

Zika Virus the Fifth Dengue Virus Serotype?

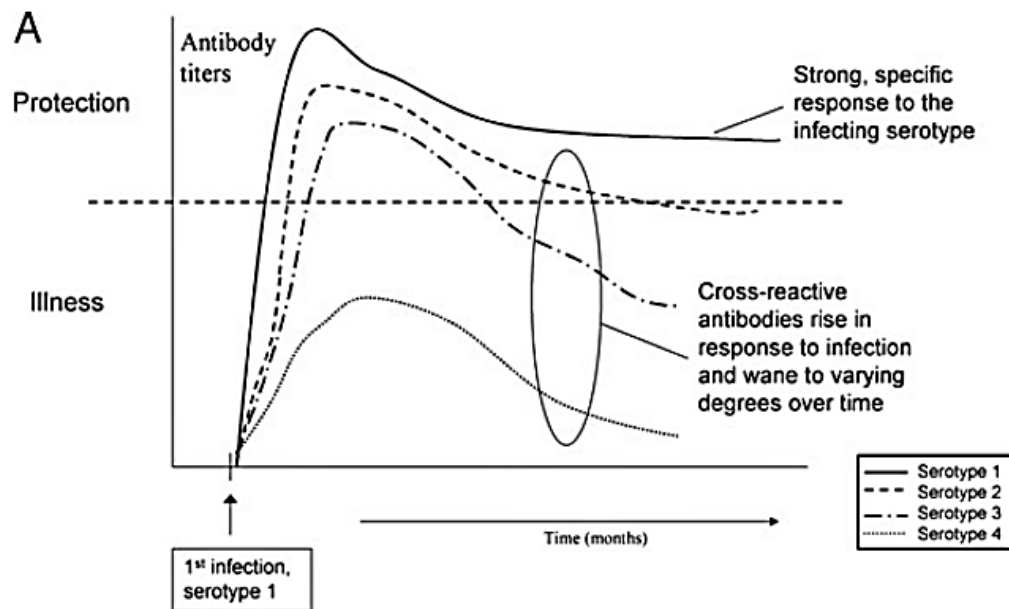
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- Dengue virus (DENV) and Zika virus (ZIKV) are both flaviviruses
- DENV has four serotypes (DENV1-4)
- ZIKV shares significant genetic similarities with DENV
- Structural similarities in envelope proteins
- ZIKV and DENV induce cross-reactive antibodies
- Implications for immune response? Disease severity?

Immunological interaction between the 4 serotypes

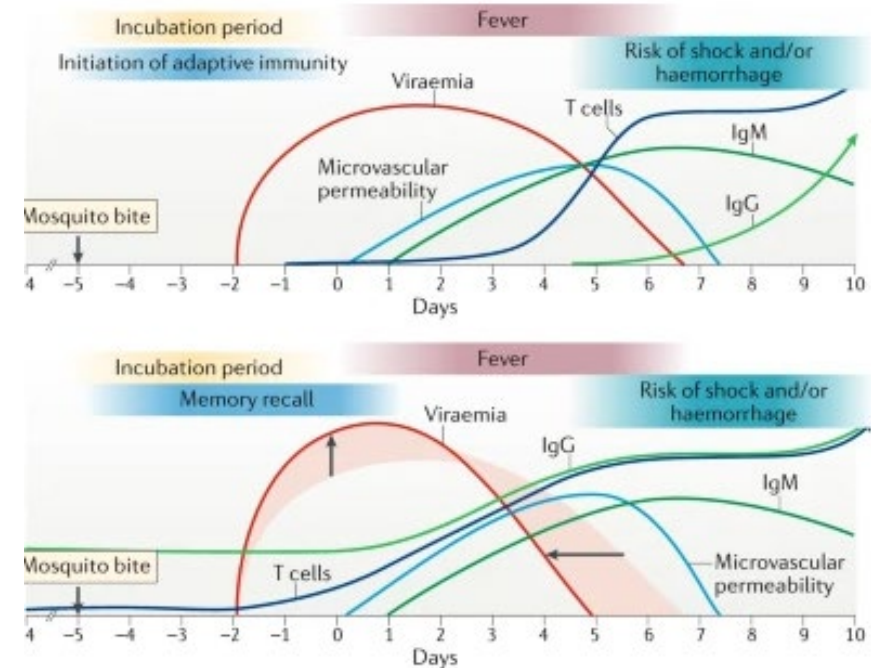
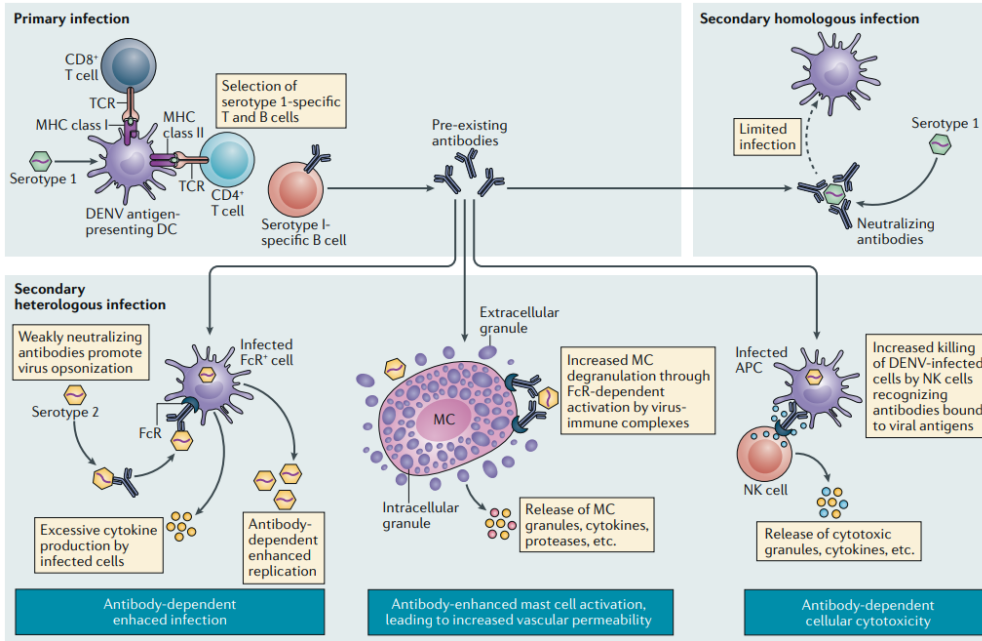
Anderson et al, A Shorter Time Interval Between First and Second Dengue Infections Is Associated With Protection From Clinical Illness in a School-based Cohort in Thailand. J Inf Dis. 2014



Primary and secondary DENV infection

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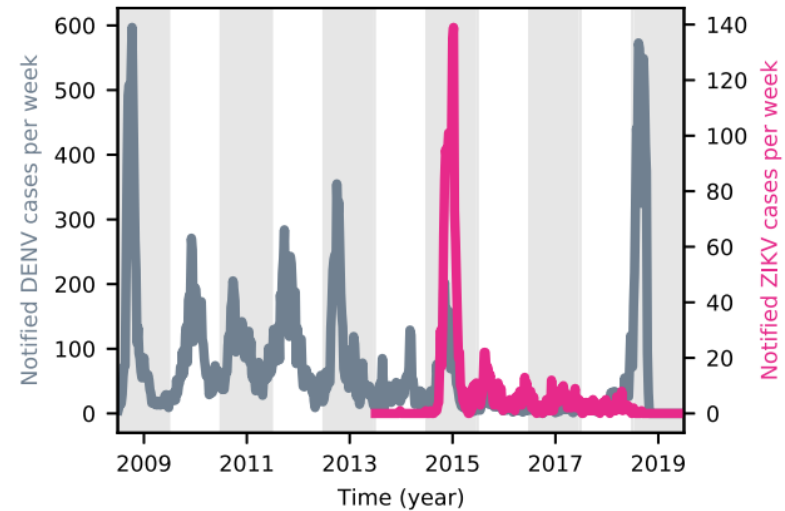
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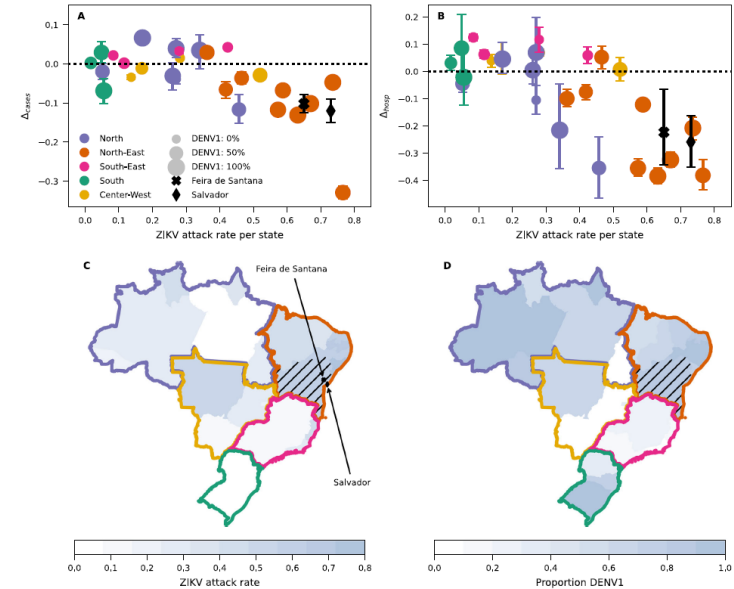
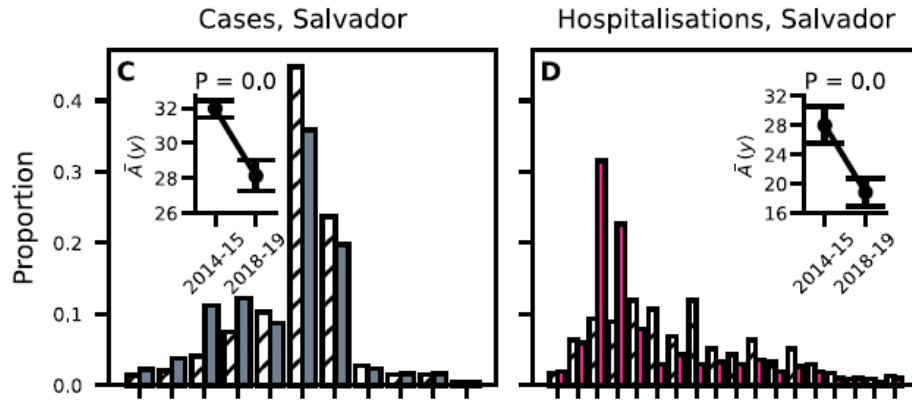
St.John et al. Nature 2019

ZIKV and DENV dynamics in Brazil

- Brazil 2015-2016 -> low DENV circulation in the 2 following years
 - Mostly DENV1 and DENV2
- Hypothesis: changes in arbovirus surveillance, control of mosquito abundance, cross-protection



Age-shift compared to pre-ZIKV era ZIKV-induced cross-reactivity can modify the age distribution of DENV cases



- A: Model with ZIKV infection only causing cross-protection, no enhancement
- B: Model with ZIKV infection modulating DENV disease severity in addition to cross-protection
- A -> age-shift towards older age of DENV cases
 - Reason: ZIKV only delays individuals to experience DENV by short-term cross-protection

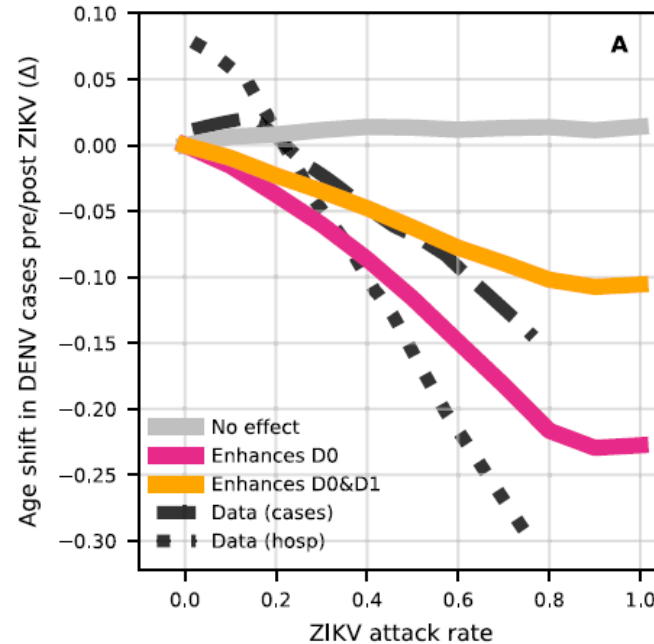
Does previous infection with ZIKV modulate DENV disease severity in addition to offering short-term protection?

Hypothesis

- 1) ZIKV behaves like a fifth DENV serotype -> enhance disease in DENV naive hosts
 - Severity of disease: 1° DENV in ZIKV+ same as 2° DENV in ZIKV-
- 2) ZIKV enhances disease in both primary and secondary DENV infections (in accordance with previous data Katzelnick et al 2020)
- shift towards younger ages in post-ZIKV DENV cases stronger in 1)

Leading role of primary DENV infections

The scenario most compatible with observed reduction in DENV case age post ZIKV is when enhancement of primary DENV infection is larger than enhancement of secondary infection



Nicaragua's large dengue epidemic 2022

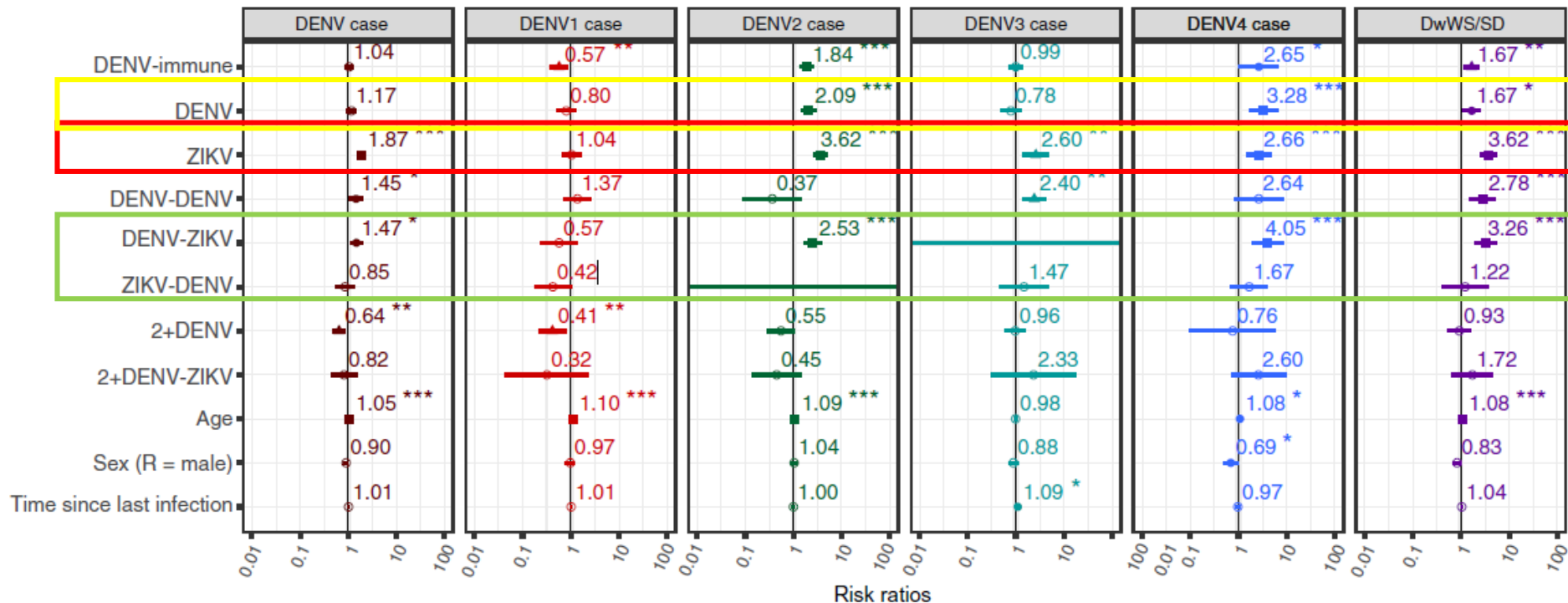
- Nicaragua Pediatric Cohort Study
- Co-circulation of DENV serotyp 1-4 (mainly 1, 4)
- 10.6 % with symptomatic dengue infection
- Population affected by ZIKV 2016
- Inclusion of data since since 2004

Previous ZIKV does not broaden protective immunity

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B

Risk of dengue disease by prior DENV and ZIKV infection histories, 2004–2023



In summary

- Prior DENV or ZIKV infections increased the crude risk of dengue cases
- Previous infection with ZIKV modulates DENV disease severity in addition to offering short-term protection
- Primary ZIKV infection is associated with the risk of symptomatic DENV2, DENV3 and DENV4 infection but not DENV1
- The number and order of DENV and ZIKV infections determined the risk of future symptomatic DENV infection

- Introduction of a monovalent ZIKV vaccine that induces immunity similar to natural ZIKV infection -> negative effect on dengue outcome in dengue-naive populations?
- Introduction of ZIKV vaccine is unlikely to broaden protective immunity in individuals with one prior DENV infection
- Even patients immune to DENV before receiving the dengue vaccine may remain at risk for severe disease

Main references

- Shifting patterns of dengue three years after Zika virus emergence in Brazil. Pinotti et al. Nature 2024
- Primary exposure to zika virus is linked with increased risk of symptomatic dengue virus infection with serotypes 2, 3, and 4 but not 1. Zambrana et al. Sci.Transl.Med 2024