

Differences Between Zika Virus Strains and their Possible Implications for Pathogenesis

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Introduction and Background

History

- Discovered in Zika Forest (Uganda, 1947)
- First case of human infection and virus characterization in 1954 (Nigeria)
- Researchers using RT-PCR analysis of serum samples determined ZIKV as cause of outbreak in Brazil
- Phylogenetic studies suggest ZIKV introduction to Brazil between May and December 2013
 - Two (2) main hypotheses were developed to explain viral emergence
 - Summer 2014: Virus introduction during World Cup Soccer Games
 - August 2014: Virus introduction during World Sprint Championships (Pacific Islands participated)

Virology

- Family: *Flaviviridae*
- Genus: *Flavivirus*
- Genome: 10.7kb (+)-sense ssRNA
- Enveloped virus
- Single polyprotein structure
 - Structural: C, prM/M, E
 - Non-structural: NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5

Clinical and Public Health Risks

- Transmission
 - Aedes aegypti*
 - Aedes albopictus*
 - Co-infection with DENV and CHIKV
- Symptoms
 - Arthralgia (joint pain)
 - Fever
 - Rash
 - Conjunctivitis
 - May also be asymptomatic
- Sexual transmission
 - Can remain 6 months in semen
- Prevalence leads to health and fertility implications
- Microcephaly
 - Abnormally small brain and cranium due to lack of neurodevelopment
- Ability to cross amniotic fluid

Objectives

- Provide a historical context for the introduction of ZIKV to the Americas
- Describe the viral vectors and their presence in the Americas
- Explore environmental constraints that could possibly limit ZIKV spread
- Understand evolutionary relationships between ZIKV strains
- Review data studying the differences in viral replication of different ZIKV strains
- Learn about how viral factors contribute ZIKV infection and pathology at the molecular level.

Research Questions and Hypotheses

1. Do environmental constraints on the vector determine evolution of Zika virus and its spread?

- Climate limits the geographical range of ZIKV vectors, mosquitoes *Aedes aegypti* and *Aedes albopictus*, thereby limiting areas with risk of infection.

2. Do molecular variations among ZIKV strains imply changes to infection pathogenesis?

- Genomic differences between ZIKV strains may influence their infectivity, replication, cell tropism, and susceptibility to immune responses. These differences may also contribute to explaining the higher incidence of microcephaly linked to ZIKV infection in Brazil.

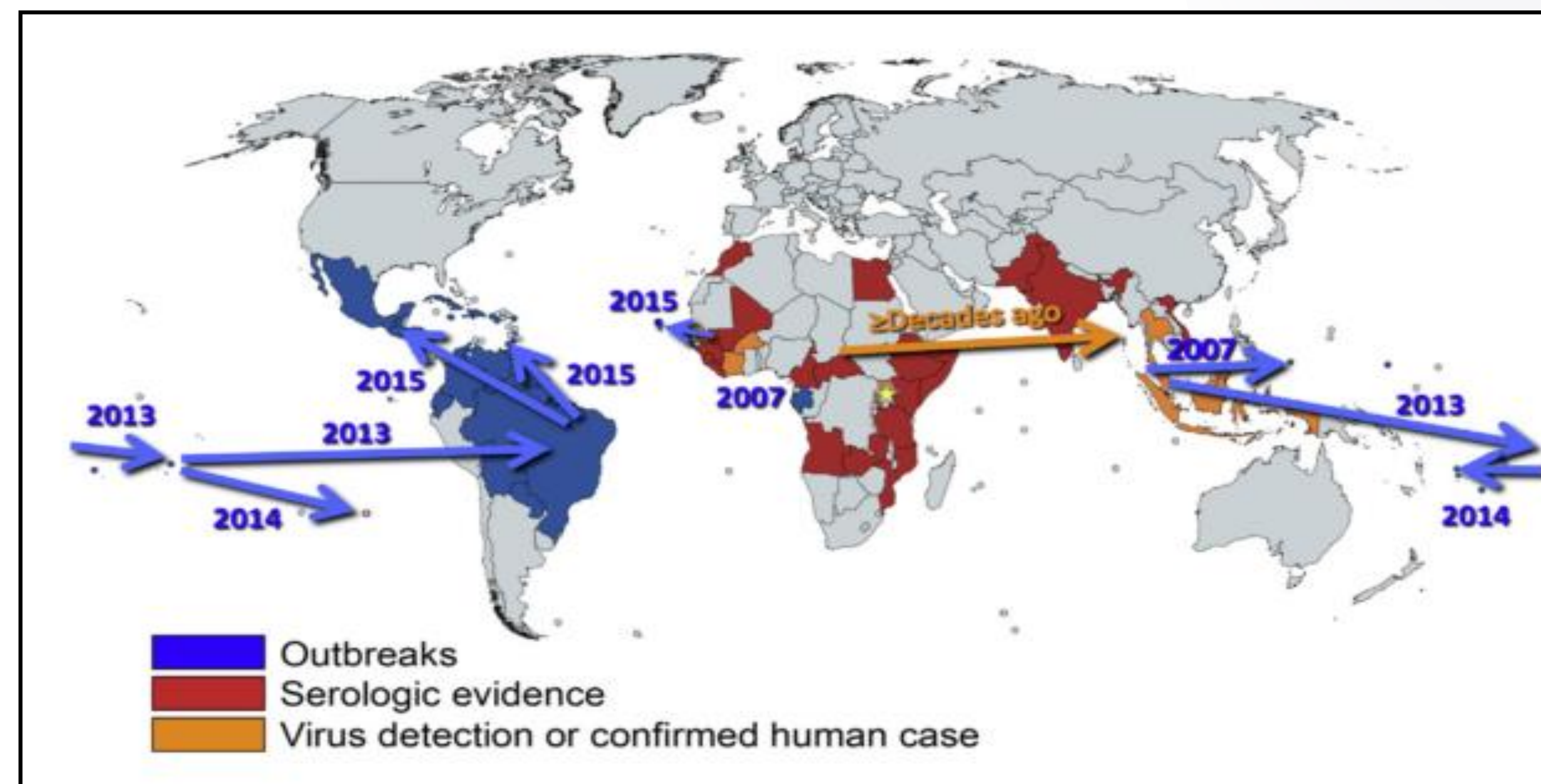


Fig. 1. Historical context of Zika virus spread worldwide. Map depicting the known distribution of ZIKV based on serosurveys, virus detection, and cases. Blue patterns show deduced spread based on phylogenetic studies. (Weaver et al., 2016)

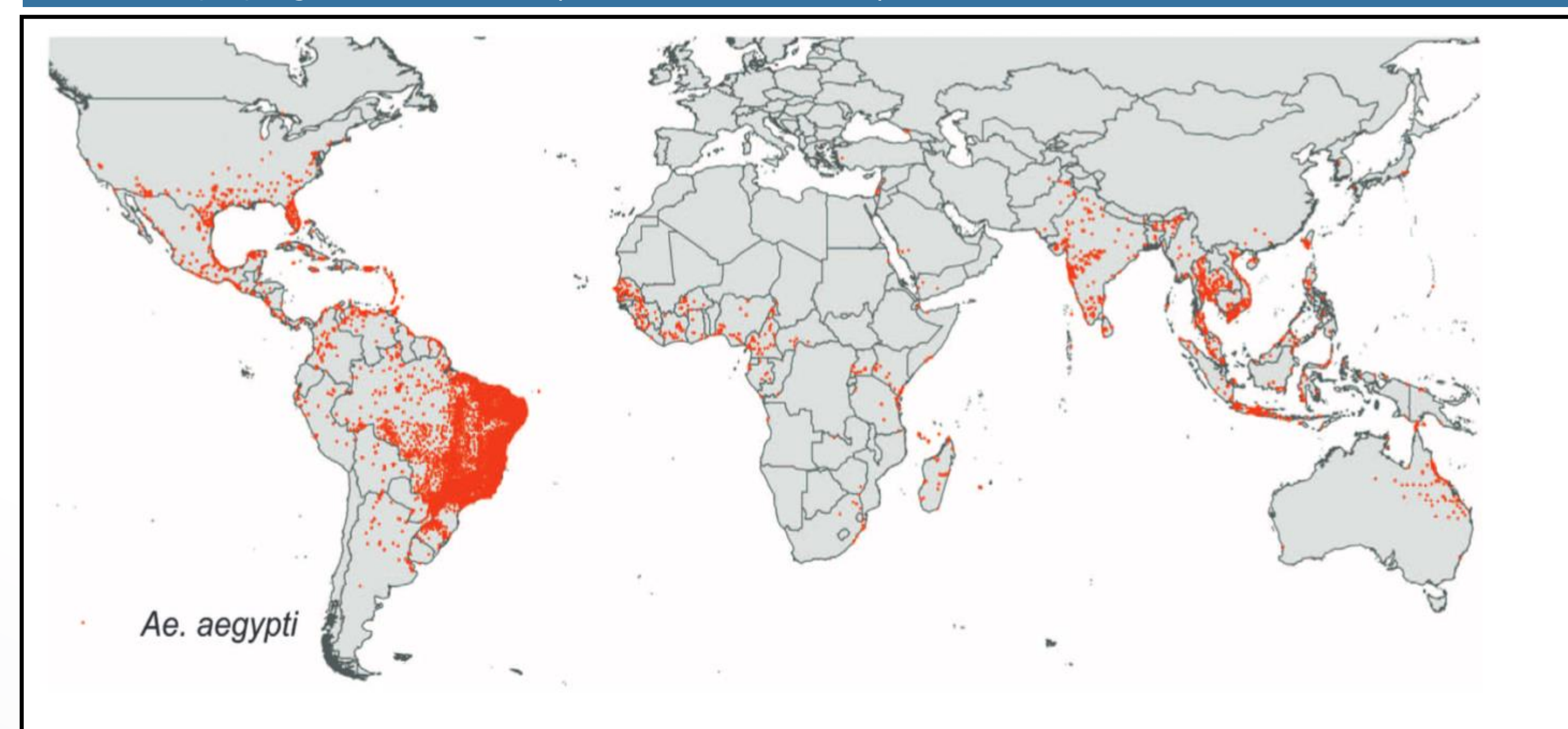


Fig. 2. Geographic distribution of *Aedes aegypti* mosquito worldwide. Occurrence points distribution of *Aedes aegypti*. Resolution of 5 km x 5 km (Kraemer et al., 2015)

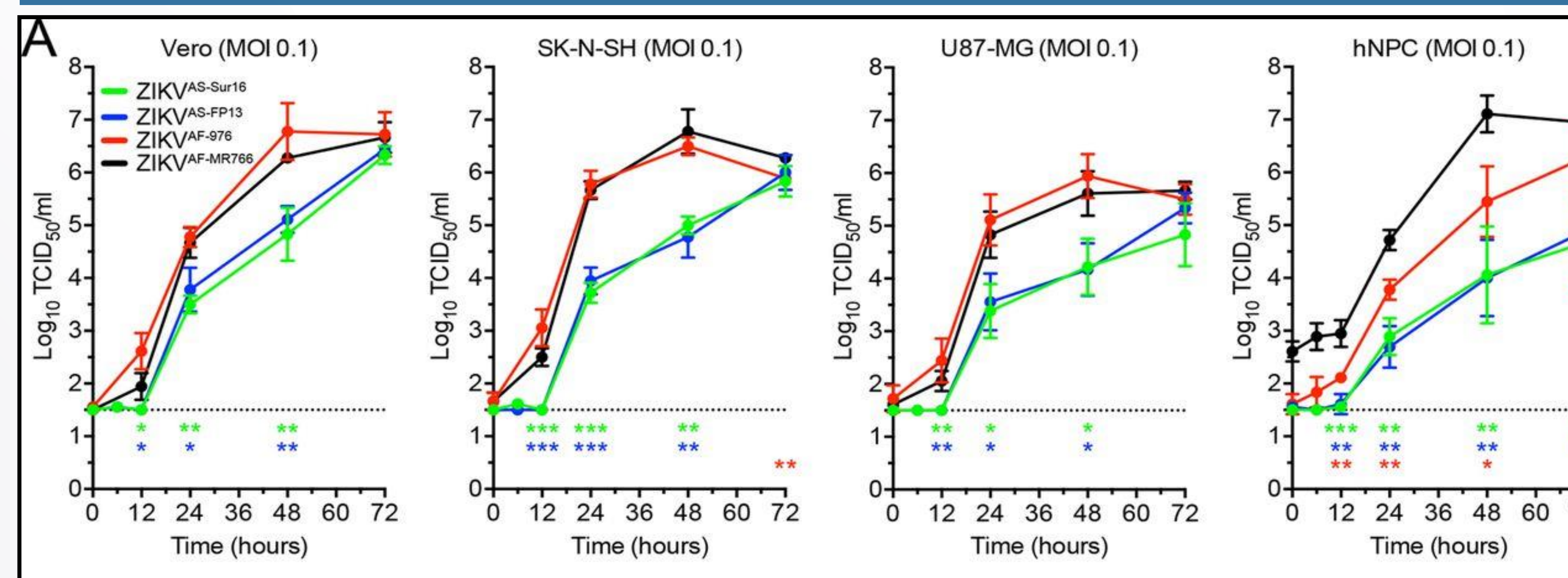


Fig. 3. Asian strains have less viral production than African strains hNPCs. Viral replication kinetics in vitro Uganda (black), French Polynesia (green) ZIKV strains. (Anfasa, et al., 2017)

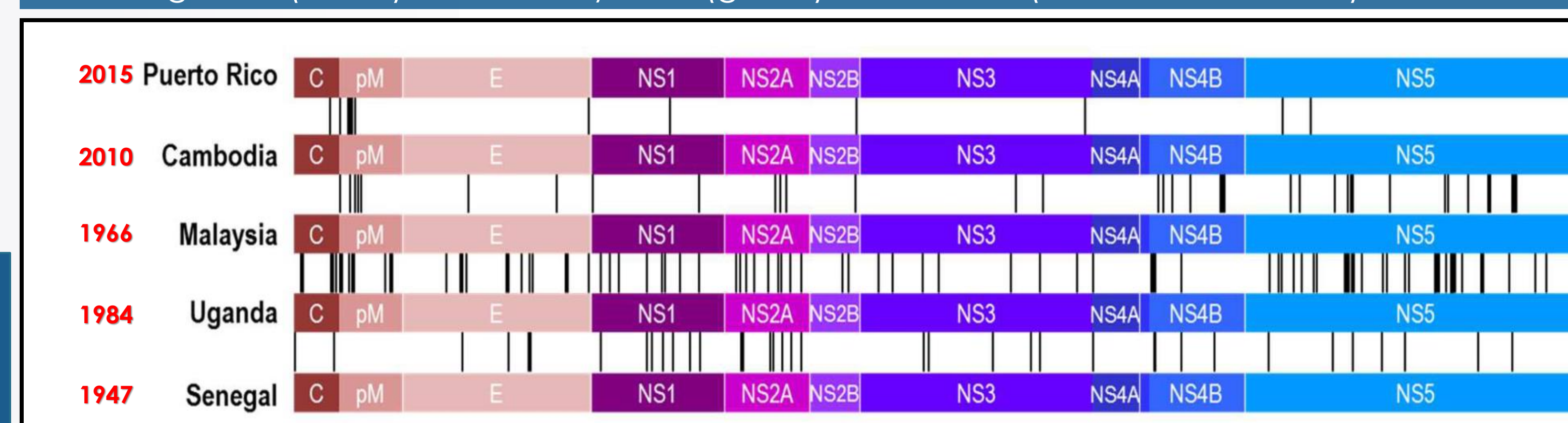


Fig. 4. Whole genome sequencing of ZIKV relate American, Asian, and African strains. Evolutionary relationship between ZIKV strains relative to amino acid comparisons between viral proteins. Reading of the map goes from bottom to top comparing the first strain to the next in ascending order. (Tripathi et al., 2017)

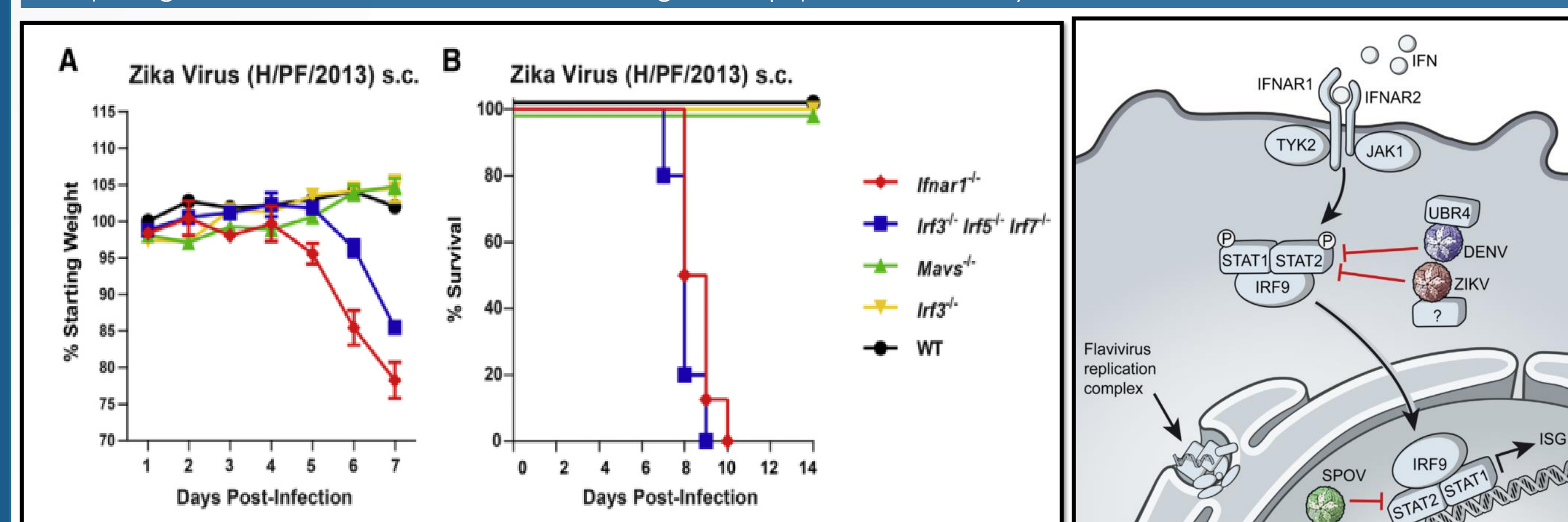


Fig. 5. IFN- α/β abrogated mice are more susceptible to disease. Five- to six-week-old mice of the indicated genotypes were inoculated with 10^2 PFU of ZIKV strain H/PP/2013 or MR 766 by a subcutaneous route (s.c.) in the footpad. A) Measure of disease progression by weight change compared to starting weight. B) Survival kinetics of infected mice (Lazear et al., 2016)

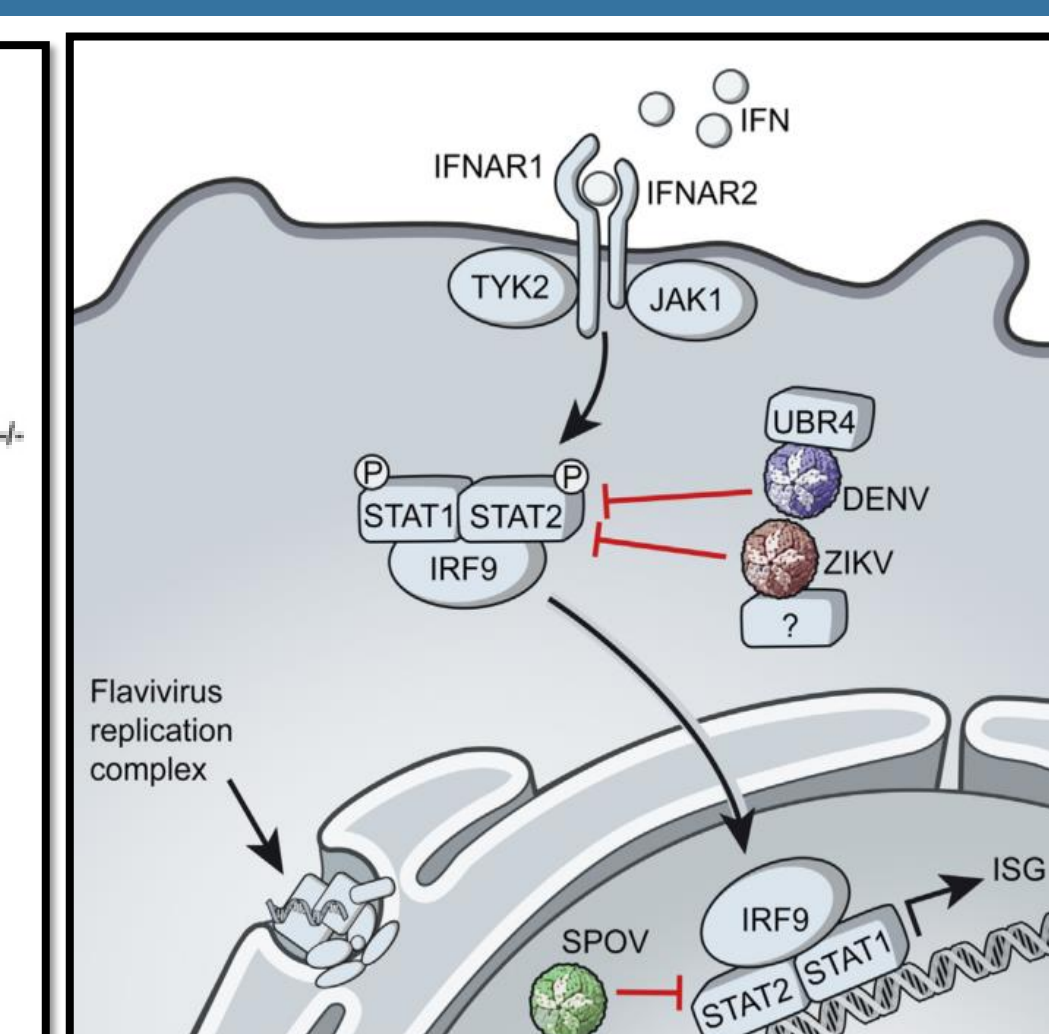


Fig. 6. Molecular mechanism of protein inhibition by ZIKV. Graphical abstract of the pathophysiology of DENV-2 and ZIKV analyzing the NS5 protein molecular mechanism. (Grant et al., 2016)

Findings

- Temperature is the primary determinant for both species in regards to suitability, followed by minimum precipitation and Enhanced Vegetation Index (EVI)
 - A. albopictus* is more reliant on precipitation and more discriminatory in selecting a water site for maturation
- Studies suggest that African strains of ZIKV show more virulence than Asian strains
- Whole genome sequencing reveals variation between Asian and African strains of ZIKV (Malaysia and Uganda)
- There are numerous mutations in the NS5 sequences between African and Asian ZIKV strains
- The NS5 protein of ZIKV interferes with the IFN α/β -mediated immune response

Conclusions

- ZIKV outbreaks are closely linked to geographical distribution of its mosquito vector
- The ZIKV strains found in the Americas are more closely related to the Asian strains than to the African strains
- There are viral factors that counteract the immune responses against ZIKV.
- Further studies are necessary to understand whether there are links between the different ZIKV strains, and their capacity to counteract the immune response.

Future Directions

- Further study the role of climate change and its impact in the geographic distribution of *Aedes* sp. and ZIKV spread
- Further study the genetic and molecular basis of ZIKV-related microcephaly in Brazil
- Explore how the differences between African, Asian, and American ZIKV strains could impact their capacity to infect neural system cells

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