AAP ZIKA ECHO

(EXTENSION FOR COMMUNITY HEALTHCARE OUTCOMES)
Housekeeping items

- For educational and quality improvement purposes, this ECHO session will be recorded.
- Project ECHO® collects participation data for each ECHO session. This data allows Project ECHO to measure, analyze, and report on the ECHO movement’s reach. Data is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.
- To protect patient privacy, please do not provide any (PHI) protected health information.
- Please mute your microphone when not speaking. If you have video capability, please enable it.
- There is a chat function in Zoom that may be used to send messages to the group. For IT help, please chat to the AAP Admin and we will assist you.
Acknowledgments

This project is supported by the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U43MC09134
Zika and Pregnancy: Should We Still Be Concerned?

Zika ECHO Lecture Series
May 21, 2018

Neil S. Silverman, M.D.
Center for Fetal Medicine and Women’s Ultrasound
Clinical Professor, Obstetrics and Gynecology
Division of Maternal-Fetal Medicine
David Geffen School of Medicine at UCLA
Roadmap

- Is Zika still a thing?
- Do we know any more about pediatric outcomes?
- What does it mean for pregnancy, and what’s up with all these guidelines?
Laboratory-confirmed symptomatic Zika virus disease cases* reported to ArboNET by states and territories—United States, 2017 (Provisional data as of April 4, 2018)

*Case counts include all symptomatic Zika virus disease cases, including cases in travelers returning from affected areas, cases acquired through presumed local mosquito-borne transmission and cases acquired through other routes. Cross hatching signifies areas with reported sustained local mosquito-borne transmission in 2017.
Current Zika Statistics (as of 3/20/18)

- 2470 pregnant travelers with laboratory evidence of Zika virus in US States and DC – vast majority imported/travel-related
  - 52 additional cases since last report date 2/20/18
  - 2286 completed pregnancies
  - 114 reported liveborn infants and 9 fetal losses with Zika related birth defects (5.3%)

- 4831 pregnant cases in US territories (mostly P. Rico) -- 4181 completed, 174 affected (4.2%)
  - 47 additional cases since 2/20/18
Thoughts on Zika’s evolution

- Morens/Fauci, JID 2017: the virus, which has existed for years in Asian countries, may have undergone viral mutations that enabled easier spread.

- Zika genotyping in Miami showed it came from Caribbean/S America; in S Texas, from Mexico.
  - Implications may be that Zika still a risk in Texas and other states, since transmission still occurring in Mexico.

- Herd immunity in high-risk countries may have lowered risk in US, but this won’t last forever as more nonimmune individuals enter a population.
  - This can create a smoldering disease risk with flares.

1. Peter Hotez, Baylor  
2. Amesh Adalja, Hopkins --- Infect Dis News 3/18
Zika as an Endemic Infection

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

- Zika evolving as an outbreak like other arboviruses: areas of endemicity but high potential (like West Nile and chikungunya) for ongoing sporadic cases and local outbreaks. (Paules C, Fauci A: JAMA 1/12/17)
Confirmed Zika Cases in Mexico by State
January 1, 2016 – April 2, 2018

Data provided by the Mexican Ministry of Health

Ag. = Aguascalientes
Quer. = Querétaro
DF = Distrito Federal
Tl. = Tlaxcala
Confirmed Zika Cases in Mexico by State
January 1, 2018 – April 2, 2018

provided by the Mexican Ministry of Health

Ag. = Aguascalientes
Quer. = Querétaro
DF = Distrito Federal
Tl. = Tlaxcala
Copyright © Taylor & Francis Group, LLC
ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2016.1177367

Guest Editorial

The Paradigm of the Paradox: Women, Pregnant Women, and the Unequal Burdens of the Zika Virus Pandemic

Lisa H. Harris, School of Medicine, University of Michigan
Neil S. Silverman, David Geffen School of Medicine, UCLA
Mary Faith Marshall, Schools of Medicine and Nursing, University of Virginia

The inequalities of outcome are, by and large, biological reflections of social fault lines
(Paul Farmer, 1999, 5)

Three paradoxes characterize the Zika virus pandemic and clinical and policy responses to it:

3. Historically, concerns for the “vulnerability” of pregnant women and fetuses have resulted in the systematic exclusion of pregnant women from research. In addition, political opposition to abortion has made it increasingly difficult to conduct research using fetal tissue. However, research on Zika virus in fetal tissue collected at the time of pregnancy termination or loss...
Pregnancy Risk Estimates

- Brasil et al: Rio cohort\(^1\)
  - Prospective study cohort of 134 symptomatic pregnant women with confirmed ZKV infection
  - Overall, 49/117 (42%) liveborn ZKV-exposed infants had abnormal findings by 1\(^{st}\) month of life [5% in ZKV(-): p < 0.001]

- Adverse outcomes seen regardless of trimester of infx
  - 55% risk if maternal infx in 1\(^{st}\), 52% if in 2\(^{nd}\), 29% if in 3\(^{rd}\)

- Updated report from US Zika Pregnancy Registry\(^2\)
  - Birth defects related to Zika in 6%, 21 in live births
  - No risk difference regarding sx; 11% risk if exposure in 1\(^{st}\) Δ

---

Pregnancy Outcomes: Recent French Territorial Data

- Outcome report from French territories in the Americas
  - 546 pregnancies, 555 fetuses/newborns (last delivered 4/17)
  - All mothers were symptomatic & had PCR-confirmed infections
  - 34% of infections in 1st trimester, 46% in 2nd, 20% in 3rd

- Neurologic and ocular abnormalities observed in 7% of fetuses/newborns overall
  - Risk by trimester: 13%, 4%, 5% for 1st, 2nd, 3rd

- Findings similar to those from US Registry

- Studies like this continue to be important and underscore need to continue surveillance for all pregnant women at-risk, including the 80% who are asymptomatic

Hoen B, et al. NEJM 3/15/18
ZODIAC Study: compiled comprehensive description of children > 12 months of age born with microcephaly (< 3rd %ile at birth) and (+) Zika IgM from Oct 2015-Jan 2016

19 infants, mean age at followup 22 months (range 19-24 months)

15/19 infants had HC ranging from 3.7-8.4 SD below the mean (avg 6.3 SD)
All of these infants were symptomatic and had developmental testing < 6 mos.

4/19 infants had HC within 1 SD of mean, all had testing results for > 6 mos.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical findings</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Seizures**,**  
Retinal abnormalities**  
Hospitalization**  
Pneumonia/Bronchitis  
Intestinal infection  
High fever  
Failure to thrive/feed | 11 (58) |
| **Functional outcomes**                                                 |         |
| Sleeping difficulties**  
Feeding difficulties**  
Impaired response to auditory stimuli (hearing  asymmetric or no response)  
Impaired response to visual stimuli  
Severe motor impairment  
Cerebral palsy*** | 10 (53) |
| **Neurologic outcomes**                                                 |         |
| Severe motor impairment  
Cerebral palsy*** | 15 (79) |
| **Total**                                                               | 23 (100)|
Zika – Education and Testing
What do we tell our pregnant patients?

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

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

- Pregnant women **should not travel** to areas with active local Zika transmission
The role of prevention

- If in an area with transmission, protection and prevention strategies are important — and repellent for 3 weeks after return from these areas

- DEET, picaridin fine for use in pregnancy
  - Consumer Reports (Sept 2017): Deet at 25-30% concentrations works best, picardin 20% (spray, not lotion), oil of lemon eucalyptus 30% (Repel better than Coleman)
Definition of Possible Zika Virus Exposure during Pregnancy

- Travel to or living in an area with Zika risk during their pregnancy or up to 8 weeks before conception
  -- (6 weeks prior to last menstrual period)

- Sex without barrier protections (male or female condoms and dental dams) with a male partner who had possible exposure to Zika within 6 months prior to sexual contact, or a female partner who had possible exposure to Zika within 8 weeks of sexual contact.
  - Sexual activity includes vaginal, anal, and oral sex, as well as sharing of sex toys
Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017

Titilope Oduyebo, MD¹; Kara D. Polen, MPH¹; Henry T. Walke, MD¹; Sarah Reagan-Steiner, MD¹; Eva Lathrop, MD¹; Ingrid B. Rabe, MBChB¹; Wendi L. Kuhnert-Tallman, PhD¹; Stacey W. Martin, MSc¹; Allison T. Walker, PhD¹; Christopher J. Gregory, MD¹; Edwin W. Ades, PhD¹; Darin S. Carroll, PhD¹; Maria Rivera, MPH¹; Janice Perez-Padilla, MPH¹; Carolyn Gould, MD¹; Jeffrey B. Nemhauser, MD¹; C. Ben Beard, PhD¹; Jennifer L. Harcourt, PhD¹; Laura Viens, MD¹; Michael Johansson, PhD¹; Sascha R. Ellington, MSPH¹; Emily Petersen, MD¹; Laura A. Smith, MA¹; Jessica Reichard, MPA¹; Jorge Munoz-Jordan, PhD¹; Michael J. Beach, PhD¹; Dale A. Rose, PhD¹; Ezra Barzilay, MD¹; Michelle Noonan-Smith¹; Denise J. Jamieson, MD¹; Sherif R. Zaki, MD¹; Lyle R. Petersen, MD¹; Margaret A. Honein, PhD¹; Dana Meaney-Delman, MD¹

Adapted for specific usage in CA: July 2017, then in Jan 2018
What informed the new testing guidelines?

- While consequences of Zika infection are better understood, accurate diagnosis continues to be challenging
  - Virus present in body fluids only transiently
  - Serologic testing (IgM) can’t always reliably time infection
  - Serology prone to false-positive results and cross-reaction with other flaviviruses
- With declining prevalence of Zika infection, probability of false-positive tests increases
- Changing epidemiology further limits diagnostic capabilities of existing tests
Zika Immunity

- Presumption has been that Zika infection confers immunity after the IgM response

- Based on experience with other flaviviruses, previous Zika infection is likely to confer prolonged, likely lifelong immunity
  - If true, prior infection would prevent risks for a future pregnancy

- However, **no commercially-available IgG testing exists**, and IgM duration limited
New guidelines – what do the changes reflect?

- As many areas in the Americas move into a 2\textsuperscript{nd} or 3\textsuperscript{rd} mosquito season after introduction of Zika virus, testing becomes more complex.

- Given the evolving epidemiology and the better-realized limitations of testing, updated testing algorithms for symptomatic and asymptomatic pregnant women emphasize a \textit{shared decision-making model}.

- Need for pre-and post-test counseling, with results interpreted in context of limitations.
New guidelines: what’s the same (mostly)?

- **Screen pregnant women for Zika exposure risk and/or symptoms** at every prenatal and hospital visit
  - Knowledge of potential exposure before and during pregnancy is critical information for test interpretation

- **Symptomatic** pregnant women with recent possible Zika exposure: testing still recommended
  - Concurrent NAT (blood/urine) and IgM as soon as possible, through 12 weeks post-exposure *(can consider if > 12 wks, but..)*

- Pregnant women with exposure and u/s findings: test

- Asymptomatic women with **ongoing** possible Zika exposure: testing still offered once/trimester
  - *NAT testing of blood and urine, not IgM (diagnostic limits)*
Asymptomatic women with recent possible Zika exposure but not ongoing exposure

- Testing now not routinely recommended for this group
- BUT: shared-decision making and consideration of local/regional epidemiologic risks important for this group
- CDC acknowledges that data indicate that while perinatal Zika risk doesn’t differ by maternal symptoms, routine testing in a low-prevalence group increases risk of false-positives in absence of any prevention or therapies
- If testing done, default to algorithm for symptomatic/no ongoing exposure: PCR and IgM

- Until recently (Jan/18): CA, FL, TX, NY kept prior guidelines
ZIKA SCREENING ALGORITHM
FOR CHILDREN AND ADULTS

IS THERE A HISTORY OF POSSIBLE ZIKA EXPOSURE?
Recent travel to an area with risk of Zika virus (see list of areas with risk of Zika virus)* OR
Recent unprotected sexual contact with:
• A male who has traveled in the past 6 months to an area with risk of Zika virus
• A female who has traveled in the past 4 weeks to an area with risk of Zika virus

IS THE PATIENT PREGNANT?

YES

DOES THE PATIENT HAVE SYMPTOM(S) OF ZIKA VIRAL DISEASE?
One or more of the following symptoms within 2 weeks of travel or sexual exposure:
• Maculopapular rash
• Fever (over 100.4°F/38°C)
• Arthralgia
• Conjunctivitis

YES

ASYMPTOMATIC PREGNANT WOMEN WITH AN EPISODE OF ZIKA EXPOSURE:
• Do not routinely test, but instead assess carefully for factors that increase the likelihood of Zika infection
• Refer to the California Zika Algorithm for a list of risk factors to consider
• A patient’s risk tolerance and decision-making regarding the pregnancy may be sufficient justification for Zika virus testing
• If choosing to test, follow testing instructions for Symptomatic Pregnant Women

IS ONGOING (DAILY OR WEEKLY) ZIKA EXPOSURE OCCURRING?

YES

SYMPTOMATIC INDIVIDUALS
• NAAT testing of serum or urine <3 weeks since symptom onset
• IGU antibody testing <12 weeks since symptom onset
• If non-negative IgM and Zika virus NAAT negative, confirm with PRT

SYMPTOMATIC PREGNANT WOMEN
• Contraindicated for dates between the 6th week and 9th week of gestation

ASYMPTOMATIC PREGNANT WOMEN WITH ONGOING POSSIBLE ZIKA EXPOSURE
• NAT testing on serum and urine 3 times during pregnancy starting with the initiation of prenatal care. Testing each trimester may be considered
• IgM testing may be considered concurrent with NAT testing but may lead to difficult interpretation of results depending on exposure history

ALL PATIENTS WITH EXPOSURE
• Recommend sexual abstinence (vaginal, anal, oral) or condom use (male or female) for all exposed patients, especially pregnant women
  ▶ ▶ Males: For at least 6 months after last potential Zika exposure
  ▶ ▶ Females: For at least 8 weeks after last potential Zika exposure
• If not pregnant, recommend delay pregnancy for the above periods of time and prescribe effective contraceptive methods
• Advise use of mosquito repellant for 3 weeks after return from an area with risk of Zika
• For counseling recommendations, see: www.bit.ly/CDPHFamilyPlan
• Areas with Risk of Zika: For asymptomatic persons, refer to CDC Areas with Risk of Zika (www.bit.ly/CDCAreaRisk). For asymptomatic pregnant women, use the WHO Zika Virus Risk Addition Table (www.bit.ly/ZikaRiskTable) 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.

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 PRT
• If CSF is collected for other purposes, NAT and IgM antibody testing should be performed on CSF. Consider CSP 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/CABirthHospitals

See CDPH guidance for lab testing: www.bit.ly/VRDZikaGuidance
For more Zika information for health professionals, see: www.bit.ly/CDPHZikaICPs
For questions about Zika virus testing or test results, contact your local health department: www.bit.ly/LHDContactInfo
Pregnancy Management

- Microcephaly and intracranial calcifications typically detected during ultrasounds in the late 2\textsuperscript{nd}/early 3\textsuperscript{rd} trimester.
  - These birth defects might be detected as early as 18-20 weeks gestation.
  - A recent study of 17 pregnancies with laboratory confirmed Zika virus infection and adverse fetal outcomes reported a \textit{median of 18 weeks} from symptom onset to prenatal diagnosis of microcephaly. \(\text{(Paara-Saavedra et al, ObGyn 7/17)}\)

- If early testing negative and 2\textsuperscript{nd} trimester or early 3\textsuperscript{rd} trimester scan normal: usual care

- If confirmed/possible maternal Zika infection, consider serial u/s q 3-4 weeks
Sexual Partner concerns/guidelines

- Extended duration of virus in semen
  - *Lancet* 6/7/16: transmission through semen 34-41 d after infection
  - *Lancet* 8/2016: Zika RNA found in semen after 90 days
  - *Eurosurveillance* 8/11/16: RNA (+) in urine up to 91 days and in semen 134 days after sx

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

- Pregnant women whose male partners have or are at risk for Zika virus infection should consider using condoms or abstaining from sexual intercourse – *duration of pregnancy*
Zika Shedding in Zika-Infected Men

- Prospective CDC study of 184 symptomatic men with confirmed Zika infection
  - Semen and urine samples obtained 2x/month for 6 months after illness onset
  - Tested by PCR for ZIKV RNA and a plaque assay for infectious ZIKV
  - Total of 1327 semen samples and 1038 urines obtained

- Zika less common in urine (4%) than semen (33%) when tested by PCR -- 61% in semen within 30 days

- Zika shedding decreased during 3 months post illness but continued for 281 days in 1 man (11% > 4 months)

- Infectious ZIKV isolated from 3/78 samples (3.8%), all within 30 days from illness, all with high viral titers
  - None of the samples with VL < 7 log 10 yielded infectious ZIKV

Mead PS, et al. NEJM 4/12/18
Zika “waiting periods” – not just pregnancy

- Timeframes to wait to get pregnant after travel to an area with a CDC travel notice *(CDC 7/17)*
  - Women -- 8 weeks    Men -- 6 months
  - If both partners traveled, wait 6 months + condoms
  - Male guidelines likely to change

- Egg and sperm donors *(ASRM, 3/16)*
  - Wait period *6 months* after infx, travel, or contact

- Blood donors *(FDA, 2/16)*
  - 4 week waiting period
Blood screening for Zika in the U.S.

- American Red Cross initiated Zika RNA screening in high-risk areas in SE US (5 states) 6/16, in all states by 12/12/16
  - (+) samples repeated in triplicate
  - ZIKV travel question removed from questionnaires 1/23/17
  - Screening protocol remains active: report – 15 months’ data
- 4.3 million samples tested: 160 initially reactive, 9 confirmed positive (1: 480,654 positive rate; PPV 5.6%)
  - 2 of (+) had local infx in FLA, 6 traveled, 1 had ZIKV vaccine
- RBC donations had higher VL than plasma
- Cost was $5.3 million per ZIKV RNA (+) blood donation

Saa P, et al. NEJM, 5/10/18
OBJECTIVE: To describe a single U.S. perinatal center’s ongoing experience with evaluating pregnant patients with potential exposure to Zika virus infection.

METHODS: This is an institutional review board-approved longitudinal observational study from January to August 2016 from a single perinatal referral center. Patients who had traveled to or had sexual contact with a person who traveled to a region with documented local patients reported insect bites and 19 (10%) patients reported symptoms. Overall, five (3% of all) patients had prenatal ultrasound findings suggestive of possible fetal Zika virus infection; all their Zika virus test results returned negative. These findings included microcephaly, echogenic intracardiac foci, and ventricular calcifications. Of the 153 Zika virus screening tests ordered, eight (5%) immunoglobulin M results returned positive or equivocal
ZIKV Pregnancy Screening Study

- Single center: 185 pregnant women screened after potential ZIKV exposure: Jan-Aug 2016
  - 91% short-term exposure, 6% sexual partner exposure
  - Pt index traveler 94%: 44% Mexico, 17% N Amer, 13% Carib
  - 47% 1st trimester exposure, 31% 2nd trimester, 17% peri
  - 10% reported symptoms (53% rash, 47% fever)
  - Possible u/s findings in 3%

- Only 1 confirmed IgM result obtained (0.5%)

- Turnaround time significantly lower for private vs public lab (median 6 vs 34 days; p < 0.001)

*Rao R et al. Obstet Gynecol 7/17*
Neonatal coordination is Critical!

Evaluation and testing of infants with possible congenital Zika virus infection

Mother with laboratory evidence of Zika virus infection during pregnancy*

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

Infant with findings consistent with congenital Zika virus syndrome

**Initial evaluation**

Infant with laboratory confirmed or probable congenital Zika virus infection

Infant negative for congenital Zika virus infection

Outpatient management and follow-up

Continue to evaluate for other causes of congenital anomalies

Infant without findings consistent with congenital Zika virus syndrome

Infant with laboratory confirmed or probable congenital Zika virus infection

Routine newborn care; additionally, perform an ABR and ophthalmology exam within one month of life

Outpatient management and follow-up

Infant negative for congenital Zika virus infection

Routine care

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

More information on the evaluation, management, and follow-up of infants with possible congenital Zika virus infection is available at www.cdc.gov/zika/hc-providers/infants-children.html.