The Interplay between Zika and other flaviviruses: overview and results from Brazil

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Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. *110*(4): 569-572, June 2015

First report of autochthonous transmission of Zika virus in Brazil

Camila Zanluca[1], Vanessa Campos Andrade de Melo[2], Ana Luiza Pamplona Mosimann[1], Glauco Igor Viana dos Santos[2], Claudia Nunes Duarte dos Santos[1]/+, Kleber Luz[3]/+

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[2]Secretaria Estadual de Saúde do Rio Grande do Norte, Natal, RN, Brasil
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In the early 2015, several cases of patients presenting symptoms of mild fever, rash, conjunctivitis and arthralgia were reported in the northeastern Brazil. Although all patients lived in a dengue endemic area, molecular and serological diagnosis for dengue resulted negative. Chikungunya virus infection was also discarded. Subsequently, Zika virus (ZIKV) was detected by reverse transcription-polymerase chain reaction from the sera of eight patients and the result was confirmed by DNA sequencing. Phylogenetic analysis suggests that the ZIKV identified belongs to the Asian clade. This is the first report of ZIKV infection in Brazil.

Key words: Zika virus - "dengue-like syndrome" - Brazil

Causal Association Between Zika and Birth Defects

Case Reports

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

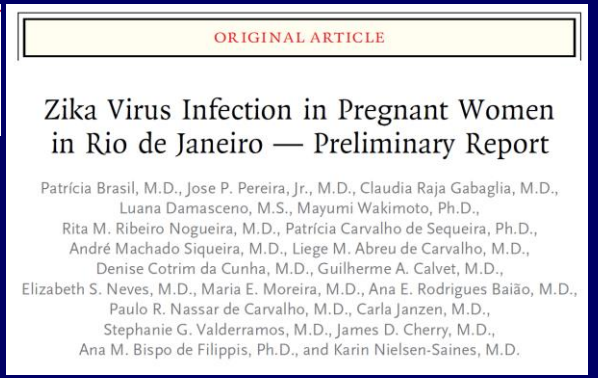
Epidemiological Studies

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

Evidence for Causality
(Rasmussen, NEJM 2014)


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 R dos Santos, Rita M R Nogueira, Amilcar Tanuri†, Ana M B de Filippis†


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.


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.

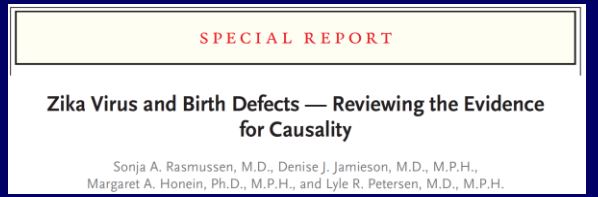

Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study

Simon Cauchemez, Marianne Besnard, Priscillia Bompard, Timothée Dub, Prisca Guillemette-Artur, Dominique Eyrolle-Guignot, Henrik Salje, Maria D Van Kerkhove, Véronique Abadie, Catherine Garel, Arnaud Fontanet*, Henri-Pierre Mallet*


RESEARCH ARTICLE

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

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


SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

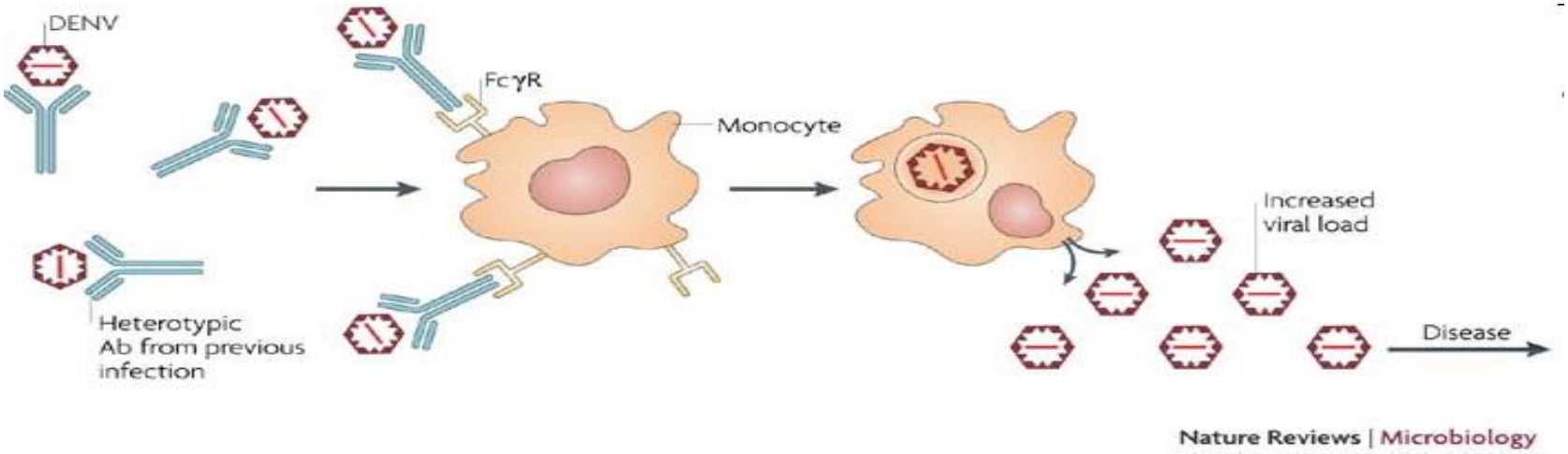
Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H., Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.


WHY ?

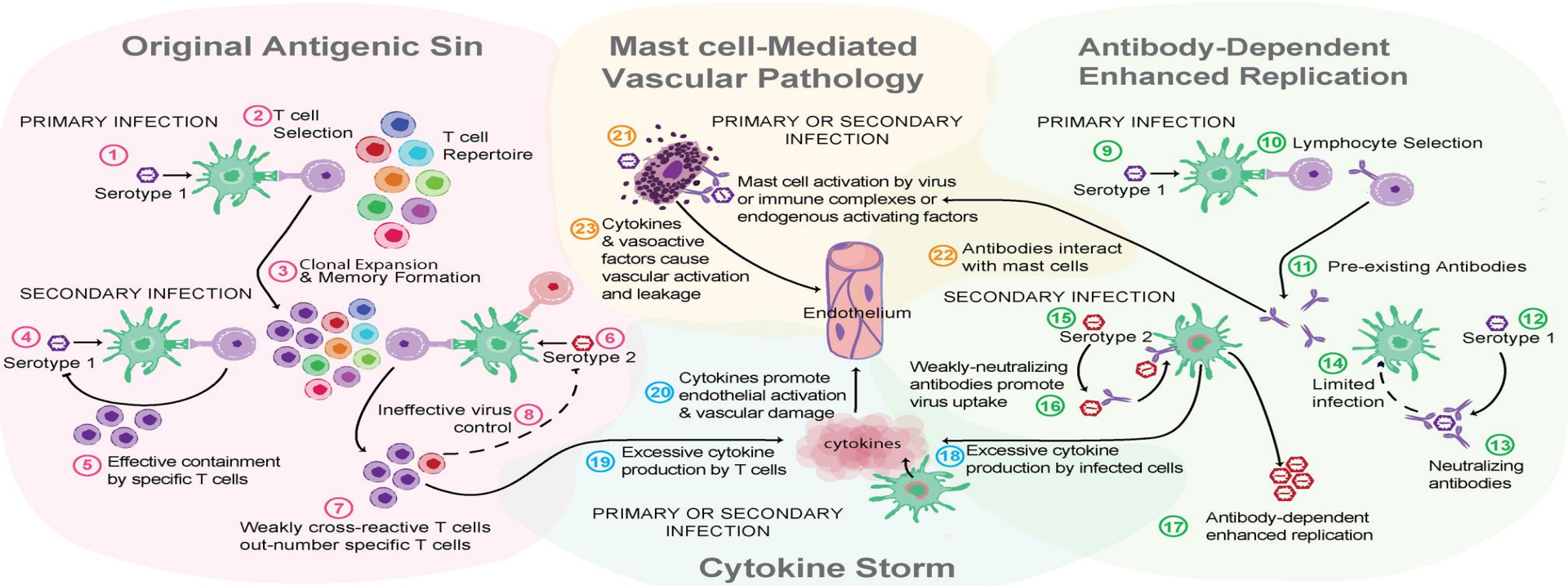
ADE or Protection

FLAVIVIRUS ANTIBODIES AND ZIKA

Model for antibody-dependent enhancement of dengue virus replication.

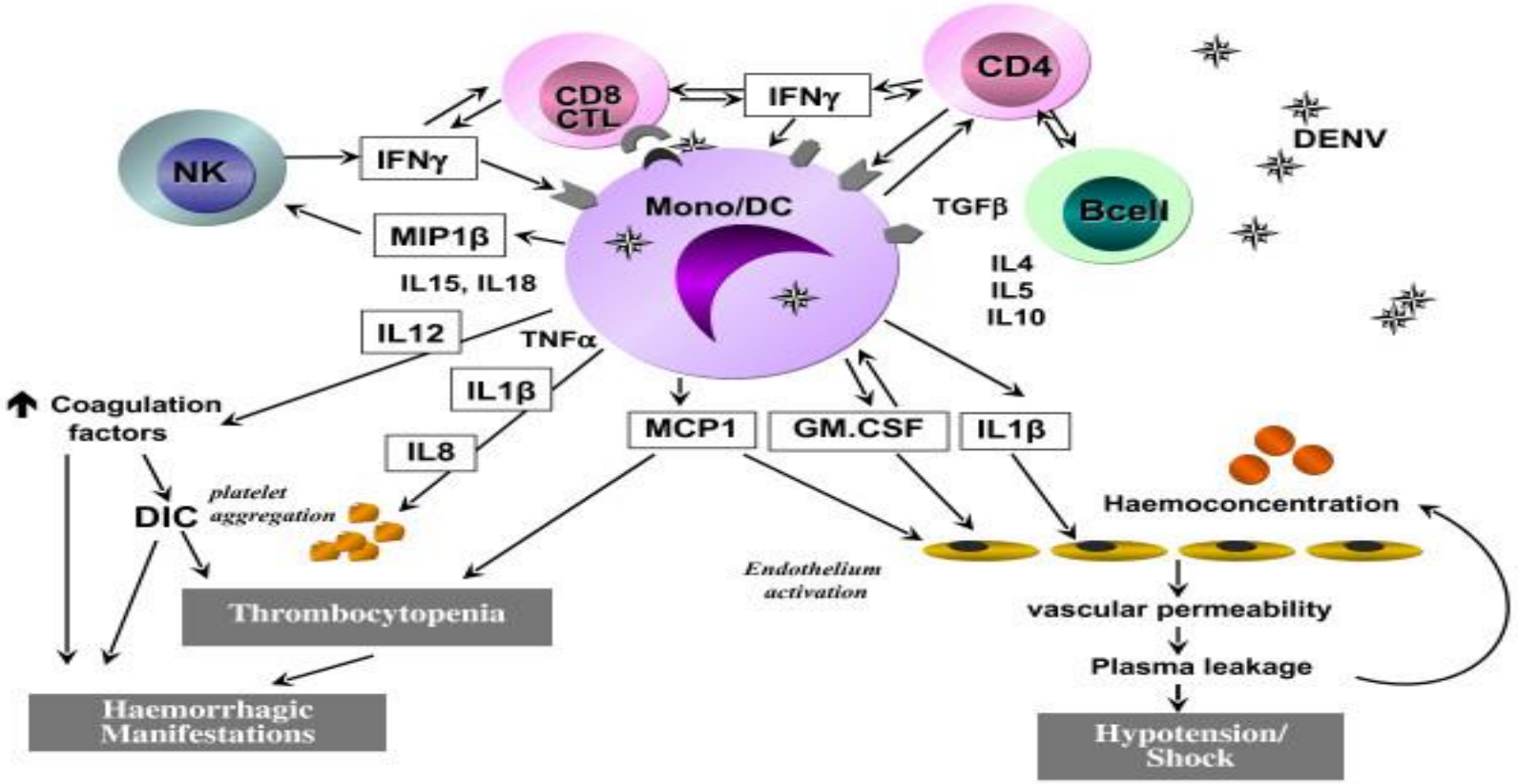


Prospects for a dengue virus vaccine
Stephen S. Whitehead, Joseph E. Blaney, Anna P. Durbin & Brian R. Murphy
Nature Reviews Microbiology 5, 518-528 (July 2007)



https://biochemwar.wordpress.com/2014/02/23/mosquito-wars-an-overview-of-dengue-fever/

Hypothetic mechanism to explain cytokine models during dengue fever.



Bozza *et al. BMC Infectious Diseases* 2008 **8**:86

nature immunology

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

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

"Most antibodies that reacted to DENV envelope protein also reacted to ZIKV. Antibodies were able to bind ZIKV but were unable to neutralize the virus and instead promoted ADE."

"Our data indicate that immunity to DENV might drive greater ZIKV replication and have clear implications for disease pathogenesis and future vaccine programs for ZIKV and DENV "

Science

REPORTS

Cite as: S. V. Bardina *et al.*, *Science* 10.1126/science.aal4365 (2017).

Enhancement of Zika virus pathogenesis by preexisting antiflavivirus immunity

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

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***These authors contributed equally to this work.**

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Zika virus (ZIKV) is spreading rapidly into regions around the world where other flaviviruses, such as dengue (DENV) and West Nile virus (WNV) are endemic. Antibody-dependent enhancement (ADE) has been implicated in more severe forms of flavivirus disease, but whether this also applies to ZIKV infection is unclear. Using convalescent plasma from DENV and WNV infected individuals, we found substantial enhancement of ZIKV infection in vitro that was mediated through IgG engagement of Fcγ receptors. Administration of DENV or WNV convalescent plasma into ZIKV-susceptible mice resulted in increased morbidity and mortality, including fever, viremia, and viral loads in spinal cord and testes. ADE may explain the severe disease manifestations associated with recent ZIKV outbreaks and highlights the need to exert great caution when designing flavivirus vaccines.

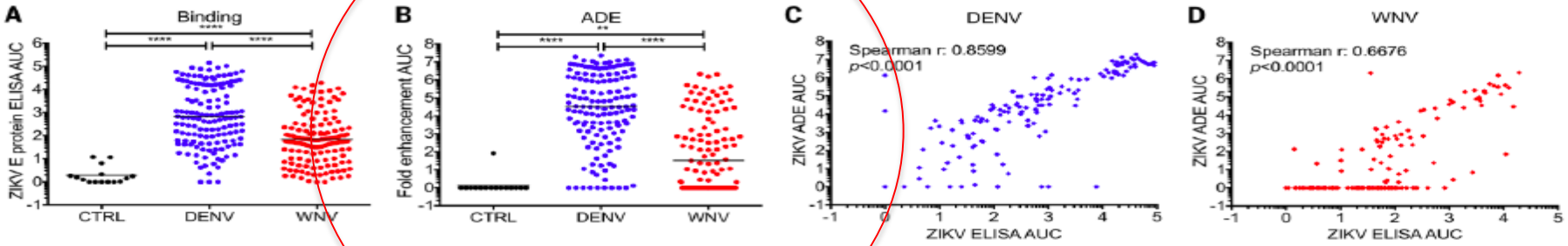


Fig. 1. ZIKV binding and enhancement of infection by DENV- and WNV-immune plasma. Plasma from seropositive DENV- ($n = 141$), WNV-infected ($n = 146$), or sero-negative control ($n = 15$) donors were evaluated for reactivity to ZIKV E protein by ELISA (**A**) or enhancement of ZIKV infection of K562 cells (**B**). Area under the curve (AUC) calculations based on serially-diluted plasma measurements are shown. (**C** and **D**) Scatter plot showing the relationship between ZIKV binding and enhancement of ZIKV infection for DENV (C) and WNV (D) immune plasma. Each point represents one donor. Significance was analyzed by nonparametric unpaired Mann-Whitney U test for (A) and (B) or by non-parametric Spearman's rank correlation for (C) and (D). $^{**}P < 0.01$; $^{****}P < 0.0001$.

ADE *in vitro*

- Common experimental phenomenon
- Without evidence of worsening the symptoms
  - Alphavirus
  - Rabies
  - Coxsackievirus B3
  - Coronavirus
  - HIV
- ADE in Flavivirus
  - Dengue heterotypic
  - Dengue homotypic (under certain concentrations)
  - YF, JEV induces Dengue ADE

Sariol, Nogueira & Vasilakis: **A tale of two viruses: Does heterologous flavivirus immunity enhance Zika disease?**
Trends in Microbiology, 2017

ADE in vivo (DENV)

- ADE of dengue *in vivo* is commonly associated to a worse clinical outcome
- Secondary dengue infections results in:
  - increased viral load
  - dramatic clinical impairment
  - cytokine storm characterized by the increase of IL-6, IL-8, IL-10, IFN-γ, IFN-α, and VEGF, combined with TNF-α, indicating a poor prognostic outcome

Sariol, Nogueira & Vasilakis: **A tale of two viruses: Does heterologous flavivirus immunity enhance Zika disease?**
Trends in Microbiology, 2017

Proposed ADE Definition

- This way *ADE would be defined as a common experimental in vitro phenomenon but a rare in vivo occurrence leading to worsening of the clinical presentation usually associated to hemodynamic changes, increased viremia, proinflamatory cytokine profile and to other detectable laboratory alterations.*

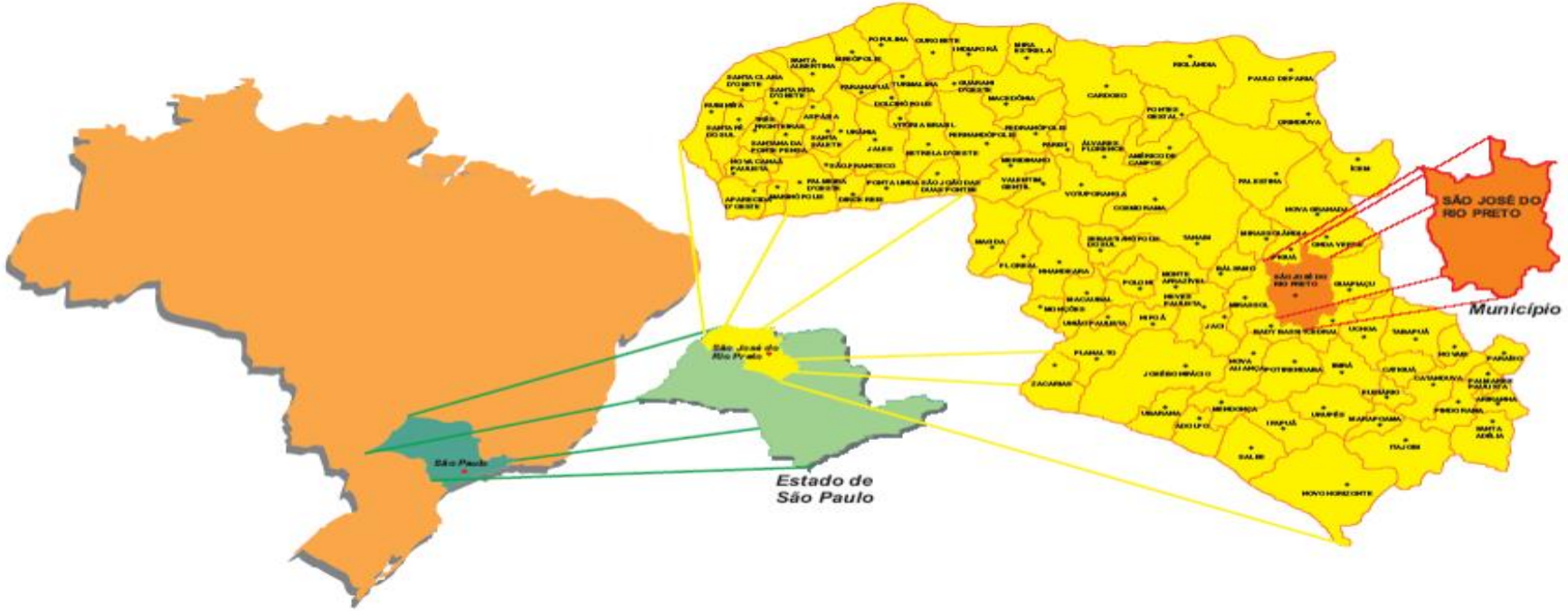
Sariol, Nogueira & Vasilakis: **A tale of two viruses: Does heterologous flavivirus immunity enhance Zika disease?** Trends in Microbiology, *in Press*

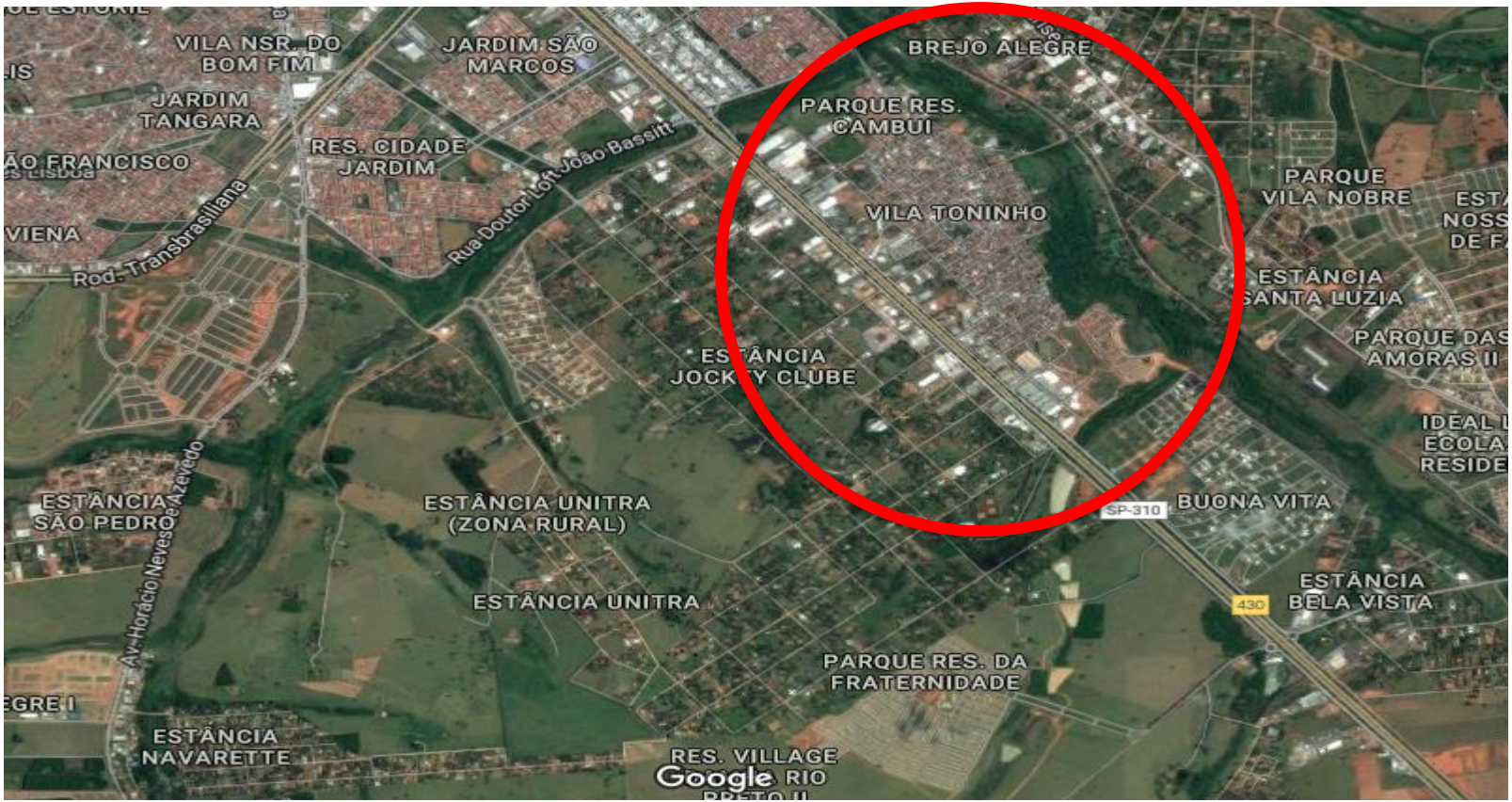
Studies in SJ Rio Preto

4 Cohorts

1 – Hospital Based
2 – Active surveillance
3 – General Population Cohort in Vila Toninho
4 – Pregnant Women

Characterization of the study area:




VILA NSR. DO BOM FIM
JARDIM SÃO MARCOS
JARDIM TANGARA
RES. CIDADE JARDIM
BREJO ALEGRE
PARQUE RES. CAMBUÍ
VILA TONINHO
PARQUE VILA NOBRE
ESTÂNCIA SANTA LUZIA
PARQUE DAS AMORAS II
Rua Doutor Lott João Bassitt
Rod. Transbrasiliana
ESTÂNCIA JOCKEY CLUBE
ESTÂNCIA SÃO PEDRO
Av. Horácio Neves de Azevedo
ESTÂNCIA UNITRA (ZONA RURAL)
ESTÂNCIA UNITRA
SP-310
BUONA VITA
430
ESTÂNCIA BELA VISTA
PARQUE RES. DA FRATERNIDADE
ESTÂNCIA NAVARETTE
RES. VILLAGE
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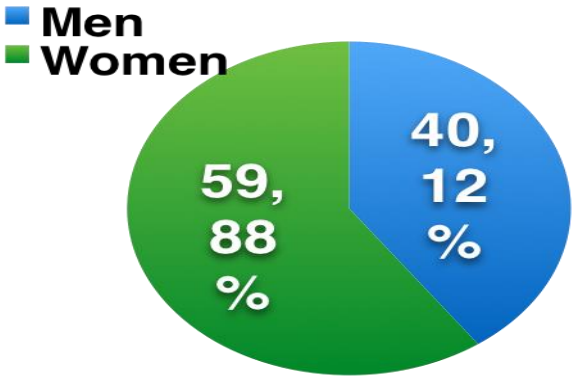
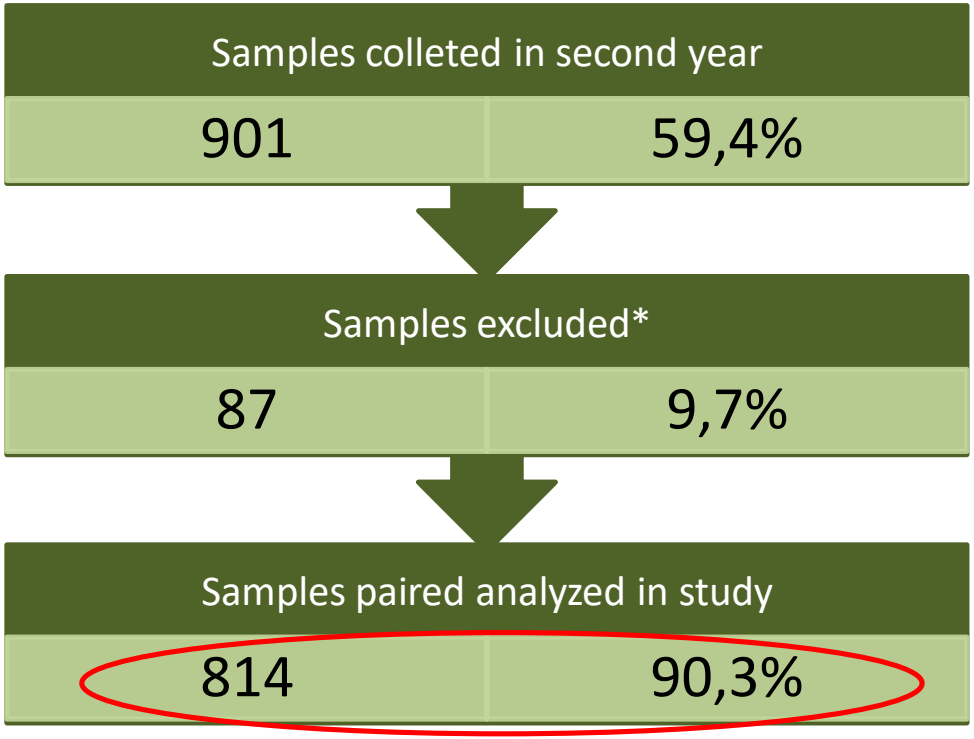
Population Profile

- **Recruitment period:** October, 2015 to April, 2016
- 1468 individuals
  - ≥ 10 years, living in Vila Toninho, São José do Rio Preto, SP, Brazil



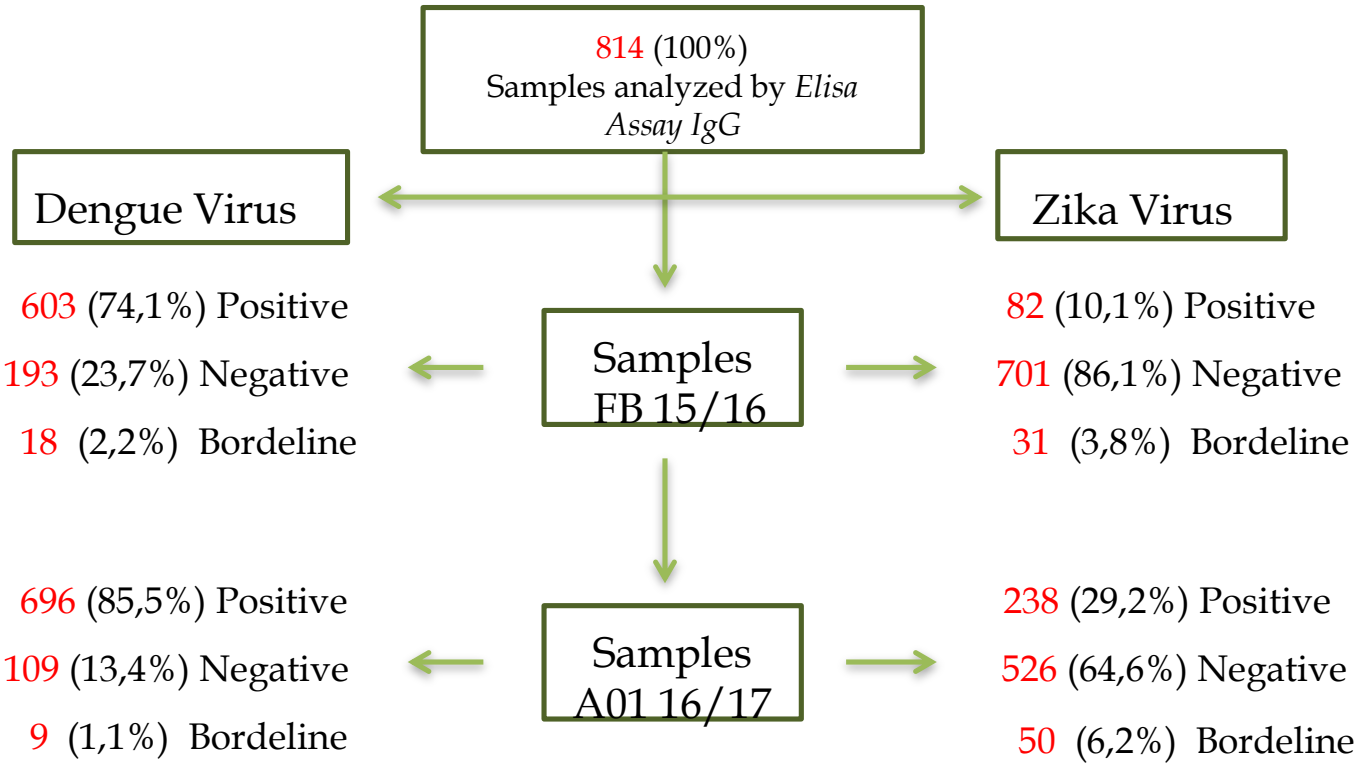
- 752 (51.22%): Caucasian
- 667 (45.44%): Married

Samples Collected in Vila Toninho



* Enrolled in a Dengue Vaccine Trial

Results:


814 (100%)
Samples analyzed by *Elisa Assay IgG*
Dengue Virus
Zika Virus
603 (74,1%) Positive
193 (23,7%) Negative
18 (2,2%) Bordeline
Samples FB 15/16
82 (10,1%) Positive
701 (86,1%) Negative
31 (3,8%) Bordeline
696 (85,5%) Positive
109 (13,4%) Negative
9 (1,1%) Bordeline
Samples A01 16/17
238 (29,2%) Positive
526 (64,6%) Negative
50 (6,2%) Bordeline

- Total: 65 Dengue-suspected cases with acute symptoms
  - RT-PCR DENV performed in 38 patients
    - 7 were positive
      - 4 DENV-2
      - 1 DENV-1
      - 1 DENV-4
      - 1 DENV-1 and -4 (co-infection)

7 Dengue confirmed

- **Concluding:**
  - 13 Dengue-confirmed cases
    - 9 during acute phase
    - 4 by seroconversion
  - 32 Dengue-presumptive cases
  - 8 Zika-confirmed cases (by seroconversion) (1 symptomatic to 19 assymptomatic*)
    - 3 were discarded (other infection confirmed)
    - 9 were not available during acute phase or late

Conclusions - I

1) High level of Dengue circulation
2) Up to 75% of DENV seropositive individuals
3) NO difference in sex regarding dengue seroprevalence
4) Difference in age (age dependent)
5) Zika seroprevalence was detected before circulation detected
6) Almost 20% of the population seroconverted to Zika
7) Symptomatic/Asymptomatic ratio up to 1: 20 (**)
    - High level of DENV ab
    - High Level YFV Ab
    - Surveillance protocol
8) 70% of the population still susceptible to Zika

Patient Study

- patients who exhibited acute febrile disease for ≤ 5 days
- PCR Assays for DENV 1-4, ZIKV, and CHIKV
- DENV IgG ELISA
- Analysis of Viral Load by qRT-PCR (DENV 2 and ZIKV)
- Analysis of Serum Cytokine Levels (interferon (IFN)-γ, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-13, and IL-17.)

Results

- No significant difference in Dengue IgG prevalence (70% and 78% in Zika and Dengue infected patients) – General Population = 67%
- Only one severe disease in dengue group.
- No difference in Zika severity in Dengue IgG+ or Dengue IgG – (even the outcome of pregnant women).

Terzian et al CID 2017

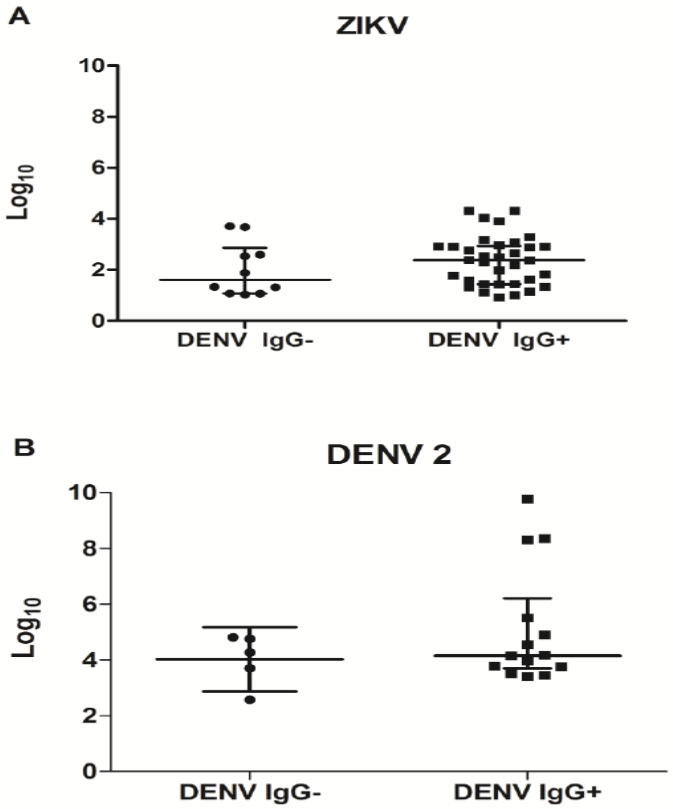
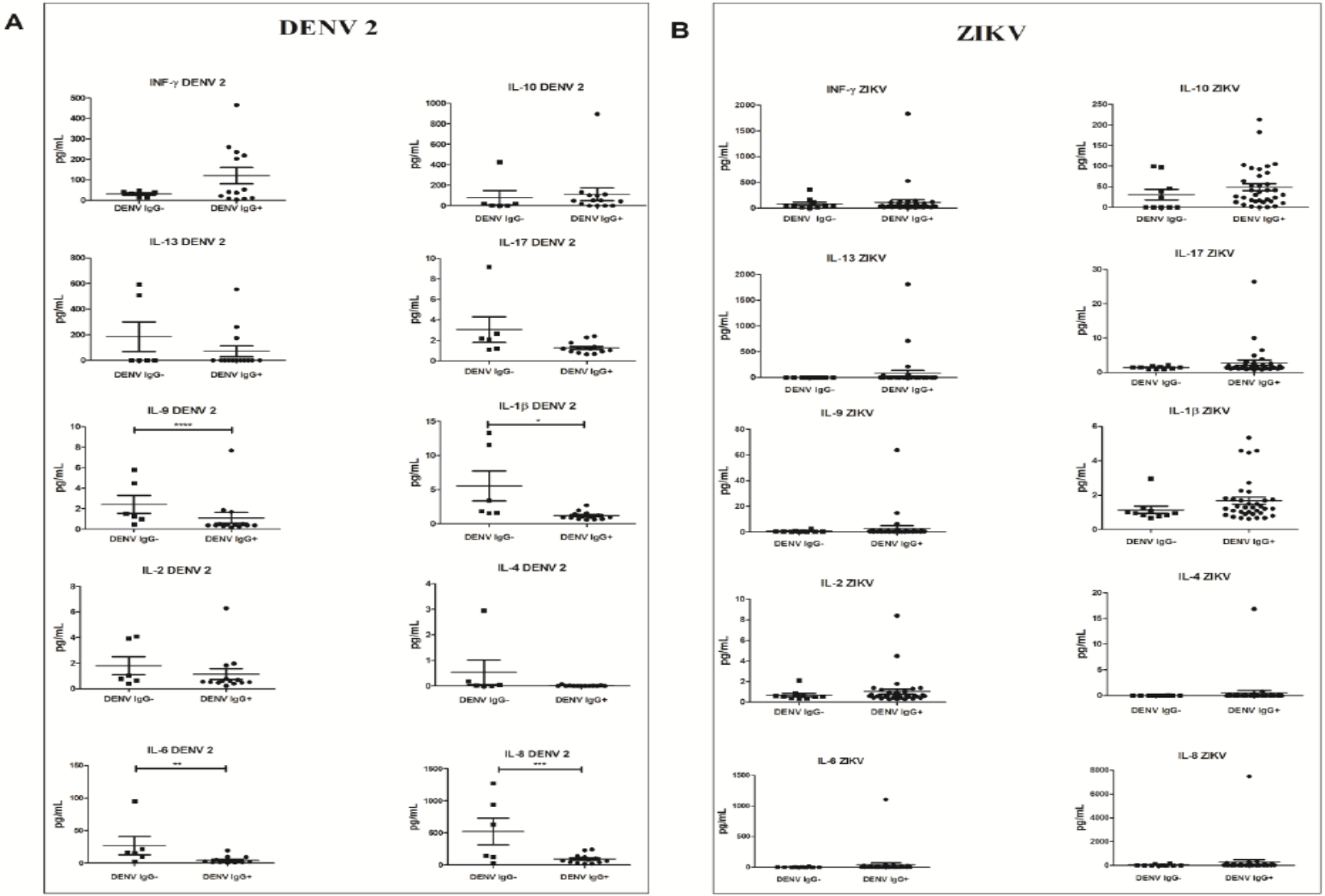


Figure 1: Viral load in ZIKV and DENV 2 patients during primary and secondary dengue infections. **(A)** Viral load quantified in ZIKV-positive patients with primary (IgG-) DENV infection (n=10) and secondary (IgG+) DENV infection (n=35). The Mann-Whitney U test demonstrated no significant difference in viral load. **(B)** Viral load quantified in DENV 2-positive patients with primary (IgG-) DENV infection (n=06) and secondary (IgG+) DENV infection (n=14). The Mann-Whitney U test demonstrated no significant difference in viral load. Median with interquartile range (IQR).


A
DENV 2
INF-γ DENV 2
IL-10 DENV 2
IL-13 DENV 2
IL-17 DENV 2
IL-9 DENV 2
IL-1β DENV 2
IL-2 DENV 2
IL-4 DENV 2
IL-6 DENV 2
IL-8 DENV 2
pg/mL
DENV IgG-
DENV IgG+
B
ZIKV
INF-γ ZIKV
IL-10 ZIKV
IL-13 ZIKV
IL-17 ZIKV
IL-9 ZIKV
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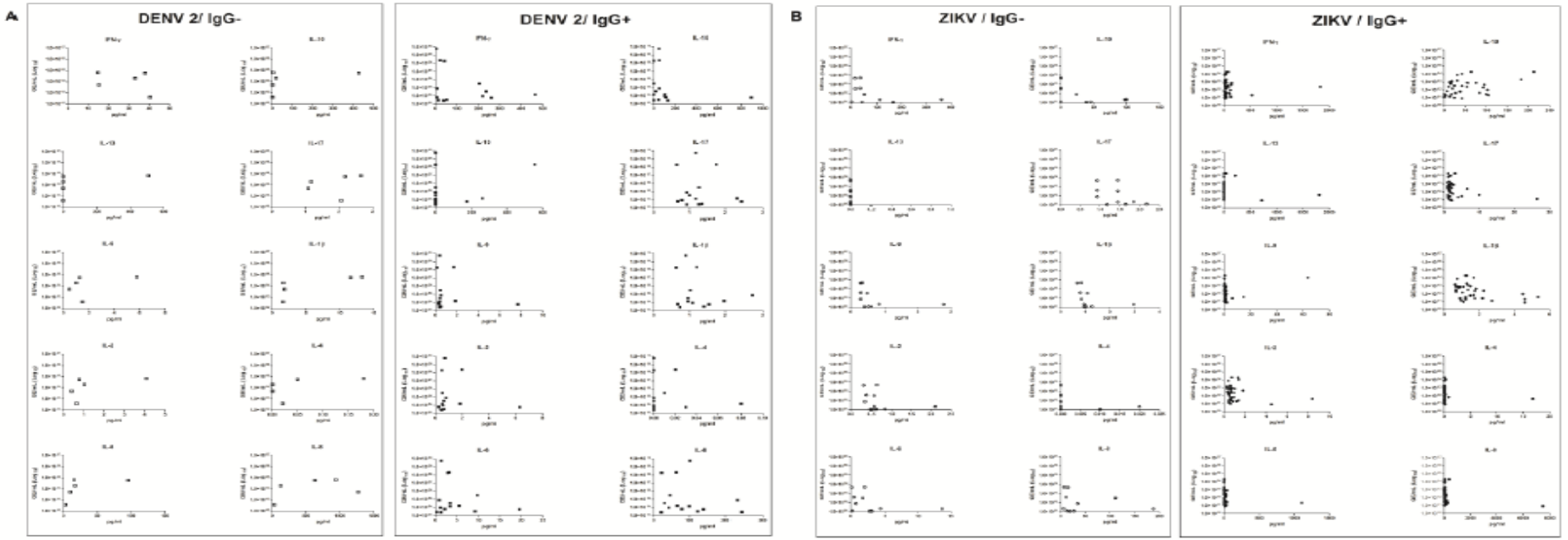
IL-2 ZIKV
IL-4 ZIKV
IL-6 ZIKV
IL-8 ZIKV


A
DENV 2/ IgG-
DENV 2/ IgG+
B
ZIKV / IgG-
ZIKV / IgG+

Clinical Infectious Diseases

MAJOR ARTICLE

Viral Load and Cytokine Response Profile Does Not Support Antibody-Dependent Enhancement in Dengue-Primed Zika Virus–Infected Patients

Ana Carolina Bernardes Terzian,[1] Alessandra Soares Schanoski,[2] Mânlio Tasso de Oliveira Mota,[1] Rafael Alves da Silva,[1] Cássia Fernanda Estofolete,[1] Tatiana Elias Colombo,[1] Paula Rahal,[3] Kathryn A. Hanley,[4] Nikos Vasilakis,[5] Jorge Kalil,[6] and Maurício Lacerda Nogueira[1]

[1]São José do Rio Preto School of Medicine, [2]Butantan Institute, and [3]Department of Biology, Institute of Biosciences, Letters, and Exact Sciences, São Paulo State University, São José do Rio Preto, Brazil; [4]New Mexico State University, Las Cruces; [5]University of Texas Medical Branch, Galveston; and [6]University of São Paulo School of Medicine, Brazil

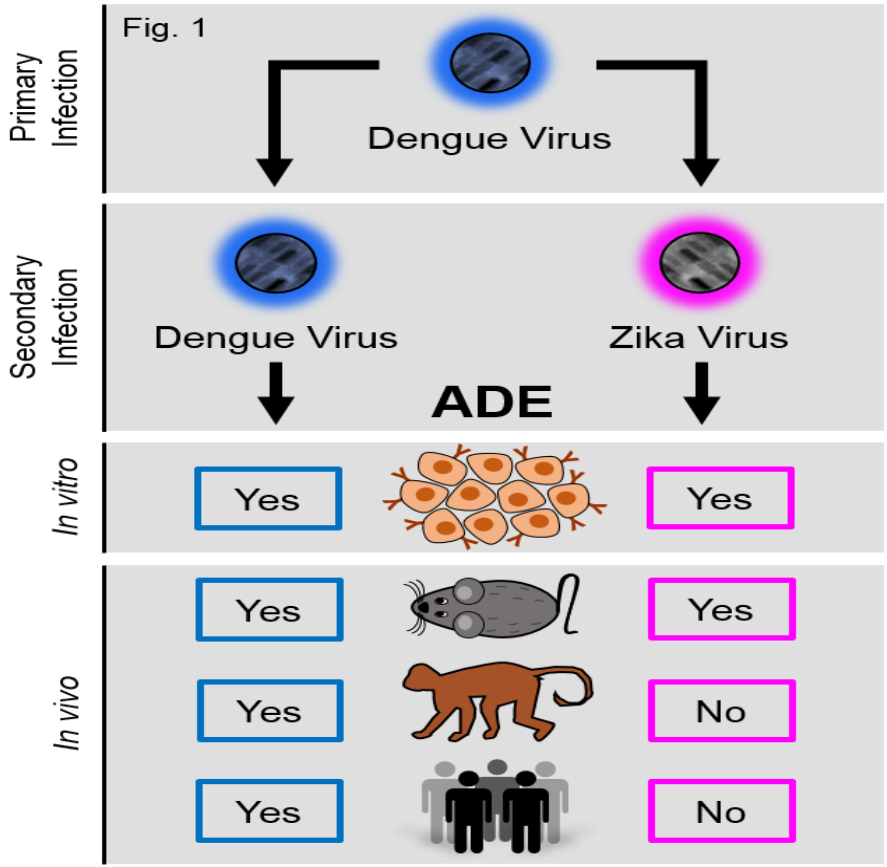
Background. The pathogenesis of severe dengue disease involves immune components as biomarkers. The mechanism by which some dengue virus (DENV)–infected individuals progress to severe disease is poorly understood. Most studies on the pathogenesis of severe dengue disease focus on the process of antibody-dependent enhancement (ADE) as a primary risk factor. With the circulation of Zika virus (ZIKV) in DENV-endemic areas, many people infected by ZIKV were likely exposed to DENV. The influence of such exposure on Zika disease outcomes remains unknown.

Methods. We investigated whether patients previously exposed to DENV exhibited higher viremia when exposed to a subsequent, heterologous dengue or Zika infection than those patients not previously exposed to dengue. We measured viral loads and cytokine profile during patients' acute infections.

Results. Neither dengue nor Zika viremia was higher in patients with prior DENV infection, although the power to detect such a difference was only adequate in the ZIKV analysis. Of the 10 cytokines measured, only 1 significant difference was detected: Levels of interleukin 1β (IL-1β) were lower in dengue-infected patients who had experienced a previous dengue infection than patients infected with dengue for the first time. However, power to detect differences between groups was low. In Zika-infected patients, levels of IL-1β showed a significant, positive correlation with viral load.

Conclusions. No signs of ADE were observed in vivo in patients with acute ZIKV infection who had prior exposure to DENV.

Keywords. ZIKV; DENV; ADE; cytokines.



Sariol, Nogueira & Vasilakis: **A tale of two viruses: Does heterologous flavivirus immunity enhance Zika disease?**
Trends in Microbiology, *2017*

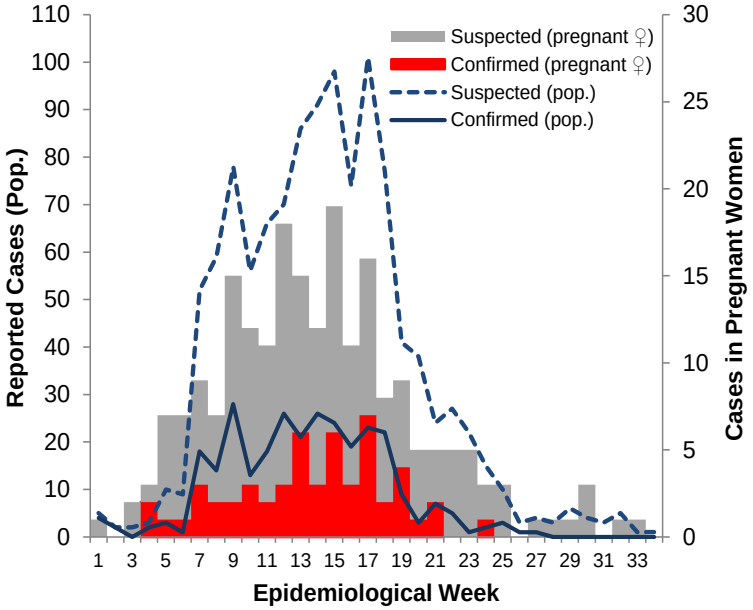
Protection ? Acute infections? Pregnant Women?

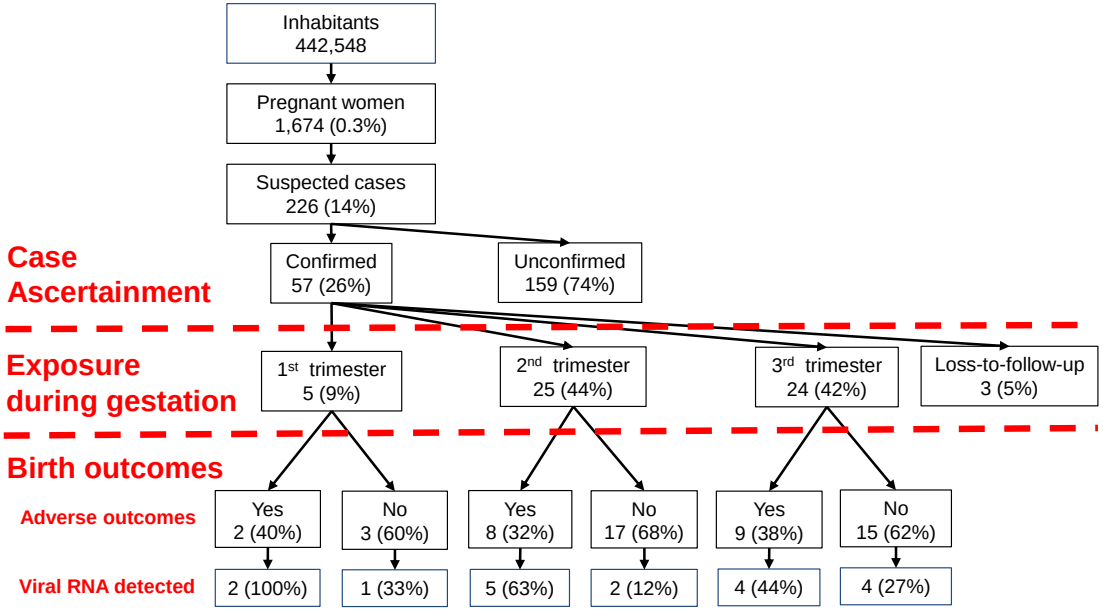
NEW QUESTIONS RAISED

And YFV vaccinated…. The search for co-factors

A ZIKA COHORT IN A DENGUE ENDEMIC AREA

Prospective Study of Pregnant Women with Symptomatic Zika Exposures during São José do Rio Preto Outbreak, February-June, 2016*





Nogueira et al, Clinical Microbiology and Infection, *accepted*

Table 4. Outcomes among Newborns of Women Exposed to ZIKV during Pregnancy

Outcomes	No. Cases	Incidence (95% CI)*
Adverse birth outcomes	15/54	28 (17 - 41)
Exposure in 1st trimester	1/4	25 (63 - 81)
Exposure in 2nd trimester	4/26	15 (5 - 33)
Exposure in 3rd trimester	10/24	42 (23 - 62)
ZIKV detected at birth	8/18	44 (23 - 67)
ZIKV not detected at birth	7/15	47 (23 - 71)
ZIKV detection at birth	18/51	35 (22 - 48)
ZIKV exposure in 1st trimester	2/4	50 (9 - 91)
ZIKV exposure in 2nd trimester	8/26	31 (15 - 50)
ZIKV exposure in 3rd trimester	8/24	33 (14 - 52)
With adverse outcomes	8/15	53 (29 - 77)
Without adverse outcomes	10/39	26 (14 - 41)

ND

*Cumulative incidence shown as cases per 100 births

Nogueira et al, Clinical Microbiology and Infection, 2018

- Clinical outcomes:
  - High rates but less severe
  - Microcephaly not observed
  - Radiological findings (17%) limited to:
    - Lenticular striated arterial vessels
    - Subependymal and choroidal cysts
    - Altered sub-tentorial measures
  - Abnormal otoacustic exam (11%)
  - Choroidoretinal atrophy (2%)

- Laboratory outcomes:
  - ZIKV RNA detected in 35%
  - All were MAC-ELISA-

- Vertical transmission rate may be >50%

Nogueira et al, Clinical Microbiology and Infection, *2018*

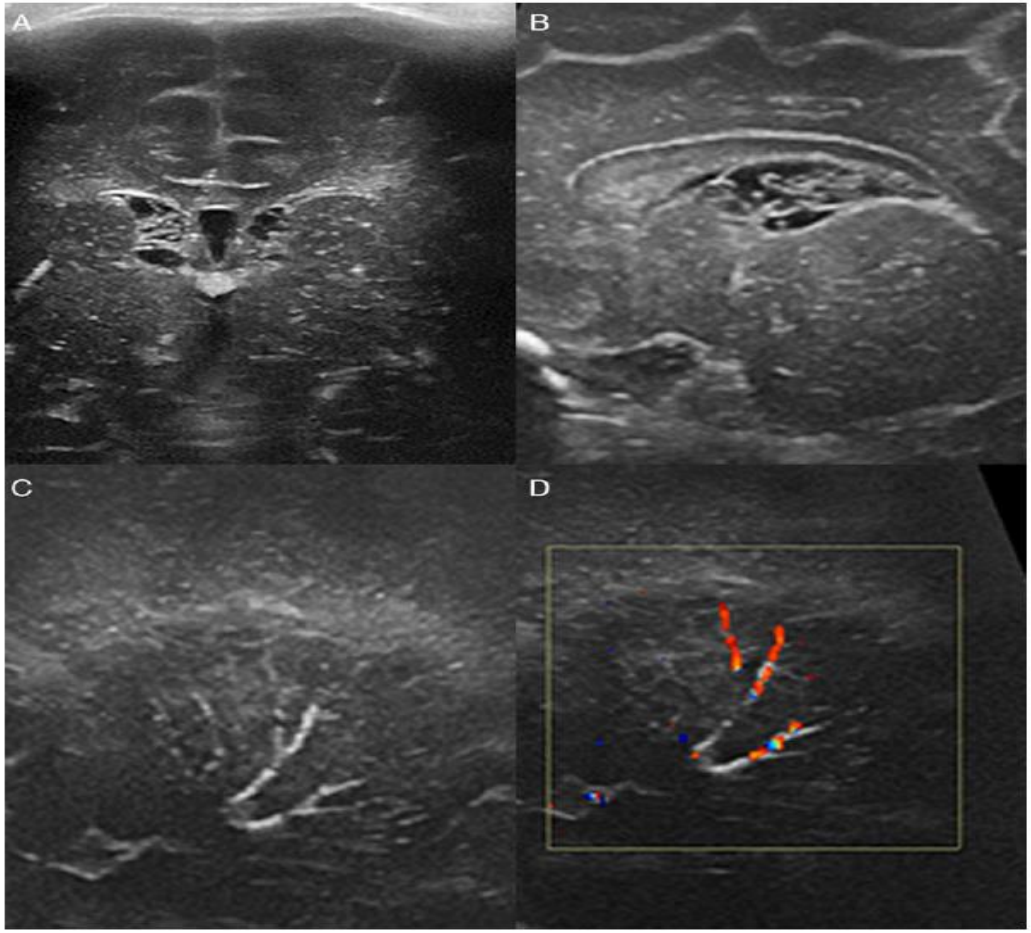


Figure 1. Neonatal transfontanellar ultrasound showing multiple small subependymal/intraventricular cysts in coronal (*A*) and sagittal views (*B*), and hyperechogenicity (mineralization) of lenticulostriate vessels in the sagittal plane at the thalamus (*C*), with vascular flow confirmed by color Doppler (*D*).

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Emerging Problems in Infectious Diseases

Zika virus infection, associated microcephaly, and low yellow fever vaccination coverage in Brazil: is there any causal link?

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Abstract

Introduction: Since the end of 2014, Zika virus (ZIKV) infection has been rapidly spreading in Brazil.

Methodology: To analyze the possible association of yellow fever vaccine with a protective effect against ZIKV-related microcephaly, the following spatial analyses were performed, using Brazilian municipalities as units: i) yellow fever vaccination coverage in Brazilian municipalities in individuals aged 15-49; ii) reported cases of microcephaly by municipality; and iii) confirmed cases of microcephaly related to ZIKV, by municipality. SaTScan software was used to identify clusters of municipalities for high risk of microcephaly.

Results: There were seven significant high risk clusters of confirmed microcephaly cases, with four of them located in the Northeast where yellow fever vaccination rates were the lowest. The clusters harbored only 2.9% of the total population of Brazil, but 15.2% of confirmed cases of microcephaly.

Conclusion: We hypothesize that pregnant women in regions with high yellow fever vaccination coverage may pose their offspring to lower risk for development of microcephaly. There is an urgent need for systematic studies to confirm the possible link between low yellow fever vaccination coverage, Zika virus infection and microcephaly.

Key words: Zika; Brazil; epidemiology.

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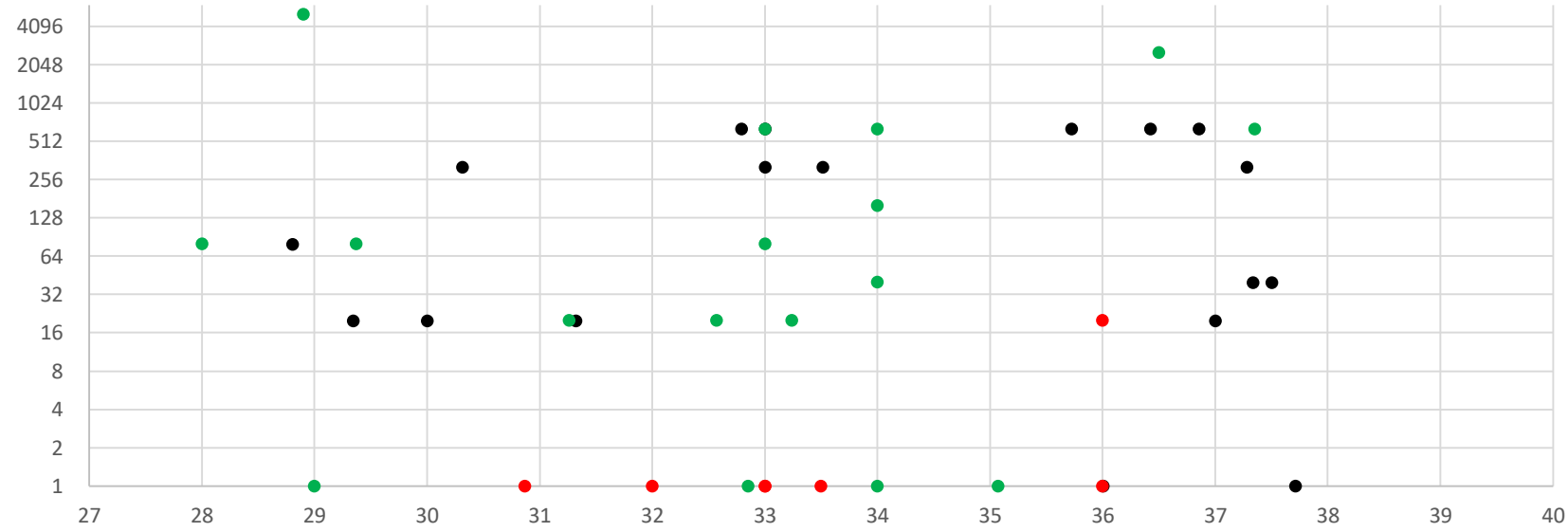
Is there a relationship between YFV Ab levels and viral load at diagnosis?



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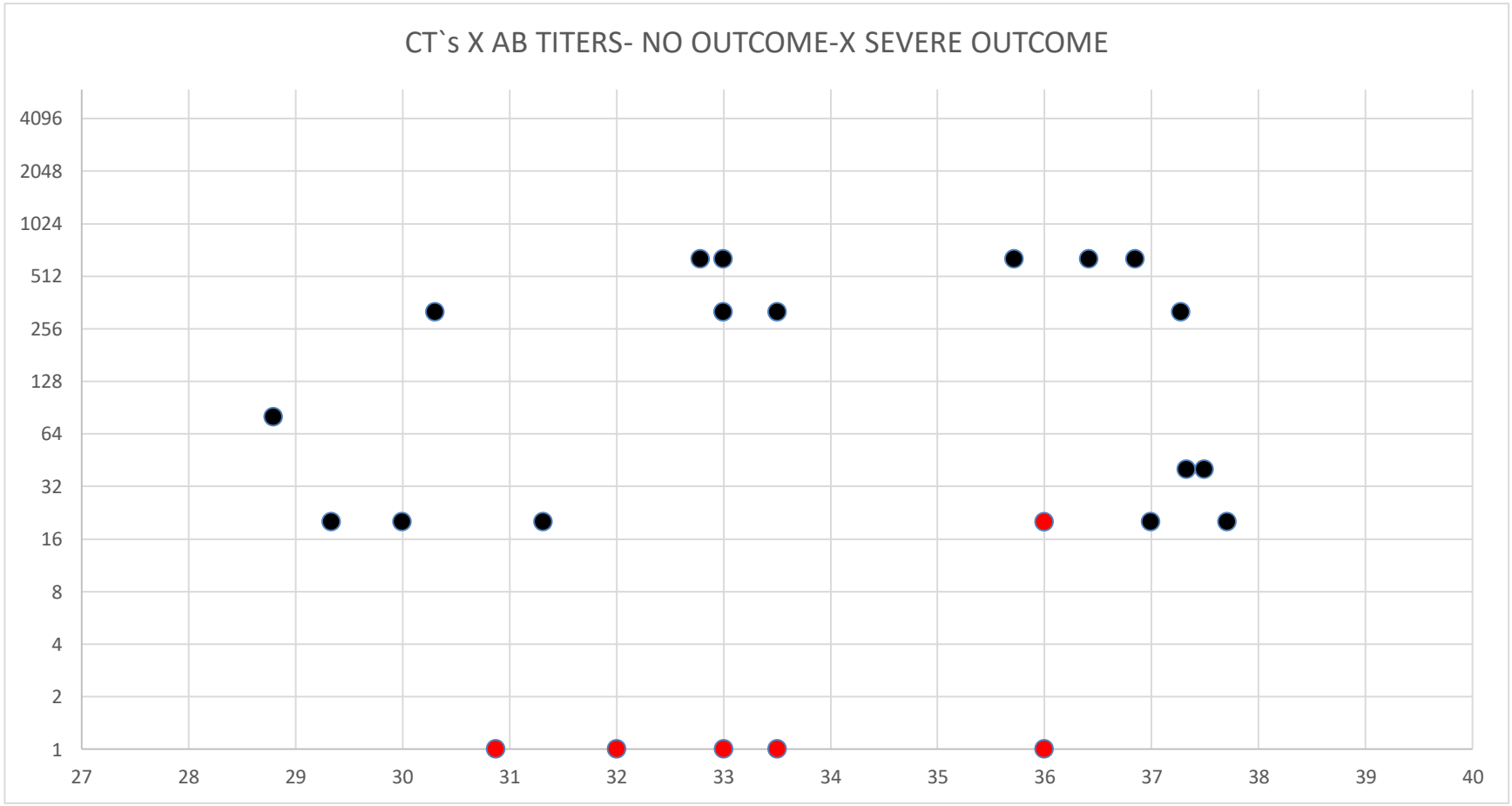

Table1. Geometric mean titer of neutralizing antibodies against Yellow Fever Virus and clinical outcomes of newborns exposed to ZIKV in pregnancy

	GeoMean	SD
Adverse Outcome	49.11*	0.021
No adverse Outcome	135.92*	0.022

* p=0.0326

Effect size = 0.26

N = 34

Patients from SJ Rio Preto and Rio de Janeiro

Conclusions - II

1) No evidence of enhancement in Zika clinical infections
2) No evidence of “clinical” ADE in pregnant women
3) There is some level of protection for Acute Zika infection induced by DENV-1 and DENV-4 serum (the two virus circulated in high levels in the years before Zika introduction).
4) No significance for DENV-3 (low levels high affinity antibodies – 10 years since last circulated) or DENV-2 (low levels of circulation in the years before Zika)
5) YFV Ab levels are CORRELATED with a better prognosis in Zika infected women.

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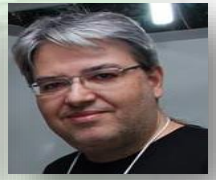

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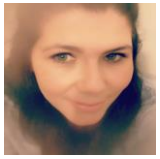

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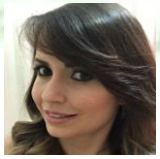

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