Zika Virus in the Primary Care Setting

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No conflicts to disclose
Objectives

- Brief overview of Zika virus
- History of Zika virus
- Current epidemiology of Zika virus
- Clinical manifestations of Zika virus infection
- Diagnosis and management of Zika virus infection
- Special considerations in pregnancy
- Reporting requirements
Zika virus

Flavivirus transmitted primarily by *Ae. Aegypti*

Spreading rapidly

Cause of significant neurological manifestations

From the CDC
1947 - ZIKV identified in a sentinel rhesus monkey in the Zika forest of Uganda

1952 - 1st human cases of ZIK detected in Uganda & United Republic of Tanzania

1960s-1980s - Human cases confirmed through blood tests, ZIKV detected in mosquitoes found in equatorial Asia

Adapted from WHO: http://www.who.int/emergencies/zika-virus/history/en/
2007- 1st ZIK outbreak in humans in Yap (previously only 14 cases documented in the world)

2013-2014- Outbreaks in 4 other groups of Pacific islands, thousands of suspected infections reveal possible association between ZIKV & congenital malformations and severe neurological & autoimmune complications

2015- ZIKV in Brazil, reports neurological disorders associated with h/o infection
Jan 2016- Intrauterine transmission of ZIKV reported, evidence supporting an association between ZIKV infection & microcephaly

Feb 2016- WHO declares a PHEIC

Aug-Sep 2016- NIAID/VRC, CVD, & Emory begin ZIKV DNA vaccine trial
Nov 2016 - WHO declares an end to the PHEIC and refocuses priorities for long-term management

Feb 2017 - More than 40 Zika vaccine candidates in the pipeline with 5 entering Phase I trials
Current Epidemiology of Zika Virus

• As of February 1, 2017, Zika virus transmission has been reported in >60 countries and territories
• In the US, local transmission has occurred in TX and FL
• As of February 8, 2017, 4,781 travel-associated cases have been reported in the US as well as 220 locally transmitted cases
Zika in the United States

As of February 1, 2017 (laboratory confirmed cases of Zika virus disease cases reported to ArboNET

Maryland 130 travel associated cases (3% of cases in the US)

Modes of Zika virus transmission

• Bite of infected mosquito (*Ae. aegypti, Ae. albopictus*)
• Vertical transmission
• Sexual transmission
  – Male-female
  – Male-male
  – Female-male
• Blood transfusion
• Close contact?
Clinical Manifestations of Zika Virus Infection

Neurological manifestations of Zika Virus Infection in adults

• Guillain-Barre Syndrome
  – Most frequent neurologic sequela reported following Zika virus infection
  – Risk increases with age
• Encephalitis
• Meningoencephalitis
• Acute myelitis
Pregnancy associated outcomes

- Fetal loss/miscarriage
- Fetal growth and brain abnormalities (microcephaly, hydrocephalus)
- Ocular findings
- Hearing loss
- Neurologic abnormalities
Congenital Zika syndrome

- Destruction of existing CNS tissue and disruption of future development
- Loss of brain volume/neurologic dysfunction
  - Hearing
  - Vision
  - Swallowing problems
  - Limb contractures
  - Developmental impairment
Diagnosis of Zika Virus Infection

- FDA has issued Emergency Use Authorization (EUA) for both the Trioplex (RT-PCR assay) and the Zika MAC-ELISA
- Molecular testing: early after symptom onset, detect viral RNA
- Serologic testing: at any time (reliably detectable 12 weeks following infection), may have significant cross-reactivity with related viruses
Testing algorithm for symptomatic individuals <14 days post onset (CDC)

2016 Zika Response: Algorithm for U.S Testing of Symptomatic Individuals*
Specimens Collected <14 days Following Symptom Onset

Test appropriate specimen by ZIKA RNA NAT

- Dengue***
  - Specimen positive for RNA patient positive for dengue virus infection.
  - Specimen negative for dengue virus RNA.

- Chikungunya***
  - Specimen positive for RNA, patient positive for chikungunya virus infection.
  - Specimen negative for chikungunya virus RNA.

- Any specimen positive, patient positive for Zika virus infection.

- All specimens negative, patient negative for Zika virus RNA.

Serological testing
Serum specimen should be tested by an anti-Zika IgM assay**

- Zika IgM ELISA interpreted as positive, equivocal, presumptive or possible Zika infection. Proceed to PRNT.

- All tests negative.
  - No further testing of specimen required.

PRNT*
Serum must be tested by CDC or CDC-designated Confirmatory Testing Lab.
See text on page 5 for possible serologic conclusions.

NOTE: Report all test results. Results should be considered in the context of symptoms, exposure risk and time point of specimen collection.

*Pregnant and non-pregnant symptomatic individuals
**Note antibody cross-reactivity to other flaviviruses complicates interpretation of the current anti-Zika IgM tests. Dengue IgM testing should be conducted for symptomatic pregnant women, individuals with a potential dengue exposure and when a presumptive other flavivirus result is obtained. See text on page 3-4 for additional information.
***Indicates testing and interpretation for the CDC Triplex assay. Note when testing urine and amniotic fluid with the CDC Triplex assay, only report the Zika result.
*PRNT confirmation is not currently routinely recommended for Puerto Rico. See page 5 for more information.
Testing algorithm for symptomatic individuals ≥ 14 days post onset (CDC)

2016 Zika Response: Algorithm for U.S. Testing of Symptomatic Individuals
Specimens Collected ≥ 14 Days Following Symptom Onset

Test specimen by an anti-Zika IgM test**

- Zika IgM ELISA interpreted as positive, equivocal, presumptive or possible Zika infection.
- All tests negative. No further testing of specimen required.***

- Patient is pregnant
  - Test available and appropriate specimen by RNA NAT for Zika only
- Patient is not pregnant
  - Forward for confirmation by PRNT*

- Any specimen positive, patient positive for Zika virus infection.
- Zika virus RNA not detected in any specimens.
  - Forward specimens for confirmation of Zika IgM by PRNT*

PRNT*:
Serum must be tested by CDC or a CDC-qualified confirmatory testing lab.
Final interpretation is made by the lab conducting the PRNT
See text on page 5 for possible serologic conclusions.

NOTE: Report all test results to the appropriate health authorities. Results should be considered in the context of symptoms, exposure risk and time point of specimen collection.

*Pregnant and non-pregnant symptomatic individuals

**Note antibody cross-reactivity to other flaviviruses complicates interpretation of the current anti-Zika IgM tests. Dengue IgM testing should be conducted for symptomatic pregnant women, individuals with a potential dengue exposure and when a presumptive other flavivirus result is obtained. See text on page 3-5 for additional information.

***Note if tests for Zika and Dengue IgM are not reactive, anti-chikungunya IgM testing should be performed for persons with chikungunya exposure risk and a clinically compatible illness.

*PRINT confirmation is not currently routinely recommended for Puerto Rico. See page 5 for more information.
Testing algorithm for asymptomatic pregnant women (CDC)


Specimens collected <14 days after return from travel or exposure

- Test all appropriate and available specimens by RNA NAT for ZIKV only

  Any specimen positive, patient positive for Zika virus infection.

  All specimens negative, patient negative for Zika virus RNA.
  Health care provider should request collection of a follow-up serum specimen 2-12 weeks following exposure or return from travel.

  Test follow-up serum by Zika IgM assay

  Zika IgM negative. No further testing of specimen required.

  Zika IgM positive, equivocal, presumptive or possible Zika infection.

  Forward for confirmation by PRNT

Specimens collected 2-12 weeks after return from travel or exposure, or from women living in areas with ongoing Zika transmission

- Test serum by Zika IgM assay

  Zika IgM ELISA interpreted as positive, equivocal, presumptive or possible Zika infection.

  Test appropriate specimens by RNA NAT for ZIKV only

  Any specimen positive, patient positive for Zika virus infection.

  All specimens negative, patient negative for Zika virus RNA.

  Forward serum for confirmation of Zika IgM by PRNT

  PRNT:
  Serum must be tested by CDC or CDC-designated confirmatory testing lab.
  Final interpretation is made by the lab conducting the PRNT
  See text on page 5 for possible serologic conclusions.

NOTE: Report all test results to the appropriate Health Authorities. Results should be considered in the context of exposure risk and time point of specimen collection.


*PRNT confirmation is not currently routinely recommended for Puerto Rico. See page 5 for more information.
Trioplex RT-PCR

- Real-time PCR assay developed by CDC for the in vitro qualitative detection on Zika virus, dengue virus, and chikungunya virus RNA
- Samples may include:
  - Serum
  - Whole blood
  - CSF
  - Urine
  - Amniotic fluid
- Should be used in accordance with CDC algorithms
Trioplex RT-PCR

• What does a positive test mean?
  – (+) test result for Zika virus indicates RNA from Zika virus was detected in the patient’s specimen
  – (+) result from any specimen collected from a patient is indicative of Zika virus infection
  – Results should always be taken in context of clinical observations, epidemiological data, travel history, etc when making a final diagnosis

• What does a negative test mean?
  – (-) test result indicates that RNA from Zika virus is not present in the specimen above the test’s limit of detection
  – (-) test result DOES NOT rule out infection and should not be used as sole basis for treatment or patient management
MAC-ELISA

- Zika IgM antibody capture enzyme-linked immunosorbent assay (Zika MAC-ELISA)
- Provides in vitro qualitative detection of human IgM antibodies to Zika virus
- Intended for use on serum of individuals meeting clinical and/or epidemiological criteria for testing (algorithm)
- Can also be used on CSF when submitted with a patient-matched serum sample (in accordance with CDC guidance)
MAC-ELISA

• What does a positive test mean?
  – (+) test indicates anti-Zika IgM antibodies were detected in the patient’s specimen
  – Positive and equivocal Zika MAC-ELISA results are NOT definitive diagnosis of Zika virus infection
    • False positives may occur due to past or present infection with related flaviviruses (dengue)
  – Confirmation by PRNT

• What does a negative test mean?
  – (-) Zika MAC-ELISA does not rule out Zika virus infection (particularly if early after symptom onset)
Reporting of test results

- When CDC performs testing, results typically sent to state/local health department within 3 weeks
- State/local health departments disseminate test results to doctors
- Doctors report test results to patients
Management of Zika Virus Infection

• No specific anti-viral
• Supportive treatment
  – Rest
  – Fluids
  – Analgesics/antipyretics
• Test for dengue and chikungunya in suspected Zika virus infections
  – Avoid aspirin and other NSAIDs until dengue can be ruled out
• Protect from further mosquito exposure during first few days of illness (reduce risk of local transmission)
• Avoid sexual transmission by using condoms or abstinence (6 months)
Special Considerations in Pregnant Women and Their Partners

- Symptomatic or asymptomatic pregnant women with serologic or molecular evidence of recent Zika virus infection should be evaluated and managed for possible adverse pregnancy outcomes and reported to the US Zika Pregnancy Registry.
Reporting Requirements

• As an arboviral disease, Zika virus is a nationally notifiable condition
• Healthcare providers are encouraged to report suspected cases to their state or local health department to facilitate diagnosis and mitigate risk of local transmission
• State and local health departments are encouraged to report laboratory-confirmed cases to CDC through ArboNET (national surveillance system for arboviral diseases)
Resources


• CDC Zika virus information for healthcare providers ➔ https://www.cdc.gov/zika/hc-providers/index.html

• CDC Zika virus reporting & surveillance ➔ https://www.cdc.gov/zika/reporting/index.html