Zika Virus Update

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Disclosures

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- FAPERJ (State of Rio de Janeiro)
- CAPES (Coord. for Improvement of Higher Education Ministry of Education Brazil)
- CNPq (Brazilian National Council for Research)

Educational Objectives:

(1) To provide general information on the biology and epidemiology of ZIKV infection
(2) To describe the recent epidemic of ZIKV in Brazil
(3) To present research findings on ZIKV mother to child transmission and maternal and neonatal outcomes
(4) To present work in progress on ZIKV transmission
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.

1.1 Information about the candidate city
Venue: The event will take place on the Lagoa Rodrigo de Freitas.
Staff: Rio de Janeiro - City: Rio de Janeiro - Population: 21,993,363

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**Zika virus in the Americas: Early epidemiological and genetic findings**

**2013 FIFA Confederations Cup**

**Copa das Confederações da FIFA Brasil 2013**

<table>
<thead>
<tr>
<th>Host country</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dates</td>
<td>15–30 June</td>
</tr>
<tr>
<td>Teams</td>
<td>8 (from 6 confederations)</td>
</tr>
<tr>
<td>Venue(s)</td>
<td>6 (in 6 host cities)</td>
</tr>
</tbody>
</table>

Final positions:
- Champions: **Brazil** (4th title)
- Runners-up: **Spain**
- Third place: **Italy**
- Fourth place: **Uruguay**

Tournament details:

Cite as: R. Faria et al., Science 10.1126/science.aab5036 (2016).
Reinfestation by *Aedes aegypti*

1930s | 1970 | 1998

Distribuição dos Municípios Infestados por *Aedes aegypti*
Brasil - 1997/2000 (*)

2,780 Mun. Infest.

3,592 Mun. Infest.

(*) Dados sujeitos à revisão
Fonte: CRFS/FUNASA/CINEP/CGVAM/COFAB
Dengue fever epidemic hits Rio de Janeiro

Infectious diseases... NBCNEWS.com

Associated Press

Sociedade

Zika, Dengue E Chicungunha

Três vírus e um mosquito

Combate ao Aedes é a melhor prevenção contra doença suspeita de provocar microcefalia
Microcephaly: In 90% of cases, responsible for developmental delay, vision and hearing impairment, and a gamut of neurologic problems, including seizures.
ZIKV identified by RT PCR in the amniotic fluid of 2 women from Paraiba, northeastern Brazil whose infants were born with microcephaly.

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities


Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.
What is Zika virus (ZIKV)?

- Zika virus is an arbovirus, a mosquito-borne ssRNA flavivirus. Known as ZIKV, the virus is in the same category as other flaviviruses such as dengue, yellow fever, Japanese Encephalitis and West Nile.

- **Origin**: Isolated from rhesus macaques in the Zika Forest, Uganda, in 1947, by the scientist GW Dick.

- Virus first identified in humans in Nigeria in the 1950s and 1960s.

  For over 60 years the virus caused sporadic outbreaks and few cases in humans were known.

  Until 2007/2013, virus identified in individuals from Africa and Asia, and studies showed antibody positivity in individuals from these areas.
ZIKV structure very similar to that of other flaviviruses:
• Nucleocapsid 25-30 nm in diameter surrounded by a host-membrane derived lipid bilayer containing envelope proteins E and M
• E protein covers most of the virion surface and is involved in replication such as host cell binding and membrane fusion

The diagnostic conundrum...

Retrospective serologic diagnosis not possible in dengue endemic areas - how to monitor asymptomatic infections?
Aedes aegypti

- ZIKV is transmitted by the infected female mosquito
- Transmitted through the saliva of the mosquito
- Primarily a daytime feeder
- Lives around human habitation
- Lays eggs and produces larvae preferentially in artificial containers

Replication and Transmission of Flaviviruses

1. Virus transmitted to human in mosquito saliva
2. Virus replicates in target organs
3. Virus infects white blood cells and lymphatic tissues
4. Virus released and circulates in blood
Replication and Transmission Flaviviruses

5. Second mosquito ingests virus with blood
6. Virus replicates in mosquito midgut and other organs, infects salivary glands
7. Virus replicates in salivary glands

Prior Zika Virus Epidemics

2007 Micronesia
- An epidemic was reported in the Yap Islands, one of the 4 states in the Archipelago of Micronesia in the Pacific Ocean. Local and U.S. Researchers identified 185 suspected cases, of which 49 were confirmed and 59 were considered probable cases. It was estimated that 5050 of 6892 islanders > 3 years of age (73% of the population) was infected during the epidemic. The majority of subjects did not develop clinical illness.

2013 – French Polynesia
- In October of 2013, French Polynesia was in the midst of a serious dengue outbreak when health authorities identified Zika Virus cases. Over 8,500 cases were identified, with approximately 11% of the population affected. Forty cases of Guillain-Barré Syndrome were reported. Unclear how Zika reached the South Pacific.
- Until this outbreak, no serious consequences of Zika Virus had been reported. Other affected islands: Cook Island, Easter Island, Vanuatu, Solomon Island and New Caledonia. Imported cases in Japan, Norway, France.
Guillain-Barré Syndrome:
Zika virus has been associated with GBS (Acute immune-mediated demyelinating polyneuropathy). An autoimmune process leading to destruction of the myelin sheaths. Treated with IVIG or plasmapheresis.
As of December 2016, there were 4,400 confirmed and probable Zika cases in the continental US.

- 65% traveled to the Caribbean
- 18% traveled to DR
The Zika Virus Grew Deadlier With a Small Mutation, Study Suggests

The New York Times

A single mutation in the prM protein of Zika virus contributes to fetal microcephaly

- A single serine to asparagine substitution (S139N) in the viral polyprotein increased ZIKV infectivity in human and mouse neural progenitor cells.
- More severe microcephaly in the mouse fetus
- Higher mortality in neonatal mice.
- Mutation arose before the 2013 epidemic in the French Polynesia.

Zika virus identified in semen of an infected patient in French Polynesia.

Potential for breast milk and blood product transmission; virus excreted in saliva, semen, milk, urine
During the Zika virus outbreak in French Polynesia, 1505 asymptomatic blood donors were screened by molecular testing for ZIKAV viremia between November 2013 to February 2014: 42 (3%) were positive for ZIKAV. Blood banks should screen for ZIKAV in endemic areas.

Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systematic review

April 10, 2017

Detection of Zika virus in saliva

Detection of Zika Virus in Urine

Ann-Claire Gourinat, Olivia O'Connor, Elodie Calvez, Cyrille Goarant, and Myrielle Dupont-Rouzeyrol

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 1, January 2015
The medians and 95th percentiles for the time until the loss of ZIKV RNA detection were 14 days (95% confidence interval [CI], 11 to 17) and 54 days (95% CI, 43 to 64), respectively, in serum; 8 days (95% CI, 6 to 10) and 39 days (95% CI, 31 to 47) in urine; and 34 days (95% CI, 28 to 41) and 81 days (95% CI, 64 to 98) in semen. Few participants had detectible ZIKV RNA in saliva or vaginal secretions.
From dengue surveillance efforts a study began...

• Since 2012 at Fiocruz Manguinhos pregnant women and their infants have been followed in a prospective cohort for the study of incidence of dengue in this population.

• In late 2015 following identification of ZIKV in Rio de Janeiro the cohort study was modified to actively screen for ZIKV by RT-PCR in blood and urine of pregnant women who presented with a rash within the last 5 days.
First detection of autochthonous Zika virus transmission in a
HIV-infected patient in Rio de Janeiro, Brazil

Guilherme A. Calvet a,b, Ana Maria B. Filippis b,c, Marcos Cesar L. Menconça a,b,1, Patrícia C. Sequeira a,b, André M. Siqueira c, Valdir A. Veiose c, Rita M. Nogueira b, Patricia Brasil a


Published: April 12, 2016
A modeling study which evaluated rainfall and other environmental & behavioral conditions in the state of Rio de Janeiro in association with screening of 10,459 serum/urine specimens for Zika, Chikungunya and Dengue by PCR (and also IgM serology for Chikungunya).

- Zika cases were more prevalent in areas of Rio with < access to municipal water (water hoarding).
- CHIKV incidence increased with increasing land urbanization in specific neighborhoods.

Rainfall Predicts Zika in Rio de Janeiro...
- with a lead time of three weeks
- Social and environmental variables predict the number of cases
- The shorter latent period of Chikungunya (2 days) in the mosquito can explain the temporal dynamics of Chikungunya and Zika (8-10 days)
- Chikungunya outcompetes Zika in the environment
- CHIKV incidence increased with % of urbanized land in neighborhoods.

Fuller et al, Plos One 2017
## Zika Virus vs. Rubella Symptoms

<table>
<thead>
<tr>
<th>Zika Virus Symptoms</th>
<th>Rubella Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Arthralgias, predominantly of the hands and feet</td>
<td>• Mild fever of 102 F (38.9 C) or lower</td>
</tr>
<tr>
<td>• Edema of the hands and feet</td>
<td>• Headache</td>
</tr>
<tr>
<td>• Low grade fever (≤ 38.5°C)</td>
<td>• Conjunctival injection</td>
</tr>
<tr>
<td>• Patchy erythema</td>
<td>• Enlarged, tender lymph nodes at the base of the skull, the back of the neck and behind the ears</td>
</tr>
<tr>
<td>• Pruritus</td>
<td>• A fine, pink rash that begins on the face and quickly spreads to the trunk and then the arms and legs, before disappearing in the same sequence- often pruriginous</td>
</tr>
<tr>
<td>• Eye pain</td>
<td>• Aching joints, especially in young women</td>
</tr>
<tr>
<td>• Conjunctival injection</td>
<td></td>
</tr>
<tr>
<td>• Dizziness</td>
<td></td>
</tr>
<tr>
<td>• Myalgias</td>
<td></td>
</tr>
<tr>
<td>• Posterior lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>• GI symptoms may occur, but are less frequent.</td>
<td></td>
</tr>
</tbody>
</table>
Proposed clinical case definition for suspected Zika cases:
Presence of rash, pruritus, conjunctival hyperemia, absence of fever, no petechiae, no anorexia.
Cerebral calcifications patient # 24

![Ultrasound image](image)

**Ultrasound and Doppler Findings in Pregnant Women with Confirmed ZIKV**

- **N = 42 patients; 12 abnormal US across gestational ages**
US sensitivity 49% and specificity 68% for association with adverse neonatal outcome. For Zika-specific adverse outcome sensitivity was 22% and specificity 98%.
26 pregnancies with known outcomes; 117 live births in 116 pregnancies (one set of twins)

** 1 Zika+ mother with a miscarriage was co-infected with Chikungunya

*** 3 infants of Zika- mothers were SGA at birth; one was born to a mother with confirmed Chikungunya infection.

Importantly, a negative result on amniocentesis does not rule out vertical transmission and CZS. Viral shedding in amniotic fluid may be transient, as demonstrated in two of our cases (Cases 4 and 11), as well as in other reports [7,8]. In cases of high suspicion for CZS, testing of the placenta and the infant after birth is a critical component of comprehensive evaluation, especially as knowledge of the full spectrum of findings in CZS continues to be elucidated.
125 pregnancies - 46% adverse pregnancy outcomes

Of 117 babies born alive, 42% found to have abnormalities

<table>
<thead>
<tr>
<th>Infant Outcomes</th>
<th>ZIKV-Exposed Live Infants (N=117)</th>
<th>ZIKV-Unexposed Live Infants (N=57)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of SGA babies</td>
<td>10/116 (8.6)</td>
<td>3/57 (5.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of Infants with Microcephaly</td>
<td>4/117 (3.4)</td>
<td>0/57</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of Infants with Microcephaly***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Proportionate microcephaly</td>
<td>2/117 (1.7)</td>
<td>0/57</td>
<td>1.0</td>
</tr>
<tr>
<td>*Disproportionate microcephaly</td>
<td>2/117 (1.7)</td>
<td>0/57</td>
<td>1.0</td>
</tr>
<tr>
<td>Total number of adverse pregnancy outcomes</td>
<td>56/125 (44.4)</td>
<td>7/57 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of adverse infant outcomes</td>
<td>49/117 (41.9)</td>
<td>3/57 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of negative pregnancy outcomes by maternal trimester of infection (including fetal demise)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>11/29 (37.9)</td>
<td>3/57 (5.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Second trimester</td>
<td>37/72 (51.4)*</td>
<td>2/55 (3.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Third trimester</td>
<td>10/44 (22.7)</td>
<td>2/22 (9.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy

Dec 2016


Early Release / June 8, 2017 / 66

Hoen, et al.

Structural CNS abnormalities reported at birth 7%

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

Table 1. Birth Outcomes and Abnormalities Observed in Fetuses and Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Trimester (N=208)</th>
<th>Second Trimester (N=252)</th>
<th>Third Trimester (N=114)</th>
<th>Total (N=553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth or death at term</td>
<td>24 (12.7)</td>
<td>4 (1.6)</td>
<td>0</td>
<td>28 (5.1)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>16 (14.9)</td>
<td>8 (3.2)</td>
<td>5 (4.4)</td>
<td>29 (5.3)</td>
</tr>
<tr>
<td>Major congenital anomaly</td>
<td>26 (12.8)</td>
<td>8 (3.2)</td>
<td>5 (4.4)</td>
<td>39 (7.0)</td>
</tr>
<tr>
<td>NTD</td>
<td>7 (3.4)</td>
<td>2 (0.8)</td>
<td>0</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>Major birth defects</td>
<td>26 (12.8)</td>
<td>8 (3.2)</td>
<td>5 (4.4)</td>
<td>39 (7.0)</td>
</tr>
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<td>Microcephaly</td>
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<td>8 (3.2)</td>
<td>5 (4.4)</td>
<td>39 (7.0)</td>
</tr>
<tr>
<td>Eye abnormalities</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Structural CNS abnormalities reported at birth 7%
### Supplementary Appendix

**Supplemental Table 2: Abnormal outcomes and/or Abnormal Findings at Birth.***

<table>
<thead>
<tr>
<th>Fetal loss</th>
<th>9 Miscarriages/Stillbirths (7.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 49/117 (42%) in 116 pregnancies with live births - 1 set twins</td>
<td></td>
</tr>
</tbody>
</table>

| Microcephaly, cerebral calcifications on CT, global cerebral atrophy, macular lesions |
| 4 microcephalies (3.4%) |
| 2 proportional/2 disproportional |

| Cerebral calcifications, ventriculomegaly, brachycephaly |
| 29 Other CNS findings (25%) |
| MRI findings: Excessive hypersignaling in T2 in the white matter, peritrigonal and tempo-parietal regions. Hypoattenuation in the diffusion sequence. |
| 15 Abnormal CNS imaging (13%) |

| Small for gestational age |
| 1 Small for gestational age alone (0.8%) |
| without CNS findings |

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![Graph](image-url)
The Brazilian Zika virus strain causes birth defects in experimental models

Cell Stem Cell
Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice

The suspected link between Zika virus (ZIKV) infection and microcephaly has raised urgent global alarm. However, there is so far no direct evidence for ZIKV infection impacting brain development. In this study, Li, Xu, and colleagues show that ZIKV replicates efficiently in the mouse embryonic brain by mainly targeting neural progenitor cells. They also show that infected brains are smaller with enlarged ventricles and a thinner cortex, consistent with a microcephalic phenotype.
Late fetal demise: Placental vascular involvement/ Focal necrotic vasculitis

Chronic villitis with fibromuscular sclerosis; marked thickening of the vessel wall

Dr. Elyzabeth Avvad Portari, IFF, Fiocruz- RJ
**Cell**

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

A mouse model of Zika virus infection in pregnancy

Zika virus infection of mice early in pregnancy results in infection of the placenta and fetal brain, causing a fetal syndrome that resembles the intrauterine growth restriction and spontaneous abortion observed in ZIKV-infected pregnant women.

Miner et al., 2016, Cell 165, 1–11
May 19, 2016 © 2016 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.cell.2016.05.006

**Cell Host & Microbe**

**Zika Virus Infects Human Placental Macrophages**

- Zika virus (ZIKV) infects and replicates in primary human placental macrophages
- ZIKV also infects human placental cytotrophoblasts, but with delayed replication kinetics
- ZIKV replication coincides with IFN and antiviral gene induction, but minimal cell death

Quicke et al., 2016, Cell Host & Microbe 20, 1–6
July 13, 2016 © 2016 Elsevier Inc.
http://dx.doi.org/10.1016/j.chom.2016.05.015
A normal, non-infected monocyte, an African Zika virus-infected cell and an Asian Zika virus-infected cell, from left to right

**Zika virus targets blood monocytes**

Two studies identify circulating monocytes as the primary cellular target of Zika virus infection in human blood. Monocytes are an ideal target as they have the potential to be used as a Trojan horse to infiltrate immune-sheltered tissues, including the placenta, testes and the brain, to spread Zika virus.

**Asian Zika virus strains target CD14⁺ blood monocytes and induce M2-skewed immunosuppression during pregnancy**

Suan-Sin Foo, Weiqlang Chen, Von Chan, James W. Bowman, Lin-Chun Chang, Younho Cheil, Ji Seung Yoo, Jiaming Ge, Genhong Cheng, Alexandre Bonnìa, Karin Nielsen-Saines, Patricia Brasil and Jae U. Jung

A normal, non-infected monocyte, an African Zika virus-infected cell and an Asian Zika virus-infected cell, from left to right

**Biomarkers and immunoprofiles associated with fetal abnormalities of ZIKV-positive pregnancies**

Suan-Sin Foo, Weiqlang Chen, Von Chan, Wai-Suet Lee, Shin-Ae Lee, Genhong Cheng, Nielsen-Saines, Patricia Brasil and Jae U. Jung

15% decline in birth rates in the city of Rio de Janeiro between September and December 2016 as compared to the prior year.

Lag time between start of the outbreak and decline in live births is a median of 40 weeks.

Eye Findings in Congenital Zika Virus Syndrome

Key Points

**Question**: Which infants exposed to Zika virus infection in pregnancy should undergo an eye examination?

**Findings**: In this case series of a cohort of 112 infants born to mothers with polymerase chain reaction-confirmed Zika virus infection, 24 (21.4%) had eye abnormalities. Ten infants (41.7%) with abnormal eye examination findings did not have microcephaly, 8 (33.3%) did not have any central nervous system findings, and 2 (8.3%) had eye abnormalities despite maternal third trimester infection.

**Meaning**: Eye abnormalities may be the only initial finding in congenital Zika virus infection, and all infants with potential Zika virus exposure should undergo screening eye examinations.
(A) Retinal pigment epithelium (RPE) mottling of the macula, left eye.
(B) Optic nerve hypoplasia and punched out, extrafoveal RPE atrophy, left eye.
(C) Punched-out, foveal RPE atrophy, right eye.
(D) Optic nerve hypoplasia and excavated chorioretinal lesion with surrounding RPE mottling, right eye.

Eye abnormalities in 24/112 (21.4%) children with PCR-confirmed congenital infection, the most common findings being optic nerve hypoplasia and chorioretinal atrophy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (%)</th>
<th>OR [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>14/24 (48.3)</td>
<td>19.1 [6.0-61]</td>
</tr>
<tr>
<td>Other CNS abnormalities</td>
<td>16/24 (66.7)</td>
<td>8.3 [1.6-41.2]</td>
</tr>
<tr>
<td>Arthrogryposis</td>
<td>7/24 (29.1)</td>
<td>29 [3.3-286]</td>
</tr>
<tr>
<td>First trimester infection</td>
<td>14/24 (58.3)</td>
<td>5.1 [1.9-13.2]</td>
</tr>
<tr>
<td>Second trimester infection</td>
<td>8/24 (33.3)</td>
<td>0.46 [0.18-1.2]</td>
</tr>
<tr>
<td>Third trimester infection</td>
<td>2/24 (8.3)</td>
<td>0.26 [0.056-1.13]</td>
</tr>
</tbody>
</table>

Table 2: Eye Abnormalities in All Infants with PCR-Positive, PCR-Negative, and PCR-Unknown Mother-Infant Pairs

![Image of the journal article pages with figures and text content related to eye abnormalities and Zika virus exposure.](https://example.com/image-url)
Visual function in infants with antenatal Zika virus exposure

Audra S. Zie, MD, MPH,a,b Jesse Tsui, MD,a,b,c Julia D. Rossetto, MD, PhD,a Stephany L. Lane, MD, PhD,b, c; Luiza M. Neves, MD,a,b,c Olivia A. Ziu, MD,a,b,c
Leonel Hartelt, MD,a José Carlos Barreto Silva Filho, MD,a,c Kristina Analfi, MD,a,b,c
Marcos Vinicius da Silva Pente, MD, PhD,a,b Sheilla Moura Pone, MD,a,b,c Nelson Moller, OT,a,b,c José Paulo Pereira Jr, MD,a,b,c Rubens Bellini, MD, PhD,a,b,c Vahid Lingjaerde Annseng, PhD,a,b,c Zihon Vasconcelos, MSc, PhD,a,b,c Patricia Brand, MD, PhD,a,b,c Rania Nitsch-Saimes, MD, MPH,a,b,c and Maria Elisabeth Lopes Moreira, MD, PhD,a,b,c

PURPOSE
To report the findings of a cross-sectional study of visual function in infants with confirmed or suspected antenatal Zika virus (ZIKV) infection seen at a single referral center in Rio de Janeiro.

METHODS
Infants were examined following the ZIKV outbreak period at Instituto Fernando Figueira/IOCruz. Visual function was considered abnormal if an infant could not fix and follow a instansiated high-contrast target (80 cm) by 3-6 months of age. Visual function and associations with structural eye abnormalities, cerebral anomalies (CNS) abnormalities, microcephaly, and nystagmus were assessed. Sensitivity and specificity of screening criteria for structural eye anomalies were assessed.

RESULTS
A total of 173 infants met inclusion criteria. Abnormal visual function was found in 52 infants (30.3%) and was significantly associated with eye abnormalities (OR = 4.1; 95% CI: 1.9-8.9), CNS abnormalities (OR = 3.5; 95% CI: 1.4-8.7), microcephaly (OR = 1.9; 95% CI: 1.0-3.7), and nystagmus (OR = 2.8; 95% CI: 1.0-7.5). Using microcephaly as screening criteria for the detection of eye abnormalities provided a sensitivity of 86.5% (95% CI: 76.4-96.3) and specificity of 62.8% (95% CI: 57.1-68.9). Using both abnormal visual function and microcephaly increased sensitivity to 100% (95% CI: 92.1-100.0) and decreased specificity to 80.5% (95% CI: 72.3-88.6).

CONCLUSIONS
Infants with suspected antenatal ZIKV infection and reduced visual function should be referred to an ophthalmologist. Visual function assessments are helpful in screening for antenatal ZIKV exposure in resource-limited settings and can identify infants who may benefit from visual habilitation. (J AAPOS 2018;22:452-456)

__Table 1. Correlation of visual function to structural findings and nystagmus__

<table>
<thead>
<tr>
<th>Structural findings</th>
<th>Total no. (%)</th>
<th>Unable no. (%)</th>
<th>Able no. (%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye abnormality</td>
<td>45 (26)</td>
<td>38 (73)</td>
<td>7 (16)</td>
<td>4.2 (1.6-11.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any CNS abnormality</td>
<td>84 (49)</td>
<td>50 (96)</td>
<td>34 (28)</td>
<td>3.5 (1.7-7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>62 (36)</td>
<td>47 (85)</td>
<td>15 (25)</td>
<td>3.1 (1.6-6.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>27 (16)</td>
<td>26 (50)</td>
<td>1 (16)</td>
<td>1.7 (0.4-7.2)</td>
<td>0.4000</td>
</tr>
<tr>
<td>None of the above</td>
<td>87 (50)</td>
<td>0 (0)</td>
<td>87 (72)</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Visual Improvement After Overplus Eyeglasses in Children with Congenital Zika Infection

Overlapping Spectrum of Retinochoroidal Scarring in Congenital Zika Virus and Toxoplasmosis Infections

Joel Carlos B. Silva Filho MD,a,b,c Julia D. Rossetto, MD, PhD,a,b,c Irena Tsui MD,a,b,c Luiza M. Neves, MD,a,b,c Luana Haefeli MD,a,b,c Isabel S.D. Garcia, MD,a,b,c Jessica Malacarne, PhD,a,b,c Natália Moller OT,a,b,c Stephanie L. Lane, MD, PhD,a,b,c Olivia A. Ziu, MD,a,b,c Marcos Vinicius da Silva Pone, MD, PhD,a,b,c Sheilla Moura Pone, MD, PhD,a,b,c Kristina Analfi, MD,a,b,c Jesse Paulo Pereira Jr, MD,a,b,c Saint Claire Gomes Jr, PhD,a,b,c Patricia Brasil, MD, PhD,a,b,c Karin Nielsen-Saines, MD, MPH,a,b,c Eshine Vasconcelos, MSc, PhD,a,b,c Maria Elisabeth Lopes Moreira, MD, PhD,a,b,c Andrea A. Ziu, MD, PhD,a,b,c
• 10.8% incidence of structural heart defects in 120 infants with PCR confirmed ZIKV exposure, 10 x the rate observed in the general population.
• No severe cardiac defects noted.
• Cardiac defects most frequently found in infants whose mothers had rash and had 2nd semester infection and infants with abnormal CNS imaging, but not necessarily microcephaly.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at ECHO (days)</th>
<th>PCR (mo)</th>
<th>PCR (ko)</th>
<th>Microcephaly</th>
<th>CNS imaging</th>
<th>Gestational age (weeks)</th>
<th>FD Echo</th>
<th>Rad. trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Girl</td>
<td>268</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Positive</td>
<td>36</td>
<td>PDA</td>
<td>2nd</td>
</tr>
<tr>
<td>2</td>
<td>Girl</td>
<td>220</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
<td>Negative</td>
<td>40</td>
<td>PDA</td>
<td>2nd</td>
</tr>
<tr>
<td>3</td>
<td>Boy</td>
<td>193</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Negative</td>
<td>40</td>
<td>VSD</td>
<td>3rd</td>
</tr>
<tr>
<td>4</td>
<td>Boy</td>
<td>1</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Negative</td>
<td>39</td>
<td>PAH</td>
<td>1st</td>
</tr>
<tr>
<td>5</td>
<td>Girl</td>
<td>178</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Positive</td>
<td>37</td>
<td>PDA</td>
<td>1st</td>
</tr>
<tr>
<td>6</td>
<td>Boy</td>
<td>2</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Positive</td>
<td>40</td>
<td>VSD</td>
<td>1st</td>
</tr>
<tr>
<td>7</td>
<td>Girl</td>
<td>86</td>
<td>Positive</td>
<td>NA</td>
<td>Yes</td>
<td>Negative</td>
<td>38</td>
<td>ASD</td>
<td>2nd</td>
</tr>
<tr>
<td>8</td>
<td>Girl</td>
<td>28</td>
<td>Negative</td>
<td>Positive</td>
<td>No</td>
<td>Positive</td>
<td>37</td>
<td>ASD</td>
<td>3rd</td>
</tr>
<tr>
<td>9</td>
<td>Girl</td>
<td>2</td>
<td>Positive</td>
<td>NA</td>
<td>Yes</td>
<td>Negative</td>
<td>35</td>
<td>LVH</td>
<td>2nd</td>
</tr>
<tr>
<td>10</td>
<td>Boy</td>
<td>35</td>
<td>Positive</td>
<td>NA</td>
<td>No</td>
<td>Negative</td>
<td>39</td>
<td>ASD</td>
<td>2nd</td>
</tr>
<tr>
<td>11</td>
<td>Boy</td>
<td>91</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
<td>Negative</td>
<td>39</td>
<td>VSD</td>
<td>2nd</td>
</tr>
<tr>
<td>12</td>
<td>Girl</td>
<td>7</td>
<td>Negative</td>
<td>Positive</td>
<td>No</td>
<td>Negative</td>
<td>38</td>
<td>POP, VSD, RESPIR</td>
<td>No sub</td>
</tr>
<tr>
<td>13</td>
<td>Boy</td>
<td>NA</td>
<td>Positive</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>37</td>
<td>VSD, POI</td>
<td>No sub</td>
</tr>
</tbody>
</table>

Maternal ZIKA Virus Disease Severity, Virus Load, Prior Dengue Antibodies, and Their Relationship to Birth Outcomes

• Analysis of 125 women with PCR+ ZIKA
• No association between Zika virus load in blood and urine and severity of maternal symptoms.
• No association between Zika virus load and pregnancy outcomes.
• No association between severity of symptoms and pregnancy outcomes.
• No association between prior dengue (IgG+ at Zika symptoms) and pregnancy outcomes: 43/98 (44%) IgG+ and 7/14 (50%) IgG neg with abnormal outcomes.
Neurodevelopment of exposed children are not included in most funding opportunities

- We may miss the window of opportunity to do something for these children
  - We need to consider the neuroplasticity in early life
  - Program of early stimulation can improve quality of life
Monkey study suggests Zika infection in infancy could cause brain damage

- Checked teratogenic capacity of 4 arboviruses: WNC, Powasan virus, CHIKV and Mayaro Virus.
- All 4 viruses caused placental infection.
- WNV and POWV caused fetal demise and replicated in fetal explants.

Chloroquine inhibits ZIKV entry in vivo and in vitro and protects against microcephaly in mouse embryos
Among 131 ZIKV in utero exposed children with imaging, neurodevelopmental and/or sensory organ assessments, 19 (14.5%) were found to have severe neurodevelopmental delay (-2SD) and/or sensory organ dysfunction.

Moreira, Nielsen-Saines, Brasil et al.

**Figure 1.** Individual Scores on the Bayley-III Scales at 12 to 18 Months of Age, According to Neuroimaging Results. Shown are the scores for cognitive, language, and motor functions on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Standard scores on the Bayley-III scales range from 55 to 145, with higher scores indicating more advanced development; the mean (±SD) score is 100±15, and a score of less than 85 indicates a developmental delay and a score less than 70 indicates severe developmental delay. The scores of 94 children who had in utero exposure to Zika virus are indicated by circles. The solid horizontal lines represent median values, and the I bars interquartile ranges.
Association between Neurodevelopmental Testing (Bayley III) at 12 to 18 months and Imaging Results in Zika Exposed Infants + Other Hearing and Eye Findings

Although a significant association was noted between normal brain imaging and higher Bayley-III scores, neuroimaging failed to predict developmental delay in 16% of children and normal development in 2% of cases.

Follow-up of babies potentially exposed to Zika during pregnancy:

1. Careful assessment of birth measures:
   - Head circumference, birth weight (10% babies SGA), length
2. Continuous monitoring of head circumference in the first year of life (secondary microcephaly has been demonstrated).
3. Follow development and feeding closely- some babies develop feeding difficulties later when primitive reflexes are lost. Neurologic follow-up needed in the first year. Some babies have seizures.
4. Trans-fontanel ultrasound recommended for babies where mothers had suspected Zika or had problems- noted not only calcifications, but also hemorrhages seen in our cohort, and brain structures missing in serious cases- if US abnormal needs additional imaging
5. Hearing assessment recommended- hearing loss reported
6. Funduscopic eye exam/ low threshold for echocardiogram
7. Testing of infant- ZIKA PCR in serum and also urine-duration of viral shedding unknown/ IgM testing of serum/ when CSF obtained- IgM in CSF
8. Long term follow-up needed (at least 2 years of age) with hearing and evaluation for later monitoring for possible learning disabilities.
Association of Infants Exposed to Prenatal Zika Virus Infection With Their Clinical, Neurologic, and Developmental Status Evaluated via the General Movement Assessment Tool

Apart from 333 neurotypical controls with normal fidgety movements at 3 to 5 months and a Bayley-III score exceeding 85 at their follow-up assessment (100% specificity), normal fidgety movements in the Rio de Janeiro cohort were associated with normal development at age 12 months, with a specificity of 96%. Conversely, the absence of fidgety movements was associated with an adverse outcome at age 12 months, with a sensitivity of 70%.
2/26/19

World must prepare for return of Zika, scientists warn

By Sarah Newey
13 SEPTEMBER 2018 - 7:57PM

Zika Is Coming

By PETER J. HUETZ APRIL 8, 2014

Microcephaly cases in Angola point to African Zika outbreak

Experts worry about the spread of the disease in a new continent, and about a sense of complacency now that Brazil’s Zika crisis has largely waned.

Organisation report reviewed by Reuters concluded in April that two cases of a potentially dangerous strain of Zika confirmed in early 2017, along with the microcephaly cases identified since then, provided “strong evidence” of a Zika-linked microcephaly cluster in Angola.

A lack of data and diagnostic testing along with a woefully inadequate Angolan health system has made tracking the outbreak difficult. But new findings from a research team in Portugal suggest it is the first on the African mainland involving the Asian strain of the disease.

41 cases of Zika and 56 cases of microcephaly as per the Angolan Ministry of Health reported in October 2018.

Zika Virus in Angola
Zika spreads rapidly in India, with 94 cases confirmed

By Swati Gupta, CNN
Updated 9:36 AM ET, Wed October 17, 2018

(CNN) — The number of people infected with the Zika virus in India has increased to 94 confirmed cases in the western state of Rajasthan, including 22 pregnant women, as of 17 October.

The first case was confirmed on September 23 and the number of people who have tested positive for the virus in the city of Jaipur has steadily grown since then.

Zika in India

This is India’s third outbreak of Zika since 2017, but is by far the biggest.

The first was reported in Ahmedabad in the western Gujarat state around January 2017 with three confirmed cases, according to the World Health Organization.

Months later in July, a second outbreak was reported in the southern state of Tamil Nadu. According to local media reports, one man tested positive for the virus. Both outbreaks were contained.