Published in final edited form as:

Curr Opin Pediatr. 2018 February ; 30(1): 105–116. doi:10.1097/MOP.0000000000000582.

Zika Clinical Updates: Implications for Pediatrics

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Abstract

Purpose of Review—Zika virus (ZIKV), a mosquito-borne flavivirus, has gained recognition over the past few years as an important new etiology of congenital infection. As a result, it is critical that pediatricians understand its epidemiology, clinical presentation, clinical sequelae, and management.

Recent findings—The recent ZIKV epidemiology, clinical presentation of acute infection in children and complications, perinatal infection, and congenital infection will be summarized in this ZIKV review. This will be followed by a brief summary on ZIKV diagnosis, management, treatment, and prevention.

Summary—The field of clinical research in ZIKV has rapidly evolved over recent months. It is critical that pediatricians continue to stay up-to-date with continuously evolving understanding of the clinical aspects of ZIKV in order to ensure optimal identification and management of affected infants and children. Given the recent changes in CDC guidelines to limit screening of asymptomatic pregnant women in the US with possible ZIKV exposure, comprehensive ZIKV clinical knowledge becomes even more crucial.

Keywords

zika virus; congenital zika syndrome; pediatric zika infection

Introduction

Prior to 2015, few could have foreseen the potential devastation that Zika virus (ZIKV) was capable of inflicting on an unsuspecting global population. Although initially discovered seven decades ago in Uganda and then followed by smaller epidemics (2007 Micronesia; 2013–2014 French Polynesia and other Pacific Islands), ZIKV had previously received scarce global attention.^{1,2–8} Following the 2015–2016 catastrophic Brazilian ZIKV epidemic and the growing recognition of an association of ZIKV with Guillain-Barre syndrome and congenital abnormalities such as microcephaly, the WHO declared ZIKV a “public health

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Disclosures and Conflict of Interest: None of the authors have no other financial relationships or conflicts of interest to disclose apart from those referred to above.

emergency” from February to November 2016.^{9–16} Extensive global research since then has led to our enhanced understanding of various clinical aspects of ZIKV infection with many new findings even since the publication of the special issue of this journal featuring Zika virus in February 2017.^{17–21}

Epidemiology

While ZIKV circulation in Latin America was recognized in Brazil in 2015, more recent mosquito phylogenetic analysis suggests that ZIKV may have arrived in Brazil as early as October 2012-to-May 2013.^{22–24} Since then, ZIKV rapidly spread throughout the Americas and the Caribbean²⁵ with transmission now reported in over 84 countries.^{23,26,27–31} Other global regions including Africa (Guinea-Bissau), Southeast Asia (Vietnam, Singapore, Philippines, Malaysia, Thailand) and the Western Pacific Regions later reported active ZIKV transmission since 2016.³² By 2017, ZIKV cases in Brazil and other Latin American countries dropped considerably with a subsequent decrease in US imported travel-cases.

The first US cases of locally transmitted ZIKV were identified in Miami, Florida in July 2016 and in Brownsville, Texas in November 2016.^{33,34,35–37} As of August 3, 2017, 185 symptomatic ZIKV cases were reported in US travelers (zero were locally transmitted) and 553 in US territories in 2017.³⁸ The number of 2017 cases are much lower than those from 2016 (5,102 US ZIKV cases including 224 acquired through local transmission and 36,079 cases in US territories).³⁸ <https://wwwnc.cdc.gov/travel/page/zika-travel-information>

The CDC created the US ZIKV Pregnancy Registry in 2016 to follow outcomes of US pregnant women.³⁹ Data from January 2016–April 2017 of over 2,500 pregnancies with laboratory evidence of possible ZIKV infection found 5% had ZIKV-associated birth defects with slight differences in rates by infection trimester.⁴⁰ However, data from our own prospective study of PCR-confirmed ZIKV Infection in Brazilian pregnant women found much higher rates of abnormalities of fetuses/infants (42%), but encompassed a wider-range of abnormalities, including both structural and functional CNS findings.⁴¹ A recent study comparing estimated birth defect prevalence in the US before (2013–2014) and after the introduction of ZIKV in the Americas found an increase from 2.86 per 1,000 to 58.8 per 1,000, approximately a 20-fold higher rate of birth defects.⁴²

The U.S. CDC and other worldwide public health authorities have issued alerts to women who are pregnant or planning to conceive, to avoid or postpone travel to countries with active ZIKV transmission and potential for ZIKV sexual transmission during and after travel. Travel warnings were issued for South Florida and Brownsville Texas, many countries/territories in Latin America/Caribbean, and some countries in the Asia Pacific region and Africa.⁴³ Additional countries in Africa and Asia are now considered a ZIKV travel risk because of a likely history of ongoing ZIV transmission for many years.^{43,44} *CDC guidelines for testing pregnant women for possible ZIKV have changed since July 2017; ZIKV testing in asymptomatic pregnant women with possible but not ongoing ZIKV exposure (travel or sexual) is no longer recommended.*^{45,46} *Pediatricians must be more vigilant and understand ZIKV risk factors and the spectrum of congenital ZIKV infection presentation.*

Zika Clinical Updates

Acute Infection

ZIKV infection is believed to be asymptomatic in up to 80% of people.^{5,47} Recent CDC studies of 197 US travelers with ZIKV in 2015–16 suggest ZIKV incubation to be 3–14 days with about half developing symptoms within 1 week.⁴⁸ Acute ZIKV infection is considered mild in the majority of patients. It is classically characterized by low grade to no fever, a maculopapular rash, arthralgia, and conjunctivitis.^{49,50–55,56,52,57} (See Fig. 1) Many patients with acute ZIKV infection do not have fever, which may be seen in only one third of patients and is typically brief and low-grade compared to chikungunya or dengue.^{52,49,58–60,56,52} Whereas, ZIKV patients may be more likely to present with conjunctivitis and a maculopapular rash, especially one accompanied by pruritis.^{52,59,61,62,41,52,63} (See Table 1)

Recent studies have attempted to evaluate the sensitivity and specificity of diagnosing ZIKV using clinical case definitions (PAHO, CDC, ECDC, WHO, Brazil Ministry of Health). One study from Brazil found that their own proposed definition of ZIKV clinical symptoms (rash, pruritis, conjunctival hyperemia, absence of fever, petechiae, anorexia) was a better predictor of ZIKV infection than the other definitions.⁶⁷ A similar Singaporean study found that many of the currently used official clinical case definitions for ZIKV lacked specificity, but rash was an important clinical characteristic.⁶⁸

Acute Infection in Children

We still know very little about acute ZIKV infection (non-congenital) in children (< 18 years of age) with few published reports.^{69–76} Prior data from the 2007 ZIKV Yap Island epidemic suggested that ZIKV-infected children may present similarly to adults with fever, rash, arthralgia, and/or conjunctivitis.^{5,69} However, it is believed that ZIKV symptomatic attack rates are lower in children, and infection is more mild in children compared to adults. Prior to late 2016, there was only one publication⁷⁷ summarizing acute ZIKV infections in children, which was a review by the CDC of six publications of 10 children with ZIKV infection from 1954–2016.^{69–78} In that initial summary report, ZIKV illness typically lasted less than one week and was characterized by fever, malaise, headache, and myalgia.⁷⁷ Gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea were more common (70%) in children, and rash was not seen.^{69,77}

A more recent CDC review of pediatric acute ZIKV cases that summarized data from 158 cases of travel-acquired ZIKV among children (1 month to 17 years of age) is now available.^{69,79} Differing from the earlier report, almost all of the children with ZIKV had rash (82%), while approximately half had fever (55%) and over one quarter had conjunctivitis (29%) and/or arthralgia (28%).⁷⁹ Additional reported symptoms included myalgia, gastrointestinal complaints, retro-orbital pain, and sore throat.⁷⁹ A smaller case series of 14 Singaporean pediatric patients (ages 6 months to 16 years) with confirmed or suspected ZIKV infection was also published.⁸⁰ They observed higher rates of fever (93%) and rash (100%) with similar rates of conjunctivitis (29%) and arthralgia (14%); GI symptoms were not commented upon although upper respiratory tract symptoms (cough, coryza) were reported

in 50%.⁸⁰ No deaths or neurologic complications were seen; although one patient with co-infection with dengue and ZIKV had hypotension and thrombocytopenia.⁸⁰

Complications of Acute Infection—The majority of acute ZIKV patients (adults and children) recover without complications. A published review of 2,382 confirmed of probable ZIKV US cases reported only 3% required hospitalization.⁸¹ Similarly, no severe ZIKV complications such as meningitis, encephalitis, septic shock, GBS, or death were observed in a recent CDC study; although two children (1 year and 4 years) were hospitalized for cough, fever, and poor oral intake.⁷⁹

In adults, unusual potential reported complications following acute ZIKV include temporary hearing impairments, dysguesia, eye abnormalities (hypertensive iridocyclitis, uveitis, acute maculopathy, acute chorioretinitis), genitourinary issues (hematospermia, prostatitis), myocarditis, and a positive ANA.^{82–90,91,92,93} Hemorrhagic complications such as severe thrombocytopenia with hematomas and mucosal bleeding have been reported but are rare in contrast to those with dengue.^{94,95,96, 91,97–104} (See Table 2)

Given ZIKV's neutropism, it is not surprising that ZIKV neurologic complications may occur including encephalopathy, meningoencephalitis, seizures, acute sensory polyneuropathy, myelitis including ADEM, and GBS.^{105,10,81,106–126} There is even a recent case report of an adolescent with a history of depression who suffered neuropsychiatric and cognitive changes for months following acute ZIKV infection.¹²⁷ Of the potential neurologic complications following ZIKV, GBS, which is a form of acute or sub-acute immune-mediated progressive flaccid paralysis and considered a medical emergency, has garnered the most attention.^{109,128–130} GBS was initially recognized as a potential complication after the French Polynesia ZIKV epidemic, where it was associated with thirty-four-fold increased risk of GBS (OR>34).^{109,111,126,109} This was followed by additional observations in Brazil of an increased incidence of GBS during the ZIKV epidemic as well as in other countries, especially in the Americas.^{9,10,110,127,112,120,81,131,132,321,331,18,119,122} One recent review of GBS cases from Brazil, Colombia, Dominican Republic, El Salvador, Honduras, Suriname, and Venezuela has suggested a two to nearly ten-fold increase in GBS cases above baseline.¹²¹

Apart from deaths from GBS, several cases of ZIKV-associated death have been reported in the literature including cases from Brazil, Colombia, Puerto Rico, and the US.^{134,81,134,105,135,136,99,101} This includes four pediatric fatalities, primarily in female teenagers.^{71,135,136} One fatality was a 15 year-old teenager with underlying sickle-cell disease (hemoglobin SC disease), who was infected with ZIKV and presented with fever, abdominal pain, myalgia, and jaundice complicated by vaso-occlusion crises culminating in severe acute respiratory distress, hemothorax, hepatic necrosis, and severe splenic sequestration.⁷¹ The fatal ZIKV Brazilian cases included two teenagers: one who presented with thrombocytopenia, anemia, and hemorrhagic manifestations and died of hypovolemic shock, and the other with likely encephalitis.^{105,135,136} The last was a 2-year-old Colombian child, with probable leukemia on autopsy, who had altered mental status, hepatomegaly, and thrombocytopenia, which evolved to disseminated intravascular coagulation, respiratory distress and shock.^{95,99}

Perinatal Transmission—As with other arboviruses such as dengue, chikungunya, and West Nile, ZIKV perinatal transmission is also possible.^{69,137–140} Two cases of acute neonatal ZIKV disease from perinatal transmission at or near delivery were reported in the literature.^{69,141} It should be noted that these infants presented much differently than congenital ZIKV infants with *in utero* ZIKV transmission. The mothers had symptomatic ZIKV infection either immediately prior to or after delivery.¹⁴¹ One infant was asymptomatic, and the other had rash and thrombocytopenia.^{69,141} A more recent 30-month follow-up report of these two infants indicated that the symptomatic infant also had mild brain lesions (subependymal cyst, lenticulo-striate vasculitis) and developed transient subclinical hepatitis that resolved after 4 months of age. However, no neurodevelopmental abnormalities were noted in either infant.¹⁴²

Congenital Infection

The potential severe teratogenic consequences of acute ZIKV infection in pregnancy has been one of the most troubling aspects of the ZIKV pandemic. We currently have a better understanding of the spectrum of abnormalities that may occur in infants after ZIKV infection in pregnancy, which may range from mild to severe, but primarily affect the central nervous system. The CDC has since created the term “congenital Zika syndrome” (CZS) to refer to the infants most severely affected by ZIKV and typically includes those with a constellation of five distinctive findings: 1) severe microcephaly (>3 SD below the mean for gestational age and gender); 2) brain abnormalities (subcortical calcifications, ventriculomegaly, cortical thinning, gyral pattern anomalies, hypoplasia of the cerebellum, or corpus callosum anomalies); 3) ocular findings; 4) congenital contractures; 5) neurologic impairment.¹⁴³ (See Fig. 2 and Table 3) There are currently nearly 3500 infants with laboratory-confirmed CZS worldwide, the majority in Brazil.¹⁴⁴

One study of Brazilian infants with ZIKV microcephaly found that 93% of infants imaged had calcifications, 69% had cortical developmental malformations (lissencephaly, pachygyria, agyria), and 66% had ventriculomegaly due to brain atrophy.¹⁴⁵ Similar if not higher rates of brain abnormalities have been noted in other studies.¹⁴⁶ More detailed phenotypic spectrum of CZS, especially facial dysmorphisms from the Zika Embryopathy Task Force-Brazilian Society of Medical Genetics is also now available.¹⁴⁷ In addition, a recent case report of two infants has also highlighted ZIKV’s potential to cause severe spinal cord injury in CZS infants.¹⁴⁸ Severe congenital contractures such as arthrogryposis have been observed in 5.7–20.7% CZS cases and may sometimes lead to bilateral congenital hip or knee dislocations.^{143,146,149} Clubfoot has also been reported in 3.8–14% of CZS cases.¹⁴³ Sensorineural hearing loss has been reported in 6% of CZS infants with microcephaly.^{150,151} Eye abnormalities were reported in 35–46% to as high as 100% of infants with microcephaly and intracerebral calcification.^{146,152–158} Ophthalmic findings described included focal retinal pigment mottling, chorioretinal atrophy, optic-nerve changes, lens subluxation, loss of foveal reflex, iris colobomas, microphthalmia, cataracts, intraocular calcifications, and myopia among others.^{143,152–155,159,160} Results from our own studies of Brazilian infants with laboratory-confirmed ZIKV exposure in utero have found eye abnormalities in over 21% of infants, particularly optic nerve and retinal abnormalities, including in some infants who did not have other CNS abnormalities.¹⁶¹ The possibility of

an increased prevalence of congenital heart disease (13.5 % with septal defects) among CZS. Infants has been raised by one study,¹⁶² while another study has reported findings of unilateral diaphragm paralysis in some CZS infants.¹⁴⁶

While many of the longer-term outcomes of infants with CZS or *in utero*-ZIKV exposure are currently being investigated, some early studies have given us preliminary insight into some of the chronic problems that many of these infants suffer from including seizures, tremors, posturing, hypertonia with spasticity, severe irritability, and dysphagia.^{41,143,163} Other studies have reported postnatal hydrocephalus and abnormalities on sleep EEGs (in spite of a lack of clinically apparent seizures) in ZIKV infants with microcephaly.^{46,163,164} A summary of ZIKV-associated outcomes with frequencies of pregnancy outcomes and infant outcomes (eye, hearing, neurologic, motor/limb, and other problems) are well detailed in a recent review.¹⁶⁵ In addition, one study of nearly fifty Brazilian infants with probable CZS and all with abnormal neuroimaging reported that common chronic issues included irritability (85%), pyramidal/extrapyramidal syndrome (56%) including hypertonia, clonus, hyperreflexia, epileptic seizures (50%), dysphagia (15%) as well as orthopedic morbidities associated with congenital clubfoot (10%) and arthrogryposis (10%).¹⁶⁶ Follow-up of infants with CZS microcephaly has also suggested that dysphagia typically appears after 3 months of age and may often times be severe with a risk of aspiration.¹⁶⁷ Another report from CDC of 13 Brazilian infants with *in utero* ZIKV-exposure without microcephaly but with significant radiographical brain abnormalities (calcifications, ventriculomegaly, cortical atrophy, cortical malformations) demonstrated the importance of following head growth closely in these infants.¹⁶³ During their postnatal course, these infants had a decreasing rate in head circumference growth, and the majority (85%) were found to have postnatal microcephaly.¹⁶³ Additional recent work from Brazil has highlighted the notable case-fatality rates for infants with ZIKV microcephaly, which were as high as 8.3–10.5%.¹⁶⁸

Many ZIKV clinical questions remain to be answered including the potential for prior ZIKV Infection to affect future fertility, neurological outcomes of ZIKV-exposed infants without CZS, chronic morbidity and mortality of CZS infants, neurological sequelae and cognitive development of infants and young children infected with ZIKV postnatally, and the potential of clinically asymptomatic infants with *in utero* ZIKV exposure to months to years later develop adverse outcomes such as hearing and eye problems as well as developmental delay.¹⁶⁵ Some have also postulated whether ZIKV-exposure in pregnancy could be a risk factor for future behavioral-developmental or neuropsychiatric diseases such as ADHD, autism or schizophrenia.¹⁶⁵

Diagnosis, Management, Treatment, Prevention Brief Updates

Diagnosis: Currently, the mainstay of ZIKV diagnosis relies on methods including reverse transcriptase-polymerase chain reaction (RT-PCR) and serology (IgM) including neutralizing antibodies via plaque reduction neutralization test (PRNT).^{63,169} Since November 2016, the CDC has recommended that serum and urine be collected from all symptomatic individuals who present <14 days after onset of their symptoms in order test via ZIKV RNA RT-PCR.¹⁷⁰ Whole blood may also allow for prolonged detection of ZIKV

RNA compared to serum alone.^{170,171} Serology (serum ZIKV IgM testing) should be done if RT-PCR testing is negative.¹⁷⁰

For patients symptomatic for more than 2 weeks prior to evaluation (ie 14 days), it is recommended that serology for ZIKV IgM (typically the (MAC-ELISA) enzyme-linked immunosorbent assay IgM antibody testing) be used to diagnose infection up to 12 weeks after illness onset.^{63,170,172} This also includes the use of PRNT to evaluate for virus-specific neutralizing antibodies in paired serum samples, which may help distinguish cross-reactive antibodies from other flavivirus infections.^{63,170,172} Serology may be positive within the first week after symptom onset (possibly as early as 4–5 days) and be present for 8–12 weeks after.^{170,173} It should be noted that there also may be some benefit to sending serum as well as whole blood and urine for ZIKV RT-PCR testing even beyond the acute phase of illness of 2 weeks because some may remain positive longer than the typical 2 week acute period.¹⁷⁰ In fact, some recent studies have documented ZIKV RT-PCR positivity more than 2 months (up to 81 days) postinfection.¹⁷⁴

For congenital ZIKV infection, recommended laboratory tests include infant serum and urine collected for ZIKV RT-PCR as well as serum Zika IgM.⁴⁶ Of note, CSF can also be used to test for ZIKV RT-PCR, ZIKV IgM while amniotic fluid and placenta tissue can be used as alternative sources to test for ZIKV RT-PCR in newborns.^{63,175}

Immunohistochemical (IHC) staining can be done to look for ZIKV antigens and RT-PCR can also be done on fixed tissues.⁶³ Cord blood testing is not recommended given risks for false positive results.⁴⁶ *Please refer to the CDC website for further detail.*

Management, Treatment, Prevention: In the vast majority of patients, acute ZIKV Infection in adults and children tends to be mild and symptoms tend to resolve within 1 week.⁶⁹ At present, there are no specific ZIKV therapies approved for use. Management of acute ZIKV Infection relies on supportive care.^{69,77} Of note, nonsteroidal anti-inflammatory drugs (NSAIDS) are not recommended until dengue virus is ruled out given overlap in presentation of ZIKV and dengue, which may pose a risk of hemorrhagic complications.⁶⁹

Management of Infants with Congenital ZIKV Infection: In August 2016, the CDC revised their definitions of infants with CZS to include those beyond that with only microcephaly and/or intracranial calcifications with additional CDC recommendations for management of infants with congenital Zika infection released in October 2017.^{46,69,176} Recommendations depend on whether infants are born to women with maternal ZIKV exposure, laboratory confirmed ZIKV infection and/or abnormalities consistent with CZS. All infants with in utero ZIKV exposure should have a comprehensive physical exam at birth as well as a postnatal head ultrasound, vision screening, and hearing screen, preferably an automated auditory brainstem response (ABR) test.^{46,177} For those with laboratory-confirmed ZIKV infection but no abnormalities on exam, infants should also have both an ophthalmologic exam and hearing screen including an ABR prior to 1 month of age.^{46,177} Normal appearing infants with negative ZIKV lab testing should continue routine newborn care.¹⁷⁷ However, we would suggest that exposed infants also have an ophthalmologic retinal exam, given findings of our recent study as described above.¹⁶¹

Infants with CZS should have a complete blood count and a metabolic panel including liver function tests, an ophthalmologist examination, an ABR hearing evaluation, and consideration for additional neuroimaging as well as evaluation for other genetic conditions and congenital infections. Feeding difficulties, sleeping, and irritability issues are common. Repeat evaluation for hypothalamic dysfunction and pituitary insufficiency, ophthalmologic exams, and ABR hearing evaluations are recommended as well as close monitoring of growth and development.¹⁷⁷ Creation of medical homes,¹⁶⁵ which offer multidisciplinary support to patients and their families, are also important as follow-up by specialists in neurology, infectious diseases, ophthalmology, audiology, early intervention and developmental specialists, physical therapy as well as sometimes GI, orthopedics, and endocrinology are often required.⁴⁶ *Further information is available on the CDC website.*

Prevention: Prevention of mosquito bites when living or traveling in regions with active ZIKV transmission is the best defense at this time. Barrier methods and insect repellents (DEET, picaridin, oil of lemon eucalyptus,) remain key components of ZIKV protection. DEET (max 30% concentration) has been the most widely tested repellent which is considered safe for usage in children 2 months of age or older.^{178,69} www.cdc.gov/zika/prevention Sexual transmission of ZIKV has also been reported even from asymptomatic carriers.^{62,179,180} ZIKV has been detected in the semen up to 80–188 days after symptom onset and for as many as 14 days in vaginal secretions.^{181–184}¹⁷⁴ Thus, it is currently recommended to practice safe sexual practices (abstaining from sexual activity or use of condoms) for at least 6 months after returning from travel from regions with circulating ZIKV for males and at least 8 weeks for females.^{56,180,185,678,185,186} The effects of ZIKV on future fertility are unknown at this time.¹⁸⁷ While ZIKV has been recovered from breastmilk,^{69,188} only one possible suspected case of postnatal ZIKV transmission breastfeeding has been reported thus far in a 5-month old infant in Venezuela.^{189,190} At this time, the CDC continues to support breastfeeding for ZIKV-infected mothers currently living in regions with active ZIKV transmission.⁶⁹ Standard precautions continue to be recommend in the care of those with ZIKV Infection.¹⁹¹ It should be noted that there was one case of secondary nonsexual ZIKV transmission possibly through mucocutaneous contact with sweat or tears of a ZIKV-infected patient with high levels of ZIKV viremia.^{134,192}

Future Vaccines and Therapeutics: Currently, there are no available licensed vaccines or drugs for the prevention or treatment of ZIKV. Multiple vaccine candidates (>40) are in preclinical phases of development and/or testing phases.^{193–195,193,196,30,196–198} Among these, the NIAID ZIKV DNA vaccine had already begun phase I clinical trials in 2016 and has advanced to phase II clinical trials as of March 2017.^{195,198–200} Some strategies that have been used to expedite drug development in ZIKV have focused on repurposing drugs by screening other FDA-approved drugs for ZIKV activity.^{201,202,203,204}

Conclusion

While the escalation in the number of ZIKV cases has subsided, particularly in Latin America and the Caribbean, it is clear the ZIKV will remain a continued global health threat for years to come with active transmission in many regions around the world. Yet, it should

be remembered that the ZIKV pandemic of 2015–16 has left tremendous societal and economic costs in its aftermath. Many of the world's poor, living in primarily urban regions in Latin America and the Caribbean, are currently struggling to care for thousands of infants with congenital ZIKV syndrome, who comprise a new generation of medically complex children.^{205206,207}

Acknowledgments

Financial Support and Sponsorship: Kristina Adachi was supported in part by grant 20164370 from the Thrasher Research Fund.

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Summary Points

- Zika virus, a mosquito-borne flavivirus, has emerged as an important new cause of congenital infections and neurologic complications such as Guillain Barre Syndrome (GBS).
- While new cases of Zika virus in the Americas have declined dramatically in 2017 compared to 2016, transmission of Zika virus will likely continue.
- Given changes in guidelines for screening asymptomatic US pregnant women, it will be even more critical for providers to understand how to appropriately identify and manage infants with or at risk for congenital Zika virus infection.
- To understand the continuously evolving Zika travel risk factors, testing, and management updates, the CDC website remains the best available resource.
<https://www.cdc.gov/zika/index.html>

Figure 1. Clinical Manifestations of Zika virus⁵²

Panel A shows a maculopapular rash on the face; Panel B, conjunctival and palpebral erythema; Panel C, retroauricular lymphadenopathy; Panel D, conjunctival injection with prominence of vasculature; Panel E, a rash on the legs, with a lacy reticular pattern; Panel F, a maculopapular rash on the inner arm; Panel G, edema of the foot, which the patient reported was painful; and Panel H, a blanching macular rash on the gravid abdomen. Source: Brasil P, Pereira JP, Jr., Raja Gabaglia C, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro – Preliminary Report. *The New England journal of medicine* 2016.

Figure 2. Neuroimaging and Classic Sequelae Seen in Congenital ZIKV Syndrome ⁴¹

MRI images of cranial facial disproportion with microcephaly. Diffuse reduction in white matter thickness with corpus callosum not identified. Diffuse pachygyria, more evident in the right parietal lobe. Supratentorial ventricular dilatation. Atrophy of the cerebellar vermix with ample communication of the fourth ventricle with the cisterna magna. Widening of the perivascular spaces of the cerebellar hemispheres, with surrounding gliosis. Panel I, disproportionate microcephaly; Panel J, arthrogryposis at birth; Panel K, redundant scalp; Panel L shows a cortical thumb; Panel M, knee fovea; and Panel N, shows the left infant retina demonstrating optic disc hypoplasia, peripapillary atrophy; macular chorioretinal atrophy with a colobomatous- like aspect with hyperpigmented halo and pigmentary mottling. Source: Brasil P, Pereira JP, Jr., Moreira ME, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro. *The New England journal of medicine*. 2016;375(24):2321–2334.

Table 1

Key Clinical Features of ZIKV Compared to Dengue and Chikungunya

Features	Zika	Dengue	Chikungunya
Fever	+ to ++	+++	+++
Maculopapular Rash	+++	+	++
Pruritus	++	−/+	−/+
Conjunctivitis	++	−	+/−
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Facial Edema	+/−	++	+
Palatal Petechiae	+/−	++	+
Hemorrhage	−	++	−
Shock	−	+	−

The table compares classic clinical features of the three arboviruses: ZIKV, dengue, and chikungunya. Source: Primarily adapted from a CDC Presentation Reference for Clinicians.⁶³ Rabe, Ingrid “Zika Virus-What Clinicians Need to Know?” presentation, Clinician Outreach and Communication Activity (COCA) Call, Atlanta, GA, January 26, 2016. With similar tables also noted in ^{64,65}

* Please note that one study of all 3 viruses of patients in Nicaragua suggested more similarities among the 3 viruses with regards to fever, conjunctivitis, arthralgia, headache.⁶⁶

Table 2**Reported Rare Complications of Acute Zika Infection**

Neurologic Complications	
•	Guillain Barre Syndrome (GBS)
•	Acute sensory polyneuropathy
•	Myelitis including ADEM
•	Meningoencephalitis
•	Encephalopathy
•	Neuropsychiatric changes
<hr/>	
Other Rare Complications	
•	Temporary hearing impairment
•	Dysguesia
•	Eye abnormalities
–	Uveitis, hypertensive iridocyclitis, acute maculopathy, acute chorioretinitis
•	Genitorurinary abnormalities
–	hematospermia, prostatitis
•	Myocarditis
•	Positive ANA
•	Hemorrhagic complications
–	Thrombocytopenia
–	Hematomas, mucosal bleeding
–	Disseminated intravascular coagulation
•	Death

Table 3**Summary of Features of Infants with Congenital Zika Syndrome**

<p>Congenital Zika Syndrome (CZS) Classic Features</p> <ul style="list-style-type: none"> • Severe microcephaly <ul style="list-style-type: none"> – >3 SD below the mean for gestational age and gender • Severe brain abnormalities <ul style="list-style-type: none"> – Subcortical calcifications – Ventriculomegaly – Cortical thinning – Gyral pattern anomalies – Hypoplasia of the cerebellum – Corpus callosum anomalies • Ocular abnormalities <ul style="list-style-type: none"> – Retinal mottling, chorioretinal atrophy, optic-nerve changes, lens subluxation, colobomas, microphthalmia, cataracts, etc • Congenital contractures <ul style="list-style-type: none"> – Arthrogryposis – Hip and knee dislocations • Severe neurologic impairment 	<p>Other Reported Findings</p> <ul style="list-style-type: none"> • Sensorineural hearing loss • Seizures, tremors • Posturing, hypertonia, hyperreflexia, spasticity • Severe irritability • Dysphagia and may include aspiration risks • Club foot • Postnatal microcephaly • Death
<p>Other Rare Findings</p> <ul style="list-style-type: none"> • Severe spinal cord injury • Unilateral diaphragm paralysis • Possible increased rates of congenital heart disease (septal defects) 	