Zika: Deet, There It Is

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THEGOS
Disclosure

• I have no financial disclosures or conflicts of interest
Lessons from Rubella...

- At peak of rubella epidemic (1964-1965):
  - 20,000 infants died from complications associated with rubella
  - 30,000 born with severe birth defects
RUBELLA (German measles) — by year, United States, 1966–1993
Objectives

• To review development of Zika epidemic
• To review risks of Zika in pregnancy
• To understand patient counseling strategies and resources
• To identify novel interventions in development for Zika diagnosis, treatment and prevention
Zika Epidemic in Review
A little history of Zika...

Zika Virus (I). Isolations and serological specificity
G. W. A. Dick, S. F. Kitchen, A. J. Haddow

DOI: https://doi.org/10.1016/S0035-9203(52)90042-4
Published: 01 September 1952
Rates of Microcephaly Over Time: the Americas and the Caribbean

Comparison of the rates of microcephaly in the Americas and Caribbean from 2010-2014 and 2015

Updated as of Epidemiological Week 52 (December 27, 2015 – January 2, 2016)

Microcephaly rates by state in Brazil (cases per 1,000 live births)

- 0.1-1.0
- 1.1-15.0
- 15.1-30.0
- 30.1-45.0
- 45.1-88.6

Countries with Zika confirmed cases

- Epi Week 52 2015
- Country limits
- Brazil State Boundaries

Data Source:
Reported from the IHR National Focal Points and through the Ministry of Health websites.

Map Production:
PAHO-WHO AD CHA IR ARO

Zika Virus

• Single stranded RNA virus
• G: Flavivirus, F: Flaviviridae
• Related to dengue, yellow fever, Japanese encephalitis and West Nile virus
• Primarily transmitted to humans by *Aedes (Stegomyia)* species mosquito
PROTECT YOUR FAMILY AND COMMUNITY:
HOW ZIKA SPREADS

Most people get Zika from a mosquito bite

A mosquito bites a person infected with Zika virus

The mosquito becomes infected

More members in the community become infected

A mosquito will often live in a single house during its lifetime

More mosquitoes get infected and spread the virus

The infected mosquito bites a family member or neighbor and infects them

Other, less common ways, people get Zika:

During pregnancy
A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika causes microcephaly, a severe birth defect that is a sign of incomplete brain development.

Through sex
Zika virus can be sexually transmitted by a man to his partners.

Through blood transfusion
There is a strong possibility that Zika virus can be spread through blood transfusions.
Zika virus

- Two recognized lineages of Zika
  - African
  - Asian

- Asian Zika strain
  - Currently circulating in western hemisphere
  - Associated with congenital Zika syndrome (CZS)

Aliota et al, 2016
Clinical Features

Zika fever

About

Fever
Rash
Joint pain
Red eyes

Symptoms

Spread through mosquito bites

Treatments
# Clinical Features: Zika virus Compared to Dengue and Chikungunya

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
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<tbody>
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<td>Fever</td>
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<td>Rash</td>
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<td>Conjunctivitis</td>
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<td>Arthralgia</td>
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<td>Myalgia</td>
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<td>Headache</td>
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<td>Hemorrhage</td>
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Reported cases of pregnant women with any lab evidence of possible Zika increased in 2016.
Pregnant women with any lab evidence of possible zika infection 2016-2017

• As of May 9, 2017:
  • 1471 Completed pregnancies with or without birth defects
  • 64 Liveborn infants with birth defects
  • 8 Pregnancy losses with birth defects

• Cases reported to the US Zika Pregnancy registry
Zika in Florida
Zika in South Texas

Brownsville, TX. Yellow shows areas where pregnant women should consider postponing travel.
Confirmed Travel-Related Zika Cases in South Carolina*

Total cases = 61 (counts are cumulative since 4/29/16)

Footnote:
* Data may not reflect the risk of Zika infection to residents in a county.
* Counties with more travelers overall are more likely to have travelers with confirmed Zika infection.
* Zika virus has not been detected in South Carolina mosquitoes as of the date this map was published.

Note: Map reflects total number of Zika cases from April 29, 2016 to February 21, 2017.
Zika in Pregnancy
CDC’s Response to Zika

Testing and interpretation recommendations\(^1\) - \(^4\) for a pregnant woman with possible exposure to Zika virus\(^*\) — United States (including U.S. territories)

**PREGNANT WOMAN**

A: Assess for possible Zika virus exposure
Evaluate for signs and symptoms of Zika virus disease

- Symptomatic: <2 weeks after symptom onset, or
- Asymptomatic and NOT living in an area with active Zika virus transmission: <2 weeks after possible exposure

 Zika virus rRT-PCR on serum and urine

- Positive Zika virus rRT-PCR on serum or urine: *Recent Zika virus infection*
- Negative Zika virus rRT-PCR on serum and urine
  - Symptomatic: Zika virus IgM and dengue virus IgM
  - Asymptomatic and NOT living in an area with active Zika virus transmission: Zika virus IgM \(>10\) weeks after exposure

- Zika virus IgM and dengue virus IgM negative: *No recent Zika virus infection*

- Zika virus IgM or dengue virus IgM positive or equivocal:
  - Presumptive recent Zika virus or dengue virus infection

- Reflex Zika virus rRT-PCR on serum and urine

- Plaque reduction neutralization test (PRNT)

- Positive Zika virus rRT-PCR on serum or urine: *Recent Zika virus infection*

- Negative Zika virus rRT-PCR on serum

B: Symptomatic: 2-12 weeks after symptom onset, or
- Asymptomatic and NOT living in an area with active Zika virus transmission: 2-12 weeks after possible exposure, or
- Asymptomatic and living in an area with active Zika virus transmission: 1st and 2nd trimester

 Zika virus IgM and dengue virus IgM\(^*\) on serum

- Dengue virus IgM positive or equivocal and Zika virus IgM negative: *Presumptive dengue virus infection*
- Zika virus IgM positive or equivocal and any result on dengue virus IgM: *Presumptive recent Zika virus or flavivirus infection*
- Zika virus IgM and dengue virus IgM negative: *No recent Zika virus infection*

- Reflex Zika virus rRT-PCR on serum and urine

- Positive Zika virus rRT-PCR on serum or urine: *Recent Zika virus infection*

- Negative Zika virus rRT-PCR on serum

- Zika virus PRNT \(>10\) and dengue virus PRNT \(<10\): *Recent Zika virus infection*
- Zika virus PRNT \(>10\) and dengue virus PRNT \(>10\): *Recent flavivirus infection, specific virus cannot be identified*
- Zika virus PRNT \(<10\): *No recent evidence of Zika virus infection*
Patient presents <2 weeks after exposure or symptom onset

• Lab testing: Zika virus RT-PCR on serum and urine
• If NEGATIVE, check Zika and Dengue IgM for symptomatic patients, Zika IgM for asymptomatic patient 2-12 weeks after exposure
• If Zika IgM or Dengue IgM positive or equivocal, plaque reduction neutralization assay performed
• Will either demonstrate recent Zika virus infection, recent other flavivivirus infection or no recent evidence of Zika
Patient presents 2-12 weeks after exposure or symptom onset

- Check Zika IgM (and Dengue IgM for symptomatic patients) for asymptomatic patient 2-12 weeks after exposure
- If Zika IgM positive or equivocal, send serum and urine specimen for reflux RT-PCR testing
- If RT-PCR of serum negative for Zika, PRNT performed
- Will either demonstrate recent Zika virus infection, recent other flavivirus infection or no recent evidence of Zika
Pregnant woman with possible exposure to Zika virus

Test for Zika virus infection

Positive or inconclusive for Zika virus infection
- Consider serial fetal ultrasounds

Negative for Zika virus infection
- Fetal ultrasound to detect abnormalities consistent with Zika virus disease
  - Fetal abnormalities consistent with Zika virus disease present
    - Retest pregnant woman for Zika virus infection
  - Fetal abnormalities consistent with Zika virus disease not present
    - Routine prenatal care
IgM persistence

• Some flavivirus infections have been reported to result in prolonged IgM responses

• Eg: Dengue IgM persists for 6 months (179 days, 95% CI 155-215) for primary infections and 4.6 months (139 days, 95% CI 119-167) after infection with another flavivirus

• Unclear significance

• Difficult to interpret timing of the infection
Testing Summary

• Timing of potential Zika exposure:
  • <2 weeks: rt-PCR for urine and serum tested first, IgM if PCR negative
  • 2-12 weeks: serum sample first for Zika and dengue IgM, PCR if sample is positive or equivocal
  • >12 weeks: Consider IgM, test PCR if any fetal abnormalities present by US

• For women living in or frequently travelling to areas with ongoing Zika transmission,
  • Consider nucleic acid (PCR) testing once per trimester
  • Consider IgM as part of pre-conception counseling*
When do delivery samples need to be sent?

• Pathology testing is not indicated in all clinical situations.

• However, it might be useful in certain situations to diagnose maternal ZIKV infection (e.g., maternal serology results consistent with recent flavivirus infection, not otherwise specified, and when maternal testing has been performed more than 12 weeks from a woman’s earliest possible exposure).

• All requests need to undergo an approval process initiated by your South Carolina state health department.
Cause and Effect?

- Increased number of cases of microcephaly in Brazil
- Zika virus detected in amniotic fluid of pregnant women whose fetus had sonographic evidence of microcephaly
- Zika virus additionally isolated in culture from amniotic fluid, placenta and fetal brain in other affected pregnancies.

De Carvalho et al 2017.
Congenital Zika Syndrome

A Lateral view of skull irregularities  
B Excessive scalp with folds  
C Lateral skull radiograph
Among US Women:

- **6% (26/442) [95% CI 4-8%] completed pregnancies had birth defects**
  - Of live births, 21/395 affected
  - 5/47 pregnancy losses were affected
- Birth defects (microcephaly ± additional brain abnormalities) noted in 6% [95% CI 4-9%] of **asymptomatic women**
- AND 6% [95% CI 3-11%] of **symptomatic women**
- No reports of birth defects among pregnancies with prenatal exposure in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester
Asymptomatic Pregnant Women with Zika

- Pacheco et al. Zika Virus Disease in Columbia, Preliminary Report (June 2016)
- Assessed patients with clinical symptoms of Zika from August 9, 2015- April 2, 2016 and all case reports of microcephaly Jan-April 2016
- 11,944 pregnant women with Zika
  - 12% cases confirmed with RT-PCR
  - In subgroup of 1850 women, 1/3 reportedly infected in 3rd TM- no infants born with apparent abnormalities
  - Between Jan- April 2016, 4/50 (8%) pregnancies with laboratory evidence of congenital Zika born to asymptomatic mothers
Guillain-Barre Syndrome

• No reports of GBS related to Zika in pregnancy to date
• GBS in pregnancy is rare
  • Incidence is 1-2 per 100,000 person-years
  • In Europe and North America, most common type is acute motor axonal neuropathy
  • Timing: 13% first trimester, 47% in second trimester, 40% in the third trimester
  • Maternal morbidity up to 10%, up to 35% of pregnant women require ICU admission for ventilator support
Can a person be infected with Zika more than once?

- Heterologous zika virus protection in macaques
- Rhesus macaque infection with prototypical ZIKV strain MR766 shown to productively infect the animal, and immunity was protective against an Asian ZIKV strain.

Zika Virus and Sexual Transmission

• Zika can be passed via sexual contact to a sexual partner
• Can be passed from a person with Zika before onset of symptoms, during symptoms and after symptoms have ended
• Any mode of unprotected intercourse
• Studies are still ongoing to determine exact duration of Zika virus in semen and vaginal fluids
  • To date, longest duration in semen = 188 days

[Website Link], Meaney-Delman et al 2016.
Male to female transmission

- In 2008, American scientist working in Senegal experienced clinical illness 6-9 days after returning home to Colorado
- Symptoms included swollen ankles, maculopapular rash on torso, extreme fatigue and headache, wrist arthralgia and subjective fever
- Wife of patient also experienced symptoms 9 days after his return home
First female-to-male sexual transmission of Zika virus

CDC Guidance for Preconception Counseling

- CDC recommends that all men with possible Zika exposure attempting conception with a partner wait to conceive at least 6 months after symptoms or possible exposure (even if asymptomatic.)
- Recommendations for women are unchanged: wait at least 8 weeks for conception from symptoms or possible Zika exposure.
- No published reports of adverse pregnancy outcome after periconceptional Zika virus infection
Periconceptional Screening

• CDC does not recommend Zika virus testing of nonpregnant patients with possible Zika virus exposure who are asymptomatic, including persons planning to attempt conception or just to assess risk of sexual transmission of Zika.

• However, for women living in or frequently travelling to areas with ongoing Zika transmission, a new health advisory notice from 5/5/17 issued states IgM testing may be considered as part of periconceptional counseling.

Novel interventions for zika diagnosis, treatment and prevention
Zika Diagnosis

• Limitations exist to current methods of diagnosing Zika infection
• National Institute of Allergy and Infectious Disease supporting research to generate antibodies to distinguish Zika from other similar viruses, eg: recombinant zika-specific proteins
Zika Treatment

• NIAID in process of testing 60 antiviral compounds against Zika
  • 15 with moderate to high activity, undergoing further testing
  • Also in process of developing neutralizing monoclonal antibodies
Zika Prevention

• Several vaccines in development
  • **DNA-based vaccine developed by NIAID’s Vaccine Research Center in Phase 1 clinical trials**
  • Purified inactivated Zika vaccine (ZPIV) developed by Walter Reed Army Institute of Research currently undergoing 3\textsuperscript{rd} of 5 Phase 1 trials
  • Live-attenuated investigational vaccine, closely related to dengue vaccine candidate. Monovalent version planned for Phase 1 trial in March 2017.
  • Investigational mRNA vaccines in development
  • Investigational vaccine using genetically engineered version of stomatitis virus in very early stages for vaccine candidacy evaluation with tissue culture and animal models
Rapid development of a DNA vaccine for Zika virus

Kimberly A. Dowd, Sung-Youl Ko, Kaitlyn M. Morabito, Eun Sung Yang, Rebecca S. Pelc, Christina R. DeMaso, L...

DOI: 10.1126/science.aai9137

You are currently viewing the abstract.
Until then...

Use Insect Repellent

Use Environmental Protection Agency (EPA)-registered insect repellents with one of the active ingredients below. When used as directed, EPA-registered insect repellents are proven safe and effective, even for pregnant and breastfeeding women.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Higher percentages of active ingredient provide longer protection</th>
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<tbody>
<tr>
<td>DEET</td>
<td></td>
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<tr>
<td>Picaridin (known as KBR 3023 and icaridin outside the US)</td>
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<td>IR3535</td>
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<tr>
<td>Oil of lemon eucalyptus (OLE) or para-menthane-diol (PMD)</td>
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<tr>
<td>2-undecaneol</td>
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Find the insect repellent that’s right for you by using EPA’s search tool*.
The take away

Stay calm and put that deet on
What we still don’t know

• When will a vaccine be ready for public use– 2020?
• Factors associated with more and less severe neonatal effects
• Second or Third trimester exposures causing microcephaly?
  • McCarthy et al, BMJ: Microcephaly risk with Zika infection is 1-13% in first trimester and negligible in 2\textsuperscript{nd}/3\textsuperscript{rd} trimesters
  • Less likely with newer data from US Zika Pregnancy Registry
Patient and provider resources

• ACOG
  • Zika toolkit

• CDC
  • Travel advisory, up to date information about areas with ongoing Zika transmission

• WHO
• DHEC
• SMFM
Thank you!