long been recognized, especially when infection occurs during the first 12 weeks of pregnancy. Brazil's vaccination program has eliminated some infections that result in congenital anomalies, such as rubella. Congenital infections can affect multiple organ systems, and many are associated with specific brain damage, including microcephaly, calcifications (predominantly periventricular, but also in the basal ganglia and in cerebral parenchyma), ventriculomegaly, neuronal migration disorders (pachygyria, polymicrogyria, lissencephaly, and schizencephaly), cerebellar hypoplasia, and white matter anomalies. Ongoing surveillance and evaluation of new cases are important to describe the phenotypic spectrum of potential Zika virus-associated congenital infections. In addition, special studies, including case-control studies, are needed to confirm the association, determine the magnitude of the potential risk, and identify other possible risk factors.

Some infants with possible Zika virus infection have been found to have **intracranial calcifications** and **abnormal eye findings**. It is not known if Zika virus infection caused any of these abnormalities.

#### Recommendations for Pregnant Women

Counsel women of reproductive age (15-44 years) about Zika signs and symptoms, possible effects on the fetus and protection against mosquito bites.

Offer serologic testing and counsel:

- Asymptomatic pregnant traveler: Asymptomatic pregnant women who have traveled to areas with ongoing Zika virus transmission. Testing can be offered two to 12 weeks after pregnant women return from travel.
- Asymptomatic pregnant women residing in areas with ongoing Zika virus transmission, testing is recommended
  - at the initiation of prenatal care with
  - follow-up testing mid-second trimester (18 weeks)
- Ill pregnant women (with clinical illness consistent with Zika virus disease),\* testing is recommended during the first week of illness.
- Women resident in areas with ongoing Zika virus transmission: discuss the continuing risk during the entire pregnancy, include recommendations for screening, testing, and management of pregnancy.
- Women traveler: Health care providers should discuss reproductive life plans, including pregnancy intention and timing, with women of reproductive age in the context of the potential risks associated with Zika virus infection.

### Recommendation for Infants

Testing for Zika virus infection is recommended for infants born to women who traveled to or resided in an area with ongoing Zika virus transmission during pregnancy who were:

- 1) diagnosed with microcephaly or intracranial calcifications detected prenatally or at birth, or
- 2) who have mothers with positive or inconclusive test results for Zika virus infection.

Zika virus infection can be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on infant serum. Serology assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies. However, since it has not been established which test is most reliable for a diagnosis in infants, **RT-PCR and IgM tests should both be performed**. Plaque-reduction neutralization testing (PRNT) can also be performed to measure virus-specific neutralizing antibodies and differentiate from other flaviviruses.

Zika virus RT-PCR and serology assays can be performed on infant serum or serum or plasma collected from the umbilical cord. If cerebrospinal fluid (CSF) specimens are available, Zika virus RT-PCR should be performed; however, CSF specimens should not be collected for the sole purpose of Zika virus testing. Other specimens that can be tested include the placenta and the umbilical cord. Histopathologic examination and immunohistochemical staining can be performed. Zika virus RT-PCR on fixed and frozen tissue should also be considered.

### Congenital Zika Virus Infection

A newborn is considered to be congenitally infected if:

- 1) Zika virus RNA is detected in any newborn specimen or during testing of amniotic fluid or the placenta, or
- 2) Zika virus IgM antibodies are detected along with confirmatory neutralizing antibody tiers that are  $\geq 4$ -fold higher than dengue virus neutralizing antibody titers in the infant serum or cerebrospinal fluid (CSF).

Testing for congenital infection is considered inconclusive if Zika virus IgM antibodies are detected but Zika virus neutralizing antibody titers are <less than four-fold higher than dengue virus neutralizing antibody titers.

Zika virus testing in newborns has **several challenges**. RT-PCR tests may not detect Zika virus RNA in a newborn who had Zika virus infection in utero if the period of viremia has passed. Serologic tests for Zika virus can often 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 newborns due to maternal antibodies that were transferred to the infant. It is important to work closely with state or territorial health departments to ensure the appropriate test is ordered and interpreted correctly.

Health care providers should **report positive or inconclusive results** to their state or territorial health department. As an arboviral disease, Zika virus disease is a nationally notifiable condition.

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 repeat hearing screen at six months of age. Continued evaluation of developmental characteristics and milestones, including head circumference, is recommended through the first year of life.

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

For infants without suspected abnormalities, health care providers should continue with routine pediatric care. If the infant has microcephaly or intracranial calcifications, health care providers should continue to evaluate and treat for other possible etiologies.

If the newborn does not have 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.

Although Zika virus RNA has been detected in breast milk, transmission of Zika infection through breastfeeding has not been documented. Based on available evidence, the benefits of breastfeeding infants outweigh any theoretical risk related to Zika virus infection.

### Guillain-Barré Syndrome

In French Polynesia a concomitant epidemic of 73 cases of Guillain-Barré syndrome and other neurologic conditions was documented in a population of approximately 270,000, which may represent complications of Zika.

### Blood Transfusions

While there have been no reports to date of Zika virus entering the U.S. blood supply, the risk of blood transmission is considered likely based on the most current scientific evidence of how Zika virus and similar viruses (flaviviruses) are spread and recent reports of transfusion-associated infection outside of the U.S. Furthermore, about four out of five of those infected with Zika virus do not become symptomatic. For these reasons, the U.S. Food and Drug Administration (FDA) is recommending that blood establishments defer blood donations from individuals in accordance with the new guidance.

***In areas without active Zika virus transmission***, the FDA recommends that donors at risk for Zika virus infection be deferred for four weeks. Individuals considered to be at risk include: those who have had symptoms suggestive of Zika virus infection during the past four weeks, those who have had sexual contact with a person who has traveled to, or resided in, an area with active Zika virus transmission

during the prior three months, and those who have traveled to areas with active transmission of Zika virus during the past four weeks.

*In areas with active Zika virus transmission*, the FDA recommends that Whole Blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. The guidance also recommends blood establishments update donor education materials with information about Zika virus signs and symptoms and ask potentially affected donors to refrain from giving blood.

## **Treatment**

The mainstays of management are bed rest and supportive care. When multiple arboviruses are co-circulating, specific viral diagnosis, if available, can be important in anticipating, preventing, and managing complications. For example, in dengue, aspirin use should be avoided and patients should be monitored for a rising hematocrit predictive of impending hemorrhagic fever, so that potentially lifesaving treatment can be instituted promptly. Patients with chikungunya virus infection should be monitored and treated for acute arthralgias and postinfectious chronic arthritis.