The Buzz on Zika:
An Update for Clinicians

March of Dimes 17th Annual Birth Conference
March 13, 2017

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Aedes aegypti

Probable Origin and Spread

- 1st discovered in Zika Forest in Uganda in 1947
  - Since then, seen in some African and Asian countries
  - Early 2000s, large outbreak in Micronesia (Yap Island): estimated 75% of all inhabitants > age 3 were infected
  - Large outbreak 2013-14 in French Polynesia, > 28K infected (11% of population), and spread to neighboring islands
- Most recently, large outbreak in NE Brazil
  - Researchers think it may be related to large intl. sporting events in Brazil: imported by travelers from Asia
  - "Perfect storm" where the vector mosquitoes also found
- Since then, the virus has spread across South and Central America, including Mexico and Puerto Rico

2015 Zika Virus Epidemic in Brazil

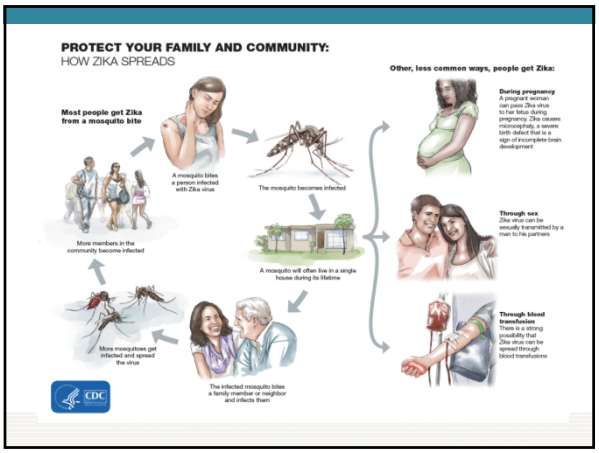
- In early 2015, health authorities in Natal, state of Rio Grande do Norte noted the presence of a syndrome similar to dengue in the population. The serologic assays were negative for dengue and Chikungunya Fever. In March 2015, the Oswaldo Cruz Institute identified Zika Virus from blood specimens. Sequencing of the virus demonstrated it originated in the South Pacific.

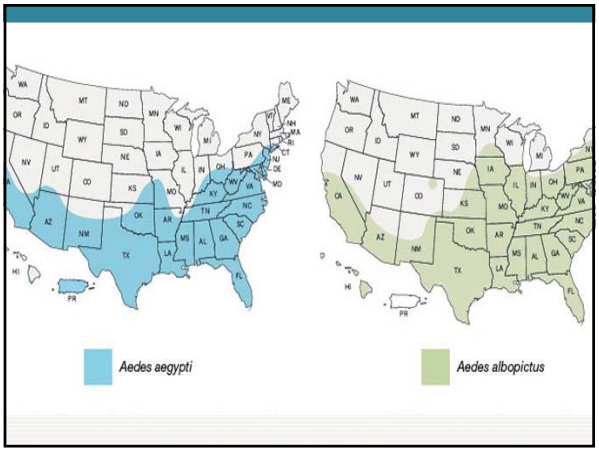
The virus was potentially introduced by tourists from the French Polynesia attending the World Cup Soccer Event in Brazil in July 2014

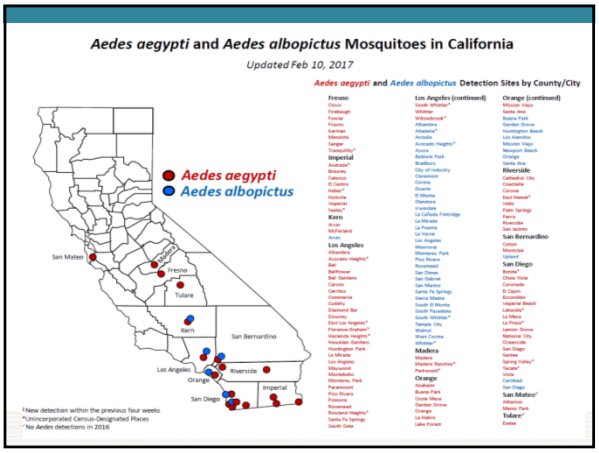
Or the Va'a Canoe event held in Rio in August 2014

Background

- Zika virus is transmitted to humans primarily through the bite of infected *Aedes* mosquito
  - Nearly all Zika outbreaks due to *aegypti* & *albopictus*
  - These are the same mosquitoes that transmit dengue and chikungunya ---all are arboviruses
    - Zika and dengue are ***flaviviruses*** – also yellow fever, West Nile, HCV (chikungunya – alphavirus)
  - The mosquito vectors typically breed in domestic water-holding containers
  - *Aegypti* -- feeds primarily on humans, multiple humans in a single meal, lives close to humans , also daytime and nighttime feeders


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
A mosquito will often live in a single house during its lifetime
The infected mosquito bites a family member or neighbor and infects them
More mosquitoes get infected and spread the virus
More members in the community become infected
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
CDC


Aedes aegypti
Aedes albopictus

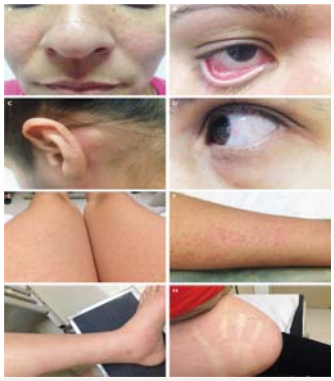

Aedes aegypti and Aedes albopictus Mosquitoes in California
Updated Feb 10, 2017
Aedes aegypti and Aedes albopictus Detection Sites by County/City
Aedes aegypti
Aedes albopictus
San Mateo
Fresno
Tulare
Kern
San Bernardino
Los Angeles
Riverside
Orange
San Diego
Imperial
¹New detection within the previous four weeks
²Unincorporated Census-Designated Places
³No Aedes detections in 2016

Zika – Disease and Risks

Clinical Disease

- About 20% of people infected with Zika virus become symptomatic
- Among those with clinical illness
  - Symptoms mild, typically develop within 1 week from exposure, lasting several days to a week
  - Characteristic clinical findings: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis.
  - Severe disease requiring hospitalization is uncommon and fatalities are rare.
- Guillain-Barré syndrome also has been reported at increased rates in patients following Zika infection

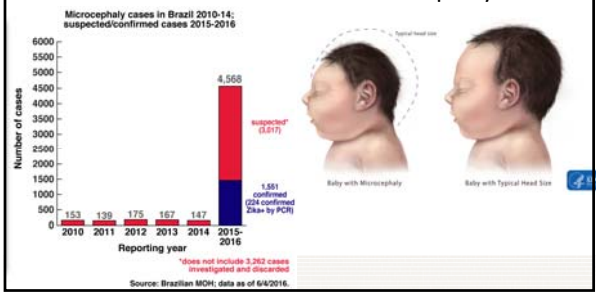
Clinical Features of Zika Virus Infection in Pregnant Women.



Brasil P et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1602412

Brazil Zika Outbreak

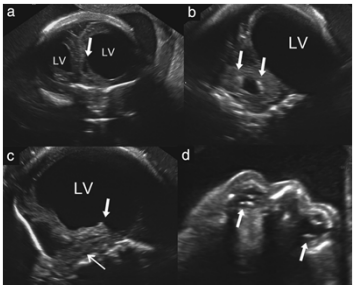
- May 2015: First infection in Brazil
- October 2015: increase in microcephaly



Microcephaly: the ***most apparent*** marker?

- Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in ***newborns***
  - On ultrasound, typically defined as **HC < 3rd %ile** for GA
- Microcephaly became an ***early trigger*** to search for Zika association, but spectrum of disease became apparent
  - Microcephaly can occur as a result of a **fetal brain disruption sequence**: this appears to be pathology of Zika infection

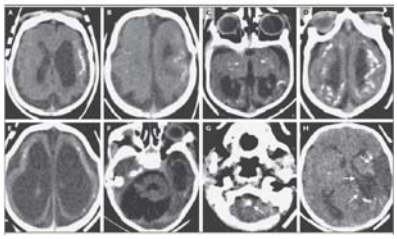
Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?



Ultrasound in Obstetrics & Gynecology
Volume 47, Issue 1, pages 6-7, 5 JAN 2016 DOI: 10.1002/uog.15831
http://onlinelibrary.wiley.com/doi/10.1002/uog.15831/full#uog15831-fig-0002

CT Scans Reveal Extensive Abnormalities

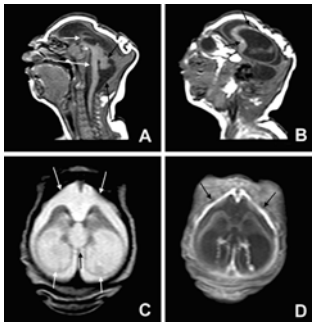
23 infants with microcephaly in Pernambuco, Brazil



- Intracranial calcifications
- Global cortical hypogyration
- Ventriculomegaly
- Global cerebellar hypoplasia

Hazin *et al*, *NEJM* April 6, 2016

Fig 3 Severe microcephaly.

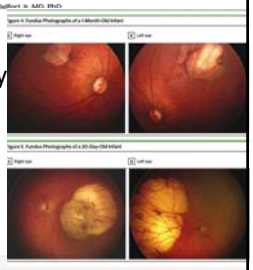


Maria de Fatima Vasco Aragao et al. BMJ 2016;353:bmj.i1901

Original Investigation

Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil

Bruno de Paula Freitas, MD; João Rafael de Oliveira Dias, MD; Juliana Prazeres, MD; Gielson Almeida Sacramento, BS; Albert Ichisang Ko, MD; Mauricio Maia, MD, PhD; Rubens Belfort Jr, MD, PhD



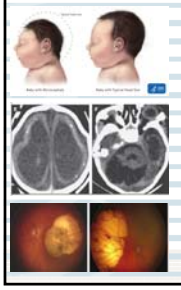
- 29 infants with microcephaly
  - 79% with suspected Zika
    - 18 in first trimester
  - 29% with ocular findings
    - Bilateral macular and perimacular lesions
    - Optic nerve abnormalities

Freitas et al, JAMA Ophthalmology online 2/9/16

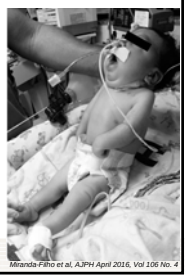
Fetal Brain Anomalies

- Microcephaly
- Hydrocephalus/hydranencephaly
- Absent structures: (CC, pons, cerebellar vermis)
- Neuronal migration disorders (lissencephaly)
- Fetal brain disruption sequence
- Cerebral calcifications
- Brain asymmetry

Zika Associated Pregnancy Outcomes



- Fetal loss/miscarriage, stillbirth
- Fetal growth abnormalities
- Fetal brain anomalies
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures
  - Neurobehavioral anomalies



Miranda-Filho et al, AJPH April 2016, Vol 106 No. 4

Surveillance and Registry Risk Estimates

- Retrospective data analysis to estimate week-by-week probability of infection (pts not ID'd prospectively) [1]
  - Birth data (n =4000) among total population (270K) compared to data from 3 Zika serosurveys (Pacific): 1200 subjects (not pregnant)
  - **"Best-fit"risk with infection in 1st trimester: 95/10,000 (1%)**
    - **Baseline 2/10,000 --- RR for 1st tri: 53.4 (6.5-1061.2); p=0.0007**
    - BUT: also with 2nd trimester: 23.2 (1.4-408); p=0.02
- Recent report from US Zika Pregnancy Registry (n = 442)
  - Birth defects related to Zika in 26 (6%), 21 in live births
  - No risk difference regarding sx; 11% risk if exposure in 1st Δ
  - As registry, selection bias possible, and Δ exposure not "pure"

1. Cauchemez S et al, Lancet 3/15/16 2. Honein M et al, JAMA 12/13/16

Prospective NEJM series, Brazil: Background

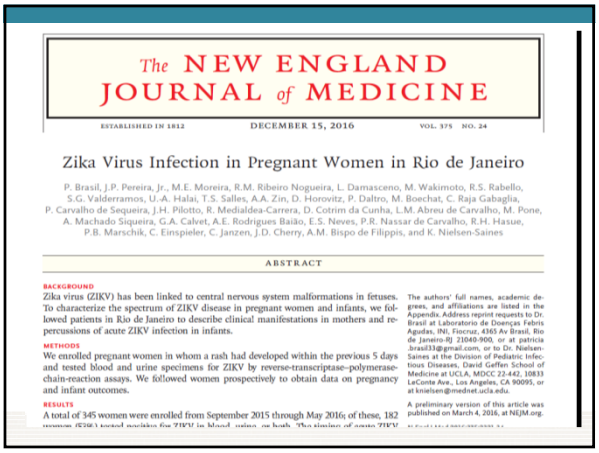
- Brazil group had been conducting surveillance for dengue in population of Rio de Janeiro since 2007
  - In 2015, noted increase in dengue-like illness with rash, coinciding with surge of similar cases in NE Brazil → ID as Zika
- Study cohort: 88 symptomatic pregnant women (9/15-2/16)
  - 82% (72/88) tested positive for ZIKV (PCR) in blood, urine, or both
  - Serial U/S done: 20-30+ weeks
  - Timing of infection: 5-38 weeks of gestation

Brasil P, et al. NEJM, online 3/4/16

Prospective NEJM series, Brazil: Results

- Of 72 women with PCR-positive test results
  - > 50% reported an ill family member; **21%: partner had been ill**
- 2 women miscarried in 1st Δ; 42 (60%) of others had u/s
  - 28 women declined u/s: either too far or fear of finding anomalies
- **Abnormal u/s results seen in 12/42 (29%) pts with Zika infx**
  - No abnormalities seen in any of the 16 Zika-negative women
  - IUGR in 5/12 fetuses (42%), with or without microcephaly
  - Cerebral calcifications in 4/12, other CNS anomalies in 2 fetuses
  - 2 IUFDs @ 30 and 38 wks: women infected at 25 and 32 wks

Brasil P, et al. NEJM, online 3/4/16



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2016 VOL. 375 NO. 24

Zika Virus Infection in Pregnant Women in Rio de Janeiro

P. Brasil, J.P. Pereira, Jr., M.E. Moreira, R.M. Ribeiro Nogueira, L. Damasceno, M. Wakimoto, R.S. Rabello, S.G. Valderramos, U.A. Halai, T.S. Salles, A.A. Zin, D. Horovitz, P. Daltro, M. Boechat, C. Raja Gabaglia, P. Carvalho de Sequeira, J.H. Pilotto, R. Medialdea-Carrera, D. Cotrim da Cunha, L.M. Abreu de Carvalho, M. Pone, A. Machado Siqueira, G.A. Calvet, A.E. Rodrigues Baião, E.S. Neves, P.R. Nassar de Carvalho, R.H. Hasue, P.B. Marschik, C. Einspieler, C. Janzen, J.D. Cherry, A.M. Bispo de Filippis, and K. Nielsen-Saines

ABSTRACT

BACKGROUND

Zika virus (ZIKV) has been linked to central nervous system malformations in fetuses. To characterize the spectrum of ZIKV disease in pregnant women and infants, we followed patients in Rio de Janeiro to describe clinical manifestations in mothers and repercussions of acute ZIKV infection in infants.

METHODS

We enrolled pregnant women in whom a rash had developed within the previous 5 days and tested blood and urine specimens for ZIKV by reverse-transcriptase–polymerase-chain-reaction assays. We followed women prospectively to obtain data on pregnancy and infant outcomes.

RESULTS

A total of 345 women were enrolled from September 2015 through May 2016; of these, 182

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brasil at Laboratorio de Doenças Febris Agudas, INI, Fiocruz, 4365 Av Brasil, Rio de Janeiro-RJ 21040-900, or at patricia.brasil31@gmail.com, or to Dr. Nielsen-Saines at the Division of Pediatric Infectious Diseases, David Geffen School of Medicine at UCLA, MDCC 22-442, 10833 LeConte Ave., Los Angeles, CA 90095, or at knielsen@mednet.ucla.edu.

A preliminary version of this article was published on March 4, 2016, at NEJM.org.

Study Overview

- Final report updates preliminary data on ZKV infection among pregnant women in Rio de Janeiro
  - Expands study cohort from 88 to 134 symptomatic women with confirmed ZKV infection
  - Fetal loss and OB complication rates and similar for Zika (+) and (-) groups (~7% and 35% respectively)
  - ZKV (+) women 10X more likely to have c/s for fetal distress and 4X more likely to need neo critical care after birth
  - Microcephaly in 4 infants: infections at 8, 12, 30, 38 weeks
  - Overall, 49/117 (42%) liveborn ZKV-exposed infants had abnormal findings in 1st month of life [5% in ZKV(-): p< 0.001]
- Adverse outcomes seen regardless of trimester of infx
  - 55% risk if maternal infx in 1st, 52% if in 2nd, 29% if in 3rd

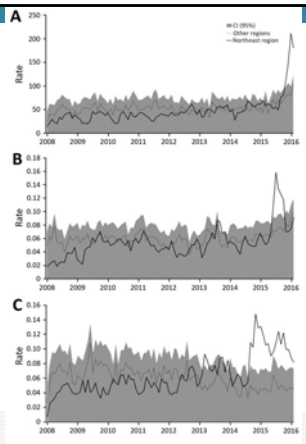
Ultrasound Findings *(supplemental data)*

- Of 58 abnormal pregnancy outcomes in ZKV (+) women
  - 9 fetal deaths: 6 in 1st trimester, 3 at 21, 36, 38 weeks
  - Of 49 surviving affected newborns, 27 (55%) had prenatal scans, with only 9/27 (33%) showing abnormalities
  - Many affected newborns with reported normal (or no) scans had functional not structural abnormalities (posturing or abnormal MRI)
- Among prenatal u/s abnormalities
  - 4/9: microcephaly +/- other anomalies
  - 1 cerebellar atrophy
  - 2 ventriculomegaly +/- calcifications
  - 1 calcifications only
  - 1 IUGR only

Increased Hospitalizations for Neuropathies in Brazil

- Recent study reported on rates of hospital admissions in Brazil for pediatric/congenital neurologic issues
  - Tracked hospital records by ICD-10 coding for "congenital malformations of the nervous system" from 1/08-2/16
- Stable mean rate until Nov 2015, when increase seen from 40 to 170 hospitalizations /100,000 live births
  - RR 4.2 (95% CI 3.8-4.6)
- Significant increases seen not just in malformations but for encephalitis, myelitis, and encephalomyelitis as well

Barcellos C et al. Emerg Infect Dis Nov 2016, online (MMWR) Sept 2016



A. Congenital malformations of nervous system per 100,00 live births

B. Guillain-Barre syndrome per 100,000 residents

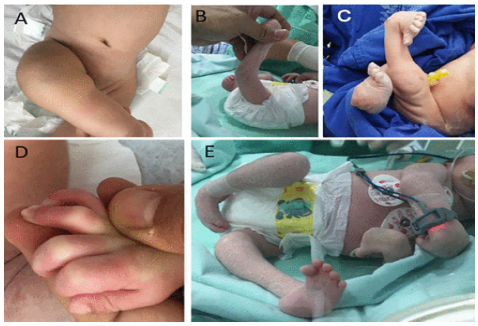
C. Encephalitis, myeleitis, encephalomyelitis per 100,000 residents

Barcellos et al,2016.

Late-Onset and Additional Problems – Newer Reports

- Update from van der Linden on 13 infants born without microcephaly but ZKV-infected -- Brazil *(MMWR 11/22/16)*
  - 11 referred for small head size but > 2SD, 2 for dev. lag (5, 7 mos).
  - 3/13 with fetal u/s issues, 6/13 maternal rash, all (+) neo ZKV (csf)
  - Neuroimaging abnormal in all: all w/ ↓ brain volume, +/or ↑ vents
  - 10 w/dysphagia, 3 w/chorioretinitis, all hypertonic
- Report on 11 newborns from Brazil *(Melo et al, JAMA Neurol 10/3/16)*
  - All with abnormal head size on prenatal u/s, but also other intracranial abnormalities
  - 6/11 had (+) amniotic fluid PCR
  - Cerebellar and gyration anomalies also seen + arthrogryposis

Zika-Related Arthrogryposis



van der Linden at al, BMJ 8/16

Zika – Where is it and where is it not?

Zika as an Endemic Infection

- Zika virus is considered endemic in some countries, and a large number of local residents are likely to be immune. However, US travelers to endemic areas may not be immune to Zika virus and infections have occurred among travelers to Asia and Africa

- Zika evolving as an outbreak like other arboviruses : areas of endemicity but high potential (like West Nile and chikungunya) for ongoing sporadic cases and local outbreaks *(Paules C, Fauci A: JAMA 1/12/17)*

Zika in the US: as of March 8, 2017

US States (5109 cases)

- Travel-associated Zika virus disease cases reported: 4813 (75 0ther/45 sexually transmitted)
  - 13 cases of Guillain-Barre syndrome
- Locally acquired vector-borne cases reported: 221

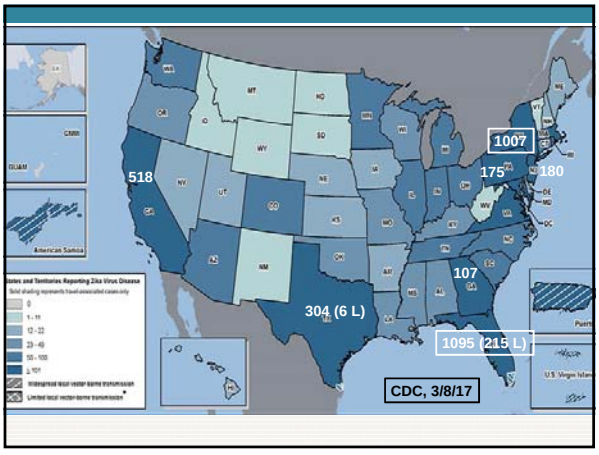
US Territories

- Travel-associated cases reported: 147
- Locally acquired cases reported: 38,099 (all but ~1100 in Puerto Rico with 993 in USVI)
  - 51 cases of Guillain-Barre syndrome

CDC.gov

Current Zika Statistics (as of 2/21/17)

- 1534 **pregnant travelers** with laboratory evidence of Zika virus in US States and DC – vast majority imported/travel-related
  - 1143 completed pregnancies
  - 47 reported liveborn infants and 5 fetal losses with Zika related birth defects
- 3225 **pregnant** cases in US territories (mostly Puerto Rico)
  - 1 liveborn infant and 1 fetal loss with Zika related birth defects
- CA --96 confirmed infections in **pregnant** women (3/10)
  - 4 liveborn infants and 0 fetal losses with Zika related birth defects



STATE OF CALIFORNIA
HEALTH AND HUMAN SERVICES AGENCY

California Department of Public Health
Division of Communicable Disease Control

CDPH

CDPH Weekly Update on Number of Zika Virus Infections in California
March 10, 2017

The following table provides the number of travel-associated infections with Zika virus in California residents in 2015–2017. CDPH is following CDC testing guidelines. This table is updated every Friday. As of March 10, 2017, there have been 518 travel-associated Zika virus infections in California.

- Total infections: 518
- New infections reported this week: 8
- Locally acquired infections: 0
- Cumulative number of infections due to sexual transmission: 6
- Cumulative number of infections in pregnant women: 96[c]
  - Liveborn infants with birth defects: 4[c]
  - Pregnancy losses with birth defects: 0[c]

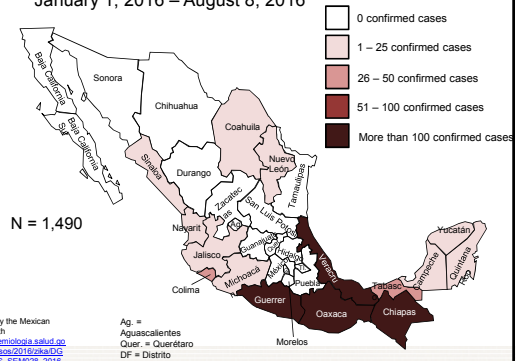
Zika virus infections in California, 2015-2017[a] (as of March 10, 2017)

County	Travel-associated [b]
Alameda (City of Berkeley)	35 (3)
Butte	2
Contra Costa	25
Fresno	6
Humboldt	2
Kern	6
Kings	1
Lake	1
Los Angeles (City of Long Beach)	113[d] (6)
Marin	8
Merced	3
Monterey	6
Napa	3
Nevada	1
Orange	33
Placer	1
Riverside	15
Sacramento	7
San Benito	1
San Bernardino	18
San Diego	85[d]
San Francisco	34
San Joaquin	7
San Luis Obispo	1
San Mateo	13
Santa Barbara	8
Santa Clara	37
Santa Cruz	3
Solano	3
Sonoma	13
Stanislaus	4
Tulare	5
Ventura	9
Yolo	6
Yuba	3
Total	518

Imported Zika Cases in California, 2015-2016

Country Traveled To	Number of Imported Cases in California
Mexico	23
El Salvador	21
Dominican Republic	15
Guatemala, Honduras	13
Puerto Rico	10
Jamaica, Nicaragua	7
Costa Rica	6
Venezuela	5
Brazil, Colombia	4
Haiti	2
American Samoa, Belize, French Polynesia, Kiribati, Saint Lucia, Trinidad	1

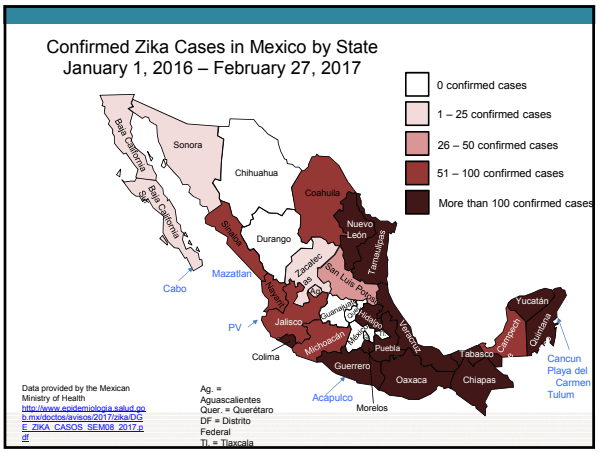
Confirmed Zika Cases in Mexico by State
January 1, 2016 – August 8, 2016

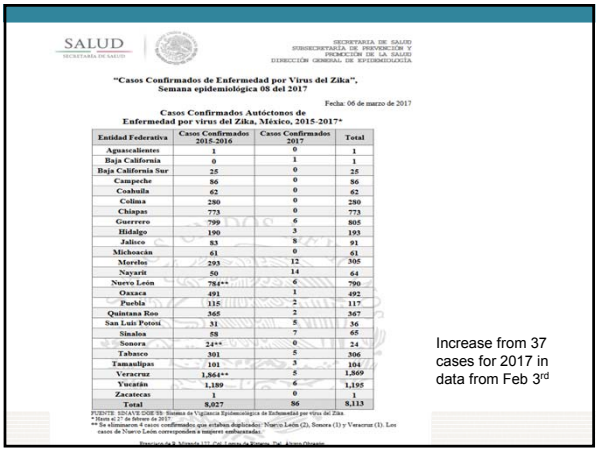


N = 1,490

Data provided by the Mexican Ministry of Health
http://www.epidemiologia.salud.gob.mx/doctos/avisos/2016/zika/DGE_ZIKA_CASOS_SEM028_2016.pdf

Ag. = Aguascalientes
Quer. = Querétaro
DF = Distrito Federal
Tl. = Tlaxcala





SALUD

SECRETARÍA DE SALUD
SUBSECRETARÍA DE PREVENCIÓN Y PROMOCIÓN DE LA SALUD
DIRECCIÓN GENERAL DE EPIDEMIOLOGÍA

"Casos Confirmados de Enfermedad por Virus del Zika", Semana epidemiológica 08 del 2017

Fecha: 06 de marzo de 2017

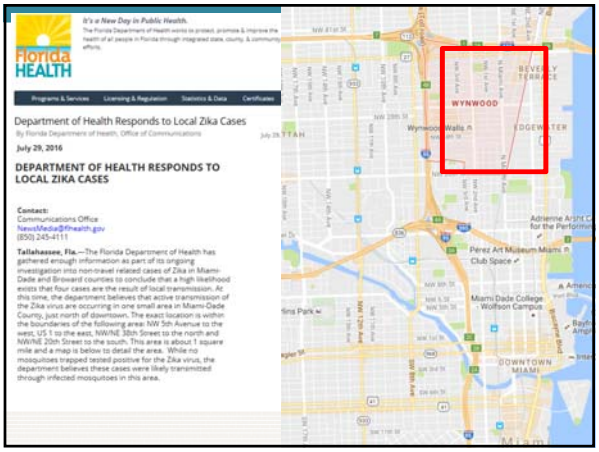
Casos Confirmados Autóctonos de Enfermedad por virus del Zika, México, 2015-2017*

Entidad Federativa	Casos Confirmados 2015-2016	Casos Confirmados 2017	Total
Aguascalientes	1	0	1
Baja California	0	1	1
Baja California Sur	25	0	25
Campeche	86	0	86
Coahuila	62	0	62
Colima	280	0	280
Chiapas	773	0	773
Guerrero	799	6	805
Hidalgo	190	3	193
Jalisco	83	8	91
Michoacán	61	0	61
Morelos	293	12	305
Nayarit	50	14	64
Nuevo León	784**	6	790
Oaxaca	491	1	492
Puebla	115	2	117
Quintana Roo	365	2	367
San Luis Potosí	31	5	36
Sinaloa	58	7	65
Sonora	24**	0	24
Tabasco	301	5	306
Tamaulipas	101	3	104
Veracruz	1,864**	5	1,869
Yucatán	1,189	6	1,195
Zacatecas	1	0	1
Total	8,027	86	8,113

FUENTE: SINAVE/DGE/SS. Sistema de Vigilancia Epidemiológica de Enfermedad por virus del Zika
* Hasta el 27 de febrero de 2017.
** Se eliminaron 4 casos confirmados que estaban duplicados: Nuevo León (2), Sonora (1) y Veracruz (1). Los casos de Nuevo León corresponden a mujeres embarazadas.

Increase from 37 cases for 2017 in data from Feb 3rd

Local Zika Transmission in Florida and Texas



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Department of Health Responds to Local Zika Cases

By Florida Department of Health, Office of Communications

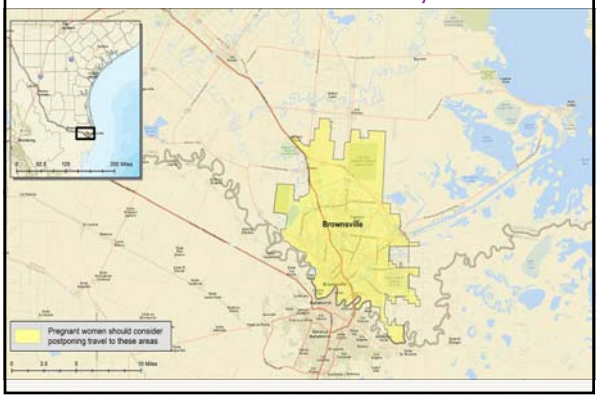
July 29, 2016

DEPARTMENT OF HEALTH RESPONDS TO LOCAL ZIKA CASES

Contact:
Communications Office
NewsMedia@flhealth.gov
(850) 245-4111

Tallahassee, Fla.—The Florida Department of Health has gathered enough information as part of its ongoing investigation into non-travel related cases of Zika in Miami-Dade and Broward counties to conclude that a high likelihood exists that four cases are the result of local transmission. At this time, the department believes that active transmission of the Zika virus are occurring in one small area in Miami-Dade County, just north of downtown. The exact location is within the boundaries of the following area: NW 5th Avenue to the west, US 1 to the east, NW/NE 38th Street to the north and NW/NE 20th Street to the south. This area is about 1 square mile and a map is below to detail the area. While no mosquitoes trapped tested positive for the Zika virus, the department believes these cases were likely transmitted through infected mosquitoes in this area.

Zika in Brownsville, TX



Local Zika Transmission in FLA, TX

- Pregnant women should avoid travel to Miami-Dade, FLA and Brownsville, TX
- Pregnant women who traveled to, lived in, or had unprotected sex with someone who lives in or traveled to these areas should be tested
  - After Aug 1, 2016 for Miami-Dade
  - After Oct 29, 2016 for Brownsville

Zika – Education and Testing

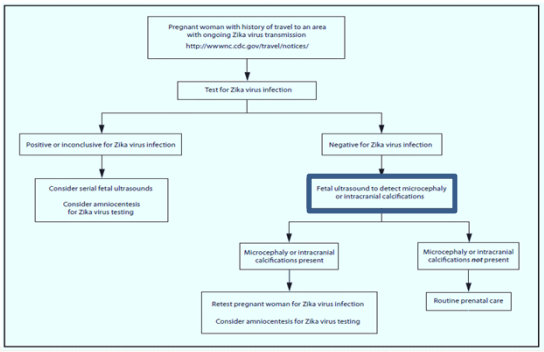
Guidance from other Viral Infections?

- Well-established risks and effects of maternal infection with rubella and CMV
- Both with greater impact with 1st trimester infection but still impact later
  - Congenital rubella in 90% of 1st Δ infections
  - CMV: 30% infection risk across pregnancy, with greater risk of severe impact with 1st Δ infection
- US prevalence of microcephaly: 6 cases per 10,000 live births (range: 2-12)
  - With Zika, risk of developmental brain abnormalities will be greater than risk of microcephaly

What do we tell our pregnant patients?

- How much fetal risk with confirmed maternal infection?
  - Based on current data, **range may be as high as 29-40%**
  - Rates are derived from methodologically diverse studies
- Despite earlier reports, recent data suggest later GA at infection does not exclude potential adverse impact
- Pregnant women **should not travel** to areas with active Zika transmission
- If in an area with transmission, protection and prevention strategies are important – ***and repellent for 3 weeks after return from these areas***
  - **DEET, picaridin most effective --- both fine for use during pregnancy**
  - Review article on repellents in Zika era: ***Wylie B, et al. ObGyn 11/16***

Testing algorithm for a pregnant woman possible Zika exposure



MMWR, 2/12/16

Morbidity and Mortality Weekly Report

Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States, July 2016

Titilope Oduyebo, MD[1]; Irogue Igbinosa, MD[2]; Emily E. Petersen, MD[1]; Kara N.D. Polen, MPH[2]; Satish K. Pillai, MD[3]; Elizabeth C. Ailes, PhD[2]; Julie M. Villanueva, PhD[2]; Kim Newsome, MPH[2]; Marc Fischer, MD[4]; Priya M. Gupta, MPH[5]; Ann M. Powers, PhD[4]; Margaret Lampe, MPH[6]; Susan Hills, MBBS[4]; Kathryn E. Arnold, MD[2]; Laura E. Rose, MTS[2]; Carrie K. Shapiro-Mendoza, PhD[2]; Charles B. Beard, PhD[4]; Jorge L. Muñoz, PhD[4]; Carol Y. Rao, ScD[7]; Dana Meaney-Delman, MD[8]; Denise J. Jamieson, MD[1]; Margaret A. Honein, PhD[2]

On July 25, 2016, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

CDC has updated its interim guidance for U.S. health care providers caring for pregnant women with possible Zika virus exposure, to include the emerging data indicating that Zika virus RNA can be detected for prolonged periods in some pregnant women. To increase the proportion of pregnant women with exposure. For asymptomatic pregnant women who live in areas without active Zika virus transmission and who are evaluated <2 weeks after last possible exposure, rRT-PCR testing should be performed. If the rRT-PCR result is negative, a Zika virus IgM antibody test should be performed 2–12 weeks after the exposure. Asymptomatic pregnant women who do not live in an area with active Zika virus transmission, who are first evalu-

Zika Testing – What's new?

- Expanded testing for pregnant women
  - Attempt to increase the proportion of pregnant women with Zika infection who receive definitive dx
  - Ask about Zika exposure (travel, sex) at each prenatal visit
    - Only test pregnant women with (+) exposure history
  - Recognizing risks of sexual transmission regardless of whether sexual partner who traveled to risk area had symptoms or not → also ask partner travel hx
  - Recognizing longer time for viral RNA detection in some pregnant women compared to nonpregnant adults
- Still no testing rec for asymptomatic partner of a pregnant woman → *still emphasize condoms thru pregnancy*

MMWR, 7/25/16

Zika Testing – What Testing should be done?

- PCR done for all pts with symptoms within **2 weeks after onset of symptoms**: test blood AND urine
- PCR for asymptomatic: **only in pregnant women with exposure in past 2 weeks** (including sex w/ male **or** female partner who traveled)
  - **If PCR on pregnant woman negative, still do antibody testing 2-12 weeks after exposure**
- All other pregnant patients with exposure (including sexual contact with traveler): testing for **Zika-specific IgM antibodies**
  - Typically develop toward the end of the first week of illness
  - **Testing in asymptomatic patients no earlier than 2 weeks after exposure (no later than 12 weeks)**
  - If Ab (+), then further testing done to confirm (PRNT)

Zika Testing – How?

- Recently emergency-approved commercially available test for PCR and has very specific role in new guidelines, especially for pregnant women
  - Cost and collection issues
  - **PCR now a test for pregnant women w/o symptoms but with exposure within 2 weeks**
- Commercial testing approved (EUA) for CDC MAC-ELISA IgM testing: TAT 5-7 days
- **No IgG test has been approved**
- Clinicians should still be aware of current guidelines for testing
  - Take a travel history of pt and partner
  - Be aware of current travel advisories (cdc.gov)

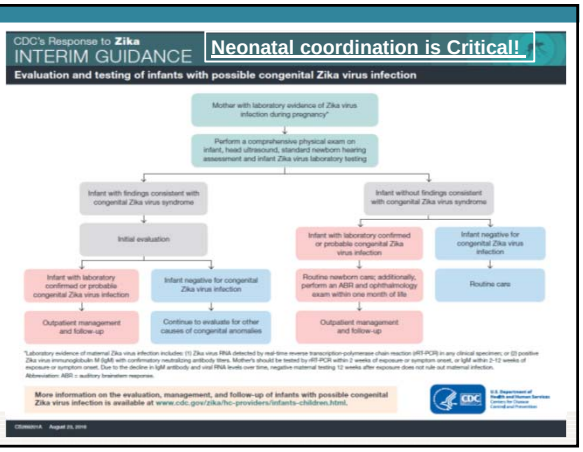
Guidance: Newborns at Risk for Congenital Infection


Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016



Sexual Transmission: What We Don't Know

- Maximum duration of virus in semen/vaginal fluids to infect a sexual partner
  - *Lancet* 6/7/16: transmission through semen 34-41 d after infection
  - *Lancet* 8/2016: Zika RNA found in semen after 90 days
  - *Eurosurveillance* 8/11/16: RNA (+) in urine up to 91 days and in semen 134 days after sx
- If Zika can be transmitted through saliva or other body fluids
- Transmission risk/duration after ***asymptomatic*** infection

Sexual Partner concerns/guidelines

- Sexual transmission of Zika virus can occur
  - Male/female, female/male, male/male all reported
- Pregnant women whose male partners have or are at risk for Zika virus infection should consider using condoms or abstaining from sexual intercourse – ***duration of pregnancy***
- Zika has recently been shown to cause testicular damage in mouse models *(Govero J, et al. Lancet Dec 15, 2016)*
  - ZKV persistence in testis/epididymis→ tissue injury resulting in diminished testosterone and inhibin B levels and oligospermia

Suggested timeframe to wait before trying to get pregnant		
Possible exposure via recent travel or sex without a condom with a partner infected with Zika		
Women		**Men**
Wait at least 8 weeks after symptoms start or last possible exposure		Wait at least 6 months after symptoms start or last possible exposure
People living in or frequently traveling to areas with Zika		
	Women	**Men**
Positive Zika test	Wait at least 8 weeks after symptoms start	Wait at least 6 months after symptoms start
No testing performed or negative test	Talk with doctor or healthcare provider	Talk with doctor or healthcare provider

CDC: Oct 3, 2016

Zika's Additional Impact on OBGYN Care

- Tissue/organ donation – including egg/sperm donors
  - Donors are **ineligible for 6 months** if dx'd with ZKVD, in an area with active transmission, or had sex with a male partner with either of those risks
  - Also applies to umbilical cord blood and placenta
  - ***FDA 3/1/16, affirmed by ASRM 3/4/16***

Zika and Blood Donation

- Zika transmission by blood transfusion has been reported
  - Major impact on blood bank capabilities: for US, initial greatest impact in Puerto Rico *(also Miami)* -- no reported cases via transfusion, but local blood collections stopped 3/1 pending PCR availability
  - FDA statement (2/16/16): 4 week waiting period for potential donors -- after illness, travel, or sexual contact
- Statement by FDA Aug 26, 2016: all U.S. blood banks to start screening for Zika : ***questionnaire screening insufficient***
  - First on list : Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina and Texas
  - All other U.S. states and territories given 3 months to comply.
- An executive for America's Blood Centers, which has more than 600 locations in the U.S. and Canada, warned that the amount of work needed to comply with the FDA's timeline was "titanic." (USNWR, Aug 2016)

Blood Donor Serologic Data – U.S.

- CDC now tracks positive Zika test results among potential blood donors
  - Presumptive viremic blood donors are people who reported no symptoms at the time of donating blood, but whose blood tested positive when screened for the presence of Zika virus RNA by the blood collection agency.
- Through March 8, 39 positive donors in US states, 318 in Puerto Rico
  - In US, majority so far in FLA (62%), with others in CA (13%), NY & TX (8% each)

Science

RESEARCH ARTICLES

Aug 4, 2016

Cite as: Abbink *et al.*, *Science* 10.1126/science.aah6157 (2016).

Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys

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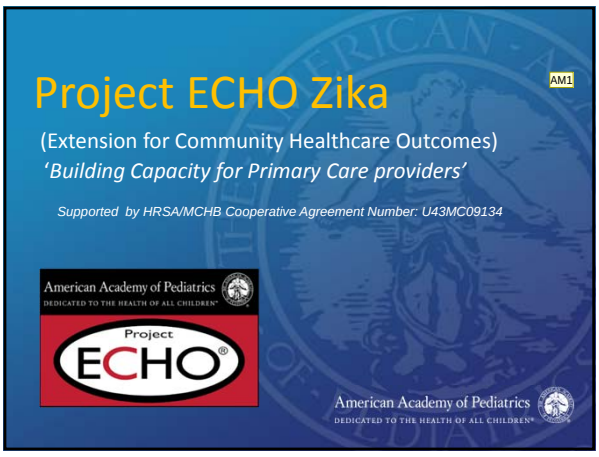
Zika virus (ZIKV) is responsible for a major ongoing epidemic in the Americas and has been causally associated with fetal microcephaly. The development of a safe and effective ZIKV vaccine is therefore an urgent global health priority. Here we demonstrate that three different vaccine platforms protect against ZIKV challenge in rhesus monkeys. A purified inactivated virus vaccine induced ZIKV-specific neutralizing antibodies and completely protected monkeys against ZIKV strains from both Brazil and Puerto Rico. Purified immunoglobulin from vaccinated monkeys conferred passive protection in adoptive transfer studies. A plasmid DNA vaccine and a single-shot recombinant rhesus adenovirus serotype 52 vector expressing ZIKV prM-Env also elicited neutralizing antibodies and completely protected monkeys against ZIKV challenge. These data support the rapid clinical development of ZIKV vaccines for humans.

Zika Resources

- CDC Zika website: www.cdc.gov/zika
- ACOG's Zika webpage: www.acog.org/zika
- CDC Zika Pregnancy Hotline for Healthcare Providers: 770-488-7100 or email ZikaPregnancy@cdc.gov for concerns related to clinical mgmt or the Zika Pregnancy Registry
- CA Dept of Public Health webpage for health care professionals
  - www.cdph.ca.gov/HealthInfo/discond/Pages/ZikaInformationforHealthProfessionals.aspx



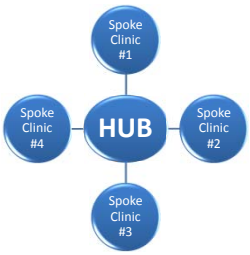
Slide 66

AM1 Capitalize "Providers"
Abigail Lea Hobson Kroening, MD, 12/12/2016

History of Project ECHO

- Developed to treat HCV in New Mexico
- HCV in New Mexico
  - Estimated number was greater than 28,000
  - In 2004, less than 5% had been treated
- Barriers to Treatment
  - Long wait lists
  - Rural location
  - Complex treatment

Hub and Spoke Model



ECHO Hub: Spokes Design

Multidisciplinary Team of Specialists at Academic Medical Centers comprise the 'HUB'

Remote and rural clinicians join via webcam or phone and are the 'SPOKES'

Faculty Members/ Representation

- James Bale, MD, FAAP/ Neurology
- Steve Caddle, MD, FAAP/ Primary Care
- Margaret Fisher, MD, FAAP/ Infectious Disease/Disaster Preparedness
- Deliana Garcia, MD/ Migrant Clinicians Network
- Dixie Griffin, MD, FAAP/ Primary Care
- Abigail Kroening, MD, FAAP/ Developmental/Behavioral Pediatrics
- Ana Medina, MD, FAAP/ Pediatrics in Puerto Rico
- Marilyn Ruiz/ Family Perspective
- Perry Sheffield, MD, FAAP/ Public and Environmental Health
- Neil Silverman, MD, FACOG/ Obstetrics and Gynecology
- Marcia Tartarella, MD/Ophthalmology

Goals

- To provide health professional education and training, through a telementoring platform
- To increase the clinical expertise of clinicians who care for children to more appropriately provide family-centered, comprehensive, coordinated, and culturally effective care in the context of a medical home for infants and families who are affected by the Zika virus

How Does an ECHO Clinic Work?

One hour sessions, at regular intervals (weekly/bi-weekly) as available:

- 5 minute intro
- 20 minutes didactic
- 30 minutes case presentations
- 5 minute summary
- Those who present cases receive a follow-up e-mail with a summary of discussion points