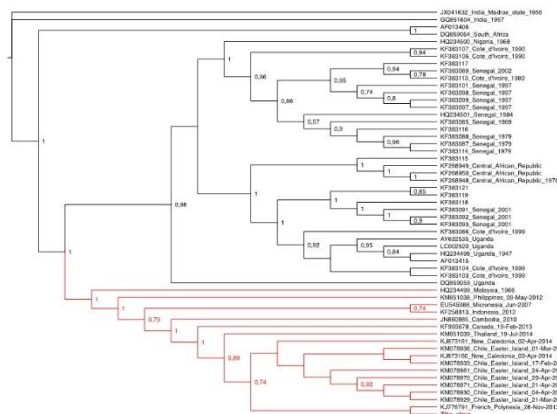


# ZIKA VIRUS: ALÉM DA MICROCEFALIA



Adriana Melo

Instituto de Pesquisa Professor Joaquim Amorim Neto – IPESQ

UNIFACISA

Instituto de Saúde Elpidio de Almeida - ISEA

- O que é o IPESQ
  
  
  
  
  
  
  
  
  
  
- Quem sou eu

# Zika virus

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- Zika virus is an arbovirus of the Flaviviridae Family. Its identification occurred in 1947 in Uganda
- The epidemic potential was perceived since 2007 in Micronesia; however, in 2013, mainly in the French Polynesia, a change in the pattern was observed, with high rates of attack, estimating the occurrence in 11% of the population
- In Brazil, since November 2014 and mainly in the beginning of 2015, the Northeast states reported a great outbreak of a new exanthematic disease.



# First isolates

- Sentinels Rhesus 1947



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*

S. F. KITCHEN,

*Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.*

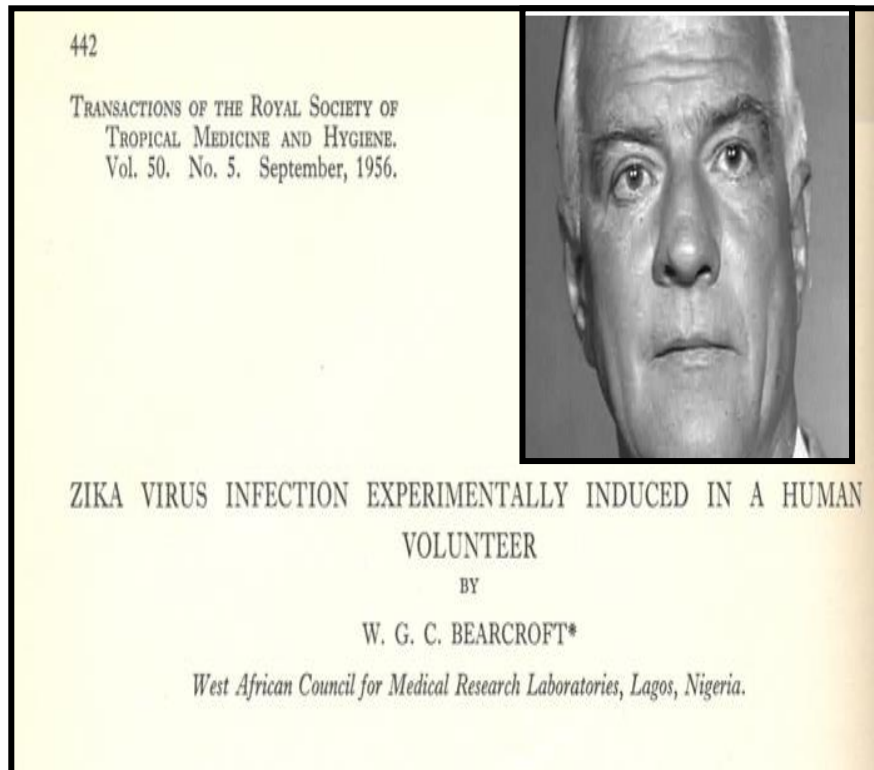
AND

A. J. HADDOW,

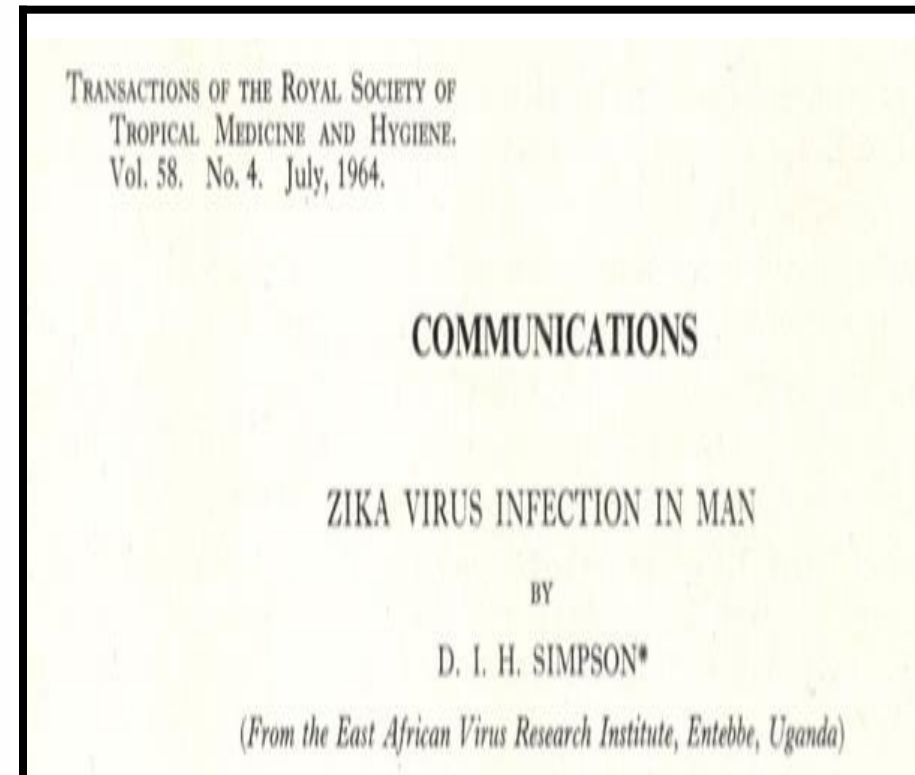
*Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.*

*(From the Virus Research Institute, Entebbe, Uganda.)*

Human cases were not observed.



Low fever and headache

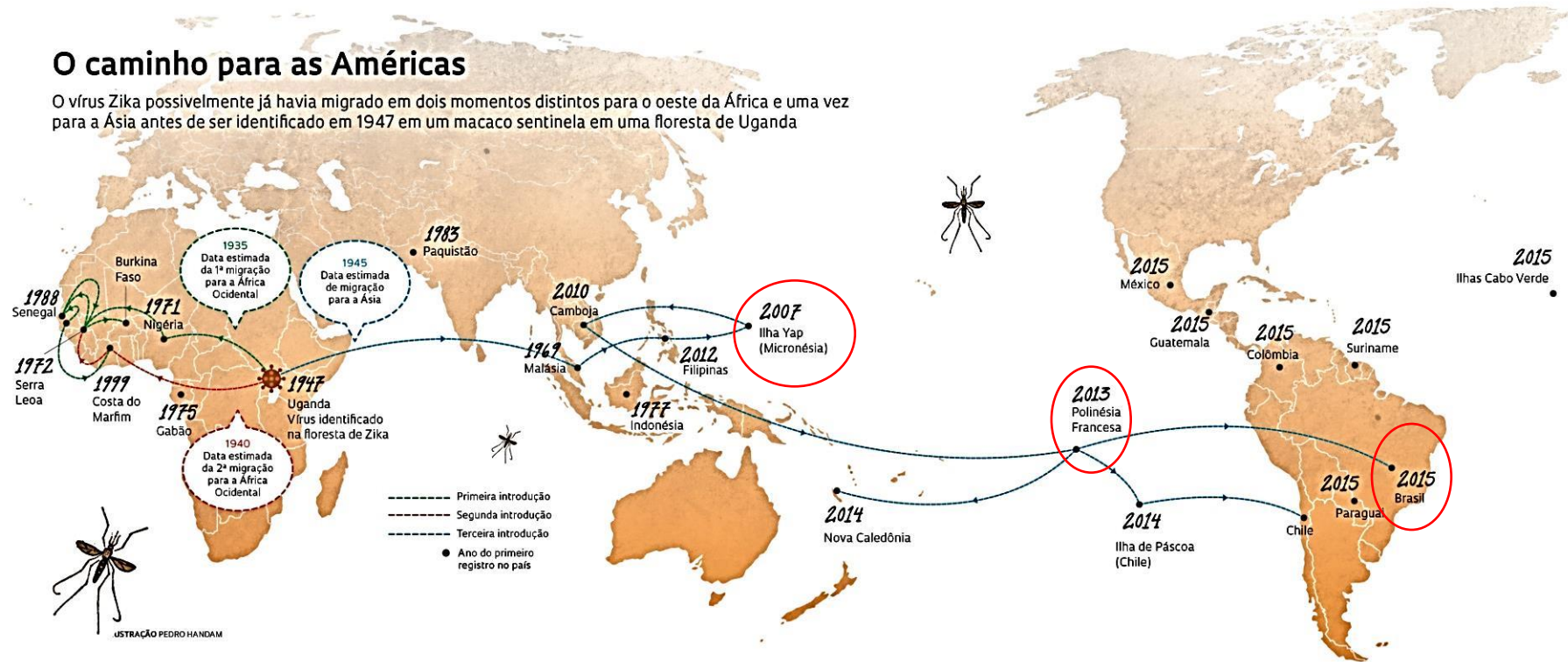


Low fever, headache and rash

# Zika outbreak

## O caminho para as Américas

O vírus Zika possivelmente já havia migrado em dois momentos distintos para o oeste da África e uma vez para a Ásia antes de ser identificado em 1947 em um macaco sentinela em uma floresta de Uganda



# New Burst of Zika virus in Americas

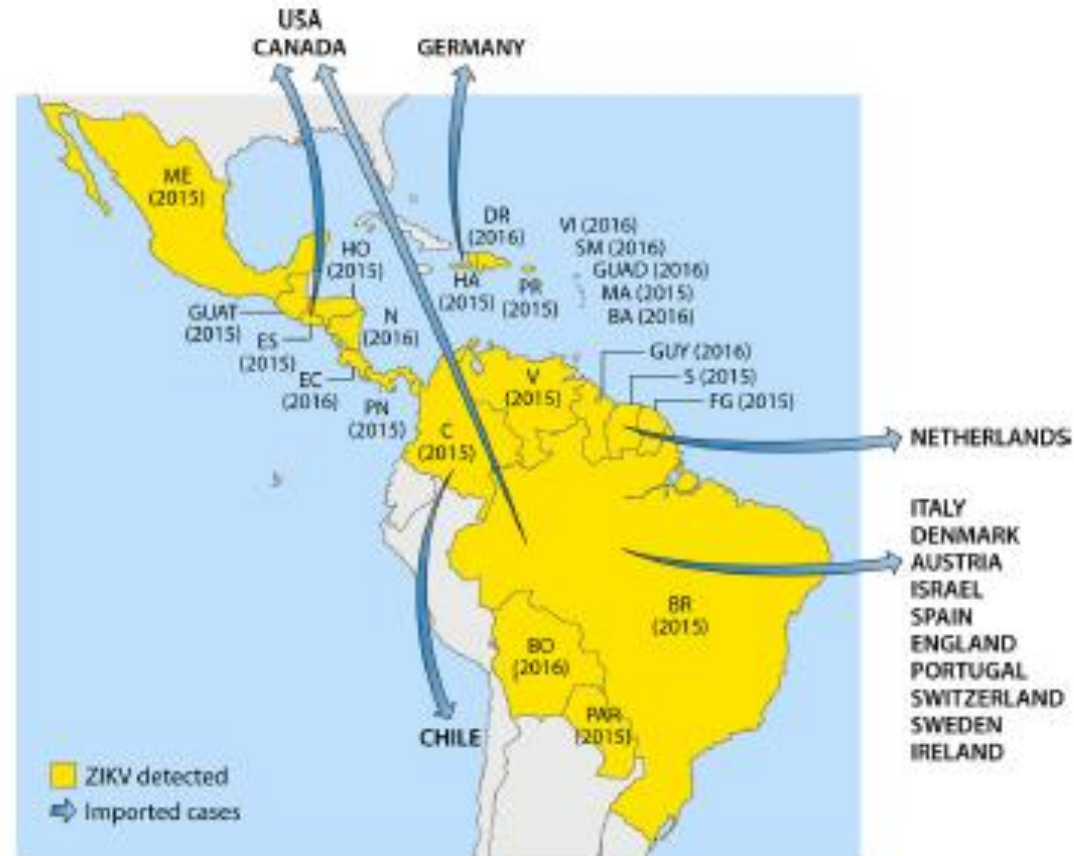


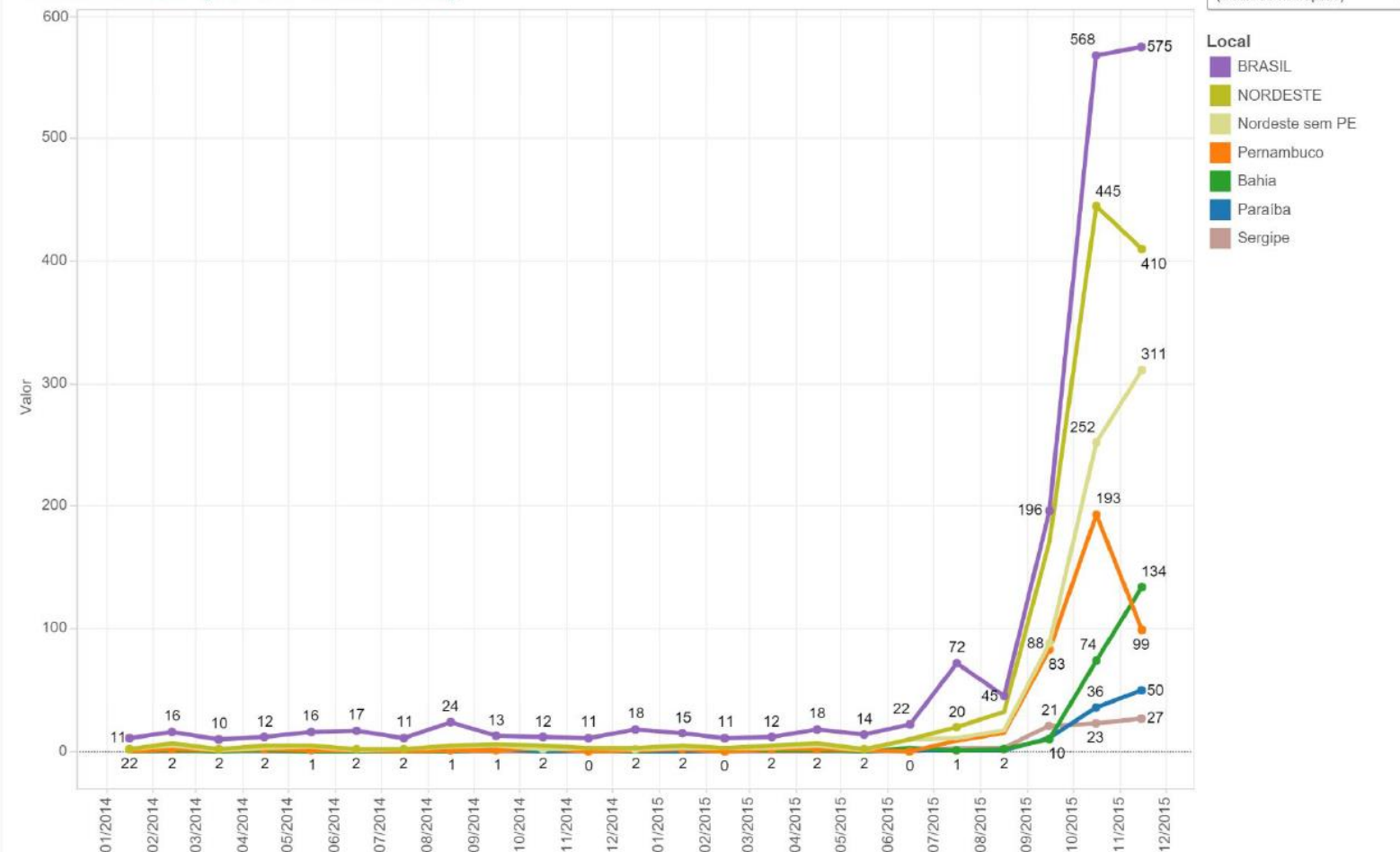
FIG 3 American countries in which ZIKV circulation has been reported up to January 2016. Abbreviations: ME, Mexico; DR, Dominican Republic; VI, Virgin Islands; SM, Saint Martin; GUAD, Guadeloupe; MA, Martinique; BA, Barbados; HA, Haiti; PR, Puerto Rico; HO, Honduras; GUAT, Guatemala; N, Nicaragua; ES, El Salvador; EC, Costa Rica; PN, Panama; V, Venezuela; GUY, Guyana; S, Suriname; FG, French Guiana; C, Colombia; BR, Brazil; BO, Bolivia; PAR, Paraguay.

# Microcephaly

## Microcefalia no Brasil - 2000 a 2015

Nascimentos totais e com microcefalia, taxa de prevalência de microcefalia (por 100.000 nascimentos) e médias móveis

### Nascimentos (com microcefalia)



**2015 – primeiros casos**  
Casos suspeitos - CP ≤ 33cm

**2016**  
CP ≤ 31.9 cm ♂  
CP ≤ 31.5 cm ♀

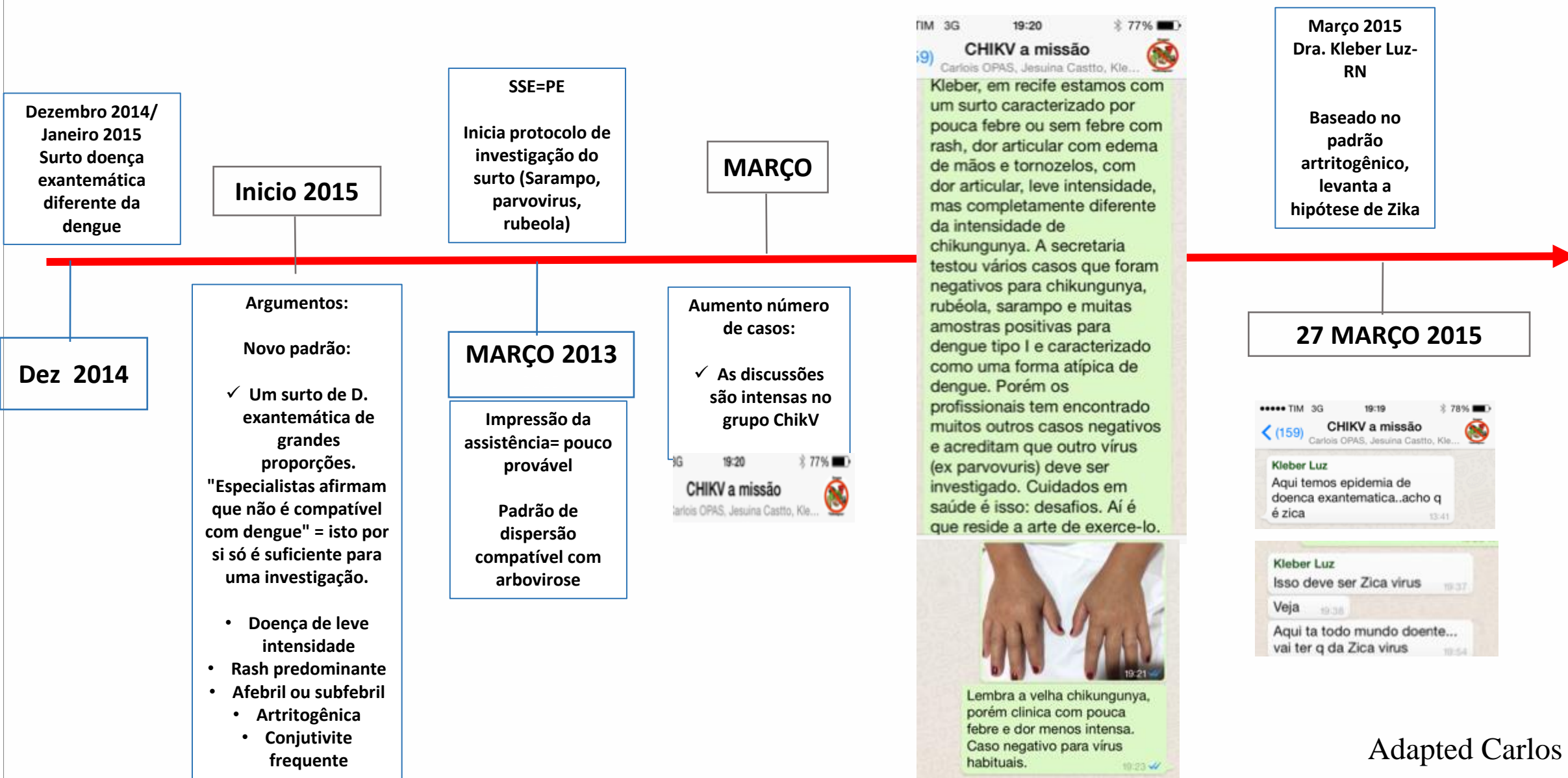


# Teorias da conspiração

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- Vacinas vencidas
- Mosquitos transgênicos
- Larvicidas

# LINHA DO TEMPO DO ZIKA VIRUS



# Casos típicos

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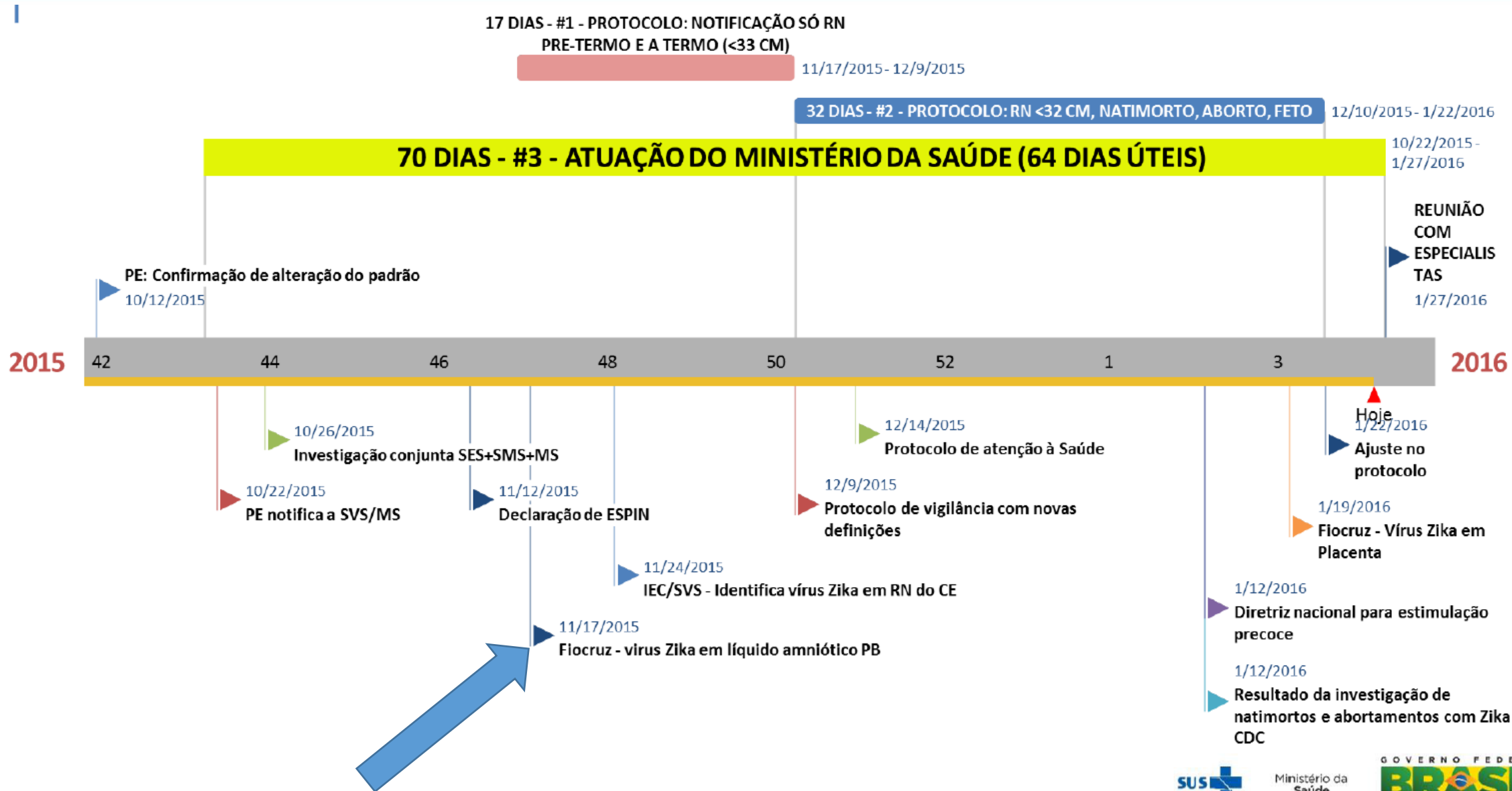


# Zika virus

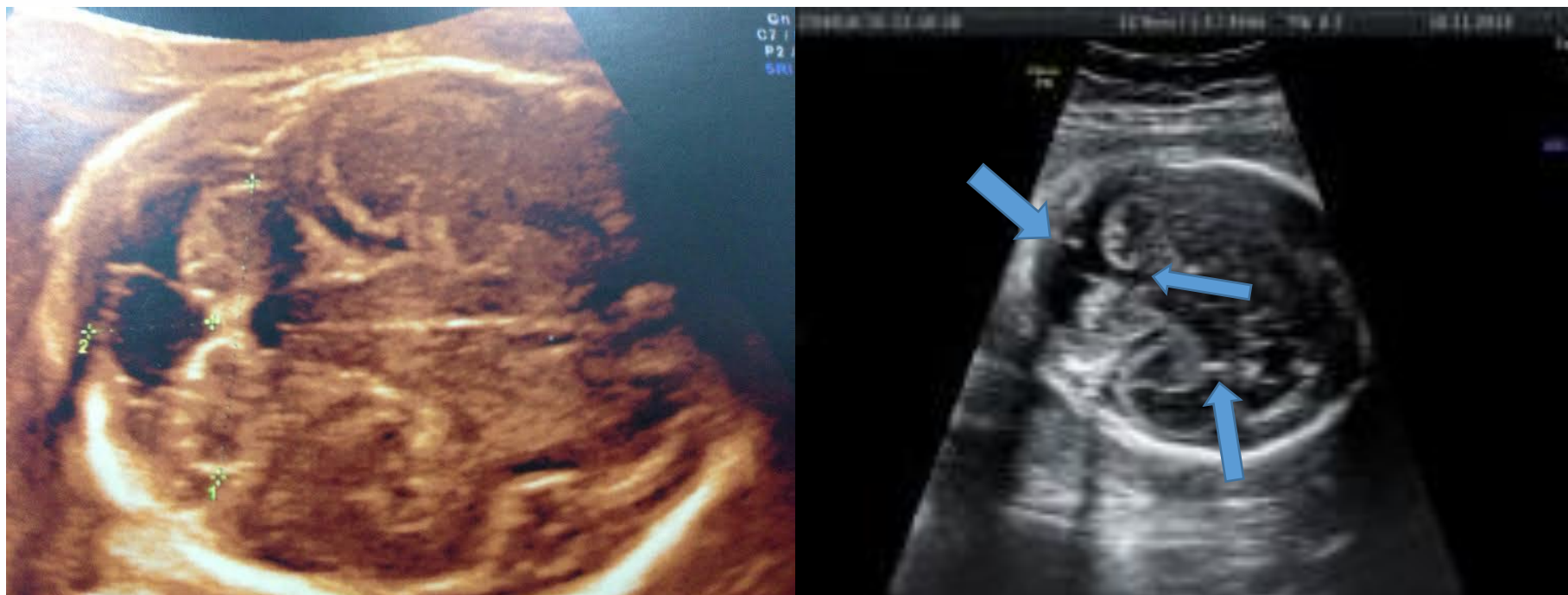
Sinais/Sintomas	Dengue	Zika	Chikungunya
Febre (duração)	Acima de 38°C (4 a 7 dias)	Sem febre ou subfebril ≤ 38°C (1-2 dias subfebril)	Febre alta > 38°C (2-3 dias)
Manchas na pele (Frequência)	Surge a partir do quarto dia 30-50% dos casos	Surge no primeiro ou segundo dia 90-100% dos casos	Surge 2-5 dia 50% dos casos
Dor nos músculos (Frequência)	+++/>+++	++/>+++	+/>+++
Dor na articulação (frequência)	+/>+++	++/>+++	+++/>+++
Intensidade da dor articular	Leve	Leve/Moderada	Moderada/Intensa
Edema da articulação	Raro	Frequente e leve intensidade	Frequente e de moderada a intenso
Conjuntivite	Raro	50-90% dos casos	30%
Cefaleia (Frequência e intensidade)	+++	++	++
Prurido	Leve	Moderada/Intensa	Leve
Hipertrofia ganglionar (frequência)	Leve	Intensa	Moderada
Discrasia hemorrágica (frequência)	Moderada	ausente	Leve
Acometimento Neurológico	Raro	Mais frequente que Dengue e Chikungunya	Raro (predominante em Neonatos)

Fonte: Carlos Brito – Professor da Universidade Federal de Pernambuco (atualização em dezembro/2015)

# LINHA DO TEMPO DA MICROCEFALIA



# Por que ZIKA?



**Outubro 2015 – Campina Grande – Paraíba - Brasil**

Vermis cerebelar hipoplásico + calcificações

60 casos similares em Pernambuco com história de rash cutâneo na gravidez

**Nota técnica da SES - PE**

## Neurotropismo

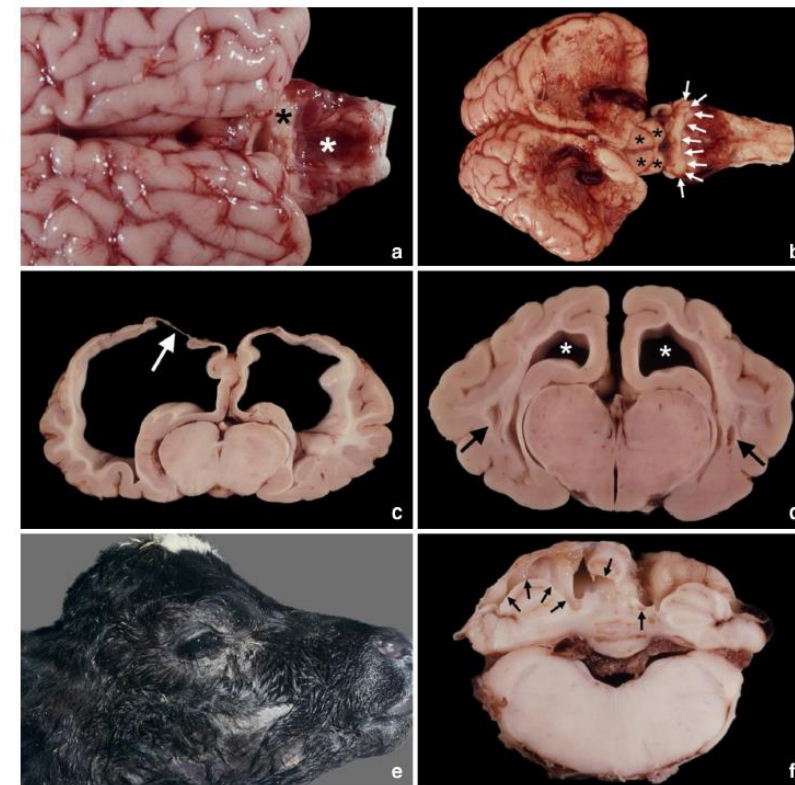
Defined diagnosis based on clinical and neurological manifestations

Diagnostic	N	%
ADEM	5	7.3
ADEM (NMO like)	1	1.5
Encephalitis	2	2,9
Meningoencephalitis	4	5,9
Meningomyelitis	1	1.5
Transverse myelitis	1	1.5
Optic neuritis	9	13.2
VI nerve palsy	1	1.5
Polyradiculoneuritis	1	1.5
Rhombencephalitis	1	1.5
Guillain-Barré syndrome	40	58.8

# Por que ZIKA?



**Figure 1** Lamb born dead with severe arthrogryposis (persistent flexion of the joints): arthrogryposis is one of the congenital abnormalities associated with viral infection.



[Javanbakht J](#) et al. 2014. Neuropathological microscopic features of abortions induced by Bunyavirus / or Flavivirus infections. [Diagn Pathol.](#)

[Agerholm JS](#) et al. 2015. Virus-induced congenital malformations in cattle. [Acta Vet Scand.](#)



# WHY ZIKA?

## November, 2015 – Campina Grande – Paraíba – Brazil

Amniocentesis and subsequent quantitative real-time polymerase chain reaction, performed after ultrasound diagnosis of fetal microcephaly and analyzed at the Oswaldo Cruz Foundation, Rio de Janeiro, Brazil (cases 1 and 2)

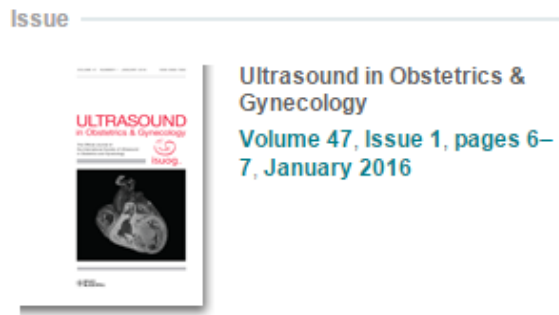
### Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?

A. S. Oliveira Melo<sup>1</sup>, G. Malinger<sup>2\*</sup>, R. Ximenes<sup>3</sup>, P. O. Szejnfeld<sup>4</sup>, S. Alves Sampaio<sup>5</sup> and A. M. Bispo de Filippis<sup>5</sup>

Article first published online: 5 JAN 2016

DOI: 10.1002/uog.15831

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FREE



## Zika Virus Associated with Microcephaly

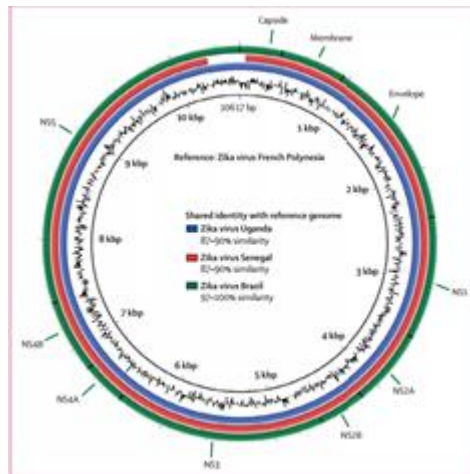
Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav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



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

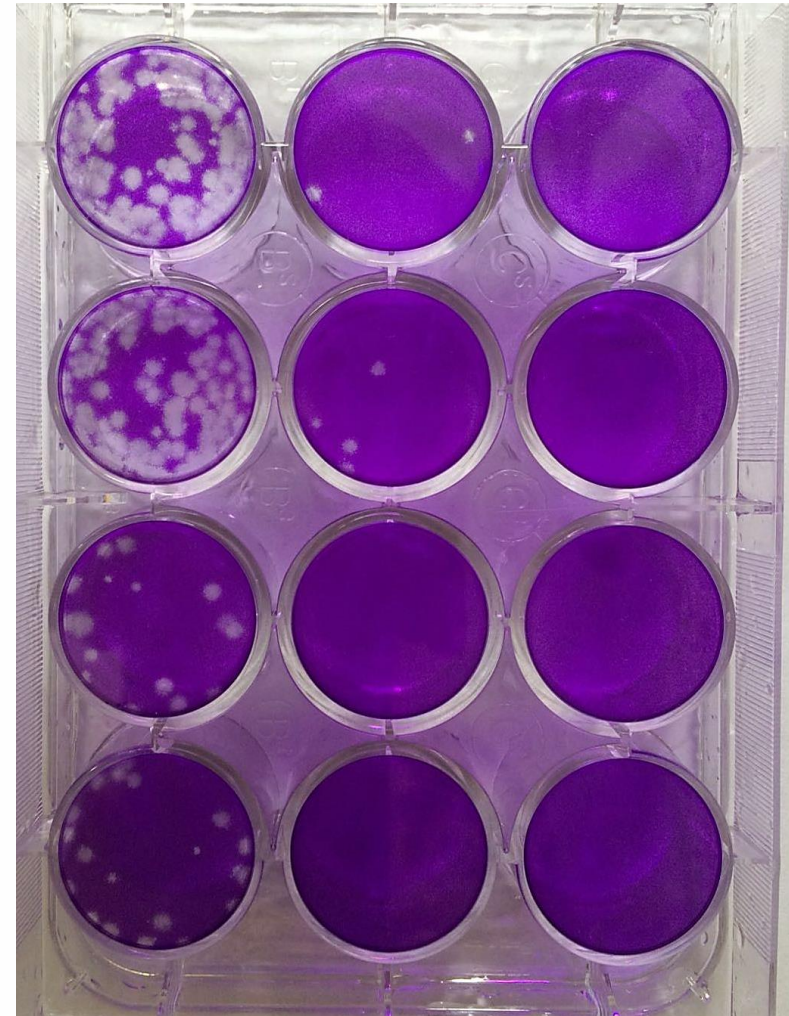
Guilherme Calvet\*, Renato S Aguiar\*, Adriana S O Melo, Simone A Sampaio, Ivano de Filippis, Allison Fabri, Eliane S M Araujo, Patricia C de Sequeira, Marcos C L de Mendonça, Louisi de Oliveira, Diogo A Tschoeke, Carlos G Schrago, Fabiano L Thompson, Patricia Brasil, Flavia B dos Santos, Rita M R Nogueira,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

**Findings** We detected the Zika virus genome in the amniotic fluid of both pregnant women. The virus was not detected in their urine or serum. Tests for dengue virus, chikungunya virus, *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus, HIV, *Treponema pallidum*, and parvovirus B19 were all negative. After sequencing of the complete genome of the Brazilian Zika virus isolated from patient 1, phylogenetic analyses showed that the virus shares 97–100% of its genomic identity with lineages isolated during an outbreak in French Polynesia in 2013, and that in both envelope and NS5 genomic regions, it clustered with sequences from North and South America, southeast Asia, and the Pacific. After assessing the possibility of recombination events between the Zika virus and other flaviviruses, we ruled out the hypothesis that the Brazilian Zika virus genome is a recombinant strain with other mosquito-borne flaviviruses.



African reference 766

Zika Br

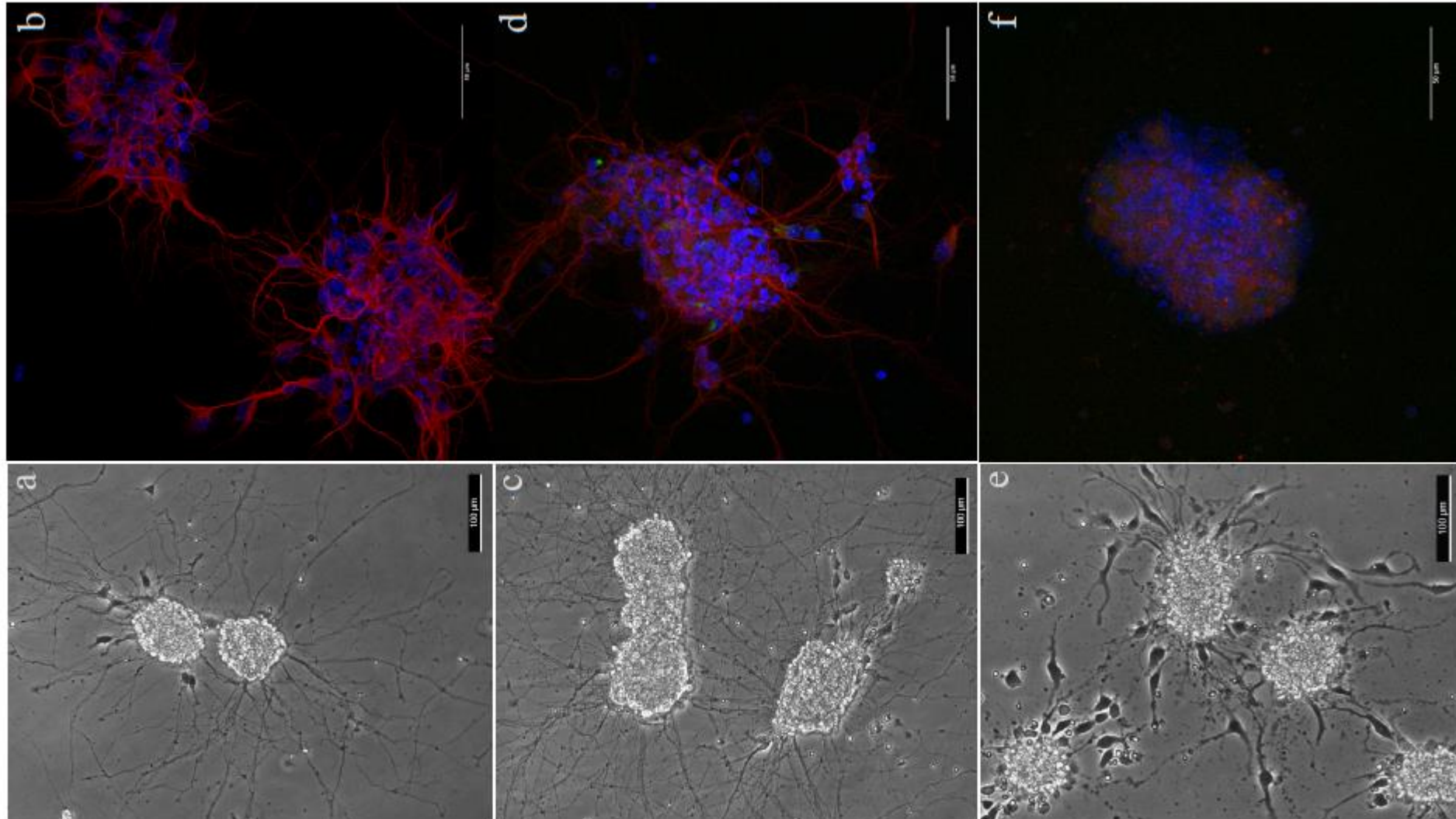


# Zika infected neurospheres

Mock

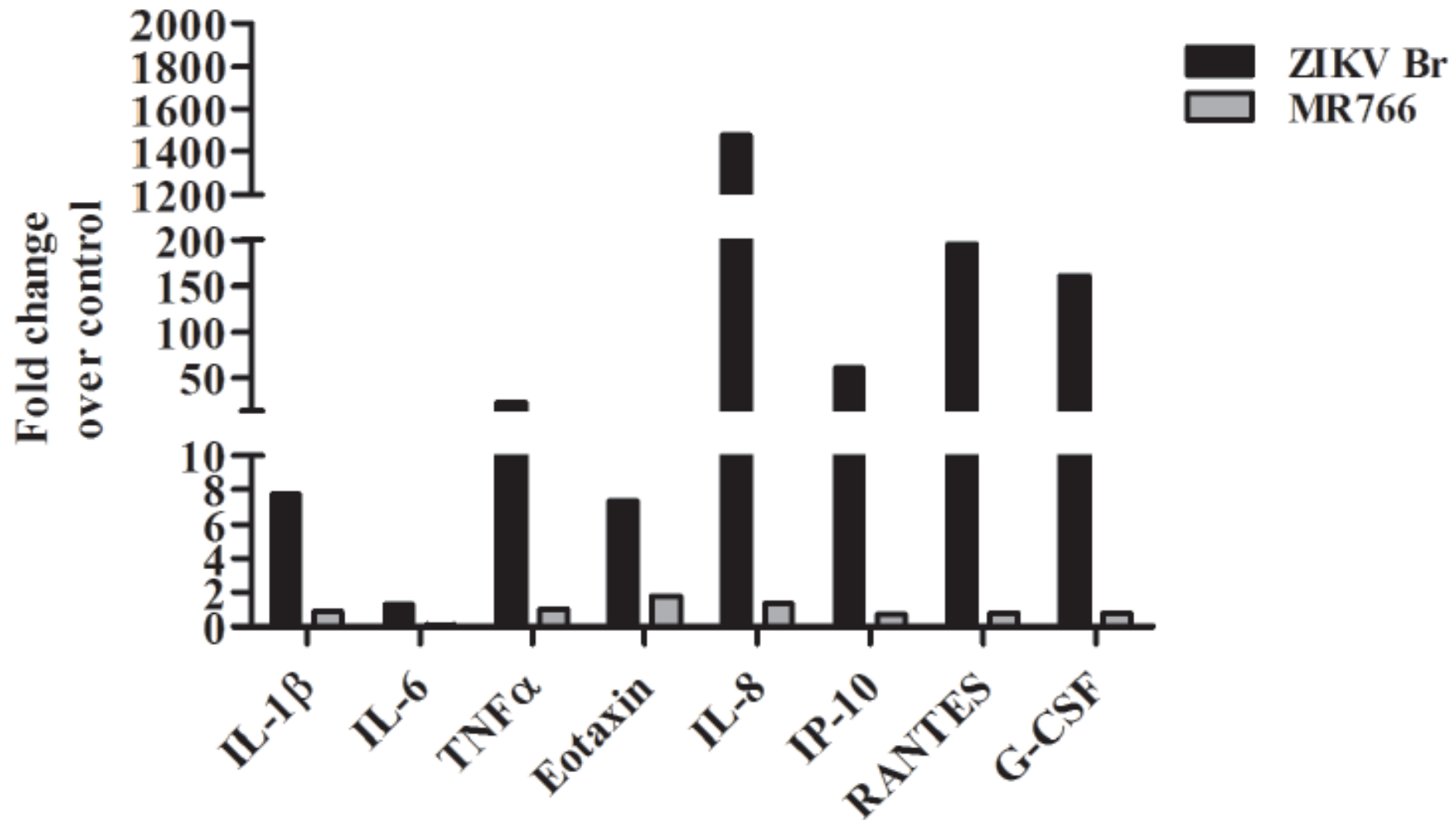
African

Zika BR



Map-2 (red) microtubule associated protein: neuronal differentiation

# Immune-activation of ZIKV Br versus African



Neurological damage (mainly brain atrophy) – 62 cases

- 59 cases - Newborns
  - 8 died less than 48 hours
  - 3 fetuses
- 13 cases detected the zika virus in amniotic fluid, cord blood or tissue (brain and placenta)



Origin

- 12 living in Campina Grande
- 50 residents of nearby cities

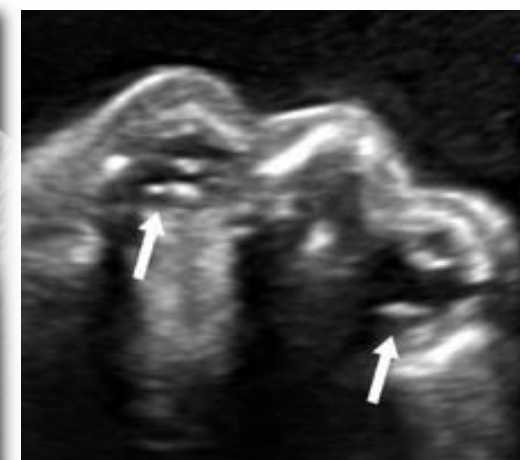
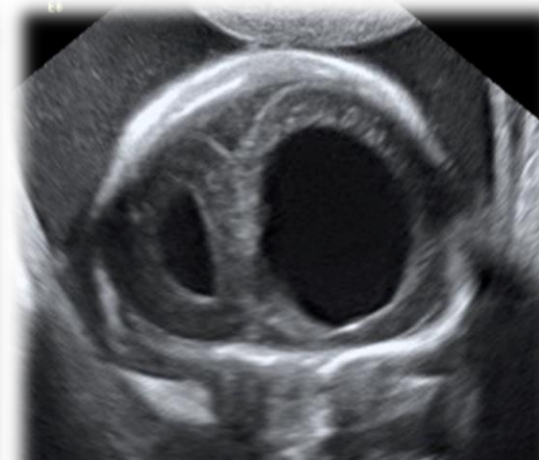
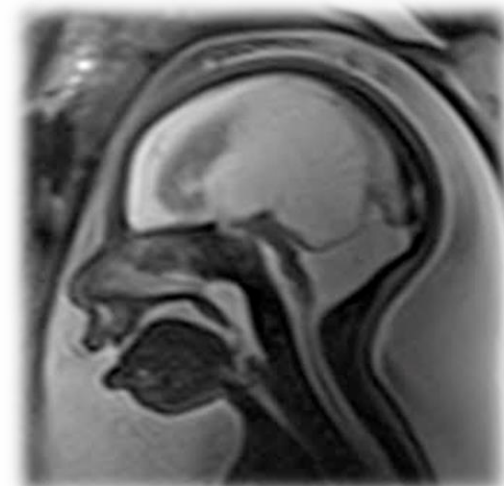


# Caso #1

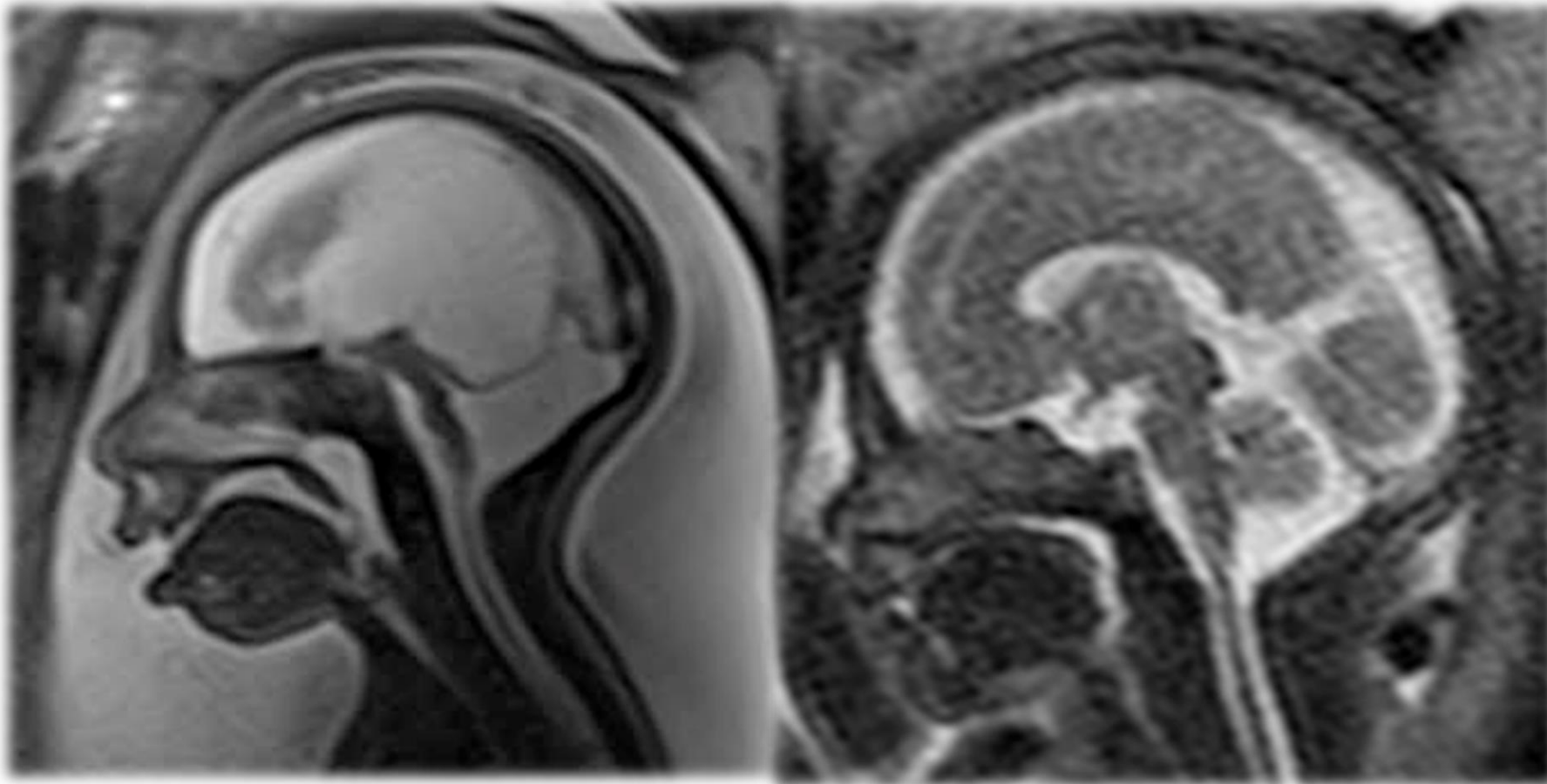
Idade gestacional ao nascer 41 semanas

Perímetro cefálico 36.5 cm (microcefalia compensada pela ventriculomegalia). Morte com - 48 horas

Um hemisfério cerebral fixado em formol, pesando 38 g

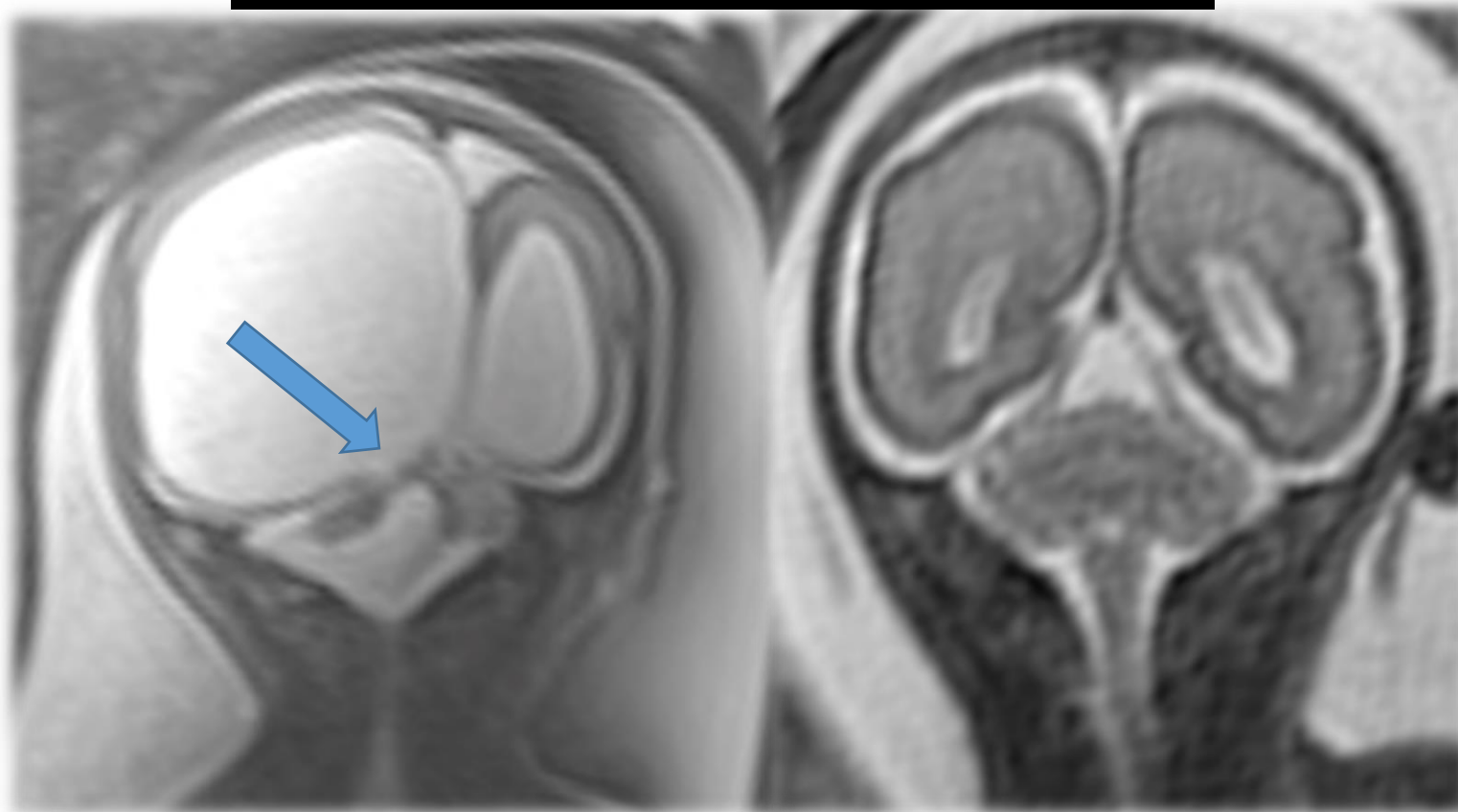


Case 1 X **Normal**



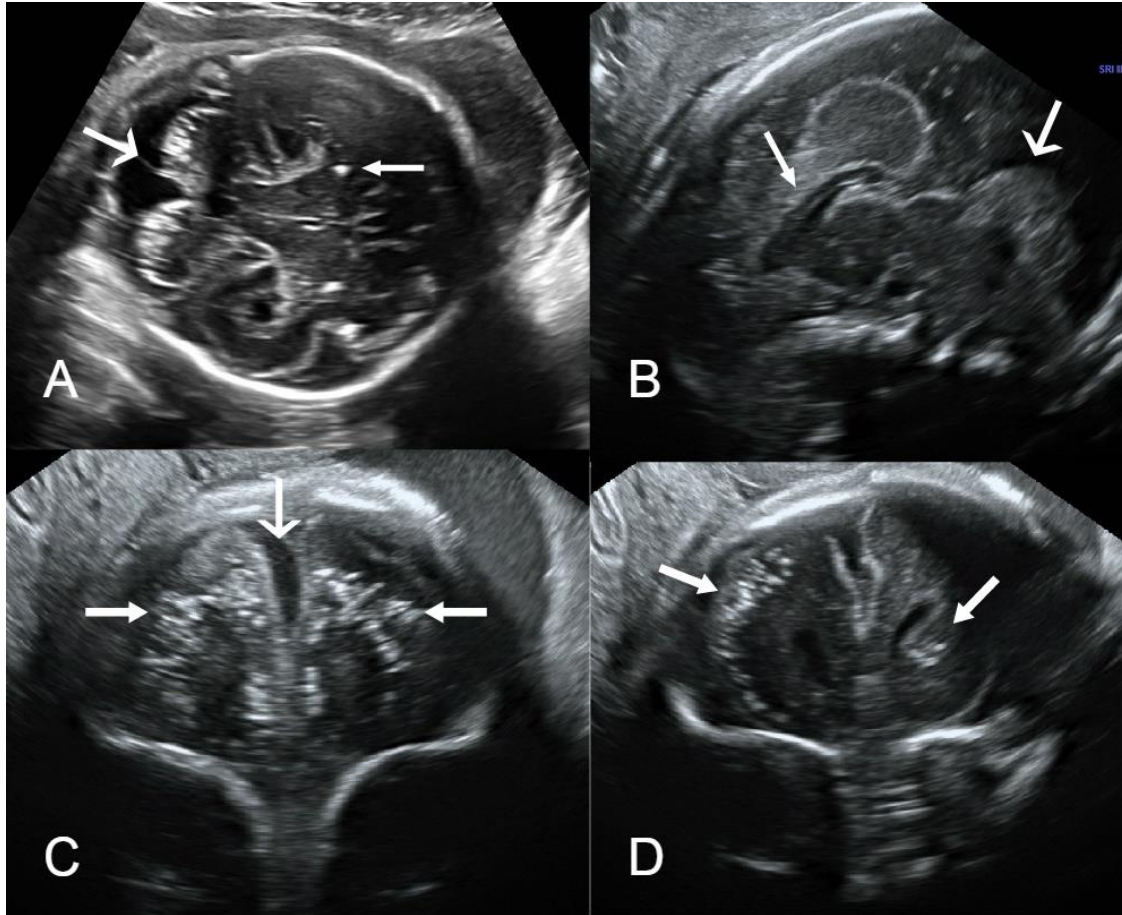
# CASE 1

Case 1 X **Normal**





# CASE 2 – symptoms 8 weeks



(a) Transabdominal axial ultrasound image shows cerebral calcifications with failure of visualization of a normal vermis (large arrow).

Calcifications are also present in the brain parenchyma (small arrow).

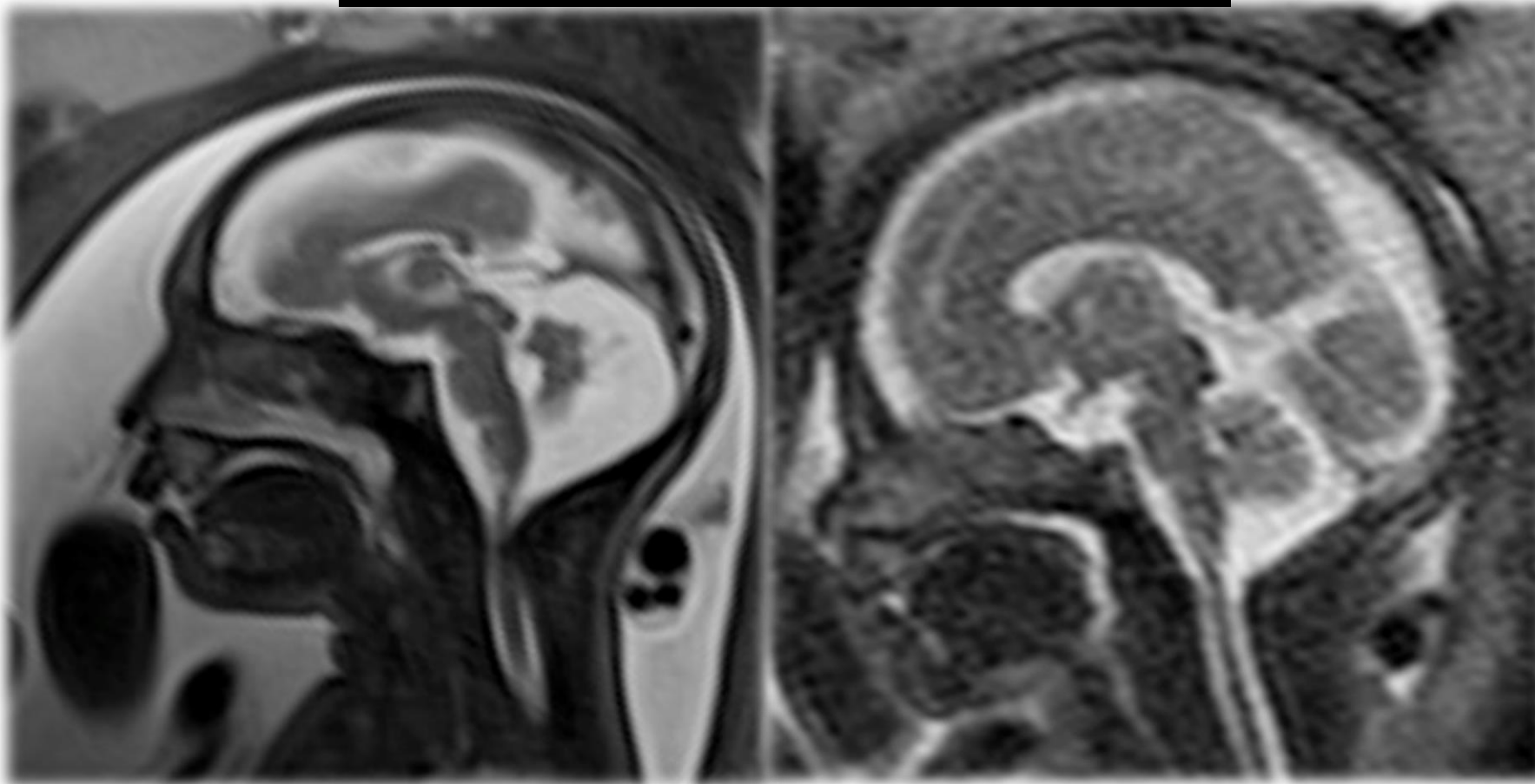
(b) Transvaginal sagittal image shows dysgenesis of the corpus callosum (small arrow) and vermian (large arrow).

(c) Coronal plane shows a wide interhemispheric fissure (large arrow) due to brain atrophy and bilateral parenchymatic coarse calcifications (small arrows).

(d) Calcifications are visible in this more posterior coronal view and can be seen to involve the caudate (arrows).

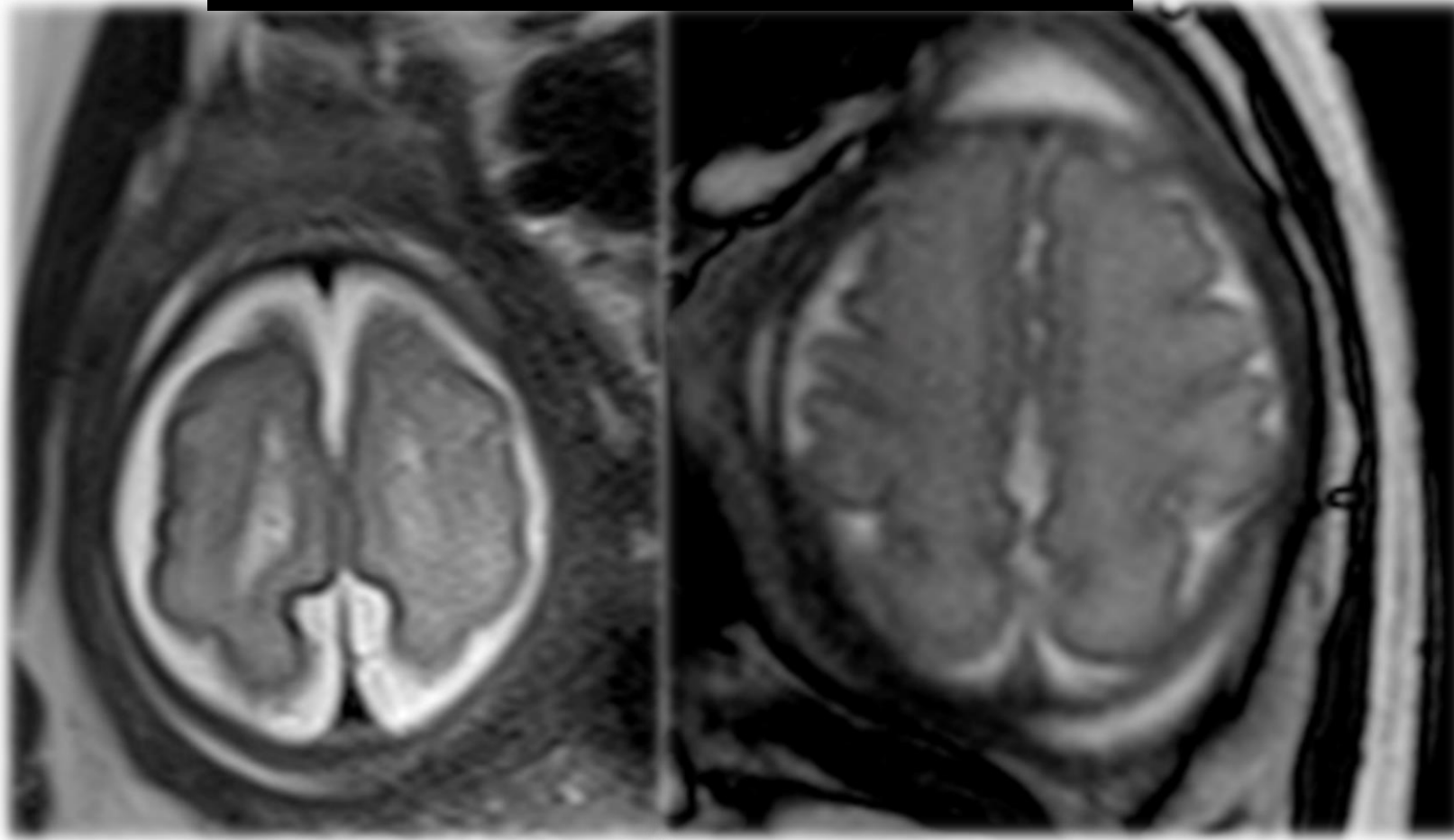
# CASE 2

Case 2 X Normal



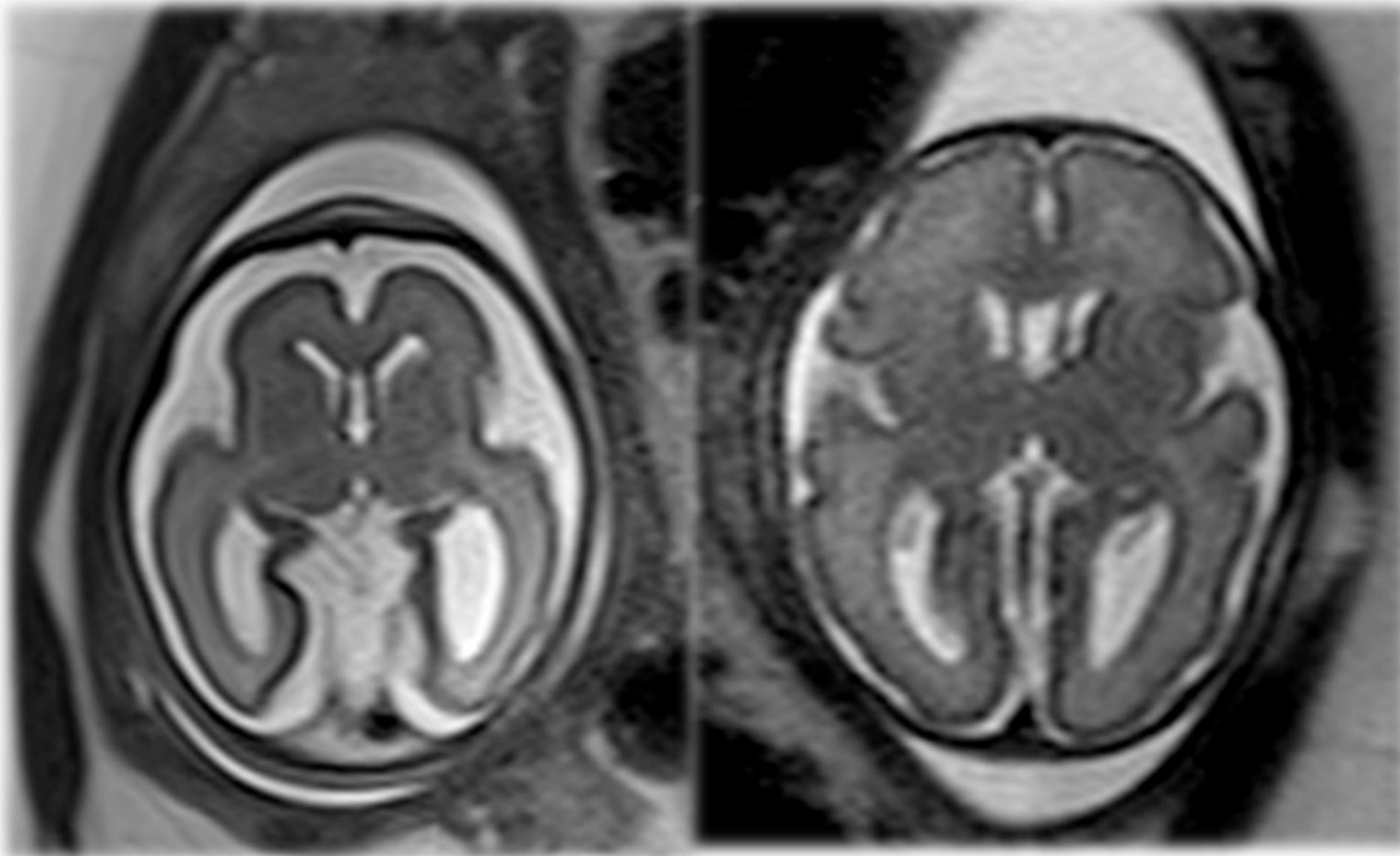
# CASE 2

Case 2 X Normal



# CASE 2

Case 2 X **Normal**



Patricia Szejnfeld

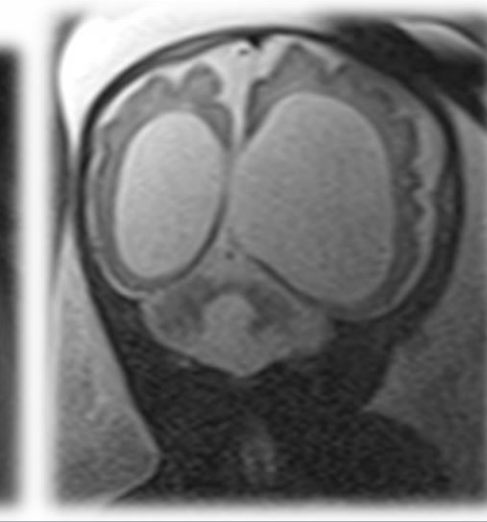
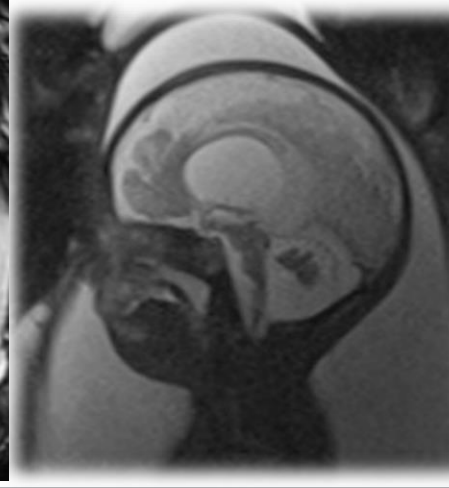
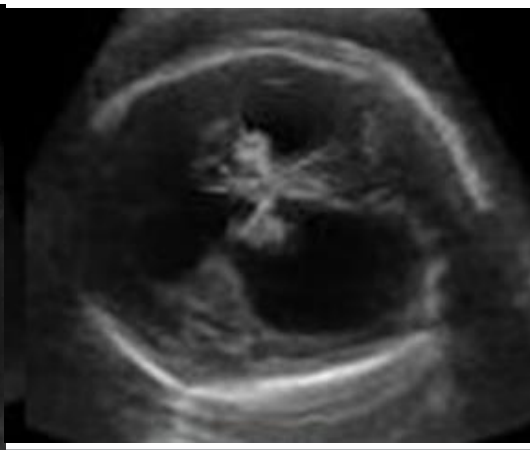
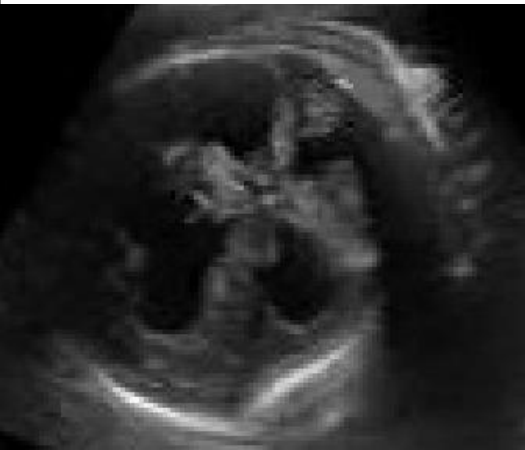


# Case # 7

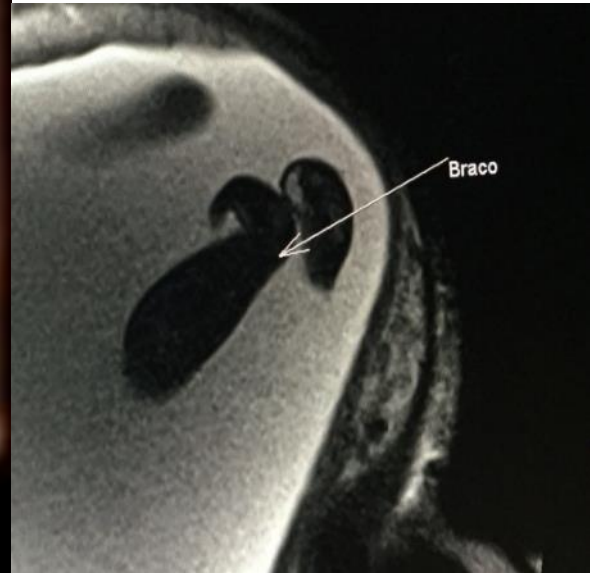
Idade gestacional ao nascimento 36 semanas

Perimetro cefálico 35 cm (microcefalia compensada pela ventriculomegalia). Morte - 48 hours

Um hemisfério cerebral fixado em formol, pesando 112g,



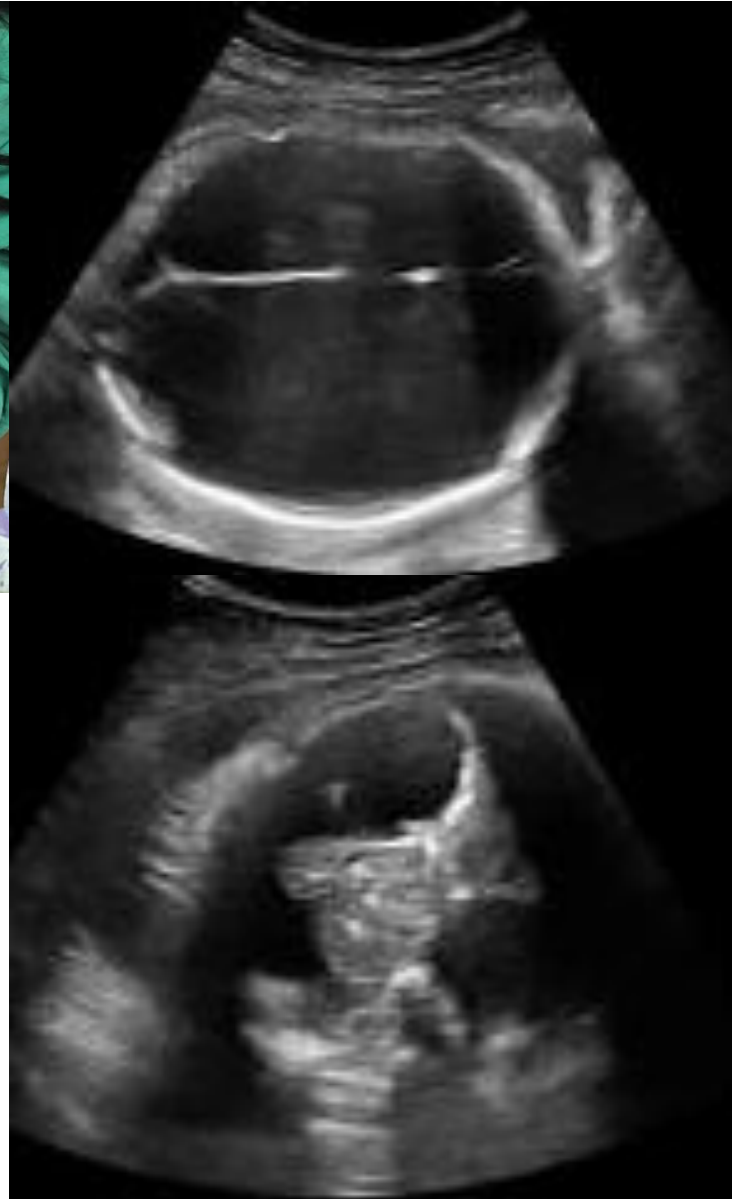
# Fetal akinesia deformation and Polyhydramnios - neurological sequelae



# Fetal akinesia deformation and Polyhydramnios - neurological sequelae



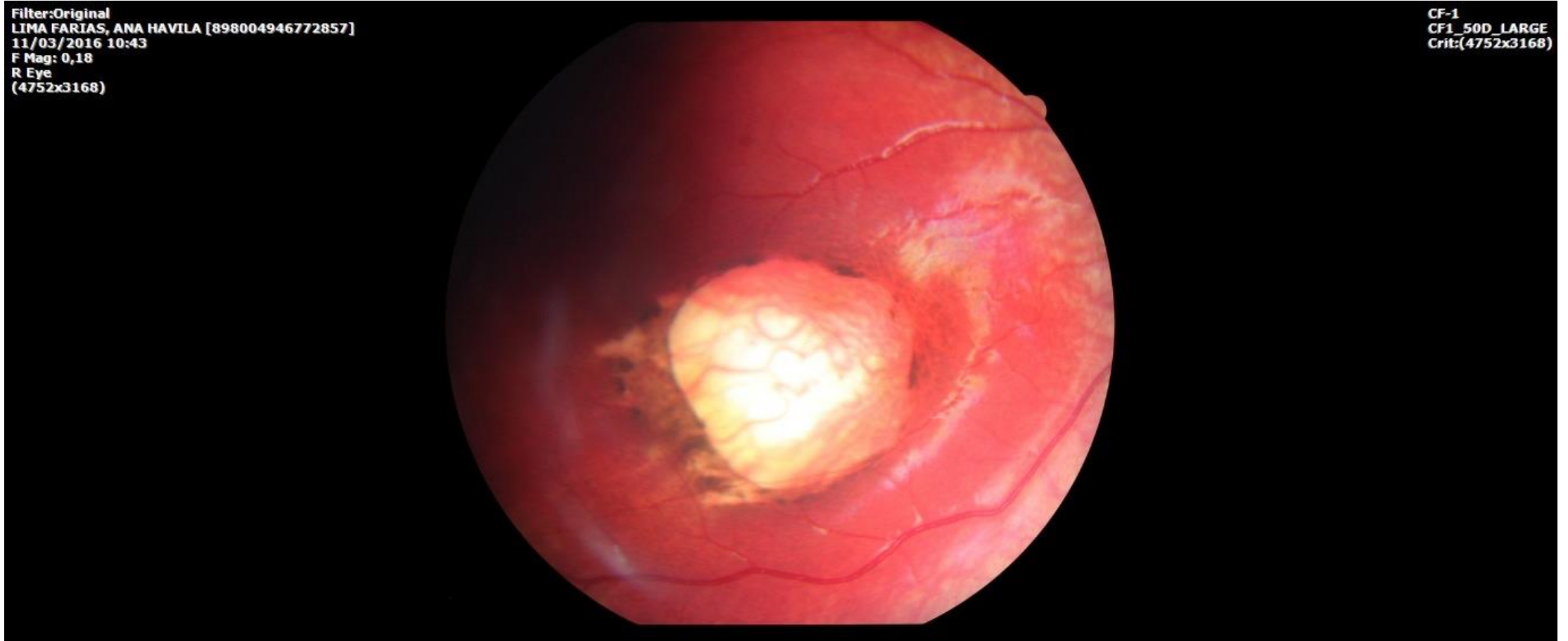
# Fetal screening: Is justified?

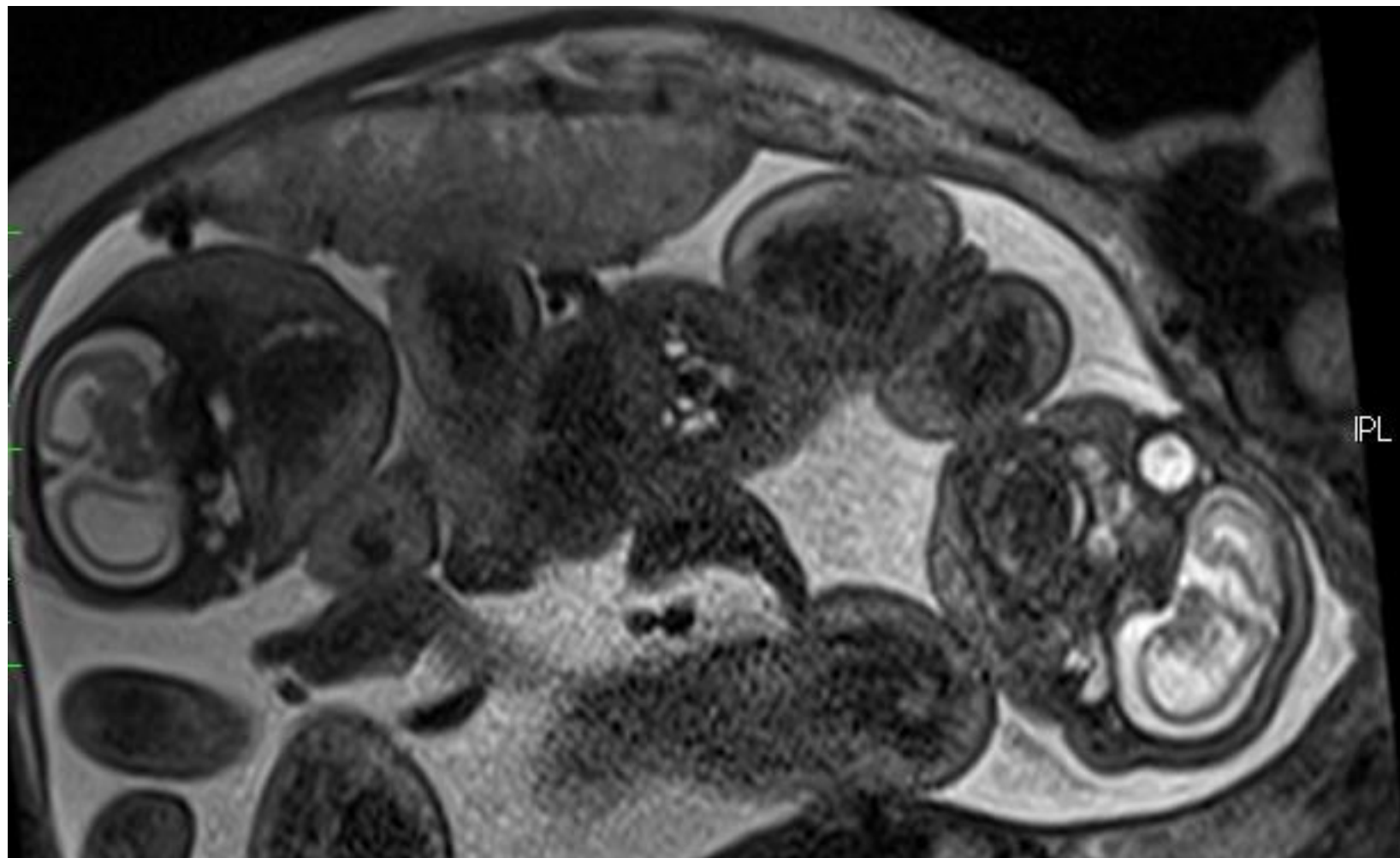


PCR + amniotic fluid



# placa de atrofia corioretiniana em região macular







# Hospital Pedro I – Campina Grande





Grupo de terapia com mães de bebês com microcefalia

# E é só microcefalia????



# E é só microcefalia????





Mães de bebês com microcefalia têm dificuldade para receber benefício do INSS

A demora para atendimento ainda é consequência da greve dos peritos do INSS.

GLOBOPLAY.GLOBO.COM

**Incidência maior nas periferias**

**Mães na maioria extremamente pobres**





# Podemos continuar de braços cruzados????



- A situação é mais grave do que está sendo vincunlada
- Qualquer situação atípica deve ser investigada
- Mortes inexplicadas estão ocorrendo em todas as faixas etárias
- Sabemos muito pouco desse vírus que está sendo considerado um dos piores vírus identificados nos últimos tempos
- Qualquer um pode ser vítima, incluindo nossas famílias (hoje e no futuro)
- O ChikV tem um alto potencial de lesão articular, aumentando o risco de doenças que culminem no afastamento do trabalho e necessidade de reabilitação (Sobrecarga do setor de reabilitação e da Previdência -- Geração de sequelados (microcefalia, encefalites, artrose, síndrome túnel do carpo...))
- É essencial que a sociedade civil, em ações conjuntas com gestão pública, universidades, estudantes vão para as ruas. Estamos em situação de Guerra.
- Cruzar os braços significa que seremos co-responsáveis por essas crianças sequeladas e pelas mortes ocorridas.
- ESTE É O MOMENTO PARA ENTENDER A DOENÇA, ANTES QUE ELA FIQUE FORA DO CONTROLE
- AS CRIANÇAS JÁ NASCIDAS SÃO VITIMAS E PRECISAMOS ESQUECER QUE SÃO NÚMEROS. É NOSSO DEVER OFERECER ASSISTÊNCIA DIGNA

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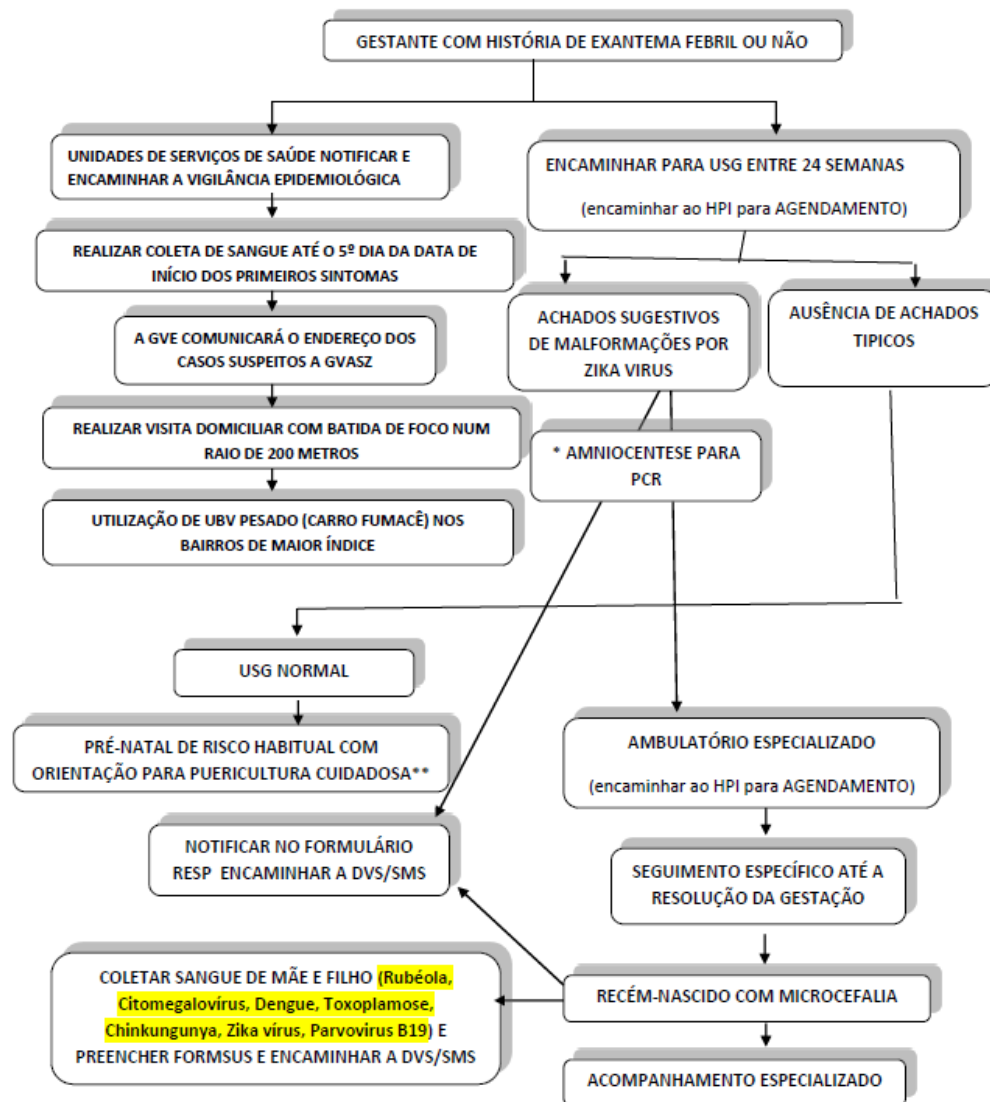
## O que o nosso grupo já descobriu?

- Parada de migração e proliferação dos neurônios motores
- Presença de células embrionárias
- Mudança em proteína

Qual nosso diferencial?

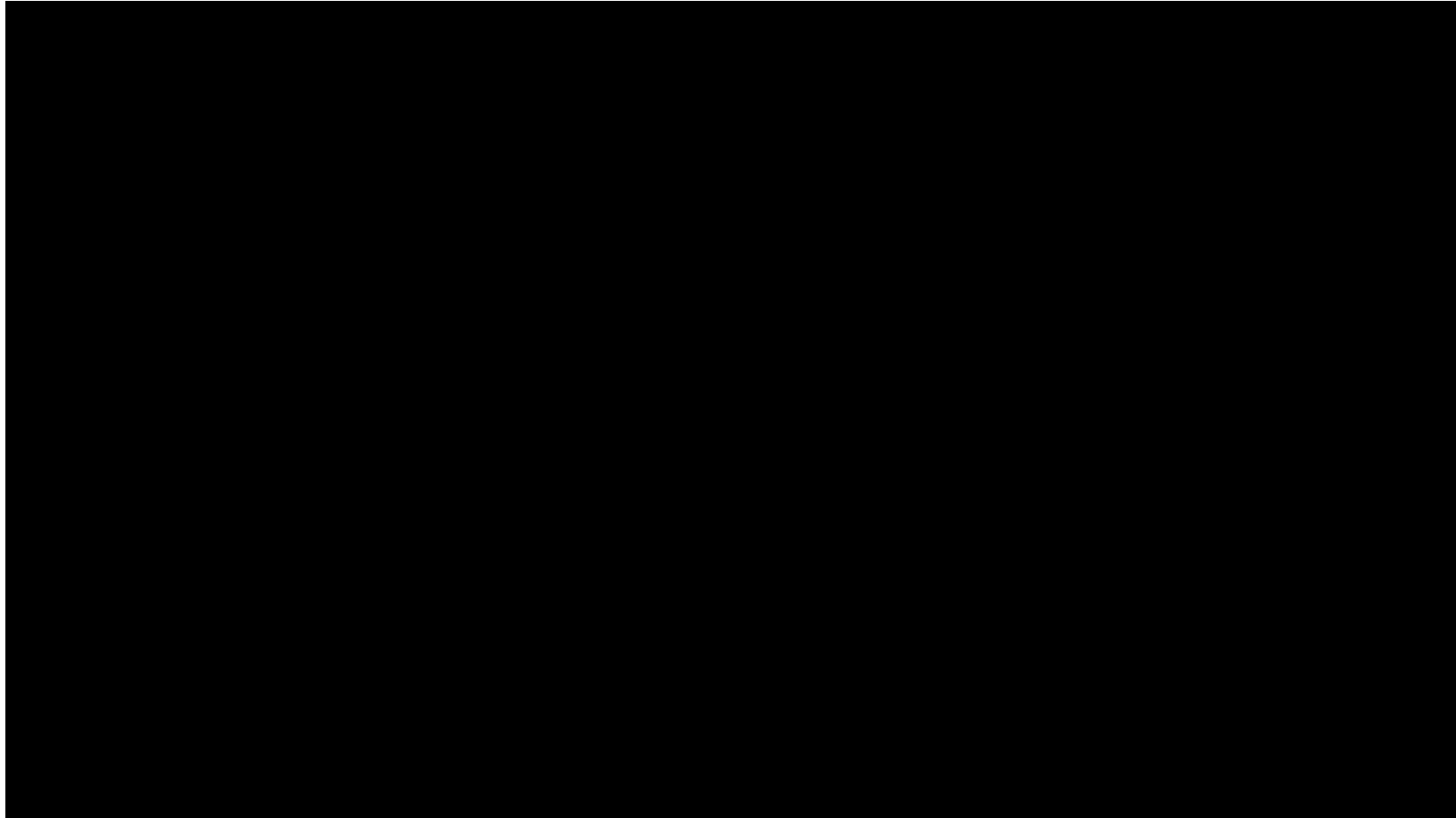
Quais os próximos passos?

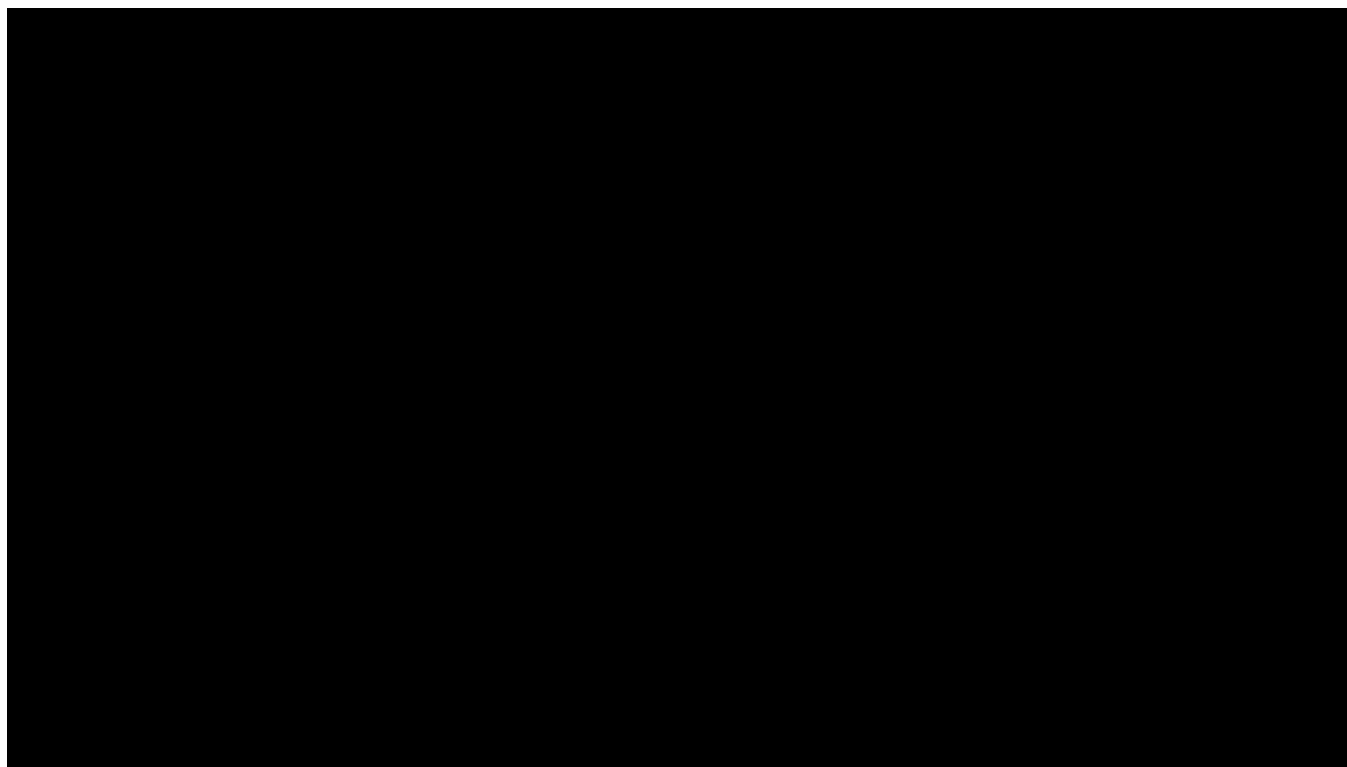
PRECEDIMENTO OPERACIONAL PADRÃO PARA MONITORAMENTO E ACOMPANHAMENTO DE CASOS DE MICROCEFALIA ASSOCIADA A EXANTEMA



# Hospital Pedro I – Campina Grande

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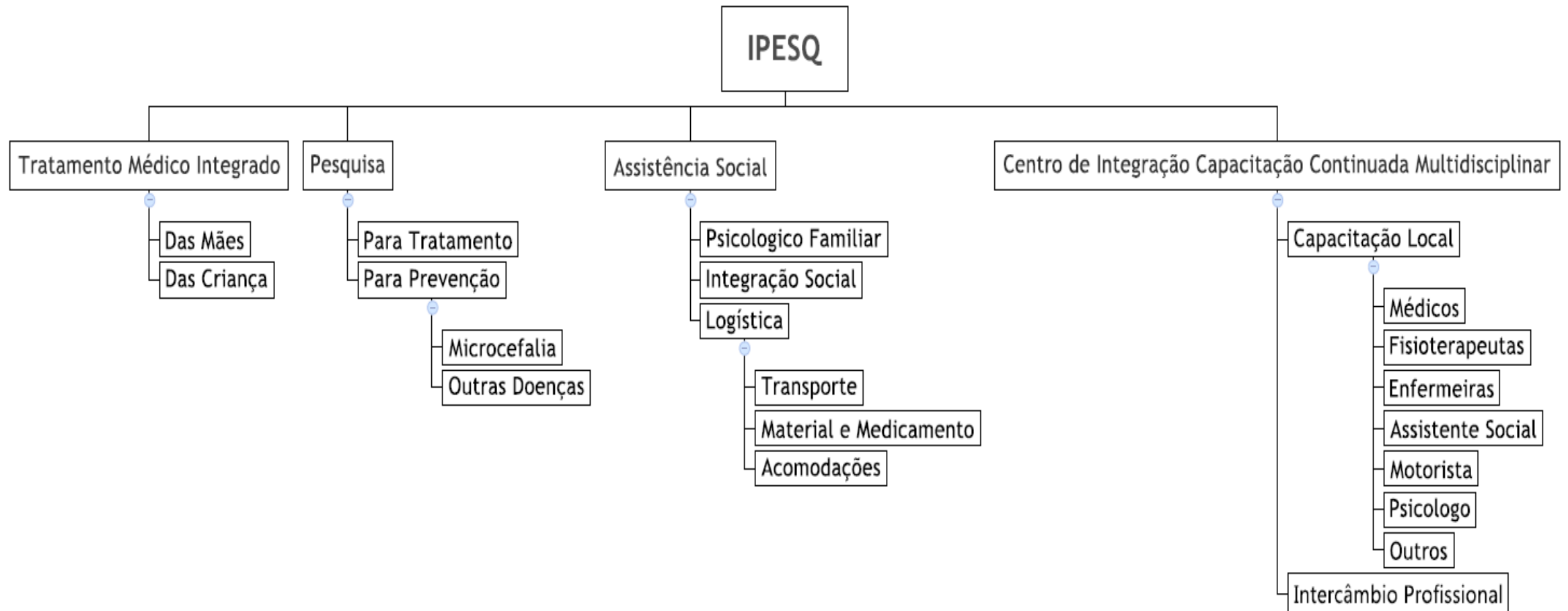




# Por que ainda não temos evidências?

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- Investimento em pesquisas
- Equipamentos necessários
- Sorologia eficiente e disponível
- Centro especializado para assistência e pesquisa





# Agradecimentos

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- Ultrasound – volunteer
- Amniocentesis - PMCG
- Magnetic Resonance - PMCG
- Ophthalmologist - volunteer
- Neurologist - volunteer
- Legist doctor – volunteer
- Radiologist – volunteer (FIDI e Instituto D’Or )
- Transportation – own resources
- Análise do material enviado – Fiocruz e UFRJ

asomelo@gmail.com



**AEDES AEGYPTI**



***IPESQ***

INSTITUTO DE PESQUISA  
PROFESSOR JOAQUIM AMORIM NETO