

## REVIEW ARTICLE

# Zika virus infection from a newborn point of view. TORCH or TORZiCH?

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ITX110418A01 • Received: 30 September 2018 • Accepted: 21 December 2018

## ABSTRACT

Zika virus (ZIKV) belongs to the group of viruses called arboviruses. Congenital Zika syndrome is a new disease with infectious teratogenic aetiology. The clinical symptoms are divided into morphological and functional. Most severe complication is the foetal brain disruption sequence that includes severe microcephaly, anomalies of the eyes and congenital contractions of joints. The aim of this paper was to review available facts about Zika virus infection from a newborn point of view in a form of the summary of all important information. Zika virus infection is a problem of past, present and future. Epidemics may occur because of global climate changes, also in countries where natural conditions for life of mosquitos are not present. This clearly indicates the need to continue developing of vaccines and specific antiviral drugs. Until this happens, we must adhere individual preventive measures. Zika virus has proven to us how it can affect the health of adults and neonates but also thinking of healthy people. Newborns with microcephaly on the front pages of the media caused in 2015 panic and fear around the world – for this reason education of people is necessary. Due to serious congenital disorders associated with ZIKV infection and global impact of virus we suggest modifying old acronym TORCH for new TORZiCH to accent the position of Zika virus.

**KEY WORDS:** newborn; Zika virus; complications; diagnosis; treatment

**ABBREVIATIONS:** **AMC:** arthrogryposis multiplex congenita; **BAEPs:** brainstem auditory evoked potentials; **CSF:** cerebrospinal fluid; **CMV:** cytomegalovirus; **FBDS:** Foetal brain disruption sequence; **GBS:** Guillain-Barré syndrome; **HSV:** herpes simplex virus; **ICH:** immunohistochemistry; **NAAT:** nucleic acid amplification test; **PRNT:** plaque reduction neutralization test; **TORCH:** most common vertically transmitted pathogens; **ZIKV:** virus Zika

## Introduction

Zika virus infection is a disease caused by virus Zika (ZIKV). In 2016, WHO declared ZIKV infection a public health emergency of international concern. Despite the great effort of scientists, we do not have an effective, specific therapy or vaccine yet. This is a summary of all important information about ZIKV infection from a comprehensive view.

Zika virus belongs to the group of viruses called arboviruses (arthropod-borne viruses). According to International Committee on Taxonomy of Viruses is ZIKV classified in genus *Flavivirus*, the family *Flaviviridae*. Viral particle is composed from nucleocapsid (+ssRNA

and C protein) and lipid bilayer (with glycoproteins M and E). It has very similar replicative cycle as other types of flaviviruses – after attaching to the receptor of host cell enters the cell through endocytosis. There are several entry factors, for example TAM family of receptor tyrosine kinases (TYRO3, AXL, and MER), T cell immunoglobulin, TIM proteins, C-type lectin receptors and the phosphatidylserine receptors (Perera-Lecoin *et al.*, 2014). Viral RNA is used for synthesis of polyprotein and it replicates itself on the surface of endoplasmic reticulum. Polyprotein is divided into three structural (C, E and M protein) and seven non-structural proteins (Bolatti *et al.*, 2010). Epidermal fibroblasts, epidermal keratinocytes and immature dendritic cells are more susceptible for ZIKV infection (Musso & Gubler, 2016).

## History

Virus itself does not have long history, because it was discovered in 1947 in Uganda during research for yellow fever virus and named after the forest where it was

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discovered (Musso & Gubler, 2016). ZIKV was the first time isolated from human (ten years old Nigerian girl) in 1954 (MacNamara, 1954). First outbreak was in 2007 in Yap State – it is one of four states in the Federated States of Micronesia, located in the Western Pacific. In 2013, 28 000 of people were infected during outbreak in French Polynesia followed by the spread to the islands in Oceania, including New Caledonia, Cook Islands and Easter Island. The first cases of infection in America were reported in 2014 in northeastern Brazil. For first months of 2015, the infection has rapidly spread across Brazil (Musso & Gubler, 2016).

According to WHO situation report, there is 84 countries with evidence of vector-borne ZIKV transmission and 64 countries where the competent vector is established but with no documented past or current ZIKV transmission. 13 countries have reported evidence of person-to-person transmission of ZIKV and 31 countries have reported microcephaly or other CNS malformations potentially associated with ZIKV infection. 23 countries have reported increased incidence of Guillain-Barré syndrome (GBS) and/or laboratory confirmation of ZIKV infection among GBS cases (WHO, 2017).

#### Transmission

The most common method is vector-borne transmission, mostly by the bite of an infected *Aedes* species mosquito. These are distributed around the world, but we can find them mostly in subtropical and tropical areas. The virus continues to spread geographically to areas where competent vectors are present. ZIKV has two different geographical lines – African and Asian, so it circulates in two different cycles – sylvatic and urban. Sylvatic cycle is between monkeys and tropical mosquitos (for example *Aedes africanus*, *Aedes furcifer-taylori*, etc.) mostly in Africa. Urban cycle is between human and domestic mosquitos (for example *Aedes aegypti* or *Aedes albopictus*) mostly in Asia (Weaver *et al.*, 2016). The most important mosquitos in transmission are *Aedes africanus*, *Aedes aegypti*, *Aedes albopictus* and *Aedes hensilli*. First isolation of ZIKV from mosquito *Aedes africanus* has been made in 1948, Uganda (Dick *et al.*, 1952).

Other methods are from mother to child (during pregnancy or around the time of birth), through sexual intercourse (vaginal, anal and oral sex) and blood transfusion. Transmission methods as organ transplantations or laboratory exposure are currently being investigated.

Transplacental transmission has been confirmed using RT-PCR for detection of ZIKV RNA in amniotic fluid of symptomatic pregnant women (Oliveira Melo *et al.*, 2016). First case of perinatal infection has been reported during outbreak in French Polynesia in 2013 (Besnard *et al.*, 2014). Zika fever is sexually transmitted disease, virus was isolated from semen of symptomatic patient with hematospermia (Musso *et al.*, 2015) and can be passed through sex from infected person to his or her partner, even if the infected person does not have symptoms. Transmission by blood derivatives was confirmed in Brazil (Motta *et al.*, 2016). The number of reported cases of ZIKV

transmission by blood products is low, even in countries with outbreaks. However, Zika virus may be present in the blood of the patient within 4 weeks after the onset of the symptoms of infection. ECDC recommends people who have been in endemic or risk areas should postpone donation of blood for at least 28 days (ECDC, 2016).

#### Symptoms

Approximately 80% of patients with ZIKV infection are asymptomatic. The most common symptoms are fever, exanthema, headache, arthritis and/or joint pain and/or muscle pain, conjunctivitis and fatigue. In tropical areas is very common that patient infected with ZIKV had been previously infected with other disease (e.g. malaria), then is very difficult to find right diagnosis (Musso & Gubler, 2016).

ZIKV can damage cells of central nervous systems directly or indirectly (through immune mechanisms). In case of transplacental infection, ZIKV infects neural progenitor cells or neural cells of retina and causes congenital Zika syndrome. In case of adult infection, ZIKV can cause paralysis due to myelitis (damage of motor neurons) or GBS. GBS or acute inflammatory demyelinating polyradiculoneuropathy is autoimmune disorder, the association between ZIKV and GBS is very well documented. One of the best evidences comes from a case control study during the outbreak in French Polynesia (Cao-Lormeau *et al.*, 2016).

#### Congenital Zika syndrome

Congenital Zika syndrome is a new disease with infectious teratogenic aetiology. The clinical symptoms that characterize this syndrome we can divide into morphological and functional. Functional anomalies are associated with a neurological deficit and can vary in severity. Morphological changes include: anomalies of the skull, brain and eyes and congenital joints contractions.

Foetal brain disruption sequence (FBDS) include severe microcephaly, prominent occipital bone, overlapping cranial sutures and redundant scalp skin, in addition to severe neurological impairment. There is extreme craniofacial disproportion with overlapping and depression of frontal bones and parietal bones. FBDS is probably a result of decreased intracranial pressure and loss in brain volume. Some of brain anomalies can be detected prenatally with ultrasonography or magnetic resonance imaging. Anomalies of brain include: increased fluid spaces (ventricular and extra-axial), diffuse subcortical calcifications, hypoplasia or aplasia of the *corpus callosum*, marked cortical thinning with abnormal gyral patterns (most consistent with polymicrogyria), decreased myelination and cerebellar or cerebellar vermis hypoplasia. The most common anomalies of eyes are microphthalmia, iris coloboma, cataracts, intraocular calcifications and posterior ocular findings (Moore *et al.*, 2017).

Microcephaly is the most important sign of congenital Zika syndrome. It is a birth defect in which occipitofrontal size of head is less than -2 standard deviation for a given age and gender, severe microcephaly is less than -3 standard deviation (according to the American Academy

of Neurology and the Practice Committee of the Child Neurology Society). Primary microcephaly occurs during pregnancy at around 32 weeks of the gestation period, when the brain fails to grow – this is caused by a gradual decrease in the production of neurons. In secondary microcephaly neonate has normal brain size at birth but failure to grow subsequently due to the loss of dendritic connections (Woods, 2004). Precise molecular mechanism of ZIKV-induced microcephaly remains elusive. During the first trimester of pregnancy virus spreads into human neural progenitor cells and surface AXL protein is important for facilitating entry. Signalling pathways in host cells are altered, mostly TLR3-mediated immune network is changed and upregulation of apoptosis plus downregulation of neurogenesis in hNPCs lead to the death of the developing neurons. Genetic, environmental, immunological and physiological factors determine transmission of ZIKV in utero and they are also involved in neurotropism (Faizan *et al.*, 2016).

Congenital contractions of joints in foetuses or infants with congenital ZIKV infection can involve one joint or multiple joints (called arthrogyriposis multiplex congenita, AMC). AMC is clinically manifested by stiffening of the joints, especially of the knees, hips and wrists. The appearance of newborns is compared to wooden dolls (Dungl *et al.*, 2005). The contours of the limbs are prolonged, cylindrical with highlighted skin algae (Sosna *et al.*, 2001). AMC may be associated with pes equinovarus, luxation of the hips and “waiter-tip” wrist position (Dungl *et al.*, 2005).

### Diagnostic methods

Scientists around the world try to understand all details about pathogenesis or immunobiology of the ZIKV and the key is adequate diagnostics, but available diagnostic methods are still limited. Only laboratory methods can confirm ZIKV infection because there is no pathognomic sign for ZIKV infection to distinguish it from other infections. Diagnosis can be made directly (evidence of viral RNA) or indirectly (evidence of antibodies). Different clinical situations and appropriate diagnostic methods with samples are described in Table 1. Up-to-date diagnostic recommendations are posted on the website <https://www.cdc.gov/zika/>.

RT-PCR, serology and virus isolation are used to identify RNA virus and viral proteins. The best method is using RT-PCR because of high specificity and sensitivity, whereas virus isolation is gold standard but requires laboratories with cell cultures. Evidence of viral RNA during acute infection by RT-PCR or NAAT provides more specific results than antibodies, but the virus can be detected only within a short time interval. There is no reference frame for initiating diagnostics (Landry & St. George, 2017).

ELISA and plaque reduction neutralization test (PRNT) are mostly used to diagnose antibodies. Diagnosis of neutralizing antibodies by PRNT has a higher specificity than ELISA detection of IgM (Saeed *et al.*, 2016). Unfortunately, the main problem of antibody diagnosis is cross-reactivity with other flaviviruses. After previous or current flavivirus infection, or even after vaccination, false positives or

**Table 1.** Possible diagnostic methods in different clinical situations according to Landry & St George, 2017 (modified).

Clinical Situations	Samples	Methods	Comments
Acute infection	serum	NAAT, IgM	NAAT is more definitive than serology if positive
	whole blood	NAAT	
	urine	NAAT	urine has higher viral load than serum, detection is possible for 14 days or longer
Recent exposure (2–12 weeks)	serum	IgM	IgM is present 2–12 weeks after acute infection
	whole blood	NAAT	positive IgM results must be confirmed with PRNT (because of cross-reactivity between flaviviruses)
Past infection	serum	IgG	possible cross-reactivity, interpretation of results can be extremely difficult
Congenital infection (foetus)	maternal serum/whole blood	IgM, IgG, NAAT	negative maternal results exclude foetal infection, unless sample is taken too soon after exposure to detect IgM or too late to detect RNA
	amniotic fluid	NAAT	positive result suggests foetal infection
Congenital infection (newborn)	maternal serum/whole blood	IgM, NAAT	
	infant serum, whole blood, urine or CSF	IgM, NAAT	necessary to obtain infant serum within 2 days of birth
	placenta, umbilical cord	NAAT, histopathology, ICH	
Congenital infection (postmortem)	fresh or formalin-fixed tissue	NAAT, histopathology, ICH	
Testing of blood donors	blood	NAAT	detection of acute viremia

NAAT– nucleic acid amplification test; PRNT– plaque reduction neutralization test; CSF– cerebrospinal fluid; ICH– immunohistochemistry

uninterpretable results are often generated. Flaviviruses with potential cross-reactivity with ZIKV antibodies are following: Dengue fever virus type 1–4, Yellow fever virus, West-Nile virus, St. Louis encephalitis, Japanese encephalitis virus and Powassan virus (Saeed *et al.*, 2016).

Detection of risk for the foetus is made primary by testing of the mother. When a baby is born to a mother with confirmed or suspected ZIKV infection, serum and whole blood of newborn, placenta, umbilical cord (plus cerebrospinal fluid if obtained for another reason) should be sent for ZIKV IgM, RT-PCR and histopathology, as appropriate (Landry & St George, 2017). Interpretation of results in newborns is described in Table 2.

It is necessary to know epidemiological history of all flavivirus diseases and vaccinations for using suitable diagnostic method and interpreting the results. This information must be provided together with the sample of biological material, also with standard data and other important information such as: date of onset of the disease, date of sampling and description of clinical signs.

ZIKV infection can be classified (Table 3) as probable (patient meets clinical and epidemiological criteria or meets laboratory criteria for probable case) or confirmed (patient meets laboratory criteria for confirmed case).

Clinical criteria are – any patient with a rash and/or fever and at least one of the following symptoms: joint pain, muscle pain, non-purulent conjunctivitis or hyperaemia.

**Table 2.** Interpretation of results from neonate’s blood, urine or CSF for evidence of congenital ZIKA virus infection (Russell, 2016).

Methods		Congenital ZIKA virus infection
RT-PCR (DNA)	ELISA (IgM)	
+	+/-	confirmed
-	+	probable
-	-	negative

**Table 3.** Diagnostic criteria for ZIKA virus infection according to Public Health Authority of the Slovak Republic, 2016.

	Criteria			
	Epidemiological	Clinical	Laboratory (for probable case)	Laboratory (for confirmed case)
probable ZIKA virus infection	+	+	-	-
	-	-	+	-
confirmed ZIKA virus infection	-	-	-	+

**Table 4.** Clinical manifestation of vertically transmitted infection according to Li *et al.*, 2016.

	CMV	toxoplasmosis	rubella	HSV	ZIKV
microcephaly	++	+	-	++	+++
calcifications	++	++	-	+	++
hydrocephalus	+	++	-	+	+
chorioretinal disease	++	++	-	+	++
systemic disease	+	-	++	++	-

CMV- cytomegalovirus; HSV- herpes simplex virus; ZIKV- Zika virus

Epidemiological criteria are – travelling in ZIKV areas two weeks before first symptoms, sexual intercourse with a person with confirmed case of infection or sexual intercourse with a person who has been in the ZIKV area in the last four weeks.

Laboratory criteria for the diagnosis of probable case is the detection of specific IgM antibodies in the serum.

Laboratory criteria for the diagnosis of confirmed case is at least one of following: detection of ZIKV nucleic acid, detection of ZIKV antigen, isolation of ZIKV, detection of serum specific IgM antibodies plus confirmation with virus-neutralization assay (Public Health Authority of the Slovak Republic, 2016).

#### Differential diagnostics

Symptoms of Zika virus infection may not be present at all, on the other hand the infection may manifest by wide range of non-specific symptoms – differential diagnostics based on clinical presentation is impossible task. Therefore, laboratory methods mostly serological tests are necessary. Infections need to be distinguished from Zika including the following: Dengue fever and chikungunyai virus, rubella, measles and parvoviruses, enteroviruses, adenoviruses and alphaviruses, leptospirosis, rickettsial infections, group A Streptococcal infection, African tick bite fever and relapsing fever and malaria (Sládečková & Rozinová, 2017).

The top in differential diagnosis for any sick neonate is the acronym TORCH – it refers to the most common vertically transmitted pathogens:

- Toxoplasmosis,
- Others (syphilis, group B Streptococcus, Listeria, Candida, etc.),
- Rubeola,
- Cytomegalovirus,
- Herpes simplex virus.

Zika virus is now considered to be part of TORCH infections (Li *et al.*, 2016). Different clinical manifestations of

vertically transmitted infection are described in Table 4. Complications may include microcephaly, periventricular calcifications, chorioretinal disease, hydrocephalus, growth retardation, hepatosplenomegaly, jaundice, thrombocytopenia and other systemic disease (Li *et al.*, 2016).

### Therapy

No approved specific antiviral therapy is available yet. Adult asymptomatic patients and patients with uncomplicated illness do not even require specific therapy. Therapeutic strategies are only symptomatic: analgesic, antipyretics, adequate hydration, plenty of rest and therapy of neurological complications. Acetaminophen is recommended to reduce fever and pain. Aspirin is contraindicated due to risk of a bleeding and Rey's syndrome in children. Non-steroidal anti-rheumatic drugs are also contraindicated due to the increased risk of haemorrhagic syndrome. Infected patients should be isolated during the first days of infection to avoid further mosquito bites.

If ZIKV infection of mother is laboratory confirmed and neonate has signs of congenital Zika syndrome, it is necessary to perform: routine physical examination, including head circumference, birth length, birth weight, gestational age assessment, head ultrasound, laboratory tests for congenital ZIKV infection, neurological examination, brainstem auditory evoked potentials (BAEPs), ophthalmologic examination of the retina, full blood count, metabolic and liver panels.

Consultation with the following specialists should be considered: infectious disease specialist to distinguish other congenital infections (for example syphilis, toxoplasmosis, rubella, CMV infection, or herpes simplex virus), neurologist for comprehensive neurologic examination and consideration of other evaluations (neuroimaging and electroencephalography), ophthalmologist for comprehensive eye exam, clinical geneticist for evaluation of other causes of congenital anomalies and confirmation of the clinical phenotype, early intervention and developmental specialists, family and supportive services, endocrinologist (thyroid testing and evaluation of hypothalamic or pituitary dysfunction), lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist (evaluation of dysphagia, management of feeding issues), orthopaedist, physiatrist, or physical therapist (the management of AMC, hypertonía, clubfoot etc.) and pulmonologist or otolaryngologist (CDC, 2017).

### Prevention

Currently, no vaccine is available to prevent ZIKV infection but NIAID has multiple vaccine candidates to prevent Zika virus infection in development and research programmes (NIAID, 2017). The most important way to prevent ZIKV infection is to protect yourself from mosquito bites. Sexual protection (using condoms) and testing of blood donors in risk areas are also necessary. Blood donation is contraindicated 28 days after returning from risk country. All travellers are encouraged to check

whether the country where the person is traveling is a risk country (with reported occurrence of the transmission ZIKV). Pregnant women and women planning pregnancy should postpone unnecessary journeys to risk countries. In risk countries it is recommended to take preventive measures to prevent mosquito bites: using repellents; children older than 2 months, pregnant and breastfeeding women should use repellents containing N, N-diethyl-m-toluamide, wearing suitable clothes (long sleeves and long pants, light colours), using mosquito nets, avoiding areas infested with mosquitoes (Public Health Authority of the Slovak Republic, 2016).

### Conclusion

Zika virus infection is a problem of past, present and future. Epidemics may occur because of global climate changes, also in countries where natural conditions for life of mosquitos are not present. This clearly indicates the need to continue developing of vaccines and specific antiviral drugs. Until this happens, we must adhere to individual preventive measures. Zika virus has proven to us how it can affect the health of adults and neonates but also thinking of healthy people. Newborns with microcephaly on the front pages of the media caused in 2015 panic and fear around the world – for this reason education of people is necessary. Due to serious congenital disorders associated with ZIKV infection and global impact of virus we suggest modifying old acronym TORCH for new TORZiCH to accent the position of Zika virus.

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