

Zika Update

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DISCLOSURE INFORMATION

AMERICAN COLLEGE OF OSTEOPATHIC INTERNISTS CONVENTION
DESERT SPRINGS, CALIFORNIA

I have no financial relationships to disclose.

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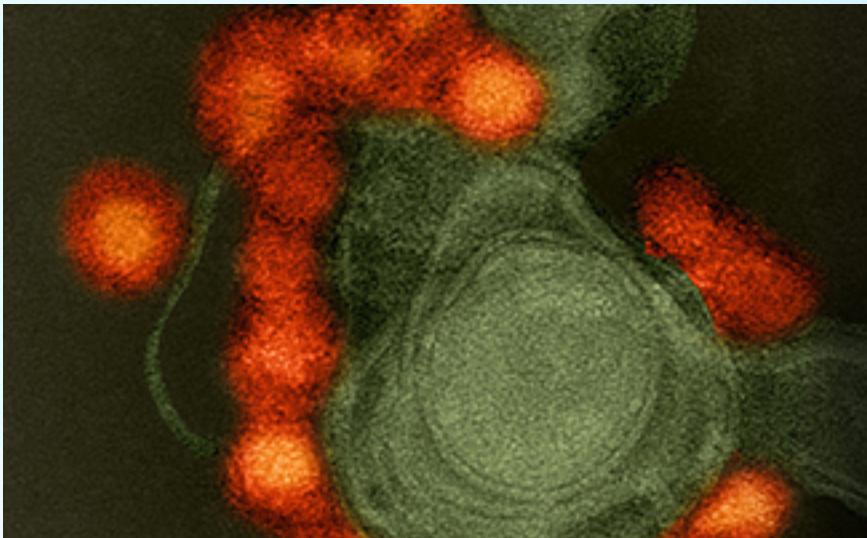
Outline

- **Overview**
- **Epidemiology**
- **Clinical Course and Disease Outcomes**
- **Clinical Guidance**
- **Diagnostics**
- **Prevention**
- **Vaccine Development**
- **Clinical Resources**

Zika Virus (ZIKV) Overview

ZIKV

- **Single stranded RNA virus**
- **Genus *Flavivirus*, family *flaviviridae***
- **Closely related to dengue, yellow fever, Japanese encephalitis (JEV), and West Nile virus (WNV)**



Transmission electron microscope image of negative-stained, Fortaleza-strain ZIKV (red), isolated from a microcephaly case in Brazil.

Photo Credit: www.niaid.nih.gov

Modes of Transmission

- **Bite from an infected *Aedes* species mosquito**
 - *Ae. aegypti* and *Ae. albopictus*
- **Maternal-fetal**
 - Intrauterine
 - Perinatal
- **Sexual transmission from ANY infected partner**
- **Laboratory exposure**
- **Probable: blood transfusion**



Vector Characteristics

Characteristic



Aedes aegypti



Aedes albopictus

Time of Blood Meal	Bite during the day and night
Number of Blood Meals	Multiple (<i>Ae. aegypti</i>), single (<i>Ae. albopictus</i>)
Preferred Host(s)	Humans (<i>Ae. aegypti</i>), humans and other mammals (<i>Ae. albopictus</i>)
Preferred Site to Lay Eggs	Containers of standing water (<i>i.e.</i> , tires, flower pots)
Vector-borne Diseases	Dengue, yellow fever, chikungunya, ZIKV
Environment	Urban (<i>Ae. aegypti</i>), urban and rural (<i>Ae. albopictus</i>)


- **Anthropophilic and anthropophagic**

Estimated Potential Range of ZIKV Vectors, United States



 *Aedes aegypti*



 *Aedes albopictus*

Incubation Period, Viremia, and Transmissibility

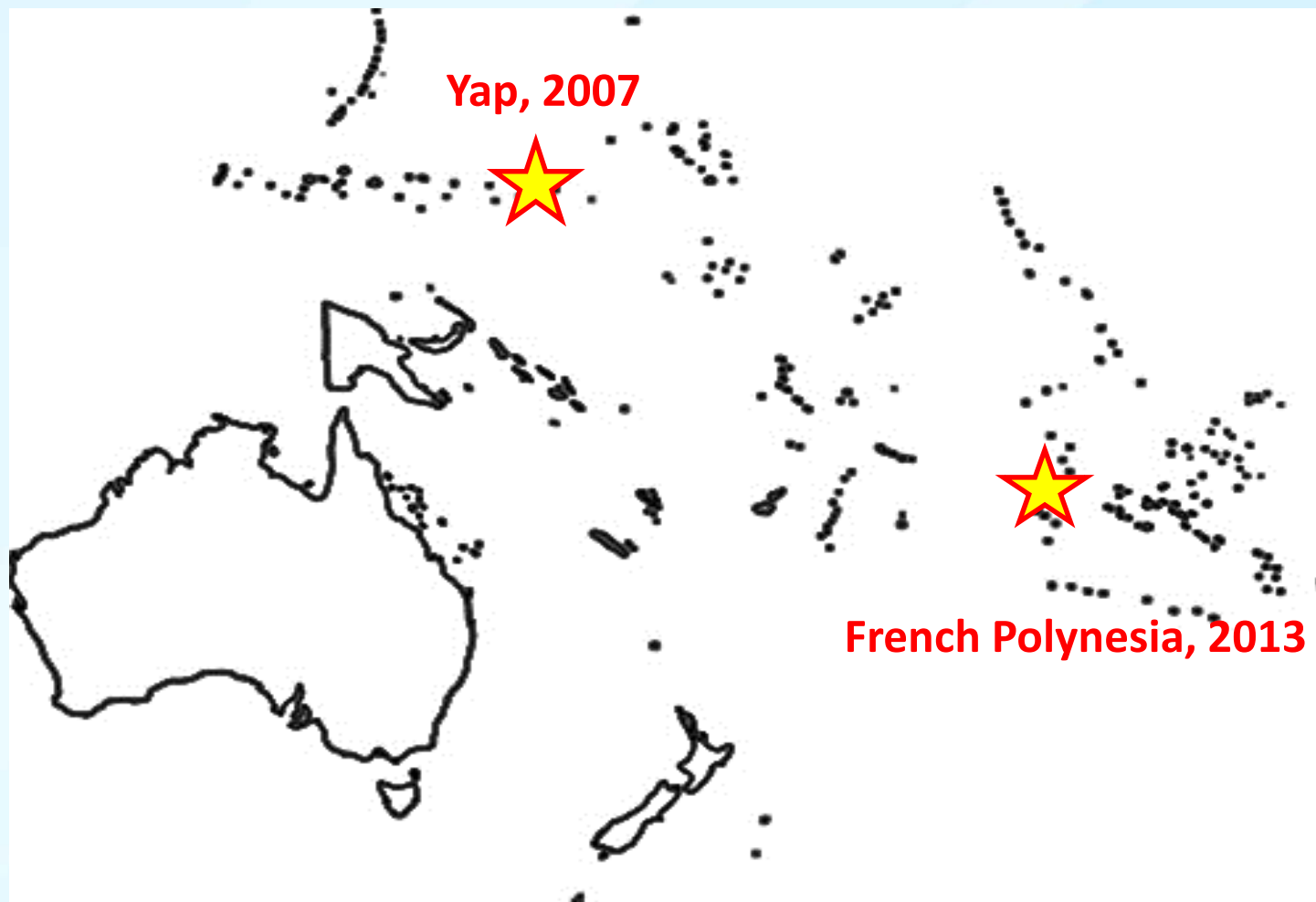
- **Incubation period: 3–14 days**
- **Viremia: few days–1 week**
- **Virus can be shed in semen and urine after viremia has resolved**
 - Viral RNA has been detected in semen as long as 188 days after illness onset
 - Duration of transmissibility not established
 - To date, cases of sexual transmission have involved exposure within a few weeks of illness onset

ZIKV Epidemiology

Where was ZIKV Discovered?



Where were the Previous Reported ZIKV Outbreaks?



<http://www.who.int/emergencies/zika-virus/timeline/en/>

Oehler E, et al. Zika virus infection complicated by Guillain-Barre syndrome — case report, French Polynesia, December 2013. *Euro Surveill*, 2014;19(9).

Cauchemez S, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15. *Lancet*, 2016;387(10033):2125-2132.

ZIKV Lineages

- **2 distinct lineages**
 - African
 - Asian
- **Despite being genetically distinct, all strains are the same serotype**
 - Identical surface antigens
 - Antibodies elicited after infection with the Asian lineage potently inhibit both Asian and African lineage strains in vitro

ZIKV Detected in the Americas (2015–2016)



Brazil, 2015

Countries and Territories with Active ZIKV Transmission: AMERICAS (current as of October 19, 2016)

- Anguilla
- Antigua and Barbuda
- Argentina
- Aruba
- The Bahamas
- Barbados
- Belize
- Bolivia
- Bonaire
- Brazil
- British Virgin Islands
- Cayman Islands
- Colombia
- Costa Rica
- Cuba
- Curaçao
- Dominica
- Dominican Republic
- Ecuador
- El Salvador
- French Guiana
- Grenada
- Guadeloupe
- Guatemala
- Guyana
- Haiti
- Honduras
- Jamaica
- Martinique
- Mexico
- Nicaragua
- Panama
- Paraguay
- Peru
- Puerto Rico
- Saba
- Saint Barthélemy
- Saint Lucia
- Saint Martin
- Saint Vincent and the Grenadines
- Saint Eustatius
- Saint Maarten
- Saint Kitts and Nevis
- Suriname
- Trinidad and Tobago
- Turks and Caicos
- United States
- U.S. Virgin Islands
- Venezuela

Countries and Territories with Active ZIKV Transmission: OUTSIDE THE AMERICAS

(current as of October 19, 2016)

■ Oceania/Pacific Islands

- American Samoa
- Fiji
- Kosrae, Federated States of Micronesia
- Marshall Islands
- New Caledonia
- Papua New Guinea
- Samoa
- Tonga

■ Africa

- Cape Verde

■ Asia

- Singapore

Novel Genetic Findings

- **Molecular clock phylogeny suggests ZIKV arrived to the Americas between May–December 2013**
- **Current epidemic strains are more closely related to the Asian lineage**
- **Significant change in amino acid and nucleotide sequences in the past 50 years**
 - All strains from the Americas have 99% nucleotide homology
- **Virus pre-membrane precursor protein has high variability**
 - Variability contributes to significant structural change
 - May partially explain the capacity to spread through the Americas

Wang, L, et al. From Mosquitos to Humans: Genetic Evolution of Zika Virus. *Cell Host and Microbe*, 2016; 19(5):561-565.

Faria NR., et al. Zika virus in the Americas: Early Epidemiological and genetic findings. *Science*, 352(6283):345-349.

Lanciott RS, Lambert AJ, Holodniv M, Saavedra S, del Carmen Castillo Signor L. Phylogeny of Zika virus in Western Hemisphere. *Emerg Infect Dis*, 2016.

Zika by the Numbers (as of October 20, 2016): WORLDWIDE

- **67 countries (since 2015)**

Characteristic	Countries (n)
Reported evidence of person-to-person transmission (sexual)	12
Reported evidence of microcephaly or other CNS malformation potentially associated with ZIKV or suggestive of congenital infection	23
Reported increased incidence of Guillain-Barré (GBS) or confirmed ZIKV in the setting of GBS	19

Zika by the Numbers (as of October 19, 2016):



US STATES



Case Classification	n
Locally acquired mosquito-borne cases	137
Travel-associated cases	3,878
Laboratory acquired cases	1
TOTAL	4,016

Zika by the Numbers (as of October 19, 2016):



US STATES



Special Classification (n=4,016)	n
Sexually-transmitted	32
Guillain-Barré syndrome	13
Pregnant women*	899
Liveborn infants with birth defects*	23
Pregnancy losses with birth defects*	5

Zika by the Numbers (as of October 19, 2016):



US STATES



State	Travel-associated cases n (%) (N=4,016)	Locally acquired cases n (%) (N=137)
Florida	708 (18)	137 (100)
New York	884 (23)	0 (0)
California	296 (8)	0 (0)
Texas	231 (6)	0 (0)

Zika by the Numbers (as of October 19, 2016): US TERRITORIES

Case Classification	n
Locally acquired mosquito-borne cases	27,314*
Travel-associated cases	88
Laboratory acquired cases	0
TOTAL	27,402

*26,798 (98%) are in Puerto Rico

Zika by the Numbers (as of October 19, 2016): US TERRITORIES

Special Classification (n=27,402)	n
Sexually-transmitted	N/A
Guillain-Barré syndrome	40
Pregnant women*	1,927
Liveborn infants with birth defects*	1
Pregnancy losses with birth defects*	1

Zika Disease Clinical Course and Outcomes

Zika Virus Infection Clinical Course

- **Clinical illness is usually mild**
- **Many infections are asymptomatic**
- **Symptoms last several days to a week**
- **Severe disease requiring hospitalization is uncommon**
- **Fatalities are rare**

Symptoms

■ Most common symptoms

- Acute onset of fever
- Maculopapular rash
- Joint pain
- Conjunctivitis

■ Other symptoms

- Muscle pain
- Headache



Differential Diagnosis

- **Based on typical clinical features, the differential diagnosis for Zika infection is broad**
 - Dengue
 - Chikungunya
 - Leptospirosis
 - Malaria
 - Rubella
 - Measles
 - Parvovirus
 - Enterovirus
 - Adenovirus
 - Other alphaviruses (*e.g.*, Mayaro, Ross River, Barmah Forest, o'nyong-nyong, Sindbis viruses)

Clinical Features: ZIKV Compared to Dengue and Chikungunya

Clinical Feature	ZIKV	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	++	++
Conjunctivitis	++	-	-
Arthralgia	++	++	+++
Myalgia	+	+++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

Adapted from Rabe, Ingrid MBChC, Mmed “Zika Virus-What Clinicians Need to Know?” (presentation, Clinical Outreach and Communication Activity (COCA) call, Atlanta, GA, January 26 2016)

Cobra C, et al. Symptoms of dengue fever in relation to host immunologic response and virus serotype, Puerto Rico, 1990-1991. *Am J Epid*, 1995; 142(11):1204.

ZIKV and Guillain-Barré Syndrome (GBS)

- **CDC research suggests a temporal and geographic relationship between GBS and ZIKV**
- **French Polynesia (2013):**
 - 38 cases of GBS occurred among an estimated 28,000 persons
 - Case-control study revealed a strong association (OR >34) between GBS and previous Zika infection
- **Case series from 7 countries (2015–2016)**
 - Increase in incidence of GBS between 100–877%
- **Brain ischemia, meningoencephalitis, and acute myelitis complicating Zika virus infection also have been reported**

Dirlikov E, et al. Guillain-Barre Syndrome During Ongoing Zika Virus Transmssion-Puerto Rico. *MMWR*, 2016; 65(34):910-914.

Oehler E, et al. Zika virus infection complicated by Guillain-Barre syndrome — case report, French Polynesia, December 2013. *Euro Surveill*, 2014;19(9).

Cao-Lormeau VM, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*, 2016; 387(10027):1531-9.

Dos Santos T, et al. Zika Virus and the Guillain-Barre Syndrome — Case Series from Seven Countries. *N Eng J Med*, Letter to the Editor, August 31, 2016.

Carteaux G, et al. Zika virus associated with meningoencephalitis. *N Engl J Med*, 2016;374:1595-1596.

Mécharles S, et al. Acute myelitis due to Zika virus infection. *Lancet* 2016; 387(10026):1481.

ZIKV in Pregnancy

- **Incidence of Zika virus infection in pregnant women is not known**
- **Infection can occur in any trimester**
- **No evidence of more severe disease compared with non-pregnant women**
- **No evidence of increased susceptibility**

CDC, *CDC Health Advisory: Recognizing, Managing, and Reporting Zika Virus Infections in Travelers Returning from Central America, South America, the Caribbean and Mexico*, 2016.

Besnard M, et al. Evidence of Perinatal Transmission of Zika Virus, French Polynesia, December 2013 and February 2014. *Euro Surveill*, 2014. 19(14):1-5.

Oliveira Melo A, et al. Zika Virus Intrauterine Infection Causes Fetal Brain Abnormality and Microcephaly: Tip of the Iceberg? *Ultrasound in Obstetrics & Gynecology*, 2016. 47(1):6-7.



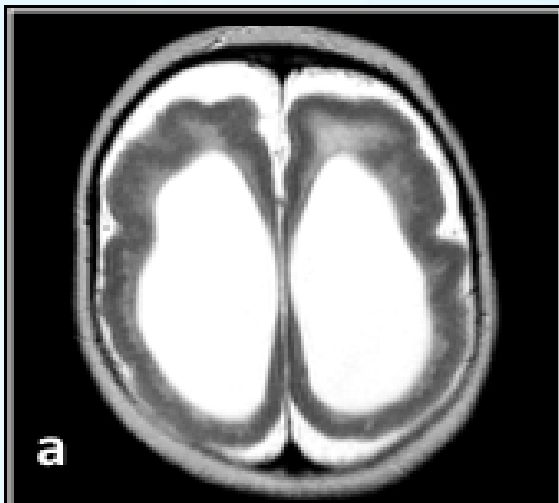
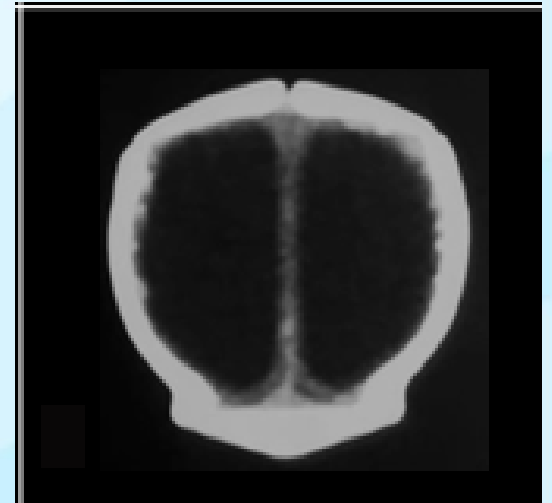
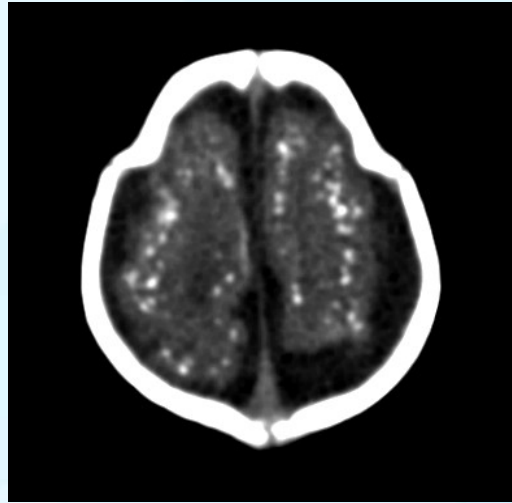
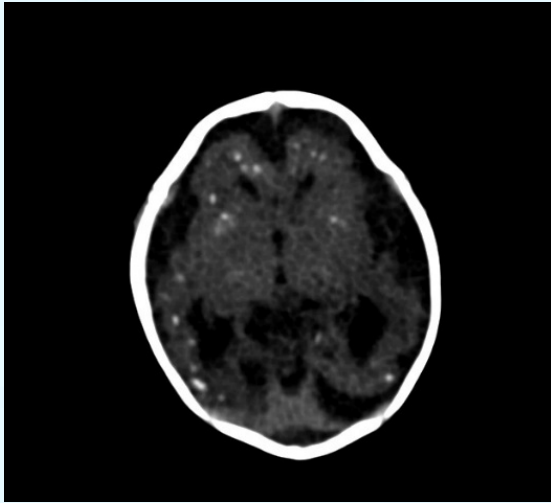
Case Definition of Microcephaly

- **Definite congenital microcephaly for live births**
 - Head circumference (HC) at birth $< 3^{\text{rd}}$ percentile for gestational age and sex
 - If HC at birth is not available, HC $< 3^{\text{rd}}$ percentile for age and sex within the first 2 weeks of life
- **Definite congenital microcephaly for still births and other pregnancy losses**
 - Postnatal HC $< 3^{\text{rd}}$ percentile for gestational age and sex
 - Prenatal HC > 3 SD below the mean on prenatal ultrasound

Congenital Zika Syndrome

- **Microcephaly**
- **Intracranial calcifications**
- **Other brain anomalies (ventriculomegaly, hydrocephalus, atrophy, etc)**
- **Eye anomalies**
- **Other anomalies (club foot, contractures)**

Congenital Zika Syndrome Brain Anomalies



ZIKV and Ocular Findings

- **Case series of 29 infants with microcephaly born to mothers with Zika virus infection during pregnancy**
 - Ocular abnormalities were found in 10/29 (34.5%)
 - 7/10 (70%) infants had bilateral disease
 - 11/17 (65%) affected eyes had focal pigment mottling of the retina and chorioretinal atrophy
 - 8/17 (47%) affected eyes had optic nerve abnormalities
- **Infants with possible congenital Zika virus infection should be screened for eye disease**

de Paula Freitas B, 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.

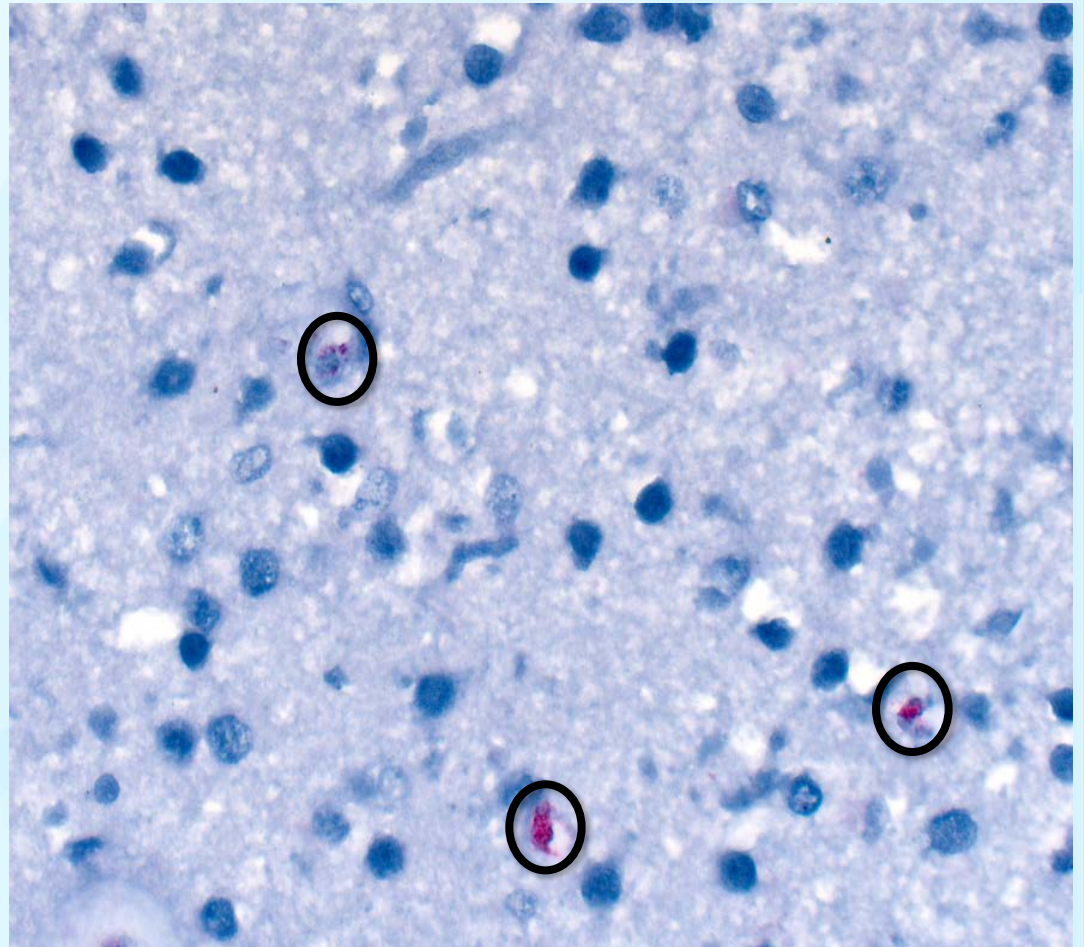
Staples JE, et al. Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection — United States, 2016. *MMWR*, 2016; 65:63–67.

Adverse Outcomes and ZIKV

- **Linked to miscarriage and stillbirth**
 - Evidence insufficient to confirm ZIKV as cause
- **Problems related to brain injury**
 - Eye abnormalities
 - Hearing impairment
 - Seizures
 - Swallowing impairment
 - Limb abnormalities
 - Severe irritability
 - Developmental delay
 - Growth abnormalities

Confirmation of ZIKV in Fetal Tissues

- **ZIKV identified in**
 - Amniotic fluid
 - Placenta
 - Brain
 - Products of conception

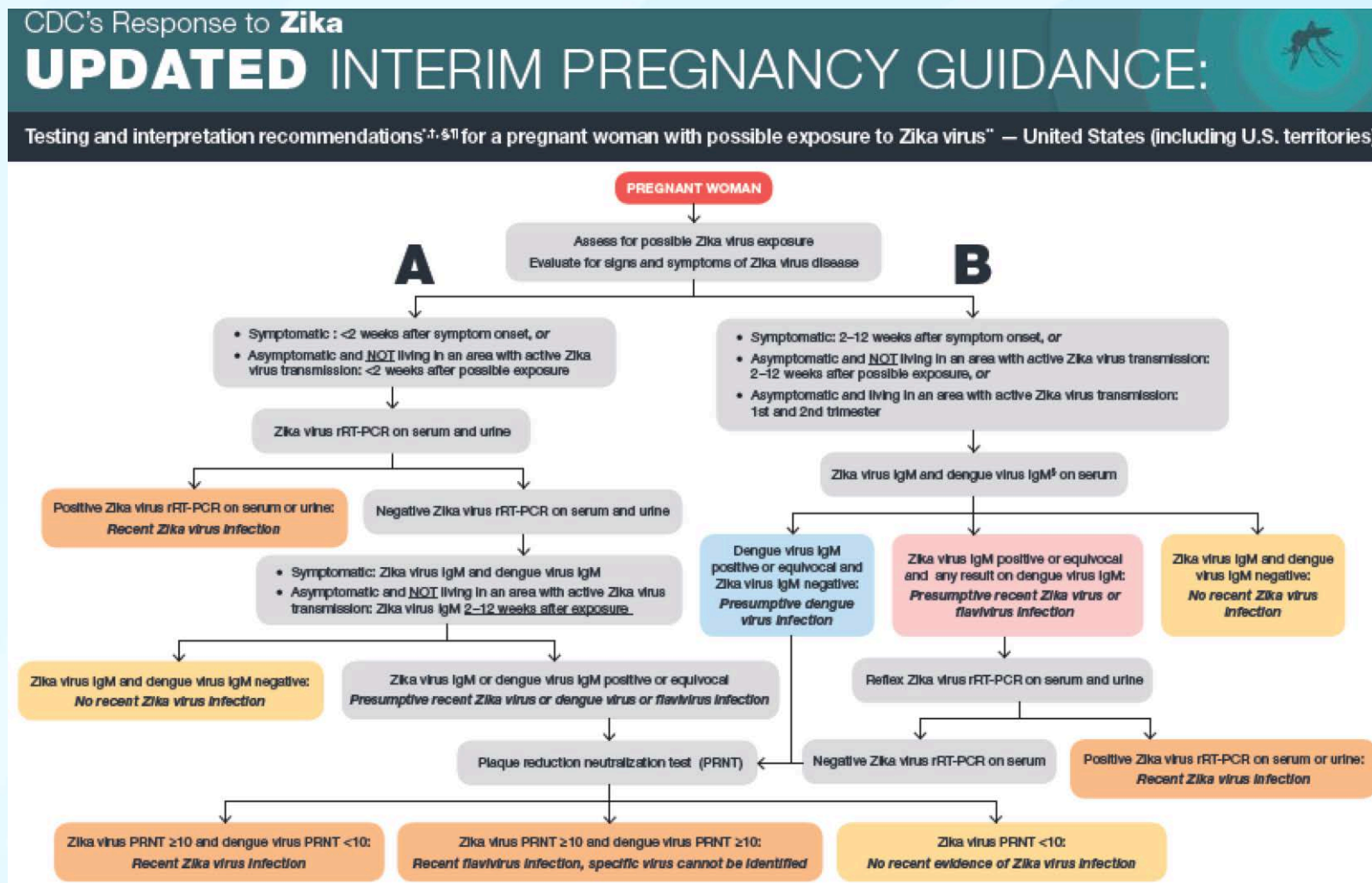


(CDC lab, Brazil clinical specimens)

Digitally-colored transmission electron micrograph (TEM) of Zika virus. Virus particles, here colored red, are 40 nm in diameter, with an outer envelope, and an inner dense core.

Zika Virus Infection Clinical Guidance

Guidance for Health Care Providers Caring for Pregnant Women with Possible ZIKV Exposure



Clinical Management of Positive or Inconclusive ZIKV Testing Results During Pregnancy

■ Antepartum

- Consider serial ultrasounds every 3–4 weeks
- Referral to maternal-fetal medicine specialist

■ Postpartum

- Histopathology of the placenta and cord
- Frozen placental tissue and cord tissue for ZIKV RNA

ZIKV and Immunocompromised Persons

- **Information is lacking on whether the risk for Zika virus infection or the severity of illness is different for people with HIV infection or other causes of immune suppression**
- **3 cases of ZIKV in HIV-infected adults (Brazil) to date**
 - Mild illnesses
- **Close clinical monitoring of HIV-infected patients with ZIKV should be considered**

Calvet GA, Filippis AM, Mendonca MC, et al. First detection of autochthonous Zika virus transmission in a HIV-infected patient in Rio de Janeiro, Brazil. *J Clin Virol* 2016;74:1-3.

Timerman A. Zika and HIV: Connecting the Science. [IASONEVOICE Stories](#) 2016 Accessed September 13, 2016.

ZIKV Diagnostics

Diagnostic Testing for Symptomatic Individuals for ZIKV

- **Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) for viral RNA in serum and urine specimens (possibly CSF or amniotic fluid) collected < 14 days after illness onset**
- **Serology for ZIKV IgM in serum (possibly CSF) collected ≥ 14 after illness onset**
- **Plaque reduction neutralization test (PRNT) for confirmation of virus-specific neutralizing antibodies in paired serum samples**
- **Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues**

Serology Cross-reactions with Other Flaviviruses

- **ZIKV IgM can be positive due to antibodies against related flaviviruses (*e.g.*, dengue and yellow fever viruses)**
- **Neutralizing antibody testing may discriminate between cross-reacting antibodies in primary flavivirus infections**
- **Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus**
- **Healthcare providers should work with state and local health departments to ensure test results are interpreted correctly**

Laboratories for Diagnostic Testing

- **Testing is performed at CDC, select commercial labs, and a few state health departments**
 - CDC is working with commercial labs to expand testing
- **Healthcare providers should contact their state, local, or territorial health department to facilitate diagnostic testing**

Zika Reporting

- **Zika virus disease and Zika virus infection without disease, including congenital Zika virus infection, are nationally notifiable conditions**
- **Report all cases to your state, local, tribal, or territorial health department**



Zika Pregnancy Registries

- **CDC established the US Zika Pregnancy Registry to collect information and learn more about pregnant women/infants with Zika virus infection**
 - Zika Active Pregnancy Surveillance System in Puerto Rico
- **Data collected will be used to update recommendations for:**
 - Clinical care
 - Services for pregnant women and families
 - Prevention of Zika virus infection during pregnancy
- **If you are a healthcare provider & have registry questions, please email or call 770-488-7100 (ask for the Zika Pregnancy Hotline). For other questions, call 800-CDC-INFO**

Zika Virus Infection Prevention

Recommendations for Prevention of Sexual Transmission

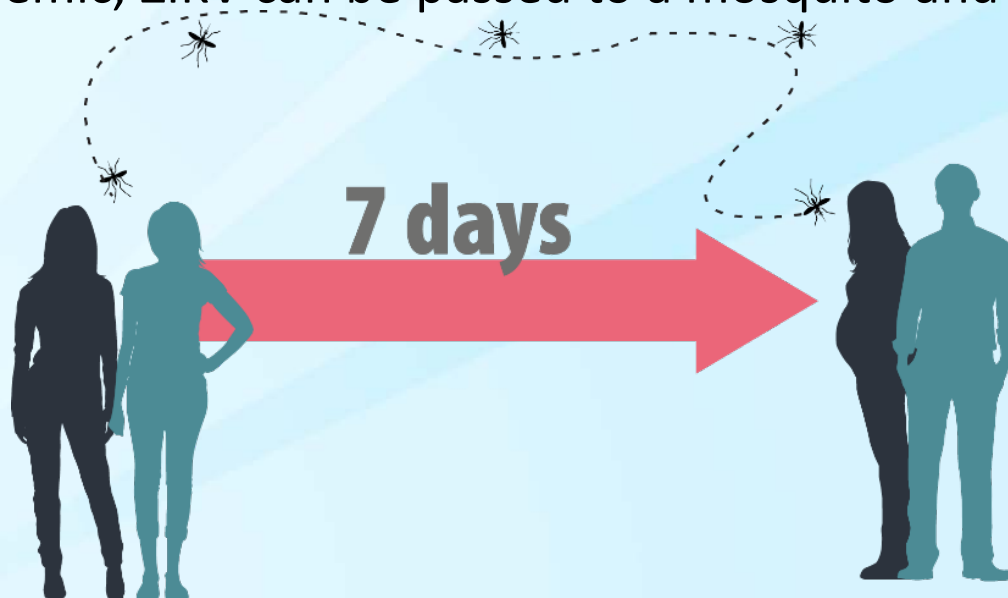
- **Couples in which a woman is pregnant**
 - Use condoms or abstain from sex throughout pregnancy
- **Couples who are not pregnant and one or both partners have traveled to or live in an area with ZIKV**
 - Use condoms (male or female) or abstain from sex (vaginal, anal, oral, and sharing of sex toys) as follows:
 - Men: At least 6 months after symptom onset or last possible exposure (if asymptomatic)
 - Women: At least 8 weeks after symptom onset or last possible exposure (if asymptomatic)

Mosquito Bite Protection

- **Wear long-sleeved shirts and long pants**
- **Stay and sleep in places with air conditioning, when possible, and use window and door screens to keep mosquitoes outside**
- **Take steps to control mosquitoes indoors and outdoors**
- **Personal protection:**
 - Use EPA-registered insect repellents with either DEET, picaridin, IR3535, or oil of lemon eucalyptus (OLE), 2-undecanone, or para-menthane-diol (PMD) and follow label directions
 - OLE and PMD should not be used in children <3 years
 - Apply sunscreen before insect repellent

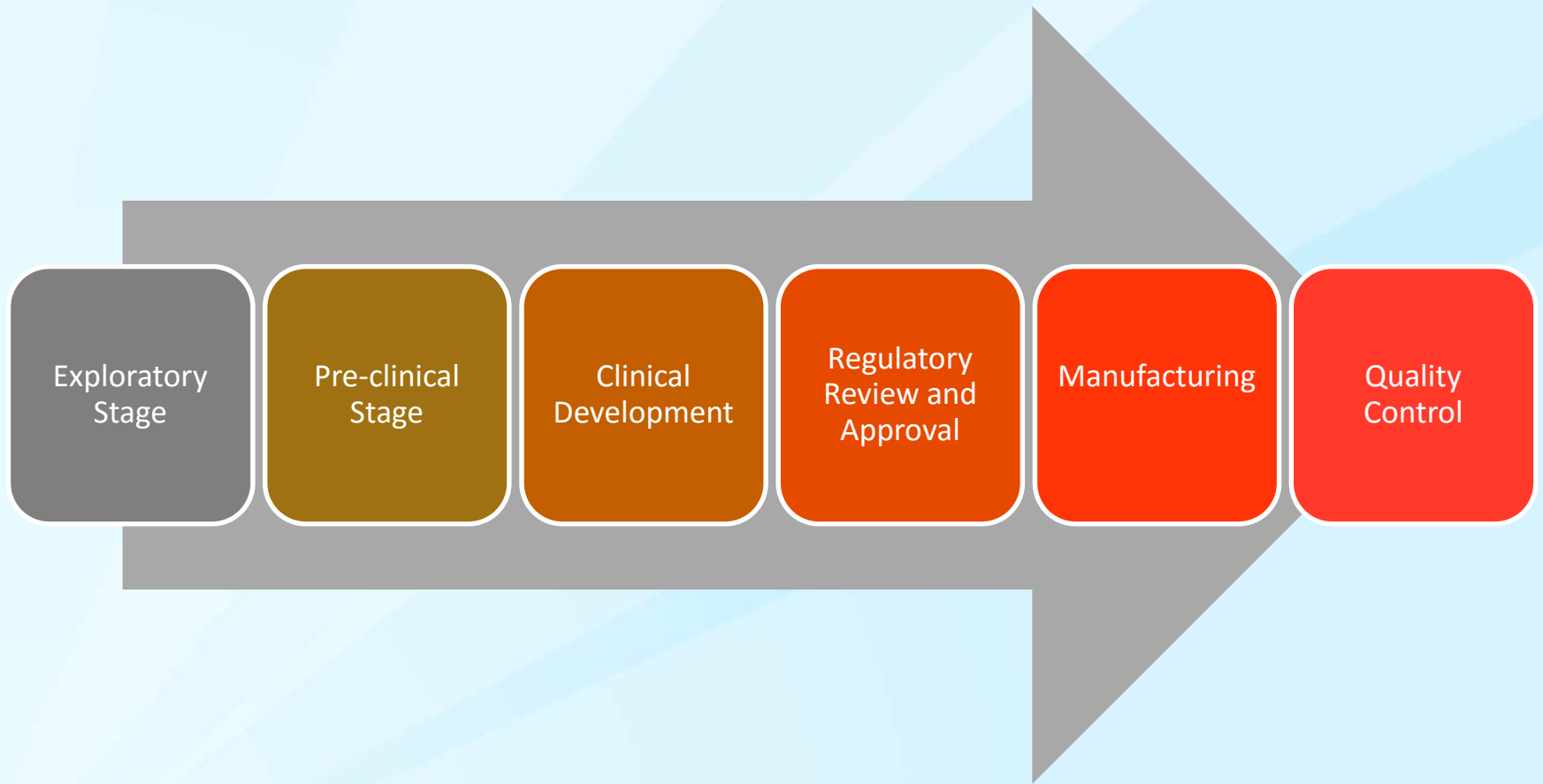
What People Infected with ZIKV or Possibly Exposed to ZIKV can do to Protect Others

- **Protect from mosquito bites for 3 weeks after leaving a Zika-affected area when ZIKV can be found in the blood**
 - 3 weeks = Incubation week + viremic week
 - When viremic, ZIKV can be passed to a mosquito and to others



ZIKV Vaccine Development

Stages in the Development of a New Vaccine



Stages in the Development of a New Vaccine



NIH/NIAID ZIKV Vaccine Candidates

- **DNA-based vaccine**
 - Similar to an investigational vaccine for WNV
 - Phase 1 clinical trial underway
- **Live-attenuated vaccine**
 - Building on a similar vaccine approach for dengue virus
 - Dengue vaccine: safe and immunogenic in early-phase trials; being evaluated in a large Phase III study in Brazil

NIH/NIAID Vaccine Candidates

- **Genetically engineered version of vesicular stomatitis virus (VSV)**
 - VSV: successfully used in an investigational Ebola vaccine
 - Plans to evaluate the ZIKV vaccine in tissue culture/animal models
- **Whole-particle inactivated vaccine**
 - Based on a similar approach used by the Walter Reed Army Institute of Research for JEV and dengue viruses

Zika Virus Infection Clinical Resources

CDC Consultation Service


- CDC maintains a 24/7 consultation service for health officials and healthcare providers caring for pregnant women with Zika virus infection (suspect or confirmed)
 - To contact the service:
 - Call: 770-488-7100
 - Email: ZIKAMCH@cdc.gov
- For other questions call:
 - 800-CDC-INFO



Additional Resources

- <http://www.cdc.gov/zika/index.html>
- <http://www.cdc.gov/zika/hc-providers/index.html>
- <http://wwwnc.cdc.gov/travel/page/zika-travel-information>

CDC's Response to Zika
For Pregnant Women: A Positive Zika Virus Test
What does it mean for me?



CDC understands that pregnant women may be worried and have questions about Zika virus. A positive test result might cause concerns, but it doesn't mean your baby will have birth defects. Learn more about what you might expect for your pregnancy if you get a positive test result for Zika.

I tested positive. What happens next?

If you get a positive test result for Zika during pregnancy, it signals to your doctor or other healthcare provider to watch your pregnancy more carefully. CDC recommends steps your doctor can take to help care for you during your pregnancy. Your doctor or other healthcare provider might do more ultrasounds or other tests to check the growth and development of your fetus and to look for signs of Zika virus infection during your pregnancy.

What are ultrasounds?

Ultrasounds are a safe and routine way for doctors or other healthcare providers to see the fetus during pregnancy. An ultrasound is usually done between 18-20 weeks of pregnancy as part of normal care. Extra ultrasounds are sometimes done later in pregnancy when doctors need more information about the fetus.

Does Zika virus cause microcephaly or other problems for the fetus?

Recently, researchers concluded that Zika virus infection during pregnancy can cause microcephaly and other severe brain defects. They are working quickly to study the full range of other potential health problems that Zika virus infection during pregnancy may cause.

Does a positive Zika virus test mean my baby will have birth defects?


Studies reported that some, but not all, babies born to women with positive Zika test results during pregnancy were born with microcephaly and other problems. At this time, we don't know how often a baby will have microcephaly or other problems if a woman is infected with Zika while she is pregnant. Your doctor or other healthcare provider will watch your pregnancy more closely if you have a positive Zika virus test.

How will my doctor or other healthcare provider know if my baby has microcephaly?

Your doctor or other healthcare provider will use ultrasound screening to look for microcephaly and other birth defects during your pregnancy. Ultrasounds can show some, but not all, problems with your baby's development during pregnancy. For example, microcephaly can sometimes be seen on the 18-20 week ultrasound but is more commonly detected later in the second trimester or early in the third trimester. To look for problems after birth, your baby's doctor will perform a careful physical exam of your baby, recommend routine hearing screening, and follow up with more exams and tests as needed.

www.cdc.gov/zika

CH2800018 June 1, 2015



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CDC's Response to Zika
ZIKA Virus Testing for Pregnant Women
Living in an Area with ZIKA



CDC understands that pregnant women may be worried and have questions about Zika virus infection during pregnancy. Learn more about Zika virus testing for pregnant women and what you might expect if you have Zika virus during your pregnancy.

What CDC knows about Zika virus and pregnancy

- Zika virus can spread from mother to fetus during pregnancy and around the time of birth.

What CDC doesn't yet know about Zika virus and pregnancy and is researching quickly to find out

- If a woman is infected during pregnancy, we don't know yet
- How the virus will affect her or her pregnancy.
- How often the virus is passed to her fetus.
- How often infection of the fetus leads to birth defects or other pregnancy problems.
- When in pregnancy the infection might lead to poor health effects for the fetus.

How can I find out if I have Zika?

If you get infected with Zika, the virus will be in your blood for about a week. If you get sick with a fever, joint pain, rash, or red eyes, doctors or other healthcare providers can take a small amount of your blood and test it for Zika virus.

After the virus clears from the blood or if you never feel sick, doctors can order a different test to look for evidence that you were infected with Zika in the last 2-12 weeks.



Symptoms

CH2800018 March 10, 2015

www.cdc.gov/zika



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Questions?



Thank you!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.