Zika Update: Findings from the U.S. Zika Pregnancy Registry and Updated Clinical Guidance

Clinician Outreach and Communication Activity (COCA)
Webinar
May 4, 2017
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Planners have reviewed content to ensure there is no bias.
Objectives

At the conclusion of this session, the participant will be able to:

- Understand the latest estimates for birth defects associated with Zika virus infection during pregnancy.
- Discuss additional considerations for evaluating and managing infants with possible congenital Zika virus infection.
- Apply the updated recommendations outlined in the additional considerations for the evaluation and management of infants with possible congenital Zika virus infection.
TODAY’S PRESENTER

Emily Petersen, MD
Medical Officer
Division of Reproductive Health
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention
Sonja Rasmussen, MD, MS
Director, Division of Public Health Information Dissemination
Editor-in-Chief, Morbidity and Mortality Weekly Report
Center for Surveillance, Epidemiology, and Laboratory Services
Centers for Disease Control and Prevention
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

Emily Petersen, MD
Centers for Disease Control and Prevention
US Zika Pregnancy Registry

Purpose of registry

» To monitor pregnancy and infant outcomes in pregnancies with laboratory evidence of possible Zika virus infection and to inform clinical guidance and public health response

- Estimate number of infants with birth defects
- Provide data to inform phenotype of congenital Zika syndrome
- Help ensure infants are linked to care
US Zika Pregnancy Registry: Inclusion Criteria

Who is included

» Pregnant women in the United States with laboratory evidence of possible Zika virus infection (regardless of whether they have symptoms) and their exposed infants

» Infants with laboratory evidence of congenital Zika virus infection (regardless of whether they have symptoms) and their mothers
Among pregnancies in the United States with laboratory evidence of possible Zika virus infection

» 6% of fetuses or infants had birth defects potentially related to Zika virus

» Similar proportion of pregnancies with birth defects (≈6%) among symptomatic and asymptomatic pregnant women

» Among women with infection in the 1st trimester of pregnancy, birth defects reported in 11%

Vital Signs MMWR: Update Previous Estimates

Morbidity and Mortality Weekly Report


Megan R. Reynolds, MPH1; Abbey M. Jones, MPH1; Emily E. Petersen, MD2; Ellen H. Lee, MD3; Marion E. Rice, MPH1,4; Andrea Bingham, PhD5; Sascha R. Ellington, MSPH2; Nicole Evert, MS6; Sarah Reagan-Steiner, MD7; Titilope Oduyebo, MD2; Catherine M. Brown, DVM8; Stacey Martin, MSE9; Nina Ahmad, MD10; Julu Bhatnagar, PhD7; Jennifer Macdonald, MPH11; Carolyn Gould, MD9; Anne D. Fine, MD3; Kara D. Polen, MPH1; Heather Lake-Burger, MPH2; Christina L. Hillard, MA1; Noemi Hall, PhD6,12; Mahsa M. Yazdy, PhD8; Karnesha Slaughter, MPH1; Jamie N. Sommer, MS10; Alys Adamski, PhD1; Meghan Raycraft, MPH1; Shannon Fleck-Derderian, MPH4,13; Jyoti Gupta, MPH11; Kimberly Newsome, MPH1; Madelyn Baez-Santiago, PhD1; Sally Slavinski, DVM3; Jennifer L. White, MPH10; Cynthia A. Moore, MD, PhD1; Carrie K. Shapiro-Mendoza, PhD2; Lyle Petersen, MD9; Coleen Boyle, PhD14; Denise J. Jamieson, MD2; Dana Meaney-Delman, MD13; Margaret A. Honein, PhD1; U.S. Zika Pregnancy Registry Collaboration
What is Added by this Report

This report features the latest data from the US Zika Pregnancy Registry

» Initial estimates were based on 442 completed pregnancies reported to the registry by September 22, 2016

» This Vital Signs report provides data on 972 completed pregnancies reported to the registry through December 27, 2016

» Analyzed subgroup of confirmed Zika virus infections

This is the largest series of infant outcomes among pregnant women with laboratory evidence of possible Zika that has been reported
USZPR Definition of Laboratory Confirmed Zika Infection

Zika virus infection can be confirmed by

» Zika virus RNA in any maternal or fetal/infant specimen detected by nucleic acid test (NAT) (e.g., rRT-PCR) OR

» Positive or equivocal Zika virus IgM with Zika virus plaque reduction neutralization test (PRNT) titer ≥10 and dengue virus PRNT <10
USZPR Definition of Possible Recent Zika Infection

Laboratory evidence of possible recent Zika virus infection

» Recent Zika virus infection detected by a Zika virus RNA nucleic acid test (NAT, e.g., [RT-PCR]) on any maternal, placental, or fetal/infant specimen or

» Detection of recent Zika virus infection or recent unspecified flavivirus infection by serologic tests on a maternal or infant specimen
  • Either positive or equivocal Zika virus IgM AND Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value; or
  • Negative Zika virus IgM, AND positive or equivocal dengue virus IgM, AND Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer
FIGURE 1. Cumulative number of pregnant women with laboratory evidence of possible recent Zika virus infection reported to the U.S. Zika Pregnancy Registry, by month of report — United States, January–December 2016 (n = 1,297)

- Total no. pregnancies reported from 50 U.S. states and the District of Columbia
Box. Birth Defects Potentially Related to Zika Virus Infection During Pregnancy and Monitored by the US Zika Pregnancy Registry for Enhanced Surveillance

**Brain Abnormalities With and Without Microcephaly**
Confirmed or possible congenital microcephaly

- Intracranial calcifications
- Cerebral atrophy
- Abnormal cortical formation (eg, polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia)
- Corpus callosum abnormalities
- Cerebellar abnormalities
- Porencephaly
- Hydranencephaly
- Ventriculomegaly/hydrocephaly (excluding “mild” ventriculomegaly without other brain abnormalities)
- Fetal brain disruption sequence (collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)
- Other major brain abnormalities including intraventricular hemorrhage in utero (excluding postnatal intraventricular hemorrhage)

**Neural Tube Defects and Other Early Brain Malformations**
Neural tube defects including anencephaly, acrania, encephalocele, spina bifida
- Holoprosencephaly (arhinencephaly)

**Eye Abnormalities**
- Microphthalmia/anophthalmia
- Coloboma
- Cataract
- Intraocular calcifications
- Chorioretinal anomalies involving the macula (eg, chorioretinal atrophy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage; excluding retinopathy of prematurity)
- Optic nerve atrophy, pallor, and other optic nerve abnormalities

**Consequences of Central Nervous System Dysfunction**
- Congenital contractures (eg, arthrogryposis, clubfoot, congenital hip dysplasia) with associated brain abnormalities
- Congenital deafness documented by postnatal audiological testing

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*a* Live births: measured head circumference (adjusted for gestational age and sex) less than the third percentile at birth or, if not measured at birth, within first 2 weeks of life. Pregnancy loss: prenatal head circumference more than 3 SDs below the mean based on ultrasound or postnatal head circumference less than the third percentile. Birth measurements are evaluated using the Intergrowth-21st standards ([http://intergrowth21.ndoxygen.ox.ac.uk/](http://intergrowth21.ndoxygen.ox.ac.uk/)) based on measurements within 24 hours of birth.
TABLE 1. Pregnancy outcomes* for 972 women with completed pregnancies† with laboratory evidence of possible recent Zika virus infection, by maternal symptom status and timing of symptom onset or exposure—U.S. Zika Pregnancy Registry, United States, December 2015–December 2016

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### TABLE 2. Postnatal neuroimaging* and infant Zika virus testing results for 895 liveborn infants in the U.S. Zika Pregnancy Registry — 50 U.S. states and the District of Columbia, 2016

<table>
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<tr>
<th>Testing</th>
<th>With birth defects</th>
<th>Without birth defects</th>
<th>Total</th>
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<tbody>
<tr>
<td>Total</td>
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<tr>
<td>Any neuroimaging reported to USZPR</td>
<td>29 (64)</td>
<td>192 (23)</td>
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<td>Positive test result on an infant specimen†,§</td>
<td>25 (56)</td>
<td>69 (8)</td>
<td>94 (11)</td>
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<td>Negative infant test results among infants with ≥1 infant specimen reported as tested</td>
<td>17 (38)</td>
<td>474 (56)</td>
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<tr>
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<td>3 (7)</td>
<td>307 (36)</td>
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<td>Neuroimaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neuroimaging reported to USZPR</td>
<td>29 (64)</td>
<td>192 (23)</td>
<td>221 (25)</td>
</tr>
<tr>
<td>Infant Zika virus testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive test result on an infant specimen</td>
<td>25 (56)</td>
<td>69 (8)</td>
<td>94 (11)</td>
</tr>
<tr>
<td>Negative infant test results among infants</td>
<td>17 (38)</td>
<td>474 (56)</td>
<td>491 (55)</td>
</tr>
<tr>
<td>No infant specimen test results reported as</td>
<td>3 (7)</td>
<td>307 (36)</td>
<td>310 (35)</td>
</tr>
<tr>
<td>tested</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Postnatal neuroimaging and Zika virus testing results are preliminary. Results should be interpreted carefully as they are based on limited data and follow-up is ongoing.


- **Any neuroimaging reported**: December 2015–August 2016: 90, September–December 2016: 150
- **No neuroimaging reported**: December 2015–August 2016: 120, September–December 2016: 80

No. of infants

Month of birth
### Postnatal Neuroimaging and Testing

**TABLE 2.** Postnatal neuroimaging* and infant Zika virus testing results for 895 liveborn infants in the U.S. Zika Pregnancy Registry — 50 U.S. states and the District of Columbia, 2016

<table>
<thead>
<tr>
<th>Testing</th>
<th>With birth defects</th>
<th>Without birth defects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>45</td>
<td>850</td>
<td>895</td>
</tr>
<tr>
<td><strong>Neuroimaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neuroimaging reported to USZPR</td>
<td>29 (64)</td>
<td>192 (23)</td>
<td>221 (25)</td>
</tr>
<tr>
<td><strong>Infant Zika virus testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive test result on an infant specimen†,§</td>
<td>25 (56)</td>
<td>69 (8)</td>
<td>94 (11)</td>
</tr>
<tr>
<td>Negative infant test results among infants with ≥1 infant specimen reported as tested</td>
<td>17 (38)</td>
<td>474 (56)</td>
<td>491 (55)</td>
</tr>
<tr>
<td>No infant specimen test results reported to USZPR</td>
<td>3 (7)</td>
<td>307 (36)</td>
<td>310 (35)</td>
</tr>
</tbody>
</table>
Baseline Prevalence of Birth Defects Observed with Zika

» Used data from birth defects surveillance systems in Massachusetts, North Carolina, and Atlanta, Georgia, during pre-Zika outbreak years (2013–2014)

» Prevalence of Zika-related birth defects before Zika outbreak in the Americas:
  
  3 out of every 1,000 births

» Proportion of infants with birth defects among completed pregnancies with confirmed Zika infection (2016):
  
  24 out of every 250 completed pregnancies

Estimated 30-fold increase in Zika-related birth defects in pregnancies with confirmed Zika infection compared with pre-Zika years
Key Vital Signs Findings

44
States reported pregnant women with evidence of Zika in 2016

about 1 in 10
Pregnant women with confirmed Zika had a fetus or baby with birth defects

only 1 in 4
Babies with possible congenital Zika infection were reported to have received brain imaging after birth
Key Vital Signs Findings

972 pregnant women with evidence of Zika completed their pregnancies in 2016, and some had babies with Zika-related birth defects:

» 5% with possible Zika had birth defects
» 10% with confirmed Zika had birth defects
» 15% with confirmed Zika in the first trimester had birth defects
Preventing Zika in Pregnant Women
What You Can Do to Help

Educate families on Zika prevention
Ask about Zika
Provide all needed tests and follow-up care
Support infants and families
Do Not Travel to Areas with Risk of Zika

» Pregnant women should **not** travel to areas with risk of Zika

There are currently 63 countries and territories worldwide, including 49 countries and territories in the Americas, with a CDC Zika Travel Notice. Countries with endemic Zika also pose a risk.

As of April 24, 2017
Do Not Travel to Areas with Risk of Zika

If a pregnant woman *must* travel, she should

» Talk with her healthcare provider before she goes
» Strictly follow steps to prevent mosquito bites during the trip
» Take steps to prevent sexual transmission
» Talk with her healthcare provider after she returns, even if she doesn’t feel sick

Prevent Mosquito Bites

If a pregnant woman lives in or travels to an area with Zika, she should

» Wear long-sleeved shirts and long pants

» Stay and sleep in places with air conditioning or that use window and door screens

» Use EPA-registered insect repellents with one of the following active ingredients:
  • DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, or 2-undecanone

» Once a week, empty and scrub, turn over, cover, or throw out items that hold water, such as trash containers, tires, buckets, toys, planters, flowerpots, birdbaths or pools
Prevent Sexual Transmission of Zika Virus

A pregnant woman whose partner lives in or has traveled to an area with risk of Zika should

» Use condoms correctly every time they have sex, or
» Not have sex

For the duration of the pregnancy, even if the pregnant woman’s partner does not have symptoms or feel sick.
Healthcare Providers Caring for Pregnant Women and Infants Should Ask about Zika Exposure during Pregnancy

- Have you traveled to an area with risk of Zika during pregnancy or just before you became pregnant?
- Have you had sex without a condom with a partner who lives in or traveled to an area with risk of Zika?
- Do you live in or do you frequently travel (daily or weekly) to an area with risk of Zika?
Who Should Be Tested for Zika?

All pregnant women (regardless of symptoms) who

» Live in or recently traveled to an area with risk of Zika that has a CDC Zika travel notice, or

» Had unprotected sex with a partner who lives in or traveled to an area with risk of Zika that has a CDC Zika travel notice

Pregnant women who live in or recently traveled to an area with risk of Zika but **without** a CDC Zika travel notice

» If they develop symptoms of Zika, or

» If their fetus has abnormalities on an ultrasound that may be related to Zika infection

Testing Infants for Zika

CDC recommends laboratory testing for

» All infants born to mothers with laboratory evidence of Zika virus infection during pregnancy

» Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a mother with a possible exposure to Zika virus, regardless of maternal Zika virus testing results
Contribute to the US Zika Pregnancy Registry

Notify health department of pregnant women and/or infants with Zika virus infection

» More information available on the U.S. Zika Pregnancy Registry website
» To contact CDC Registry staff, call the CDC Emergency Operations Center watch desk at 770-488-7100 and ask for the Zika Pregnancy Hotline or email ZIKApregnancy@cdc.gov.
» For non-urgent requests, call 800-CDC-INFO (800-232-4636)
Thank you!

For more information, please visit:

www.cdc.gov/vitalsigns/index.html
www.cdc.gov/zika

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.
Additional Considerations for Evaluation and Management of Infants with Possible Congenital Zika Virus Infection

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Editor-in-Chief, Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
Evaluation and Management of Infants with Possible Congenital Zika Virus Infection


Kate Russell, MD1,2; Sara E. Oliver, MD1,3; Lillianne Lewis, MD1,4; Wanda D. Barfield, MD5; Janet Cragan, MD6; Dana Meaney-Delman, MD7; J. Erin Staples, MD, PhD8; Marc Fischer, MD8; Georgina Peacock, MD9; Titilope Oduyebo, MD3; Emily E. Petersen, MD5; Sherif Zaki, MD, PhD10; Cynthia A. Moore, MD, PhD6; Sonja A. Rasmussen, MD11; Contributors

http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
Update Posted April 2017: Additional Considerations

• Additional Considerations for Evaluation and Management of Infants with Possible Zika Virus Infection
  » Neuroimaging
  » Zika virus testing

Infants with Possible Congenital Zika Virus Infection

• Born to mothers with laboratory evidence of possible Zika virus infection
• With abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link*

*An epidemiologic link includes travel to or residence in an area with risk of Zika, or sex without a condom with a partner who traveled to or lived in such an area
Initial Evaluation of Infants with Possible Congenital Zika Virus Infection

• Comprehensive physical exam
  » Head circumference, weight, length measurements
  » Neurologic assessment

• Standard newborn hearing assessment

• Head ultrasound

• Zika virus laboratory testing
Initial Evaluation of Infants with Possible Congenital Zika Virus Infection

• Comprehensive physical exam
  » Head circumference, weight, length measurements
  » Neurologic assessment
• Standard newborn hearing assessment
• Head ultrasound
• Zika virus laboratory testing
Congenital Zika Syndrome

- Distinct pattern of birth defects in fetuses and infants of women infected during pregnancy
- Birth defects that make up the congenital Zika syndrome
  - Severe microcephaly with partially collapsed skull
  - Thin cerebral cortex with subcortical calcifications
  - Macular scarring and focal pigmentary retinal mottling
  - Congenital contractures
  - Marked early hypertonia and symptoms of extrapyramidal involvement
Congenital Zika Syndrome without Microcephaly at Birth

- Microcephaly from congenital infection can occur after birth
- The full spectrum of poor outcomes caused by Zika virus infection during pregnancy remains unknown

Linden V, Pessoa A, Dobyns WB, et al. Description of 13 Infants Born During October 2015–January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth — Brazil
New Vital Signs Report

Zika Virus: Protecting Pregnant Women and Babies

44 States reported pregnant women with evidence of Zika in 2016

about 1 in 10 Pregnant women with confirmed Zika had a fetus or baby with birth defects

only 1 in 4 Babies with possible congenital Zika infection were reported to have received brain imaging after birth
Infants with Possible Congenital Zika Virus Infection: Neuroimaging

Current Interim Guidance

• A head ultrasound is recommended before hospital discharge for infants with possible Zika virus infection
Infants with Possible Congenital Zika Virus Infection: Neuroimaging

Current Interim Guidance
- A head ultrasound is recommended before hospital discharge for infants with possible Zika virus infection

Additional Considerations
- For an infant with a small or absent anterior fontanelle and poor visualization of the intracranial anatomy on ultrasound, other imaging should be considered
Initial Evaluation of Infants with Possible Congenital Zika Virus Infection

- Comprehensive physical exam
  - Head circumference, weight, length measurements
  - Neurologic assessment
- Standard newborn hearing assessment
- Head ultrasound
- Zika virus laboratory testing
Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

Current Interim Guidance

Testing for Zika virus infection is recommended for infants

- Born to mothers with laboratory evidence of possible Zika virus infection
- With clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link*

*An epidemiologic link includes travel to or residence in an area with risk of Zika, or sex without a condom with a partner who traveled to or lived in such an area
Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

Current Interim Guidance

Testing for Zika virus infection is recommended for infants

- Born to mothers with laboratory evidence of possible Zika virus infection
- With clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link*

Additional Considerations

Testing for Zika virus infection should be considered for infants

- Born to mothers with an epidemiologic link for whom
  - There is concern about infant follow-up care
  - Maternal testing was not performed before delivery and exposure was >12 weeks before delivery, or
  - Maternal testing was negative but was performed on a specimen obtained >12 weeks after maternal exposure

*An epidemiologic link includes travel to or residence in an area with risk of Zika, or sex without a condom with a partner who traveled to or lived in such an area.
Timing of Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

Current Interim Guidance

- CDC recommends testing specimens collected from infants within 2 days after birth.
  
  » If specimens are collected later, it may be difficult to distinguish congenital from postnatally acquired infection in areas with risk of Zika.
Timing of Laboratory Testing of Infants with Possible Congenital Zika Virus Infection

Current Interim Guidance

- CDC recommends testing specimens collected from infants within 2 days after birth.
  - If specimens are collected later, it may be difficult to distinguish congenital from postnatally acquired infection in areas with risk of Zika

Additional Considerations

- Testing specimens collected within the first few weeks to months after birth may still be useful in the evaluation for infants with possible congenital Zika virus infection, particularly among infants born in areas without risk of Zika
Testing of Cerebrospinal Fluid (CSF)

Current Interim Guidance

• If cerebrospinal fluid (CSF) is obtained for other studies, Zika NAT (nucleic acid testing) for Zika virus RNA and Zika virus IgM should be performed on CSF
Testing of Cerebrospinal Fluid (CSF)

Current Interim Guidance

- If cerebrospinal fluid (CSF) is obtained for other studies, NAT testing for Zika virus RNA and Zika virus IgM should be performed on CSF.

Additional Considerations

- Testing CSF for Zika virus RNA and IgM antibody should be considered for infants with clinical findings of possible congenital Zika syndrome but whose initial laboratory tests are negative on serum and urine.
Interpretation of Laboratory Test Results of Infants with Possible Congenital Zika Virus Infection

Laboratory Testing for Infants with Possible Congenital Zika Virus Infection

• Plaque Reduction Neutralization Test (PRNT) can be performed at 18 months to confirm a congenital Zika virus infection after maternal IgG has waned
Possible Limitations of Infant Zika Virus Laboratory Testing

- Case reports of infants with clinical findings consistent with possible congenital Zika virus syndrome in whom Zika virus lab results were negative
- Potential explanations include
  - The clinical findings are due to another cause
  - Testing was incomplete, performed on suboptimal specimens, or performed too late
  - The fetus failed to mount an IgM antibody response
Maintain a Level of Suspicion

- For infants without laboratory evidence of Zika virus infection but for whom suspicion for congenital Zika virus infection remains, HCPs should
  - Evaluate for other causes of congenital infection
  - Consider an ophthalmology exam and auditory brainstem response (ABR) hearing test
  - Consider performing other evaluation and follow up in accordance with CDC interim guidance for the evaluation and management of infants with possible congenital Zika syndrome
Zika Care Connect: Improving Access to Clinical Services

- Provider Network for Families Affected by Zika
  - Maternal-fetal medicine, mental health services, audiology, radiology, pediatric ophthalmology, pediatric neurology, developmental pediatrics, infectious disease, and endocrinology
- Laboratory Testing Web Portal for Healthcare Providers
  - Identify laboratories offering Zika testing

HelpLine: 1-844-677-0447 (toll-free)
Website: www.zikacareconnect.org
Summary

- Infants with possible congenital Zika virus infection
  - Neuroimaging
  - Criteria, timing, and specimens for Zika testing
  - Possible limitations
Thank you!

For more information, please visit:

www.cdc.gov/vitalsigns/index.html  
www.cdc.gov/zika

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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