




Zika Virus, Pregnancy and Sex: Up-to-Date Information for Los Angeles Health Care Providers

March 15, 2016

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Disclosures

There is no commercial support for today's activity

None of the speakers or planners for today's meeting have disclosed any financial interests related to the content of the meeting

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Zika Virus Webinar Overview

- How Zika virus is transmitted
- The epidemiology of Zika virus outbreaks
- The clinical presentation and treatment
- The diagnostic testing and procedures
- The potential complications of Zika virus in pregnancy
- How Zika virus infection can be prevented




Zika Virus, Pregnancy, and Sex

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Medical Epidemiologist
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Zika Virus Transmission and Epidemiology



Zika Virus

- Single stranded RNA virus isolated in 1947 from a rhesus monkey in Zika forest in Uganda
- Genus *Flavivirus* – closely related to viruses that cause West Nile, dengue, Chikungunya, yellow fever, and Japanese Encephalitis
- Transmitted to humans by *Aedes* species mosquitoes primarily by *A. aegypti*, *A. albopictus* may also be competent vector

Dick, et al. Trans R Soc Trop Med Hyg 1952;46: 509-20.

Global *Aedes aegypti* Distribution

https://en.wikipedia.org/w/index.php?title=Zika_virus&printable=yes

Zika Virus Epidemiology

- Before 2007 – sporadic human disease cases reported from Africa and southeast Asia
- 2007 – first outbreak reported on Yap Island, Federated States of Micronesia
- 2013-14 – Major epidemics in reported from French Polynesia, New Caledonia, the Cook Islands and Easter Island
- 2015- widespread transmission Americas and Brazil

Duffy, et al. N Engl J Med 2009; 360:2536-43.
Cao-Lormeau, et al. EID 2014; 20: 1085-6

Countries with Zika Virus Transmission, March 11, 2016

- 37 countries and territories in the Americas
- 5 Pacific Islands
- Cape Verde

<http://wwwnc.cdc.gov/travel/notices>

As of March, 2016

Zika Virus Transmission

- Primarily mosquito-human-mosquito
 - Infected persons viremic for ~1 week during which they can infect a mosquito that bites them
- Other modes of transmission
 - Intrauterine and intrapartum
 - Sexual
 - Transfusion-associated
 - Laboratory
- Virus found in urine, saliva, and breast milk but evidence of transmission from those fluids

Clinical Illness, Diagnosis and Management

Zika Virus Clinical Illness

- Only 20% of infections symptomatic
- Onset 3-12 days after exposure
- Symptomatic illness mild, lasting <1 week
- Rare hospitalizations; no deaths
- Guillain-Barré Syndrome (GBS) may occur after symptomatic/asymptomatic

Symptom	Percent
Rash	77%
Myalgia	77%
Arthralgia	73%
Fever	73%
Eye pain	67%
Chills	67%
Headache	63%
Sore throat	40%
Petichiae	33%
Conjunctivitis	27%

http://www.cdc.gov/mmwr/volumes/65/wr/mm6506a2.htm?_a_cid=mm6506a2.htm_w



Clinical Features of Zika Compared with Dengue and Chikungunya

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





Management of Suspect Zika Virus Infection

- No specific antiviral therapy
- Supportive treatment (rest, fluids, analgesics, antipyretics)
- Avoid aspirin and other NSAIDs until dengue is ruled out to reduce the risk of hemorrhage



Zika Virus Laboratory Testing and Surveillance



Laboratory Testing Indications

- Individuals who traveled to Zika endemic area and with symptoms of acute Zika virus infection that occur within 2 weeks of exposure*
- Asymptomatic pregnant women 2-12 weeks after exposure
- Fetal microcephaly and/or intracranial calcifications on ultrasound with mother with travel history to Zika affected area
- Infant with microcephaly after maternal exposure or confirmed/inconclusive maternal infection
- Symptomatic sexual partner without travel history of acutely symptomatic case-patient with travel history to Zika affected area
- GBS after potential Zika virus exposure

*Symptoms of acute Zika virus infection are defined as 2 or more of the following: fever, maculopapular rash, arthralgia, or conjunctivitis



Laboratory Testing for Zika Virus

- RT-PCR – detection of virus RNA
 - RT-PCR testing of serum, urine, CSF, amniotic fluid, fixed tissue
 - Recent symptomatic infection within 7 days of onset for serum, urine PCR positive up to 30 days
- Serology (IgM) – Test >4 days after illness onset or 2-12 weeks after potential exposure if asymptomatic
- Immunohistochemistry – detect virus from tissue and placenta



Challenging Issues of Laboratory Testing for Zika Virus

- Zika is closely related to other flaviviruses
 - Cross-reactivity with other flaviviruses; test for dengue and Chikungunya and report if Yellow Fever or JE vaccine
 - Plaque reduction neutralization test identifies Zika specific antibodies and compares to other closely related viruses, must be completed on all positive IgM specimens
- Tests currently available at California Department of Public Health
 - Confirmatory testing of positive serological results at CDC
 - Delays in test results



Zika Virus Laboratory Testing Procedures Los Angeles County (LAC), March 3, 2016 (1)

- Pre-approval from Public Health is not required for Zika testing
- Zika Virus Testing and Report Form must be completely filled out – must accompany specimen
- Zika Virus Lab Requisition Form must be completely filled out and one form for each specimen type



Zika Virus Laboratory Testing Procedures, March 3, 2016 (2)

- Zika suspects meeting the following criteria should be reported to Acute Communicable Disease Program (ACDC) by phone for Zika test coordination
 - Pregnant traveler with fetal ultrasound evidence of microcephaly and/or intracranial calcifications or fetal loss
 - Infant with microcephaly and/or calcifications and evidence of maternal Zika infection
 - Symptomatic woman without travel history who had unprotected sex with a symptomatic male traveler from Zika affected area
 - Traveler to Zika affected area with GBS diagnosis



Zika Virus in the United States- as of March 9, 2016

- No local transmission in the U.S.
- From 2011–2014, 11 confirmed Zika cases in travelers returning to the U.S.
- 193 travel- associated cases in U.S. confirmed by CDC as of March 9, 2016
- 11 cases in California in 2016; 4 cases in Los Angeles County
- 173 cases of local transmission and 1 travel associated case in US Territories- most cases in Puerto Rico
- With current CDC backlog for testing, number of U.S. cases will increase



Zika Surveillance in Los Angeles County (LAC)

- To date, over 200 requests for testing approved
 - 4 positive; 43 negative; 154 pending results
- Public Health Laboratory receiving 15 – 20 Zika test requests per day
 - > 80% are asymptomatic pregnant women who traveled to an affected country
 - 46% report travel to Mexico; and 4-8% each to Guatemala, Honduras, Costa Rica, El Salvador



Zika Virus Testing and Follow-up in LAC

- Public Health Laboratory will report positive and negative Zika tests to medical provider
- ACDC will conduct case investigations laboratory confirmed Zika cases
- For pregnant women with positive Zika testing
 - ACDC will coordinate perinatal testing with obstetrician
 - Requires cord blood and placental specimens
 - Public Health will work with family and pediatrician to follow Zika infected newborn through 1st year of life
 - Recommended hearing and ophthalmologic evaluation
 - Developmental assessment
 - Additional Zika testing as necessary



Prevention of Zika Virus Infection and of Local Zika Transmission



Prevention of Zika Infection

- No vaccine or medication to prevent infection or disease
- Pregnant women should avoid travel to Zika affected areas
- Primary prevention measure is to reduce mosquito exposure
 - Insect repellent with an EPA registered ingredient (DEET, Picaridin, IR3535)
 - Repellents safe for use by pregnant women
 - Most can be used on children aged >2 months
 - Wear long sleeves and pants; may treat with permethrin
 - Stay in places with air conditioning or screens



LA County Patient Information

WARNING

Zika Virus Disease

Areas of Central and South America, the Caribbean, and Mexico have mosquitoes that can cause Zika virus disease. If you're pregnant, your baby may be born with birth defects if you get infected with Zika.

Traveling South of the United States

Check for signs of Zika (a fever, rash, etc.)

Returning to the United States

Check for signs of Zika (a fever, rash, etc.)

Zika Virus Disease

1. What is Zika virus disease?

2. How does Zika disease spread?

3. What are the symptoms?

4. What is known about Zika being pregnant?

5. How can you prevent getting Zika disease?

<http://publichealth.lacounty.gov/acd/VectorZika.htm>

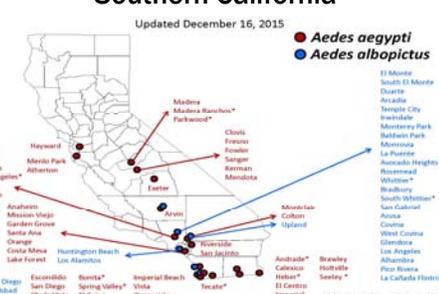


A. aegypti & A. albopictus in Southern California

Updated December 16, 2015

Legend:

- *Aedes aegypti*
- *Aedes albopictus*



*Not Incorporated Census Designated Places



Reducing Risk of Local Zika Transmission

- Control *Aedes* mosquito populations
 - Mosquito and Vector Control Districts
 - Surveillance (trapping) for *Aedes*
 - Investigation of complaints & targeted larvicide and adulticide treatment
 - New control technologies
 - Public education
 - Public actions
 - Identify and reduce standing water around homes
 - Contact vector control if multiple day time mosquito bites





Zika Vaccine Development

- Congenital infection makes Zika a priority for vaccine development
- No Zika vaccines currently in advanced development
- Existing flavivirus vaccines (YF, JE, dengue) may serve as a platform
- Sanofi Pasteur & biotech firms developing vaccine candidates
- Licensure and use likely 3 – 10 years away



Zika and Pregnancy: Update --March 15, 2016

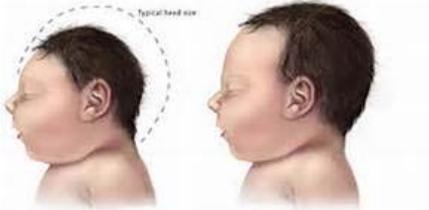


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Aedes aegypti

Photo: CDC/ Prof. Frank Hadley Collins, Dir., Cntr. for Global Health and Infectious Diseases, Univ. of Notre Dame. PHIL 9261

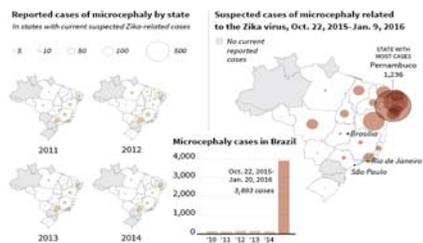


Baby with Microcephaly Baby with Typical Head Size



Microcephaly and other Risks

- To date, over 4700 cases of suspected microcephaly have been attributed to Zika in Brazil from mid-2015 through Jan 2016 (20X ↑ from baseline): *CDC 2/19/16*

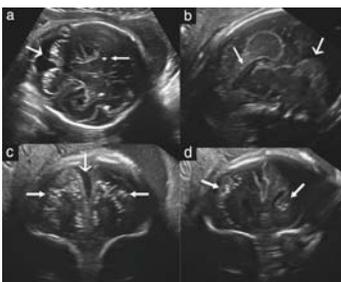


Source: Brazil Ministry of Health, CDC, Associated Press

Microcephaly: the most apparent marker?

- Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in **newborns**
 - On ultrasound, typically defined as HC < 3rd %ile for GA, though some authors define as < 1st %ile (3 SD), to increase specificity
 - Definitions/cutoffs for this diagnosis are evolving**
- Microcephaly became an **early trigger** to search for Zika association, but spectrum of disease became apparent
 - 2 early cases of Zika isolation from amniotic fluid of fetuses with microcephaly: fetuses also had white matter atrophy, calcifications, ventriculomegaly (*Oliviaira Melo et al. Ultrasound Obstet Gynecol Jan 2016*)
- Polynesia outbreak in 2014: data showed higher rates of fetal CNS abnormalities in some women seropositive for Zika, though none had had symptoms (*Euro Ctr Dis Prev Control 2015*)

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?



Ultrasound in Obstetrics & Gynecology
Volume 47, Issue 1, pages 6-7, 5 JAN 2016 DOI: 10.1002/uog.15831
<http://onlinelibrary.wiley.com/doi/10.1002/uog.15831/full#uog15831-fig-0001>

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?

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But, does Zika **cause** pregnancy problems?

- Until recently, *association* with infection and microcephaly
- Recent data linking presence of virus to brain tissue of fetus aborted @ 32 weeks (NEJM online 2/12/16)
 - Slovenian health worker, likely infx 1st Δ, EFW @ 3rd %ile
 - Autopsy: agyria and diffuse calcium deposits through white matter
 - Brain wt 84gm (< 4SD), **Zika RNA found in brain only via PCR**
- Also association with chorioretinitis in newborns with microcephaly (JAMA Ophtho online 2/11/16)
 - Seen in 35% of 29 newborns w/ microcephaly in Brazil
 - 80% of newborns' mothers had sx c/w Zika
 - Other infections excluded by neonatal serology
- 2 recent CDC cases associating maternal infection with miscarriage (2/12/16)

Additional recent CDC reports from Brazil

- Since Nov 2015, CDC has been developing assays for Zika virus testing in formalin-fixed, paraffin-embedded (FFPE) tissue samples
 - Working with task force from Brazil Ministry of Health
- In Dec 2015, FFPE samples analyzed from 4 pregnancies with adverse outcomes from N. Brazil
 - 2 newborns with microcephaly (born at 36 & 38 weeks) who died within 20 hrs of birth, and 2 Sabs @ 11, 13 wks
 - All 4 mothers had clinical signs of Zika infection in 1st trimester, with no signs of active infection at delivery
 - No mothers were tested for Zika antibodies
- Specimens from all 4 cases were positive for Zika antigens by RT-PCR (2 newborn brains, 1 placenta, 2 POC)
 - Dengue PCR was negative, TORCH serologies in mothers negative
 - Viral antigen in glial cells in brain, and in chorionic villi from 1 SAB

MMWR. Feb 19, 2016

Zika Virus Associated with Microcephaly.
 Mlakar J, et al.
 N Engl J Med
 2016; 374:951-958
 March 10, 2016

The JAMA Network

From: Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil
 JAMA Ophthalmol. Published online February 09, 2016. doi:10.1001/jamaophthalmol.2016.0267

Figure Legend:
 Fundus Photographs of a 1-Month-Old Boy The right (A) and left (B) eyes have paramacular superotemporal round chorioretinal atrophy surrounded by a hyperpigmented halo and hyperpigmented mottling.

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The JAMA Network

From: Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil
 JAMA Ophthalmol. Published online February 09, 2016. doi:10.1001/jamaophthalmol.2016.0267

Figure Legend:
 Fundus Photographs of a 20-Day-Old Infant The right eye has optic disc hypoplasia, peripapillary nasal atrophy, and an excavated nasal round lesion with a hyperpigmented halo, with a colobomatous-like aspect (A), and the left eye has optic disc hypoplasia, peripapillary nasal atrophy, and a retinal nasal lesion with a similar pattern (B).

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Recent NEJM series, Brazil: Background

- Brazil group had been conducting surveillance for dengue in population of Rio de Janeiro since 2007
 - In 2015, noted increase in dengue-like illness with rash, coinciding with surge of similar cases in NE Brazil → ID as Zika
 - Expanded cohort study to pregnant women at any GA w/rash that had developed within previous 5 days
- Study cohort: 88 women (9/15-2/16)
 - 82% (72/88) tested positive for ZIKV (PCR) in blood, urine, or both
 - U/S done before 20 wks, 20-30 wks, and > 30 wks
 - Timing of infection: 5-38 weeks of gestation
 - ZIKV+ women more likely to have rash (58% v 13%), conjunctivitis (58% v 13%), lymphadenopathy (40% v 7%)

Brasil P, et al. NEJM, online 3/4/16

Clinical Features of Zika Virus Infection in Pregnant Women.



Brasil P et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1602412

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Recent NEJM series, Brazil: Results

- Of 72 women with PCR-positive test results
 - 60 (+) blood (83%), 46 (+) urine (64%), 34 (+) both samples
 - > 50% reported an ill family member; **21%: partner had been ill**
- 2 women miscarried in 1st Δ; 42 (60%) of others had u/s
 - 28 women declined u/s: either too far or fear of finding anomalies
- **Abnormal u/s results seen in 12/42 (29%) pts with Zika infx**
 - No abnormalities seen in any of the 16 Zika-negative women
 - IUGR in 5/12 fetuses (42%), with or without microcephaly
 - Cerebral calcifications in 4/12, other CNS anomalies in 2 fetuses
 - 2 IUFDs @ 30 and 38 wks: women infected at 25 and 32 wks
- To date, 8/42 women have delivered, with findings confirmed

Brasil P, et al. NEJM, online 3/4/16

Current Pregnancy Statistics, U.S.

- Timeline of guidelines:
 - Jan 15, 2016: travel alert
 - Jan 19: 1st interim guidelines, revised to expand testing Feb 5
- From 8/1/15 to 2/10/16, CDC received 257 requests for Zika testing of pregnant women, 59% symptomatic
 - As of Feb 17, 9 pregnant travelers with lab-confirmed ZKVD with an additional 10 under investigation: **no native cases**
 - Of those 9, all were symptomatic
 - 2 were early Sabs and 2 EAbs
 - 3 live births: 2 healthy, 1 with severe microcephaly
 - 2 ongoing, no known complications, 18 and 34 wks GA
- No Zika-related hospitalizations or deaths among women

MMWR. Feb 26, 2016

What do we tell our pregnant patients?

- *Despite earlier reports, recent data suggest later GA at infection does not exclude potential adverse impact*
- **Since there is neither vaccine or prophylactic medication available, CDC recommends that all pregnant women strongly consider postponing travel to areas with active Zika virus transmission**
- Providers and patients should be aware of CDC website with current travel advisories
 - <http://www.cdc.gov/zika/geo/index.html>
- If in an area with transmission, protection and prevention strategies are important
 - Repellent, screens/netting, long sleeves and pants
 - DEET, picaridin, oil of lemon eucalyptus, IR353

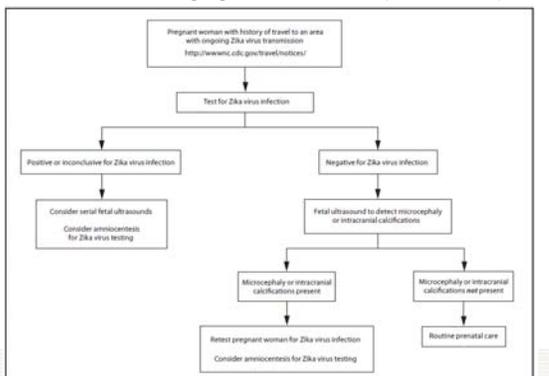
Ultrasound surveillance

- Microcephaly difficult to diagnose before 22 weeks
 - If exposure early (esp. if symptomatic), could potentially see intracranial findings short of microcephaly before 20-22 weeks: *evolving spectrum of disease*
 - Using CMV as model, likely need at least 6 weeks post exposure to see possible impact on u/s
- Current guidelines not prescriptive
- If Zika serology negative and reasonably-timed post-exposure ultrasound is normal, then routine surveillance is appropriate

Recent SMFM Statement on Microcephaly (Feb 2016)

- o Statement is prompted by concerns regarding dx of microcephaly in potentially Zika-exposed pregnancies
- o If the HC on prenatal ultrasound is > 2SD below the mean
 - This level should trigger detailed evaluation of fetal intracranial anatomy
 - *Recognizes process may be a spectrum before microcephaly apparent*
 - Followup as indicated but no sooner than 3-4 weeks [NB: take maternal serology results into account]
- o Isolated fetal microcephaly should be defined as fetal HC ≥ 3SD below mean for GA
- o Dx of pathologic microcephaly is certain at ≥ 5SD below mean

Updated Interim guidance: Testing algorithm for a pregnant woman with history of travel to an area with ongoing Zika virus transmission (MMWR 2/12/16)



Additional questions (evolving data)

- o When is safe to get pregnant after travel?
 - No clear data: at least 1 month after return, 2 months prudent?
- o What about a pregnant woman's sexual partner?
 - Sexual transmission of Zika virus can occur, although there are limited data about the risk: 14 cases under current study in US (2/29)
 - Recent statement from CDC (Feb 16) regarding male risks
 - 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**
 - CDC-cited early citation (3/2/16): ZKV-infected symptomatic male (by blood PCR) had convalescent-phase urine, blood and semen testing (Citing: Atkinson B et al. *Emerg Infect Dis J*, May 2016)
 - Only semen was PCR+ at 27 and 62 days after febrile illness
 - Does not prove infectious virus present

Zika: Potential Blood/Organ/Tissue Transmission

- o 2 possible cases of transmission through blood transfusion in Brazil (ECDC, Jan 2016)
 - Documented transfusion transmission of other flaviviruses (dengue, WNV): *NEJM 2003, MMWR 2010*
 - Blood donations positive for ZIKV viral RNA by nucleic acid testing (NAT) were detected during the French Polynesia outbreak in 2013-2014 (*Intl J Infect Dis, Dec 2015*)
- o Potential living donors of human cells, tissues should be considered **ineligible for 6 months** if dx'd with ZKVD, in an area with active transmission, or had sex with a male partner with either of those risks
 - **Includes semen, umbilical cord blood, placenta**

FDA 3/1/16, affirmed by ASRM 3/4/16

FDA Statement on Blood Transfusion: 2/16/16

- o Donor history questionnaire should assess prospective donors for a history of residence in or travel to an area with active transmission of ZIKV in the past 4 weeks.
- o Recommendation to defer for 4 weeks donors at risk for ZIKV infection as follows:
 - Defer for 4 weeks after resolution of symptoms in a donor with a history of confirmed ZIKV infection.
 - Defer for 4 weeks after resolution of symptoms a donor who reports *symptoms suggestive of ZIKV* that arose within 2 weeks of departure from an area with active transmission
 - Defer a donor for 4 weeks after last sexual contact with a man who has been diagnosed with ZIKV or who traveled to or resided in an area with active transmission of ZIKV in the 3 months prior to that instance of sexual contact.
 - Defer a donor for 4 weeks from the date of his or her departure, after travel to or residence in an area with active transmission

Indications for Zika testing	IgM serology ¹ (serum, CSF)	RT-PCR ² (serum, urine, or other sample types)	Call Public Health to report suspect case 213-240-7943
Pregnancy-associated			
Symptomatic pregnant traveler (2 or more of fever, maculopapular rash, arthralgia, non-purulent conjunctivitis)	YES	YES	NO
Asymptomatic pregnant traveler	YES ³	NO	NO
Pregnant traveler with ultrasound evidence of fetal microcephaly (occipitofrontal circumference <3 rd percentile for age and gender) and/or calcifications ⁴ OR fetal loss ⁵	YES	YES	YES
Infant with microcephaly and/or calcifications and evidence of maternal Zika virus infection ⁶	YES	YES ⁷	YES
Infant with no apparent defect and evidence of maternal Zika virus infection ⁶	YES	YES	YES
Symptomatic pregnant woman without travel history who had unprotected sex with a symptomatic male traveler from Zika affected area	YES	YES	YES
In Non-Pregnant Patients:			
Traveler with Guillain-Barre Syndrome diagnosis	YES	NO	YES
Symptomatic non-pregnant traveler (male or female) (2 or more of fever, maculopapular rash, arthralgia, non-purulent conjunctivitis)	YES	YES	NO

¹ For those symptomatic, collect serum for IgM 24 days post symptom onset
² Collect serum within 7 days of symptom onset; urine within 30 days of symptom onset
³ Collect sample between 2-12 weeks of return
⁴ Consider testing amniotic fluid
⁵ Additional specimens will be requested: e.g. placenta, fetal tissues
⁶ Positive or inconclusive Zika virus serology
⁷ Additional specimens will be requested: e.g. cord blood, placenta/umbilical cord tissue, CSF

March 3, 2016

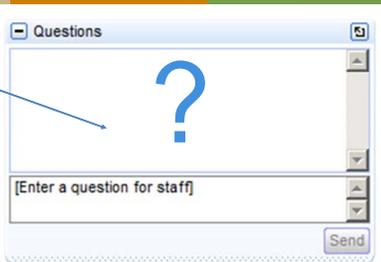
LAC DPH Health Update: Zika Virus Infection Update #3-Revised Instructions for Zika Testing and Reporting in Los Angeles County

Questions

Type your questions into the Question Pane

If you can't see the Question Pane, click on +

If you can't see the control Panel, click on the blue flower or the orange arrow



Zika Resources

- Acute Communicable Disease Control Program
 - Phone during business hours: 213-240-7941 or after hours: 213- 974-1234
- Zika laboratory testing forms
 - <http://publichealth.lacounty.gov/acd/docs/ZikaInfoTestReq.pdf>
- Zika webinar information publichealth.lacounty.gov/acd/zikawebinar.htm
- CDC Zika virus site: <http://www.cdc.gov/zika/>
 - For clinicians: <http://www.cdc.gov/zika/hc-providers/index.html>
 - Travel notices: <http://wwwnc.cdc.gov/travel/notices>
- LAC DPH Zika virus site: <http://publichealth.lacounty.gov/acd/VectorZika.htm>
- PAHO Zika virus site: http://www.paho.org/hq/index.php?option=com_topics&view=article&id=427&Itemid=41484&lang=en

Thank you for attending the Zika webinar

Reminder

- You will get an email in an hour with a link to request CME/Certificate of attendance.
- If you want to claim CME right away, visit the Zika Webinar homepage which also has handouts, links to Zika resources and the archived webinar. publichealth.lacounty.gov/acd/zikawebinar.htm

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