Emergence of Congenital Zika Syndrome

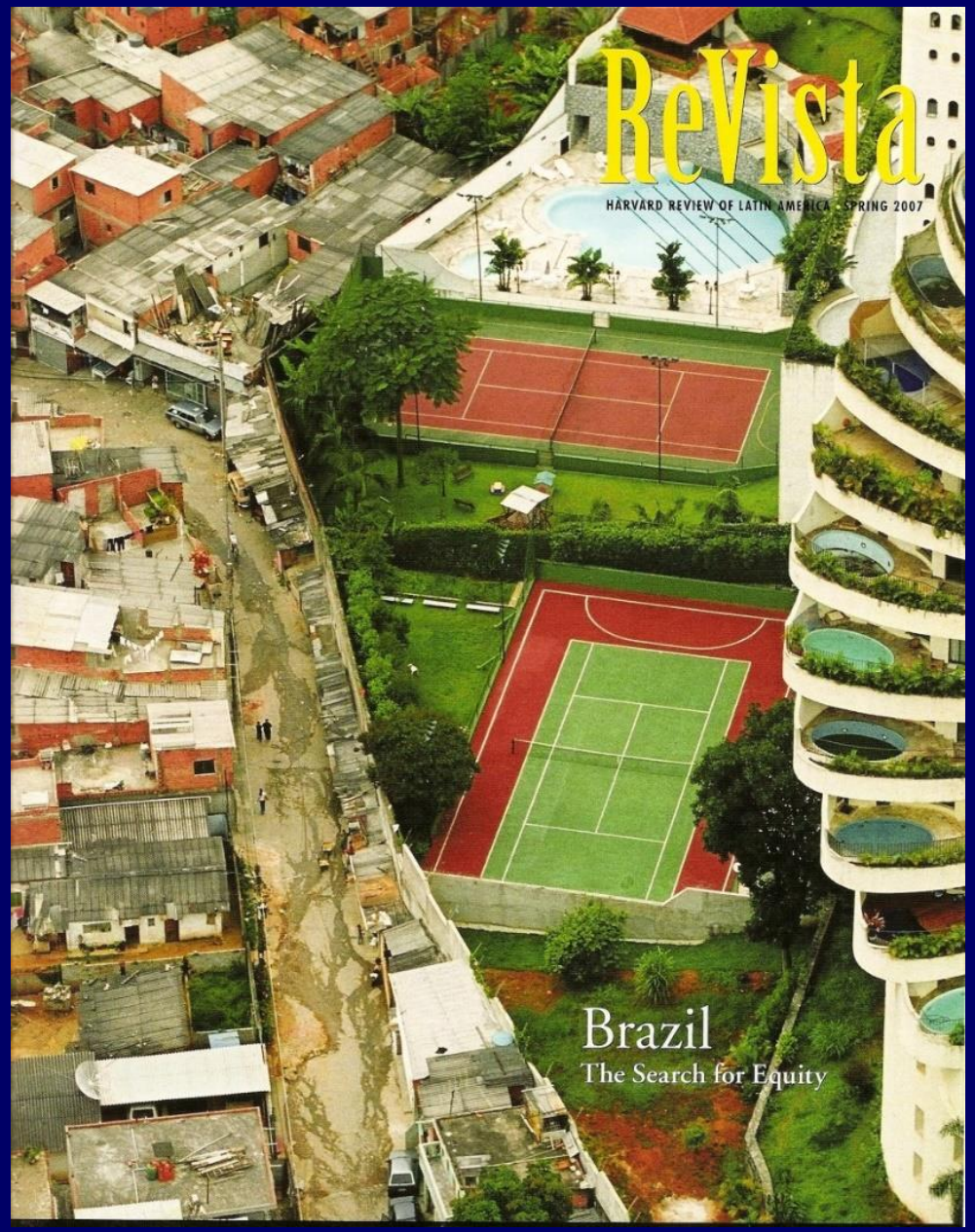
XVII Congresso SADI
Mar del Plata, Argentina
June 16, 2017

Oswaldo Cruz Foundation (Fiocruz)
Brazilian Ministry of Health
Salvador, Brazil

Yale School of Public Health
Epidemiology of Microbial Diseases
New Haven, USA

Overview

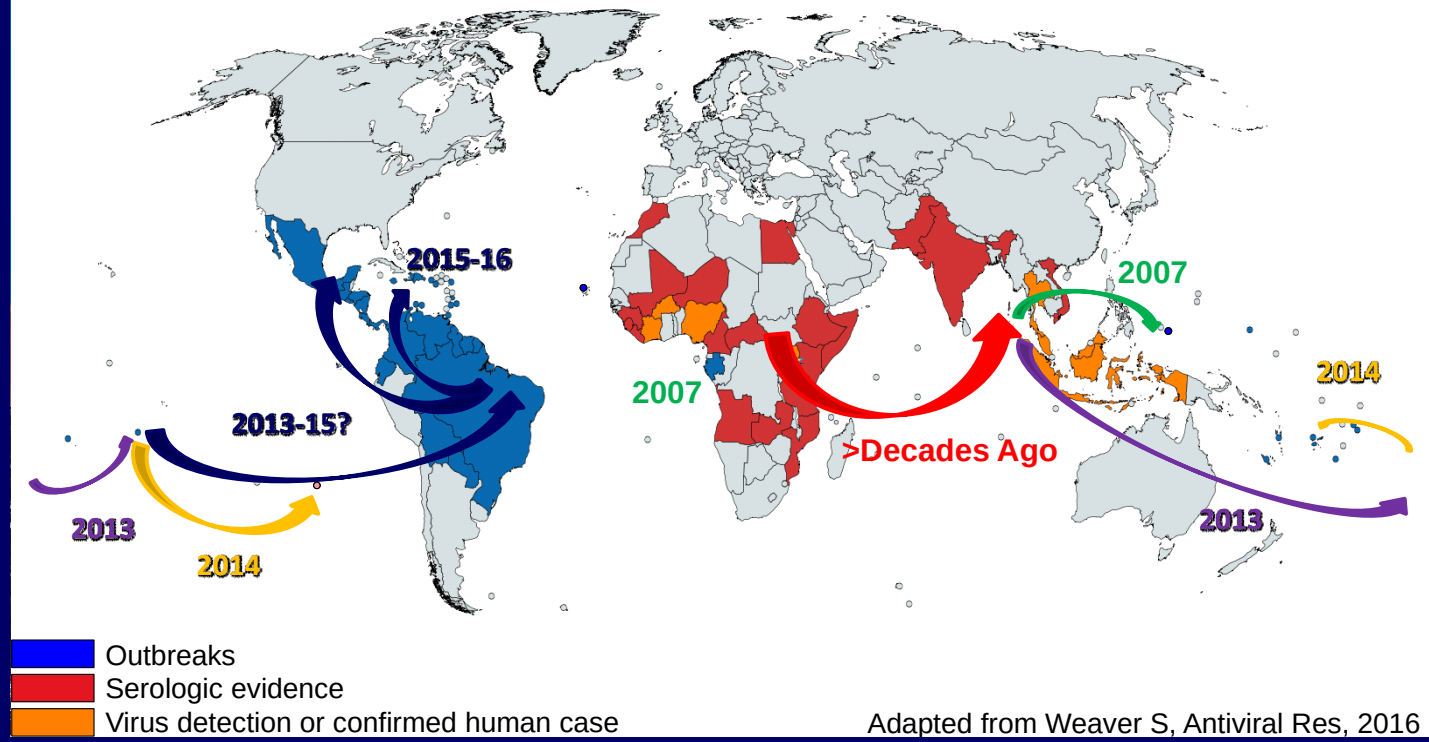
- Introduction of Zika into the Americas
- What is congenital zika syndrome?
- Does risk and severity vary across and within populations?
- How do you screen for and diagnose congenital zika syndrome?
- Questions and future challenges



Zika Virus

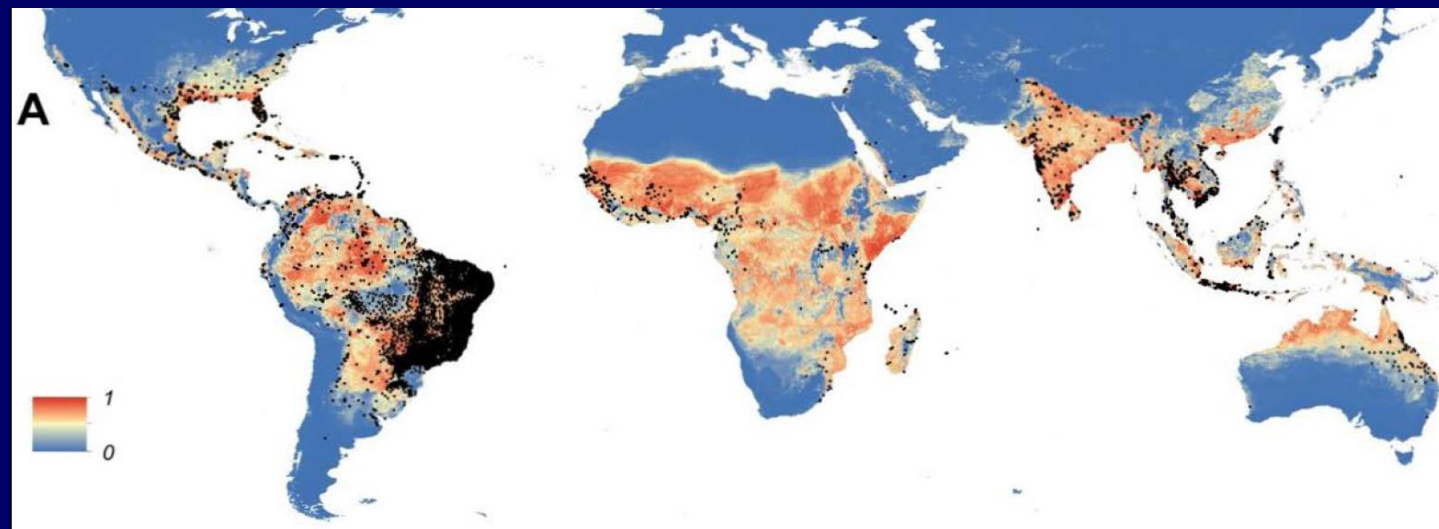
- SS +sense RNA virus
  - Genus Flavivirus (DENV, YFV, WNV)
  - High serologic cross-reactivity
- 1° transmission is mosquito-borne
  - *Aedes* genus, including *A. aegypti*
  - Documented sexual transmission
- Limited to sylvatic setting
  - Isolated in 1947
  - Sylvatic *Aedes*, non-human primates
  - <20 human cases before 2007
- Global pandemic and introduction to the Americas in 2015

Spread of Zika Virus: 1947-2016



Adapted from Weaver S, Antiviral Res, 2016

"Perfect Storm": Global Distribution of Aedes aegypti

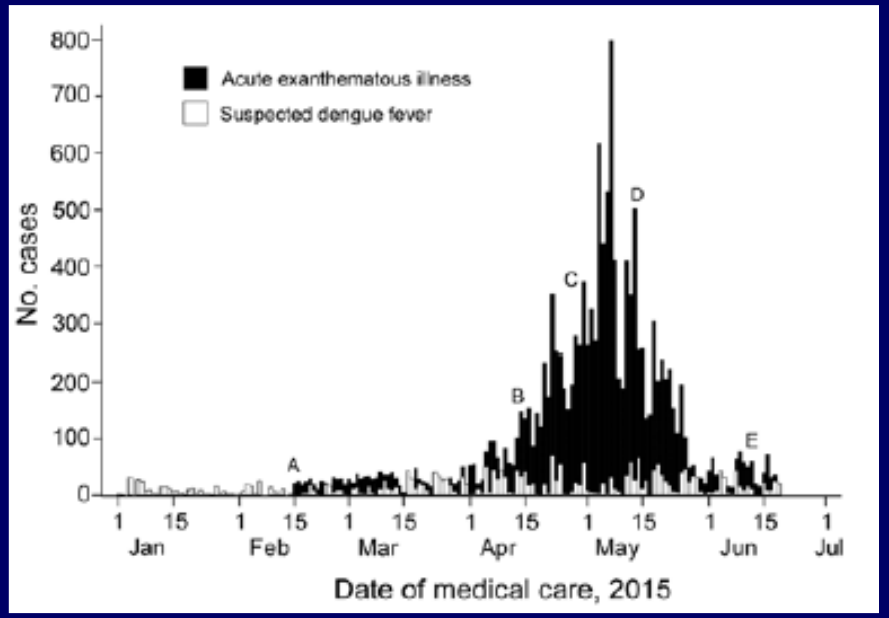


Timeline of the Zika Outbreak in Salvador, Brazil

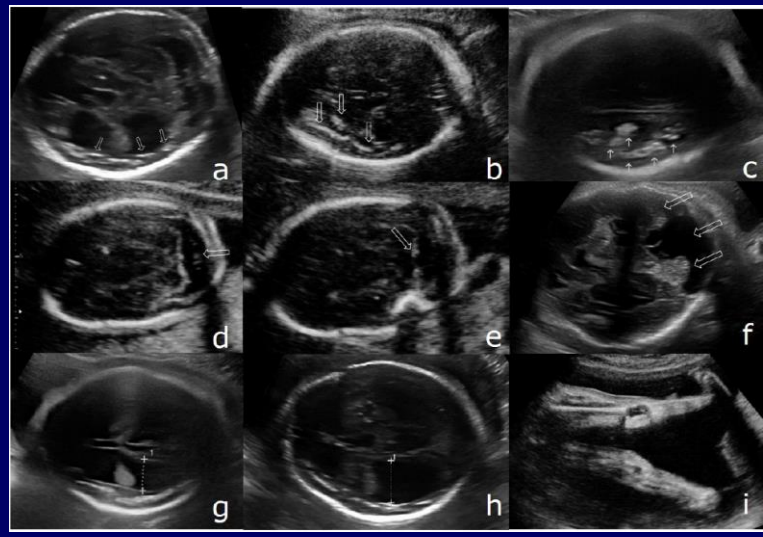
- Feb-Jun 2015: Outbreak of acute exanthematous illness
- Mar 2015: Zika detected
- April-Jul 2015: Cluster of GBS
- Jul-Set 2015: Obstetricians identified abnormalities on routine UTS of pregnant women
- Oct 2015: Increase detected of newborns with microcephaly

Outbreak of Exanthematous Illness Associated with Zika, Chikungunya, and Dengue Viruses, Salvador, Brazil

Cristiane W. Cardoso,[1] Igor A.D. Paploski,[1] Mariana Kikuti, Moreno S. Rodrigues, Monaise M.O. Silva, Gubio S. Campos, Silvia I. Sardi, Uriel Kitron, Mitermayer G. Reis, Guilherme S. Ribeiro



20 wk 26 wk 35 wk



Sarno Uts Ob Gyn, 2016

Microcephaly Epidemic in Brazil

Case Reports

- Zika detected fetuses w/ abnormalities (Oliveira Melo, Uts Ob Gyn 2016)
- Aborted fetuses, stillbirths (Mlakar, NEJM, 2016, Martines, MMWR 2016)
- Hydrops fetalis and fetal demise (Sarno, PLoS NTD, 2016)

Epidemiological Studies

- 29% adverse fetal outcomes (Brasil, NEJM, 2016)
- 1% risk of microcephaly after 1st trimester exposure (Cauchemez, Lancet, 2016)
- OR 56 for association of Zika and microcephaly (de Araújo, Lancet ID, 2016)

Causal Association with Birth Defects

(Rasmussen, NEJM 2014)

BRIEF REPORT

Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

RESEARCH ARTICLE

Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise

Manoel Sarno[1,2], Gielson A. Sacramento[3], Ricardo Khouri[3], Mateus S. do Rosário[1], Federico Costa[2,3,4], Gracinda Archanjo[1], Luciane A. Santos[3], Nivison Nery, Jr.[3], Nikos Vasilakis[5], Albert I. Ko[3,4]*, Antonio R. P. de Almeida[1,2]

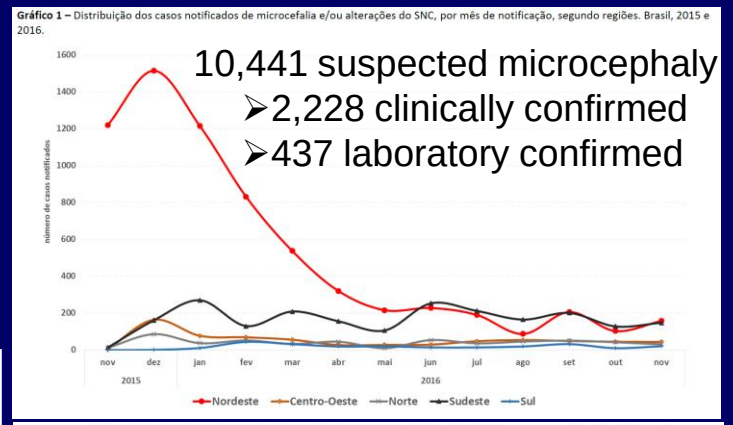
ORIGINAL ARTICLE

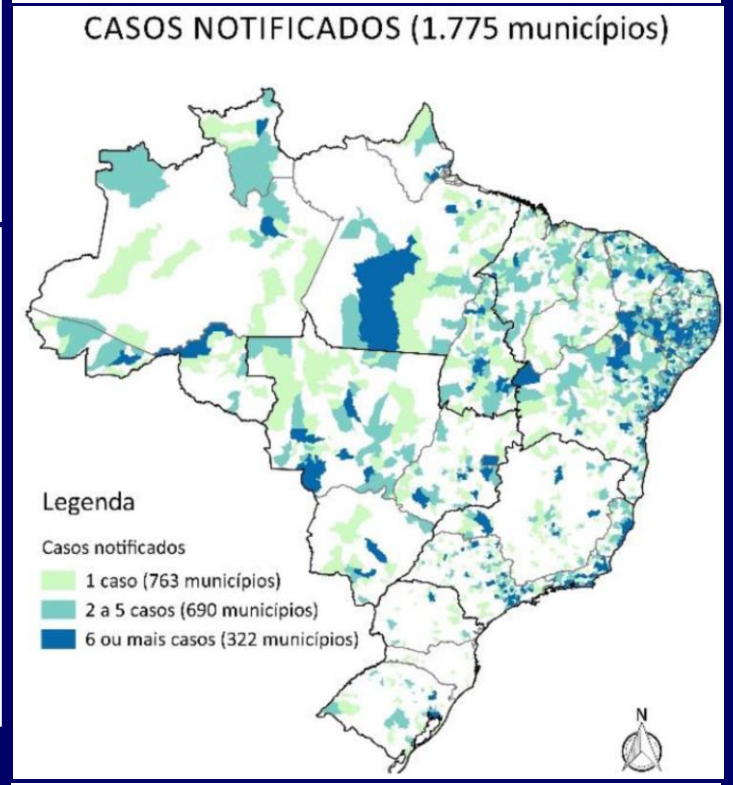
Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

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.

Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study

*Thalia Velho Barreto de Araújo, Laura Cunha Rodrigues, Ricardo Arraes de Alencar Ximenes, Demócrito de Barros Miranda-Filho, Ulisses Ramos Montarroyos, Ana Paula Lopes de Melo, Sandra Valongueiro, Maria de Fátima Pessoa Militão de Albuquerque, Wayner Vieira Souza, Cynthia Braga, Sinval Pinto Brandão Filho, Marli Tenório Cordeiro, Enrique Vazquez, Danielle Di Cavalcanti Souza Cruz, Cláudio Maierovitch Pessanha Henriques, Luciana Caroline Albuquerque Bezerra, Priscila Mayrelle da Silva Castanha, Rafael Dhalia, Ernesto Torres Azevedo Marques-Júnior, Celina Maria Turchi Martelli, on behalf of investigators from the Microcephaly Epidemic Research Group, the Brazilian Ministry of Health, the Pan American Health Organization, Instituto de Medicina Integral Professor Fernando Figueira, and the State Health Department of Pernambuco**





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.

Brazil-Yale Studies on Zika

- Microcephaly outbreak investigation in Salvador
  - Enrolled and following >1000 mother-newborn pairs
  - Risk factors and prognosis for CZS
- Prospective studies of Zika-exposed pregnant women in São José do Rio Preto
- NIH-Fiocruz ZIP Study
  - Nine international sites
  - 10,000 pregnant women in 1st trimester
- Community-based cohort studies in Salvador
  - Following 2,400 slum residents
  - Transmission dynamics
  - Role of pre-exisiting flavivirus immunity

Zika in Infants and Pregnancy (ZIP) Study

- Sponsored by NIH and Oswaldo Cruz Foundation (Fiocruz) of Brazil
- Prospective cohort study of 10,000 pregnant women
- Following women for incidence of Zika infection
- Following infants through at least one year of age
- Key endpoints: pregnancy outcomes, congenital anomalies, other developmental abnormalities

AS Fauci/NIAID

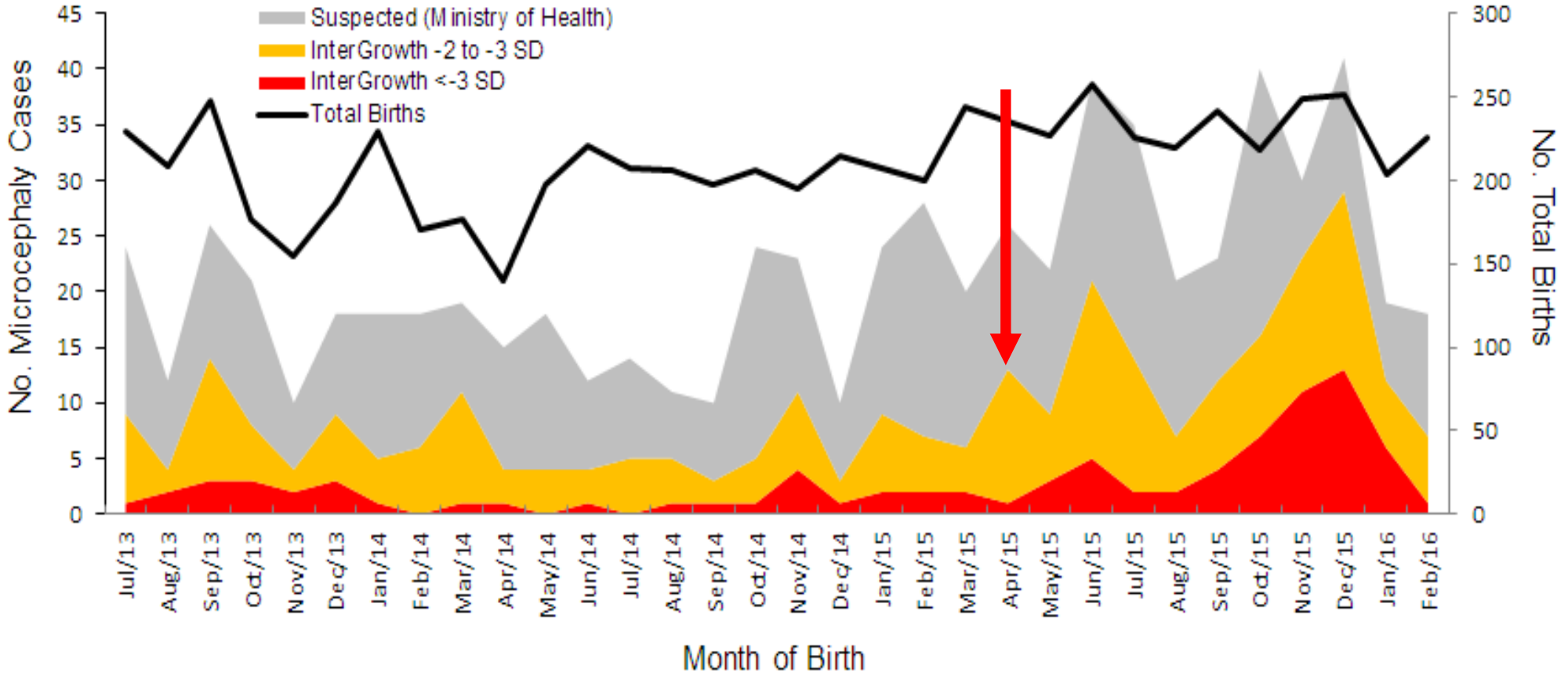
*additional areas to be added

Fiocruz-Yale Community Site

What is Congenital Zika Syndrome?

Investigation of the Microcephaly Outbreak in Salvador, Brazil

Surveillance at Hospital Geral Roberto Santos



Microcephaly Cases: Presentation at Birth

Characteristics	No.	No. (%) or median (IQR)
Gestational age (wk)	40	39 (38-40)
Axial hypertonia	33	19 (58)
Uncoordinated swallowing	40	8 (20)
Lower extremity arthrogryposis	40	7 (18)
Talipes equivarus	40	3 (8%)
Abnormal OAE	31	14 (45%)
Ocular lesions	33	14 (42%)
Seizures	40	5 (12%)
In-hospital death	40	3 (8%)

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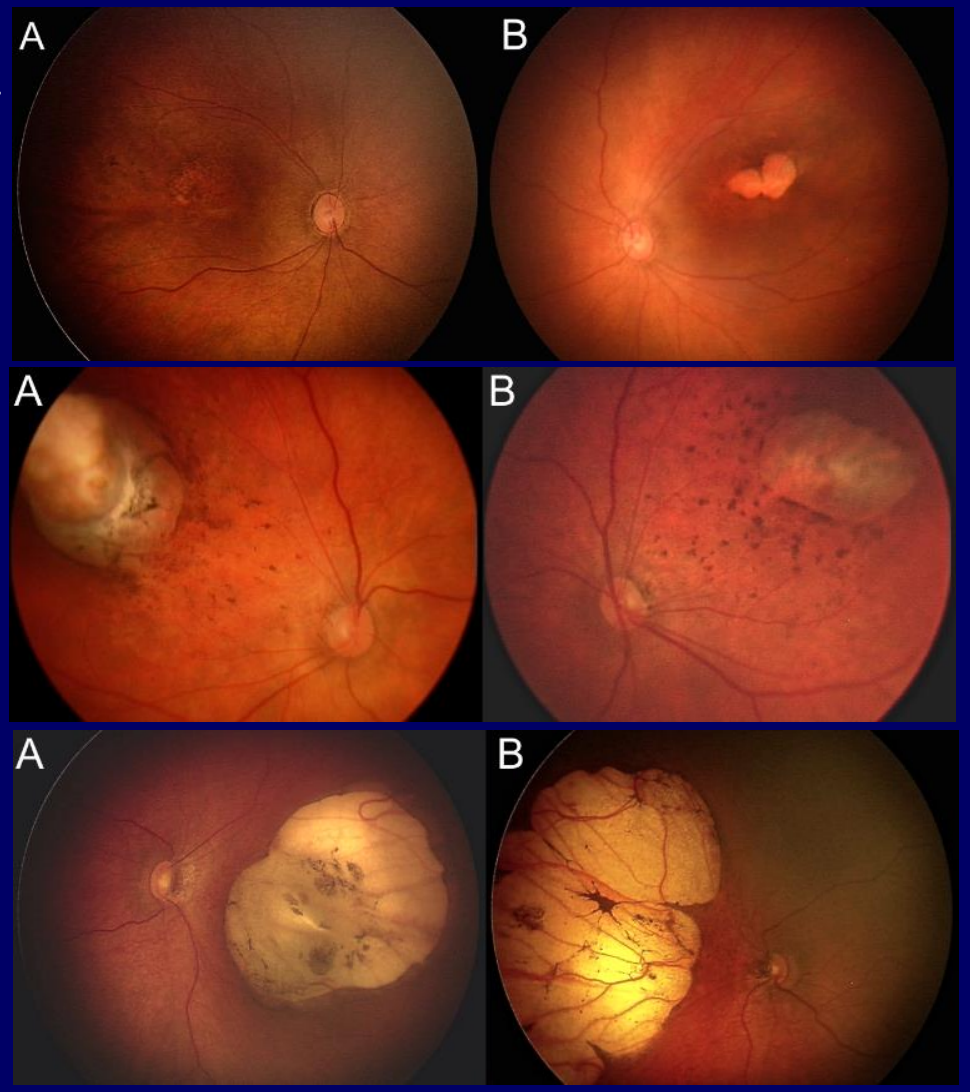
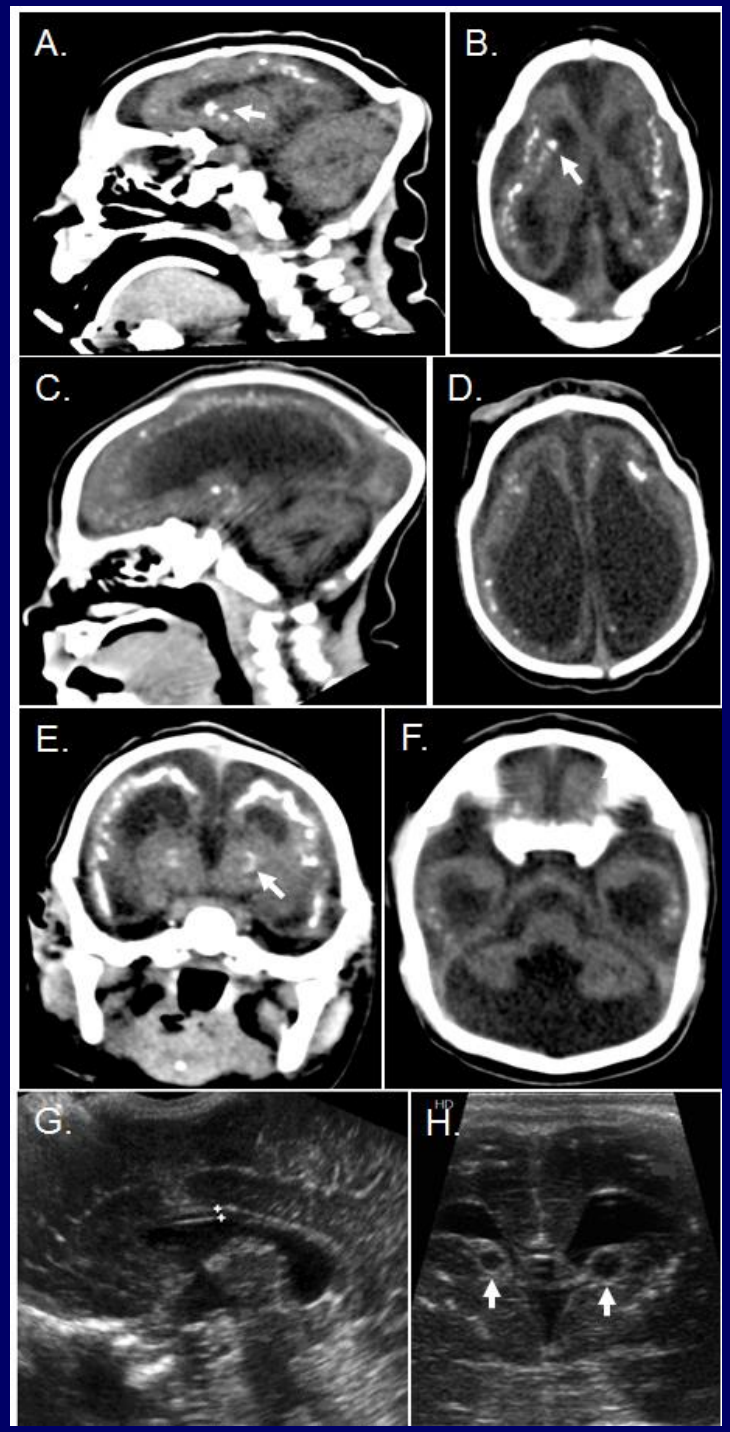
Original Investigation

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

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

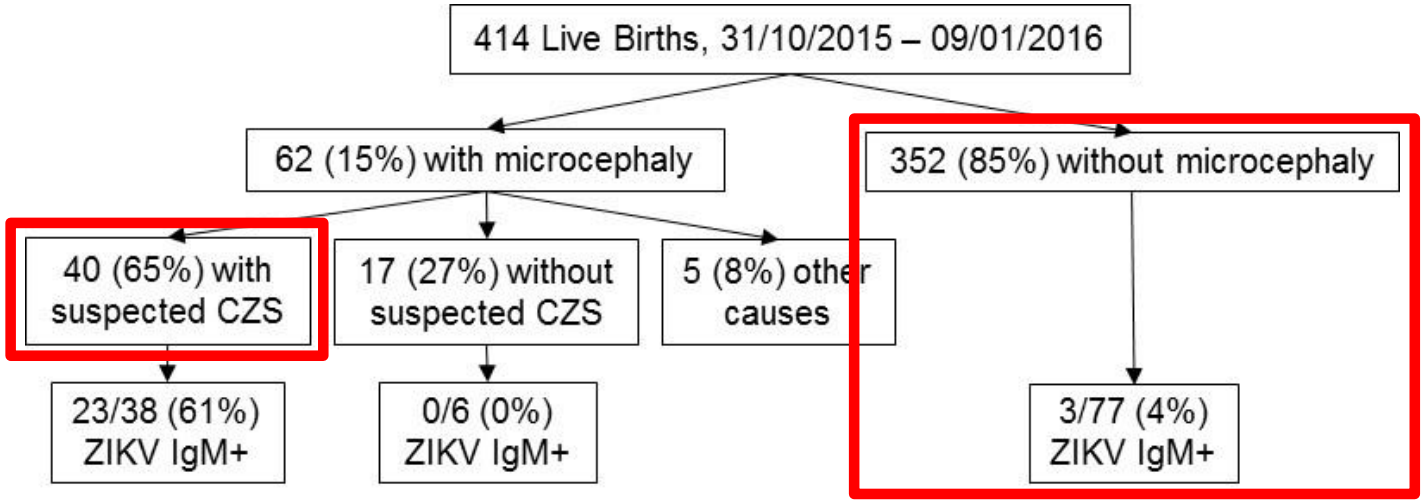


Findings	Total (N=38)
Ventriculomegaly	34 (89%)
Subependymal cysts	14 (42%)
Parenchymal calcifications	35 (92%)
Subcortical	32 (84%)
Periventricular	12 (32%)
Basal ganglia	24 (63%)
Thalamic	17 (45%)
Brainstem	12 (32%)
Stippled	31 (82%)
Laminar	12 (32%)
Simplified gyral pattern	31 (82%)
Corpus callosum dysgenesis	24 (63%)
Reduced cerebellar volume	10 (29%)



Microcephaly Outbreak in Salvador, Brazil

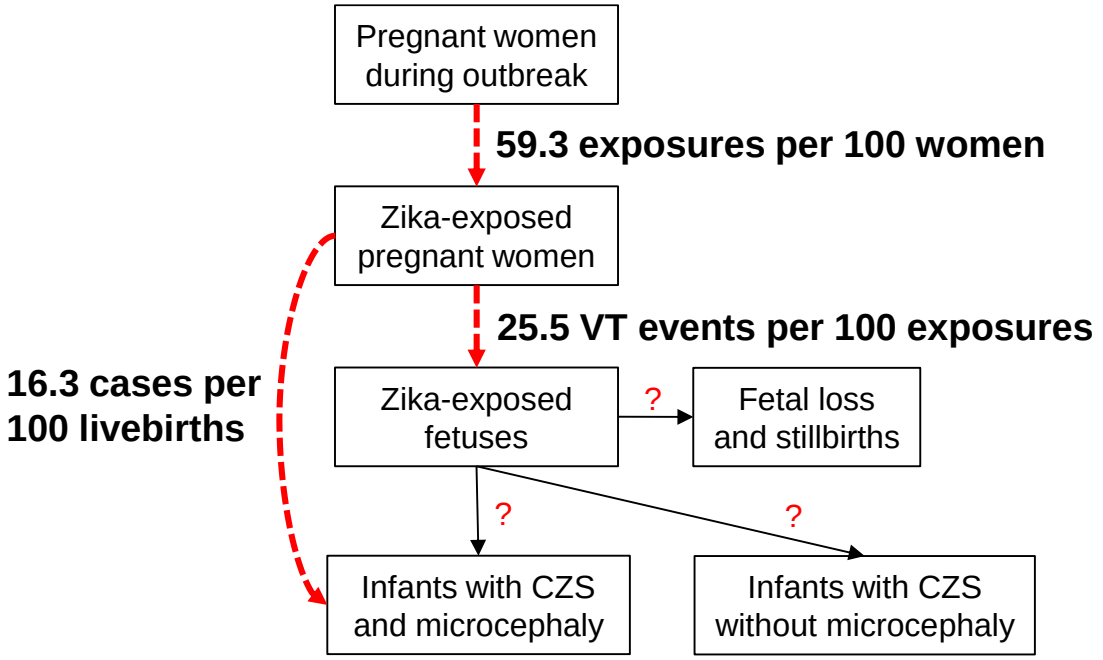
Case-Control Investigation



100% of 34 mothers had ZIKV neutralizing antibodies

55% of 45 mothers had ZIKV neutralizing antibodies

Estimated Risk for Vertical Transmission and Acquiring CZS



Suspected cases: 9.7% total births

- **61% ZIKV IgM in cord blood**
- **13% ZIKV RNA detected**

Annals of Internal Medicine

IDEAS AND OPINIONS

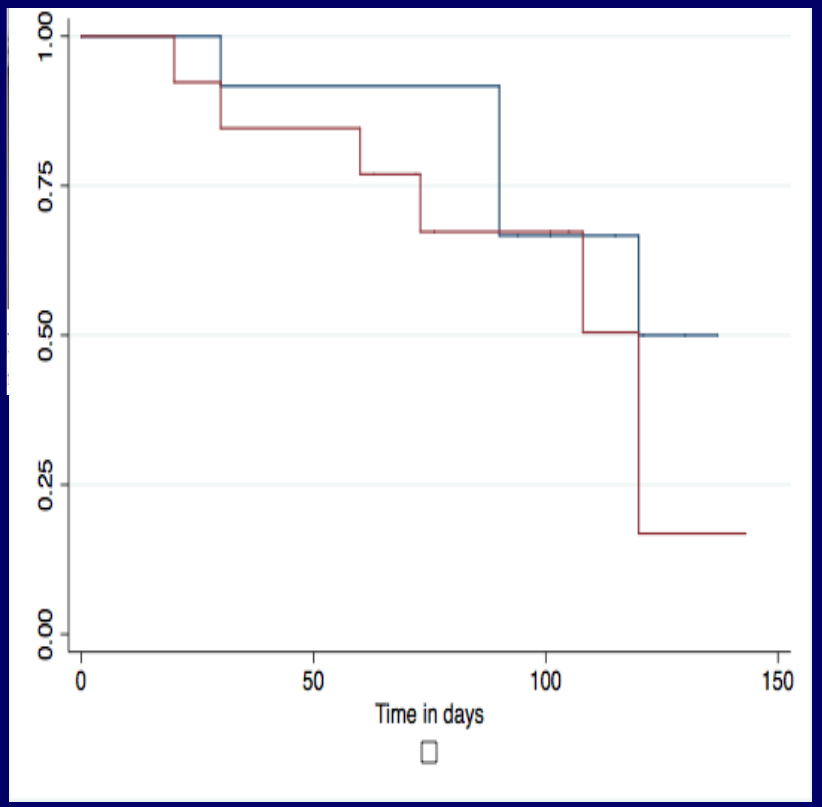
Emergence of Congenital Zika Syndrome: Viewpoint From the Front Lines

Federico Costa, PhD; Manoel Sarno, MD, PhD; Ricardo Khouri, PhD; Bruno de Paulo Freitas, MD; Isadora Siqueira, MD, PhD; Guilherme S. Ribeiro, MD, PhD; Hugo C. Ribeiro, MD; Gubio S. Campos, PhD; Luiz C. Alcântara, PhD; Mitermayer G. Reis, MD, PhD; Scott C. Weaver, PhD; Nikos Vasilakis, PhD; Albert I. Ko, MD; and Antonio Raimundo Almeida, MD

Congenital Glaucoma
De Freitas, Ophthalmology, 2016

- High Zika exposure rates (60%) during the epidemic
- High rates of vertical transmission (25%) and severe outcomes (16%) in Salvador and Northeast Brazil
- Distinct from other congenital infections
  - ➢ Pathology restricted to CNS & placenta in contrast with TORCHS
  - ➢ Severity and specific lesions (ocular, arthrogryposis, cysts)
- Prognosis is likely to be poor.

Onset of Seizures after Birth



Does Risk and Severity of CZS Vary Across and Within Populations?

World Health Organization

SITUATION REPORT

ZIKA VIRUS
MICROCEPHALY
GUILLAIN-BARRÉ SYNDROME

2 FEBRUARY 2017

DATA AS OF 1 FEBRUARY 2017

Figure 1. Cumulative number of countries and territories by WHO region[1] reporting mosquito-borne Zika virus transmission for the first time by year (2007–2014), and by month from 1 January 2015 to 1 February 2017

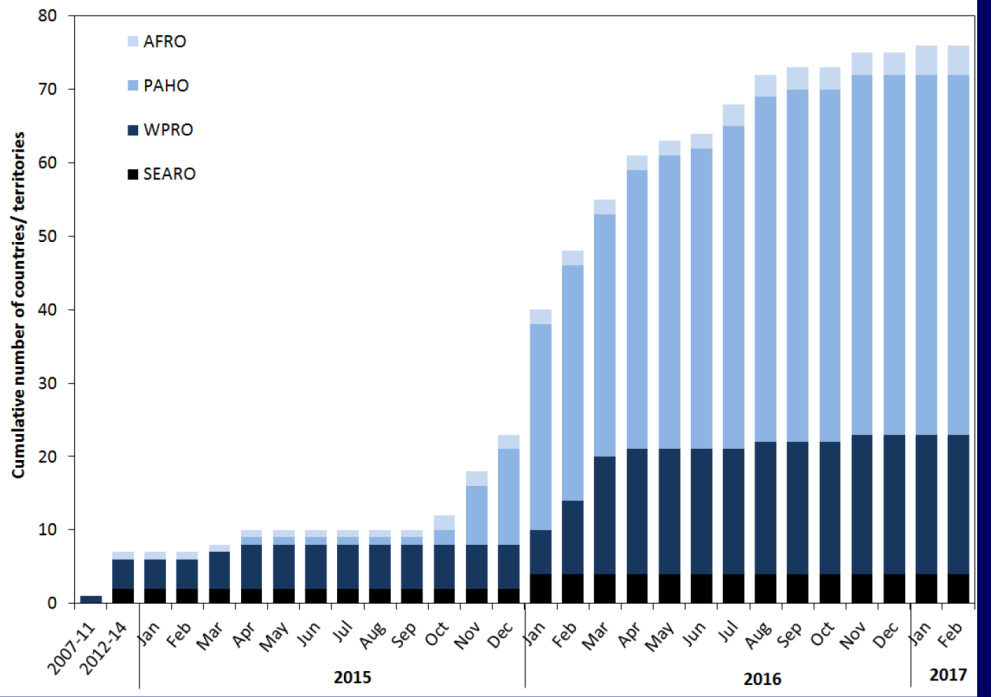


Table 3. Countries and territories that have reported microcephaly and/or CNS malformation cases potentially associated with Zika virus infection

Reporting country or territory	Number of microcephaly and/or CNS malformation cases suggestive of congenital Zika virus infections or potentially associated with a Zika virus infection	Probable location of infection
Argentina	2[2]	Argentina
[illegible]	14[3]	[illegible]
Brazil	2366[4]	Brazil
Cabo Verde	9	Cabo Verde
Canada	2	Undetermined
Colombia	86[5]	Colombia
Costa Rica	2	Costa Rica
Dominican Republic	22[6]	Dominican Republic
El Salvador	4	El Salvador
French Guiana	16[7]	French Guiana
French Polynesia	8	French Polynesia
Grenada	1	Grenada
Guadeloupe	13[8]	Guadeloupe
Guatemala	15[9]	Guatemala
Haiti	1	Haiti
Honduras	2	Honduras
Marshall Islands	1	Marshall Islands
Martinique	19[8]	Martinique
Nicaragua	2[10]	Nicaragua
Panama	5	Panama
Paraguay	2[11]	Paraguay
Puerto Rico	11[12]	Puerto Rico
Slovenia	1[13]	Brazil
Spain	2	Colombia, Venezuela (Bolivarian Republic of)
Suriname	4	Suriname
Thailand	2	Thailand
Trinidad and Tobago	1	Trinidad and Tobago
United States of America	42[14]	Undetermined**
Viet Nam	1	Viet Nam

***The probable locations of three of the infections were Brazil (one case), Haiti (one case) and Mexico, Belize or Guatemala (one case).*

MICROCEFALIA - GUINÉ-BISSAU, ASSOCIAÇÃO COM O VÍRUS ZIKA, CASOS CONFIRMADOS
****

Uma mensagem / Una mensaje / de ProMED-PORT Data: Terça-feira, 05 de dezembro de 2016

A Guiné-Bissau registou 11 casos de microcefalia em recém nascidos desde o início do ano [2016] provocados pelos vírus Zika, Dengue e chikungunya, anunciou hoje o diretor do Instituto Nacional de Saúde do país, Plácido Cardoso.

10/5/2016 Thailand reports first two cases of Zika birth defects | Global development | The Guardian

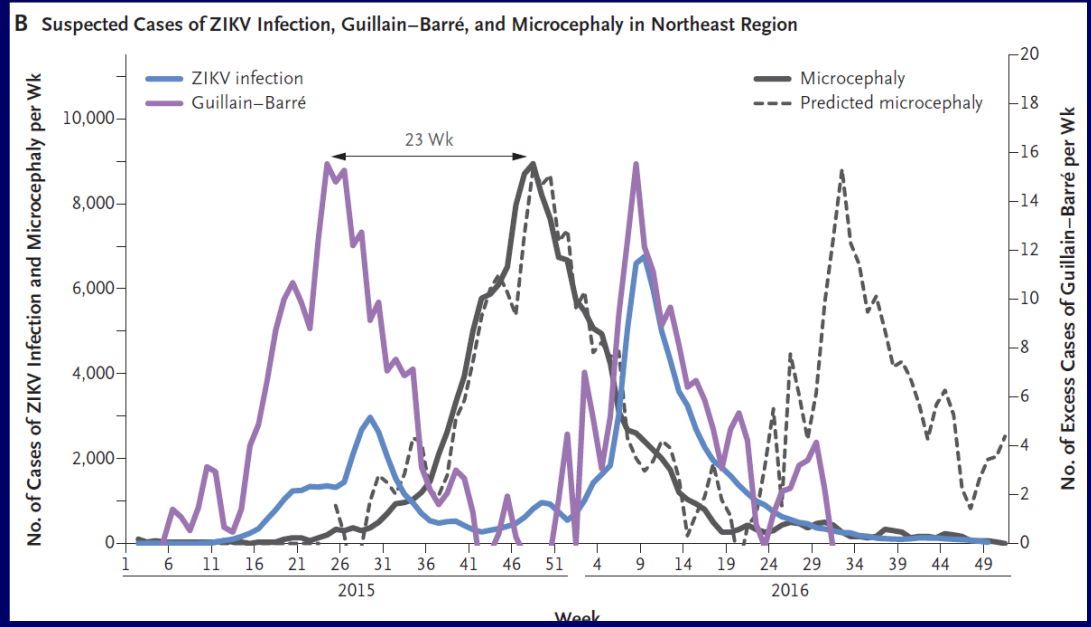
theguardian

Thailand reports first two cases of Zika birth defects

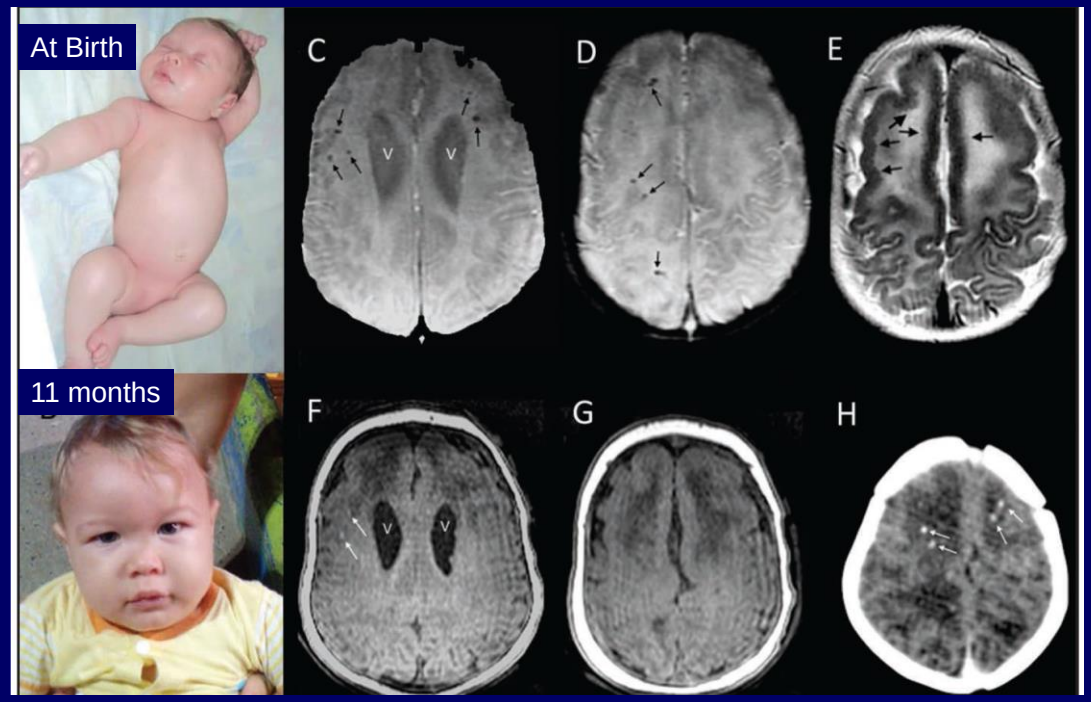
Two babies born with 'small heads' are first confirmed cases of microcephaly linked to the mosquito-borne Zika virus in south-east Asia

Variation in Severity and Risk of Zika Congenital Syndrome

- Rio de Janeiro cohort (NEJM, 2016)
  - ➢ 42% with adverse outcomes after symptomatic illness
  - ➢ 3% microcephaly among 117 live births
- Surveillance in Colombia (NEJM, 2016)
  - ➢ 4 cases of microcephaly and no defects among ~600 newborns of women exposed in 3rd trimester
- Surveillance in US (MMWR, 2017)
  - ➢ 10% of 250 infants with Zika-associated birth defects
- Smaller numbers of microcephaly cases as the epidemic spread in Brazil in 2016 (NEJM, 2016)
- Increasing reports of CZS in infants without microcephaly and with less severe findings



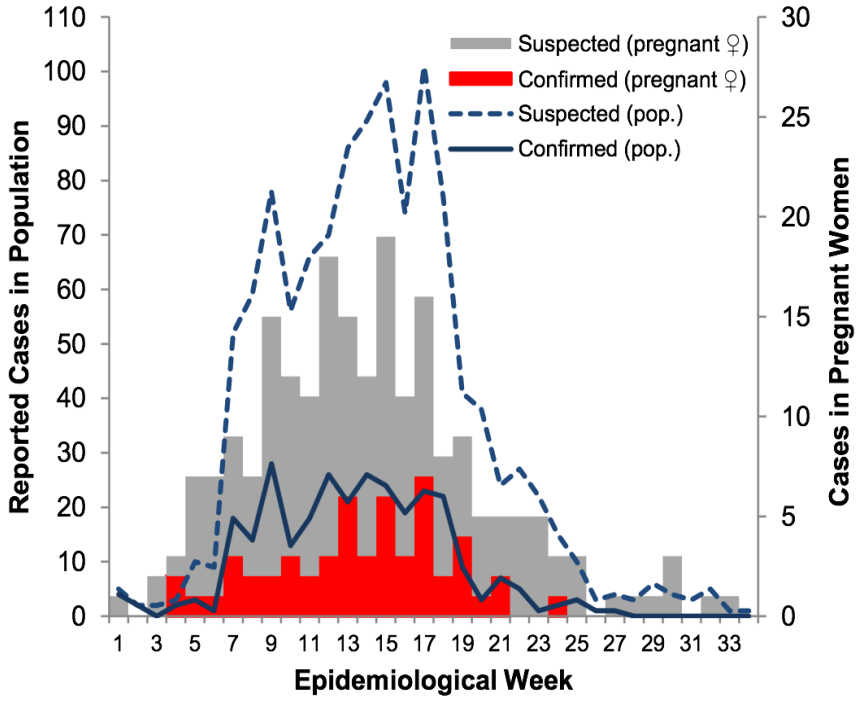
De Oliveira, NEJM, 2016



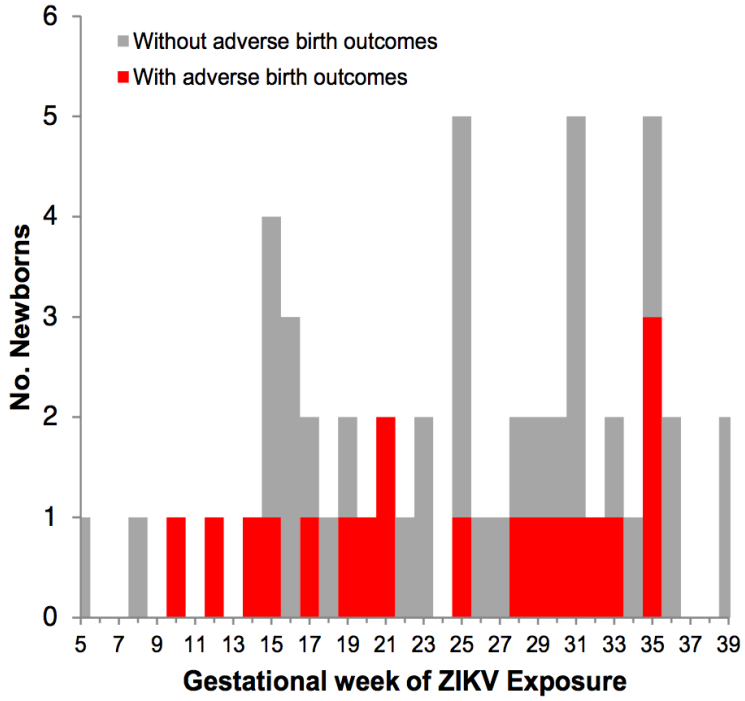
MMWR, 2016

Prospective Study of Pregnant Women with Confirmed Zika Infection São José do Rio Preto Outbreak, February-June, 2016

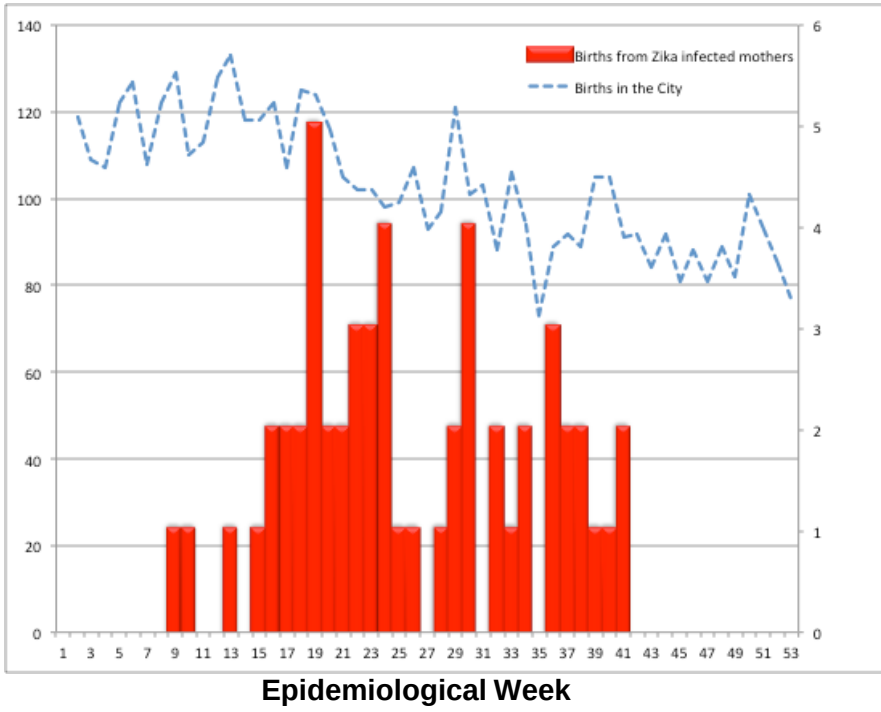
Timeline of the Outbreak



Exposure during Gestation



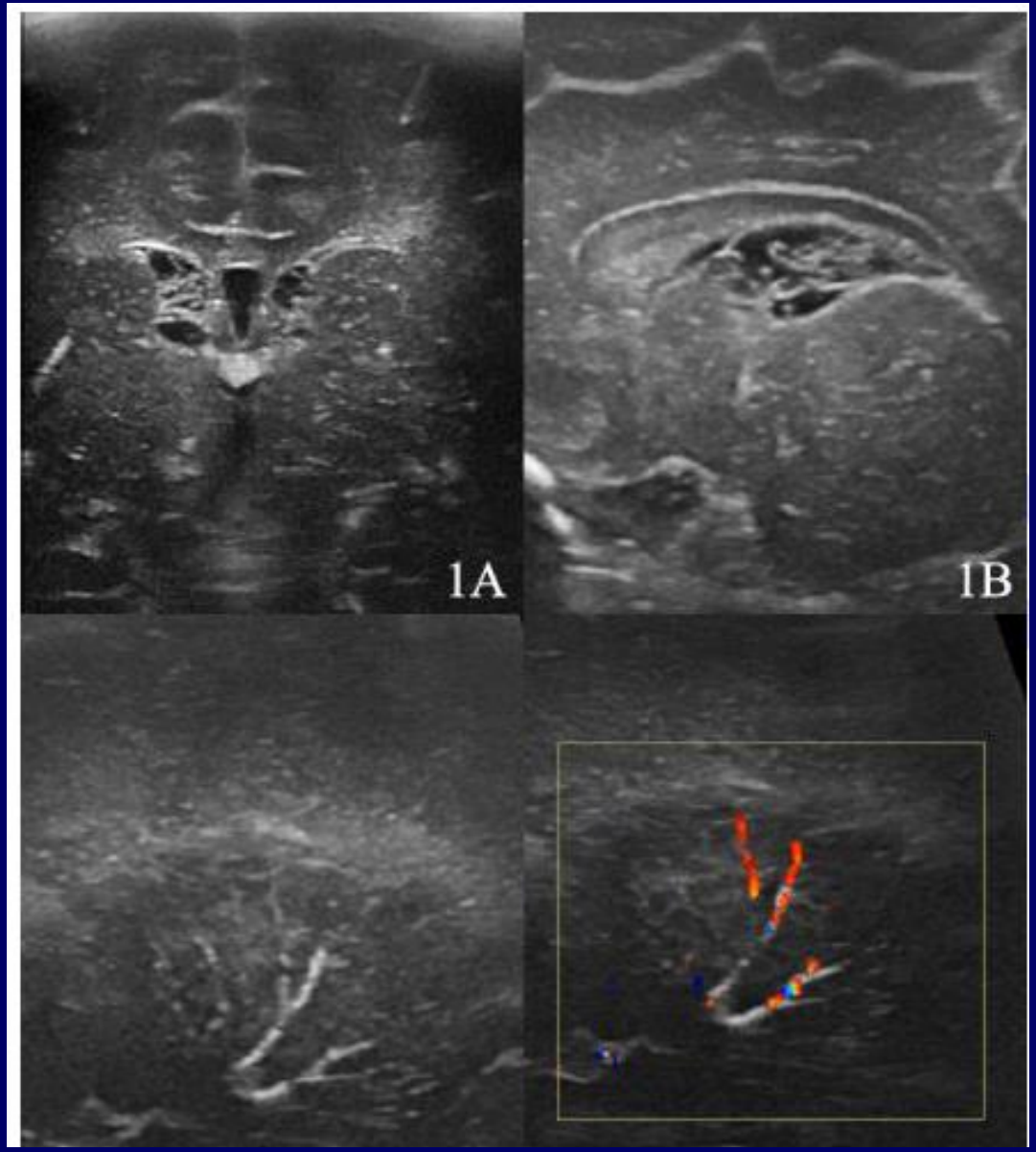
Timeline of Births



- Population 442,548
- 1,674 pregnant women
- 54 confirmed Zika cases

PI: Maurício Nogueira, Faculdade de Medicina de São José do Rio Preto (FAMERP)

Infant Outcomes of Zika-Exposed Pregnant Women, Sao Jose do Rio Preto



Lenticulate vasculopathy

Souza, CID 2016

Outcomes	Rates
Adverse birth outcomes	28% (15/54)
1st trimester exposure	25% (1/4)
2nd trimester exposure	15% (4/26)
3rd trimester exposure	42% (10/24)
ZIKV detected at birth	35% (18/51)
With adverse outcomes	53% (8/14)
Without adverse outcomes	25% (10/40)

Less severe presentations of CZS (N=15)

- No adverse fetal outcomes
- No microcephaly cases among newborns
- Abnormal OAE (6)
- Choroidoretinal atrophy (2)
- Subependymal cysts, lenticulostriate vasculopathy (7)
- Intracranial bleed (1)

Factors That May Influence Vertical Transmission and Clinical Outcomes?

- Strain-specific factors
  - African vs Asian genotypes
- Exposure-related factors
  - Herd immunity
  - Timing of exposure during gestation
  - Mosquito vs sexual exposures
  - Symptomatic vs inapparent infections
- Host factors
  - Cofactors: nutrition, co-infections
  - Maternal and fetal innate response
  - Transfer of maternal antibodies
- Prior flavivirus exposure protects or enhances Zika infection?
  - Implications for vaccine development
  - No clinical correlates to date for enhancement

Spotlight

Dengue Antibody and Zika: Friend or Foe?

Anna P. Durbin[1,*]

Zika virus is a mosquito-borne *Flavivirus* related to dengue that is rapidly spreading through the Americas. This outbreak is occurring in dengue-endemic areas where the population has acquired antibodies to dengue. Recent studies reveal that preexisting dengue antibodies may have opposite effects on Zika infection, transmission, and clinical outcome. Discerning these effects is critical to a better understanding of Zika pathogenesis and the prevention of future outbreaks.

Structural basis of potent Zika–dengue virus antibody cross-neutralization

Giovanna Barba-Spaeth[1,2*], Wanwisa Dejnirattisai[3*], Alexander Rouvinski[1,2*], Marie-Christine Vaney[1,2*], Iris Medits[4], Arvind Sharma[1,2], Etienne Simon-Lorière[5,6], Anavaj Sakuntabhai[5,6], Van-Mai Cao-Lormeau[7], Ahmed Haouz[8,9], Patrick England[9,10], Karin Stiasny[4], Juthathip Mongkolsapaya[3,11], Franz X. Heinz[4], Gavin R. Screaton[3] & Félix A. Rey[1,2]

Dengue Virus Envelope Dimer Epitope Monoclonal Antibodies Isolated from Dengue Patients Are Protective against Zika Virus

J. A. Swanstrom,[a] J. A. Plante,[a] K. S. Plante,[b] E. F. Young,[a,c] E. McGowan,[c] E. N. Gallichotte,[a,c] D. G. Widman,[a] M. T. Heise,[b,c] A. M. de Silva,[c] R. S. Baric[a,c]

Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus

Wanwisa Dejnirattisai[1], Piyada Supasa[1–3], Wiyada Wongwiwat[1], Alexander Rouvinski[4,5], Giovanna Barba-Spaeth[4,5], Thaneeya Duangchinda[6], Anavaj Sakuntabhai[7,8], Van-Mai Cao-Lormeau[9], Prida Malasit[2,6], Felix A Rey[4,5], Juthathip Mongkolsapaya[1,2]& Gavin R Screaton[1]

Enhancement of Zika virus pathogenesis by preexisting antiflavivirus immunity

Susana V. Bardina,[1*] Paul Bunduc,[1*] Shashank Tripathi,[1,2*] James Duehr,[1*] Justin J. Frere,[1] Julia A. Brown,[1] Raffael Nachbagauer,[1] Gregory A. Foster,[3] David Krysztof,[3] Domenico Tortorella,[1] Susan L. Stramer,[3] Adolfo García-Sastre,[1,2,4†] Florian Krammer,[1†] Jean K. Lim[1†]

How Do You Screen for and Diagnose Congenital Zika Syndrome?

Diagnostic Needs for Zika Clinical Decision Making

- Acute disease and sequelae
  - ➢ Acute illness
  - ➢ GBS and atypical neurological manifestations
- Blood bank security (cost, ~US$8 per unit)
- Congenital zika syndrome
  - Counseling women of childbearing age
  - Symptomatic illness during pregnancy
  - Asymptomatic exposure during pregnancy
  - Newborns with *in utero* exposure to Zika
  - Infants exposed during gestation but not diagnosed at birth

Lack of Adequate Zika Diagnostics

Viral isolation: Limited to research purposes

RNA detection: 12 EUA approved kits in US

- Viremia not be prolonged in pregnant women
- Low sensitivity in newborns

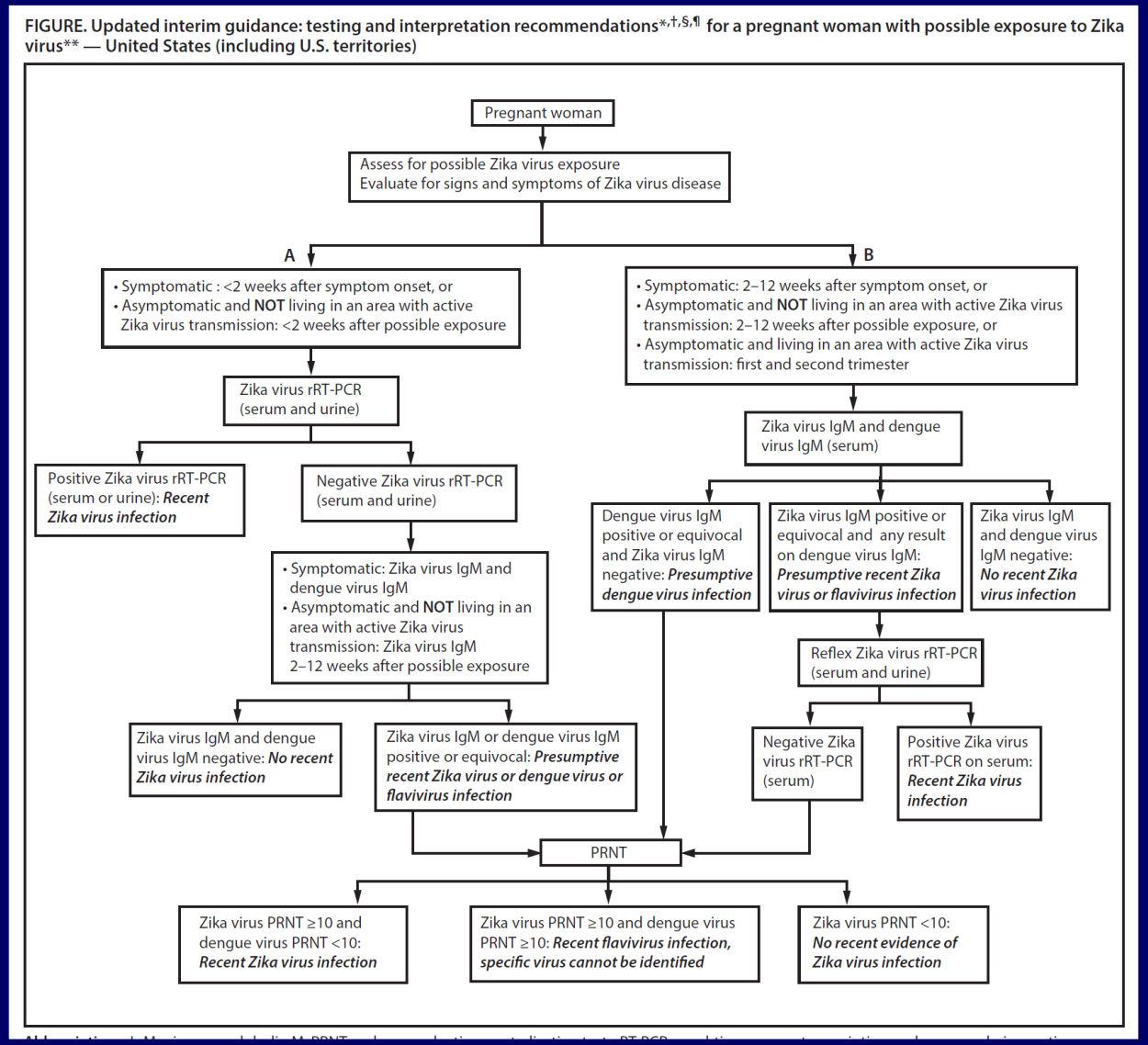
IgM ELISA: Anti-whole virus, NS1 and E

- Low specificity with prior flavivirus exposure
- Low sensitivity (60%) in newborns
- Sensitivity lower for 1st trimester exposures

IgG assays: None approved

Plaque reduction neutralization titers (PRNT)

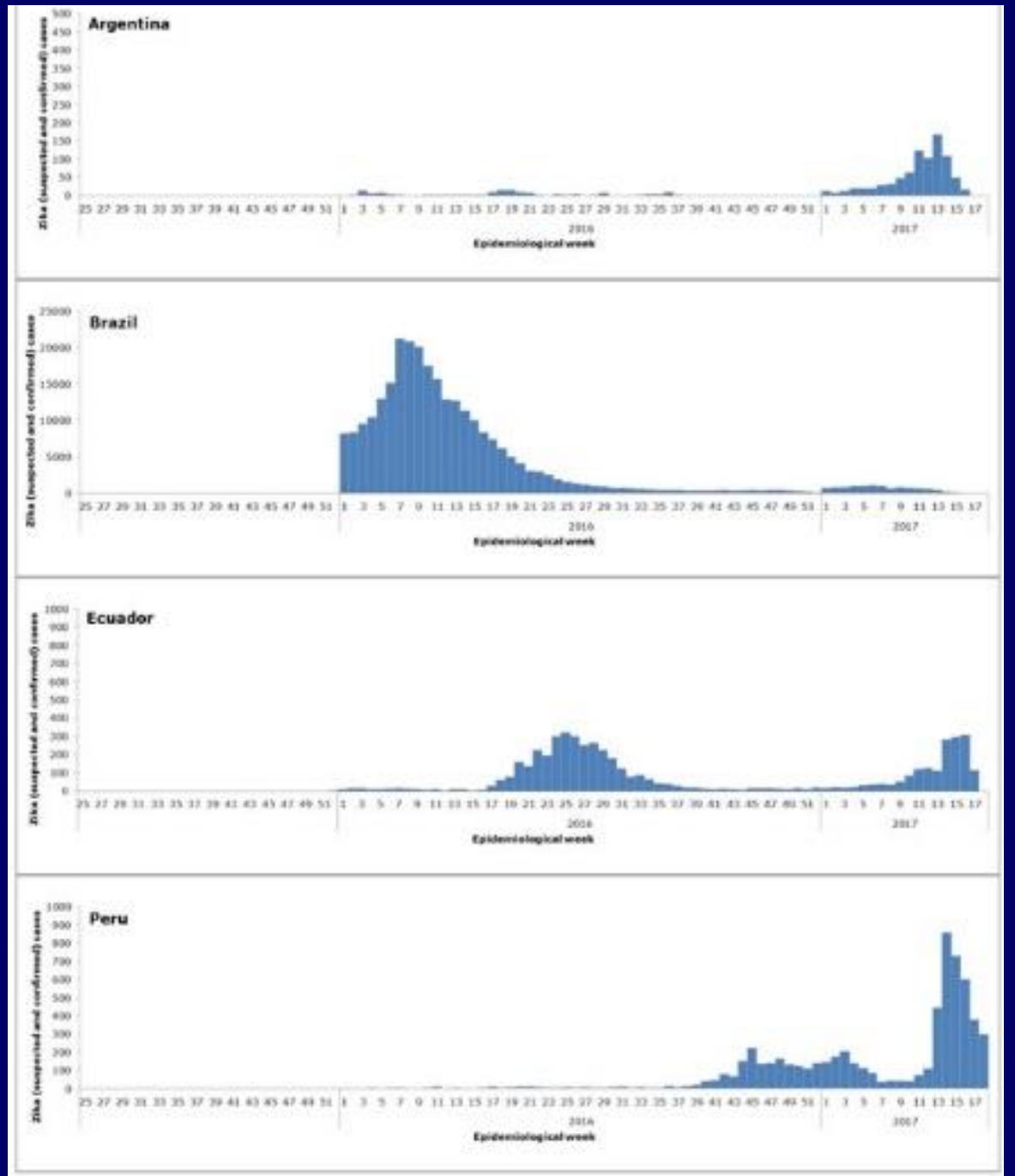
- Few laboratories can perform this assay
- Unclear specificity in dengue endemic regions



Congential Zika Syndrome: Questions

- Why risk and severity varies significantly across regions and within populations? Prior dengue exposure?
- Lack of diagnostics is the key barrier to mounting effective screening & counseling.
- New antivirals will be difficult to evaluate.
- No effective prevention:
  - Several vaccine candidates in clinical trials
  - Use of monoclonal antibodies for prophylaxis?
- Will Zika return to regions that experienced epidemics due to herd immunity?
- There remains large populations of susceptible women of child bearing age in the Americas and likely in Asia and Africa.

Suspected Zika cases, 2015-2017, PAHO



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Support:
Brazilian National Research Council
Oswaldo Cruz Foundation
NIAID R01 AI052473, U01AI088752
FIC R01 TW009504, R25 TW009338
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