

# Pathogens of Pandemics: Emerging Viruses including Zika

Julie E. Mangino, MD, FSHEA  
Professor of Internal Medicine  
Division of Infectious Diseases  
Medical Director, Department of Clinical Epidemiology  
The Ohio State University Wexner Medical Center

## Objectives

- To share what is known about ZIKV
  - Epidemiology
  - Transmission
  - Treatment
  - Prevention
- To share how the ZIKV and other arthropod infections (dengue, chikungunya) are being more commonly diagnosed in US and the Americas
  - How they are similar and different

Author: CDC



## ZIKV is a Flavivirus.....

- Flavi-viruses replicate in nerve cells near inoculation site and spread to lymph nodes and bloodstream
- ZIKV is detected in blood on day of illness onset
- Other important Flavi-viruses:
  - Dengue
  - Yellow fever
  - West Nile Virus
  - St. Louis and Japanese encephalitis viruses
- Infection acts like Chikungunya, also associated with a recent outbreak in the Americas (2014)



## History of Zika Virus(ZIKV)

- April 1947: fever in a Rhesus monkey in a cage on a tree platform in Zika Forest, Uganda (study yellow fever)
  - Rhesus monkey serum inoculated into mice; all sick
  - Transmissible agent: RNA virus in mouse brains
- 1948 ZIKV isolated from Aedes mosquitos in same forest
- 1956 Transmission of ZIKV by artificially fed *A. aegypti* mosquitoes to mice and monkey
- 1970s: ZIKV isolated in Nigeria during 1970s
  - 10 yr old boy w/ fever HA and body aches

## History of Zika Virus Continued



Manuel Almagro Rivas [CC BY-SA],  
via Wikimedia Commons

- **1951-1981:**
  - Africa: Uganda Tanzania, Egypt, Sierra Leone, Ivory Coast
  - Asia: India, Malaysia, Philippines, Thailand, Vietnam, Indonesia
  - Serologic evidence of human ZIKV infections in 1952; 14 cases

## History of Zika Virus Continued



Manuel Almagro Rivas [CC BY-SA],  
via Wikimedia Commons

- **2007 Yap Island Outbreak:** outside Asia/Africa
  - Boorman: transmission of ZIKV to mice and monkeys by *A aegypti* in a lab; 900 cases (8K population)

## History of Zika Virus Continued



Manuel Almagro Rivas [CC BY-SA],  
via Wikimedia Commons

- **2013-15 French Polynesia ZIKV outbreak:**
  - Concomitant with dengue epidemic
    - 28,000 ZIKV infx; 11% of population reported
  - Guillain Barre syndrome (GBS) in 40/72 infected pts
    - Weak arms legs, face muscles and swallowing issues
    - Serious cases affects breathing
    - Symptoms last months
    - Rare 3-6 cases/100K in the US

## How Zika virus spread from Africa

- **1947:** Discovered in Uganda
- **1977-78:** Pakistan, Malaysia, Indonesia
- **2007:** Yap, Micronesia
- **2013:** French Polynesia
- **2015:** Brazil

Source: Lancaster University

# **Zika Virus Recent Epidemiology**

- **Aug 2014: How did ZIKV get to Brazil?**
  - ? Human travel/transport via blood of athletes (French Polynesia) in Rio de Janeiro (2014 Soccer World Cup)
- **May 2015**
  - Pan American Health Organization issued alert regarding 1st confirmed ZIKV infection in Brazil.
- **Oct 2015: Drastic increase in microcephaly among infants born to mothers in NE Brazil**
  - Amniotic fluid from 2 showed ZIKV.
- **Dec 2015: locally transmitted case of ZIKV detected in Puerto Rico.**
  - Brazil: Preliminary estimates of 440K to 1.3 million cases through December 2015

# ZIKV

- Feb 2016: WHO declared ZIKV an international public health emergency
  - Pregnant women giving birth to babies with birth defects (microcephaly) w/ poor pregnancy outcomes.
    - Knowledge of the link evolving
- 2/8/16 CDC EOC activated; issued a Travel Alert (Level 2-Practice Enhanced Precautions) to regions/certain countries (South/Central America) w/ ongoing ZIKV transmission
  - Increased risk in defined settings or risk factors;
  - Certain high risk populations (pregnant) may wish to delay travel to these destinations
  - If male partner in region w/ ZIKV transmission, abstain from sex or use condoms

## All Countries and Territories with Active Zika Virus Transmission

Reported active transmission

Map showing all countries and territories with active Zika virus transmission. The map is color-coded to indicate the status of transmission:

- Dark Gray:** Reported active transmission

Key countries and territories shown include:

- Mexico
- Belize
- Honduras
- Guatemala
- El Salvador
- Costa Rica
- Nicaragua
- Panama
- Colombia
- Ecuador
- Venezuela
- French Guiana
- Suriname
- Brazil
- Peru
- Bolivia
- Paraguay
- Argentina
- Chile
- Cuba
- Haiti
- Dominican Rep.
- St. Martin
- St. Maarten
- US Virgin Is.
- St. Bartholomew
- Anguilla
- St. Kitts
- Nevis
- St. Vincent & the Grenadines
- Barbados
- Trinidad & Tobago
- Guyana
- Suriname
- French Guiana
- Marshall Is.
- Kiribati
- Micronesia
- Papua New Guinea
- Samoa
- American Samoa
- Tonga
- Fiji
- New Caledonia
- New Zealand

CDC May 26 2016

**States and Territories Reporting Zika Virus Disease**  
Number of cases by state or territory (2015-2016)

Number of Cases	Shading Description
0-2	White
3-4	Light Grey
5-6	Medium Grey
7+	Dark Grey

Area with local vector-borne transmission

**US Territories:** Locally acquired 1301 (Puerto Rico, Am Samoa, Virgin Islands)

## How does Zika virus spread?

- By *Aedes aegypti* and *Aedes albopictus* ?
- Both of these mosquitoes carry
  - Dengue
  - Chikungunya virus
- Lay eggs in standing water: buckets, bowls, animal dishes, flower pots, vases
- Bite mostly during the daytime
  - Like to live indoors and outdoors *near people*
- Mosquitos become infected when feeding on someone already infected with the virus
  - Bite and spread to others



Author: CDC

<http://www.cdc.gov/zika/transmission/index.html>

## First ZIKV cases in Brazil

- Confirmed in 8 pts
  - All with maculopapular rash and pain
  - Headache, retro-orbital pain, myalgia
  - Joint pain
  - Fever in 2/8 >100.4
- Retrospective analysis from multiple areas



Author: CDC

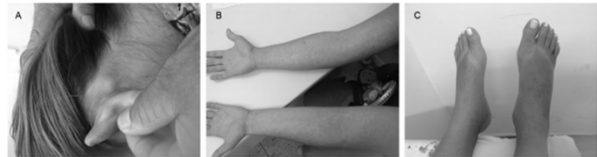
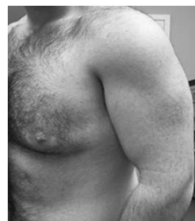


Fig. 3 Zika virus clinical findings in patients from Natal, state of Rio Grande do Norte, Brazil. A: lymphadenopathy; B: maculopapular rash; C: periarticular swelling.

Zanluca, C. First report of autochthonous tm of ZIKV in Brazil  
Mem Inst Oswaldo Cruz, June 2015 Rio de Janeiro Vol 110 (4) 569-72

## Symptoms and Complications

- ~ 1 in 5 people become ill
  - Most are unaware of ZIKV infection
- Symptoms:
  - Fever
  - Rash (95%)
  - Joint pain
  - Conjunctivitis
  - Muscle pain (myalgia) and headache.
- Incubation (exposure to symptoms)= ~ 2-7 days after bite
- Symptoms last up to a week and is usually mild
  - Similar to dengue and chikungunya
  - ZIKV is in blood for only a few days
- Severe disease is uncommon; death is rare
- Likely protected from future infections



<http://www.cdc.gov/zika/symptoms/index.html>

## Sexual Transmission

- Initial reports:
  - 1- M to F TM 3 days before ZIKV symptom onset (2011)
  - 2- M developed symptoms 2 d after travel; M partner of 10 yrs developed symptoms 5 d later in Dallas, Tx (4/2016)
  - 3- ZIKV isolated from semen 14 and 62d after illness
    - RT PCR testing of blood collected same time as semen did not detect ZIKV; no sexual contacts
    - Duration of persistence of ZIKV in semen is unknown
- Correct and consistent use of latex condoms reduces sexual transmission of many infections

Foy BD et al. Probable non-vector-borne TM of ZIKV, Colorado USA. *Emerg Inf Dis* 2011;17:880-2.  
Musso et al. Potential sexual TM of ZIKV. *Emerg Inf Dis* 2015;21:359-361.  
Atkinson B et al. Detection of ZIKV in Semen letter. *Emerg Inf Dis* May 2016.  
D'Ortenzio E et al. Evidence of Sexual TM of Zika. *NEJM* June 2 2016 374;22:2195-2198.

## Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus-US 2016

**BOX.** Recommendations for prevention of sexual transmission of Zika for couples in which a man has traveled to or resides in an area with active Zika transmission

- Couples in which a woman is pregnant should use condoms consistently and correctly or abstain from sex for the duration of the pregnancy.
- Couples concerned about sexual transmission\*
- Couples in which a man had confirmed Zika infection or clinical illness consistent with Zika disease should consider using condoms or abstaining from sex for at least 6 months after onset of illness.
- Couples in which a man traveled to an area with active Zika transmission but did not develop symptoms of Zika virus disease should consider using condoms or abstaining from sex for at least 8 weeks after departure from the area.
- Couples in which a man resides in an area with active Zika transmission but has not developed symptoms of Zika virus disease might consider using condoms or abstaining from sex while active transmission persists.

\* Couples who do not desire pregnancy should use the most effective contraceptive methods to be used correctly and consistently in addition to condoms, which also reduce the risk for sexually transmitted infections. Couples planning conception have a number of factors to consider, which are discussed in more detail in the following: Petersen EE, Polen KN, Meaney-Delman D, et al. Update: interim guidance for health care providers caring for women of reproductive age with possible Zika virus exposure—United States, 2016.

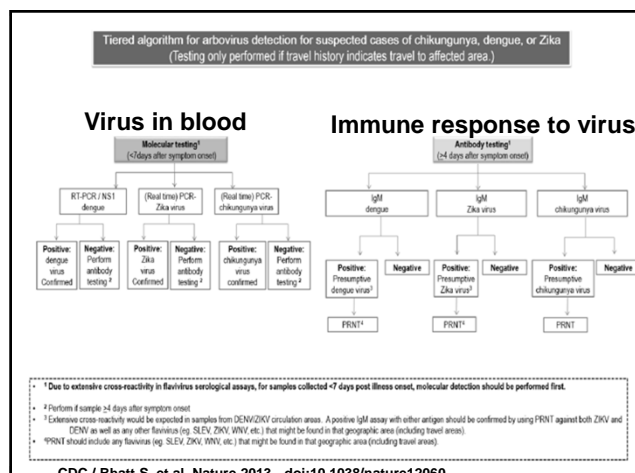
MMWR Morb Mortal Wkly Rep 2016. Published online March 25, 2016.

## Diagnostic Testing of ZIKV

- Preliminary diagnosis is based on a patient's clinical features, places and dates of travel/activities.
- Date of onset of symptoms is very important for testing purposes and included on the CDC form
- Testing options:
  - Serum for PCR and antibody
  - Cerebrospinal fluid
  - Urine for PCR testing if <14d from onset of symptoms in conjunction with serum testing
  - Amniotic fluid and histopathologic tissue (i.e. formalin fixed or frozen, umbilical cord and/or placenta)

MMWR interim Guidance for ZKV testing of Urine May 13 2016

MMWR Interim Guidance for ZKV Ab testing June 3 2016



## ZIKV Adverse Effects

- Most have no AE as 80% asymptomatic
- Pregnancy
  - Congenital syndromes (1<sup>st</sup> case in US May 31, 2016)
    - Disruption of brain development
    - Microcephaly, craniofacial disproportion, spasticity
    - Sight and hearing abnormalities
    - Impaired growth
- Guillain Barre Syndrome (GBS): immune system attacks nerves, ascending weakness and temporary paralysis
- Acute myelitis

Kleber de Oliveira MMWR March 11, 2016/ 65 (9) 242; Costello A. Bulletin of the WHO 2016 94:406  
Mecharles S et al. 2016 thelancet.com Published online March 3, 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)00644-9](http://dx.doi.org/10.1016/S0140-6736(16)00644-9)

## Transmission of ZIKV other than mosquito

What is known.....

### Blood transfusion

- No confirmed blood transfusion infx in US
- Multiple blood transfusion infx in Brazil
- Laboratory exposure
- Organ or tissue transplantation

What is NOT known?

- How long is ZIKV definitively present in semen?
- One case (6/2/2016) via oral sex?
- If a woman can transmit to her sex partners?
- Other bodily fluids i.e. saliva or vaginal fluid?

D'Ortenzio E et al. Evidence of Sexual TM of ZKV *NEJM* 375;22 June 2 2016

## Treatment of ZIKV

- No vaccine is available to prevent or treat ZIKV
  - NIH is tweaking a vaccine begun for West Nile ? 9/1/16
- No antivirals available for ZIKV disease.
  - Studies in mice by BioCryst ongoing
  - 15/62 drugs screened have "some degree of activity"
- Treatment is supportive and includes rest, fluids, analgesics and antipyretics
  - Fever should be treated with acetaminophen
- Aspirin and other NSAID are not typically used in pregnancy, specifically avoid until dengue is ruled out to reduce the risk for hemorrhage

## Dengue



Author: CDC






- Before 1970 only 9 countries
- Endemic in over 100 countries; 3.6 billion are at risk
- Endemic throughout the tropics
- Sporadic outbreaks in so, HI, TX and FL
- 30 fold increase in incidence over last 50 yrs
  - 25% of infected develop symptoms
  - 96 million cases in 2010
    - 13 million cases in the Americas
    - Brazil has the most cases

CDC / Bhatt S, et al. Nature 2013 - doi:10.1038/nature12060

## Dengue

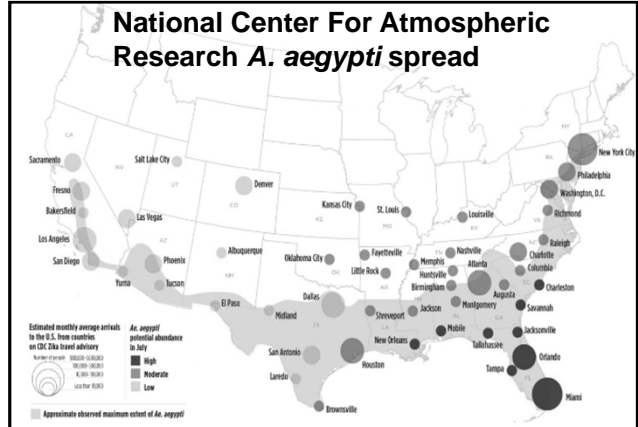
- Four closely related dengue viruses
  - *Aedes aegypti* primarily; *Aedes albopictus* in HI in 2001
- Endemic in Puerto Rico, Latin America, SE Asia and Pacific Islands
  - 100 million cases per year worldwide
- Symptoms: acute febrile illness
  - High fever, severe HA, pain behind eyes, joint pain, muscle and bone pain, rash and mild bleeding.
- Dengue hemorrhagic fever: fever 2-7d then vomiting abdominal pain, SOB; capillary leak syndrome (ascites, pleural effusions, MOSF) and death
  - Low platelets, bruising, bleeding
  - Treat with acetaminophen, no aspirin, fluids

## Aedes Mosquitoes: 100 million cases of mosquito borne diseases/year

VIRUS	<i>Aedes aegypti</i> 	<i>Aedes albopictus</i>
Dengue 1-4	X	X
Chikungunya	X	X
Yellow Fever	X	
Zika	X	
		
		

Images from CDC

## National Center For Atmospheric Research *A. aegypti* spread



National Center for Atmospheric Research (NCAR)  
(Image based on data mapped by Olga Wilhelm, NCAR GIS program)

## Chikungunya Virus (CHIKV)

- Mosquito Born; isolated in Tanzania '53
- Name means "that which bends up"

## Crippling Virus Set to Conquer Western Hemisphere



Author: CDC

16 MAY 2014 VOL 344 SCIENCE www.sciencemag.org

public health

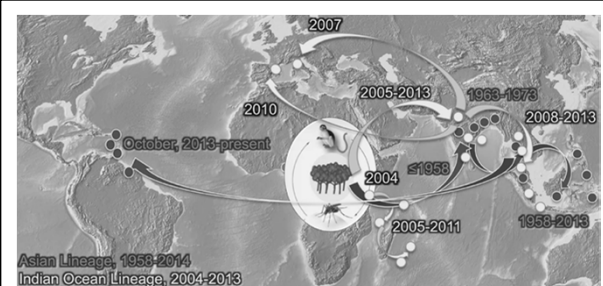
Chikun-What? A New Mosquito-Borne Virus Lands In The U.S.

by MICHAEL E. DOUGLEFF

July 03, 2014 3:08 AM ET

23 After Months of Slinking Across the Border, Chikungunya Transmitted in the U.S.

www.pbs.org

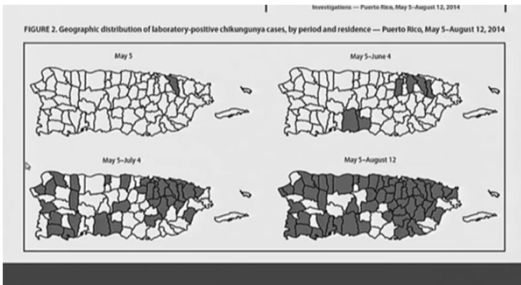


## Epidemiology of CHIKV

- Asian Lineage
  - Primarily transmitted by *Aedes aegypti*
- Indian Ocean Lineage
  - Adapted to *Aedes albopictus*

Image source: PLOSNTD 2014;8:e2921

## MMWR 12/5/2014 CHIKV on Puerto Rico



- Cases of outbreak with blue showing residents of an imported case
- Over 3 months, CHIKV spread with 10K suspected cases
- And 2K tested positive

## Pathogenesis of CHIKV

- Infects musculoskeletal tissues
- Triggers inflammatory cell infiltration
  - Monocytes, macrophages, NK cells, and T cells
- Chronic disease
  - Persistent infection in tissues
  - Pro-inflammatory immune response

J Immun 2010;184:5914-5927

## Chikungunya Acute Presentation

Symptom or Sign	Frequency Range (% of Symptomatic Pts)
Fever	76-100
Polyarthralgias	71-100
Headache	17-74
Rash	28-77
Myalgias	46-72
Back Pain	34-50
Nausea	50-69
Vomiting	4-59
Polyarthrititis	12-32
Conjunctivitis	3-56

- 3-7 day incubation

- High morbidity, low mortality

- ~ 80% develop significant symptoms

Table adapted from: Preparedness and Response for Chikungunya Virus Introduction in the Americas. CDC/PAHO 2011

## Chikungunya vs Dengue

Clinical Signs	Chikungunya	Dengue
Fever	Common	Common
Rash	Day 1–4	Day 5–7
Retro-orbital Pain	Rare	Common
Arthralgia	Consistent	Rare
Arthritis	Common	Absent
Myalgia	Common	Common
Tenosynovitis	Common	Absent
Hypotension	Possible	Common
Minor Bleeding	Rare	Common
Outcome	Arthralgia for months to years	Possible fatigue for weeks
Thrombocytopenia	Early and mild	Delayed and possibly severe

Table adapted from: Curr Infect Dis Rep 2011;13:218-228



## Chronic Chikungunya Disease

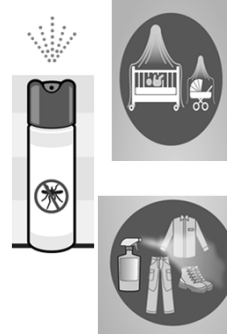
### Subacute (2 to 3 months)

- Symptom relapse after initial improvement
- Polyarthritis, tenosynovitis, Raynaud's
- Depression, fatigue, weakness

### Chronic (> 3 months)

- 15 to 50% of patients
- Distal polyarthritis and tenosynovitis
  - Previously injured joints and bones
- Occasionally develop a destructive arthritis
  - Rheumatoid arthritis-like polyarthritis
- Fatigue, depression, and loss of quality of life

## Prevention



### Community level

- Habitat control with larvicides and insecticides
  - Challenging to sustain
- Avoid mosquitos and areas with ongoing transmission.

### Personal protective measures:

- Air conditioning
- Screens on windows/doors
- Mosquito repellants (picaridin, IR<sub>3535</sub>®, DEET 20-30%)
- Long sleeved shirts and pants
- Protect infected people from further mosquito exposure within the first week of illness.

[http://www.cdc.gov/chikungunya/pdfs/fs\\_mosquito\\_bite\\_prevention\\_travelers.pdf](http://www.cdc.gov/chikungunya/pdfs/fs_mosquito_bite_prevention_travelers.pdf)

## Zika Virus Summary

- *Aedes aegypti* is the most important vector in outbreaks of ZIKV, Dengue, CHIKV
  - Recent increased incidence; spread to new areas
  - Defer blood donors w/ symptoms or travel (FDA)
- Overlapping geographic areas and similar features of diseases make testing for all diseases important
- No antivirals, but clinical management for severe dengue until proven otherwise
  - Await vaccines for dengue and chikungunya
- Prevent to reduce mosquito exposure; avoid all standing water, use air-conditioning, screens, avoid travel if not essential and pregnant

Kirkpatrick BD. [www.ScienceTranslationalMedicine.org](http://www.ScienceTranslationalMedicine.org) 3/16/2016

## References

- Zika Virus CDC Homepage [cdc.gov](http://cdc.gov)
- Interim Guidelines for Pregnant Women During a Zika Virus Outbreak – United States, 2016
- Practice Advisory: Interim Guidance for Care of Obstetric Patients During a Zika Virus Outbreak
- Q&A for Obstetrical Health Care Providers: Pregnant Women and Zika Virus Infection
- Possible Association Between Zika Virus Infection and Microcephaly – Brazil, 2015
- <http://www.who.int/emergencies/zika-virus/en/>
- <https://www.nejm.org>
- <http://jama.jamanetwork.com/journal.aspx>
- Rasmussen, SA et al. Zika Virus and Birth Defects- Reviewing the Evidence for Causality. *NEJM* April 13, 2016

### **Drs. Anthony Fauci (NIAID), Tom Friedan (CDC)**

- Unknowns that research must address: questions about molecular makeup of virus, immune response needed, and appropriate animal models.
- “Cautious optimism” that a vaccine against the virus can be developed....a candidate could be tested before the end of 2016; the difference between developing a product to be tested and getting it approved and distributed. That, would likely be several years away at best. That work, as well as CDC’s responses, can’t be completed without resource support “in the form of the supplement the president asked for”. (AF)
- “Nothing about Zika control is quick and easy.” (TF)

Science Speaks: A Project of the Center for Global Health Policy  
March 10, 2016

### **US Policy and Funding June 1 2016**

- WHO: “one of the most profound transformations in the Organization’s history,” with agreement by member states at 69th World Health Assembly to launch a new “Health Emergencies Programme” with a starting budget of \$494 million. It follows news from the World Bank that it will launch a \$500 million insurance fund to fight pandemics — with the first \$50 million commitment coming from Japan.
- While no dollar response exists yet to Obama Admin’s February request for \$1.9 billion to address Zika and its impacts, \$510 million diverted from Ebola responses to Zika efforts is unlikely to be replaced; neither the Senate \$1.1 billion proposal, nor the House’s proposed \$622 million reallocation of existing funds includes paying that back.

### **Infection Prevention**



Department of Clinical Epidemiology

Image authors: Serenity, Stanis 70 and CDC

## **Zika: a primer on vector-borne & perinatal infections**

**Michael Cackovic, MD**  
Assistant Professor  
Department of Obstetrics & Gynecology  
Division of Maternal-Fetal Medicine  
The Ohio State University Wexner Medical Center

## Learning objectives

- Discuss the threat of Zika and vector born disease in pregnancy
- Use Zika as a model for discussing viral disease in ultrasound and pregnancy
- Discuss the media impact of Zika and how it affects obstetrics and health care



## Zika Transmission

- Primarily through bite of infected *Aedes* mosquito
- Zika viral RNA found in blood, semen, urine, saliva, CSF, amniotic fluid, breast milk
- Maternal-fetal transmission can occur through intrauterine transmission resulting in congenital infection as well as intrapartum transmission from a viremic mom
- Transmission through breast milk has not been observed, however other flaviviruses have been reported
- Transmissible via blood products

## Zika Outbreaks

- Initial outbreak Brazil: FEB-JUN2015
- Bahia State, capital of Salvador: heart of Brazilian epidemic
- Ideal climate: wet, hot, humid
- Attack rate: 5.5 cases/10,000 inhabitants (0.05%)
- “10 to 20-fold increase” in microcephaly; 6/10,000 incidence
- OCT2015- 14 Brazilian states affected
- DEC2015- 1.3M people infected

## Zika Outbreaks

- 400-9000 fetal transmission cases
- Initially: 4180 suspected cases of microcephaly: 3448 cases under investigation, 270 confirmed
- Now: 641 cases *confirmed*, 1687 examined
- Presence of Zika *confirmed* in 17 cases of microcephaly
- 2014: 3M births in Brazil, 150 cases microcephaly (0.005%)
- Compare to USA: 4M births, 2500 cases (0.06%)
- Bias- heightened awareness of Zika

## Zika Outbreaks

- OCT2015: First case reported in Columbia
- 51,473 suspected cases by 3MAR2016
- 6300 confirmed cases in pregnancy
- No microcephaly cases; 32 “other” findings
- French Polynesia: 17 cases/32,000 people (0.0005%)

## Zika in the USA

- Mosquito-borne transmission has not yet been confirmed in the USA
- JAN, 2016-Hawaii: microcephalic fetus born to woman who lived in Brazil during pregnancy
- FEB, 2016- Texas: sexually-transmitted transmission
- 691 cases thus far/206 pregnant/11 STIs (8June)
- US territories: 1305/166 pregnant (8June)
- 30+ US states may be at risk this summer

## Zika in the media

- Pandemic virus!
- Causes severe developmental abnormality!
- No cure; no vaccine!
- No readily available work-up!
- It is COMING!!
- PubMed: 931 Zika articles, 25 published from 1952-2009; 716+ published in 2016

## Clinical manifestations

- Has been found in pathologic specimens of fetal losses; not known if cause
- No evidence to suggest pregnant women are more susceptible
- Rate of vertical transmission is unknown
- Thus far, no developmental complications in healthy babies with postnatal exposure

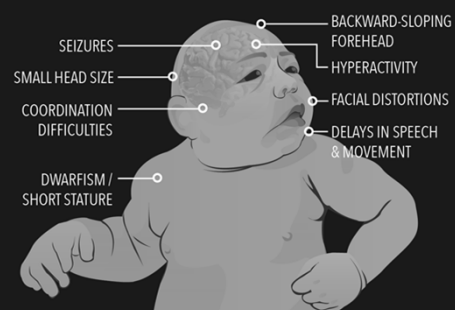
## Public health emergency of international concern

- Declared by WHO on 01FEB2016
- 3 criteria:
  1. constitute a health risk to other countries through international spread
  2. potentially require a coordinated response because it is unexpected, serious or unusual
  3. have implications beyond the affected country that could require immediate action

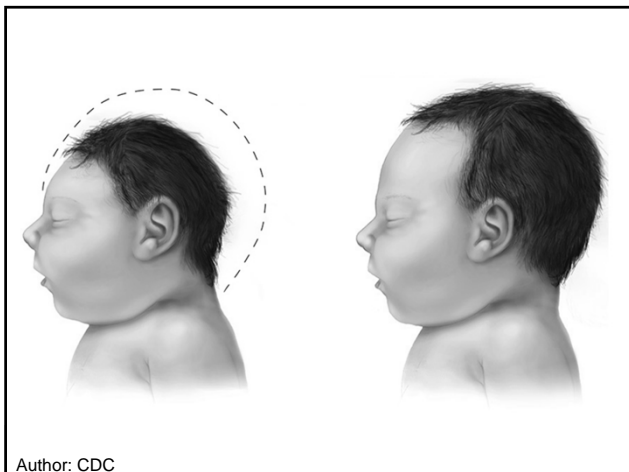
## Public health emergency of international concern

- No standard case definition of microcephaly; needs to be standardized within affected areas as well as Africa and Asia
- Research on neurological effects: viral/toxins/environmental effects. Post mortem analysis, case-controls, other studies.
- Precautionary measures for flaviviruses/arboviruses in general: dengue, chikungunya
- Diagnostic tests: seroprevalence studies not requiring Ag presence
- Vector control

### SYMPTOMS OF MICROCEPHALY



Author: Beth.herlin  
CC BY-SA 4.0



## Mechanisms of cytopathology

- **Indirect damage:** when certain viruses attack the placenta, they may spark a powerful immune response from the mother. Inflammation-triggering molecules spread from the infection, and some may end up in the fetus. Its tissues may then swell and become damaged, and may even die off (HSV).
- **Direct damage:** the virus infects fetuses very early in development, creating a bigger disruption to rapidly dividing cells as they give rise to the brain.

## Ionizing radiation

- Injures developing embryo due to cell death or chromosomal injury
- Dose dependent; stage of development
- 10-18 weeks: period of greatest sensitivity for developing brain
- Most Zika infections in pregnancy with adverse fetal effect occurred 7-13 weeks up to 18 weeks

## Microcephaly

- Clinical significance is small brain
- HC less than 2 or 3 SD below the mean
- 2 SD: 2.5% of population
- 3 SD: better correlation with MR
- Primary- arrest in brain development
- Secondary- acquired insult to the brain
- US Collaborative Perinatal Project: 1.6/1000 livebirths

## Microcephaly

- Little information is available on the intrauterine natural history of microcephaly
- Becomes more obvious in utero as gestation progresses
- Rarely made before third trimester
- Little is known about what occurs during 1<sup>st</sup> and 2<sup>nd</sup> trimesters
- CDC: <3% for gestational age

## Microcephaly

- 20-33% genetic
- Environmental: rubella, CMV, HSV, toxoplasmosis, VZ
- Drugs: EtOH, hydantoin, vitamin A, cocaine, methylmercury, solvents, CO, radiation
- Maternal PKU
- Isolated v. Extensive differential
- Initial case reports in Brazil implicate fetal brain disruption sequence in Zika

## How do viruses cause microcephaly?

- **CMV**- series of steps over weeks; CMV first infects the wall of the uterus. Then it moves to specific placental cells. From the placenta, the virus can travel into the amniotic sac, and then to the fetus itself.
- If cytomegalovirus reaches the fetus early in development, the infection can cause serious harm, especially to the brain. The fetus's immune system has barely developed at that point, while the brain is already growing rapidly.

## How do viruses cause microcephaly?

- Once cytomegalovirus enters the fetal brain, it waits for a few days. Only after the brain has begun to mature do the viruses start multiplying inside stem cells that will later give rise to neurons.

## Rubella

- 100 years ago, believed to be mild febrile illness
- Thought nasty rash was the worst part
- 1940's- Norman Gregg questioned surge of infants with congenital cataracts at Royal Alexandra Hospital in Sydney, Australia
- He found 90% of moms of sick babies had been infected with rubella during first trimester

## Rubella

- 1969- vaccine introduced
- 1964- worldwide pandemic: 12.5 million cases, 11,000 fetal deaths, 20,000 cases congenital rubella syndrome
- Vertical transmission thru hematogenous spread with viremia; 5-7d after inoculation
- Maternal blood → Placenta → Fetal vascular system  
cytopathic damage to blood vessels/ischemia results
- Two proposed mechanisms for cytopathology:  
viral-induced inhibition of cell division –and- direct cytopathic effect (apoptosis)
- 38-100% risk of infection in first trimester

## CMV

- 1-2% seroconvert in pregnancy
- #1 infectious disease causing microcephaly, developmental delay and birth defects in pregnancy
- 13% of affected babies will have syndrome
- As with rubella, adverse fetal effects in first trimester
- Both: sensorineural hearing loss, chorioretinitis, and neurologic effects including microcephaly and CP



## CMV

- Congenital CMV infection: 40,000 infants born yearly in USA
- Maternal transmission to fetus most common with primary maternal infection → anti-CMV Ab appear; virus becomes latent (periodic reactivation)
- Most common vertical transmission: virus infects placental cytotrophoblasts which then affect embryo/fetus- virus then replicates in multiple tissues
- Evidence to suggest transmission from maternal genital tract
- Rate of vertical transmission: 36.5%/40.1%/65%
- 16.4% 3weeks prior to conception to 3 weeks after

## Zika - Differential diagnosis

- Dengue, Zika, Chikungunya
- Seronegative Rheumatoid Arthritis, African Tick Bite Fever, enteric fever, leptospirosis, malaria, relapsing fever, Ross River virus, measles, Rubella, Epstein-Barr virus, Meningococcus
- Dengue and Zika have similar transmission cycles

## Dengue

- Vertical transmission has been reported *probably* with maternal infection within 10d of delivery up to 11d of life
- Pregnancy does not increase severity nor incidence of dengue. Does not appear to cross the placenta.
- Breastfeeding as mode of transmission is possible

## Chikungunya

- Nosocomial transmission reported
- Vertical transmission: 48% transmitted at time of delivery with maternal viremia
- CD: not protective
- No evidence of congenital infection

## **Zika - neurotoxicity**

- 1940's- animal studies revealed neural cell death
- Causal relationship cannot be proven with epidemiologic studies
- Cape Verde, 2015-2016: 7000 cases, no microcephaly
- One case-controlled study in French Polynesia with Guillain-Barre syndrome
- 41/42 cases had antibody to Zika compared to 35/98 controls; no association with dengue

Cao-Lormeau et al. Lancet. 29FEB2016

## **Guillain-Barre syndrome**

- French Polynesia case-control study
- OR >34 between GBS and prior Zika infection
- Acute motor axonal neuropathy subtype
- Meningoencephalitis and acute myelitis reported (French West Indies)

## **Zika neurotoxicity**

- Seen as intense neurotropic virus targeting neural progenitor cells and neuronal cells in all stages of maturity
- WHO: process to identify new congenital syndrome to define spectrum of clinical manifestations and neurological abnormalities
- Scope of syndrome will expand as further info and follow-up becomes available.

## **Fetal brain disruption sequence**

- Described in 1990 by Bonnemann & Meinecke
- Exogenous insult to developing brain
- Vascular or infectious: disrupts normal development
- Severe microcephaly, scalp rugae, overlapping cranial sutures

## Lancet

- Retrospective data 2013-15 in French Polynesia
- Serological and surveillance data to estimate probability of infection
- Used 2 SD; one perinatal center
- 66% population infected, 270,000 people
- 8 cases microcephaly
- 5 terminated 26-31 weeks; no testing!

Caucmeze, et al Lancet. 16MAR2016

## Zika-case reports

- 2 reported cases peripartum transmission (French Polynesia): one with thrombocytopenia and rash, one asymptomatic
- One case of transmission from monkey bite in Indonesia (could not r/o mosquito transmission)
- Transmission through breast milk not reported although virus has been found in breast milk in high titers
- Two laboratory infections have been reported

## Zika-case reports

- 2 cases Zika intrauterine infection with microcephaly, brain calcifications, abnormal CC, decreased brain parenchyma diagnosed in 3<sup>rd</sup> trimester
- 29 weeks with microcephaly, ventriculomegaly and calcifications after normal 14 and 20 week scans
- Prospective study: 12/42 women (29%) with Zika had US abnormalities with 7/42 (17%) microcephaly, cerebral atrophy, or brain calcifications

Oliveira Melo et al. US Obst Gynecol. 2016

Mikar et al. NEJM. 2016

Brasi et al. NEJM. 2016

## Zika-case reports

- Finnish woman on vacation in Mexico, Guatemala, and Belize in NOV2015 infected with Zika at 11 weeks
- 16-21 weeks: HC decreased from 47<sup>th</sup> to 24<sup>th</sup>%
- Findings: dilated ventricles, absent CSP suggesting ACC, no calcifications
- ToP at 21 weeks
- Autopsy: grossly normal fetus, no classic histologic features of viral encephalitis
- Viral load highest in brain, placenta and membranes and cord

## Zika-case reports

- PCR negative: parvo, HSV, toxo, HSV, CMV, varicella
- Maternal IgM negative for CMV, parvo, rubella, toxo
- Guatemalan strain- different than other Zika types

Driggers, et al. NEJM. 2016

## CDC: Zika is a teratogen

- Potential teratogens have been assessed based on Shepherd's criteria for "proof" of human teratogenicity to prove causality
- No flavivirus has ever been definitively shown to be teratogenic
- Shepherd's criteria have been used in teratogen litigation as well as to assess other teratogens

## Shepherd's criteria

1. Proven exposure to agent at one or more critical times during prenatal development
2. Consistent findings by  $\geq 2$  high-quality epidemiologic studies, controlling bias/confounders, sufficient numbers
3. Careful delineation of clinical cases; a specific defect or syndrome is helpful if present
4. Rare environmental exposure that is associated with a rare defect

## Shepherd's criteria

5. Teratogenicity in experimental animals is important but not essential
6. Biologically plausible
7. Proof in an experimental system that an agent acts in an unaltered state

### **Evaluation and management of pregnant women**

- Test pregnant women with clinical illness suggestive of Zika during or within two weeks of travel using Zika PCR and IgM
- For women without clinical illness during or within two weeks of travel: offer Zika IgM 2-12 weeks after travel
- In endemic area: asymptomatic pts should be offered IgM at first visit and again in late second trimester

### **Evaluation and management of pregnant women**

- Fetal evaluation consists of US, preferably at 18-20 weeks
- Targeted: intracranial calcifications, microcephaly and brain abnormalities
- Serial scans for maternal infection or inconclusive findings
- CDC: negative IgM at 12 weeks after travel may not r/o disease but may eliminate need for serial US

## **Summary**

- Prevention, prevention, prevention, because...
- We just don't know yet
- Brazil is the key; possibly Columbia
- Don't let the media replace good medicine
- It will be years until we have good answers