

ZIP Study: Understanding the Impact of Zika Virus on Pregnancy and Child Outcomes

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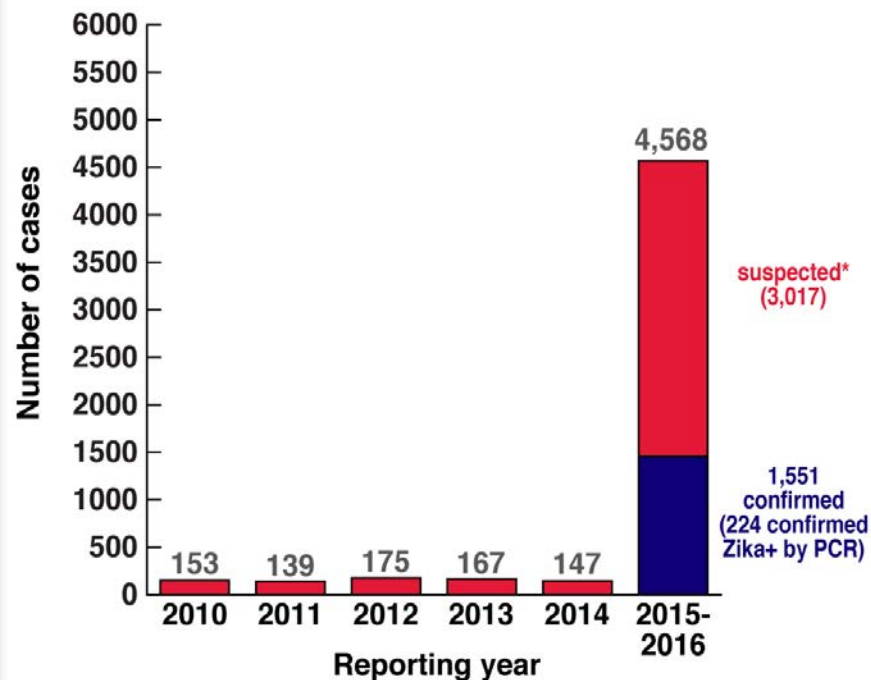
Eunice Kennedy Shriver National Institute
of Child Health and Human Development



Brazil Zika Outbreak

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

Microcephaly cases in Brazil 2010-14;
suspected/confirmed cases 2015-2016

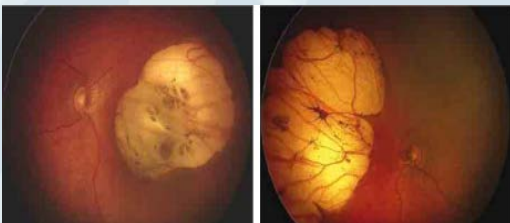
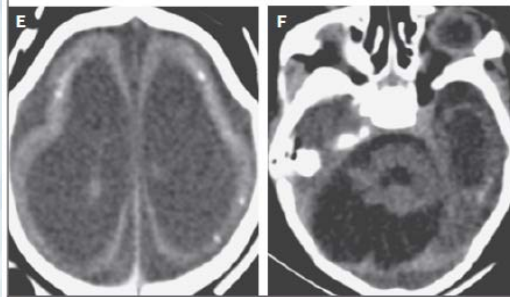
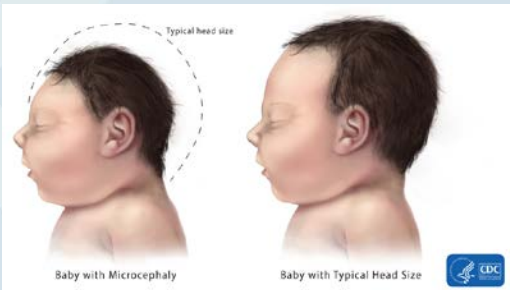


*does not include 3,262 cases investigated and discarded

Source: Brazilian MOH; data as of 6/4/2016.



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





The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

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

- 88 women with rash
 - 82% Zika positive
- 58% (n=44) Zika+ followed with ultrasound
- 29% with fetal abnormalities
- 17% with microcephaly, atrophy, calcifications



Fetal Brain Anomalies

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

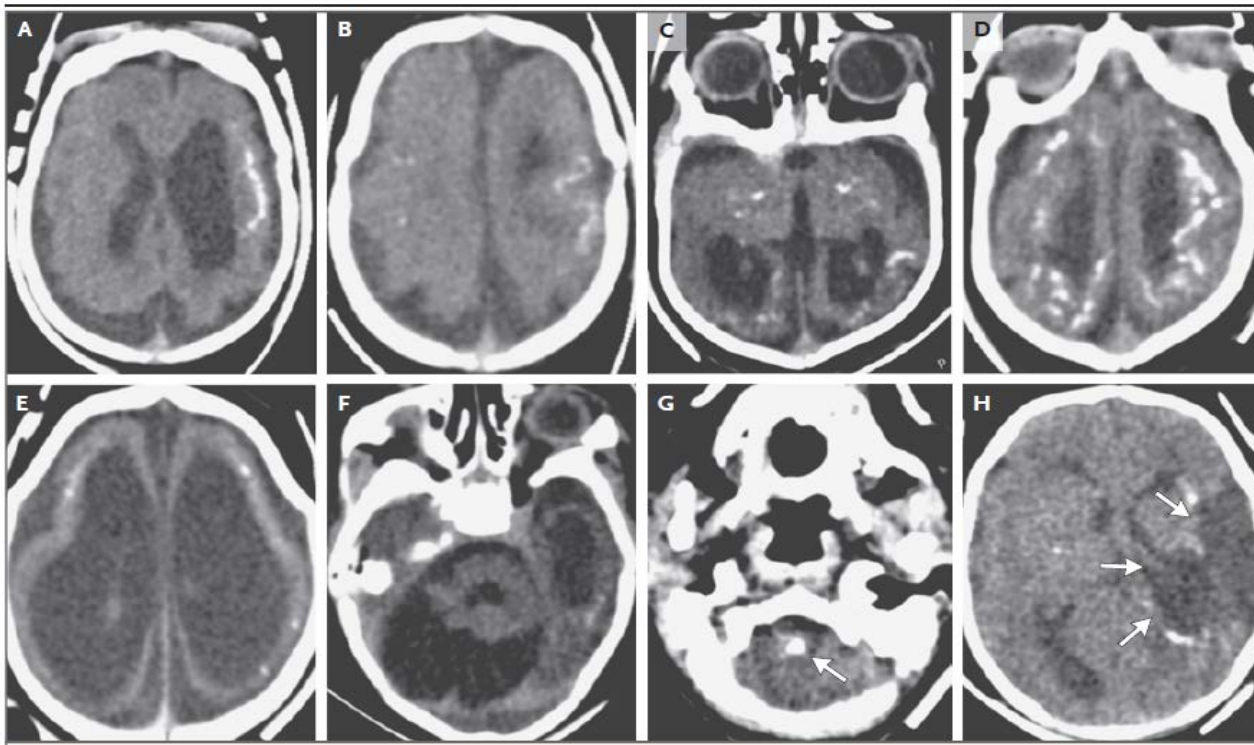




CT Scans Reveal Extensive Abnormalities

23 infants with microcephaly in Pernambuco, Brazil

The NEW ENGLAND JOURNAL of MEDICINE



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

Hazin *et al*, *NEJM* April 6, 2017



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 Icksang Ko, MD; Maurício 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

Figure 4. Fundus Photographs of a 1-Month-Old Infant

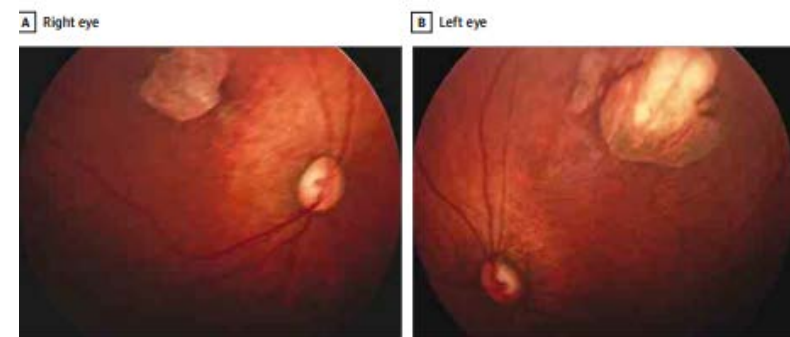
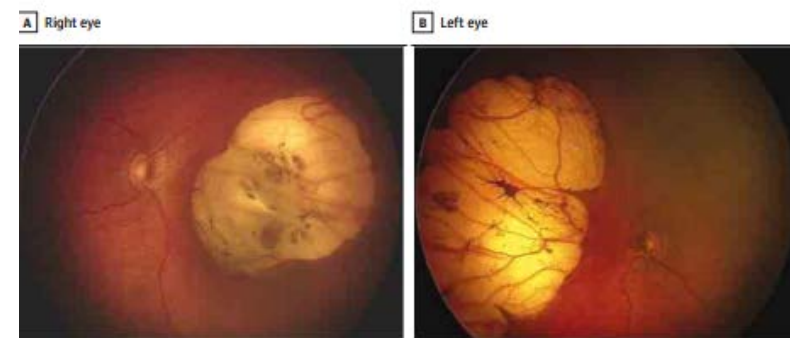


Figure 5. Fundus Photographs of a 20-Day-Old Infant





Asymptomatic Zika Infection

- Case report from Brazil
- Upper and lower limb spasms
- CT: cerebral calcifications, ventriculomegaly, lissencephaly
- Ocular exam: chorioretinal scar

Ventura et al, Lancet online 6/7/16



Chorioretinal scar on the macular region with no associated optic disc findings in an infant without microcephaly



Long Term Outcomes: Unknown

- Long term function:
motor and sensory abnormalities
- Anticipate a spectrum of outcomes:
 - Developmental delay
 - Intellectual impairments
 - Mental disorders – autism, schizophrenia, etc
 - Motor abnormalities



Zika and Timing of Infection



First trimester

Second trimester

Third trimester



Blastocyst



Week 0

13

20

30

40

25 days



100 days



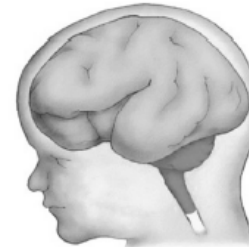
5 months



6 months



8 months



9 months





Risk not limited to 1st trimester

ORIGINAL ARTICLE

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

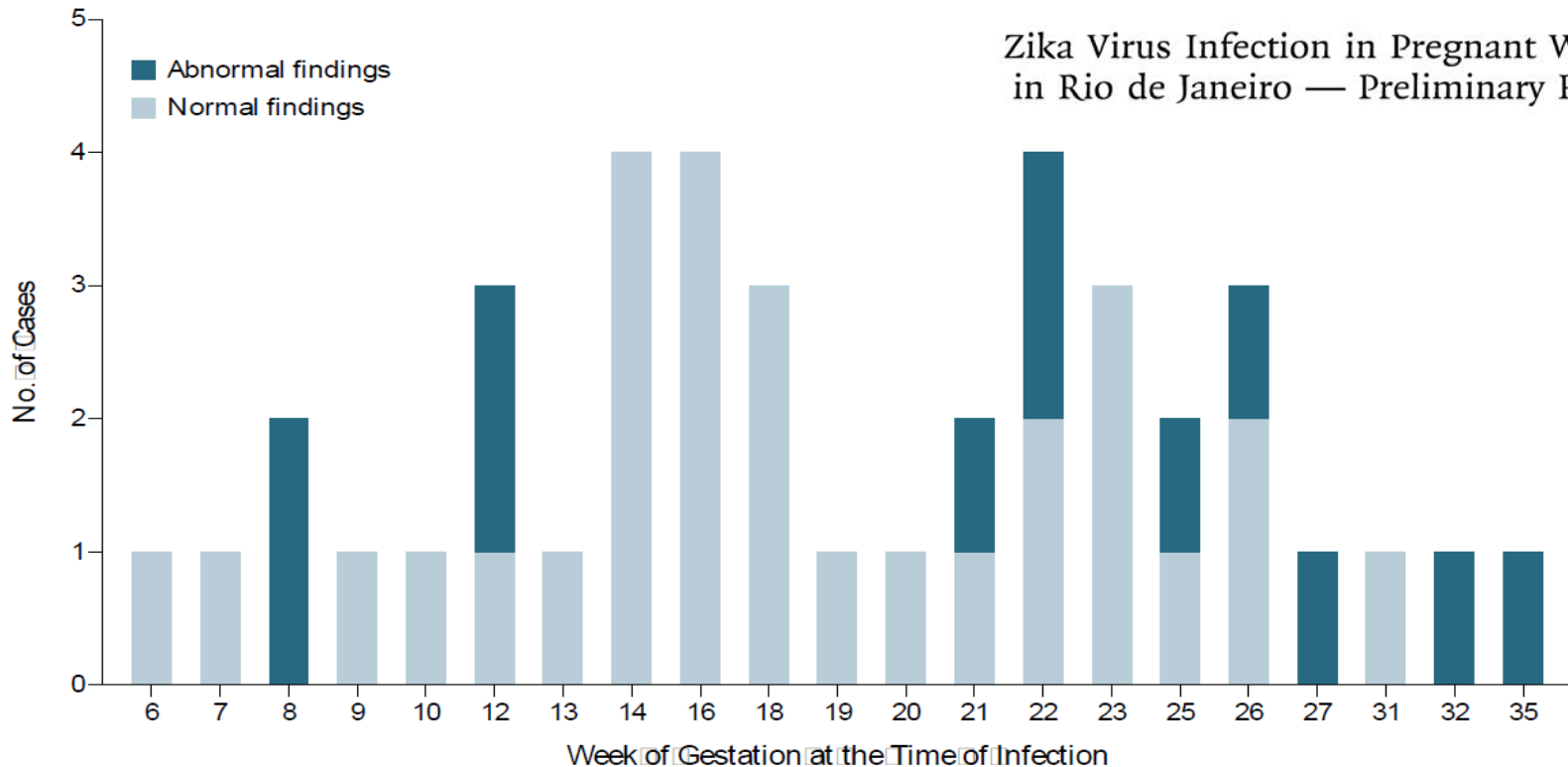


Figure 2. Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings. Twelve of 42 women (29%) in whom fetal ultrasonography was performed had abnormal findings.

Zika Research Gaps: Pregnancy and Pregnancy Outcomes

- Risk of infection in pregnancy
 - Modeling estimates microcephaly risk of 1-13% from 1st trimester infection *NEJM Johansson 6/8/16*
- Outcome from asymptomatic infection
- Sequelae of Zika exposed and infected infants without microcephaly
- Long-term reservoirs for Zika
- Evaluation, management, treatment for children exposed to Zika in utero

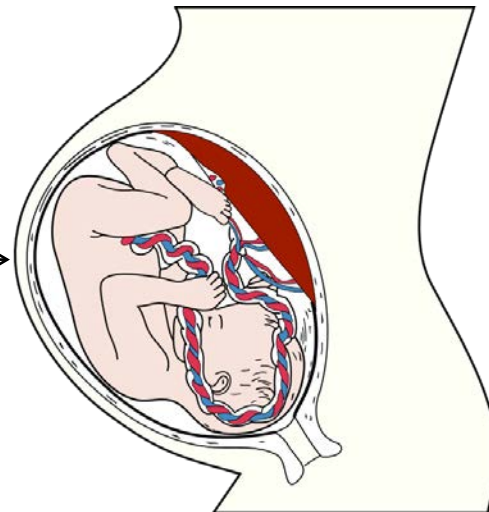


Modes of Transmission



Modes of Transmission

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

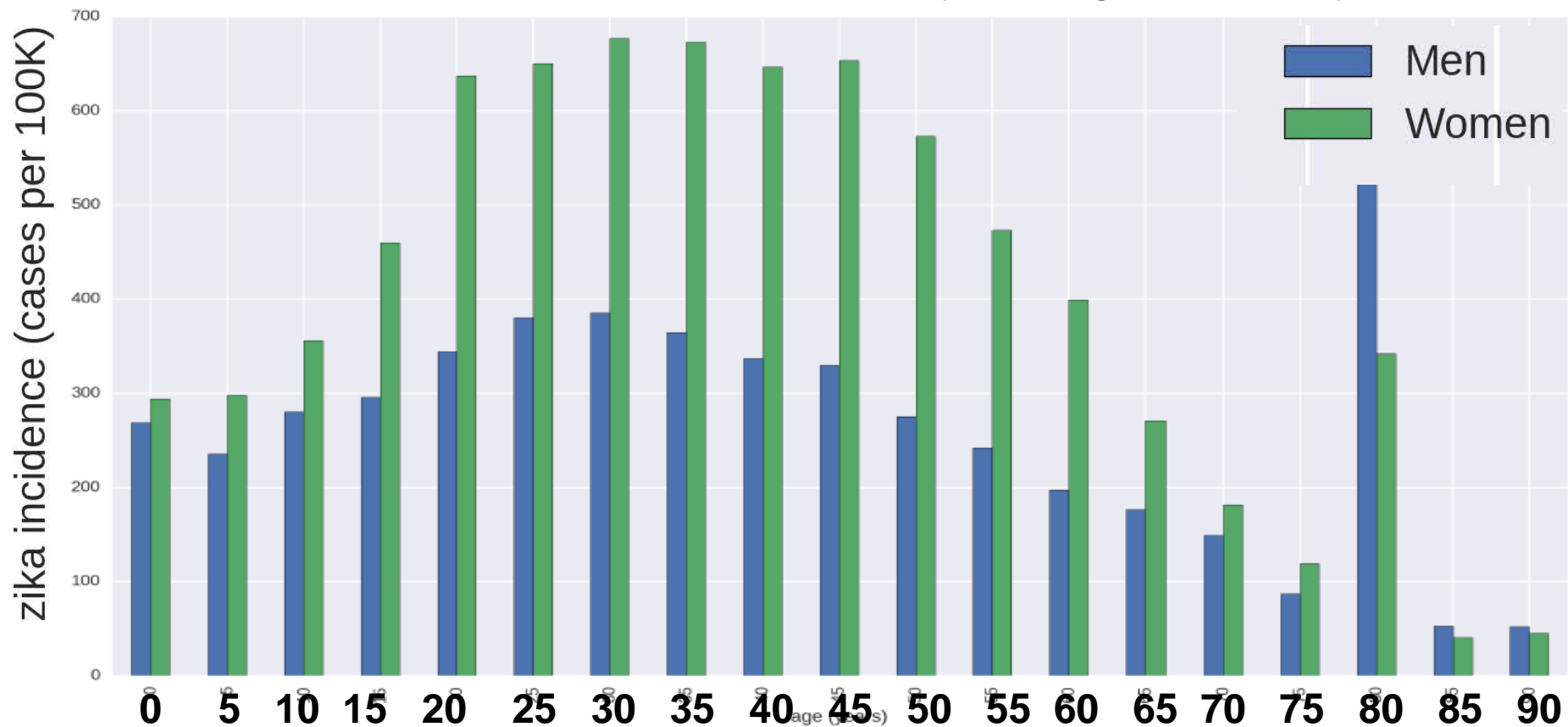




Could increased incidence of ZIKV in women be caused by sexual transmission?

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 Coelho et al, *The Lancet Infectious Disease* May 25, 2016



Sexual Transmission: What We Don't Know

- Transmission for asymptomatic infection
- For how long after the infection semen can infect a sexual partner
 - *Lancet* 6/7/16: transmission 34-41 d after infection
- If a woman with Zika can pass the virus to her sex partners
- If Zika can be transmitted through saliva



Zika and Viremia



Pregnancy: Prolonged Viremia

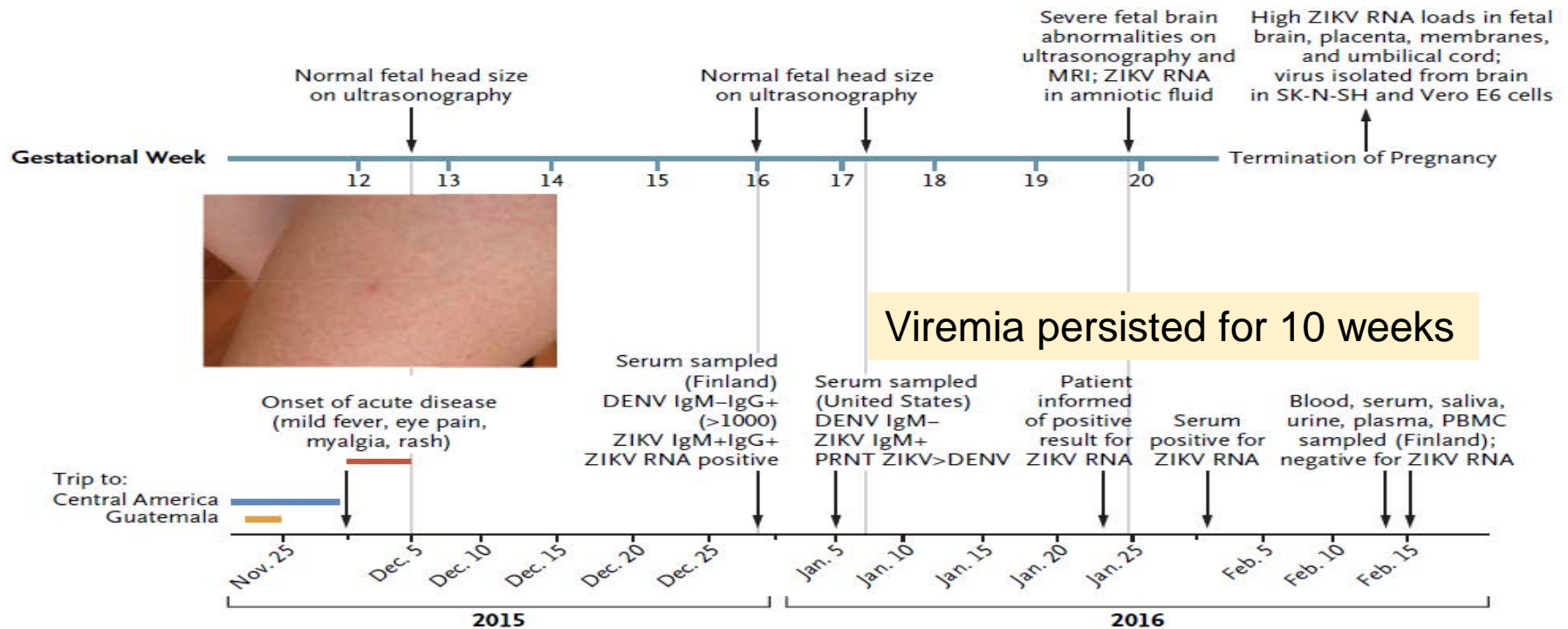
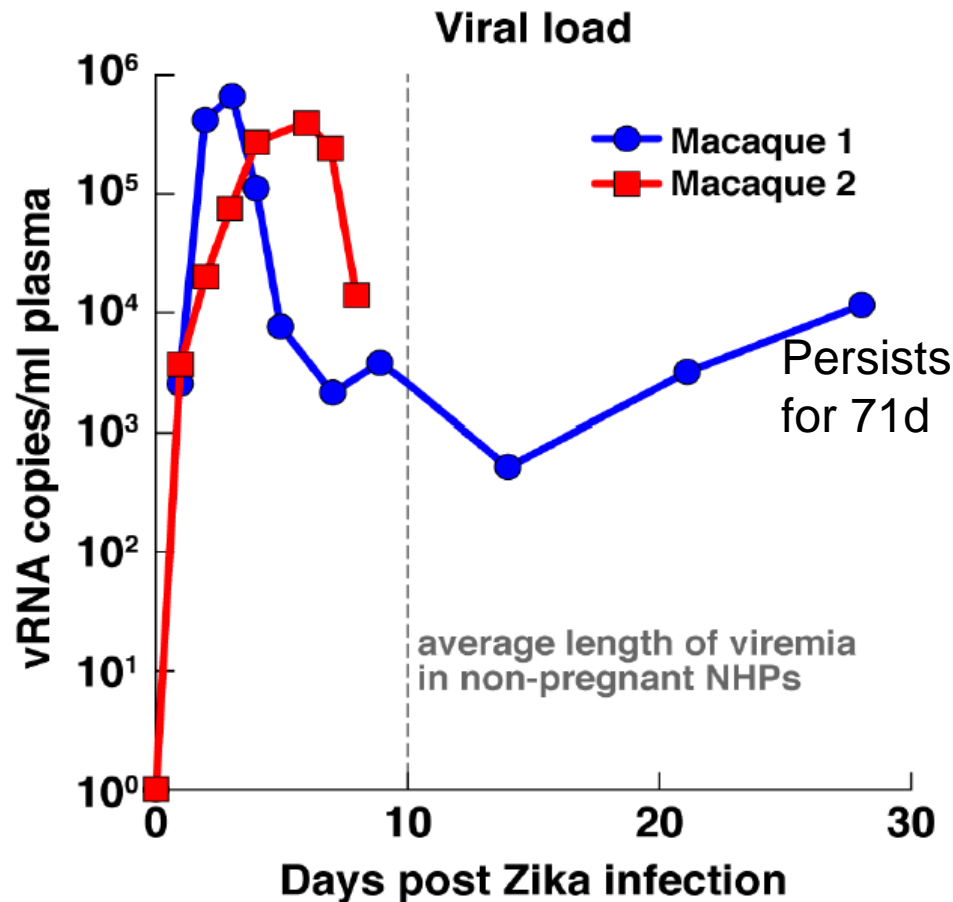


Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.

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.



Pregnancy: Prolonged Viremia



Virus is likely from fetus

- 1) Virus in plasma, not urine, suggesting the maternal immune system was able to contain virus replication
- 2) Viral variants detected near the end of the "typical" viremia (d7) are distinct from those in "prolonged" viremia (d21). This would be seen if the fetus was infected with a small number of transmitted/founder viruses from the mother during the initial burst of virus replication



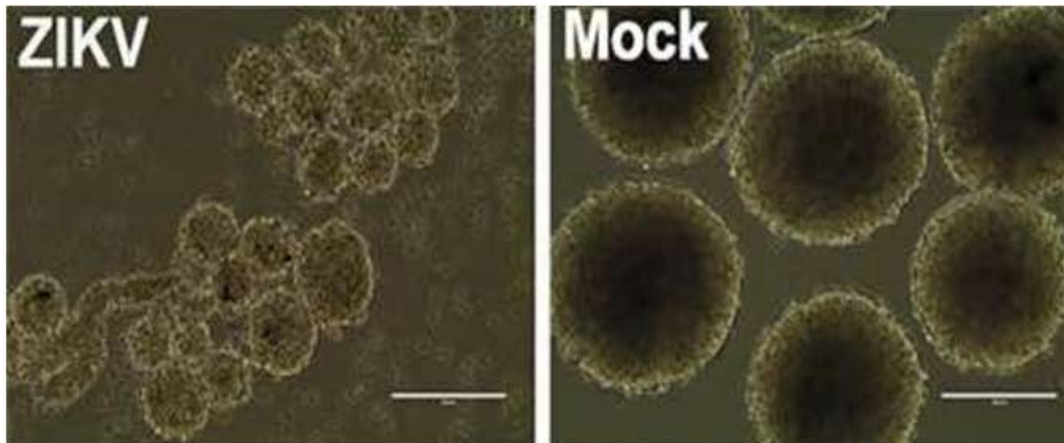
How Might Zika Virus Affect the Fetus?



Proposed Mechanism

- ZIKV directly infects human cortical neural progenitor cells with high efficiency, resulting in stunted growth, transcriptional dysregulation and cell death

Garcez et al, Science 4/14/16
Tang et al, Cell Stem Cell 4/4/16
Cugola et al, Nature Res Letter 5/11/16



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 in significantly reduced size. Credit: UC San Diego Health

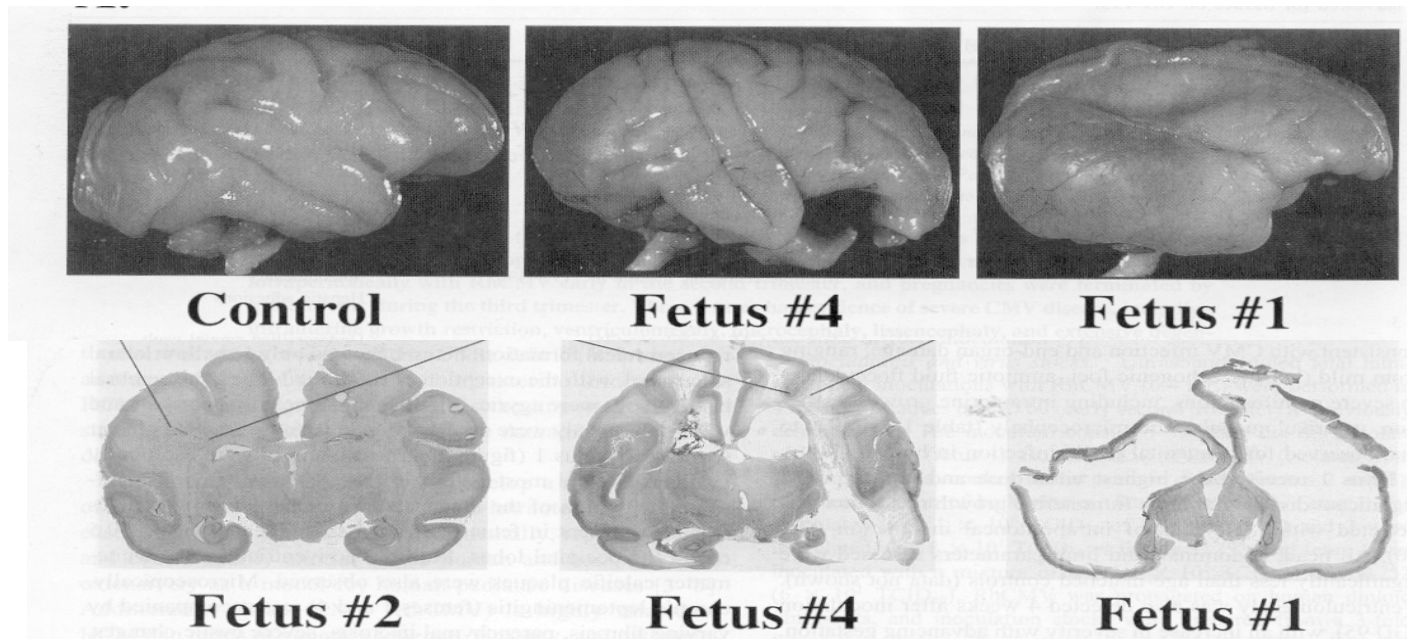


Impact on Fetal Brain: Congenital CMV

4 rhesus macaques infected in second trimester

Direct virus-mediated damage to the developing CNS

- Loss of neural progenitor cells (early gestation infection>damage)
- Loss of supporting vasculature in the CNS





What Are We Doing to Address This Public Health Emergency?

Guidance Documents

- Travel
- Pregnancy
- Reproductive planning

Zika Virus



Language: English ▾

ZIKA & PREGNANCY



Pregnant women

ABOUT ZIKA VIRUS DISEASE

Zika virus disease is caused by Zika virus and is spread to people primarily through infected *Aedes* mosquitoes...

AREAS WITH ZIKA

Countries and territories with active Zika virus transmission...

SYMPTOMS, DIAGNOSIS, & TREATMENT

Most common symptoms are fever, rash, joint pain, or red eyes...

FOR HEALTH CARE PROVIDERS

Clinical evaluation, disease, diagnostic testing, obstetricians, pediatricians...

Spotlight

[What you should know about Zika virus and sexual transmission](#)

At A Glance - Zika in the U.S. (as of April 6, 2016)

US States


- Travel-associated Zika virus disease cases reported: 346
- Locally acquired vector-borne cases reported: 0
- Of the 346 cases reported, 32 were pregnant women, 7 were sexually transmitted, and 1 had Guillain-Barré syndrome

US Territories

- Travel-associated cases reported: 3
- Locally acquired cases reported: 351
- Of the 354 cases reported, 37 were pregnant women and 1 had Guillain-Barré syndrome

[More >](#)

What's New

- [April 1, 2016: Zika Action Plan Summit](#)
- [April 1, 2016: Doctor's visit checklist: For Pregnant Women who Travel to an area with Zika](#)
 [PDF - 2 pages]
- [April 1, 2016: Doctor's visit checklist: For Pregnant Women who Travel to an area with Zika](#)



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



Initial ZIP Study Sites





ZIP Cohort Study

- Recruitment through prenatal clinics and community outreach
- Enrollment early in pregnancy with monthly assessments during pregnancy
- Clinical information and biospecimens will be collected
- Infants will be evaluated within 48 hours of birth and at 3, 6, and 12 months





Zika Cohort Study

Followed through pregnancy

<13 wks gestation
Offered enrollment
into cohort study

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

All children
followed: those
with and without
anomalies

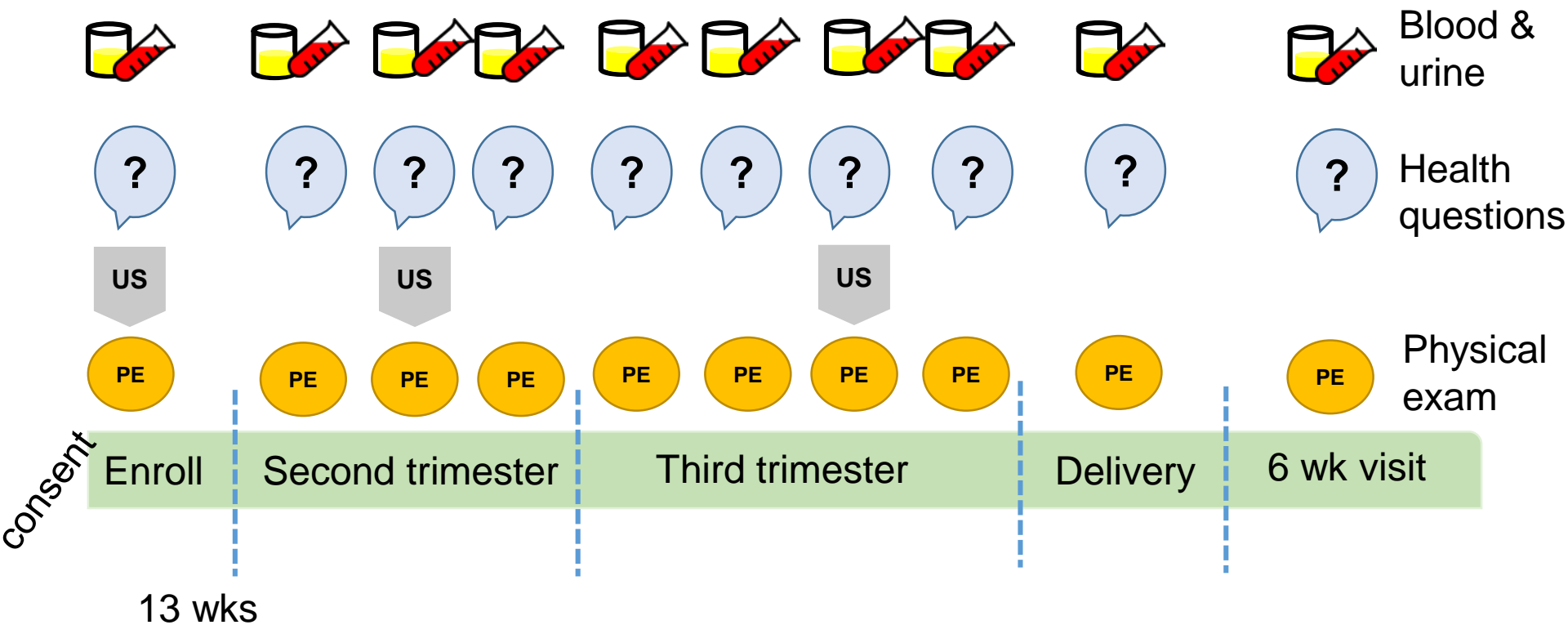
Cofactors:

- environmental exposures
- co/prior infections
- toxins



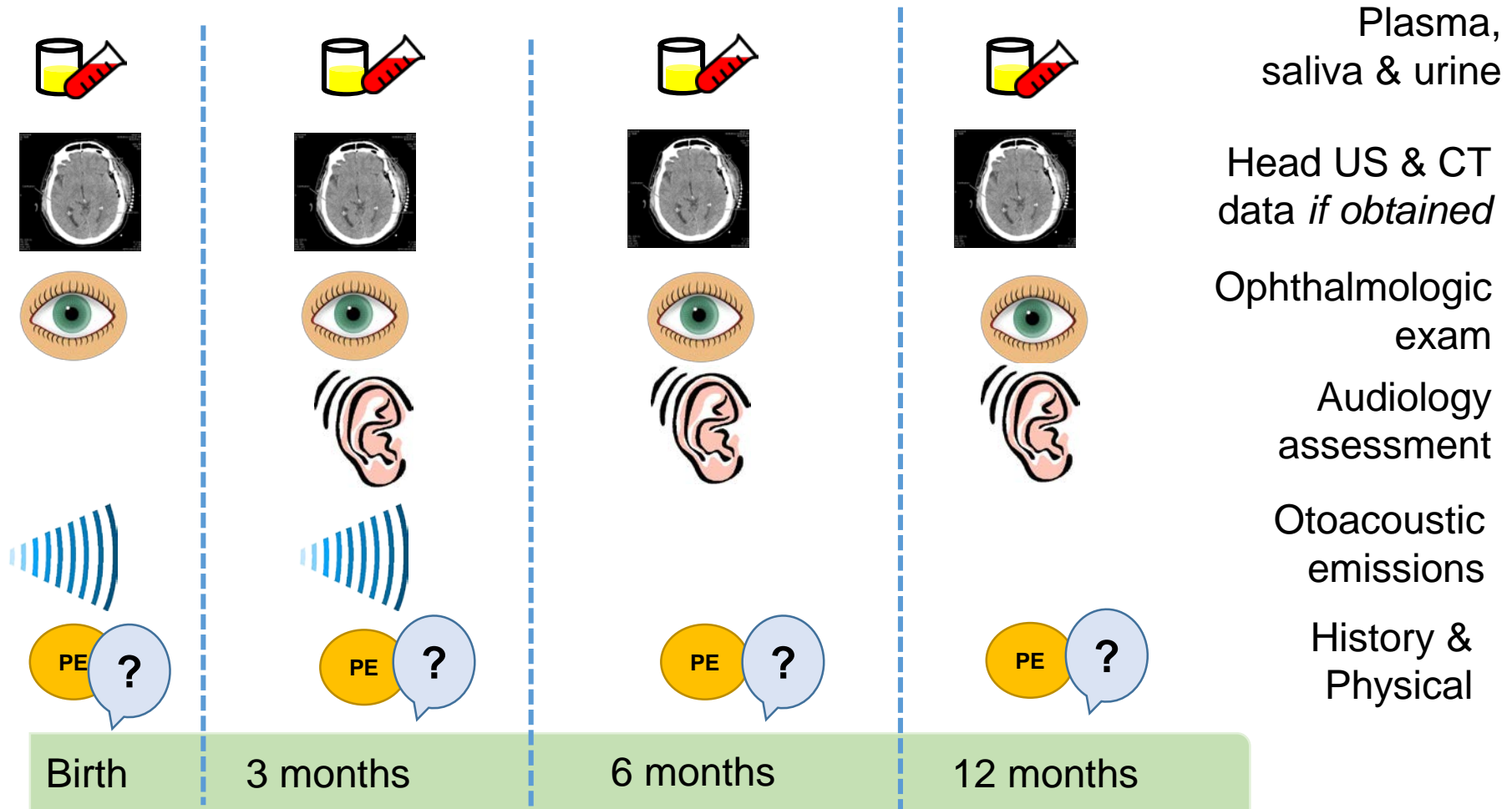


Zika Cohort Study Template: Pregnancy





Zika Cohort Study Template: Infant





Workshop Focused on the Children

- September 2016 in Bethesda, Maryland
- Define the evidence to understand how prenatal Zika virus infection affects child development and to identify strategies for evaluation, management, and treatment



Photo attribution: Agência Brasil



Questions?