

Unexpected Arrivals !

Shruti Patel

Infectious Diseases Fellow

Wright State University

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

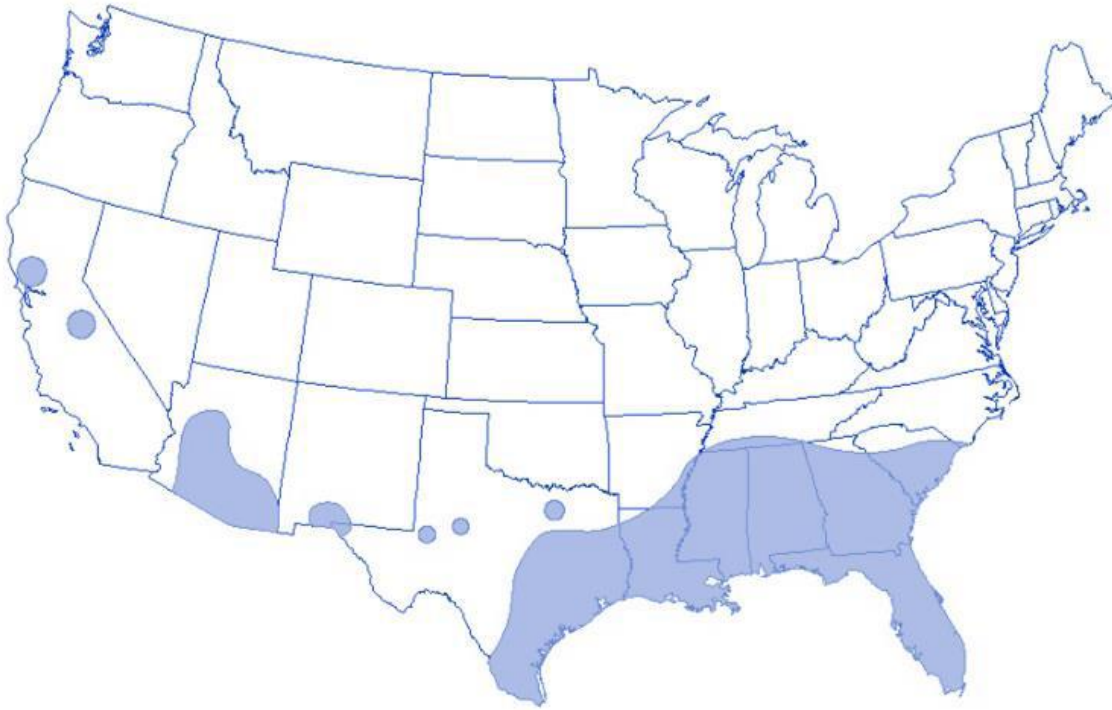


Aedes aegypti

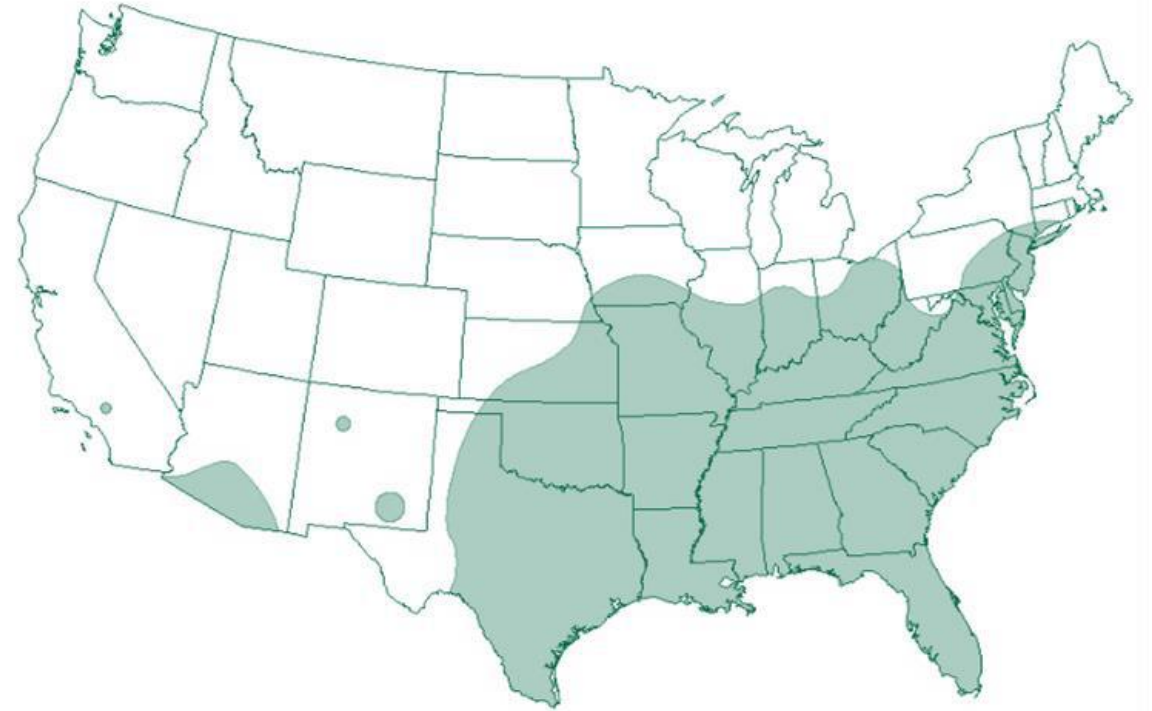


Aedes albopictus

Distribution of *Aedes* spp. Mosquitoes in United States



Aedes aegypti

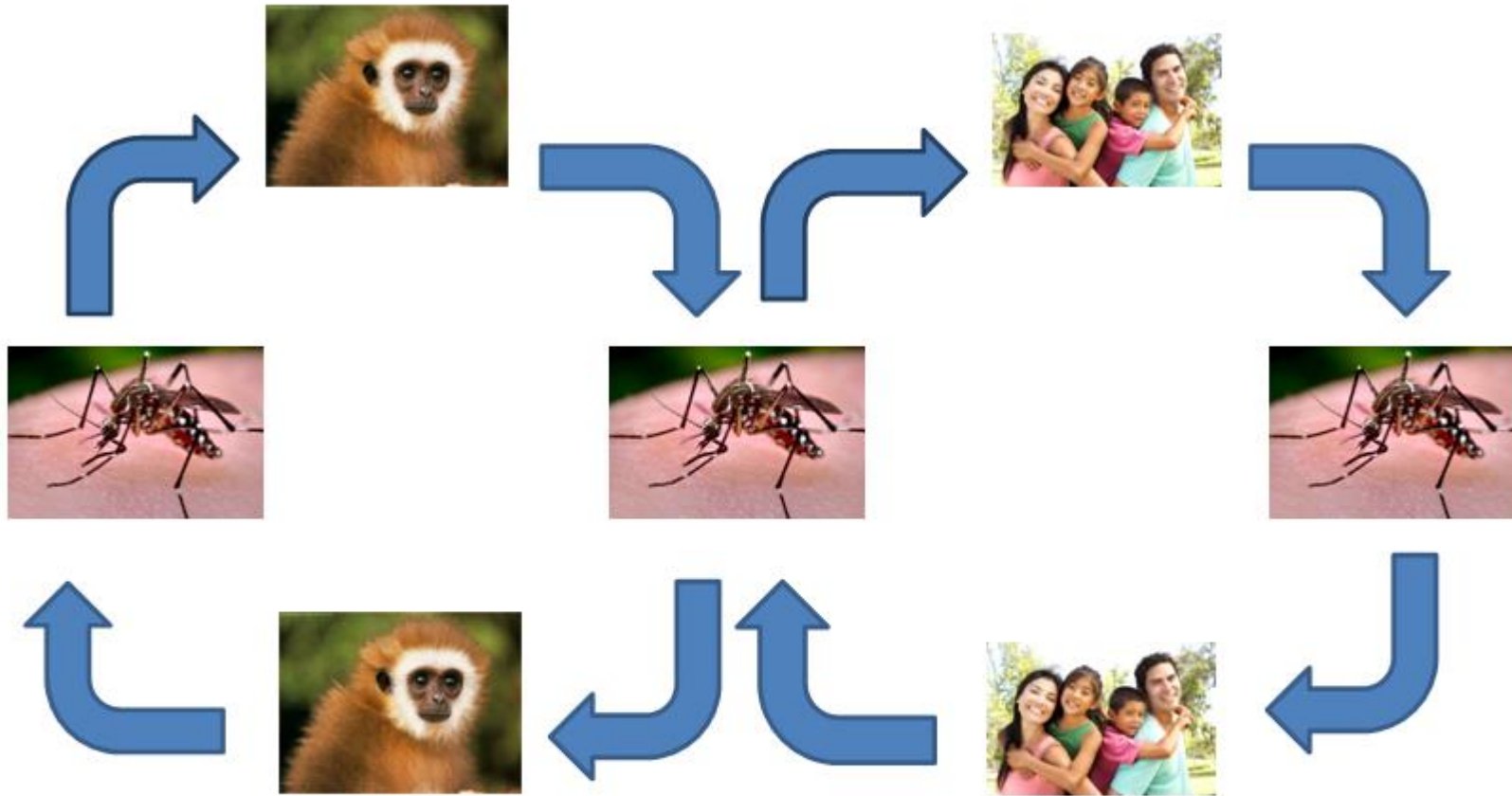


Aedes albopictus

Transmission

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

Transmission Cycle



Jungle Cycle

Urban Cycle

Epidemiology

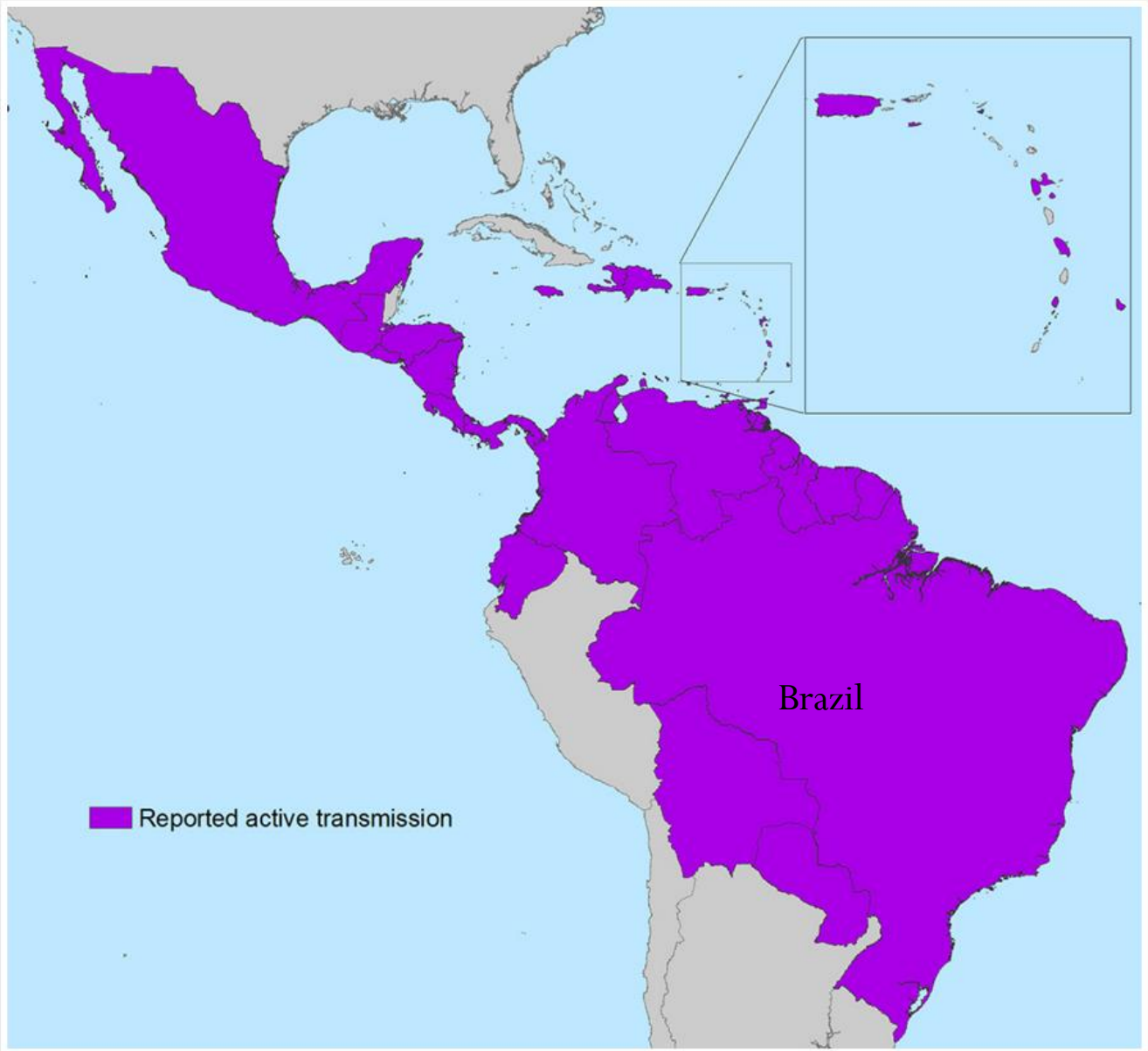
- First discovered from a monkey in the Zika Forest, Uganda in 1947
- It was confined to only Africa and south east Asia until 2007
- (14 cases)
- First locally acquired case in western hemisphere in Easter Island in 2014
- Now locally acquired cases in South America, Central America, the Caribbean, Mexico, and the US territory of Puerto Rico.

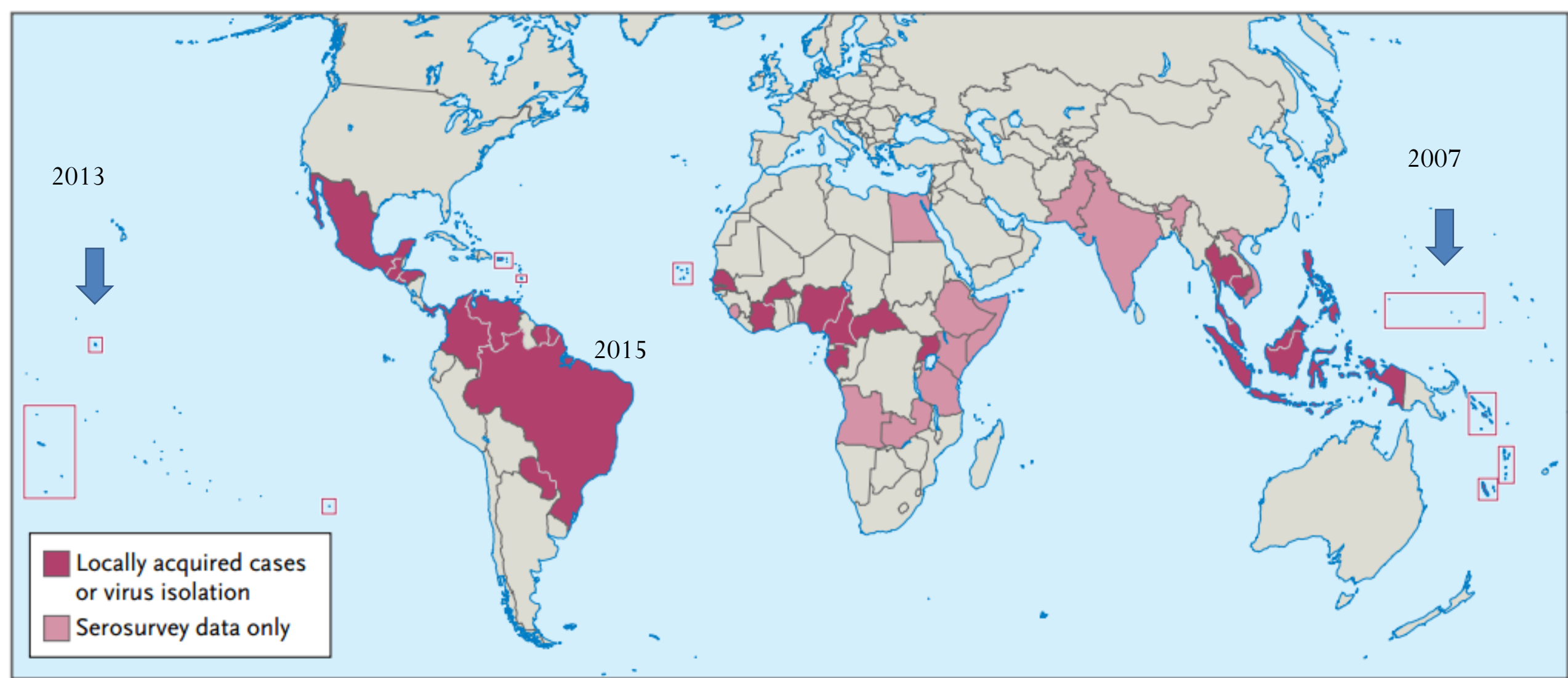
Figure 2. Countries with reported confirmed autochthonous cases of Zika virus infection in 2015, as of 4 December

- EU/EEA Member States, including outermost regions
- Other countries and territories
- ▨ Affected countries
- Maritime zone for non-visible affected areas
- Maritime zone for non-visible not affected areas



Countries with Active Transmission of Zika Virus





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)
- Febuary 2016:Cabo verde – 7081 cases (No neurological complications)

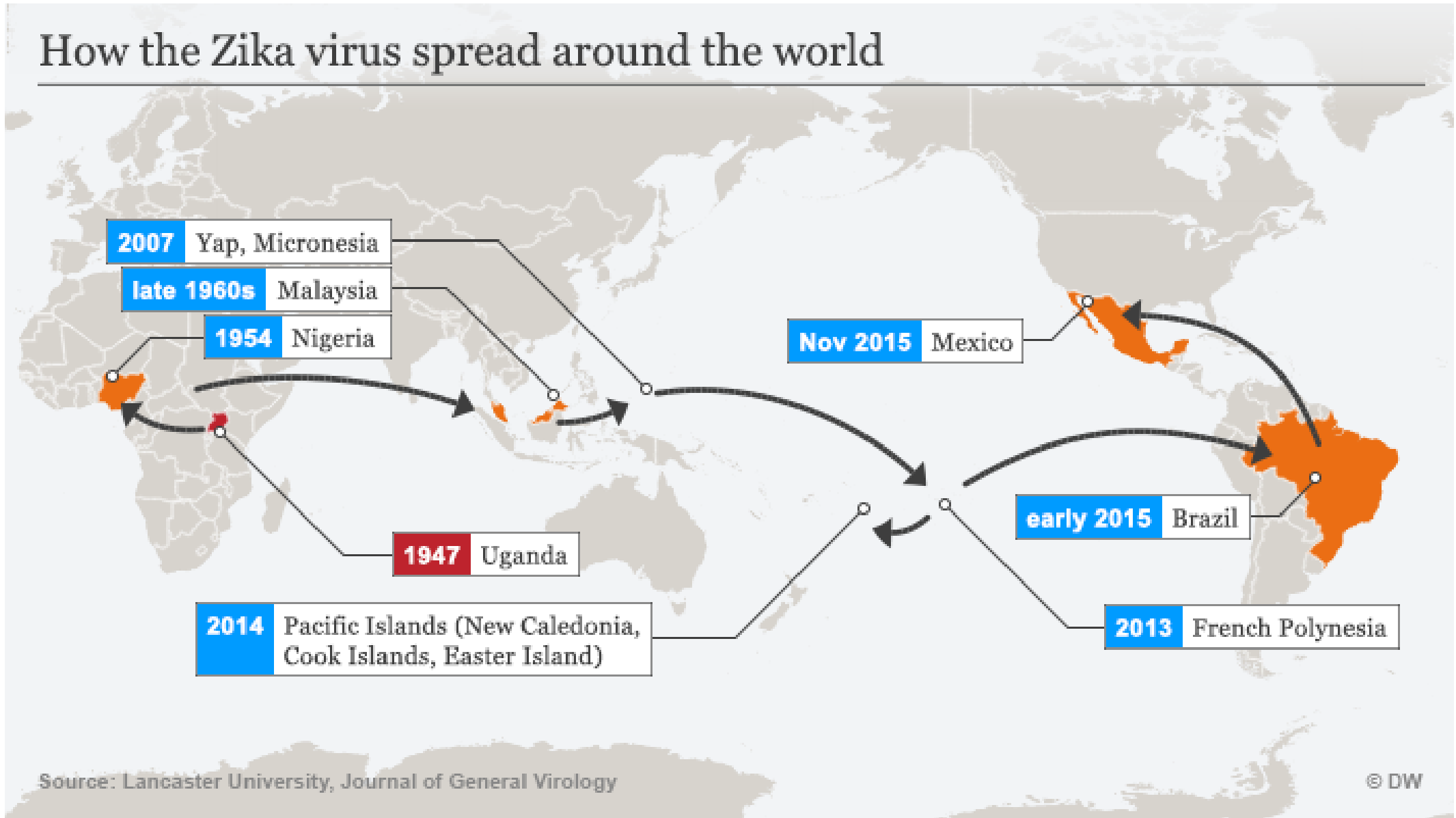
Figure 1. The temporal and geographical distribution of Zika virus from 1947 to February 2016. Dates refer to events reported in the published literature (cited in the text), or drawn from WHO's Event Information Site (EIS).

Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)



Outbreaks

How the Zika virus spread around the world



Dengue, chikungunya and Zika and mass gatherings: What happened in Brazil, 2014

Travel Medicine and Infectious Disease (2015) xx, 1–2



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.



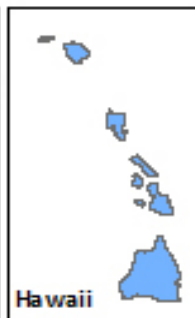
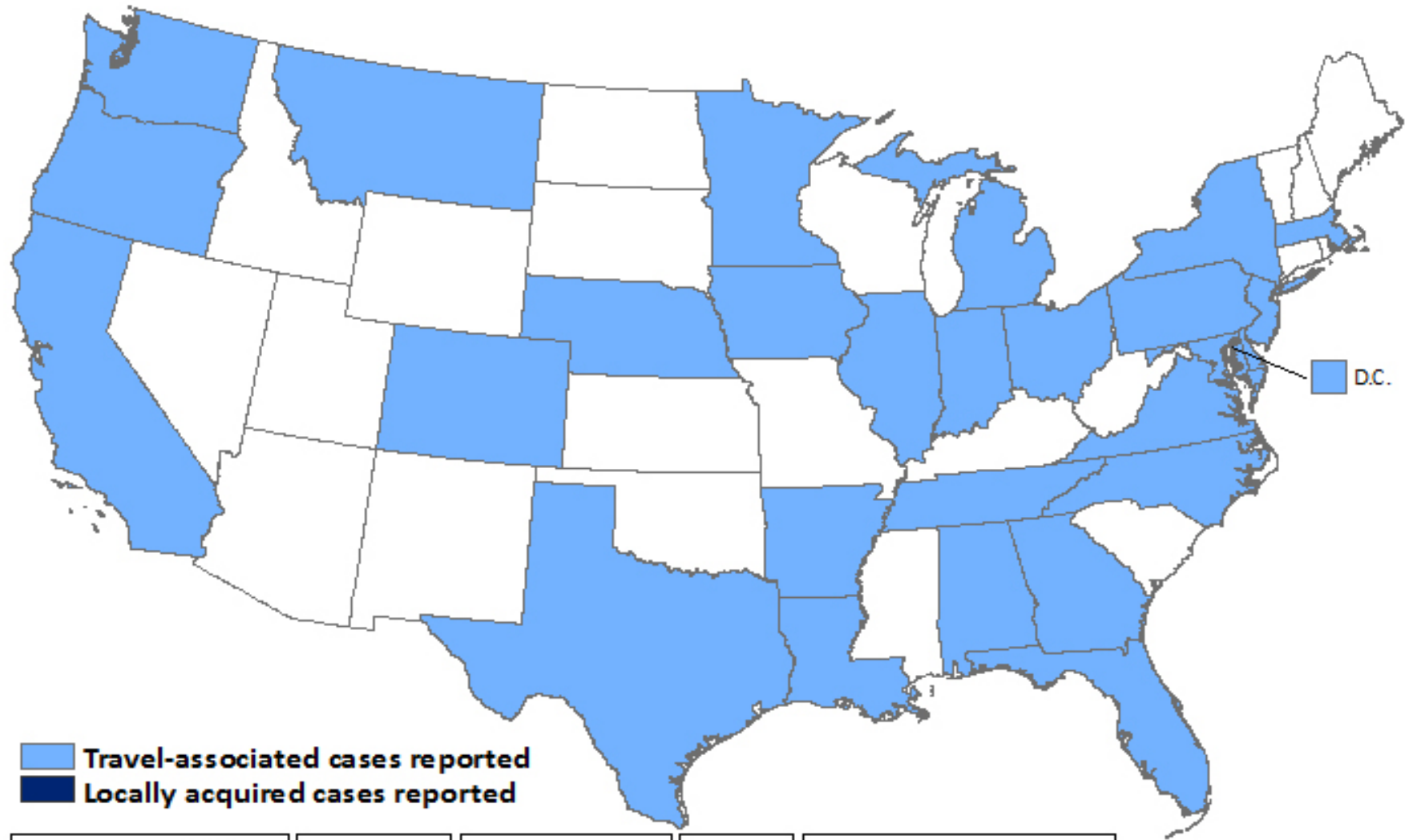
Zika virus in united states

- **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

Note: Rates based on serosurvey on Yap Island, 2007 (population 7,391) Duffy M. N Engl J Med 2009

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

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-

Why is Zika virus important ?

- Possible association with Microcephaly in infants and implications in pregnant women
- Complications like Guillian-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

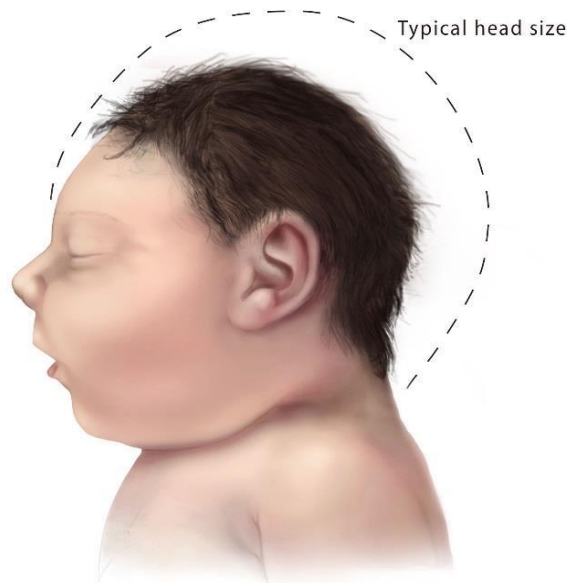
(Centers for Disease Control and Prevention, *CDC Health Advisory: Recognizing, Managing, and Reporting Zika Virus Infections in Travelers Returning from Central America, South America, the Caribbean and Mexico*, 2016. Besnard, M., et al., Evidence of Perinatal Transmission of Zika Virus, French Polynesia, December 2013 and February 2014. *Euro Surveill*, 2014. 19(14): p. 1-5. Oliveira Melo, A., et al., Zika Virus Intrauterine Infection Causes Fetal Brain Abnormality and Microcephaly: Tip of the Iceberg? *Ultrasound in Obstetrics & Gynecology*, 2016. 47(1): p. 6-7.)

Zika Virus and Microcephaly

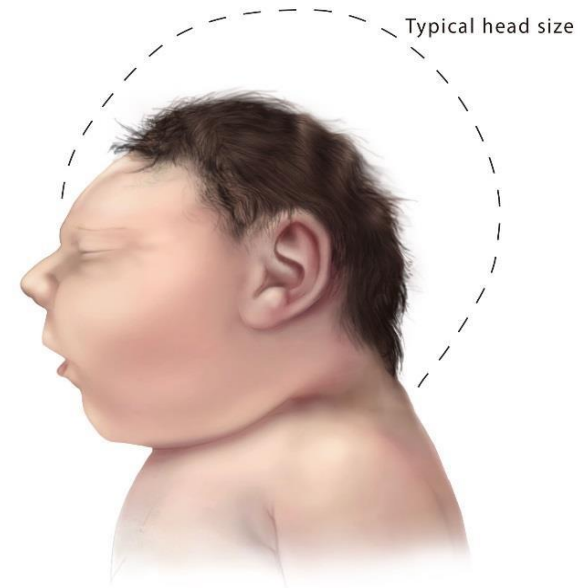
- Clinical findings of small head circumference in infants compared to same sex and age
- Lead to cognitive and neurological issues



Baby with Typical Head Size



Baby with Microcephaly



Baby with Severe Microcephaly

Etiology of Microcephaly

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

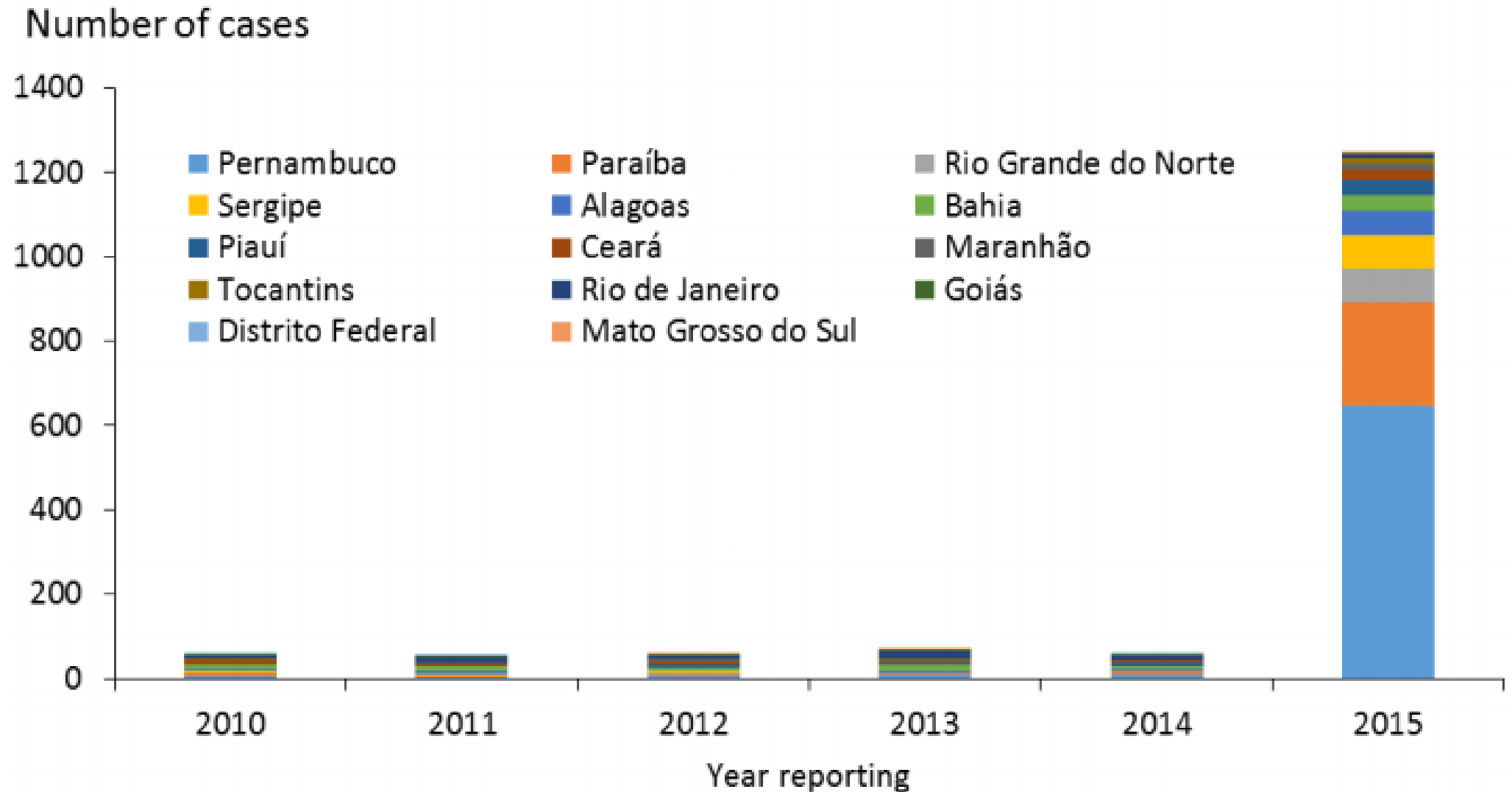
Outbreaks in Brazil

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/MS – 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



Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study

- 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

Feb 10, 2016

Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D.,
Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc.,
Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D.,
Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D.,
Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

- 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, enteroviruse, Toxoplasma, rubella, lymphocytic choriomeningitis
- ZIKV genome sequence showed identity (99.7%) with strain isolated from patient from French Polynesia in 2013.

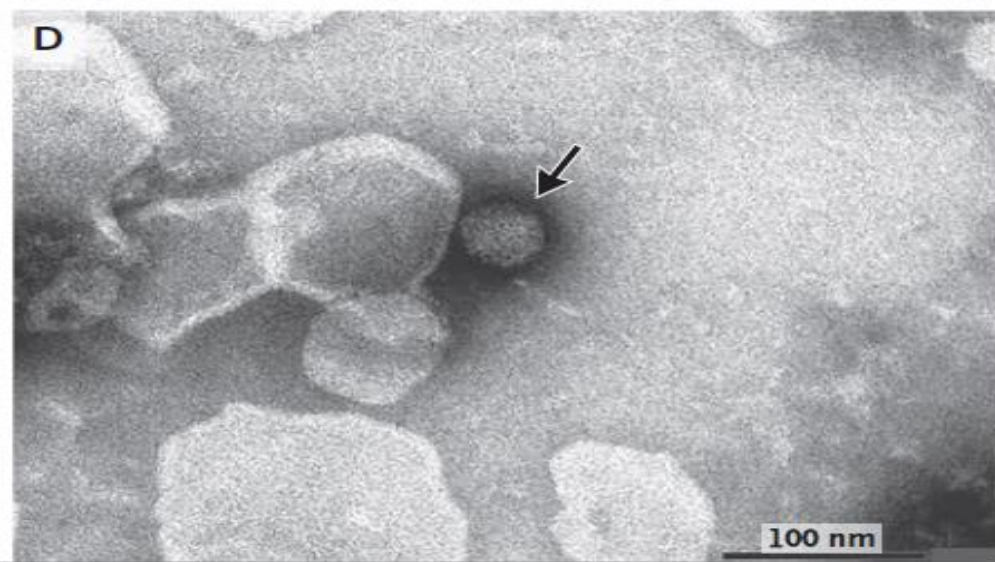
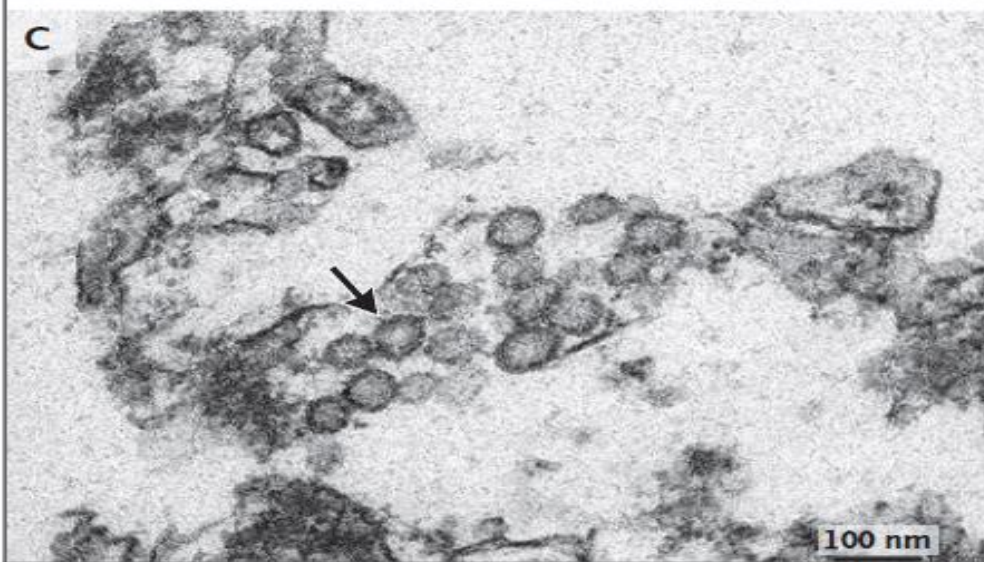
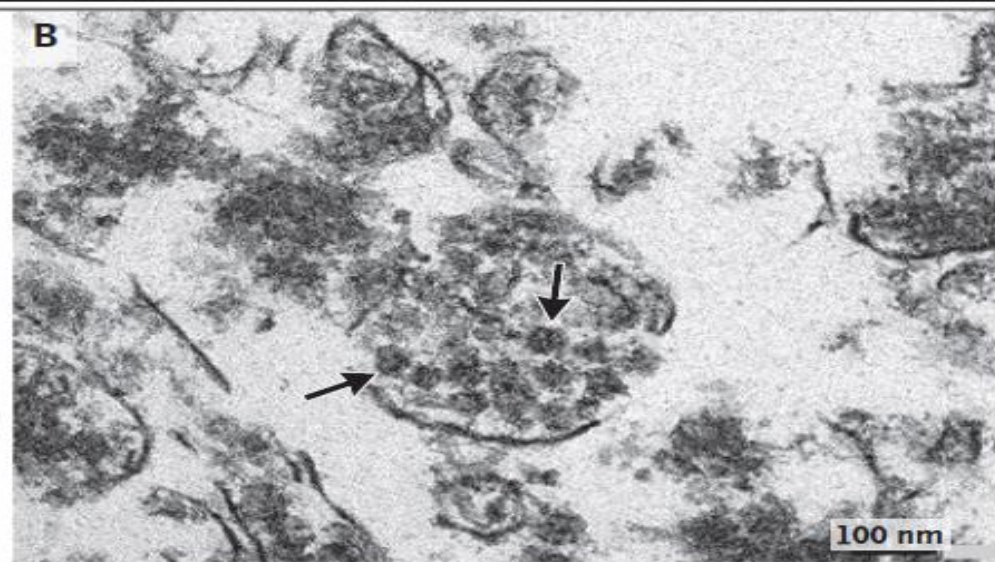
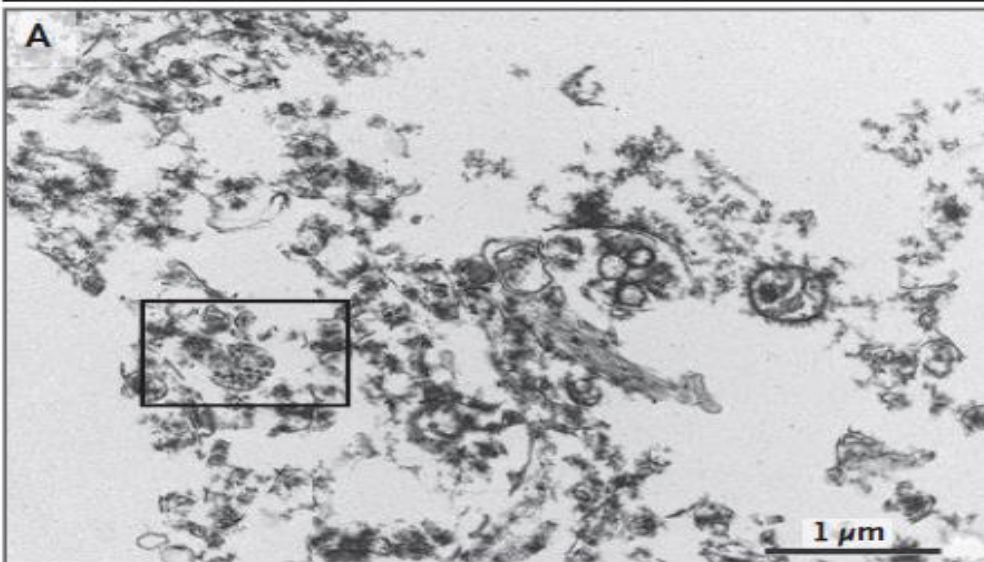


Figure 3. Electron Microscopy of Ultrathin Sections of Fetal Brain and Staining of a Flavivirus-like Particle.

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).

Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses — Brazil, 2015



Weekly / February 19, 2016 / 65(06):159–160

- 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

Guillain-Barre Syndrome

- French Polynesia outbreak : 8750 suspected cases, 383 PCR confirmed cases , Coincided with a dengue outbreak
 - 42 Guillain-Barre syndrome
- Brazil outbreak: 1708 cases of Guillain Barre syndrome Simultaneous outbreaks of CHIKV and Dengue
- El salvador in one month – 46 cases of Guillain Barre syndrome

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuquerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché**

THE LANCET

Available online 2 March 2016
In Press, Corrected Proof — Note to users

- First study to confirm link between Zika virus infection and Guillian 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 Areas With Ongoing Zika Virus Transmission

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 IG-M antibodies

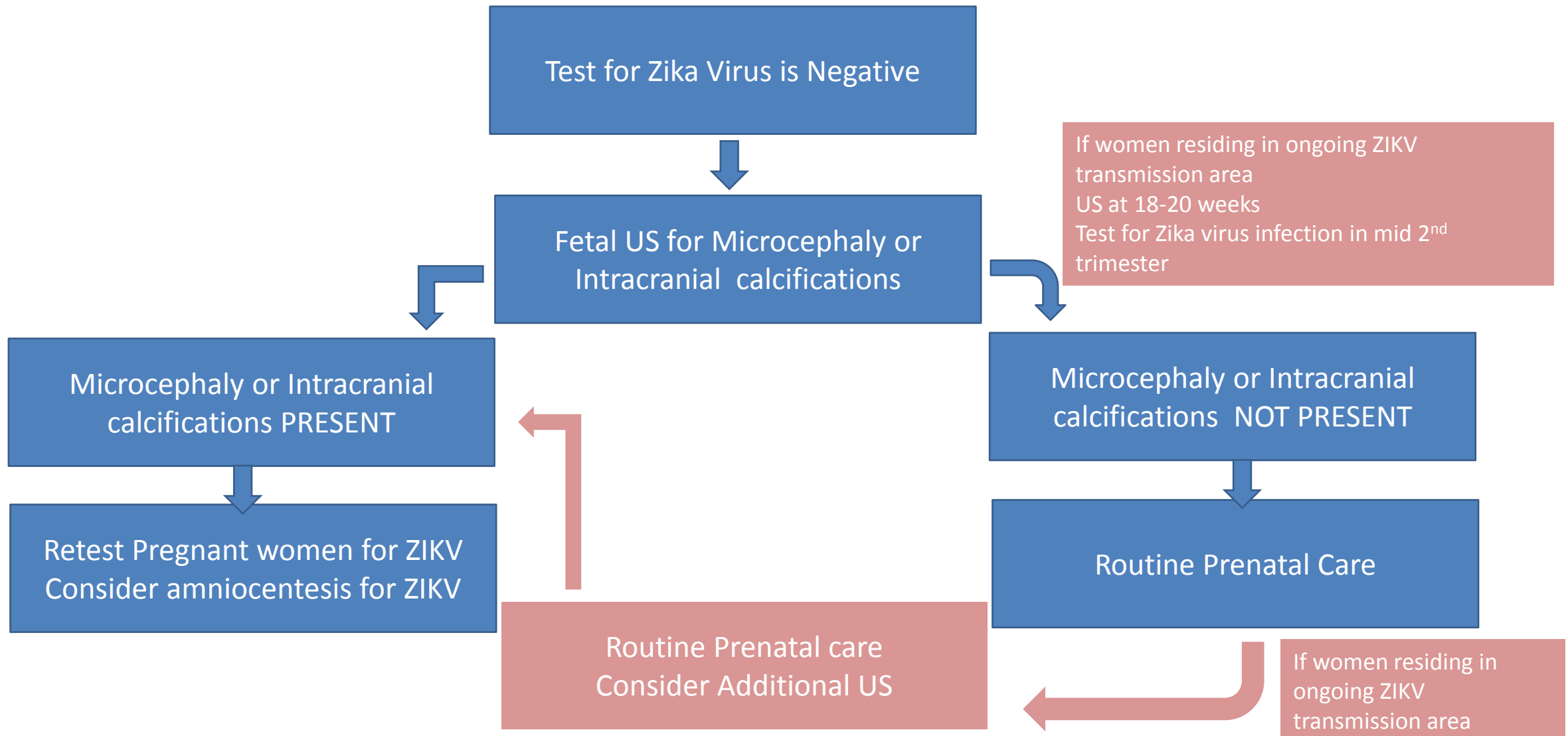
Positive or inconclusive for Zika Virus infection

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

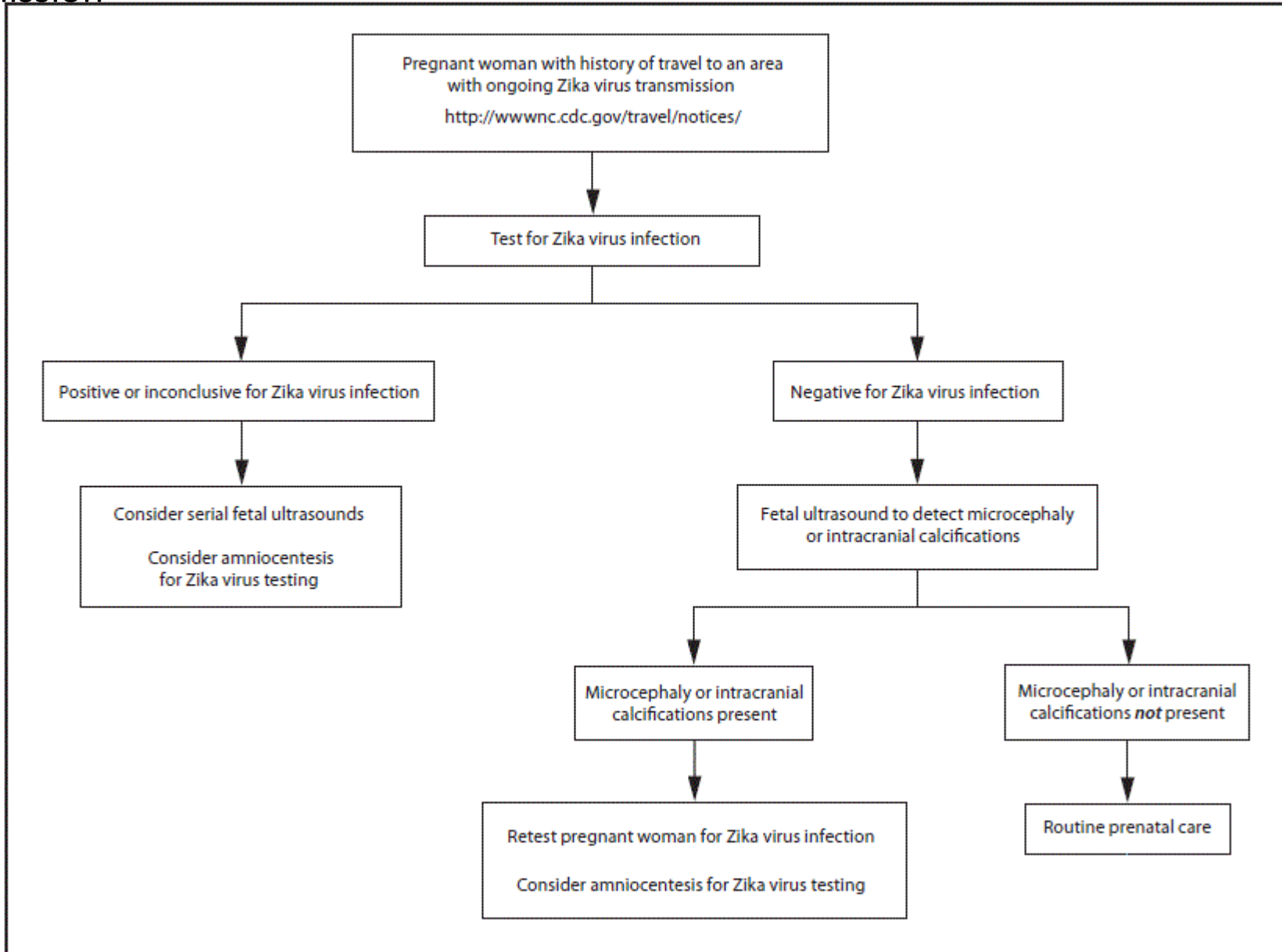
Symptomatic:
2 or more of following symptoms:
Fever, Rash, Arthralgia, conjunctivitis

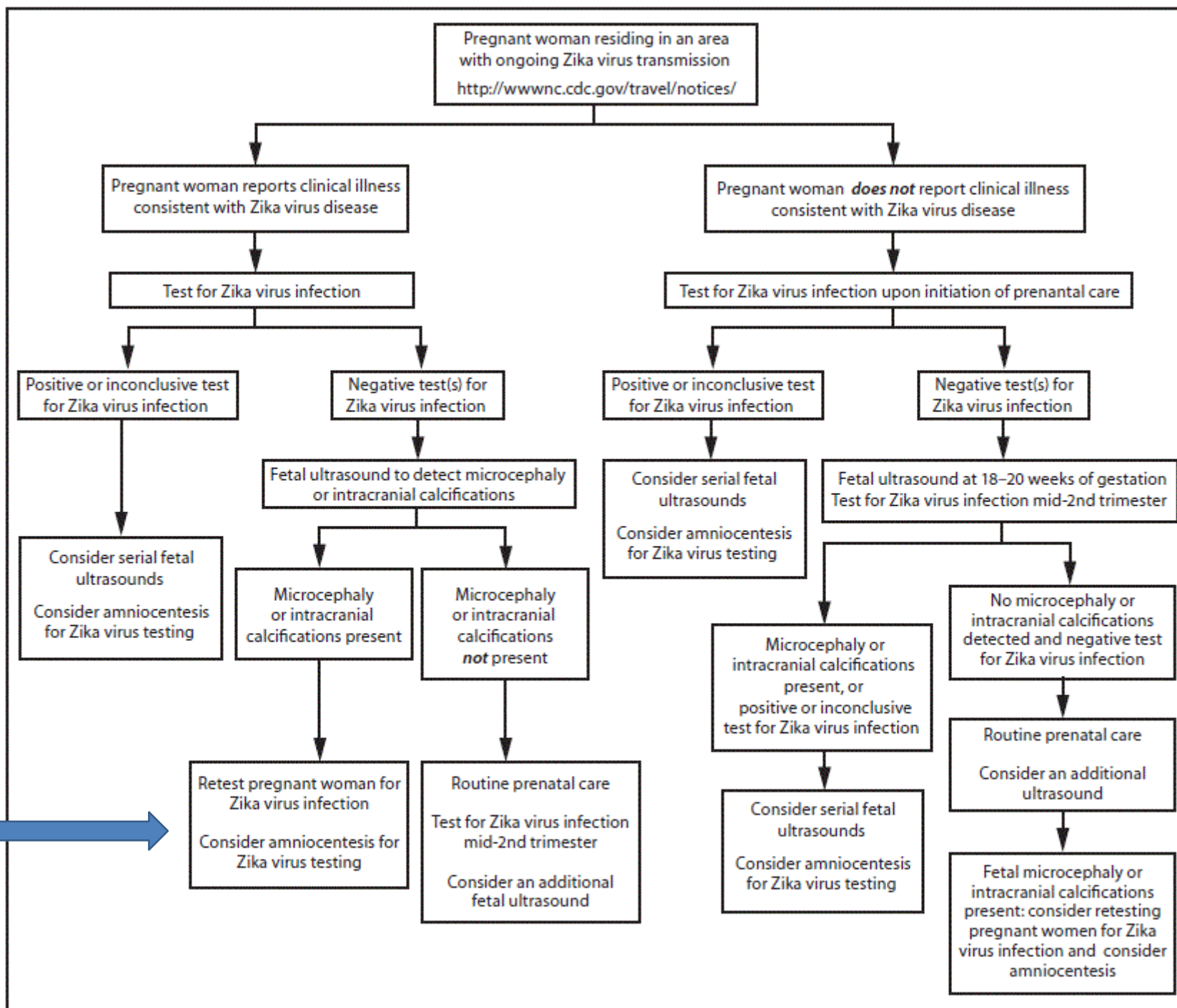
Pregnant women With **History Of Travel or Residing in Areas** With Ongoing Zika Virus Transmission





Guidelines for Pregnant women with history of Travel to an area with ongoing Zika Virus Transmission





Evaluation of Pregnant female residing in Area with Ongoing Zika Transmission

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



**Update: Interim Guidelines for Healthcare Providers
Caring for Infants and Children with Possible Zika
Virus Infection — United States, February 2016**

Infants whose mother travelled to resided in an area with ongoing Zika virus transmission during Pregnancy

Microcephaly or intracranial calcification detected prenatally or at birth

No microcephaly or birth defect but Mother with positive or inconclusive ZIKV infection

Thorough physical exam and perform Zika Virus testing in infant
RT-PCR, IgM, IgG, Neutrizing 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

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.

Centers for Disease Control and Prevention



Update: Interim Guidelines for Prevention of Sexual Transmission of Zika Virus – United States, 2016

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 exists 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**

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- 3: Martines RB, Bhatnagar J, Keating MK, Silva-Flannery L, Muehlenbachs A, Gary J, Goldsmith C, Hale G, Ritter J, Rollin D, Shieh WJ, Luz KG, Ramos AM, Davi HP, Kleber de Oliveria W, Lanciotti R, Lambert A, Zaki S. Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses - Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. 2016 Feb 19;65(6):159-60.
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