Zika Outbreak

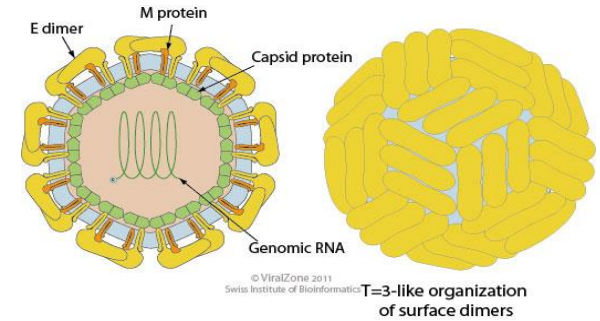
Brazil 2015

Fernando A. Bozza, M.D. Ph.D.

Evandro Chagas National Institute of Infectious Disease
Oswaldo Cruz Foundation (Fiocruz)
Ministry of Health, Rio de Janeiro, Brazil

Fernando.bozza@ini.fiocruz.br

Background



- 1947 – First viral isolation from blood of Rhesus monkey. Zika forest, Uganda;

TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 46. No. 5. September, 1952.

COMMUNICATIONS

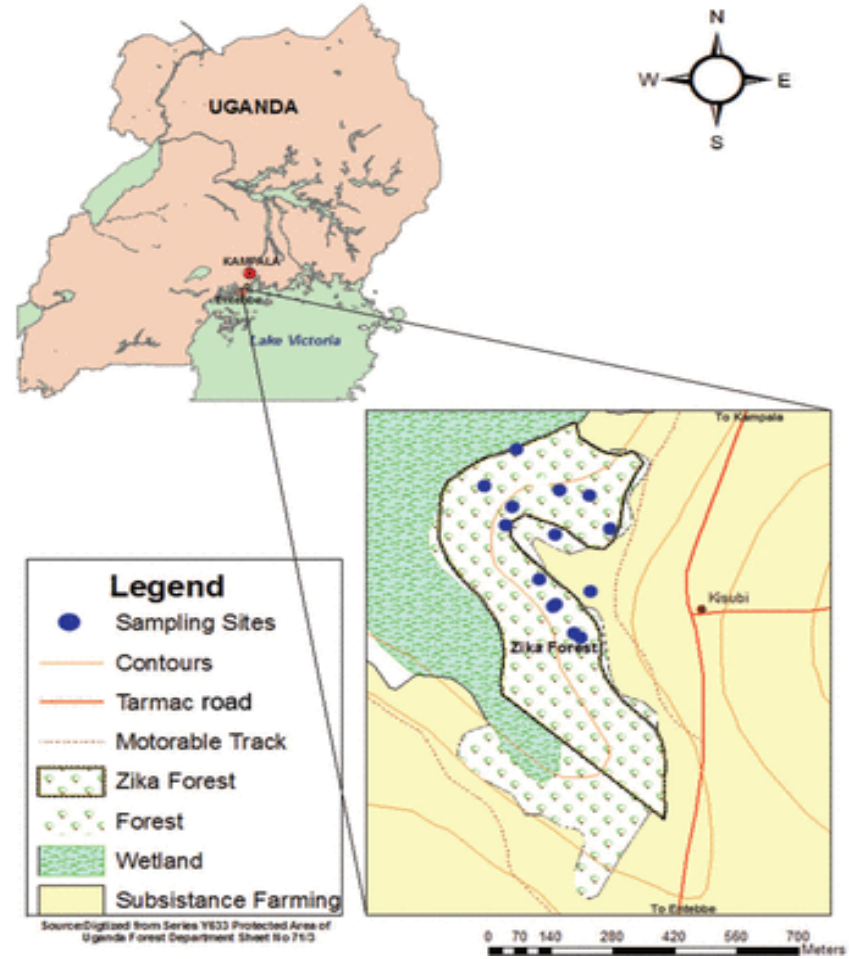
ZIKA VIRUS

(I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

G. W. A. DICK,

The National Institute for Medical Research, London



Background

- 1952 – First human cases Nigeria;

ZIKA VIRUS : A REPORT ON THREE CASES OF HUMAN INFECTION DURING AN EPIDEMIC OF JAUNDICE IN NIGERIA

BY

F. N. MACNAMARA*

Acting Director, Virus Research Institute, Yaba, Nigeria

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.
Vol. 48. No. 2. March, 1954.

Zika Virus

Virus phylogenetically close to other flavivirus transmitted by mosquitoes

Dengue, yellow fever, West Nile Fever, Japanese Encephalitis virus, Ilhéus, Rocio and St. Louis

Molecular epidemiology

RNA virus with a serotype and two genotypes: African and Asian.

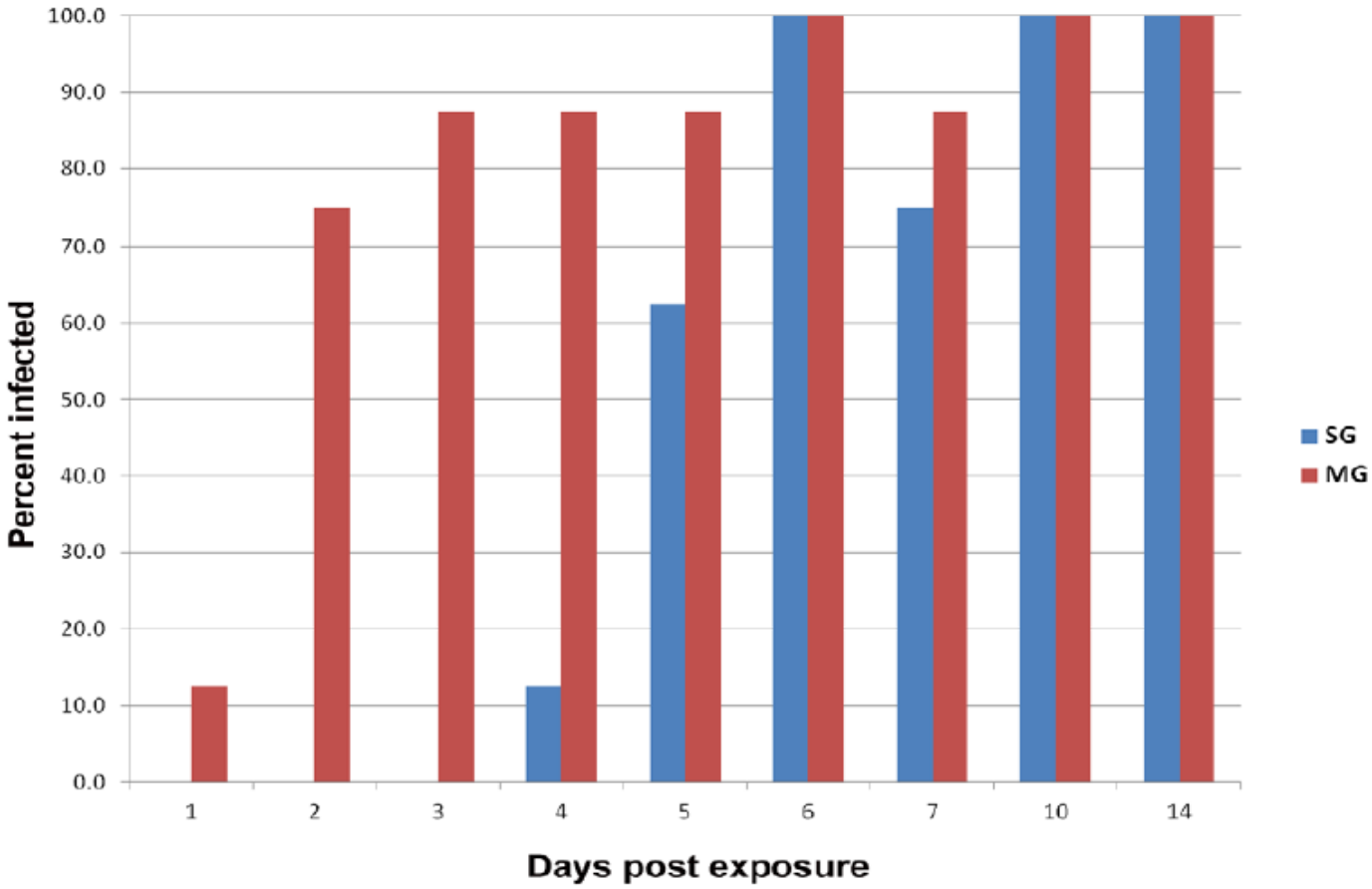
Isolation in the genus Aedes

Ae. Aegypti, Ae. africanus, Ae. apicoargenteus, Ae. luteocephalus, vitattus Ae, andAe. furcifer

Transmission

Oral Susceptibility of Singapore *Aedes* (*Stegomyia*) *aegypti* (Linnaeus) to Zika Virus

MeiZhi Irene Li[☯], Pei Sze Jeslyn Wong[☯], Lee Ching Ng, Cheong Huat Tan*



Midguts and salivary glands infection rates of ZIKV in Ae. Aegypti (n=120) at different days post-infectious bloodmeal

PLOS | NEGLECTED TROPICAL DISEASES

Transmission

Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

Fonte: Euro Surveill. 2014;19(13):pii=20751

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]

Fonte: Euro Surveill. 2014;19(14):pii=20761

Transmission

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

Fonte: Emerg Infect Dis. 2011

Potential Sexual Transmission of Zika Virus

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

Fonte: Emerging Infectious Diseases Vol. 21, No. 2, 2015

Epidemiology

- *Between 1947 and 2007 cases reported in Africa and Asia: no severe forms, no epidemic behavior*
- *First cases outside of Asia and Africa*

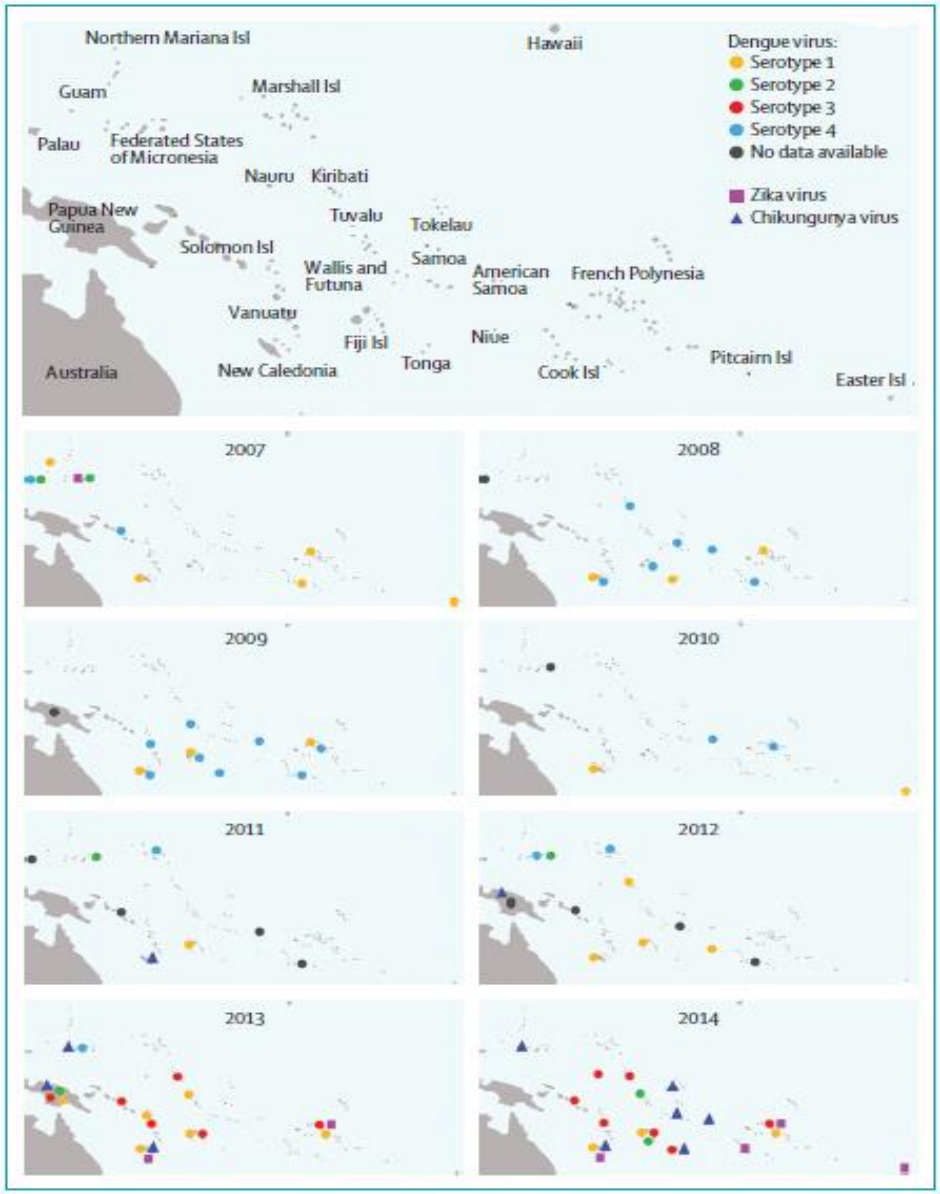
  2007: outbreak in Yap Islands, Micronesia, (8000 cases)

  2013: French Polynesia epidemic (~ 30,000 cases)

  2014: simultaneous outbreak in the Pacific: dengue, chik and zika

  2014: 1st detection in the Americas, Easter Island, Chile, 2014

Epidemiology



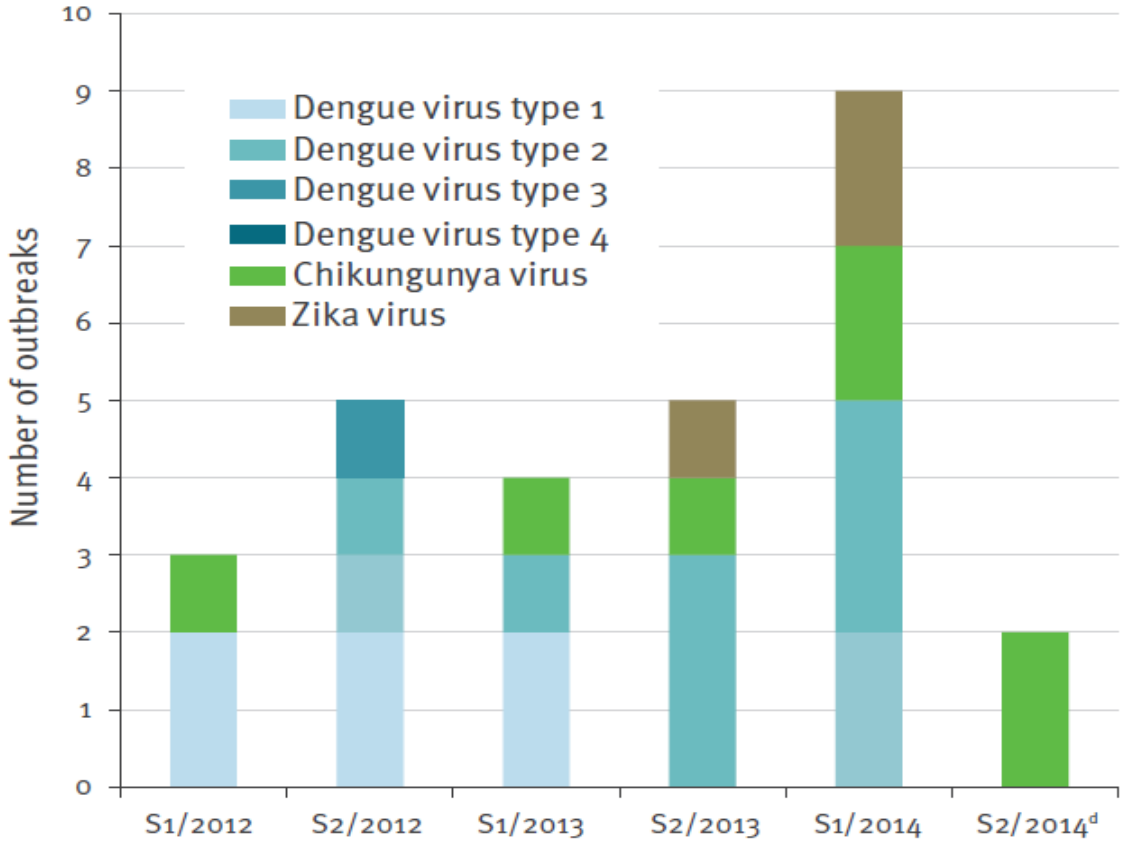
Emerging Arbovirus

Pacífic, 2007 - 2014

Fonte: The Lancet Vol 384 November 1, 2014

Epidemiology

Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012–2014



Co-infection with Zika and Dengue Viruses in 2 Patients, New Caledonia, 2014

Myrielle Dupont-Rouzeyrol, Olivia O'Connor, Elodie Calvez, Maguy Daures, Michèle John, Jean-Paul Grangeon, Ann-Claire Gourinat

Fonte: Euro Surveill. 2014;19(41):pii=20929

Epidemiology

Zika Virus Outbreak, Bahia, Brazil

Gubio S. Campos, Antonio C. Bandeira, Silvia I. Sardi

Authors affiliations: Federal University of Bahia, Salvador, Bahia, Brazil (G.S. Campos, S.I. Sardi); Hospital Aliança, Salvador (A.C. Bandeira)

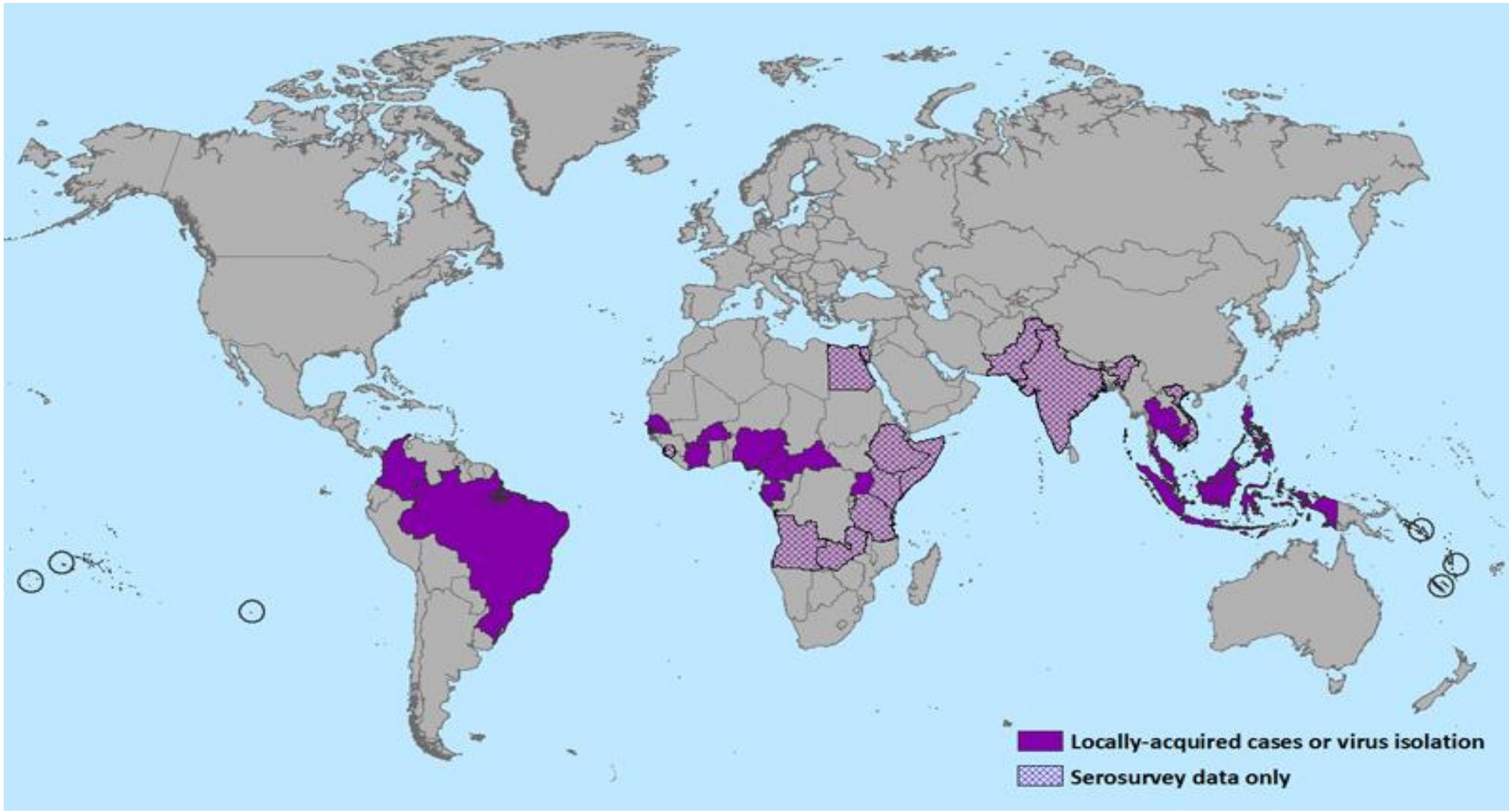
DOI: http://dx.doi.org/10.32301/eid2110.150847

- **March 26th 2015 – first case series of Zika vírus infection (trought PCR).**

Reverse transcription PCR result for Zika virus (no.)	Mean (SD) patient age, y	Patient sex, F/M	No. (%)			
			Rash	Fever	Myalgia	Headache
Positive (7)	33 (15)	6/1	6 (85.7)	3 (43)	4 (57.1)	3 (43)
Negative (17)	31 (8.5)	12/5	12 (70.6)	6 (35.3)	9 (53)	11 (64.7)

Emerging Infectious Diseases Vol. 21, No. 10, October 2015

Vírus Zika Circulation



Fonte: CDC, outubro 2015.

Confirmed Zika virus cases in Brasil, 2015.

North
Roraima
Pará

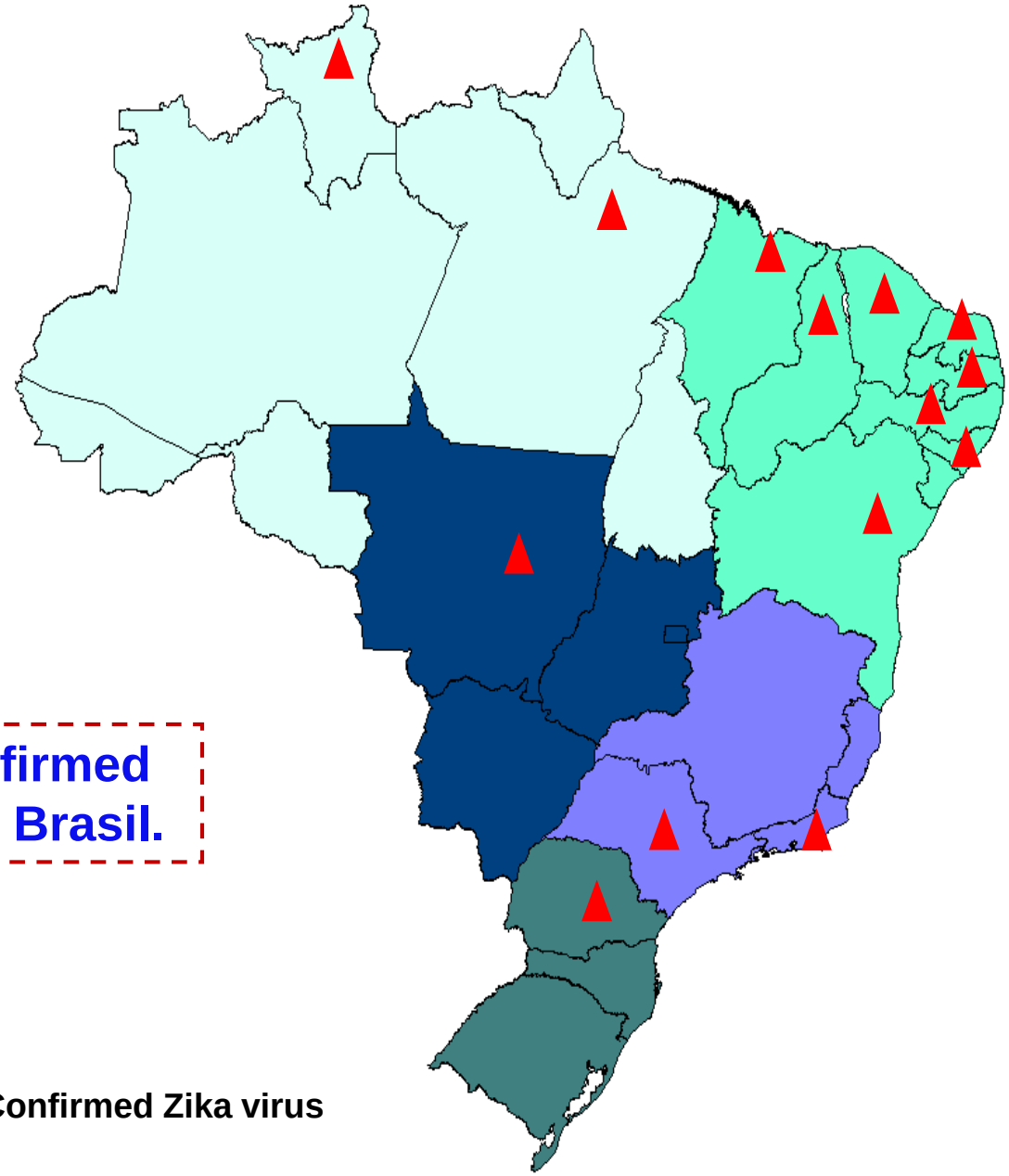
Northeast
Maranhão
Piauí
Ceará
RN
Paraíba
Pernambuco
Alagoas
Bahia

Southeast
Rio de Janeiro
São Paulo

Center east
Mato Grosso

South
Paraná

14 states with confirmed Zika virus cases in Brasil.



Last updated in October 2015

Confirmed Zika virus

Confirmed Zika virus cases in Brasil, 2015.

Zika Vírus	SINAN NET	FORMSUS	BOLETIM
Rondônia	2	0	-
Acre	0	3	-
Amazonas	0	0	-
Roraima	25	349	-
Amapá	0	0	-
Para	97	65	-
Tocantins	37	10	-
NORTE	**161**	**427**	**-**
Maranhão	36	130	-
Piauí	4	25	-
Ceará	587	0	-
Rio Grande do Norte	228	6.177	-
Paraíba	116	81	-
Pernambuco	2	0	-
Alagoas	485	383	-
Sergipe	0	0	-
Bahia	19.369	77	56.318
NORDESTE	**20.827**	**6.873**	**56.318**

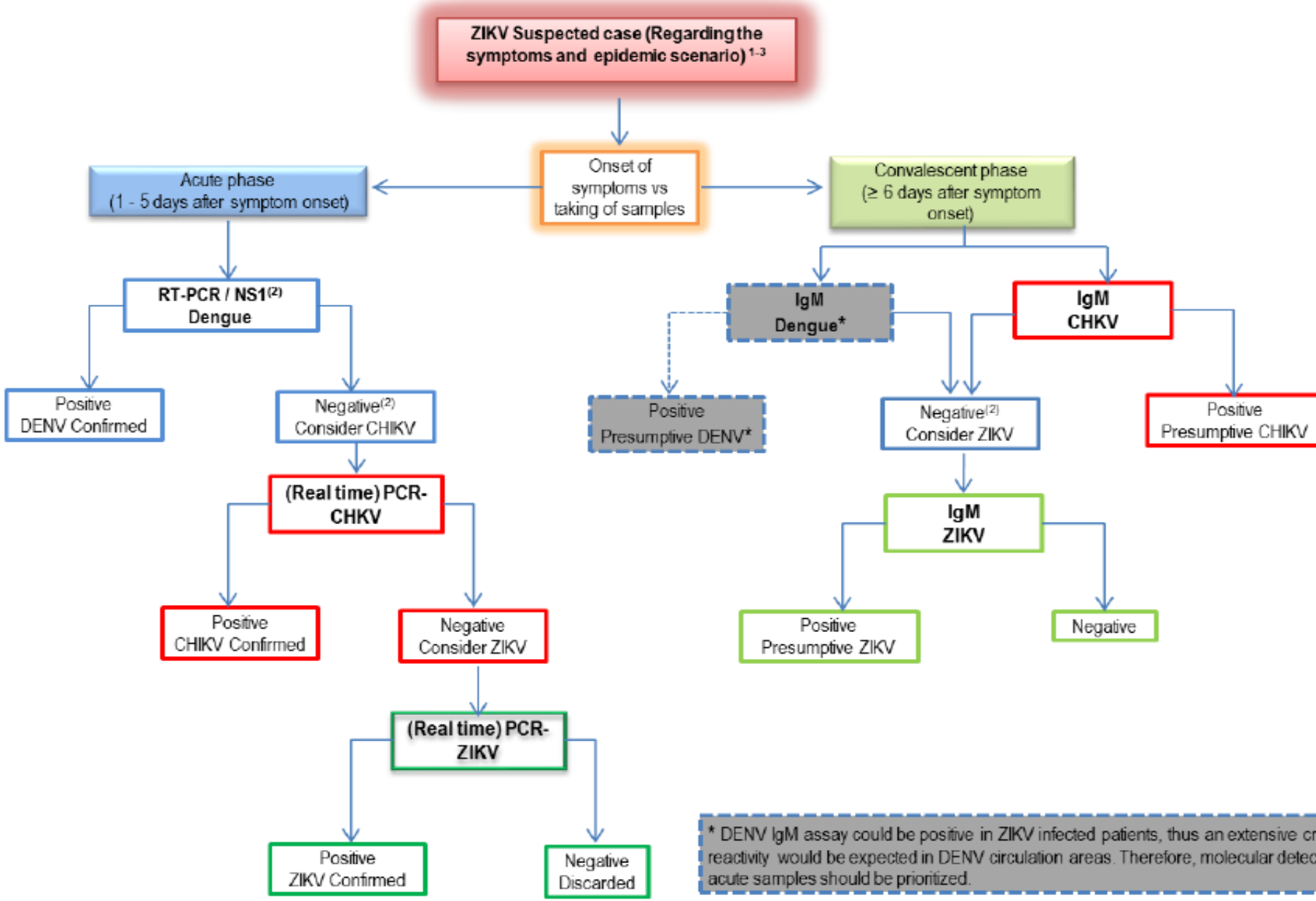
Zika Vírus	SINAN NET	FORMSUS	BOLETIM
Minas Gerais	3	0	-
Espirito Santo	2	0	-
Rio de Janeiro	208	1	-
São Paulo	61	0	-
SUDESTE	**274**	**1**	**-**
Paraná	8	0	-
Santa Catarina	0	0	-
Rio Grande do Sul	2	0	-
SUL	**10**	**0**	**-**
Mato Grosso do Sul	5	0	-
Mato Grosso	17	0	-
Goiás	1	10	-
Distrito Federal	8	0	-
CENTRO-OESTE	**30**	**10**	**-**
BRASIL	**21.302**	**7.311**	**56.318**

[1]Banco disponível em 06/10/2015; [2]FormSus acessado em 08/10/2015; [3]Boletim nº7 de 02/10/2015

Zika virus dection and isolation

- Real time RT-PCR
  - Serum, up to 5 days after the onset of ilness (it may be considered up to 7 days)
  - Urine, up to 12 days after the onset of ilness
- Serology
  - It may be positive from 7 days after onset
  - Often cross-reactive with Dengue tests
- Isolation
  - Efforts may be made in RT-PCR positive samples in mosquito cells (C6/36)

Algorithm for ZIKV detection



Manifestações Clínicas

The NEW ENGLAND JOURNAL of MEDICINE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

* Cases of measured and subjective fever are included.

Fonte: N Engl J Med 2009;360:2536-43.

Clinical Characteristics

Zika confirmed cases
Fiocruz, 2015 (n=58)

- Rash: 56
- Febre: 36
- Cefaléia: 34
- Artralgia: 33
- Prurido: 32
- Mialgia: 28
- Dor retro orbital: 23

Conjuntivite: 22

Adenomegalia: 16

Edema articular: 13

Náusea: 9

Vômito: 3

Diarréia: 1

Clinical Characteristics

General review

Current Zika virus epidemiology and recent epidemics

Infections par le virus Zika et épidémies récentes

Comparison of symptoms for dengue fever, chikungunya, and Zika.
Clinique comparée de la dengue, du chikungunya et du Zika.

Symptoms	Dengue	Chikungunya	Zika
Fever	++++	+++	+++
Myalgia/arthralgia	+++	++++	++
Edema of extremities	0	0	++
Maculopapular rash	++	++	+++
Retro-orbital pain	++	+	++
Conjunctivitis	0	+	+++
Lymphadenopathies	++	++	+
Hepatomegaly	0	+++	0
Leukopenia/thrombopenia	+++	+++	0
Hemorrhage	+	0	0

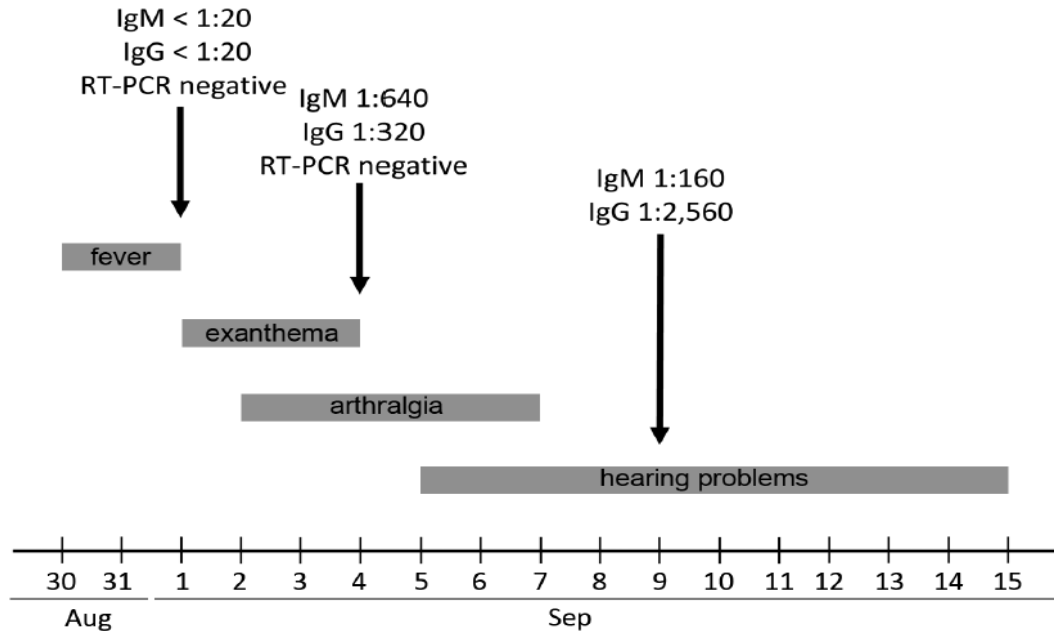
Fonte: S. Ioos et al. / Médecine et maladies infectieuses 44 (2014) 302–307

Complications

Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013

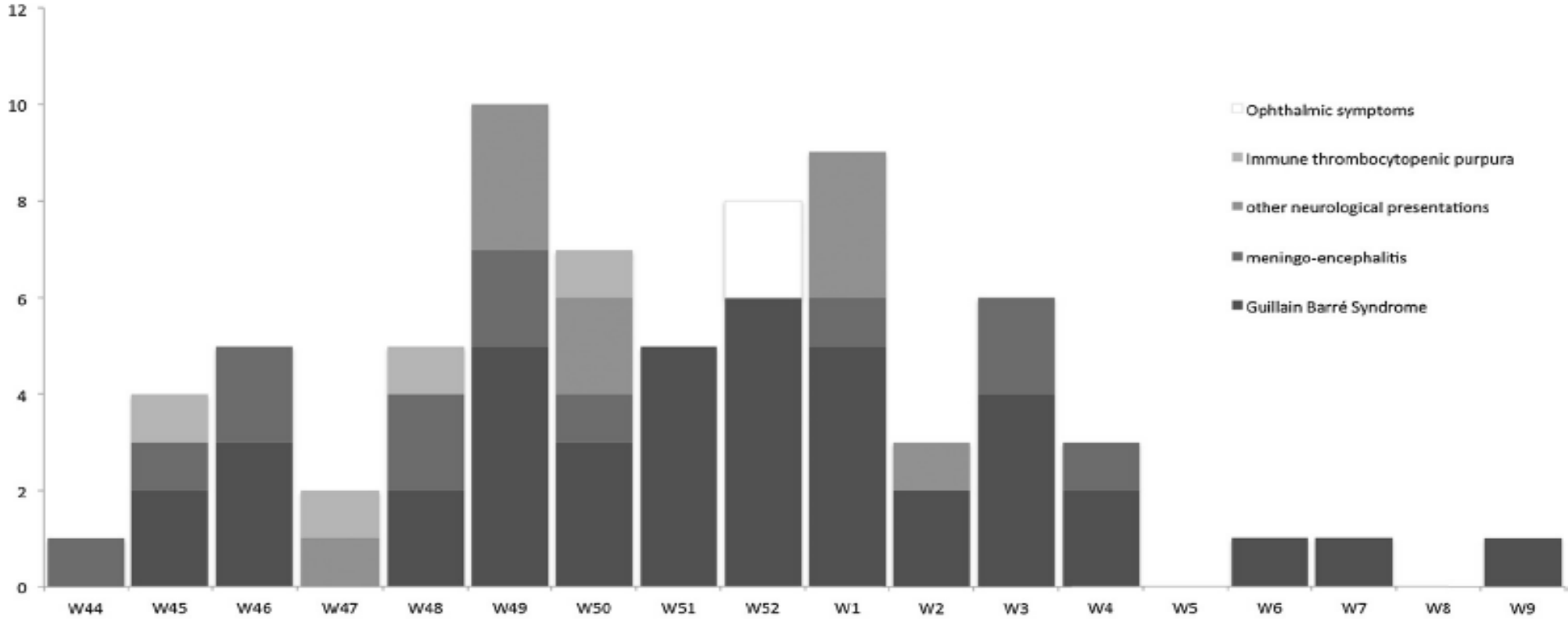
Fonte: Euro Surveill. 2014;19(9):pii=20720

Acute Zika Virus Infection after Travel to Malaysian Borneo, September 2014



Fonte: Emerging Infectious Diseases Vol. 21, No. 5, May 2015

Complications



*** Guillain-Barré Syndrome (GBS), immune thrombocytopenic purpura (ITP), meningo-encephalitis (ME)**

Source: Bulletin de Veille Sanitaire, bureau de veille sanitaire, week 8- 2014

Fonte: S. Ioos et al. / Médecine et maladies infectieuses 44 (2014) 302–307

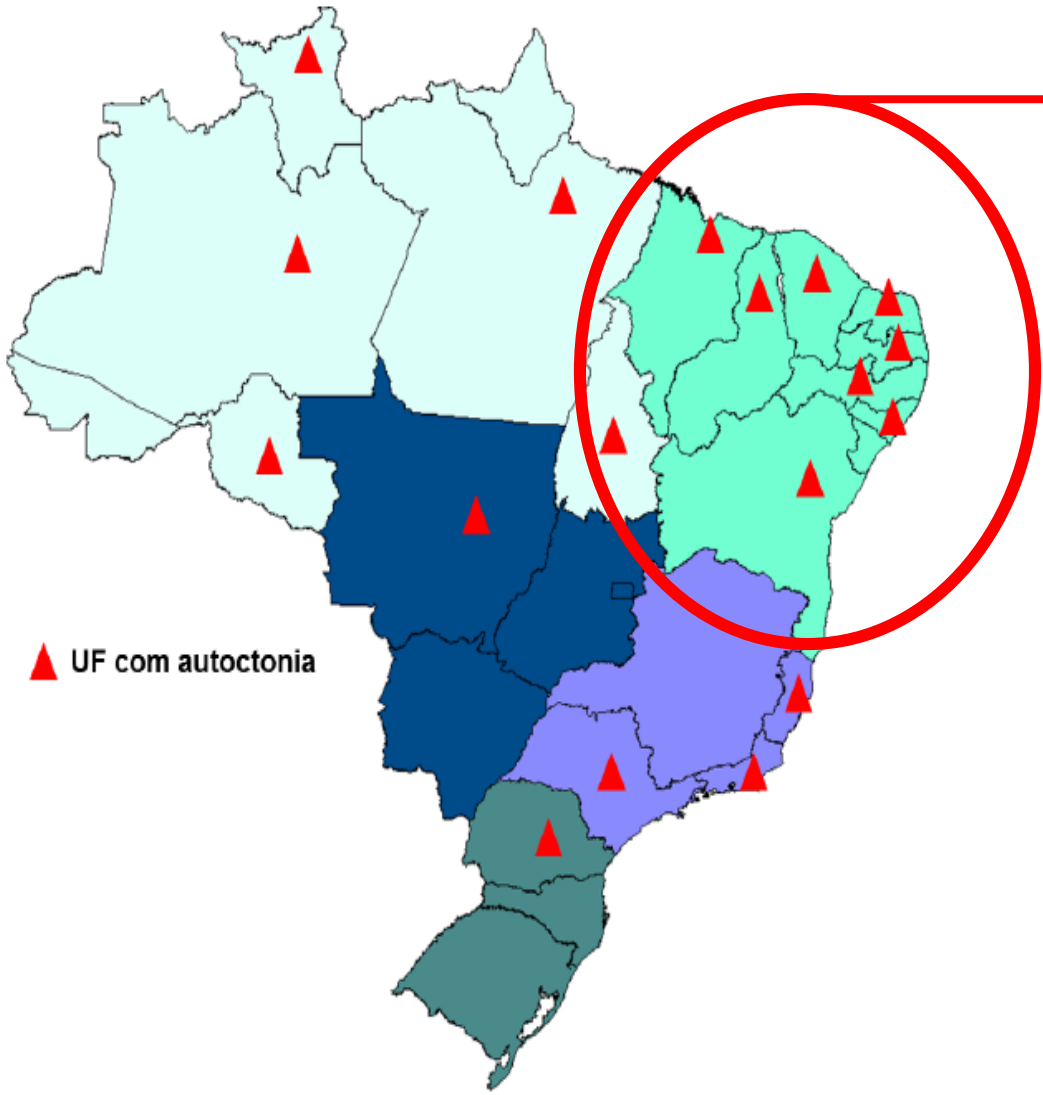
Microcephaly

October 22: reported by SES / PE 26 cases of newborns with microcephaly in different public and private hospitals in different regions of the state.

Newborns with head circumference (HC) lower than expected for age and gender.

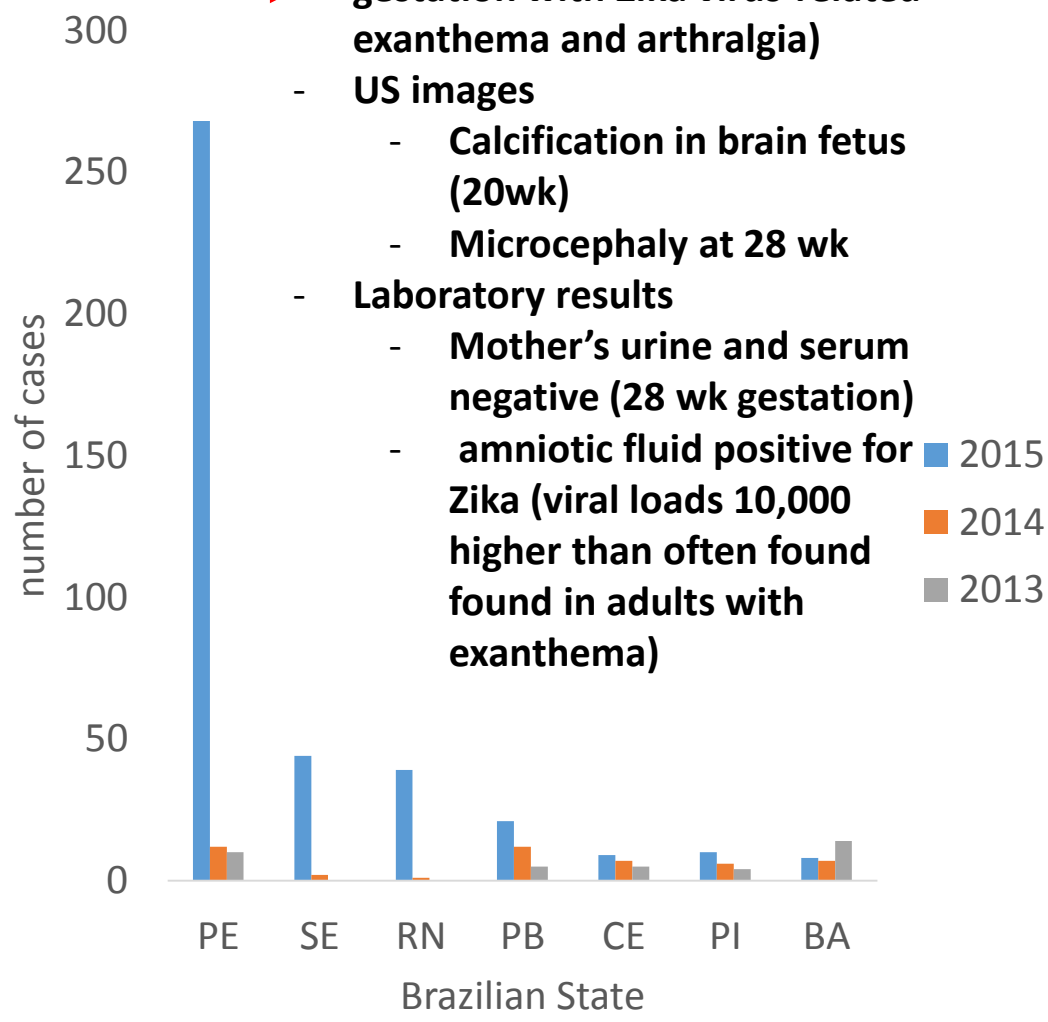
November 12: the Ministry of Health declared Emergency in Public Health based on microcephaly of occurrence

Brazilian States with confirmed Zika virus detection and Microcephaly cases



Direct link

- **Two pregnants (18-19 wk gestation with Zika virus-related exanthema and arthralgia)**
- **US images**
  - **Calcification in brain fetus (20wk)**
  - **Microcephaly at 28 wk**
- **Laboratory results**
  - **Mother's urine and serum negative (28 wk gestation)**
  - **amniotic fluid positive for Zika (viral loads 10,000 higher than often found found in adults with exanthema)**



Peso: 4.140g Estatura: 48cm **PC: 31cm**


cute

Possible antiviral interventivos against zika virus infection (by rational)

- ***Broad spectrum antivirals***
  - **Ribavirin** - Controversial effects towards Dengue. Not recommended during pregnancy – including prior to 6 mo and to male partners
  - **Favipiravir** - Effective against YFV and WNV. No data on pregnancy displayed. It has been used during the Ebola outbreak (any evidence of safety in pregnant?)
- ***Successful therapies to other Flavivirus (HCV-driven therapy)***
  - **Ribavirin** (mentioned above)
  - **Ledipasvir** (iNS5A, fosfoprotein) and **Sofosbuvir** (iNS5B, RNA polymerase) - No adequate and well-controlled study in humans. In animal reproduction studies, no evidence of adverse developmental outcomes
  - **Paritaprevir** (iNS3/4A, serine protease), **ombitasvir** (iNS5A, fosfoprotein) and **dasabuvir** (NS5B, RNA polymerase)- No adequate and well-controlled study in humans. In animal reproduction studies, no evidence of adverse developmental outcomes. Used in combination with ritonavir (besides an HIV protease inhibitor, it blocks a human CYP3A to slow down the other drugs metabolism)
  - **Non-** and **PEG-IFN** – Effective against Dengue 2 infection in macques. Not recommended during pregnancy
- ***Other viral protease inhibitors?***
  - ***Caveat:*** *HIV protease is an Asp-protease, whereas Flavivirus protease is a Ser-protease*

Opportunities

- Epidemiological studies
  - Retrospective analysis of microcephaly cases
  - Prospective analysis of serological status.
  - Pregnant cohort
  - Neurological complications
- Clinical management
  - Experimental intervention protocol for pregnant and non-pregnant zika virus-infected individuals (driven by the discussion from the previous slide)
- Technological development
  - Antivirals (screen a library of compounds from synthetic, natural and biotechnological origins)
  - Immunotherapy
  - Specific serological tests (virus immunome)