Summary

- Flavivirus, belongs to Spondweni serogroup
- Vector: mosquito, Aedes species; human to human transmission occurs (sexually)
- Main clinical presentation: Artralgia/ rash, Febrile disease, neurological syndrome (AR, FD, NS), conjunctivitis, congenital syndrome
- WHO declared the Zika virus epidemic in the Americas a Public Health Emergency of International Concern (PHEIC), because of its association with microcephaly and other neurodevelopmental disorders

Virus

Zika virus (ZIKV) is a member of the virus family Flaviviridae, genus Flavivirus. It is a 40-nm virus and has icosahedral symmetry. ZIKV has a non-segmented, single-stranded, positive sense RNA genome.

Transmission

Prior to the 2007 outbreak in the Yap islands (Micronesia), no outbreaks and only 14 cases of human ZIKV disease had been recorded, although sero-surveillance studies in Africa had already indicated anti-ZIKV antibody presence of ca. 6% in some populations. The Yap outbreak indicated that the virus could now spread in human communities and establish a so-called urban transmission cycle. The biggest epidemic occurred in 2015-2017 in the Americas with spread to several countries in Asia. In 2016 the incidence peaked in the Americas and declined substantially throughout 2017 and 2018 probably due to herd immunity. In 2020, a total of 87 countries have had evidence of autochthonous transmission of Zika virus.

The reservoir of ZIKV are primates, both human and non-human. The virus is primarily transmitted by mosquitoes from the genus Aedes, most commonly Aedes aegypti. However sexual transmission of the virus (male to female, male to male, female to male) from symptomatic or asymptomatic persons is now well established. Uncertainty remains over the duration of infectivity of one person.

Table 4 A brief history of Zika virus infections

1947	ZIKV was first detected from rhesus monkey in Uganda.
1952	First human case has been identified in Uganda.
1968	ZIKV has been reported from Nigeria.
1951-1981	Incidences of this virus have been reported from various countries of Asia and Africa.
2007	The first outbreak was reported in Yap Islands, part of the Federated States of Micronesia. Prior to this event, no outbreaks and only 14 cases of human Zika virus disease had been documented worldwide. Zika virus infection is estimated to be asymptomatic in 80% of cases.
2012-2014	Cases have been reported from Thailand.
2013	The virus spread to French Polynesia with an estimated 28 000 cases. ZIKV rapidly spreads to the Cook Islands and Easter Island. An association of Zika virus with Guillain Barré Syndrome is observed.
2015	Zika virus infection was first diagnosed in Brazil. It was found to be associated with microcephaly in the infants of mothers with suspected ZIKV infection.
February 2016	WHO declares the Zika virus epidemic in the Americas a Public Health Emergency of International Concern (PHEIC) because of its association with microcephaly and other neurodevelopmental disorders.
2015-2017	Epidemic in the Americas with 500.000 symptomatic cases reported at the peak of the pandemic in 2016

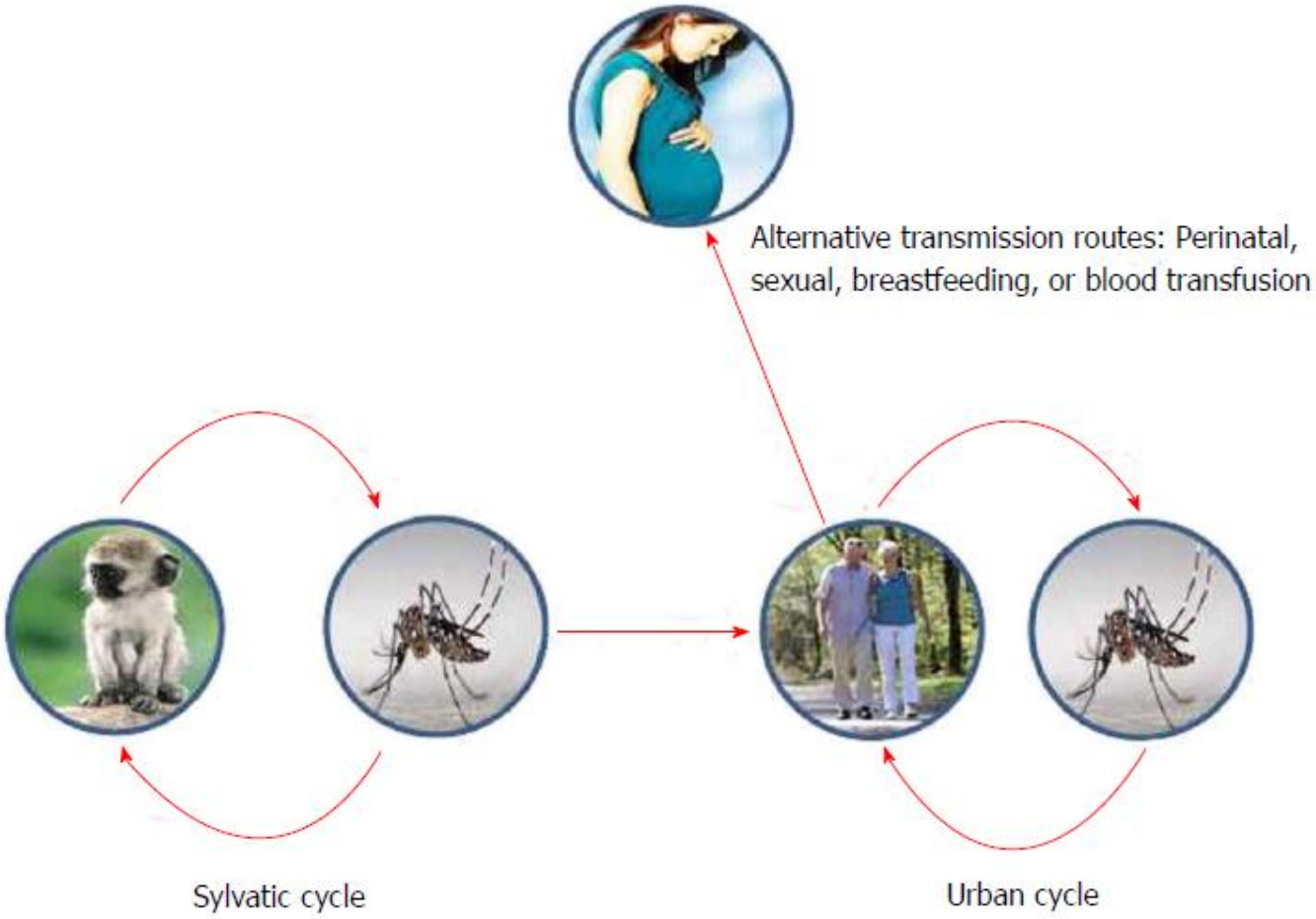


Figure: Important transmission routes of Zika virus (Blázquez A-B et al, World J Virol)

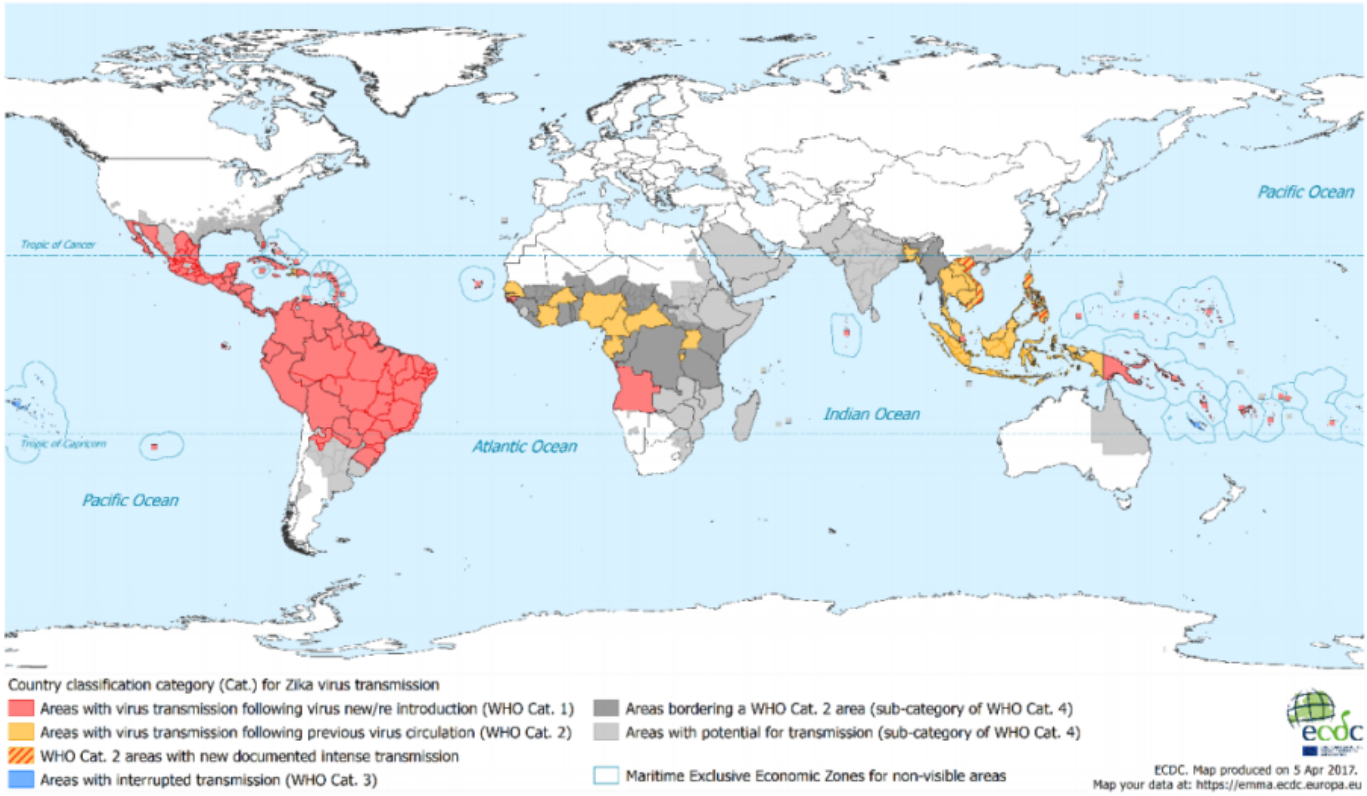


Figure: Global transmission of Zika virus, ECDC April 2017

Clinical aspects

Symptomatic ZIKV infections

After a mosquito bite, the incubation period is 3-12 days, with a mean of 5.9 days (95% credible interval, CrI: 4.4–7.6), and 95% of people who developed symptoms doing so within 11.2 days (95% CrI: 7.6–18.0) after infection. Approximately 20% of patients are symptomatic. They can present with acute onset of low-grade fever with maculopapular rash, arthralgia or non-purulent conjunctivitis. These symptoms feature in the (E)CDC case definition. Other commonly reported clinical manifestations are lymphadenopathy and ulcers on the mucous membrane are less common. Thrombocytopenia, palatal petechiae, and uveitis have been reported. In adults, ZIKV infection generally produces very mild disease. Infants and young children may present with irritability, walking with a limp, difficulty moving an extremity. There may be pain on palpation, or pain with active or passive movement of the affected joint.

Guillain Barré syndrome

Guillain-Barré Syndrome (GBS) is a post-infectious peripheral autoimmune neuropathy, characterized by progressive weakness of the limbs and absent or depressed deep tendon reflexes and cyto-albuminologic dissociation in cerebrospinal fluid (CSF) examination. Several electro-myographic (EMG) types exist. Up to 25% of those affected may require mechanical ventilation. Mortality is estimated at 3-5%. Global incidence of GBS varies from 0.8-1.9/ 100,000.

The incidence of ZIKV-associated GBS is estimated to be 2 tot 3 cases per 10,000 ZIKV infections. The median time before onset of neurological symptoms was 6 days.

Neurodevelopmental disorders

The most disconcerting finding is the association of ZIKV infection with neurodevelopmental disorders. Health care personnel and authorities in Brazil observed a sharp increase in the number of neonates born with congenital microcephaly and found an epidemiological association with the ZIKV epidemic which hit Brazil early in 2015.

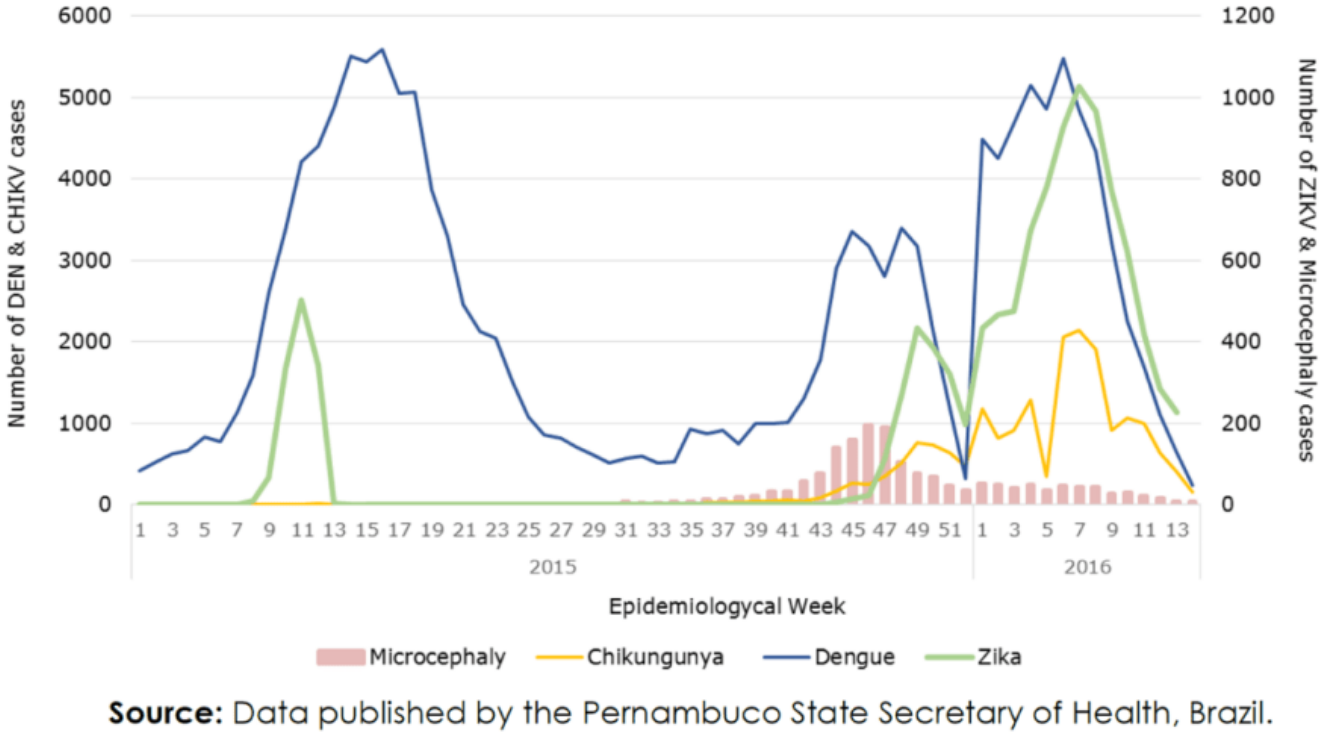


Figure: Temporal association of microcephaly cases in newborns and Zika virus epidemic in Brazil (www.paho.org)

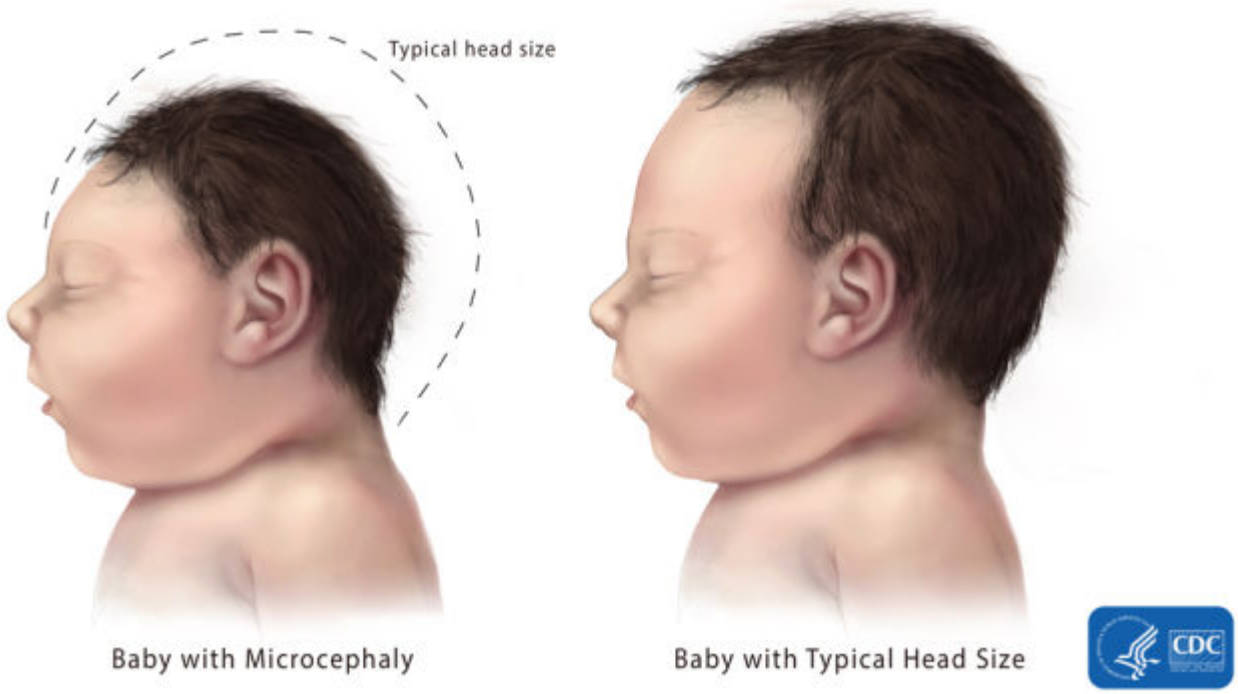


Figure: Microcephaly, from www.cdc.gov/ncbddd/birthdefects/microcephaly.html

Microcephaly is defined as Head Circumference (HC) at birth less than the 3rd percentile for gestational age and sex

Maternal-fetal ZIKV transmission can occur in all trimesters of pregnancy. There is no suggestion that pregnant women are more susceptible to ZIKV infection and there is no evidence of greater severity of this infection during pregnancy.

20-30% Of foetuses and neonates will become infected when mothers are infected during pregnancy. This will lead to foetal loss in 14%, to congenital Zika syndrome in 21% with microcephaly in about half the cases. 80-90% of all foetuses exposed to Zika (not necessarily vertically infected) will be asymptomatic during the first weeks of life. Follow-up is needed to know whether longer term sequalae (learning difficulties, …) in this last group will occur. Not just the brain that is affected in the congenital zika syndrome: infants from ZIKV infected mothers frequently show retinal defects, such as chorioretinal atrophy surrounded by a hyperpigmented halo and hyperpigmented mottling. Hence, the neurodevelopmental disorders observed in neonates and children after ZIKV infection of the mother can be referred to as Zika virus congenital syndrome.

Significance of asymptomatic ZIKV infections and sexual transmission

At present, approximately 80% of ZIKV infected patients are thought to have no clinical manifestations of infection. In areas where suitable mosquito vectors are present, these patients will add to the reservoir and fuel the epidemic. It is estimated that 1% of ZIKV infections reported in Europe and the United States were acquired through sexual transmission. ZIKV RNA is detected up to 3è0 days after onset of symptoms, but shedding of infective virus is unlikely to occur after 30 days from the onset of illness.

Diagnosis

Laboratory diagnosis is needed to confirm the diagnosis of ZIKV infection.

Specific laboratory diagnosis is based on detection of viral RNA from clinical specimens by RT-PCR. The window of detection in blood samples is a period of 1–5 days after the start of symptoms. However, the sensitivity of RT- PCR is estimated to be 40 %. Because of the longer persistence of the virus in urine, RT-PCR on urine can be attempted up to the 15th day after the start of symptoms. Seroconversion (detection of anti-ZIKV IgM antibodies) is thought to occur from the 4th day after infection and IgG a little later. Seroconversion occurs on average at 9 days and 95% by 14 days

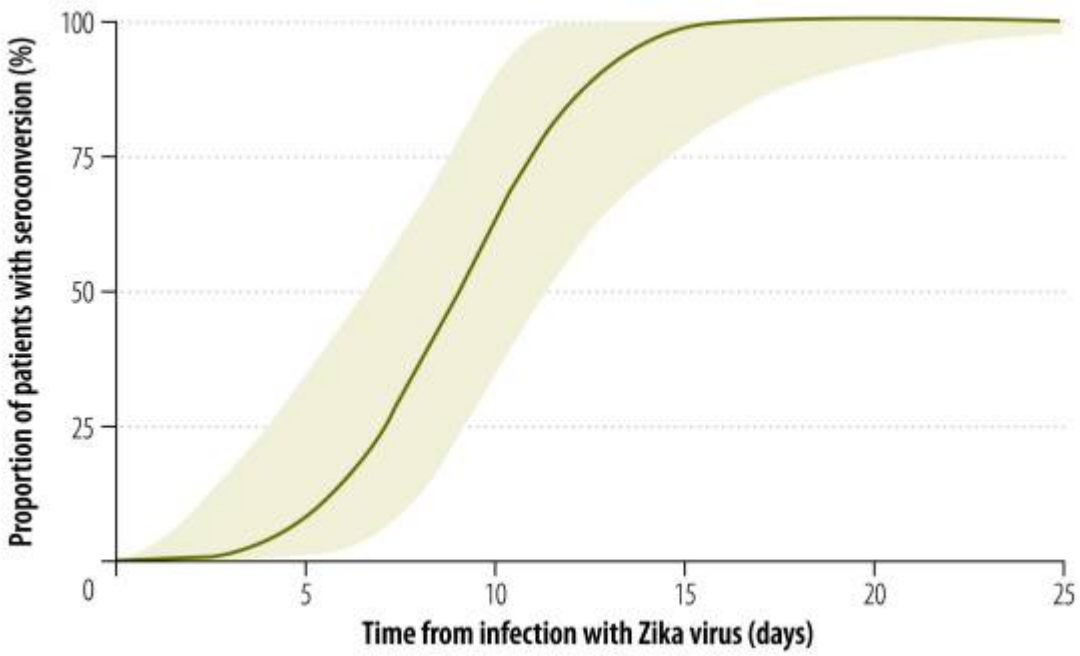


Figure: Time to seroconversion in Zika virus infection (Lessler et al, Bull WHO)

As with other serological tests for flavivirus infections, cross-reactivity of ZIKV antibody detection assays can yield false positive results; in endemic areas this may be a significant problem, because of possible simultaneous or previous circulation of other flaviviruses. Virus neutralization tests can be used to increase specificity.

Treatment

General

There is no specific antiviral treatment for treating ZIKV. Antipyretics or analgesics can be used for symptom relief. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should not be used until dengue has been ruled out. NSAIDs should not be used in pregnant women beyond the 32nd week of gestation because of the risk of early closure of the arterial duct.

Management of pregnant women

Current CDC recommendations for the management of pregnant women with ZIKV infection include:

- Use of serial ultrasound examinations.
- In case of a confirmed diagnosis of fetal microcephaly, amniocentesis should be considered from the 15th week of pregnancy onwards.

Management of microcephaly/ ZIKV congenital syndrome

There is no specific treatment for microcephaly. Microcephaly may be accompanied by epilepsy, cerebral palsy, delayed cognitive, motor and speech development and hearing and eyesight problems. Since each child develops complications of different type and severity (eg. respiratory, neurological and motor problems), follow-up by specialists in different fields is warranted

Guillain Barré Syndrome

Treatment of GBS in the acute phase consists of immunotherapy, such as plasmapheresis or application of human immunoglobulin (IVIG, dose: 400 mg/ kg of body weight per day, for a period of 5 days). IVIG is relatively simple to administer, however expensive and can be difficult to obtain. The best results of IVIG or plasmapheresis are obtained when it is started within the first 2 weeks after the onset of neurological symptoms. Use of corticosteroids as a stand-alone treatment does not accelerate the recovery or alter the long-term result.

Prevention

A vaccine is not yet available.