Zika Virus Update


Sociedade

ALERTA NA SAÚDE

Microcefalia já é epidemia

Ministério admite que número de casos deve aumentar e mais estados podem ser afetados

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Disclosures

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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

David Geffen School of Medicine

Mattel Children's Hospital UCLA

UCLA Children's Discovery and Innovation Institute

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.


GUTO MORETO

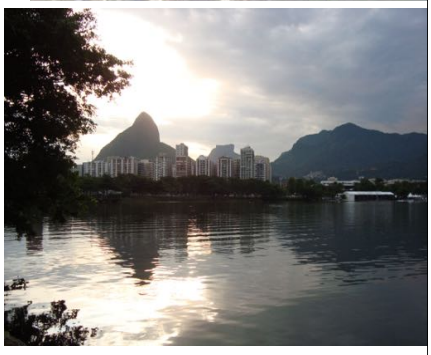
OMS: alerta mundial sobre Zika

A OMS divulgou alerta global sobre a epidemia de zika e microcefalia no Brasil. O Ministério da Saúde deve concluir hoje plano de combate ao *Aedes*. Grávidas sofrem com sensação de impotência diante do risco de microcefalia. PÁGINA 29

Preocupação. Luana Rodrigues, grávida de 7 meses

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



Science

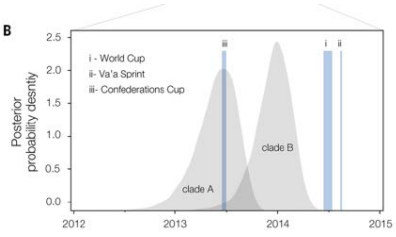
Cite as: N. R. Faria *et al.*, *Science* 10.1126/science.aaf5036 (2016).

Zika virus in the Americas: Early epidemiological and genetic findings

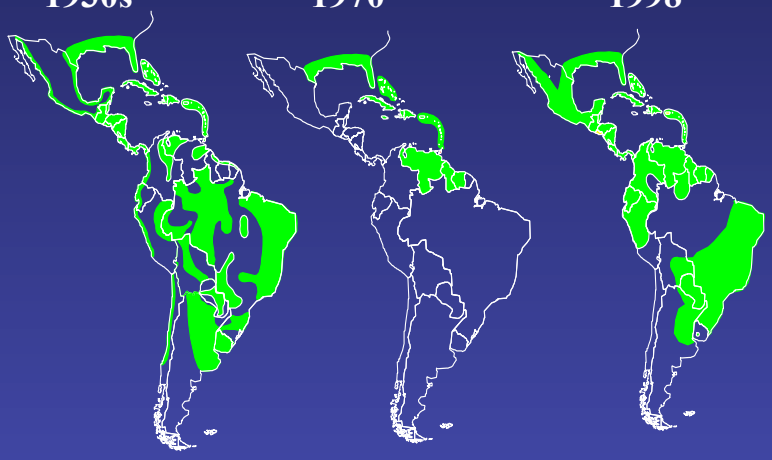
2013 FIFA Confederations Cup

Copa das Confederações da FIFA
Brasil 2013

Tournament details	
Host country	Brazil
Dates	15–30 June
Teams	8 (from 6 confederations)
Venue(s)	6 (in 6 host cities)
Final positions	
Champions	Brazil (4th title)
Runners-up	Spain
Third place	Italy
Fourth place	Uruguay
Tournament statistics	



Reinfestation by *Aedes aegypti*



Distribuição dos Municípios Infestados por *Aedes aegypti*

Brasil - 1997/2000 (*)

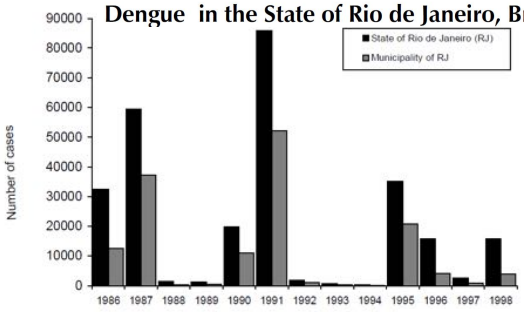
2.780 Mun. Infest.

3.592 Mun. Infest.

(*)Dados sujeitos à revisão
Fonte: CR's/FUNASA/CENEPI/CGVAM/COFAB

FUNASA

Dengue in the State of Rio de Janeiro, Brazil, 1986-1998



Souce: Secretary of Health of the State of Rio de Janeiro
Secretary of Health of the Municipality of Rio de Janeiro

Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. *94*(3): 297-304, May/Jun. 1999

Dengue fever epidemic hits Rio de Janeiro

Officials: Outbreak has killed at least 47, and perhaps twice that

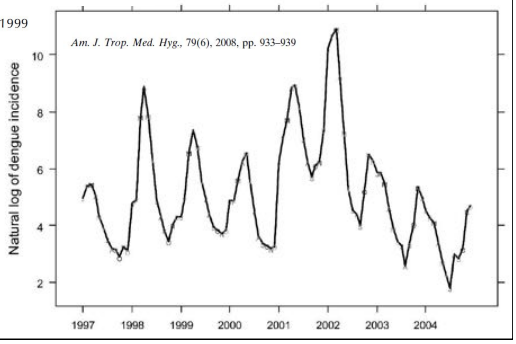
Infectious diseases on NBCNEWS.com

Associated Press
updated 3/20/2008 8:08:19 PM ET

Time Series Analysis of Dengue Incidence in Rio de Janeiro, Brazil

Paula M. Luz,* Beatriz V. M. Mendes, Claudia T. Codeço, Claudio J. Struchiner, and Alison P. Galvani

Am. J. Trop. Med. Hyg., 79(6), 2008, pp. 933–939



Los Angeles Times
$2.00 DESIGNATED AREAS HIGHER © 2016 WST
THURSDAY, APRIL 21, 2016
latimes.com

On the frontline of Brazil's war with Zika, a mother's first question: 'How big is the head?'

By ALEXANDRA ZAVIS | Photos by KATIE FALKENBERG

CAMPINA GRANDE, BRAZIL | APRIL 21, 2016

Quinta-feira 3.12.2015 — Sociedade — O GLOBO

RISCO DE MICROCEFALIA

Grávidas e o medo do zika

Ministério da Saúde conclui hoje plano de combate ao mosquito vilão das gestantes

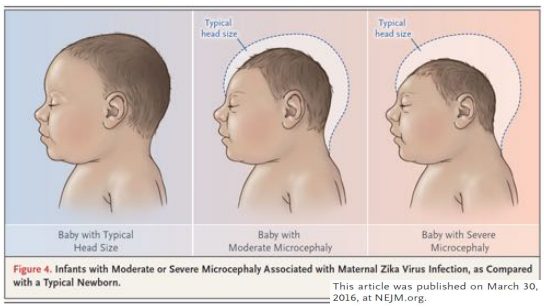


Figure 4. Infants with Moderate or Severe Microcephaly Associated with Maternal Zika Virus Infection, as Compared with a Typical Newborn.

This article was published on March 30, 2016, at NEJM.org.

DOI: 10.1056/NEJMra1602113

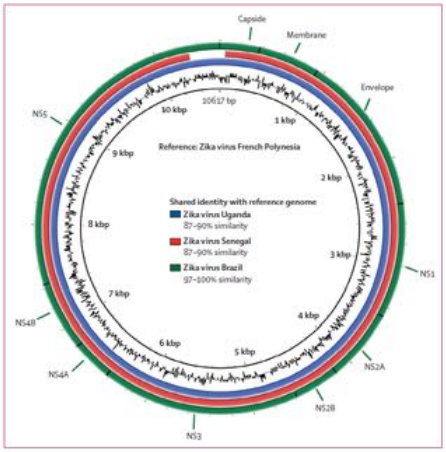
Sudden increase in the number of infants born with microcephaly in the state of Pernambuco in 2015 with number of cases 20 times greater than expected.

Microcephaly: In 90% of cases, responsible for developmental delay, vision and hearing impairment, and a gamut of neurologic problems, including seizures.

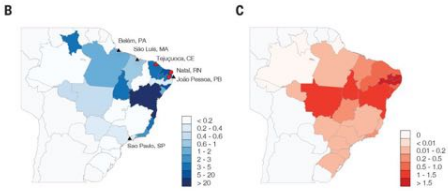
Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study

Guilherme Calvet*, Renato S Aguiar*, Adriana S O Melo, Simone A Sampaio, Ivano de Filippis, Allison Fabri, Eliane S M Araujo, Patricia C de Sequeira, Marcos C L de Mendonça, Louisi de Oliveira, Diogo A Tschoeke, Carlos G Schrago, Fabiano L Thompson, Patricia Brasil, Flavia B dos Santos, Rita M R Nogueira, Amilcar Tanuri†, Ana M B de Filippis†

www.thelancet.com/infection **Published online February 17, 2016**



ZIKV identified by RT PCR in the amniotic fluid of 2 women from Paraiba, northeastern Brazil whose infants were born with microcephaly.



N. R. Faria *et al.*, *Science* 5/science.aaf5036 (2016).

Table 2. Bradford Hill Criteria for Evidence of Causation as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies*

Criterion	Evidence	Criterion Met?
Strength of association	A recent epidemiologic study from French Polynesia suggests a strong association between prenatal Zika virus infection and microcephaly (estimated risk ratio, approximately 50).[2] The substantial increase in the number of cases of microcephaly and other brain anomalies that have been associated with the Zika virus outbreak in Brazil suggests a strong association.[1,2]	Yes
Consistency	Two epidemiologic studies, one from Brazil and one from French Polynesia,[2,14] support the association between prenatal Zika virus infection and microcephaly and other serious brain anomalies. The observed increase in the number of cases of microcephaly after outbreaks of Zika virus infection in Brazil and French Polynesia, as well as preliminary reports of cases in Colombia, support consistency.[1,2,42] Case reports of Zika virus infection in fetuses or infants with microcephaly or other brain anomalies who were born to mothers who traveled to areas of active Zika virus transmission support consistency.[16,18,19]	Yes
Specificity	Other causes of microcephaly exist; however, on the basis of clinical descriptions that are available for a small number of infants with presumed congenital Zika virus infection,[20] the clinical phenotype linked to the Zika virus appears to be an unusual form of microcephaly that is consistent with the fetal brain disruption sequence.	Yes
Temporality	Zika virus infection in mothers during pregnancy precedes the finding of microcephaly or other brain anomalies in fetuses or infants.[14-20] Zika virus outbreaks in Brazil and French Polynesia preceded the increase in the number of cases of microcephaly.[1,2]	Yes
Biologic gradient	Infection is a phenomenon that is either present or absent; there is no dose–response relationship. No data are available regarding whether women with an increased viral load have a higher risk of adverse pregnancy or birth outcomes.	NA
Plausibility	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus and rubella virus).[26] Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[28] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of on immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
Coherence	No results in an animal model of effects of Zika virus on pregnancy have yet been published, but animal models have shown that Zika virus is neurotropic,[27,28] a finding that is consistent with prenatal Zika virus infection causing microcephaly and other brain anomalies. Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[28] a finding that is consistent with a causal relationship between Zika virus infection and microcephaly.	Yes
Experiment	No experimental animal model of Zika virus teratogenicity is available.	No
Analogy	No other flavivirus has been shown to definitively cause birth defects in humans,[4] but flaviviruses, Wesselsbron and Japanese encephalitis viruses, have been shown to cause stillbirth and brain anomalies in animals.[43] Findings are similar to those seen after prenatal infection with other viral teratogens (e.g., cytomegalovirus, rubella virus).[26]	Yes

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H., Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

This article was published on April 13, 2016, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities

R.W. Driggers, C.-Y. Ho, E.M. Korhonen, S. Kuivanen, A.J. Jääskeläinen, T. Smura, A. Rosenberg, D.A. Hill, R.L. DeBiasi, G. Vezina, J. Timofeev, F.J. Rodriguez, L. Levanov, J. Razak, P. Iyengar, A. Hennenfent, R. Kennedy, R. Lanciotti, A. du Plessis, and O. Vapalahti

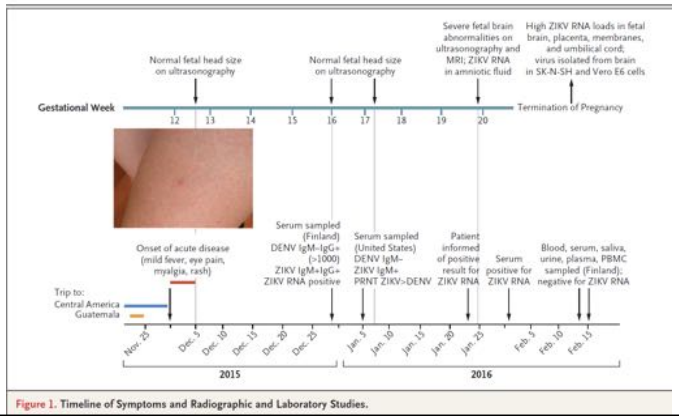


Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.

Pan American Health Organization / World Health Organization

Zika cases and congenital syndrome associated with Zika virus reported by countries and territories in the Americas, 2015 - 2017
Cumulative cases
Data as of March 2017

Country/Territory	Zika Cases (Suspected/ Confirmed)	Confirmed congenital syndrome associated with Zika virus infectiond	Tx incidência Zika	Population X 10	Number of live births/year	Prevalence rate Microcephaly per 10,000 live birth
Brazil[14]	346.475	2.386	165	209.553	3.084.620	7,7
Colombia[10]	107.206	128	220	48.650	479.141	2,7
Dominican Republi	5.241	54	49	10.708	138.224	3,9
Guatemala[4]	4.354	37	26	16.674	386.195	1,0
Martinique[7]	36.701	22	9.268	396	5.441	40,4
French Guiana[7]	10.803	17	3.914	276	6.247	27,2
Guadeloupe[7]	31.227	14	6.616	472	5.758	24,3
Bolivia (Plurination	1.029	14	9,4	10.971	255.405	0,5
Puerto Rico[9]	39.339	12	1.069	3.681	40.123	3,0
Panama[5]	4.659	5	117	3.990	74.254	0,7
El Salvador[3]	11.574	4	188	6.147	107.081	0,4
Costa Rica	7.874	2	161	4.881	78.486	0,3
Nicaragua	2.060	2	33	6.184	113.847	0,2
Paraguay[16]	664	2	10	6.725	116.592	0,2
Honduras	32.403	2	396	8.190	193.775	0,1
Argentina[15]	2.279	2	5	44.060	738.318	0,0
Saint Martin[7]	3.415	1	9.486	36	627	15,9
Haiti[8]	2.960	1	27	10.916	249.212	0,0
Mexico[2]	8.113	1	6	128.624	2.463.420	0,0

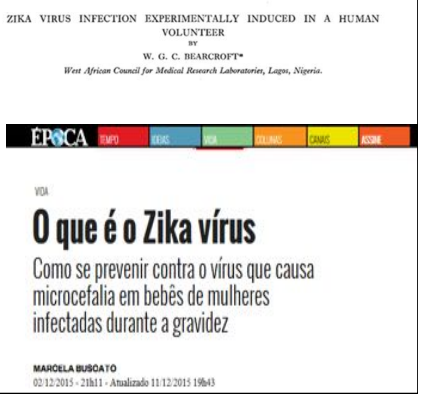
Courtesy Carlos Brito, Patricia Brasil

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.


ZIKA VIRUS INFECTION EXPERIMENTALLY INDUCED IN A HUMAN VOLUNTEER

BY

W. G. C. BEARCROFT*

West African Council for Medical Research Laboratories, Lagos, Nigeria.

ÉPOCA

VIDA

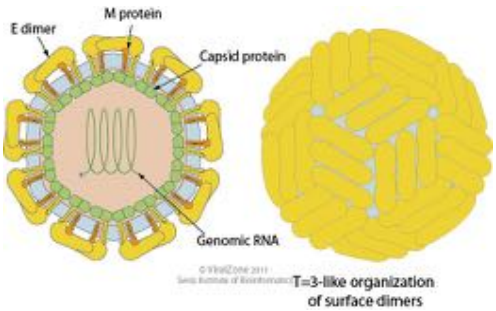
O que é o Zika vírus

Como se prevenir contra o vírus que causa microcefalia em bebês de mulheres infectadas durante a gravidez

MARCELA BUSCATO

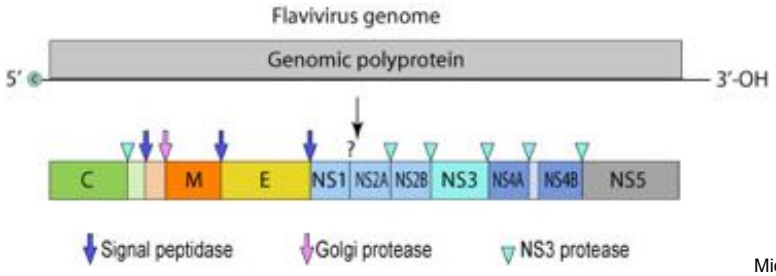
02/12/2015 - 21h11 - Atualizado 11/12/2015 19h43

Structure of ZIKV: Virion and genome



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



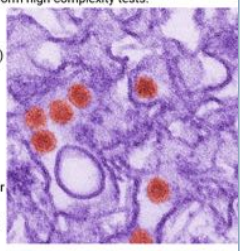
Microbe Wiki, 2015

The diagnostic conundrum…

FDA Approves New CDC Laboratory Test for Zika Virus

By IDSE News Staff

The FDA issued an Emergency Use Authorization (EUA) for a diagnostic tool for Zika virus that will be distributed to qualified laboratories and, in the United States, those who are certified to perform high-complexity tests.



The test, called the Centers for Disease Control and Prevention (CDC) Zika Immunoglobulin M (IgM) Antibody Capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA), detects antibodies to Zika virus infection. These IgM antibodies appear in the blood of an individual infected with Zika virus beginning four to five days after the start of illness and last for about 12 weeks. The test is intended to be used on blood samples from people with a history of symptoms associated with Zika virus and/or individuals who have recently traveled to an area during a time of active Zika transmission.

	Dengue IgG
1	positivo
2	positivo
3	positivo
4	positivo
5	positivo
6	positivo
7	positivo
8	positivo
9	positivo
10	positivo
11	positivo
12	positivo
13	negativo
14	positivo
15	indeterminado
16	positivo
17	positivo
18	positivo
20	positivo
22	positivo
23	positivo
25	positivo
26	positivo
27	positivo
28	positivo
29	positivo
30	negativo
31	positivo
32	positivo
34	positivo
36	positivo
37	positivo
38	positivo
42	positivo
43	positivo
44	positivo
45	positivo
46	positivo
47	positivo
48	positivo
49	negativo
50	positivo
52	positivo
53	negativo
54	positivo
55	positivo
57	negativo
58	positivo
59	positivo
60	positivo

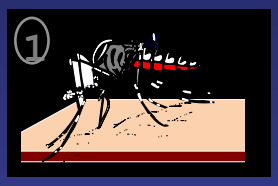
Retrospective serologic diagnosis not possible in dengue endemic areas- how to monitor asymptomatic infections?

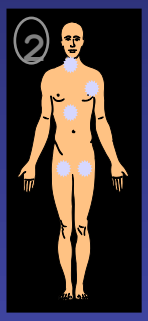
Aedes aegypti

- 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

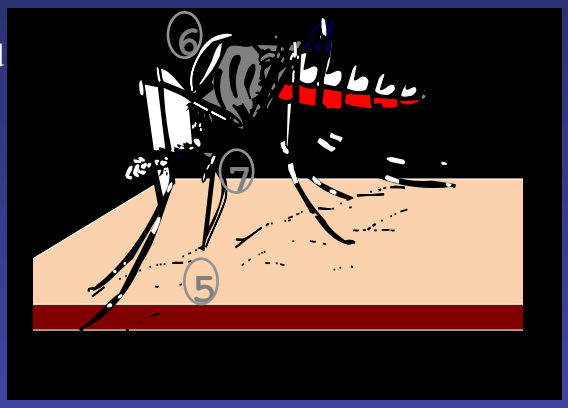
1. Virus transmitted to human in mosquito saliva
2. Virus replicates in target organs
3. Virus infects white blood cells and lymphatic tissues
4. Virus released and circulates in blood





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

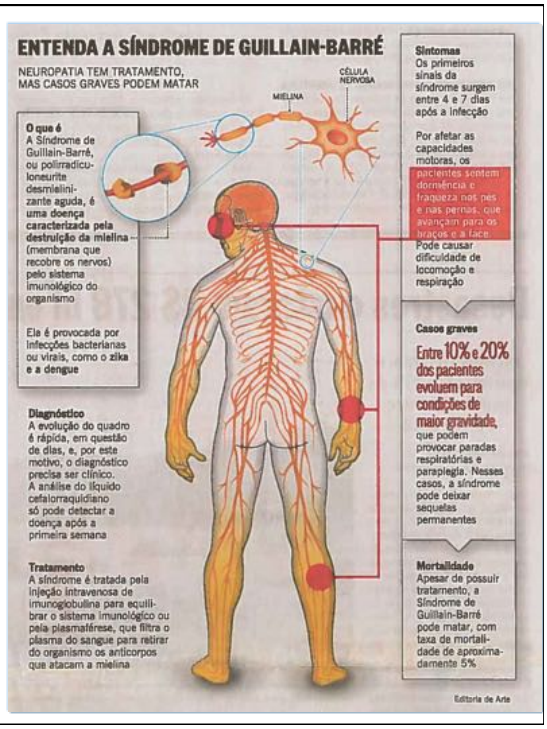
2007 Micronesia

- 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 idenfied 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 leding to destruction of the myelin sheaths. Treated with IVIG or plasmapheresis.



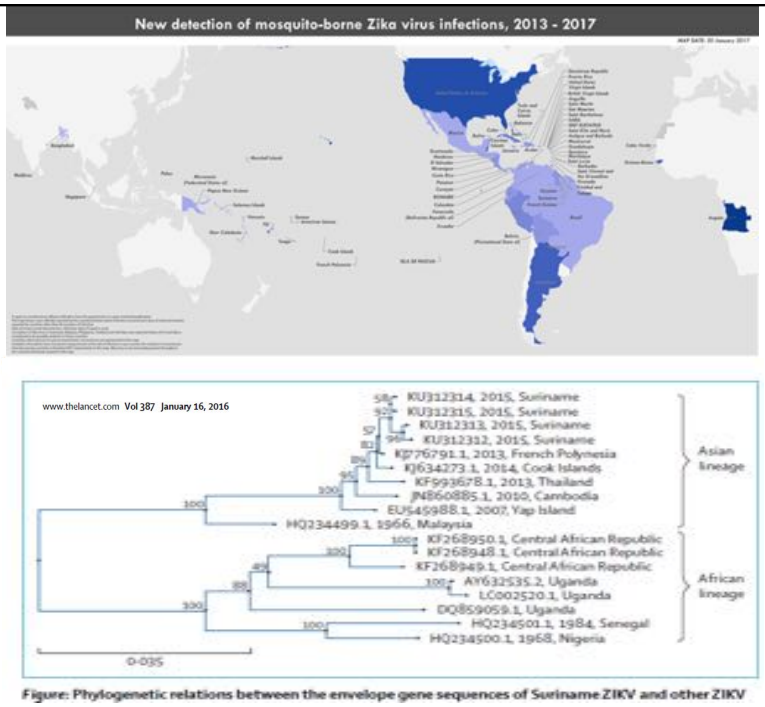
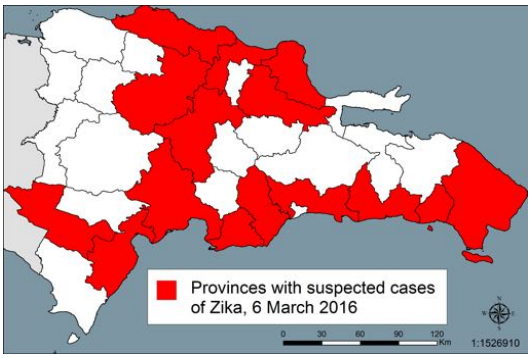


Figure: Phylogenetic relations between the envelope gene sequences of Suriname ZIKV and other ZIKV

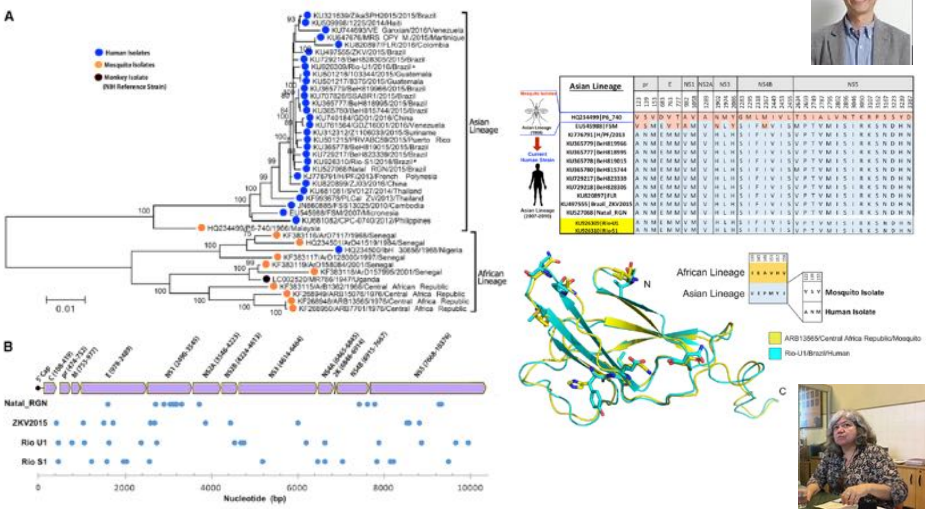
Dominican Republic



- 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

From Mosquitos to Humans: Genetic Evolution of Zika Virus

Cell Host & Microbe
Commentary
dx.doi.org/10.1016/j.chom.2016.04.006



Lulan Wang,[1,2,3,10] Stephanie G. Valderramos,[1,4,10] Aiping Wu,[2,3] Songying Ouyang,[1,5] Chunfeng Li,[1] Patricia Brasil,[6] Myrna Bonaldo,[7] Thomas Coates,[8] Karin Nielsen-Saines,[9] Taijiao Jiang,[2,3,*] Roghiyh Aliyari,[1,*] and Genhong Cheng[1,2,3,*]

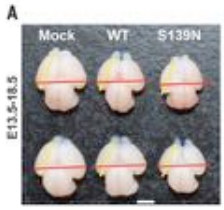
The Zika Virus Grew Deadlier With a Small Mutation, Study Suggests

The New York Times

ZIKA

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

Ling Yuan,[1,2,*] Xing-Yao Huang,[2,*] Zhong-Yu Liu,[2,*] Feng Zhang,[1,2,*] Xing-Liang Zhu,[1,2,*] Jiu-Yang Yu,[2,*] Xue Ji,[3] Yan-Peng Xu,[3] Guanghui Li,[1,3] Cui Li,[1,3] Hong-Jiang Wang,[3] Yong-Qiang Deng,[3] Menghua Wu,[4] Meng-Li Cheng,[3,5] Qing Ye,[3] Dong-Yang Xie,[3,5] Xiao-Feng Li,[3] Xiangxi Wang,[6] Weifeng Shi,[7] Baoyang Hu,[4] Pei-Yong Shi,[8] Zhiheng Xu,[1,2,9]† Cheng-Feng Qin[3]†



- 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.

Science 17 Nov 2017:
Vol. 358, Issue 6365, pp. 933-936

Probable Non–Vector-borne Transmission of Zika Virus, Colorado, USA

Brian D. Foy, Kevin C. Kobylinski, Joy L. Chilson Foy, Bradley J. Blitvich, Amelia Travassos da Rosa, Andrew D. Haddow, Robert S. Lanciotti, and Robert B. Tesh

Emerging Infectious Diseases • Vol. 10, No. 2, May 2011

In 2008, a case of sexual transmission of Zika virus was documented. A university biologist from the Colorado State University Arthropod-borne and Infectious Diseases Laboratory, visited Senegal and acquired Zika Fever. A few days after returning to the USA he fell ill with Zika, but not before having vaginal intercourse with his wife. His wife subsequently showed symptoms of Zika infection 10 days later.

Potential Sexual Transmission of Zika Virus

Didier Musso, Claudine Roche, Emilie Robin, Tuxuan Nhan, Anita Teissier, Van-Mai Cao-Lormeau

Emerging Infectious Diseases • Vol. 21, No. 2, February 2015

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

RAPID COMMUNICATIONS

Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014

D Musso (dmusso@ilm.pf)[1], T Nhan[1], E Robin[1], C Roche[1], D Bierlaire[2], K Zisou[1], A Shan Yan[1], V M Cao-Lormeau[1], J Broult[2]

Euro Surveill. 2014;19(14):pii=20761. Available online: http://www.eurosurveillance.org/

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.

PLOS | NEGLECTED TROPICAL DISEASES

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

April 10, 2017

Susannah Colt[1], Maria N. Garcia-Casal[2], Juan Pablo Peña-Rosas[2], Julia L. Finkelstein[1], Pura Rayco-Solon[2], Zita C. Weise Prinzo[2], Saurabh Mehta[1]*

Journal of Clinical Virology 68 (2015) 53–55

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Short communication

Detection of Zika virus in saliva

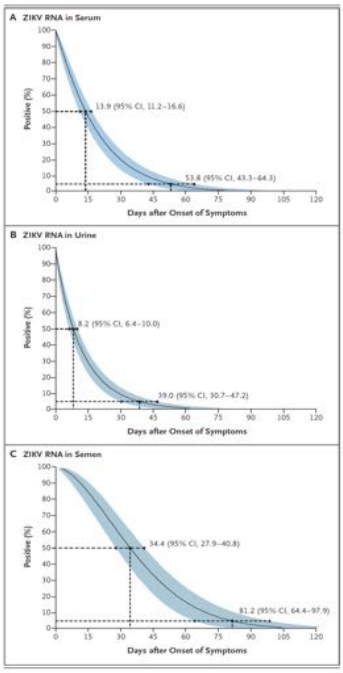
Didier Musso[a,b,*], Claudine Roche[b], Tu-Xuan Nhan[a], Emilie Robin[a], Anita Teissier[b], Van-Mai Cao-Lormeau[b]

DISPATCHES

Detection of Zika Virus in Urine

Ann-Claire Gourinat,[1] Olivia O'Connor,[1] Elodie Calvez, Cyrille Goarant, and Myrielle Dupont-Rouzeyrol

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 1, January 2015



ORIGINAL ARTICLE

Persistence of Zika Virus in Body Fluids — Preliminary Report

Gabriela Paz-Bailey, M.D., Ph.D., Eli S. Rosenberg, Ph.D., Kate Doyle, M.P.H., Jorge Munoz-Jordan, Ph.D., Gilberto A. Santiago, Ph.D., Liore Klein, M.S.P.H., Janice Perez-Padilla, M.P.H., Freddy A. Medina, Ph.D., Stephen H. Waterman, M.D., M.P.H., Carlos Garcia Gubern, M.D., Luisa I. Alvarado, M.D., and Tyler M. Sharp, Ph.D.

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 detectable ZIKV RNA in saliva or vaginal secretions.

This article was published on February 14, 2017, at NEJM.org.

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.

Journal of Clinical Virology 74 (2016) 1–3

Contents lists available at ScienceDirect

Journal of Clinical Virology

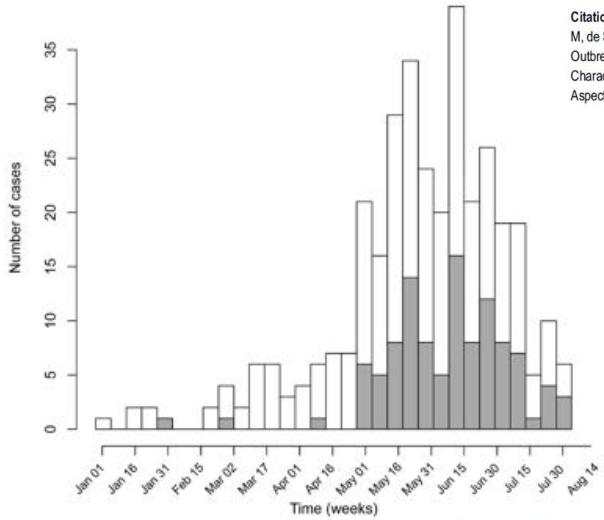
journal homepage: www.elsevier.com/locate/jcv

First detection of autochthonous Zika virus transmission in a HIV-infected patient in Rio de Janeiro, Brazil

Guilherme A. Calvet[a,*], Ana Maria B. Filippis[b,1], Marcos Cesar L. Mendonça[b,1], Patricia C. Sequeira[b,1], Andre M. Siqueira[a], Valdilea G. Veloso[c], Rita M. Nogueira[b], Patrícia Brasil[a]

PLOS | NEGLECTED TROPICAL DISEASES

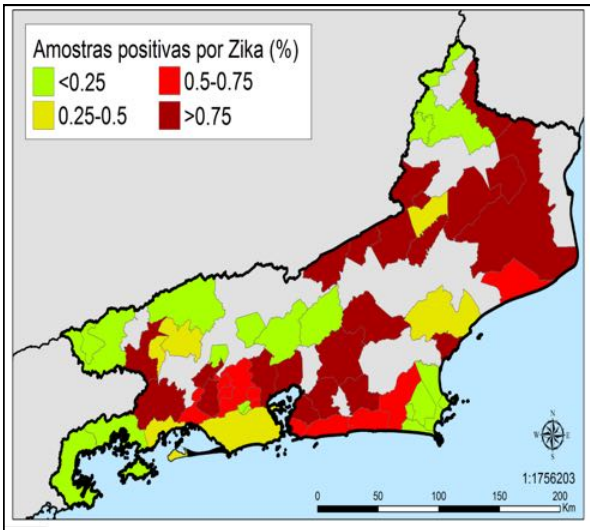
ZIKA Virus Outbreak in Rio de Janeiro



Citation: Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC, Nobre A, et al. (2016) Zika Virus Outbreak in Rio de Janeiro, Brazil: Clinical Characterization, Epidemiological and Virological Aspects. PLoS Negl Trop Dis 10(4): e0004636.

Fig 2. Time series for number of cases confirmed (gray background) and not confirmed (white background) for ZIKV between January 1, 2015 and July 31, 2015 in Rio de Janeiro State.

Published: April 12, 2016



PLOS ONE

November 16, 2017

Behavioral, climatic, and environmental risk factors for Zika and Chikungunya virus infections in Rio de Janeiro, Brazil, 2015-16

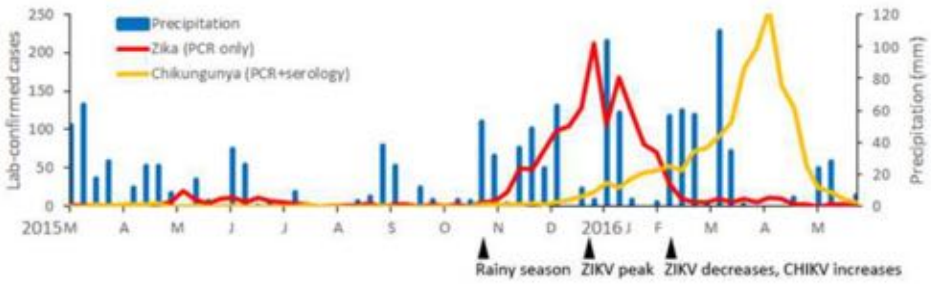
Trevon L. Fuller[1]*, Guilherme Calvet[2]*, Camila Genaro Estevam[2]*, Jussara Rafael Angelo[2]*, Gbenga J. Abiodun[3], Umme-Aiman Halai[4]*, Bianca De Santis[1], Patricia Carvalho Sequeira[2], Eliane Machado Araujo[2], Simone Alves Sampaio[2], Marco Cesar Lima de Mendonça[2], Allison Fabri[2], Rita Maria Ribeiro[2], Ryan Harrigan[1], Thomas B. Smith[1,4], Claudia Reja Gabaglia[5], Patricia Brasil[2], Ana Maria Bispo de Filippis[2], Karin Nielsen-Saines[6]

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

- Arthralgias, predominantly of the hands and feet
- Edema of the hands and feet
- Low grade fever (≤ 38.5ºC),
- Patchy erythema
- Pruritus
- Eye pain
- Conjunctival injection
- Dizziness
- Myalgias
- Posterior lymphadenopathy
- GI symptoms may occur, but are less frequent.

- Mild fever of 102 F (38.9 C) or lower
- Headache
- Conjunctival injection
- Enlarged, tender lymph nodes at the base of the skull, the back of the neck and behind the ears
- 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
- Aching joints, especially in young women

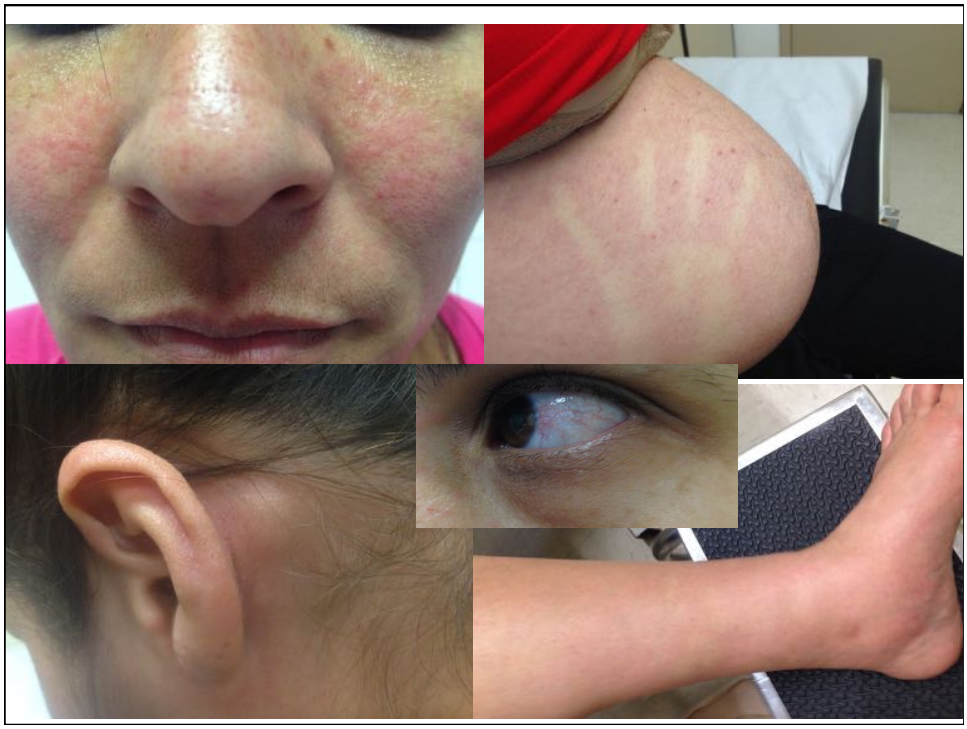


Table 1. Baseline Demographic and Clinical Characteristics of Women in the Pregnancy Cohort.*

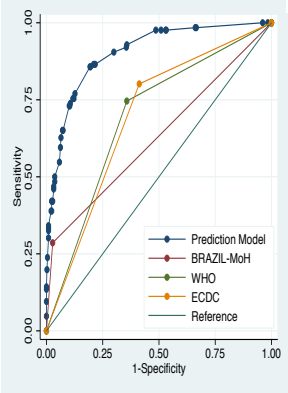
Variable	ZIKV-Positive Women (N=134)	ZIKV-Negative Women (N=73)	P Value†
Demographics			
Age — yr			0.57‡
Median (IQR)	31 (26–34)	29 (25.5–34)	
Range	16–46	17–41	
Other family members ill — no./total no. (%)	44/115 (38.3)	15/60 (25.0)	0.09
Partner ill — no./total no. (%)	14/103 (13.6)	4/53 (7.5)	0.30
Use of repellent — no./total no. (%)	48/80 (60.0)	52/63 (82.5)	0.006
History of dengue — no./total no. (%)	33/127 (26.0)	20/69 (29.0)	0.74
Socioeconomic status — no./total no. (%)§			
Income ≤2× minimum wage	48/108 (44.4)	28/63 (44.4)	1.0
Income >2 to ≤5× minimum wage	38/108 (35.2)	21/63 (33.3)	0.87
Income >5× minimum wage	22/108 (20.4)	14/63 (22.2)	0.85
Week of gestation at time of infection			
Median (IQR)	24.5 (18–31)	27 (23–31)	0.23‡
Range	5–39	7–36	
Distribution — no. (%)			
0 to ≤13 wk	26 (19.4)	4 (5.5)	0.15
14 to ≤28 wk	72 (53.7)	41 (56.2)	1.0
≥29 wk	36 (26.9)	28 (38.4)	0.45
Symptoms — no./total no. (%)			
Rash¶			
Any	134/134 (100)	73/73 (100)	0.24‡
Median duration (IQR)	5 (4–7)	4 (3–6.5)	
Range	1–16	1–12	
Macular	57/134 (42.5)	37/73 (50.7)	0.31
Maculopapular	57/134 (42.5)	19/73 (26.0)	0.02
Other	20/134 (14.9)	17/73 (23.3)	0.18
Pruritus	116/129 (89.9)	64/73 (87.7)	0.64
Arthralgia or arthritis	81/130 (62.3)	51/73 (69.9)	0.29
Conjunctival injection	73/127 (57.5)	29/72 (40.3)	0.03
Headache	69/127 (54.3)	47/73 (64.4)	0.18
Fatigue or malaise	66/127 (52.0)	55/73 (75.3)	0.002
Retro-orbital pain	53/131 (40.5)	29/73 (39.7)	1.0
Myalgia	53/130 (40.8)	43/69 (62.3)	0.005
Lymphadenopathy	48/125 (38.4)	19/70 (27.1)	0.12
Localized	22/39 (56.4)	5/10 (50.0)	0.74
Generalized	17/39 (43.6)	5/10 (50.0)	0.74
Paresthesia	36/100 (36.0)	26/67 (38.8)	0.75
Edema	54/99 (54.5)	37/73 (50.7)	0.64
Fever, body temperature ≥37.5°C	34/124 (27.4)	42/72 (58.3)	<0.001
Duration <24 hr	10/20 (50.0)	12/23 (52.2)	1.0
Duration ≥24 to <72 hr	10/20 (50.0)	11/23 (47.8)	1.0

RESEARCH ARTICLE

Accuracy of Zika virus disease case definition during simultaneous Dengue and Chikungunya epidemics

José Ueleres Braga[1,2]*, Clarisse Bressan[3‡], Ana Paula Razal Dalvi[1‡], Guilherme Amaral Calvet[3], Regina Paiva Daumas[1], Nadia Rodrigues[1], Mayumi Wakimoto[3], Rita Maria Ribeiro Nogueira[4], Karin Nielsen-Saines[5], Carlos Brito[6], Ana Maria Bispo de Filippis[4¤], Patricia Brasil[3¤]

June 26, 2017



Proposed clinical case definition for suspected Zika cases:
Presence of rash, pruritus, conjunctival hyperemia, absence of fever, no petechiae, no anorexia.

This article was published on March 4, 2016, at NEJM.org.

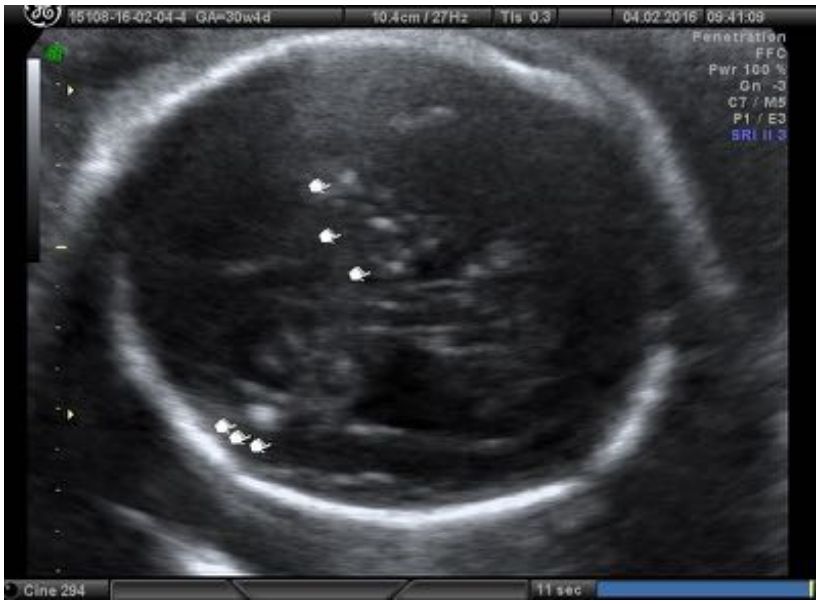
The NEW ENGLAND JOURNAL of MEDICINE

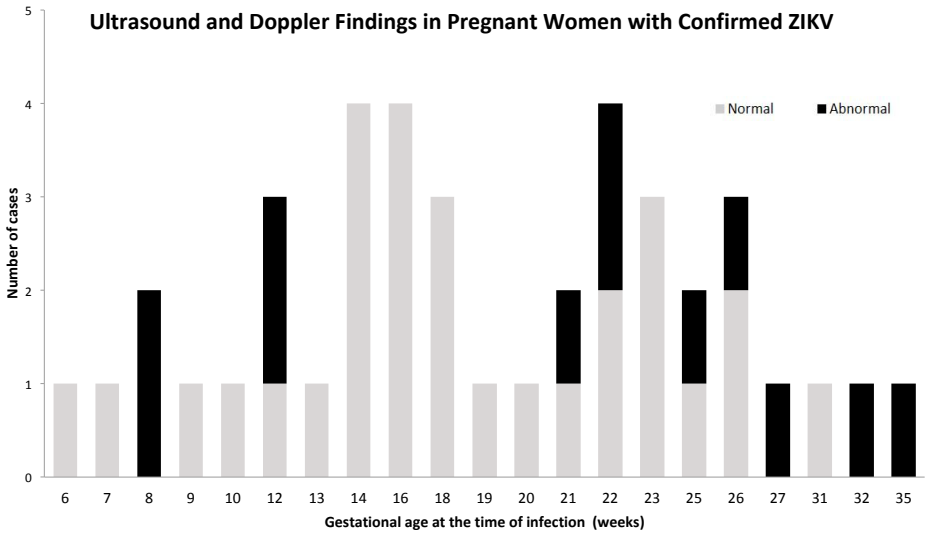
ORIGINAL ARTICLE

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

Patrícia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D., Luana Damasceno, M.S., Mayumi Wakimoto, Ph.D., Rita M. Ribeiro Nogueira, M.D., Patrícia Carvalho de Sequeira, Ph.D., André Machado Siqueira, M.D., Liege M. Abreu de Carvalho, M.D., Denise Cotrim da Cunha, M.D., Guilherme A. Calvet, M.D., Elizabeth S. Neves, M.D., Maria E. Moreira, M.D., Ana E. Rodrigues Baião, M.D., Paulo R. Nassar de Carvalho, M.D., Carla Janzen, M.D., Stephanie G. Valderramos, M.D., James D. Cherry, M.D., Ana M. Bispo de Filippis, Ph.D., and Karin Nielsen-Saines, M.D.

Cerebral calcifications patient # 24





N = 42 patients; 12 abnormal US across gestational ages

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

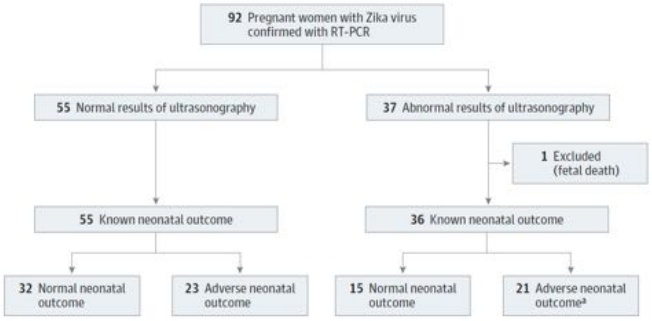
* EEG denotes electroencephalogram, and CT computed tomography.

JAMA Network | Open

Original Investigation | Obstetrics and Gynecology

Association of Prenatal Ultrasonographic Findings With Adverse Neonatal Outcomes Among Pregnant Women With Zika Virus Infection in Brazil

Jose Paulo Pereira Jr, MD; Karin Nielsen-Saines, MD; Jeffrey Sperling, MD; Melanie M. Maykin, MD; Luana Damasceno, PharmD; Renan Fonseca Cardozo, MD; Helena Abreu Valle, MD; Beatriz Ribeiro Torres Dutra, MD; Helder Dotta Gama, MD; Kristina Adachi, MD; Andrea A. Zin, MD, PhD; Irena Tsui, MD; Zilton Vasconcelos, PhD; Patricia Brasil, MD, PhD; Maria E. Moreira, MD, PhD; Stephanie L. Gaw, MD, PhD



US sensitivity 49% and specificity 68% for association with adverse neonatal outcome. For Zika-specific adverse outcome sensitivity was 22% and specificity 98%.

JAMA Network Open. 2018;1(8):e186529. doi:10.1001/jamanetworkopen.2018.6529 December 28, 2018

Clinical Infectious Diseases IDSA hivma

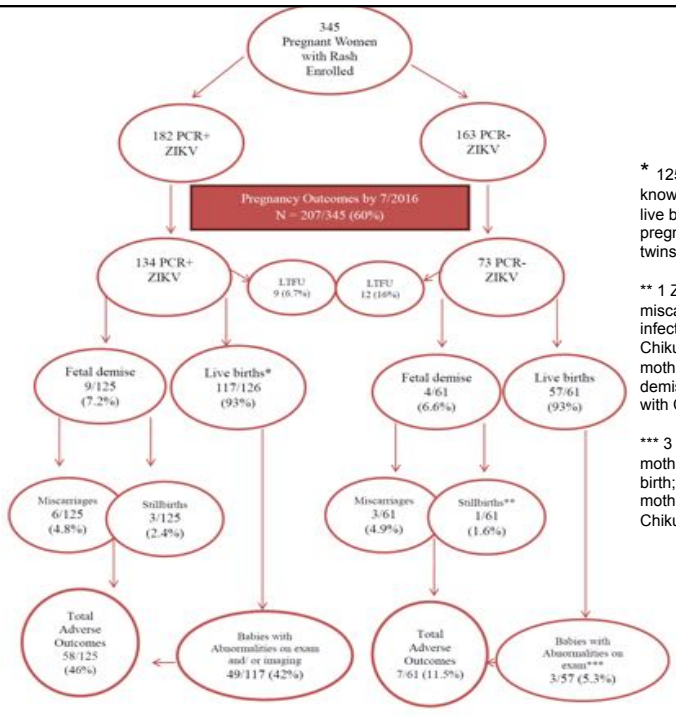
Advance articles alert

07 January 2019 - 08 January 2019

The Role of Amniocentesis in the Diagnosis of Congenital Zika Syndrome

Jose Paulo Pereira Jr., MD[1]*;Melanie M. Maykin, MD[2]*; Zilton Vasconcelos, PhD[1]; Elyzabeth Avvad-Portari, MD, PhD[1]; Andrea A. Zin, MD, PhD[1]; Irena Tsui, MD[3]; Patricia Brasil, MD, PhD[4]; Karin Nielsen-Saines, MD[5]; Maria E. Moreira, MD, PhD[1]; Stephanie L. Gaw, MD, PhD[2]

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.

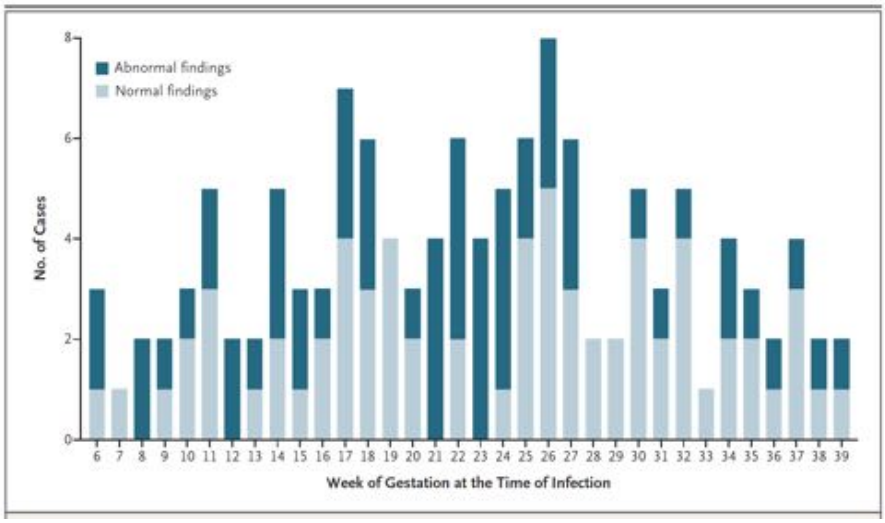


* 125 pregnancies with known outcomes; 117 live births in 116 pregnancies (one set of twins)

** 1 ZIKA+ mother with a miscarriage was co-infected with Chikunguya; 2 ZIKV- mothers with fetal demise were infected with Chikungunya

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

125 pregnancies- 46% adverse pregnancy outcomes



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

Infant Outcomes	ZIKV- Exposed Live Infants (N=117) *	ZIKV-Unexposed Live Infants (N=57)	P Value*
Number of SGA babies	10/116 (8.6)	3/57 (5.3)	0.06
Number of Infants with Microcephaly	4/117 (3.4)	0/57	0.31
Number of Infants with Microcephaly*** Proportionate microcephaly Disproportionate microcephaly	2/117 (1.7) 2/117 (1.7)	0/57 0/57	1.0 1.0
Total number of adverse pregnancy outcomes Total number of adverse infant outcomes	~~58/ 125 (46.4)~~ 49/117 (41.9)	7/ 61 (11.5) 3/57 (5.3)	<0.001 <0.001
Number of negative pregnancy outcomes by maternal trimester of infection (including fetal demise) First trimester Second trimester Third trimester	11/20 (55.0) 37/72 (51.4)* 10/34 (29.4)	3/4 (75.0) 2/35 (5.7) 2/22 (9.1)	<0.01 <0.01 <0.01

JAMA | Original Investigation

Dec 2016

Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy

Margaret A. Honein, PhD; April L. Dawson, MPH; Emily E. Petersen, MD; Abbey M. Jones, MPH; Ellen H. Lee, MD; Mahsa M. Yazdy, PhD; Nina Ahmad, MD; Jennifer Macdonald, MPH; Nicole Evert, MS; Andrea Bingham, PhD; Sascha R. Ellington, MSPH; Carrie K. Shapiro-Mendoza, PhD; Titilope Oduyebo, MD; Anne D. Fine, MD; Catherine M. Brown, DVM; Jamie N. Sommer, MS; Jyoti Gupta, MPH; Philip Cavicchia, PhD; Sally Slavinski, DVM; Jennifer L. White, MPH; S. Michele Owen, PhD; Lyle R. Petersen, MD; Coleen Boyle, PhD; Dana Meaney-Delman, MD; Denise J. Jamieson, MD; for the US Zika Pregnancy Registry Collaboration

10% rate of structural birth defects in registry

Morbidity and Mortality Weekly Report

On April 4, 2017, this report was posted as an MMWR Early Release on the MMWR website (https://www.cdc.gov/mmwr).

Vital Signs: Update on Zika Virus–Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure — U.S. Zika Pregnancy Registry, 2016

5% rate of structural birth defects in registry

Early Release / June 8, 2017 / 66

Characteristic	No. with brain abnormalities and/or microcephaly¶	No. with NTDs and early brain malformations, eye abnormalities, or consequence of CNS dysfunction without brain abnormalities or microcephaly	Total no. with ≥1 birth defect	Total no. of completed pregnancies	Percentage with Zika virus –associated birth defect (95% CI**)
Any laboratory evidence of recent possible Zika virus infection††					
Total	108	14	122	2,549	5 (4–6)
Recent NAT-confirmed Zika virus infection in maternal, placental, fetal, or infant specimen§§§§					
Total	71	9	80	1,508	5 (4–7)
Timing¶¶¶¶ of symptoms or specimen collection date***					
First trimester†††	18	4	22	276	8 (5–12)
Second trimester§§§	34	2	36	726	5 (4–7)
Third trimester¶¶¶	17	3	20	494	4 (3–6)

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas *Hoen, et al.*

The NEW ENGLAND JOURNAL of MEDICINE

Table 4. Birth Outcomes and Abnormalities Observed in the Fetuses and Infants.*

Variable	Time of ZIKV Infection			
	First Trimester (N=189)	Second Trimester (N=252)	Third Trimester (N=114)	Total (N=555)
	no. of fetuses or infants (%)			
Birth outcome				
Stillborn or not carried to term	24 (12.7)	4 (1.6)	0	28 (5.0)
Miscarried	11 (5.8)	0	0	11 (2.0)
Not carried to term because of voluntary termination of pregnancy	1 (0.5)	0	0	1 (0.2)
Not carried to term because of termination of pregnancy for medical reasons	9 (4.8)	1 (0.4)	0	10 (1.8)
Stillborn	3 (1.6)	3 (1.2)	0	6 (1.1)
Live-born	165 (87.3)	248 (98.4)	114 (100)	527 (95.0)
No prenatal ultrasonography after ZIKV infection†	13 (6.9)	28 (11.1)	55 (48.2)	96 (17.3)
Abnormalities observed				
Neurologic or ocular birth defects‡	24 (12.7)	9 (3.6)§	6 (5.3)	39 (7.0)
Microcephaly¶	19 (10.1)	8 (3.2)	5 (4.4)	32 (5.8)
Severe	7 (3.7)	2 (0.8)	0	9 (1.6)
Moderate: disproportionate	4 (2.1)	2 (0.8)	3 (2.6)	9 (1.6)
Moderate: proportionate	8 (4.2)	4 (1.6)	2 (1.8)	14 (2.5)
Intracranial calcifications	8 (4.2)	0	0	8 (1.4)
Ventriculomegaly	7 (3.7)	1 (0.4)	0	8 (1.4)
Lissencephaly	2 (1.1)	0	0	2 (0.4)
Other brain abnormalities	8 (4.2)	1 (0.4)	0	9 (1.6)
Neural-tube defects	1 (0.5)	0	0	1 (0.2)
Eye abnormalities	0	0	0	0
Consequences of central nervous system dysfunction	1 (0.5)	0	1 (0.9)	2 (0.4)
Other birth defects	2 (1.1)	3 (1.2)	1 (0.9)	6 (1.1)
Chromosomal defects	0	1 (0.4)‖	0	1 (0.2)
Skeletal abnormalities	2 (1.1)	1 (0.4)	1 (0.9)	4 (0.7)
Other	0	1 (0.4)	0	1 (0.2)
Congenital Zika syndrome	13 (6.9)	3 (1.2)	1 (0.9)	17 (3.1)

Structural CNS abnormalities reported at birth 7%

Supplementary Appendix

ORIGINAL ARTICLE
ZIKV Infection in Pregnant Women in Rio de Janeiro
December 15, 2016 | P. Brasil and Others
Preliminary Report Published Online: March 4, 2016

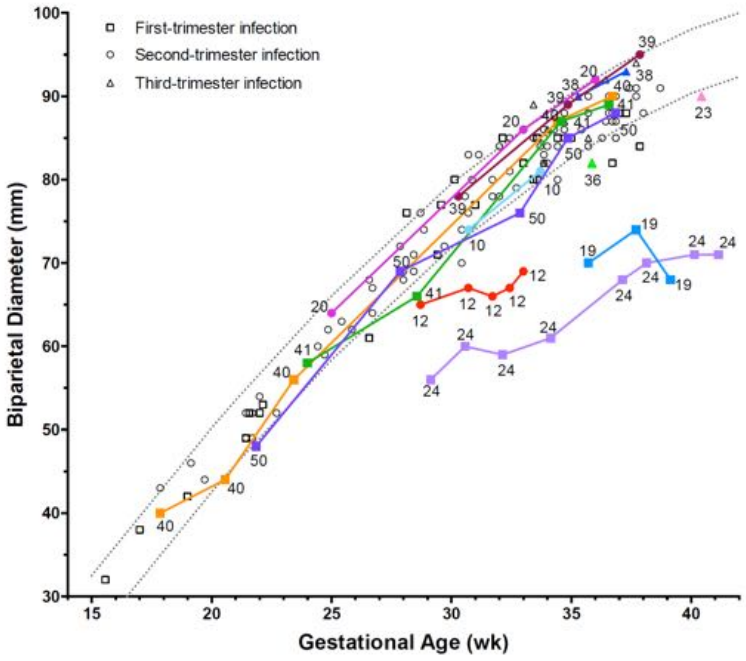
Supplemental Table 2: Abnormal outcomes and/ or Abnormal Findings at Birth.*

n = 58/125 (46%)

Fetal loss	9 Miscarriages/ Stillbirths (7.2%)

n = 49/117 (42%) in 116 pregnacies with live births- 1 set twins

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%) abnormal neurologic exam w/ or without CNS abnormal imaging
MRI findings: Excessive hypersignaling in T2 in the white matter, peritrigonal and tempo-parietal regions. Hyposignaling in the diffusion sequence.	15 Abnormal CNS imaging (13%)
Small for gestational age	1 Small for gestational age alone (0.8%) without CNS findings

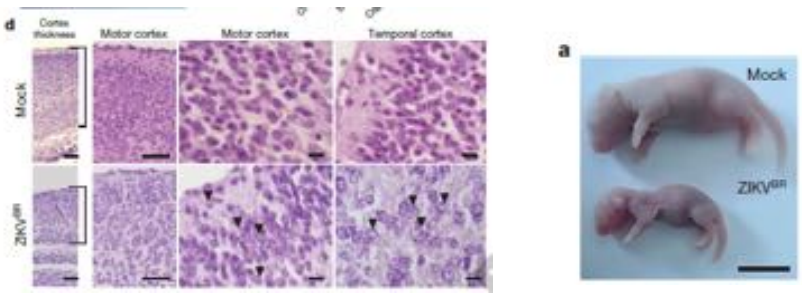


LETTER

Cugola *et al*, 2016

doi:10.1038/nature18296

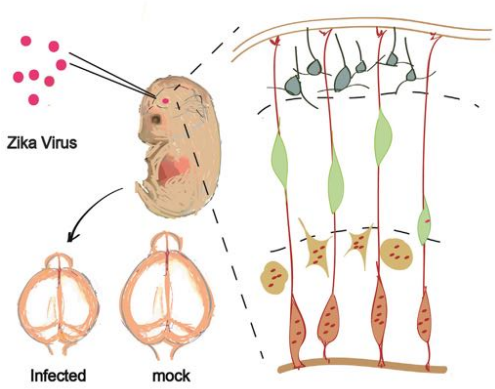
The Brazilian Zika virus strain causes birth defects in experimental models



Short Article

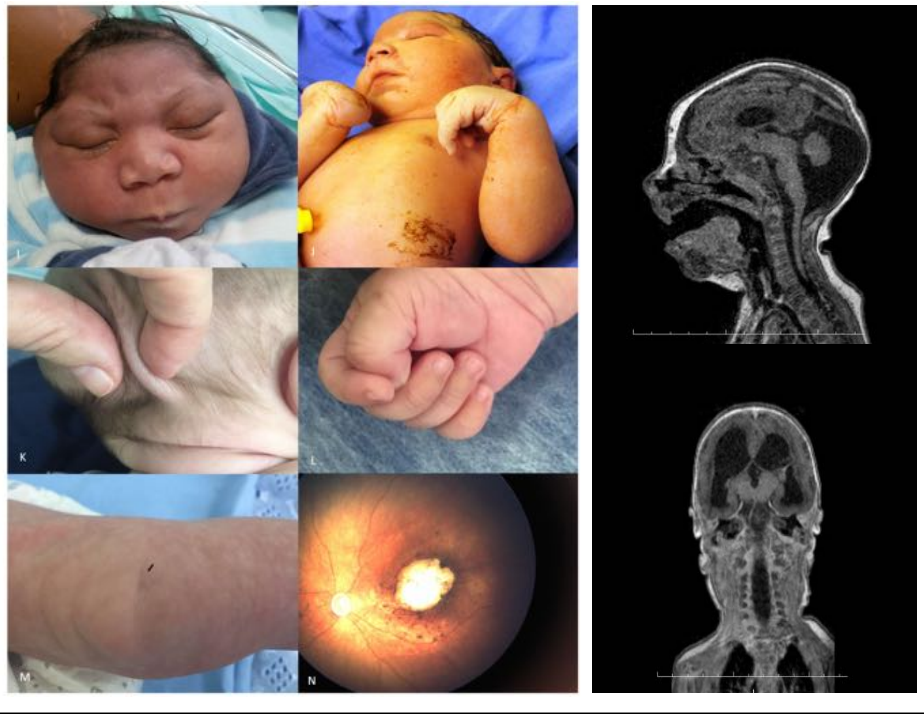
Cell Stem Cell

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

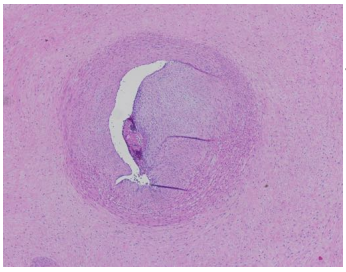


The suspected link between Zika virus (ZIKV) infection and microcephaly has raised urgent global alarm. However, there is so far no direct evidence for ZIKV infection impacting brain development. In this study, Li, Xu, and colleagues show that ZIKV replicates efficiently in the mouse embryonic brain 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.

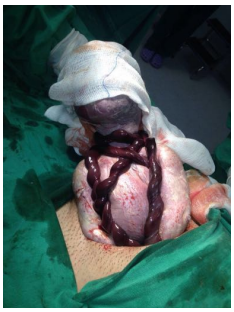
Li et al., 2016, Cell Stem Cell *19*, 1–7
August 4, 2016
http://dx.doi.org/10.1016/j.stem.2016.04.017

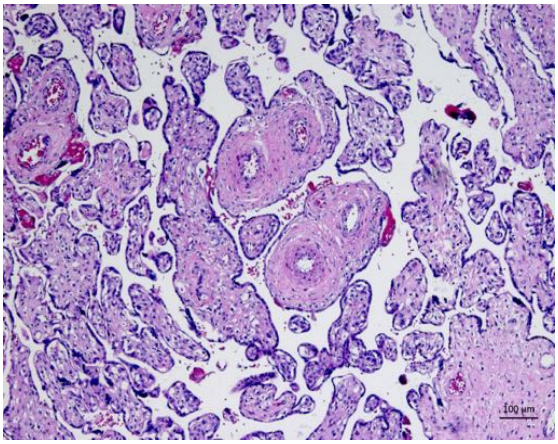


Late fetal demise: Placental vascular involvement/ Focal necrotic vasculitis



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

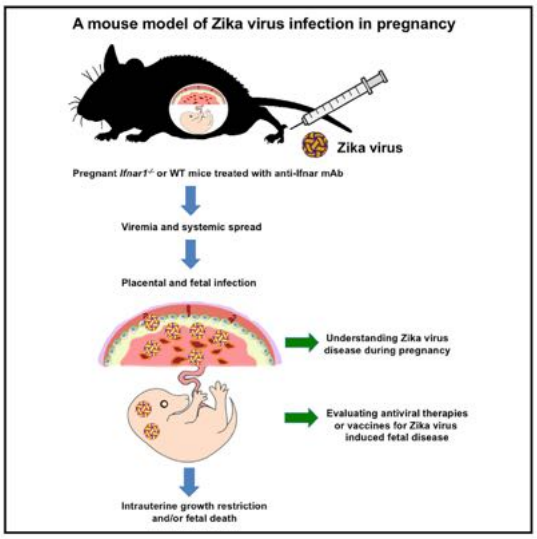




Dr. Elyzabeth Avvad Portari, IFF, Fiocruz- RJ

Cell

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

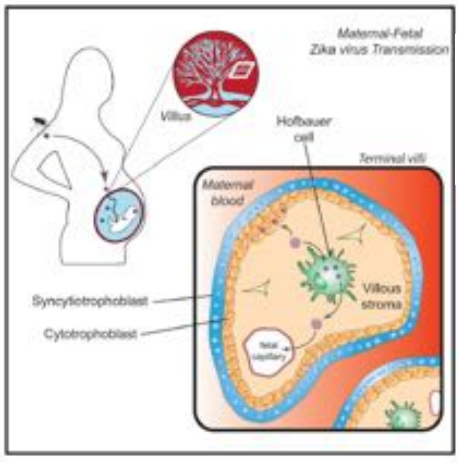


Zika virus infection of mice early in pregnancy results in infection of the placenta and fetal brain, causing a fetal syndrome that resembles the intrauterine growth restriction and spontaneous abortion observed in ZIKV-infected pregnant women.

Miner et al., 2016, Cell *165*, 1–11
May 19, 2016 © 2016 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.cell.2016.05.008

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*, 1–8
July 13, 2016 © 2016 Elsevier Inc.
http://dx.doi.org/10.1016/j.chom.2016.05.015

news & views

VIRUS PATHOGENESIS

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 placenta, testes and the brain, to spread Zika virus.

nature microbiology

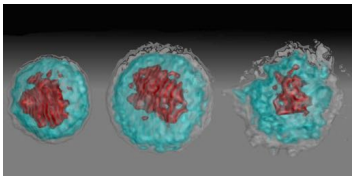
ARTICLES

DOI: 10.1038/s41564-017-0016-3

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

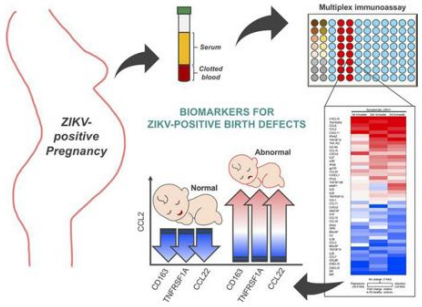
Suan-Sin Foo[1], Weiqiang Chen[1], Yen Chan[2], James W. Bowman[1], Lin-Chun Chang[1], Younho Choi[1], Ji Seung Yoo[1], Jianning Ge[1], Genhong Cheng[3], Alexandre Bonnin[4], Karin Nielsen-Saines[5], Patrícia Brasil[6] and Jae U. Jung[1]*

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,[1] Weiqiang Chen,[1] Yen Chan,[2] Wai-Suet Lee,[1,3] Shin-Ae Lee,[1] Genhong Cheng,[4] Nielsen-Saines,[5] Patrícia Brasil,[6] and Jae U. Jung[1]



JCI Insight. 2018;3(21):e124152. https://doi.org/10.1172/jci.insight.124152.

Zika outbreak may have led to fewer births in Rio de Janeiro

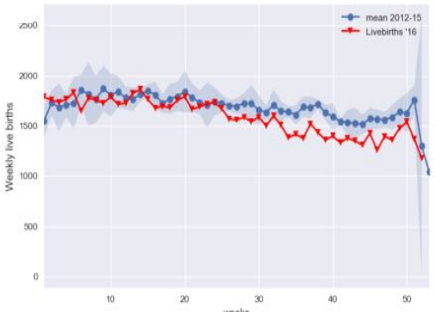
DAILY NEWS 24 April 2017

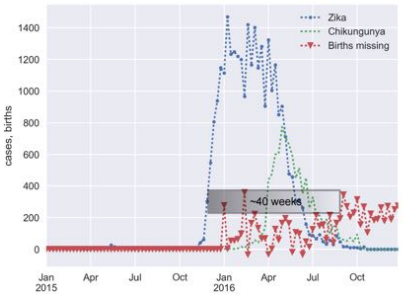
Can Zika account for the missing babies?

Flávio Codeço Coelho[a,*], Margaret Armstrong[a,b], Valeria Saraceni[c], Cristina Lemos[c]

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





bioRxiv preprint first posted online Apr. 12, 2017; doi: http://dx.doi.org/10.1101/126557.

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.

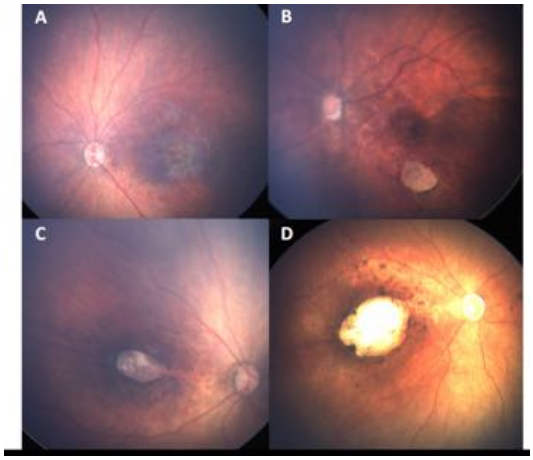
Meaning Eye abnormalities may be the only initial finding in congenital Zika virus infection, and all infants with potential Zika virus exposure should undergo screening eye examinations.

Published online July 17, 2017

JAMA Pediatrics | Original Investigation

Screening Criteria for Ophthalmic Manifestations of Congenital Zika Virus Infection

Andrea A. Zin, MD, PhD; Irena Tsui, MD; Julia Rossetto, MD, PhD; Zilton Vasconcelos, MSc, PhD; Kristina Adachi, MD; Stephanie Valderramos, MD, PhD; Umme-Aiman Halai, MD, MPH; Marcos Vinicius da Silva Pone, MD, PhD; Sheila Moura Pone, MD, PhD; Joel Carlos Barros Silveira Filho, MD; Mitsue S. Aibe, MD; Ana Carolina C. da Costa, PhD; Olivia A. Zin, MD; Rubens Belfort Jr, MD, PhD; Patricia Brasil, MD, PhD; Karin Nielsen-Saines, MD, MPH; Maria Elisabeth Lopes Moreira, MD, PhD



(A) Retinal pigment epithelium (RPE) mottling of the macula, left eye.
(B) Optic nerve hypoplasia and punched out, extra-foveal 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.

	Number (%)	OR [CI]
Microcephaly	14/24 (48.3)	19.1 [6.0-61]
Other CNS abnormalities	16/24 (66.7)	4.3 [1.6-11.2]
Arthrogryposis	7/24 (29.1)	29 [3.3-256]
First trimester infection	14/24 (58.3)	5.1 [1.9-13.2]
Second trimester infection	8/24 (33.3)	0.46 [0.18-1.2]
Third trimester infection	2/24 (8.3)	0.26 [0.056-1.18]

Zin et al, Jama Pediatrics

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Eye Findings in Infants With Suspected or Confirmed Antenatal Zika Virus Exposure

Irena Tsui, Maria Elisabeth Lopes Moreira, Julia D. Rossetto, Zilton Vasconcelos, Stephanie L. Gaw, Luiza M. Neves, Olivia A. Zin, Lorena Haefeli, Joel Carlos Barros Silveira Filho, Saint Clair Gomes Jr, Kristina Adachi, Marcos Vinicius da Silva Pone, Sheila Moura Pone, Jose Paulo Pereira Jr, Rubens Belfort, Vaithilingaraja Arumugaswami, Patricia Brasil, Karin Nielsen-Saines and Andrea A. Zin

Pediatrics originally published online September 13, 2018; originally published online September 13, 2018;

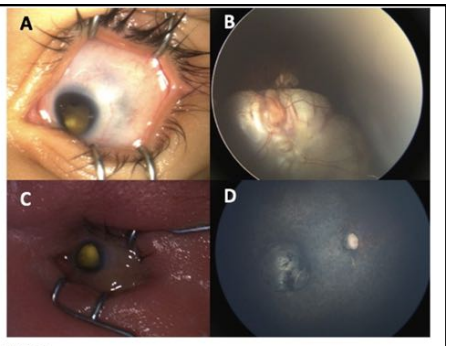


FIGURE 3
Uncommon presentations of ZIKV. A, Eye with microcornea and inferior iris coloboma. B, Large ON coloboma extending into the retina. C, Eye with microcornea and microphthalmia. D, Eye with ON atrophy, severe retinal vessel attenuation, and macular chorioretinal scarring.

TABLE 2 Eye Abnormalities in All Infants, RT-PCR–Positive Mother-Infant Pairs, and RT-PCR Unconfirmed Mother-Infant Pairs

	Total ZIKV Cases (N = 224), n (%)	RT-PCR–Positive (N = 156), n (%)	RT-PCR Unconfirmed (N = 68), n (%)
Any eye abnormality	57 (25.4)	32 (20.5)	25 (36.8)
Bilateral disease	51 (22.8)	31 (19.9)	20 (29.4)
Any ON abnormality	44 (19.6)	26 (16.7)	18 (26.5)
ON cupping and/or pallor	35 (15.6)	19 (12.2)	16 (23.5)
ON hypoplasia	12 (5.4)	9 (5.7)	3 (4.4)
ON coloboma	1 (0.5)	1 (0.6)	0 (0)
Any retina abnormality	37 (16.5)	23 (14.7)	14 (20.6)
Chorioretinal atrophy	22 (9.8)	15 (9.6)	7 (10.3)
Pigment mottling	20 (8.9)	12 (7.7)	8 (11.8)
Colobomatous	2 (0.9)	1 (0.6)	1 (1.5)
Severe vessel attenuation	1 (0.5)	0 (0)	1 (1.5)
Abnormal eye finding with normal physical examination	5 (2.2)	4 (2.6)	1 (1.5)

Eye abnormalities were not mutually exclusive.

Visual function in infants with antenatal Zika virus exposure

Andrea A. Zin, MD, PhD,[a,e] Irena Tsui, MD,[b,e] Julia D. Rossetto, MD, PhD,[a] Stephanie L. Gaw, MD, PhD,[c] Luiza M. Neves, MD,[a,d] Olivia A. Zin, MD,[d] Lorena Haefeli, MD,[a] Joel Carlos Barros Silveira Filho, MD,[c] Kristina Adachi, MD,[b] Marcos Vinicius da Silva Pone, MD, PhD,[a] Sheila Moura Pone, MD, PhD,[a] Natalia Molleri, OT,[a] Jose Paulo Pereira Jr, MD,[a] Rubens Belfort, MD, PhD,[f] Vaithilingaraja Arumugaswami, PhD,[b] Zilton Vasconcelos, MSc, PhD,[a] Patricia Brasil, MD, PhD,[g] Karin Nielsen-Saines, MD, MPH,[b] and Maria Elisabeth Lopes Moreira, MD, PhD[a]

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 Fernandes Figueira/FIOCRUZ. Visual function was considered abnormal if an infant could not fix and follow a standardized high-contrast target (10 cm) by 3-6 months of age. Visual function and associations with structural eye abnormalities, central nervous system (CNS) abnormalities, microcephaly, and nystagmus were assessed. Sensitivity and specificity of screening criteria for structural eye abnormalities was assessed.

RESULTS A total of 173 infants met inclusion criteria. Abnormal visual function was found in 52 infants (30.0%) and was significantly associated with eye abnormalities (40/52; OR = 44.2; 95% CI, 16.6-117.6), CNS abnormalities (50/52; OR = 64.0; 95% CI, 14.7-277.6), microcephaly (44/52; OR = 31.5; 95% CI, 12.7-77.8), and nystagmus (26/52; OR = 120.0; 95% CI, 15.6-924.5). Using microcephaly as screening criteria for the detection of eye abnormalities provided a sensitivity of 88.9% (95% CI, 76.0-96.3) and specificity of 82.8% (95% CI, 75.1-88.9). 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, 72.5-86.9).

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)

J AAPOS. 2018 Dec;22(6):452-456.e1. doi: 10.1016/j.jaapos.2018.07.352. Epub 2018 Oct 22.

Table 1. Correlation of visual function to structural findings and nystagmus

Structural findings	Total no. (%) [n = 173]	Fix-and-follow visual function: Unable, no. (%) [n = 52]	Able, no. (%) [n = 121]	OR (95% CI)	*P* value
Eye abnormality	45 (26)	38 (73)	7 (6)	44.2 (16.6-117.6)	<0.0001
Any CNS abnormality	84 (49)	50 (96)	34 (28)	64.0 (14.7-277.6)	<0.0001
Microcephaly	62 (36)	44 (85)	18 (15)	31.5 (12.7-77.8)	<0.0001
Nystagmus	27 (16)	26 (50)	1 (0.8)	120.0 (15.6-924.5)	<0.0001
None of the above	87 (50)	0 (0)	87 (72)	1	-

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. Silveira Filho MD[a]; Julia D. Rossetto, MD, PhD[b,c]; Irena Tsui MD[d], Luiza M. Neves MD[b], Lorena Haefeli MD[b]; Isabel S.D. Garcia, MD[b], Jocieli Malacarne, PhD[b], Natalia Molleri OT[b], Stephanie L. Gaw[e], MD, PhD; Olivia A Zin, MD[f]; Marcos Vinicius da Silva Pone, MD[b], PhD; Sheila Moura Pone, MD, PhD[b]; Kristina Adachi[d], MD; Jose Paulo Pereira Jr, MD[b]; Saint Claire Gomes Jr, PhD[b]; Patricia Brasil, MD, PhD[g]; Karin Nielsen-Saines, MD,MPH[d]; Zilton Vasconcelos, MSc, PhD[b]; Maria Elisabeth Lopes Moreira, MD, PhD[b]; Andrea A. Zin, MD, PhD[b]

PLOS | NEGLECTED TROPICAL DISEASES

March 26, 2018

RESEARCH ARTICLE

Cardiac findings in infants with in utero exposure to Zika virus- a cross sectional study

Dulce H. G. Orofino[1,2☯*], Sonia R. L. Passos[3☯], Raquel V. C. de Oliveira[3☯], Carla Verona B. Farias[1‡], Maria de Fatima M. P. Leite[1‡], Sheila M. Pone[4‡], Marcos V. da S. Pone[4‡], Helena A. R. Teixeira Mendes[2,3‡], Maria Elizabeth L. Moreira[5‡], Karin Nielsen-Saines[6‡]

- 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 1. Characteristics of 13 patients with abnormal ECHO findings.

Patient	Sex	Age at ECHO (days)	PCR (m) [a]	PCR (n) [b]	Microcephaly	CNS imaging [c]	Gestational age (weeks)	2D-Echo	Rash-trimester
1	Girl	288	Positive	Positive	Yes	Positive	36	PDA [d]	2nd
2	Girl	220	Positive	Positive	No	Negative	40	PDA	2nd
3	Boy	132	Positive	Positive	No	Negative	40	VSD [e]	2nd
4	Boy	1	Positive	Positive	Yes	Positive	39	PAH [f]	1st
5	Girl	178	Positive	Positive	Yes	Positive	37	PDA	1st
6	Boy	2	Positive	Positive	Yes	Positive	40	VSD	1st
7	Girl	96	Positive	NA	Yes	Negative	38	ASD [g]	2nd
8	Girl	28	Negative	Positive	No	Positive	37	ASD	3rd
9	Girl	2	Positive	NA	Yes	Negative	35	LVH [h]	2nd
10	Boy	55	Positive	NA	No	Negative	39	ASD	2nd
11	Boy	91	Positive	Positive	No	Negative	39	VSD	2nd
12	Girl	7	Negative	Positive	No	Negative	38	POF [i], VSD, RSPB [j]	No rash
13	Boy	NA [k]	Positive	NA	No	NA	37	VSD, POF	No rash

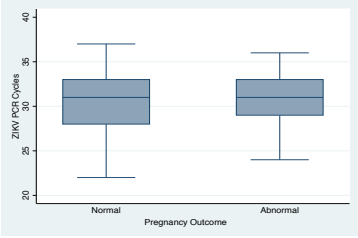
Maternal Zika Virus Disease Severity, Virus Load, Prior Dengue Antibodies, and Their Relationship to Birth Outcomes

Clinical Infectious Diseases

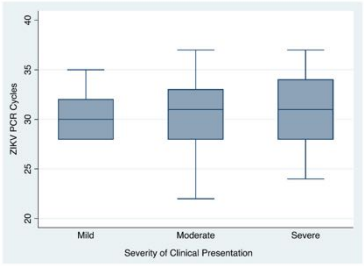
MAJOR ARTICLE

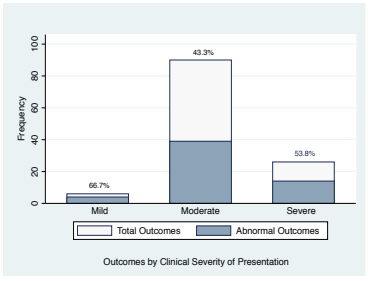
CID 2017

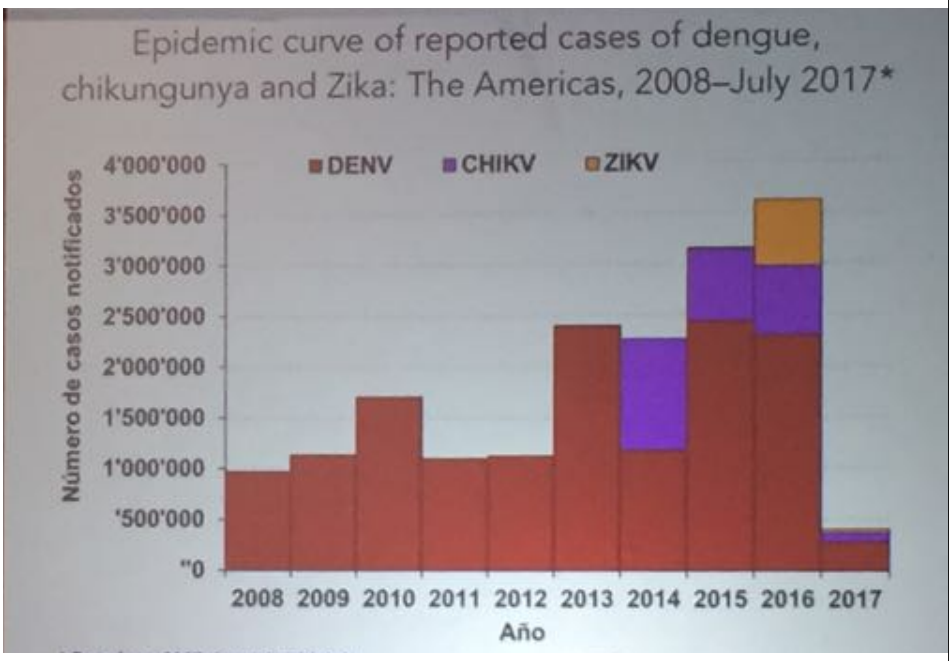
Umme-Aiman Halai,[1] Karin Nielsen-Saines,[1] Maria Lopes Moreira,[2] Patricia Carvalho de Sequeira,[2] Jose Paulo Pereira Junior,[2] Andrea de Araujo Zin,[2] James Cherry,[1] Claudia Raja Gabaglia,[3] Stephanie L. Gaw,[4] Kristina Adachi,[1] Irena Tsui,[1] Jose Henrique Pilotto,[2] Rita Ribeiro Nogueira,[2] Ana Maria Bispo de Filippis,[1] Patricia Brasil[2]



- 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





Science Translational Medicine

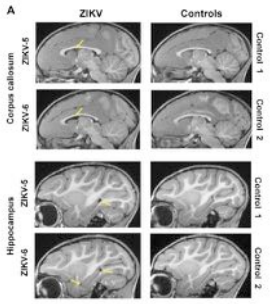
Postnatal Zika virus infection is associated with persistent abnormalities in brain structure, function, and behavior in infant macaques

Mavigner *et al., Sci. Transl. Med.* **10**, eaao6975 (2018) 4 April 2018

Zika Exposure Even after Birth May Lead to Brain Damage

A monkey study heightens concerns about widespread harm from the virus

Monkey study suggests Zika infection in infancy could cause brain damage



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

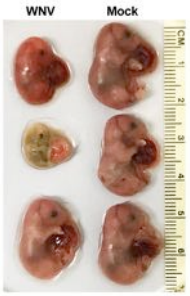
EMERGING INFECTIONS

Zika virus–related neurotropic flaviviruses infect human placental explants and cause fetal demise in mice

Platt *et al., Sci. Transl. Med.* **10**, eaao7090 (2018) 31 January 2018

- 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.

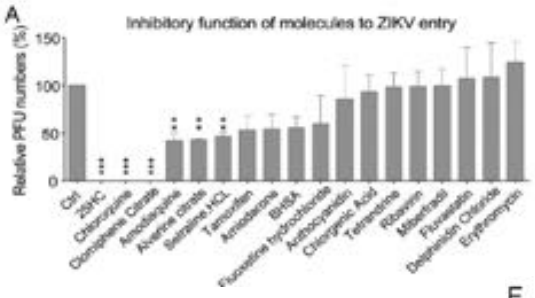
WNV caused fetal CNS malformations in mice



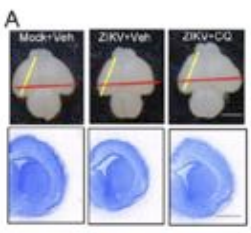
Chloroquine, a FDA-approved Drug, Prevents Zika Virus Infection and its Associated Congenital Microcephaly in Mice

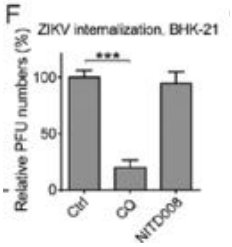
Chunfeng Li [a,b,1], Xingliang Zhu [c,1], Xue Ji [d,1], Natalie Quanquin [e], Yong-Qiang Deng [b], Min Tian [f,b], Roghiyh Aliyari [e], Xiangyang Zuo [a], Ling Yuan [c], Shabbir Khan Afridi [c], Xiao-Feng Li [b], Jae U. Jung [g], Karin Nielsen-Saines [h], Frank Xiao-Feng Qin [a,*], Cheng-Feng Qin [b,d,**], Zhiheng Xu [c],***, Genhong Cheng [a,e,****]

EBioMedicine 24 (2017) 189–194



Chloroquine inhibits ZIKV entry in vivo and in vitro and protects against microcephaly in mouse embryos





Neurodevelopment in Infants Exposed to Zika Virus In Utero

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 ser organ dysfunctic

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Moreira, Nielsen-Saines, Brasil et al.

N ENGL J MED 379;24 NEJM.ORG DECEMBER 13, 2018

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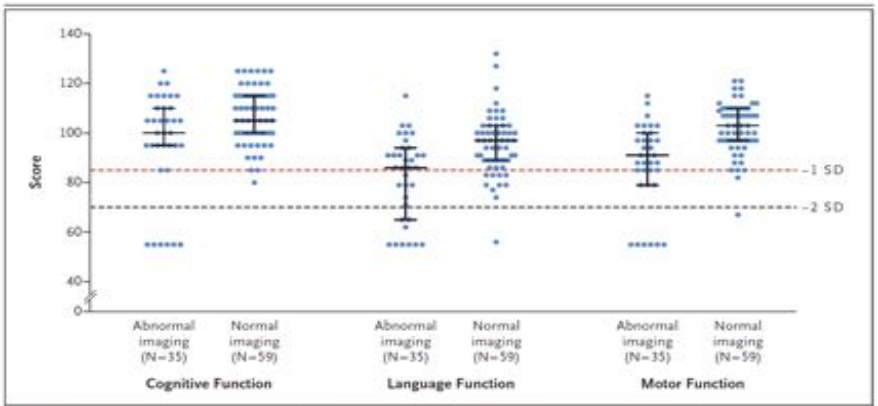


Figure 1. Individual Scores on the Bayley-III Scales at 12 to 18 Months of Age, According to Neuroimaging Results.
Shown are the scores for cognitive, language, and motor functions on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Standard scores on the Bayley-III scales 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

Neurological and Imaging Assessments (N=94)	Normal (above 85)	%	Between 1 and 2SD (71-85)	%	OR	95% CI	P Value	Below 2 SD (70 and below)	%	OR	95% CI	P Value
All with Imaging and Bayley												
Bayley assessments (N=94)	59	62.8%	24	25.5%	0.73	(0.60,0.88)	<0.01	11	11.7%	0.80	(0.70, 0.91)	<0.01
Cognitive (N=94)	83	88.3%	5	5.3%	0.84	(0.73,0.90)	0.01	6	6.4%	0.84	(0.76, 0.93)	<0.01
Language(N=94)	69	73.4%	15	16.0%	0.77	(0.64,0.92)	0.01	10	10.6%	0.79	(0.70, 0.89)	<0.01
Motor (N=94)	76	80.9%	11	11.7%	0.75	(0.64,0.88)	<0.01	7	7.4%	0.86	(0.77, 0.95)	<0.01
Normal Imaging												
Bayley assessments (N=59)	44	46.8%	13	11.4%				2	2.1%			
Cognitive (N=59)	56	59.6%	3	2.3%				0	0.0%			
Language(N=59)	49	52.1%	9	9.1%				1	1.1%			
Motor (N=59)	54	57.4%	4	3.4%				1	1.1%			
Abnormal Imaging												
Bayley assessments (N=35)	15	15.9%	11	11.7%				9	9.6%			
Cognitive (N=35)	27	28.7%	2	2.1%				6	6.4%			
Language(N=35)	20	21.2%	6	6.4%				9	9.6%			
Motor (N=35)	22	23.4%	7	7.4%				6	6.4%			

Other Assessments	Normal (N)	%	Abnormal (N)	%
Hearing (N=49)	43	88%	6	13%
Eye (N=112)	105	94%	7	6%

*Odds Ratio (OR), 95% Confidence Interval (95% CI), and p value obtained from logistic regression, with either -1 SD or - 2 SD vs normal Bayley-III as the outcome, and normal vs. abnormal imaging as the exposure.

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.

Moreira, Nielsen-Saines, Brasil, NEJM, Dec 12, 2018

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.

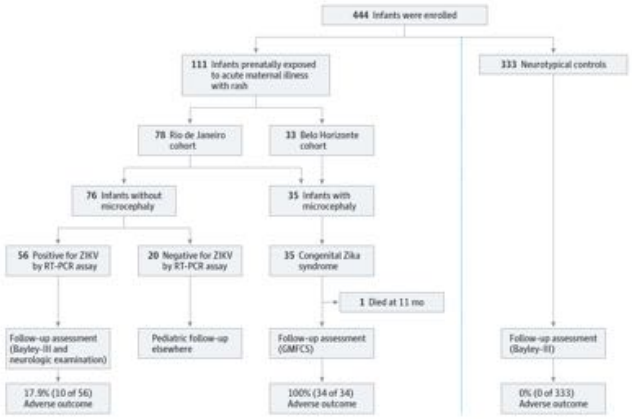
Original Investigation | Pediatrics

Association of Infants Exposed to Prenatal Zika Virus Infection With Their Clinical, Neurologic, and Developmental Status Evaluated via the General Movement Assessment Tool

Christa Einspieler, PhD; Fabiana Utsch, MD; Patricia Brasil, MD; Carolina Y. Panvequio Aizawa, MS; Colleen Peyton, PhD; Renata Hydee Hasue, PhD; Fernanda Françoso Genovesi, MS; Luana Damasceno, MS; Maria Elisabeth Moreira, MD; Kristina Adachi, MD; Peter B. Marschik, PhD; Karin Nielsen-Saines, MD, MPH; for the GM Zika Working Group

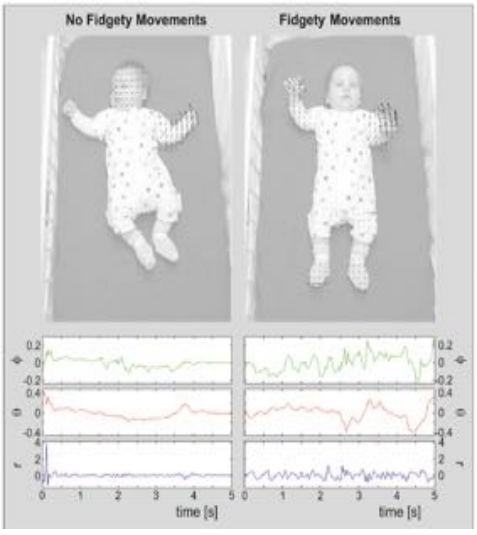
JAMA Network Open

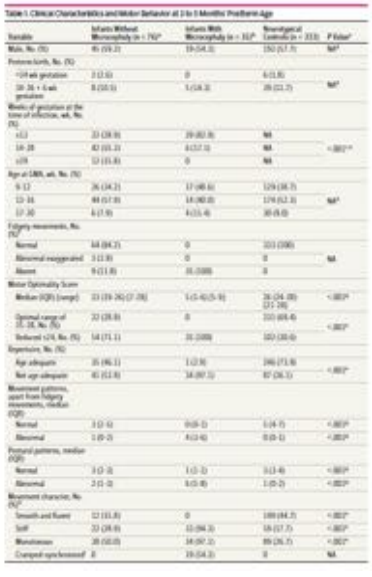
Figure. Prospective Cohort of Infants Prenatally Exposed to Acute Maternal Illness With Rash and Neurotypical Controlsa



Adverse outcomes included neurologic deficits and/or abnormal Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) results as defined in the text. Positive and negative for Zika virus by reverse transcriptase–polymerase chain reaction assay plus infants referred for congenital Zika syndrome. GMFCS indicates Gross Motor Function Classification System.

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%.





The Telegraph

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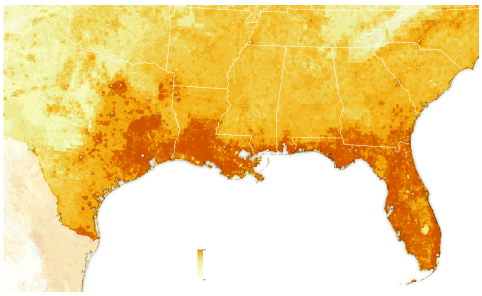
World must prepare for return of Zika, scientists warn

The Opinion Pages | OP-ED CONTRIBUTOR

Zika Is Coming

By PETER J. HOTEZ APRIL 8, 2016



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By Sarah Newey

13 SEPTEMBER 2018 • 7:57PM

The New York Times

africa.com

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.

CDC > Home > Travel Notices

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.

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- Ana Bispo de Filippis
- Guilherme Calvet
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