The Evolving Buzz on Zika and Pregnancy: An Update for Clinicians

August 19, 2016
Webinar Instructions:

1. Everyone will be muted on entry.
2. Questions can be typed in the Q&A Box and addressed at the end.
3. The meeting is being recorded and a link will be posted on the CMQCC and CDPH websites.
The Evolving Buzz on Zika and Pregnancy: An Update for Clinicians

August 19, 2016

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The Buzz on Zika in Pregnancy
August 19, 2016

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Background

- Zika virus is transmitted to humans primarily through the bite of infected *Aedes* mosquito
  - Nearly all Zika outbreaks due to *aegypti* & *albopictus*
  - These are the same mosquitoes that transmit dengue and chikungunya
  - The mosquito vectors typically breed in domestic water-holding containers
  - *Aegypti* -- feeds primarily on humans, multiple humans in a single meal, lives close to humans, also daytime and nighttime feeders
PROTECT YOUR FAMILY AND COMMUNITY:
HOW ZIKA SPREADS

Most people get Zika from a mosquito bite

A mosquito bites a person infected with Zika virus

The mosquito becomes infected

A mosquito will often live in a single house during its lifetime

More members in the community become infected

More mosquitoes get infected and spread the virus

The infected mosquito bites a family member or neighbor and infects them

Other, less common ways, people get Zika:

During pregnancy
A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika causes microcephaly, a severe birth defect that is a sign of incomplete brain development

Through sex
Zika virus can be sexually transmitted by a man to his partners

Through blood transfusion
There is a strong possibility that Zika virus can be spread through blood transfusions

CDC
POTENTIAL ZIKA MOSQUITO RANGE

37 STATES

SOURCE: CENTERS FOR DISEASE CONTROL AND PREVENTION
Zika – Disease and Risks
Clinical Disease

- About 20% of people infected with Zika virus become symptomatic (*but % based on earlier outbreaks*)

- Among those with clinical illness
  - Symptoms mild, typically develop within 1 week from exposure, lasting several days to a week
  - Characteristic clinical findings: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis.
  - Severe disease requiring hospitalization is uncommon and fatalities are rare.

- Guillain-Barré syndrome also has been reported at increased rates in patients following Zika infection
  - 50% increase in cases in Colombia since Oct 2015
Clinical Features of Zika Virus Infection in Pregnant Women.
Brazil Zika Outbreak

- May 2015: First infection in Brazil
- October 2015: Increase in microcephaly

**Microcephaly cases in Brazil 2010-14; suspected/confirmed cases 2015-2016**

- 1,551 confirmed (224 confirmed Zika+ by PCR)
- 4,568 suspected* (3,017)

*does not include 3,262 cases investigated and discarded

Source: Brazilian MOH; data as of 6/4/2016.
Microcephaly: the most apparent marker?

- Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in newborns
  - On ultrasound, typically defined as $HC < 3^{rd} \%ile$ for GA

- Microcephaly became an early trigger to search for Zika association, but spectrum of disease became apparent
  - Microcephaly can occur as a result of a fetal brain disruption sequence: this appears to be pathology of Zika infection

- Polynesia outbreak in 2014: higher rates of fetal CNS abnormalities in some women who tested positive for Zika, though none had had symptoms (Euro Ctr Dis Prev Control 2015)
Fetal Brain Anomalies

- Microcephaly
- Hydrocephalus/hydranencephaly
- Absent structures: (CC, pons, cerebellar vermis)
- Neuronal migration disorders (lissencephaly)
- Fetal brain disruption sequence
- Cerebral calcifications
- Brain asymmetry
Zika Associated Pregnancy Outcomes

- Fetal loss/miscarriage, stillbirth
- Fetal growth abnormalities
- Fetal brain anomalies
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures
  - Neurobehavioral anomalies

Miranda-Filho et al, AJPH April 2016, Vol 106 No. 4
Slide courtesy of NICHD.
Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?
Fig 4 Microlissencephaly.
Fig 3 Severe microcephaly.

Maria de Fatima Vasco Aragao et al. BMJ
2016;353:bmj.i1901
Prospective NEJM series, Brazil: Background

- Brazil group had been conducting surveillance for dengue in population of Rio de Janeiro since 2007
  - In 2015, noted increase in dengue-like illness with rash, coinciding with surge of similar cases in NE Brazil → ID as Zika

- Study cohort: 88 symptomatic pregnant women (9/15-2/16)
  - 82% (72/88) tested positive for ZIKV (PCR) in blood, urine, or both
  - Serial U/S done: 20-30+ weeks
  - Timing of infection: 5-38 weeks of gestation

Brasil P, et al. NEJM, online 3/4/16
Prospective NEJM series, Brazil: Results

- Of 72 women with PCR-positive test results
  - > 50% reported an ill family member; 21%: partner had been ill

- 2 women miscarried in 1st Δ; 42 (60%) of others had u/s
  - 28 women declined u/s: either too far or fear of finding anomalies

- Abnormal u/s results seen in 12/42 (29%) pts with Zika infx
  - No abnormalities seen in any of the 16 Zika-negative women
  - IUGR in 5/12 fetuses (42%), with or without microcephaly
  - Cerebral calcifications in 4/12, other CNS anomalies in 2 fetuses
  - 2 IUFDs @ 30 and 38 wks: women infected at 25 and 32 wks

*Brasil P, et al. NEJM, online 3/4/16*
Pregnancy: Prolonged Viremia

Viremia persisted for 5 weeks

Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.

This timeline highlights the symptoms of Zika virus (ZIKV) infection in the mother (bottom row) and the corresponding radiographic and laboratory findings in the fetus (top row). The inset photograph shows the mother’s rash at the time of the onset of the acute illness. DENV denotes dengue virus, MRI magnetic resonance imaging, PBMC peripheral-blood mononuclear cells, and PRNT plaque-reduction neutralization test.
Long Term Pregnancy Outcomes: Evolving

- Emerging reports and series of long-term functional motor and sensory abnormalities
  - van der Linden et al, *BMJ 8/16*: 7 infants with microcephaly and abnormal MRI: also with arthrygryposis: neurologic not muscular
  - Pestorius et al, CDC, 8/4/16: “late-onset microcephaly” in series from Brazil: normal head size at birth, abnormal by 6 months

- Anticipate a spectrum of outcomes?
  - Developmental delay
  - Intellectual impairments
  - Mental disorders – autism, schizophrenia, etc
  - Motor abnormalities
Zika-Related Arthrogryposis

van der Linden at al, BMJ 8/16
Zika – Where is it and where is it not?
Zika in the US
(as of August 10, 2016)

US States and DC
- Travel-associated Zika virus disease cases reported: 1955 (22 sexually transmitted)
  - 6 cases of Guillain-Barre syndrome
- Locally acquired vector-borne cases reported: 33*
- No Zika-related hospitalizations or deaths among women
  - 1 recent Zika-attributable death in Utah (elderly traveler)

US Territories
- Travel-associated cases reported: 31
- Locally acquired cases reported: 6587 (all but 112 in Puerto Rico)
  - 20 cases of Guillain-Barre syndrome

CDC ; *Florida DOH 8/17/16
Zika Pregnancy Statistics  
(as of August 11, 2016)

**US States and DC**
- 529 pregnant travelers with laboratory evidence of Zika virus— all imported/travel-related, no native cases
  - 16 reported liveborn infants and 5 fetal losses with Zika related birth defects

**US Territories**
- 691 pregnant cases (mostly Puerto Rico)
  - 1 liveborn infant and 1 fetal loss with Zika related birth defects

**California** (as of August 12, 2016)
- 24 pregnant cases
  - 2 liveborn infant and 0 fetal losses with Zika related birth defects
Imported Zika Cases in California, 2015-2016

California Department of Public Health

N = 153 (as of August 12, 2016)
CDPH Weekly Update on Number of Zika Virus Infections in California
August 12, 2016

The following table provides the number of travel-associated infections with Zika virus in California residents in 2015 and 2016. CDPH is following CDC testing guidelines. This table is updated every Friday. As of August 12, 2016, there have been 153 travel-associated Zika virus infections in California.

- Total infections: 153
- Cumulative number of infections due to sexual transmission: 1
- Cumulative number of infections in pregnant women: 24
  - Liveborn infants with birth defects: 2
  - Pregnancy losses with birth defects: 0

### Zika virus infections in California, 2015-2016 (as of August 12, 2016)

<table>
<thead>
<tr>
<th>County</th>
<th>Travel-associated</th>
<th>Locally acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alameda</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Contra Costa</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fresno</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Kern</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lake</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Marin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Merced</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Monterey</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Napa</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Orange</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Riverside</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sacramento</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>San Bernardino</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>San Diego</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>San Francisco</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>San Joaquin</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>San Mateo</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Santa Clara</td>
<td>11</td>
<td>0</td>
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<td>Santa Cruz</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Solano</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sonoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stanislaus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Tulare</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Yolo</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Yuba</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>153</strong></td>
<td>0</td>
</tr>
</tbody>
</table>
## Imported Zika Cases in California, 2015-2016

<table>
<thead>
<tr>
<th>Country Traveled To</th>
<th>Number of Imported Cases in California</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>36</td>
</tr>
<tr>
<td>El Salvador</td>
<td>22</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>15</td>
</tr>
<tr>
<td>Guatemala, Honduras</td>
<td>31</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>13</td>
</tr>
<tr>
<td>Jamaica, Nicaragua</td>
<td>27</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>7</td>
</tr>
<tr>
<td>Venezuela</td>
<td>5</td>
</tr>
<tr>
<td>Brazil, Colombia</td>
<td>8</td>
</tr>
<tr>
<td>Haiti</td>
<td>2</td>
</tr>
<tr>
<td>American Samoa, Belize, French Polynesia, Kiribati, Saint Lucia, Trinidad</td>
<td>7</td>
</tr>
</tbody>
</table>

Note: Individuals may have traveled to more than one country.

California Department of Public Health
Culex sp. mosquitoes as a Zika risk?

- Recent reports from Brazil suggested *Culex* (Southern house) mosquito as source of Zika transmission (also West Nile virus)

- Latest research from UT Galveston (Aug 4): *Culex* NOT an efficient vector for Zika transmission and confirmed *Aedes aegypti* to be

  - Researchers captured both species in wild and fed infected blood, measured Zika in bodies and saliva of mosquitoes
  - Released data ahead of upcoming publication as public health issue
Confirmed Zika Cases in Mexico by State
January 1, 2016 – August 8, 2016

- Sonora
- Chihuahua
- Coahuila
- Durango
- Nuevo León
- Yucatán
- Oaxaca
- Guerrero
- Chiapas
- Colima
- Jalisco
- Nayarit
- Tabasco
- Puebla
- Morelos
- Aguascalientes
- Querétaro
- Distrito Federal
- Tlaxcala

0 confirmed cases
1 – 25 confirmed cases
26 – 50 confirmed cases
51 – 100 confirmed cases
More than 100 confirmed cases

Data provided by the Mexican Ministry of Health
Case data is reported at the municipality level. 
Shading does not indicate a uniform or specific 
distribution of cases within a particular municipality. 
States in Mexico have between 5 and 570 
municipalities, depending on the state.

**Confirmed Zika cases by municipio -- Mexico**
Epi Week 25; data July 4, 2016

- 1 to 5 cases
- 6 to 10 cases
- 11 to 50 cases
- 51 to 100 cases
- 100 to 150 cases

- New municipality reporting cases
- Municipality reporting new cases
Local Zika Transmission in Florida
DEPARTMENT OF HEALTH RESPONDS TO LOCAL ZIKA CASES

Tallahassee, Fla.—The Florida Department of Health has gathered enough information as part of its ongoing investigation into non-travel related cases of Zika in Miami-Dade and Broward counties to conclude that a high likelihood exists that four cases are the result of local transmission. At this time, the department believes that active transmission of the Zika virus are occurring in one small area in Miami-Dade County, just north of downtown. The exact location is within the boundaries of the following area: NW 5th Avenue to the west, US 1 to the east, NW/NE 38th Street to the north and NW/NE 20th Street to the south. This area is about 1 square mile and a map is below to detail the area. While no mosquitoes trapped tested positive for the Zika virus, the department believes these cases were likely transmitted through infected mosquitoes in this area.
Local Zika Transmission in Florida (August 17, 2016)

• 33 cases of locally-acquired Zika infection
  – 4 original cases (Miami-Dade and Broward)
    o 23 additional cases
  – 5 cases (Miami-Dade)
  – 1 case (Palm Beach)

• Florida DOH believes transmission still limited to 1-square mile in Wynwood

• Door to door outreach and sampling ongoing

• Mosquito abatement and reduction ongoing
Zika – Education and Testing
What do we tell our pregnant patients?

- How much fetal risk with confirmed maternal infection?
  - Based on current data, the range may be as high as 29%
  - Rates are derived from methodologically diverse studies

- Despite earlier reports, recent data suggest later GA at infection does not exclude potential adverse impact

- Pregnant women should not travel to areas with active Zika transmission

- If in an area with transmission, protection and prevention strategies are important – and repellent for 3 weeks after return from these areas
  - DEET, picaridin most effective --- both fine for use during pregnancy
Testing algorithm for a pregnant woman possible Zika exposure

Pregnant woman with history of travel to an area with ongoing Zika virus transmission

Test for Zika virus infection

Positive or inconclusive for Zika virus infection

Consider serial fetal ultrasounds
Consider amniocentesis for Zika virus testing

Negative for Zika virus infection

Fetal ultrasound to detect microcephaly or intracranial calcifications

Microcephaly or intracranial calcifications present

Retest pregnant woman for Zika virus infection
Consider amniocentesis for Zika virus testing

Microcephaly or intracranial calcifications not present

Routine prenatal care
Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States, July 2016

Titilope Odiete, MD; Iroge Igbinosa, MD; Emily E. Petersen, MD; Kara N.D. Polen, MPH; Satish K. Pillai, MD; Elizabeth C. Ailes, PhD; Julie M. Villanueva, PhD; Kim Newsome, MPH; Marc Fischer, MD; Priya M. Gupta, MPH; Ann M. Powers, PhD; Margaret Lampe, MPH; Susan Hills, MBBS; Kathryn E. Arnold, MD; Laura E. Rose, MTS; Carrie K. Shapiro-Mendoza, PhD; Charles B. Beard, PhD; Jorge L. Muñoz, PhD; Carol Y. Rao, ScD; Dana Meany-Delman, MD; Denise J. Jamieson, MD; Margaret A. Honein, PhD

On July 25, 2016, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).

CDC has updated its interim guidance for U.S. health care providers caring for pregnant women with possible Zika virus exposure, to include the emerging data indicating that Zika virus RNA can be detected for prolonged periods in some pregnant women. To increase the proportion of pregnant women with exposure. For asymptomatic pregnant women who live in areas without active Zika virus transmission and who are evaluated <2 weeks after last possible exposure, rRT-PCR testing should be performed. If the rRT-PCR result is negative, a Zika virus IgM antibody test should be performed 2–12 weeks after the exposure. Asymptomatic pregnant women who do not live in an area with active Zika virus transmission, who are first evalu-
Practice Advisory on Zika Virus

In the Zika Practice Advisory
- **Background** (Updated: August 3, 2016)
- **Travel Restrictions** (Updated: August 3, 2016)
- **Prevention** (Updated: August 3, 2016)
- **Reproductive Counseling** (Updated: August 3, 2016)
- **Testing, Evaluation, and Management of Pregnant and Postpartum Women** (Updated: August 3, 2016)
- **Reporting and the U.S. Pregnancy Registry** (Updated: August 3, 2016)
- **Infection Control Considerations** (Updated: August 3, 2016)
- **Zika and Blood Transfusion** (Updated: August 3, 2016)
- **References** (Updated: August 3, 2016)
Zika Testing – What’s new (this time)?

- Expanded testing for pregnant women
  - Attempt to increase the proportion of pregnant women with Zika infection who receive definitive dx
  - Ask about Zika exposure (travel, sex) at each prenatal visit
    - Only test pregnant women with (+) exposure history
  - Recognizing risks of sexual transmission regardless of whether sexual partner who traveled to risk area had symptoms or not also ask partner travel hx
  - Recognizing longer time for viral RNA detection in some pregnant women compared to nonpregnant adults

- Still no testing for asymptomatic partner of a pregnant woman still emphasize condoms thru pregnancy
Zika Testing – What Testing should be done?

- PCR done for all pts with symptoms within **2 weeks after onset of symptoms**: test blood AND urine
- PCR for asymptomatic: **only in pregnant women with exposure in past 2 weeks** (including sex w/ male or female partner who traveled)
  - If PCR on pregnant woman negative, still do antibody testing 2-12 weeks after exposure
- All other pregnant patients with exposure (including sexual contact with traveler): testing for **Zika-specific IgM antibodies**
  - Typically develop toward the end of the first week of illness
  - **Testing in asymptomatic patients no earlier than 2 weeks after exposure (no later than 12 weeks)**: TAT 2-3 weeks
  - If Ab (+), then further testing done to confirm
Should I request a test for Zika virus from my doctor?

Did you or your sexual partner travel from one of the countries or territories affected by Zika virus within the past two weeks?

**NO**

You don’t need a test.

**YES**

Are you pregnant?

**NO**

Did you or your partner experience any of the following symptoms during your travels or within two weeks of travel?

- Fever
- Rash
- Joint pain
- Conjunctivitis

**YES**

Pregnant women can request a Zika diagnostic test anytime from two to 12 weeks after they return from a Zika virus-affected area. They should request a test immediately if they experience symptoms like fever, rash, joint pain or conjunctivitis.

Pregnant women get PCR test if travel or other exposure within 2 weeks, even if no symptoms (including sex with male partner who traveled), then antibody test if PCR negative.

Go to your doctor, who will determine, based on your travel dates, activities and symptoms, whether or not to request a Zika virus test. It could also be malaria, Chikungunya virus or other diseases, so medical attention is necessary no matter what it turns out to be.
Zika Testing – How?

- Emergency-approved commercially available test for PCR has a very specific role in new guidelines, especially for pregnant women
  - Cost and collection issues
  - PCR now a test for pregnant women w/o symptoms but with exposure within 2 weeks

- One company recently approved for CDC MAC-ELISA IgM testing: advertised TAT 5-7 days
  - Again, collection protocol needs to be followed

- Clinicians should still be aware of current guidelines for testing
  - Take a travel history of pt and partner
  - Be aware of current travel advisories (cdc.gov)
Sexual Transmission: What We Don’t Know

- For how long after the infection semen/vaginal fluids can infect a sexual partner
  - *Lancet* 6/7/16: transmission through semen 34-41 d after infection
  - *Lancet* 8/2016: Zika RNA found in semen after 90 days
  - *Eurosurveillance* 8/11/16: RNA (+) in urine up to 91 days and in semen 134 days after sx

- If Zika can be transmitted through saliva or other bodily fluids
- Transmission risk/duration after *asymptomatic* infection
Sexual Partner concerns/guidelines

- Sexual transmission of Zika virus can occur
  - Male/female, female/male, male/male all reported

- Pregnant women whose male partners have or are at risk for Zika virus infection should consider using condoms or abstaining from sexual intercourse – *duration of pregnancy*
<table>
<thead>
<tr>
<th>Possible exposure via recent travel or sex without a condom with a man infected with Zika</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zika symptoms</strong></td>
<td>Wait at least 8 weeks after symptoms start</td>
<td>Wait at least 6 months after symptoms start</td>
</tr>
<tr>
<td><strong>No Zika symptoms</strong></td>
<td>Wait at least 8 weeks after exposure</td>
<td>Wait at least 8 weeks after exposure. Talk with your healthcare provider</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People living in areas with Zika</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zika symptoms</strong></td>
<td>Wait at least 8 weeks after symptoms start</td>
<td>Wait at least 6 months after symptoms start</td>
</tr>
<tr>
<td><strong>No Zika symptoms</strong></td>
<td>Talk with doctor or healthcare provider</td>
<td>Talk with doctor or healthcare provider</td>
</tr>
</tbody>
</table>
Zika’s Additional Impact on OBGYN Care

○ Tissue/organ donation – including egg/sperm donors
  • Donors are **ineligible for 6 months** if dx’d with ZKVD, in an area with active transmission, or had sex with a male partner with either of those risks
  • Also applies to umbilical cord blood and placenta
  • *FDA 3/1/16, affirmed by ASRM 3/4/16*

○ Blood donation
  • Major impact on blood bank capabilities: for US, greatest impact in Puerto Rico (*also Miami*) -- no reported cases via transfusion, but local blood collections stopped 3/1 pending PCR
  • Investigational use of Zika PCR for PRBCs/WB (Apr 4)
  • FDA statement (2/16/16): 4 week waiting period for potential donors -- after illness, travel, or sexual contact
Zika in Pregnancy: Evaluating the Impact on the Fetus and Neonate

Desiree LaBeaud, MD, MPH
Associate Professor
Pediatric Infectious Disease
Stanford University
Mother with laboratory evidence of Zika virus infection during pregnancy

Perform a comprehensive PE, head U/S, hearing test, and Zika testing (Box 1)

Infant with findings c/w congenital Zika syndrome

Initial evaluation (Box 2)

Laboratory confirmed or probable congenital Zika

Outpatient management (Box 3)

Infant negative for congenital Zika

Evaluate and treat other causes

No findings c/w congenital Zika syndrome

Laboratory confirmed or probable Zika virus infection

Routine care of infant and FU on any clinical findings; hearing and ophtho exam within one month

Outpatient management and follow up (Box 4)

Infant negative for Zika

Routine care

For possible congenital Zika virus infection

- Test infant serum for Zika virus RNA, Zika virus immunoglobulin M (IgM) and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. The initial sample should be collected either from the umbilical cord or directly from the infant within 2 days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.
- Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus reverse transcription-polymerase chain reaction (RT-PCR) on fixed and frozen tissue.
- If not already performed during pregnancy, test mother’s serum for Zika virus IgM and neutralizing antibodies, and IgM and neutralizing antibodies for other potentially cross-reacting viruses as appropriate.

*Indications for testing for congenital infection include 1) an infant with microcephaly or intracranial calcifications born to a woman who traveled to or resided in an area with Zika virus transmission while she was pregnant or who had unprotected sex during her pregnancy with a man who experienced symptoms of acute Zika virus infection within 2 weeks of returning to an area with Zika virus transmission, or 2) an infant born to a mother with a positive or inconclusive test result for Zika virus infection.
Table 1: Specimen Collection and Storage of specimens for Zika virus testing in infants (updated 2/26/16)

<table>
<thead>
<tr>
<th>Specimen</th>
<th>When to Collect</th>
<th>Preferred Amount</th>
<th>Container</th>
<th>Storage and Shipment Conditions</th>
<th>Tested at CDC</th>
<th>Tested at VRDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (infant)†</td>
<td>&lt;2 days post onset</td>
<td>≥2 ml (one tube preferred)</td>
<td>red or tiger top tube</td>
<td>cold</td>
<td>serology, PCR</td>
<td>serology, PCR</td>
</tr>
<tr>
<td>Serum (mother)</td>
<td>at time of collection of infant serum</td>
<td>≥2 ml (one tube preferred)</td>
<td>red or tiger top tube</td>
<td>cold</td>
<td>serology, PCR</td>
<td>serology, PCR</td>
</tr>
<tr>
<td>CSF</td>
<td>if collected for other studies</td>
<td>≥1 ml</td>
<td>sterile cryovial</td>
<td>cold</td>
<td>serology, PCR</td>
<td>N/A</td>
</tr>
<tr>
<td>Amniotic Fluid</td>
<td>when available</td>
<td>≥1 ml</td>
<td>sterile cryovial</td>
<td>frozen</td>
<td>PCR</td>
<td>N/A</td>
</tr>
<tr>
<td>Cord Blood</td>
<td>when available</td>
<td>0.5-1 ml</td>
<td>sterile cryovial</td>
<td>cold or frozen</td>
<td>PCR</td>
<td>serology, PCR</td>
</tr>
<tr>
<td>Placental/Fetal Tissue§</td>
<td>when available</td>
<td>0.5-1.0 cm</td>
<td>sterile container</td>
<td>both a.) cold formalin fixed and b.) frozen tissues</td>
<td>HP, IHC, PCR</td>
<td>N/A</td>
</tr>
</tbody>
</table>

† Infant serum or cord blood are acceptable specimens for serological and PCR testing.


Evaluation for all infants with possible congenital Zika virus infection

- **Physical Examination**
  - Comprehensive physical examination, including careful measurement of occipitofrontal circumference, length, weight, and assessment of gestational age.
  - Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions.

- **Additional Clinical Evaluation**
  - Cranial ultrasound
  - Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth.
  - Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth.
  - Other evaluations specific to the infant’s clinical presentation.
Mother with laboratory evidence of Zika virus infection during pregnancy

Perform a comprehensive PE, head U/S, hearing test, and Zika testing (Box 1)

Infant with findings c/w congenital Zika syndrome

Initial evaluation (Box 2)

Laboratory confirmed or probable congenital Zika

Outpatient management (Box 3)

Infant negative for congenital Zika

Evaluate and treat other causes

No findings c/w congenital Zika syndrome

Laboratory confirmed or probable Zika virus infection

Routine care of infant and FU on any clinical findings; hearing and ophtho exam within one month

Outpatient management and follow up (Box 4)

Infant negative for Zika

Routine care

Box 2: Further evaluation for infants with lab-confirmed Zika and abnormalities c/w congenital Zika

Consults:

- Pediatric neurologist to determine appropriate brain imaging
- Pediatric infectious disease specialist and testing for other congenital infections
- Ophthalmologist for comprehensive eye exam and evaluation for possible cortical visual impairment prior to discharge from the hospital or within 1 month of birth.
- Endocrinologist for evaluation for hypothalamic or pituitary dysfunction.
- Clinical geneticist or dysmorphologist
- Consider: Orthopedist, PT, pulmonologist, GI, lactation, nutrition, Speech/OT, ENT

Testing:

- Complete blood count with platelet count and liver function and enzyme tests
- Perform auditory brainstem response to assess hearing
Mother with laboratory evidence of Zika virus infection during pregnancy

Perform a comprehensive PE, head U/S, hearing test, and Zika testing (Box 1)

Infant with findings c/w congenital Zika syndrome

Initial evaluation (Box 2)

Infant negative for congenital Zika syndrome

Laboratory confirmed or probable congenital Zika

Evaluate and treat other causes

No findings c/w congenital Zika syndrome

Laboratory confirmed or probable Zika virus infection

Routine care of infant and FU on any clinical findings; hearing and ophtho exam within one month

Outpatient management and follow up (Box 4)

Infant negative for Zika

Routine care

Box 3: Outpatient management of congenital Zika syndrome

- Establish medical home with PCP visits monthly for first 6 months
- Follow growth and development; provide routine immunizations, anticipatory guidance, and psychosocial support; and ensure infants receive necessary testing and consultations.
- Neurologic examination by the primary care provider at 1 and 2 months of age.
  - Refer to neurology for any abnormalities, or concerns.
- Refer to developmental specialist and early intervention services.
- Repeat comprehensive ophthalmologic exam at age 3 months
  - Refer to ophthalmology for any abnormal findings, or concerns.
- Repeat auditory brainstem response testing at age 4–6 months
  - Refer to audiology for any abnormal findings, or concerns.
- Repeat testing for hypothyroidism at age 2 weeks and 3 months, even if the initial results were normal.
  - Refer to endocrinology for any abnormal findings.
- Provide family and supportive services.
Mother with laboratory evidence of Zika virus infection during pregnancy

Perform a comprehensive PE, head U/S, hearing test, and Zika testing (Box 1)

Infant with findings c/w congenital Zika syndrome

Initial evaluation (Box 2)

Laboratory confirmed or probable congenital Zika

Outpatient management (Box 3)

Box 4: Outpatient management of laboratory confirmed Zika without abnormalities c/w congenital Zika

- Establish medical home with PCP visits
  - Follow growth parameters, and perform developmental screening at each well child visit.
  - Emphasize anticipatory guidance for families regarding developmental milestones, feeding and growth, sleep and irritability, and abnormal movements

- Screen development: Use a standardized, validated developmental screening tool at 9 months as currently recommended, or earlier for any concerns.

- Referral to ophthalmology for comprehensive eye exam within one month of birth. Perform vision screening and assess visual regard at every well child visit, and refer to ophthalmology for any abnormal findings, or concerns.

- Perform auditory brainstem response within one month of birth. Consider repeat auditory brainstem response at 4–6 months or perform behavioral diagnostic testing at 9 months of age and refer to audiology for any abnormal findings, or concerns.

- Provide family and supportive services.
Mother with laboratory evidence of Zika virus infection during pregnancy

Perform a comprehensive PE, head U/S, hearing test, and Zika testing (Box 1)

Infant with findings c/w congenital Zika syndrome

Initial evaluation (Box 2)

Laboratory confirmed or probable congenital Zika syndrome

Laboratory confirmed or probable Zika virus infection

Routine care of infant and FU on any clinical findings; hearing and ophtho exam within one month

Infant negative for congenital zika

Evaluate and treat other causes

Outpatient management (Box 3)

Outpatient management and follow up (Box 4)

Infant negative for congenital Zika

Laboratory confirmed or probable congenital Zika

Routine care of infant and FU on any clinical findings; hearing and ophtho exam within one month

<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant clinical exam</th>
<th>Before hospital discharge</th>
<th>Infant testing</th>
<th>2 wks.</th>
<th>1 mo.</th>
<th>2 mos.</th>
<th>3 mos.</th>
<th>4–6 mos.</th>
<th>9 mos.</th>
<th>12 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory evidence of Zika virus infection*</td>
<td>No evidence of abnormalities</td>
<td>Routine newborn care: PE, HC, weight/length, and neurologic exam Hearing screen Head US Infant Zika virus testing (Table 1)</td>
<td>Negative for Zika virus infection</td>
<td>Routine care, including monitoring of OFC and development at every well child visit and age-appropriate developmental screening</td>
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<tr>
<td>Abnormalities consistent with congenital Zika syndrome</td>
<td>As above plus: Consider transfer to hospital with subspecialty care CBC, metabolic panel, LFTs, ophthalmology exam ABR</td>
<td>Negative for Zika virus infection*</td>
<td>Laboratory evidence of Zika virus infection</td>
<td>Ophthalmology exam ABR</td>
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<td>Consider repeat ABR Behavioral audiology if ABR not done at 4–6 mos.</td>
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<td></td>
<td>Monitoring of OFC and development at every visit and age-appropriate developmental screening (Box 4)</td>
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<td>Evaluate for other causes of congenital anomalies Further management as clinically indicated</td>
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<td></td>
<td>Laboratory evidence of Zika virus infection*</td>
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<td></td>
<td>Thyroid screen Neurologic exam Neurologic exam Thyroid screen, ophthalmology exam Repeat ABR</td>
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<td></td>
<td>Routine preventive health care including monitoring of feeding and growth Routine and congenital infection-specific anticipatory guidance Referral to specialists, including evaluation of other causes of congenital anomalies as needed (Box 3)</td>
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</tr>
</tbody>
</table>

advanced neuroimaging (Box 2)
<table>
<thead>
<tr>
<th>Not tested, or tested outside of appropriate window</th>
<th>No evidence of abnormalities</th>
<th>Maternal Zika virus testing</th>
<th>Perform infant Zika virus testing if evidence of Zika virus infection on maternal testing*</th>
<th>Outpatient management for appropriate infant clinical exam and test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormalities consistent with congenital Zika syndrome</td>
<td>As above, plus: Consider transfer to hospital with subspecialty care. CBC, metabolic panel, LFTs, ophthalmology exam ABR Consider advanced neuroimaging Infant Zika virus testing (Table 1)</td>
<td>Negative for Zika virus infection Laboratory evidence of Zika virus infection*</td>
<td>Evaluate for other causes of congenital anomalies Further management as clinically indicated</td>
<td>Refer to outpatient management for infant with abnormalities consistent with congenital Zika syndrome</td>
</tr>
</tbody>
</table>
Zika Resources

- ACOG’s Zika webpage: [www.acog.org/zika](http://www.acog.org/zika)
- CDC Zika Pregnancy Hotline for Healthcare Providers: 770-488-7100 or email ZikaPregnancy@cdc.gov for concerns related to clinical management
- CA Department of Public Health webpage for health care professionals
  - [www.cdph.ca.gov/zika](http://www.cdph.ca.gov/zika) see Information for Health Professionals

QUESTIONS?