Os Arbovírus

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Depto de Microbiologia- ICB/USP

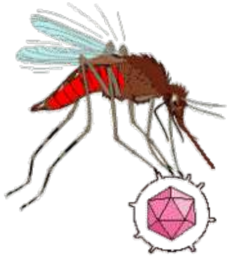
Arboviroses

ARBOVÍRUS: *arthropode-borne viruses*

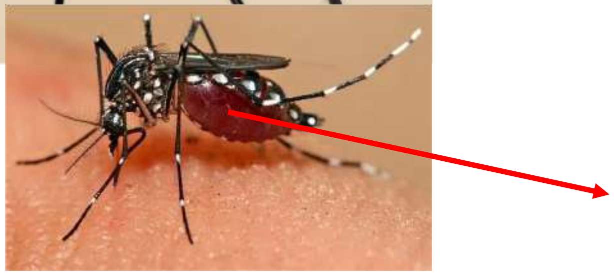
Transmissão

São ARBOVÍRUS

Arthopod Borne Viruses



Aedes aegypti



- Febre amarela
- Dengue
- Zika

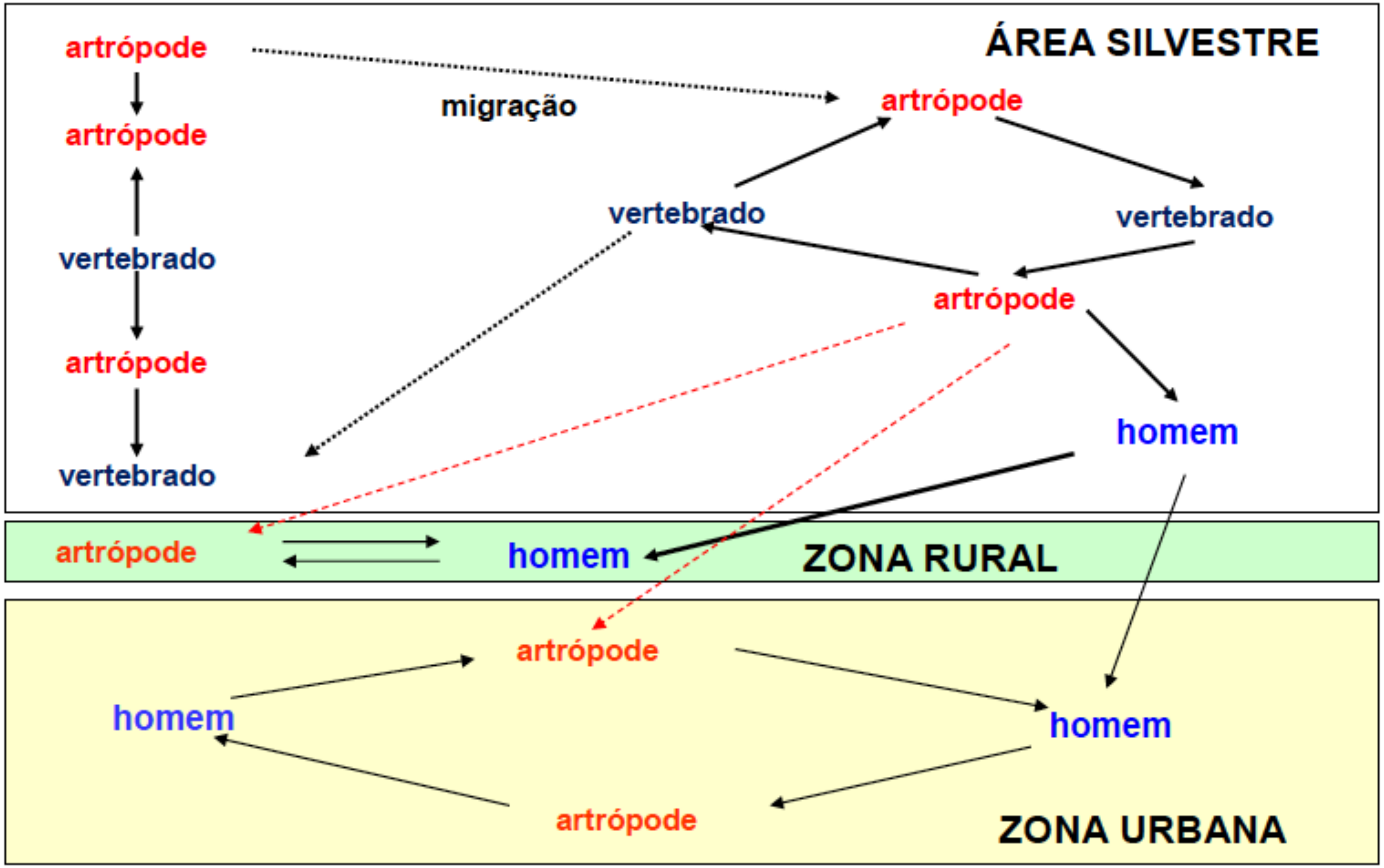
→ *Flaviviridae*
Arbovírus do Grupo B

- Chikungunya

→ *Togaviridae*
Arbovírus do Grupo A

Arboviroses

Ciclo de transmissão



Arboviroses

Família *Flaviviridae*

- Conhecida desde o início do século.
- Seu primeiro membro, o vírus da febre amarela (YF), foi reconhecido como um agente filtrável, em 1927.
- O nome tem origem na palavra latina *flavus* = amarelo.
- Possui quatro gêneros (60 espécies), com vírus que infectam humanos e animais:
  - Flavivírus
  - Pestivírus
  - Hepacivírus
  - Pegivírus

Arboviroses

O gênero *Flavivírus*

- **Pelo menos 73 sorotipos ≠, 40 já foram associados a doenças humanas.**
- **Os mais importantes são:**

Dengue 1
Dengue 2
Dengue 3
Dengue 4
} Sorogrupo DEN
62 a 77% de identidade

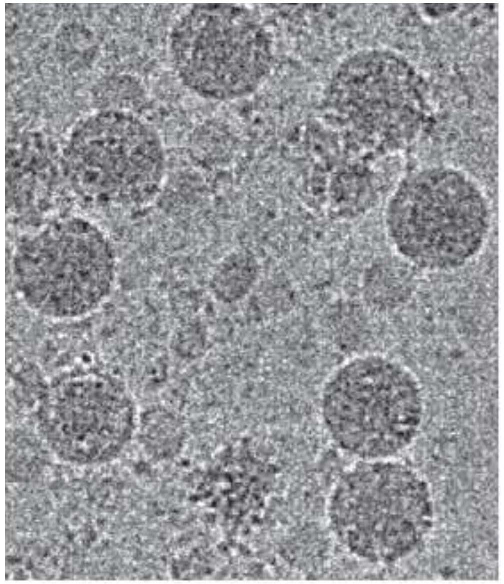
Febre amarela → Sorotipo único

West Nile
Encefalite de Saint Louis
Encefalite Japonesa
} Sorogrupo JE
72 a 93% de identidade

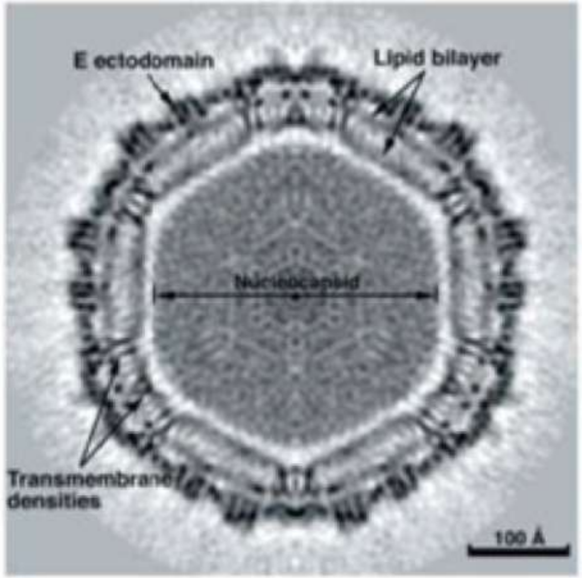
"Tick-borne" encefalite → Sorogrupo TBE
77 a 96% de identidade

FLAVIVIRIDAE

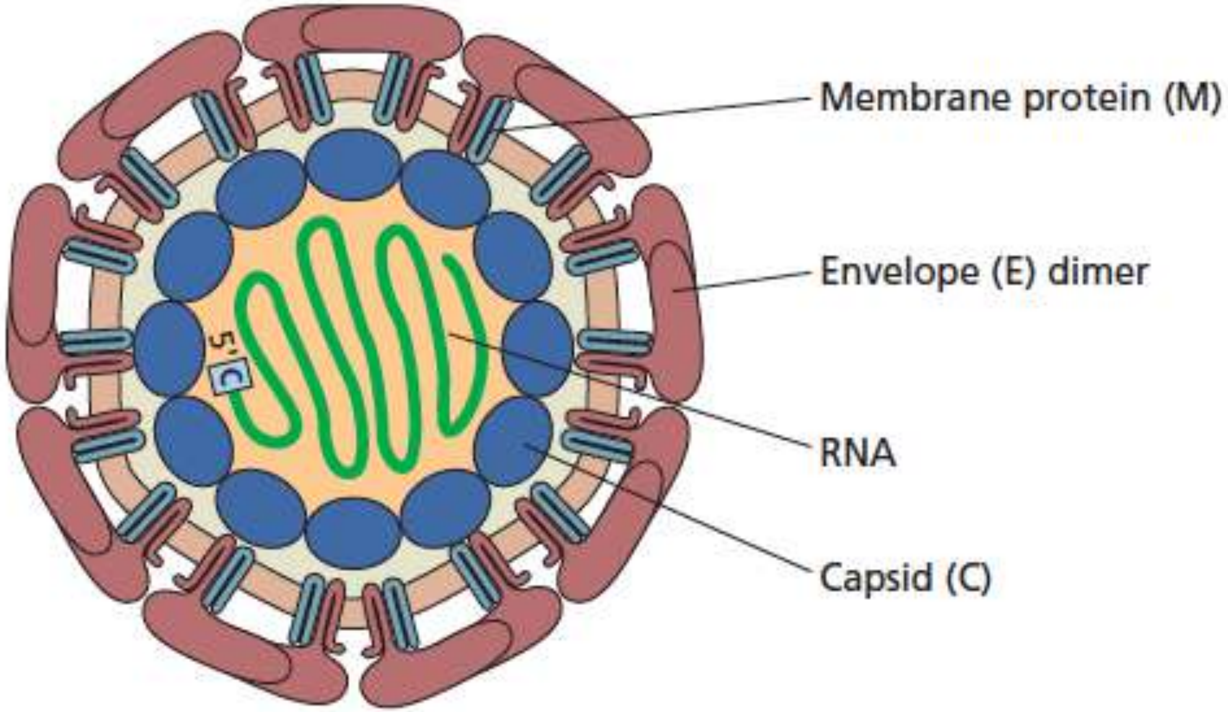
Envelopados, icosaédricos, (+)ss RNA



cryo-electron microscopy (cryo-EM)



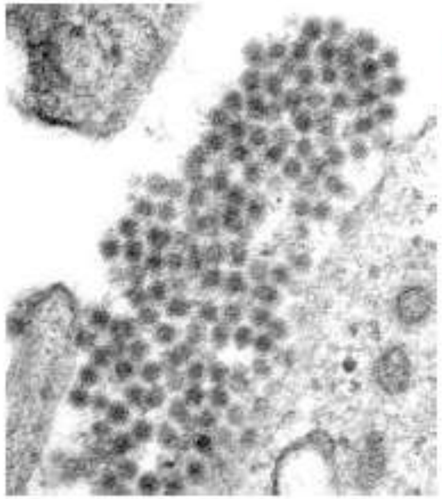
Zhang et al., Nat Struct Biol., 2003



Flint, Racaniello, Rall, Skalka. Principles of Virology. 2015

40 a 60 nm

Arboviroses



Febre amarela
Dengue
Zika

Chikungunya: Togaviridae

Família:	*Flaviviridae*
Gênero:	*Flavivírus*
Transmissão:	vetor artrópode - *Haemagogus janthinomis e Aedes aegypti*
Hospedeiros:	*Silvestre - macacos; Urbano - homem*
Partículas virais:	Esféricas 45 nm, envelopadas
Proteínas estruturais:	glicoproteína E ; nucleoproteína: C; membrana: M
Genoma:	ss-RNA polaridade positiva

FLAVIVIRIDAE

***Flavus, latim*=amarelo**

Family *Flaviviridae*

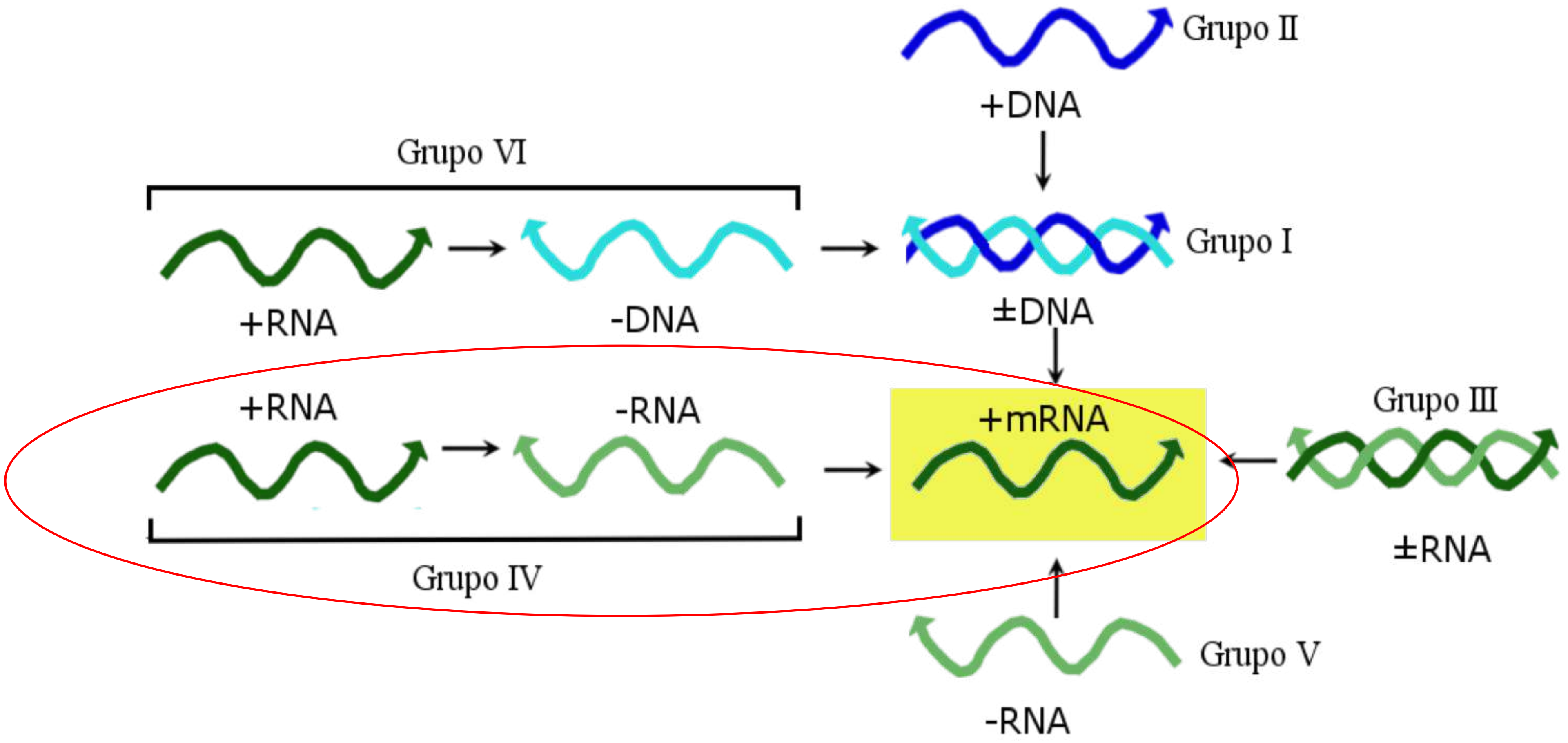
Genera	Examples
Flavivirus	Yellow fever virus
	Dengue virus
	West Nile virus
Hepacivirus	Hepatitis C virus
	GB virus B
Pestivirus	Bovine viral diarrhea virus
Pegivirus	GB virus A, C, D

Flint, Racaniello, Rall, Skalka. Principles of Virology. 2015

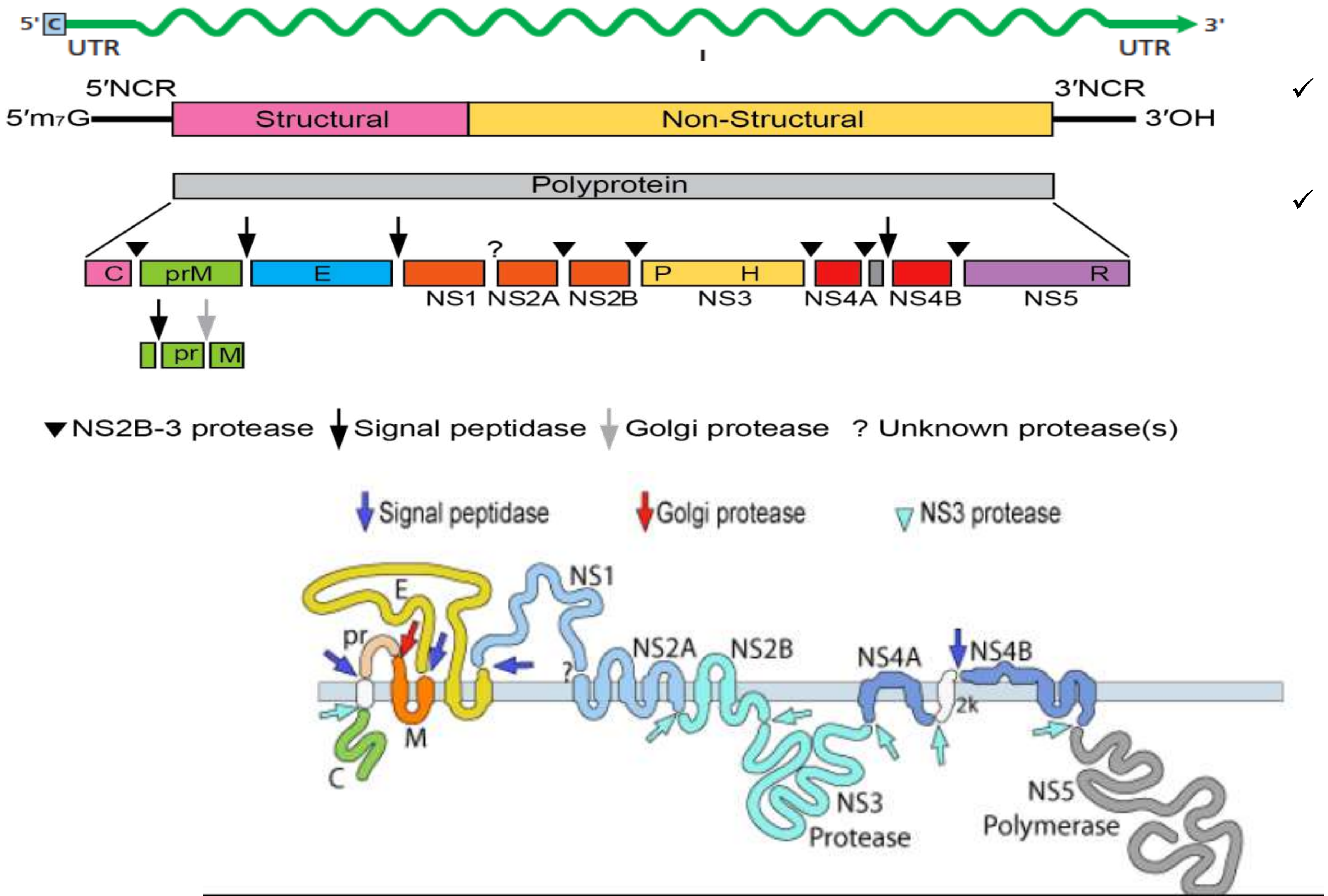
- ✓ Vírus da Febre amarela
- ✓ Vírus da Hepatite C
- ✓ Vírus da Dengue
- ✓ Vírus da Zika
- ✓ Vírus da encefalite japonesa
- ✓ Vírus da encefalite St Louis
- ✓ Vírus do Oriente do Nilo *(West Nile)*
- ✓ Vírus da encefalite do carrapato

FLAVIVIRIDAE

(+)ss RNA, classe IV de Baltimore



FLAVIVIRIDAE: (+)ss RNA, 11 Kb, RNA 5’CAP



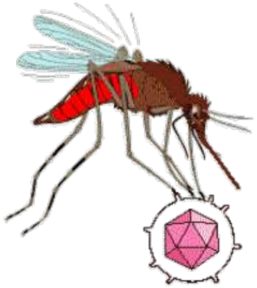
- ✓ 3 genes prot. estruturais
- ✓ 7 genes prot. não-estruturais

Vírus da Febre amarela

1888, Carlos Finlay, Cuba

1901, Walter Reed e James Carroll

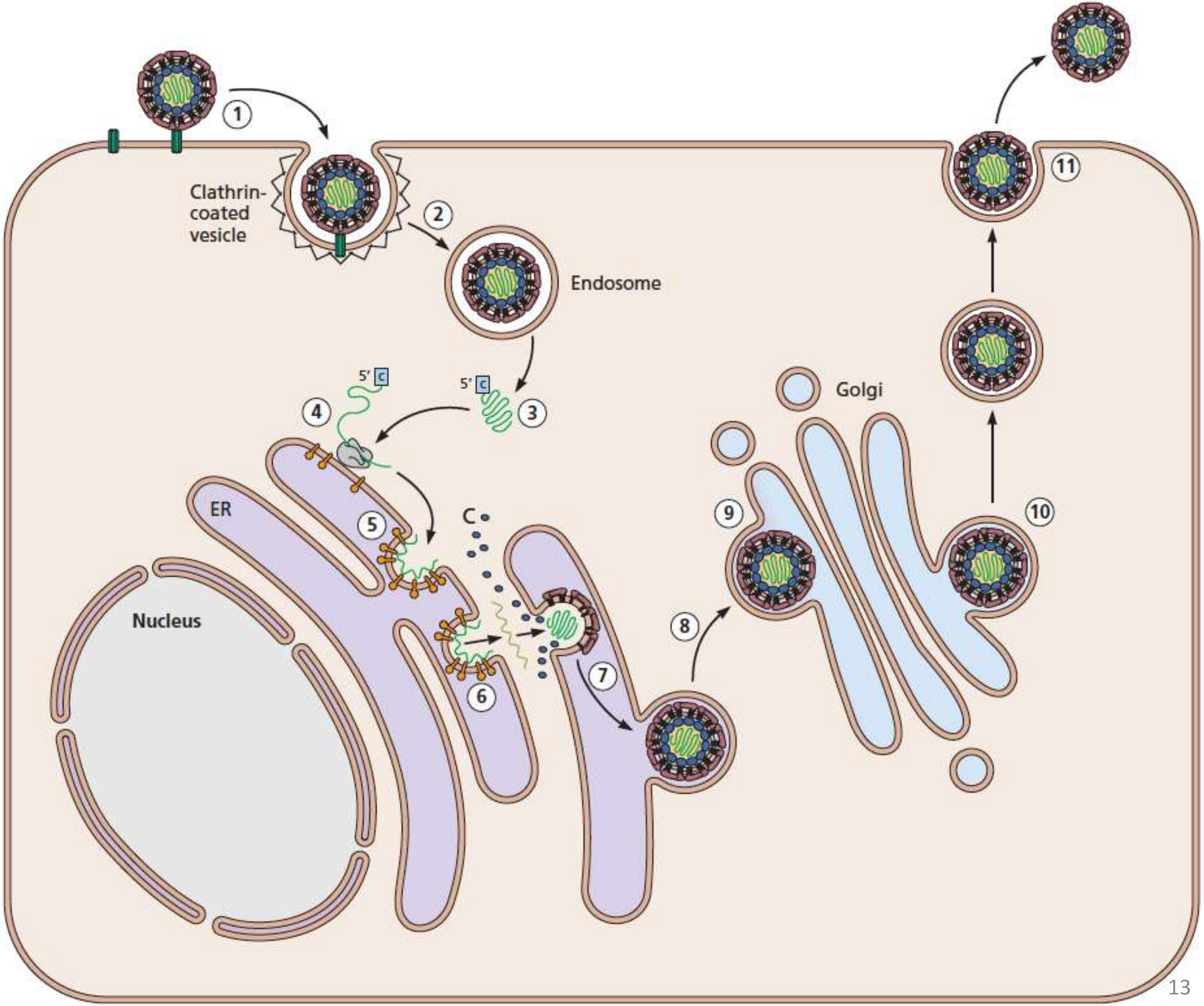
1903, Oswaldo Cruz, RJ, Brasil



Ciclo Viral

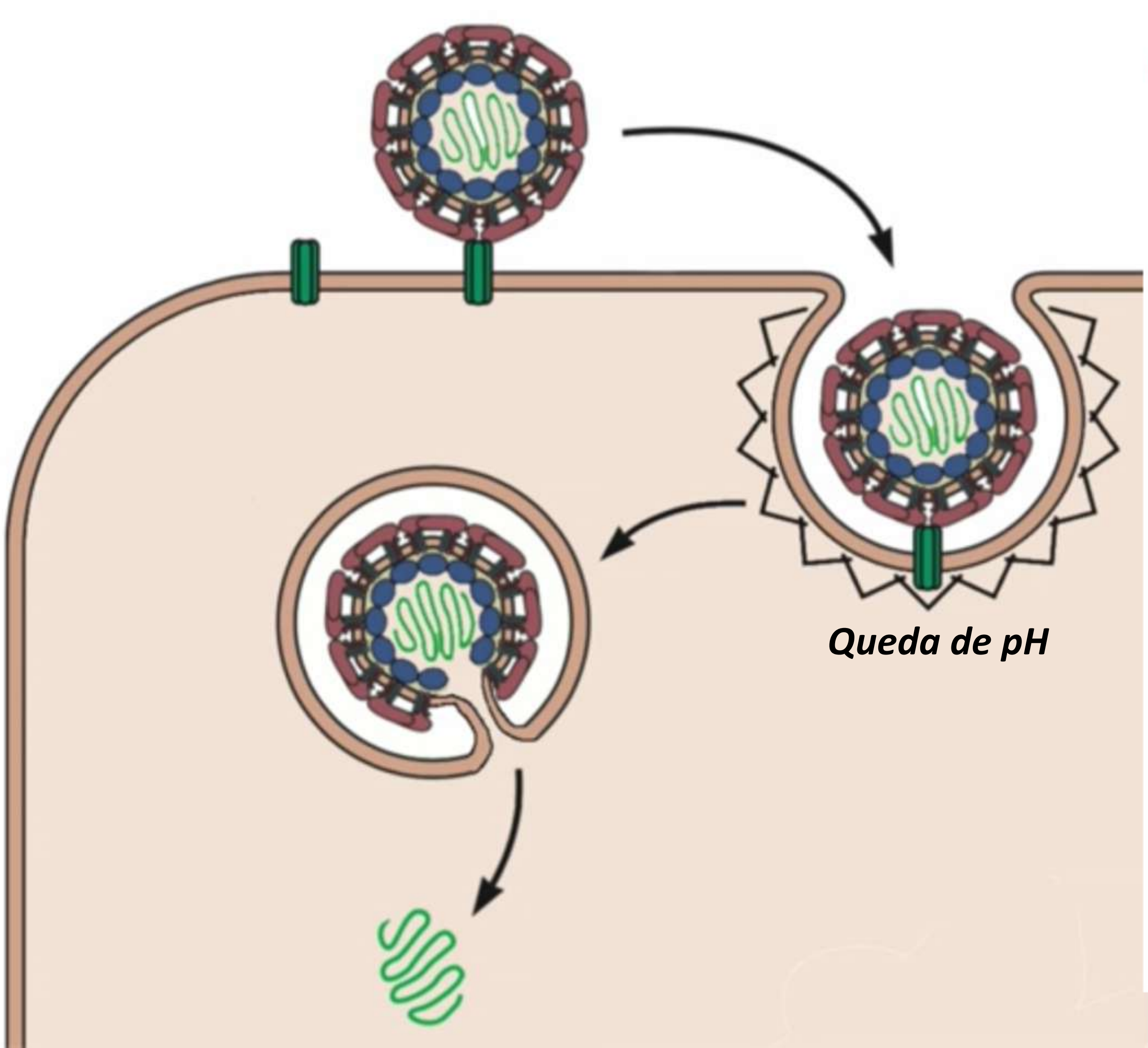
Etapas

- ✓ Adesão: (1)
- ✓ Entrada e desnudamento: (2, 3)
- ✓ Replicação e síntese de proteínas virais: (4, 5, 6)
- ✓ Montagem: (7, 8)
- ✓ Maturação: (9,10)
- ✓ Liberação: (11)



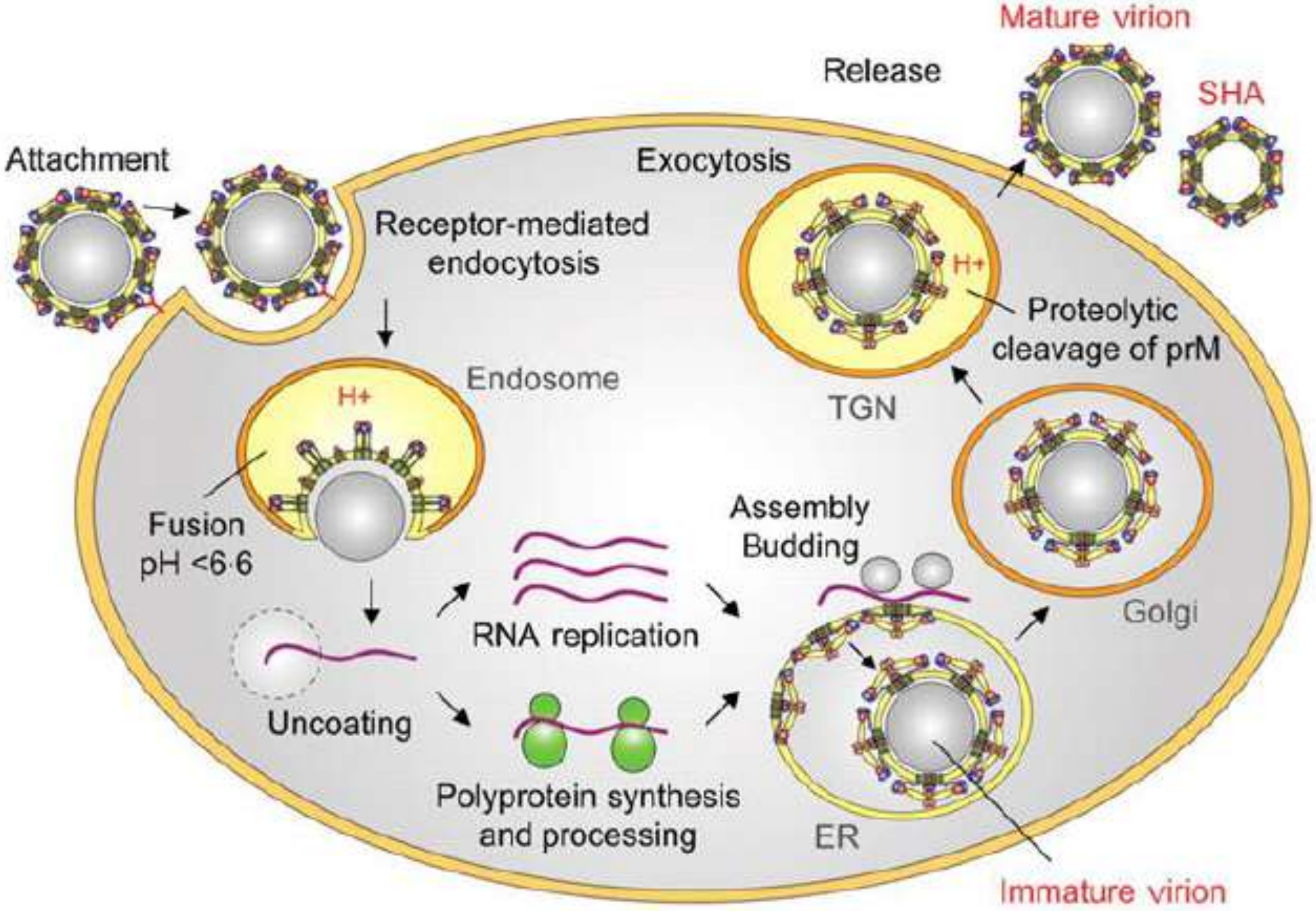
Flint, Racaniello, Rall, Skalka. Principles of Virology. 2015

Adesão e desnudamento



Arboviroses

Replicação dos Flavivírus



doi: 10.1099/vir.0.82210-0 *J Gen Virol October 2006 vol. 87 no. 10 2755-2766*

Etapas

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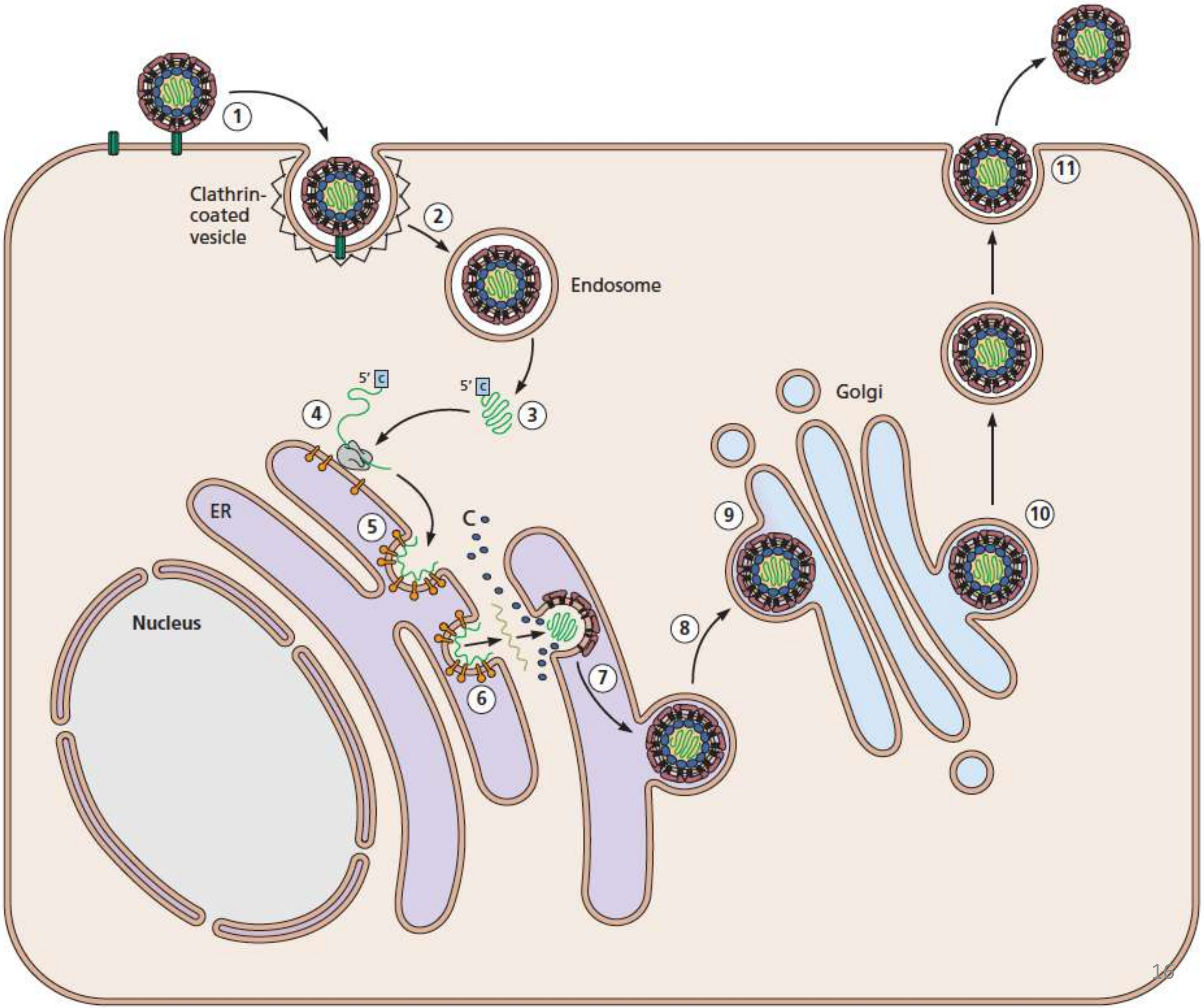
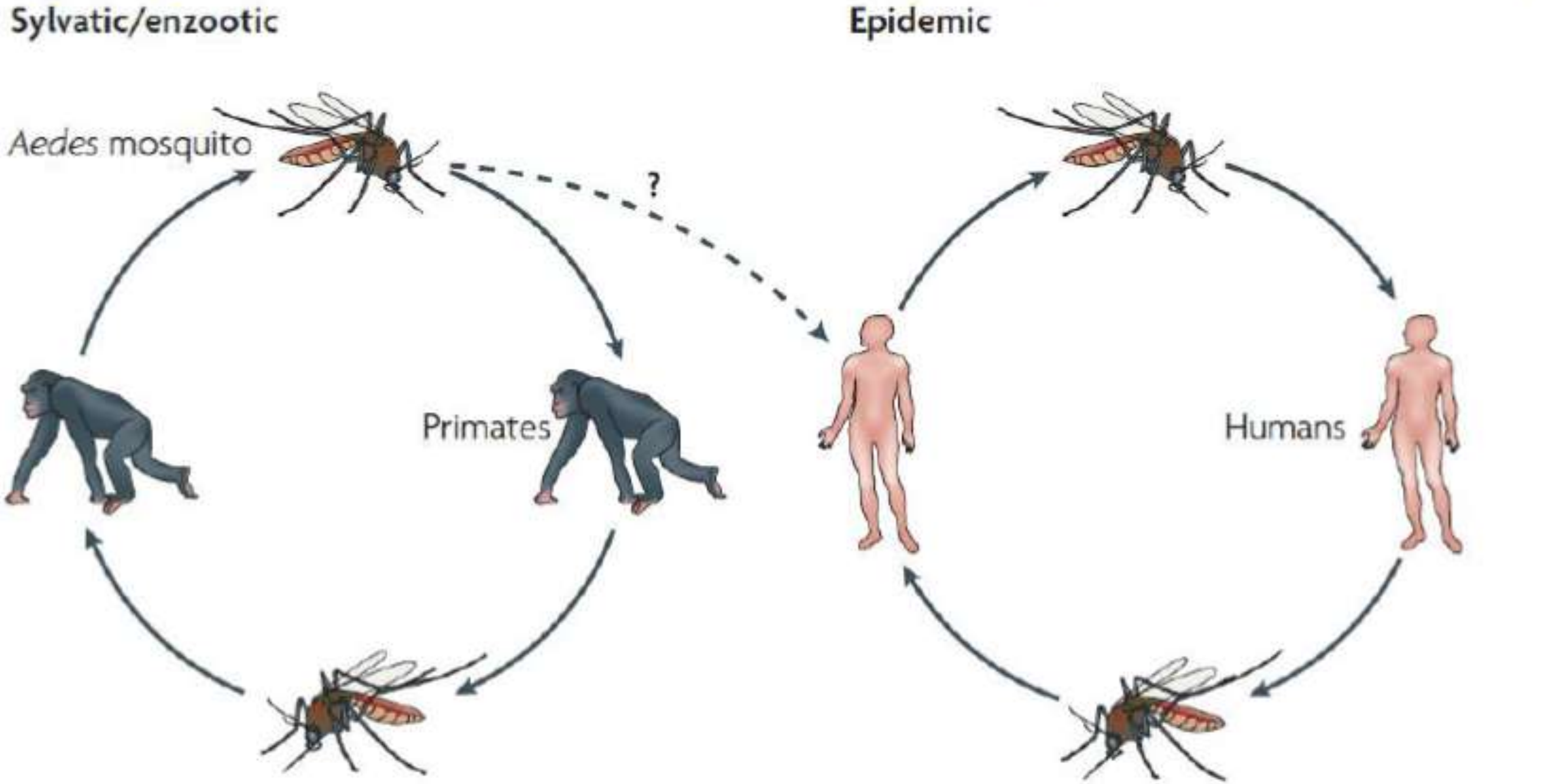


Arboviroses

Replicação e transmissão do DENV, YFV (e outros arbovírus)

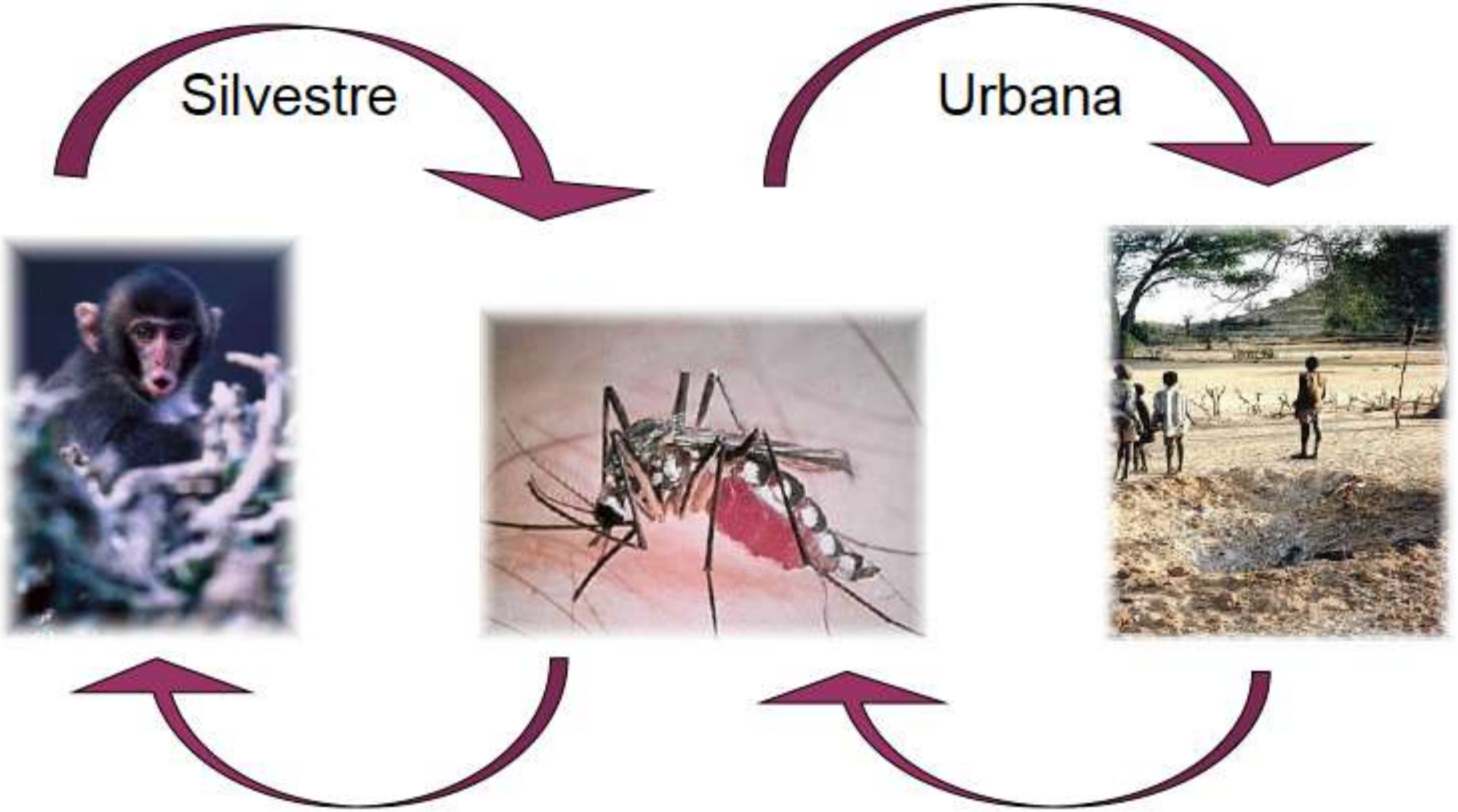


1- O mosquito infectado pica o hospedeiro e libera o vírus pela saliva.
2- O vírus replica-se nos órgãos alvos do hospedeiro.
3- O vírus infecta os linfócitos e tecidos linfáticos.
4- O vírus é liberado na circulação sanguínea.

5- Um segundo mosquito pica o hospedeiro infectado.
6- O mosquito ingere o vírus com o sangue. O vírus multiplica-se no trato digestivo do mosquito.
7- O vírus passa para as glândulas salivares, replica-se e será liberado da próxima vez que o inseto se alimentar.

Arboviroses

Febre amarela

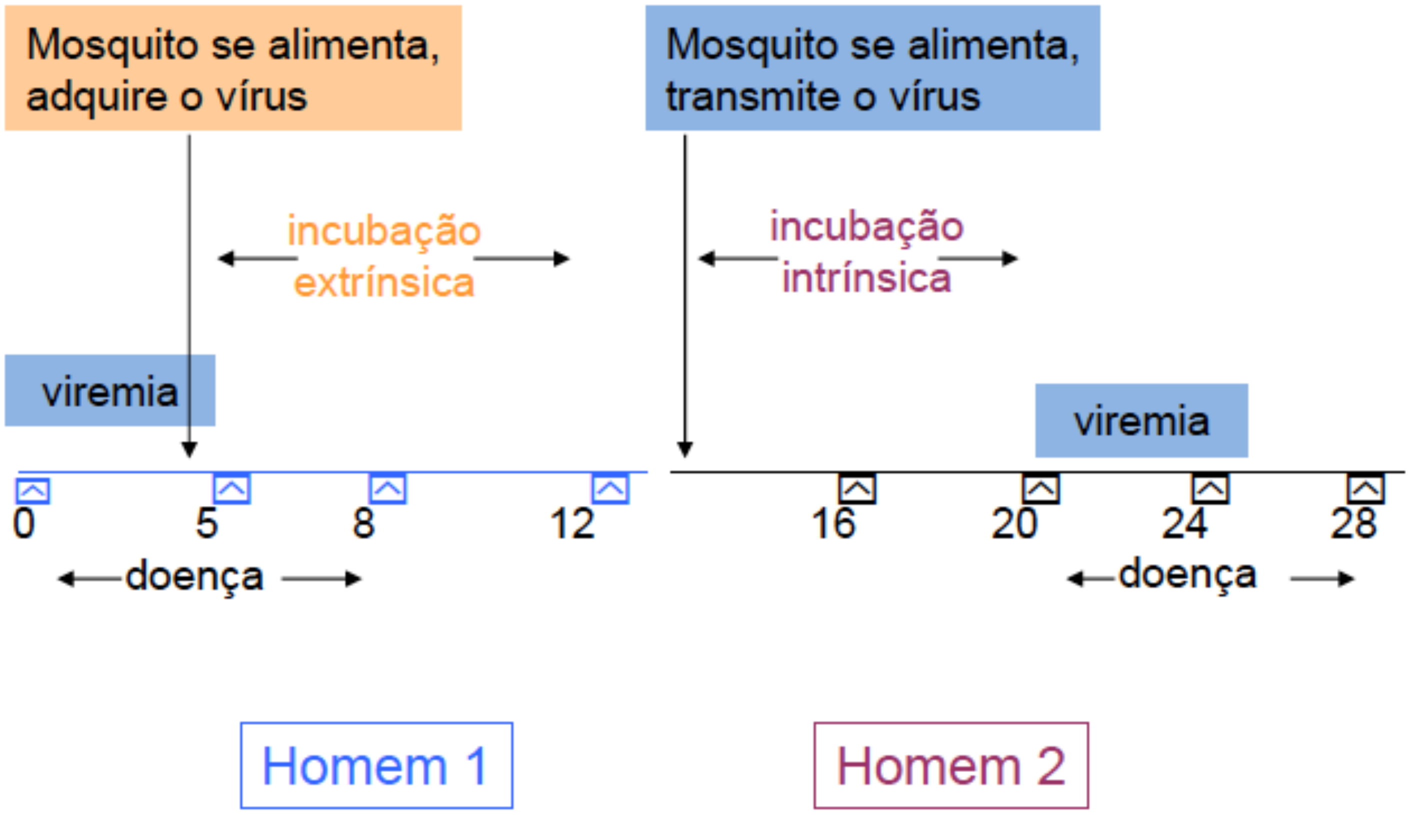


Haemagogus janthinomis
Aedes albopictus

Aedes aegypti

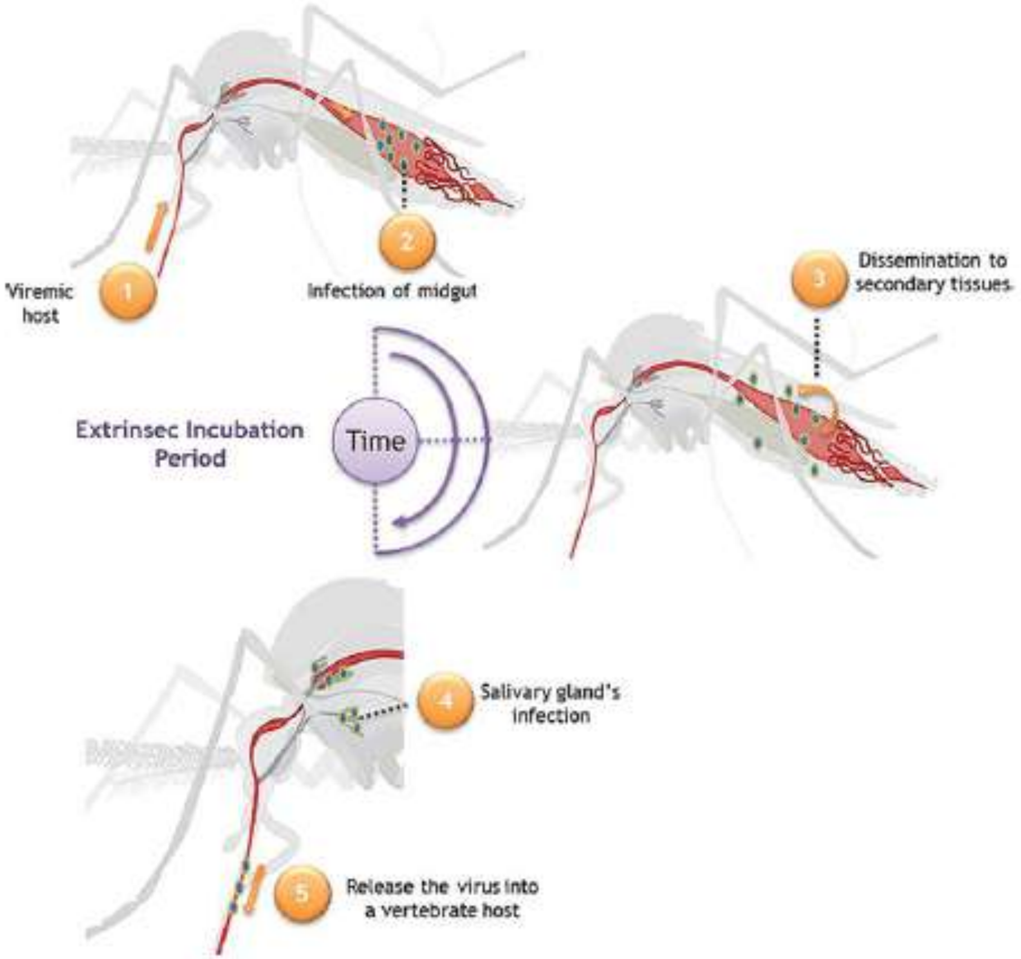
Arboviroses

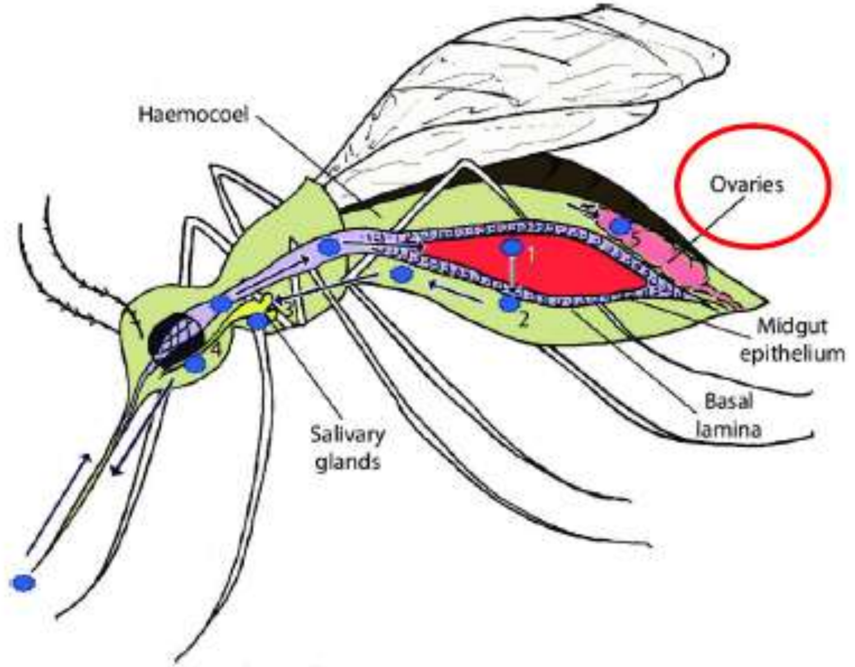
Transmissão da dengue por *A. aegypti*



Arboviroses

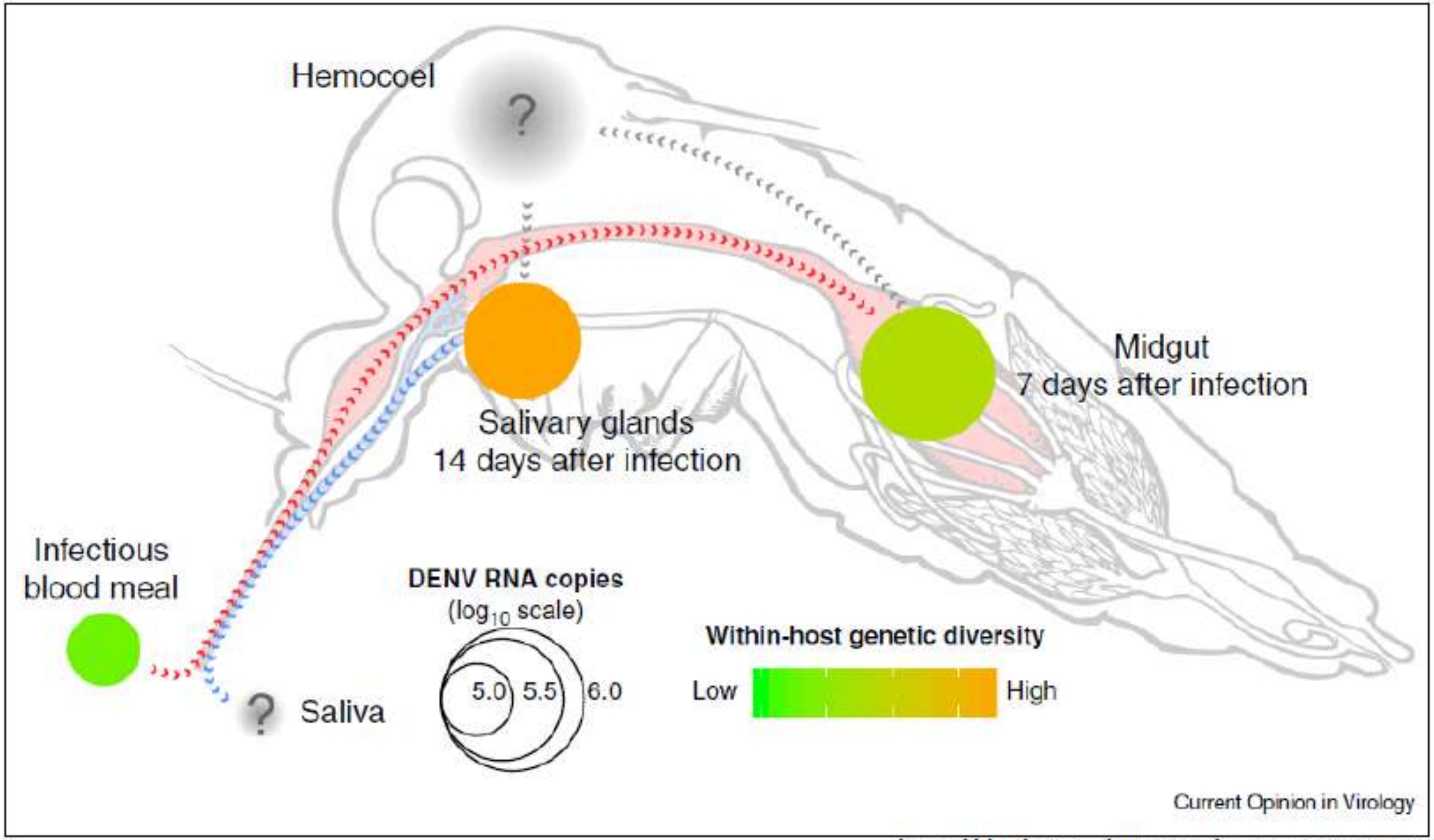
Incubação extrínseca





Arboviroses

Incubação extrínseca



http://dx.doi.org/10.1016/j.coviro.2016.07.013

Arboviroses

Prevenção

- Controle do hospedeiro artrópode



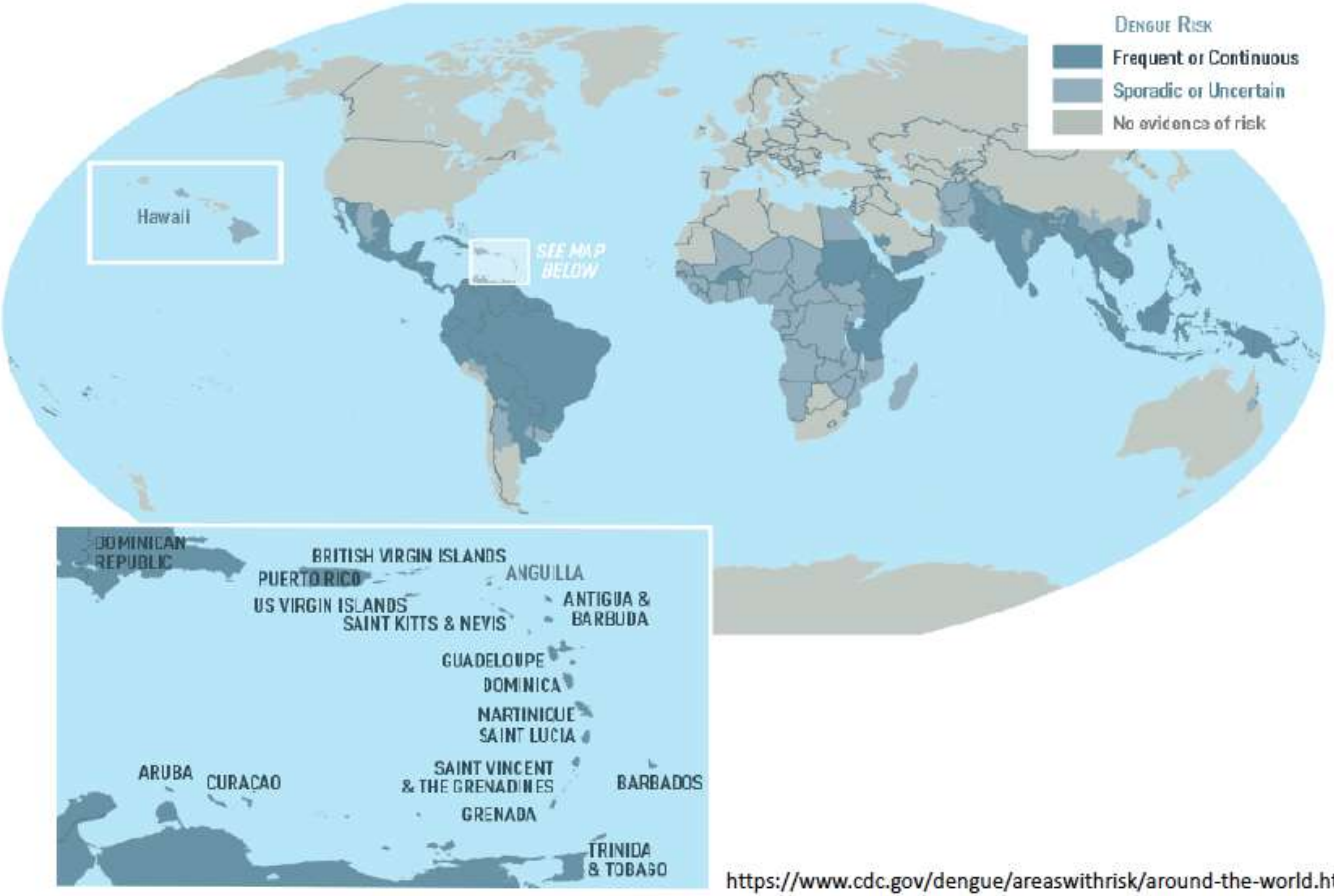
Arboviroses

Prevenção

1970

Arboviroses

Dengue



https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html

Arboviroses

Febre Amarela

https://www.cdc.gov/yellowfever/maps/south_america.html

Arboviroses

Prevenção

Febre Amarela

- Vacinação preventiva da população:

  Vacina de vírus atenuados 17D

Zika: início

509

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.

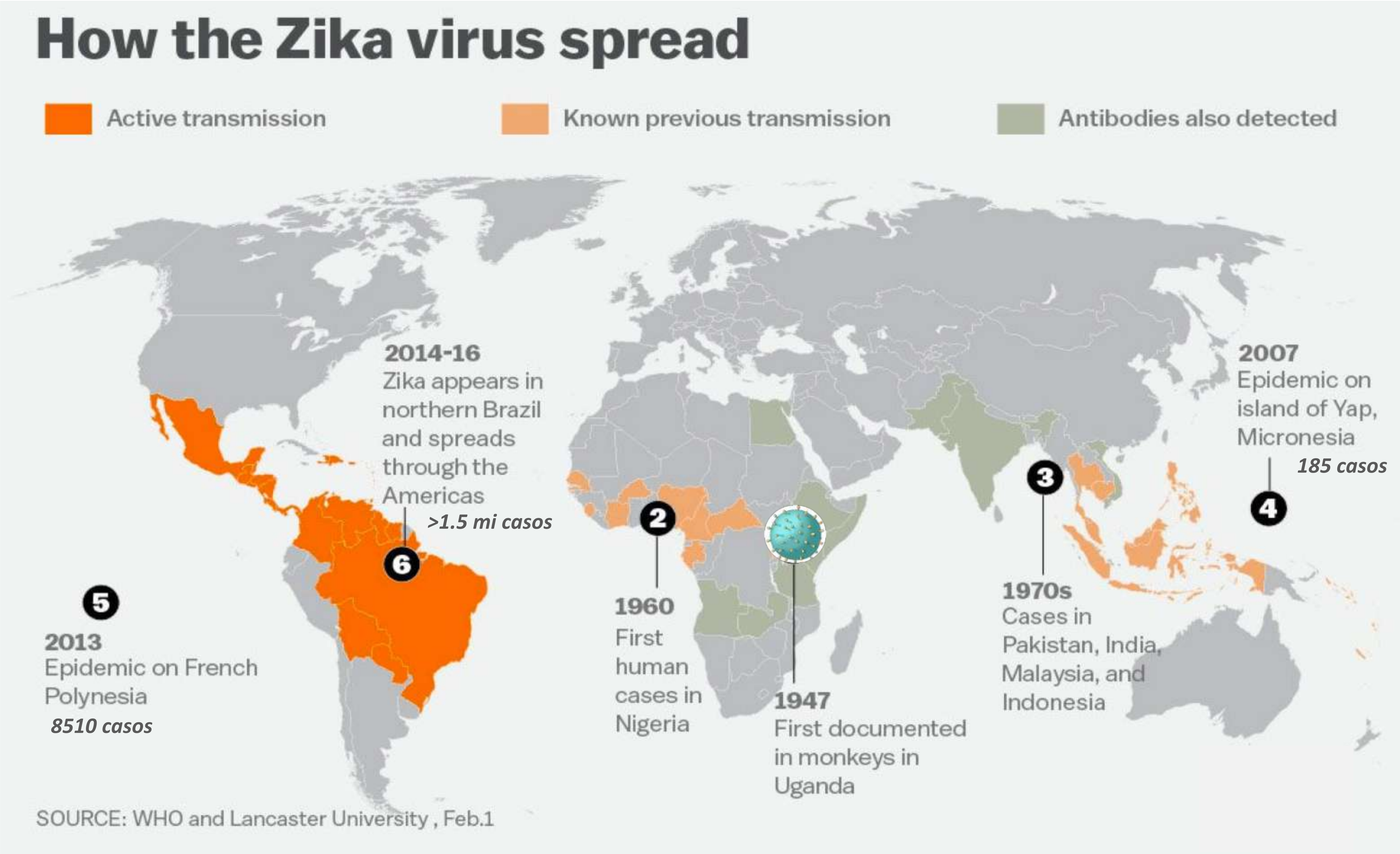
AND

A. J. HADDOW,

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

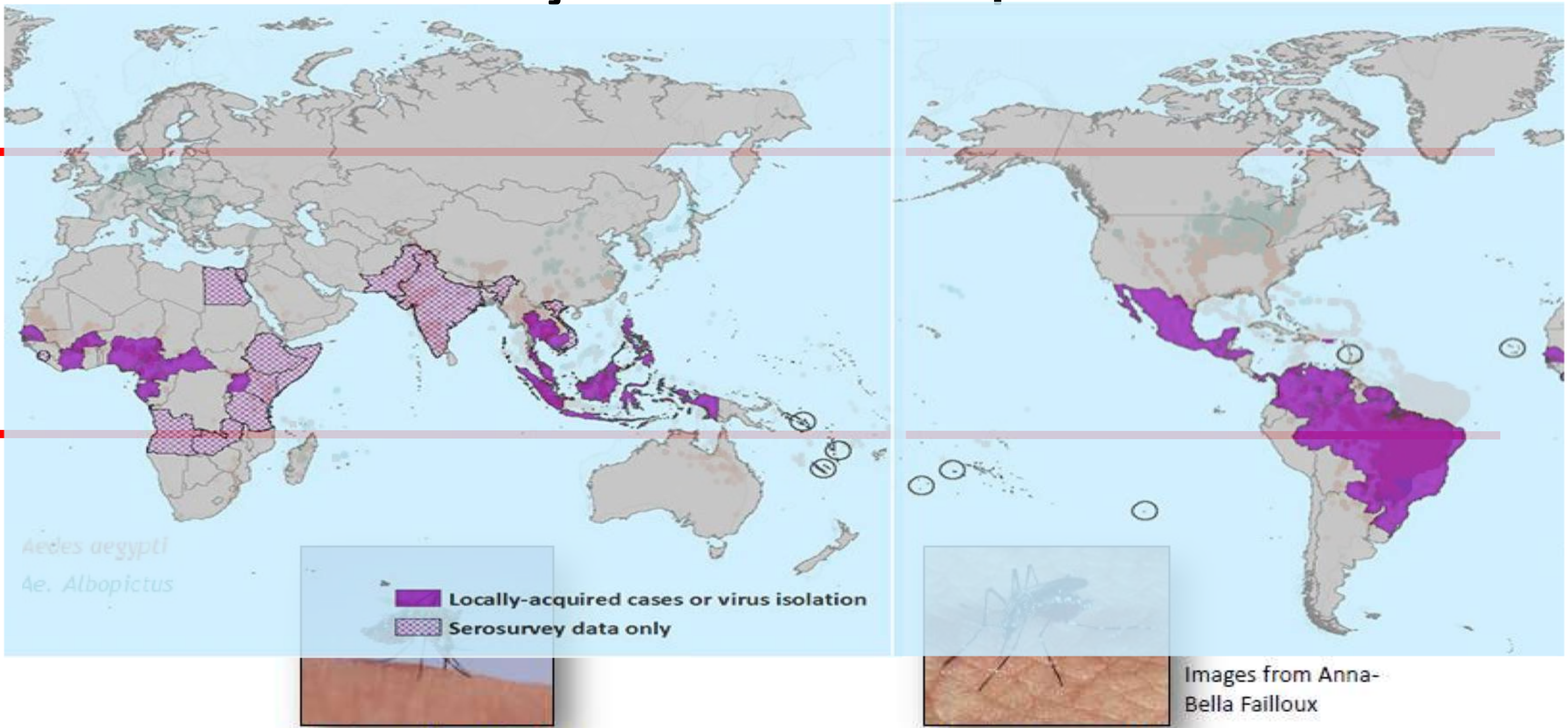
(From the Virus Research Institute, Entebbe, Uganda.)

Zika foi isolado pela primeira vez de um macaco sentinela, Rhesus, MR-766.



Adaptado de Loos et al., Med Mal Infect, 2014

Distribuição do Vetor Artrópode



Images from Anna-Bella Failloux

Aedes albopictus

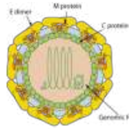
CHIKV, DENV, ZIKV, YFV

Aedes aegypti

CHIKV, DENV, ZIKV, YFV

http://healthintelligence.drupalgardens.com/content/visualizing-global-distribution-aedes-aegypti-and-ae-albopictus

+


E dimer
M protein
C protein

Sintomas

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Mark R. Duffy, D.V.M., M.P.H., Tai-Ho Chen, M.D., W. Thane Hancock, M.D., M.P.H., Ann M. Powers, Ph.D., Jacob L. Kool, M.D., Ph.D., Robert S. Lanciotti, Ph.D., Moses Pretrick, B.S., Maria Marfel, B.S., Stacey Holzbauer, D.V.M., M.P.H., Christine Dubray, M.D., M.P.H., Laurent Guillaumot, M.S., Anne Griggs, M.P.H., Martin Bel, M.D., Amy J. Lambert, M.S., Janeen Laven, B.S., Olga Kosoy, M.S., Amanda Panella, M.P.H., Brad J. Biggerstaff, Ph.D., Marc Fischer, M.D., M.P.H., and Edward B. Hayes, M.D.

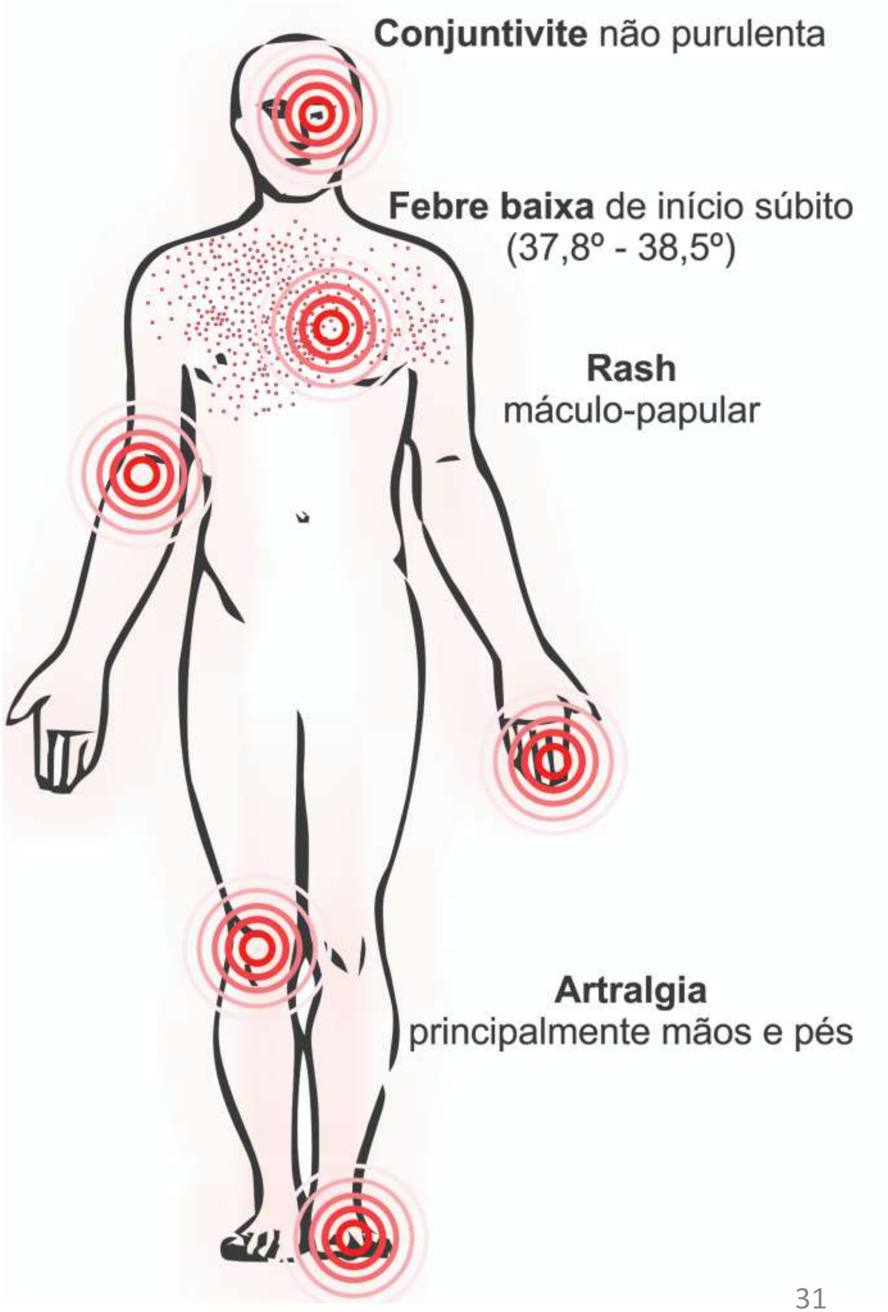
Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

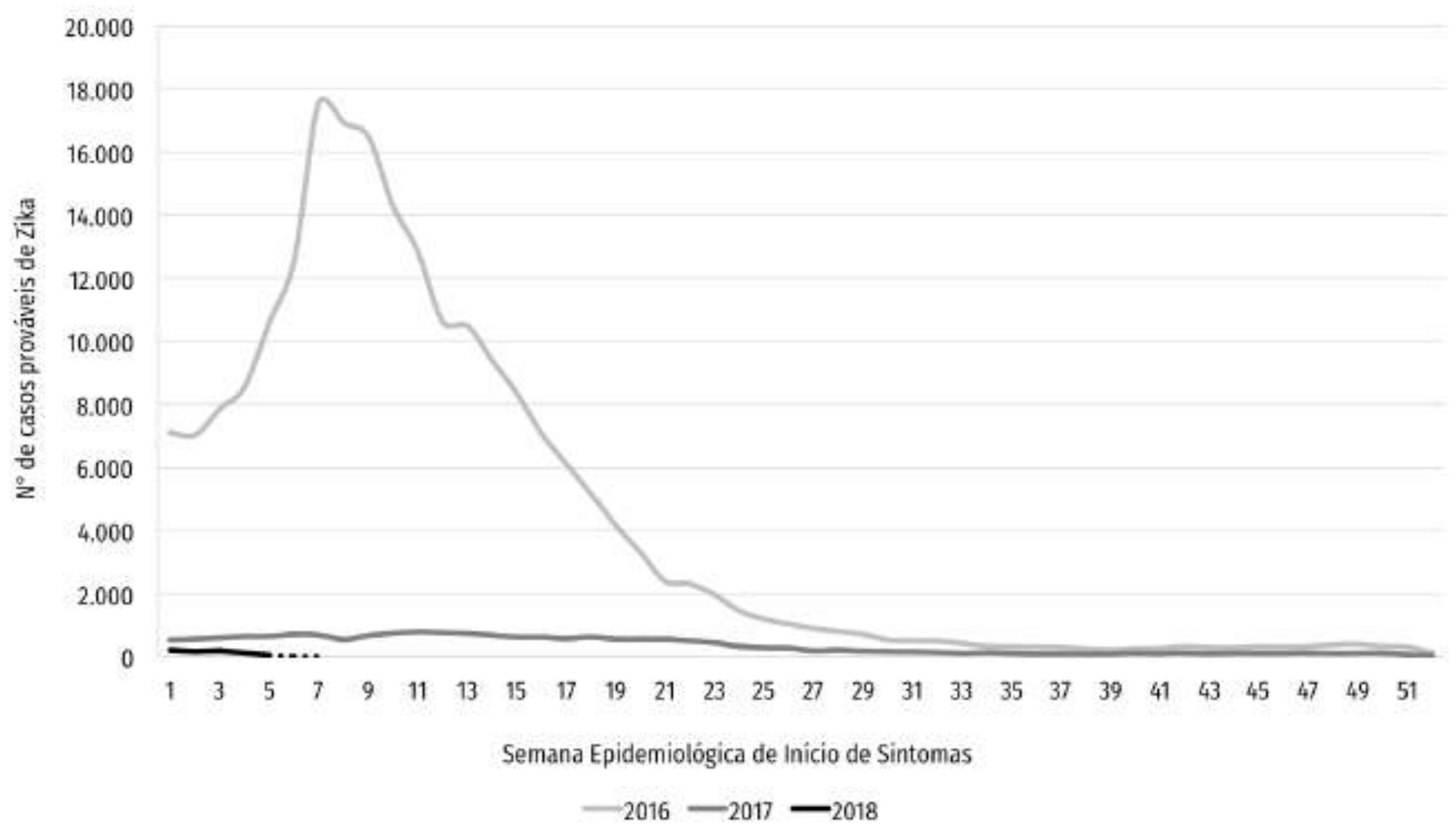
Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

Duffy et al., NEJM, 2009

Incubação:
2-10 dias
Sintomas:
2-7 dias e são leves
Morte raro

Guillain-Barre

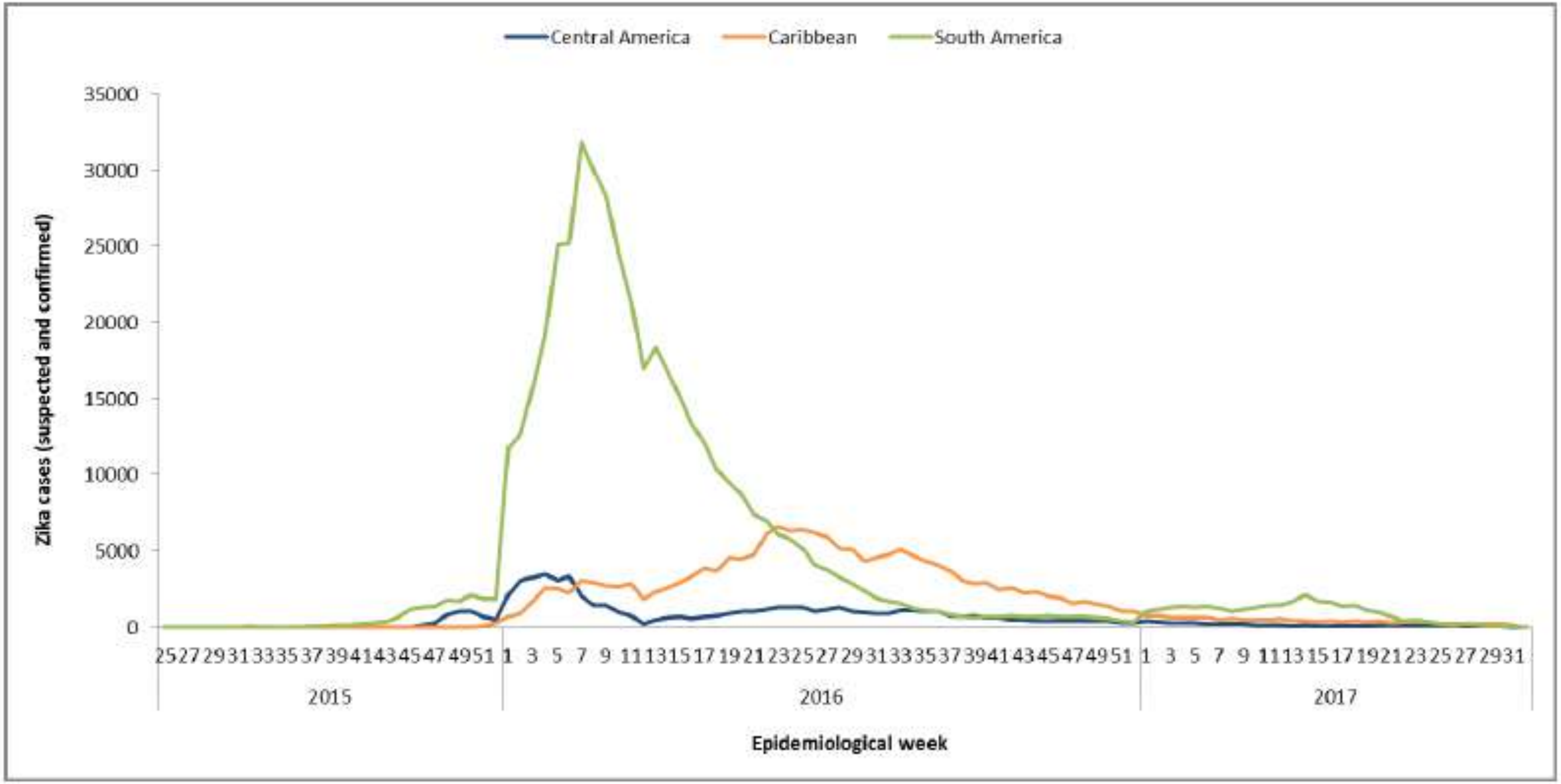




Fonte: Sinan NET (banco de 2016 atualizado em 23/06/2017; de 2017, em 23/01/2018; e de 2018, em 19/02/2018). Dados sujeitos a alteração.

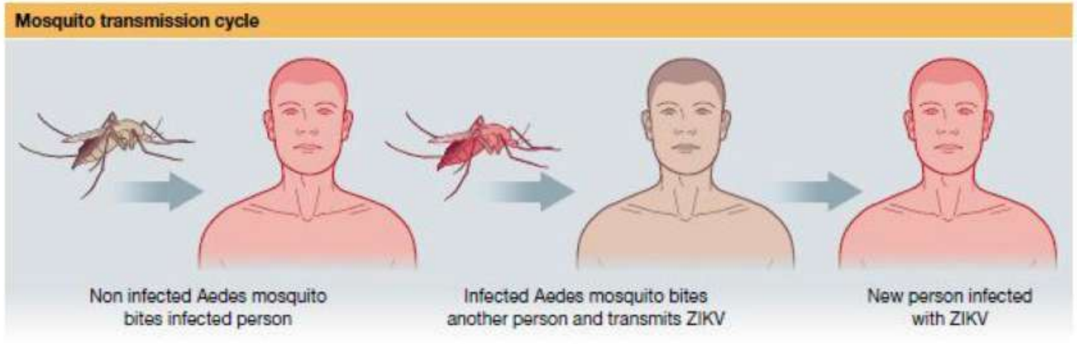
FIGURA 3 **Casos prováveis de febre pelo vírus Zika, por semana epidemiológica de início de sintomas, Brasil, 2017 e 2018**

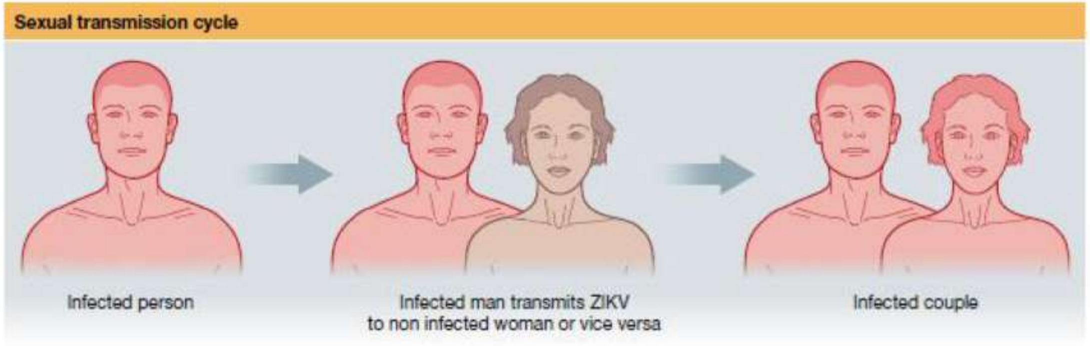
Figure 4. Distribution of suspected and confirmed Zika cases by EW and sub-region. Region of the Americas, 2015 – 2017 (as of EW 32).[14]



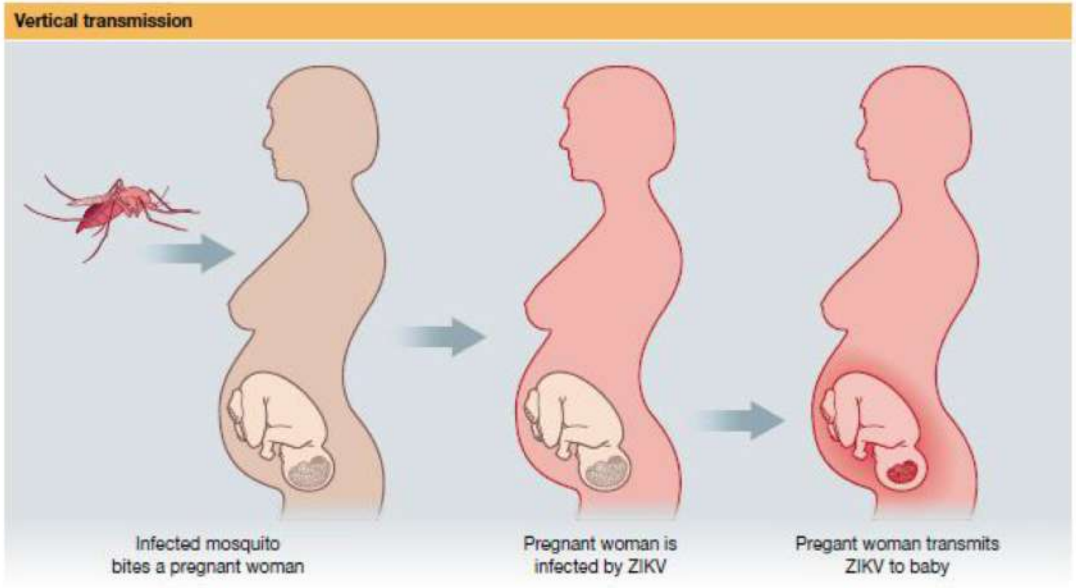
Source: Data provided by countries and territories of the Americas and reproduced by PAHO/WHO

Transmissão do ZIKV





Russo et al., Cell Microbiol 2017



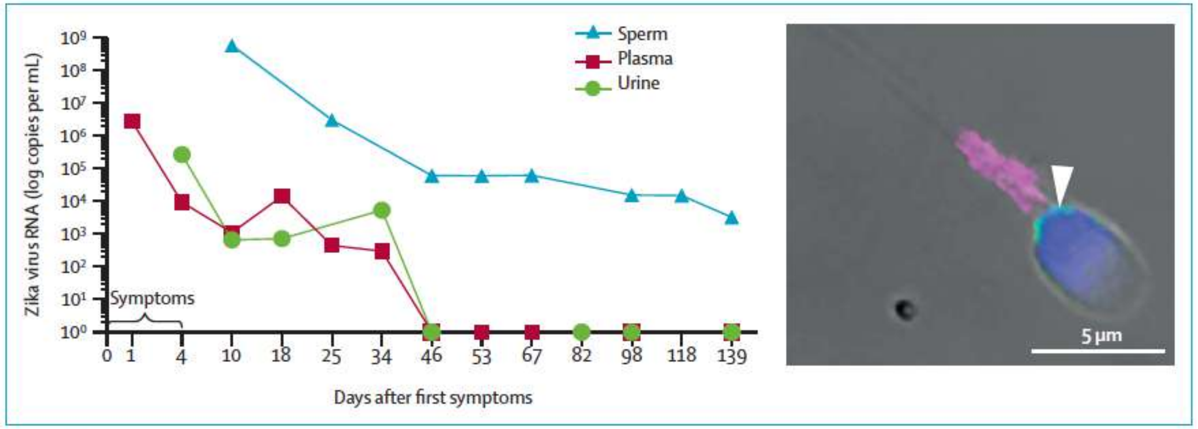
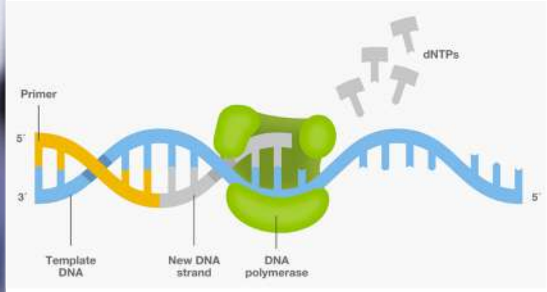


Figure: Zika virus infects spermatozoa

Mansuy et al., Lancet 2016

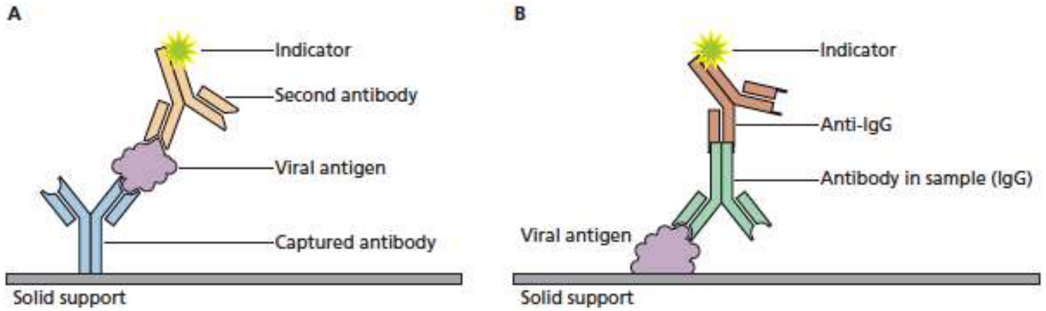
Diagnóstico laboratorial do ZIKV

PCR



Sangue
Urina
Sêmen
Saliva

ELISA



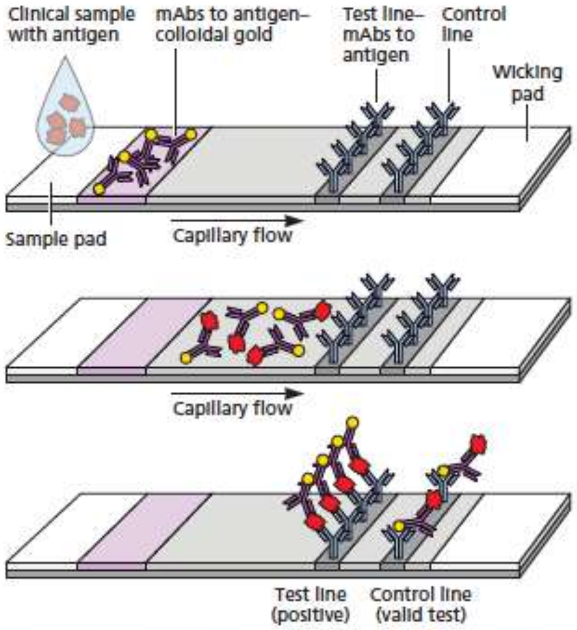


Figure 2.17 Lateral flow immunochromatographic assay.

FLOW IMMUNOCROMATOGRAFIA

Flint, Racaniello, Rall, Skalka. Principles of Virology. 2015

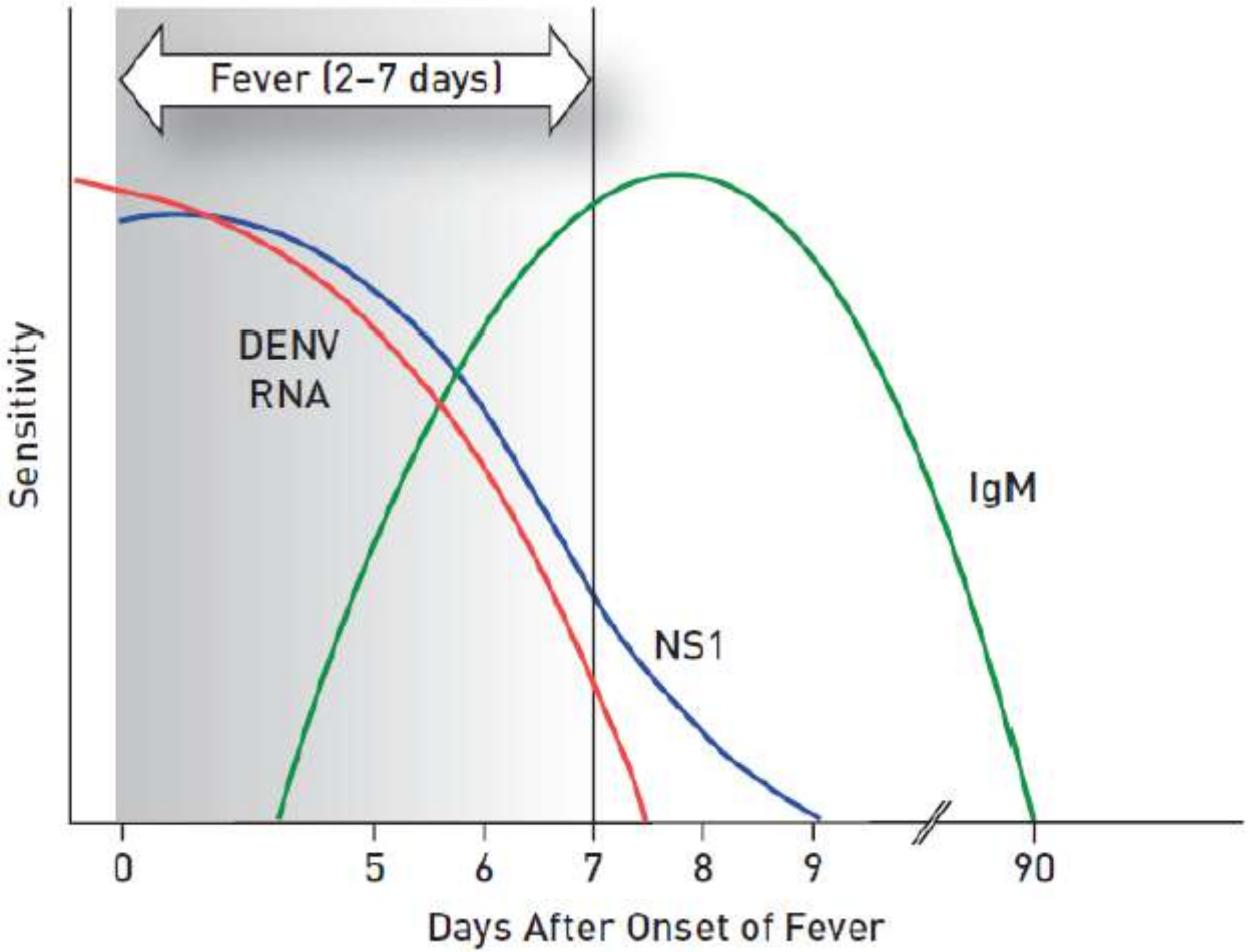
Arboviroses

Diagnóstico Laboratorial e Prevenção

- Diagnóstico Laboratorial
  - Isolamento viral em culturas de células de macaco (Vero ou LLC-MK2)
  - Soroneutralização
  - Imunofluorescência
  - Ensaio imunoenzimático (ELISA)
  - RT-PCR – hibridação
  - PCR

Arboviroses

Dengue: Diagnóstico Laboratorial



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Dengue: Diagnóstico Laboratorial

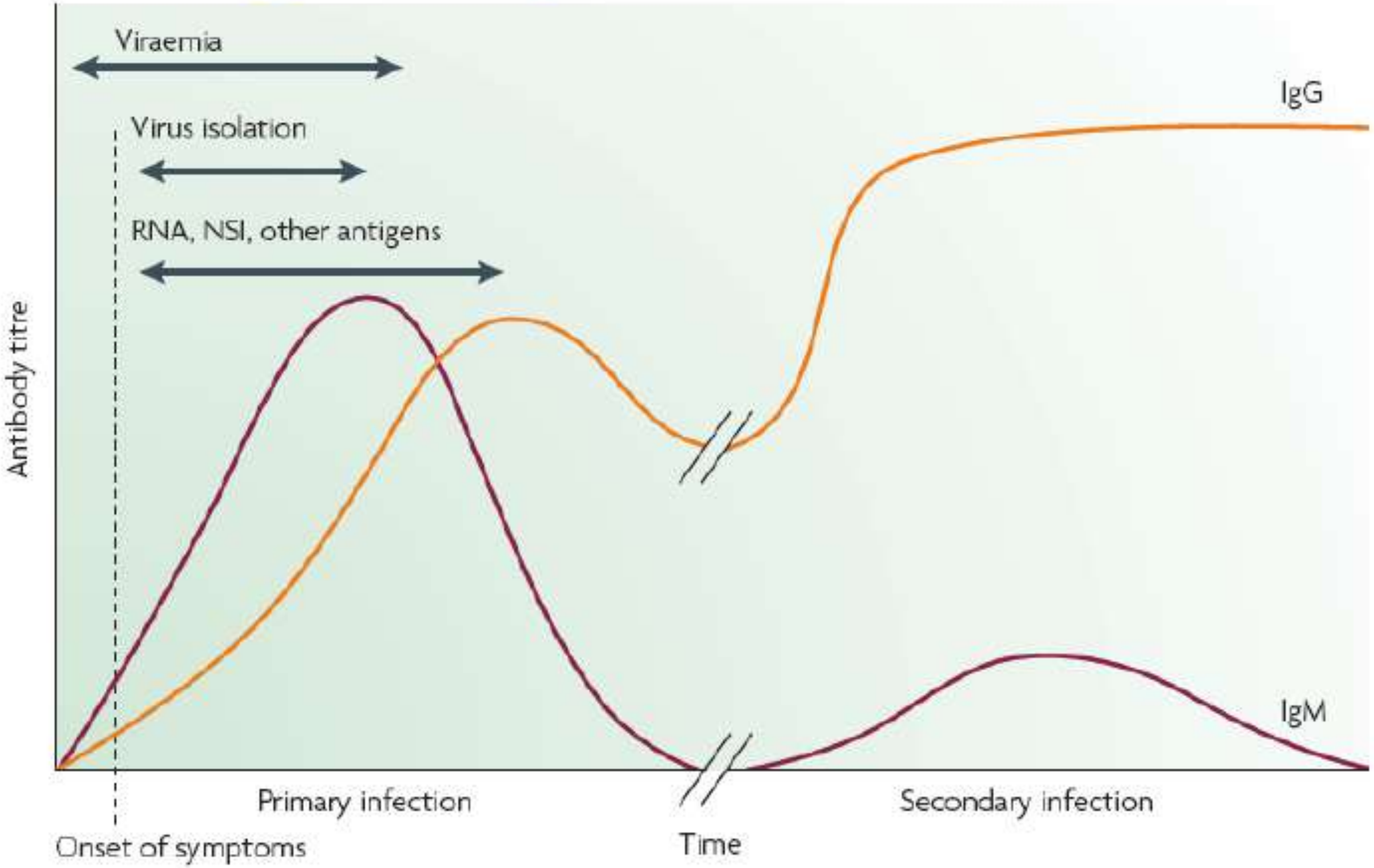


Figure 2 | **Major diagnostic markers for dengue infection.** The titre of the IgM and IgG response varies, depending on whether the infection is a primary or secondary infection.

doi:10.1038/nrmicro2459

Arboviroses

Dengue: Diagnóstico Laboratorial

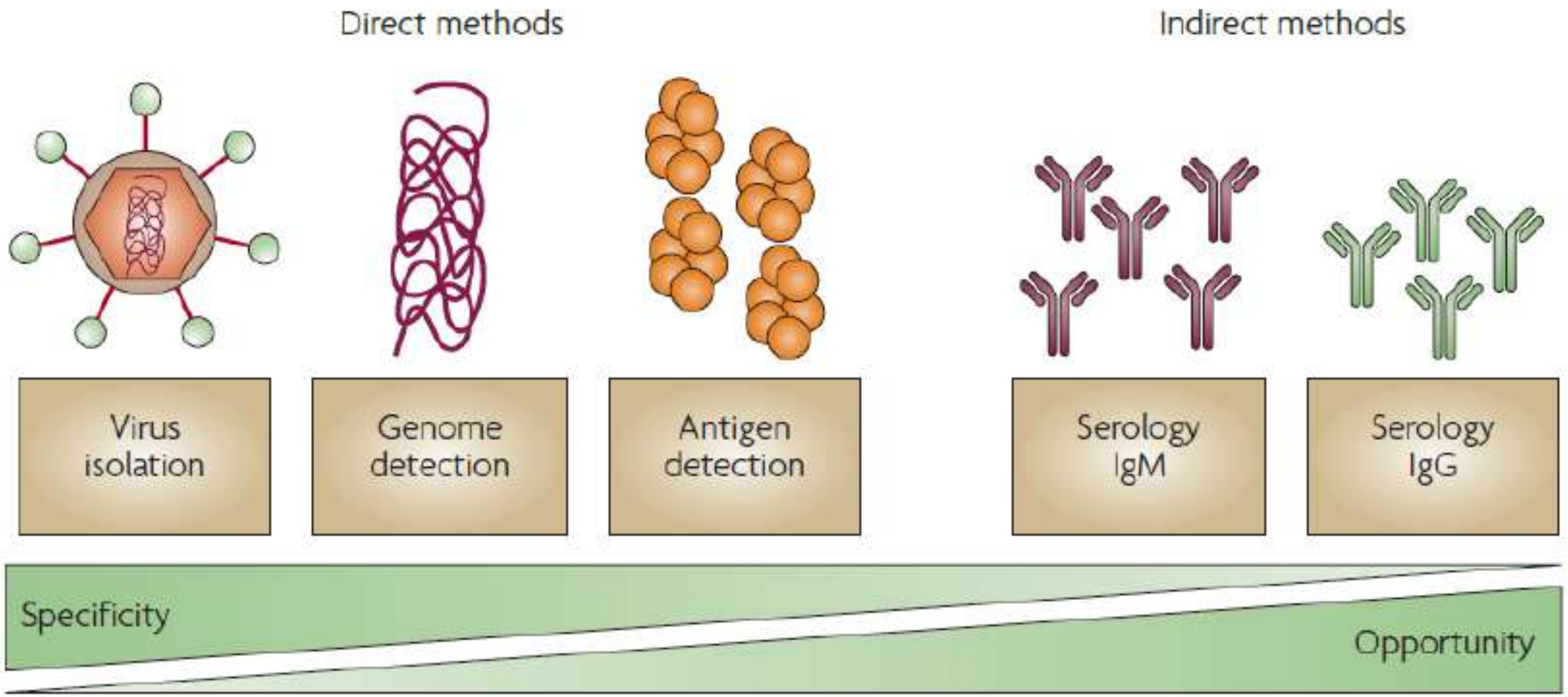


Figure 1 | **Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections.** Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.

doi:10.1038/nrmicro2459

Arboviroses

Dengue: Diagnóstico Laboratorial

Table 1 | **Advantages and limitations of different dengue diagnostic tests**

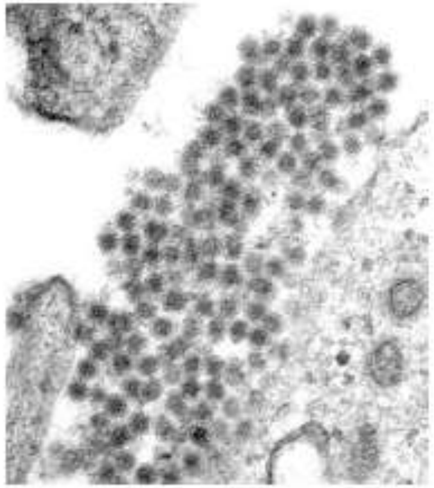
Diagnostic tests	Advantages	Limitations
Viral isolation and identification	• Confirmed infection • Specific • Identifies serotypes	• Requires acute sample (0–5 days post onset) • Requires expertise and appropriate facilities • Takes more than 1 week • Does not differentiate between primary and secondary infection • Expensive
RNA detection	• Confirmed infection • Sensitive and specific • Identifies serotype and genotype • Results in 24–48 hours	• Potential false-positives owing to contamination • Requires acute sample (0–5 days post onset) • Requires expertise and expensive laboratory equipment • Does not differentiate between primary and secondary infection
Antigen detection		
Clinical specimens (for example, using blood in an NS1 assay)	• Confirmed infection • Easy to perform • Less expensive than virus isolation or RNA detection	• Not as sensitive as virus isolation or RNA detection
Tissues from fatal cases (for immunohistochemistry, for example)	• Confirmed infection	• Not as sensitive as virus isolation or RNA detection • Requires expertise in pathology
Serological tests		
IgM or IgG seroconversion	• Confirmed infection • Least expensive • Easy to perform	• IgM levels can be low in secondary infections • Confirmation requires two or more serum samples • Can differentiate between primary and secondary infection*
IgM detection (single sample)	• Identifies probable dengue cases • Useful for surveillance, tracking outbreaks and monitoring effectiveness of interventions	• IgM levels can be low in secondary infections

*Primary infection: IgM-positive and IgG-negative (if samples are taken before day 8–10); secondary infection: IgG should be higher than 1,280 haemagglutination inhibition in convalescent serum.

doi:10.1038/nrmicro2459

ARBOVIROSES “EMERGENTES”

Arboviroses Emergentes

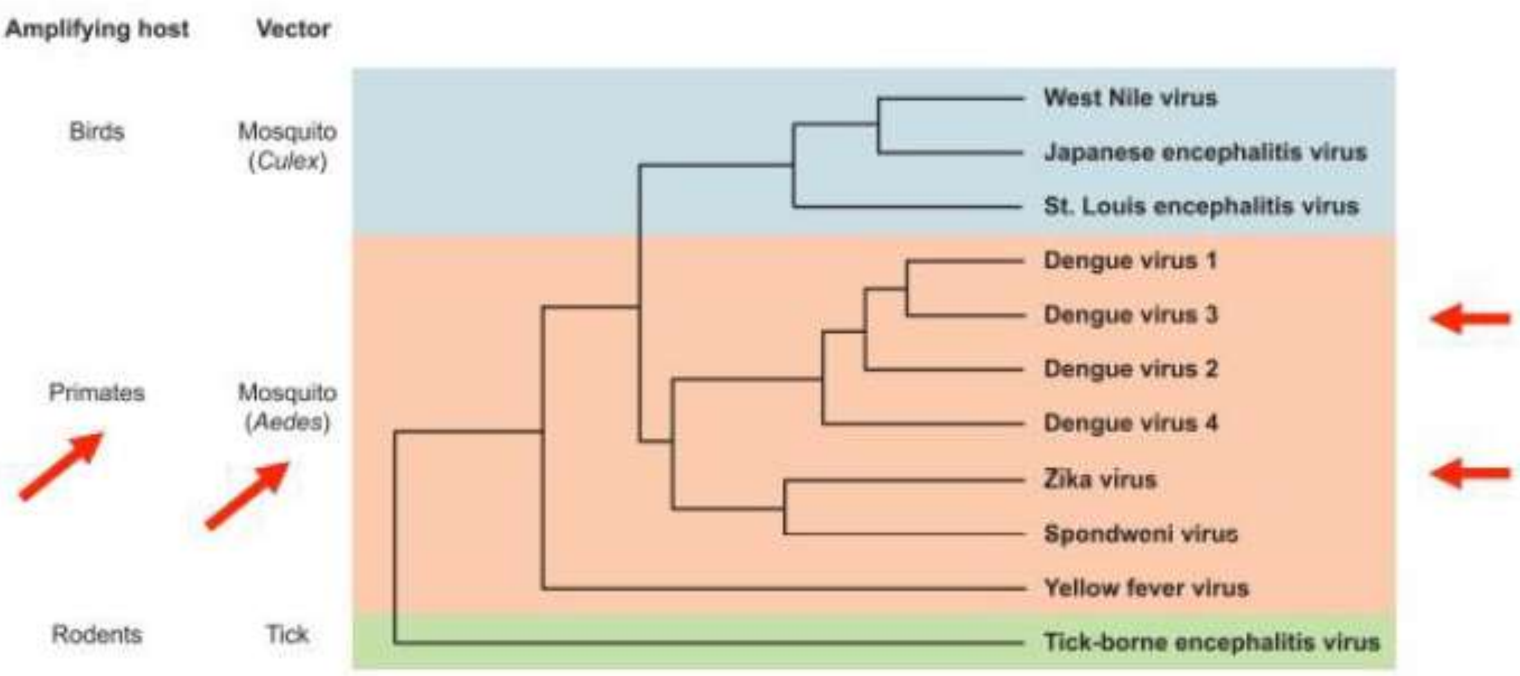


Zika Vírus

Família:	*Flaviviridae*
Gênero:	*Flavivirus*
Transmissão:	vetor artrópode - *Aedes aegypti*
Partículas virais:	esférico 45 nm, envelopado
Proteínas estruturais:	glicoproteína E ; nucleoproteína: C; membrana: M
Genoma:	ss-RNA polaridade positiva

Arboviroses Emergentes: Zika Vírus

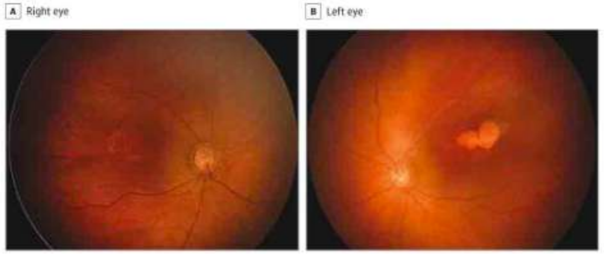
Zika virus is a flavivirus that is closely related to Dengue virus



Síndrome Congênita do Zika Vírus

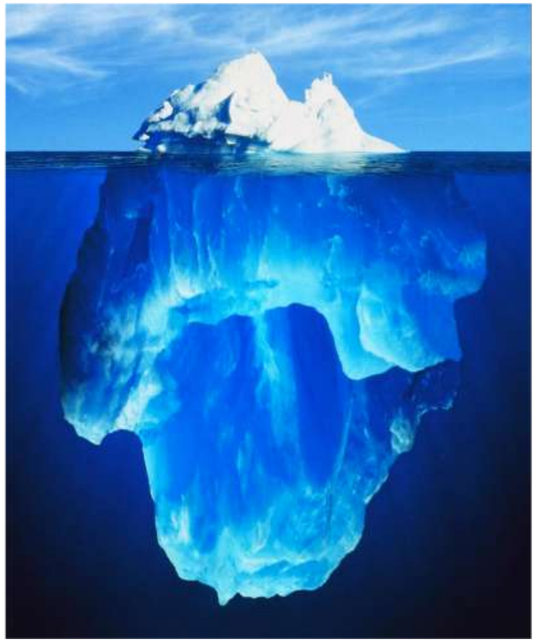
Microcefalia

Anormalidades olhos



Freitas et al., 2016

IUGR



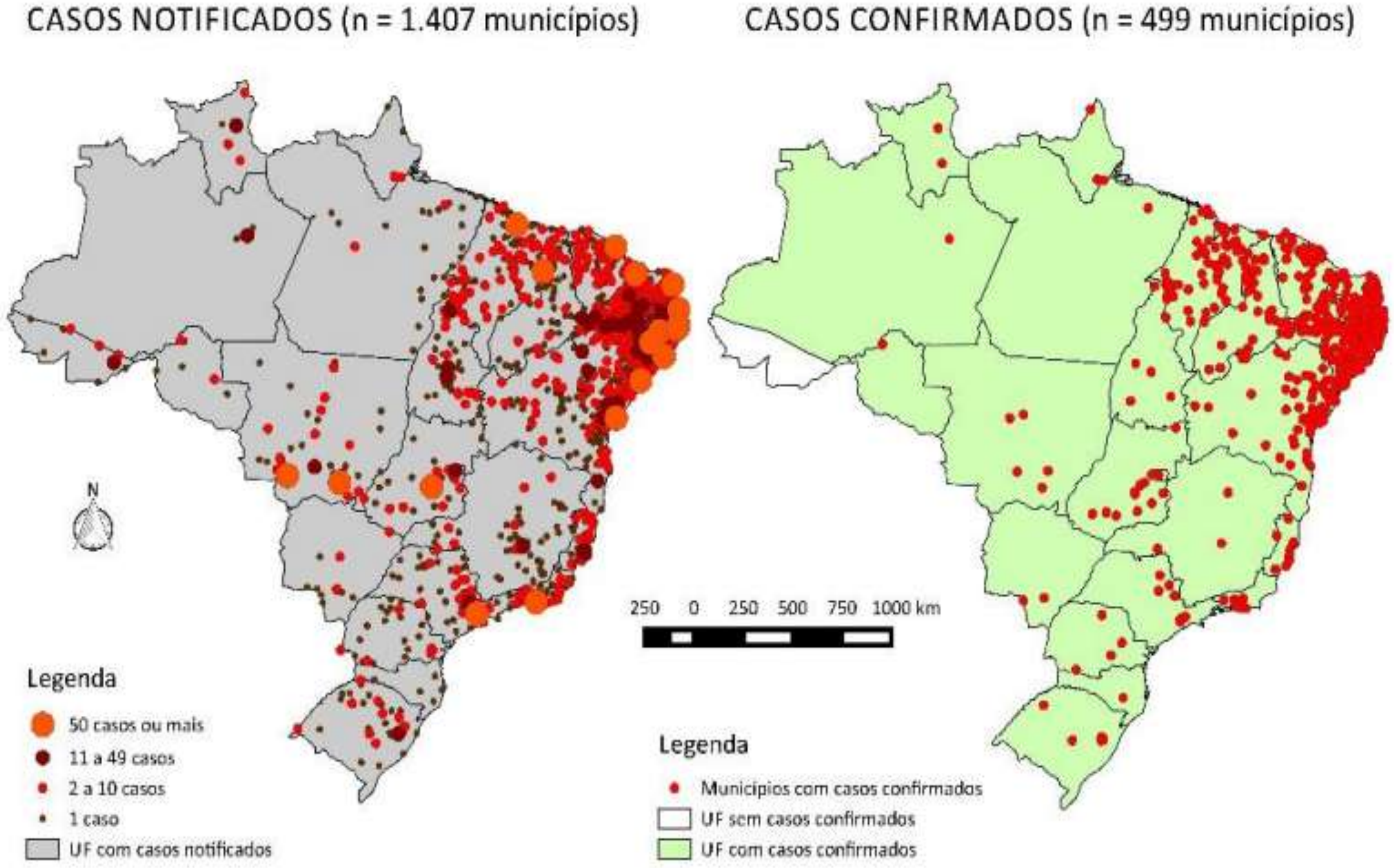
Microcalcificações

Oliveira et al., 2016

Artrogripose

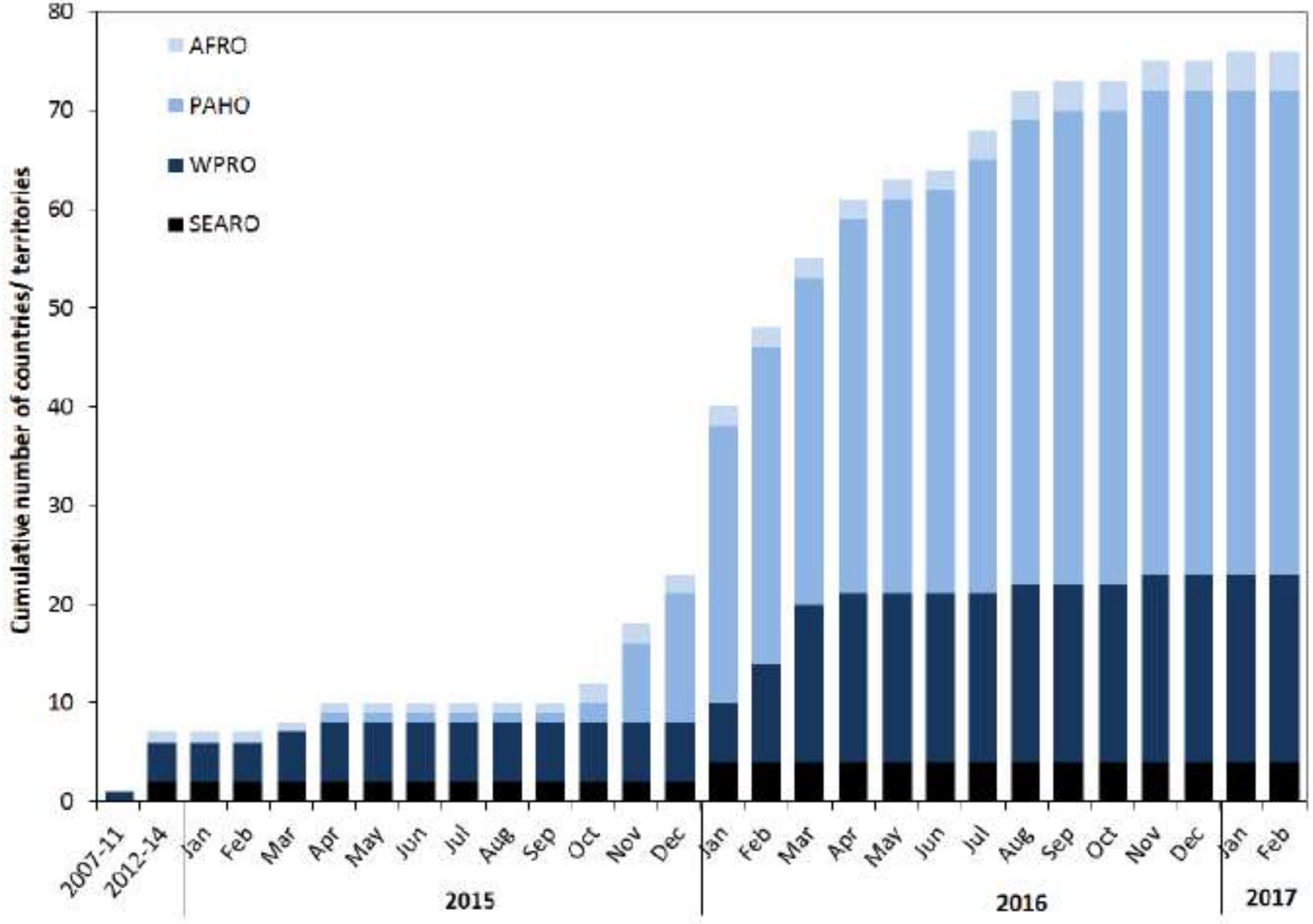
Alvino et al., 2016

Figura 1 – Distribuição espacial com casos notificados e confirmados de microcefalia e/ou alteração do SNC, Brasil, até a SE 19/2016.



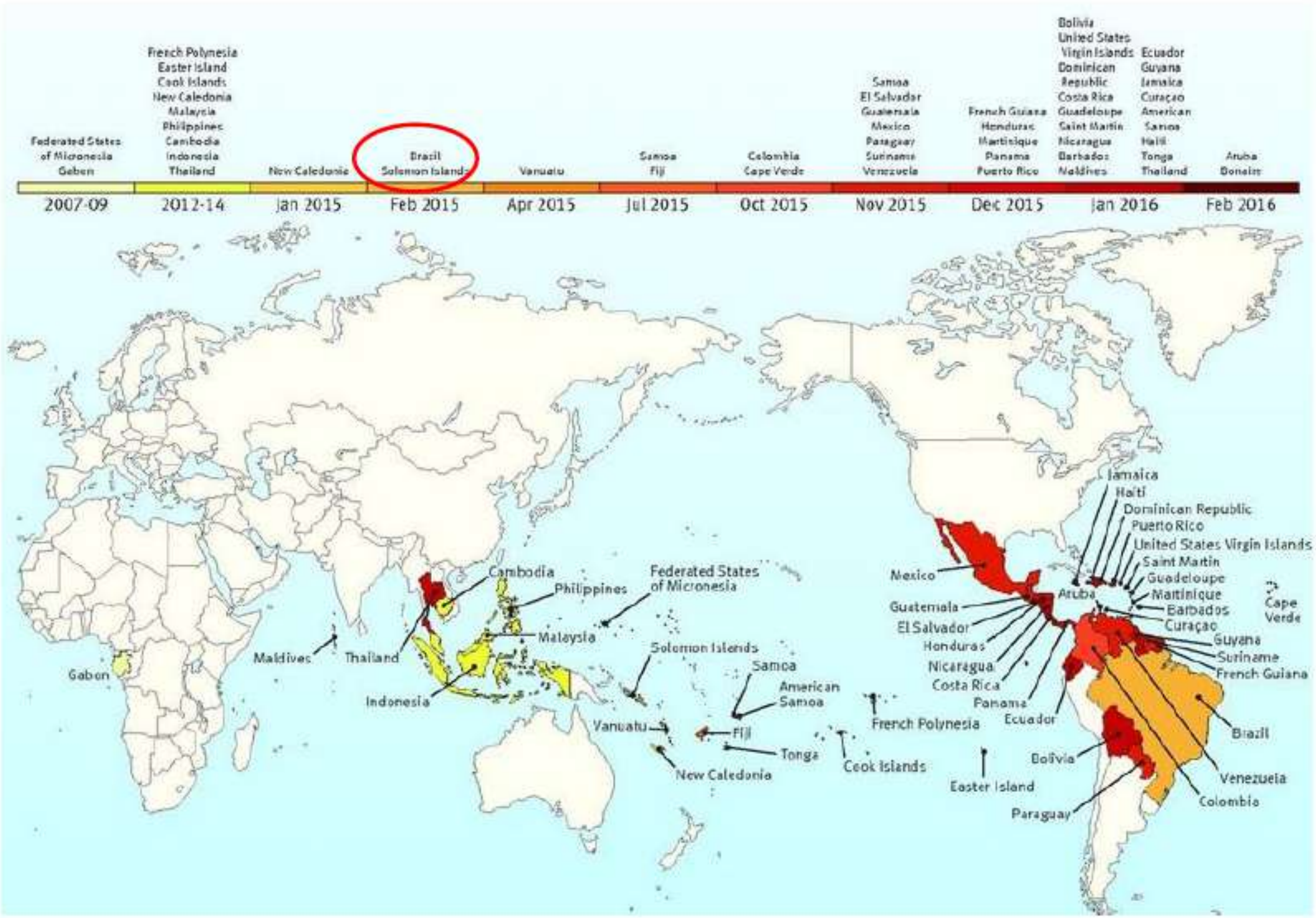
Arboviroses Emergentes: Zika Vírus

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



http://apps.who.int/iris/bitstream/10665/254507/1/zikasitrep2Feb17-eng.pdf?ua=1

Arboviroses Emergentes: Zika Vírus



World Health Organization

SITUATION REPORT

ZIKA VIRUS
MICROCEPHALY
GUILLAIN-BARRÉ SYNDROME
20 OCTOBER 2016

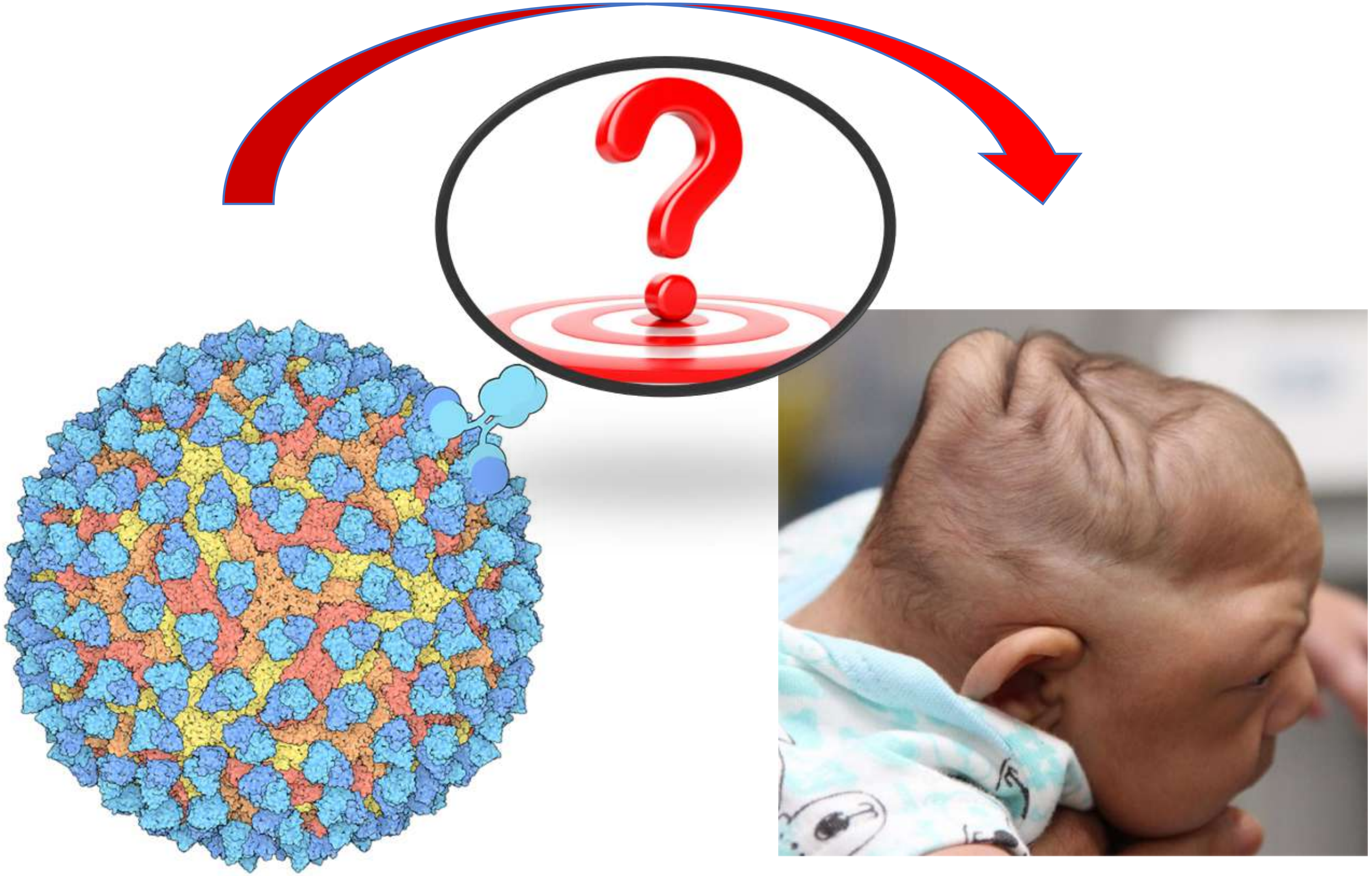
DATA AS OF 19 OCTOBER 2016

Brasil:
Síndrome Congênita do Zika
2017: 89% menos casos
2981 para 330 casos

Table 3. Countries and territories reporting 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 infections or potentially associated with a Zika virus infection	Probable location of infection
Brazil	2033[2]	Brazil
Cabo Verde	9	Cabo Verde
Canada	1	Undetermined
Costa Rica	1	Costa Rica
Colombia	46[3]	Colombia
Dominican Republic	10[4]	Dominican Republic
El Salvador	4	El Salvador
French Guiana	10[5]	French Guiana
French Polynesia	8	French Polynesia
Grenada	1	Grenada
Guatemala	17[6]	Guatemala
Haiti	1	Haiti
Honduras	1	Honduras
Marshall Islands	1	Marshall Islands
Martinique	12[6]	Martinique
Panama	5	Panama
Paraguay	2[7]	Paraguay
Puerto Rico	2[8]	Puerto Rico
Slovenia	1[9]	Brazil
Spain	2	Colombia, Venezuela (Bolivarian Republic of)
Suriname	1	Suriname
Thailand	2	Thailand
United States of America	28[10]	Undetermined*

The probable locations of three of the infections were Brazil (1 case), Haiti (1 case) and Mexico, Belize or Guatemala (1 case).



Zika Virus Infection of the Central Nervous System of Mice

By

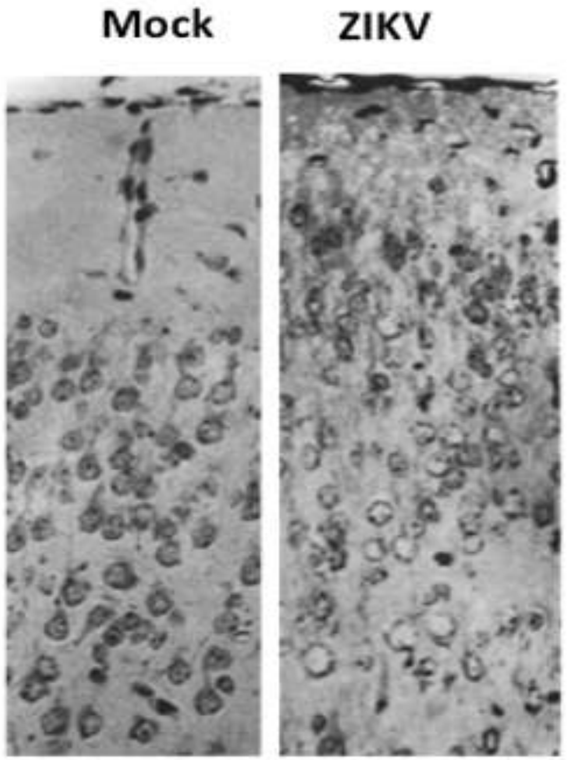
T. M. Bell, E. J. Field, and H. K. Narang

Medical Research Council, Demyelinating Diseases Unit, Newcastle General Hospital, Newcastle upon Tyne, England

With 8 Figures

Received February 10, 1971

Archiv für die gesamte Virusforschung 35, 183—193 (1971)



- ✓ Vírus da Febre amarela
- ✓ Vírus da Hepatite C
- ✓ Vírus da Dengue
- ✓ Vírus da Zika
- ✓ Vírus da encefalite japonesa
- ✓ Vírus da encefalite St Louis
- ✓ Vírus do Oriente do Nilo *(West Nile)*
- ✓ Vírus da encefalite do carrapato

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

Brasil et al., NEJM, 2016

88 gestantes:

42 ZIKV positivas:

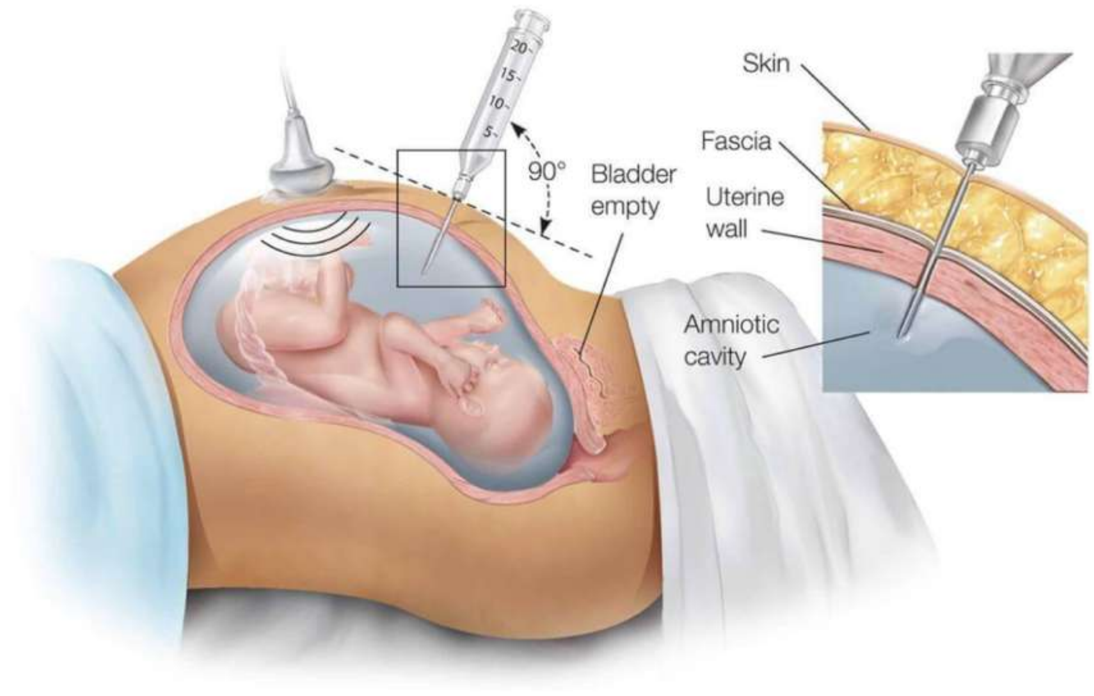
29% anormalidades fetais:

IUGR, microcefalia, calcificações no cérebro, alterações na circulação placentária, morte fetal

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†

Calvet et al.,Lancet, 2016



2 gestantes (18 e 10 sem. gest./infecção Zika), fetos com microcefalia:

28 semanas: genoma do ZIKV no liquido amniótico

The NEW ENGLAND JOURNAL of MEDICINE

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.

Mlakar et al.,NEJM, 2016

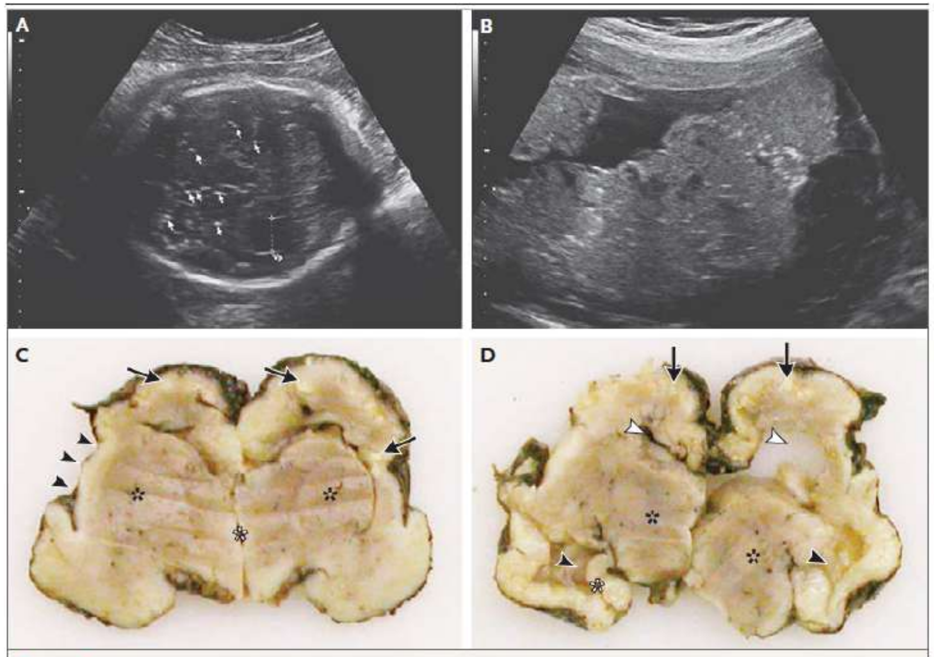


Figure 1. Prenatal Ultrasonographic Images and Photographs of Coronal Slices of Brain.

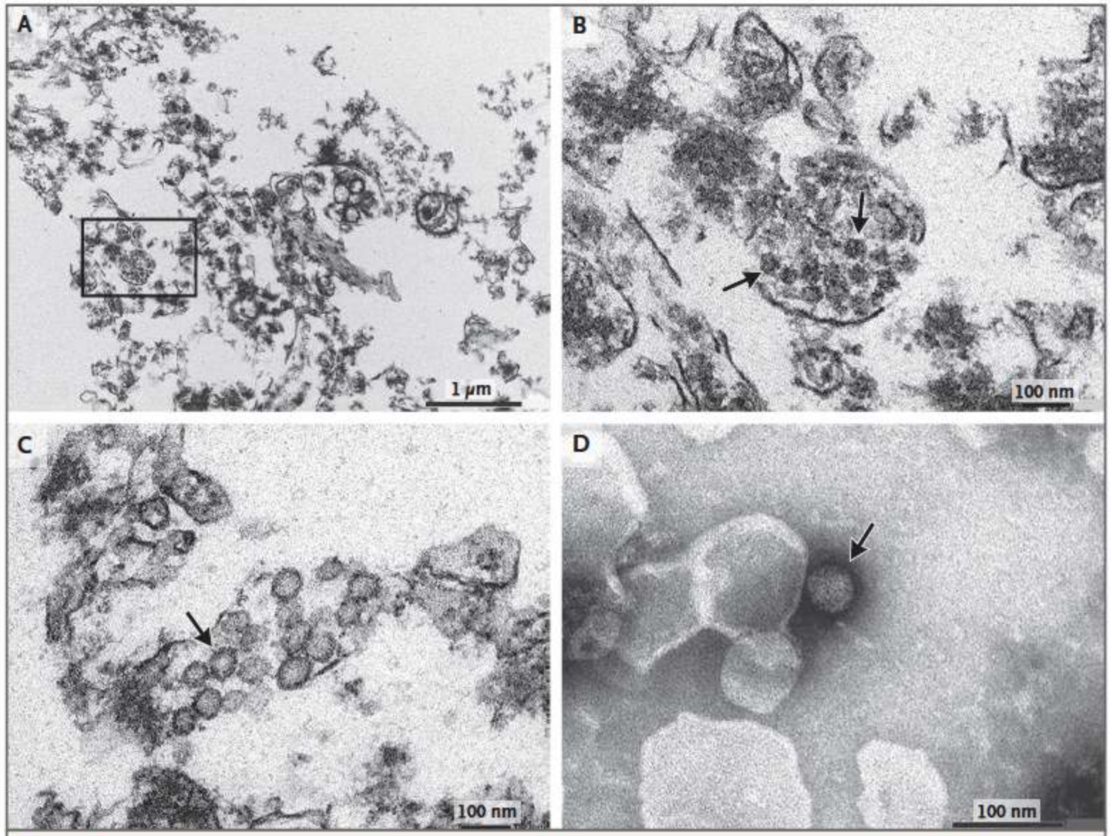
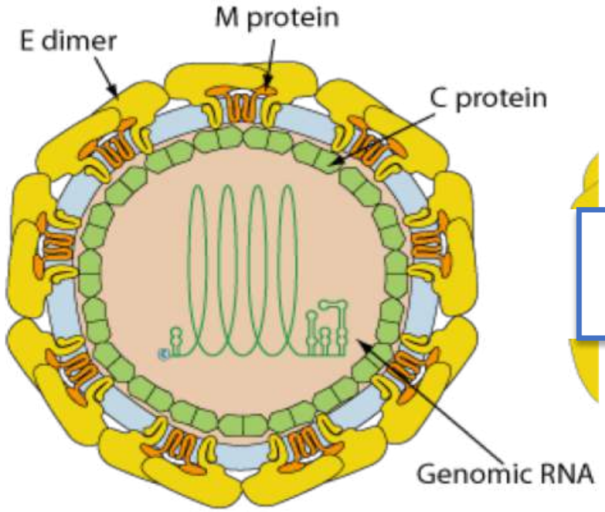


Figure 3. Electron Microscopy of Ultrathin Sections of Fetal Brain and Staining of a Flavivirus-like Particle.

Microcefalia, agiria, hidrocefalia, microcalcificações no cérebro e placenta, leve inflamação cortical.

PCR + ZIKV no cérebro

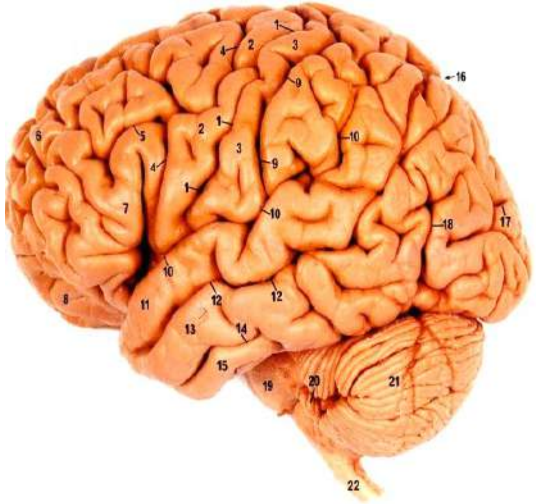


ZIKV

Microcefalia Congênita

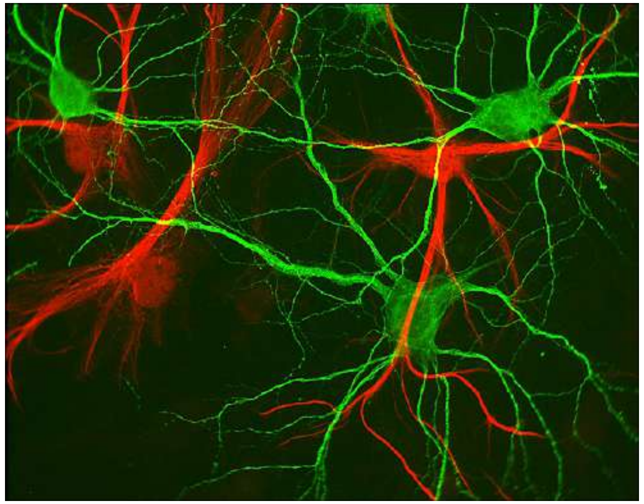
Modelos para estudar doenças que afetam o SNC

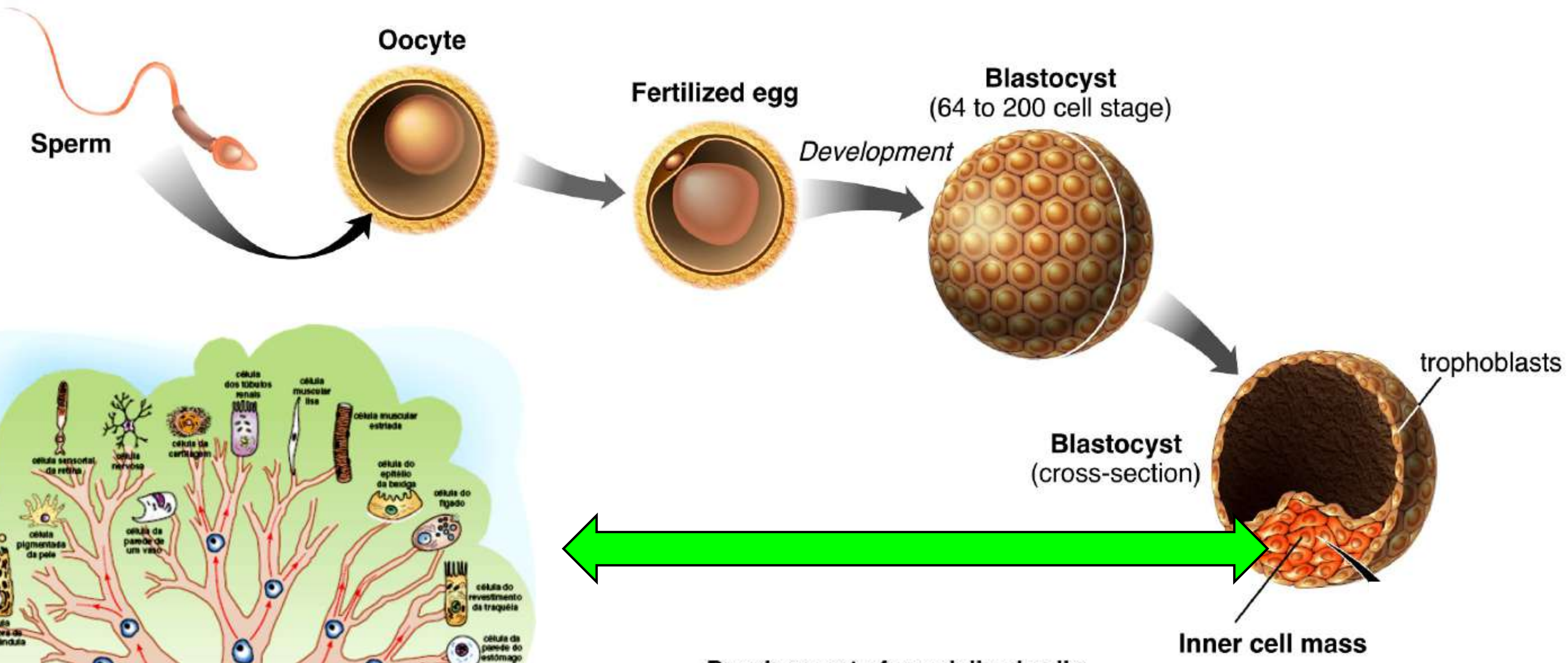
Cérebro Post-mortem

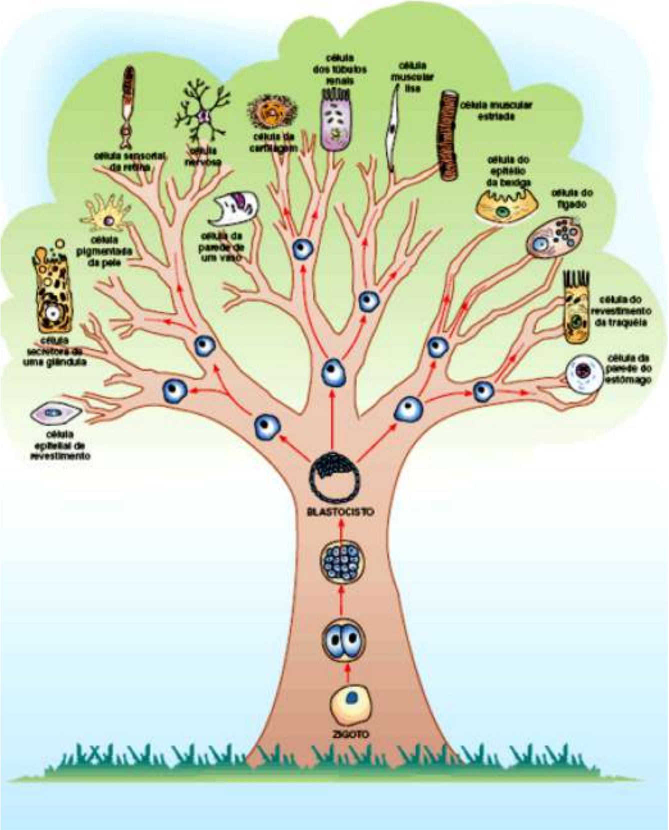


Modelo Animal

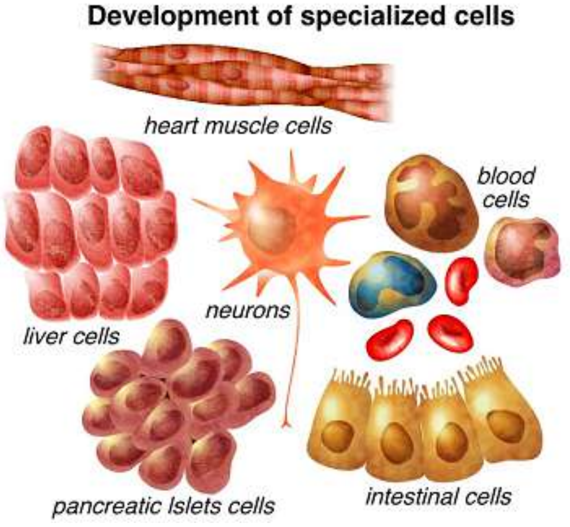
Cultura de células

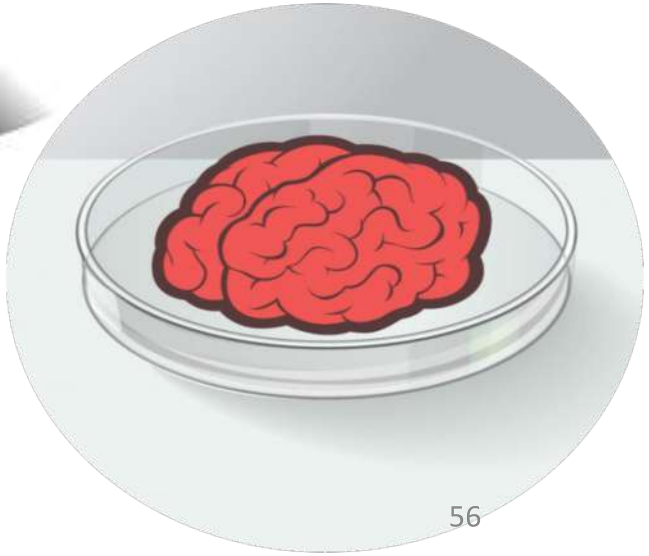




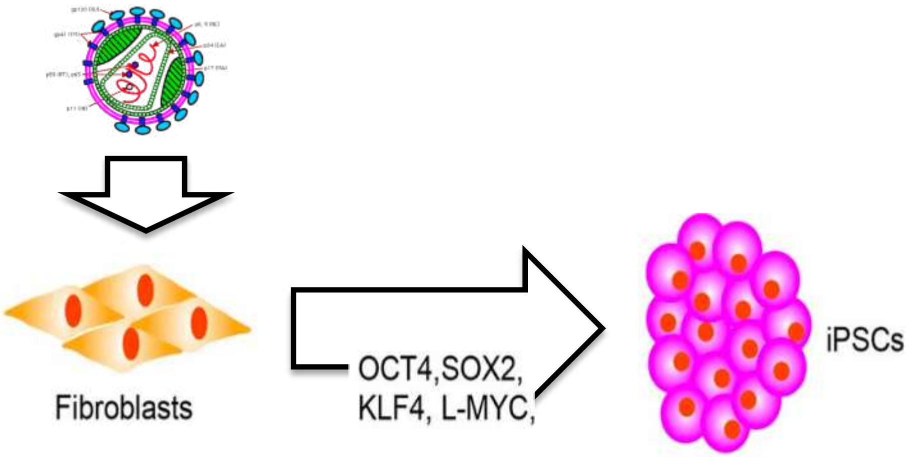


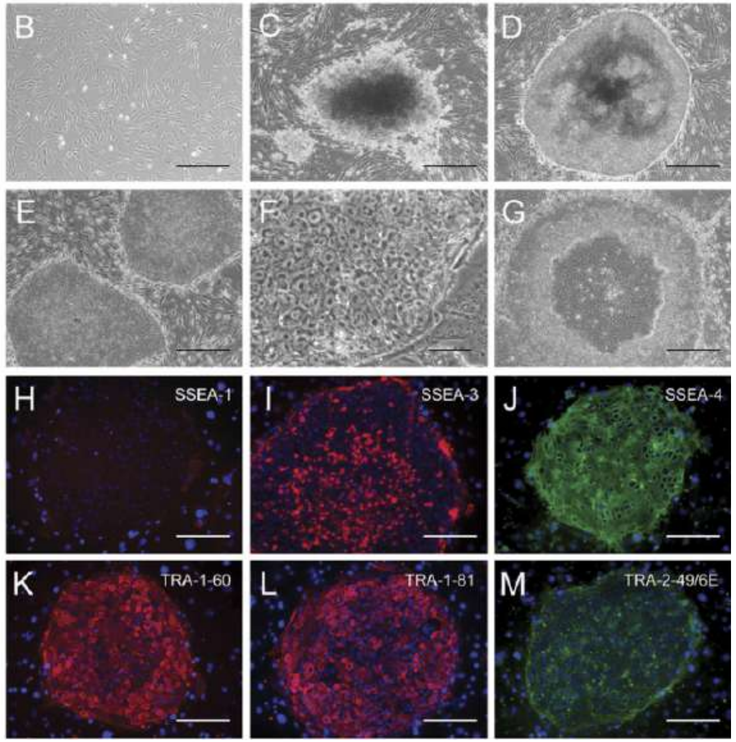
Célula-tronco





Células Pluripotentes induzidas (iPSC)



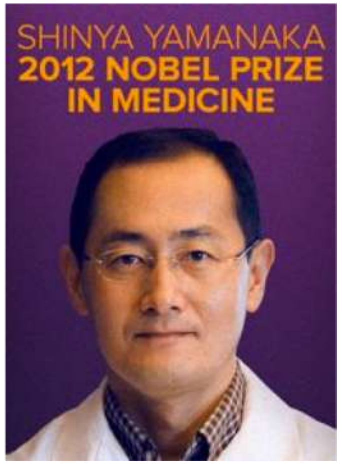


Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Takahashi, Yamanaka, Cell, 2006

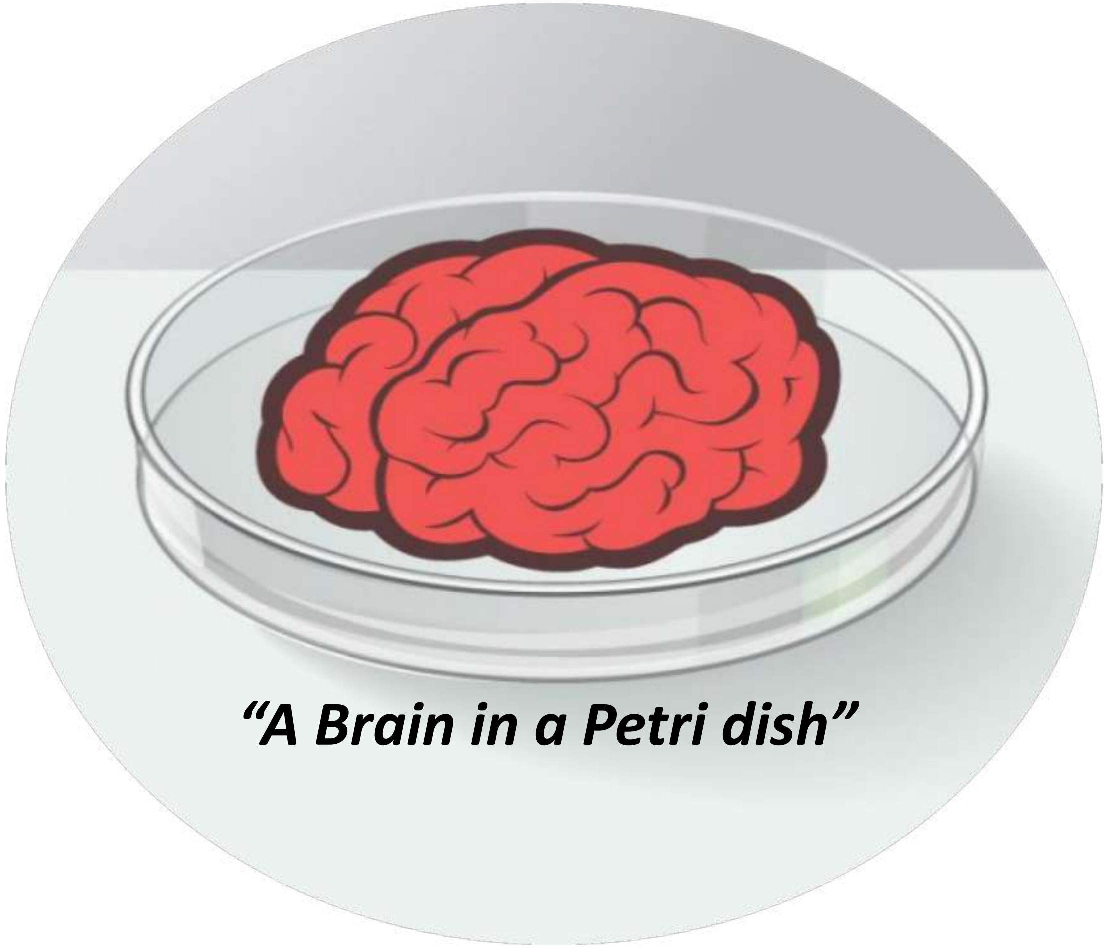
Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Takahashi et al., Cell, 2007



Modelagem de Doenças que afetam o SNC

”Mini-cérebros”: versão simplificada da realidade



“A Brain in a Petri dish”

Modelagem de Doenças do SNC usando células da polpa do dente de leite

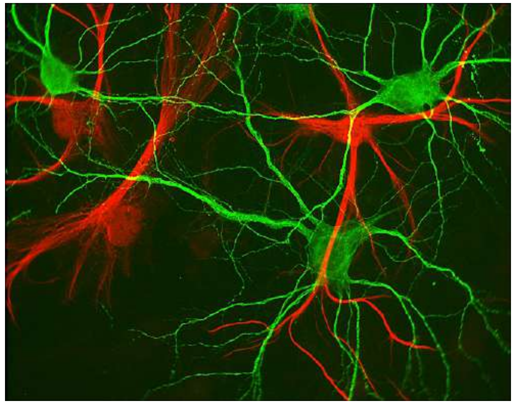
Céls da polpa do dente

iPSC

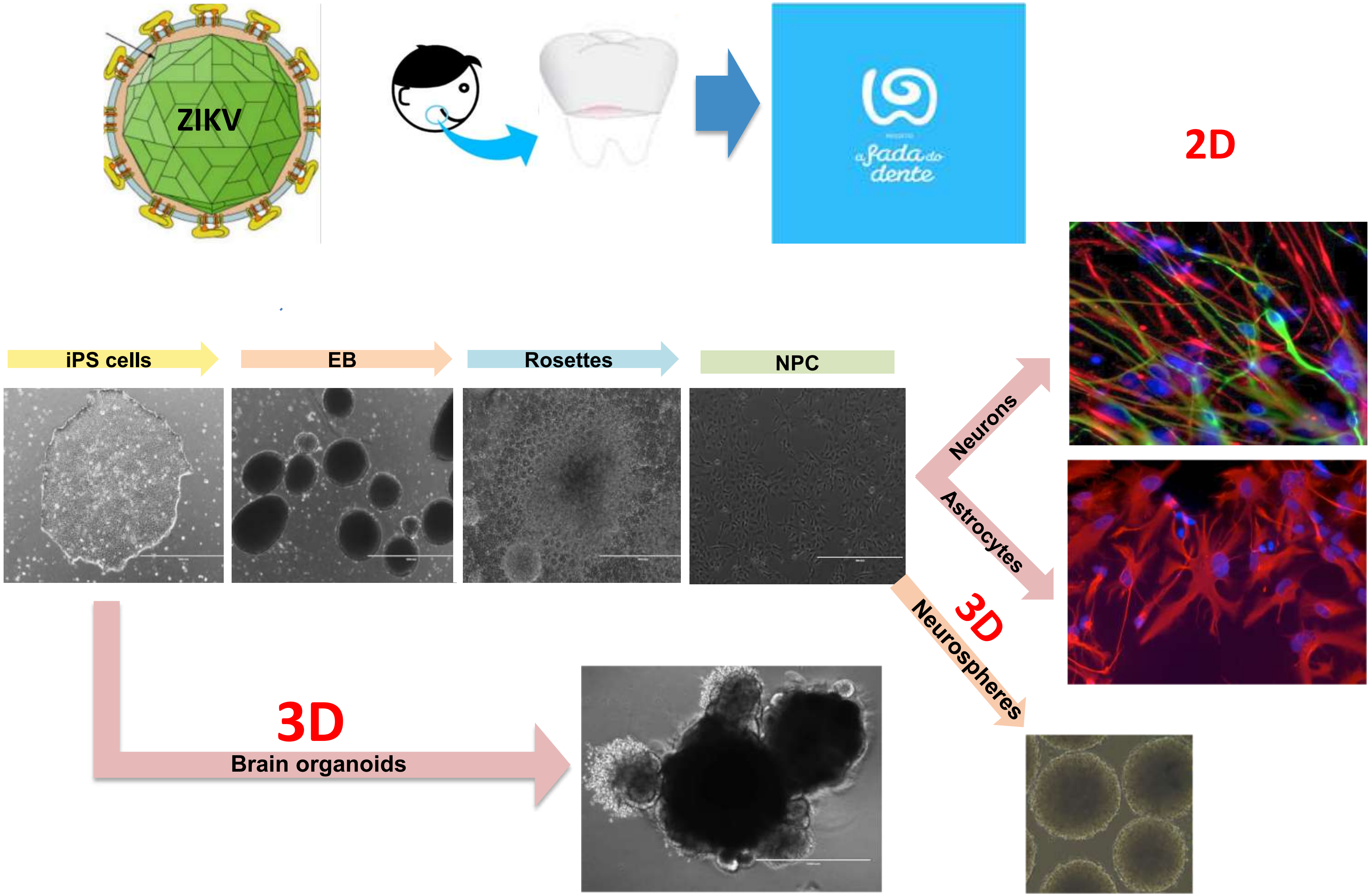
Beltrão-Braga et al., Cell Transplantation, 2011

PROJETO
a fada do dente

Neuronios e células gliais



“Disease in a dish”



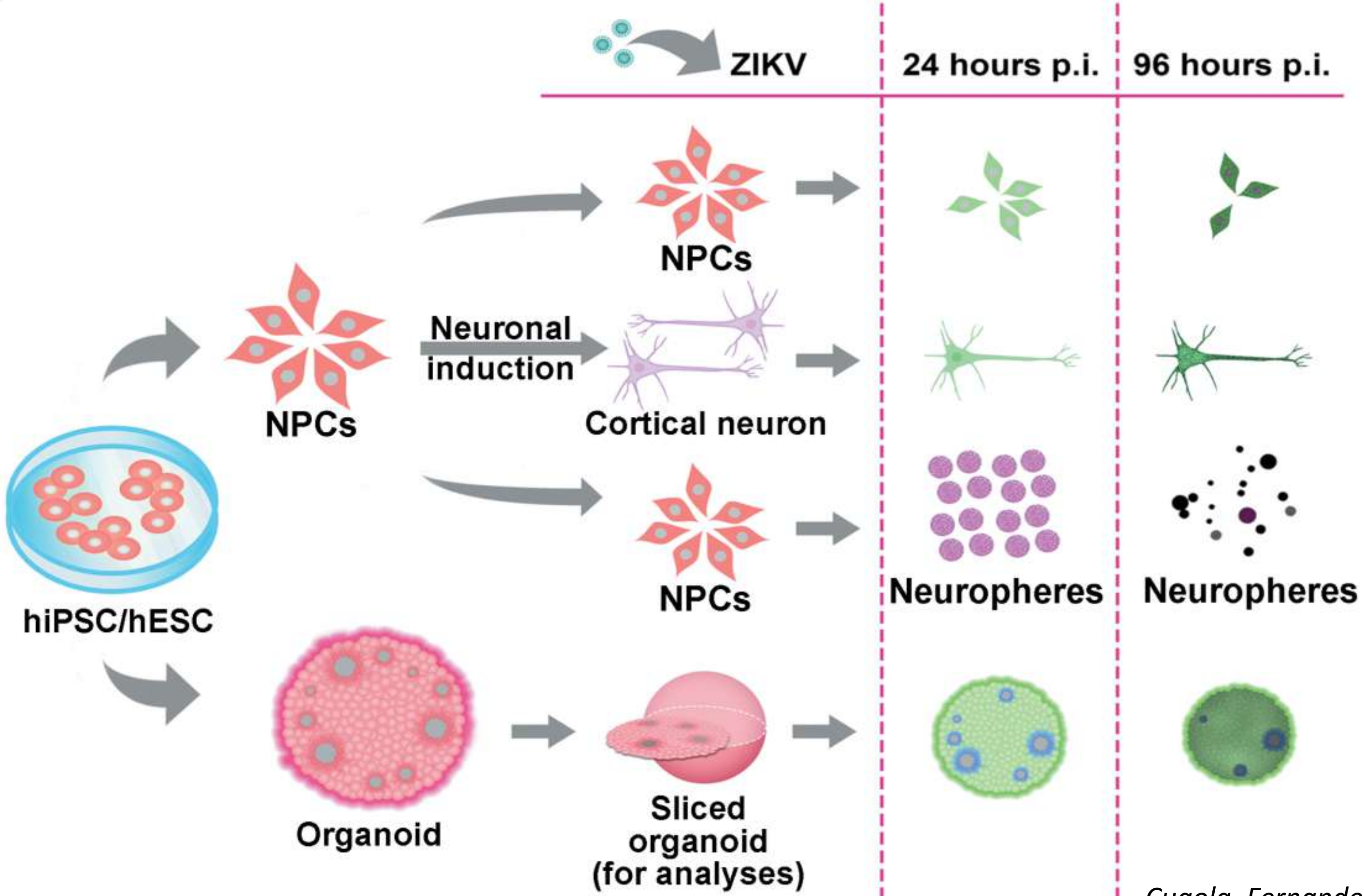
LETTER

nature

doi:10.1038/nature18296

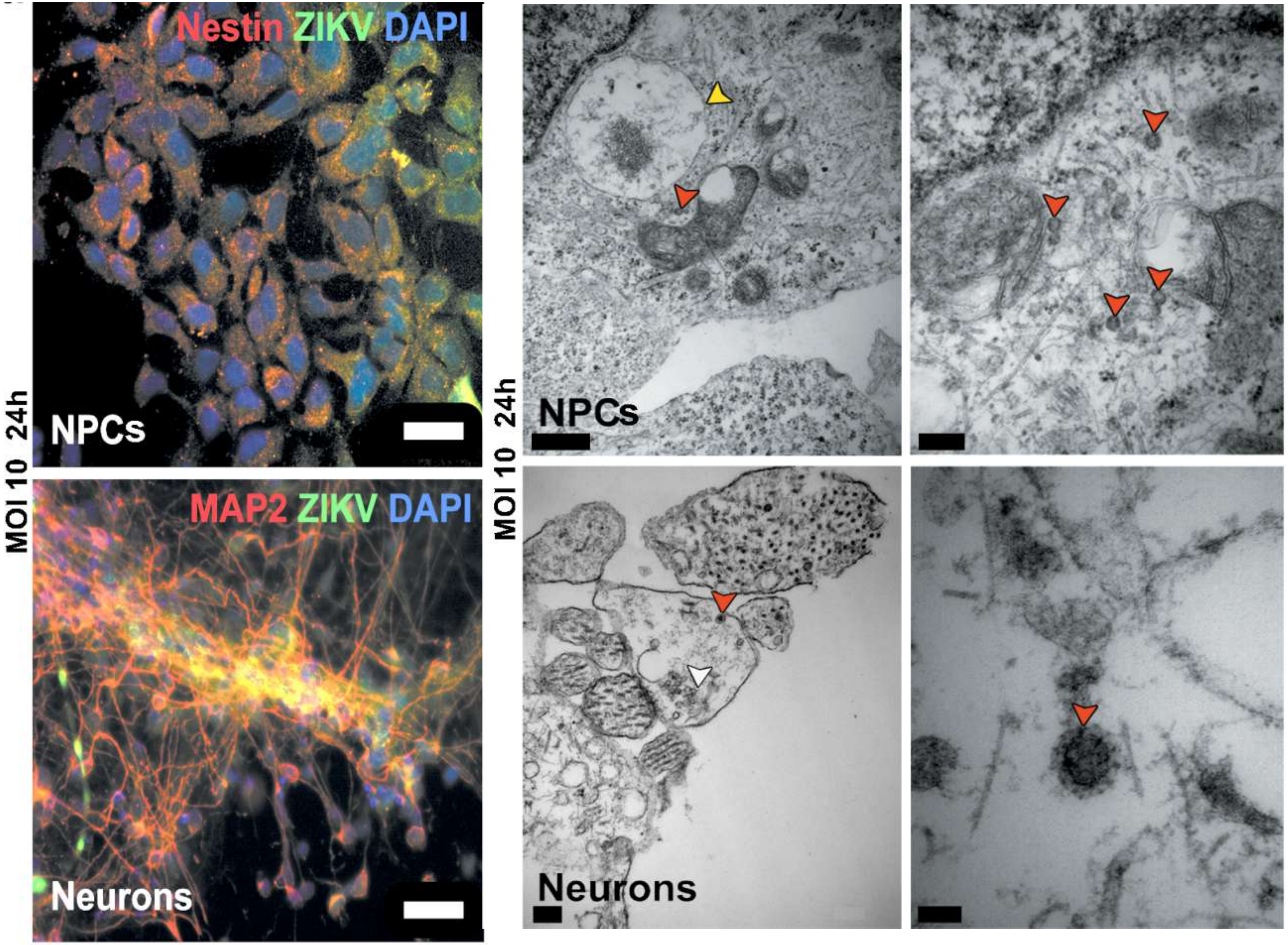
The Brazilian Zika virus strain causes birth defects in experimental models

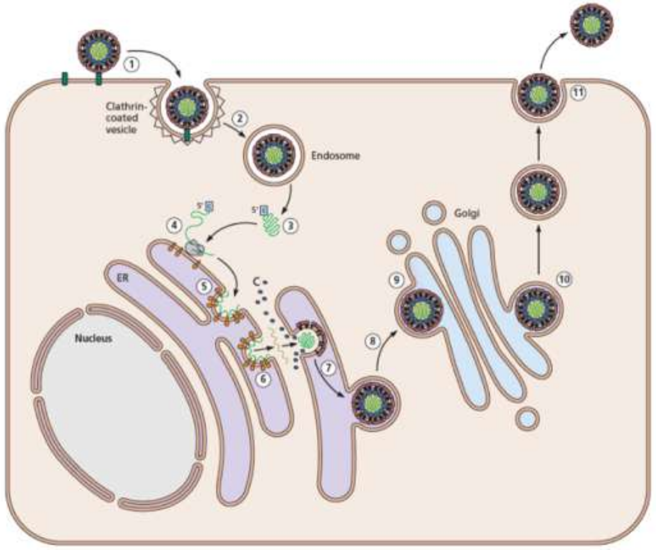
Fernanda R. Cugola[1]*, Isabella R. Fernandes[1,2]*, Fabiele B. Russo[1,3]*, Beatriz C. Freitas[2], João L. M. Dias[1], Katia P. Guimarães[1], Cecília Benazzato[1], Nathalia Almeida[1], Graciela C. Pignatari[1,3], Sarah Romero[2], Carolina M. Polonio[4], Isabela Cunha[4], Carla L. Freitas[4], Wesley N. Brandão[4], Cristiano Rossato[4], David G. Andrade[4], Daniele de P. Faria[5], Alexandre T. Garcez[5], Carlos A. Buchpigel[5], Carla T. Braconi[6], Erica Mendes[6], Amadou A. Sall[7], Paolo M. de A. Zanotto[6], Jean Pierre S. Peron[4], Alysson R. Muotri[2] & Patricia C. B. Beltrão-Braga[1,8]



Cugola, Fernandes, Russo, et al. Nature 2016

ZIKV infecta NPC e neurônios e se replica em vesículas

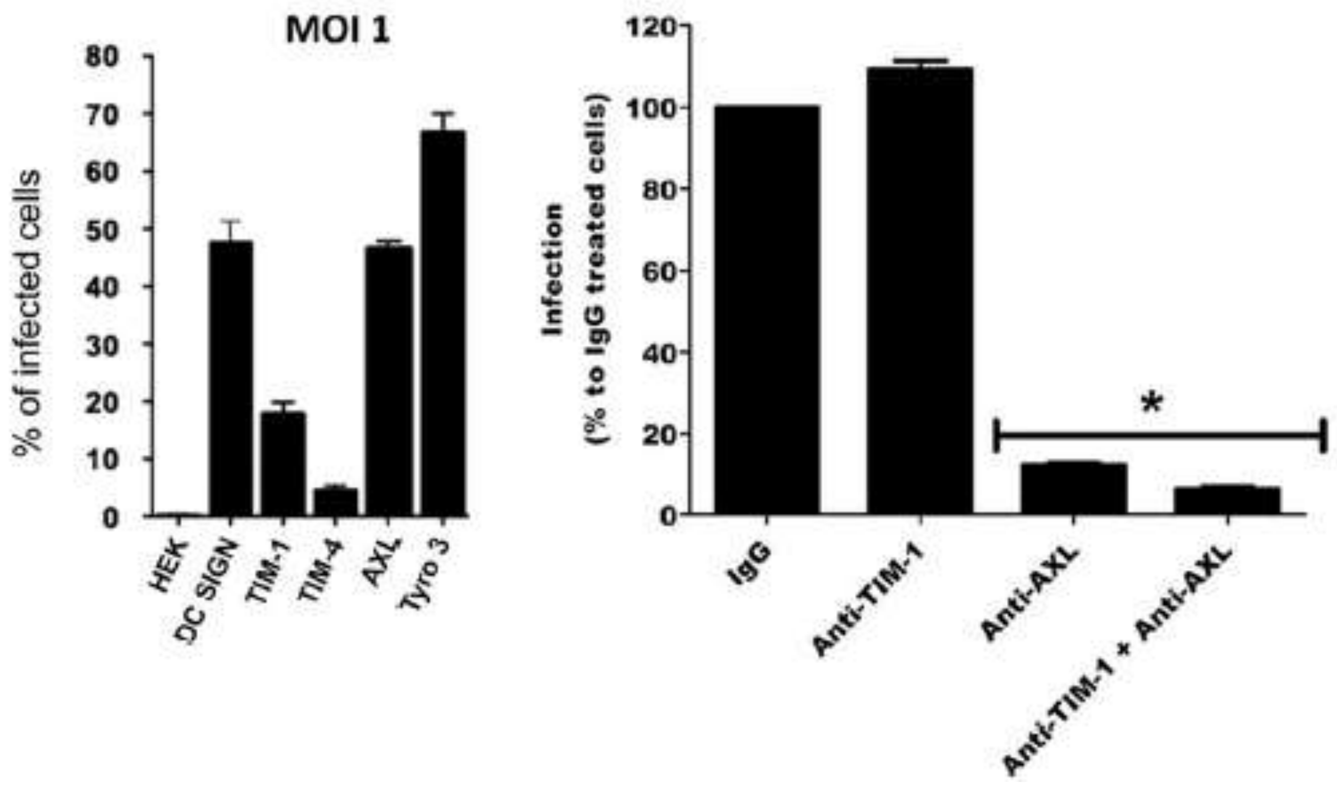




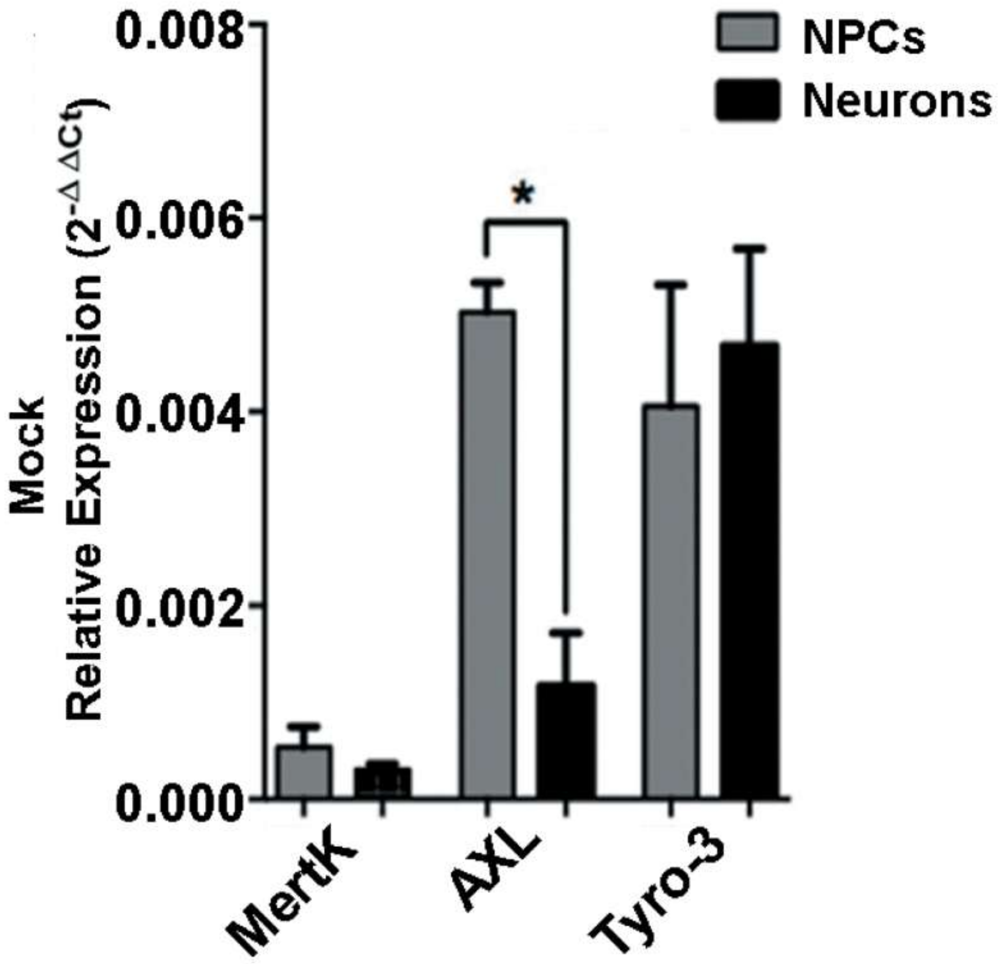
NPC e neurônios tem receptores TAM na superfície

Biology of Zika Virus Infection in Human Skin Cells

Rodolphe Hamel,[a] Ophélie Dejarnac,[b] Sineewanlaya Wichit,[a] Peeraya Ekchariyawat,[a] Aymeric Neyret,[c] Natthanej Luplertlop,[d] Manuel Perera-Lecoin,[a] Pornapat Surasombatpattana,[e] Loïc Talignani,[a] Frédéric Thomas,[a] Van-Mai Cao-Lormeau,[f] Valérie Choumet,[g] Laurence Briant,[c] Philippe Desprès,[h] Ali Amara,[b] Hans Yssel,[i] Dorothée Missé[a]

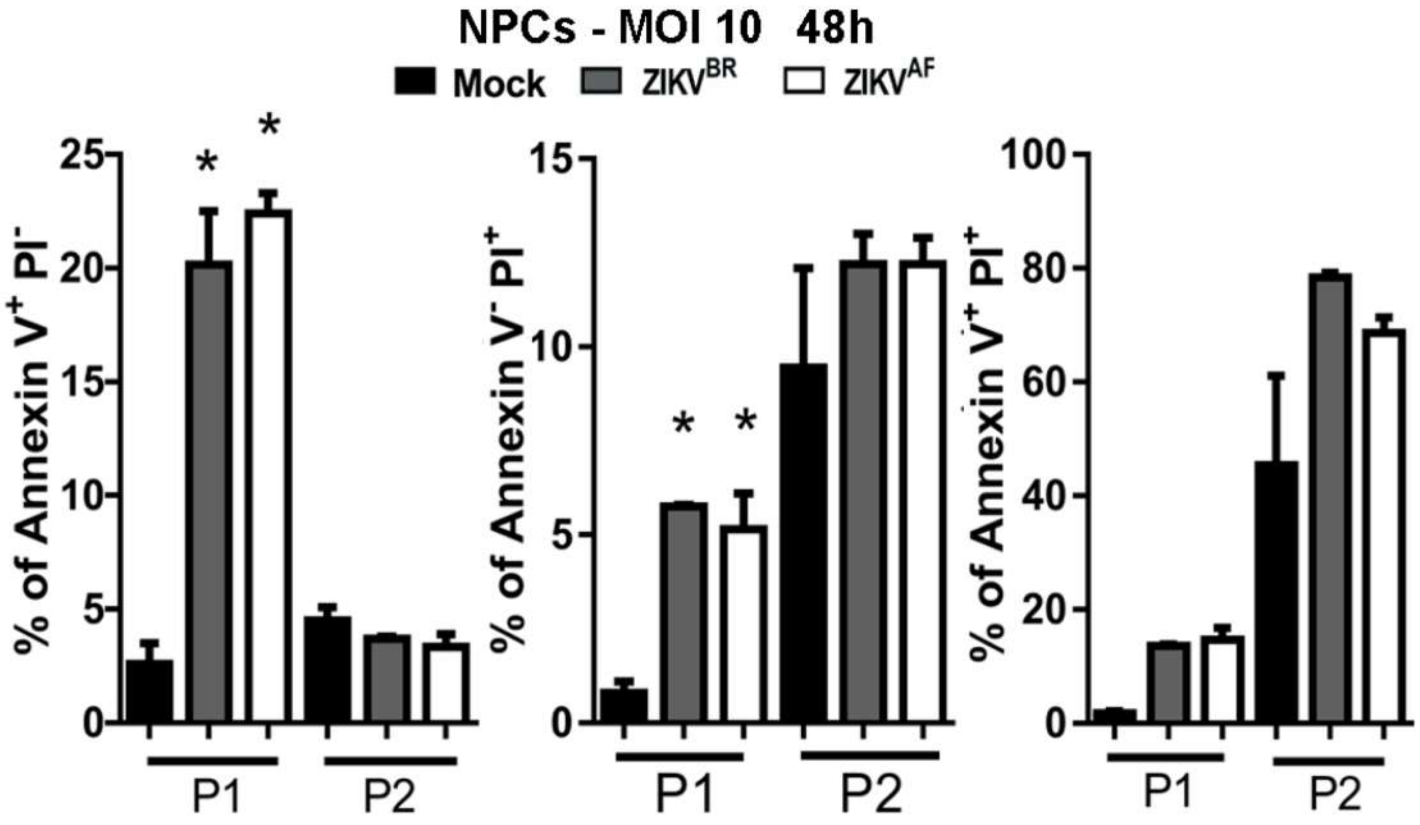


Hamel et al. JVI, 2015

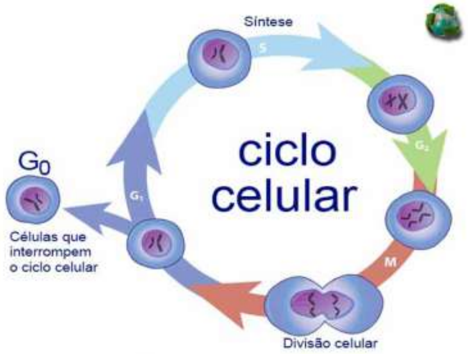


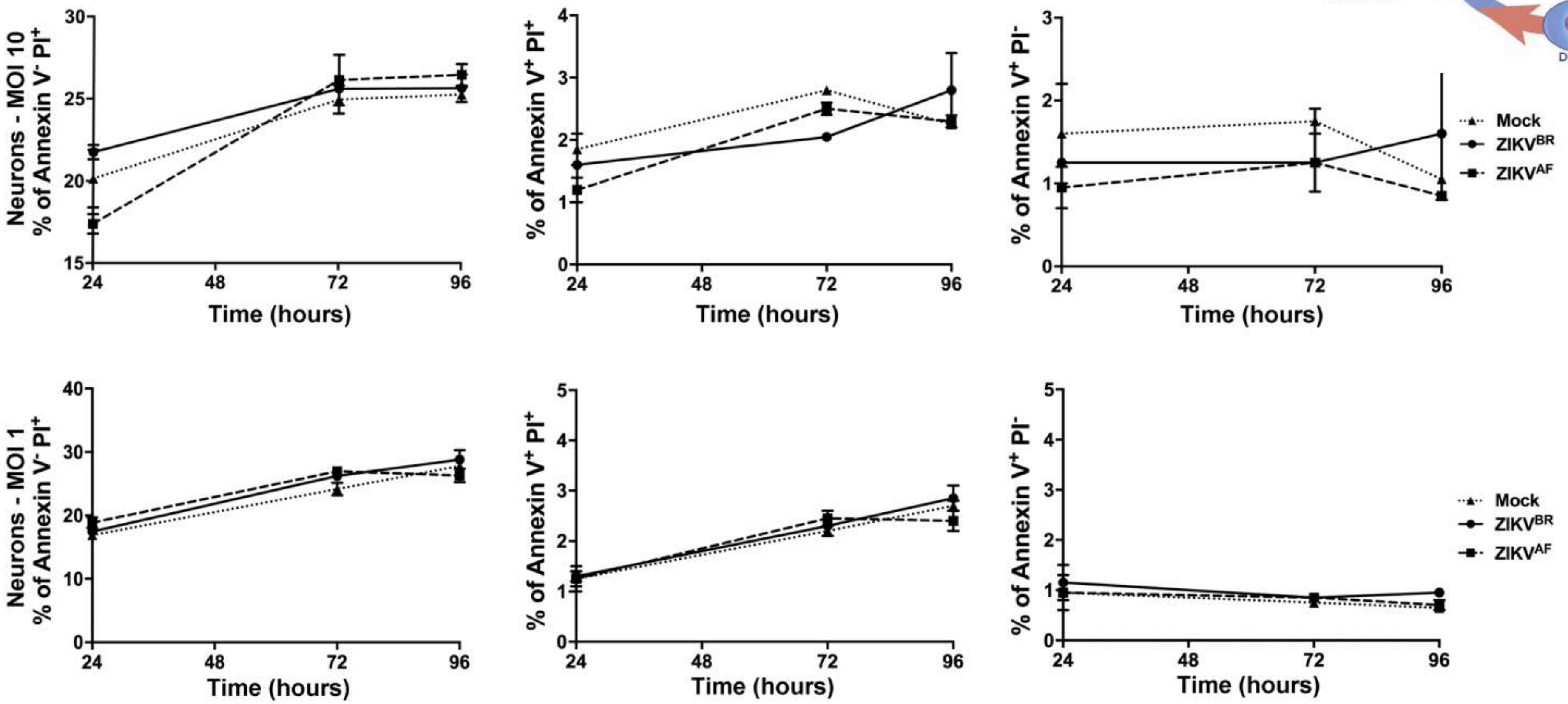
Cugola, Fernandes, Russo, et al. Nature 2016

NPC infectadas morriam por apoptose

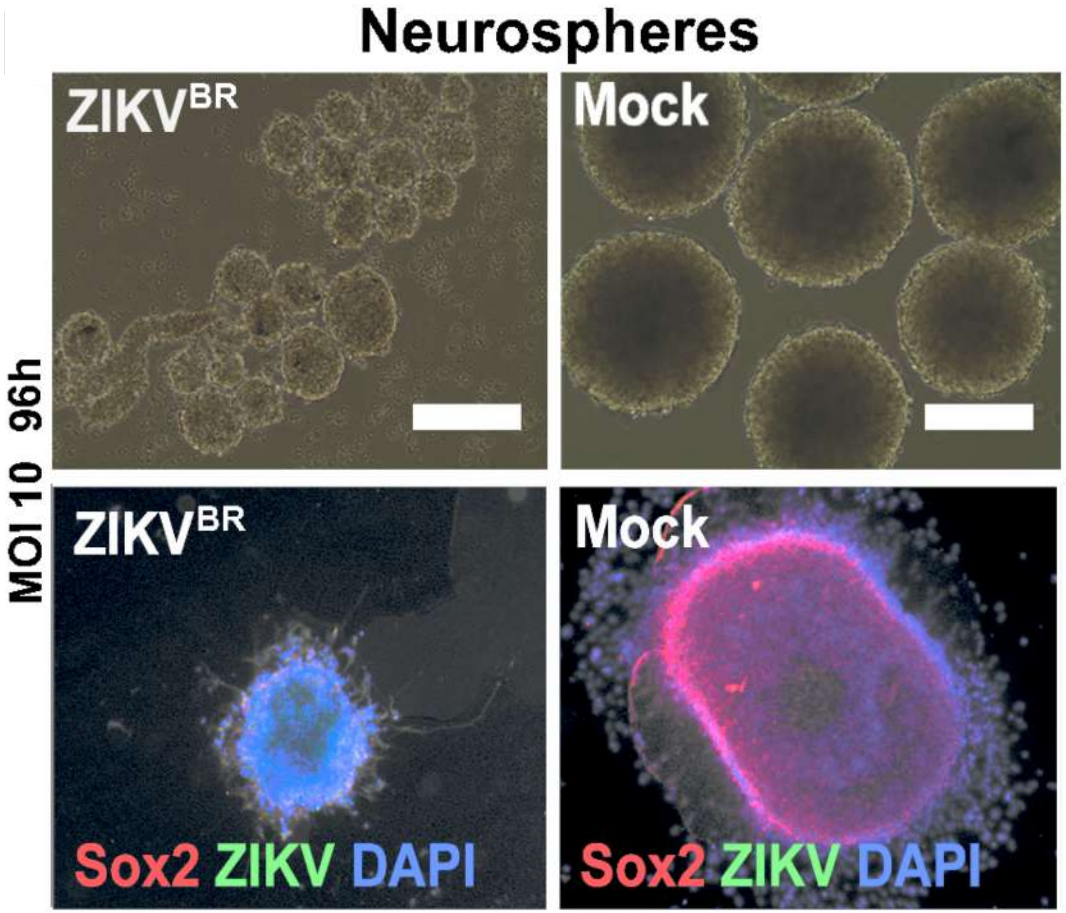


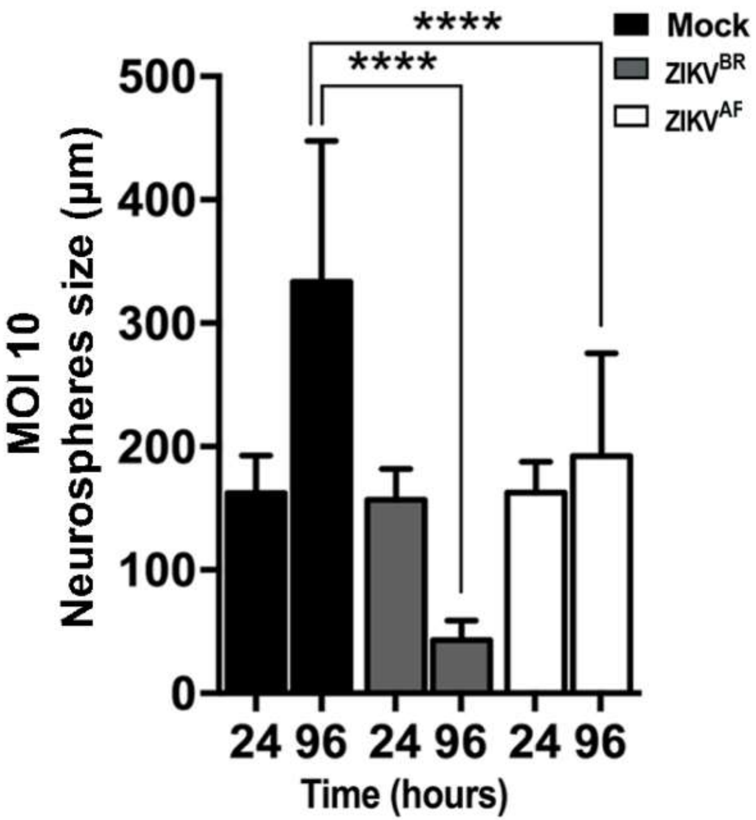
Neurônios não entravam em apoptose



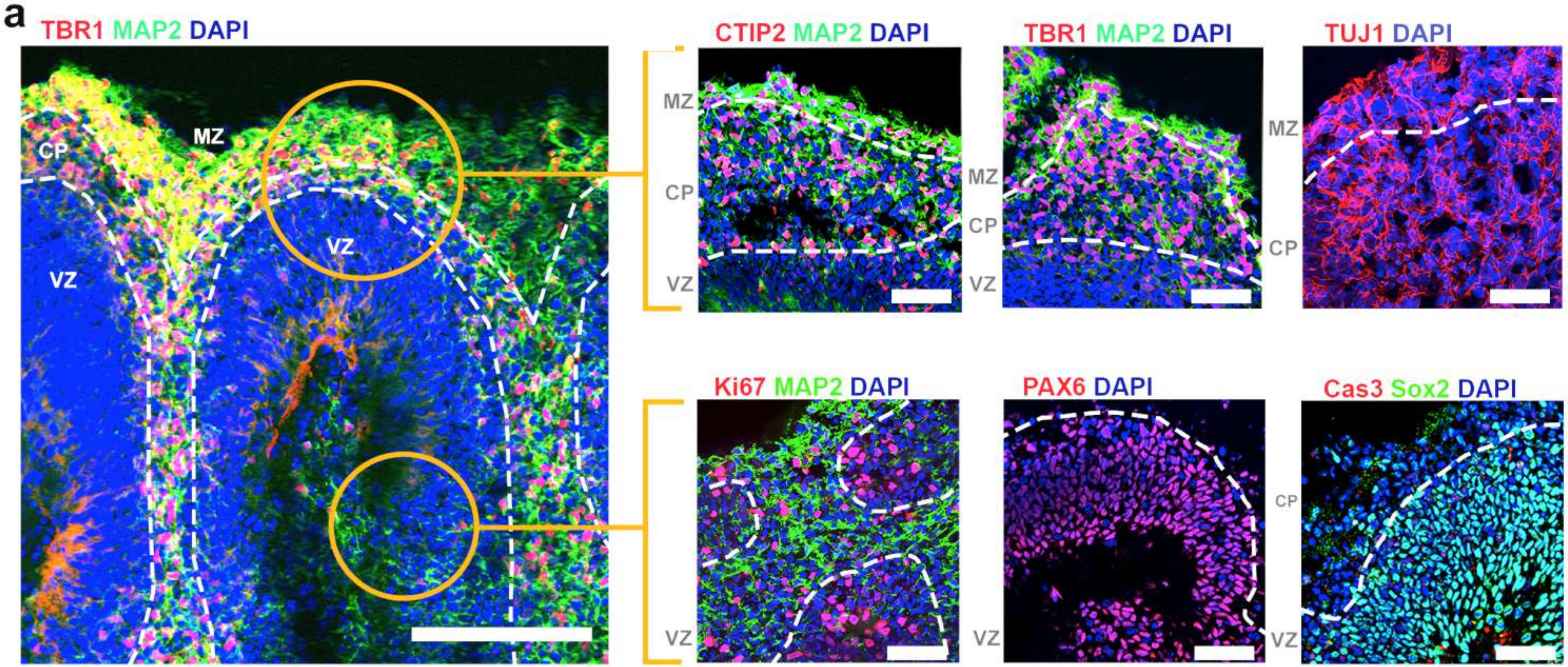


Neuroesferas diminuiram de tamanho em 4 dias e as células não migravam

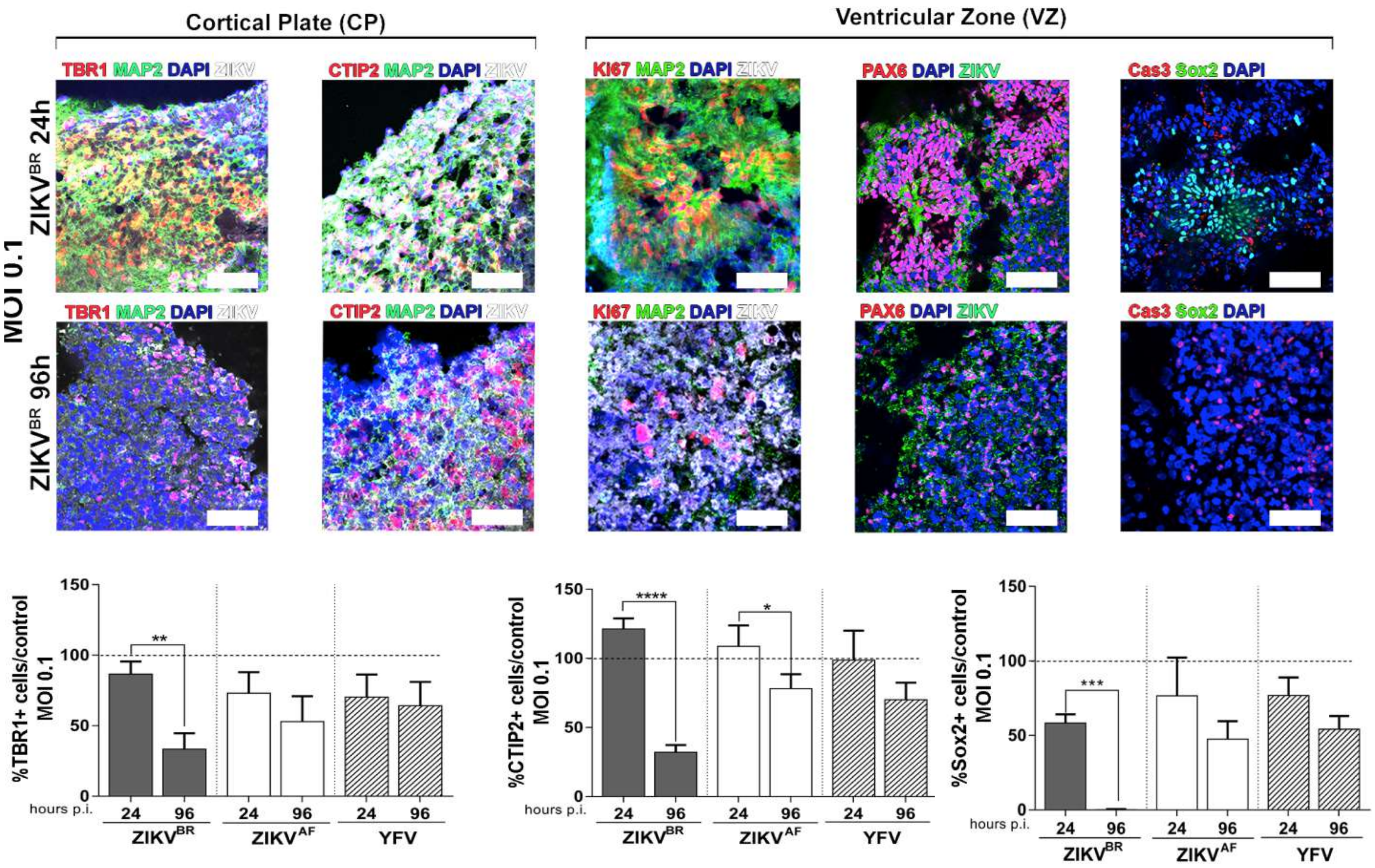




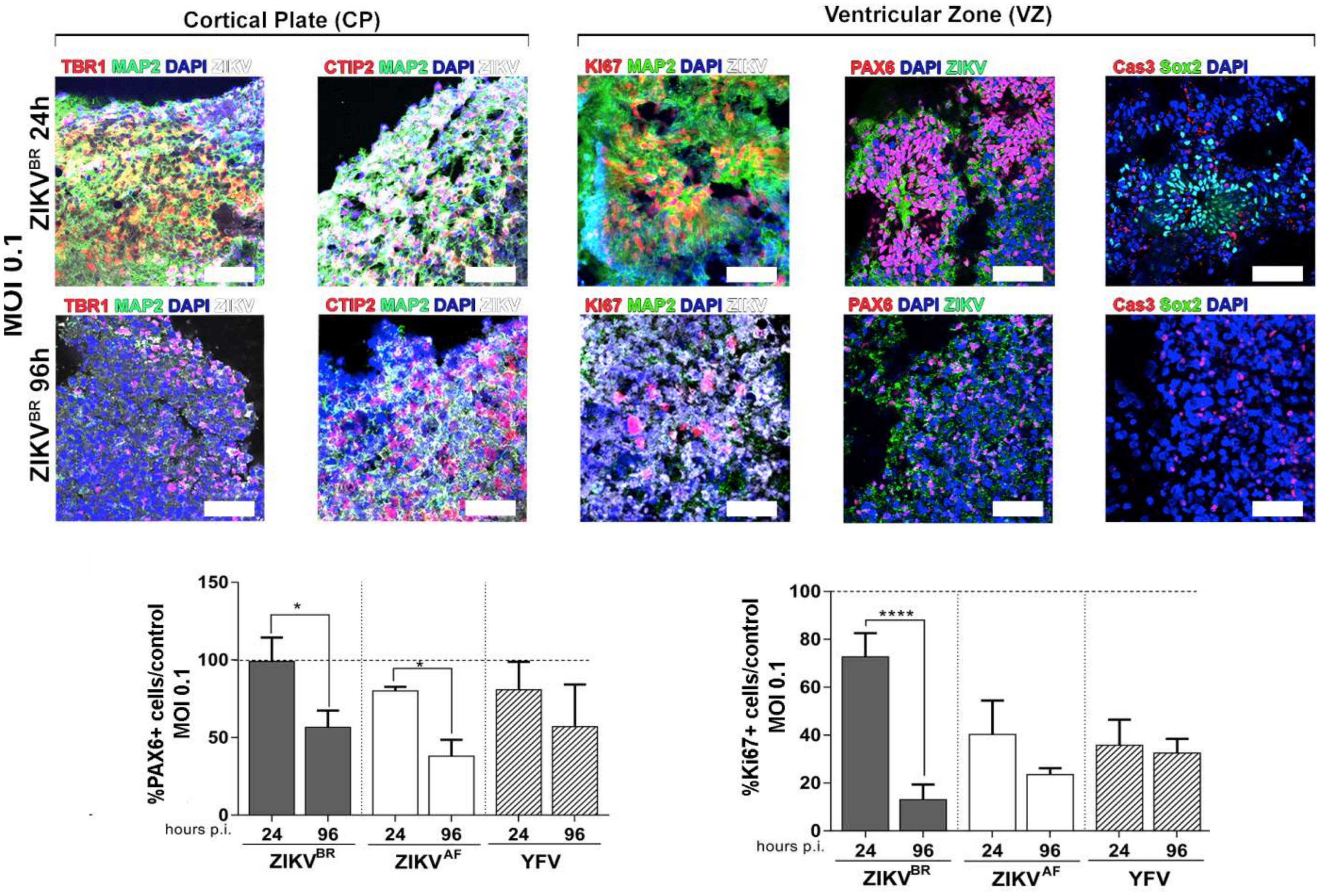
ZIKV infecta organóides cerebrais, na placa cortical e na região ventricular



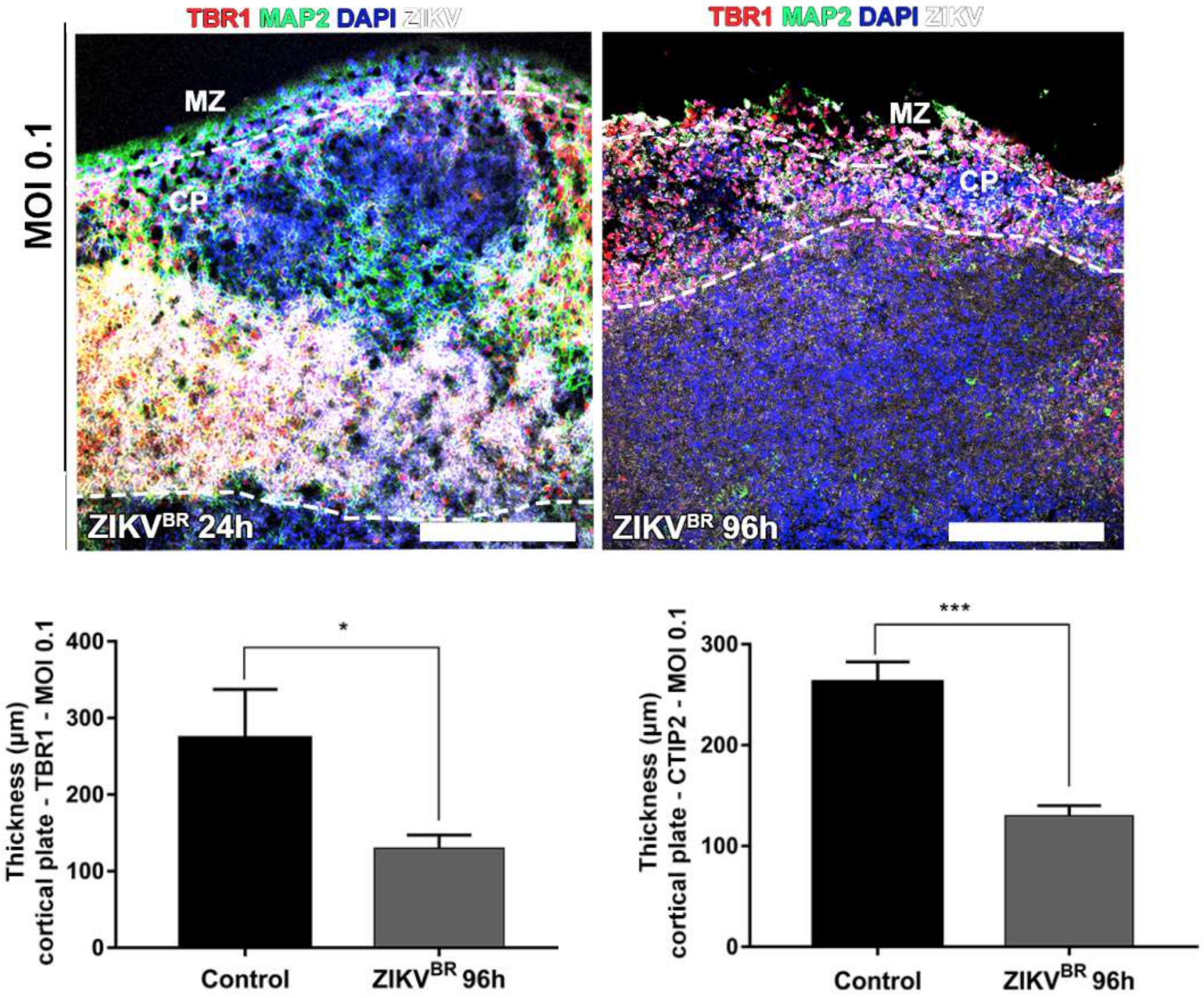
Células progenitoras do córtex e NPC diminuiram em número 96 h p.i.



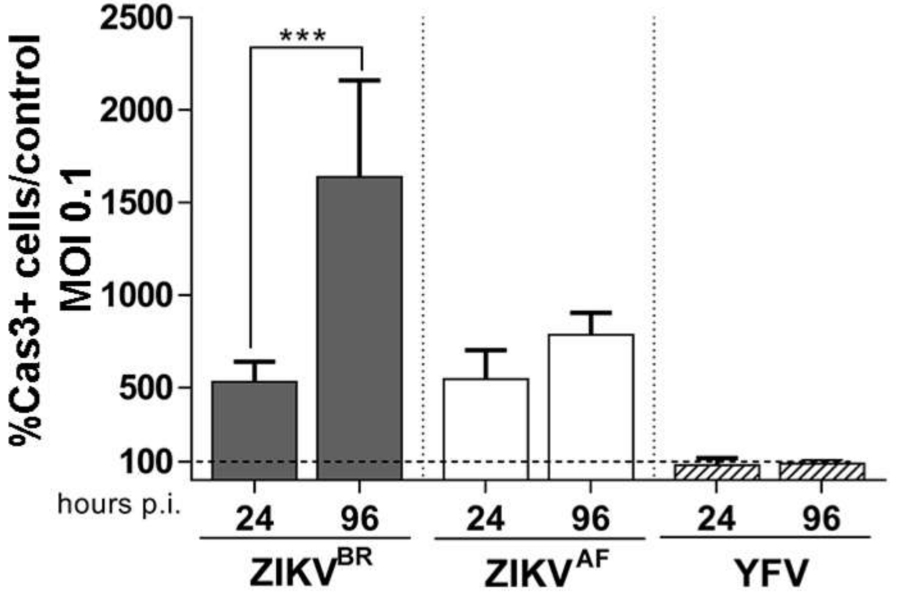
Células mitóticas diminuiram em número 96h p.i.

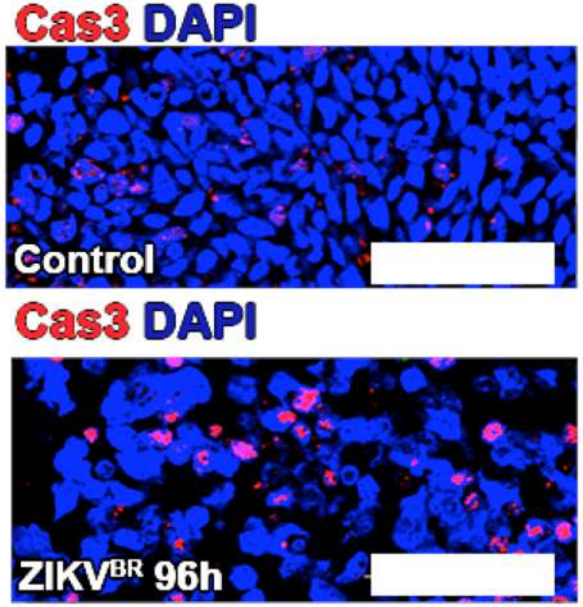


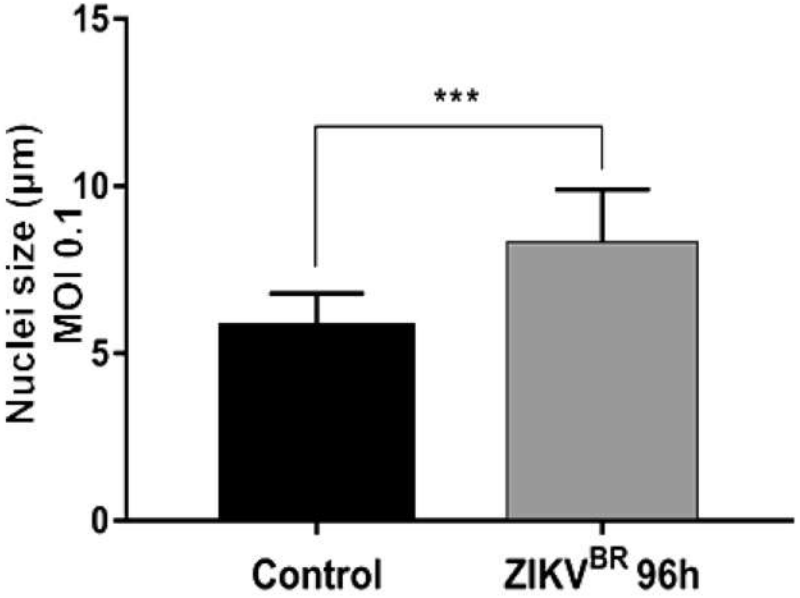
Camada cortical estava menor em 96h p.i.



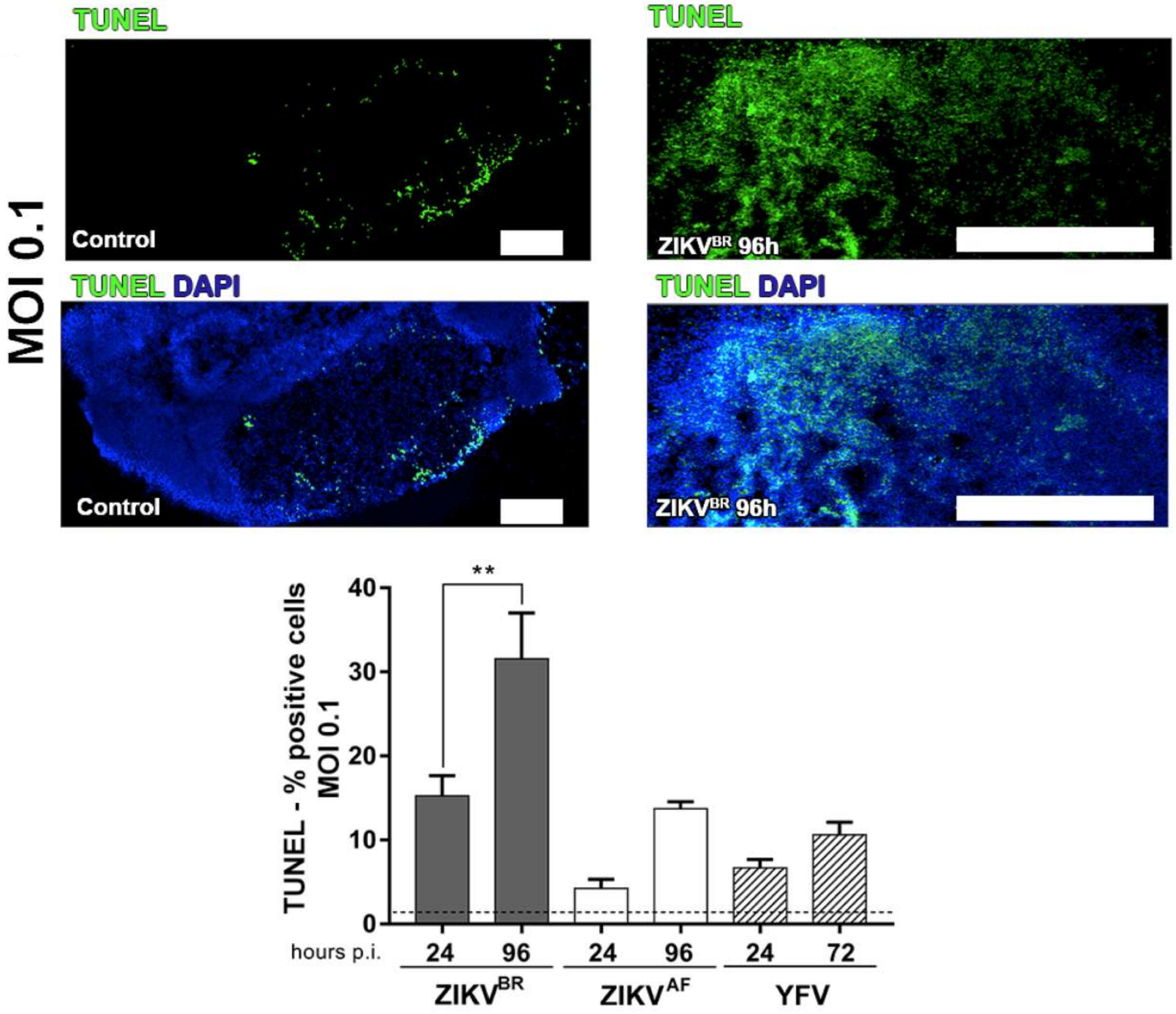
Número de células em apoptose aumentou 96h p.i.



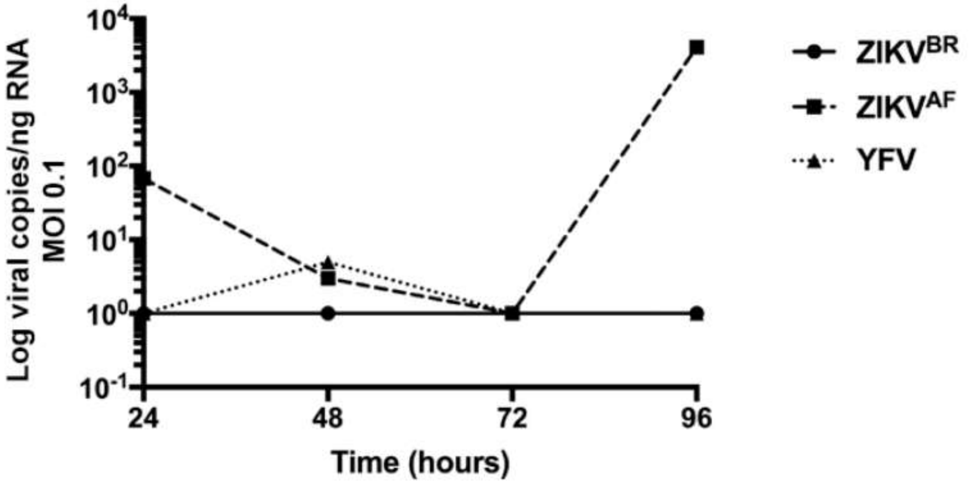


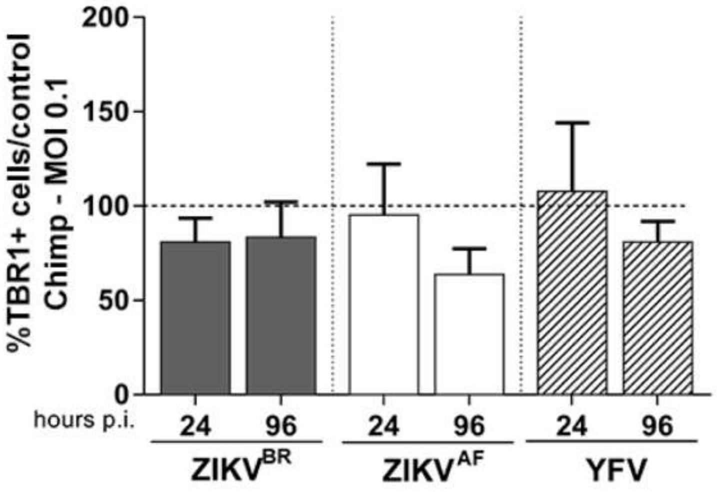


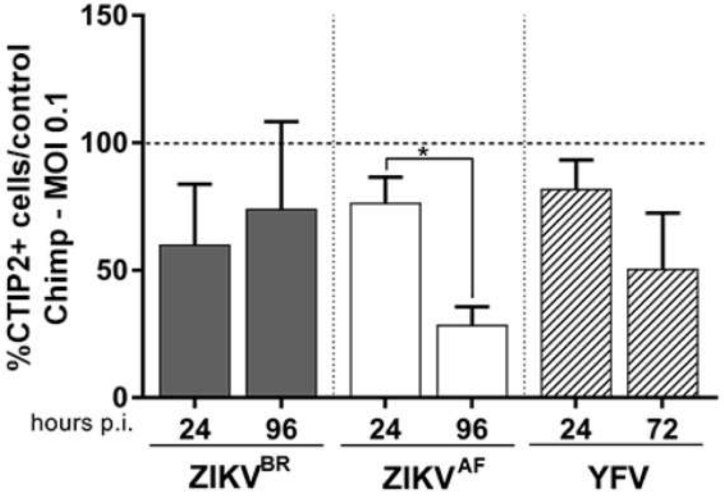
Efeito citopático viral?


TUNEL
TUNEL
MOI 0.1
Control
ZIKV^BR 96h
TUNEL DAPI
TUNEL DAPI
Control
ZIKV^BR 96h
**
TUNEL - % positive cells
MOI 0.1
40
30
20
10
0
hours p.i.
24
96
24
96
24
72
ZIKV^BR
ZIKV^AF
YFV

Em *"mini-cérebros"* de chimpanzé o comportamento entre as cepas brasileira e africana foi o inverso!







Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

Hengli Tang,[1,11,*] Christy Hammack,[1,11] Sarah C. Ogden,[1,11] Zhexing Wen,[2,3,11] Xuyu Qian,[2,4,11] Yujing Li,[9] Bing Yao,[9] Jaehoon Shin,[2,5] Feiran Zhang,[9] Emily M. Lee,[1] Kimberly M. Christian,[2,3] Ruth A. Didier,[10] Peng Jin,[9] Hongjun Song,[2,3,5,6,7,*] and Guo-li Ming[2,3,5,6,7,8,*]

Zika virus impairs growth in human neurospheres and brain organoids

Patricia P. Garcez,[1,2*] Erick Correia Loiola,[2†] Rodrigo Madeiro da Costa,[2†] Luiza M. Higa,[3†] Pablo Trindade,[2†] Rodrigo Delvecchio,[3] Juliana Minardi Nascimento,[2,4] Rodrigo Brindeiro,[3] Amilcar Tanuri,[3] Stevens K. Rehen[2,1*]

Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure

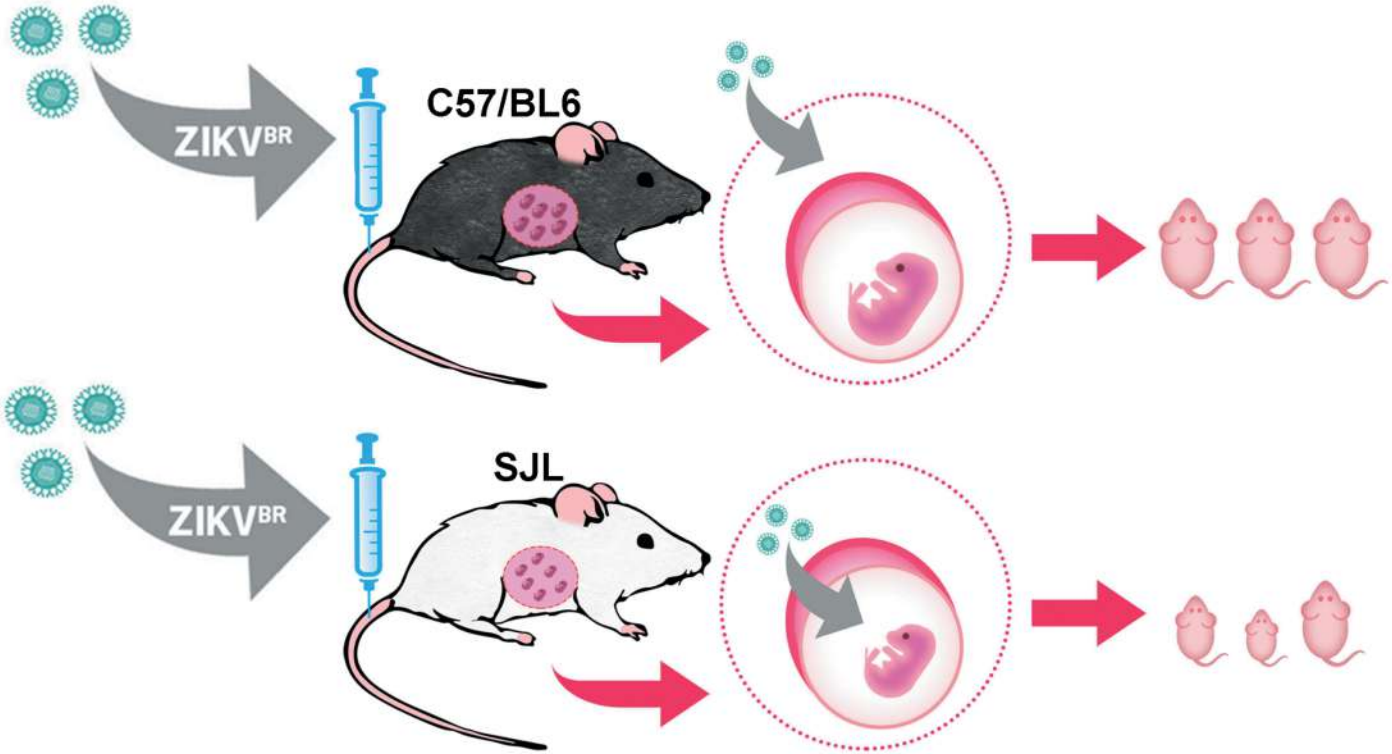
Xuyu Qian,[1,2,18] Ha Nam Nguyen,[1,3,4,18] Mingxi M. Song,[1,9] Christopher Hadiono,[1,10] Sarah C. Ogden,[11] Christy Hammack,[11] Bing Yao,[12] Gregory R. Hamersky,[5] Fadi Jacob,[1] Chun Zhong,[1,4] Ki-jun Yoon,[1,4] William Jeang,[1,14] Li Lin,[12] Yujing Li,[12] Jai Thakor,[1] Daniel A. Berg,[1] Ce Zhang,[1,4] Eunchai Kang,[1,4] Michael Chickering,[1] David Nauen,[1,6] Cheng-Ying Ho,[15,16] Zhexing Wen,[1,4] Kimberly M. Christian,[1,4] Pei-Yong Shi,[17] Brady J. Maher,[5,7] Hao Wu,[13] Peng Jin,[12] Hengli Tang,[11] Hongjun Song,[1,3,4,8,*] and Guo-li Ming[1,3,4,7,8,*]

Cell Stem Cell

Brief Report

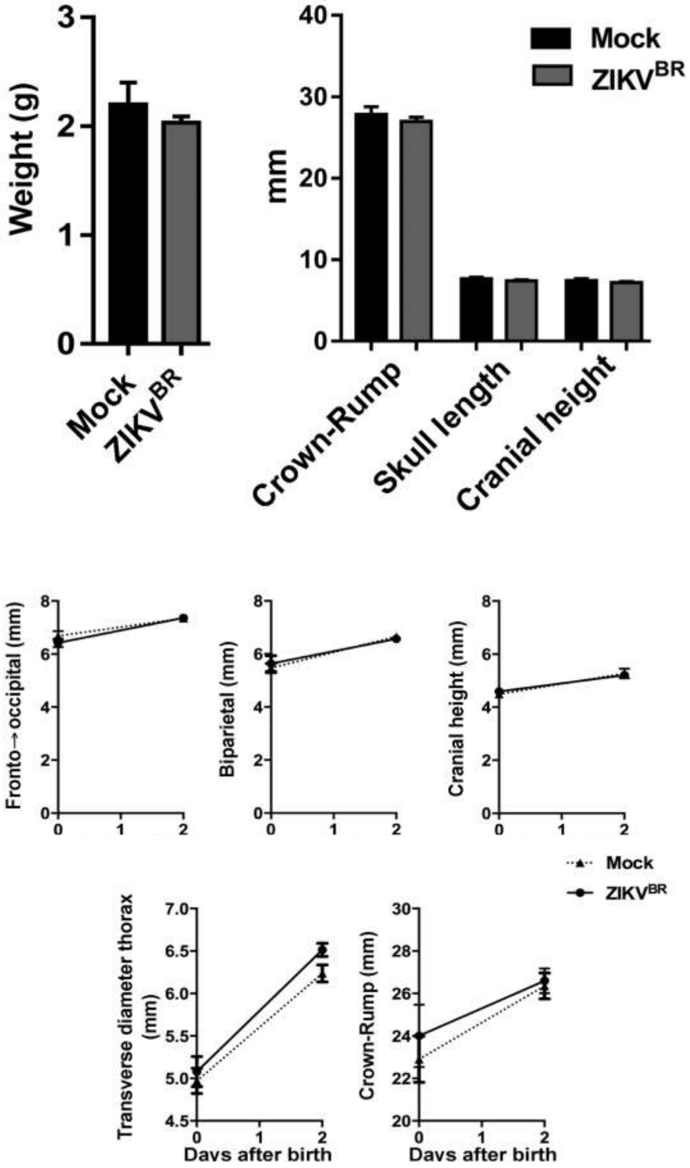
Expression Analysis Highlights AXL as a Candidate Zika Virus Entry Receptor in Neural Stem Cells

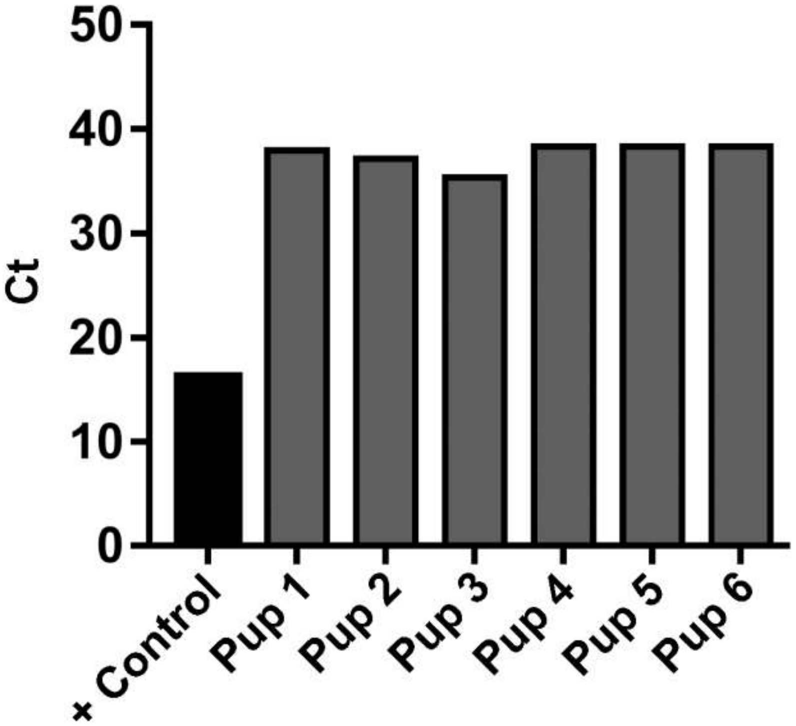
ZIKV é capaz de cruzar a placenta e infectar os fetos?



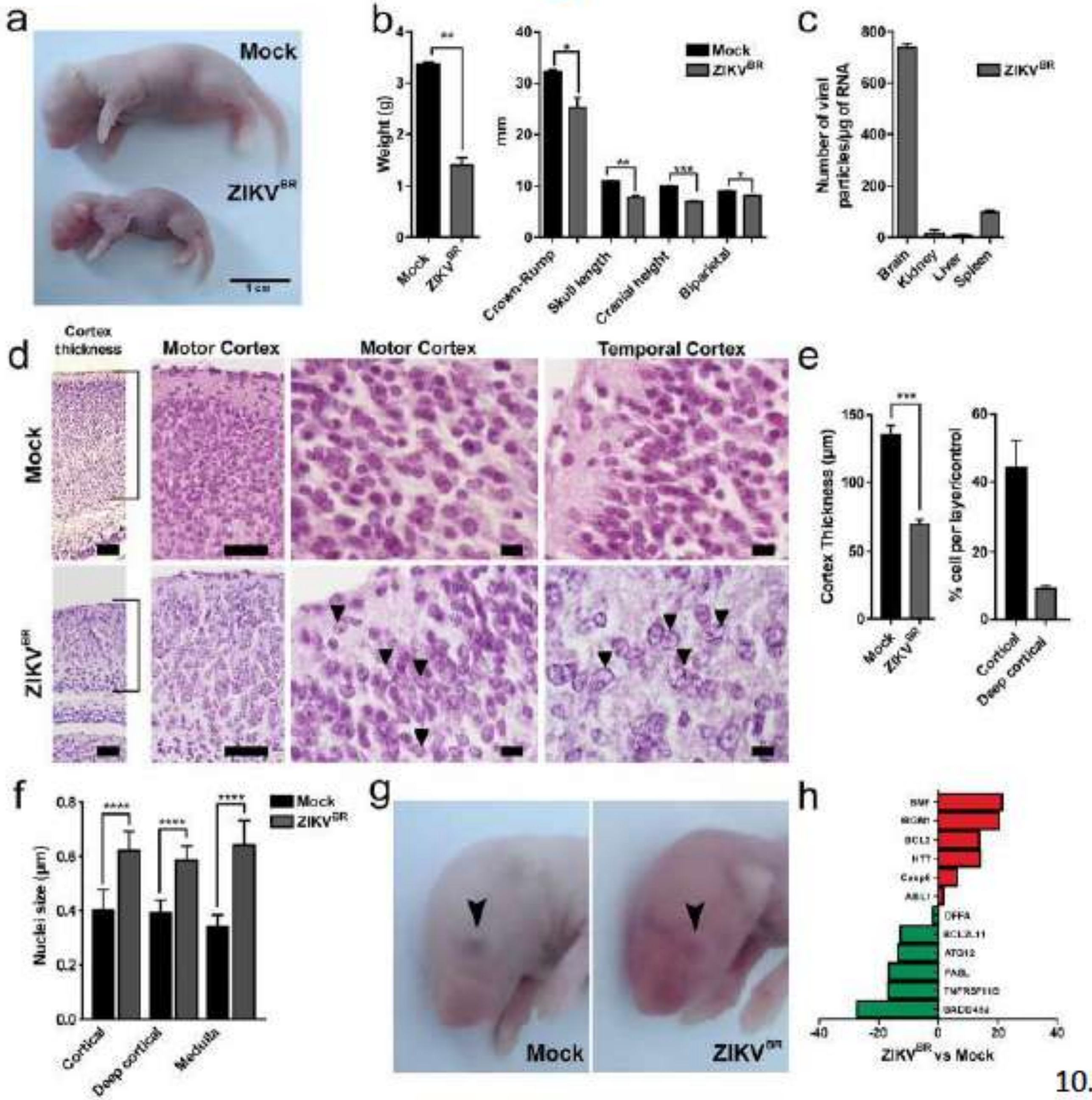
Cugola, Fernandes, Russo, et al. Nature 2016

C57/BL6 não são susceptíveis ao ZIKV





Arboviroses Emergentes: Zika Vírus



10.1038/nature18296

Zika Virus Infection of the Central Nervous System of Mice

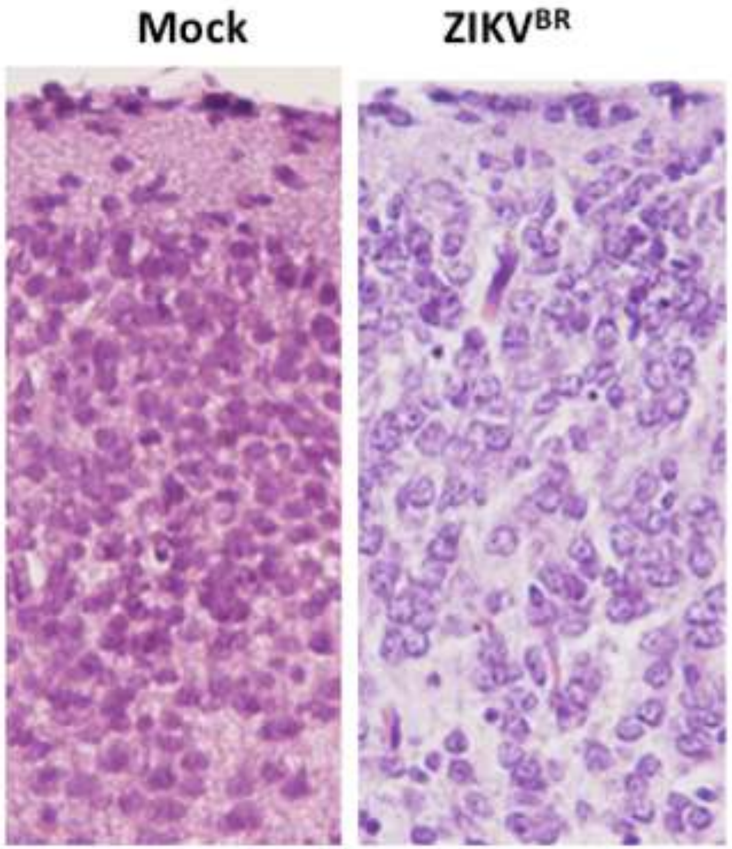
By

T. M. Bell, E. J. Field, and H. K. Narang

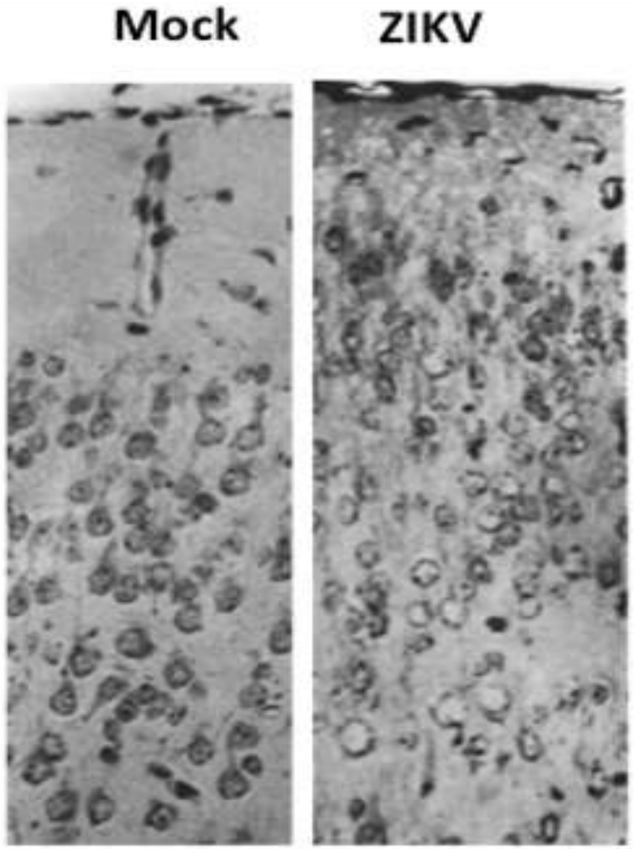
Medical Research Council, Demyelinating Diseases Unit, Newcastle General Hospital, Newcastle upon Tyne, England

With 8 Figures

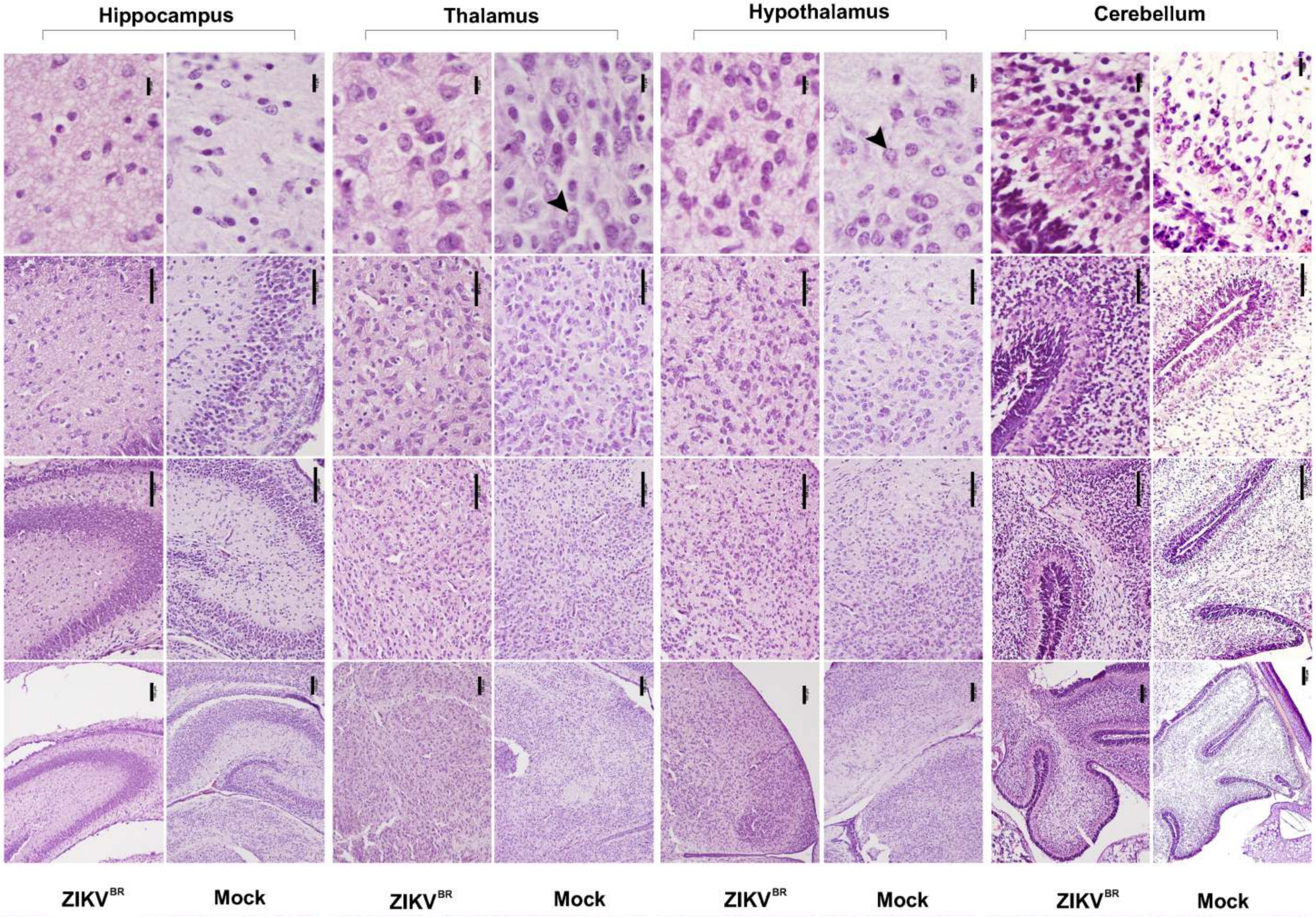
Received February 10, 1971



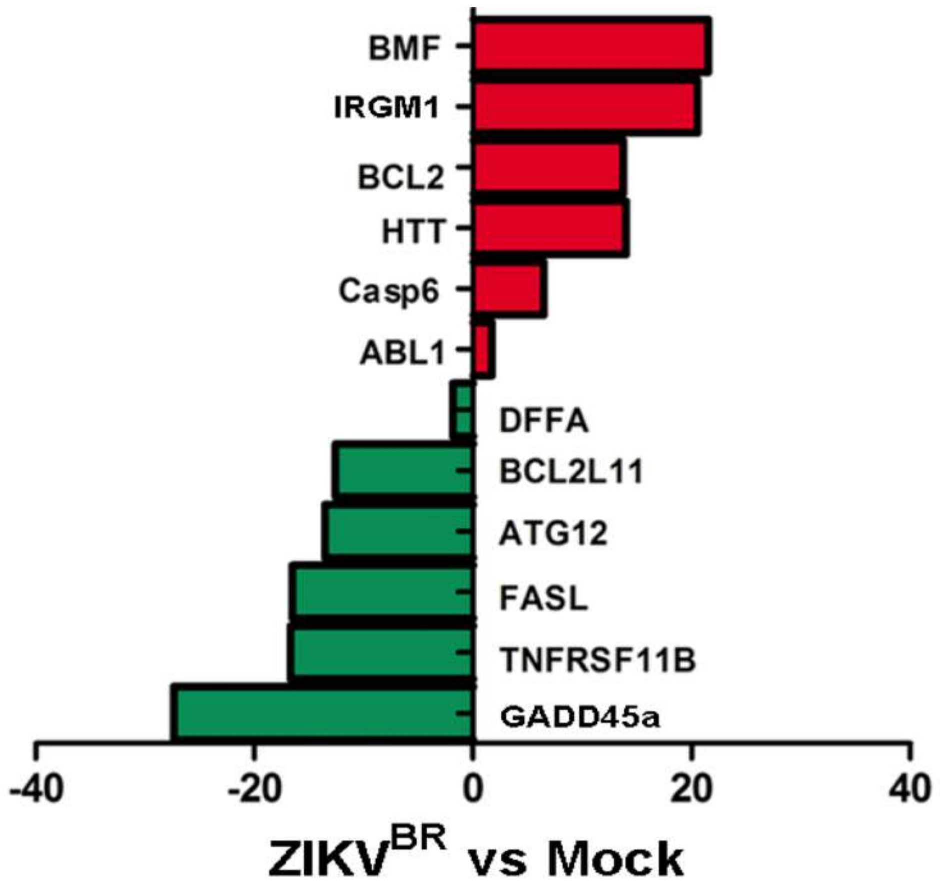
Cugola et al.

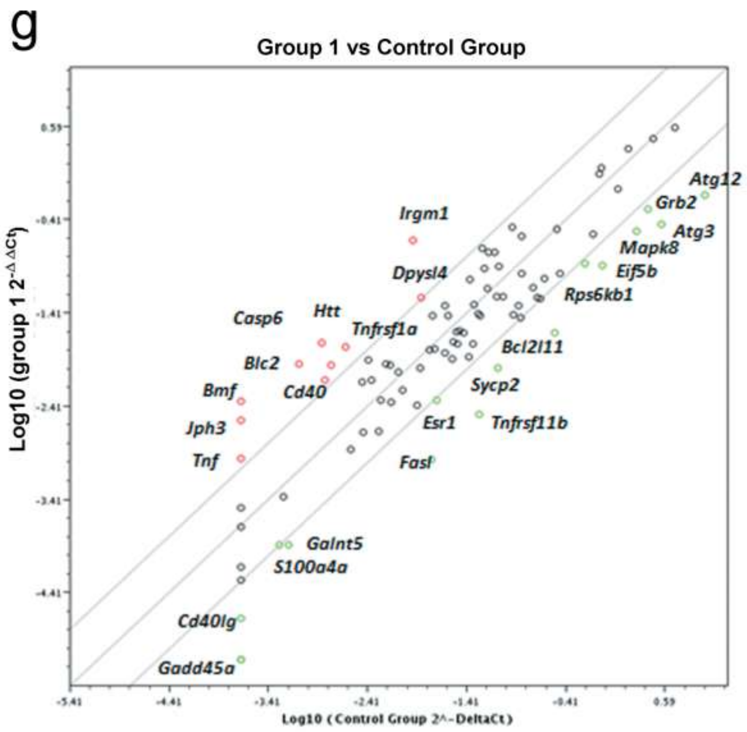


Bell et al, 1971


Hippocampus
Thalamus
Hypothalamus
Cerebellum
ZIKV^BR
Mock
ZIKV^BR
Mock
ZIKV^BR
Mock
ZIKV^BR
Mock

Genes relacionados à apoptose e autofagia estão desregulados no cérebro dos filhotes





had been circulating in Southeast Asia for many years (*10*, *12*). Why was microcephaly not recognized earlier? Besides the potential impact of herd immunity and the lack of diagnostics and surveillance in epidemic areas, one plausible hypothesis is that ZIKV has acquired some adaptive mutations to become more virulent to the human fetal brain. Some preliminary results from cell lines indicate strain-specific effects

Science REPORTS

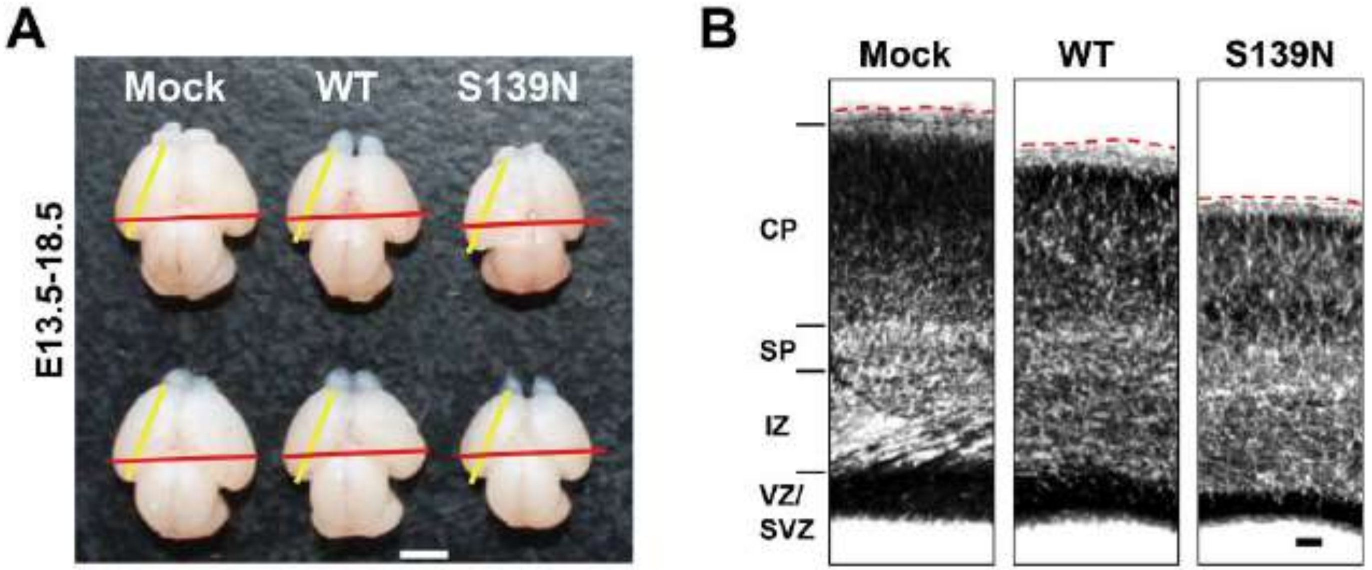
Cite as: L. Yuan *et al*., *Science* 10.1126/science.aam7120 (2017).

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

Yuan et al., Science, 2017

mutação ZIKV S139N

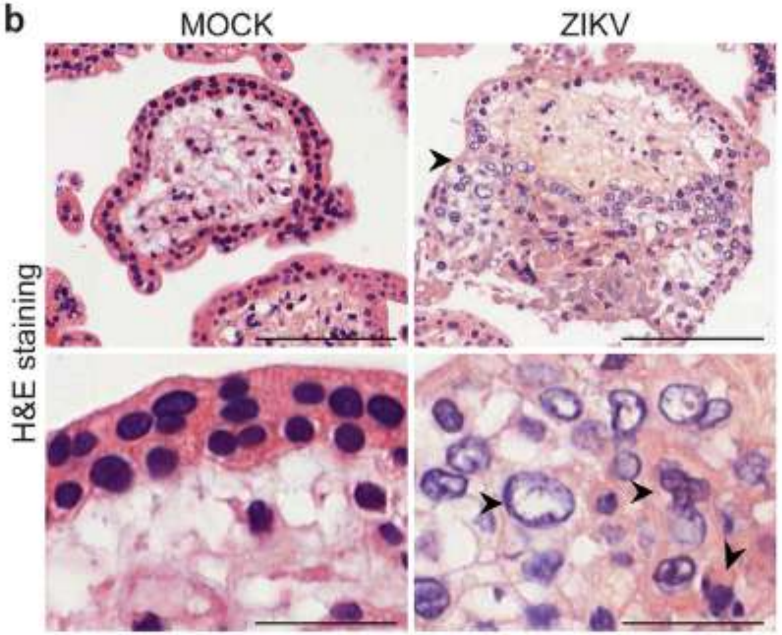
Serina / asparagina

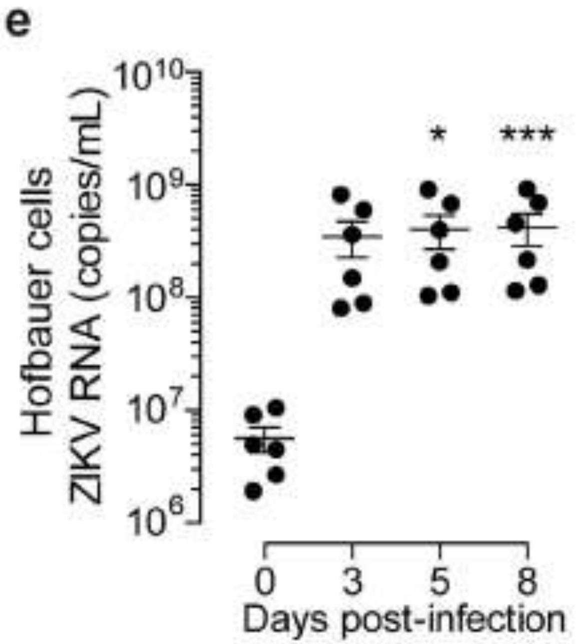


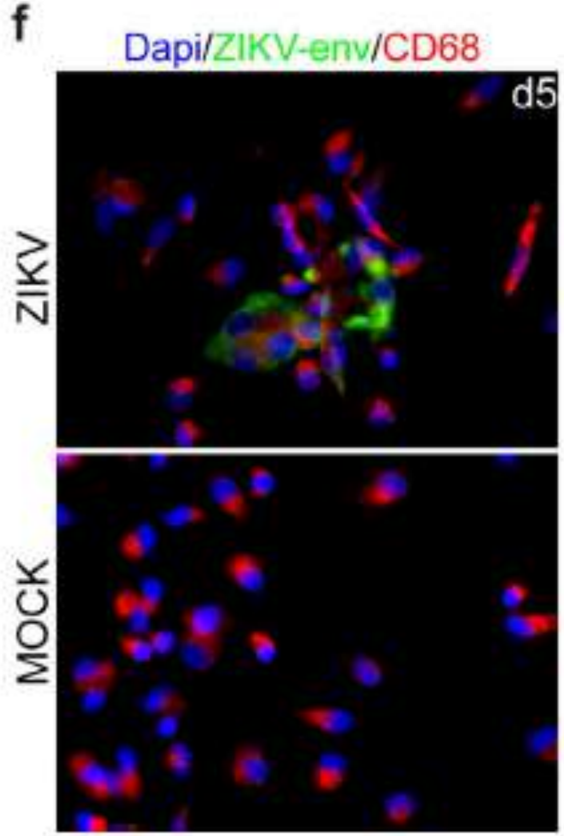
ZIKV infecta células da placenta e macrófagos (Hofbauer)

ZIKA virus reveals broad tissue and cell tropism during the first trimester of pregnancy

Hicham El Costa[1,2,*], Jordi Gouilly[1,*], Jean-Michel Mansuy[2], Qian Chen[1], Claude Levy[3], Géraldine Cartron[4], Francisco Veas[5], Reem Al-Daccak[6], Jacques Izopet[1,2] & Nabila Jabrane-Ferrat[1]



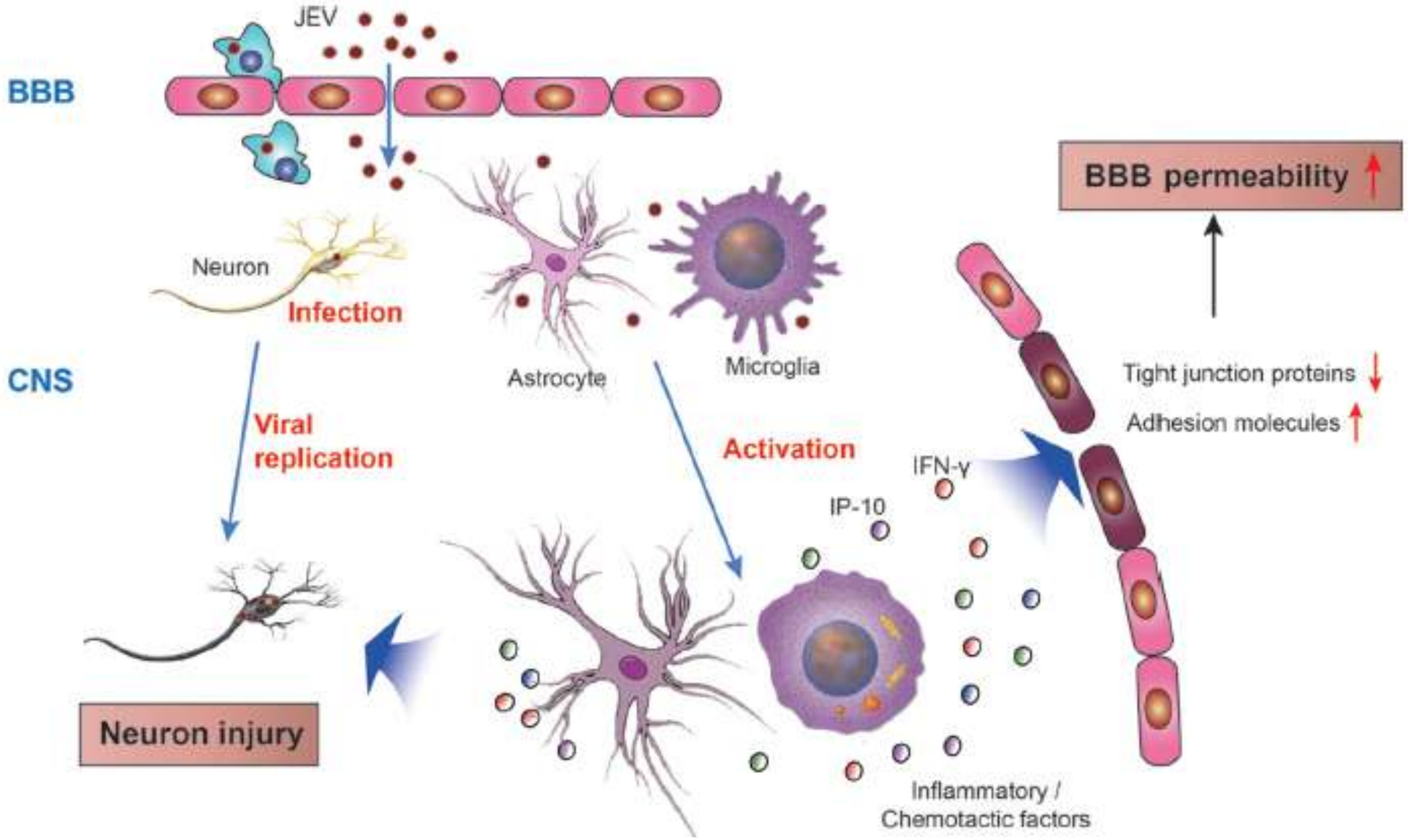




Costa et al., Sci Rep, 2016

Viral Infection of the Central Nervous System and Neuroinflammation Precede Blood-Brain Barrier Disruption during Japanese Encephalitis Virus Infection

Li et al., JIV, 2015



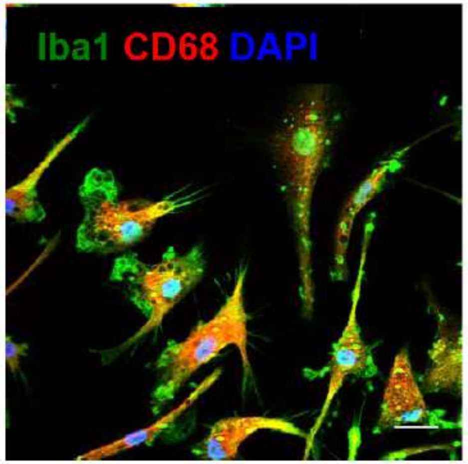
”Mediadores inflamatórios, particularmente IFN-gama, tem um papel central aumentando a permeabilidade da Barreira Hematoencefálica na infecção por JEV, diminuindo a expressão de proteínas das junções ocludentes”.

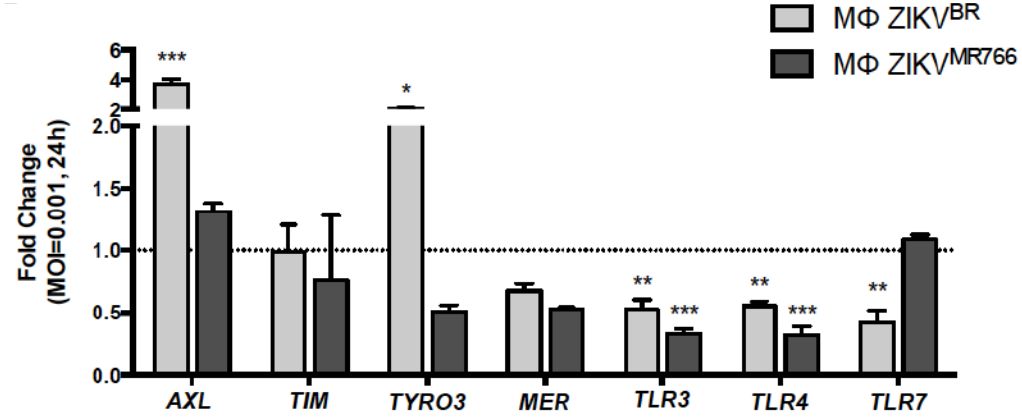
ORIGINAL ARTICLE

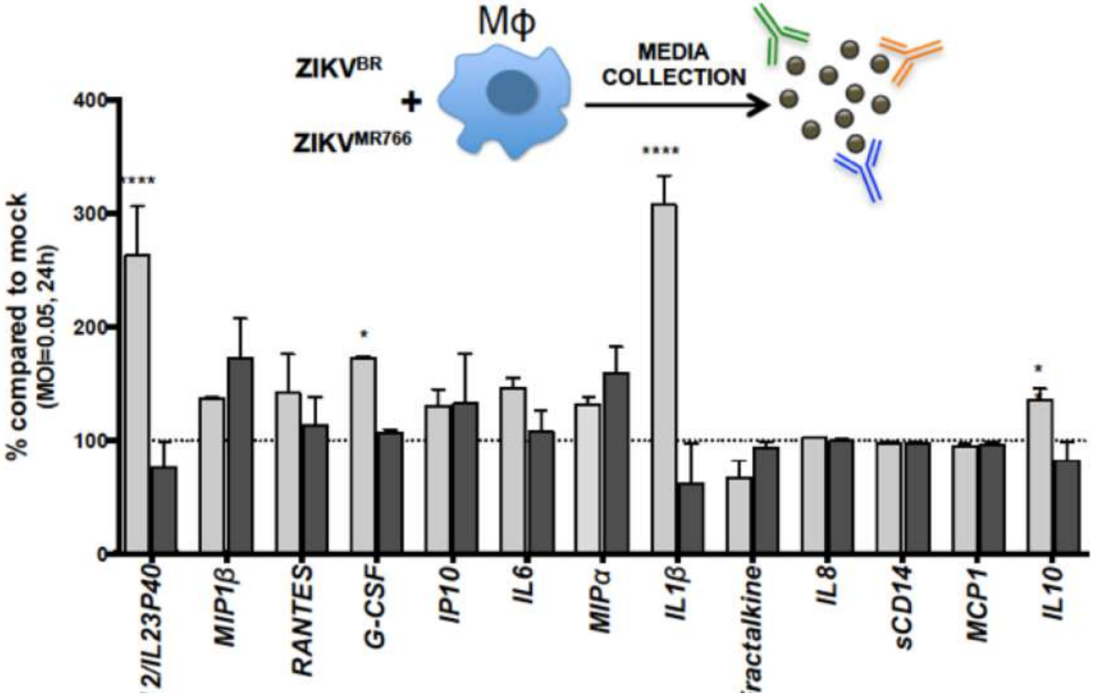
Modeling neuro-immune interactions during Zika virus infection

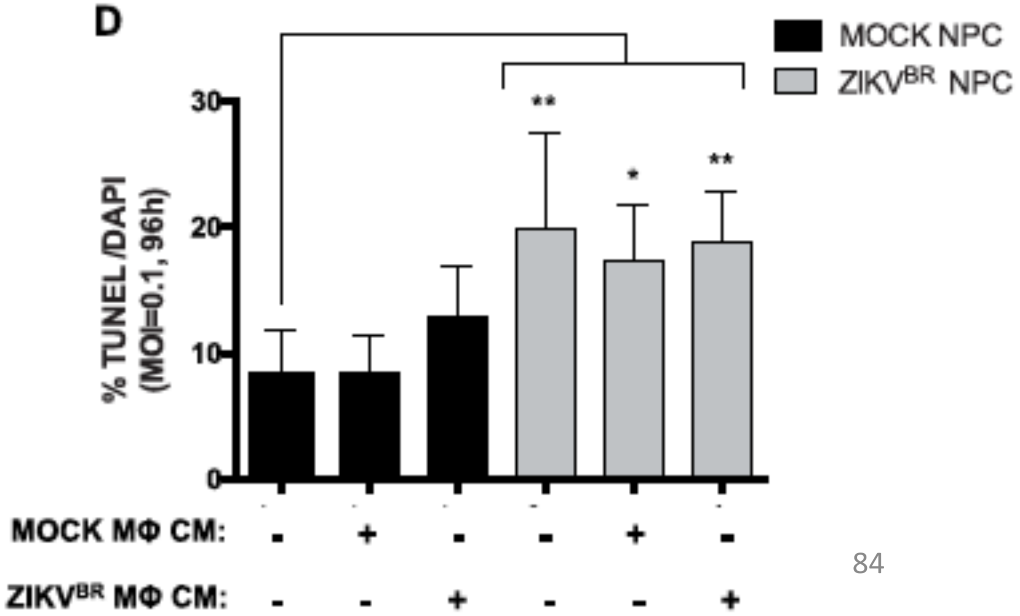
Pinar Mesci[1,2,†], Angela Macia[1,2,†], Christopher N. LaRock[3], Leon Tejwani[1,2]
Isabella R. Fernandes[1,2], Nicole A. Suarez[1,2], Paolo M. de A. Zanotto[4],
Patricia C.B. Beltrão-Braga[5,6,7], Victor Nizet[3] and Alysson R. Muotri[1,2,*]

Mesci et al., Hum Mol Gen, 2018







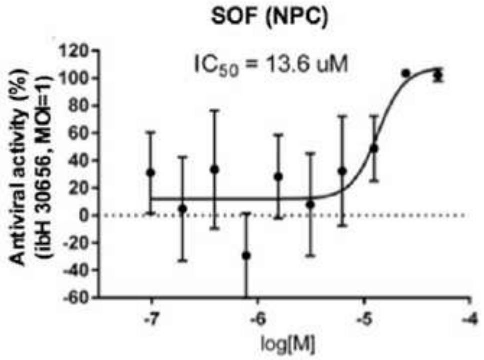


Blocking Zika virus vertical transmission

Pinar Mesci[1], Angela Macia[1], Spencer M. Moore[1], Sergey A. Shiryaev[2], Antonella Pinto[2], Chun-Teng Huang[2], Leon Tejwani[1], Isabella R. Fernandes[1], Nicole A. Suarez[1], Matthew J. Kolar[3], Sandro Montefusco[4], Scott C. Rosenberg[5,6], Roberto H. Herai[7], Fernanda R. Cugola[8,9,10], Fabiele B. Russo[8,9,10], Nicholas Sheets[11], Alan Saghatelian[3], Sujan Shresta[11], Jeremiah D. Momper[12], Jair L. Siqueira-Neto[4], Kevin D. Corbett[5], Patricia C. B. Beltrão-Braga[8,9,10], Alexey V. Terskikh[2] & Alysson R. Muotri[1]

Mesci et al., Sci Rep, 2018

a



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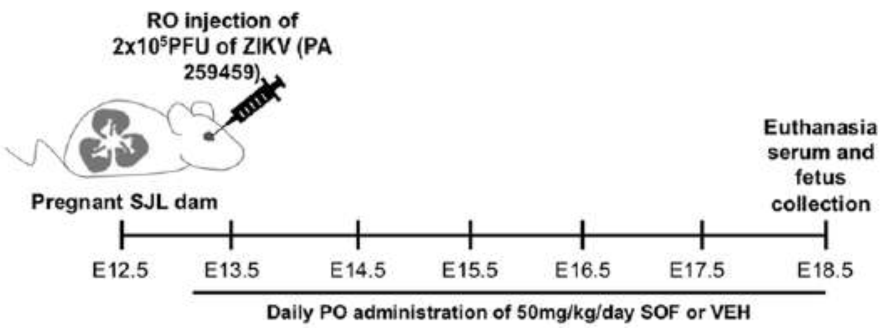

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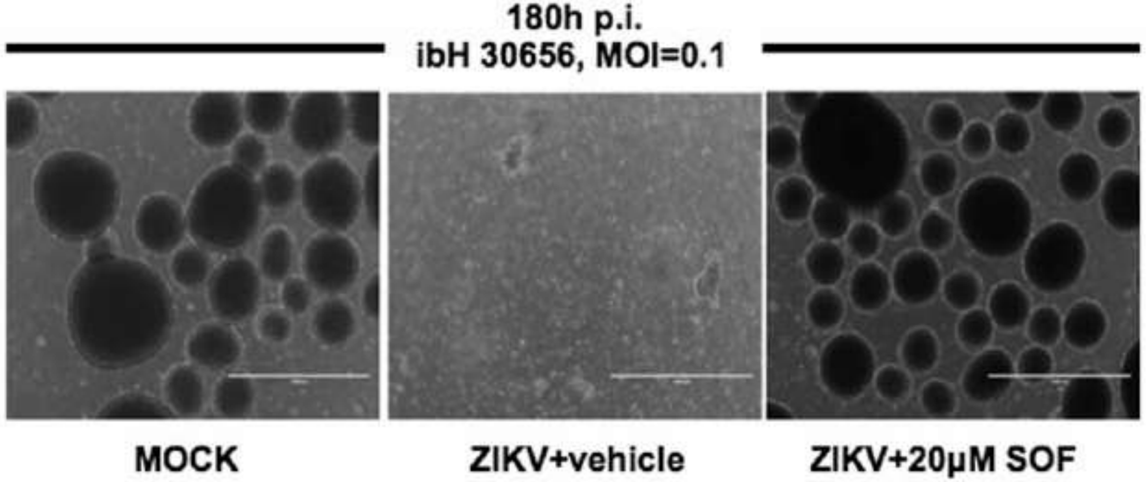

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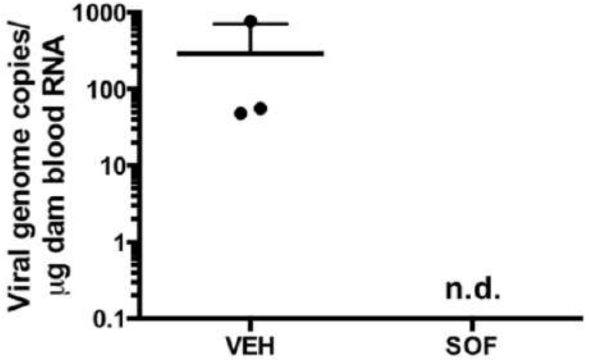


First Travel-Associated Congenital Zika Syndrome in the US: Ocular and Neurological Findings in the Absence of Microcephaly

Camila V. Ventura, MD; Maria Paula Fernandez, MD; Ivan A. Gonzalez, MD; Delia M. Rivera-Hernandez, MD; Roberto Lopez-Alberola, MD; Maria Peinado, MD; Angelica A. Floren, MD; Patricia A. Rodriguez, MD; Basil K. Williams Jr., MD; Gabriela de la Vega Muns, MD; Ana J. Rodriguez, RN; Catherin Negron, BA; Brenda Fallas; Audina M. Berrocal, MD

Ventura et al.,Ophtal Surgery, 2016

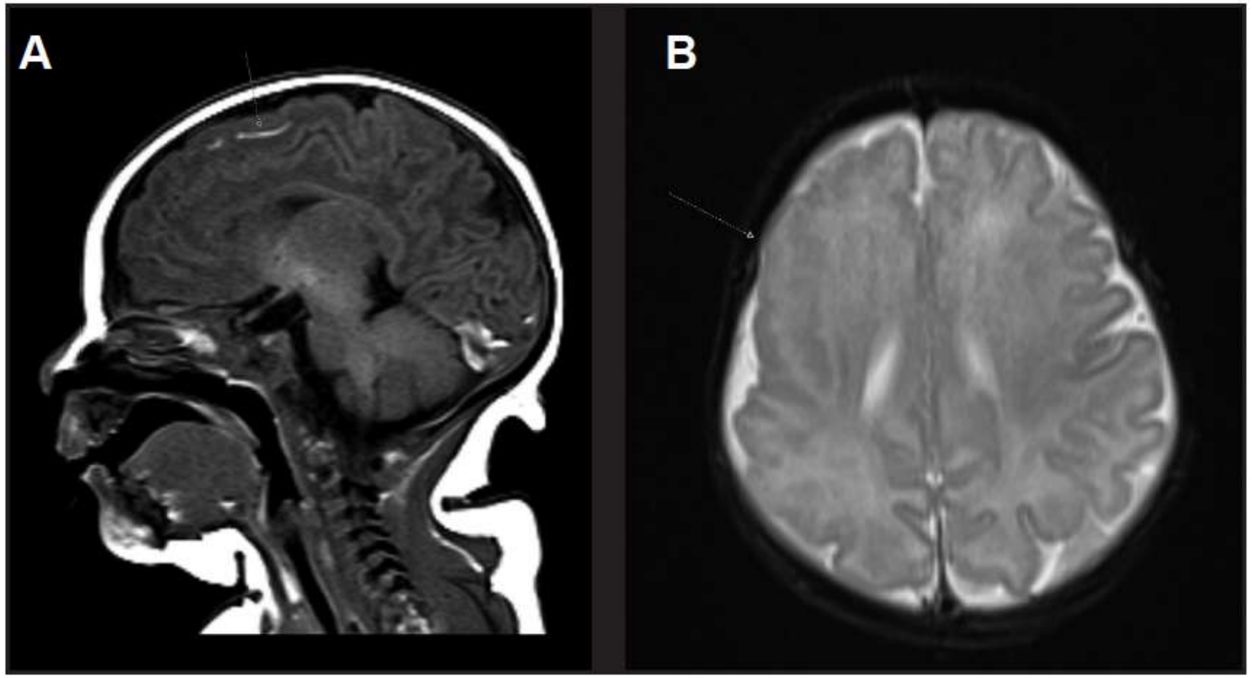


Figure 1. MRI of the brain of a baby with congenital Zika infection showing (A) an area of tubular increased T1 signal in the left subcortical white matter of the frontal lobe, suggesting intraparenchymal calcification, and (B) right cortical abnormality compared to contralateral hemisphere, with smooth appearance of the frontal and anterior superior temporal lobes.

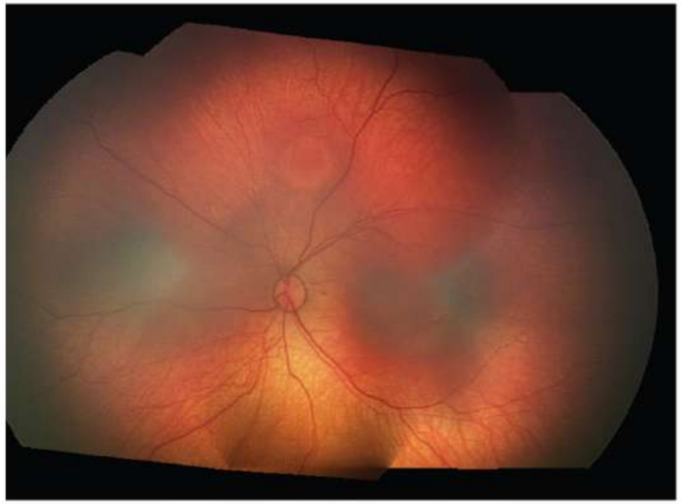
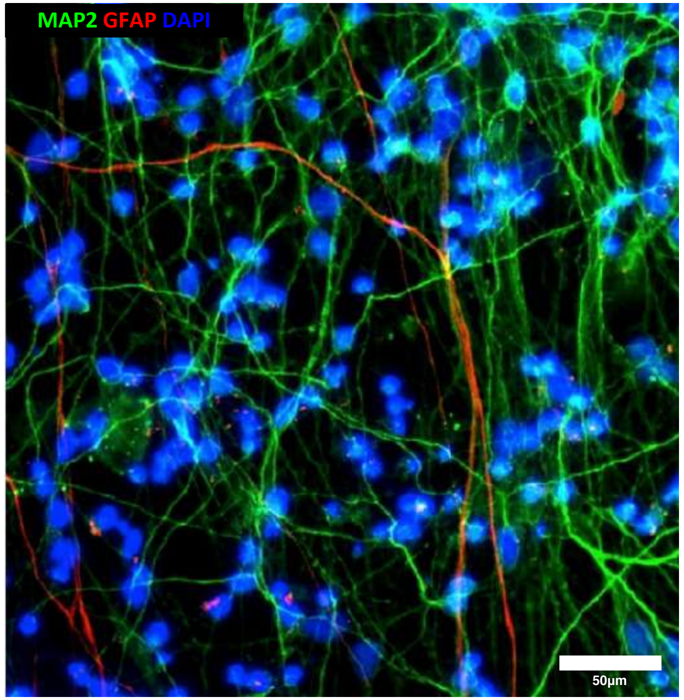
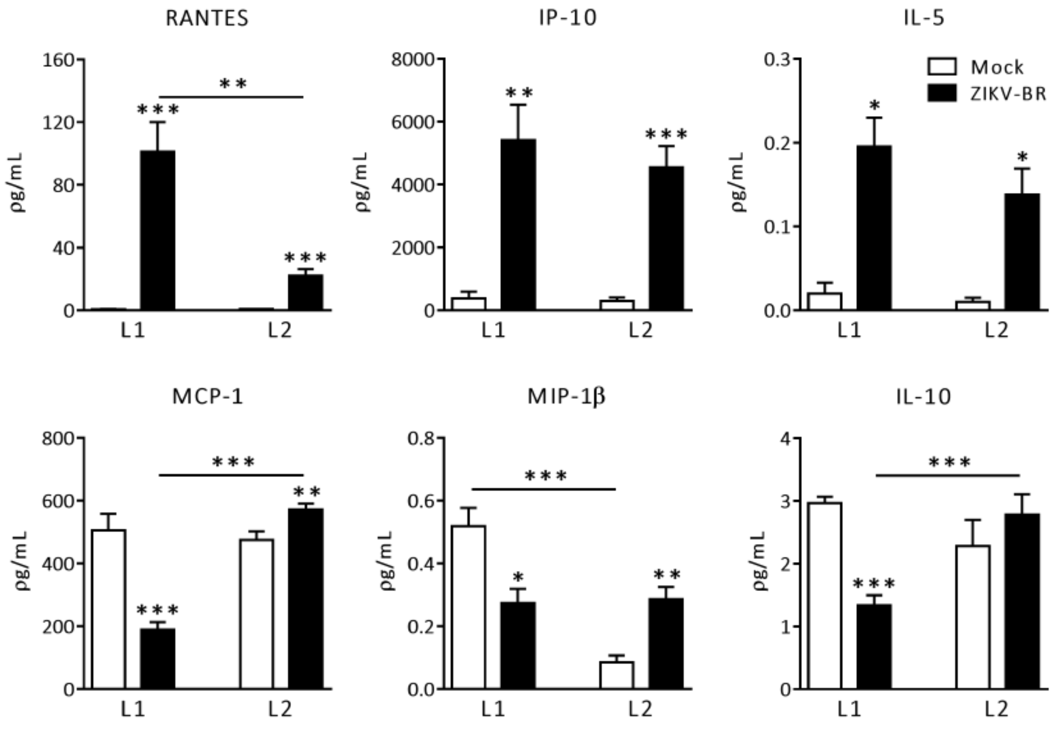
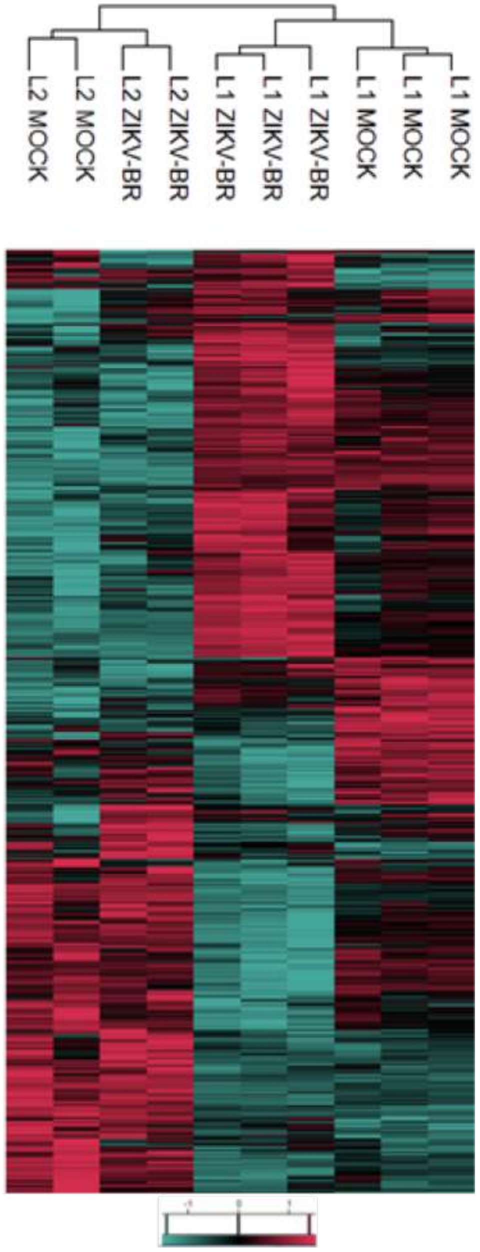


Figure 2. Fundus image of the left eye of a baby with congenital Zika infection showing a hypopigmented lesion located in the superior quadrant.

Resposta do ZIKV depende do hospedeiro







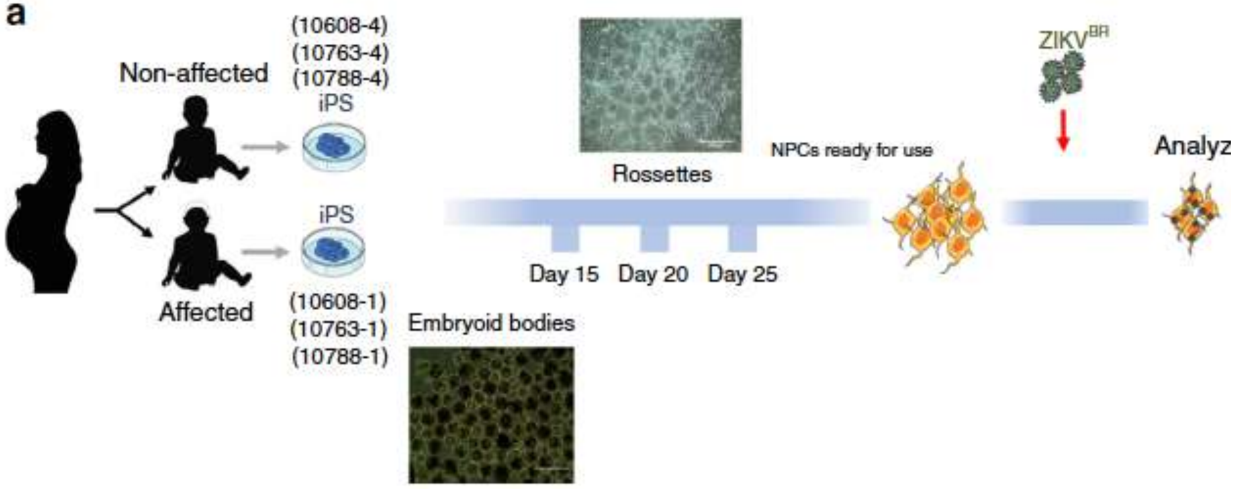
Rosa-Fernandes, 2019

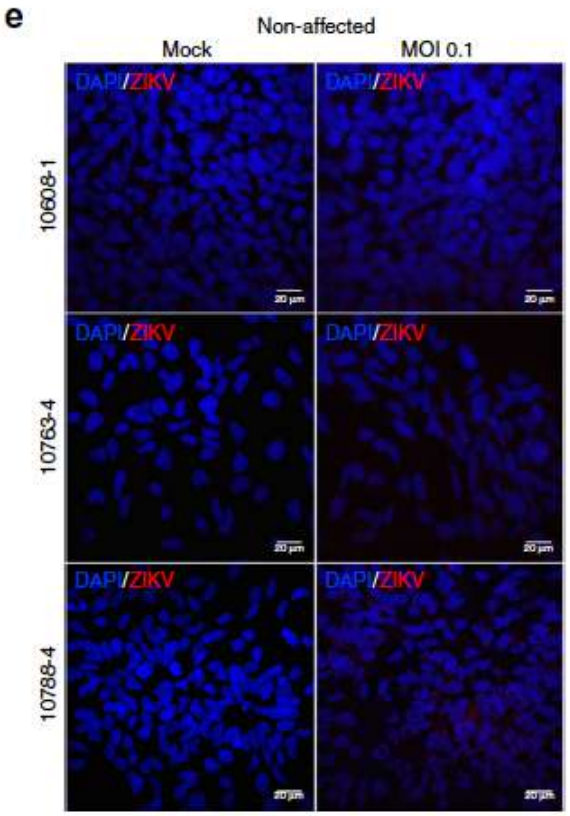
ARTICLE

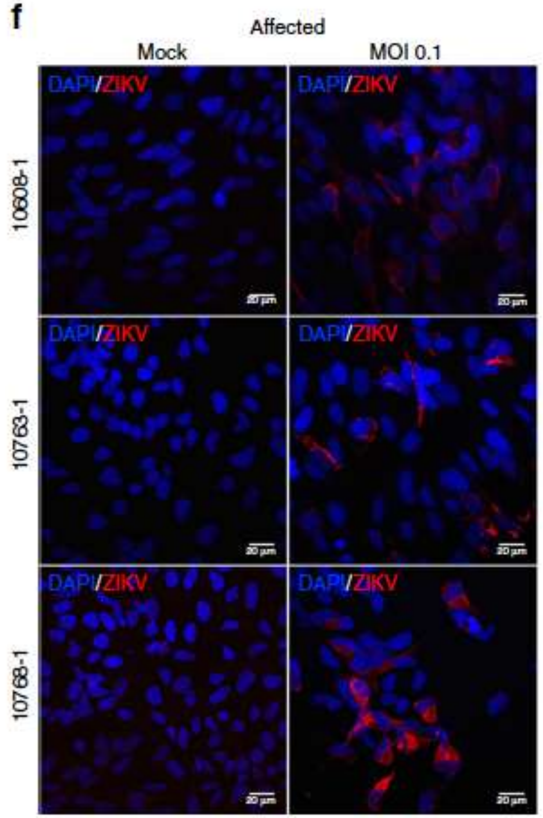
DOI: 10.1038/s41467-017-02790-9 OPEN

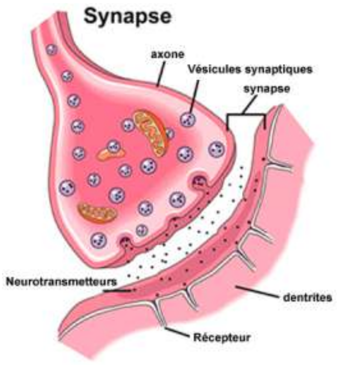
Discordant congenital Zika syndrome twins show differential in vitro viral susceptibility of neural progenitor cells

Luiz Carlos Caires-Júnior et al.#

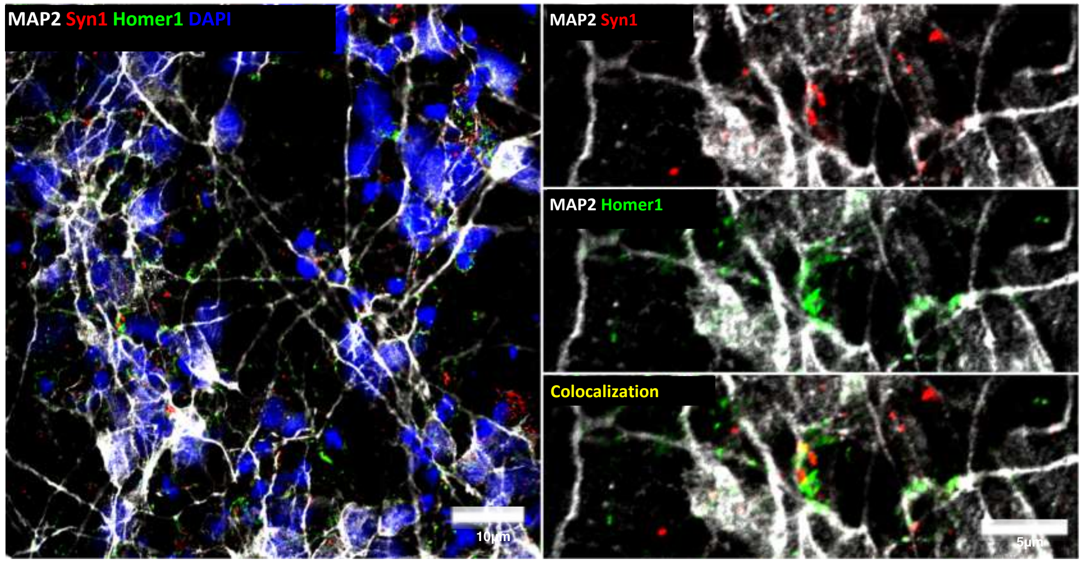


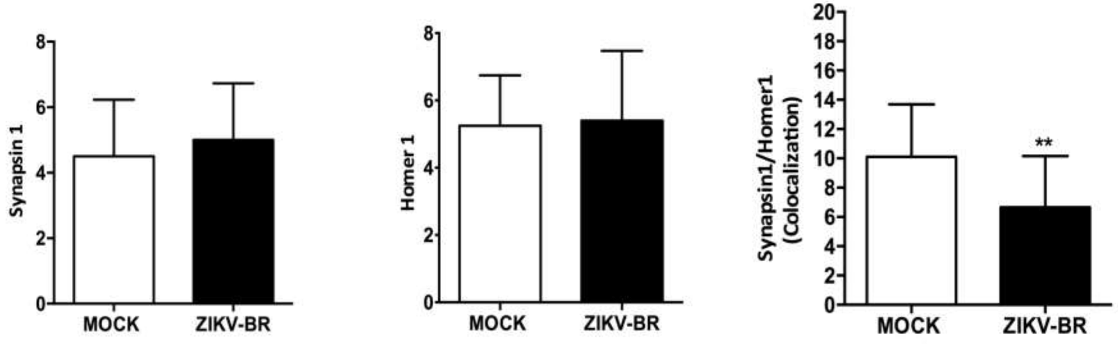


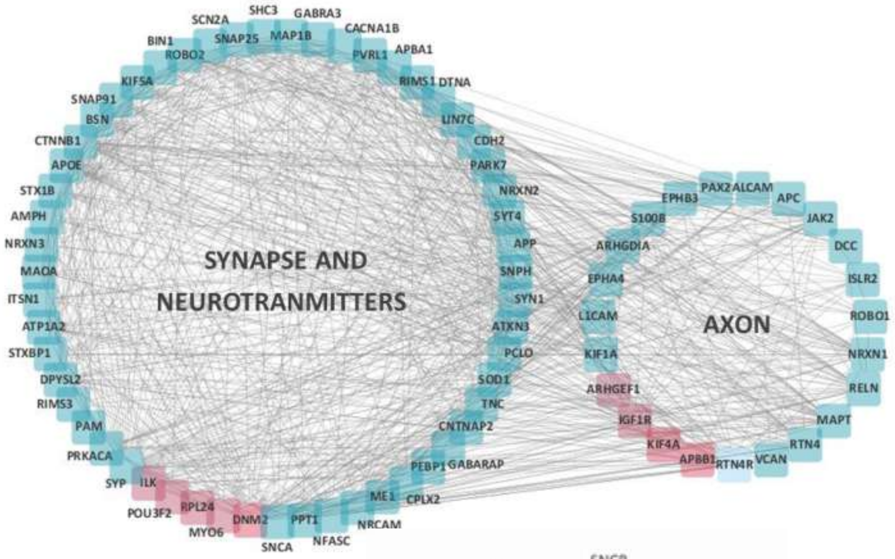


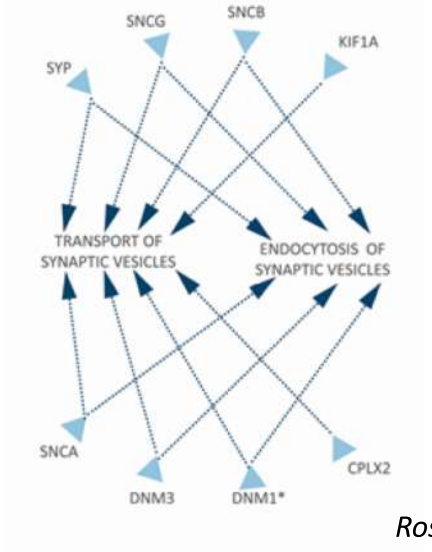


A neurogênese é afetada pelo ZIKV



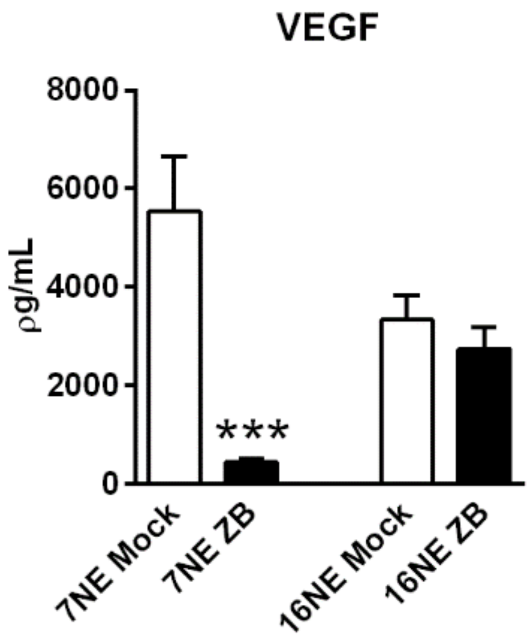


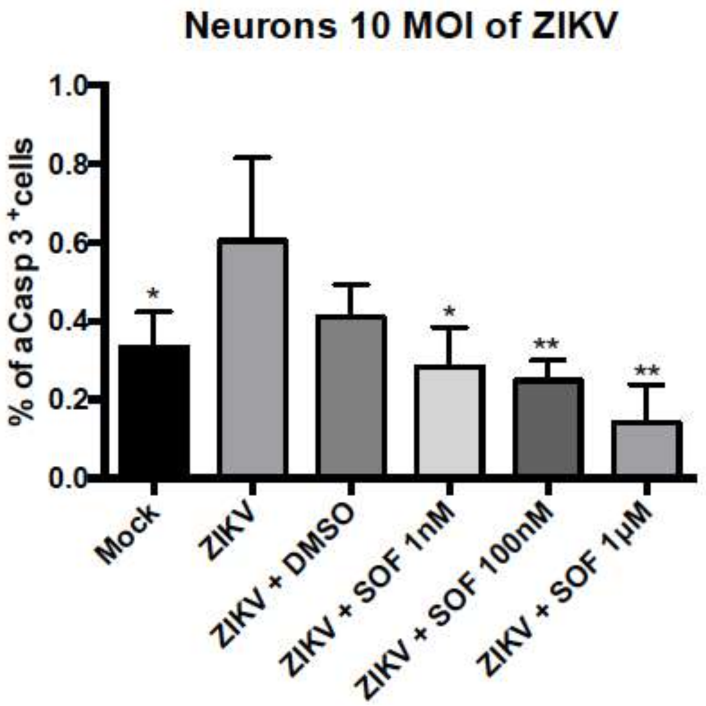


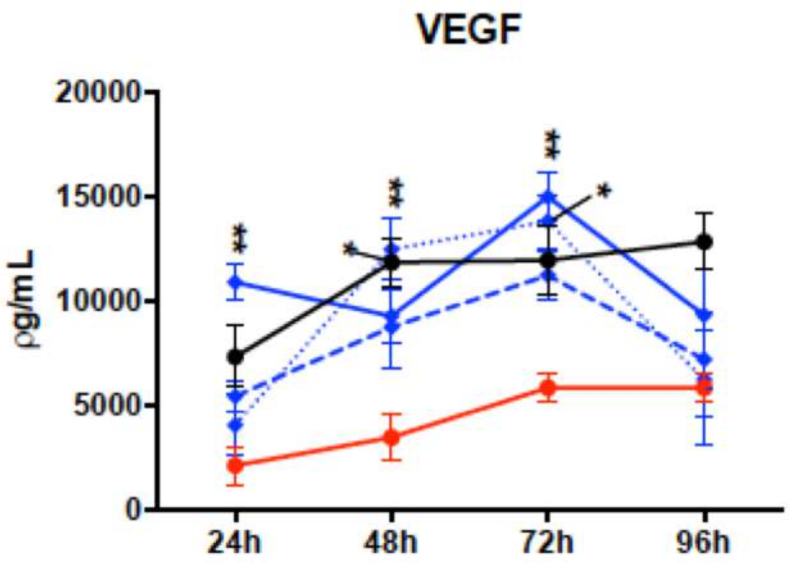


Rosa-Fernandes, 2019

SOF restaura os níveis de VEGF







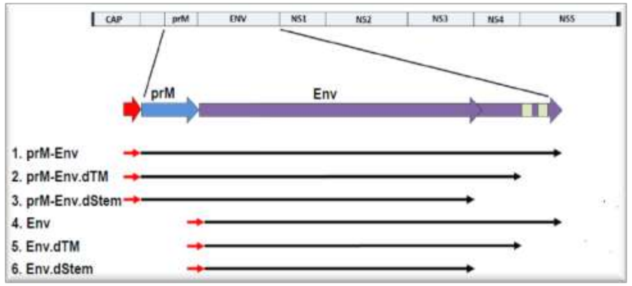
Vacina

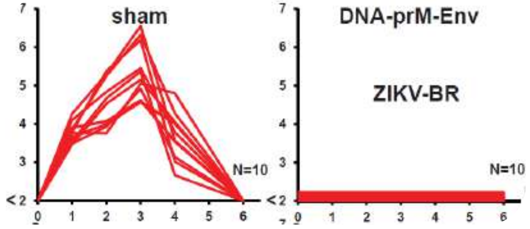
LETTER

doi:10.1038/nature18952

Vaccine protection against Zika virus from Brazil

Rafael A. Larocca[1]*, Peter Abbink[1]*, Jean Pierre S. Peron[2], Paolo M. de A. Zanotto[2], M. Justin Iampietro[1], Alexander Badamchi-Zadeh[1], Michael Boyd[1], David Ng'ang'a[1], Marinela Kirilova[1], Ramya Nityanandam[1], Noe B. Mercado[1], Zhenfeng Li[1], Edward T. Moseley[1], Christine A. Bricault[1], Erica N. Borducchi[1], Patricia B. Giglio[1], David Jetton[1], George Neubauer[1], Joseph P. Nkolola[1], Lori F. Maxfield[1], Rafael A. De La Barrera[3], Richard G. Jarman[3], Kenneth H. Eckels[3], Nelson L. Michael[3], Stephen J. Thomas[3] & Dan H. Barouch[1,4]

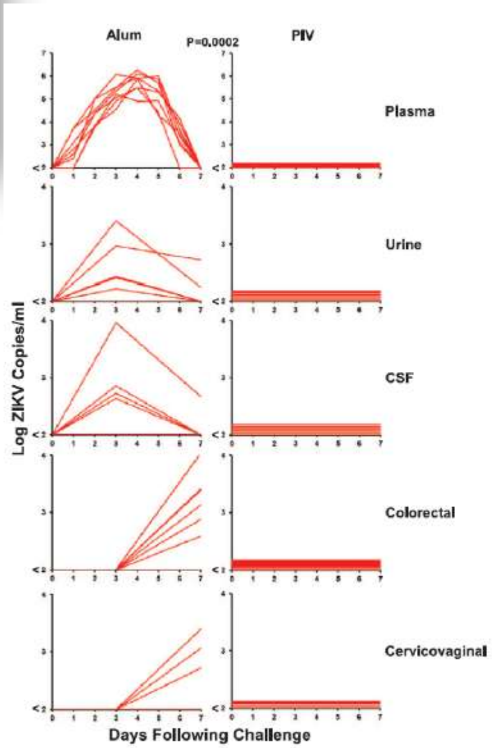




VACCINES

Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys

Peter Abbink,[1]* Rafael A. Larocca,[1]* Rafael A. De La Barrera,[2] Christine A. Bricault,[1] Edward T. Moseley,[1] Michael Boyd,[1] Marinela Kirilova,[1] Zhenfeng Li,[1] David Ng'ang'a,[1] Ovini Nanayakkara,[1] Ramya Nityanandam,[1] Noe B. Mercado,[1] Erica N. Borducchi,[1] Arshi Agarwal,[1] Amanda L. Brinkman,[1] Crystal Cabral,[1] Abishek Chandrashekar,[1] Patricia B. Giglio,[1] David Jetton,[1] Jessica Jimenez,[1] Benjamin C. Lee,[1] Shanell Mojta,[1] Katherine Molloy,[1] Mayuri Shetty,[1] George H. Neubauer,[1] Kathryn E. Stephenson,[1] Jean Pierre S. Peron,[3] Paolo M. de A. Zanotto,[3] Johnathan Misamore,[4] Brad Finneyfrock,[4] Mark G. Lewis,[4] Galit Alter,[5] Kayvon Modjarrad,[2,6] Richard G. Jarman,[2] Kenneth H. Eckels,[2] Nelson L. Michael,[2] Stephen J. Thomas,[2]† Dan H. Barouch[1,5]†‡



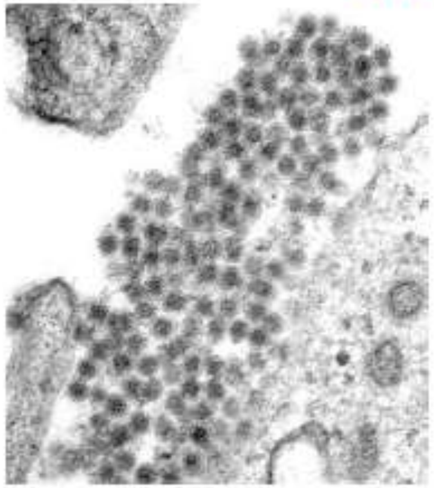
	Status	Type of vaccine
Inovio	In phase 1 clinical trials	DNA vaccine
National Institutes of Health	In phase 1 clinical trials	DNA vaccine; live vesicular stomatitis virus recombinant (early R&D); live attenuated Zika virus (early R&D)
Walter Reed Army Institute of Research and Sanofi Pasteur	In phase 1 clinical trials	Whole, purified, inactivated virus
Butantan Institute	In phase 1 clinical trials; early stage research	Live, dengue virus-vectored vaccine expressing precursor membrane and envelope proteins; purified inactivated virus
Bharat	Preclinical animal studies	Purified inactivated virus; virus-like particle expressing polyprotein
NewLink Genetics	Preclinical animal studies	Purified inactivated virus
PaxVax	Preclinical animal studies	Purified inactivated virus
Novavax	Preclinical animal studies	Protein nanoparticle vaccine
Replikins	Preclinical animal studies	Synthetic peptide vaccine
Pharos Biologicals	Preclinical animal studies	DNA vaccine
Bio-Manguinhos	Early stage research	Purified inactivated virus; yellow fever 17DD chimera; virus-like particle; DNA
US Centers for Disease Control and Prevention	Early stage research	Virus-like particle expressing Zika virus DNA; live adenovirus recombinant
CureVac	Early stage research	Thermostable mRNA-based vaccine
Geovax	Early stage research	Live modified vaccinia ankara recombinant
GlaxoSmithKline	Early stage research	Self-amplifying mRNA platform; whole, inactivated virus
Hawaii Biotech	Early stage research	Alhydrogel and recombinant protein
Oxford University	Early stage research	Live adenovirus recombinant
Protein Sciences	Early stage research	Recombinant envelope protein
Sanofi	Early stage research	Yellow fever 17D chimera
Sementis	Early stage research	Live poxvirus recombinant
Themis Bioscience	Early stage research	Live measles recombinant
Valneva	Early stage research	Purified inactivated virus
Mayo Clinic Vaccine Research Group	Early stage research	Naturally processed and HLA-presented Zika virus peptides packaged with biodegradable nanoparticles
Moderna	Early stage research	Lipid nanoparticle-delivered mRNA
Emergent Biosolutions	Early stage research	Inactivated, whole virus
Institut Pasteur of Shanghai	Early stage research	Recombinant subunit virus-like particle
Takeda	Early stage research	Alum adjuvanted, inactivated whole virus
Jenner Institute	Early stage research	Simian adenovirus vector
VBI Vaccines	Early stage research	Virus-like particle containing envelope and non-structural 1 proteins
Vaxart	Early stage research	Recombinant oral vaccine

R&D=research and development.

Table: Zika vaccines in development

Poland et al., Lancet, 2018

Arboviroses Emergentes



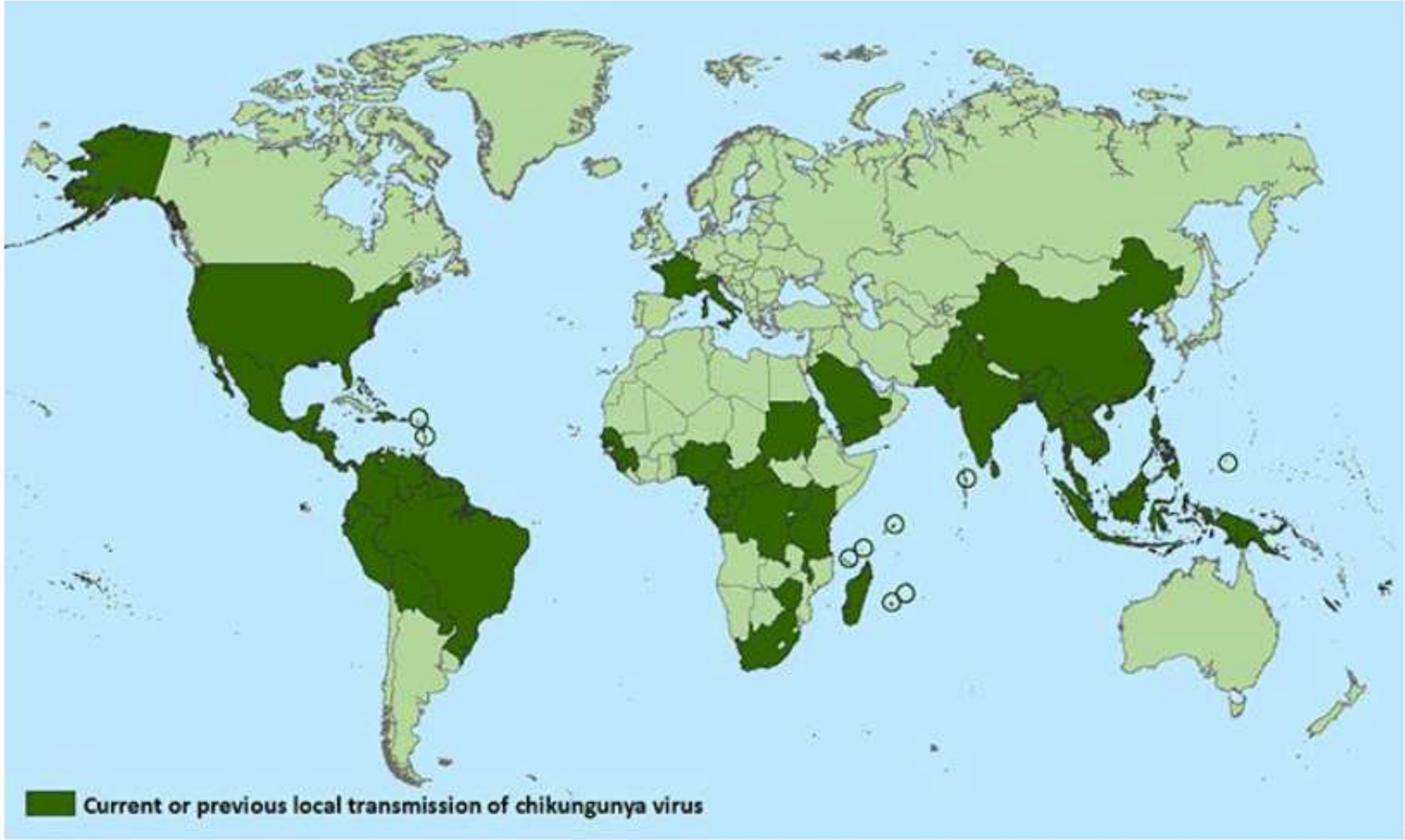
Chikungunya (Tanzania 1952)

Mayaro (Trinidad in 1954) (Genótipos D e L)

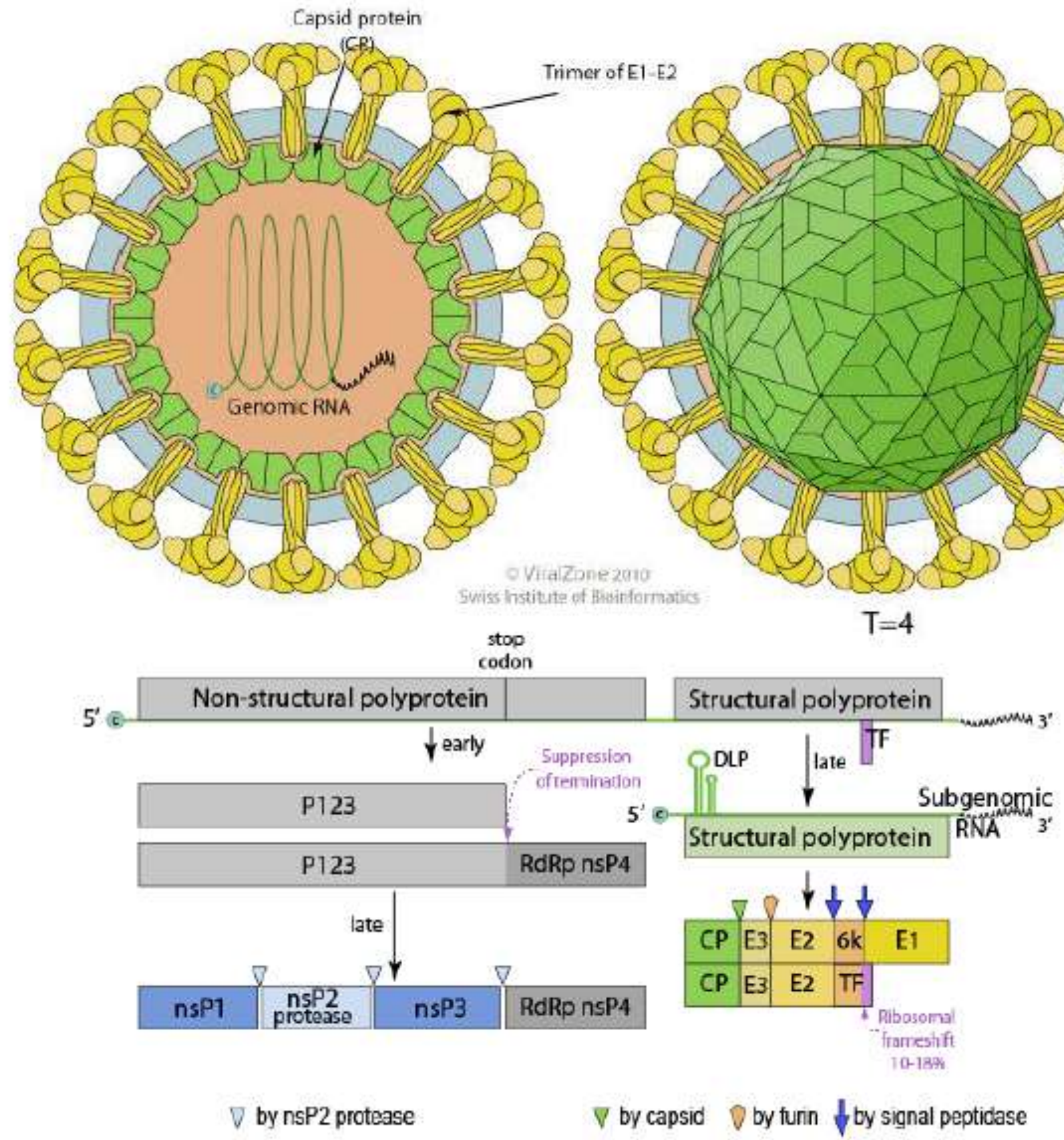
(Ross River virus, O'nyong'nyong virus, and Semliki Forest Virus (SFV)

Família:	*Togaviridae*
Gênero:	*Alphavirus*
Transmissão:	vetor artrópode - *Aedes aegypti* ((*Ae. furcifer, Ae. taylori e Ae. luteocephalus*)
Partículas virais:	esférico 60-70 nm, envelopado
Proteínas estruturais:	E2,E3, CP, 6k e TF
Genoma:	ss-RNA polaridade positiva 11.6 kb

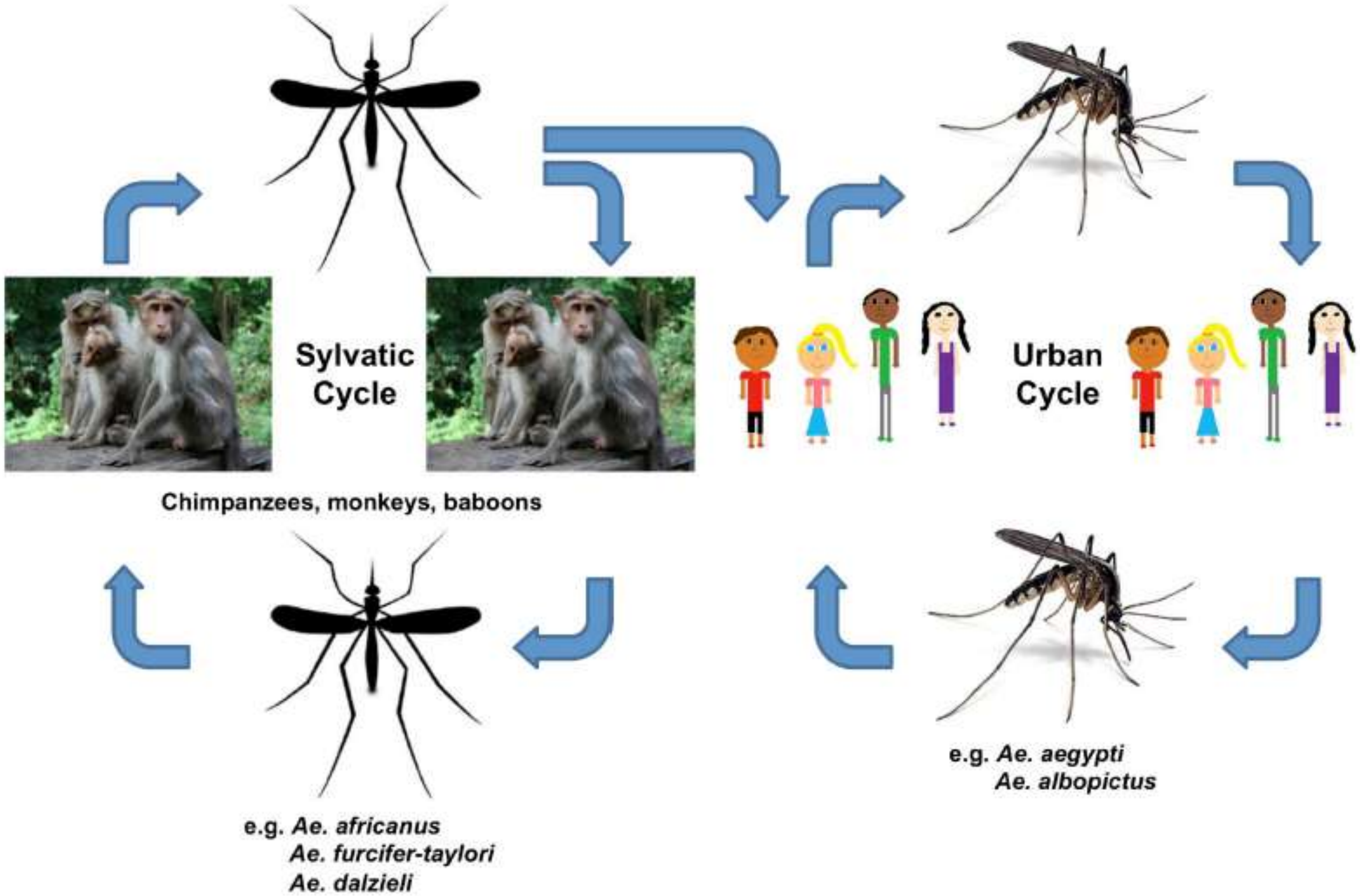
Arboviroses Emergentes: Chikungunya



Arboviroses Emergentes: Chikungunya



Arboviroses Emergentes: Chikungunya



PRINCIPAIS **SINTOMAS**

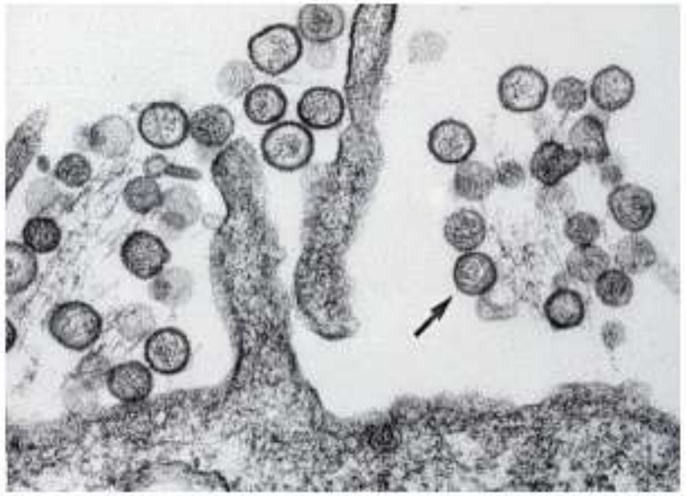
	DENGUE	CHIKUNGUNYA	ZIKA
FEBRE	**Sempre presente: alta e de início imediato**	**Quase sempre presente: alta e de início imediato**	**Pode estar presente: baixa**
ARTRALGIA (DORES NAS ARTICULAÇÕES)	**Quase sempre presente: dores moderadas**	**Presente em 90% dos casos: dores intensas**	**Pode estar presente: dores leves**
RASH CUTÂNEO (MANCHAS VERMELHAS NA PELE)	**Pode estar presente**	**Pode estar presente: se manifesta nas primeiras 48 horas** (normalmente a partir do 2º dia)	**Quase sempre presente: se manifesta nas primeiras 24 horas**
PRURIDO (COCEIRA)	**Pode estar presente: leve**	**Presente em 50 a 80% dos casos: leve**	**Pode estar presente: de leve a intensa**
VERMELHIDÃO NOS OLHOS	**Não está presente**	**Pode estar presente**	**Pode estar presente**

https://agencia.fiocruz.br/zika-chikungunya-e-dengue-entenda-diferen%C3%A7as

Arboviroses Emergentes...

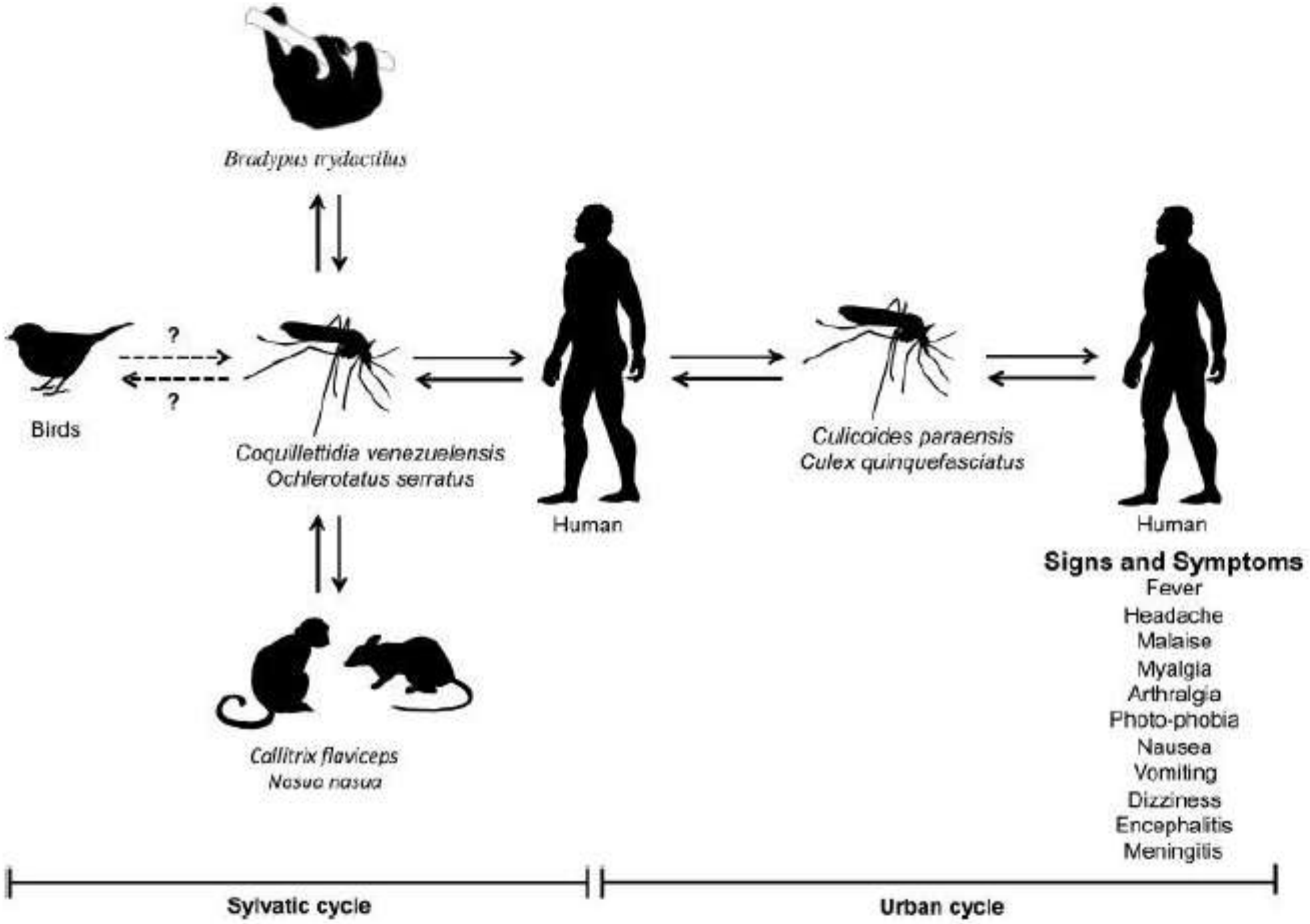
É bom ficarmos atentos!!!

Outras Arboviroses: Oropouche



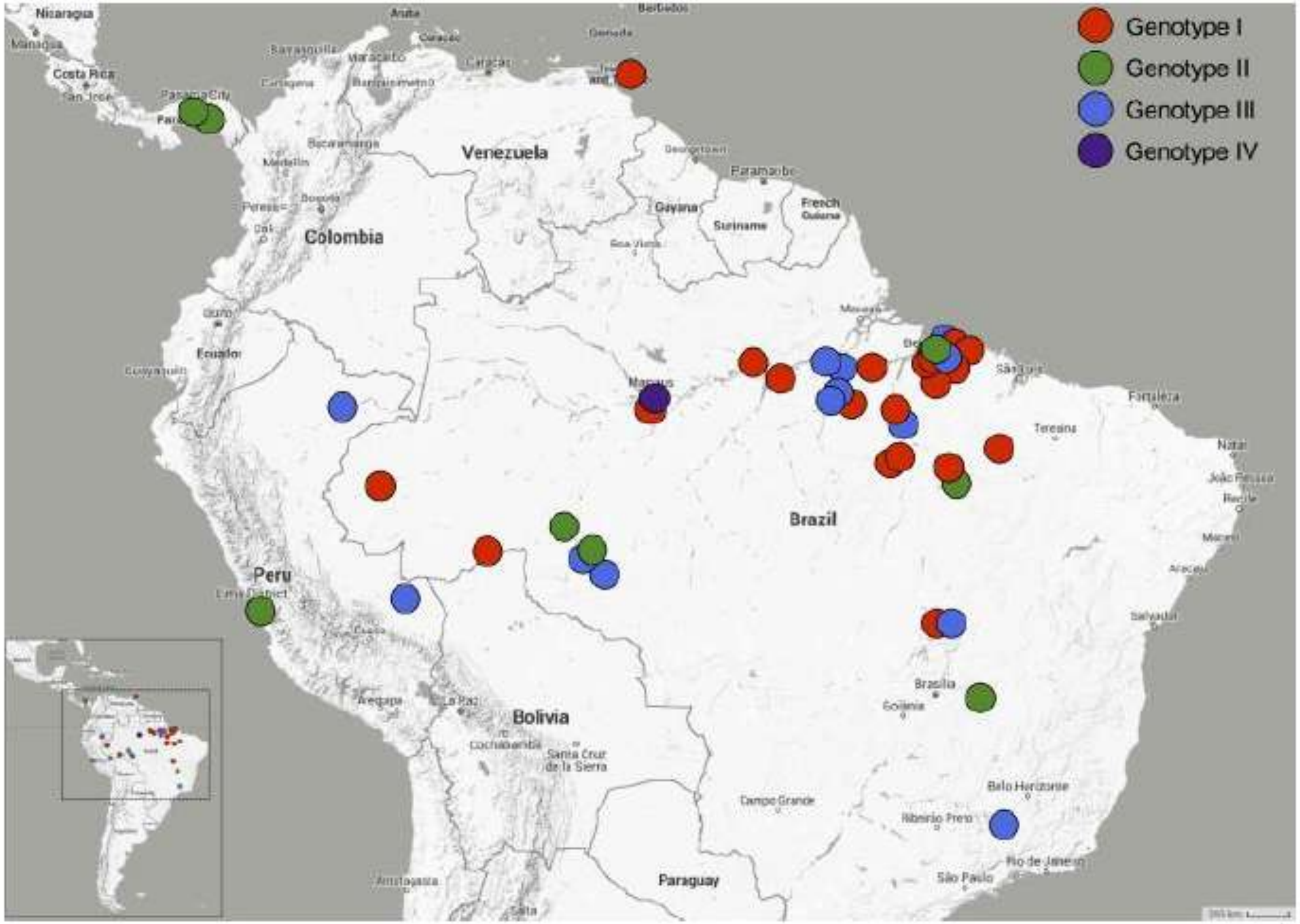
Família:	*Bunyaviridae* (Gênero *Orthobunyavirus*)
Transmissão:	hospedeiro vertebrado, sem vetor artrópode
Partículas virais:	esférico, 80-110 nm
Proteínas estruturais:	glicoproteínas: G1, G2 ; nucleoproteína: N
Genoma:	ss-RNA, trisegmentado, polaridade negativa

Outras Arboviroses: Oropouche



10.4269/ajtmh.16-0672

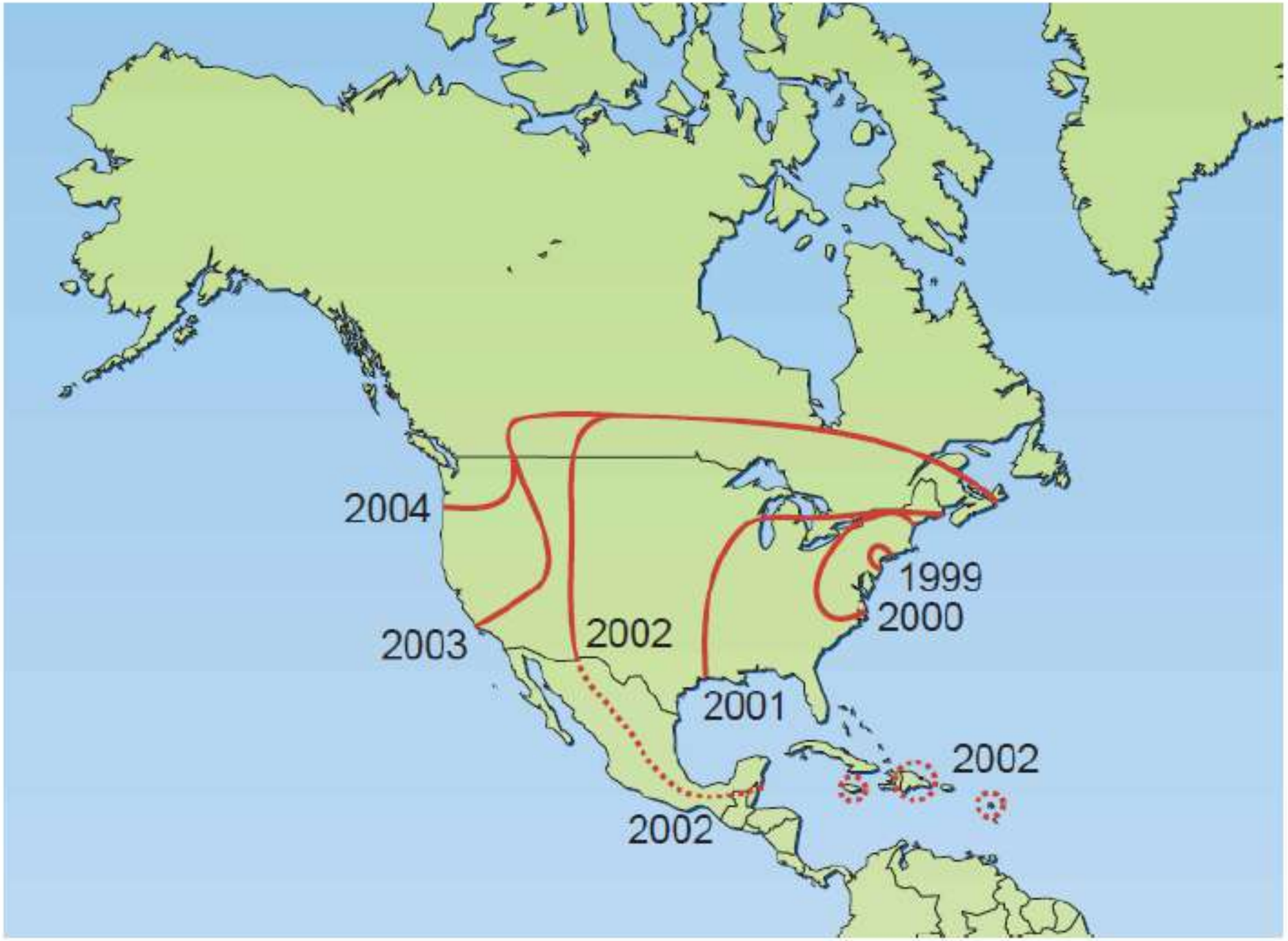
Outras Arboviroses: Oropouche



10.4269/ajtmh.16-0672

Arboviroses Emergentes: West Nile (flavivírus)

West Nile virus (WNV)



Arboviroses Emergentes: West Nile (flavivírus)

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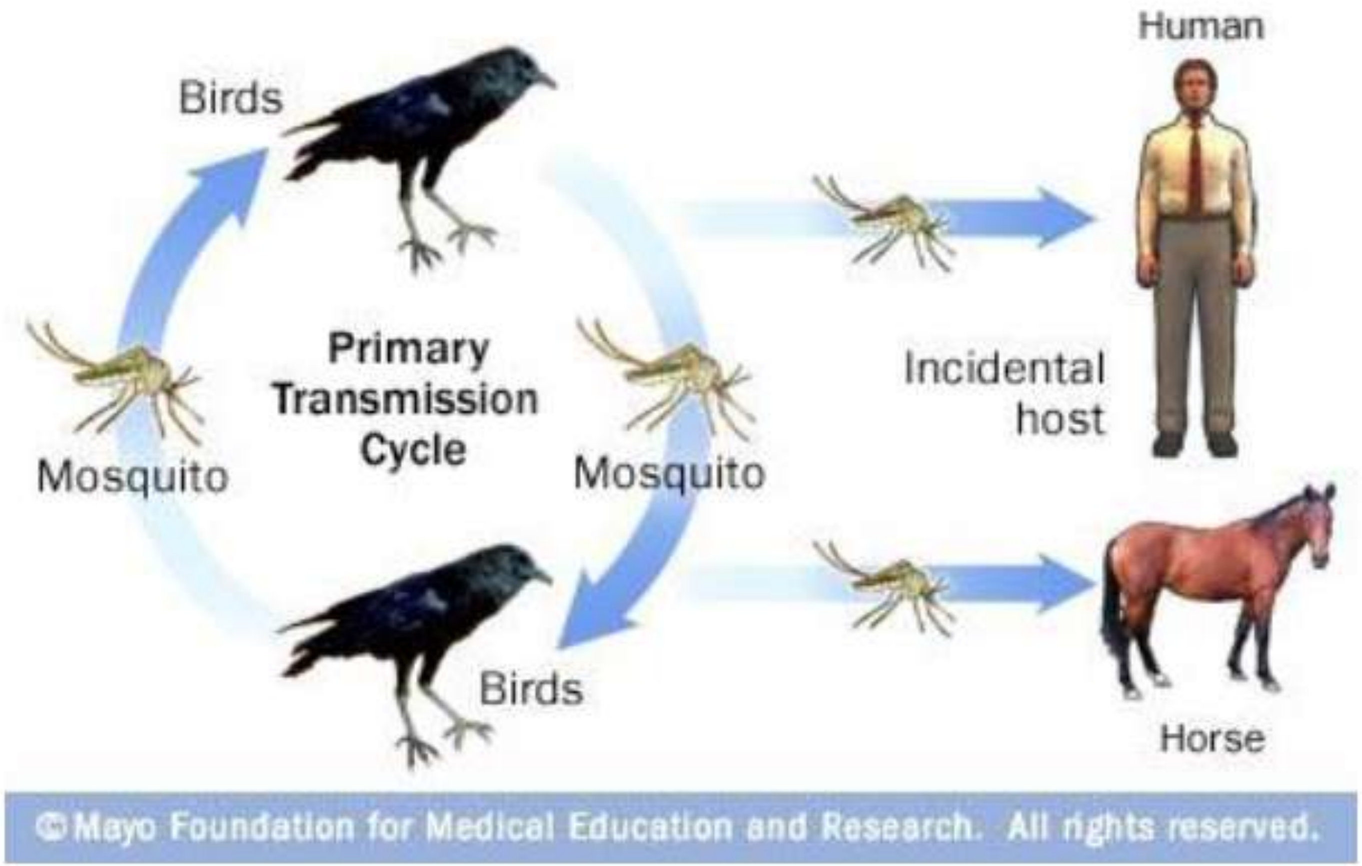
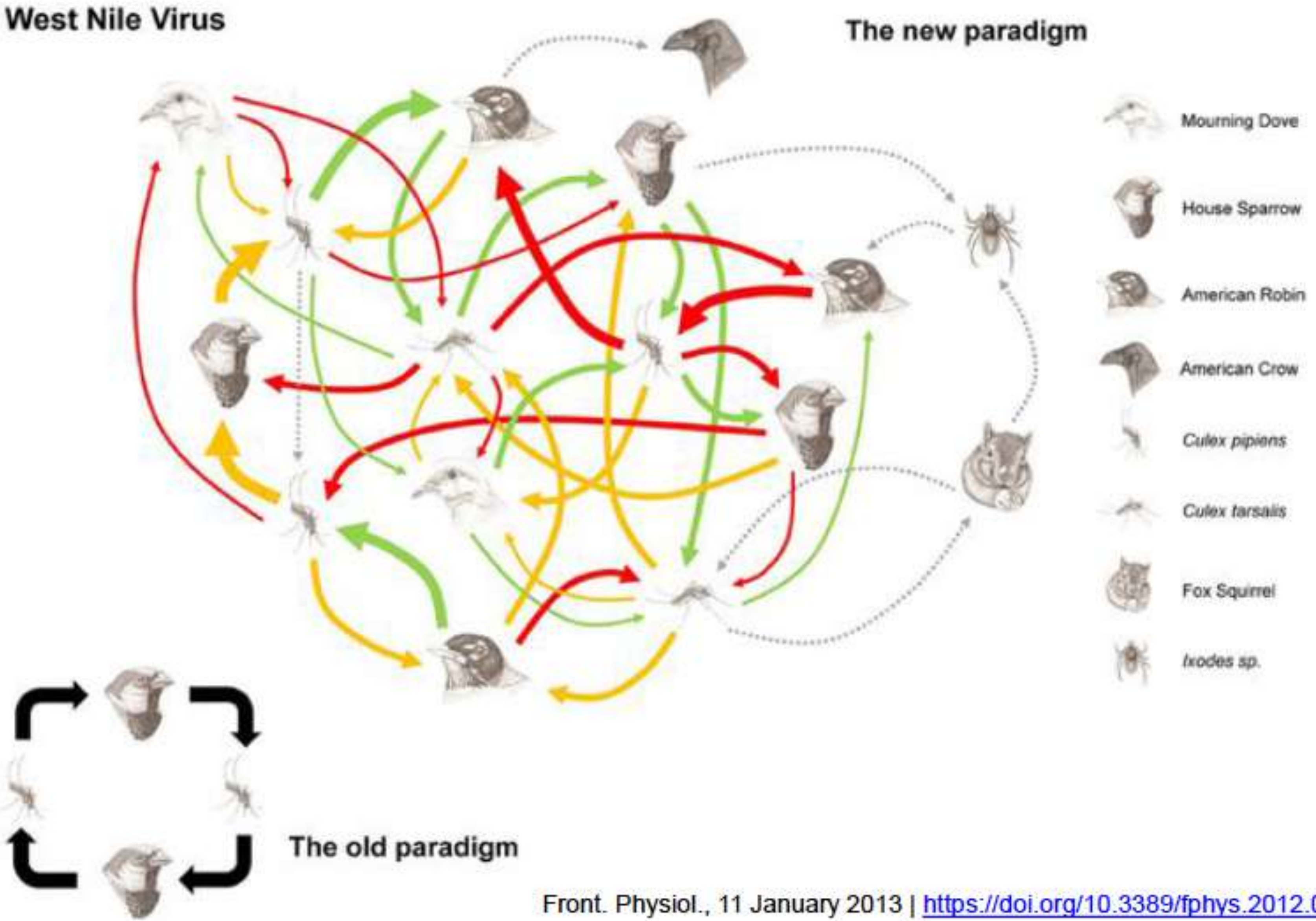
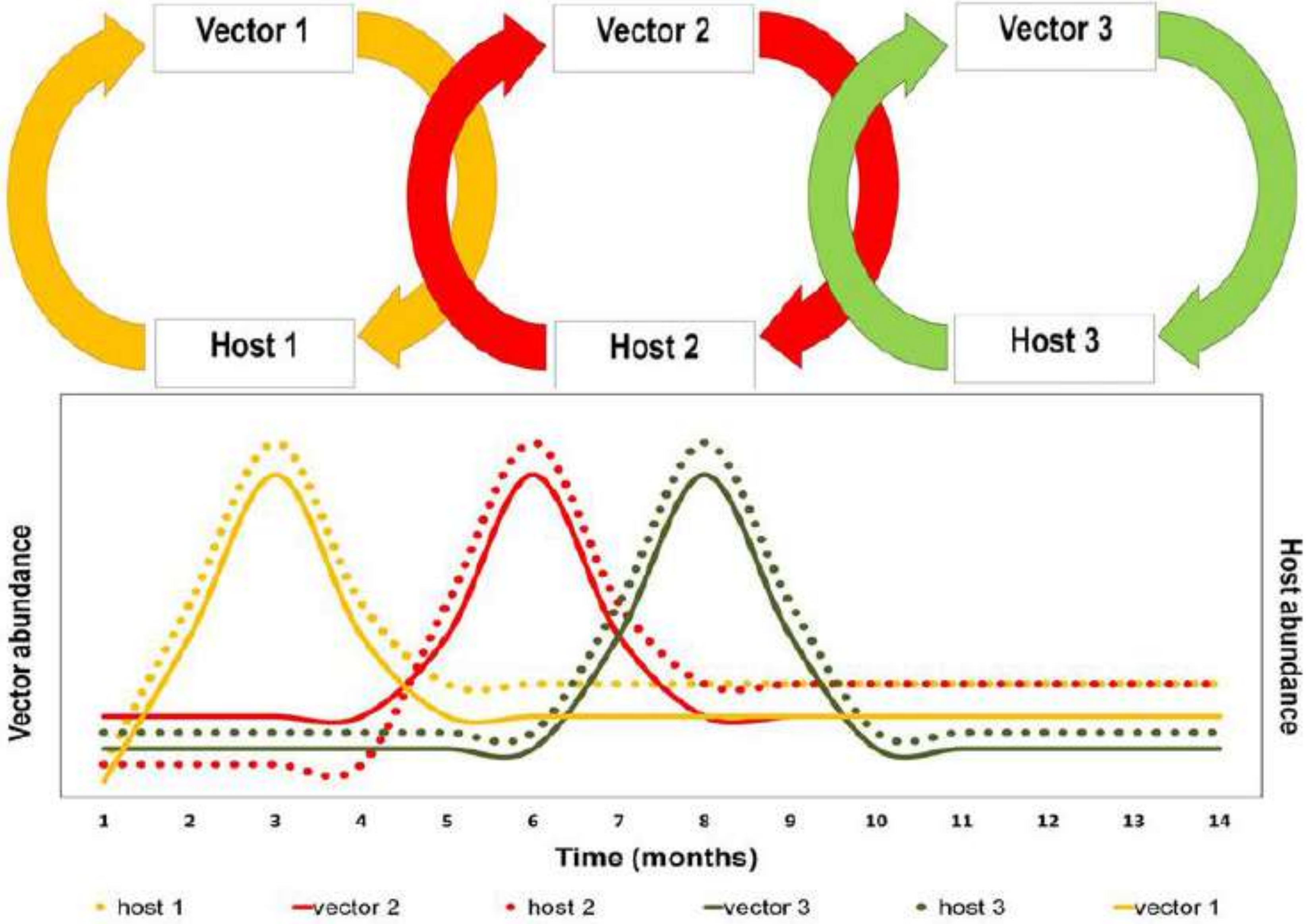


Arboviroses:
ciclos de transmissão mais complexos?



Front. Physiol., 11 January 2013 | https://doi.org/10.3389/fphys.2012.00493

Arboviroses:
ciclos de transmissão mais complexos?



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VÍRUS EMERGENTES

Alterações nas populações de hos[illegible] ambiente podem expandir os nichos para [illegible]

COVID-19

Exemplos:

- Poliomielite e sane[illegible]
- Varíola e Sar[illegible] [illegible]o
- Hantaví[illegible] [illegible]áticas (Sin nombre vírus, 1993)
- Ae[illegible]
- Ba[illegible]