The Buzz on Zika: An Update for Clinicians
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Facts and impact

Where is it now?

Counseling, testing, and surveillance

PACLAC 2017

ZIKA TODAY
Aedes aegypti
Background

- Zika virus is transmitted to humans primarily through the bite of infected *Aedes* sp. mosquito
  - Nearly all Zika outbreaks due to *aegypti* & *albopictus*
  - These are the same mosquitoes that transmit dengue and chikungunya
    - Dengue and Zika are flaviviruses (YF); chikungunya: alphavirus
    - West Nile also arbovirus/flavivirus, but spread by Culex sp.
  - The mosquito vectors typically breed in domestic water-holding containers
  - *Aegypti* -- high “vectorial capacity”: 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 mosquitoes get infected and spread the virus

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

More members in the community become infected

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
Centers for Disease Control and Prevention
Aedes aegypti and Aedes albopictus Mosquitoes in California Detection Sites by County/City
Updated May 12, 2017

Counties with **Aedes aegypti** only:
Fresno, Imperial, Madera, Riverside, San Mateo, Tulare

Both **Aedes aegypti** and **Aedes albopictus**:
Kern, Los Angeles, Orange, San Bernardino, San Diego
Zika – Disease and Risks
Clinical Disease

- About 20% of people infected with Zika virus become symptomatic
- 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
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**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
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<tbody>
<tr>
<td>2010</td>
<td>153</td>
</tr>
<tr>
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<td>175</td>
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<tr>
<td>2013</td>
<td>167</td>
</tr>
<tr>
<td>2014</td>
<td>147</td>
</tr>
<tr>
<td>2015-2016</td>
<td>4,568</td>
</tr>
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</table>

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

*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 $\text{HC} < 3^{\text{rd}} \% \text{ile}$ 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
Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?
CT Scans Reveal Extensive Abnormalities

23 infants with microcephaly in Pernambuco, Brazil

- Intracranial calcifications
- Global cortical hypogyration
- Ventriculomegaly
- Global cerebellar hypoplasia

Hazin et al, NEJM April 6, 2016
Fig 3 Severe microcephaly.
Fetal Brain Anomalies

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

- Emerging reports and series of long-term functional motor and sensory abnormalities
  - Pestorius et al, CDC, 8/4/16: “late-onset microcephaly” in series from Brazil: normal head size at birth, abnormal by 6 months

- Update on 13 infants **born without microcephaly** but ZKV-infected (Brazil)
  - Neuroimaging abnormal in all: all w/ ↓ brain volume, +/- ↑ vents
  - 11 referred for small head size but > 2SD, 2 for devel. lag (5, 7 mos)
  - 10 w/dysphagia, 3 w/chorioretinitis, all hypertonic  *(MMWR 11/16)*

- Anticipate a spectrum of outcomes?
  - Developmental delay
  - Intellectual impairments
  - Motor abnormalities
Marked early hypertonia and symptoms of extrapyramidal involvement

- Loss of upper motor and alpha motor neurons can result in hypertonia, or increase in muscle tone.
- Increased resistance is apparent when the arms and legs are extended.
- Hyperextension of the back and tightly clenched fists are often seen.

Sources: [http://neuroscience.uth.tmc.edu/s3/chapter06.html](http://neuroscience.uth.tmc.edu/s3/chapter06.html) and [http://www.slideshare.net/peso88888/neonatal-examination-45813957](http://www.slideshare.net/peso88888/neonatal-examination-45813957)
Zika-Related Arthrogryposis

van der Linden at al, BMJ 8/16
29 infants with microcephaly
  - 79% with suspected Zika
    - 18 in first trimester
  - 29% with ocular findings
    - Bilateral macular and perimacular lesions
    - Optic nerve abnormalities

Freitas et al, JAMA Ophthalmology online 2/9/16
Ophtho criteria for CZS

- First ophthalmological examination has to be performed within 30 days of birth.
  - **Red Reflex Test** does **NOT** work for diagnosis in cases of CZS
  - 72 patients with CZS -- normal RRT

- **SIGNS**: Focal pigment mottling of the retina and circular lesions of chorioretinal atrophy including the macula, along with optic nerve abnormalities
  - Identified in 30% of newborns with microcephaly (Frietas et al, JAMA Ophtho 2/16)

- **UNIQUE CHORIORETINAL ATROPHY**
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
Pregnancy Risk Estimates

- Brasil et al (NEJM, 12/16): Rio cohort
  - Expands prospective study cohort from 88 to 134 symptomatic pregnant women with confirmed ZKV infection
  - Overall, 49/117 (42%) liveborn ZKV-exposed infants had abnormal findings by 1st month of life [5% in ZKV(-): p< 0.001]

- Adverse outcomes seen regardless of trimester of infx
  - 55% risk if maternal infx in 1st, 52% if in 2nd, 29% if in 3rd

- Recent report from US Zika Pregnancy Registry (n = 442)
  - Birth defects related to Zika in 26 (6%), 21 in live births
  - No risk difference regarding sx; 11% risk if exposure in 1st Δ
  - As registry, selection bias possible, and Δ exposure not “pure”

Zika – Where is it and where is it not?
As of May 2017: CDC.gov

Reported active Zika virus transmission
No reported active Zika virus transmission

Data as of 14 December 2016

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

British Virgin Islands
US Virgin Islands
Saint Martin
Sint Maarten
Saint Barthélemy
Anguilla
Saba
Sint Eustatius

St. Kitts and Nevis
Montserrat
Antigua & Barbuda
Guadeloupe
Dominica
Martinique
Saint Lucia
St. Vincent and the Grenadines
Grenada
Trinidad and Tobago
Barbados
Zika as an Endemic Infection

- Zika virus is considered **endemic** in some countries, and a large number of local residents are likely to be immune. However, US travelers to endemic areas may not be immune to Zika virus and infections have occurred among travelers to Asia and Africa.

- Zika evolving as an outbreak like other arboviruses: areas of endemicity but high potential (like West Nile and chikungunya) for ongoing sporadic cases and local outbreaks  *(Paules C, Fauci A: JAMA 1/12/17)*
Zika in the US: as of May 10, 2017

US States/DC (5273 cases): 110 in 2017

- Travel-associated Zika virus disease cases reported: 4830 (48 sexually transmitted: 7 in CA)
  - Locally acquired vector-borne cases reported: 224
  - In 2017: all travel cases so far

US Territories

- Travel-associated cases reported: 147 (0 in 2017)
- Locally acquired cases reported: 36581 (including 493 so far in 2017)
  - 51 cases of Guillain-Barre syndrome
Current Zika Statistics (as of 4/25/17)

• 1793 pregnant travelers with laboratory evidence of Zika virus in US States and DC – vast majority imported/travel-related
  o 1409 completed pregnancies
  o 58 reported liveborn infants and 8 fetal losses with Zika related birth defects

• 3700 pregnant cases in US territories (mostly Puerto Rico)

• CA --117 confirmed infections in pregnant women (5/12)
  o 5 liveborn infants and 0 fetal losses with Zika related birth defects
Laboratory-confirmed symptomatic Zika virus disease cases* reported to ArboNET by states and territories—United States, 2017 (Provisional data as of May 10, 2017)

*Case counts include all symptomatic Zika virus disease cases, including cases in travelers returning from affected areas, cases acquired through presumed local mosquito-borne transmission and cases acquired through other routes. Cross hatching signifies areas with reported local mosquito-borne transmission in 2017.
CDPH Weekly Update on Number of Zika Virus Infections in California
May 12, 2017

The following table provides the number of travel-associated infections with Zika virus in California residents during 2015–2017. CDPH is following CDC testing guidelines. This table is updated every Friday. As of May 12, 2017, there have been 541 travel-associated Zika virus infections in California.

- Total infections: 541
- New infections reported this week: 2
- Locally acquired infections: 0
- Cumulative number of infections due to sexual transmission: 7
- Cumulative number of infections in pregnant women: 117
  - Liveborn infants with birth defects: 5
  - Pregnancy losses with birth defects: 0

<table>
<thead>
<tr>
<th>County</th>
<th>Travel-associated 2015-2016</th>
<th>Travel-associated 2017</th>
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</thead>
<tbody>
<tr>
<td>Alameda</td>
<td>35</td>
<td>0</td>
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<tr>
<td>(City of Berkeley)</td>
<td>(3)</td>
<td></td>
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<tr>
<td>Butte</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Contra Costa</td>
<td>26</td>
<td>2</td>
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<tr>
<td>Fresno</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Humboldt</td>
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<td>0</td>
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<tr>
<td>Kern</td>
<td>5</td>
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<tr>
<td>Kings</td>
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<td>Lake</td>
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<tr>
<td>Los Angeles</td>
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<td>7</td>
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<tr>
<td>(City of Long Beach)</td>
<td>(6)</td>
<td></td>
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<tr>
<td>Marin</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Mendocino</td>
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<td>1</td>
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<tr>
<td>Merced</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Monterey</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Napa</td>
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<td>Nevada</td>
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<td>Orange</td>
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<td>Placer</td>
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<td>Sacramento</td>
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<td>San Benito</td>
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<td>San Bernardino</td>
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<td>San Diego</td>
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<td>4</td>
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<table>
<thead>
<tr>
<th>County</th>
<th>2015-2016</th>
<th>2017</th>
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<td>San Francisco</td>
<td>29</td>
<td>6</td>
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<td>San Joaquin</td>
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<td>San Luis Obispo</td>
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<td>San Mateo</td>
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<td>0</td>
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<td>Sonoma</td>
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<td>Stanislaus</td>
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<td>Tulare</td>
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<td>Ventura</td>
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<tr>
<td>Yuba</td>
<td>3</td>
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<tr>
<td>Total</td>
<td>503</td>
<td>38</td>
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Imported Zika Cases in California, 2015-17
(n = 539, through May 5, 2017)

<table>
<thead>
<tr>
<th>Country Traveled To</th>
<th>Number of Imported Cases in California (%)</th>
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<tbody>
<tr>
<td>Mexico</td>
<td>195 (36%)</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>61 (11%)</td>
</tr>
<tr>
<td>Guatemala</td>
<td>49 (9%)</td>
</tr>
<tr>
<td>El Salvador</td>
<td>37 (7%)</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>26 (5%)</td>
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These 5 countries account for 68% of travel cases in CA

Median age 35

66% in women
Confirmed Zika Cases in Mexico by State
January 1, 2016 – August 8, 2016

N = 1,490

Data provided by the Mexican Ministry of Health
Confirmed Zika Cases in Mexico by State
January 1, 2016 – May 8, 2017

Data provided by the Mexican Ministry of Health

Ag. = Aguascalientes
Quer. = Querétaro
DF = Distrito Federal
Tl. = Tlaxcala
Increase from 37 cases for 2017 in data from Feb 3rd

To date: 62 local cases in pregnant women

<table>
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<tr>
<th>Entidad Federativa</th>
<th>Casos Confirmados 2015-2016</th>
<th>Casos Confirmados 2017</th>
<th>Total</th>
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<td>Aguascalientes</td>
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<tr>
<td>Baja California</td>
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<td>2</td>
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<tr>
<td>Baja California Sur</td>
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<td>26</td>
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<tr>
<td>Campeche</td>
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<td>92</td>
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<td>Coahuila</td>
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<td>62</td>
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<td>Colima</td>
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<td>Chiapas</td>
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<td>Nayarit</td>
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<td>97</td>
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<td>Puebla</td>
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<tr>
<td>Quintana Roo</td>
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<td>Veracruz</td>
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<td>Yucatán</td>
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<td>Zacatecas</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>8,573</strong></td>
<td><strong>162</strong></td>
<td><strong>8,735</strong></td>
</tr>
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</table>
Local Zika Transmission in Florida and Texas
Local Zika Transmission in FLA, TX

- Pregnant women should avoid travel to Miami-Dade, FLA and Brownsville, TX
- Pregnant women who traveled to, lived in, or had unprotected sex with someone who lives in or traveled to these areas should be tested
  - After Aug 1, 2016 for Miami-Dade
  - After Oct 29, 2016 for Brownsville
- **BUT: Biggest risk in U.S. still remains travel exposure**
Zika – Education and Testing
Guidance from other Viral Infections?

- Well-established risks and effects of maternal infection with rubella and CMV
- Both with greater impact with 1\textsuperscript{st} trimester infection but still impact later
  - Congenital rubella in 90% of 1\textsuperscript{st} infection
  - CMV: 30% infection risk across pregnancy, with greater risk of severe impact with 1\textsuperscript{st} infection
- US prevalence of microcephaly: 6 cases per 10,000 live births (range: 2-12)
  - With Zika, risk of developmental brain abnormalities will be greater than risk of microcephaly
What do we tell our pregnant patients?

- How much fetal risk with confirmed maternal infection?
  - Based on current data, range may be as high as 29-40%
  - 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 Oduyebo, MD1; Irogue Igbinosa, MD2; Emily E. Petersen, MD1; Kara N.D. Polen, MPH2; Satish K. Pillai, MD3; Elizabeth C. Ailes, PhD2; Julie M. Villanueva, PhD3; Kim Newsome, MPH2; Marc Fischer, MD4; Priya M. Gupta, MPH5; Ann M. Powers, PhD4; Margaret Lampe, MPH6; Susan Hills, MBBS4; Kathryn E. Arnold, MD2; Laura E. Rose, MTS3; Carrie K. Shapiro-Mendoza, PhD1; Charles B. Beard, PhD4; Jorge L. Muñoz, PhD4; Carol Y. Rao, ScD7; Dana Meaney-Delman, MD8; Denise J. Jamieson, MD1; Margaret A. Honein, PhD2

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-
Zika Testing – What’s new?

- 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 rec for asymptomatic partner of a pregnant woman still emphasize condoms thru pregnancy

MMWR, 7/25/16
Zika Testing – What Testing should be done?

- **PCR**: tests for the *virus* (acute testing), antibodies: test for *previous exposure* to the virus
  
  - PCR done for all pts with symptoms, and for all pregnant women with exposure — within **2 weeks**: test blood AND urine
    
    - Exposure includes 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)
    - If Ab (+), then further testing done to confirm (PRNT)
Zika Testing – How?

- Recently emergency-approved commercially available tests for PCR and IgM
  - Cost and collection issues
  - Shorter turnaround time (5-7 days) than public health labs
  - No “control” on testing
  - Confirmatory IgM testing still goes to public health labs

- **No IgG test has been approved**

- 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)
CDC Zika Testing Update: HAN 5/5/17
-- Guidance related to prolonged IgM responses

- Revised guidance based on newer data from Puerto Rico showing IgM persistence > 12 weeks (like other flavivirus infections) – **87% were still (+) at 2 months**
  - In one subset of pts, median time for IgM to first negative Zika IgM after infection of 4 months (range 8-210 days)

- Revisions mostly apply to asymptomatic pregnant women living in or frequently traveling to areas with local Zika transmission

- Also address “consideration” of Zika antibody testing before pregnancy for women who may have been exposed

CDC Revised Testing Guidelines – May 5, 2017

- Add **Zika PCR testing every trimester** to IgM for asymptomatic pregnant women at high risk of ongoing exposure (unless a previous PCR was +)
  - Detection of IgM may not always represent recent infection
  - Could be positive in a woman infected before pregnancy

- **Screen pregnant women for Zika exposure risk** at every prenatal visit and test promptly with PCR for sx

- **Consider Zika Ab testing before pregnancy** in women with possible pre-conception exposure
  - This does not imply a “safe” period to get pregnant, but can help determine if someone is actually infected during pregnancy
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

• Zika has recently been shown to cause testicular damage in mouse models (Govero J, et al. Lancet Dec 15, 2016)
  - ZKV persistence in testis/epididymis → tissue injury resulting in diminished testosterone and inhibin B levels and oligospermia
<table>
<thead>
<tr>
<th>Possible exposure via recent travel or sex without a condom with a partner infected with Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Wait at least 8 weeks after symptoms start or last possible exposure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People living in or frequently traveling to areas with Zika</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>Positive Zika test</td>
<td>Wait at least 8 weeks after symptoms start</td>
</tr>
<tr>
<td>No testing performed or negative test</td>
<td>Wait at least 6 months after symptoms start</td>
</tr>
<tr>
<td></td>
<td>Talk with doctor or healthcare provider</td>
</tr>
<tr>
<td></td>
<td>Talk with doctor or healthcare provider</td>
</tr>
</tbody>
</table>

CDC: Oct 3, 2016
Guidance: Newborns at Risk for Congenital Infection

CDC has updated its interim guidance for U.S. health care providers caring for infants born to mothers with possible Zika virus infection during pregnancy. Laboratory testing is recommended for infants born to mothers with laboratory evidence of Zika virus infection during pregnancy and for infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results. Congenital Zika syndrome is a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes microcephaly, intracranial calcifications, or other brain anomalies, or eye anomalies, among others. Recommended infant laboratory evaluation includes both molecular (real-time reverse transcription–polymerase chain reaction [rRT-PCR]) and serologic (immunoglobulin M [IgM]) testing. Initial samples should be collected directly from the infant in the first 2 days of life, if possible; testing of cord blood is not recommended. A positive infant serum or urine rRT-PCR test result confirms congenital Zika virus infection. Positive Zika virus IgM testing, with a negative rRT-PCR result, indicates probable congenital Zika virus infection. In addition to infant Zika virus testing, initial evaluation of all infants born to mothers with laboratory evidence of Zika virus infection during pregnancy should include a comprehensive physical examination, including a neurologic examination, postnatal head ultrasound, and standard newborn hearing screen. Infants with laboratory evidence of congenital Zika virus infection should have a comprehensive ophthalmologic exam and hearing assessment by auditory brainstem response (ABR) testing before 1 month of age. Recommendations for follow-up of infants with laboratory evidence of congenital Zika virus infection depend on whether abnormalities consistent with congenital Zika syndrome are present. Infants with abnormalities consistent with congenital Zika syndrome should have a coordinated evaluation by multiple specialists within the first month of life; additional evaluations will be needed within the first year of life, including assessment of vision, hearing, feed- ing, growth, and neurodevelopmental and endocrine function. Families and caregivers will also need ongoing psychosocial support and assistance with coordination of care. Infants with laboratory evidence of congenital Zika virus infection without apparent abnormalities should have ongoing developmental monitoring and screening by the primary care provider; repeat hearing testing is recommended. This guidance will be updated when additional information becomes available.

Zika virus infection during pregnancy is a cause of microcephaly and other serious brain anomalies (8); however, the clinical spectrum of the effects of Zika virus infection during pregnancy is not yet known. A wide range of neurologic abnormalities, in addition to microcephaly, has been observed among infants with presumed or confirmed congenital Zika virus infection (2,6). Reported neuroimaging findings include intracranial calcifications; ventriculomegaly and extracranial fluid; abnormal gyral patterns (e.g., polymicrogyria); decreased brain parenchymal volume; cortical atrophy and malformation; hypoplasia of the cerebellum, cerebellar vermis or brainstem; delayed myelination; and thinning or hypoplasia of the corpus callosum (3,6). Neurologic abnormalities apparent on examina- tion of these infants have included hypertonia, hypotonia, spasticity, hypreflexia, severe irritability, and seizures (2,6). Zika virus appears to primarily target neural progenitor cells resulting in cell death and disruption of neuronal proliferation, migration, and differentiation, which slows brain growth and affects neural cell viability (7–9). Ocular findings reported in infants with presumed or confirmed congenital Zika virus
CDC’s Response to Zika

INTERIM GUIDANCE

Neonatal coordination is Critical!

Evaluation and testing of infants with possible congenital Zika virus infection

Mother with laboratory evidence of Zika virus infection during pregnancy*

- Perform a comprehensive physical exam on infant, head ultrasound, standard newborn hearing assessment and infant Zika virus laboratory testing

Infant with findings consistent with congenital Zika virus syndrome

- Initial evaluation
  - Infant with laboratory confirmed or probable congenital Zika virus infection
    - Outpatient management and follow-up
  - Infant negative for congenital Zika virus infection
    - Continue to evaluate for other causes of congenital anomalies

Infant without findings consistent with congenital Zika virus syndrome

- Infant with laboratory confirmed or probable congenital Zika virus infection
  - Routine newborn care; additionally, perform an ABR and ophthalmology exam within one month of life
  - Outpatient management and follow-up

- Infant negative for congenital Zika virus infection
  - Routine care

*Laboratory evidence of maternal Zika virus infection includes: (1) Zika virus RNA detected by real-time reverse transcription-polymerase chain reaction (rRT-PCR) in any clinical specimen; or (2) positive Zika virus immunoglobulin M (IgM) with confirmatory neutralizing antibody titers. Mother’s should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or IgM within 2-12 weeks of exposure or symptom onset. Due to the decline in IgM antibody and viral RNA levels over time, negative maternal testing 12 weeks after exposure does not rule out maternal infection.

Abbreviation: ABR = auditory brainstem response.

## Implementing CDC Guidance for Infant and Placental Zika Virus Testing and Infant Head Ultrasound

Based on maternal Zika virus exposure and laboratory test results

### Notes:
1. This tool summarizes general CDC guidance for the following scenarios. The tool only addresses live births. Please consult CDC or your state or local health department for case-specific questions. Health departments should adapt CDC guidance depending on local capacity and circumstances.
2. Infant serum and urine should be tested for Zika virus by Zika NAT and infant serum for Zika virus IgM antibodies. If IgM is obtained, it can also be tested. Please refer to the published guidance for more information.
3. Placental testing includes testing of formalin-fixed or formalin-fixed, paraffin-embedded placenta, umbilical cord, and fetal membranes by ZIKV RT-PCR. Microscopic evaluation of fixed tissues is conducted in selected cases. Please note that a positive RT-PCR result from placental testing cannot distinguish between maternal and fetal infection; therefore, a positive RT-PCR result from the placenta can confirm maternal Zika infection but cannot be used to confirm congenital Zika infection in the infant. Negative NAT results on placental tissue do not exclude maternal Zika virus infection, as the duration of ZIKV persistence in the placenta is unknown and the samples evaluated may not reflect the placenta as a whole. Refer to the website for further guidance.

### Timing of Zika virus exposure relative to timing of maternal specimen collection

<table>
<thead>
<tr>
<th>Test results and interpretation of maternal specimens (serum, urine, and whole blood)</th>
<th>EXPOSURE WITHIN ANY TIME PERIOD</th>
<th>ALL EXPOSURE WITHIN 12 WEEKS OF SPECIMEN COLLECTION</th>
<th>INFANT TESTING</th>
<th>PLACENTAL TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ZIKV infection</td>
<td>NAT positive OR non-negative Zika IgM, Zika PRINT ≥ 10, and dengue PRINT &lt; 10</td>
<td>Presumptive recent ZIKV or flavivirus infection non-negative Zika IgM, PRINT pending</td>
<td>Additional Maternal Testing: Follow up PRINT results, if indicated according to lab guidance. If maternal IgM is inconclusive, repeat qMx testing in accordance with EUA.</td>
<td>Placental Testing: Should be considered to aid in maternal diagnosis.</td>
</tr>
<tr>
<td>Recent flavivirus infection, specific virus cannot be identified OR non-negative Zika IgM AND Zika PRINT &gt; 10, and dengue PRINT ≥ 10</td>
<td>Neurimaging: Head ultrasound should be performed before hospital discharge.</td>
<td>Additional Maternal Testing: Recommended. Specimens should be collected within 2 days of birth.</td>
<td>Placental Testing: Fix and store placenta until maternal PRINT results are available. Based on maternal PRINT result interpretation, refer to appropriate column.</td>
<td></td>
</tr>
<tr>
<td>No evidence of ZIKV infection</td>
<td>Zika IgM negative OR non-negative Zika IgM, Zika PRINT &lt; 10</td>
<td>Presumptive recent ZIKV or flavivirus infection non-negative Zika IgM, PRINT pending</td>
<td>Additional Maternal Testing: Follow up PRINT results, if indicated according to lab guidance. If maternal IgM is inconclusive, repeat qMx testing in accordance with EUA.</td>
<td>Placental Testing: Should be considered to aid in maternal diagnosis.</td>
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<tr>
<td>Presumptive recent ZIKV or flavivirus infection non-negative Zika IgM, PRINT pending</td>
<td>Neurimaging: Head ultrasound should be performed before hospital discharge.</td>
<td>Additional Maternal Testing: Recommended. Specimens should be placed within 2 days of birth.</td>
<td>Placental Testing: Should be considered to aid in maternal diagnosis.</td>
<td></td>
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</tbody>
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### Infant Testing

- **Neurimaging:** Head ultrasound should be performed before hospital discharge.
- **Infant Testing:** Recommended; specimens should be collected within 2 days of birth.
- **Infant Testing:** Recommended; specimens should be collected within 2 days of birth. Consider testing CSF if serum and urine results are negative.
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### Placental Testing

- **Neurimaging:** Head ultrasound should be performed before hospital discharge.
- **Placental Testing:** Not indicated; no added diagnostic value given known maternal Zika diagnosis.
- **Placental Testing:** Should be considered to aid in maternal diagnosis.
- **Placental Testing:** Fix and store placenta until maternal PRINT results are available. Based on maternal PRINT result interpretation, refer to appropriate column.
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### Additional Testing

- **Neurimaging:** Head ultrasound should be performed before hospital discharge.
- **Infant Testing:** Specimens should be collected within 2 days of birth. Decision to test the infant can be deferred until maternal test results are available. Based on maternal PRINT result interpretation, refer to appropriate column.
- **Infant Testing:** Specimens should be collected within 2 days of birth and stored. Decision to test the infant can be deferred until maternal test results are available.

### Infant outcome

- **Infant outcome:** Neuroimaging: Head ultrasound should be performed before hospital discharge.
- **Infant outcome:** Infants should be collected within 2 days of birth.

### Abbreviations

- CT: Computed Tomography
- EUA: Emergency Use Authorization
- IgM: Immunoglobulin M
- MRI: Magnetic Resonance Imaging
- NAT: Nucleic Acid Test (includes RT-PCR; PRINT: RPA-Reduction Neutralization Test; hF-PCR: Real-Time Reverse Transcription-Polymerase Chain Reaction; hF-PCR: Reverse Transcription-Polymerase Chain Reaction; ZIKV: Zika virus.

### Authorship

1. Please contact CDC Zika Pregnancy Hotline at 770-488-1100 or cdczika@cdc.gov.
2. Possible Zika virus exposure is defined as travel to or residence in an area with risk of Zika virus or without a condom during sexual activity with someone who traveled to or resided in an area with risk of Zika.
3. Start and end date of exposure are both within the 12-week testing window.
4. Non-negative serology/titer variability by assay and example include positive, equivocal, presumptive positive, or possible positive results. For explanation of a specific interpretation and information on each case, refer to the CDC’s Zika virus guidance website (https://www.cdc.gov/zika/), under the “Guideline” tab for the specific assay. Inoculational maternal IgM should be retested in accordance with EUA. If the inoculational maternal IgM cannot be reconciled, refer to the relevant exposure category “Clinical” column, and base decision to test placenta on maternal and infant test results.

### References

6. If infant testing is done is should be performed before placental testing, if possible. If [1] infant IgM is positive for ZIKA, or [2] infant IgM is positive or equivocal AND infant or maternal PRINT is positive for ZIKA, but not for dengue, then there is a need for maternal testing. If either maternal test results are obtained, placental testing may provide another opportunity to identify maternal infection that would otherwise be unaccompanied.

### Additional Information

- [CDC Zika Virus Pregnancy Outcomes website](https://www.cdc.gov/zika/)
Assessment and Testing for Zika in Pregnant Women and their Newborns: Information for Birth Hospitals (June 1, 2017)

Zika Basics: Zika virus infection during pregnancy has been linked to problems such as miscarriage, stillbirth, potential long-term impacts and Zika-associated birth defects among 10% of pregnant women with laboratory confirmed Zika infection. For more information on Zika, please see CDPH Zika Questions and Answers and CDPH Zika Virus Information for Health Care Providers.

Standard precautions are recommended to prevent the spread of Zika in healthcare settings. CDC recommendations are available for healthcare providers, including pregnant women, to help prevent exposure to Zika virus in healthcare settings.

Definition of Possible Zika Virus Exposure During Pregnancy:
- Travel to or living in an area with risk of Zika during their pregnancy or up to 8 weeks before conception.
- Sex without a condom with a male partner who had possible exposure to Zika within 6 months prior to sexual contact, or a female partner within 8 weeks of sexual contact.
Note: Most people with Zika virus infection don’t know they have it; only about 20% have symptoms.

1) Assess All Pregnant Women for Possible Zika Virus Exposure and Test for Zika, as indicated:
- All pregnant women should be assessed for possible Zika virus exposure (see above) at each prenatal care visit and at hospital admission. In-hospital assessment for possible Zika exposure should be incorporated as part of the medical/nursing intake process for all pregnant women for both antepartum and delivery admissions.
- For pregnant women with a possible exposure history or known laboratory evidence of Zika virus.
Note: Most people with Zika virus infection don’t know they have it; only about 20% have symptoms.

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- For pregnant women with a possible exposure history or known laboratory evidence of Zika virus
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 mgmt or the Zika Pregnancy Registry
- CA Dept of Public Health webpage for healthcare professionals
  - [www.cdph.ca.gov/HealthInfo/discond/Pages/ZikaInformationforHealthProfessionals.aspx](http://www.cdph.ca.gov/HealthInfo/discond/Pages/ZikaInformationforHealthProfessionals.aspx)
ZIKA INFORMATION FOR HEALTH PROFESSIONALS

Clinical Tools

- Zika Screening Algorithm
- Patient Exposure Self-Assessment...In Spanish
- Risk-Based Testing for Local Transmission
- Evaluation and Follow-up Procedures for Suspected Congenital Zika Virus Infection - Fetus, Newborn, and Infant

Zika Virus Testing

- Laboratory Testing Information
- Viral & Rickettsial Disease Laboratory
- CDC Zika Testing Provider Resource Page
- FAQs for Testing

Provider Resources

- FAQs for Health Care Providers
- FAQs for Infection Control Practices
- Zika and Pregnancy: Info for Clinicians

CDC Guidance