

# **Zika Virus**

## **for Pediatric Providers**

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Bay Area Infectious Disease Conference  
for Perinatal and Pediatric Providers  
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# Disclosures

- None

## Disclaimer

Recommendations subject to change based on CDC and CDPH. See their websites for the most up to date information and recommendations:

- <https://www.cdc.gov/zika/>
- <https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Zika.aspx>

# Objectives

1. Identify risks for Zika transmission and infection.
2. Recognize clinical features of Zika infection – congenital and pediatric
3. Use Zika testing algorithms to identify children at risk for congenital Zika infection and understand long term care of affected children.

# **THE RISE OF ZIKA VIRUS**

# Zika Virus – Origins

## Zika Virus (I). Isolations and serological specificity

G. W. A. Dick, S. F. Kitchen, A. J. Haddow

*Transactions of The Royal Society of Tropical Medicine and Hygiene*, Volume 46, Issue 5, 1 September 1952, Pages 509–520,

[https://doi.org/10.1016/0035-9203\(52\)90042-4](https://doi.org/10.1016/0035-9203(52)90042-4)

**Published:** 01 September 1952

- 1947 – New virus identified in rhesus monkey placed in Zika forest of Uganda; named Zika virus (ZIKV).
- 1948 – Zika virus recovered from *Aedes africanus* mosquito caught in Zika forest.
- 1962-1963 – First human case of Zika virus infection – Uganda.



Frontline - <http://apps.frontline.org/zika/>



EPA/STR

WHO – The History of Zika Virus timeline

Petersen et al, “Zika Virus”, NEJM, April 21, 2016

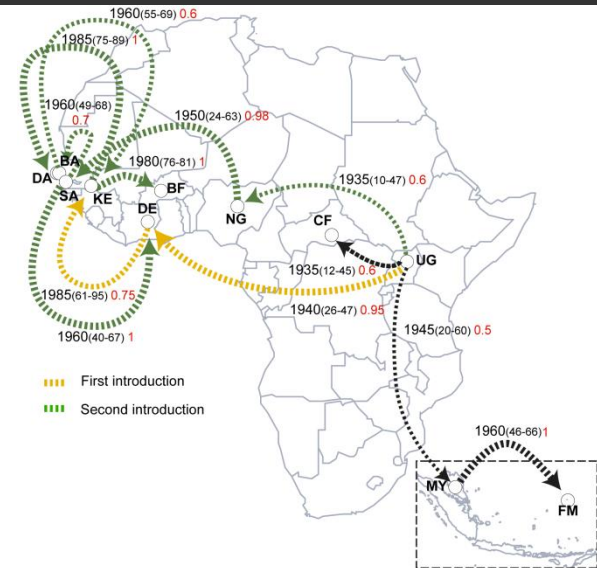
Gubler, et al, “History and Emergence of Zika Virus”, JID 2017:216

# Zika Virus – History

- 1964 – Researcher in Uganda infected with Zika
  - Has “mild” febrile illness.
- 1960s-1980s – Human cases confirmed through blood tests.
  - No deaths or hospitalizations.
  - Disease moves from Uganda to western Africa and Asia.
- 1969-1983 – Zika virus detected in mosquitoes found in equatorial Asia
  - India, Indonesia, Malaysia, Pakistan
- **Only 13 naturally acquired cases reported in 57 years.**

## Molecular Evolution of Zika Virus during Its Emergence in the 20th Century

Oumar Faye Caio C. M. Freire Atila Iamarino Ousmane Faye Juliana Velasco C. de Oliveira  
Mawlouth Diallo Paolo M. A. Zanotto Amadou Alpha Sall



WHO – The History of Zika Virus timeline  
Petersen et al, “Zika Virus”, NEJM, April 21, 2016

Frontline - <http://apps.frontline.org/zika/>

# Zika Virus – First Outbreak

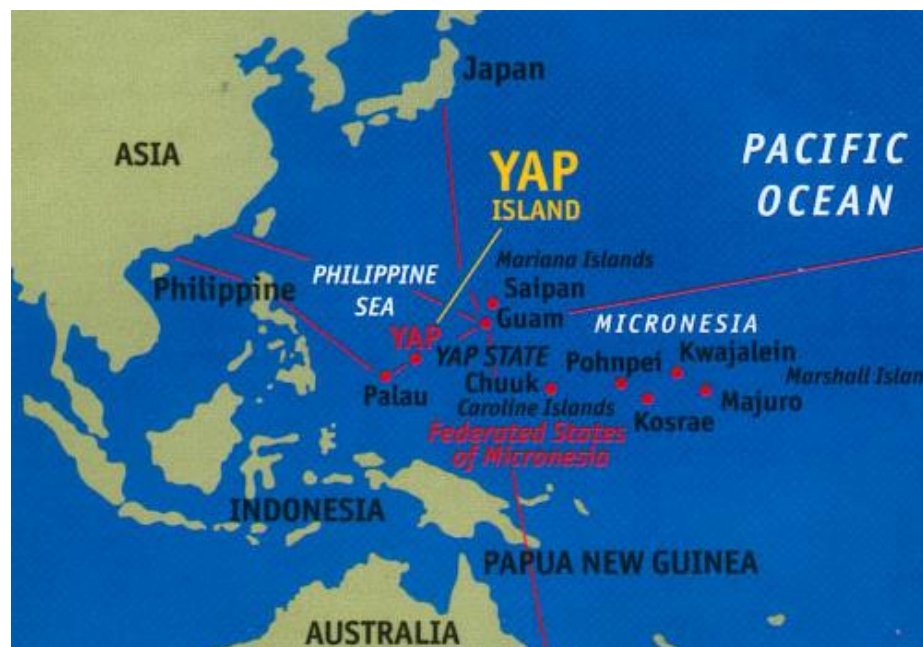
ORIGINAL ARTICLE

## Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Duffy et al, NEJM, June 11 2009



Wikipedia



<http://www.dankainmicronesia.com/islands.html>

- Apr-May 2007 – Yap Island, Federated States of Micronesia
- Outbreak of rash, conjunctivitis, arthralgia
- Zika virus RNA or specific ZIKV neutralizing antibody detected
- 49 confirmed, 59 probable cases of Zika virus disease
- ~73% Yap residents infected
  - ~18% symptomatic
- No deaths or hospitalizations.
- First cases outside Africa and Asia.

# Zika Virus – Early Outbreaks

- More Outbreaks
  - French Polynesia (2013, 2014)
  - New Caledonia (2014)
  - Easter Island (2014)
  - Cook Islands (2014)
- Dec 2013, Feb 2014 – Evidence of perinatal transmission of ZIKV in French Polynesia
  - Two mothers and their newborns infected with ZIKV.
  - Suspected transplacental transmission or during delivery.
- March 2014 – ZIKV detected in blood of asymptomatic blood donors (French Polynesia)



# Zika Virus – The Americas

- March 2015 – Outbreak of exanthematous illness identified in Bahia, Brazil.
  - Campos et al – identified ZIKV in sera of patients
  - Outbreak Feb to June 2015
  - By Dec 2015 – estimated 1.3 million suspected cases
- By March 2016, spread to 33 countries and territories in the Americas

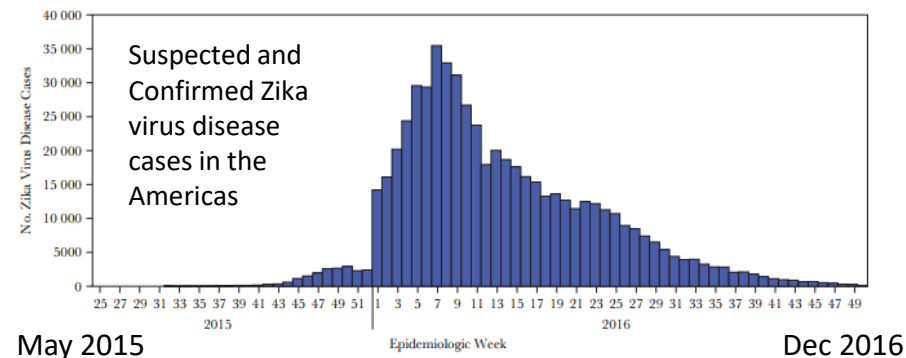


Figure 2. Suspected and confirmed Zika virus disease cases in the Americas reported to the Pan American Health Organization [24] by epidemiological week, May 2015 to December 2016.

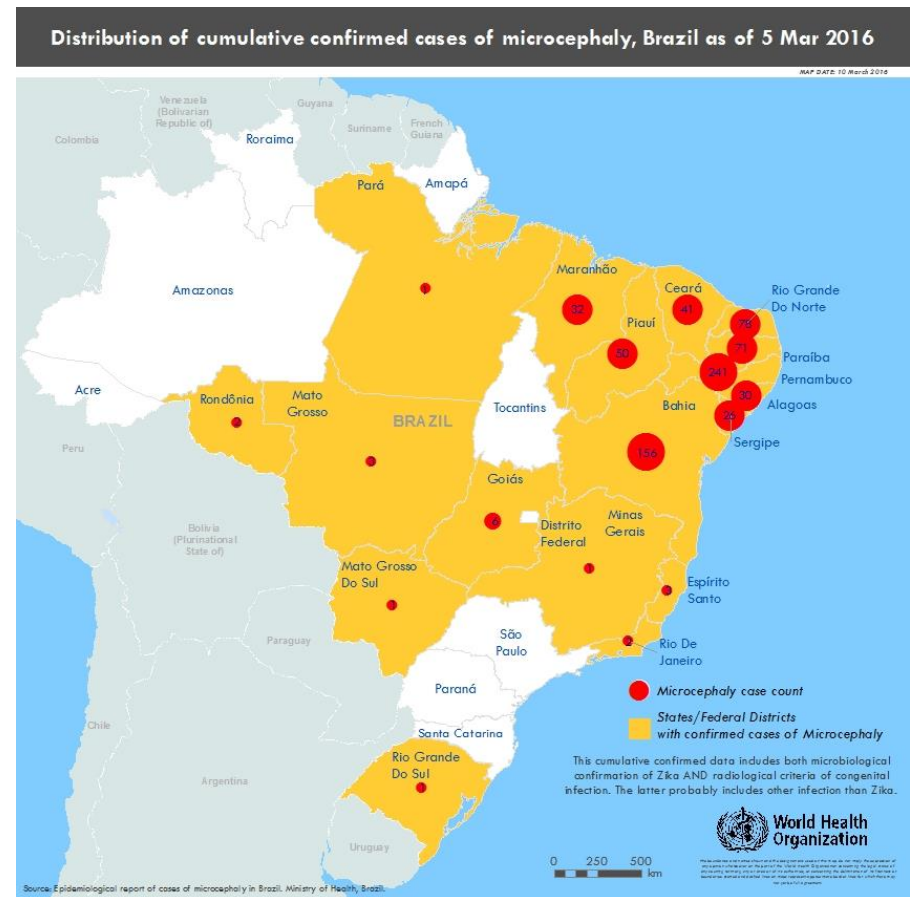
Campos et al, Emerg Inf Dis, Oct 2015

Petersen et al, "Zika Virus", NEJM, April 21, 2016

Hills et al, "Epidemiology of Zika Virus Infection", JID 2017:216

# Microcephaly in Infants in Brazil

- By Sept 2015 – noted increase in infants born with microcephaly.
- By Feb 2016 > 4,300 cases of microcephaly.
  - Overlap with Zika outbreak areas.
  - Also noted in French Polynesia
  - WHO declares Public Health Emergency of International Concern



March 10, 2016 – WHO

## BRIEF REPORT

## Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D.,  
Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc.,  
Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D.,  
Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D.,  
Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

## SUMMARY

A widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 in South and Central America and the Caribbean. A major concern associated with this infection is the apparent increased incidence of microcephaly in fetuses born to mothers infected with ZIKV. In this report, we describe the case of an expectant mother who had a febrile illness with rash at the end of the first trimester of pregnancy while she was living in Brazil. Ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta. After the mother requested termination of the pregnancy, a fetal autopsy was performed. Microcephaly (an abnormally small brain) was observed, with almost complete agyria, hydrocephalus, and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. ZIKV was found in the fetal brain tissue on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, with consistent findings on electron microscopy. The complete genome of ZIKV was recovered from the fetal brain.

Case report of severe fetal brain injury associated with Zika virus infection in a woman pregnant in Brazil in Feb 2015.

Woman sick during end of 1<sup>st</sup> trimester.

Abnormal fetal ultrasound at 29 weeks gestation.

ZIKV detected by RT-PCR in fetal brain tissue on autopsy.

## SPECIAL REPORT

**Zika Virus and Birth Defects — Reviewing the Evidence for Causality**

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,  
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

## SUMMARY

The Zika virus has spread rapidly in the Americas since its first identification in Brazil in early 2015. Prenatal Zika virus infection has been linked to adverse pregnancy and birth outcomes, most notably microcephaly and other serious brain anomalies. To determine whether Zika virus infection during pregnancy causes these

birth outcomes. Addressing these questions will improve our ability to reduce the burden of the effects of Zika virus infection during pregnancy.

POTENTIAL RELATIONSHIP  
BETWEEN ZIKA VIRUS INFECTION  
AND BIRTH DEFECTS

## RESEARCH

**Zika Virus RNA Replication and Persistence in Brain and Placental Tissue**

Julu Bhatnagar, Demi B. Rabeneck, Roosecelis B. Martines, Sarah Reagan-Steiner, Yokabed Ermias, Lindsey B.C. Estetter, Tadaki Suzuki, Jana Ritter, M. Kelly Keating, Gillian Hale, Joy Gary, Atis Muehlenbachs, Amy Lambert, Robert Lanciotti, Titilope Oduyebo, Dana Meaney-Delman, Fernando Bolaños, Edgar Alberto Parra Saad, Wun-Ju Shieh, Sherif R. Zaki

Emerging Infectious Diseases, March 2017

“Sufficient evidence has accumulated to infer a causal relationship between prenatal Zika virus infection and microcephaly and other severe brain abnormalities.”

Zika virus exhibits neurotropism. Found evidence of Zika virus replication and persistence in fetal brain and placenta.

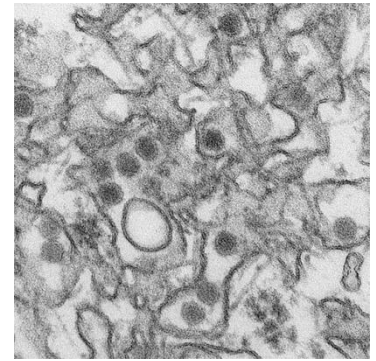
“Never before in history has there been a situation where a bite from a mosquito could result in a devastating malformation.”

Dr. Tom Frieden

CDC Director, April 13, 2016

# **ZIKA VIRUS AND TRANSMISSION**

# Zika Virus



ZIKV, C. Goldsmith/CDC

- Single stranded RNA virus, *Flavivirus*
  - Arbovirus = **Ar**thropod-**borne virus**
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Mosquito-borne transmission – ***Aedes* sp.**
  - *Aedes aegypti* and *Aedes albopictus*



*Aedes aegypti*



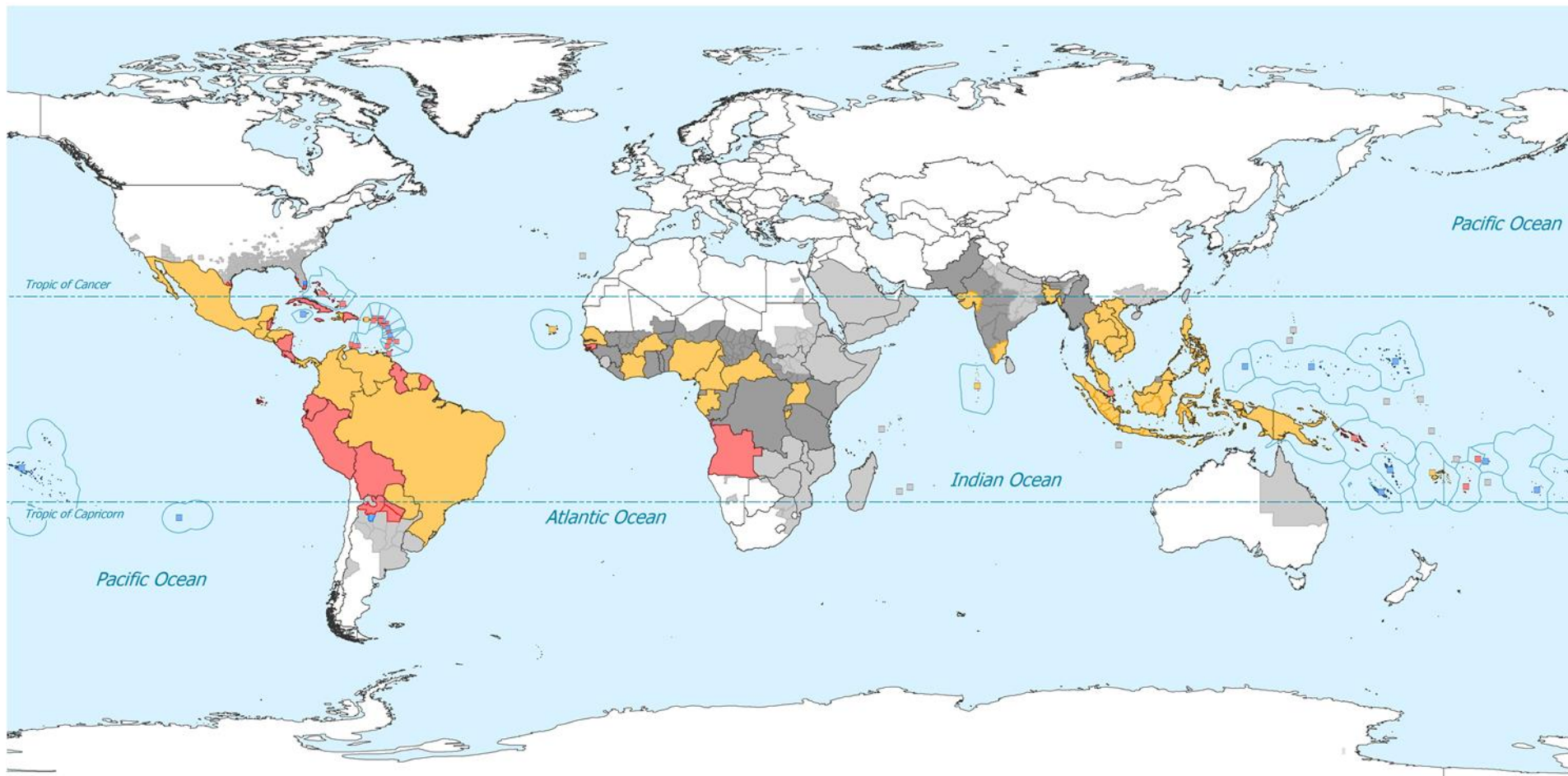
*Aedes albopictus*

**Daytime biting mosquitoes.**

**Feed indoors and outdoors.**



# Current Zika transmission worldwide



Country classification category (Cat.) for Zika virus transmission

- Areas with virus transmission following virus new/re introduction (WHO Cat. 1)
- Areas with virus transmission following previous virus circulation (WHO Cat. 2)
- Areas with interrupted transmission (WHO Cat. 3)

- Areas bordering a WHO Cat. 2 area (sub-category of WHO Cat. 4)
- Areas with potential for transmission (sub-category of WHO Cat. 4)

Maritime Exclusive Economic Zones for non-visible areas



ECDC. Map produced on 19 Dec 2017.  
Map your data at: <https://emma.ecdc.europa.eu>

**December 19, 2017**

**European Centre for Disease Prevention and Control**

<https://ecdc.europa.eu/en/publications-data/current-zika-transmission-worldwide>



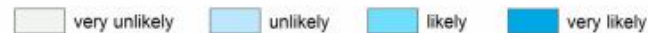
# ESTIMATED range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2017\*



*Aedes aegypti* mosquitoes



Mosquitoes' ability to live and reproduce



*Aedes aegypti* mosquitoes are more likely to spread Zika, dengue, chikungunya, and other viruses than other types of mosquitoes such as *Ae. albopictus* mosquitoes.

*Aedes albopictus* mosquitoes



Mosquitoes' ability to live and reproduce



## These maps DO NOT show

- Exact locations or numbers of mosquitoes living in an area
- Risk or likelihood that these mosquitoes will spread viruses

## These maps show

- CDC's best estimate of the potential range of *Ae. aegypti* and *Ae. albopictus* in the United States
- Areas where mosquitoes are or have been previously found

<https://www.cdc.gov/zika/pdfs/Zika-mosquito-maps.pdf>

As of Sept 20, 2017

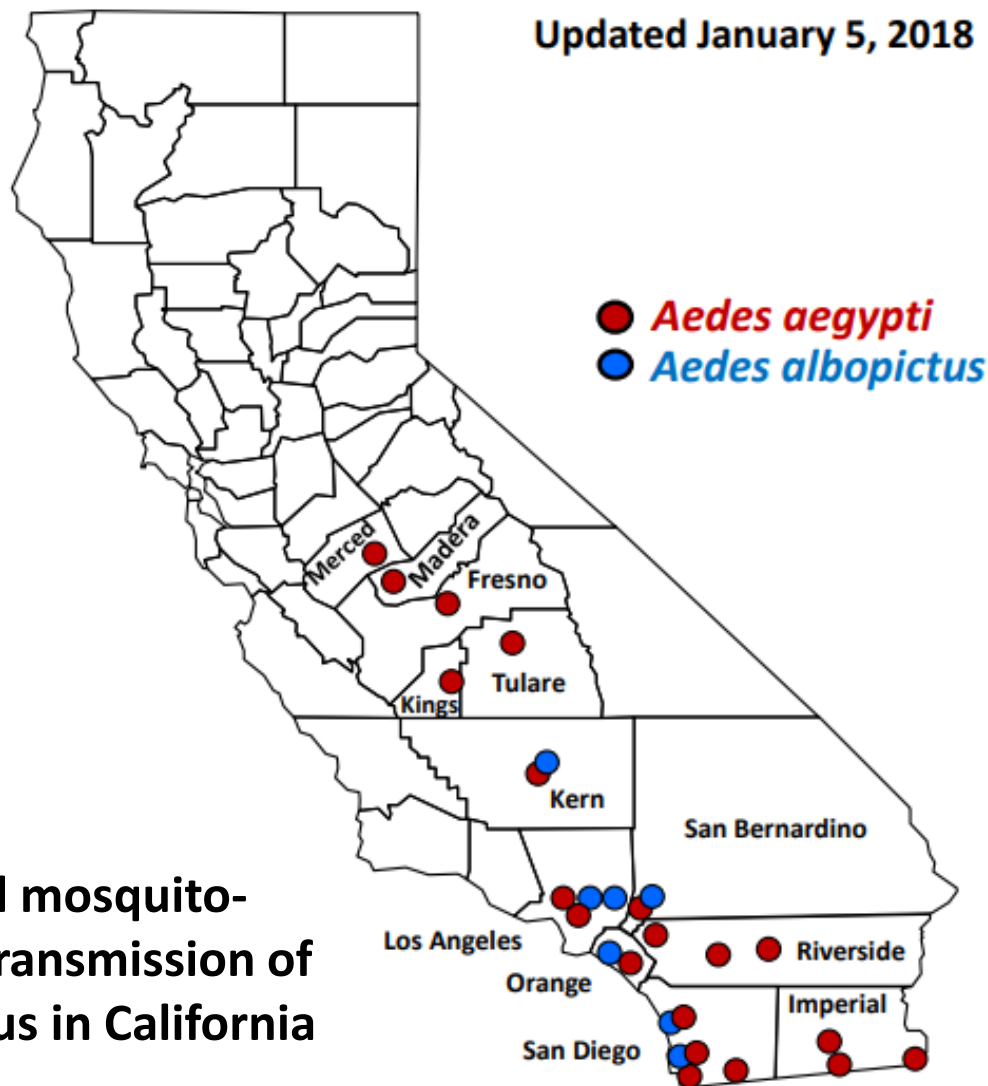


U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

# *Aedes aegypti* and *Aedes albopictus* Mosquitoes in California

## Detection Sites by County/City

Updated January 5, 2018



**Counties with *Aedes aegypti* only:**  
Fresno, Imperial, Kings, Madera, Riverside, Merced, Tulare

**Both *Aedes aegypti* and *Aedes albopictus*:**  
Kern, Los Angeles, Orange, San Bernardino, San Diego

See pages 2 and 3 for *Aedes* detections by city or census-designated place in each county.

**No local mosquito-borne transmission of Zika virus in California to date.**

CA Dept Public Health

# Risk of Local Zika Virus Transmission by County

Extremely Low Risk

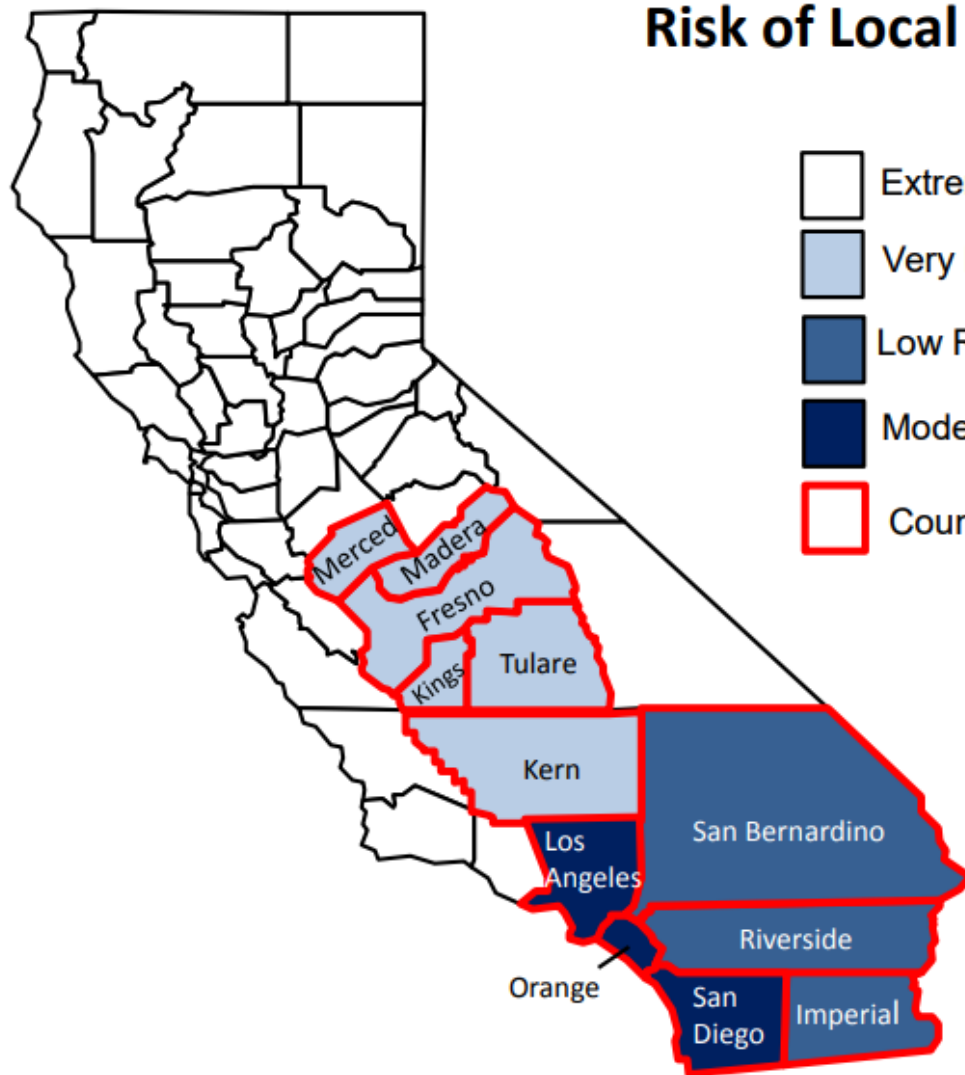
Very Low Risk

Low Risk

Moderate Risk

County with *Aedes* mosquitoes detected\*

\*Zika virus vectors: *Aedes aegypti* and/or *Aedes albopictus*



**Local risk is based on the following factors within a given county:**

- 1) distribution and abundance of *Aedes* mosquitoes
- 2) number of travel-associated Zika cases
- 3) population of county
- 4) distance from U.S.– Mexico border

Risk of local transmission in a county may change in response to factors 1 and 2, or if local Zika virus transmission increases in northern Mexico.



## Seasonal Risk of Local Zika Virus Transmission in California

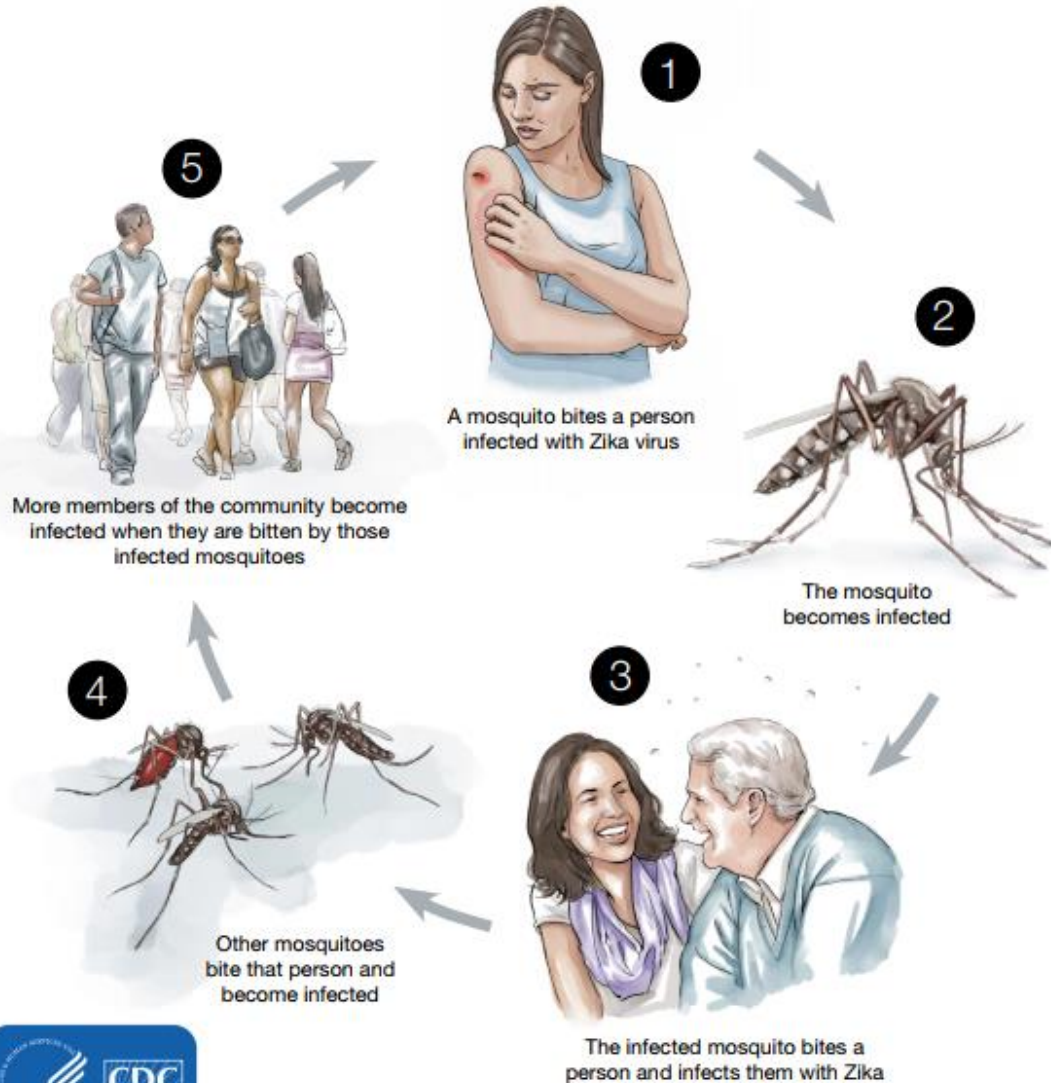


# PROTECT YOUR FAMILY AND COMMUNITY

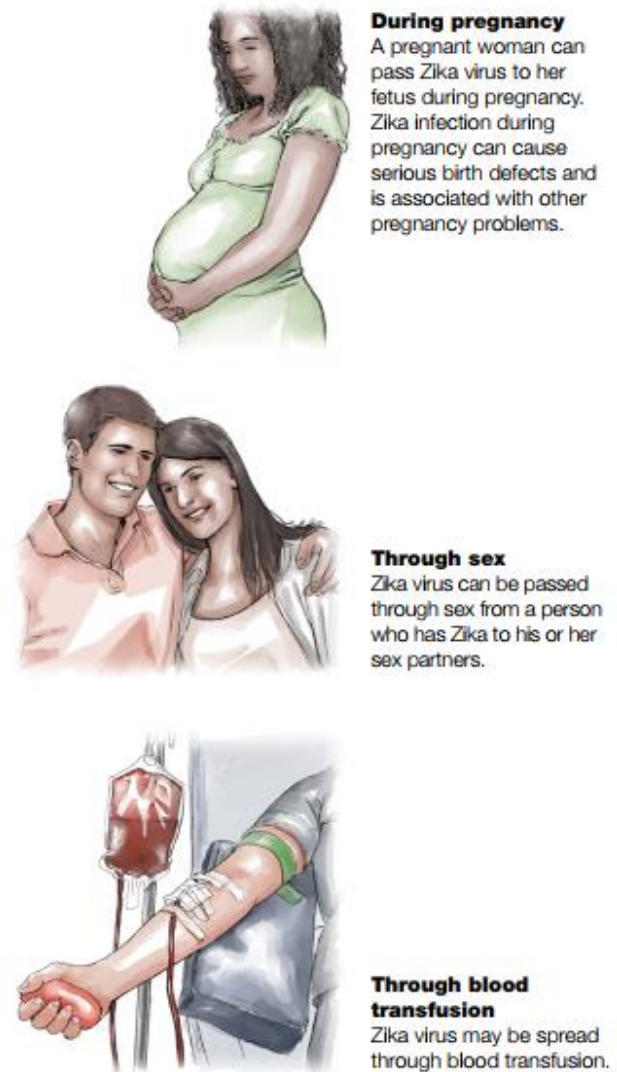
## HOW ZIKA SPREADS

Accessible Version: <https://www.cdc.gov/zika/transmission/index.html>

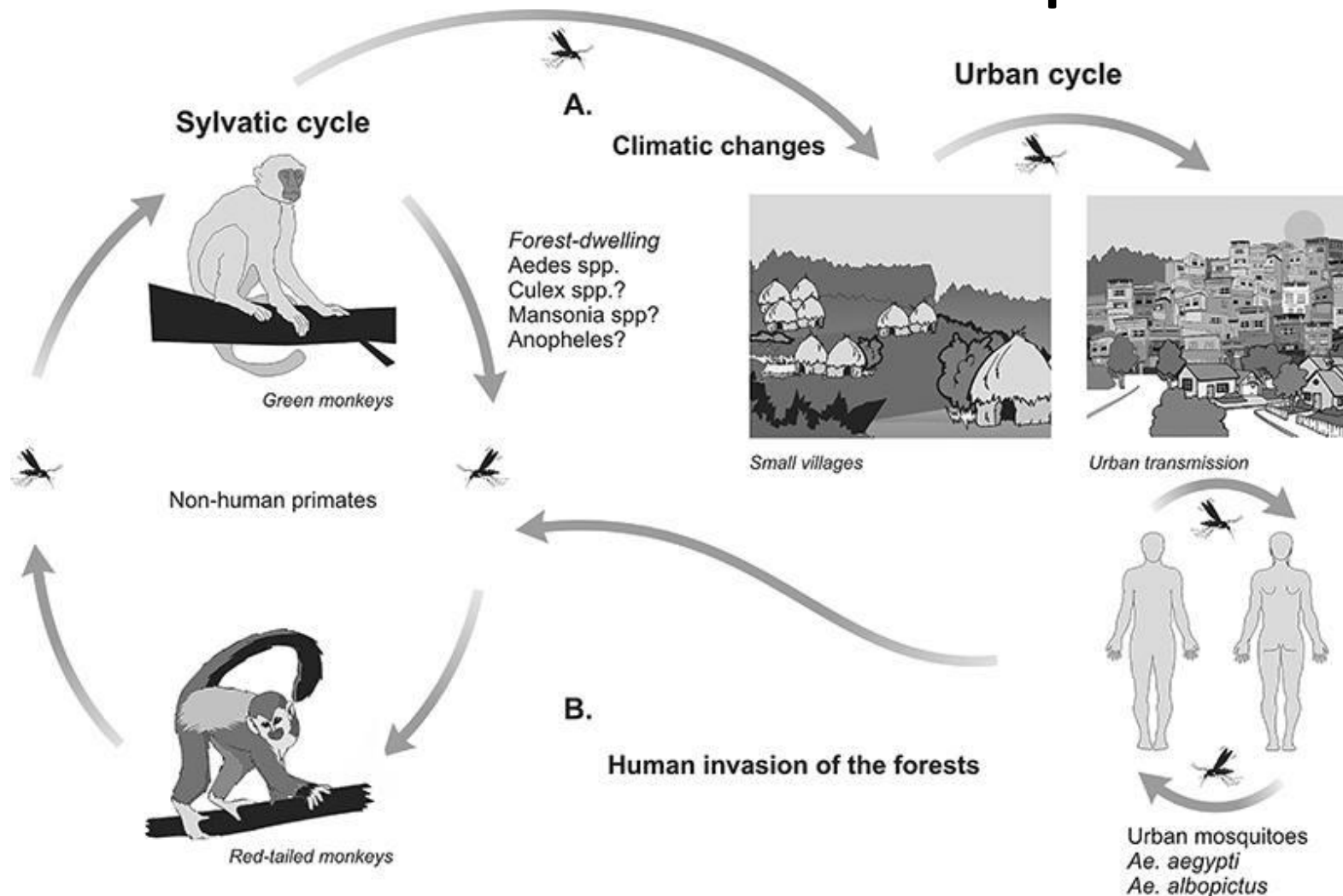
### Most people get Zika from a mosquito bite



### Other ways people get Zika



# Zika Transmission - Mosquitoes



Slavov et al, "Overview of Zika virus infection in regards to Brazilian epidemic," Brazilian Journal of Medical and Biological Research, 2016.

# Zika Transmission – Maternal-Child

- In utero / transplacental
  - Confirmed
  - Mothers with evidence of infection.
  - Fetus can be affected.
- Peripartum
  - Two cases in French Polynesia 2013-2014
  - Mothers sick around time of delivery, infants infected (one asymptomatic, one transient hepatitis)



## **During pregnancy**

A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika infection during pregnancy can cause serious birth defects and is associated with other pregnancy problems.

- Breastfeeding ??
  - Zika virus detected in breast milk
  - No transmission documented yet

# Zika Transmission - Horizontal

- Sexual transmission
  - Male to female, female to male, male to male
  - Vaginal, anal, oral, sex toys
- Time to loss of detectable virus:

Source	Median	95%
Serum	2 weeks	54 days
Urine	8 days	39 days
Semen	34 days	81 days

- Semen: virus detected in one case up to 188 days after illness onset!



## Through sex

Zika virus can be passed through sex from a person who has Zika to his or her sex partners.

- Urine, saliva – no cases of transmission
- Abstinence / condoms after illness onset
  - Women: 8 weeks
  - Men: 6 months

# Zika Transmission – Other

- Blood transfusion ??
  - No confirmed cases in US
  - Rare reports of blood/platelet transmission in Brazil
    - under investigation
  - French Polynesia outbreak:
    - 2.8% of asymptomatic blood donors tested positive for Zika virus
  - Zika virus screening of blood supply in US



**Through blood transfusion**

Zika virus may be spread through blood transfusion.

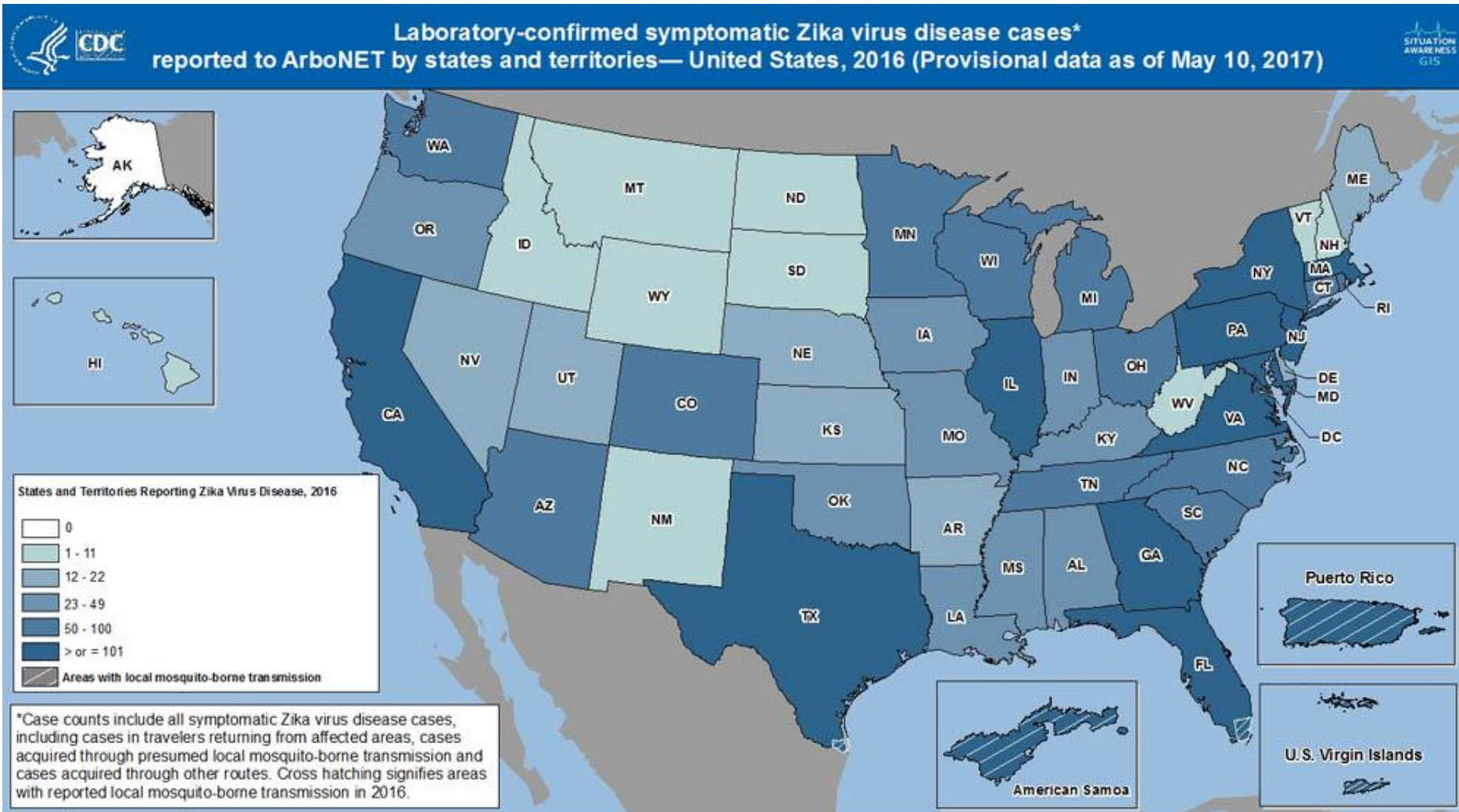
No confirmed reported Zika virus transmission in healthcare settings in U.S.

- One lab-acquired case as of June 15, 2016 (Penn – needle stick injury).



# Zika in the US 2016

<https://www.cdc.gov/zika/reporting/2016-case-counts.html>



## States:

5,102 symptomatic Zika virus cases reported  
4,830 cases from returning travelers from affected areas  
224 cases from local mosquito-borne transmission (in Florida and Texas)  
48 cases from other routes (46 sexual, 1 lab, 1 person-to-person)

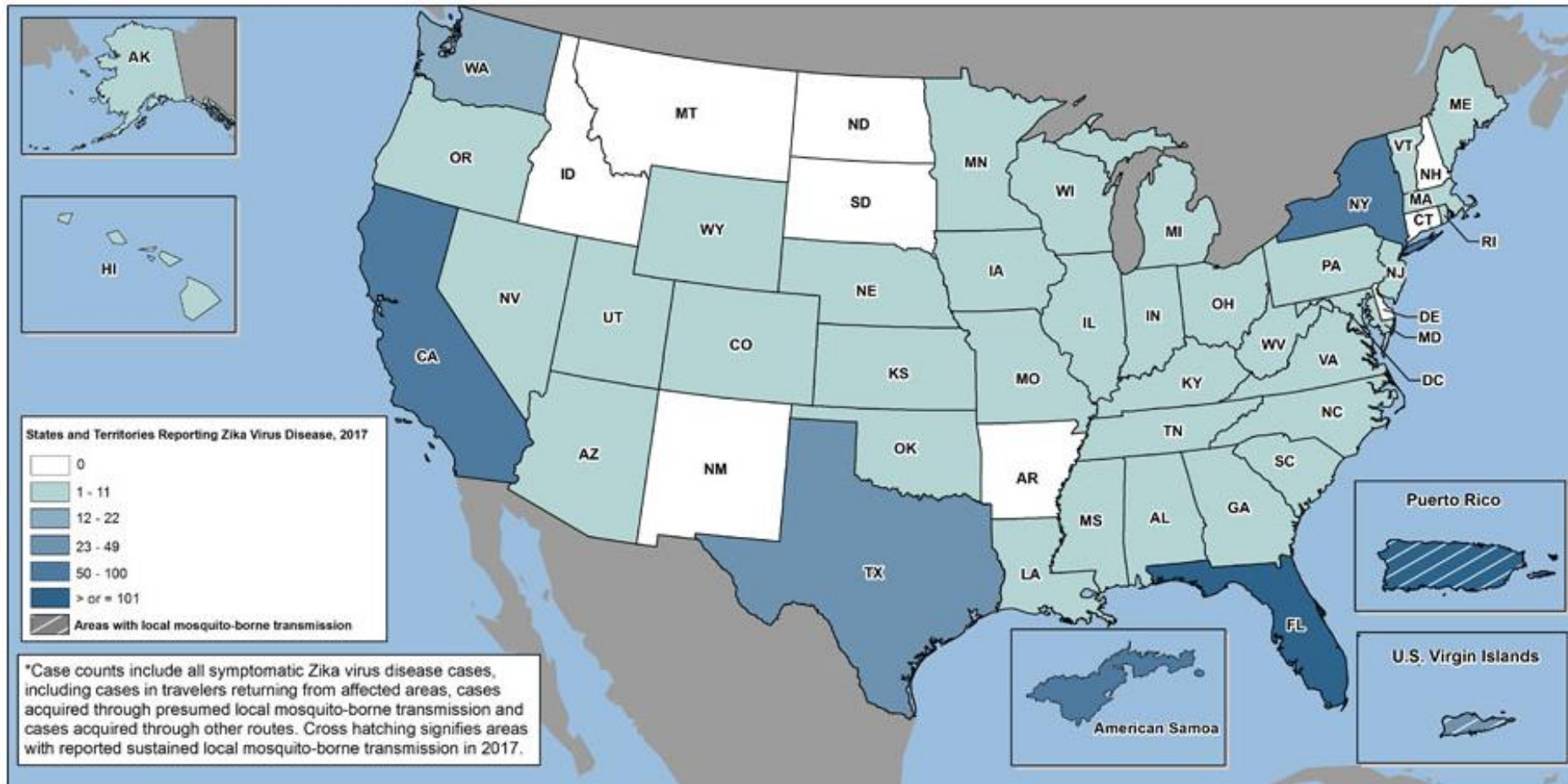
## Territories:

36,079 cases  
142 travelers  
35,937 mosquito  
0 other routes

# Zika in the US 2017

<https://www.cdc.gov/zika/reporting/2017-case-counts.html>

Laboratory-confirmed symptomatic Zika virus disease cases\* reported to ArboNET by states and territories— United States, 2017 (Provisional data as of January 10, 2018)



States:

407 symptomatic Zika virus cases reported  
398 cases from returning travelers from affected areas  
4 case from local mosquito-borne transmission  
5 cases from sexual transmission

Territories:

631 cases  
1 travelers  
630 mosquito  
0 other routes

# CDPH Monthly Update on Number of Zika Virus Infections in CA as of January 5, 2018

## Travel-associated infections with Zika virus in CA residents during 2015-2017

<b>Total Infections</b>	<b>634</b>
Cumulative number of infections due to sexual transmission	9
Cumulative number of infections in pregnant women	168
Cumulative number of completed pregnancies	142
Live-born infants with birth defects	10

<b>Snapshot of Bay Area County residents with Zika Virus Infection during 2015-2017</b>	<b>2015-2016</b>	<b>2017</b>	<b>Total</b>
Alameda	32	7	<b>39</b>
City of Berkeley	3	3	<b>6</b>
Contra Costa	26	4	<b>30</b>
San Francisco	29	11	<b>40</b>
<b>TOTAL</b>	<b>90</b>	<b>25</b>	<b>115</b>

<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TravelAssociatedCasesofZikaVirusinCA.pdf>

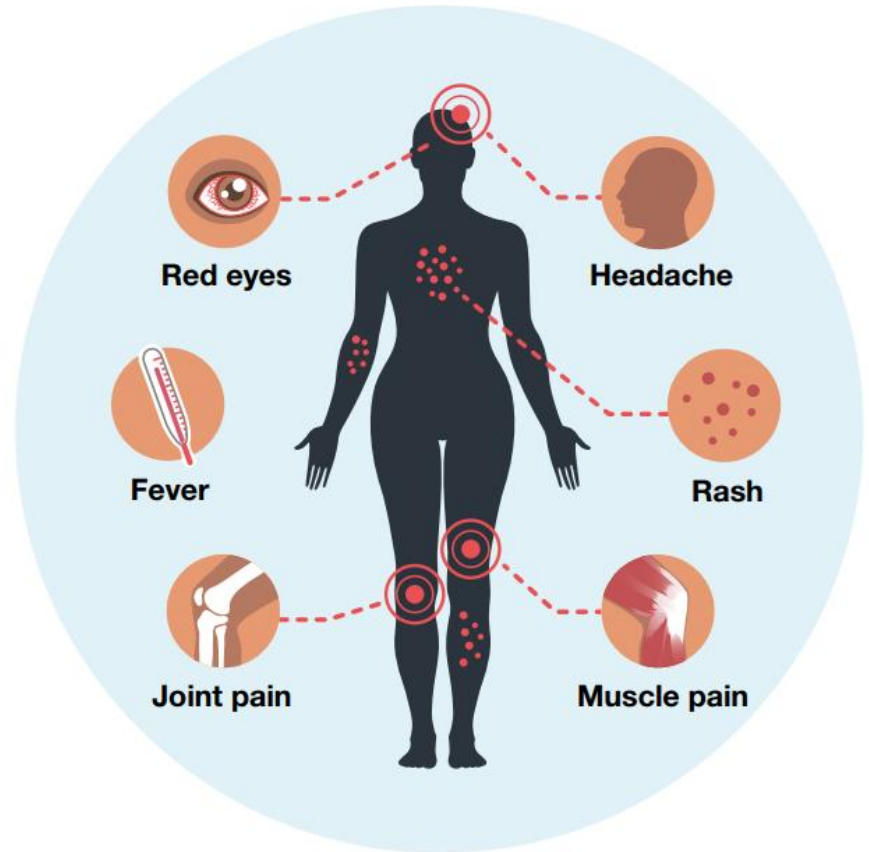
# **ZIKA VIRUS DISEASE, DIAGNOSIS AND MANAGEMENT**

# Incubation and Viremia

- Incubation period: ~3 - 14 days
- Viremia: a few days to 1 week
  - Longer in some pregnant women
- Virus remains in semen and urine longer than in blood.
- Most infections are **asymptomatic** (~80%).

# Clinical Disease

- Usually mild illness:
  - Acute onset fever
  - Maculopapular rash
  - Joint pain / arthralgia
  - Conjunctivitis
  - (Headache)
  - (Muscle pain / myalgia)
- Symptoms last several days to a week.
- Severe disease uncommon.
- Fatalities rare.
- Once infected, likely protected.
- Guillain-Barre syndrome reported



CDC



## Reported clinical symptoms among confirmed Zika virus disease cases

Symptoms	N (n=31)	%
Macular or papular rash	28	90%
Subjective fever	20	65%
Arthralgia	20	65%
Conjunctivitis	17	55%
Myalgia	15	48%
Headache	14	45%
Retro-orbital pain	12	39%
Edema	6	19%
Vomiting	3	10%

**Yap Island, 2007**

Duffy M. N Engl J Med 2009



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

# Clinical features: Zika virus compared to dengue and chikungunya

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

Rabe, Ingrid MBChB,  
MMed “Zika Virus- What  
Clinicians Need to Know?”  
(presentation, Clinician  
Outreach and  
Communication Activity  
(COCA) Call, Atlanta, GA,  
January 26 2016)



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



# Zika virus and Pregnancy

- Pregnant women can be infected by
  - Mosquito bite
  - Unprotected sex with infected partner (with or without symptoms).
- No evidence of increased susceptibility or more severe disease.
  - Clinical disease is similar in pregnant and nonpregnant persons.
- Previous infection may confer immunity for future pregnancies.
- Avoid travel to Zika virus risk areas.

# Clinical Management

- **No antiviral treatment available.**
- Supportive care
  - Rest
  - Drink fluids to prevent dehydration
  - Antipyretics – acetaminophen
  - Avoid aspirin and NSAIDs until dengue ruled out (due to risk of bleeding)

# Diagnosis

- Based on clinical features, places and dates of travel, and activities.
- Laboratory diagnosis – detecting viral nucleic acid or specific IgM and neutralizing antibodies.
- Reporting: Nationally notifiable condition.
  - Report suspected cases to state or local health departments.

## ZIKA LABORATORY TESTING GUIDANCE

9/20/2017

Appropriate Clinical Specimens for Laboratory Testing of Suspected Cases					
	Symptomatic Suspect Cases or Asymptomatic Pregnant Women				
	Serum	Whole Blood <sup>§</sup> (EDTA)	CSF	Urine <sup>§</sup>	Other <sup>¶</sup>
RT-PCR <sup>§</sup>	YES	YES	YES	YES	YES
Serology: IgM with PRNT confirmation <sup>†</sup>	YES	NO	YES	NO	YES

<sup>¶</sup> CDC will consider testing other specimen types (e.g., saliva, placental tissue, umbilical cord, fetal and other tissues) on a case by case basis.

<sup>§</sup> RT-PCR is the preferred method. Urine and whole blood have been shown to be preferred specimens for confirming an acute case.

<sup>†</sup> PRNT (plaque-reduction neutralization test) may confirm cross-reactive IgM tests by measuring virus-specific neutralizing antibodies.

Contact local public health dept for testing.

Suspect cases: VRDL tests for Zika, Chikungunya, Dengue

### RT-PCR

- Serum/blood, CSF – w/in 14 days of illness onset (symptomatic case) or last potential exposure (asymptomatic pregnant woman)
- Urine – w/in 21 days of illness onset (SC), w/in 14 days of last exposure (APW)
- Amniotic fluid (amniocentesis)

### IgM and PRNT

- Asymptomatic pregnant women – 2 to 12 weeks after last possible exposure
- Symptomatic cases: >3 days after illness onset, up to 12 weeks after

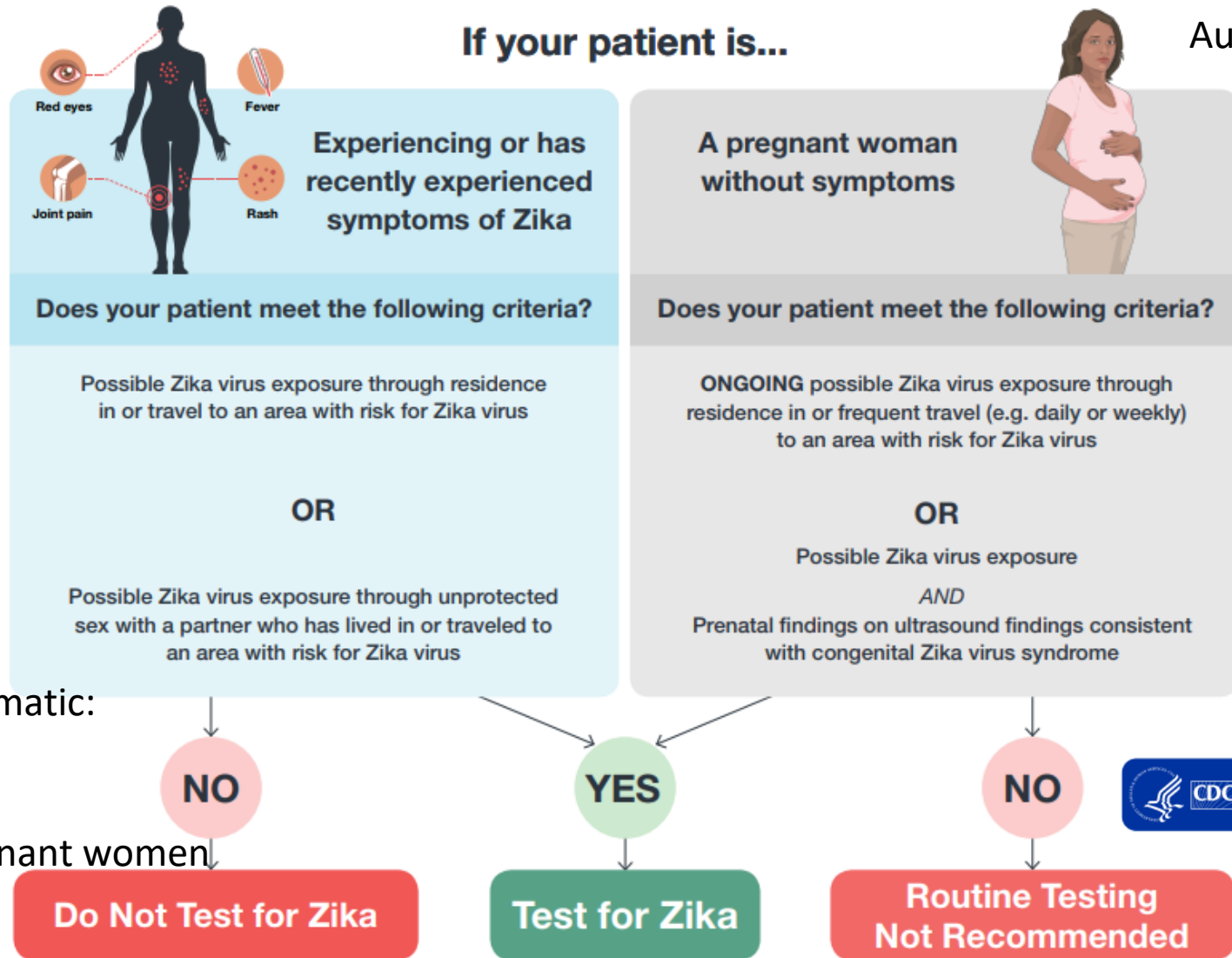
# WHEN TO TEST FOR **ZIKA VIRUS**



As a healthcare provider, you decide if a patient should be tested for Zika virus infection. The algorithm below will help you determine whether or not to test your patient for Zika virus infection.

Aug 25, 2017

**If your patient is...**



**ONGOING exposure**

No Asymptomatic:

- Men
- Children
- Non-pregnant women



# **ZIKA VIRUS TESTING GUIDANCE: SYMPTOMATIC NON-PREGNANT INDIVIDUALS WITH POSSIBLE ZIKA VIRUS EXPOSURE**

Testing Re

CDC's Response to **Zika**

## **UPDATED INTERIM PREGNANCY GUIDANCE: SYMPTOMATIC PREGNANT WOMEN WITH POSSIBLE ZIKA VIRUS EXPOSURE**

Accessible Version: <https://www.cdc.gov/zika/laboratories/lab-guidance.html>

Testing Recomm

CDC's Response to **Zika**

## **UPDATED INTERIM PREGNANCY GUIDANCE: ASYMPTOMATIC PREGNANT WOMEN WITH POSSIBLE ZIKA VIRUS EXPOSURE**

### Testing Recommendations and Interpretation of Results for Healthcare Providers

ASK PREGNANT WOMEN ABOUT

Positive Zi

WHOM to test?

WHEN to test?

WHICH tests?

RESULTS and ADDITIONAL tests

ACUTE ZIKA

INTERPRETATION Abbreviations: IgM =

1. NAT testing is not re
2. Acceptable specim urine. Repeat NAT + virus NAT testing sh compatible illness.

INTERPRETATION

- Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test
1. Ask about type and duration of Zika virus exp before the current pregnancy might limit later can help inform testing decisions. Some patie
  2. Possible Zika virus exposure includes travel to <https://www.cdc.gov/travel/page/zika-travel-information> period (8 weeks before conception [6 weeks] during pregnancy or the periconceptional per risk for Zika virus transmission.
  3. Zika virus testing is not routinely recommend confirmed Zika virus infection by either NAT a and Zika virus PRNT ≥10 and dengue virus PI
  4. This algorithm also applies to pregnant wome prenatal ultrasound findings consistent with o
  5. The duration of detectable Zika virus in preg suggest NAT may remain positive for several virus IgM antibodies are most likely to be det

<https://www.cdc.gov/mmwr>

ASK PREGNANT WOMEN ABOUT

Travel to or residence in any areas with risk for Zika virus transmission before and during the current pregnancy<sup>1,2</sup>  
Possible sexual exposure before and during the current pregnancy • A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy<sup>3</sup> • Symptoms of Zika virus disease during current pregnancy (e.g., fever, rash, conjunctivitis, arthralgia) • If symptoms are reported, refer to symptomatic algorithm.

Before testing, discuss testing limitations and potential risks of misinterpretations for test results.

WHOM to test?

Asymptomatic pregnant women with ongoing possible Zika virus exposure<sup>4</sup>

Asymptomatic pregnant women with recent possible Zika virus exposure, without ongoing exposure:  
**Testing not routinely recommended, but should be considered.**  
If considering testing, base decisions on patient preferences and values, clinical judgment, a balanced assessment of risks and expected outcomes, and jurisdiction's recommendations  
If testing is conducted, follow algorithm for symptomatic pregnant women using timeframe from last possible exposure.

WHEN to test?

Three times during pregnancy<sup>5</sup>  
First test at initiation of prenatal care.

WHICH tests?

Zika virus NAT (serum and urine)

RESULTS

Positive Zika virus NAT<sup>6</sup>

Negative Zika virus NAT

INTERPRETATION

ACUTE ZIKA VIRUS INFECTION

NO ZIKA VIRUS RNA DETECTED. ZIKA VIRUS INFECTION DURING PREGNANCY CANNOT BE RULED OUT.<sup>7</sup>

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test

1. Ask about type and duration of Zika virus exposure before and during the current pregnancy. Exposure prior to the current pregnancy may limit interpretation of Zika IgM antibody results; pretest counseling can help inform testing decisions.
2. Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (<https://www.cdc.gov/travel/page/zika-travel-information>) during pregnancy or the periconceptional period (8 weeks before the last menstrual period), or sex without a condom during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.
3. Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive/equivocal Zika virus or dengue virus IgM and Zika virus PRNT ≥10 and dengue virus PRNT <10 results).
4. Persons with ongoing possible exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk for Zika virus transmission.
5. The interval for Zika virus NAT testing during pregnancy is unknown. Preliminary data suggest that NAT might remain positive for several weeks after infection in some pregnant women. For women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits. The proportion of fetuses and infants with Zika virus-associated birth defects is highest among women with first and early second trimester infections; therefore, conducting all NAT testing during the first and second trimesters might be considered

- to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester; therefore, testing every trimester might be considered.
  6. Despite the high specificity of NAT, false positive NAT results have been reported. If both serum and urine specimens are NAT positive, interpretation should be acute Zika virus infection. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection. If repeat NAT testing is negative, results are indeterminate and healthcare providers should perform IgM antibody testing on a specimen collected ≥2 weeks after the initial specimen collection. For laboratory interpretation, see Table 1.
  7. A negative Zika virus NAT result does not exclude infection during pregnancy because it represents a single point in time. Zika virus RNA levels decline over time, and the duration of the presence of Zika virus RNA in serum and urine following infection vary among pregnant women. Despite Zika virus IgM test limitations (e.g., cross-reactivity with other flaviviruses and prolonged detection for months, presenting challenges in determining the timing of infection), which should be discussed as part of pretest counseling, patients may still choose to receive Zika virus IgM testing.
- Note: For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/Flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.

[https://www.cdc.gov/mmwr/volumes/66/wr/mm6629e1.htm?cid=mm6629e1\\_w](https://www.cdc.gov/mmwr/volumes/66/wr/mm6629e1.htm?cid=mm6629e1_w)



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

CS267383-A July 24, 2017





KAREN L. SMITH, MD, MPH  
Director and State Public Health Officer

State of California—Health and Human Services Agency  
**California Department of Public Health**



EDMUND G. BROWN JR.  
Governor

**August 2, 2017**

**Updated Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure**

Background

On July 24, 2017, CDC released updated [Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure – United States and U.S. Territories](https://www.cdc.gov/mmwr/volumes/66/wr/mm6629e1.htm) (<https://www.cdc.gov/mmwr/volumes/66/wr/mm6629e1.htm>). These recommendations update the prior CDC guidance in response to two developments in the Zika outbreak. First, the number of people with Zika infection in the Americas is declining and therefore a lower occurrence of disease could lead to a higher proportion of false-positive test results. Second, emerging data show that Zika virus IgM antibodies can persist for months in some pregnant women, making it difficult for healthcare providers to use Zika IgM test results to determine whether an infection occurred during or before the current pregnancy. Both the CDC and CDPH emphasize a shared-decision making model for testing and screening pregnant women, with testing decisions considered in accordance with patient preferences, risk tolerance, and clinical judgement and in line with state or local jurisdictional recommendations.

CDC has updated recommendations in four areas, and CDPH is updating the following Zika testing recommendations accordingly, with one notable discretionary difference:

**August guidance differed from CDC with respect to pregnant women without ongoing exposure.**

<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/UpdatedZikaGuidanceforHCPsCaringforPregnantWomen.pdf>



KAREN L. SMITH, MD, MPH  
Director and State Public Health Officer

State of California—Health and Human Services Agency  
California Department of Public Health



EDMUND G. BROWN JR.  
Governor

**Date: January 10, 2018**

**To: California Health Care Providers**

**From: California Department of Public Health**

**Updated Guidance for Health Care Providers: Assessment and Testing for Zika Virus Infection in Pregnant Women and their Newborns**

- I. **Background:** The impact of Zika virus infection in pregnancy remains a great concern. Pregnant women should have access to Zika virus testing, including testing of asymptomatic pregnant women when appropriate.

Nearly half of all California Zika cases to date have reported travel to Mexico and many others have reported travel to other Central and South American countries. In 2017, Mexico has reported declining numbers of cases and the incidence of new Zika infections in California has substantially declined. These factors together lead to a lower pre-test probability of infection when considering testing pregnant women and their newborns. As of November 24, 2017, 162 pregnant women with travel-associated Zika infection have been reported in California since 2015. Of these, 136 women have had completed pregnancies and 9 infants have been born with microcephaly and other Zika-associated anomalies. More than half of the infants born in California with Zika-associated birth defects were born to Zika-exposed mothers who were asymptomatic for Zika infection.

Based on the changing epidemiology of Zika virus infections in California since 2015, together with input from specialty organizations, CDPH is updating recommendations for the assessment and testing of pregnant women and their newborns for Zika virus infection. These updates align CDPH recommendations with current CDC interim guidance<sup>a,b</sup>. See the [CDPH Zika webpage](#) for [tools](#) and resources to implement this guidance in California.

As of January 10, 2018, CDPH and CDC recs are now aligned.

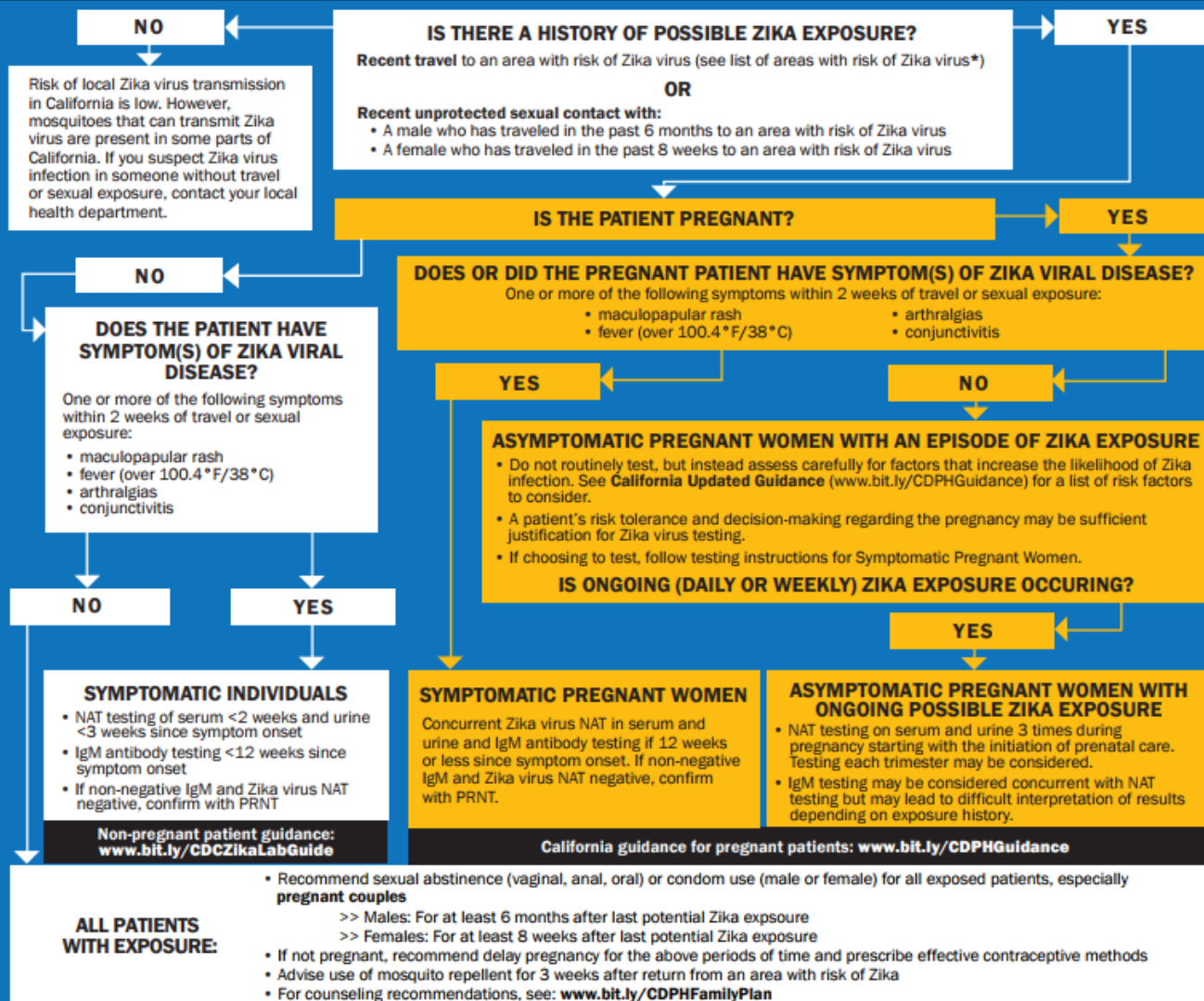




# ZIKA SCREENING ALGORITHM



## FOR CHILDREN AND ADULTS



\*AREAS WITH RISK OF ZIKA: For symptomatic persons, refer to [CDC Areas with Risk of Zika](http://www.bit.ly/CDCRiskAreas) ([www.bit.ly/CDCRiskAreas](http://www.bit.ly/CDCRiskAreas)). For asymptomatic pregnant women, use the [WHO Zika Virus Classification Table](http://www.bit.ly/WHOZikaTable) ([www.bit.ly/WHOZikaTable](http://www.bit.ly/WHOZikaTable)) WHO risk classification "Category 1" and "Category 2" countries to help limit the risk of false positive test results. Only Texas and Florida have experienced transmission in the U.S., but transmission is not ongoing at this time.



# ZIKA SCREENING ALGORITHM



## FOR INFANTS

### INFANT ZIKA VIRUS TESTING FOR SUSPECTED CONGENITAL ZIKA VIRUS INFECTION

Indications for testing include maternal exposure history plus any of the following:

- Maternal laboratory evidence of Zika virus infection
- Infant findings consistent with congenital Zika syndrome regardless of maternal test results

Newborn specimen collection:

- Zika virus NAT testing on infant serum and urine and Zika virus IgM antibody testing on infant serum. If non-negative IgM and negative Zika virus NAT, confirm with PRNT.
- If CSF is collected for other purposes, NAT and IgM antibody testing should be performed on CSF.
- For infants with findings consistent with congenital Zika syndrome with unknown etiology, consider CSF for Zika virus NAT and IgM antibodies.

Birth hospitals may consider collecting infant specimens for concurrent Zika virus testing if maternal testing is being done: [www.bit.ly/CABirthingHospitals](http://www.bit.ly/CABirthingHospitals)

See CDPH guidance for lab testing: [www.bit.ly/VRDLZikaGuidance](http://www.bit.ly/VRDLZikaGuidance)

For more Zika information for health professionals, see: [www.bit.ly/CDPHZikaHCPs](http://www.bit.ly/CDPHZikaHCPs)

For questions about Zika virus testing or test results, contact your local health department: [www.bit.ly/LHDCContactInfo](http://www.bit.ly/LHDCContactInfo)

[www.bit.ly/AlgorithmCDPH](http://www.bit.ly/AlgorithmCDPH)  
(All links are case sensitive)

<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaAlgorithmPoster.pdf>

# CDPH: Who to test? (adults)

Who to Test?	When and with what tests?
<b>Non-pregnant symptomatic</b> patient with possible Zika exposure <ul style="list-style-type: none"><li>• recent travel to area with risk of Zika virus or</li><li>• recent unprotected sexual contact with recent traveler to area with risk of Zika virus (male w/in 6 months, female w/in 8 weeks)</li></ul>	<ul style="list-style-type: none"><li>• NAT testing of serum &lt;2 wks and urine &lt;3 wks since symptom onset</li><li>• IgM antibody testing &lt;12k wks since symptom onset</li><li>• If non-neg IgM and ZIKV NAT neg, confirm with PRNT</li></ul>
<b>Symptomatic pregnant</b> woman with possible Zika exposure	<ul style="list-style-type: none"><li>• Concurrent ZIKV NAT in serum and urine and IgM antibody testing if ≤12 wks since symptom onset</li><li>• If non-neg IgM and ZIKV NAT neg, confirm with PRNT</li></ul>

# CDPH: Who to test? (adults)

Who to Test?	When and with what tests?
<b>Asymptomatic pregnant</b> woman with <b>an episode</b> of Zika exposure (without ongoing exposure)	<ul style="list-style-type: none"><li>• Do not routinely test, but assess carefully for risk factors that increase likelihood of Zika infection. Test based on risk tolerance.</li><li>• If choosing to test, follow instructions for Symptomatic Pregnant Woman</li></ul>
<ul style="list-style-type: none"><li>• Risk Factors</li></ul>	<ul style="list-style-type: none"><li>• Local Zika transmission at time of exposure</li><li>• Unprotected sexual exposure to partner with travel to Zika-risk area</li><li>• Longer duration of travel (&gt;4wk) or multiple sexual exposures</li><li>• Higher risk activities (outdoor)</li><li>• Known mosquito bites</li><li>• Lack of protective clothing and insect repellent on regular basis</li><li>• Compromised integrity of housing</li><li>• Other household members with Zika infection</li><li>• High risk patient occupation (lab worker)</li><li>• Recipient of recent transfusions or transplants</li></ul>

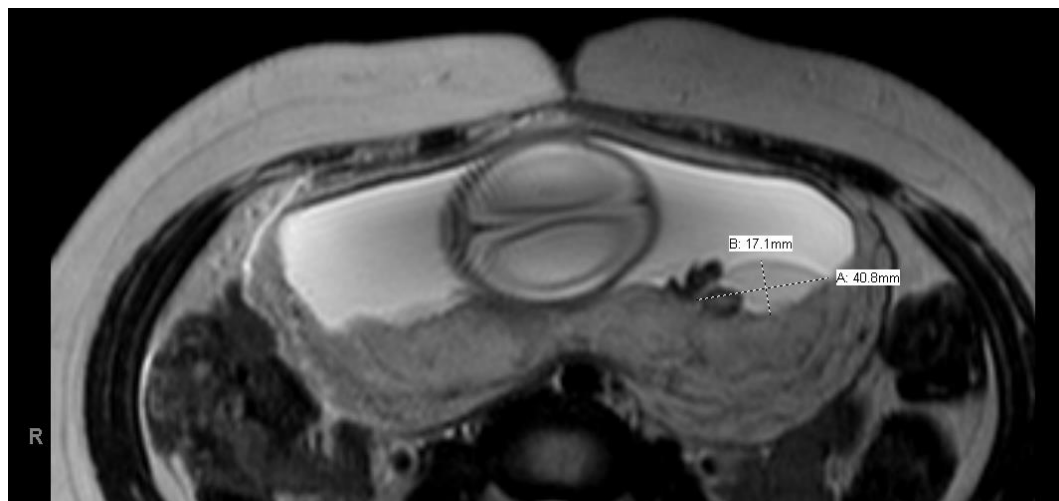
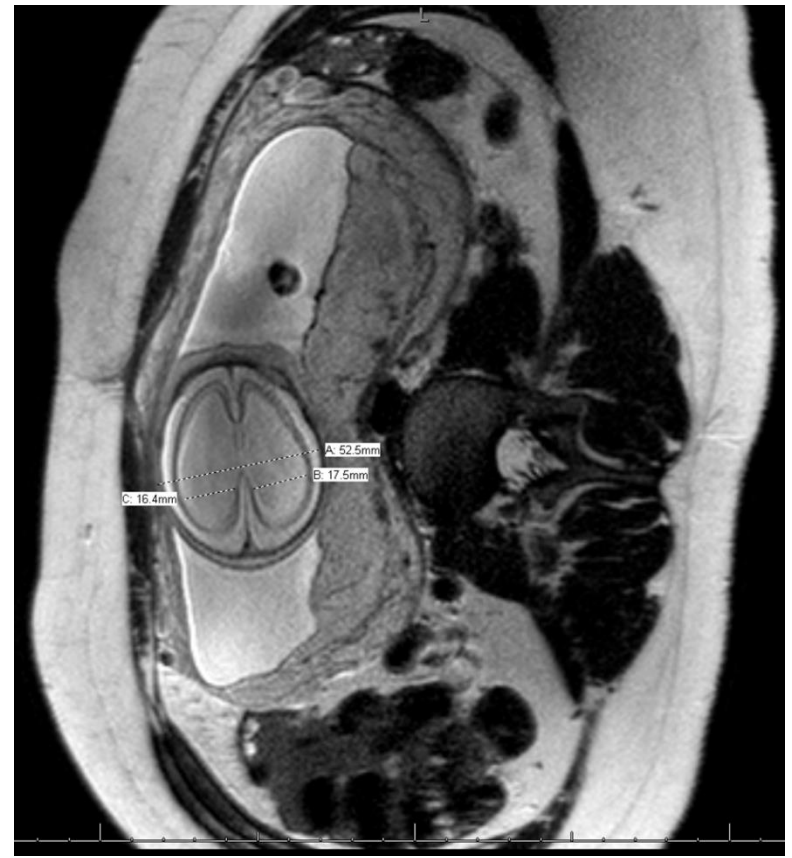
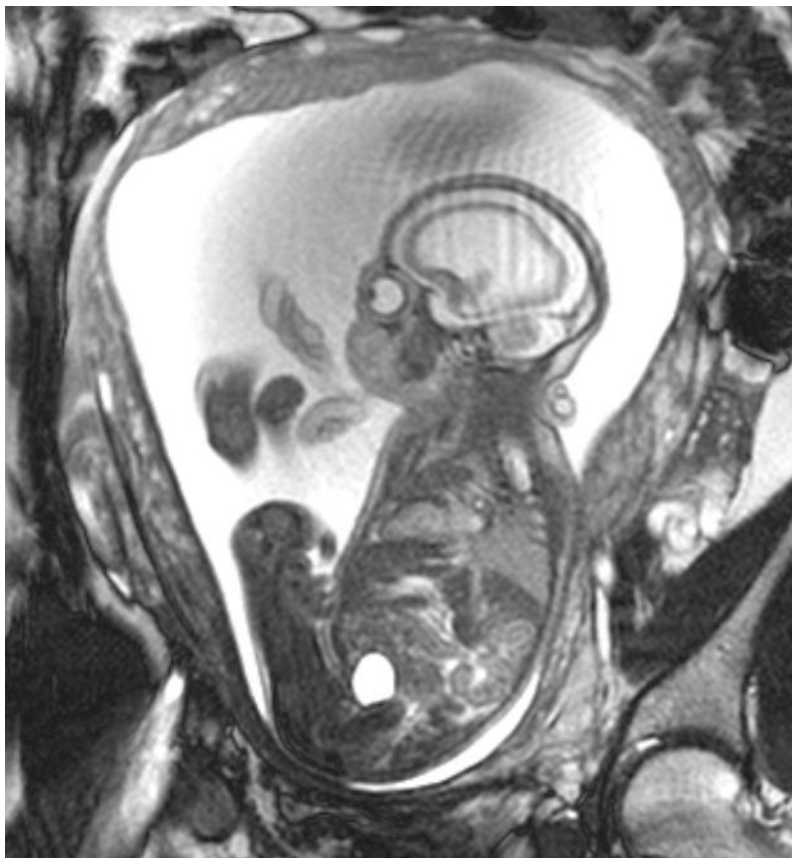
# CDPH: Who to test? (adults)

Who to Test?	When and with what tests?
<b>Asymptomatic Pregnant</b> Woman with <b>ongoing</b> (daily or weekly) possible Zika exposure	<ul style="list-style-type: none"><li>• NAT testing of serum and urine 3 times during pregnancy. Consider qTrimester testing.</li><li>• IgM testing may be considered with NAT testing, but may have difficult interpretation depending on exposure history.</li></ul>
<b>Pregnant</b> woman with recent possible Zika exposure and <b>fetal prenatal ultrasound</b> with findings consistent with <b>congenital Zika virus syndrome</b> .	<ul style="list-style-type: none"><li>• Testing to include both NAT and IgM tests.</li><li>• If amniocentesis performed, send NAT testing of amniotic fluid.</li></ul>
Case by case: 1) Symptomatic mothers with probable Zika virus infection and 2) mother with infant/fetus with possible Zika virus-associated birth defects but no definitive diagnosis of Zika virus infection during pregnancy.	<ul style="list-style-type: none"><li>• Pathology testing of placental tissues</li><li>• Placental Zika virus testing – on a case by case basis in consultation with Public Health.</li></ul>

# Case

- 25 yo woman had positive pregnancy test in Sept 2015 in El Salvador.
- Developed fever and rash in Oct 2015, lasting about 2 weeks, recovered completely.
- First trimester ultrasound revealed twin pregnancy but single fetal demise.
- Moved to U.S. in Jan 2016. Fetal ultrasound abnormal.
- Fetal MRI Feb 2016:





# Case



- TORCH evaluation negative
- Zika IgM equivocal
- Infant born full term via NSVD, Apgars 8 and 9
- HC 28.5 cm (<<5%)
- Other abnormalities on exam

# Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy

Dec 13, 2016

Margaret A. Honein, PhD; April L. Dawson, MPH; Emily E. Petersen, MD; Abbey M. Jones, MPH; Ellen H. Lee, MD; Mahsa M. Yazdy, PhD; Nina Ahmad, MD; Jennifer Macdonald, MPH; Nicole Evert, MS; Andrea Bingham, PhD; Sascha R. Ellington, MSPH; Carrie K. Shapiro-Mendoza, PhD; Titilope Oduyebo, MD; Anne D. Fine, MD; Catherine M. Brown, DVM; Jamie N. Sommer, MS; Jyoti Gupta, MPH; Philip Cavicchia, PhD; Sally Slavinski, DVM; Jennifer L. White, MPH; S. Michele Owen, PhD; Lyle R. Petersen, MD; Coleen Boyle, PhD; Dana Meaney-Delman, MD; Denise J. Jamieson, MD; for the US Zika Pregnancy Registry Collaboration

- Data for pregnant women in the US Zika Pregnancy Registry (USZPR).
- Women with lab evidence of possible Zika infection:
  - About 6% of fetuses or infants had birth defects potentially related to Zika virus.
  - Birth defects similar for symptomatic and asymptomatic women: ~6%
  - Birth defects in ~11% of women with exposure or symptoms in 1<sup>st</sup> trimester.

# Congenital Zika Syndrome

Distinct pattern of congenital anomalies and problems unique to fetuses and infants infected with Zika virus before birth - five main features:

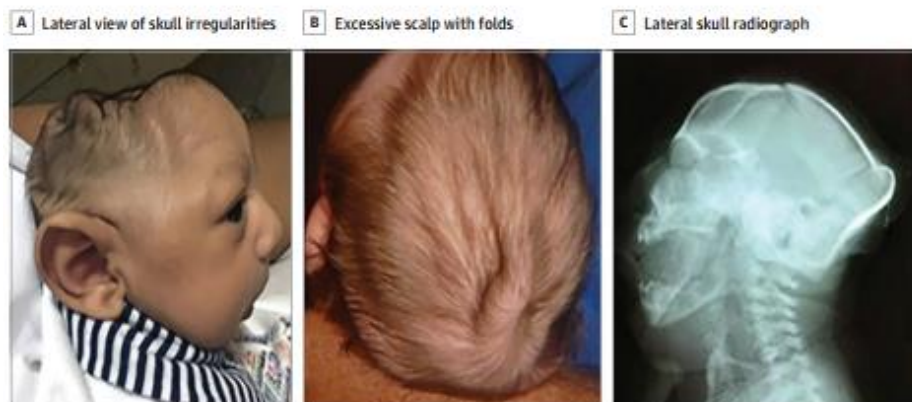
1. Severe microcephaly in which skull has partially collapsed
2. Decreased brain tissue with a specific pattern of brain damage, including subcortical calcifications
3. Damage to the back of the eye, including macular scarring and focal pigmentary retinal mottling
4. Congenital contractures, such as clubfoot or arthrogryposis
5. Hypertonia restricting body movement soon after birth

# Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

Cynthia A. Moore, MD, PhD; J. Erin Staples, MD, PhD; William B. Dobyns, MD; André Pessoa, MD; Camila V. Ventura, MD; Eduardo Borges da Fonseca, MD, PhD; Erlane Marques Ribeiro, MD, PhD; Liana O. Ventura, MD; Norberto Nogueira Neto, MD; J. Fernando Arena, MD, PhD; Sonja A. Rasmussen, MD, MS

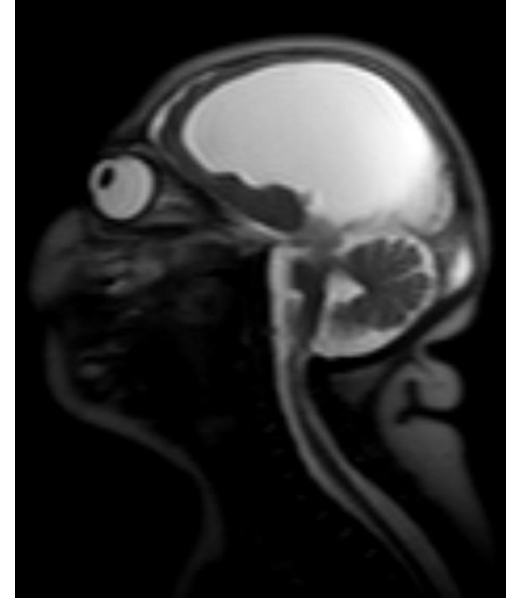
- Cranial Morphology: Fetal brain disruption sequence (FBDS)
  - Severe microcephaly
  - Overlapping cranial sutures
  - Prominent occipital bone
- Redundant scalp skin (excess nuchal skin)
- Severe neurological impairment
- Can have craniofacial disproportion with depression of frontal bones and parietal bones.
- Suspected due to loss of brain volume and decrease in intracranial pressure.

Figure 1. Cranial Morphology Supporting Fetal Brain Disruption Sequence Phenotype in Congenital Zika Syndrome



# Congenital Zika Syndrome

- Brain Anomalies
  - Diffuse, primarily subcortical calcifications
  - Increased fluid spaces (ventricular, extra-axial)
  - Marked cortical thinning with abnormal gyral patterns (polymicrogyria)
  - Hypoplasia or absence of corpus callosum
  - Decreased myelination
  - Cerebellar or cerebellar vermis hypoplasia



- Case: Postnatal ultrasound
  - Marked hydrocephalus and thinning of cortical mantle
  - Redundant skin in posterior neck



# Congenital Zika Syndrome

- Ocular Anomalies
  - Structural eye anomalies (microphthalmia, coloboma)
  - Cataracts
  - Intraocular calcifications
  - Posterior ocular findings, macular scarring
  - Chorioretinal atrophy, focal pigmentary mottling of retina, optic nerve atrophy/anomalies
- Congenital contractures
  - Arthrogryposis multiplex congenita, arthrogryposis
  - Clubfoot
  - Bilateral congenital hip dislocation

Figure 4. Infants With Congenital Zika Infection, Microcephaly, and Arthrogryposis

A Multiple contractures with knee dislocation B Multiple contractures including right talipes equinovarus



A, Newborn infant with bilateral contractures of the hips and knees, bilateral talipes calcaneovalgus, and anterior dislocation of the knees. Hips are bilaterally dislocated. B, Newborn infant with bilateral contractures of the shoulders, elbows, wrists, hips, knees, and right talipes equinovarus. Hips are bilaterally dislocated.

Moore et al, JAMA Pediatrics, March 2017  
MMWR October 20, 2017

# Congenital Zika Syndrome

- Neurological Sequelae and Prognosis
  - Likely to be severely impaired.
  - Motor, cognitive disabilities, seizures, swallowing difficulties -> failure to thrive, vision loss, sensorineural hearing loss
  - Irritability, excessive crying, hypertonia and spasticity, dysphagia, occasionally hypotonia.
  - Abnormal EEG, tremors and posturing (extrapyramidal dysfunction), epilepsy, abnormal tone or movements



# ZIKA SCREENING ALGORITHM



## FOR INFANTS

### INFANT ZIKA VIRUS TESTING FOR SUSPECTED CONGENITAL ZIKA VIRUS INFECTION

Indications for testing include maternal exposure history plus any of the following:

- Maternal laboratory evidence of Zika virus infection
- Infant findings consistent with congenital Zika syndrome regardless of maternal test results

Newborn specimen collection:

- Zika virus NAT testing on infant serum and urine and Zika virus IgM antibody testing on infant serum. If non-negative IgM and negative Zika virus NAT, confirm with PRNT.
- If CSF is collected for other purposes, NAT and IgM antibody testing should be performed on CSF.
- For infants with findings consistent with congenital Zika syndrome with unknown etiology, consider CSF for Zika virus NAT and IgM antibodies.

Birth hospitals may consider collecting infant specimens for concurrent Zika virus testing if maternal testing is being done: [www.bit.ly/CABirthingHospitals](http://www.bit.ly/CABirthingHospitals)

See CDPH guidance for lab testing: [www.bit.ly/VRDLZikaGuidance](http://www.bit.ly/VRDLZikaGuidance)

For more Zika information for health professionals, see: [www.bit.ly/CDPHZikaHCPs](http://www.bit.ly/CDPHZikaHCPs)

For questions about Zika virus testing or test results, contact your local health department: [www.bit.ly/LHDCContactInfo](http://www.bit.ly/LHDCContactInfo)

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(All links are case sensitive)

<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ZikaAlgorithmPoster.pdf>

# CDPH: Who to test? (newborns)

Who to Test?	Collect tests within first 2 days of life:
<ol style="list-style-type: none"><li>1) Infants born to mothers with laboratory evidence of possible Zika virus infection during pregnancy</li><li>2) Infants with clinical findings suggestive of congenital Zika syndrome and possible maternal Zika virus exposure during pregnancy, regardless of maternal testing results.</li></ol>	<ul style="list-style-type: none"><li>• NAT of serum and urine and IgM concurrently.<ul style="list-style-type: none"><li>• If non-neg IgM and negative Zika virus NAT, confirm with PRNT.</li></ul></li><li>• If CSF collected for other purposes, send for NAT and IgM antibody testing.</li><li>• For infants with clinical findings consistent with congenital Zika syndrome with unknown etiology, consider testing CSF for Zika virus NAT and IgM antibodies.</li></ul>

# Infant Zika Testing

- Collect samples within 2 days of life (ideally).
- Consider sending infant specimens for concurrent testing if maternal testing is to be done.
- Consider Placental storage/fixation if needed for testing

# ZIKA VIRUS: COLLECTION AND SUBMISSION OF SPECIMENS FOR ZIKA VIRUS TESTING AT TIME OF BIRTH



## General Information

Laboratory testing for congenital Zika virus infection is recommended for infants born to mothers with laboratory evidence of Zika virus infection during pregnancy, and for infants who have abnormal clinical findings suggestive of congenital Zika virus syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results.

For infants born to mothers with risk factors for maternal Zika virus infection (travel to or residence in [an area of Zika virus](#) transmission or sex with a partner with travel to or residence in such an area) for whom maternal testing was not performed before delivery, assessment of the infant, including comprehensive physical exam and careful measurement of head circumference, neurologic assessment as well as newborn hearing screen should be performed. In addition, based on the level of possible maternal Zika virus exposure (e.g., duration and type of exposure, use of prevention measures, intensity of Zika virus transmission at the location of travel), the provider should consider whether

further evaluation of the newborn for possible congenital Zika virus infection is warranted, in which case a head ultrasound and ophthalmologic assessment should be considered. Based on results of the evaluation, testing of the infant for Zika virus infection could be considered.

Testing of placental tissue specimens by Zika virus reverse-transcription polymerase chain reaction (RT-PCR) is conducted at CDC's Infectious Diseases Pathology Branch (IDPB). Zika virus RT-PCR on placental tissues from women with possible Zika virus exposure can be considered for diagnostic purposes for symptomatic pregnant women and women with infants with possible Zika virus-associated birth defects without a definitive diagnosis of laboratory-confirmed Zika virus infection during pregnancy. For asymptomatic pregnant women who have recent possible Zika virus exposure but without ongoing possible exposure, similar to the updated recommendations for testing of non-tissue clinical specimens (e.g., serum and urine), testing of placental tissues is not routinely recommended.

**IMPORTANT: Pre-approval is required prior to submission of any tissue specimens.**  
For pre-approval please contact [pathology@cdc.gov](mailto:pathology@cdc.gov).

### Healthcare Providers:

- Please make sure that your state, territorial, tribal, or local health department has been notified and has received pre-approval from CDC for submission and shipment of tissue specimens before they are collected and sent.
  - » Institutions with surgical pathology available: Please consult surgical pathology regarding appropriate collection and processing of tissue specimens for Zika virus testing.
  - » Institutions without surgical pathology available: Please see table below for general guide on collection of tissue specimens for Zika virus testing.
- Specimens should **ONLY** be sent to CDC directly from health departments. CDC's Zika Pregnancy Hotline (770-488-7100; or email [zikapregnancy@cdc.gov](mailto:zikapregnancy@cdc.gov)) is available 24/7 to healthcare providers and health departments for consultation regarding management of pregnant women and infants with possible

- Pre-approval is required prior to submission of all tissue specimens (i.e., placenta, umbilical cord). Please contact [pathology@cdc.gov](mailto:pathology@cdc.gov) to obtain pre-approval. Additional clinical and epidemiologic information may be requested, see <https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html> for minimum required information for pre-approval. If you have additional questions for the Infectious Diseases Pathology Branch, please call 404-639-3133.
- If you have additional questions for the Arboviral Diseases Branch, please call 970-221-6400.

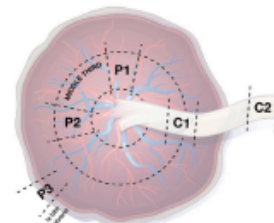


Figure: Collecting placental specimen

### Reporting of Results:



- Infant serum
- Placental and fetal membranes
- Umbilical cord
- Infant urine

Specimen Type	General Instructions	Notes	Storage	Shipping
Infant serum	At least 1.0 mL  Transfer serum to a plastic tube measuring approximately 50 mm tall and 15 mm in diameter (e.g., 1.8 mL cryotube or 2.0 mL microtube) with screw cap and secure with thermoplastic, self-sealing lab film.	For antibody and rRT-PCR testing, specimens should be kept cold (2–8 °C) or frozen (–70 °C).  For virus isolation testing, specimens should be frozen as soon as possible (–70 °C).	For cold specimens, the sample should be placed in an insulated container with adequate ice packs to ensure specimen ("cold chain") integrity.  For frozen specimens, ship the sample on enough dry ice to ensure specimens remain frozen until received.	Arboviral Diseases Branch Diagnostic Laboratory Centers for Disease Control and Prevention 3156 Rampart Road Fort Collins, Colorado 80521  More information about collecting, handling, and shipping is available <a href="#">here</a> .
Placenta and fetal membranes	At least 2 full thickness sections (0.5–1 cm x 3–4 cm in depth) from middle third of placental disk and at least 1 from the placental disk margin  One 5 x 12 cm strip of fetal membranes taken from the area of rupture and including a small bite of the edge of the disk.  Please include sections of the placental disk, fetal membranes, and pathologic lesions when possible.  (Please reference the figure on page one.)	Please sample both maternal and fetal side of the placenta.  Label all specimens to identify location of sample.	Fix specimens in formalin  Volume of formalin used should be about 10x the volume of tissue. Place in 10% neutral buffered formalin for 3 days (72 hours). After fixation, if not paraffin-embedded, tissues should be transferred to 70% ethanol for long term storage and shipping.  Storage and shipping at room temperature.	Infectious Diseases Pathology Branch Centers for Disease Control and Prevention 1600 Clifton Rd. NE, MS G-32 Atlanta GA 30329-4027  Get <a href="#">more instructions regarding collecting and shipping tissue specimens</a> .
Umbilical cord	At least two representative 2.5 cm segments of cord	Label specimen to identify location of sample (e.g., if proximal, middle, and distal to umbilical cord insertion site on the placenta).	Fix specimens in formalin  Volume of formalin used should be about 10x the volume of tissue. Place in 10% neutral buffered formalin for 3 days (72 hours). After fixation, if not paraffin-embedded, tissues should be transferred to 70% ethanol for long term storage and shipping  Storage and shipping at room temperature.	Infectious Diseases Pathology Branch Centers for Disease Control and Prevention 1600 Clifton Rd. NE, MS G-32 Atlanta GA 30329-4027  Get <a href="#">more instructions regarding collecting and shipping tissue specimens</a> .
Infant urine	Provide 0.5–1.0 mL of the specimen in a sterile screw capped vial secured with a small piece of thermoplastic, self-sealing lab film. Please ensure a tight seal as leaking specimens cannot be accepted.	Sterile specimen is not required	For rRT-PCR testing, specimens should be kept cold (2–8 °C) or frozen (–20 °C) for storage and shipping.  For frozen specimens, ship the sample on enough dry ice to ensure specimens remain frozen until received.	Arboviral Diseases Branch Diagnostic Laboratory Centers for Disease Control and Prevention 3156 Rampart Road Fort Collins, Colorado 80521  Get more information about <a href="#">collecting, handling, and shipping</a> .

# Case – Infant testing results

- VRDL:
  - Zika IgM >1:10 **detected**, PCR not detected
  - Dengue IgM not detected, PCR not detected
- CDC:
  - Zika PRNT >1280 (positive)
  - Dengue PRNT >1280 (positive)

# **MANAGEMENT OF NEWBORNS EXPOSED TO ZIKA VIRUS**

## Update: Interim Guidance for the Diagnosis, Evaluation, and Management of Infants with Possible Congenital Zika Virus Infection — United States, October 2017

Tolulope Adebajo, MD<sup>1,2</sup>; Shana Godfred-Cato, DO<sup>3</sup>; Laura Viens, MD<sup>4</sup>; Marc Fischer, MD<sup>5</sup>; J. Erin Staples, MD, PhD<sup>5</sup>; Wendi Kuhnert-Tallman, PhD<sup>6</sup>; Henry Walke, MD<sup>7</sup>; Titilope Oduyebo, MD<sup>8</sup>; Kara Polen, MPH<sup>9</sup>; Georgina Peacock, MD<sup>10</sup>; Dana Meaney-Delman, MD<sup>6</sup>; Margaret A. Honein, PhD<sup>9</sup>; Sonja A. Rasmussen, MD<sup>11</sup>; Cynthia A. Moore, MD, PhD<sup>9</sup>; Contributors

- Most up to date recommendations by CDC so far.
- CDPH refers to CDC recommendations for management and evaluation.

# More recent findings

- Eye findings in infants without microcephaly or other brain anomalies.
- Postnatal onset microcephaly in infants born with normal head circumferences
- Postnatal onset hydrocephalus in infants born with microcephaly
- Abnormalities on sleep EEG in some infants with microcephaly who did not have recognized seizures.
- Diaphragmatic paralysis in infants born with microcephaly and arthrogryposis.

# Updated management for possible maternal Zika virus exposure scenarios

Who needs further testing/evaluation?	Who does not?
Infants with clinical findings consistent with congenital Zika syndrome regardless of maternal testing results	Infants without clinical findings consistent with congenital Zika syndrome who were born to mothers without laboratory evidence of possible Zika virus <ul style="list-style-type: none"><li>• Routine pediatric care</li></ul>
Infants without clinical findings consistent with congenital Zika syndrome who were born to mothers with laboratory evidence of possible Zika infection	



# Standard Evaluation

- All infants born to mothers with possible Zika virus exposure during pregnancy should receive a **standard evaluation** at birth and at each subsequent well-child visit:
  - Comprehensive physical exam (with growth parameters)
  - Age-appropriate vision screening and developmental monitoring and screening using validated tools
  - Newborn hearing screen at birth (preferably ABR)

# MEASURING HEAD CIRCUMFERENCE



Typical Head Size

Typical Head Size



**Baby with Typical Head Size**



**Baby with Microcephaly**



**Baby with Severe Microcephaly**

- Use a measuring tape that cannot be stretched
- Securely wrap the tape around the widest possible circumference of the head
  - » Broadest part of the forehead above eyebrow
  - » Above the ears
  - » Most prominent part of the back of the head

- Take the measurement three times and select the largest measurement to the nearest 0.1 cm
- Head circumference measurements should be taken on the first day of life because commonly-used birth head circumference reference charts by age and sex are based on measurements taken before 24 hours of age

**For more information: [www.cdc.gov/zika](http://www.cdc.gov/zika)**



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**TABLE. Interpretation of results of laboratory testing of infant's blood, urine, and/or cerebrospinal fluid for evidence of congenital Zika virus infection**

**Infant test result\***

<b>NAT</b>	<b>IgM</b>	<b>Interpretation</b>
Positive	Any result	Confirmed congenital Zika virus infection <sup>†</sup>
Negative	Nonnegative	Probable congenital Zika virus infection <sup>§,¶</sup>
Negative	Negative	Congenital Zika virus infection unlikely <sup>§,**</sup>

**Abbreviations:** IgM = immunoglobulin M; NAT = nucleic acid test.

\* Infant serum, urine, or cerebrospinal fluid.

<sup>†</sup> Distinguishing between congenital and postnatal infection is difficult in infants who live in areas where there is ongoing transmission of Zika virus and who are not tested soon after birth. If the timing of infection cannot be determined, infants should be evaluated as if they had congenital Zika virus infection.

<sup>§</sup> Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology results, clinical findings consistent with congenital Zika syndrome, and any confirmatory testing with plaque reduction neutralization testing.

<sup>¶</sup> If Zika virus plaque reduction neutralization test is negative, this suggests that the infant's Zika virus IgM test is a false positive.

\*\* Congenital Zika virus infection is unlikely if specimens are collected within the first few days after birth and the clinical evaluation is normal; however, health care providers should remain alert for any new findings of congenital Zika virus infection.

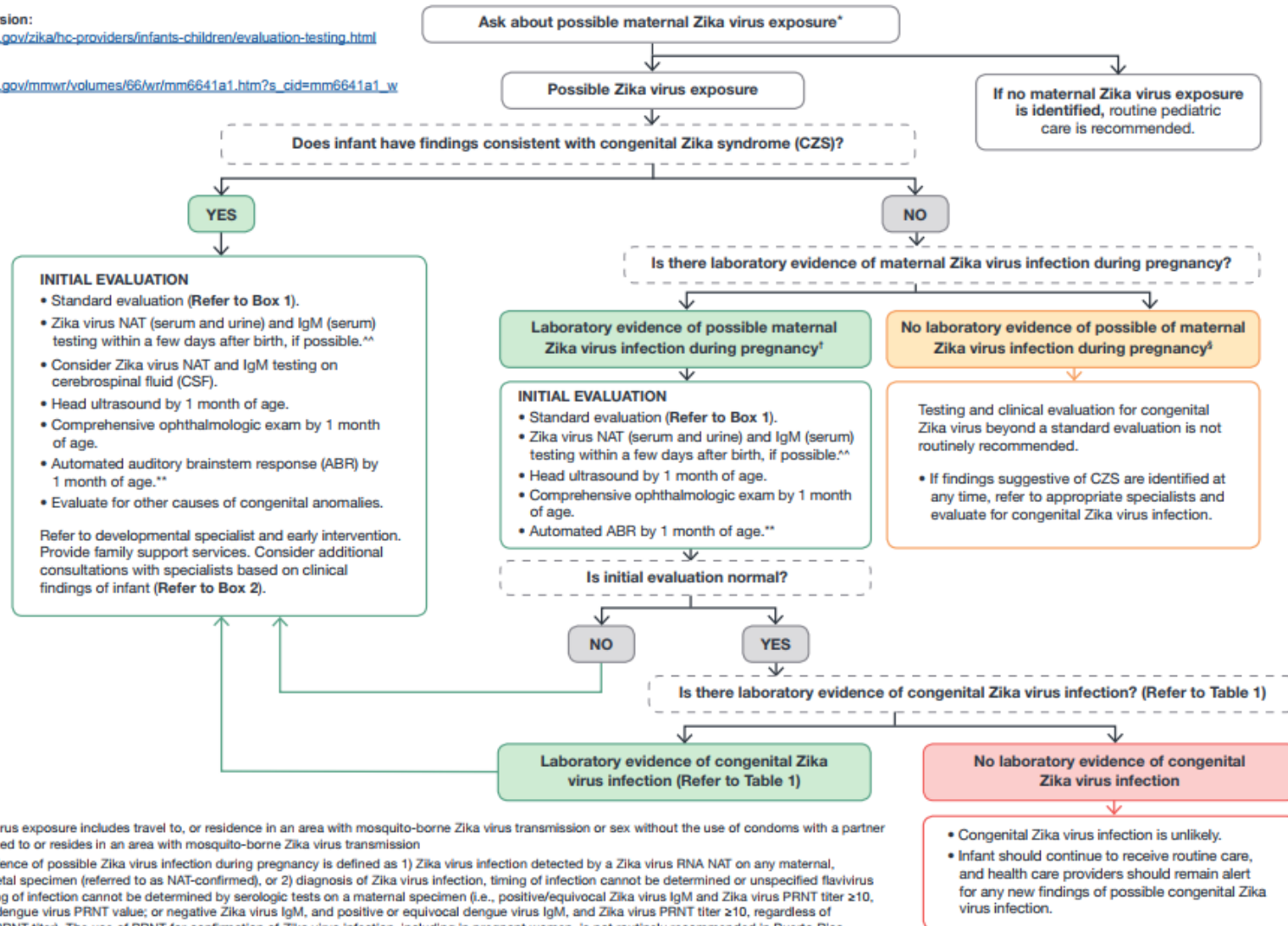
# EVALUATION FOR INFANTS WITH POSSIBLE CONGENITAL ZIKA VIRUS INFECTION

Accessible Version:

<https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-testing.html>

MMWR:

[https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm?s\\_cid=mm6641a1\\_w](https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm?s_cid=mm6641a1_w)



\* Possible Zika virus exposure includes travel to, or residence in an area with mosquito-borne Zika virus transmission or sex without the use of condoms with a partner who has traveled to or resides in an area with mosquito-borne Zika virus transmission

† Laboratory evidence of possible Zika virus infection during pregnancy is defined as 1) Zika virus infection detected by a Zika virus RNA NAT on any maternal, placental, or fetal specimen (referred to as NAT-confirmed), or 2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified flavivirus infection, timing of infection cannot be determined by serologic tests on a maternal specimen (i.e., positive/equivocal Zika virus IgM and Zika virus PRNT titer  $\geq 10$ , regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer  $\geq 10$ , regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women, is not routinely recommended in Puerto Rico (<https://www.cdc.gov/zika/laboratories/lab-guidance.html>).

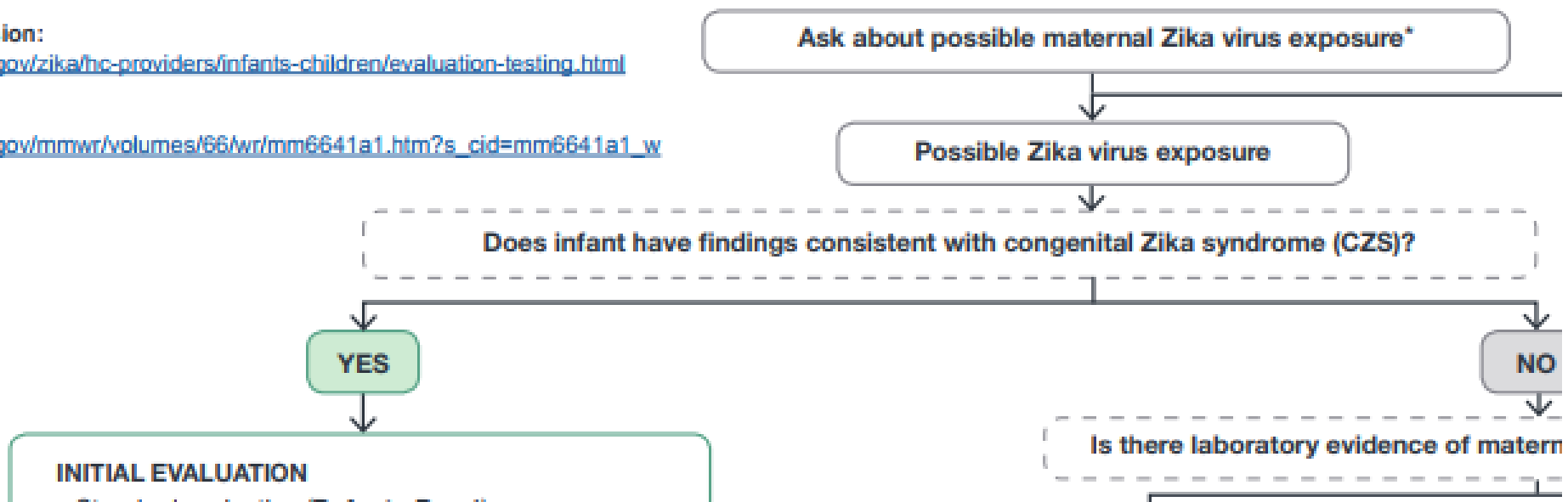
‡ This group includes women who were never tested during pregnancy as well as those whose test result was negative because of issues related to timing or sensitivity and specificity of the test. Because the latter issues are not easily discerned, all mothers with possible exposure to Zika virus during pregnancy who do not have laboratory evidence of possible Zika virus infection, including those who tested negative with currently available technology, should be considered in this group.

\*\* Automated ABR by 1 month of age if newborn hearing screen passed but performed with otoacoustic emission (OAE) methodology

^^ If CSF is obtained for other purposes, Zika virus NAT and IgM antibody testing should be performed on CSF.



Version:  
<https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-testing.html>  
[https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm?s\\_cid=mm6641a1\\_w](https://www.cdc.gov/mmwr/volumes/66/wr/mm6641a1.htm?s_cid=mm6641a1_w)



**Infants with abnormalities consistent WITH congenital Zika syndrome born to mothers with possible Zika exposure in pregnancy**

# Infants with abnormalities consistent WITH congenital Zika syndrome born to mothers with possible Zika exposure in pregnancy

YES

## INITIAL EVALUATION

- Standard evaluation (**Refer to Box 1**).
- Zika virus NAT (serum and urine) and IgM (serum) testing within a few days after birth, if possible.<sup>^^</sup>
- Consider Zika virus NAT and IgM testing on cerebrospinal fluid (CSF).
- Head ultrasound by 1 month of age.
- Comprehensive ophthalmologic exam by 1 month of age.
- Automated auditory brainstem response (ABR) by 1 month of age.<sup>\*\*</sup>
- Evaluate for other causes of congenital anomalies.

Refer to developmental specialist and early intervention. Provide family support services. Consider additional consultations with specialists based on clinical findings of infant (**Refer to Box 2**).

**\*\* ABR needed if initial was otoacoustic emissions methodology.**

**Infants with abnormalities consistent WITH congenital Zika syndrome born to mothers with possible Zika exposure in pregnancy**

## **Management**

- Refer to developmental specialist and early intervention services.
- Provide family support services.
- Consider additional consultations with:
  - Infectious diseases specialist
  - Clinical geneticist
  - Neurologist
  - Other clinical specialists based on clinical findings of infant



# Infants with abnormalities consistent **WITH** congenital Zika syndrome born to mothers with possible Zika exposure in pregnancy

## Consult with Specialists

- **Infectious Diseases** – r/o congenital infections, help with Zika testing/counseling
- **Neurologist** – by 1 mo, comprehensive evaluation, consider advanced neuroimaging, EEG
- **Ophthalmologist** – by 1 mo, comprehensive eye exam
- **Geneticist** – confirm phenotype, evaluate for other causes of microcephaly or congenital anomalies
- **Early intervention and developmental specialists**
- **Family and supportive services**

## Other specialists as indicated:

- **Endocrine** – hypothalamic or pituitary dysfunction, thyroid testing
- **Orthopedist, physiatrist, PT** – hypertonia, clubfoot, arthrogryposis
- **Pulmonologist, ENT** – aspiration concerns

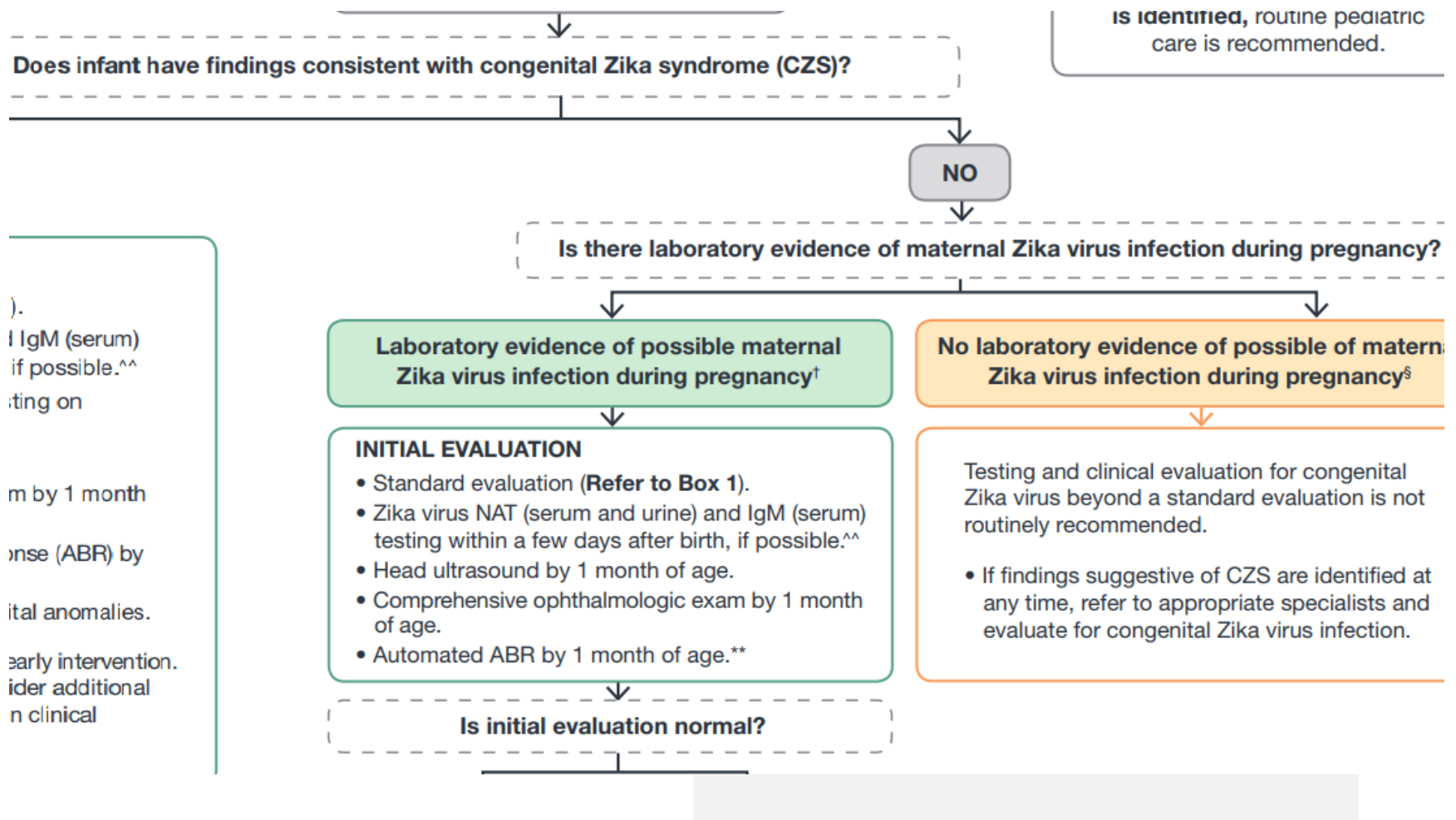
# Local Services

- Early Start – CA
  - <http://www.dds.ca.gov/earlystart/index.cfm>
- Regional Center – CA
  - <http://www.dds.ca.gov/RC/index.cfm>
- California Children's Services
  - <http://www.dhcs.ca.gov/services/ccs/Pages/default.aspx>
- Family Resource Centers Network of California
  - <http://www.frcnca.org/>
- Maternal, Child and Adolescent Health (CDPH)
  - <https://www.cdph.ca.gov/Programs/CFH/DMCAH/Pages/default.aspx>
- Regional Perinatal Programs of CA (CDPH)
  - <https://www.cdph.ca.gov/Programs/CFH/DMCAH/RPPC/Pages/Default.aspx>

# **Infants with abnormalities consistent WITH congenital Zika syndrome born to mothers with possible Zika exposure in pregnancy**

## **Further management**

- Respiratory distress/failure or fails to wean from ventilator -  
> evaluate for diaphragmatic paralysis
- Monitor feeding for swallowing dysfunction, dysphagia
- Signs of increased ICP -> neuroimaging for postnatal hydrocephalus
- Establish medical home for coordination of care and to ensure abnormal findings are addressed
  - Routine pediatric care with standard evaluation, immunizations, etc.
- f/u eye exams as needed as per ophthalmologist
- No need for 4-6 mo ABR
  - no delayed-onset hearing loss noted thus far



**Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with lab evidence of possible Zika virus infection during pregnancy**

# **Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with lab evidence of possible Zika virus infection during pregnancy**

## **Initial Evaluation**

- Standard evaluation (PE incl. growth parameters [wt/ht/HC], vision and developmental screen, newborn hearing screen)
- Zika virus NAT and IgM testing
- Head ultrasound by age 1 month
- Comprehensive ophthalmologic exam by age 1 month
- Automated ABR by age 1 month
  - if initial screen was otoacoustic emission methodology

If initial evaluation is not normal, follow recommendations for infants with congenital Zika syndrome findings.

### INITIAL EVALUATION

- Standard evaluation (**Refer to Box 1**).
- Zika virus NAT (serum and urine) and IgM (serum) testing within a few days after birth, if possible.<sup>^^</sup>
- Consider Zika virus NAT and IgM testing on cerebrospinal fluid (CSF).
- Head ultrasound by 1 month of age.
- Comprehensive ophthalmologic exam by 1 month of age.
- Automated auditory brainstem response (ABR) by 1 month of age.<sup>\*\*</sup>
- Evaluate for other causes of congenital anomalies.

Refer to developmental specialist and early intervention. Provide family support services. Consider additional consultations with specialists based on clinical findings of infant (**Refer to Box 2**).

### Laboratory evidence of possible maternal Zika virus infection during pregnancy<sup>†</sup>

### INITIAL EVALUATION

- Standard evaluation (**Refer to Box 1**).
- Zika virus NAT (serum and urine) and IgM (serum) testing within a few days after birth, if possible.<sup>^^</sup>
- Head ultrasound by 1 month of age.
- Comprehensive ophthalmologic exam by 1 month of age.
- Automated ABR by 1 month of age.<sup>\*\*</sup>

### Is initial evaluation normal?

NO

YES

Is there laboratory evidence

**Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with lab evidence of possible Zika virus infection during pregnancy**

## **Further Management**

- Standard evaluations
  - Routine pediatric care, immunizations, etc.
  - Be vigilant for signs associated with congenital Zika syndrome, refer if concerned.
    - Impaired visual acuity/function
    - Hearing problems
    - Developmental delay
    - Delay in head growth



# **Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with lab evidence of possible Zika virus infection during pregnancy**

## **Further Management**

- If laboratory evidence of congenital Zika virus infection (positive Zika virus NAT or nonnegative Zika virus IgM with confirmatory neutralizing antibody testing)
  - Follow recommendations for infants with clinical findings of congenital Zika syndrome, even in absence of clinical abnormalities.
- If no laboratory evidence of congenital Zika virus infection:
  - Congenital Zika virus infection is unlikely.
  - Continue routine care. Remain alert for new findings of congenital Zika virus infection.

- Zika virus NAT (serum and urine) and IgM (serum) testing within a few days after birth, if possible.<sup>^^</sup>
- Consider Zika virus NAT and IgM testing on cerebrospinal fluid (CSF).
- Head ultrasound by 1 month of age.
- Comprehensive ophthalmologic exam by 1 month of age.
- Automated auditory brainstem response (ABR) by 1 month of age.<sup>\*\*</sup>
- Evaluate for other causes of congenital anomalies.

Refer to developmental specialist and early intervention. Provide family support services. Consider additional consultations with specialists based on clinical findings of infant (**Refer to Box 2**).

### Laboratory evidence of possible maternal Zika virus infection during pregnancy<sup>†</sup>

#### INITIAL EVALUATION

- Standard evaluation (**Refer to Box 1**).
- Zika virus NAT (serum and urine) and IgM (serum) testing within a few days after birth, if possible.<sup>^^</sup>
- Head ultrasound by 1 month of age.
- Comprehensive ophthalmologic exam by 1 month of age.
- Automated ABR by 1 month of age.<sup>\*\*</sup>

Is initial evaluation normal?

NO

YES

Is there laboratory evidence of congenital Zika virus infection? (**Refer to Table 1**)

### Laboratory evidence of congenital Zika virus infection (**Refer to Table 1**)

### No laboratory evidence of possible of maternal Zika virus infection during pregnancy<sup>§</sup>

Testing and clinical evaluation for congenital Zika virus beyond a standard evaluation is not routinely recommended.

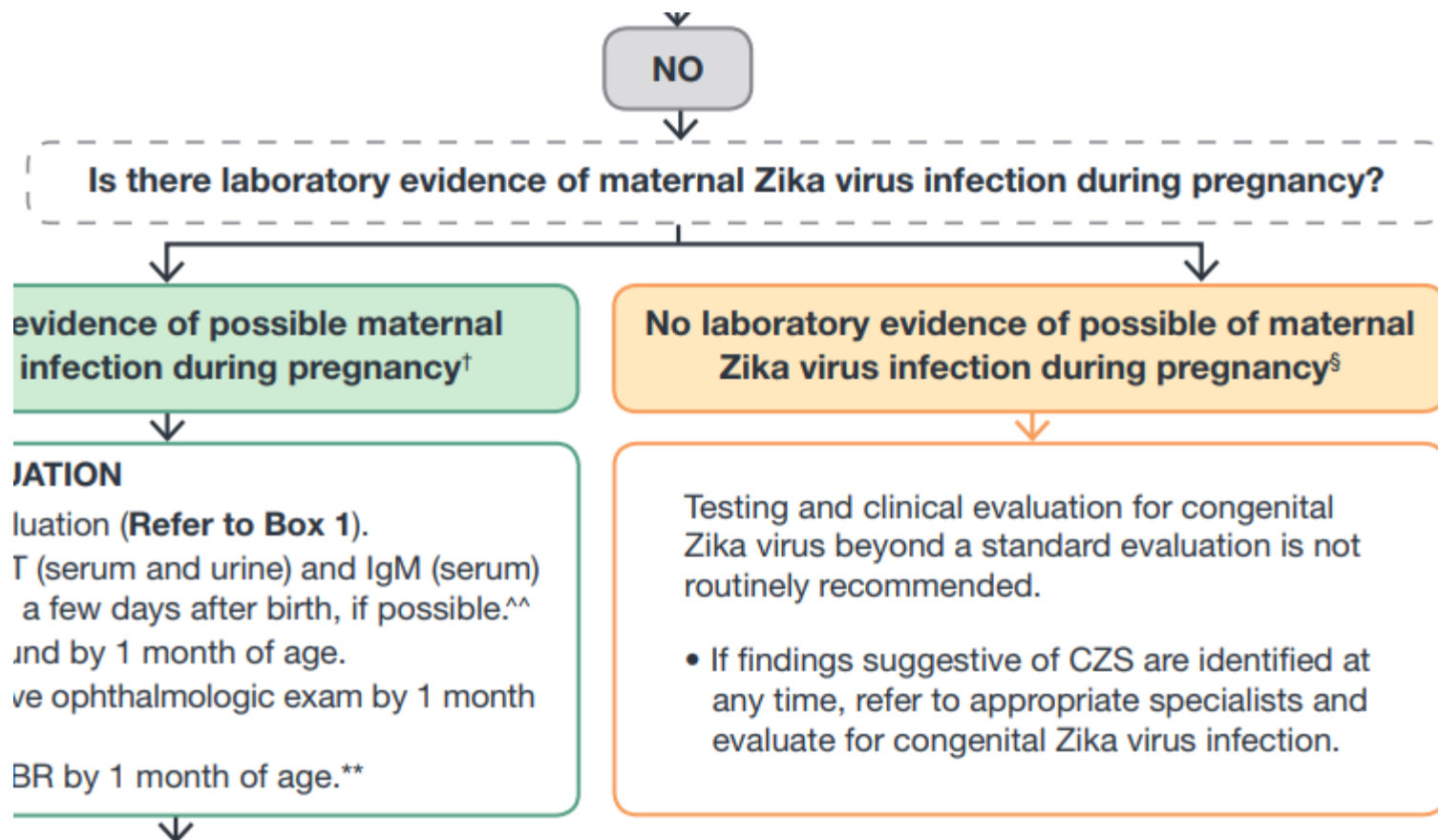
- If findings suggestive of CZS are identified at any time, refer to appropriate specialists and evaluate for congenital Zika virus infection.

### No laboratory evidence of congenital Zika virus infection

- Congenital Zika virus infection is unlikely.
- Infant should continue to receive routine care, and health care providers should remain alert for any new findings of possible congenital Zika virus infection.

is exposure includes travel to, or residence in an area with mosquito-borne Zika virus transmission or sex without the use of condoms with a partner d to or resides in an area with mosquito-borne Zika virus transmission

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**Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with possible Zika virus exposure during pregnancy but without lab evidence of possible Zika virus infection during pregnancy**

**Infants WITHOUT findings consistent with congenital Zika syndrome born to mothers with possible Zika virus exposure during pregnancy but without lab evidence of possible Zika virus infection during pregnancy**

## **Initial and Further Management**

- Standard evaluation (PE incl. growth parameters [wt/ht/HC], vision and developmental screen, newborn hearing screen)
- Zika testing not routinely recommended unless abnormal findings are identified.
- If any findings consistent with congenital Zika syndrome are identified, refer to appropriate specialists and perform evaluation for infants with findings consistent with congenital Zika syndrome.

# Reporting Zika

- Zika virus infections are nationally notifiable conditions.
- Report lab confirmed and symptomatic cases of Zika to local health departments.
  - They should report to ArboNET.
- US Zika Pregnancy Registry
  - <https://www.cdc.gov/pregnancy/zika/research/registry.html>

# General patient advice about Zika virus

- Avoid traveling to Zika risk areas while pregnant.
- There is no treatment or vaccine for Zika (yet).
  - Treat symptoms with supportive care.
- Prevent mosquito bites while traveling to Zika risk areas.
  - Keep skin covered (long sleeves, etc.), sleep under mosquito bed or in air conditioned rooms.
  - Use mosquito repellent (DEET, etc.)



# PROTECT YOURSELF from MOSQUITO BITES

Mosquitoes spread Zika and other viruses



## Daytime is the most dangerous

Mosquitoes that spread Zika are aggressive daytime biters. They can also bite at night.



## Use insect repellent It works!

Look for the following active ingredients:

- DEET • PICARIDIN • IR3535
- OIL of LEMON EUCALYPTUS
- PARA-MENTHANE-DIOL



## Wear protective clothes

Wear long-sleeved shirts and long pants or use insect repellent. For extra protection, treat clothing with permethrin.



## Mosquito-proof your home

Use screens on windows and doors. Use air conditioning when available. Once a week empty and scrub, turn over, cover, or throw out items that hold water outside your home.

Distributed by:



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Health and Human Services  
Centers for Disease  
Control and Prevention



For more information: [www.cdc.gov/zika](http://www.cdc.gov/zika)  
[www.cdph.ca.gov/zika](http://www.cdph.ca.gov/zika)



# Insect Repellent: What Pregnant & Breastfeeding Women Need to Know



Protect your family - prevent insect bites



Repellents will keep mosquitoes and other insects from biting you. This will reduce your chance of getting a disease like **Zika**, which can cause severe birth defects in your unborn baby.

Insect repellents registered by the Environmental Protection Agency (EPA) are **safe** and **effective** to use, even for pregnant and breastfeeding women, when used as directed by the label instructions.

## Do:

- Read and follow label directions before applying repellent
- Use only enough repellent to cover your clothes and exposed skin
- Apply sunscreen first if you are going outdoors, then apply repellent
- Apply repellent for children—spray on your own hands first and then put it on the child
- Wash your clothes and bathe after using insect repellent and returning indoors

The California Department of Public Health

Don't:

# “Top 5 Things Everyone Needs to Know About Zika” [CDC]

1. Zika primarily spreads through infected mosquitoes. You can also get Zika through sex.
2. The best way to prevent Zika is to prevent mosquito bites.
3. Zika is linked to birth defects.
4. Pregnant women should not travel to areas with risk of Zika.
5. Returning traveler's infected with Zika can spread the virus through mosquito bites and sex.

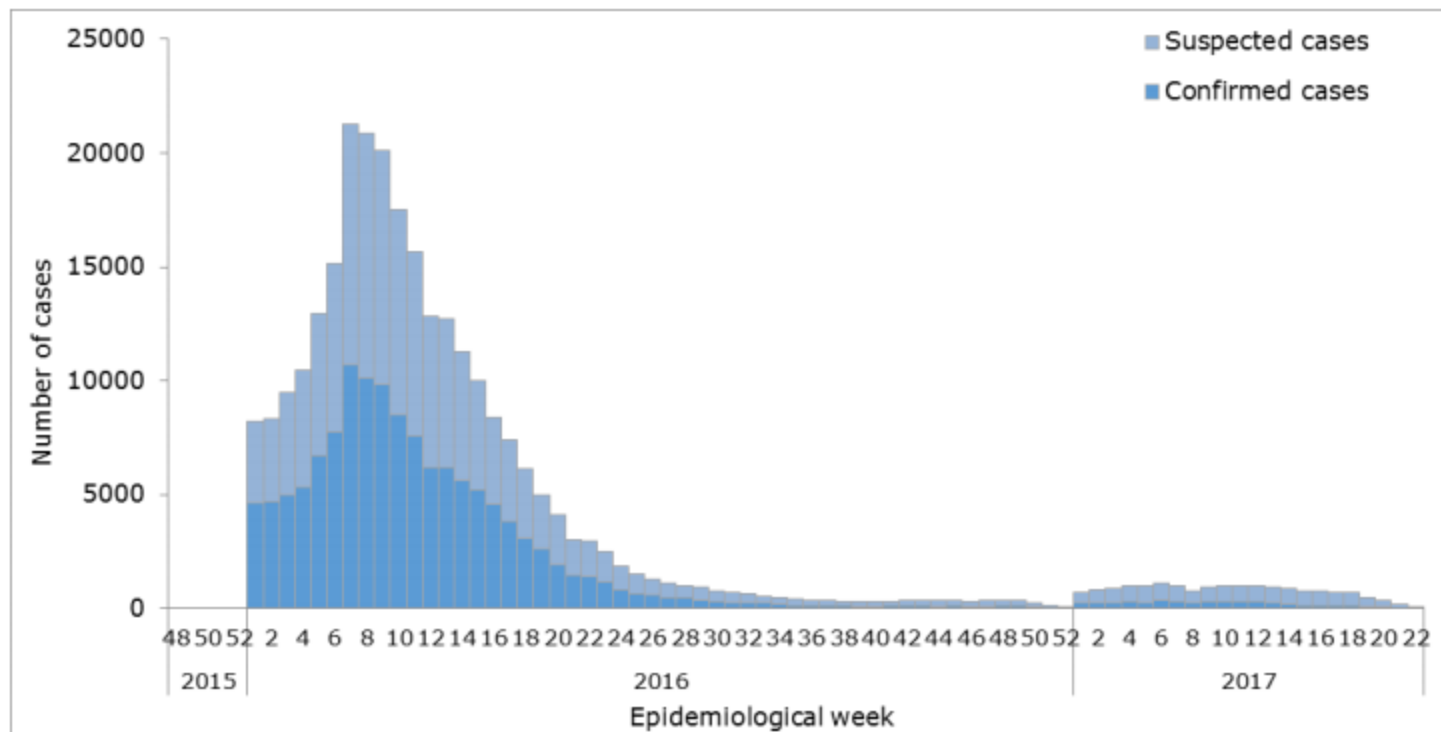
# Hope?

## Zika-Epidemiological Report Brazil



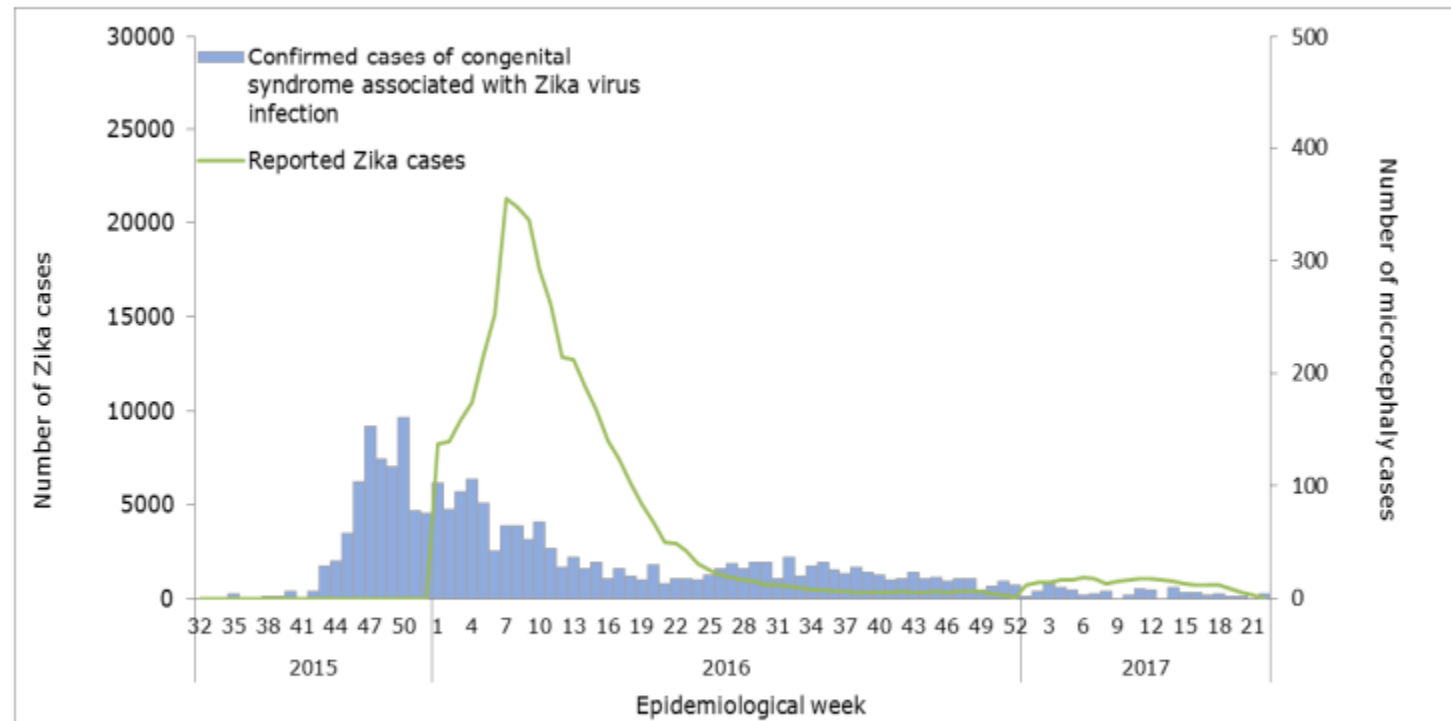
25 September 2017

**Figure 1.** Suspected and confirmed cases of Zika by epidemiological week. Brazil. EW 48 of 2015 to EW 22 of 2017.<sup>1</sup>



Source: Data provided by the Brazil Ministry of Health to PAHO/WHO<sup>2</sup>

**Figure 6.** Total confirmed cases of congenital syndrome associated with Zika virus infection by EW. Brazil. EW 32 of 2015 to EW 22 of 2017.



Source: Data provided by the Brazil Ministry of Health to PAHO/WHO<sup>10</sup>

# For more information:

Centers for Disease Control and Prevention (CDC)

- <https://www.cdc.gov/zika/>

CA Dept of Public Health (CDPH)

- <https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Zika.aspx>

# Additional Sources

- World Health Organization: [www.who.int/topics/zika/en/](http://www.who.int/topics/zika/en/)
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