Congenital Zika Virus Infections

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ABSTRACT

Zika virus (ZIKV) is an arthropod-borne flavivirus transmitted through bites of the *Aedes* mosquitoes. Infected mothers can vertically transmit ZIKV to their fetuses, particularly during the first and second trimesters. Infections beginning during early gestation can cause congenital Zika virus syndrome (CZS), which may be marked by arrested development and/or altered healing in the nervous system. There can be microcephaly, craniosynostosis, intracranial calcifications, ventriculomegaly, low brain volume and/or cortical atrophy, and hypoplasia/altered myelination in the corpus callosum, cerebellum, and brainstem. There may also be altered development with polymicrogyria, pachygyria, and lissencephaly. Clinically, infants with CZS may show facial dysmorphism, pulmonary hypoplasia, altered growth and development, hypertonia, hyperreflexia, limb contractures, and arthrogryposis multiplex. Perinatal infections can present with irritability, seizures, eye involvement, and sensorineural hearing loss (SNHL). Congenital zika virus syn and perinatal infections contrast with those acquired after birth, which usually have a relatively milder course. Overall, the mortality rate can reach 4–6%. Laboratory evaluation can include polymerase chain reactions on serum, cerebrospinal fluid, and urine; testing for immunoglobulin M (IgM); and plaque reduction neutralization tests (PRNTs) to confirm the specificity of these Zika virus IgM (ZIKV IgM) antibodies. Unfortunately, no specific treatment is available; most measures are largely supportive.

Keywords: Congenital Zika syndrome, Newborn, Real-time reverse transcription-polymerase chain reaction, Magnetic resonance imaging, Zika virus infection.

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INTRODUCTION

Zika virus (ZIKV) was first isolated from a sentinel primate in Uganda in 1947.[1] It is a mosquito-borne virus named after the Zika Forest in Central Africa.[2,3] It circulated unnoticed in some regions in Africa and Southeast Asia until 2007, until an outbreak was recorded in the Yap Island in Micronesia.[4,5] The virus has since spread to parts of Central and South America and the Caribbean.[6–8] A major epidemic was seen in Brazil in 2015.[9,10] The incidence has gradually risen with new cases now having been reported from nearly 80 countries worldwide.[11–14]

The term congenital zika virus syndrome (CZS) has been used to describe the complicated clinical course seen in neonates born to mothers infected with ZIKV.[15–17] Several prospective cohort studies have shown that fetal ZIKV exposure *in utero* is associated with adverse birth outcomes and neurologic sequelae.[18–20] Unlike postnatal ZIKV infections after birth and in adults, congenital infections tend to be more severe and may be associated with neurological and multi-system complications.[13,21] In this article, we have focused on these vertically transmitted ZIKV infections.[22]

Zika Virus: Classification and Structure

Zika virus belongs to the Flaviviridae family of positive-strand RNA viruses that includes human pathogens such as the mosquito-transmitted dengue virus, West Nile virus, Japanese encephalitis virus, yellow fever virus, and the tick-borne encephalitic virus.[23–31] Flaviviruses are enveloped viruses containing an RNA genome of about 11 kilobase (kB).[32] There are multiple copies of a capsid protein, which is surrounded by an icosahedral shell consisting of 180 copies each of the envelope glycoprotein (about 500 amino acids) and a membrane protein (about 75 amino acids its precursor of about 165 amino acids); both are anchored in a lipid

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membrane.[32–36] There are seven non-structural proteins that are needed for replication, assembly, and for antagonizing the host innate immune responses.[37–40]

Flaviviruses evolve through three stages, including immature, mature, and fusogenic.[41,42] These are non-infectious, infectious, and host membrane–binding states, respectively.[39] The immature "spiky" immature particle is assembled in the ER and is non-infectious.[43] It matures through conformational changes of the surface

glycoproteins into a "smooth" particle in the low-pH environment of the trans-Golgi network.[44] The fusogenic stage is marked by an endosomal fusion loop seen in conditions with acidic pH.[45]

In this group of viruses, ZIKV specifically contains a typical flavivirus genome that is 10.8 kB long (Fig. 1).[44] The RNA is translated into a single polyprotein (3,423 amino acids) that is processed into the 3 above-mentioned structural proteins.[46] The capsid contains four α helices with a long pre-α1 loop and forms dimers; the pre-α1 loop contributes to the tighter association of dimeric assembly.[35,36,47,48] The membrane protein contains two loops that anchor it to the membrane.[43] Finally, the envelope protein is comprised of four domains; the stem-transmembrane domain anchors the protein into the membrane.[39] The seven non-structural proteins are labeled NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Interestingly, some of these proteins regulate viral replication.[49] The structural proteins form the virus particle, whereas the non-structural proteins assist in the replication and packaging of the genome.[50] The generation of the 10 individual proteins from the polyprotein is regulated by viral and host proteases, and the efficiency of furin, a host protease that cleaves the viral targets.[51,52]

Epidemiology

ZIKV is transmitted to humans primarily through the bites of infected *Aedes* mosquitoes, particularly those of the species *Ae. aegypti* and *Ae. albopictus*.[53] These mosquitoes live near human habitations and frequently get infected with viruses such as Zika, chikungunya, and dengue after biting infected persons who are viremic such as during the first week of infection.[54] These mosquitoes lay eggs in standing water such as near the edges of lakes and ponds, in plants in swamps and marshes, or in containers that hold water such as buckets, bowls, and animal dishes.[55] These mosquitoes bite humans and can transfer the viruses to other hosts.[56]

A pregnant woman can pass ZIKV to her fetus during pregnancy or the perinatal period.[57] Zika virus has also been found in mother's own milk, although viral transmission through breast milk has not been confirmed yet.[58] Flavivirus nucleic acid has been detected in breast milk.[59] However, we do not know the long-term effects of postnatal ZIKV transmission.[60] The benefits of breastfeeding may outweigh the risk of transmission through breast milk, and the Centers for Disease Control and Prevention (CDC) continue to encourage mothers to breastfeed even if they lived/traveled to endemic areas or were infected with ZIKV.[61]

Zika virus can be sexually transmitted from an infected person to his or her partners.[62] Many individuals with minimal symptoms can be infectious; studies suggest that ZIKV can be passed from an infected persons before the onset of symptoms, during acute illness, or after apparent clinical recovery.[63] Studies are on to determine
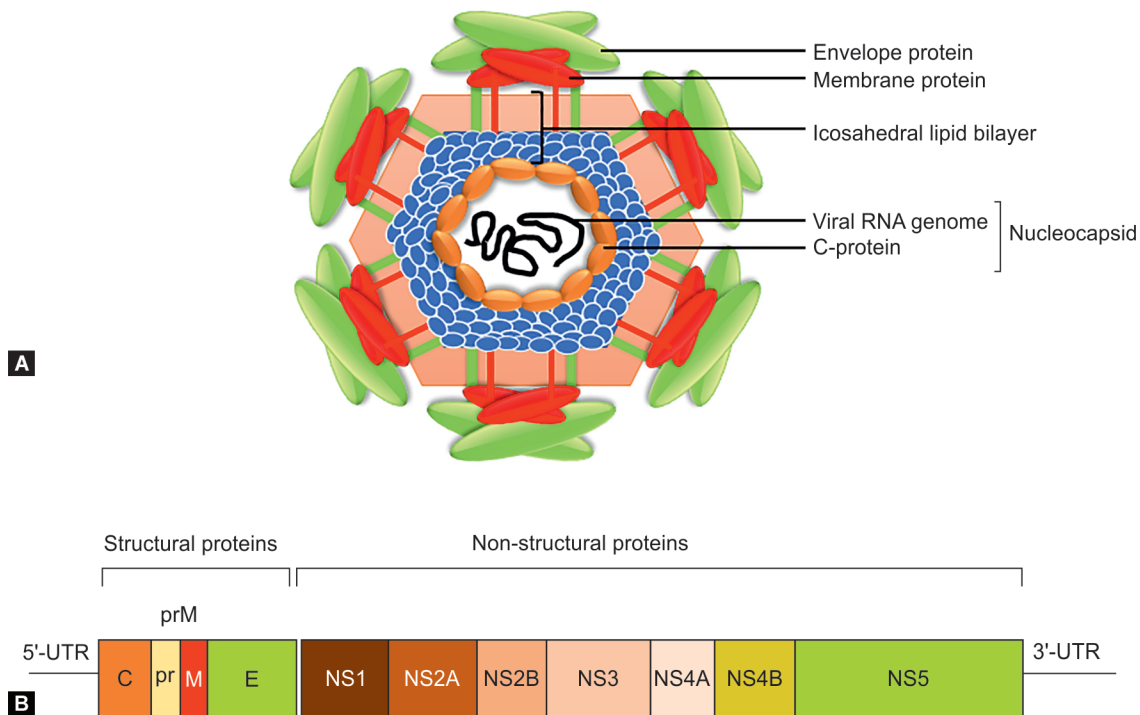
Figs 1A and B: (A) Schematic illustration of ZIKV: Zika virions are enveloped, 18–45 nanometer icosahedral structures. The genome is a positive strand RNA enclosed in a capsid and surrounded by a membrane. The RNA contains 10,794 nucleotides encoding 3,419 amino acids. (B) The ZIKV genome. The 10.8 kB long genome is translated into a single polyprotein, which is then processed into a capsid protein (C), an envelope glycoprotein (E) and membrane protein (proM, processed to M), and 7 non-structural proteins that are labeled NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. UTR = Untranslated region; prM = uncleaved pro-membrane protein; C = capsule; E = envelope; NS = non-structural protein. The mature ZIKV particle is about 50-nm in diameter. It has 180 copies of the E and M proteins embedded in the membrane. The E protein is comprised of four domains: A stem-transmembrane domain pair and three ectodomains I, II, and III seen outside of the membrane. The E protein exists as a dimer and predominates on the surface of the virion with the smaller M protein residing underneath. The M protein has a smaller extracellular region and a stem-transmembrane domain. Three E proteins dimers lie parallel to one another in a raft configuration, with the virion having a total of 30 rafts. The non-structural proteins assist in replication and packaging of the genome.

the duration for which ZIKV remains detectable in semen and vaginal fluid of infected individuals, and their infectivity.[64] The virus may remain detectable in semen longer than in other body fluids such as vaginal fluids, urine, blood, conjunctival fluid, and amniotic fluid.[65,66]

Reports from Brazil and other countries have documented the presence of ZIKV in blood donated for transfusions.[67] During the French Polynesian outbreak, 2.8% of blood donors tested positive for ZIKV.[68] There are some reports of laboratory-acquired ZV infections, although the route of transmission could not always be established.[69] There is a need to investigate these reports because ZIKV diagnostic testing and laboratory research have expanded with increased risk of occupational exposure to laboratory workers and biomedical researchers.[70] The emergency committee of the World Health Organization (WHO) announced ZIKV disease as a Public Health Emergency of International Concern in 2016 and triggered the exploration of global involvement to define the pathophysiology and deal with the related clinical challenges.[71]

Pathophysiology

The mechanisms of the ZIKV passage across the placental barrier, the association between viremia and the development of CZS, and the exact timing of placental and fetal infection with maternal viremia are still not clear.[72] ZIKV can infect placental macrophages, trophoblasts, and endothelial cells, and then enter the fetus from these cells.[73] In infected fetuses, ZIKV has been isolated from the brain and cerebrospinal fluid.[21] However, the impact of placental infection in defining the syndrome's severity has not been confirmed yet.[74]

ZIKV infections of the fetal brain can damage the neuronal progenitor cells and interrupt neuronal proliferation, migration, and differentiation.[75] These events may slow or interrupt brain growth beginning at 20 weeks of gestation.[76,77] The risk of neurodevelopmental abnormalities in infected fetuses is the highest when maternal infection appears during the first and second trimesters of pregnancy because it is a crucial period for brain development.[78] Interestingly, some neonates who were exposed to ZIKV *in utero* did not show obvious abnormalities at birth but developed impairments over time.[79,80] In these infants, ZV replication may have continued after birth and interrupted brain growth.[79] Clearly, ZIKV-exposed fetuses need continued, comprehensive follow-up after birth.[81]

Histopathology

ZIKV is a neurotropic virus that specifically attacks neural progenitor cells.[82,83] Electron micrographs show ZIKV as dense particles in the damaged endoplasmic reticulum (ER) in these cells. This ER stress/ unfolded protein response not only suppresses the proliferation of cortical progenitor cells but also damages mature neurons in the cerebral cortex.[83,84] Specific groups of enveloped structures with a bright interior resembling the residue of replication complex also support ZIKV replication in the neonatal brain.[39]

Zika infections in the developing brain may manifest with diffuse arachnoiditis with ependymitis and vasculitis.[85] Some foci show meningoencephalitis, ventriculomegaly or an *ex vacuo* hydrocephalus, microcephaly with lissencephaly, and cerebellar hypoplasia.[86] An additional spectrum of parenchymal lesions was observed involving the whole hemispheric wall namely the cortical plate (CP), the intermediate, and the ventricular zones. The CP lesions consisted in a loss of lamination with radial glia disruption, focal polymicrogyria, neuronal loss, chromatin fragmentation with numerous apoptotic residues and mineralization.[86] The loss of lamination can disrupt radial glia and cause a diffuse loss of neurons.

Necrotic lesions can be seen in the subcortical region in the vicinity of damaged vessels.[86] The loss of cortical neurons has been linked with ZIKV-associated microcephaly.[87] Several neurobiological studies have shown increased cell death and the impaired cell cycle leading to a decreased neural progenitor cell proliferation, causing a decrease in the number of cortical neurons.[88] In addition to ER stress, ZIKV infection can cause chromatin change and necroptosis.[89] Viral particles have been observed in basal/ apical progenitor cells, neurons in the cortical plate, and in the ventricular and subventricular zones.[90] The loss of callosal fibers and longitudinal tracts has been identified as a cause of the cerebral atrophy and the ventricular enlargement.[91] The disruption of the hypothalamic and pituitary axis can cause adrenal gland atrophy.[92]

Immunohistochemical studies may show T-lymphocytic and histiocytic meningitis with abundant cerebral astroglial and macrophagic reactions.[85] Vasculitis is marked by the presence of swollen endothelial cells surrounded by active microglia and astrocytes.[93,94] In the cerebellum, the width of the external and the internal granular layers was reduced.[85] The neurons were shrunken and contained fragmented chromatin (karyorrhexis).[95,96] Macrophages and numerous hypertrophic astrocytes were present.[96] In the spinal cord, the astrocytic and macrophagic reaction was mild and neurons were spared.[83] The longitudinal tracts were missing. Glial fibrillary acidic protein-reactive antibody confirmed the astroglial nature of the gliosis seen close to the necrotic regions in the subventricular and in the intermediate zones.[21]

In situ hybridization shows ZIKV particles within the cerebral parenchyma mainly in the ventricular/subventricular zone and in the cortical plate.[77] The neuronal precursor cell is the main target for ZIKV leading to cell death, although, neuronal cells in all stages of maturity can be affected.[82] These changes can explain the microcephaly and poor cortical gyration.[97] Moreover, viral cerebritis can affect cerebral embryogenesis and result in microcephaly or other central nervous system abnormalities.[85,98]

There may be inflammatory changes in other organs. The placenta may contain a Hofbauer cells hyperplasia with signs of inflammation.[99] Truncal vessels may show fibromuscular hypertrophy causing a narrowing of the lumen.[85] Some cases may show features of acute chorioamnionitis, villitis, and funisitis.[100] Some studies have shown an interstitial lymphocytic infiltrate in the testes.[101]

Clinical Manifestations

The full CZS spectrum is evolving with the recognition of the following subtle manifestations in growing infants:

- Fetal growth restriction.[102–107]
- Congenital anomalies in 7–40% of infants.[108–111] Central nervous system findings include large ventricles, microcephaly, and intracranial calcifications.[112] Some infants show craniosynostosis, low brain volume and/or cortical atrophy (Fig. 2), and hypoplasia/ altered myelination in the corpus callosum, cerebellum, and brainstem. There may also be altered structural development with polymicrogyria, pachygyria, and lissencephaly. Clinically, infants with CZS may show facial dysmorphism, pulmonary hypoplasia, altered growth and development, hypertonia, hyperreflexia, limb contractures, and arthrogryposis multiplex.
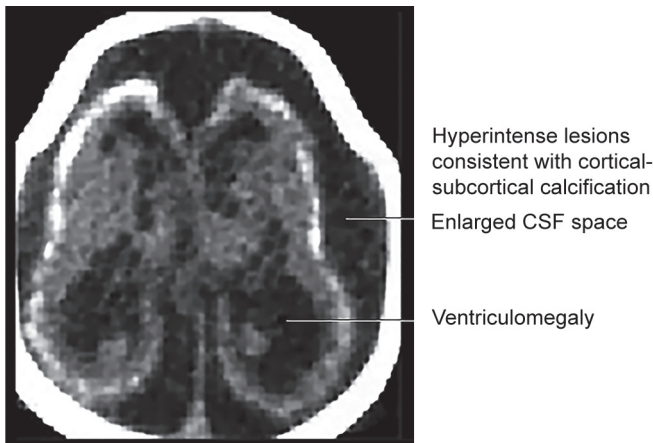
Fig. 2: Axial CT image of an infant with congenital ZIKV infection and severe microcephaly shows cerebral atrophy with ventriculomegaly, prominent cerebrospinal fluid space, and extensive, punctate cortico–subcortical calcifications.

- Perinatal infections can present with irritability, seizures, eye involvement, and sensorineural hearing loss (SNHL). Congenital Zika syndrome and perinatal infections contrast with those acquired after birth, which usually have a relatively milder course.
- Fetal/perinatal death.[113]

There are five signs that have recorded frequently in infants with CZS as follows:

- Decreased brain tissue with subcortical calcifications.
- Microcephaly.
- Hypertonia with limitations of body movement seen shortly after birth.
- Congenital joint contractures such as arthrogryposis and clubfoot.
- Eye lesions, such as focal retinal pigmentary mottling and macular scarring.

The following findings are relatively more specific to CZS:[114] (a) Partially collapsed skull with severe microcephaly, (b) subcortical calcifications with thin cerebral cortices, (c) focal pigmentary retinal mottling with macular scarring, (d) congenital contractures and arthrogryposis, and (e) severe early hypertonia.[115]

Microcephaly

The incidence of microcephaly has varied across studies. In some small cohorts, up to 90% of cases of CZV had microcephaly, and most cases have severe congenital microcephaly.[98,116] Other studies have shown lower incidence figures, with only 5–9% of infants with CZS having a small head circumference.[117] In a large cohort, Cauchemez et al.[103] estimated the frequency of microcephaly to be about 95 per 10,000 women infected during the first trimester. Severe microcephaly has been noted in 7–9% of all infants with CZS.[100,108,113,118–123] About 10% had moderate microcephaly.[106]

Microcephaly has been traditionally defined as an occipital head circumference (OHC; measured between occipital protuberance and glabella) that is 2 standard deviations (SDs) less than the average for gestational age (GA) or corrected GA. Severe microcephaly is defined as an OHC below 3 SDs.[124] It can be a primary abnormality seen at birth or a secondary failure of head growth that develops over time.[121,125] Proportionate microcephaly is a restriction of head circumference similar to that of length and weight. Infants

with disproportionate microcephaly have a restricted head circumference but a normal weight and length.[126]

Infants with CZS frequently show disproportionate craniofacial dimensions where the face appears larger compared to a small head.[127] Up to 78% of infants with CZV infections develop craniosynostosis;[107,114] many show *cutis gyrata* where the continuously growing redundant scalp tissue begins to show folds over the cranium that is not growing any further.[115] A CZS-associated microcephaly may reflect a less-than-normal number of gray matter neurons with reduced brain volume. Microcephaly is usually seen when ZV infections occur early in pregnancy; however, proportionate microcephaly has been observed in the offspring of women infected as late as the third trimester of pregnancy.[128,129] In rare instances, microcephaly has been noted to resolve over time.[129]

Infants with CZV-related microcephaly frequently have seizures, cerebral palsy, and neurodevelopmental abnormalities. Many infants have abnormal facies, thin cerebral cortex on cranial imaging, macular scarring, focal pigmentary retinal changes, SNHL, irritability, hypertonia, hyperreflexia, and congenital contractures and talipes equinovarus due to decreased movements *in utero*.[97,130] In one cohort, 6% of infants had congenital anomalies, and 9% had neurodevelopmental abnormalities such as developmental delay, hearing loss, and seizures.[103] Neuroimaging showed major structural lesions in 42% and minor abnormalities in 24%. The physical (neurological) examination was abnormal in 21%. Nine percent were small-for-gestational age (SGA). Eye abnormalities were recorded in 7%, dysphagia in 3%, hearing defects in 3%, clinically evident or subclinical seizures (abnormal electroencephalogram) in 3%, and minor abnormalities in 10%.[100]

Ocular Manifestations

About 25% of infants with CZS showed eye abnormalities, which was considerably higher than the 6–7% incidence in the general population.[131,132] These findings included macular abnormalities; focal pigmentary retinal changes; chorioretinal atrophy, and optic nerve abnormalities such as optic nerve hypoplasia, increased cup-disk ratio, and pallor.[133–136] Other changes included pigmentary clumping, coloboma, subretinal hemorrhages, vascular tortuosity, and abnormal retinal vessels with focal vascular dilation.[137–140] Iris colobomas, microcornea, microphthalmia, lens subluxation, cataracts, intraocular calcification, congenital glaucoma, strabismus, and nystagmus were also seen in some infants.[141–145] The eye findings in CZS were not progressive.[132] Cortical visual impairment was the most likely cause of the loss of vision in infants with CZS.[146,147] Major visual impairment in CZS was seen in 30%. However, the rate of visual impairment was as high as 84% when the associated eye findings were included.[148]

Other Abnormalities

Sensorineural hearing loss is seen in 7–12%.[104] Arthrogryposis and club foot have been reported and are likely neurogenic in origin due to fixed posture *in utero*.[149] Other clinical signs of CZS include hypertonia, hyperreflexia, irritability, feeding difficulties, and dysphagia.[150] Seizures may occur due to underlying brain malformations, but may also be present in children without apparent CNS abnormalities with a median age of onset of a seizure is 4 months.[106,151] The seizures are usually refractory with poor initial control with medical therapy. Notably, 30–40% of infants with CZS are SGA.[107,130] Congenital heart disease (CHD) occurs in 10–15% and is mostly non-severe, such as secundum atrial septal defect (ASD), patent ductus arteriosus (PDA), and small

muscular or peri-membranous ventricular septal defect (VSD) and few had hemodynamically significant CHD defect such as large membranous VSD.[152,153]

Perinatal Infections

Infants infected around the time of birth develop acute encephalopathy and can present with irritability, seizures, eye involvement, and SNHL.

Postnatal Infections

Most patients remain asymptomatic. A small minority develops a mild course of fever, rash, and conjunctivitis.[58,154,155]

Neuroimaging

Imaging can detect neurological abnormalities such as intracranial calcifications, ventriculomegaly, low brain volume, delayed myelination, polymicrogyria, pachygyria, lissencephaly, corpus callosum, brainstem, cerebellar thinning or hypoplasia, large cisterna magna, and increased extra-axial fluid spaces.[156,157]

Intracranial calcifications due to ZIKV are seen the most frequently at the junction of the cortical and subcortical white matter. Notably, these lesions differ from the punctate lesions caused by cytomegalovirus. However, calcification may occur in the periventricular region, basal ganglia, thalamus, brainstem, and cerebellum.[158] These calcifications may diminish in number, size, or density with age in most children,[159] although these changes do not correlate with clinical improvement as most patients; these patients may still develop severe neurological sequelae. Notably, 40% of infants with hydrocephalus may require a ventriculoperitoneal shunt. Cranial ultrasound is an important screening tool but it often needs to be followed up with magnetic resonance imaging (MRI) for detailed evaluation. CT scans can detect intracranial calcifications while MRI is better for structural brain disease. A negative sonographic examination in infants who have seizures, microcephaly, and tone abnormalities should be followed by a more extensive neurological evaluation by specialists and a specific imaging evaluation.

Evaluation

A detailed evaluation as detailed in the following list is needed for infants with ZIKV infections confirmed by maternal laboratory test and clinical evidence of CZI such as microcephaly and/or other congenital anomalies:[160]

- Physical examination including anthropometric measurements (head circumference, length, and weight), neurologic abnormalities, and dysmorphic findings assessment.
- Laboratory testing, including complete blood counts, and a metabolic panel with liver function tests.
- Head ultrasound.
- Hearing test using auditory brainstem response to assess hearing.
- Eye examination by an experienced ophthalmologist before or shortly after discharge from the hospital.
- Other specialties consultation (a) neurologist; (b) infectious disease specialist; (c) clinical geneticist; (d) early intervention and developmental specialists; and (v) family and supportive services.
- Other optional consultations (a) orthopedist, (b) physiatrist, (c) physical and/or occupational therapists, (d) lactation specialist, (e) nutritionist; (f) gastroenterologist; (g) speech or

occupational therapist; (h) endocrinologist for evaluation; (i) pulmonologist; (j) otolaryngologist; and (k) cardiologist.

The WHO and CDC define microcephaly as occipitofrontal circumference (OFC) above 2 SDs below the mean or below the third percentile for gender, age, and GA at birth.[124,161,162] Severe microcephaly is a HC below 3 SDs below the mean.[161] Both CDC and WHO recommend detailed clinical assessments before making a diagnosis of microcephaly to decide the plans for follow-up.[124]

Laboratory Evaluation

The following infants should be tested:[160]

- The mother has evidence of ZIKV infections during pregnancy.
- There are clinical or neuroimaging findings suggestive of CZS with maternal or paternal possible exposure, regardless of maternal ZIKV laboratory status.

The postnatal laboratory tests include the following:[160,163]

- Serum and or urine for ZIKV RNA using real-time reverse transcriptase-polymerase chain reaction (rRT-PCR).
- Serum Zika virus immunoglobulin M (IgM) using enzyme-linked immunosorbent assay (ELISA).
- Cerebrospinal fluid (CSF; if available) for ZV RNA by rRT-PCR and ZIKV IgM.[160,163] Early samples can distinguish between congenital, perinatal, and postnatal infection. Cord blood should not be used as it may yield false-positive results.[160]
- Plaque reduction neutralization test (PRNT) detects specific neutralizing antibodies of the Zika and dengue viruses which is not available for routine use. It can confirm the specificity of IgM antibodies against the ZV, which can rule out a false-positive IgM test. For a positive or presumptive positive or possible positive or equivocal result without PRNT of the mother's sample, a ZV PRNT on the infant's initial sample is of great help. If the neonatal PRNT is initially positive, a repeat PRNT test should be done after the age of 18 months to differentiate true initial fetal infection from maternal passive transfer of antibodies, at which time maternally acquired antibodies will have waned.

Maternal serum should be checked for ZIKV IgM and its neutralizing antibodies. To distinguish from other arboviruses, the infants should be tested for dengue virus IgM and its neutralizing antibodies. The interpretation of these results is complex because of the cross-reaction between Zika and dengue antibodies. Neutralization assays can confirm or exclude the result. Histopathologic assessment of the placenta and umbilical cord can add more information.

Interpretation and Diagnosis

Confirmed diagnosis: In the first few days of life, ZIKV RNA present in the serum, urine, or CSF are collected, regardless of IgM antibodies being positive or negative.[160]

Probable diagnosis: A negative PCR while IgM against ZIKV is positive which indicates probable ZIKV infection. The IgM result may be false-positive due to cross-reacting IgM antibodies or may be a result of a non-specific reactivity.[164] Mother testing results are very important in this regard. Therefore, a positive IgM in the infant makes congenital ZIKV infections very likely if the maternal ZVI is confirmed. While the presence of CSF IgM is very suggestive of congenital ZIKV infections.[164]

Diagnosis unlikely: The congenital infection is unlikely if both PCR and IgM are negative.[160] A negative PCR result alone cannot rule out

congenital infection transient viremia as it is not known the period of postnatal viral shedding of *in utero* infected newborns. Some authors suggest the viremic period can reach up to 67 days after birth.[165] There is a need for evidence to definitively excluded CZV infection based on negative rRT-PCR and IgM, in infants with known ZV exposure. A negative newborn PCR test may be due to the absence of virus shedding in the urine despite confirmed maternal infection exposure. Moreover, a negative IgM test may be due to delay IgM antibodies release as in congenital rubella and CMV infection.

Differential Diagnosis

Infants suspected to have ZIKV infections should be evaluated for rubella, cytomegalovirus, and toxoplasmosis. Infections other than ZIKV infections frequently show hepatosplenomegaly, thrombocytopenia, and skin lesions.[10,81,128] A detailed evaluation of other causes of microcephaly is also required.

Management

The management is supportive as there is no specific antiviral treatment for CZS. The supportive care needs to focus on (a) seizures; (b) feeding difficulties; (c) hypertonia; and (d) hearing loss.

Parents should be provided with key sets of information. Maternal transmission of ZIKV to the fetus may occur during labor and delivery. There are reports of two cases of intrapartum ZIKV transmission from mothers infected within 2–3 days of delivery to the infant. However, these infants were not symptomatic, while the others showed thrombocytopenia and a widespread rash.[58,166,167] ZIKV has been detected in breast milk, but there is no documented evidence of transmission in breast milk.[154]

Testing both the mother and the baby is indicated during the first 14 days after birth if the mother is exposed to ZIKV within 14 days of delivery with ≥2 of the following; (a) rash, (b) conjunctivitis, (c) arthralgia, (d) fever.[166] If either or both newborn's or mother's symptoms developed within the first week of birth, both newborn serum and urine ZIKV using real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) should be obtained. However, if available, urine from both the mother and newborn should be obtained in the 2nd week and should be evaluated by Zika rRT-PCR. A positive laboratory test confirms the diagnosis.

If the rRT-PCR is negative 3 days after maternal symptoms, test for ZIKV IgM and neutralizing antibody titers. A positive test is suggestive of the diagnosis. Maternal ZIKV IgM and neutralizing antibody titers should be assessed if the newborn is symptomatic, and the mother is asymptomatic. Possible ZIKV exposure is not an indication of lumber puncture, but if the CSF is available for other reasons, a testing for ZIKV RNA using rRT-PCR is appropriate action.[166]

Follow-up

- The general pediatrics services should focus on (a) monitoring growth parameters such as weight, length/height, and HC; (b) routine immunizations; (c) anticipatory guidance; (d) psychosocial support; (e) other necessary testing services; and (f) consultations with other specialist services as needed.[160]
- Follow-up with experts in (a) hearing and vision; (b) neurology, focusing on seizures, tone abnormalities, and *ex vacuo* hydrocephalus; (c) developmental services; (d) feeding difficulties, breathing difficulties, choking, or coughing with feeding and assessment for dysphagia; (e) nutrition; and (f) continued supportive services and palliative care.

Prognosis

The prognosis of newborns with CZI is uncertain. The reported mortality rate among live-born infants with confirmed and probable CZI in Brazil is 4–6%.[150]

The prognosis of severe CZS with microcephaly and severe other cerebral abnormalities is very poor. However, the prognosis of milder forms is not known.[112] Nearly 1/3 of the children are either below average developmental scores or have neurosensory abnormalities such as abnormal eye examinations and/or hearing assessments during the second and third years of life.[129] Approximately 29% scored below average in a minimum of one developmental assessment, especially language assessments and 2% of children may be in the autism spectrum disorder during the second year of life.

The presence or absence of structural and functional neurologic abnormalities at birth may not predict later neurodevelopmental outcomes.[129,133] Approximately ½ of abnormal neurologic examination or abnormal neuroimaging findings at birth may develop normally in the follow-up assessments in their second or third years of life. About 25% of patients who appeared asymptomatic at birth may have delayed neurodevelopmental outcomes with or without abnormal hearing or ophthalmologic outcomes on follow-up.

Prevention

Protection against Zika virus infections during pregnancy:

- Avoid travel to areas with mosquito transmission of ZV.[168–176]
- Protection against mosquito bites.[177,178]
- Protection against sexual transmission for a partner who traveled to or lives in an area with a risk of ZV.
- Adherence to standard infection-prevention precautions.

Guidance for couples planning pregnancy:

- Reproductive-age couples in the affected areas should know the risks of transmission of ZV, the consequences of ZVI during pregnancy, and they should consider the possibility of delaying pregnancy.[171,174]
- Partners planning to conceive better to avoid or may postpone travel to areas where mosquito transmission of ZVI is likely unless the travel is very essential.[179]
- Wait for a minimum of 3 months after a potential exposure prior to a trial of conception with the use of abstinence or condoms during this period.[180]
- Those with infertility treatment who require to use of donor sperm or donor egg should only obtain these gametes from laboratories following FDA recommendation for screening guidelines and avoid donors traveling to risky places within 6 months of donation.[180] If they are using their own gametes same testing and timing recommendations of the FDA should be followed.[113]

REFERENCES

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg 1952;46(5):509–520. DOI: 10.1016/0035-9203(52)90042-4.
2. Grard G, Caron M, Mombo IM, et al. Zika virus in Gabon (Central Africa) – 2007: A new threat from *Aedes albopictus*? PLoS Negl Trop Dis 2014;8(2):e2681. DOI: 10.1371/journal.pntd.0002681.
3. Qian X, Qi Z. Mosquito-borne flaviviruses and current therapeutic advances. Viruses 2022;14(6):1226. DOI: 10.3390/v14061226.
4. Gubler DJ, Vasilakis N, Musso D. History and emergence of Zika virus. J Infect Dis 2017;216(Suppl. 10):S860–S867. DOI: 10.1093/infdis/jix451.

5. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med 2009;360(24):2536–2543.DOI: 10.1056/NEJMoa0805715.

6. Ikejezie J, Shapiro CN, Kim J, et al. Zika virus transmission – Region of the Americas, May 15, 2015–December 15, 2016. MMWR Morb Mortal Wkly Rep 2017;66(12):329–334. DOI: 10.15585/mmwr.mm6612a4.

7. Rodriguez–Diaz CE, Garriga–Lopez A, Malave–Rivera SM, et al. Zika virus epidemic in Puerto Rico: Health justice too long delayed. Int J Infect Dis 2017;65:144–147. DOI: 10.1016/j.ijid.2017.07.017.

8. Morris JK, Dolk H, Duran P, et al. Use of infectious disease surveillance reports to monitor the Zika virus epidemic in Latin America and the Caribbean from 2015 to 2017: Strengths and deficiencies. BMJ Open 2020;10(12):e042869. DOI: 10.1136/bmjopen-2020-042869.

9. Lowe R, Barcellos C, Brasil P, et al. The Zika virus epidemic in Brazil: From discovery to future implications. Int J Environ Res Public Health 2018;15(1):96. DOI: 10.3390/ijerph15010096.

10. Yan G, Pang L, Cook AR, et al. Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore. Emerg Infect Dis 2018;24(8):1565–1568. DOI: 10.3201/eid2408.171883.

11. Chang C, Ortiz K, Ansari A, et al. The Zika outbreak of the 21st century. J Autoimmun 2016;68:1–13. DOI: 10.1016/j.jaut.2016.02.006.

12. Aubry M, Teissier A, Huart M, et al. Zika virus seroprevalence, French Polynesia, 2014–2015. Emerg Infect Dis 2017;23(4):669–672. DOI: 10.3201/eid2304.161549.

13. Aliota MT, Bassit L, Bradrick SS, et al. Zika in the Americas, year 2: What have we learned? What gaps remain? A report from the Global Virus Network. Antiviral Res 2017;144:223–246. DOI: 10.1016/j.antiviral.2017.06.001.

14. Bragazzi NL, Alicino C, Trucchi C, et al. Global reaction to the recent outbreaks of Zika virus: Insights from a Big Data analysis. PLoS One 2017;12(9):e0185263. DOI: 10.1371/journal.pone.0185263.

15. Freitas DA, Souza–Santos R, Carvalho LMA, et al. Congenital Zika syndrome: A systematic review. PLoS One 2020;15(12):e0242367. DOI: 10.1371/journal.pone.0242367.

16. Paixao ES, Cardim LL, Costa MCN, et al. Mortality from congenital Zika syndrome: Nationwide cohort study in Brazil. N Engl J Med 24 2022;386(8):757–767. DOI: 10.1056/NEJMoa2101195.

17. Nithiyanantham SF, Badawi A. Maternal infection with Zika virus and prevalence of congenital disorders in infants: systematic review and meta-analysis. Can J Public Health 2019;110(5):638–648. DOI: 10.17269/s41997-019-00215-2.

18. Curcio AM, Shekhawat P, Reynolds AS, et al. Neurologic infections during pregnancy. Handb Clin Neurol 2020;172:79–104. DOI: 10.1016/B978-0-444-64240-0.00005-2.

19. Nogueira ML, Nery Junior NRR, Estofolete CF, et al. Adverse birth outcomes associated with Zika virus exposure during pregnancy in Sao Jose do Rio Preto, Brazil. Clin Microbiol Infect 2018;24(6):646–652. DOI: 10.1016/j.cmi.2017.11.004.

20. Antoniou E, Orovou E, Andronikidi PE, et al. Congenital Zika infection and the risk of neurodevelopmental, neurological, and urinary track disorders in early childhood: A systematic review. Viruses 2021;13(8):1671. DOI: 10.3390/v13081671.

21. Waldorf KMA, Nelson BR, Stencel–Baerenwald JE, et al. Congenital Zika virus infection as a silent pathology with loss of neurogenic output in the fetal brain. Nat Med 2018;24(3):368–374. DOI: 10.1038/nm.4485.

22. Ades AE, Soriano–Arandes A, Alarcon A, et al. Vertical transmission of Zika virus and its outcomes: A Bayesian synthesis of prospective studies. Lancet Infect Dis 2021;21(4):537–545. DOI: 10.1016/S1473-3099(20)30432-1.

23. Neufeldt CJ, Cortese M, Acosta EG, et al. Rewiring cellular networks by members of the Flaviviridae family. Nat Rev Microbiol 2018;16(3):125–142. DOI: 10.1038/nrmicro.2017.170.

24. Mazeaud C, Freppel W, Chatel–Chaix L. The multiples fates of the flavivirus RNA genome during pathogenesis. Front Genet 2018;9:595. DOI: 10.3389/fgene.2018.00595.

25. Lee H, Halverson S, Ezinwa N. Mosquito-borne diseases. Prim Care 2018;45(3):393–407. DOI: 10.1016/j.pop.2018.05.001.

26. Bogovic P, Strle F. Tick-borne encephalitis: A review of epidemiology, clinical characteristics, and management. World J Clin Cases 2015;3(5):430–441. DOI: 10.12998/wjcc.v3.i5.430.

27. Petersen LR, Brault AC, Nasci RS. West Nile virus: Review of the literature. JAMA 2013;310(3):308–315. DOI: 10.1001/jama.2013.8042.

28. Back AT, Lundkvist A. Dengue viruses: An overview. Infect Ecol Epidemiol 2013;3, DOI: 10.3402/iee.v3i0.19839.

29. Sharma KB, Vrati S, Kalia M. Pathobiology of Japanese encephalitis virus infection. Mol Aspects Med 2021;81:100994. DOI: 10.1016/j.mam.2021.100994.

30. Barrett AD, Higgs S. Yellow fever: A disease that has yet to be conquered. Annu Rev Entomol 2007;52:209–229. DOI: 10.1146/annurev.ento.52.110405.091454.

31. Dubrau D, Tortorici MA, Rey FA, et al. A positive-strand RNA virus uses alternative protein–protein interactions within a viral protease/cofactor complex to switch between RNA replication and virion morphogenesis. PLoS Pathog 2017;13(2):e1006134. DOI: 10.1371/journal.ppat.1006134.

32. Zhang X, Zhang Y, Jia R, et al. Structure and function of capsid protein in flavivirus infection and its applications in the development of vaccines and therapeutics. Vet Res 2021;52(1):98. DOI: 10.1186/s13567-021-00966-2.

33. Therkelsen MD, Klose T, Vago F, et al. Flaviviruses have imperfect icosahedral symmetry. Proc Natl Acad Sci U S A 2018;115(45):11608–11612. DOI: 10.1073/pnas.1809304115.

34. Bressanelli S, Stiasny K, Allison SL, et al. Structure of a flavivirus envelope glycoprotein in its low-pH-induced membrane fusion conformation. EMBO J 2004;23(4):728–738. DOI: 10.1038/sj.emboj.7600064.

35. Tan TY, Fibriansah G, Kostyuchenko VA, et al. Capsid protein structure in Zika virus reveals the flavivirus assembly process. Nat Commun 2020;11(1):895. DOI: 10.1038/s41467-020-14647-9.

36. Shang Z, Song H, Shi Y, et al. Crystal structure of the capsid protein from Zika virus. J Mol Biol 2018;430(7):948–z62. DOI: 10.1016/j.jmb.2018.02.006.

37. Valente AP, Moraes AH. Zika virus proteins at an atomic scale: How does structural biology help us to understand and develop vaccines and drugs against Zika virus infection? J Venom Anim Toxins Incl Trop Dis 2019;25:e20190013. DOI: 10.1590/1678-9199-JVATITD-2019-0013.

38. Lee LJ, Komarasamy TV, Adnan NAA, et al. Hide and seek: The interplay between Zika virus and the host immune response. Front Immunol 2021;12:750365. DOI: 10.3389/fimmu.2021.750365.

39. Sirohi D, Kuhn RJ. Zika virus structure, maturation, and receptors. J Infect Dis 2017;216(Suppl. 10):S935–S944. DOI: 10.1093/infdis/jix515.

40. Sironi M, Forni D, Clerici M, et al. Nonstructural proteins are preferential positive selection targets in Zika virus and related flaviviruses. PLoS Negl Trop Dis 2016;10(9):e0004978. DOI: 10.1371/journal.pntd.0004978.

41. Newton ND, Hardy JM, Modhiran N, et al. The structure of an infectious immature flavivirus redefines viral architecture and maturation. Sci Adv 2021;7(20):eabe4507. DOI: 10.1126/sciadv.abe4507.

42. Moureau G, Cook S, Lemey P, et al. New insights into flavivirus evolution, taxonomy and biogeographic history, extended by analysis of canonical and alternative coding sequences. PLoS One 2015;10(2):e0117849. DOI: 10.1371/journal.pone.0117849.

43. DiNunno NM, Goetschius DJ, Narayanan A, et al. Identification of a pocket factor that is critical to Zika virus assembly. Nat Commun 2020;11(1):4953. DOI: 10.1038/s41467-020-18747-4.

44. Sirohi D, Chen Z, Sun L, et al. The 3.8 A resolution cryo-EM structure of Zika virus. Science 2016;352(6284):467–470. DOI: 10.1126/science.aaf5316.

45. Franca R, Silva JM, Rodrigues LS, et al. New anti-flavivirus fusion loop human antibodies with Zika virus-neutralizing potential. Int J Mol Sci 2022;23(14):7805. DOI: 10.3390/ijms23147805.

46. Song W, Zhang H, Zhang Y, et al. Identification and characterization of Zika virus NS5 methyltransferase inhibitors. Front Cell Infect Microbiol 2021;11:665379. DOI: 10.3389/fcimb.2021.665379.

47. Dong S, Xiao MZX, Liang Q. Modulation of cellular machineries by Zika virus-encoded proteins. J Med Virol 2023;95(1):e28243. DOI: 10.1002/jmv.28243.

48. Roos WH, Ivanovska IL, Evilevitch A, et al. Viral capsids: Mechanical characteristics, genome packaging and delivery mechanisms. Cell Mol Life Sci 2007;64(12):1484–1497. DOI: 10.1007/s00018-007-6451-1.

49. Yu Y, Gao C, Wen C, et al. Intrinsic features of Zika virus non-structural proteins NS2A and NS4A in the regulation of viral replication. PLoS Negl Trop Dis 2022;16(5):e0010366. DOI: 10.1371/journal.pntd.0010366.

50. Barnard TR, Abram QH, Lin QF, et al. Molecular determinants of flavivirus virion assembly. Trends Biochem Sci 2021;46(5):378–390. DOI: 10.1016/j.tibs.2020.12.007.

51. Izaguirre G. The proteolytic regulation of virus cell entry by furin and other proprotein convertases. Viruses 2019;11(9):837. DOI: 10.3390/v11090837.

52. Braun E, Sauter D. Furin-mediated protein processing in infectious diseases and cancer. Clin Transl Immunology 2019;8(8):e1073. DOI: 10.1002/cti2.1073.

53. Zhou TF, Lai ZT, Liu S, et al. Susceptibility and interactions between IS mosquitoes and Zika viruses. Insect Sci 2021;28(5):1439–1451. DOI: 10.1111/1744-7917.12858.

54. Paixao ES, Teixeira MG, Rodrigues LC. Zika, chikungunya and dengue: The causes and threats of new and re-emerging arboviral diseases. BMJ Glob Health 2018;3(Suppl. 1):e000530. DOI: 10.1136/bmjgh-2017-000530.

55. Chitolina RF, Anjos FA, Lima TS, et al. Raw sewage as breeding site to *Aedes* (*Stegomyia*) *aegypti* (Diptera, culicidae). Acta Trop 2016;164:290–296. DOI: 10.1016/j.actatropica.2016.07.013.

56. Du S, Liu Y, Liu J, et al. *Aedes* mosquitoes acquire and transmit Zika virus by breeding in contaminated aquatic environments. Nat Commun 22 2019;10(1):1324. DOI: 10.1038/s41467-019-09256-0.

57. Zanluca C, de Noronha L, dos Santos CND. Maternal–fetal transmission of the zika virus: An intriguing interplay. Tissue Barriers 2018;6(1):e1402143. DOI: 10.1080/21688370.2017.1402143.

58. Colt S, Garcia–Casal MN, Pena–Rosas JP, et al. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systematic review. PLoS Negl Trop Dis 2017;11(4):e0005528. DOI: 10.1371/journal.pntd.0005528.

59. Mann TZ, Haddad LB, Williams TR, et al. Breast milk transmission of flaviviruses in the context of Zika virus: A systematic review. Paediatr Perinat Epidemiol 2018;32(4):358–368. DOI: 10.1111/ppe.12478.

60. Adams Waldorf KM, Olson EM, Nelson BR, et al. The aftermath of Zika: Need for long-term monitoring of exposed children. Trends Microbiol 2018;26(9):729–732. DOI: 10.1016/j.tim.2018.05.011.

61. Sampieri CL, Montero H. Breastfeeding in the time of Zika: A systematic literature review. PeerJ 2019;7:e6452. DOI: 10.7717/peerj.6452.

62. Mead PS, Hills SL, Brooks JT. Zika virus as a sexually transmitted pathogen. Curr Opin Infect Dis 2018;31(1):39–44. DOI: 10.1097/QCO.0000000000000414.

63. Murray JS. Understanding Zika virus. J Spec Pediatr Nurs 2017;22(1). DOI: 10.1111/jspn.12164.

64. Counotte MJ, Kim CR, Wang J, et al. Sexual transmission of Zika virus and other flaviviruses: A living systematic review. PLoS Med 2018;15(7):e1002611. DOI: 10.1371/journal.pmed.1002611.

65. Nicastri E, Castilletti C, Liuzzi G, et al. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill 2016;21(32):30314. DOI: 10.2807/1560-7917.ES.2016.21.32.30314.

66. Vanegas H, Gonzalez F, Reyes Y, et al. Zika RNA and flavivirus-like antigens in the sperm cells of symptomatic and asymptomatic subjects. Viruses 2021;13(2):152. DOI: 10.3390/v13020152.

67. Magnus MM, Esposito DLA, Costa VAD, et al. Risk of Zika virus transmission by blood donations in Brazil. Hematol Transfus Cell Ther 2018;40(3):250–254. DOI: 10.1016/j.htct.2018.01.011.

68. Musso D, Nhan T, Robin E, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill 2014;19(14): DOI: 10.2807/1560-7917.es2014.19.14.20761.

69. Hills SL, Morrison A, Stuck S, et al. Case series of laboratory-associated Zika virus disease, United States, 2016–2019. Emerg Infect Dis 2021;27(5):1296–1300. DOI: 10.3201/eid2705.203602.

70. Shugart JM, Brown CK. Zika virus presents an ongoing occupational health hazard for laboratory and biomedical research workers. Appl Biosaf 2019;24(1):8–9. DOI: 10.1177/1535676018818562.

71. Gulland A. Zika virus is a global public health emergency, declares WHO. BMJ 2016;352:i657. DOI: 10.1136/bmj.i657.

72. Chiu CF, Chu LW, Liao IC, et al. The mechanism of the Zika virus crossing the placental barrier and the blood–brain barrier. Front Microbiol 2020;11:214. DOI: 10.3389/fmicb.2020.00214.

73. Arruda LV, Salomao NG, Alves FAV, et al. The innate defense in the Zika-infected placenta. Pathogens 2022;11(12): DOI: 10.3390/pathogens11121410.

74. Rabelo K, de Souza LJ, Salomao NG, et al. Zika induces human placental damage and inflammation. Front Immunol 2020;11:2146. DOI: 10.3389/fimmu.2020.02146.

75. Ferraris P, Cochet M, Hamel R, et al. Zika virus differentially infects human neural progenitor cells according to their state of differentiation and dysregulates neurogenesis through the Notch pathway. Emerg Microbes Infect 2019;8(1):1003–1016. DOI: 10.1080/22221751.2019.1637283.

76. King EL, Irigoyen N. Zika virus and neuropathogenesis: The unanswered question of which strain is more prone to causing microcephaly and other neurological defects. Front Cell Neurosci 2021;15:695106. DOI: 10.3389/fncel.2021.695106.

77. Gurung S, Reuter N, Preno A, et al. Zika virus infection at mid-gestation results in fetal cerebral cortical injury and fetal death in the olive baboon. PLoS Pathog 2019;15(1):e1007507. DOI: 10.1371/journal.ppat.1007507.

78. Zorrilla CD, García IG, Fragoso LG, et al. Zika virus infection in pregnancy: Maternal, fetal, and neonatal considerations. J Infect Dis 2017;216(Suppl. 10):S891–S896. DOI: 10.1093/infdis/jix448.

79. Shao Q, Herrlinger S, Yang SL, et al. Zika virus infection disrupts neurovascular development and results in postnatal microcephaly with brain damage. Development 2016;143(22):4127–4136. DOI: 10.1242/dev.143768.

80. Wheeler AC. Development of infants with congenital Zika syndrome: What do we know and what can we expect? Pediatrics 2018;141(Suppl. 2):S154–S160. DOI: 10.1542/peds.2017-2038D.

81. Gazeta RE, Bertozzi A, Dezena R, et al. Three-year clinical follow-up of children intrauterine exposed to Zika virus. Viruses 2021;13(3): DOI: 10.3390/v13030523.

82. Rothan HA, Fang S, Mahesh M, et al. Zika Virus and the metabolism of neuronal cells. Mol Neurobiol 2019;56(4):2551–2557. DOI: 10.1007/s12035-018-1263-x.

83. van den Pol AN, Mao G, Yang Y, et al. Zika virus targeting in the developing brain. J Neurosci 2017;37(8):2161–2175. DOI: 10.1523/JNEUROSCI.3124-16.2017.

84. Alfano C, Gladwyn–Ng I, Couderc T, et al. The unfolded protein response: A key player in Zika virus-associated congenital microcephaly. Front Cell Neurosci 2019;13:94. DOI: 10.3389/fncel.2019.00094.

85. Beaufrere A, Bessieres B, Bonniere M, et al. A clinical and histopathological study of malformations observed in fetuses infected by the Zika virus. Brain Pathol 2019;29(1):114–125. DOI: 10.1111/bpa.12644.

86. Melo AS, Aguiar RS, Amorim MM, et al. Congenital Zika virus infection: Beyond neonatal microcephaly. JAMA Neurol 2016;73(12):1407–1416. DOI: 10.1001/jamaneurol.2016.3720.

87. Li C, Wang Q, Jiang Y, et al. Disruption of glial cell development by Zika virus contributes to severe microcephalic newborn mice. Cell Discov 2018;4:43. DOI: 10.1038/s41421-018-0042-1.

88. Souza BS, Sampaio GL, Pereira CS, et al. Zika virus infection induces mitosis abnormalities and apoptotic cell death of human neural progenitor cells. Sci Rep 23 2016;6:39775. DOI: 10.1038/srep39775.

89. Wen C, Yu Y, Gao C, et al. RIPK3-dependent necroptosis is induced and restricts viral replication in human astrocytes infected with Zika virus. Front Cell Infect Microbiol 2021;11:637710. DOI: 10.3389/fcimb.2021.637710.

90. Lin MY, Wang YL, Wu WL, et al. Zika virus infects intermediate progenitor cells and post-mitotic committed neurons in human fetal brain tissues. Sci Rep 2017;7(1):14883. DOI: 10.1038/s41598-017-13980-2.

91. Vhp L, Aragao MM, Pinho RS, et al. Congenital zika virus infection: A review with emphasis on the spectrum of brain abnormalities. Curr Neurol Neurosci Rep 2020;20(11):49. DOI: 10.1007/s11910-020-01072-0.

92. Ferreira LL, Aguilar Ticona JP, Silveira–Mattos PS, et al. Clinical and biochemical features of hypopituitarism among brazilian children with Zika virus-induced microcephaly. JAMA Netw Open 2021;4(5):e219878. DOI: 10.1001/jamanetworkopen.2021.9878.

93. Enlow W, Bordeleau M, Piret J, et al. Microglia are involved in phagocytosis and extracellular digestion during Zika virus encephalitis in young adult immunodeficient mice. J Neuroinflammation 2021;18(1):178. DOI: 10.1186/s12974-021-02221-z.

94. Garcez PP, Stolp HB, Sravanam S, et al. Zika virus impairs the development of blood vessels in a mouse model of congenital infection. Sci Rep 2018;8(1):12774. DOI: 10.1038/s41598-018-31149-3.

95. Merfeld E, Ben–Avi L, Kennon M, et al. Potential mechanisms of Zika-linked microcephaly. Wiley Interdiscip Rev Dev Biol 2017;6(4):e273. DOI: 10.1002/wdev.273.

96. Sher AA, Glover KKM, Coombs KM. Zika virus infection disrupts astrocytic proteins involved in synapse control and axon guidance. Front Microbiol 2019;10:596. DOI: 10.3389/fmicb.2019.00596.

97. Brasil P, Pereira JP Jr, Moreira ME, et al. Zika virus infection in pregnant women in Rio de Janeiro. N Engl J Med 2016;375(24):2321–2334. DOI: 10.1056/NEJMoa1602412.

98. Krauer F, Riesen M, Reveiz L, et al. Zika virus infection as a cause of congenital brain abnormalities and Guillain–Barre syndrome: Systematic review. PLoS Med 2017;14(1):e1002203. DOI: 10.1371/journal.pmed.1002203.

99. Schwartz DA. Viral infection, proliferation, and hyperplasia of Hofbauer cells and absence of inflammation characterize the placental pathology of fetuses with congenital Zika virus infection. Arch Gynecol Obstet 2017;295(6):1361–1368. DOI: 10.1007/s00404-017-4361-5.

100. Rosenberg AZ, Yu W, Hill DA, et al. Placental pathology of Zika virus: Viral infection of the placenta induces villous stromal macrophage (Hofbauer cell) proliferation and hyperplasia. Arch Pathol Lab Med 2017;141(1):43–48. DOI: 10.5858/arpa.2016-0401-OA.

101. Almeida RDN, Braz-de-Melo HA, Santos IO, et al. The cellular impact of the ZIKA virus on male reproductive tract immunology and physiology. Cells 2020;9(4):1006. DOI: 10.3390/cells9041006.

102. Walker CL, Merriam AA, Ohuma EO, et al. Femur-sparing pattern of abnormal fetal growth in pregnant women from New York City after maternal Zika virus infection. Am J Obstet Gynecol 2018;219(2):187.e1–187.e20. DOI: 10.1016/j.ajog.2018.04.047.

103. Cauchemez S, Besnard M, Bompard P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: A retrospective study. Lancet 2016;387(10033):2125–2132. DOI: 10.1016/S0140-6736(16)00651-6.

104. van der Linden V, Pessoa A, Dobyns W, et al. Description of 13 infants born during October 2015–January 2016 With congenital Zika virus infection without microcephaly at birth – Brazil. MMWR Morb Mortal Wkly Rep 2016;65(47):1343–1348. DOI: 10.15585/mmwr.mm6547e2.

105. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell 2016;18(5):587–590. DOI: 10.1016/j.stem.2016.02.016.

106. Gilmore EC, Walsh CA. Genetic causes of microcephaly and lessons for neuronal development. Wiley Interdiscip Rev Dev Biol 2013;2(4):461–478. DOI: 10.1002/wdev.89.

107. Driggers RW, Ho CY, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med 2016;374(22):2142–2151. DOI: 10.1056/NEJMoa1601824.

108. Schuler–Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly – Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65(3):59–62. DOI: 10.15585/mmwr.mm6503e2.

109. Reynolds MR, Jones AM, Petersen EE, et al. Vital signs: Update on Zika virus-associated birth defects and evaluation of all U.S. infants with congenital Zika virus exposure – U.S. Zika Pregnancy Registry, 2016. MMWR Morb Mortal Wkly Rep 2017;66(13):366–373. DOI: 10.15585/mmwr.mm6613e1.

110. Hoen B, Schaub B, Funk AL, et al. Pregnancy outcomes after ZIKV infection in French territories in the Americas. N Engl J Med 2018;378(11):985–994. DOI: 10.1056/NEJMoa1709481.

111. Rice ME, Galang RR, Roth NM, et al. Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection – U.S. territories and freely associated states, 2018. MMWR Morb Mortal Wkly Rep 2018;67(31):858–867. DOI: 10.15585/mmwr.mm6731e1.

112. Jurado KA, Simoni MK, Tang Z, et al. Zika virus productively infects primary human placenta-specific macrophages. JCI Insight 2016;1(13): DOI: 10.1172/jci.insight.88461.

113. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. N Engl J Med 2016;374(10):951–958. DOI: 10.1056/NEJMoa1600651.

114. Rasmussen SA, Jamieson DJ, Honein MA, et al. Zika virus and birth defects: Reviewing the evidence for causality. N Engl J Med 2016;374(20):1981–1987. DOI: 10.1056/NEJMsr1604338.

115. Miner JJ, Cao B, Govero J, et al. Zika virus infection during pregnancy in mice causes placental damage and fetal demise. Cell 2016;165(5):1081–1091. DOI: 10.1016/j.cell.2016.05.008.

116. Moura da Silva AA, Ganz JS, Sousa PD, et al. Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. Emerg Infect Dis 2016;22(11):1953–1956. DOI: 10.3201/eid2211.160956.

117. Miranda–Filho Dde B, Martelli CM, Ximenes RA, et al. Initial description of the presumed congenital Zika syndrome. Am J Public Health 2016;106(4):598-600. DOI: 10.2105/AJPH.2016.303115.

118. Calvet G, Aguiar RS, Melo ASO, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: A case study. Lancet Infect Dis 2016;16(6):653–660. DOI: 10.1016/S1473-3099(16)00095-5.

119. Microcephaly Epidemic Research G. Microcephaly in infants, Pernambuco state, Brazil, 2015. Emerg Infect Dis 2016;22(6):1090–1093. DOI: 10.3201/eid2206.160062.

120. Martines RB, Bhatnagar J, Keating MK, et al. Notes from the field: Evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses – Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65(6):159–160. DOI: 10.15585/mmwr.mm6506e1.

121. Sarno M, Sacramento GA, Khouri R, et al. Zika virus infection and stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. PLoS Negl Trop Dis 2016;10(2):e0004517. DOI: 10.1371/journal.pntd.0004517.

122. WHO. Zika virus and complications: Questions and answers. World Health Organization. 2023. http://www.who.int/features/qa/zika/en/. Accessed on: January 2023.

123. Cordeiro MT, Pena LJ, Brito CA, et al. Positive IgM for Zika virus in the cerebrospinal fluid of 30 neonates with microcephaly in Brazil. Lancet 2016;387(10030):1811–1812. DOI: 10.1016/S0140-6736(16)30253-7.

124. Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: The newborn cross-sectional study of the INTERGROWTH-21st project. Lancet 2014;384(9946):857–868. DOI: 10.1016/S0140-6736(14)60932-6.

125. Meneses JDA, Ishigami AC, de Mello LM, et al. Lessons learned at the epicenter of Brazil's congenital Zika epidemic: Evidence from 87 confirmed cases. Clin Infect Dis 2017;64(10):1302–1308. DOI: 10.1093/cid/cix166.

126. Chi JG, Dooling EC, Gilles FH. Gyral development of the human brain. Ann Neurol 1977;1(1):86–93. DOI: 10.1002/ana.410010109.

127. Tsui I, Moreira MEL, Rossetto JD, et al. Eye findings in infants with suspected or confirmed antenatal Zika virus exposure. Pediatrics 2018;142(4): DOI: 10.1542/peds.2018-1104.

128. Pool KL, Adachi K, Karnezis S, et al. Association between neonatal neuroimaging and clinical outcomes in Zika-exposed infants from Rio de Janeiro, Brazil. JAMA Netw Open 2019;2(7):e198124. DOI: 10.1001/jamanetworkopen.2019.8124.

129. Adachi K, Romero T, Nielsen–Saines K, et al. Early clinical infancy outcomes for microcephaly and/or small for gestational age Zika-exposed infants. Clin Infect Dis 2020;70(12):2663–2672. DOI: 10.1093/cid/ciz704.

130. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr 2017;171(3):288–295. DOI: 10.1001/jamapediatrics.2016.3982.

131. Moreira MEL, Nielsen–Saines K, Brasil P, et al. Neurodevelopment in infants exposed to Zika virus in utero. N Engl J Med 2018;379(24):2377–2379. DOI: 10.1056/NEJMc1800098.

132. Zin AA, Tsui I, Rossetto J, et al. Screening criteria for ophthalmic manifestations of congenital Zika virus infection. JAMA Pediatr 2017;171(9):847–854. DOI: 10.1001/jamapediatrics.2017.1474.

133. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol 2016;134(5):529–535. DOI: 10.1001/jamaophthalmol.2016.0267.

134. Moshfeghi DM, de Miranda HA 2nd, Costa MC. Zika virus, microcephaly, and ocular findings. JAMA Ophthalmol 2016;134(8):945. DOI: 10.1001/jamaophthalmol.2016.1303.

135. Ventura CV, Maia M, Travassos SB, et al. Risk factors associated with the ophthalmoscopic findings identified in infants with presumed Zika virus congenital infection. JAMA Ophthalmol 2016;134(8):912–918. DOI: 10.1001/jamaophthalmol.2016.1784.

136. Miranda HA II, Costa MC, Frazao MAM, et al. Expanded spectrum of congenital ocular findings in microcephaly with presumed Zika infection. Ophthalmology 2016;123(8):1788–1794. DOI: 10.1016/j.ophtha.2016.05.001.

137. de Oliveira Dias JR, Ventura CV, Borba PD, et al. Infants with congenital Zika syndrome and ocular findings from Sao Paulo, Brazil: Spread of infection. Retin Cases Brief Rep 2018;12(4):382–386. DOI: 10.1097/ICB.0000000000000518.

138. Ventura LO, Ventura CV, Lawrence L, et al. Visual impairment in children with congenital Zika syndrome. J AAPOS 2017;21(4):295–299.e2. DOI: 10.1016/j.jaapos.2017.04.003.

139. Ventura CV, Ventura LO, Bravo–Filho V, et al. Optical coherence tomography of retinal lesions in infants with congenital Zika syndrome. JAMA Ophthalmol016;134(12):1420–1427. DOI: 10.1001/jamaophthalmol.2016.4283.

140. Ventura CV, Maia M, Bravo–Filho V, et al. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet 2016;387(10015):228. DOI: 10.1016/S0140-6736(16)00006-4.

141. Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol 2016;79(1):1–3. DOI: 10.5935/0004-2749.20160002.

142. de Paula Freitas B, Ko AI, Khouri R, et al. Glaucoma and congenital Zika syndrome. Ophthalmol 2017;124(3):407–408. DOI: 10.1016/j.ophtha.2016.10.004.

143. Melo ASO, Malinger G, Ximenes R, et al. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: Tip of the iceberg? Ultrasound Obstet Gynecol 2016;47(1):6–7. DOI: 10.1002/uog.15831.

144. Yepez JB, Murati FA, Pettito M, et al. Ophthalmic manifestations of congenital Zika syndrome in Colombia and Venezuela. JAMA Ophthalmol 2017;135(5):440–445. DOI: 10.1001/jamaophthalmol.2017.0561.

145. Ventura LO, Ventura CV, Dias NC, et al. Visual impairment evaluation in 119 children with congenital Zika syndrome. J AAPOS 2018;22(3):218.e1–222.e1. DOI: 10.1016/j.jaapos.2018.01.009.

146. Zin AA, Tsui I, Rossetto JD, et al. Visual function in infants with antenatal Zika virus exposure. J AAPOS 2018;22(6):452.e1–456.e1. DOI: 10.1016/j.jaapos.2018.07.352.

147. Vercosa I, Carneiro P, Vercosa R, et al. The visual system in infants with microcephaly related to presumed congenital Zika syndrome. J AAPOS 2017;21(4):300.e1–304.e1. DOI: 10.1016/j.jaapos.2017.05.024.

148. Leal MC, Muniz LF, Ferreira TS, et al. Hearing loss in infants with microcephaly and evidence of congenital Zika virus infection – Brazil, November 2015 – May 2016. MMWR Morb Mortal Wkly Rep 2016;65(34):917–919. DOI: 10.15585/mmwr.mm6534e3.

149. Franca GV, Schuler–Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: A case series of the first 1501 livebirths with complete investigation. Lancet 27 2016;388(10047):891–897. DOI: 10.1016/S0140-6736(16)30902-3.

150. Alves LV, Mello MJG, Bezerra PG, Alves JGB. Congenital Zika syndrome and infantile spasms: Case series study. J Child Neurol 2018;33(10):664–666. DOI: 10.1177/0883073818780105.

151. Cavalcanti DD, Alves LV, Furtado GJ, et al. Echocardiographic findings in infants with presumed congenital Zika syndrome: Retrospective case series study. PLoS One 2017;12(4):e0175065. DOI: 10.1371/journal.pone.0175065.

152. Besnard M, Eyrolle–Guignot D, Guillemette–Artur P, et al. Congenital cerebral malformations and dysfunction in fetuses and newborns following the 2013 to 2014 Zika virus epidemic in French Polynesia. Euro Surveill 2016;21(13). DOI: 10.2807/1560-7917.ES.2016.21.13.30181.

153. Orofino DHG, Passos SRL, de Oliveira RVC, et al. Cardiac findings in infants with in utero exposure to Zika virus: A cross sectional study. PLoS Negl Trop Dis 2018;12(3):e0006362. DOI: 10.1371/journal.pntd.0006362.

154. Read JS, Torres–Velasquez B, Lorenzi O, et al. Symptomatic Zika virus infection in infants, children, and adolescents living in Puerto Rico. JAMA Pediatr 2018;172(7):686–693. DOI: 10.1001/jamapediatrics.2018.0870.

155. Vouga M, Baud D. Imaging of congenital Zika virus infection: The route to identification of prognostic factors. Prenat Diagn 2016;36(9):799–811. DOI: 10.1002/pd.4880.

156. Culjat M, Darling SE, Nerurkar VR, et al. Clinical and imaging findings in an infant with Zika embryopathy. Clin Infect Dis 2016;63(6):805–811. DOI: 10.1093/cid/ciw324.

157. Soares de Oliveira–Szejnfeld P, Levine D, Melo AS, et al. Congenital brain abnormalities and Zika virus: What the radiologist can expect to see prenatally and postnatally. Radiology 2016;281(1):203–218. DOI: 10.1148/radiol.2016161584.

158. Petribu NCL, Aragao MFV, van der Linden V, et al. Follow-up brain imaging of 37 children with congenital Zika syndrome: Case series study. BMJ 2017;359:j4188. DOI: 10.1136/bmj.j4188.

159. Adebanjo T, Godfred–Cato S, Viens L, et al. Update: Interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection – United States, October 2017. MMWR Morb Mortal Wkly Rep 2017;66(41):1089–1099. DOI: 10.15585/mmwr.mm6641a1.

160. World Health Organization. Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero. World Health Organization. 2016. Available at: https://apps.who.int/iris/handle/10665/204475. Accessed on: 2 January 2023.

161. Petersen LR, Jamieson DJ, Powers AM, et al. Zika Virus. N Engl J Med 2016;374(16):1552–1563. DOI: 10.1056/NEJMra1602113.

162. Prevention CfDCa. Congenital microcephaly case definitions. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/zika/public-health-partners/microcephaly-case-definitions.html Accessed on: 2 January 2023.

163. Rabe IB, Staples JE, Villanueva J, et al. Interim guidance for interpretation of Zika virus antibody test results. MMWR Morb Mortal Wkly Rep 2016;65(21):543–546. DOI: 10.15585/mmwr.mm6521e1.

164. Oliveira DB, Almeida FJ, Durigon EL, et al. Prolonged shedding of Zika virus associated with congenital infection. N Engl J Med 2016;375(12):1202–1204. DOI: 10.1056/NEJMc1607583.

165. Besnard M, Lastere S, Teissier A, et al. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014;19(13):20751. PMID: 24721538.

166. Centers for Disease Control and Prevention. Questions and answers for healthcare providers caring for infants and children with possible Zika virus infection. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/zika/hc-providers/index.html. Accessed on: 2 January 2023.

167. Fleming–Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection – United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65(7):182–187. DOI: 10.15585/mmwr.mm6507e1.

168. Throckmorton L, Hancher J. Management of travel-related infectious diseases in the emergency department. Curr Emerg Hosp Med Rep 2020;8(2):50–59. DOI: 10.1007/s40138-020-00213-6.

169. Management of Patients in the Context of Zika Virus: ACOG COMMITTEE OPINION, Number 784. Obstet Gynecol Sep 2019;134(3):e64–e70. DOI: 10.1097/AOG.0000000000003399.

170. Burke RM, Pandya P, Nastouli E, et al. Zika virus infection during pregnancy: What, where, and why? Br J Gen Pract 2016;66(644): 122–123. DOI: 10.3399/bjgp16X683917.

171. European Centre for Disease Prevention and Control. Rapid risk assessment – Zika virus disease epidemic: Potential association with microcephaly and Guillain–Barre syndrome (first update). Available at: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf Accessed on: 2 January 2023.

172. World Health Organization. WHO statement on the 2nd meeting of IHR Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. World Health Organization. 2016. Available at: http://www.who.int/mediacentre/news/statements/2016/2nd-emergency-committee-zika/en/. Accessed on: 2 January 2023.

173. Centers of Disease Control and Prevention. CDC issues advice for travel to the 2016 Summer Olympic Games. Centers of Disease Control and Prevention. 2016. Available at: http://www.cdc.gov/media/releases/2016/s0226-summer-olympic-games.html. Accessed on: 2 January 2023.

174. Cetron M. Revision to CDC's Zika travel notices: Minimal likelihood for mosquito-borne Zika virus transmission at elevations above 2,000 meters. MMWR Morb Mortal Wkly Rep 2016. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6510e1er.htm. Accessed on: 2 January 2023.

175. Centers for Disease Control and Prevention. CDC Guidance for travel and testing of pregnant women and women of reproductive age for Zika virus infection related to the investigation for local mosquito-borne Zika virus transmission in Miami-Dade and Broward counties, Florida Atlanta, Georgia, United States. Available at: https://emergency.cdc.gov/han/han00393.asp. Accessed on: 2 January 2023.

176. Centers for Disease Control and Prevention. Interim Guidance for Protecting Workers from Occupational Exposure to Zika Virus Centers for Disease Control and Prevention. 2016. Available at: http://www.cdc.gov/niosh/topics/outdoor/mosquito-borne/pdfs/osha-niosh_fs-3855_zika_virus_04-2016.pdf#page=1. Accessed on: January 2, 2023.

177. Ndeffo–Mbah ML, Parpia AS, Galvani AP. Mitigating prenatal Zika virus infection in the Americas. Ann Intern Med 2016;165(8):551–559. DOI: 10.7326/M16-0919.

178. Centers for Disease Control and Prevention. CDC and OSHA issue interim guidance for protecting workers from occupational exposure to Zika virus. Centers for Disease Control and Prevention. 2016. Available at: https://www.cdc.gov/media/releases/2016/s0422-interim-guidance-zika.html. Accessed on: 2 January 2023.

179. US Food and Drug Administration. Donor screening recommendations to reduce the risk of transmission of Zika virus by human cells, tissues, and cellular and tissue-based products. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/donor-screening-recommendations-reduce-risk-transmission-zika-virus-human-cells-tissues-and-cellular US Food and Drug Administration. 2016. Accessed on: 2 January 2023. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf

180. American College of Obstetricians and Gynecologists. Practice advisory interim guidance for care of obstetric patients during a Zika virus outbreak. Reproductive counseling. American College of Obstetricians and Gynecologists. http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak#counseling. Accessed on: 2 January 2023.