

# Epidemiology of Microcephaly in Brazil

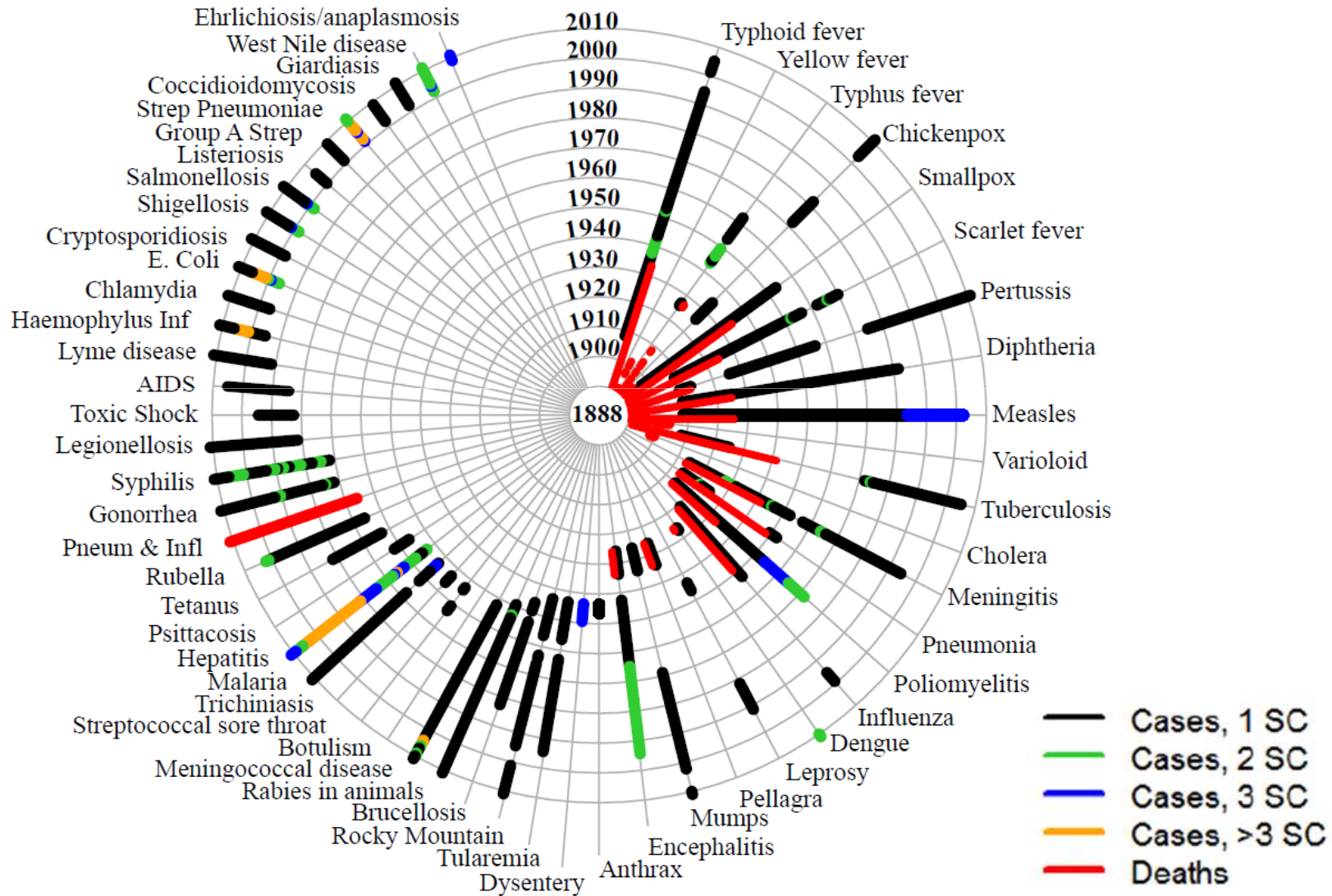
Workshop  
March, 2016



# A new congenital syndrome? Zika virus infection?

- Clusters of new phenotype of neonatal syndrome
- Timeline
- Microcephaly
  - Causality, Correlation vs Coincidence
- Ongoing studies
  - Case control
  - Cohort studies

# History of disease reporting in the US



# The New York Times

SUNDAY, FEBRUARY 7, 2016

Washington Edition  
 After 10 days and another week of...  
 ...the...  
 ...the...  
 ...the...

ers Was  
 to Accept  
 Problems  
 Initially Saw  
 servative Plot

STEVE EDER  
 DAVE PHILIPPS  
 ...reports of secret  
 ...to hide long delays  
 ...blame-blowers said as  
 ...veterans had died  
 ...appointments. And  
 ...was demanding an-

mounting evidence of  
 ...the Department of Veter-  
 ...ria. Senator Bernie  
 ...was the chairman of  
 ...Veterans Affairs Com-  
 ...mittee, regarded the  
 ...as overblown, and as  
 ...conservatives to weak-  
 ...en the country's largest so-  
 ...ciety.  
 ...right now, as we  
 ...sported effort to un-  
 ...e V.A., Mr. Sanders  
 ...said, two weeks after  
 ...was picked up by na-  
 ...tional organizations. "You  
 ...out there now — Koch  
 ...and others — who want  
 ...to change the nature of  
 ...either make major  
 ...changes to these institu-  
 ...tions, or  
 ...away with them."

scandal deepened: The  
 ...of veterans affairs re-  
 ...ports showed major  
 ...deficiencies of V.A. hospi-  
 ...tals. An Obama administra-  
 ...tion revealed "significant  
 ...systemic leadership  
 ...deficiencies in the hospi-  
 ...tal system."  
 ...leaders eventually  
 ...resigned, becoming criti-  
 ...cism and ultimately  
 ...Senator John Mc-  
 ...Carthy, an Arizona Republican,  
 ...introduced legislation to draft a bi-

...aid on page 17  
  
 ...during a debate  
 ...from his rivals.

## Medical Mystery With a Global Reach



An *Aedes aegypti* mosquito, the carrier of Zika virus, which has island-hopped for years eastward across the Pacific.

### Search to Explain Birth Defects in Brazil Led to Zika Virus

This article is by **Donald G. McNeil Jr.**, **Simon Romero** and **Sabrina Torres**.  
 Something strange was happening last August in the maternity wards of Recife, a seaside city perched on Brazil's east Atlantic coast, when the country jolted into the Atlantic.  
 "Doctors, pediatricians, semaphores, they started finding this thing we never had seen," said Dr. Celina M. Turchi, an infectious diseases researcher at the Oswaldo Cruz Foundation, a prominent scientific institution in Brazil.  
 "Children with normal faces up to the eyebrows, and then you have an forehead and very strange heads," she recalled, referring to the condition known as microcephaly. "The doctors were saying, 'Well, it's new. Not today' and, 'Oh, that's strange, because I saw that!'"  
 Adults from their uterine appearance, many of the babies showed defects.  
 "They said," Dr. Turchi said, "they looked well. They just didn't seem to be it."  
 Doctors were stumped.  
 They did not know it then, but they were seeing the first wave of a hurly-burly wave: A little-known

pathogen — the Zika virus, carried by mosquitoes — had been circulating in Brazil for at least a year. It would later become the chief suspect in the hunt to work out what had happened in those newborns.  
 "Since then, those tiny babies have led the World Health Organization to declare a public health emergency. They have prompted warnings to pregnant women in several countries where the virus is circulating, even to refrain from unprotected

sex with men who have visited those countries, following a report of sexual transmission of the virus in Dallas last week.  
 They have led health ministers of five countries to say something as unlikely as that rain had ever caused a fetus: Women, please delay having children.  
 The virus now threatens the economies of fragile nations and the 2016 Summer Olympics in Rio de Janeiro. It has opened a new front in the debate in heavily Roman Catholic countries about a woman's right to birth control and abortion.  
 And the children stricken with microcephaly, or abnormally small heads, have doctors everywhere asking: What is this virus? How could it have been around for almost 70 years without us realizing its power? What do we tell our patients about a bug that can hide in a mosquito's proboscis and a man's semen, even in human saliva or urine? What do we tell young women who ask if their unborn babies are safe?  
 "This epidemic is an unfolding story," said Dr. Anthony S. Fauci, director of the National Institutes of Health.

Continued on Page 16



A Brazilian soldier inspected a water cask in a yard looking for mosquito larvae in Recife, where doctors saw a startling increase in birth defects.

Medical mystery with a global reach ...  
 Search to Explain Birth Defects in Brazil Led to Zika Virus

<http://www.nytimes.com/2016/02/07/health/zika-virus-brazil-how-it-spread-explained.html? r=0>

# Primary Microcephaly-causes

## Causes

Genetic

Environmental

Toxic exposures

Foetal alcohol syndrome

Radiation

Clinical/**Infections**

**TORCH** Infections:

**T**oxoplasmosis,

**O**ther (Syphilis, Varicella-zoster,  
Parvovirus B19),

**R**ubella,

**C**ytomegalovirus (CMV), and

**H**erpes infections.



Calcifications  
suggest infectious  
origin



# Microcephaly

## Definition

- Reduced head circumference of  $<32$  cm
- Morphological abnormalities

## Known Causes

Genetic

Toxic-Metabolic

Including Fetal Alcohol  
Syndrome

Environmental

Infectious



## Congenital infection?

- Cerebral abnormalities (dysgenesis, calcifications)
- High number of microcephaly cases within few weeks/short time
- Geographical spread
- Cluster

≠ transmission mechanisms of ToRCHeS (Toxoplasmosis, Rubeola, CMV, Herpes, Syphilis)

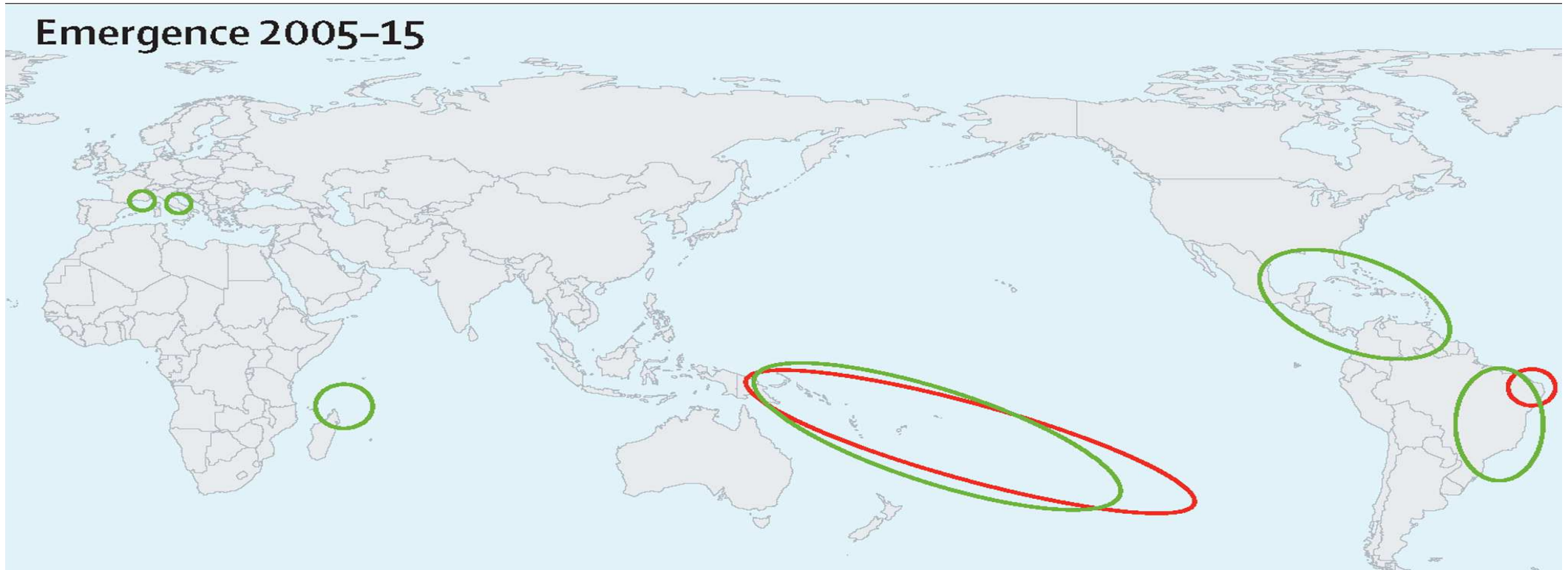
## Arboviruses?

- Dengue
- Chikungunya
- Zika???

Perinatal transmission → neonatal infection?

1947	Zika virus isolated in a Rhesus monkey at Zika forest in Uganda. Arbovirus - Flavivirus family.
1952	First human case of Zika
1960	Sporadic human cases in Asia and Africa
2007	First outbreak in Micronesia/ Pacific, with Exanthema, conjunctivitis and arthralgia
2013-14	Outbreaks in French Polynesia, associated with cases of Guillan Barré syndrome

# Zika virus: following Dengue and Chikungunya?

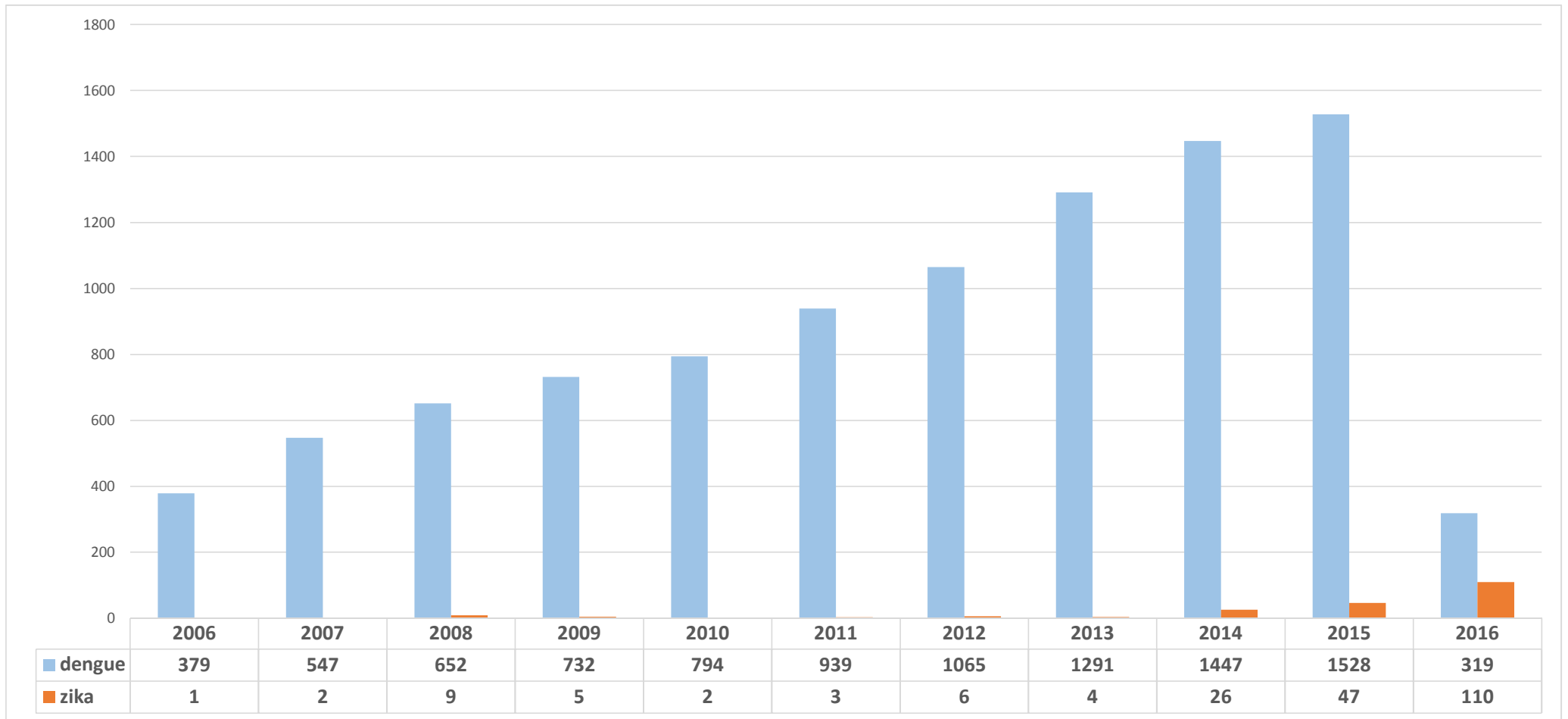


*The Lancet*. Volume 386, Issue 9990, Pages 243-244 (July 2015)

DOI: 10.1016/S0140-6736(15)61273-9



# Pubmed: 'Dengue' vs 'Zika' (past 10 yrs)



REVIEW **OPEN**

# Global research priorities for infections that affect the nervous system

Chandy C. John<sup>1</sup>, H el ene Carabin<sup>2</sup>, Silvia M. Montano<sup>3</sup>, Paul Bangirana<sup>4</sup>, Joseph R. Zunt<sup>5</sup> & Phillip K. Peterson<sup>6</sup>

[Nature](#). 2015 Nov 19;527(7578):S178-86. doi: 10.1038/nature16033

# Timeline – microcephaly in live births in Metropolitan Recife, 2015



<sup>1</sup> Health Secretary of Pernambuco State

<sup>2</sup> Health Surveillance Secretary of the Ministry of Health

<sup>3</sup> Pan-American Health Organization (PAHO)

# Rapid communication

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

➤ **3 mothers with their children RT-PCR positive**

[www.eurosurveillance.org](http://www.eurosurveillance.org)

Article published: 3 April 2014, Besnard et al

# Evidence

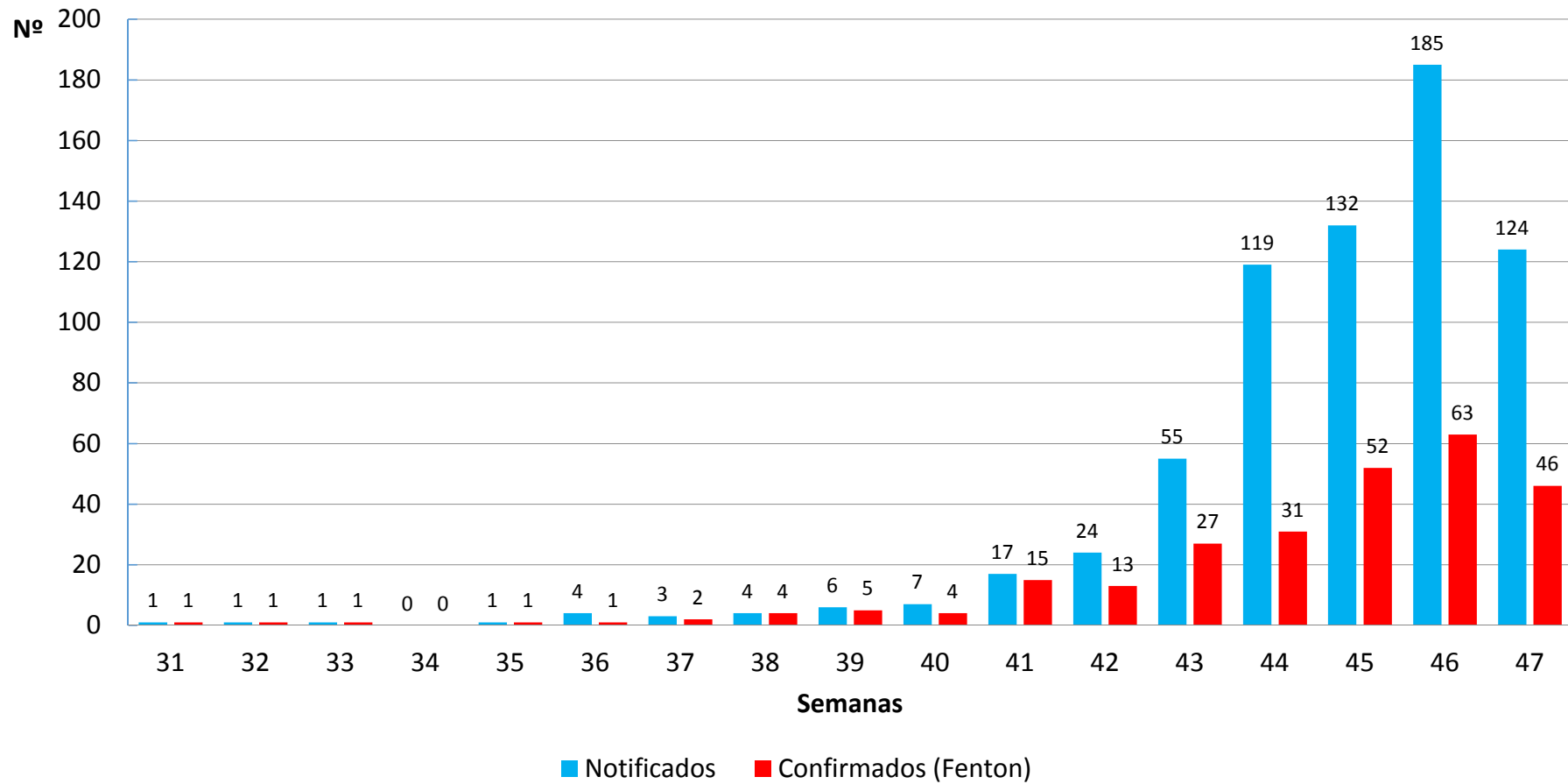
- Increase in occurrence of suspected cases of infectious microcephaly
- Period of major Zika circulation in the North-East corresponded to first gestational months of the women
- Nervous system alteration of the children, compatible with infectious disease
- Neurotropism of Zika virus and other Flaviviruses in literature
- Virus detection in amniotic fluid of pregnant women and one still birth

# Distribution of notifications of suspected cases of microcephaly in Brazil - Feb 13, 2016

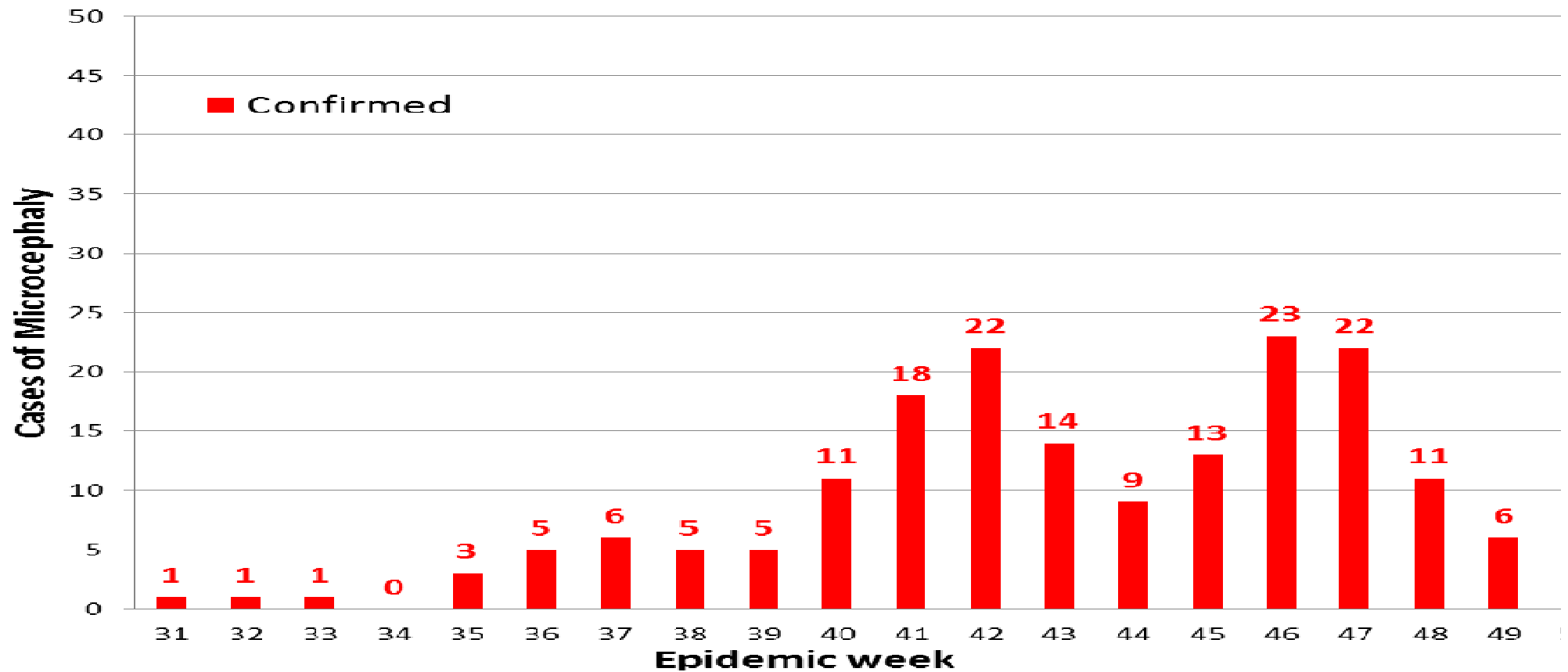


By The New York Times | Source: Brazil's Ministry of Health

# Microcephaly in live births – Pernambuco State, 1/08/2015 - 12/12/2015

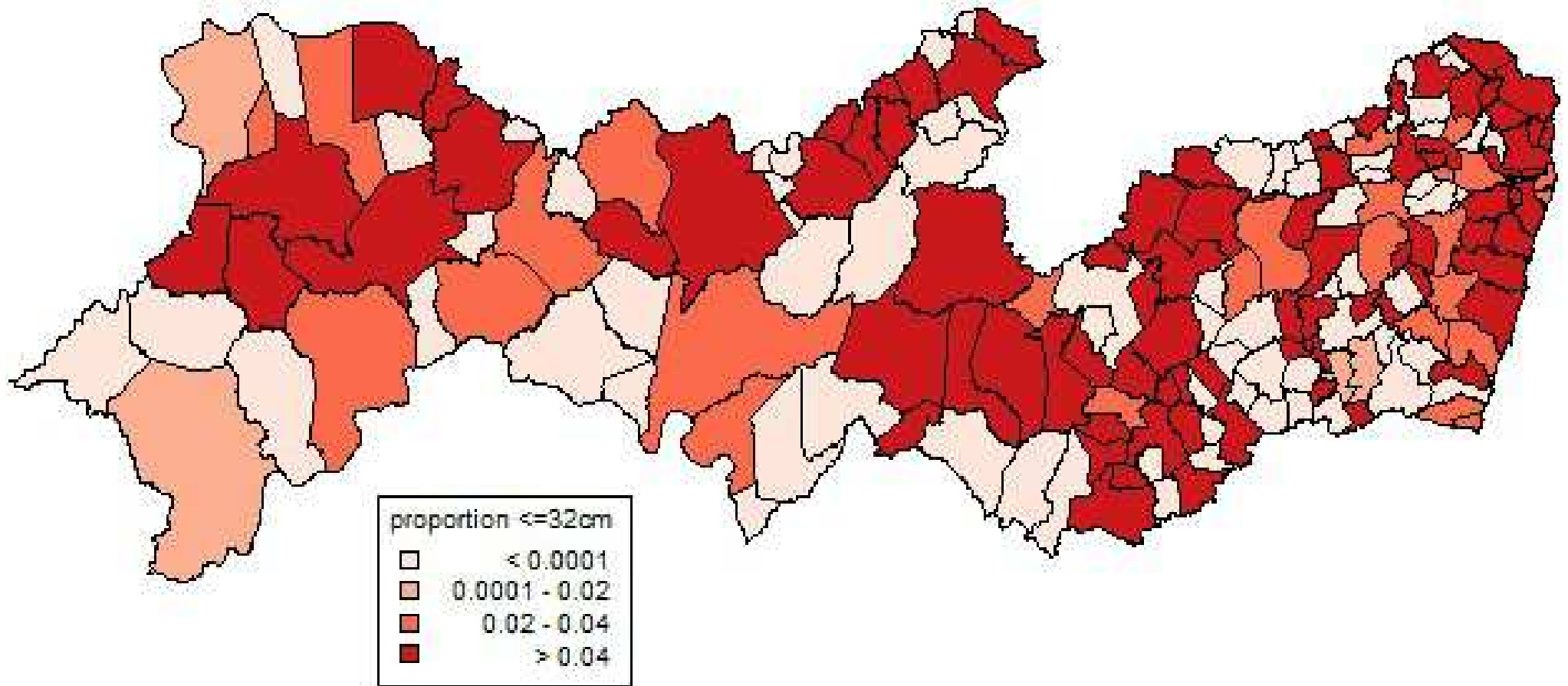


# Microcephaly in live births – Pernambuco State, 1/08/2015 – 12/12/2015





# Spatial distribution of suspected microcephaly in Pernambuco State, November 2015





## Letter to the editor

**Zika and microcephaly: causation, correlation, or coincidence?**

- ZIKV neurotropism:
    - ZIKV crosses blood-brain barrier - intraperitoneally injected mice: Dick, 1952
    - Progression of disease in directly infected mice brains: Bell, 1972
  - ZIKV cell pathomechanism - autophagy:
    - Autophagy: cell-protective mechanism against unwanted material, but:
    - ZIKV “hijacks” for viral replication → “Virus factories” intracytoplasmic inclusions
  - Pathogenesis of microcephaly – centrosomes:
    - Abnormal function & amplification of centrosomes (mitosis, regulatory functions, vesicle trafficking): Thornton, 2009; Marthiens, 2013
- Microcephaly in fetal ZIKV infection due to ?link autophagy & centromes

# Research

## Projects by Microcephaly Epidemic Research Group (MERG)



**Case series**



**Case-control**



**Cohort**



**Pregnant  
women  
with rash**



**Neonates with  
congenital  
abnormalities**

## Publications of MERG – online shortly

Microcephaly in Pernambuco State – Epidemiological characteristics and evaluation of diagnostic criteria	Cadernos de Saude Publica (Reports in Public Health), 2016 (accepted)
Initial Description of the Presumed Congenital Zika Syndrome.	American Journal of Public Health, 2016 (in press)
Head computed tomography findings in infants with congenital microcephaly due to prenatal Zika virus infection	Submitted 2016 (under review)
The epidemic of Microcephaly in Brazil: description of 104 cases, 2016.	Submitted, 2016 (under review)

# Acknowledgments

## MERG Team

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Universidade Federal de Pernambuco, Recife  
(UFPE)  
Universidade de Pernambuco (UPE), Recife  
State Secretariat of Health, Pernambuco  
Mother-Child Institute Pernambuco (IMIP) and  
other state and municipal hospitals  
Ministry of Health, Brazil  
Pan-American Health Organization, Brazil  
PAHO, Washington  
Epidemiology and Population Health, London  
School of Hygiene & Tropical Medicine,  
London



## MERG Protocols (other publications & updates soon...)

<http://scf.cpqam.fiocruz.br/merg/index.php/documentos/3-protocolos>





# References

Tetro JA. Zika and microcephaly: causation, correlation, or coincidence? *Microbes and Infection*, Institut Pasteur, 2016, p 1-2.

McNEIL Jr. DG et al. Short Answers to Hard Questions About Zika Virus. *New York Times*, updated February 24, 2016, accessed online on 27/02/2016 under

<http://www.nytimes.com/interactive/2016/health/what-is-zika-virus.html? r=0>