Zika Virus: The Evolving Epidemic

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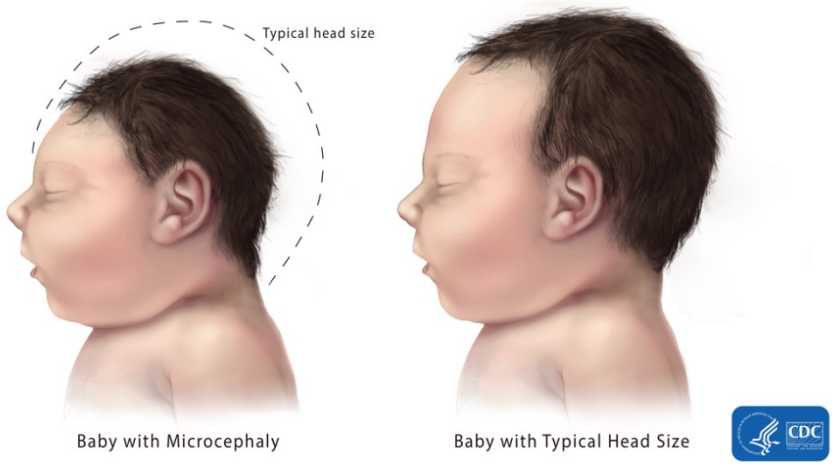
Zika Virus

Aedes aegypti

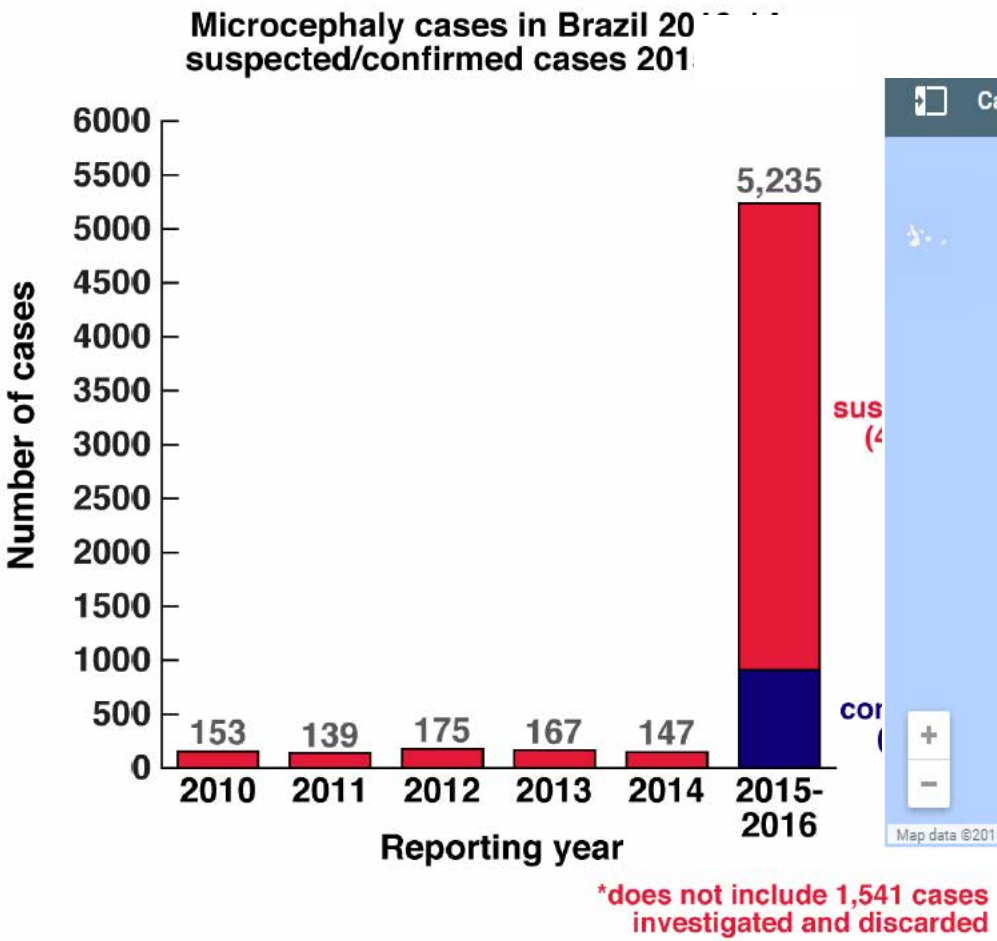
- First discovered in 1947 in Zika forest in Uganda isolated from febrile Rhesus Macaques
- Arbovirus of the genus Flavivirus
- 1952: first human cases detected
- Sporadic infections reported in tropical Africa, Southeast Asia, and the Pacific Islands

Brazil Zika And Congenital Malformations

- May 2015: First infection in Brazil
- ~500,000 to 1.5 million Zika virus cases by December 2015
- September 2015: increase in microcephaly in north-east region



Number Of Microcephaly Cases By Year, Brazil, 2000 -2016



Source: Brazilian MOH; data as of 3/26/2016.

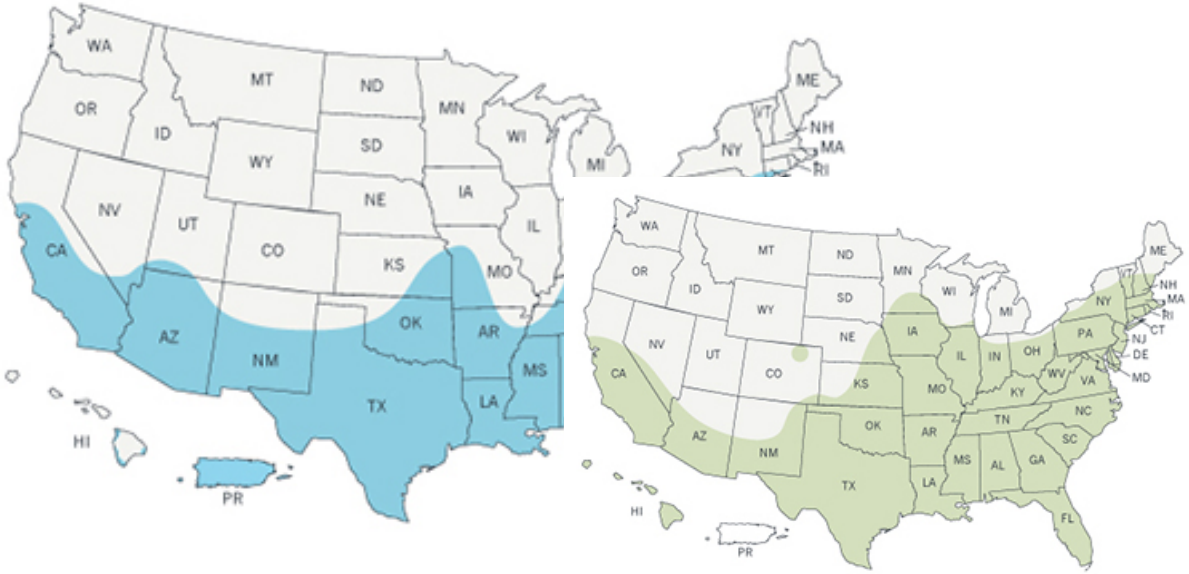
Source: Ministério da Saúde eandSecretarias Estaduais de Saúde (update in 20/02/2016)

Presented at PAHO meeting 03/01/2016 by Giovanni Evelino Coelho
Ministry of Health - Brazil

Caribbean and South America

American Samoa	Argentina	Aruba	Barbados
Belize	Bolivia	Bonaire	Brazil
Cape Verde	Colombia	Costa Rica	Cuba
Curacao	Dominica	Dominican Republic	Ecuador
El Salvador	Fiji	French Guiana	Guadeloupe
Guatemala	Guyana	Grenada	Haiti
Honduras	Jamaica	Kosrae	Marshall Islands
Martinique	Mexico	New Caledonia	Nicaragua
Panama	Papua New Guinea	Paraguay	Peru
Puerto Rico	Saint Barthelemy	Saint Lucia	Saint Martin
Saint Vincent	Samoa	Sint Maarten	Suriname
Tonga	Trinidad and Tobago	US Virgin Islands	Venezuela

Estimated Range Aedes aegypti and Aedes albopictus in the United States, 2016

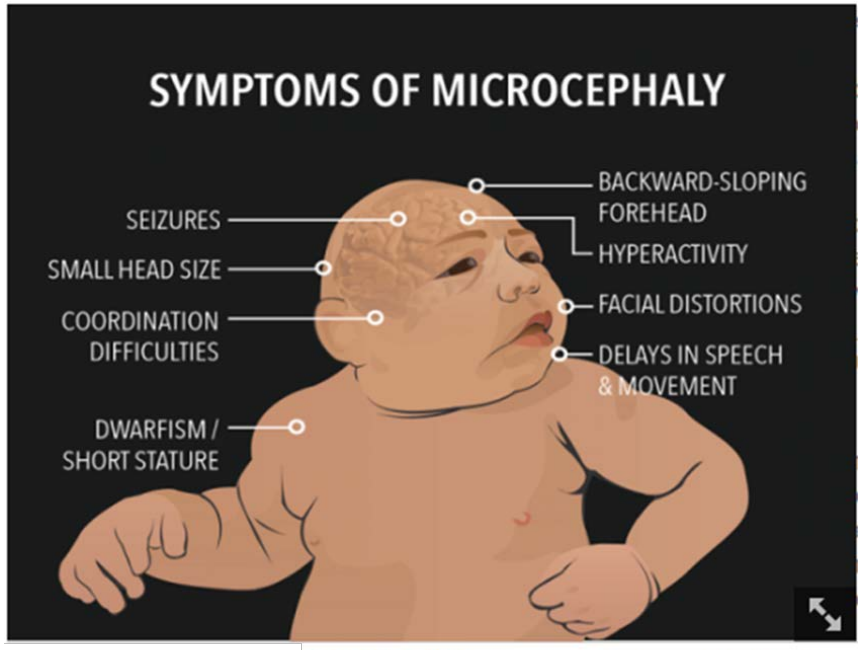


Aedes aegypti *Aedes albopictus*

These maps show CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States.

Microcephaly: Causes and Risk Factors

- U.S. prevalence: 2-12/10,000 livebirths
- Unknown
- Genetic mutations
- Exposures during pregnancy:
  - Infections, such as toxoplasmosis, rubella, or cytomegalovirus (“TORCHS”)
  - Severe malnutrition
  - Exposures to alcohol, certain drugs, or toxic chemicals
- Interruption of the blood supply to the baby’s brain during development



Angela Laguipo, Tech Times | February 13, 1:31 AM

Centers for Disease Control and Prevention
MMWR

***MMWR: 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

- Zika virus confirmed in postmortem brain, amniotic fluid or placental tissue in infants with microcephaly

THE LANCET Infectious Diseases
Published online February 18, 2016

- Detection and Sequencing of Zika Virus from Amniotic Fluid of Fetuses with Microcephaly in Brazil: a Case Study

  G Calvet, AM de Filippis, et al.

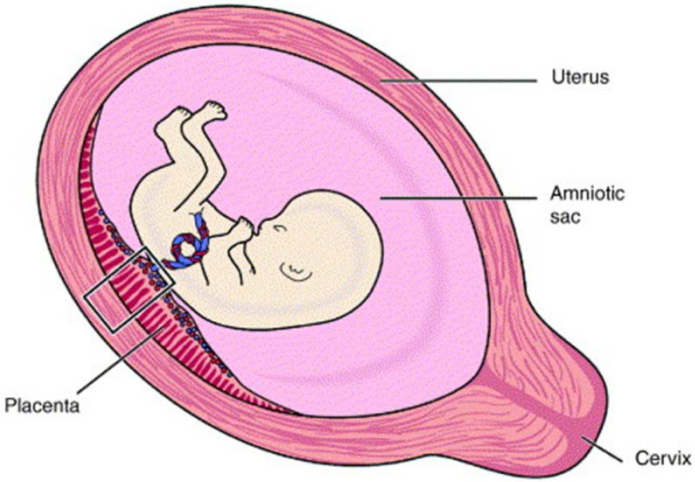
- Zika Genome detected in amniotic fluid of two pregnant women from Paraiba State In NE Brazil whose fetus had been diagnosed with microcephaly

- Complete Zika virus genome from one sample and genome fragments from the second

Modes of Transmission

Modes Of Transmission

- Vector born
- Sexual
- Mother to infant
- Blood donation/transfusion
- Organ transplant donors

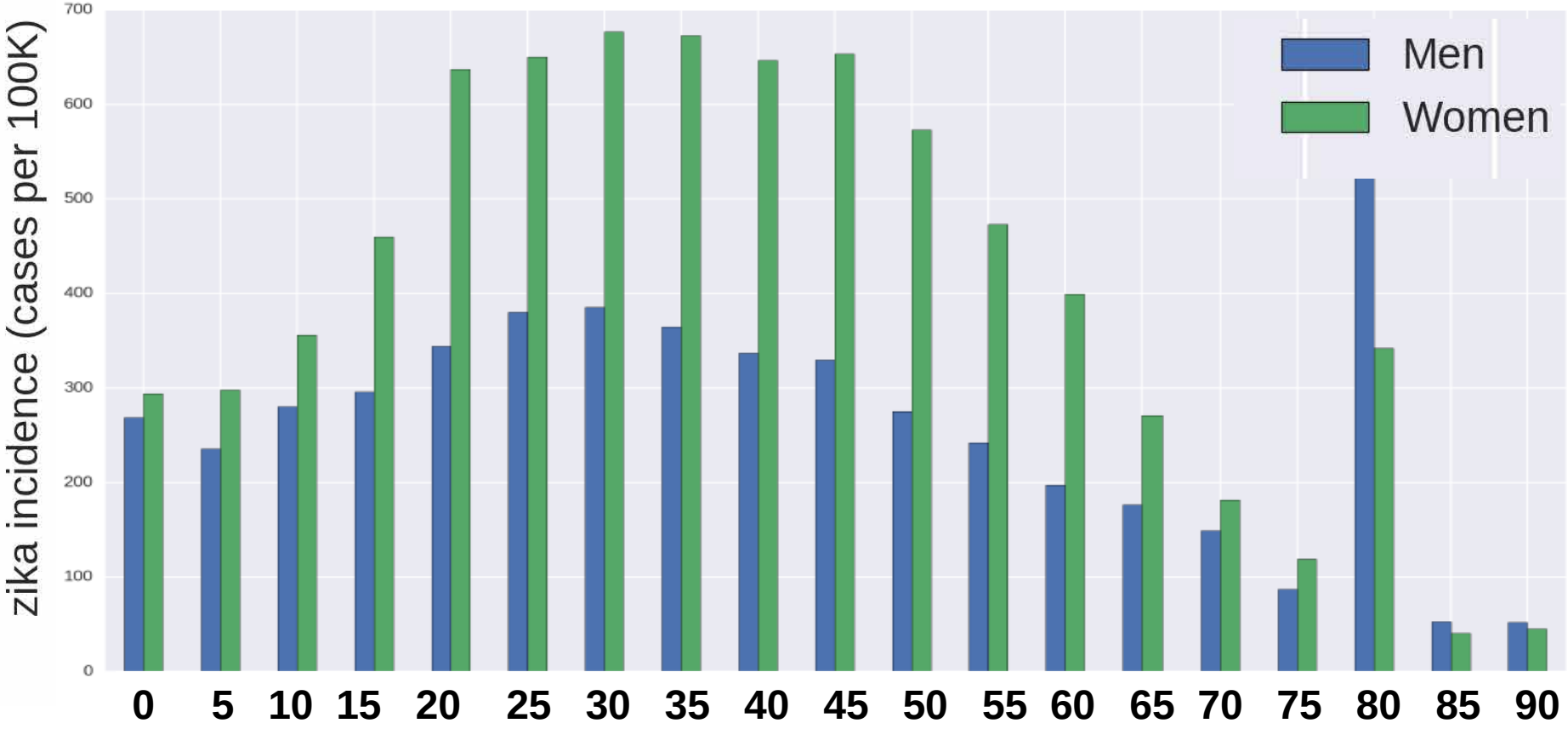


William Britt HHS presentation March 28, 2016

Could increased incidence of ZIKV in women be caused by sexual transmission?

Zika incidence in men and women by age class, excludes pregnant women

90% more cases per 100,000 women in sexually active group (15-65 years)



Codeco Coelhoa et al, The Lancet Infectious Disease May 25, 2016

Pregnant?

- Do not travel to areas where Zika virus is spreading.
- If you must travel to these areas, talk to your doctor first.
- Strictly follow steps to prevent mosquito bites during your trip.
- If you have a male partner who lives in or has traveled to an area with Zika, either use condoms the right way every time you have vaginal, oral, or anal sex, or do not have sex during the pregnancy.

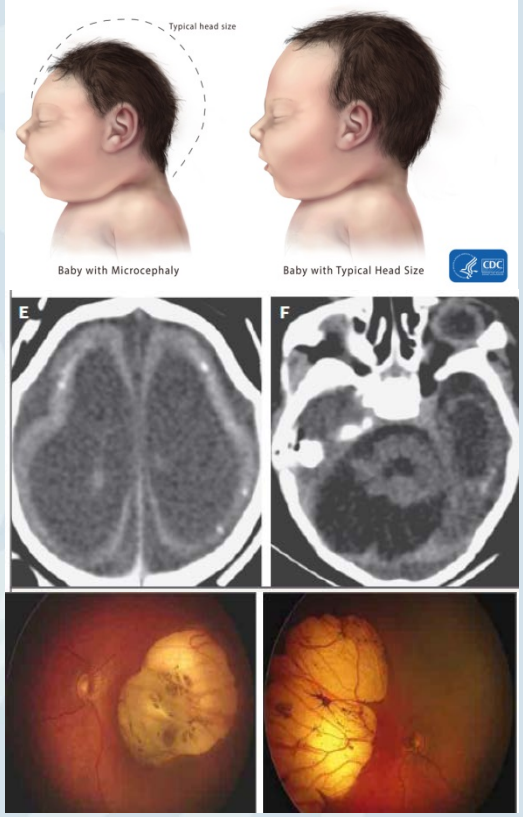
Trying to become pregnant?

- Before you travel, talk to your doctor about your plans to become pregnant and the risk of getting Zika.
- Strictly follow steps to prevent mosquito bites during your trip.

Before you travel, check the CDC travel website frequently for the most up-to-date recommendations. http://wwwnc.cdc.gov/Travel

Zika Associated Adverse Outcomes

Range of adverse outcomes



- Fetal loss/miscarriage
- Stillbirth
- Fetal brain anomalies
- Eye abnormalities

Spectrum Of Teratogenic Effects Of Zika

- IUGR
- Miscarriage/stillbirth
- Eyes: cataracts, chorioretinitis
- Brain:
  - Microcephaly
  - Hydrocephalus/hydranencephaly
  - Absent structures: (CC, pons, cerebellar vermis, etc)
  - Neuronal migration disorders (lissencephaly)
  - Fetal brain disruption sequence
  - Cerebral calcifications
  - Brain asymmetry

- Neurologic: hypertonia, swallowing problems, arthrogryposis (joint contractures), seizures
- Neurodevelopment?

Affected Fetus With Documented Zika Infection

Driggers et al, NEJM

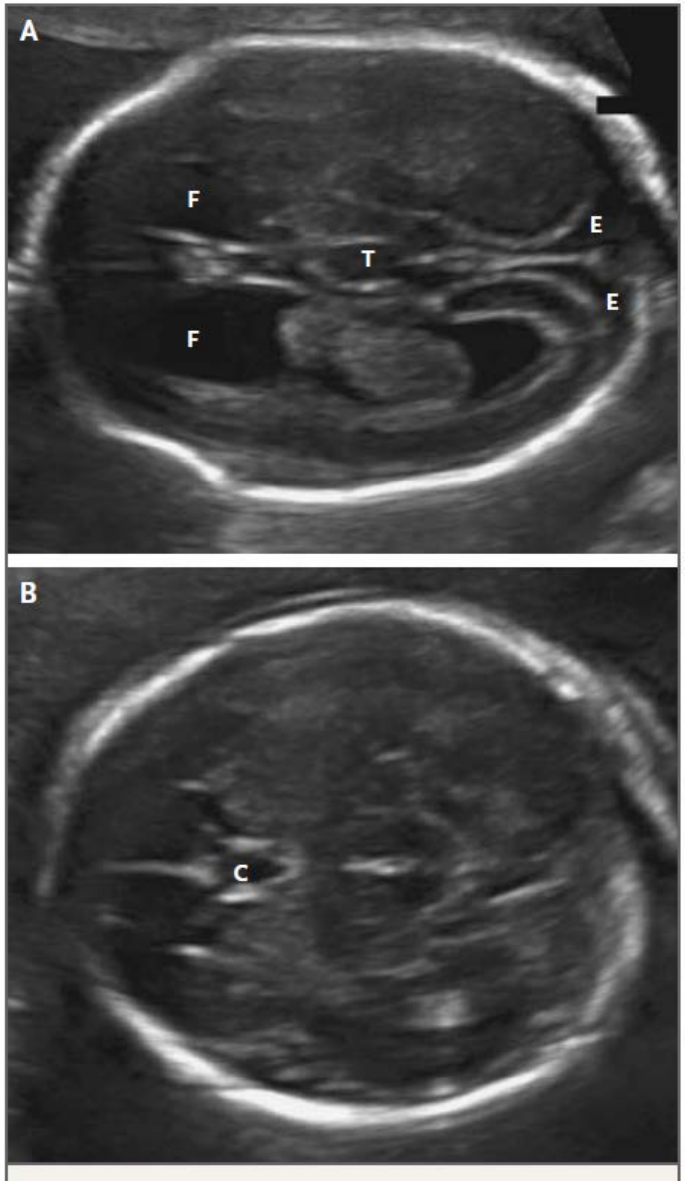


Figure 2. Fetal Ultrasonography at 19 Weeks of Gestation.

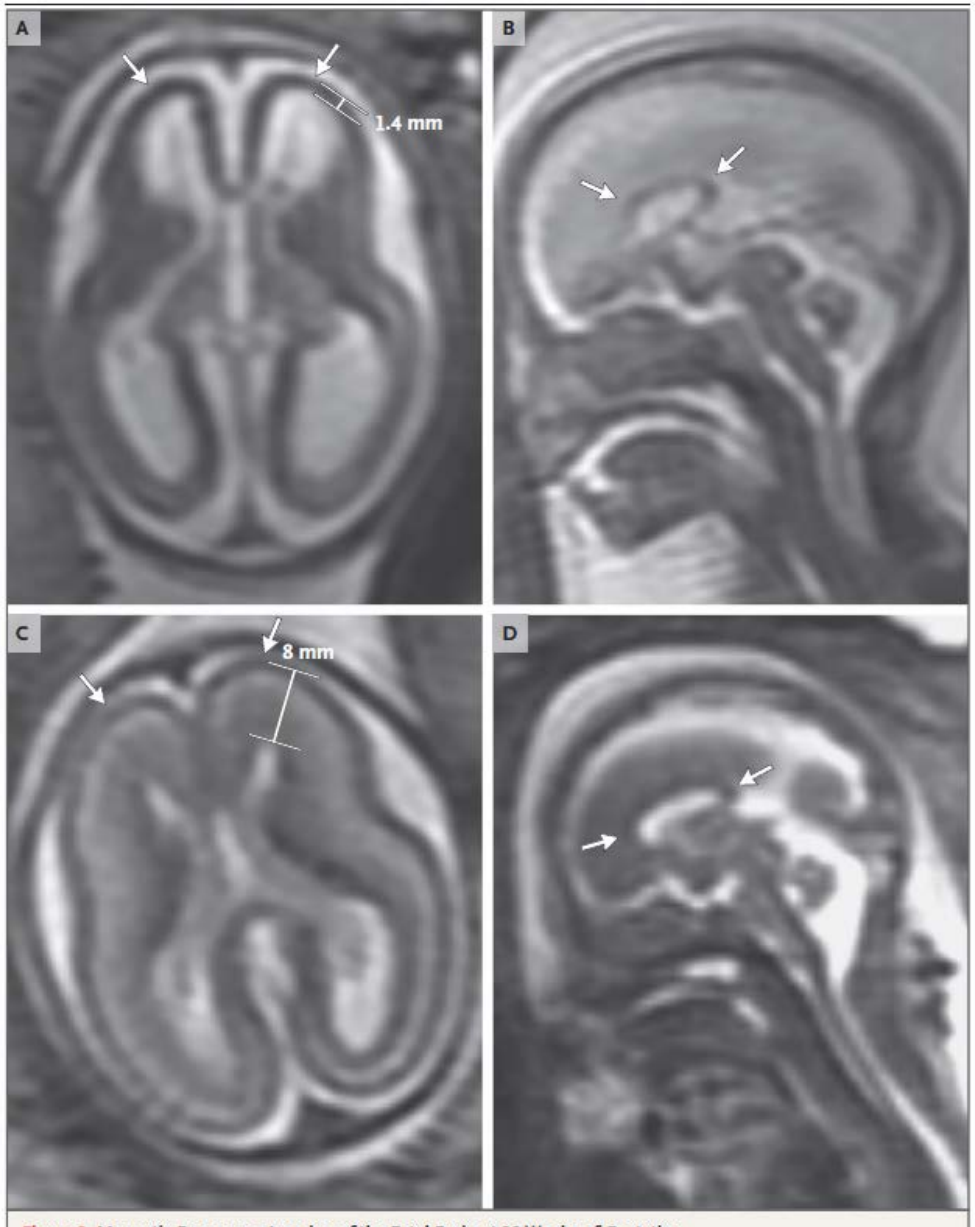
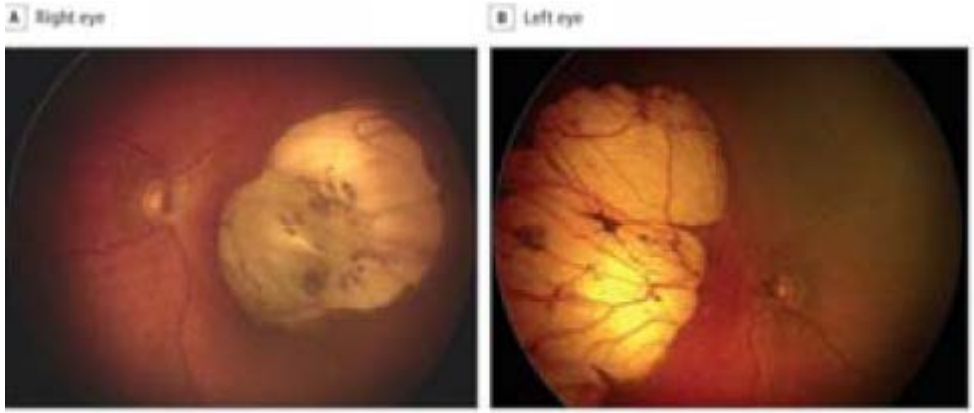


Figure 3. Magnetic Resonance Imaging of the Fetal Brain at 19 Weeks of Gestation.

Adverse Fetal Outcomes Not Limited To Microcephaly

- JAMA Ophthalmology BP Freitas, R Belfort et al.
  - February 2016
  - Ocular findings Congenital Infection in Salvador Brazil



Fundus Photographs of a 20-Day-Old Infant

Zika Virus: First Cohort Study

- Study of 42 Zika+ pregnant women in Brazil followed with serial ultrasound:

Table 2. Ultrasonographic Features of Fetuses and Findings at Birth.*

Fetus No.	Week of Gestation at Infection	Week of Gestation at Ultrasound Examination	Abnormal Findings on Doppler Ultrasonography	Findings at Birth
19	8	35	Microcephaly, cerebral calcifications, abnormal middle cerebral artery, intrauterine growth restriction	Microcephaly, cerebral calcifications on CT, global cerebral atrophy, macular lesions
40	8	20	Choroid plexus cyst, cerebellar atrophy (transverse diameter <5th percentile)	Still in utero
24	12	29	Microcephaly, cerebral calcification, Blake's cyst, agenesis vermis, club foot, intrauterine growth restriction	Still in utero
41	12	24	Mega cisterna magna (>95th percentile)	Still in utero
39	21	30	Cerebellar and cerebral right periventricular calcifications	Still in utero
17	22	26	Middle cerebral artery flow <5th percentile	Still in utero
12	22	27	Microcephaly, placental insufficiency as assessed by Doppler study, oligohydramnios, intrauterine growth restriction	Small for gestational age, head circumference proportional to body size, macular lesions
10	25	30	Normal first ultrasonogram, fetal death detected at 36 weeks on repeat ultrasonogram	Stillbirth
36	26	35	Microcephaly, abnormal umbilical artery flow (>95th percentile on the pulsatile index), intrauterine growth restriction	Small for gestational age, head circumference proportional to body size
38	27	35	Cerebral calcifications, ventriculomegaly, brachycephaly	Still in utero
2	30	34	None	Normal at birth
3	31	33	None	Normal at birth
53	32	38	Fetal death	Stillbirth
23	35	40	Anhydramnios, intrauterine growth restriction	Normal growth measure, poor sucking reflex, EEG abnormalities

29% with fetal anomalies

17% with microcephaly, atrophy, or calcifications

Brasil et al, NEJM

Risk May Not Be Limited To 1st Trimester

ORIGINAL ARTICLE

Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

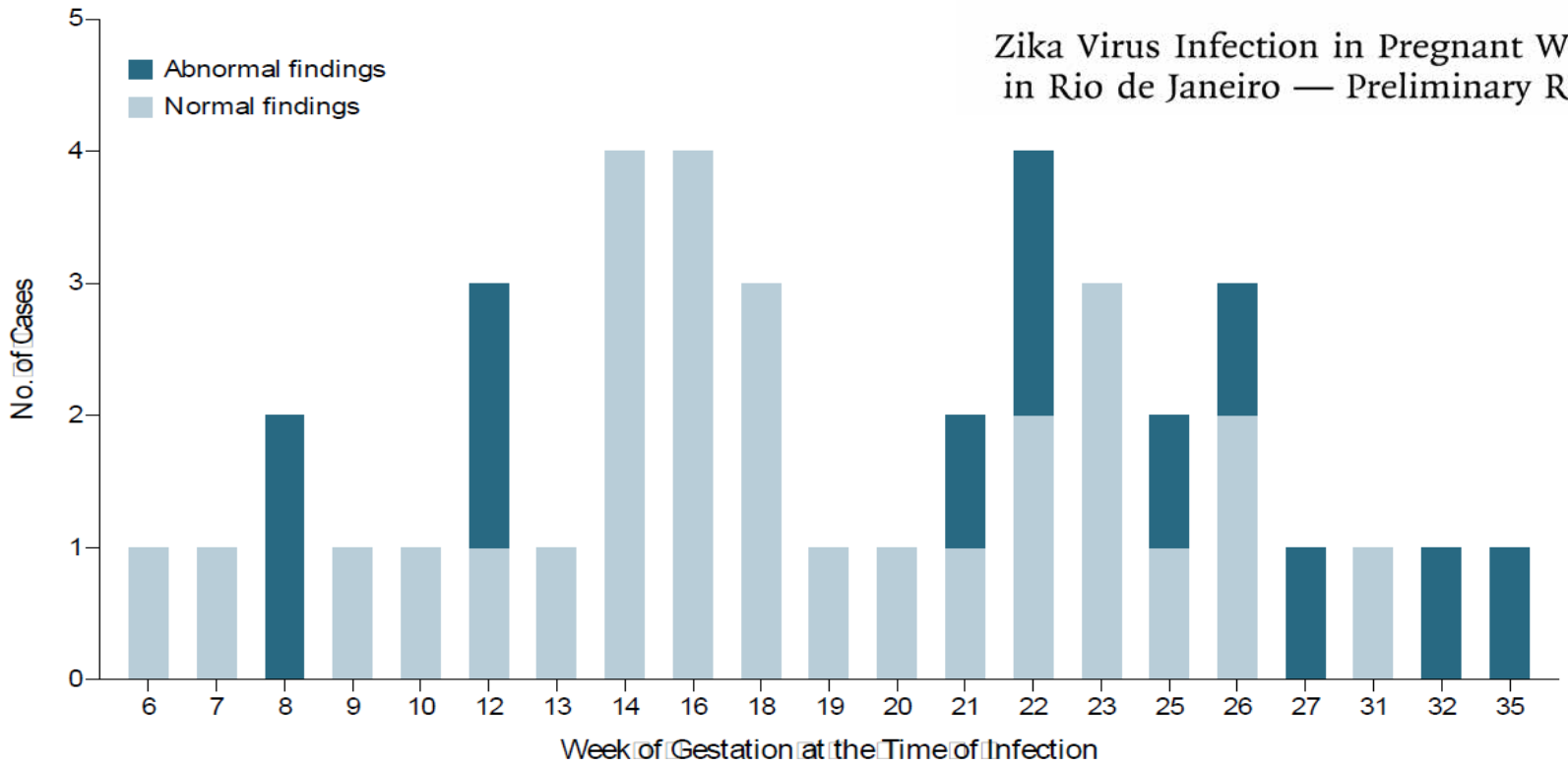


Figure 2. Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings. Twelve of 42 women (29%) in whom fetal ultrasonography was performed had abnormal findings.

The NEW ENGLAND JOURNAL of MEDICINE

Brasil et al, NEJM online 3/4/16

WHO Update: New Findings

- Unpublished data from Colombia and Panama suggest other systems affected
  - Cardiac
  - Digestive
  - Genitourinary

http://www.who.int/bulletin/volumes/94/6/16-176990

Diagnostic Challenge

The NEW ENGLAND JOURNAL of MEDICINE

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities

Rita W. Driggers, M.D., Cheng-Ying Ho, M.D., Ph.D

March 30, 2016

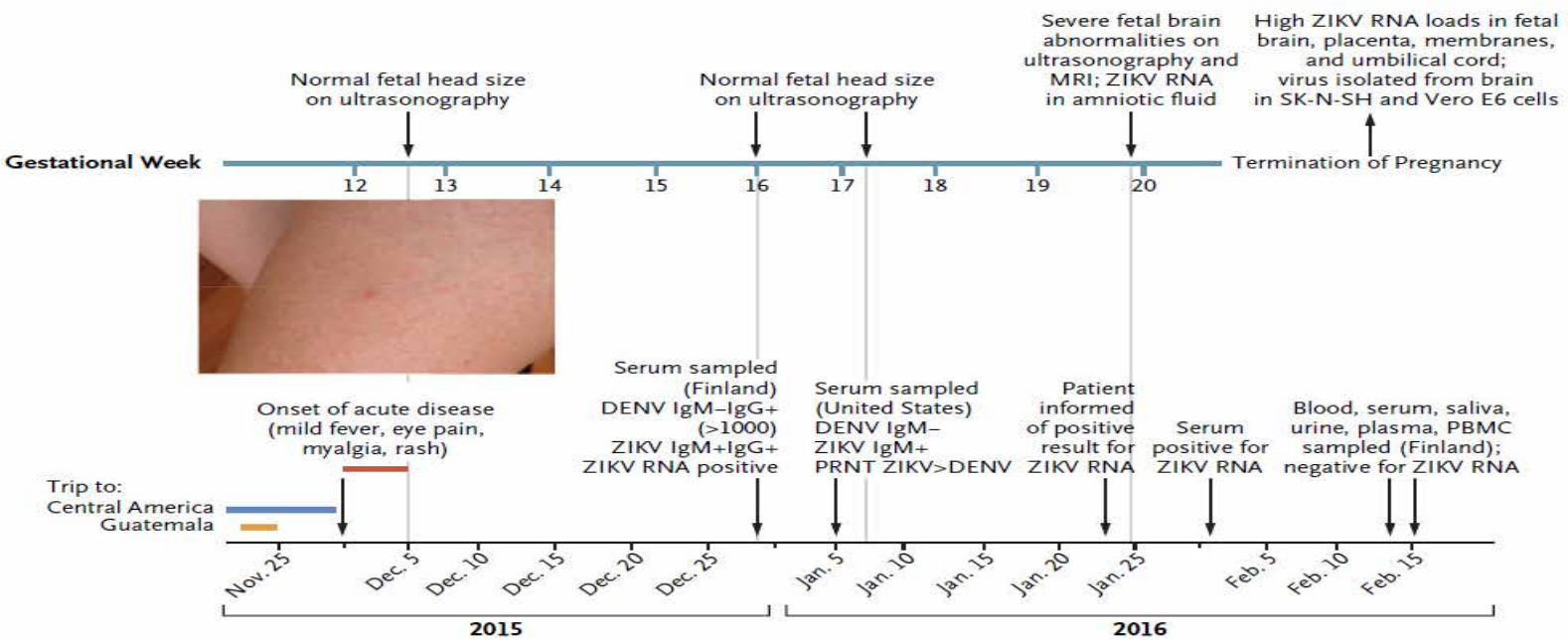


Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.
This timeline highlights the symptoms of Zika virus (ZIKV) infection in the mother (bottom row) and the corresponding radiographic and laboratory findings in the fetus (top row). The inset photograph shows the mother's rash at the time of the onset of the acute illness. DENV denotes dengue virus, MRI magnetic resonance imaging, PBMC peripheral-blood mononuclear cells, and PRNT plaque-reduction neutralization test.

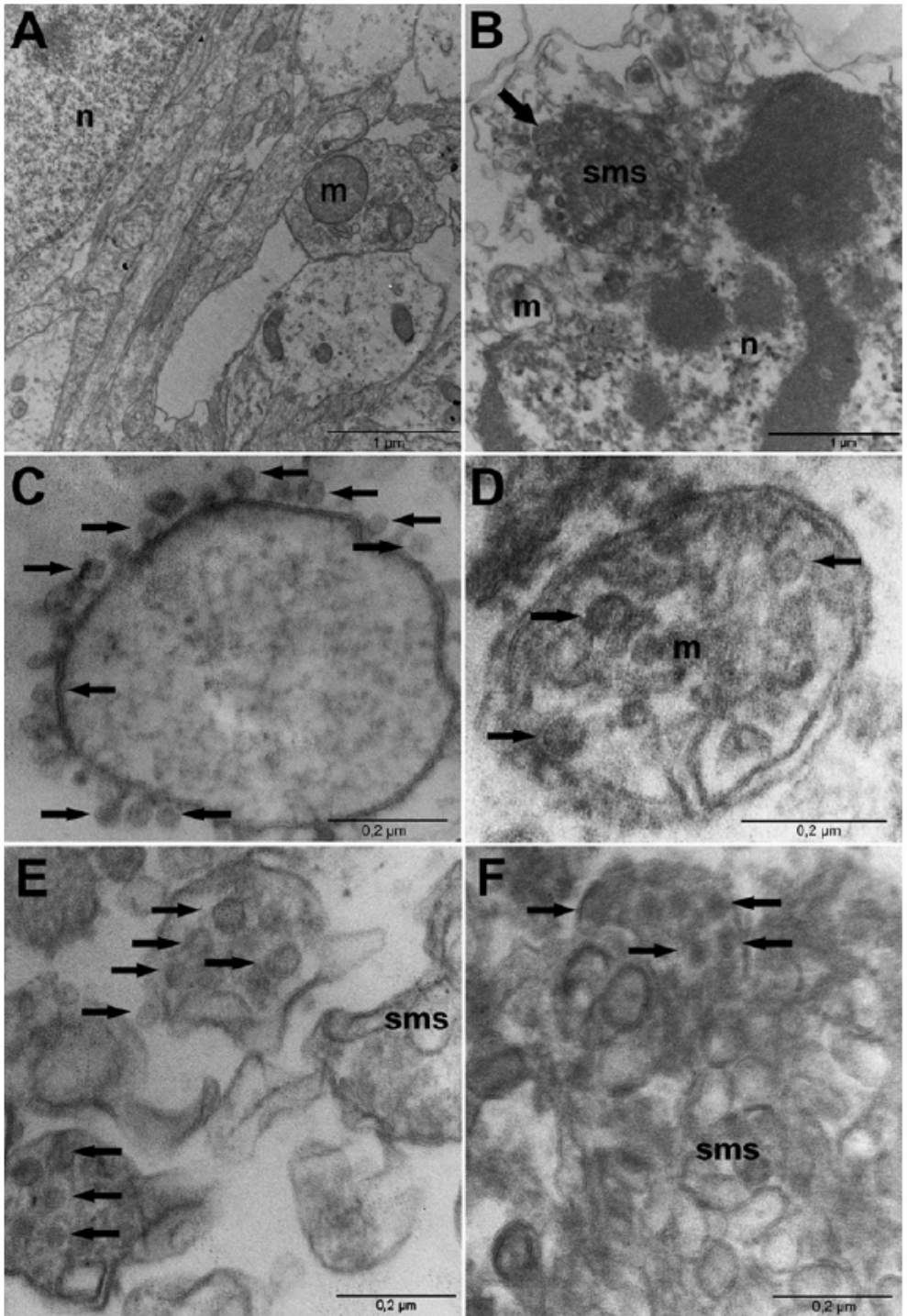
Potential Mechanisms

Zika Kills Developing Human Brain Cells

- Zika Virus infects
- Human Cortical Neural Progenitor cells
- Attenuates their Growth more efficiently compared to mature cortical neurons
- Causing dysregulation and cell Death
- Zika Virus also Impairs Growth in

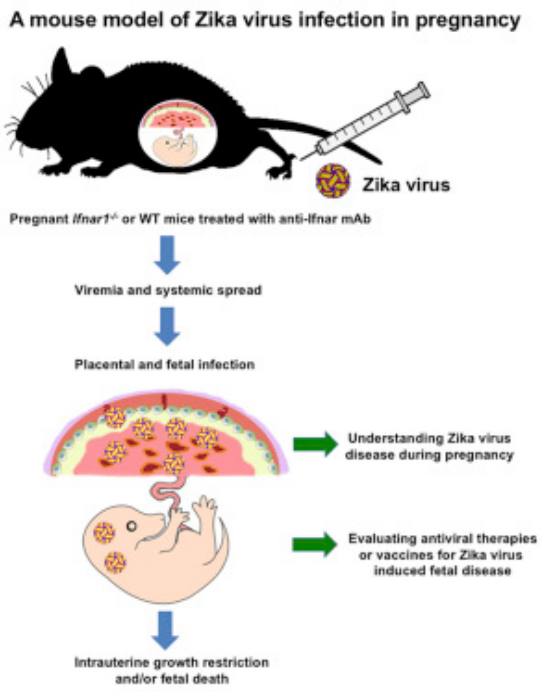
Human Neurospheres and

Brain Organoids



Garcez et al, Science
H Tang, G Ming et al., Cell

Mouse Model Zika In Utero Transmission

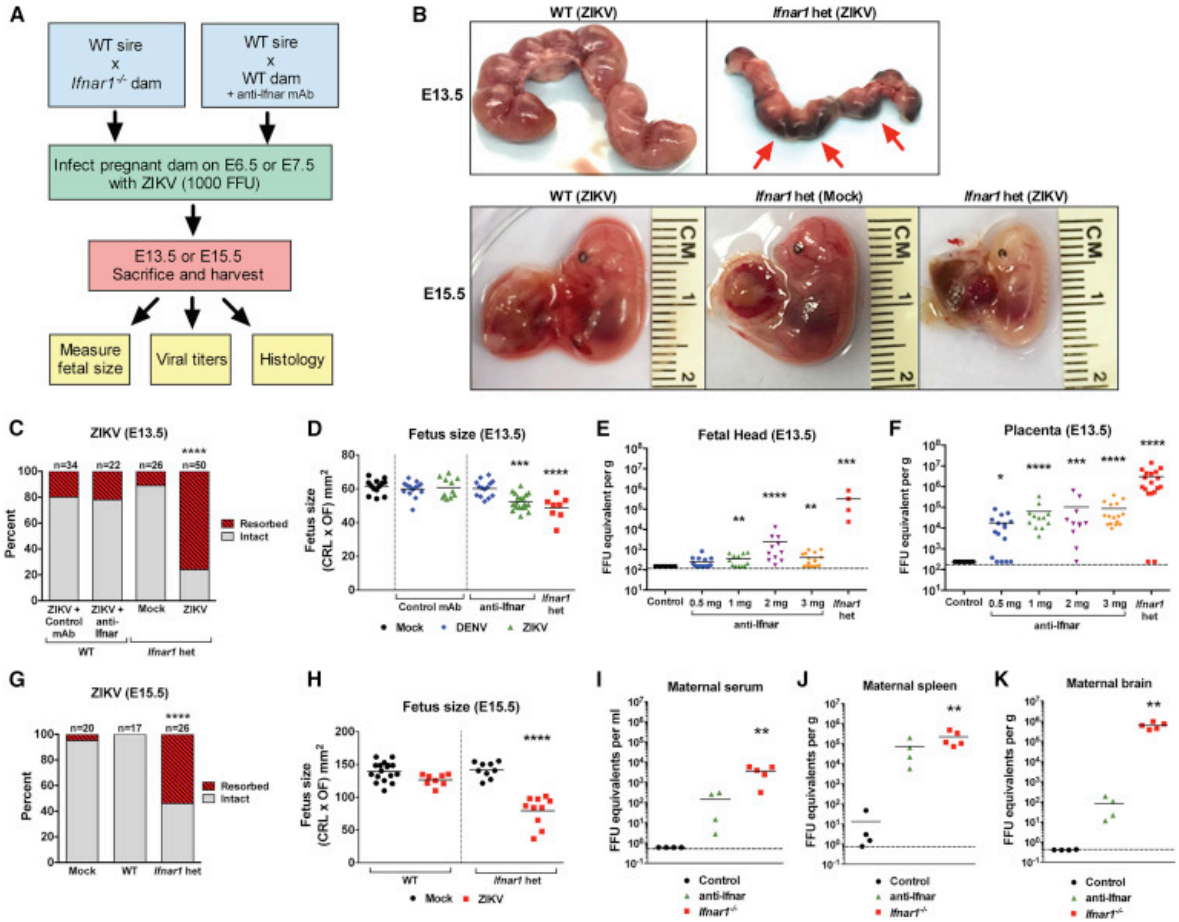


Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise

Jonathan J. Miner, Bin Cao, Jennifer Govero, Amber M. Smith, Estefania Fernandez, Omar H. Cabrera, Charise Garber, Michelle Noll, Robyn S. Klein, Kevin K. Noguchi, Indira U. Mysorekar, Michael S. Diamond

null, Volume 165, Issue 5, 2016, 1081–1091

Mouse Model Zika In Utero Transmission



Jonathan J. Miner, Bin Cao, Jennifer Govero, Amber M. Smith, Estefania Fernandez, Omar H. Cabrera, Charise Garber, Michelle Noll, Robyn S. Klein, Kevin K. Noguchi, Indira U. Mysorekar, Michael S. Diamond

null, Volume 165, Issue 5, 2016, 1081–1091

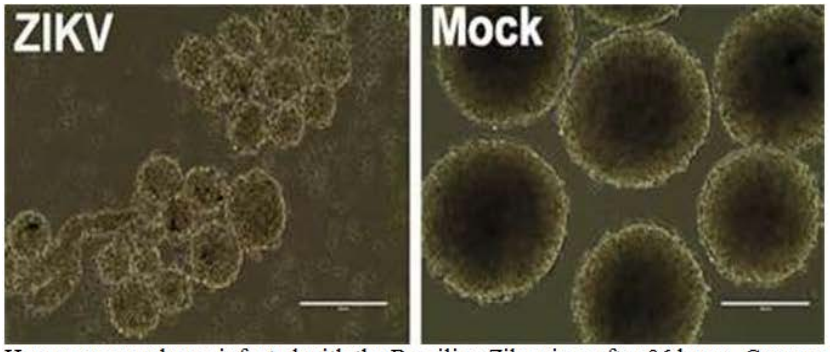
http://dx.doi.org/10.1016/j.cell.2016.05.008

NATURE

RESEARCH LETTER

Fernanda Cugola, Isabella Fernandes et. al. Published online May 11, 2016

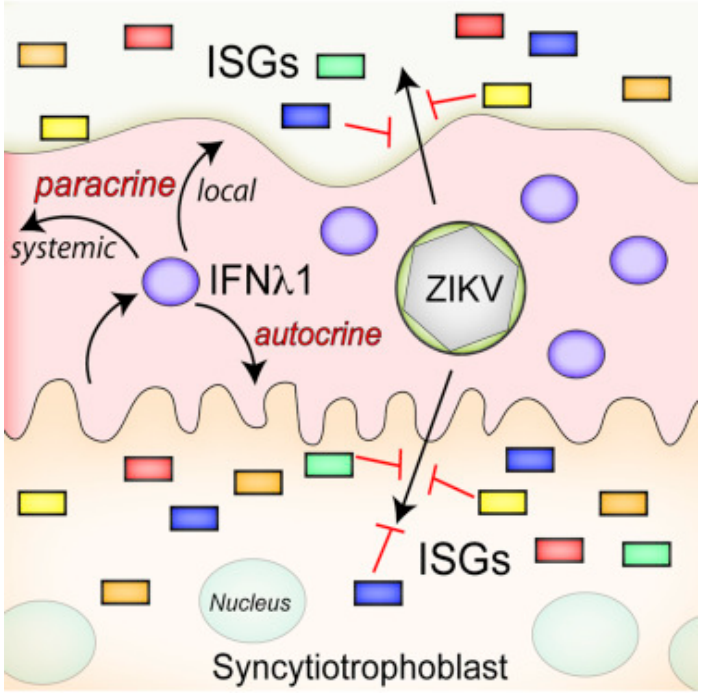
- The Brazilian Zika Virus strain causes birth defects in experimental models
  - ZIKV crosses the placenta
  - Targets cortical progenitor cells
  - Induces cell death by apoptosis and autophagy



Human neurospheres infected with the Brazilian Zika virus after 96 hours. Compared to mock-infected controls, the neurospheres show dramatic cell death with arrested growth, resulting is significantly reduced size. Credit: UC San Diego Health

Zika and the Placenta

Primary Human Trophoblasts

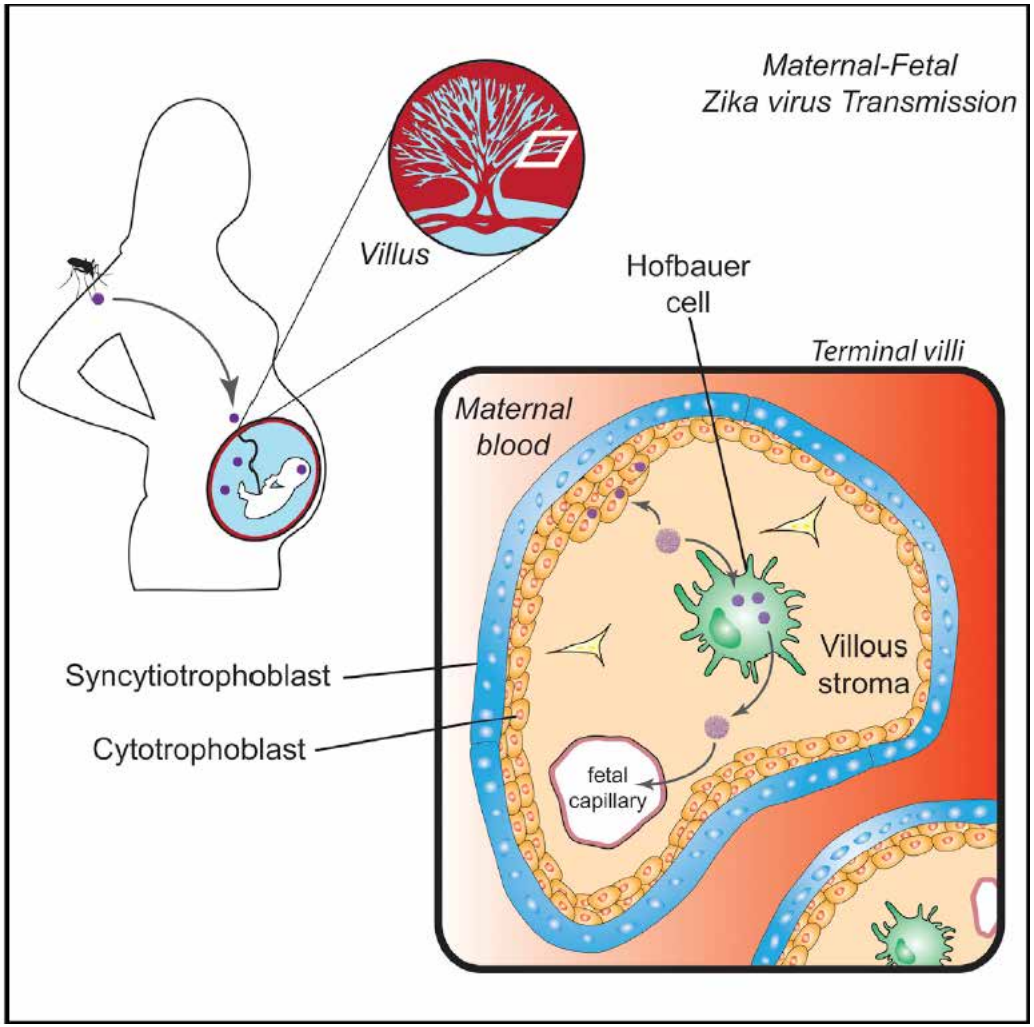


Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection

Avraham Bayer, Nicholas J. Lennemann, Yingshi Ouyang, John C. Bramley, Stefanie Morosky, Ernesto Torres De Azeved Marques Jr., Sara Cherry, Yoel Sadovsky, Carolyn B. Coyne

null, Volume 19, Issue 5, 2016, 705–712

http://dx.doi.org/10.1016/j.chom.2016.03.008



Zika virus PR type replicates in primary human placental macrophages, Hofbauer cells and lesser extent cytotrophoblasts

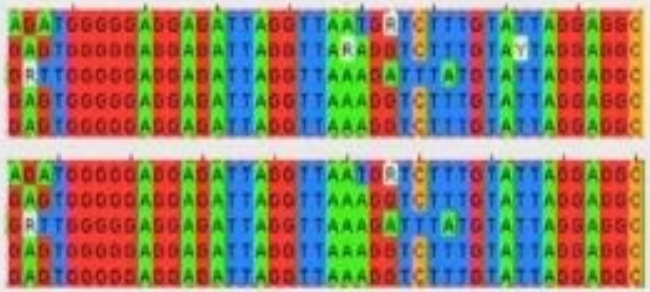
Suggesting that Zika virus gains access to the fetal compartment by directly infecting placental cells and disrupting the placental barrier

Quicke et. al. May 2016

Three hypotheses as to why Zika virus causes new clinical syndromes

Mike Diamond

- Zika virus has evolved at the sequence level



New strain
(African versus Asian)

- Different host populations: unique human genetics

New people

- Pre-existing immunity to a related flavivirus predisposes to more severe Zika virus infection

New immune background

Zika: Research Gaps Related to Pregnancy and Pregnancy Outcomes

- Risk of infection in pregnancy
- Sequelae of Zika exposed and infected infants without microcephaly
- Diagnostics
- Long-term reservoirs for Zika
- Treatment
- Vaccine

PAR-16-106 - Rapid Assessment of Zika Virus (ZIKV) Complications (R21)

- Open March 20, 2016 and expires on March 1, 2019
- Applications accepted on a rolling basis, beginning on April 20, 2016

Provides an expedited (rapid) funding mechanism for research on Zika virus (ZIKV) and its complications given the urgent need to determine whether ZIKV infection causes microcephaly and other congenital abnormalities in babies and the potential rapid spread of ZIKV to the United States.

Zika in Infants and Pregnancy (ZIP) Cohort Study

- Multi-site, multi-country prospective observational cohort study
- To determine the risks of Zika infection during pregnancy on maternal and fetal outcomes while controlling for potential confounders
- 10,000 women planned
- 4 current sites, additional sites planned
- Standardized protocol, data collection
- Supported by NICHD, NIAID, NIEHS and Fundacao Oswaldo Cruz-Fiocruz

Zika cohort study

<13 wks gestation
Offered enrollment into cohort study

Followed through pregnancy

- Zika infection - symptomatic
- Zika infection - asymptomatic
- No Zika infection

All children followed: those with and without anomalies

Cofactors:
- environmental exposures
- co/prior infections
- toxins

Acknowledgments

- Cathy Spong
- Bill Britt
- Mike Diamond
- Melissa Parisi
- Christine Rogers

Questions?