Unexpected Arrivals!

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Objectives

- Epidemiology
- Transmission
- Outbreaks
- Clinical manifestation
  - Zika Virus in Pregnancy
  - Zika Virus and Microcephaly
- Diagnosis
- Management
- Prevention
History

- Single stranded RNA virus

- Genus *Flavivirus*, Family *Flaviviridae*

- It is closely related to dengue, yellow fever, Japanese encephalitis and West Nile virus.
Vectors

- *Aedes species* including *Aedes aegypti* and *Aedes Albopictus*
  - Also transmits Dengue and Chikungunya
    - Frequent co infections with these viruses
- Day time biters
- Lay eggs on standing water in or near house like Buckets, bowls, flower vases, pots
Distribution of Aedes spp. Mosquitoes in United States

Aedes aegypti

Aedes albopictus
Transmission

- Mosquito bites
- Mother to fetus
  - Intrauterine
  - Perinatal
- Blood Transfusion
- Sexual transmission
- Laboratory exposure
- Theoretical
  - Breast milk
  - Organ and Tissue transplant
Epidemiology

- First discovered from a monkey in the Zika Forest, Uganda in 1947
- It was confined to only Africa and south east Asia until 2007
  - (14 cases)
- First locally acquired case in western hemisphere in Easter Island in 2014
- Now locally acquired cases in South America, Central America, the Caribbean, Mexico, and the US territory of Puerto Rico.
Figure 2. Countries with reported confirmed autochthonous cases of Zika virus infection in 2015, as of 4 December
Countries with Active Transmission of Zika Virus

Brazil

CDC: Updated Feb 29.
Countries with Past or Current Evidence of Zika Virus Transmission (as of December 2015).

Anthony S. Fauci, M.D., and David M. Morens, M.D.
January 13, 2016 | DOI: 10.1056/NEJMp1600297
Zika History and Outbreak

- 1952: First case of human Zika virus infection in Uganda
- 2007: Yap Island, Micronesia
- 2013-2014: 4 Pacific islands: French Polynesia, Easter Island, the Cook Islands, and New Caledonia: 8750 suspected cases and 383 confirmed cases
- 2015-2016: Brazil: 440000 to 1300000 cases in 2015 including confirmed cases
- 2015: Columbia: 3,700 suspected (578 confirmed)
- January 2016: Suriname 1,107 suspected (308 confirmed)
- February 2016: Cabo Verde – 7081 cases (No neurological complications)
Figure 1. The temporal and geographical distribution of Zika virus from 1947 to February 2016. Dates refer to events reported in the published literature (cited in the text), or drawn from WHO’s Event Information Site (EIS).

Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)
2015 – outbreak of Zika virus started in state of Rio Grande do Norte and state of Bahia

Phylogenetic analysis showed that Zika virus sequences obtained belonged to the Asian lineage with 99% identity with a sequence from a Zika virus isolate from French Polynesia

No Zika virus endemic Pacific country competed during the FIFA cup

Another hypothesis: Virus invaded Brazil through another event that was held in Rio de Janeiro in August 2014, the “Va’a World Sprint Championship canoe race” where 4 Pacific countries (French Polynesia, New Caledonia, Cook Islands and Easter Islands) were involved

Or traveler from Chile in FIFA CUP.
Zika virus in united states

- US States
  - Travel-associated Zika virus disease cases reported: 153
  - Locally acquired vector-borne cases reported: 0

- US Territories
  - Travel-associated cases reported: 1
  - Locally acquired cases reported: 107
  - (Puerto Rico, US virgin Island, Samoa Island)
Zika Virus Incidence and Attack Rate

- Infection rate: 73%
- Symptomatic attack rate among infected: 18%
- All age groups affected
- Adults more likely to present for medical care
- No severe disease, hospitalizations, or deaths

Clinical Manifestations

- Mild or Asymptomatic Dengue like illness
- Severe illness causing hospitalization or death is rare
- Incubation period : 2 weeks
- Symptoms:
  - Fever, chills
  - Maculopapular rash
  - Conjunctivitis
  - Headache
  - Myalgia, Arthralgia
## Clinical features comparison

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
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<td>Fever</td>
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<td>Hemorrhage</td>
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Why is Zika virus important?

- Possible association with Microcephaly in infants and implications in pregnant women

- Complications like Guillain-Barre Syndrome
Pregnancy and Zika Virus

- Limited information available
- Existing data show:
  - No evidence of increased susceptibility
  - Infection can occur in any trimester
  - Incidence of Zika virus infection in pregnant women is not known
  - No evidence of more severe disease compared with non-pregnant people

Zika Virus and Microcephaly

- Clinical findings of small head circumference in infants compared to same sex and age
- Lead to cognitive and neurological issues
Etiology of Microcephaly

- Infectious causes
  - Cytomegalovirus
  - Herpes simplex virus
  - Rubella,
  - Varicella
  - Toxoplasmosis
  - HIV
  - Syphilis
  - Enterovirus
- Toxin exposure
  - Alcohol, tobacco, marijuana, cocaine, heroin
Outbreaks in Brazil

Figure 1. States with laboratory-confirmed cases Zika virus disease, Brazil, 2015, as of 23 November 2015

ECDC. Map produced on 7 Dec 2015. Administrative boundaries: ©EuroGeographics, ©UN-FAO
Data on the courtesy of MoH Brazil (VS/M5 – Last Update: 23 Nov 2015)
Figure 3. Notified cases of microcephaly in Brazil from 2010 to 2015, with 14 states under investigation, as of 28 November 2015.

Baseline of notification of microcephaly for Brazil: 2010 (n=153), 2011 (n=139), 2012 (n=175), 2013 (n=167) and 2014 (n=147).
Microcephaly incidence

- 150 - 200 children per year were born with microcephaly in Brazil from 2010 to 2014

- 1,248 suspected cases of microcephaly have been identified across 14 of the 26 states of Brazil, of which 509 cases were reported between 21 and 28 November 2015

- Unusual increase (20 folds) in microcephaly in newborns in 2015
Zika Virus and Microcephaly

• Brazil reported > 5200 cases of suspected microcephaly temporally linked with current Zika outbreak

• French Polynesia: 17 cases of neurologic malformations among fetus and newborns were temporally linked to 2013-2014 outbreak

• Investigation ongoing
• 2 Pregnant female with possible infection with Zika virus during pregnancy (At 10 and 18 weeks respectively)
• US guided amniocentesis at 28 weeks
• RT-PCR was positive for Zika Virus in amniotic fluid
• Serum and urine was negative
• Tests for dengue, chikungunya, Toxoplasma, rubella, CMV, HSV, HIV, Syphilis, and parvovirus B19 were all negative.
• Sequencing of the complete genome of the Brazilian Zika virus isolated from patient 1, phylogenetic analyses showed that the virus shares 97-100% of its genomic identity with lineages isolated during an outbreak in French Polynesia in 2013.
• 1 infant with microcephaly
• 2 Infant with severe ventriculomegaly, Microphthalmia, cataracts and severe arthrogryposis
Women lived in Brazil until 28 weeks of gestation
Possible Zika Virus infection at week 13
US at 29 and 32 weeks: IUGR, microcephaly and other brain abnormalities
Termination at week 32 and autopsy of fetus and placenta performed
Electron microscopy of brain: spherical virus particles similar to Flaviviridae family
Microbiology: RT PCR from brain sample positive for ZIKV
Negative for Dengue, yellow fever, west nile virus, tick borne encephalitis, CHIKV, CMV, VZV, HSV, parvo B19, enterovirus, Toxoplasma, rubella, lymphocytic choriomeningitis
ZIKV genome sequence showed identity (99.7%) with strain isolated from patient from French Polynesia in 2013.
Figure 3. Electron Microscopy of Ultrathin Sections of Fetal Brain and Staining of a Flavivirus-like Particle.
Panel A shows a damaged brain cell with a cluster of dense virions located in the disrupted endoplasmic reticulum. Remains of membranes derived from different cellular compartments and filamentous structures are also seen. A magnified view of the boxed area with virions clearly visible (arrows) is shown in Panel B. Panel C shows a group of enveloped structures with a bright interior, presumably indicating viral replication (arrow). Panel D shows a negatively stained viral particle with morphologic characteristics consistent with those of Flaviviridae viruses (arrow).
4 pregnant female in Brazil with Zika Virus infection during pregnancy
2 infants born with Microcephaly and died within 20 hours
2 Miscarriages ( at 11 and 13 weeks )
Samples from brain, autopsy tissue and products of conception from fetal losses
Positive RT-PCR for Zika Virus from brain and fetal loss tissue
Significant histopathological changes in brain
Parenchymal calcification and necrosis
Tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV were negative in the two mothers
Zika Virus Infection Among U.S. Pregnant Travelers — August 2015–February 2016

- 9 Pregnant female in US
- No hospitalization or deaths among pregnant women
- 2 early pregnancy loss
- 2 Elective terminations
- 3 Live births: 2 healthy infants, 1 with severe microcephaly
- 2 pregnancy continued without known complications
Guillian-Barre Syndrome

- French Polynesia outbreak: 8750 suspected cases, 383 PCR confirmed cases, Coincided with a dengue outbreak
  - 42 Guillian-Barre syndrome

- Brazil outbreak: 1708 cases of Guillian Barre syndrome Simultaneous outbreaks of CHIKV and Dengue

- El Salvador in one month – 46 cases of Guillian Barre syndrome
First study to confirm link between Zika virus infection and Guillain Barre syndrome

- Zika virus infection IgM positive - (93%) of GBS patients and (17%) in control group
- Neutrilizing antibody response in (100% of 42) of GBS patients and (56% of 98) in control group
- Transient illness suggesting Zika virus infection with median of 6 days
- No indication of increased recent infection with Dengue
- Past history with Dengue is common with all patients
- Electrophysiological findings: Acute motor axonal neuropathy (AMAN) type
- Incidence rate of 24 in 100,000 patients compare to 1-4 in 100,000 patient in world.
Diagnosis

- There are **no commercially available diagnostic tests** for Zika virus disease. Zika virus testing is performed at the CDC Arbovirus Diagnostic Laboratory and a few state health departments.

- In 2016, **Zika virus disease became a nationally notifiable condition**. Healthcare providers are encouraged to report suspected Zika cases to their state or local health department.

- FDA had issued Emergency use authorization for Zika Virus Diagnostic tool (EUA)
Diagnosis

- **Virus Antigen**
  - RT-PCR – for viral RNA in serum collected ≤7 days after illness onset

- **Serology**
  - IgM and neutralizing antibodies in serum collected ≥4 days after illness onset
  - Plaque reduction neutralization test (PRNT) for ≥4-fold rise in virus-specific neutralizing antibodies in paired sera
  - Only available at CDC

- **Immunohistochemical (IHC) staining** for viral antigens or RT-PCR on fixed tissues
Serology cross reaction with other viruses

- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (dengue and yellow fever viruses)

- Neutralizing antibody (PRNT) testing may discriminate between cross-reacting antibodies in primary flavivirus infections

- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus
Testing through CDC

- No commercially-available diagnostic tests

- Testing performed at CDC and a few state health departments

- CDC is working to expand laboratory diagnostic testing in states

- Suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infections
Process to get tested through CDC

- Patient consent to test for Zika Virus
- Notify local or state health department and CDC about collection and shipment of specimen
- Contact CDC at zika_adb_epi@cdc.gov
- Submit CDC form 50.34 with all specimens. Test order name enter “Zika virus”.
- Questions for tissue specimen submission: email pathology@cdc.gov.
Types of specimen can be tested

- Serum
  - Acute: 3-10 days after onset of symptoms
  - Convalescent: 2-3 weeks after acute serum sample
- Fresh frozen tissue
- CSF
- Testing results available in 4-14 days to STATE HEALTH DEPARTMENT

- CDC Additional assistance: DVBD Arbovirus Diagnostic and Reference Laboratory at 970-221-6400
Zika Virus Disease Surveillance

- Zika virus is a nationally notifiable disease

- Health care providers should report suspected cases to their state health department

- State health department are requested to report laboratory confirmed cases to CDC
Management

- No specific antiviral treatment available
- Treatment supportive: Rest, IV fluids, Analgesics, Antipyretics
- Suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infections
- Aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce risk of hemorrhage
Differential Diagnosis for Zika Virus

- Dengue
- Chikungunya
- Leptospirosis
- Malaria
- Rickettsia
- Parvovirus
- Group A streptococcus
- Rubella
- Measles
- Adenovirus
- Enterovirus
Update: Interim Guidance for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016
Evaluation

- Ask about travel history

- If positive travel history ask about symptoms for Zika Virus and test for infection.

- Pregnant women with male partners who have Zika virus infection or exposure should use condoms or abstain from sexual activity for the duration of pregnancy.
Pregnant women with history of travel to an area with Zika Virus Transmission

Symptomatic:
(2 or more symptoms within 2 weeks of travel)
- RT-PCR or IgM

Asymptomatic: IgM

Test for Zika Virus Infection
RT-PCR or IgM antibodies

Positive or inconclusive for Zika Virus infection

Consider serial fetal ultrasounds
Consider amniocentesis for Zika virus testing

Inconclusive test: IgM positive with neutralizing Ab titers that are < 4 fold higher than dengue virus neutralizing Ab titers

Symptomatic:
2 or more of following symptoms:
Fever, Rash, Arthralgia, conjunctivitis
Pregnant women With History Of Travel or Residing in Areas With Ongoing Zika Virus Transmission

- **Test for Zika Virus is Negative**
  - If women residing in ongoing ZIKV transmission area
    - US at 18-20 weeks
    - Test for Zika virus infection in mid 2nd trimester
- **Fetal US for Microcephaly or Intracranial calcifications**
  - Microcephaly or Intracranial calcifications PRESENT
    - Retest Pregnant women for ZIKV
      - Consider amniocentesis for ZIKV
  - Microcephaly or Intracranial calcifications NOT PRESENT
    - Routine Prenatal Care
      - If women residing in ongoing ZIKV transmission area

- **Routine Prenatal care**
  - Consider Additional US
Guidelines for Pregnant women with history of Travel to an area with ongoing Zika Virus Transmission

Pregnant woman with history of travel to an area with ongoing Zika virus transmission

Test for Zika virus infection

Positive or inconclusive for Zika virus infection

Consider serial fetal ultrasounds
Consider amniocentesis for Zika virus testing

Negative for Zika virus infection

Fetal ultrasound to detect microcephaly or intracranial calcifications

Microcephaly or intracranial calcifications present

Retest pregnant woman for Zika virus infection
Consider amniocentesis for Zika virus testing

Microcephaly or intracranial calcifications not present

Routine prenatal care
Evaluation of Pregnant female residing in Area with Ongoing Zika Transmission

- Offer serologic testing
  - At initiation of prenatal care
  - During follow up of mid 2nd trimester

- Routine US for all pregnant female at 18-20 weeks and if negative consider repeating US
Clinical Management During Pregnancy

- Positive or inconclusive Zika virus testing results
  - **Antepartum**
    - Consider serial ultrasounds every 3–4 weeks
    - Referral to maternal-fetal medicine specialist is recommended
  - **Postpartum**
    - Histopathologic examination of the placenta and umbilical cord
    - Testing of frozen placental tissue and cord tissue for Zika virus RNA
    - Testing of cord serum for Zika and dengue virus IgM and neutralizing antibodies
Guidelines for breast feeding

- Zika virus RNA has been identified in breast milk
- No cases of Zika transmission associated with breastfeeding have been reported
- Mothers are encouraged to breast feed their infants
- With current evidence, benefits of breast feeding outweigh theoretical risks
Pregnant women considering Travel

- Pregnant women in any trimester should consider postponing travel to areas where Zika virus transmission is ongoing.

- If they must travel, consider talking to health care provider and take steps to prevent mosquito bites.
Infants whose mother travelled to and resided in an area with ongoing Zika virus transmission during pregnancy:

- Microcephaly or intracranial calcification detected prenatally or at birth:
  - Thorough physical exam and perform Zika Virus testing in infant:
    - RT-PCR, IgM, IgG, Neutralizing Ab, histologic evaluation of placenta or cord
    - Negative Test > Evaluate for other causes
    - Positive or inconclusive test for Zika Virus Infection in Infant > Additional clinical evaluation, report case, assess for long term sequelae

- No microcephaly or birth defect but Mother with positive or inconclusive ZIKV infection:
  - Additional clinical evaluation, report case, assess for long term sequelae
  - Negative Test > Evaluate for other causes
Evaluation in infants with congenital Zika Virus Infection

BOX 2. Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection

For all infants with possible congenital Zika virus infection, perform the following:

- Comprehensive physical examination, including careful measurement of occipitofrontal circumference, length, weight, and assessment of gestational age.
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions. Full body photographs and photographic documentation of any rash, skin lesions, or dysmorphic features should be performed. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant’s clinical presentation.

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram).
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections. Consider consulting a pediatric infectious disease specialist.
- Complete blood count with platelet count and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

Sexual Transmission

- First reported case in 2012 in US researcher got Zika virus infection while doing research in Senegal transmits to his wife.
- Zika Virus can be sexually transmitted by a man to his sex partners.

What we do not know:
- How long virus persists in semen
- Whether women can transmit it
- Whether it can be transmitted from oral sex
- Whether infected asymptomatic men can transmit infection
Men and their pregnant sex partners:
- Should abstain from sexual activity or consistently use condoms during sex
- Pregnant women should discuss their partner’s possible exposure with their health care providers.

Men and their non pregnant sex partners:
- If concerns for Zika Virus infection, consider condoms or abstain from sex
Prevention

- No vaccines exist to prevent Zika virus infection
- EPA registered Mosquitoes Repellents – Contains 20% or more DEET (Off!, Cutter, Sawyer, Ultrathon)
  - DEET and permethrin, are safe and effective for pregnant women
- Permethrin Treated clothing and gears
- House screens, Mosquitoes bed nets
- Air-conditioning
- Long sleeves and full clothing
Future course of Zika Virus in Americas

- Virus will continue to spread in areas with vectors
- Travel associated cases will introduce virus to U.S states
- It may result in some local transmission and outbreak
- Air conditioning and colder climate might interrupt further spread
Learning points

• If suspected in pregnant female, consider serial US and amniocentesis for virus detection

• Diagnosis available at CDC and some state health departments

• Symptomatic Treatment

• Pregnant women in any trimester should consider postponing travel to areas where Zika is present
References


