Zika Virus Update: The Forgotten Pandemic

Naushad Amin, MD, FAAFP

ACTIVITY DISCLAIMER

The material presented here is being made available by the American Academy of Family Physicians for educational purposes only. Please note that medical information is constantly changing; the information contained in this activity was accurate at the time of publication. This material is not intended to represent the only, nor necessarily best, methods or procedures appropriate for the medical situations discussed. Rather, it is intended to present an approach, view, statement, or opinion of the faculty, which may be helpful to others who face similar situations.

The AAFP disclaims any and all liability for injury or other damages resulting to any individual using this material and for all claims that might arise out of the use of the techniques demonstrated therein by such individuals, whether these claims shall be asserted by a physician or any other person. Physicians may care to check specific details such as drug doses and contraindications, etc., in standard sources prior to clinical application. This material might contain recommendations/guidelines developed by other organizations. Please note that although these guidelines might be included, this does not necessarily imply the endorsement by the AAFP.
DISCLOSURE

It is the policy of the AAFP that all individuals in a position to control content disclose any relationships with commercial interests upon nomination/invitation of participation. Disclosure documents are reviewed for potential conflict of interest (COI), and if identified, conflicts are resolved prior to confirmation of participation. Only those participants who had no conflict of interest or who agreed to an identified resolution process prior to their participation were involved in this CME activity.

All individuals in a position to control content for this session have indicated they have no relevant financial relationships to disclose.

The content of my material/presentation in this CME activity will not include discussion of unapproved or investigational uses of products or devices.

Naushad Amin, MD, FAAFP

Assistant Professor, Department of Family Medicine, University of Central Florida College of Medicine, Orlando

Dr. Amin earned his medical degree at Dow Medical College, Karachi, Pakistan, where he was an avid polio campaigner for the World Health Organization (WHO). He completed his family medicine residency at Florida Hospital South, Orlando. Following residency, he worked as a hospitalist and served as vice-chairman of the Department of Family Medicine at Holmes Regional Medical Center, Melbourne, Florida. In 2017, he completed a global health fellowship at the University of San Francisco California, Contra Costa. As an assistant professor of family medicine at the University of Central Florida (UCF) College of Medicine, Orlando, he has been involved with multidisciplinary student-run outpatient clinics and the annual UCF Global Health Conference.

Within the field of global health, Dr. Amin is focused on medical education, capacity building, and research, with an emphasis on noncommunicable disease. Increasingly, his passion for global health has led him to work extensively with marginalized populations in countries including Peru, Malawi, Uganda, and Kenya. As a point-of-care ultrasound (POCUS) instructor, he has conducted several POCUS workshops, both in the United States and abroad. He is also a frequent presenter at international global health conferences.
Learning Objectives

1. Counsel patients planning on traveling to areas with known cases of Zika virus to take necessary precautions to prevent infection.

2. Recognize clinical manifestations of Zika viral infection, distinguishing it from other infections (e.g. dengue fever, West Nile), and diagnose accordingly.

3. Establish detailed, practice-based plans for responding to complex medical emergencies that include protocols to report notifiable diseases in the community of practice.

4. Counsel patients who are in relationships that might lead to pregnancy and who are planning on traveling to areas with known cases of Zika virus to take necessary precautions to prevent infection, both during and after travel.

Audience Engagement System

Step 1

Step 2

Step 3
Case Study

A 44 year old school teacher, started feeling fatigued with arthralgia and myalgia, soon after returning from a mission trip from Haiti. Day 8 she noticed macular rash on her face and chest. Next day she had a low grade fever of 101 F and noticed bilateral conjunctivitis, periorbital pressure and bilateral wrist pain. She was seen at a local urgent care where she remembers to be bitten by a mosquito on her thigh while in Haiti. She received oral prednisone and antibiotics. Later she was tested positive for Zika on PCR and negative for Dengue and Chikungunya.

• What advice would you give to a patient prior to travel to areas with active Zika virus infection?
• What diagnostic tools and approach would you use?
• What are some of the complications associated with Zika Virus infection?

Epidemiology

ZIKV discovered in 1947 in Ugandan Zika forest.
Epidemiology

Spread of Zika Virus from Africa

• First large outbreak of ZIKV was in Yap in 2007

Within 3 years, an estimate of 73% of Yap’s population got infected with ZIKV.
Epidemiology

ZIKV:

Flavivirus
RNA Virus
Approximately 40 nm in diameter
Contains membrane protein E and M
Enveloped

Epidemiology

TRANSMISSION:
- Mosquito bites Aedes aegypti and A. albopictus
- Mother to child
- Sexual contact
- Blood transfusion
- FDA has recommended donor screening, donor deferral and product management.
- Lab exposure
Epidemiology

- Geographical mapping of Aedes aegypti and A. albopictus
Epidemiology

• Geographical areas with Active Zika Virus Transmission as of June 30, 2016

![Map of Active Zika Virus Transmission](image)

Epidemiology

![Map of Areas with Risk of Zika](image)

**Map Legend**
- Purple: Country or territory that has ever reported Zika cases** (past or current)
- Light purple: Areas with low likelihood of Zika infection because of high elevation (above 6,500 feet/2,000 meters)
- Yellow: Country with mosquito* but no reported Zika cases**
- Green: Country or territory with no mosquitoes that spread Zika

* Aedes aegypti

** Locally acquired, mosquito-borne Zika cases
Poll Question #1

Which of the following is the most common clinical presentation in a patient infected with Zika virus?

A. Fever.
B. Maculopapular rash.
C. Arthralgia.
D. Conjunctivitis.
E. Asymptomatic

Clinical signs and symptoms

- Mostly asymptomatic ~80%
- Incubation period is likely 3-12 days
- Fever
- Maculopapular rash
- Conjunctivitis
- Arthralgia
- Less commonly myalgias and headaches
- Neurological symptoms including Guillain-Barre Syndrome
- Microcephaly
Clinical signs and symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash</td>
<td>90%</td>
</tr>
<tr>
<td>Fever</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital ache</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
</tr>
</tbody>
</table>

Duffy M. N Engl J Med 2009 Total n=31

Differential Diagnosis

Dengue
Malaria
Leptospirosis
Group A Streptococcus
Measles
Rubella
Parvovirus
Enterovirus
Adenovirus
Chikungunya

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Poll Question #2

Zika virus testing is recommended for all except:

A. Anyone with possible exposure to Zika or Dengue virus with recent symptoms
B. Preconception screening.
C. Asymptomatic pregnant women with ongoing exposure to above viruses
D. Pregnant mother with positive prenatal ultrasound findings consistent with congenital Zika infection.

Who should you test?

• Anyone with possible exposure to Zika or Dengue virus with recent symptoms
• Symptomatic pregnant women with possible exposures
• Asymptomatic pregnant women with ongoing exposure to above viruses
• Pregnant mother with positive prenatal ultrasound findings consistent with congenital Zika infection.

Zika virus testing is not routinely recommended for
• Non-pregnant asymptomatic patients
• Preconception screening.
Zika Virus disease is a nationally notifiable condition.

Diagnostic tools and approach

• Complete CDC submission form (50.34)
• Include date of onset of symptoms
• Date of specimen collected
• Pertinent travel history
• Specimen origin field = select HUMAN
• Test order name field = select ARBOVIRUS
• Add email
• Add brief clinical history
Diagnostic tools and approach

- **Nucleic Acid Amplification test (NAAT)**
  - Highest sensitivity in serum during the first week of illness
  - Urine sample should be performed up to 14 days of illness
  - CSF specimen

- **ELISA**
  - Virus specific immunoglobulin M (IgM)
    - Cross-reactivity exist among other flavivirus eg. Dengue and Yellow fever.
  - Plaque reduction neutralization test (PRNT)

Diagnostic tools and approach in Non-Pregnant Symptomatic Patient

![Diagnostic flowchart for non-pregnant symptomatic patient]
Diagnostic tools and approach in Pregnant Symptomatic Patient

Asymptomatic pregnant women with recent travel to zika endemic area

No routine testing needed

Asymptomatic pregnant women with current Zika exposure

Test with NAT three times during pregnancy. First test at the initial prenatal visit

Positive NAT results indicates active Zika infection.
Congenital Zika Syndrome

- Severe microcephaly
- Decrease brain tissue
- Impaired visual and auditory response to stimuli
- Joints deformities and contractures such as club foot
- Hypertonia
- Non febrile seizures

The Zika Outcomes and Development in Infants and Children (ZODIAC) investigation
Microcephaly


Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

<table>
<thead>
<tr>
<th>Gestational Age at Birth</th>
<th>Reference Chart</th>
</tr>
</thead>
<tbody>
<tr>
<td>33–43 Weeks</td>
<td>INTERGROWTH-21st Newborn Size at Birth Chart [🔗]</td>
</tr>
<tr>
<td></td>
<td>A tool for calculating centiles for head circumference for infants 33–42 weeks is available.</td>
</tr>
<tr>
<td>24–32 Weeks</td>
<td>INTERGROWTH-21st Very Preterm Size at Birth References [🔗]</td>
</tr>
<tr>
<td></td>
<td>A tool for calculating centiles for head circumference for infants 24–32 weeks is also available from this site.</td>
</tr>
<tr>
<td>&lt;24 Weeks</td>
<td>INTERGROWTH-21st Fetal Growth Standards [🔗]</td>
</tr>
</tbody>
</table>

The International Very Preterm Size at Birth Reference Charts

Head circumference (cm) Girls

<table>
<thead>
<tr>
<th>Gestational age (weeks + days)</th>
<th>3rd</th>
<th>5th</th>
<th>10th</th>
<th>20th</th>
<th>25th</th>
<th>30th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
<th>97th</th>
</tr>
</thead>
<tbody>
<tr>
<td>24+0</td>
<td>19.16</td>
<td>19.62</td>
<td>20.09</td>
<td>22.09</td>
<td>24.09</td>
<td>24.66</td>
<td>25.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+1</td>
<td>19.28</td>
<td>19.65</td>
<td>20.22</td>
<td>22.22</td>
<td>24.22</td>
<td>24.78</td>
<td>25.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+2</td>
<td>19.41</td>
<td>19.78</td>
<td>20.34</td>
<td>22.34</td>
<td>24.34</td>
<td>24.91</td>
<td>25.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+3</td>
<td>19.54</td>
<td>19.90</td>
<td>20.47</td>
<td>22.47</td>
<td>24.47</td>
<td>25.04</td>
<td>25.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+4</td>
<td>19.66</td>
<td>20.03</td>
<td>20.60</td>
<td>22.60</td>
<td>24.60</td>
<td>25.16</td>
<td>25.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+5</td>
<td>19.79</td>
<td>20.16</td>
<td>20.72</td>
<td>22.72</td>
<td>24.72</td>
<td>25.29</td>
<td>25.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24+6</td>
<td>19.92</td>
<td>20.28</td>
<td>20.85</td>
<td>22.85</td>
<td>24.85</td>
<td>25.42</td>
<td>25.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25+0</td>
<td>20.04</td>
<td>20.41</td>
<td>20.98</td>
<td>22.98</td>
<td>24.98</td>
<td>25.54</td>
<td>25.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Ultrasound screening for fetal microcephaly following Zika virus exposure

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

Prenatal Ultrasound (HC)

- <2SD
- >2SD
- >3 SD

- Repeat q 3-4 weeks
- Detailed Neurosonographic Exam
- Isolated microcephaly
- >5 SD
- Pathologic microcephaly

Practice Advisory: Updated Interim Guidance for Care of Women of Reproductive Age During a Zika Virus Outbreak

- 1st ultrasound 3-4 weeks after symptom onset or exposure or 18-20 weeks in endemic area
- Serial ultrasounds q3-4 weeks with diagnosed infection (IgM, PCR)
- If negative for infection, consider 2nd ultrasound and if negative, return routine prenatal care

Updated June 23, 2016

http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak

Head Circumference

http://www.fetal.com/Screening/s03%20Standard%20Examination.html
Technique

• Find cervical spine in long axis
  • Turn probe 90 degrees to find occipito-frontal axis
  • Identify landmarks

Microcalcifications  Ventriculomegaly
Large Subarachnoid Space

Simplified convolution pattern
Agenesis of Corpus Collosum

Visual Ultrasound for Ultrasound in Obstetrics and Gynecology

Sloping forehead

Visual Ultrasound for Ultrasound in Obstetrics and Gynecology
Treatment

• No specific antiviral are available against ZIKV

• Supportive care
  • Rest
  • Hydration
  • Acetaminophen for analgesic and antipyretic effects
  • Avoid Aspirin and NSAIDS

Prevention

• Vector control

• Prevention of sexual transmission
  • Condom use throughout pregnancy

• Screening of blood product

• Reducing travel exposure

• Pregnant women of all trimesters should avoid travel to destinations with active ZikV infection.
Vector Control

- Everyone can control mosquitos!!!
- Local government uses Integrated Mosquito Management [IMM]
  - Track mosquito population and viruses they carry
  - Determine the efficacy of EPA-approved insecticides.
  - Dispose of illegally dumped tires, clean up and maintenance of public places, storm drainage etc.
  - Use of larvicides and adulticides.

Poll Question #3

Which of the following is NOT true regarding vector control?

A. Oil of lemon eucalyptus is not an EPA approved insect repellent.
B. EPA approved insect repellents should not be used if infant younger than 2 months of age.
C. Do not use oil of lemon of eucalyptus (OLE) or para-methane-diol (PMD) products for children under 3 years of age.
D. Treat clothing and gears with permethrin and avoid direct skin contact.
Vector Control

• Public role:

  • Use EPA approved insect repellent
    • Follow product label
    • Reapply often as directed
    • Do not use if infant younger than 2 months of age
    • Do not use oil of lemon eucalyptus (OLE) or para-methane-diol (PMD) products for children under 3 years of age.
    • Do not apply repellent directly on a child’s face or irritated skin.

Environment Protection Agency (EPA) registered insect repellents.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Some brand name examples*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEET</td>
<td>Off, Cutter, Sawyer, Ultrathon</td>
</tr>
<tr>
<td>Picaridin, also known as KDR 3023, Bayrepel, and icaridin</td>
<td>Cutter Advanced, Skin So Soft Bug Guard Plus, Autan (outside the United States)</td>
</tr>
<tr>
<td>Oil of lemon eucalyptus (OLE) or para-methane-diol (PMD)</td>
<td>Repel</td>
</tr>
<tr>
<td>IR3535</td>
<td>Skin So Soft Bug Guard Plus Expedition, SkinSmart</td>
</tr>
</tbody>
</table>

* Insect repellent brand names are provided for your information only. The Centers for Disease Control and Prevention and the U.S. Department of Health and Human Services cannot recommend or endorse any name brand products.
Vector Control

• Protect children:
  • Dress to cover arms and legs as well.
  • Use mosquito netting over cribs, stroller, and baby carriers

• Treat clothing and gears with permethrin. Do not apply directly on the skin.

Vector Control

Prevent home invasion

• Use mosquito screen,
• Air conditioning, if possible
• Avoid water pooling
Prevention via Sexual Transmission

- Infected men can transmit ZikV up to 41 days\(^1\) and infected women up to 11 days\(^2\) from the onset of symptoms
- Transmission can occur among both genders infected with Zika virus.
- All pregnant women should use barrier methods or abstain from sex during pregnancy if their partners live in or travel to areas with presence of Zika virus.
- Similar guidelines for non pregnant couples.
  - Barriers include both male and female condoms and dental dams

Prevention of Transmission

- Screening of blood transfusion products.
  - FDA has recommended donor screening, donor deferral and product management.

- Reducing travel exposure
  - Pregnant women of all trimesters should avoid travel to destinations with active ZikV infection.
Perinatal Counseling

| Uncertainty in Data regarding Zika Virus effect during pregnancy | Ultrasound examination has limitation and may not rule in or out congenital Zika syndrome |
| All pregnant patient at risk should be offered detailed options and counseling | If Zika virus testing is indicated, physician should provide pretest counseling |
| Several testing may be required with complexity of interpretation | Provider should discuss each type of test in detail |

Case study continues

A 44 year old school teacher, started feeling fatigued with arthralgia and myalgia, soon after returning from a mission trip from Haiti. Day 8 she noticed macular rash on her face and chest. Next day she had a low grade fever of 101 F and noticed bilateral conjunctivitis, periorbital pressure and bilateral wrist pain. She was seen at a local urgent care where she remembers to be bitten by a mosquito on her thigh while in Haiti. She received oral prednisone and antibiotics. Later she was tested positive for Zika on PCR and negative for Dengue and Chikungunya.

Positive serum, saliva and sputum RT-PCR.
Positive IgM and negative RT-PCR on spinal fluid analysis
Case study continues
In the meantime, she develops bilateral upper and lower extremities paranesthesia. She was hospitalized where:

• CT scans MRI were essentially normal.
• LP was performed and was positive for IgM for ZikV.
• Nerve conduction studies showed bilateral mild radial sensory neuropathy and right tibial motor nerve conduction abnormality.

A diagnosis of sensory-motor variant of GBS was made and she was treated with plasmapheresis and IVIG with partial symptoms improvement.

Practice Changing Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with Zika virus is a nationally notifiable condition.</td>
<td>A</td>
</tr>
<tr>
<td>All pregnant women infected or presumptively infected with Zika virus should be offered comprehensive options counseling, including a thorough discussion of pregnancy continuation, terminations of pregnancy, and adoption.</td>
<td>B</td>
</tr>
<tr>
<td>Counsel patients to use environment protection agency (EPA) registered insect repellents.</td>
<td>A</td>
</tr>
</tbody>
</table>
If you think you are too small to make a difference, you haven’t spend a night with a mosquito.

Thank you.

Contact Information

drnaushadamin@Hotmail.com
Questions
Reference and Resources

- Turmel JM, Abgueguen P, Hubert B, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet 2016;387:2501
- Duffy M. N Engl J Med 2009 Zika virus outbreak on Yap Island, federated states of Micronesia
- American College of Obstetricians and Gynecologists, http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisor-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak