Evolution of Emergence and Expansion of Zika virus; differences from Dengue and Chikungunya (and Yellow fever)

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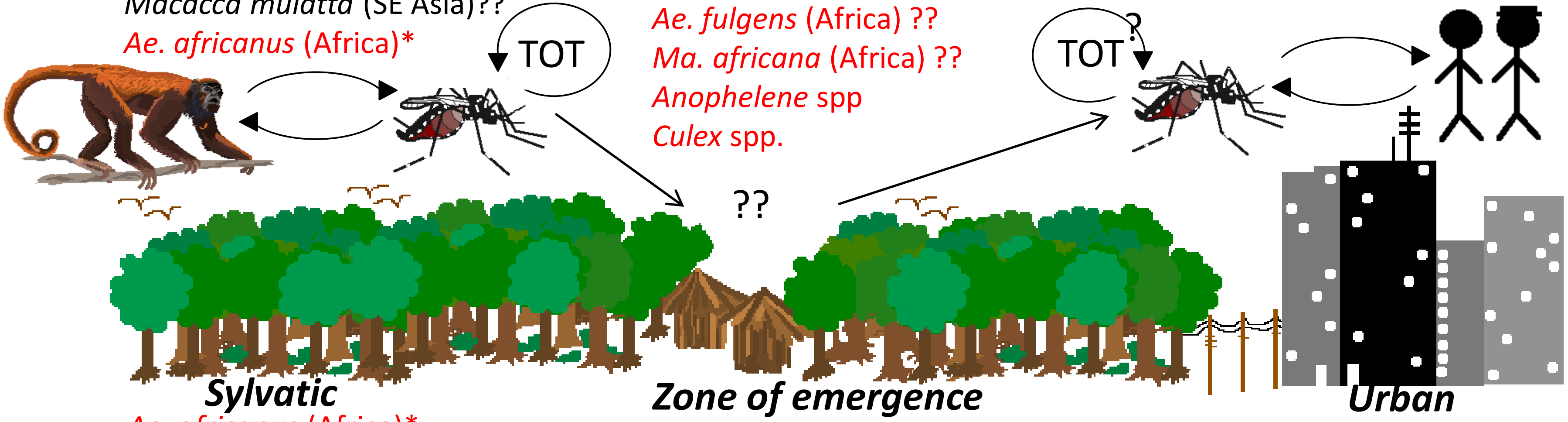
Zika and Chikungunya Transmission Cycles

CHIKV

Cercopithecus spp. (Africa)
Pan troglodytes (Africa)
Papio spp. (Africa)
Erythrocybus patas (Africa)
Galago senegalensis (Africa) ??
Xerus erythropus (Africa) ??
Scotophyllus spp (Africa) ??
Pongo borneo (SE Asia)??
Macacca mulatta (SE Asia)??
Ae. africanus (Africa)*

Ae. furcifer (Africa)*
Ae. dalzieli (Africa)
Ae. irritans (Africa)
Ae. luteocephalus (Africa)*
Ae. neoafricanus (Africa)
Ae. taylori (Africa)*
Ae. vittatus (Africa)
Ae. fulgens (Africa) ??
Ma. africana (Africa) ??
Anophelene spp
Culex spp.

Homo sapiens
Ae. aegypti aegypti (global)
Ae. albopictus



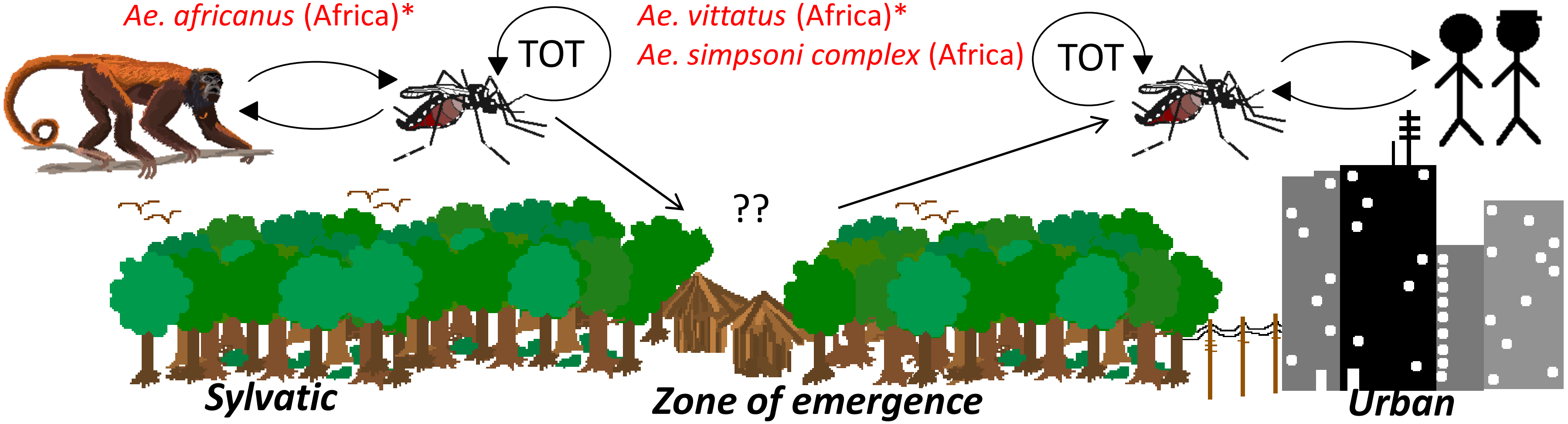
ZIKV

Ae. africanus (Africa)*
Ae. dalzieli (Africa)
Ae. furcifer (Africa)*
Ae. luteochephalus (Africa)*
Ae. vittatus (Africa)
Rhesus spp (Africa)
Chlorocebus sabaeus (Africa)
Cercopithecus spp (Africa)
Colobus guereza (Africa)
Erythrocebus patas (Africa)
Pongo borneo (SE Asia) *??*

Ae. apicoargenteus (Africa)
Ae. furcifer (Africa)*
Ae. hirsitus (Africa)
Ae. metallicus (Africa)
Ae. opok (Africa)
Ae. taylori (Africa)*
Ae. unilineatus (Africa)
Ma. uniformis (Africa)
An. coustani (Africa)
Cx. perfuscus (Africa)

Ae. aegypti aegypti (global)
Ae. albopictus ??
Ae. polynensiensis (Polynesia)
Ae. hensilii (Polynesia)
Homo sapiens

Dengue and Yellow Fever Transmission Cycles



YFV

Alouatta spp (S. America)
Colobus spp (Africa)
Cercopithecus spp. (Africa)
G. senegalensis (Africa)
H. janthinomys (S. America)
H. leucocelaenus (S. America)
S. chloropterus (S. America)
Ae. africanus (Africa)*

Ae. bromeliae (Africa)
Ae. furcifer (Africa)*
Ae. taylori (Africa)*
Ae. africanus (Africa)
Ae. luteocephalus (Africa)*
Ae. metallicus (Africa)
Ae. opok (Africa)
Ae. vittatus (Africa)*
Ae. simpsoni complex (Africa)

Homo sapiens
Ae. aegypti aegypti (global)

Sylvatic

Zone of emergence

Urban

DENV

Ae. luteochephalus (Africa)
Ae. furcifer (Africa)
Ae. niveus spp. (SE Asia)
Chlorocebus sabaeus (Africa)
Papio papio (Africa)
Erythrocebus patas (Africa)
Macaca fascicularis (SE Asia)
Macaca nemestrina (SE Asia)
Presbytis spp (SE Asia)

Ae. furcifer (Africa)
Ae. albopictus (SE Asia)

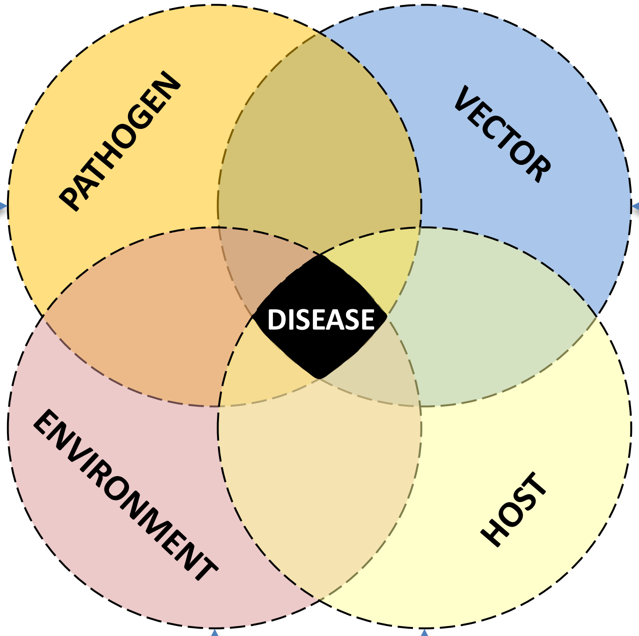
Ae. aegypti aegypti (global)
Ae. albopictus (global)
Ae. polynensiensis (Polynesia)
Homo sapiens

Vasilakis etal. (2011), Nature Reviews Microbiology 9:532-541; Hanley etal (2013), Infection Genetics and Evolution 19C:292-311

Factors Influencing Virus Evolution Emergence

VIRAL GENOMIC DATA
- Deep sequencing to detect emerging variants
- Population structure and evolution
- Virulence and vector competence markers
- Host/ vector adaptation

VECTOR ECOLOGY AND POPGEN DATA
- Microsatellite data
- Genetic markers
- Vector distribution and gene flow
- Vector competency/capacity
- Vector habitat
- Vector feeding preference



Modelling and risk analysis

ENVIRONMENTAL DATA
- Temperature and wind
- Weather and climate predictions
- Vegetation
- Land use change predictions
- Behavioral/cultural change predictions

HOST DATA
- Tracked movement
- Gene flows
- Habitat data
- immunity

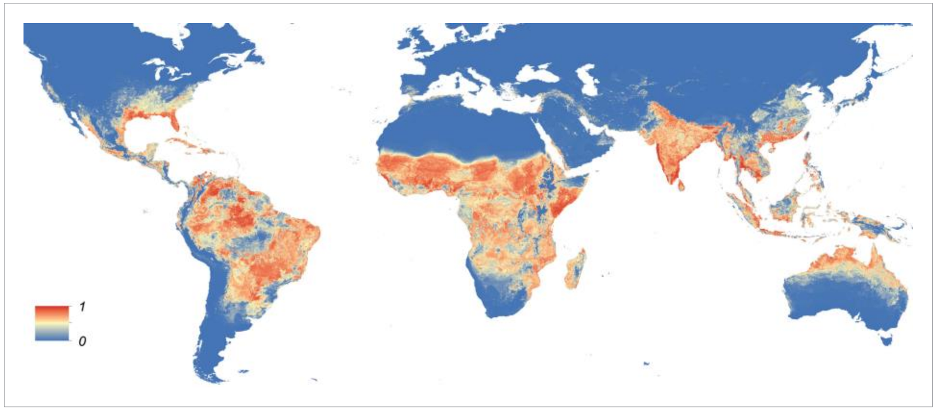
Mosquito Vectors

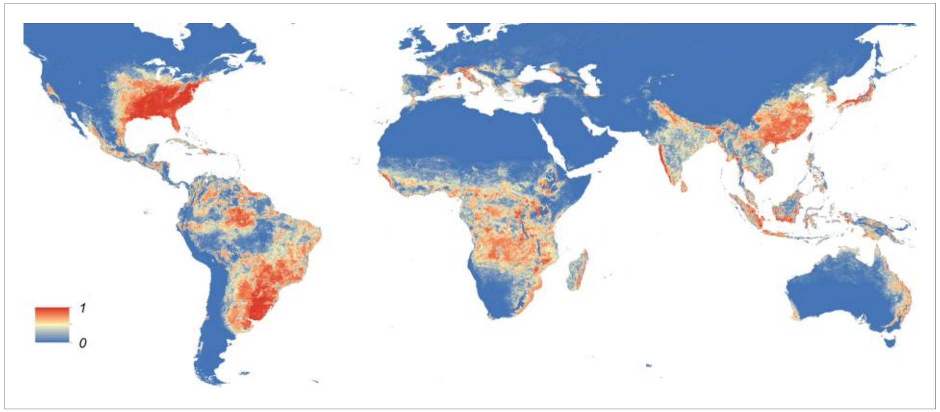
Aedes (Stegomyia) *aegypti*

Originated in sub-Saharan Africa, spread throughout the tropics centuries ago from West Africa

Aedes (Stegomyia) *albopictus*

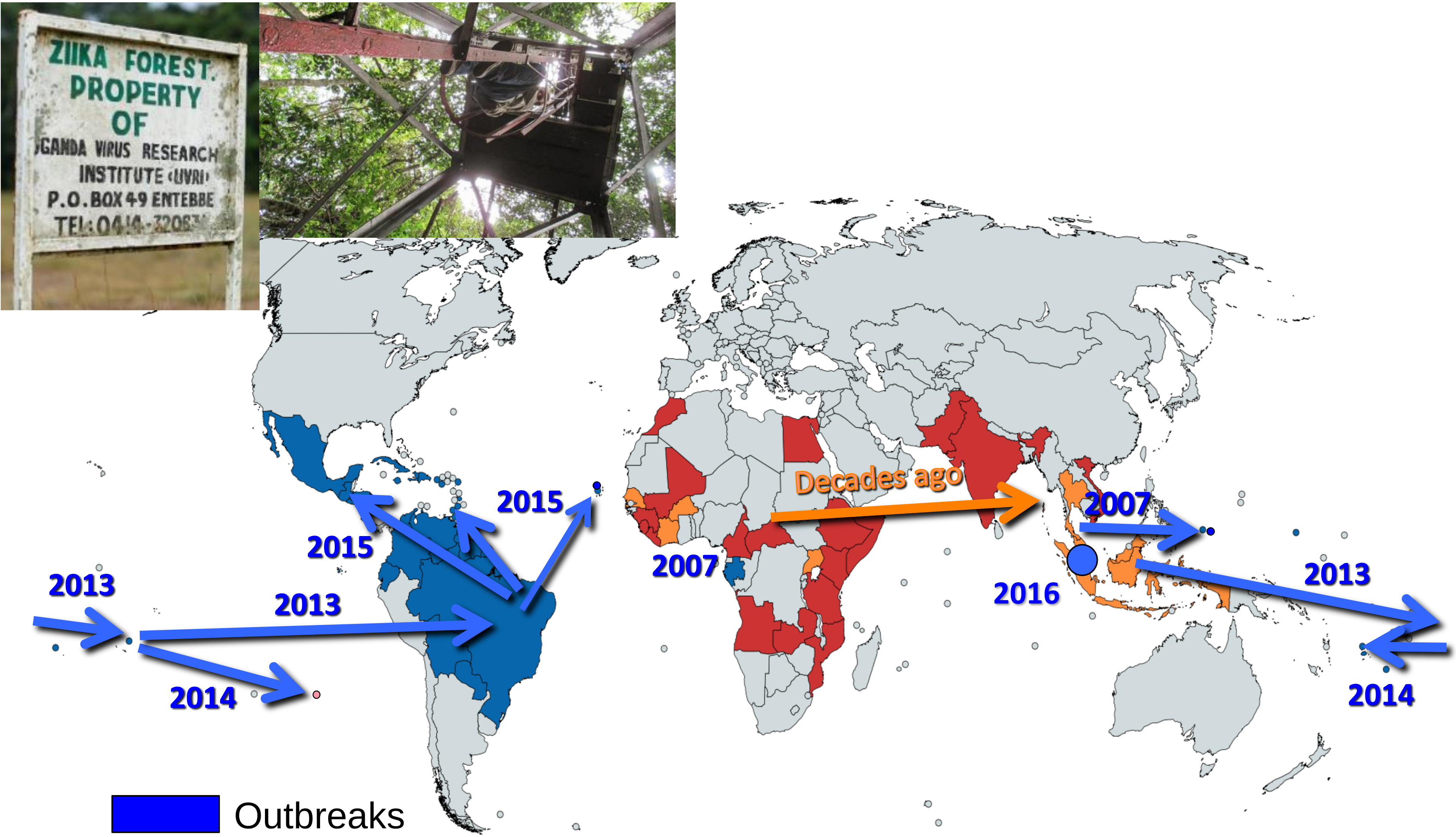
Originated in Asia, spread to the Americas, Africa and Europe beginning in 1985





Kraemer, M.U., et al., 2015. The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. albopictus*. Elife 4.

Origin and Spread of Zika Virus



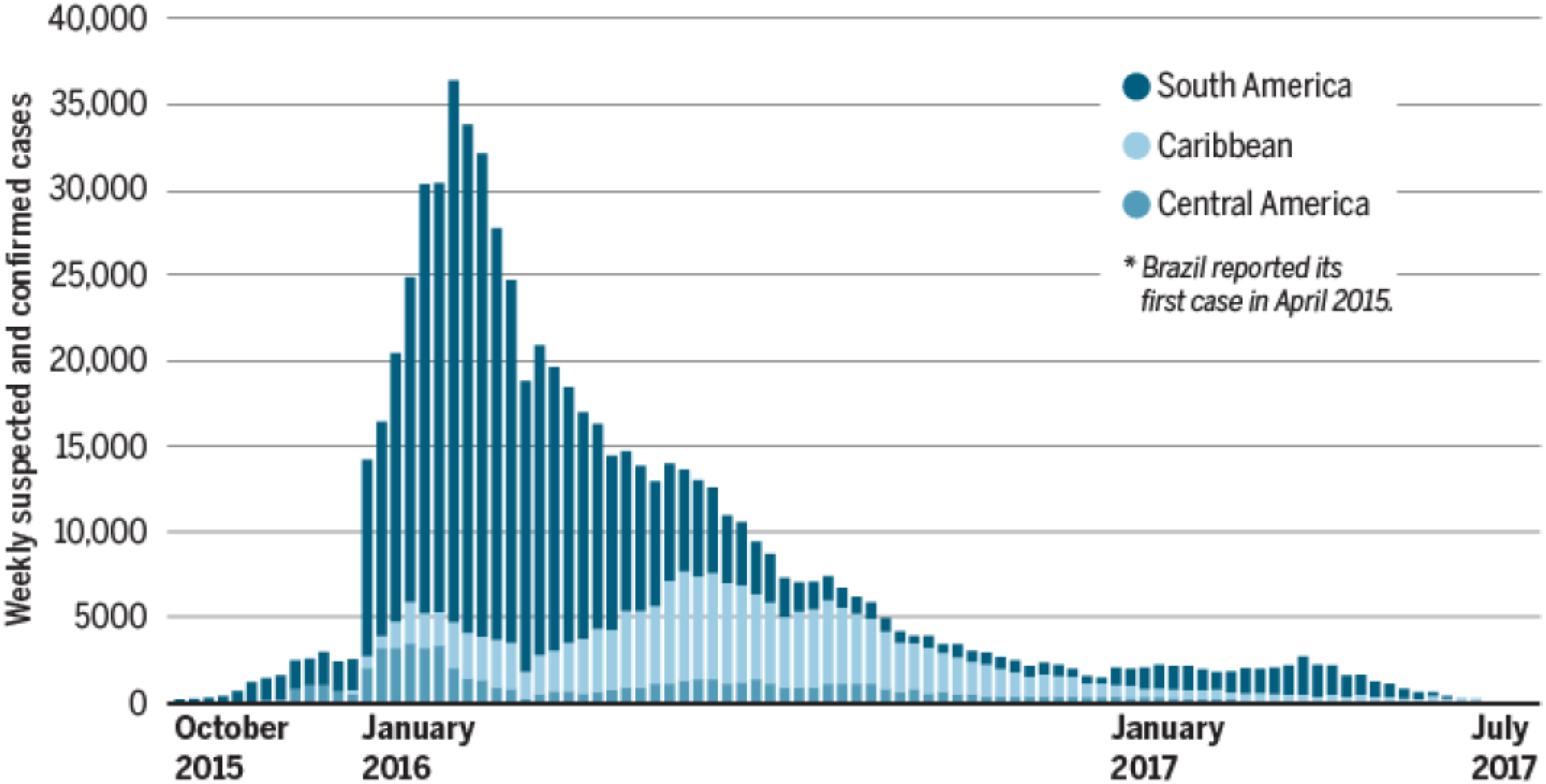
🟦 Outbreaks

🟥 Serologic evidence

🟧 Virus detection or confirmed human case

Weaver SC, et al. Antiviral Res. 2016. 130:69-80.

ZIKV Epidemic in the New World

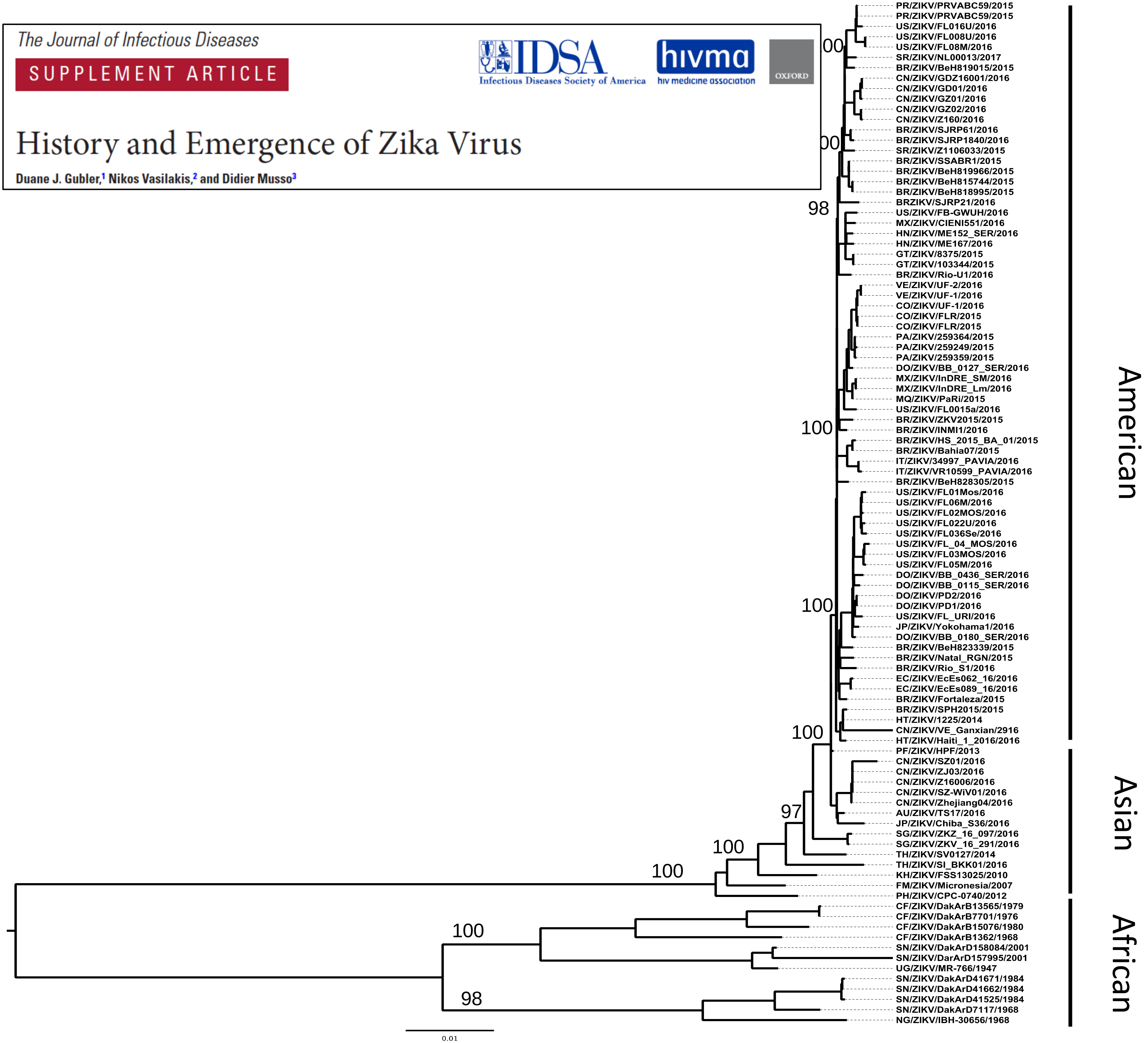


CREDITS: (GRAPHIC) J. YOU/SCIENCE; (DATA) PAN AMERICAN HEALTH ORGANIZATION/WORLD HEALTH ORGANIZATION

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

History and Emergence of Zika Virus

Duane J. Gubler,[1] Nikos Vasilakis,[2] and Didier Musso[3]



Hypotheses For the Recent ZIKV Emergence

1. ZIKV underwent adaptive evolution to enhance infectivity of urban *Aedes* (*Stegomyia*) spp. vectors (like chikungunya virus, in which the Indian Ocean lineage underwent a series of *Ae. albopictus*-adaptive mutations from 2005-2009.

2. ZIKV underwent adaptive evolution to enhance human viremia (which would not only enhance transmission efficiency, but could increase the risk of transplacental fetal transmission).

3. The stochastic introduction of ZIKV into naïve populations in the South Pacific allowed for sufficient levels of amplification to facilitate the introduction into Brazil (assisted by increased global travel, expansion of tropical cities and *Ae. aegypti* populations; e.g. no change or difference among ZIKV strains in epidemic potential or virulence).

ZIKV Evolution for Urban Transmission and increased Virulence?

LETTER

doi:10.1038/nature22365

Evolutionary enhancement of Zika virus infectivity in *Aedes aegypti* mosquitoes

Yang Liu[1,2,3]*, Jianying Liu[1,3]*, Senyan Du[1]*, Chao Shan[4]*, Kaixiao Nie[1], Rudian Zhang[1,2], Xiao-Feng Li[5], Renli Zhang[3], Tao Wang[3,6], Cheng-Feng Qin[5], Penghua Wang[7], Pei-Yong Shi[4] & Gong Cheng[1,3]

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

Ling Yuan,[1,2]* Xing-Yao Huang,[3]* Zhong-Yu Liu,[3]* Feng Zhang,[1,2]* Xing-Liang Zhu,[1,2]* Jiu-Yang Yu,[3]* Xue Ji,[3] Yan-Peng Xu,[3] Guanghui Li,[1,2] Cui Li,[1,2] Hong-Jiang Wang,[3] Yong-Qiang Deng,[3] Menghua Wu,[4] Meng-Li Cheng,[3,5] Qing Ye,[3] Dong-Yang Xie,[3,5] Xiao-Feng Li,[3] Xiangxi Wang,[6] Weifeng Shi,[7] Baoyang Hu,[4] Pei-Yong Shi,[8] Zhiheng Xu,[1,2,9]† Cheng-Feng Qin[3]†

Variation in *Aedes aegypti* Mosquito Competence for Zika Virus Transmission

Christopher M. Roundy,[1] Sasha R. Azar,[1] Shannan L. Rossi, Jing H. Huang, Grace Leal,
Ruimei Yun, Ildefonso Fernandez-Salas, Christopher J. Vitek, Igor A.D. Paploski, Uriel Kitron,
Guilherme S. Ribeiro, Kathryn A. Hanley, Scott C. Weaver, Nikos Vasilakis

Fig. 1A

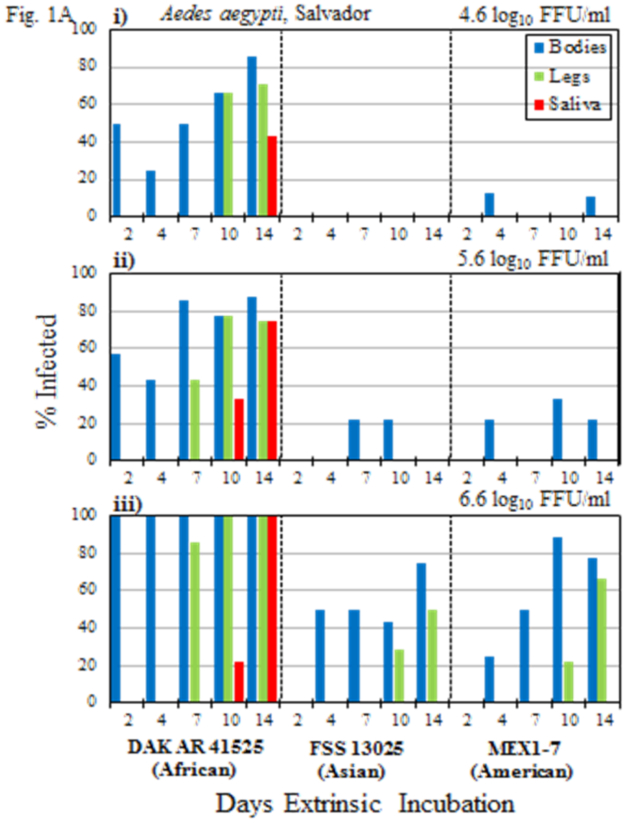


Fig. 1B

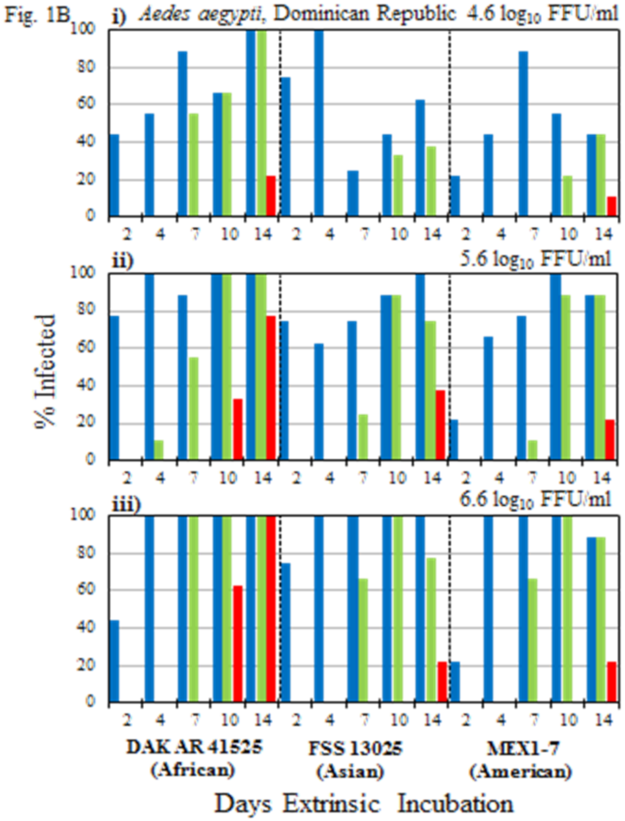
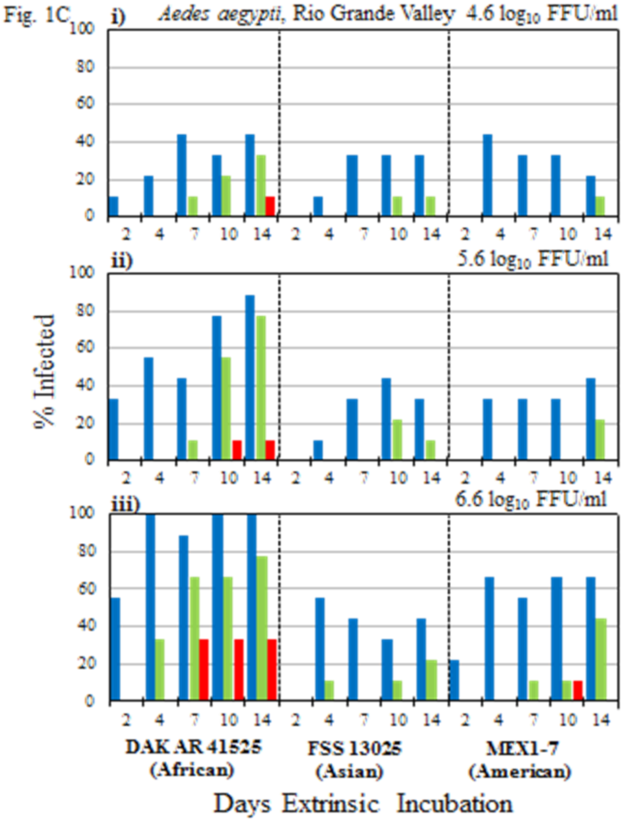


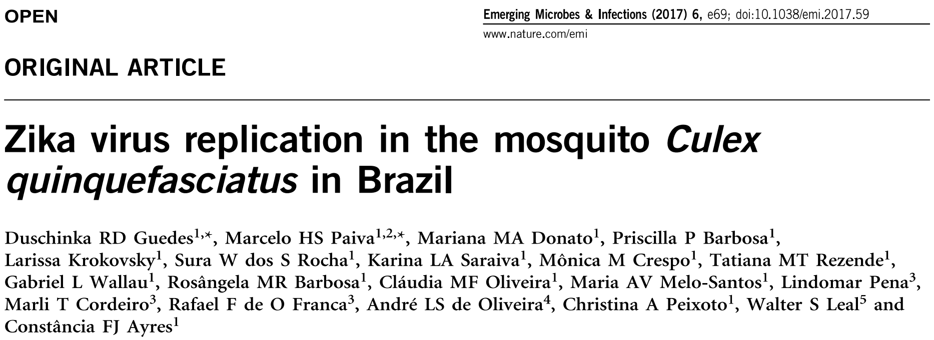
Fig. 1C



African ZIKV strains are typically more infectious for *Ae. aegypti* and more virulent for mice than Asian or American strains

Could the introduction of an African ZIKV strain lead to another major outbreak with a higher incidence of severe outcomes?

Cx. quinquefasciatus as a potential ZIKV vector?



OPEN

Emerging Microbes & Infections (2017) 6, e69; doi:10.1038/emi.2017.59
www.nature.com/emi

ORIGINAL ARTICLE

Zika virus replication in the mosquito *Culex quinquefasciatus* in Brazil

Duschinka RD Guedes[1,*], Marcelo HS Paiva[1,2,*], Mariana MA Donato[1], Priscilla P Barbosa[1], Larissa Krokovsky[1], Sura W dos S Rocha[1], Karina LA Saraiva[1], Mônica M Crespo[1], Tatiana MT Rezende[1], Gabriel L Wallau[1], Rosângela MR Barbosa[1], Cláudia MF Oliveira[1], Maria AV Melo-Santos[1], Lindomar Pena[3], Marli T Cordeiro[3], Rafael F de O Franca[3], André LS de Oliveira[4], Christina A Peixoto[1], Walter S Leal[5] and Constância FJ Ayres[1]

OPEN

Emerging Microbes & Infections (2016) 5, e102; doi:10.1038/emi.2016.102
www.nature.com/emi

ORIGINAL ARTICLE

Culex pipiens quinquefasciatus: a potential vector to transmit Zika virus

Xiao-xia Guo[1,*], Chun-xiao Li[1,*], Yong-qiang Deng[2,*], Dan Xing[1], Qin-mei Liu[1], Qun Wu[1], Ai-juan Sun[1], Yan-de Dong[1], Wu-chun Cao[3], Cheng-feng Qin[2] and Tong-yan Zhao[1]

1. **“The Cts of the (Recife) *Cx. quinquefasciatus*-positive pools when screened by RT-qPCR were 37.6 (sample 5), 38.0 (sample 17) and 38.15 (sample 163).”**

2. **These titers are several orders of magnitude lower than transmission-competent *Ae. aegypti* or *Ae. albopictus.***

3. **Some populations of *Cx. quinquefasciatus* may be competent vectors but vectorial capacity has not been demonstrated based on serial human biting.**

Cx. quinquefasciatus as a potential ZIKV vector?

OPEN

Emerging Microbes & Infections (2016) 5, e102; doi:10.1038/emi.2016.102
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ORIGINAL ARTICLE

Culex pipiens quinquefasciatus: a potential vector to transmit Zika virus

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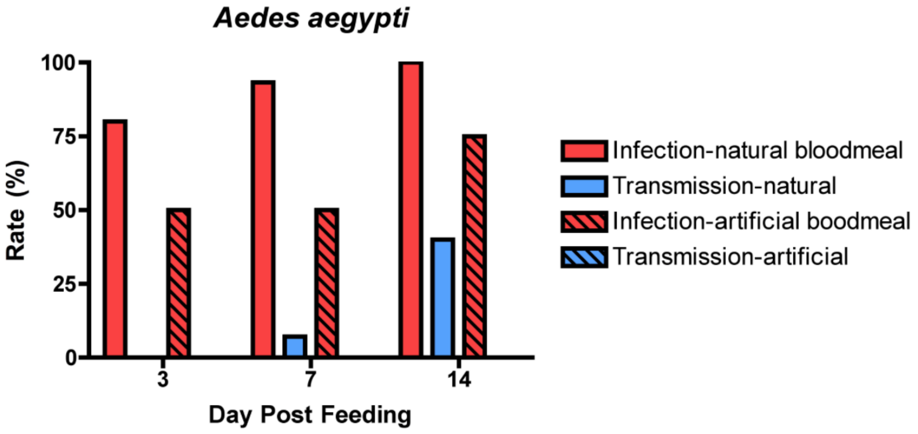
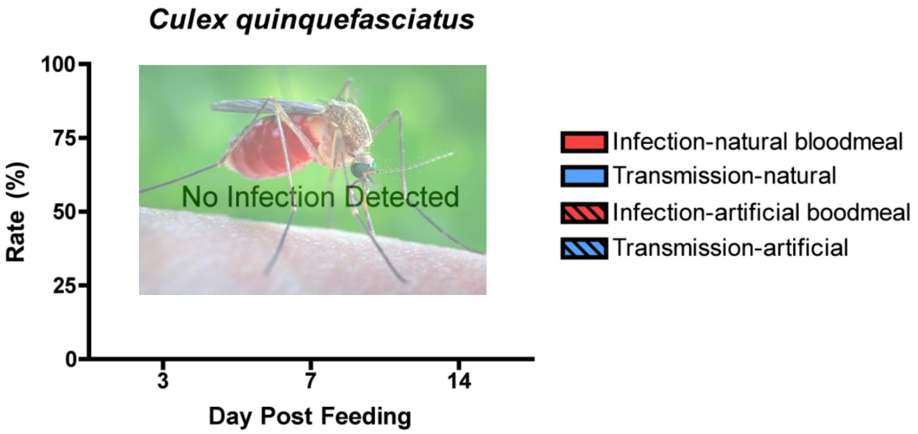


Hart CE, Roundy CM, Azar SR, Huang JH, Yun R, Reynolds E, Leal G, Nava MR, Vela J, Stark PM, Debboun M, Rossi S, Vasilakis N, Thangamani S, Weaver SC. Zika Virus Vector Competency of Mosquitoes, Gulf Coast, United States. Emerg Infect Dis. 2017. 23.

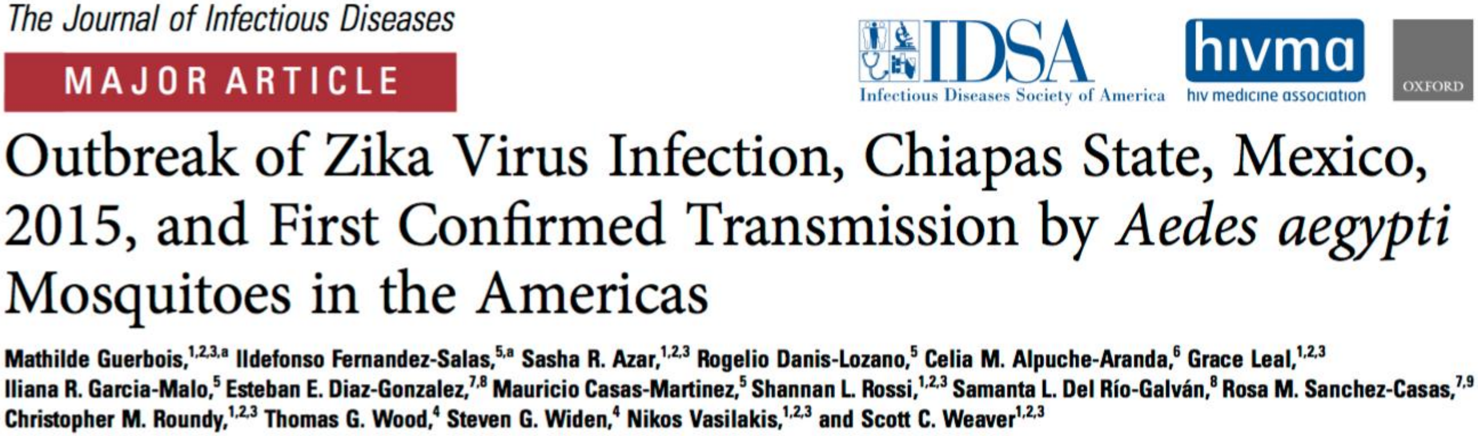
Huang, Y.S., et al., 2016. *Culex* Species Mosquitoes and Zika Virus. Vector Borne Zoonotic Dis.

Amraoui, F.,et al., 2016. *Culex* mosquitoes are experimentally unable to transmit Zika virus. Euro Surveill 21.

Fernandes, R.S., et al., 2016. *Culex quinquefasciatus* from Rio de Janeiro Is Not Competent to Transmit the Local Zika Virus. PLoS Negl Trop Dis 10, e0004993.



Direct Incrimination of *Ae. aegypti* but not *Cx. quinquefasciatus* during epidemic ZIKV transmission



The Journal of Infectious Diseases

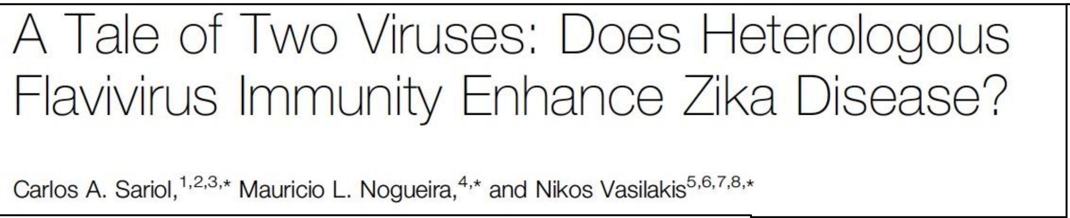
MAJOR ARTICLE

Outbreak of Zika Virus Infection, Chiapas State, Mexico, 2015, and First Confirmed Transmission by *Aedes aegypti* Mosquitoes in the Americas

Mathilde Guerbois,[1,2,3,a] Ildefonso Fernandez-Salas,[5,a] Sasha R. Azar,[1,2,3] Rogelio Danis-Lozano,[5] Celia M. Alpuche-Aranda,[6] Grace Leal,[1,2,3] Iliana R. Garcia-Malo,[5] Esteban E. Diaz-Gonzalez,[7,8] Mauricio Casas-Martinez,[5] Shannan L. Rossi,[1,2,3] Samanta L. Del Río-Galván,[8] Rosa M. Sanchez-Casas,[7,9] Christopher M. Roundy,[1,2,3] Thomas G. Wood,[4] Steven G. Widen,[4] Nikos Vasilakis,[1,2,3] and Scott C. Weaver[1,2,3]

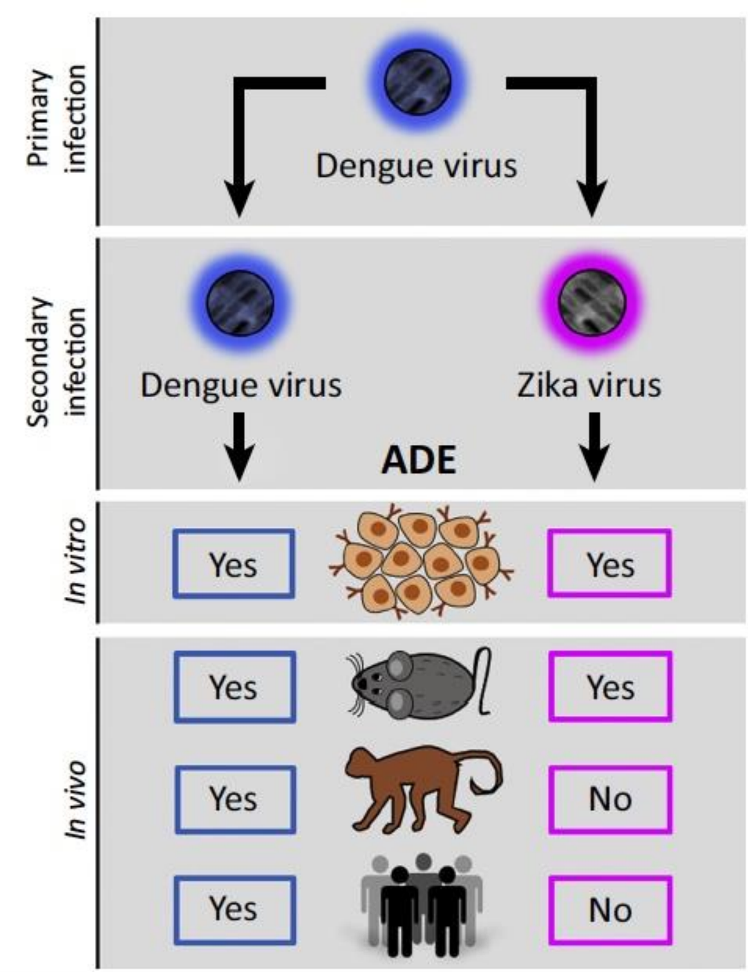
- Of 796 mosquitoes collected in and around the homes of Zika patients, *Aedes aegypti* yielded ZIKV detection by RT-PCR in 15 of 55 pools (27.3%).
- No ZIKV was detected in *Culex quinquefasciatus* mosquitoes, which were similar in abundance to *Ae. aegypti*

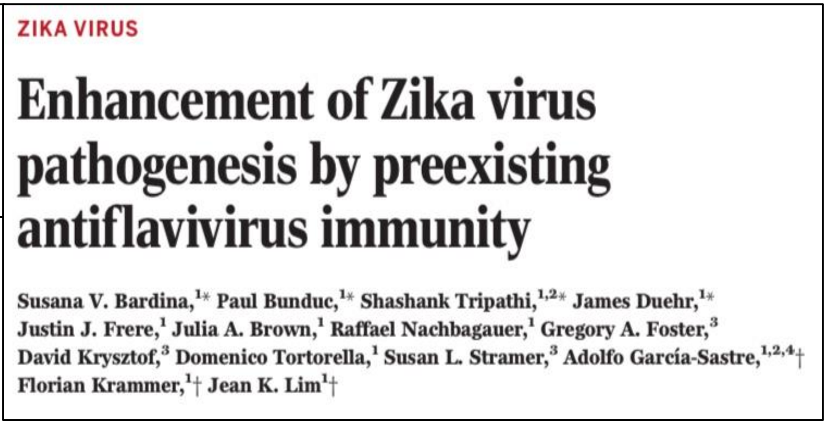
ZIKV Evolution for Urban Transmission and increased Virulence?



A Tale of Two Viruses: Does Heterologous Flavivirus Immunity Enhance Zika Disease?

Carlos A. Sariol,[1,2,3,*] Mauricio L. Nogueira,[4,*] and Nikos Vasilakis[5,6,7,8,*]





ZIKA VIRUS

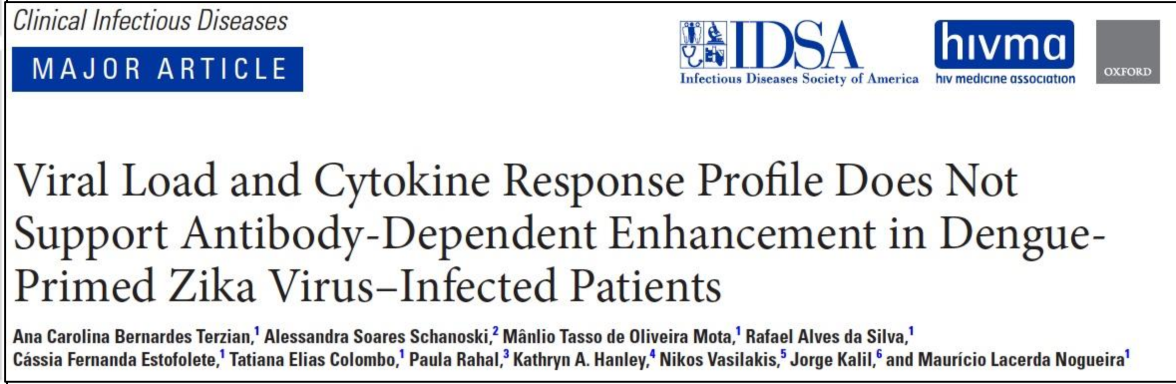
Enhancement of Zika virus pathogenesis by preexisting antiflavivirus immunity

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]†

Received 8 Dec 2016 | Accepted 19 Apr 2017 | Published 23 Jun 2017 DOI: 10.1038/ncomms15674 OPEN

Zika virus pathogenesis in rhesus macaques is unaffected by pre-existing immunity to dengue virus

Petraleigh Pantoja[1,2,*], Erick X. Pérez-Guzmán[2,*], Idia V. Rodríguez[1], Laura J. White[3], Olga González[1], Crisanta Serrano[2], Luis Giavedoni[4], Vida Hodara[4], Lorna Cruz[1], Teresa Arana[2], Melween I. Martínez[1], Mariah A. Hassert[5], James D. Brien[5], Amelia K. Pinto[5], Aravinda de Silva[3] & Carlos A. Sariol[1,2,6]



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

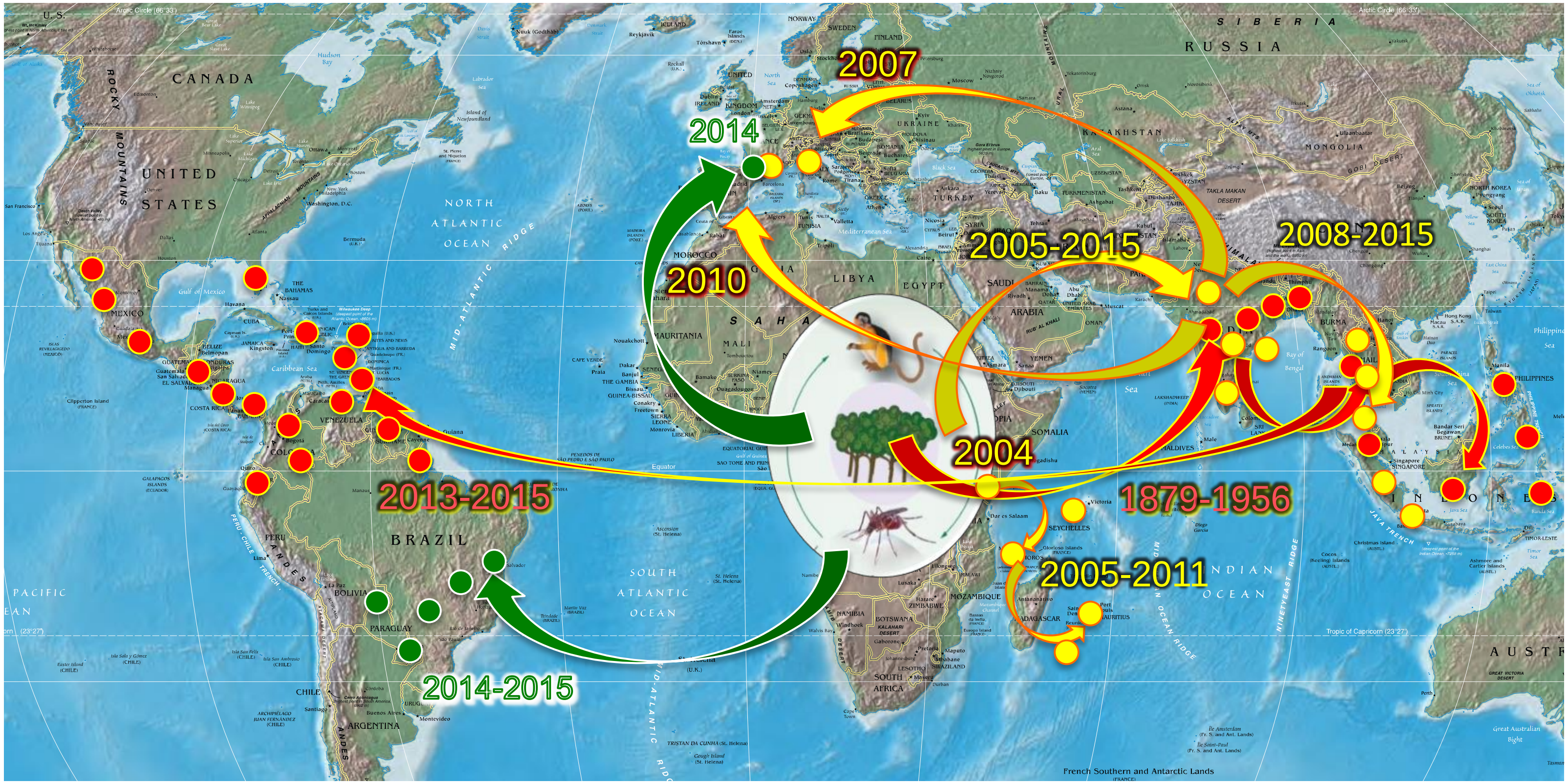
hivma hiv medicine association

OXFORD

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

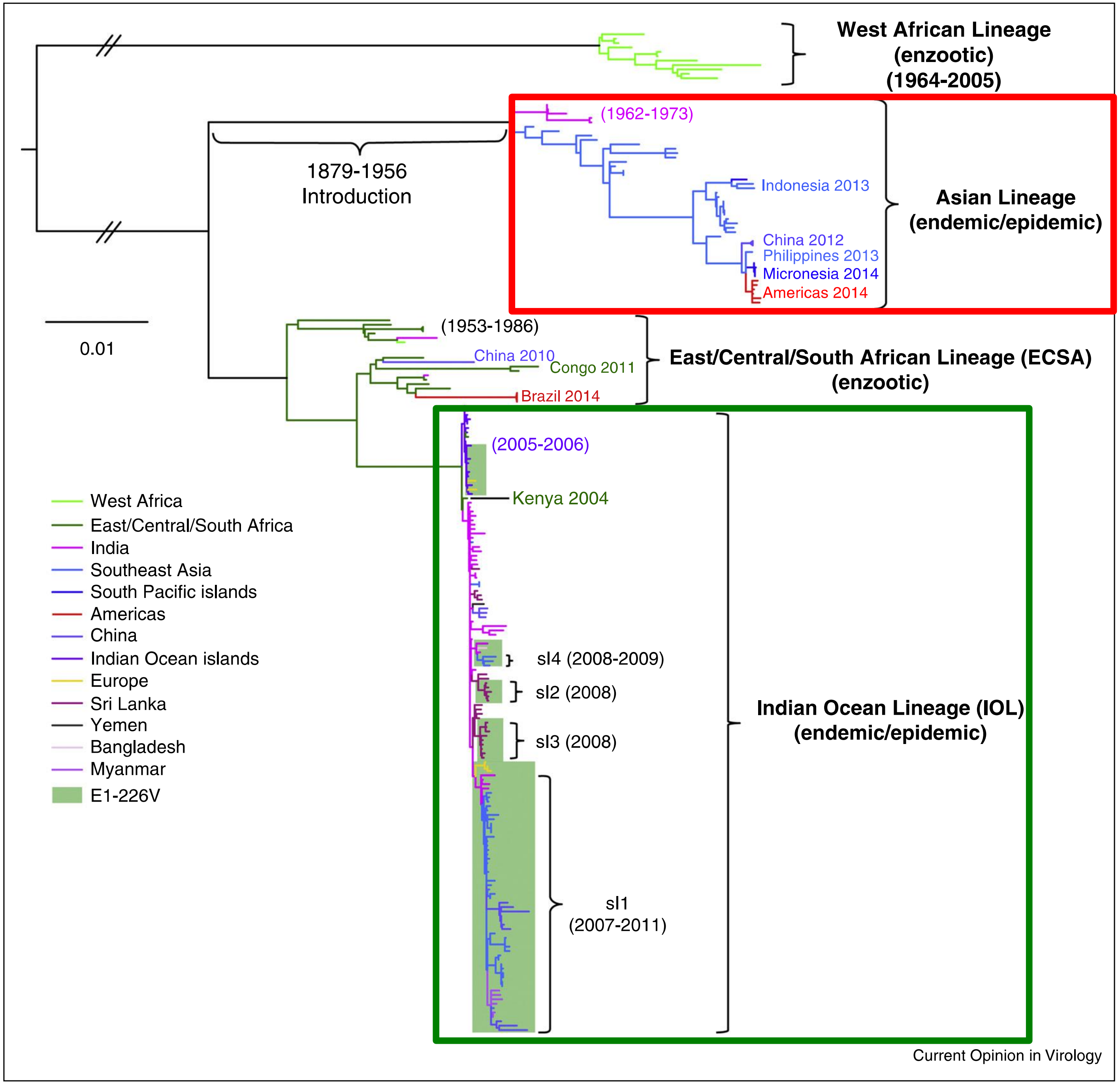
Ana Carolina Bernardes Terzian,[1] Alessandra Soares Schanoski,[2] Mânlio Tasso de Oliveira Mota,[1] Rafael Alves da Silva,[1] Cássia Fernanda Estofolete,[1] Tatiana Elias Colombo,[1] Paula Rahal,[3] Kathryn A. Hanley,[4] Nikos Vasilakis,[5] Jorge Kalil,[6] and Maurício Lacerda Nogueira[1]

Origin and Spread of CHIKV



ECSA lineage
Asian lineage
Indian Ocean Lineage

E1-A226V only found in IOL



Current Opinion in Virology

Tsetsarkin KA, Chen R, Weaver SC. Curr Opin Virol. 2016. 16:143-50.

Ae. albopictus - Adaptive Mutations

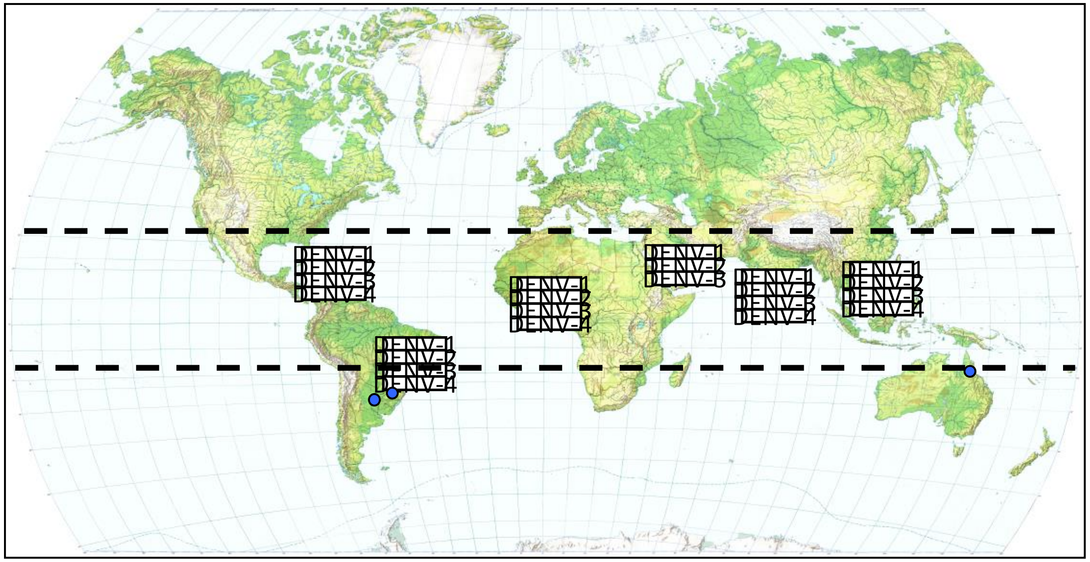
Lineage	First appearance	Protein	Substitution	Fitness for *Ae. albopictus* infection	Fitness for *Ae. aegypti* infection
IOL	2005	E1	A226V	40-fold increase	Slight decrease
IOL (SL1)	2007	E2	K252Q	8-fold increase	No effect
IOL (SL2 partial)	2008	E2	K233E	6-fold increase	No effect
IOL (SL3B)	2008	E2/E3	R198Q/S18F (synergistic)	16-fold increase	No effect
IOL (SL4)	2009	E2	L210Q	5-fold increase	No effect
Asian	Never	E1	A226V	No effect	Not done
Asian	Never	E2	K252Q	decrease	Slight increase
Asian	Never	E2	K233E	decrease	Slight increase
Asian	Never	E2/E3	R198Q/S18F (synergistic)	decrease	Slight decrease
Asian	Never	E2	L210Q	decrease	Not done

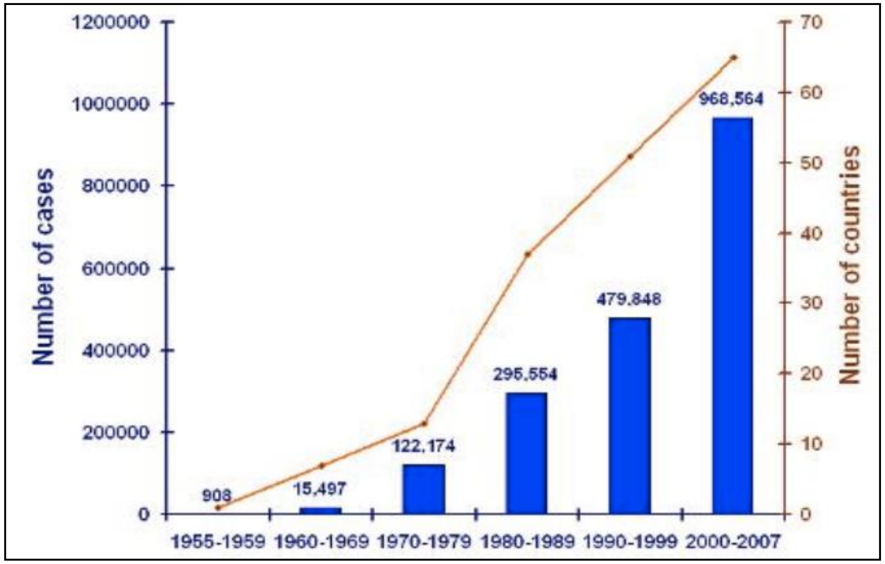
None of the E2 mutations depend on E1-226V for penetrance

Tsetsarkin KA, et al. Nat Commun. 2014. 5:4084.
Chen, R and Weaver, SC, unpublished

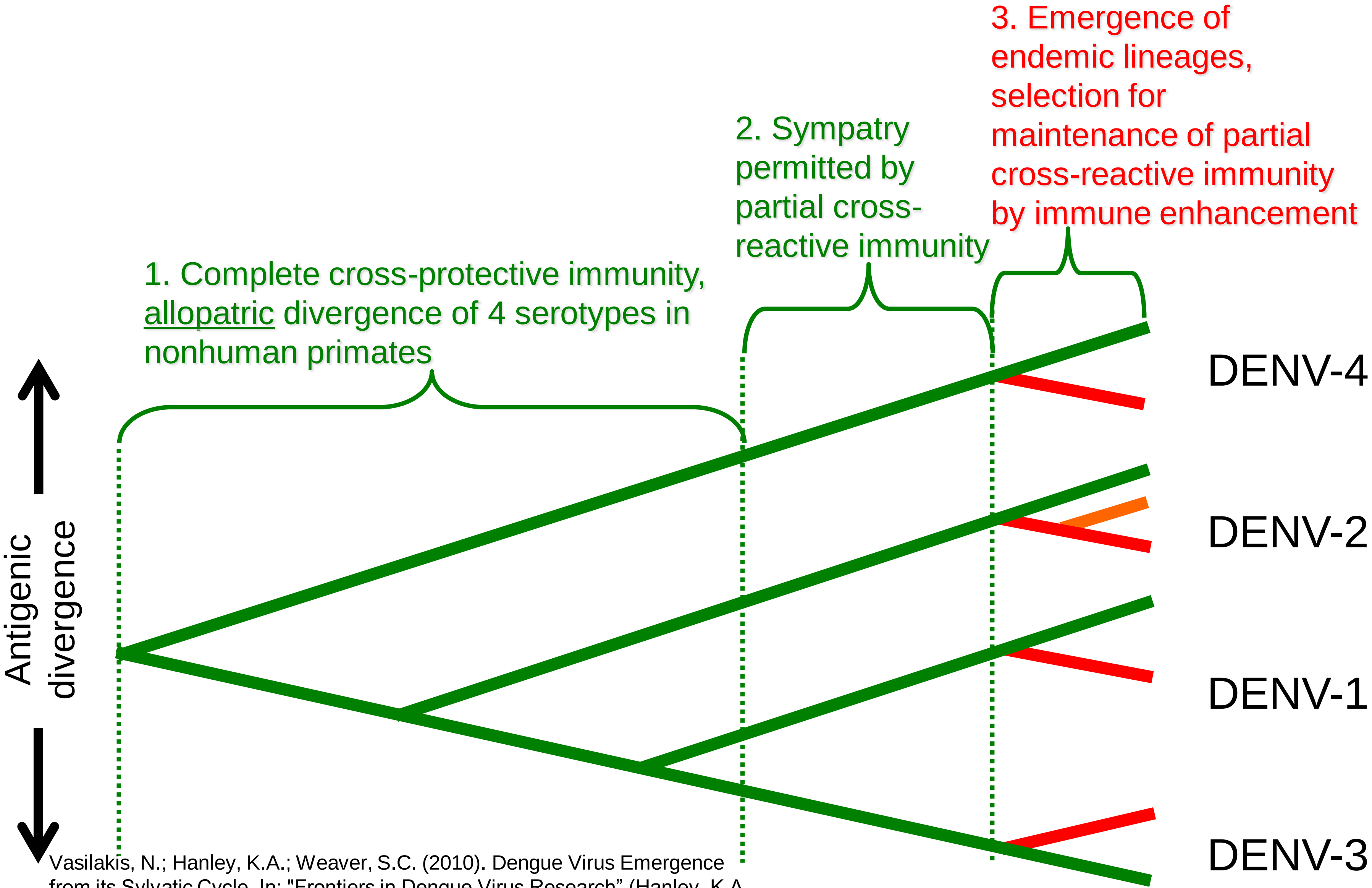
Dengue

- **Over 2.5 billion people – over 40% of the world's population – are at risk, estimated 390 mil infections annually.**
- **Rapid, unplanned urbanization, air travel, increasing populations of *Ae. aegypti* and contact with people**
- **Increased transmission and human travel have led to hyperendemicity**
- **Infection predisposes individuals to DHF upon secondary, heterotypic infection.**
- **Without proper treatment, DHF case fatality rate can exceed 20%.**
- **First vaccine (Sanofi-Pasteur) licensed in several countries**



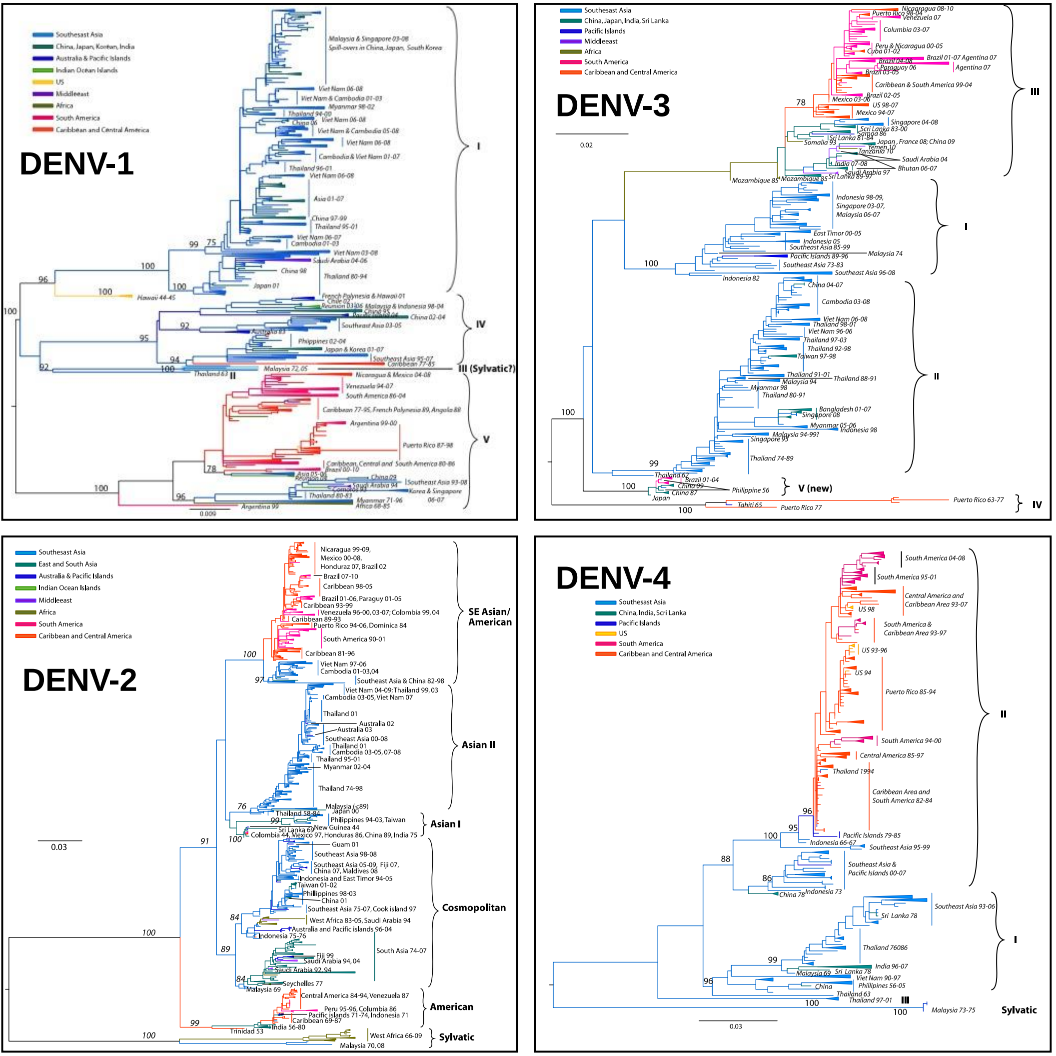


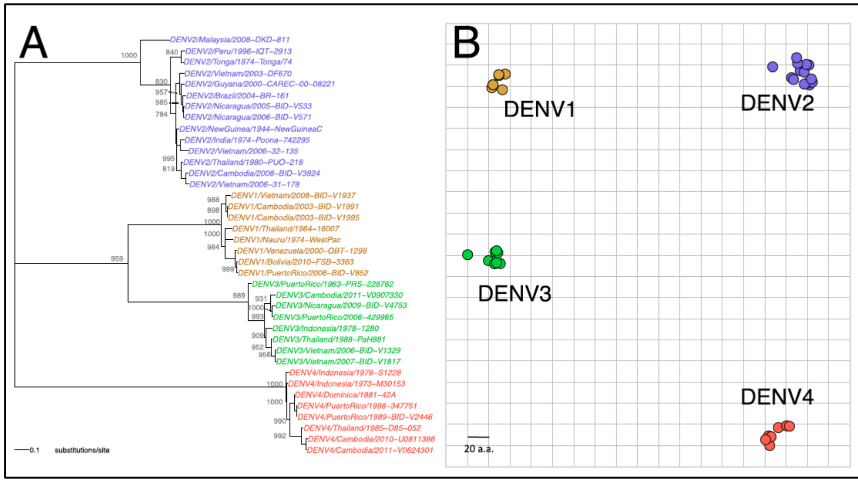
Phases of DENV Evolution

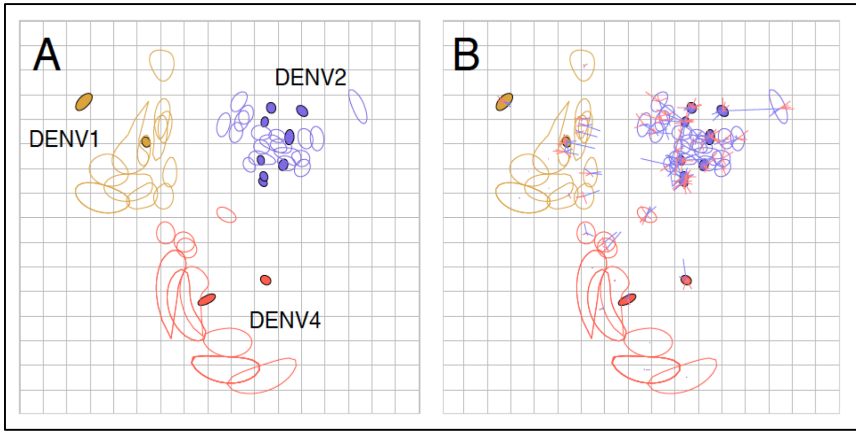


Vasilakis, N.; Hanley, K.A.; Weaver, S.C. (2010). Dengue Virus Emergence from its Sylvatic Cycle. In: "Frontiers in Dengue Virus Research" (Hanley, K.A. and Weaver, S.C., Eds). Caister Academic Press

DENV Diversity







Genetically, geographically, and temporally diverse DENV cluster loosely by type, but many are as similar antigenically to a virus of a different type as to some viruses of the same type

Antigenic Cartography Consortium   Katzelnick *et al. Science 2015*

Chen & Vasilakis. *Quo tu et quo vadis.* (2011) *Viruses* ***3****:1562-1608*

Dengue Virus Emergence

1. **Did dengue emergence depend on adaptation to human reservoir hosts or peridomestic mosquito vectors vectors?**

   Experimental studies do not support adaptation to peridomestic vectors or human reservoir hosts. Vasilakis *et al. (2007*). *Virology* 358:402-412; Hanley *et al*. *EID (in peer review)*

2. **Do evolutionary processes among sylvatic DENV-2 facilitate emergence?**

   Sylvatic DENV evolves in a similar manner to human DENV, and the dynamics of mutation, replication and selection are similar across its host range.

   Vasilakis etal (*2007). J.* Virol 81:9591 – 9595

3. **Could sylvatic DENV re-emerge? Do unrecognized spill over epidemics occur in urban settings?**

   Yes, congruent with amplification cycles.

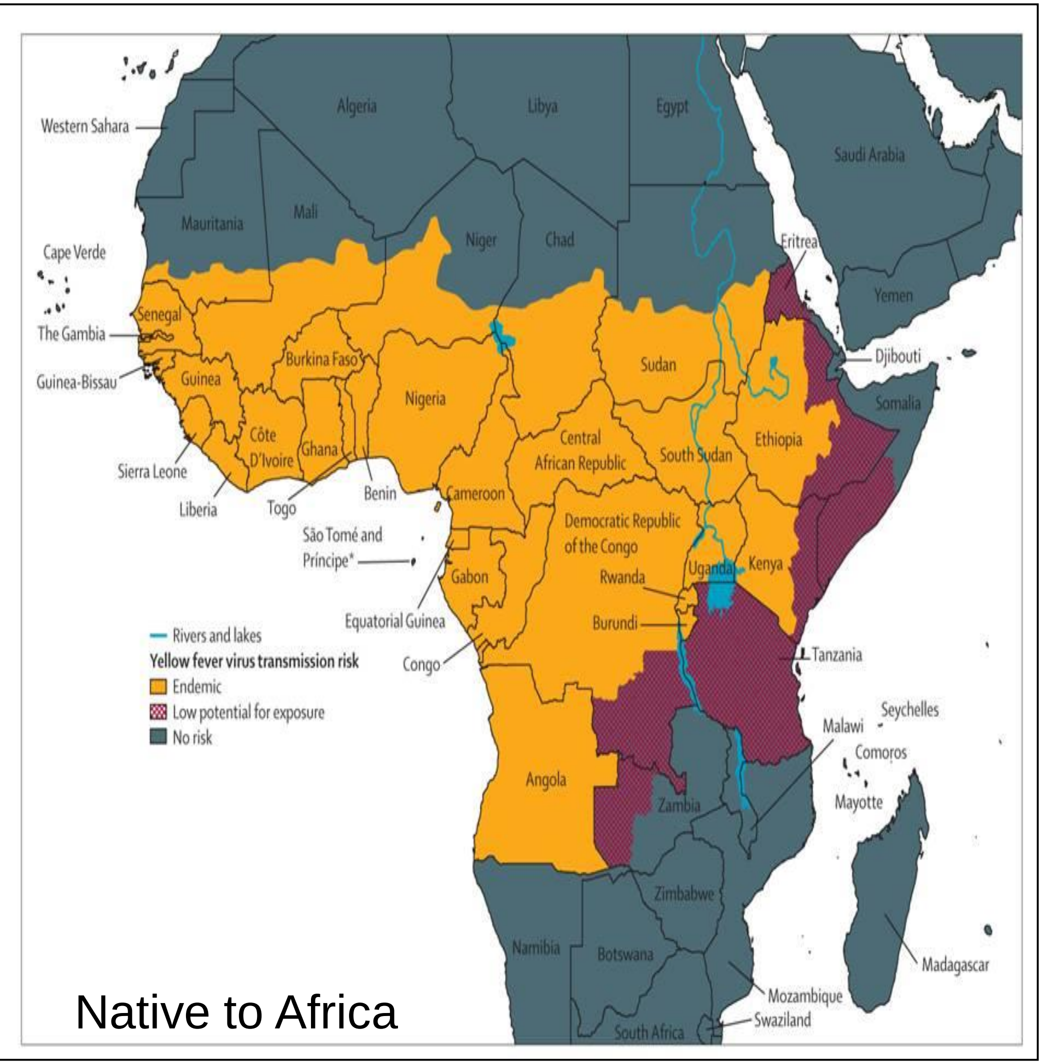
   Vasilakis, Tesh & Weaver (2008), *EID 14:502-504;* Cardosa *et al (2009) PLoS NTD 3, e423;* Franco *et al.* (2012), *PLoS NTD 5, e1251*; Monlun *et al.* (1992)*,* Med. Mal. Infect. 22, 718-721); Saluzzo *et al. (1986), Trans R Soc Trop Med Hyg* 80, 5; and others

4. **How easily can dengue re-emerge from the sylvatic cycle in the face of natural immunity or vaccination?**

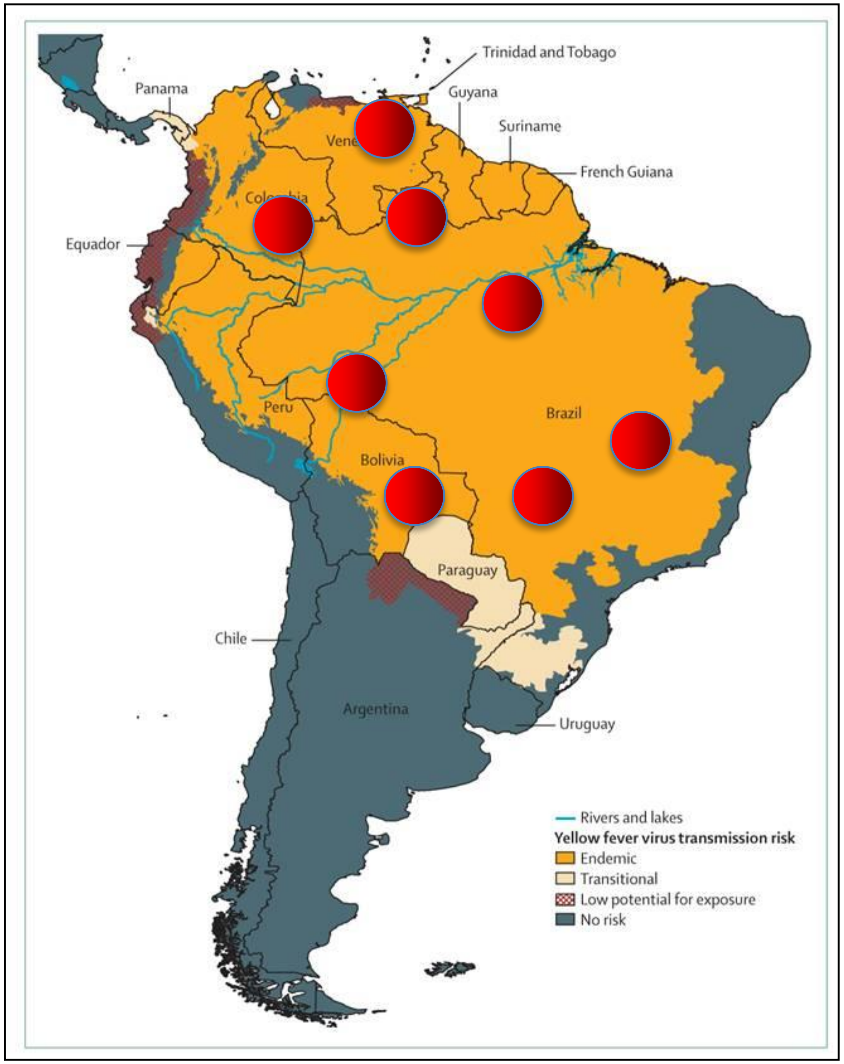
   Emergence potential of sylvatic DENV is restrained by vaccination and homotypic immunity. Vasilakis *et al. (2008).* Am. J. Trop. Med. Hyg*.* 79:128 – 132; Durbin *et al. (2013). Virology 439:34 - 41*

Sylvatic dengue can re-emerge into the human transmission cycle at any time!

Yellow Fever



Native to Africa

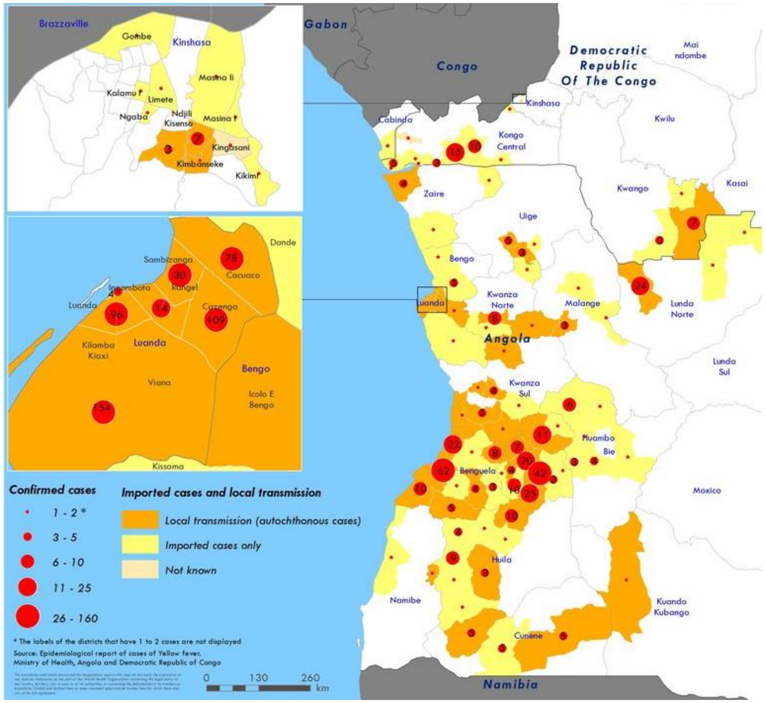


Source: Center for Disease Control, Atlanta GA; http://www.cdc.gov/yellowfever/maps/africa.html

Recent/current Yellow Fever Outbreaks

Africa

- December, 2015-June, 2016, urban transmission mainly by *A. aegypti*
- 884 confirmed cases, 381 fatal, Angola and DR Congo
- Exported cases as far as China (risk for establishment?)
- 12M doses of 17D vaccine distributed (19M requested, shortage led to dose sparing to 1/5 normal amount)

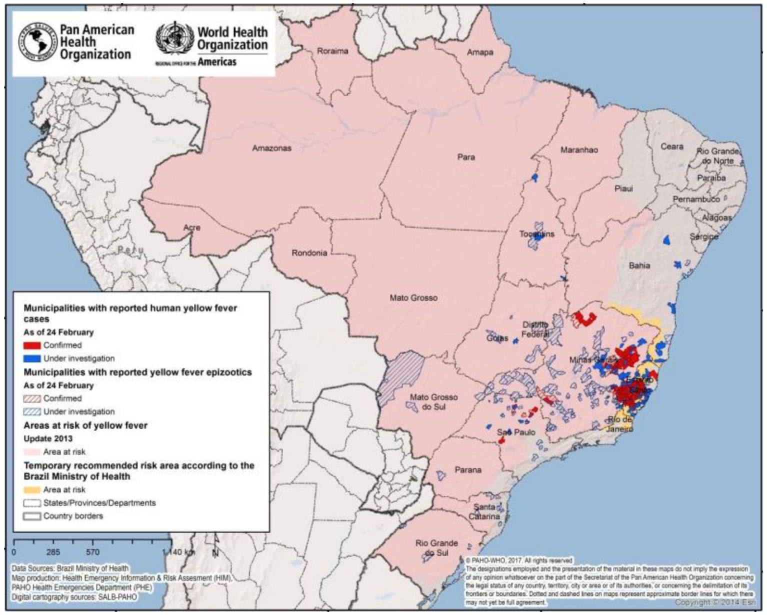


* The labels of the districts that have 1 to 2 cases are not displayed

Source: Epidemiological report of cases of Yellow fever. Ministry of Health, Angola and Democratic Republic of Congo

Brazil

- December 2016-present, epizootic spillover infections, 916 suspected, 326 confirmed cases, 109 of these fatal
- Potentially high risk for initiation of urban transmission
  - Limited vaccine coverage in major urban centers highly permissive for dengue, Zika, chikungunya



Data Sources: Brazil Ministry of Health
Map production: Health Emergency Information & Risk Assesment (HIM), PAHO Health Emergencies Department (PHE)
Digital cartography sources: SALB-PAHO

Emergence into the urban transmission cycle: Comparisons with DENV, CHIKV, YFV

1. Yellow fever virus: Originated in Africa and emerged into the urban cycle following the domestication of *Ae. aegypti*; transport of *Ae. aegypti* and infected persons aboard sailing ships centuries ago, especially during to the slave trade, resulted in regular introductions into the Americas and establishment of enzootic circulation (but why not in Asia?)
2. Dengue viruses: Originated in Southeast Asia, diversified into 4-5 serotypes while still in the enzootic cycle (possibly selected by immune enhancement). Enzootic spillover and emergence into the urban cycles followed by transport throughout the tropics on sailing ships centuries ago; spillback of DENV-2 into an enzootic cycle in West Africa (but why not in the Americas?)
3. Chikungunya virus: Originated in Africa and emerged repeatedly into the urban cycle following the domestication of *Ae. aegypti* there; transport of *Ae. aegypti* and infected persons aboard sailing ships resulted in regular introductions into Asia and the Americas centuries ago but no documented establishment of enzootic circulation outside of Africa.

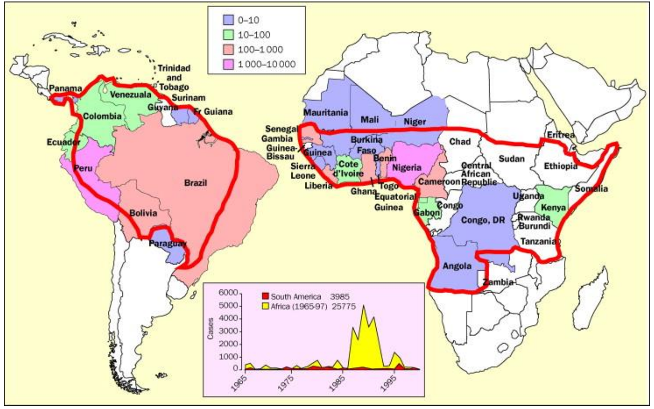
J. E. Bryant, et a., *PLoS Pathog* **3**, e75 (2007); E. Wang *et al.*, *J. Virol.* **74**, 3227-3234 (2000); S. M. Volk *et al.*, *J. Virology* **84**, 6497-6504 (2010). S. B. Halstead, *Emerg Infect Dis* **21**, (2015).

Risks for Spillback into Permanent Enzootic Cycles

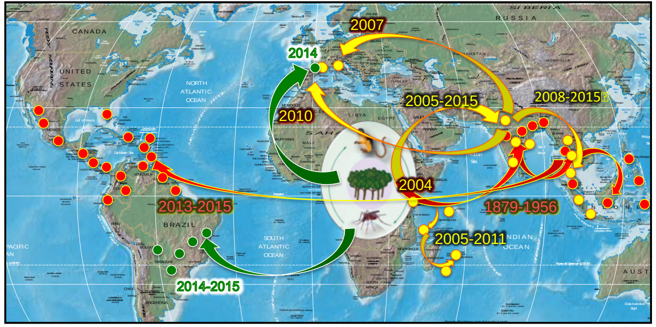
- Yellow fever virus: ½ (Americas but not Asia)
- Dengue viruses: ½ (Africa for DENV-2, none detected in the Americas)
- CHIKV: 0/2 (none detected in Asia or the Americas)
- Zika virus? No direct evidence in Asia but very limited surveillance

But independent enzootic circulation is difficult to distinguish from temporary spillback unless sufficient divergence between enzootic and human strains can be detected, or epizootics in nonhuman primates suggests the presence of an enzootic cycle

Enzootic yellow fever



Recent chikungunya virus spread



Role of Flavivirus Cross-immunity for the Absence of Sylvatic DENV and possibly ZIKV in the Americas?

Saint Louis Encephalitis virus
Rocio virus
Yellow fever virus
Dengue virus (1 – 4)
West Nile virus
Aroa
Naranjal
Bussuquara
Iguape
Cacipacore
Ilheus

✓ **Heterologous immunity protects against DENV?**

- DENV-immune NHP survived or exhibited prolonged survival time after lethal challenge of YFV (Theiler & Anderson, 1975)
- prior exposure to heterologous flavivirus infection ↑ the inapparent/apparent infection ratio in humans (Monath etal, 1984)
- secondary flavivirus infection ↑ heterologous Abs to other viruses of the same group (Theiler & Casals 1958)
- exposure to ZIKV in humans protected for YFV (Bearcroft 1956)
  …but immunization to YFV did not protect against ZIKV (Bres etal 1963)
- Indian immigrants and troops who had resided in India (‘seasoned’) prior to arrival in S. America were less affected to YFV epidemics (Ashcroft, 1979; Wallbridge, 1891)

✓ **…but not all heterologous immunity is protective**

- WNV, BANV & ZIKV not protective vs YFV (rhesus NHP)
- WSLV & ZIKV were protected (Vervet NHP) (Henderson etal, 1970)

And Now What?

- ✓ **Comprehensive ecological and epidemiological studies**

- ✓ **Given the similarities with YFV and the increased levels of human DENV, CHIKV and ZIKV transmission in the Americas, opportunities for the establishment of a sylvatic cycle will increase [??]**

- ✓ **Even if DENV, ZIKAV and CHIKV can not establish a sylvatic transmission cycle amomg NHPs in the neotropics, elucidation of the underlying reasons would greatly enhance our understanding of the mechanisms of arbovirus emergence as well as its limitations**

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