CSTE-hosted VBD Webinar: The Emergence and Geographic Spread of *Aedes*-Transmitted Diseases

August 17, 2017
2:00-3:00 pm Eastern Standard Time

Council of State and Territorial Epidemiologists

Webinar Housekeeping

CSTE

Webinar Housekeeping

- **Today's webinar is being recorded**
  - The webinar recording and presentation slides will be available in the webinar library on CSTE's website: http://www.cste.org/?page=WebinarLibrary
- **All lines have been muted**
- **There will be a question-and-answer session at the end of the webinar**
  - To ask a question, please use the Q&A box on the right side of your screen

Emergence and Geographic Spread of *Aedes*-Transmitted Viruses

Duane J Gubler, ScD, FAAAS, FIDSA, FASTMH
Emeritus Professor
Program in Emerging Infectious Diseases,
Duke-NUS Medical School, Singapore,
Chairman, Global Dengue & Aedes-Transmitted Diseases Consortium

CSTE Webinar, 17 Aug, 2017

Disclosure

Provided consultation and advice on dengue to:

Sanofi Pasteur
Takeda
Inviragen
NIH
Merck
GSK
Janssen
Globavir
Novartis
Hawaii Biotech
Bayer

Patent holder of Takeda vaccine
Investor in Takeda Pharmaceuticals

Emergence and Geographic Spread of *Aedes*-transmitted Viruses

Talk Outline

- History of emergence
- Basic epidemiology
- Changing epidemiology
- Other viruses/ yellow fever
- Drivers of emergence
- Prevention and Control
- Conclusions

Emergent Arboviruses Currently Causing Urban Epidemics Transmitted by Aedes (Stegomyia) Species Mosquitoes

- Flaviviruses
  - Dengue
  - Zika
  - Yellow fever
- Alphaviruses
  - Chikungunya

Emergence into the urban transmission cycle: Comparisons among YFV, DENV, ZIKV & CHIKV

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

Chikungunya virus: Originated in Africa and emerged repeatedly into the urban cycle following the domestication of *Ae. aegypti*; 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).D.J. Gubler, CABI, Chapter 1, 2014.

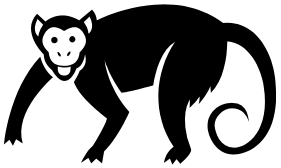
Emergence into the urban transmission cycle: Comparisons with DENV, YFV, ZIKV & CHIKV

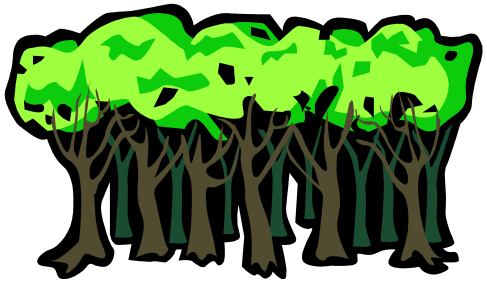
Zika virus: Originated in Africa and spread throughout sub-continent, maintained in an enzootic cycle with spillover into the peridomestic environment and sporadic/silent transmission to humans. Introduced to Asia transmitted sporadically/silently to humans by Ae. aegypti and Ae albopictus (?) throughout the region, but no documented establishment of enzootic circulation outside of Africa

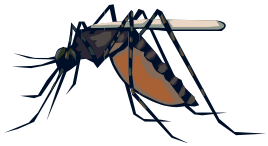
Dengue viruses: Originated in Southeast Asia, diversified into 4-5 serotypes while still in mosquitoes or the enzootic cycle. Enzootic spillover and emergence into village and urban cycles followed by regular introductions to urban areas throughout the tropics on sailing ships centuries ago; spillback of DENV-2 into an enzootic cycle in West 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)

Sub-Saharan Africa/Asia



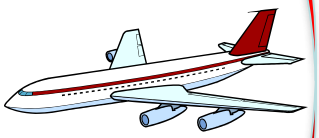


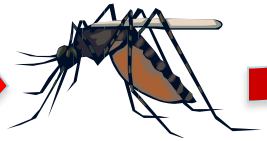


Aedes spp.

No known barriers to initial host range changes

Ae. aegypti aegypti
Ae. albopictus





TSETSARKIN, K. A., CHEN, R., SHERMAN, M. B. & WEAVER, S. C. 2011. *Curr Opin Virol,* 1**,** 310-317.

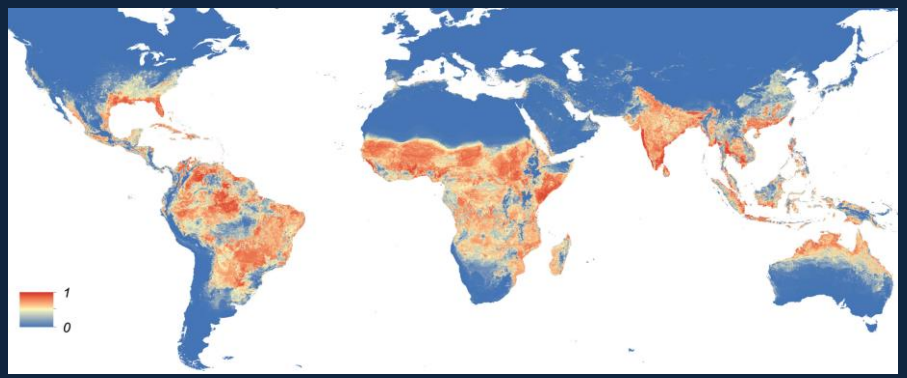
Urban *Aedes* Virus Vectors

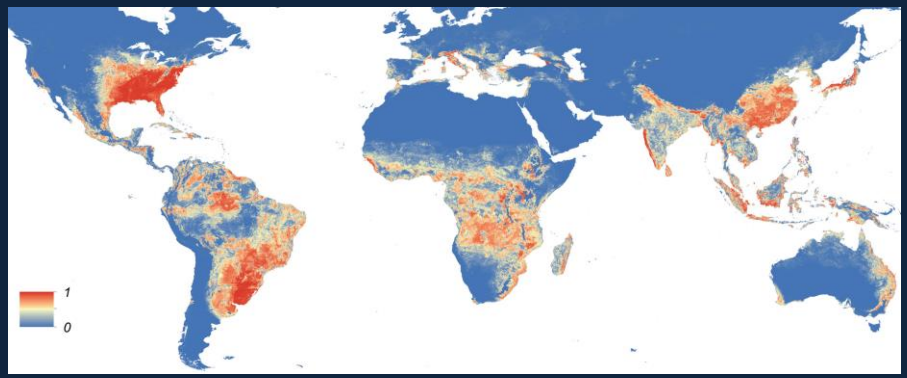
Ae.aegypti

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

Ae.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.

Aedes Urban Endemic/Epidemic Vectors

Aedes aegypti aegypti

- Tropical and subtropical
- Feeds almost exclusively on humans
- Takes multiple bloodmeals within a gonotrophic cycle (0.76-0.63 blood meals per day) for both egg production and energy needs
- Exploits artificial water containers near houses as larval habitats
- Adult females found mostly inside houses
- Feeds during the daytime

Aedes albopictus

- Tropicical, subtropical and temperate regions
- Feeds opportunistically
- Usually takes a single bloodmeal within a gonotrophic cycle
- Uses artificial and natural larval habitats
- Varied levels of anthrophily and endophily
- Feeds during the daytime

Other Potential Urban/Peridomestic Mosquito Vectors

Pacific and Asia

- *Aedes polynesiensis*
- *Aedes hensilii*
- *Aedes malayensis*
- Other *Aedes scutellaris* species

Other *potential vectors*

- Aedes triseriatus
- Aedes spp

Principal Clinical Syndromes Caused by Arboviruses

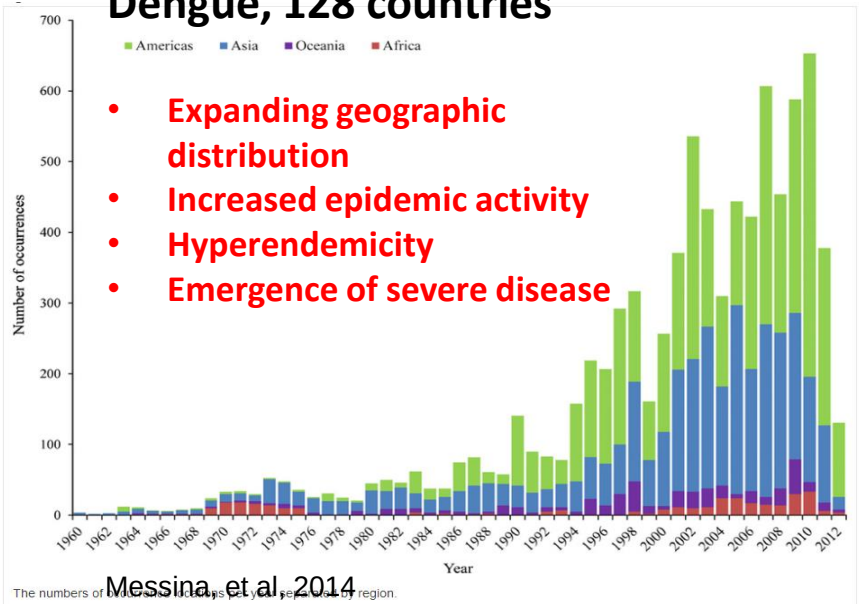
- Systemic Febrile Illness
  - Dengue
  - Yellow fever
  - Zika
  - Chikungunya
- Hemorrhagic Fever
  - Dengue
  - Yellow fever
- Meningoencephalitis
  - Zika

Spectrum of Dengue, Zika, Yellow Fever and Chikungunya Disease Overlaps

Symptoms	Dengue	Yellow Fever	Zika	Chikungunya
Fever	++++	++++	+++	++++
Myalgyias/arthralgias	+++	+++	++	++++
Edema	++	++	++	-
Rash	++	++	+++	++
Retro-orbital pain	+++	++	+++	+
Conjunctivitis	-	-	+++	+
Lymphadenopathy	++	++	+	++
Hepatomegaly	++	+++	?	++
Leukopenia	+++	+++	+	+++
Thrombocytopenia	+++	+++	-	+
Hemorrhage	++	+++	-	+
Neurologic	+	+	++++	+

The Changing Epidemiology of Aedes Transmitted Diseases

Dengue, 128 countries

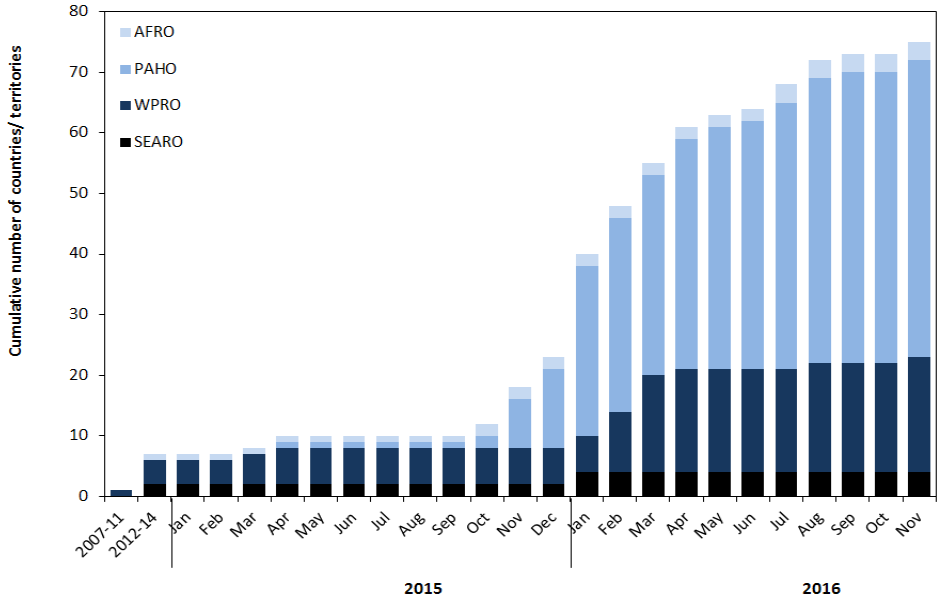


- Expanding geographic distribution
- Increased epidemic activity
- Hyperendemicity
- Emergence of severe disease

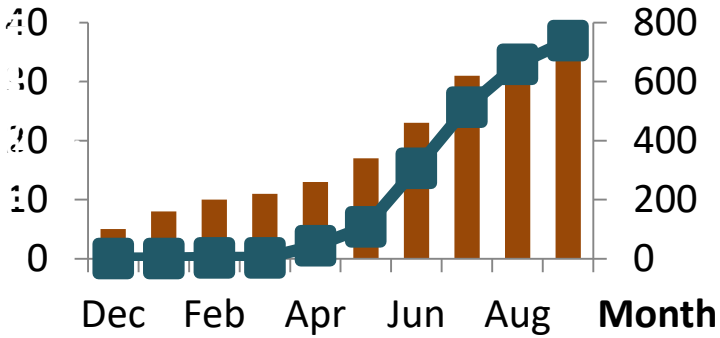
Messina, et al, 2014

The numbers of endemic countries per year, separated by region.

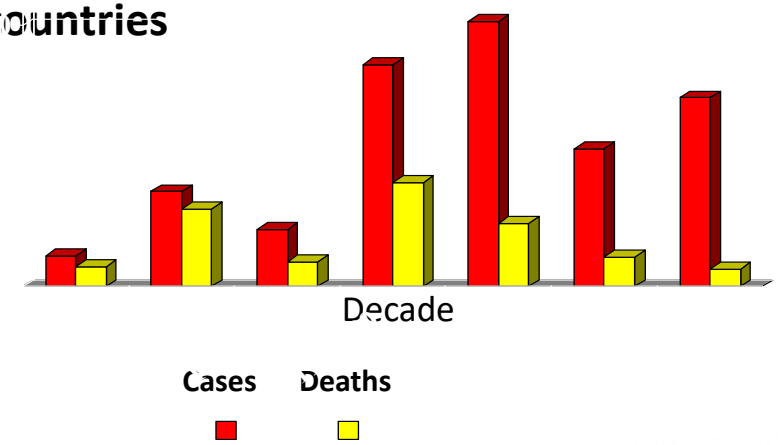
Zika, 79 countries



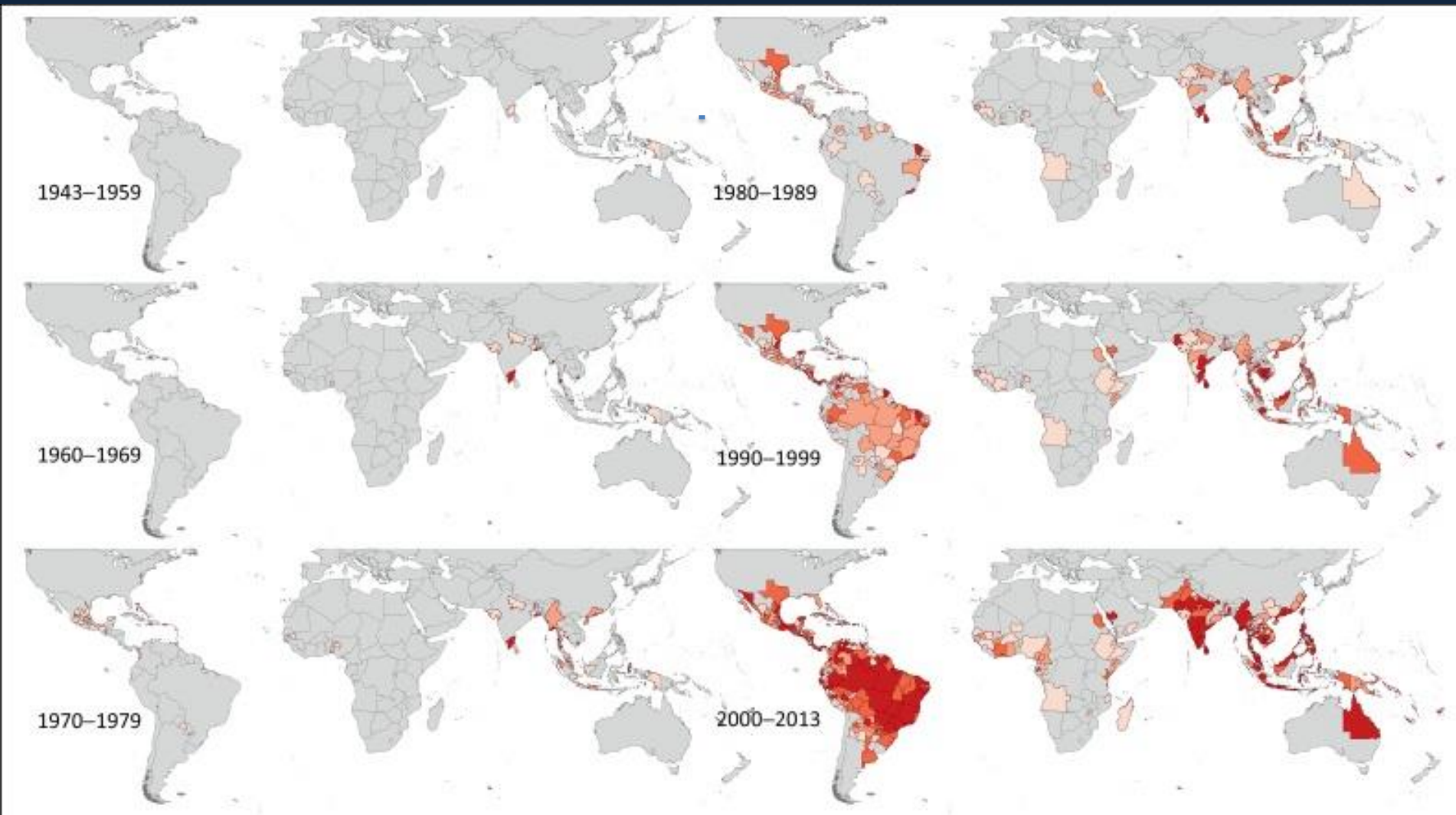
Chikungunya
37 countries*



Yellow Fever Cases and Deaths Reported to WHO, by Decade, 1950-2016
42 countries

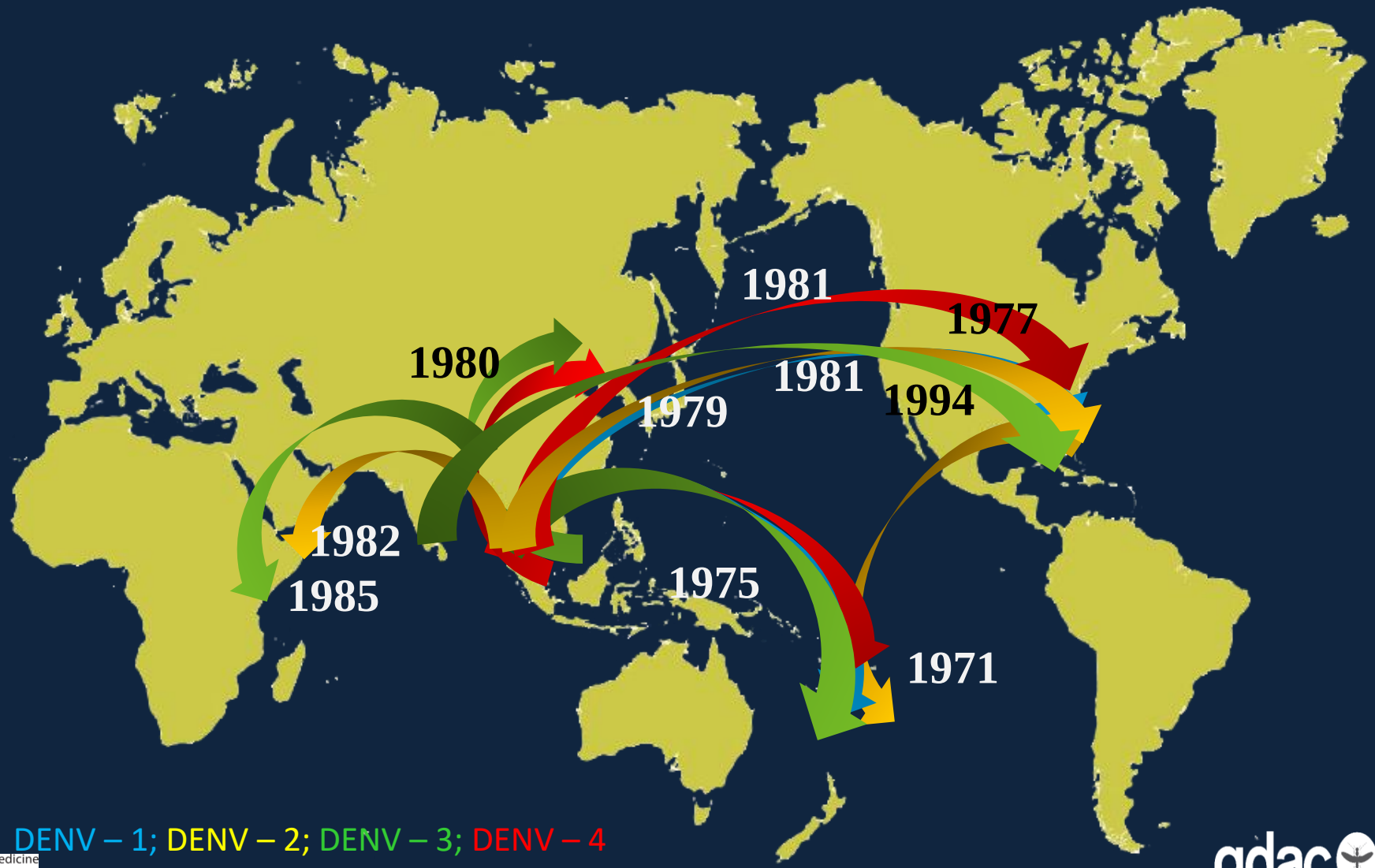


Global Spread of Dengue Viruses



Courtesy, Simon Hay

Global spread of dengue virus serotypes, 1970-2000

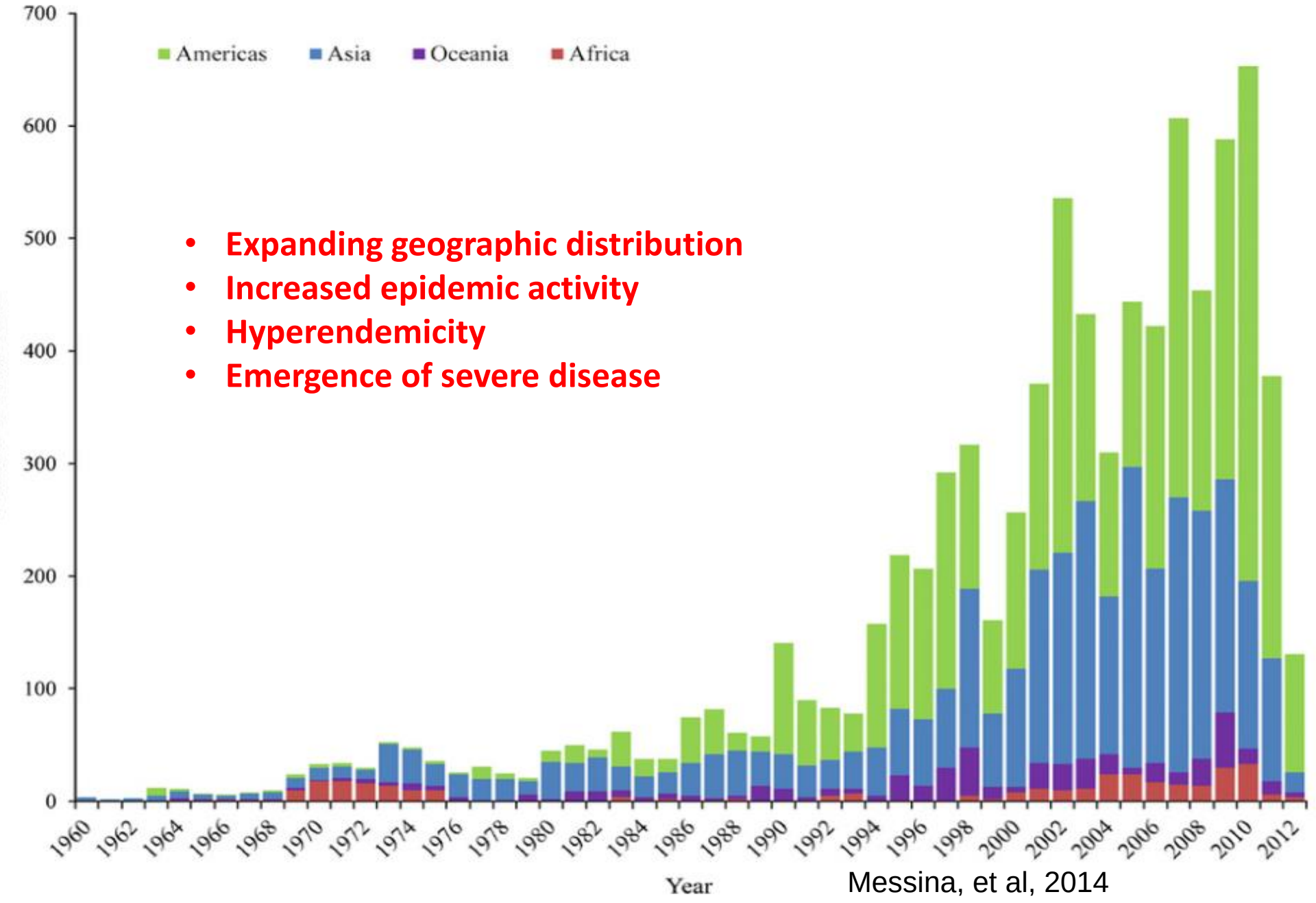


DENV – 1; DENV – 2; DENV – 3; DENV – 4

Global distribution of dengue virus serotypes, 1970

Global distribution of dengue virus serotypes, 2017

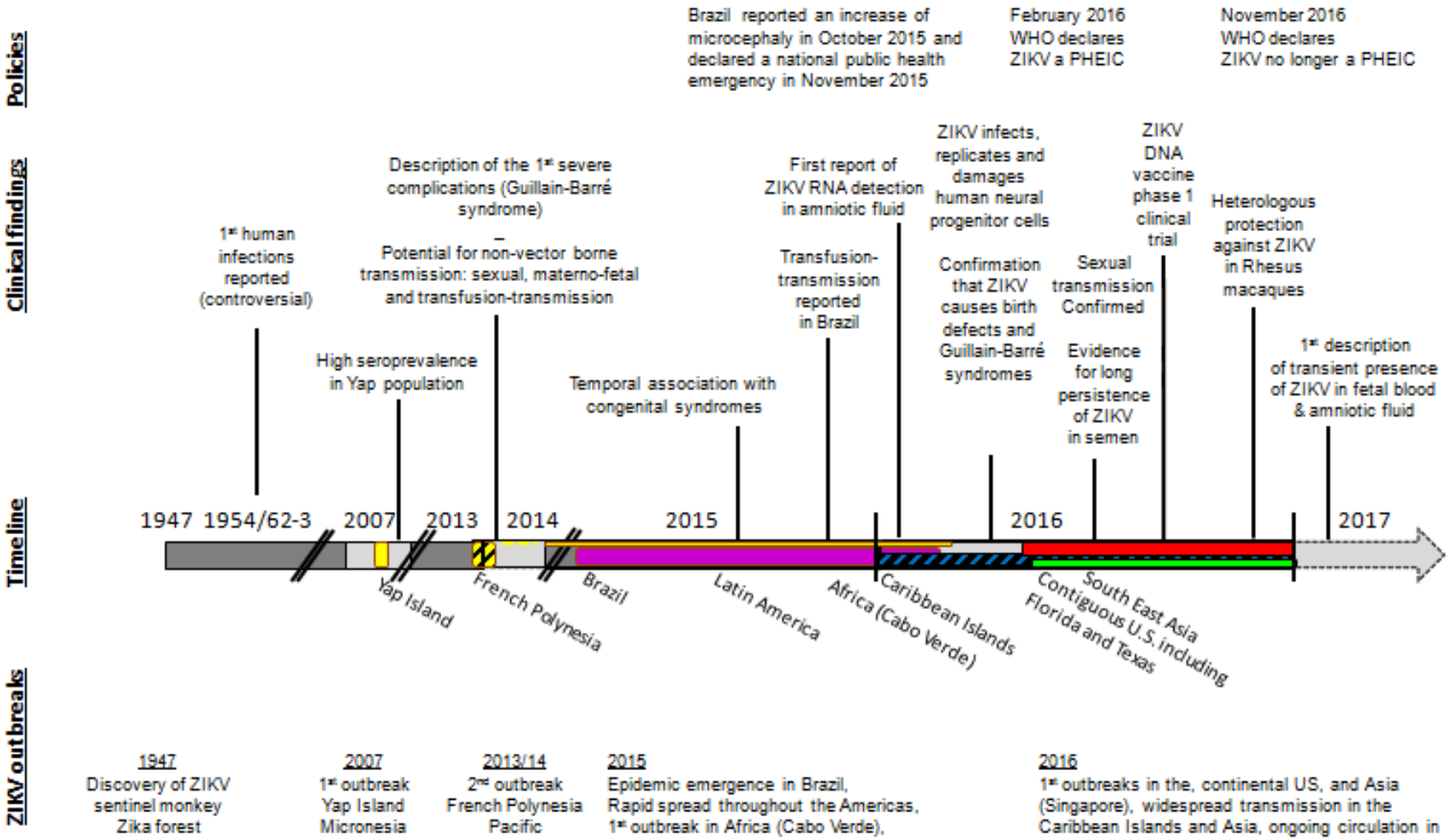
The Changing Epidemiology of Dengue



- **Expanding geographic distribution**
- **Increased epidemic activity**
- **Hyperendemicity**
- **Emergence of severe disease**

Messina, et al, 2014

Zika Emergence Timeline



Baud, et al, Lancet, 2017

Other Arboviruses with Potential for Urban Emergence

- Flavivuruses
  - Yellow fever
  - Spondweni
  - Wesselsbron
  - Sepik
  - Edge Hill
  - Kedougou
  - Tembusu

Other Arboviruses with Potential for Urban Emergence

- Alphaviruses
  - Ross River
  - Barmah Forest
  - Mayaro
  - O'nyong nyong
  - Sinbis
  - VEE
  - Me Tri

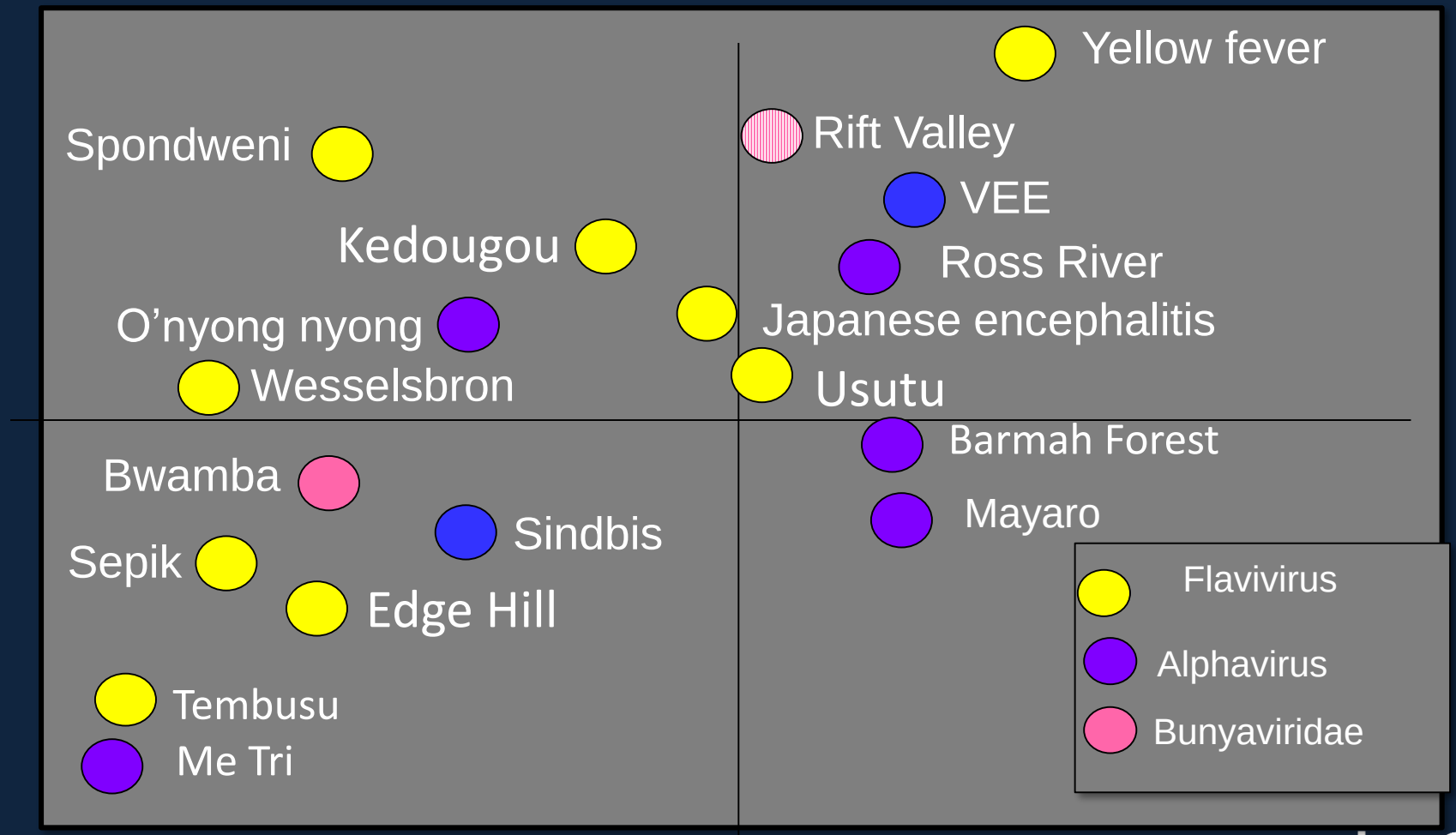
Other Arboviruses with Potential for Urban Emergence

- Bunyaviruses
  - Rift Valley Fever
  - Bwamba

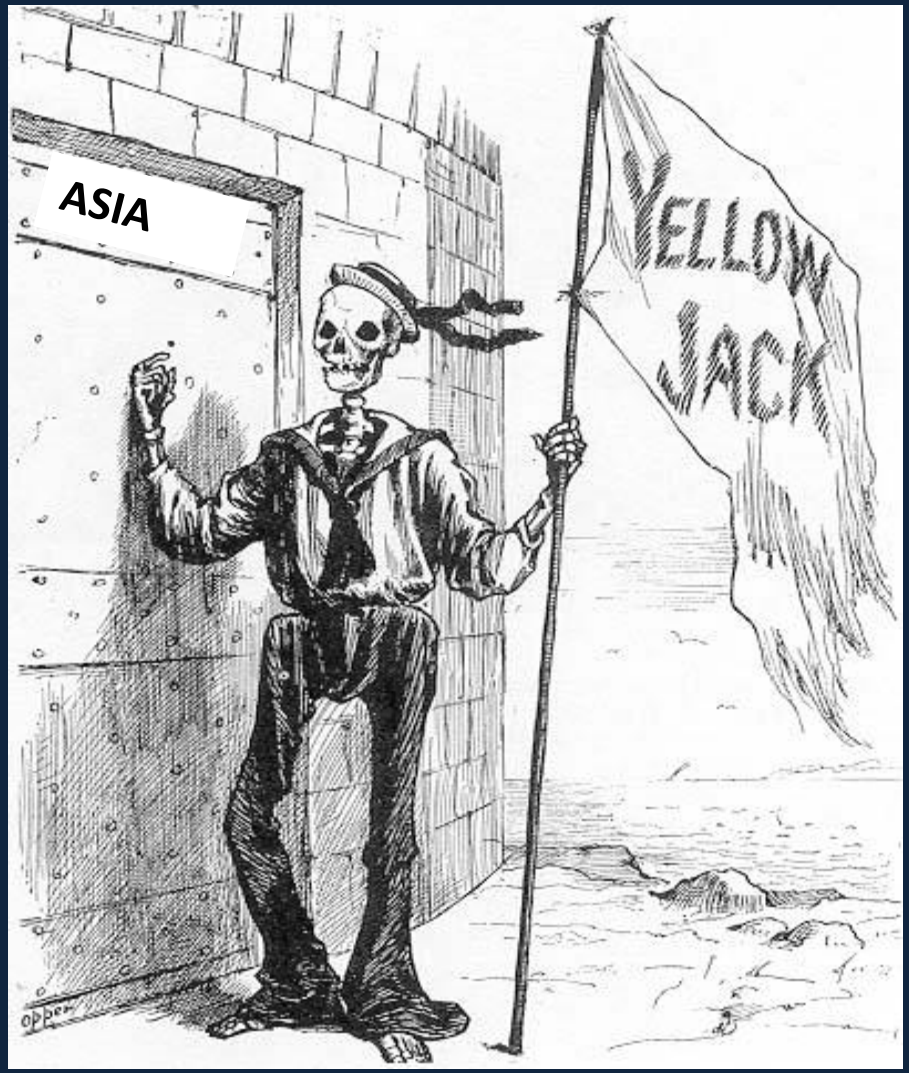
Novel Modes of Transmission

- Transfused blood
- Transplacental transmission
- Sexual
- Urine?”
- Saliva?

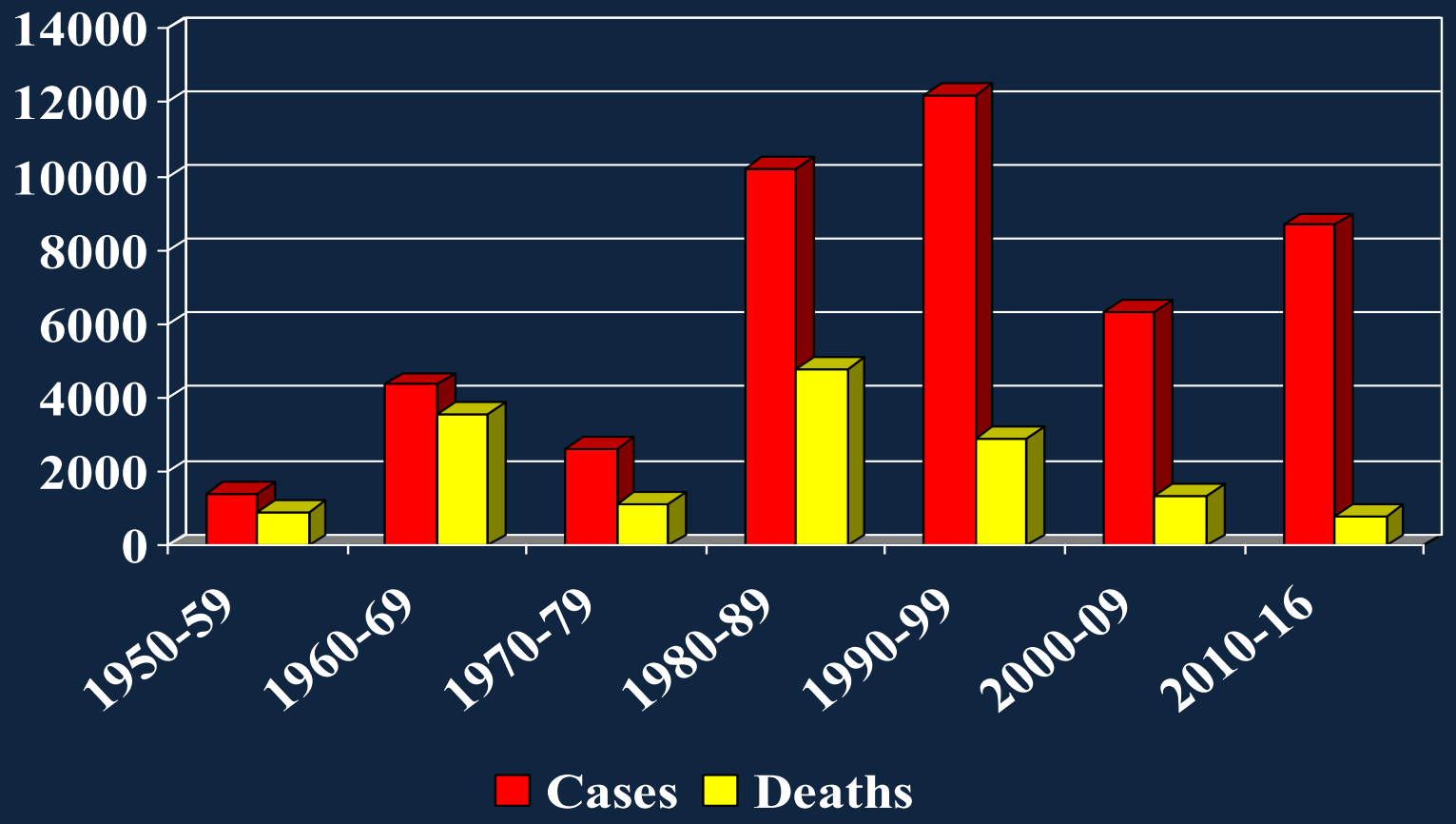
Other Arboviruses with Potential for Urban Emergence



Pandemic yellow fever: the next global threat?

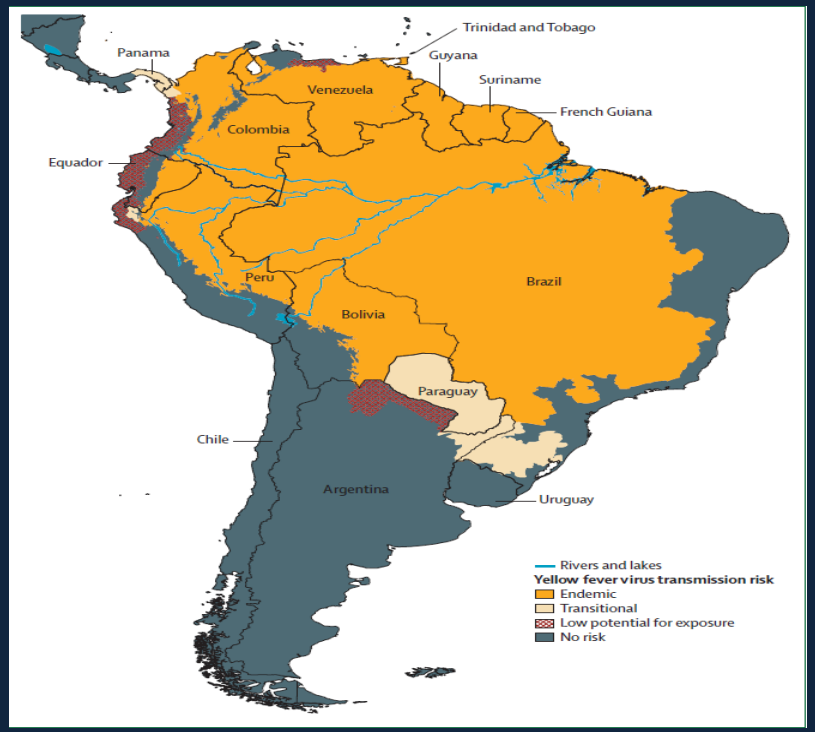


Yellow Fever Cases and Deaths Reported to WHO, by Decade, 1950-2016

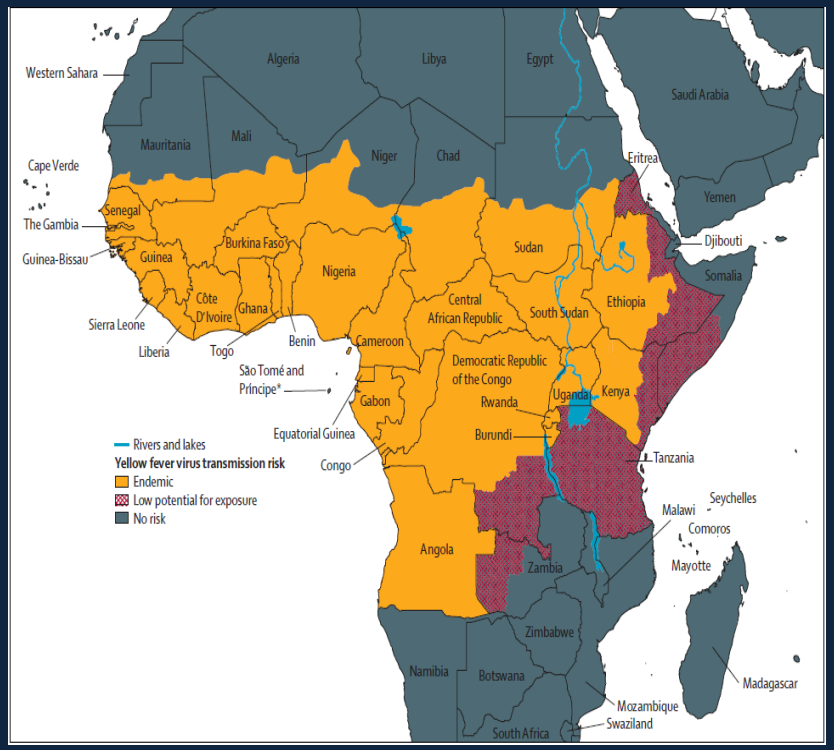


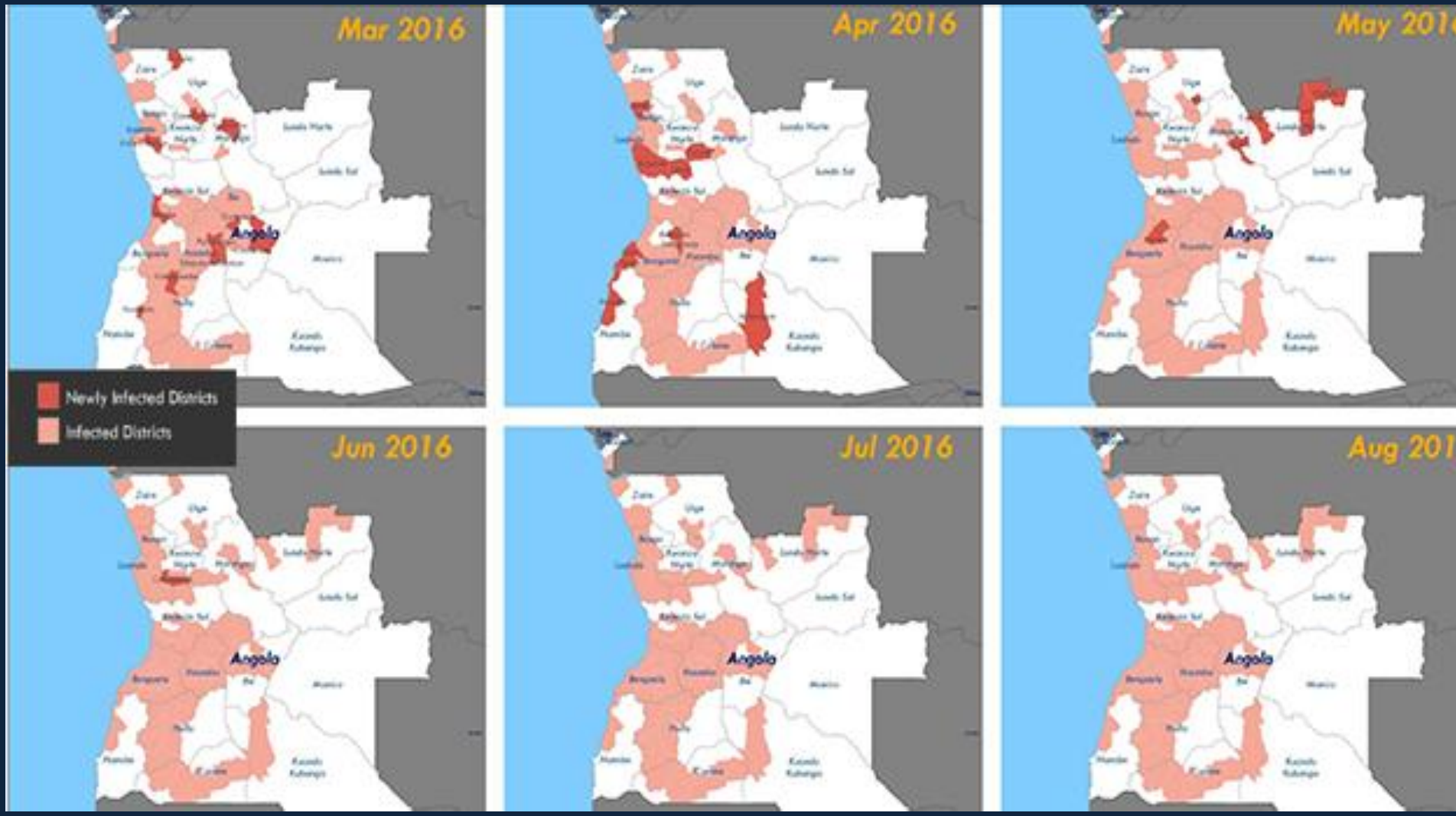
YF Endemic zones

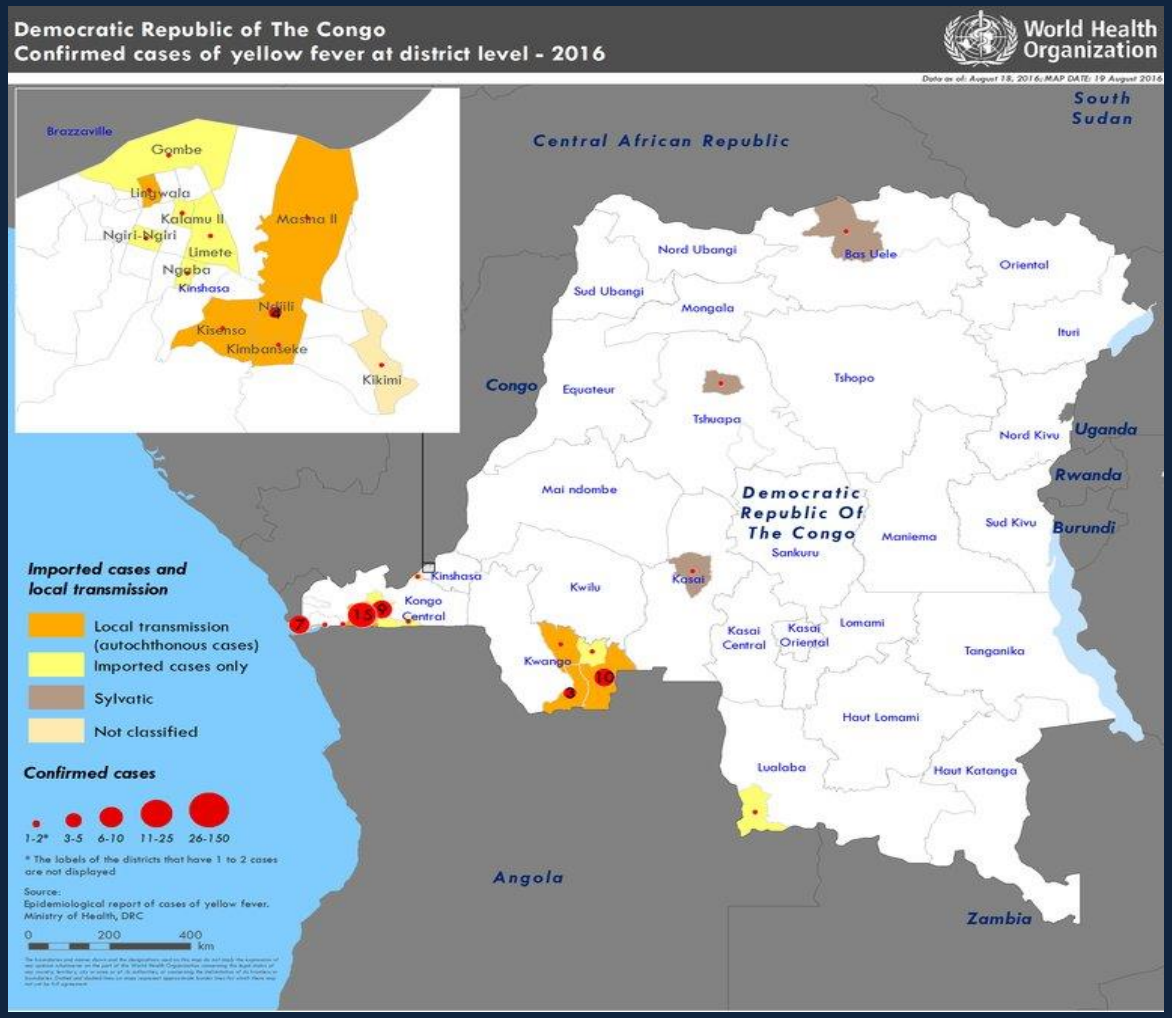
SOUTH AMERICA



AFRICA



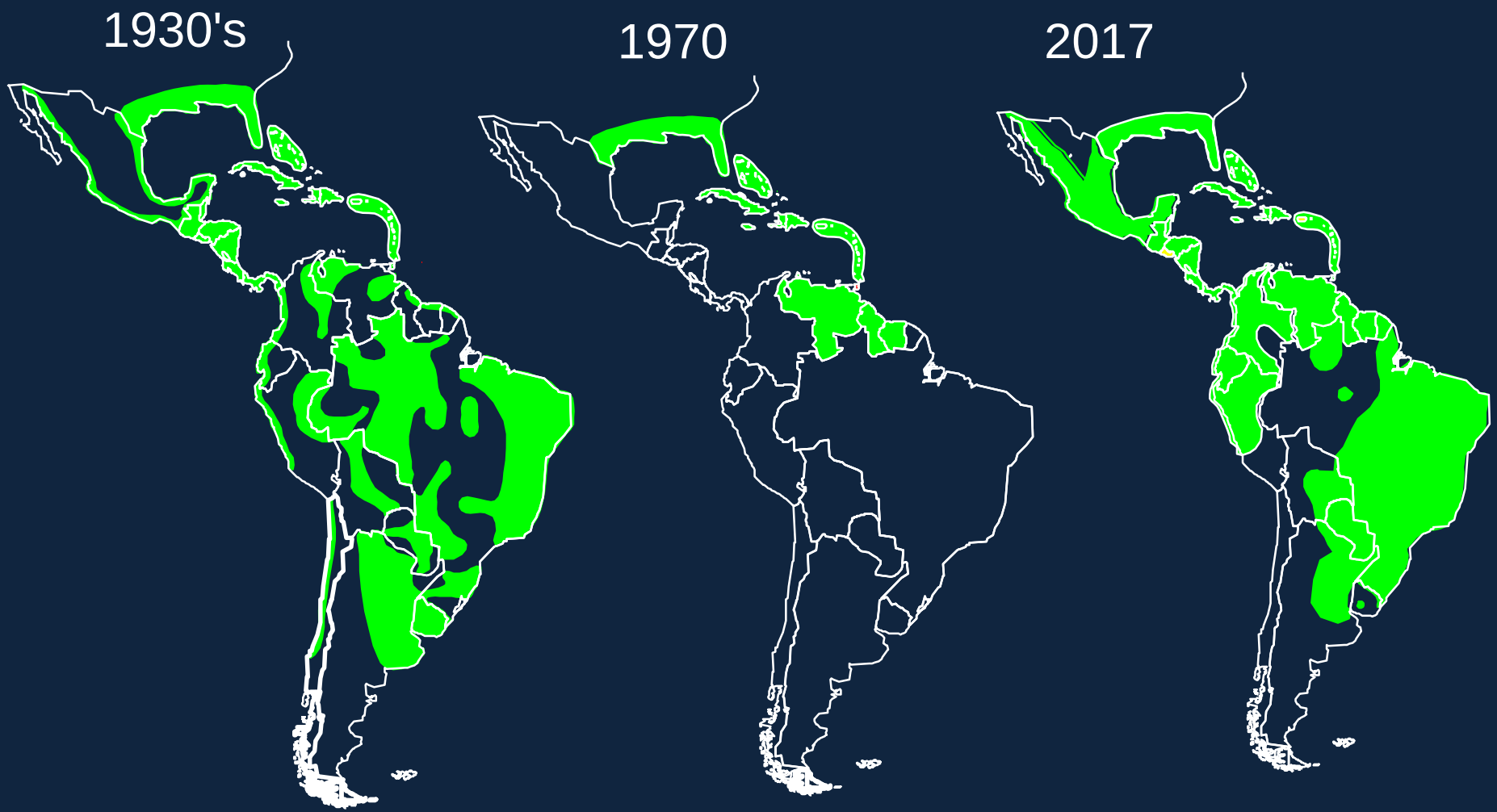

Mar 2016
Apr 2016
May 2016
Jun 2016
Jul 2016
Aug 2016
Newly Infected Districts
Infected Districts
Angola


Democratic Republic of The Congo
Confirmed cases of yellow fever at district level - 2016
World Health Organization
Data as of: August 18, 2016; MAP DATE: 19 August 2016
Brazzaville
Gombe
Lingwala
Kalamu II
Masina II
Ngiri-Ngiri
Limete
Ngaba
Kinshasa
Ndjili
Kisenso
Kimbanseke
Kikimi
South Sudan
Central African Republic
Nord Ubangi
Bas Uele
Oriental
Sud Ubangi
Mongala
Ituri
Congo
Equateur
Tshopo
Tshuapa
Nord Kivu
Uganda
Rwanda
Mai ndombe
Democratic Republic Of The Congo
Sud Kivu
Burundi
Maniema
Sankuru
Kwilu
Kasai
Kongo Central
Kasai Central
Kasai Oriental
Lomami
Kwango
Tanganika
Haut Lomami
Lualaba
Haut Katanga
Angola
Zambia
Imported cases and local transmission
Local transmission (autochthonous cases)
Imported cases only
Sylvatic
Not classified
Confirmed cases
1-2* 3-5 6-10 11-25 26-150
* 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, DRC
0 200 400 km

Yellow fever in China

- Date: March 14, 2016, Monday
- Source: Source: Xinhua |
- Health officials yesterday [13 Mar 2016] confirmed the first imported yellow fever case in China.
- The patient, a 32-year-old man from east China's Zhejiang Province, experienced stage one symptoms of the disease last Tuesday [8 Mar 2016] while in Luanda, capital of Angola, the National Health and Family Planning Commission said.
- He sought medical treatment after returning home on Thursday, and is now said to be in a "relatively serious" condition, with weakened liver and kidney functions.

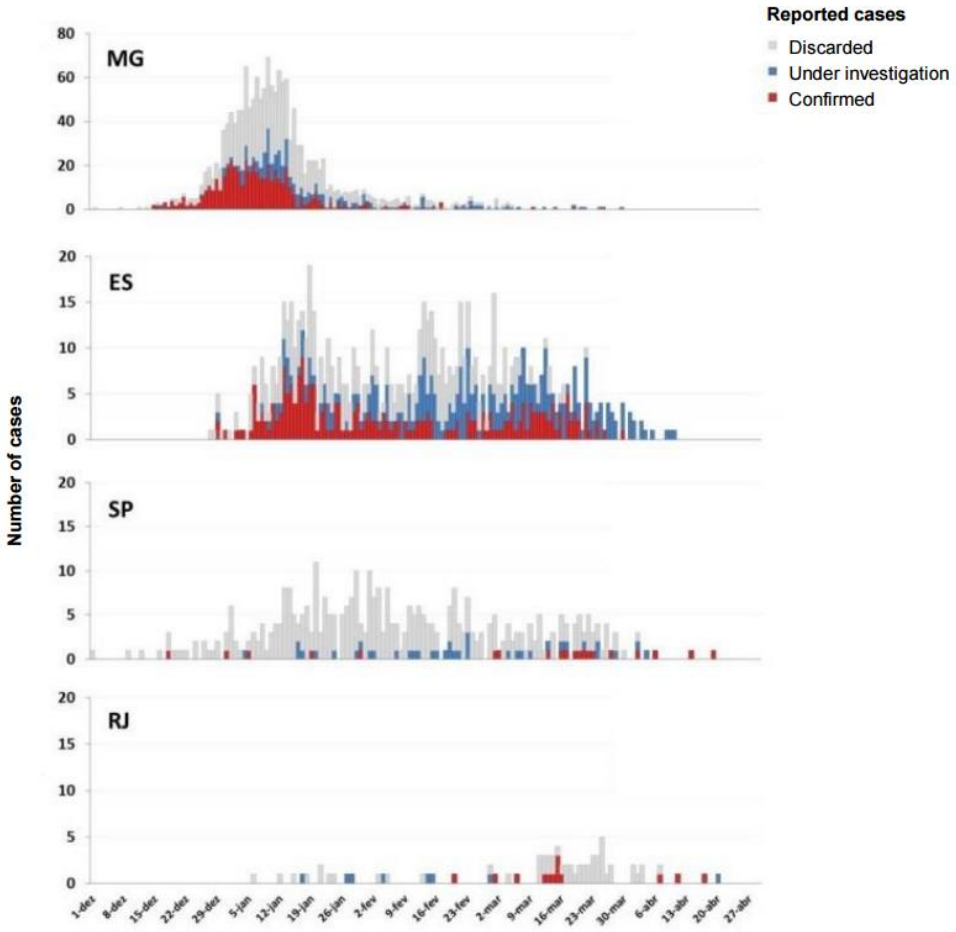
Aedes aegypti Distribution in the Americas



Adapted from Gubler, 1998

Potential for Urban Yellow Fever Epidemics in the Americas

Figure 1. Distribution of reported yellow fever cases by date of symptoms onset and probable state of infection. Brazil, 1 December 2016 to 18 May 2017.



MG: Minas Gerais, SP: São Paulo, ES: Espírito Santo, RJ: Rio de Janeiro.

Source: Data published by the Brazil Ministry of Health and reproduced by PAHO/WHO

Figure 2. Geographic location of suspected and probable cases of yellow fever reported in Minas Gerais, 2016 – 2017

Jan 9,

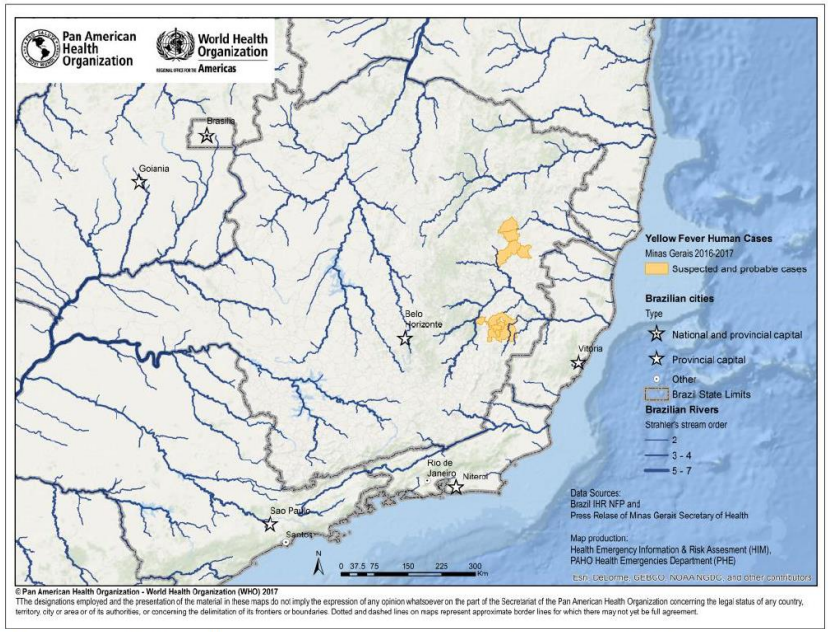


Figure 2. Geographic location of suspected and probable cases of yellow fever reported i Minas Gerais and Espiritu Santo, 2016 – 2017

Jan 18

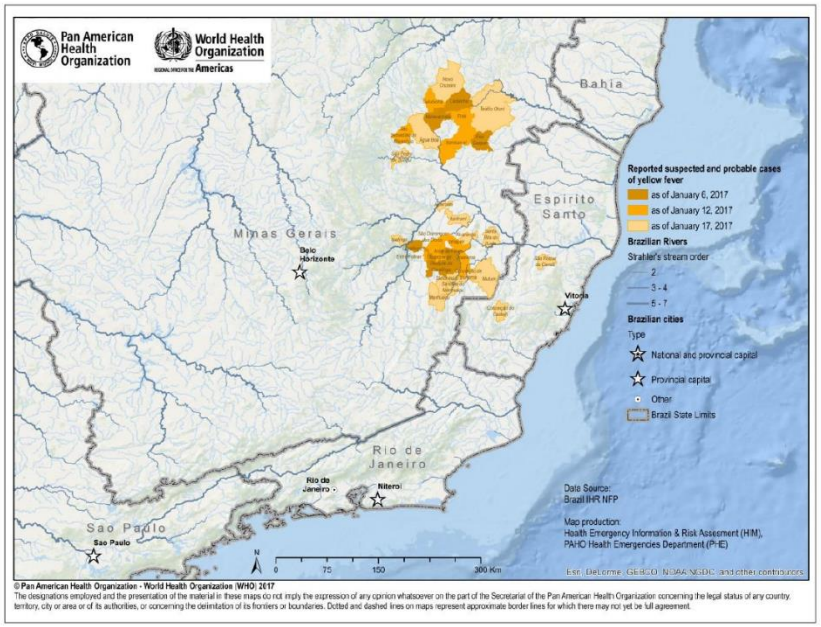
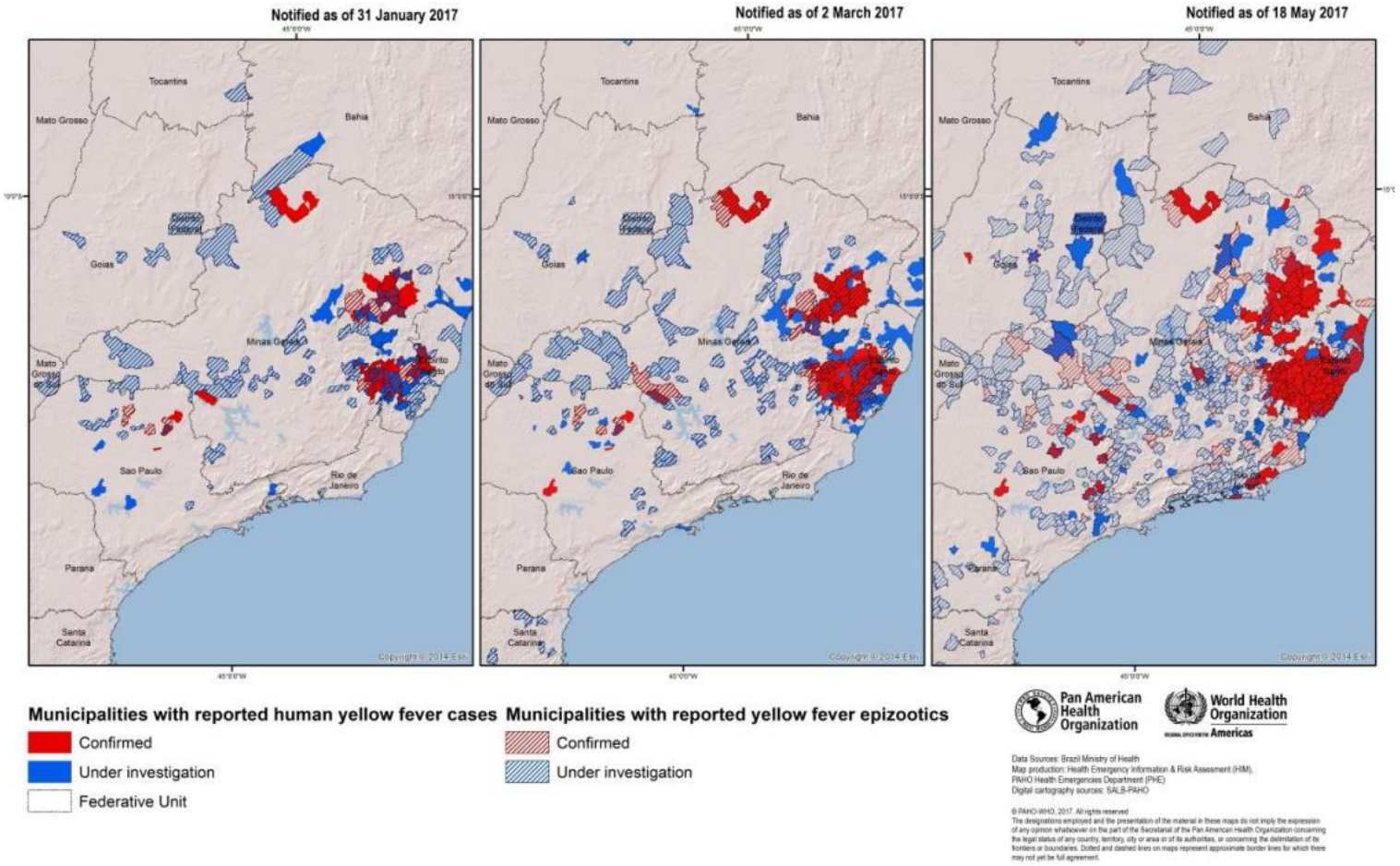
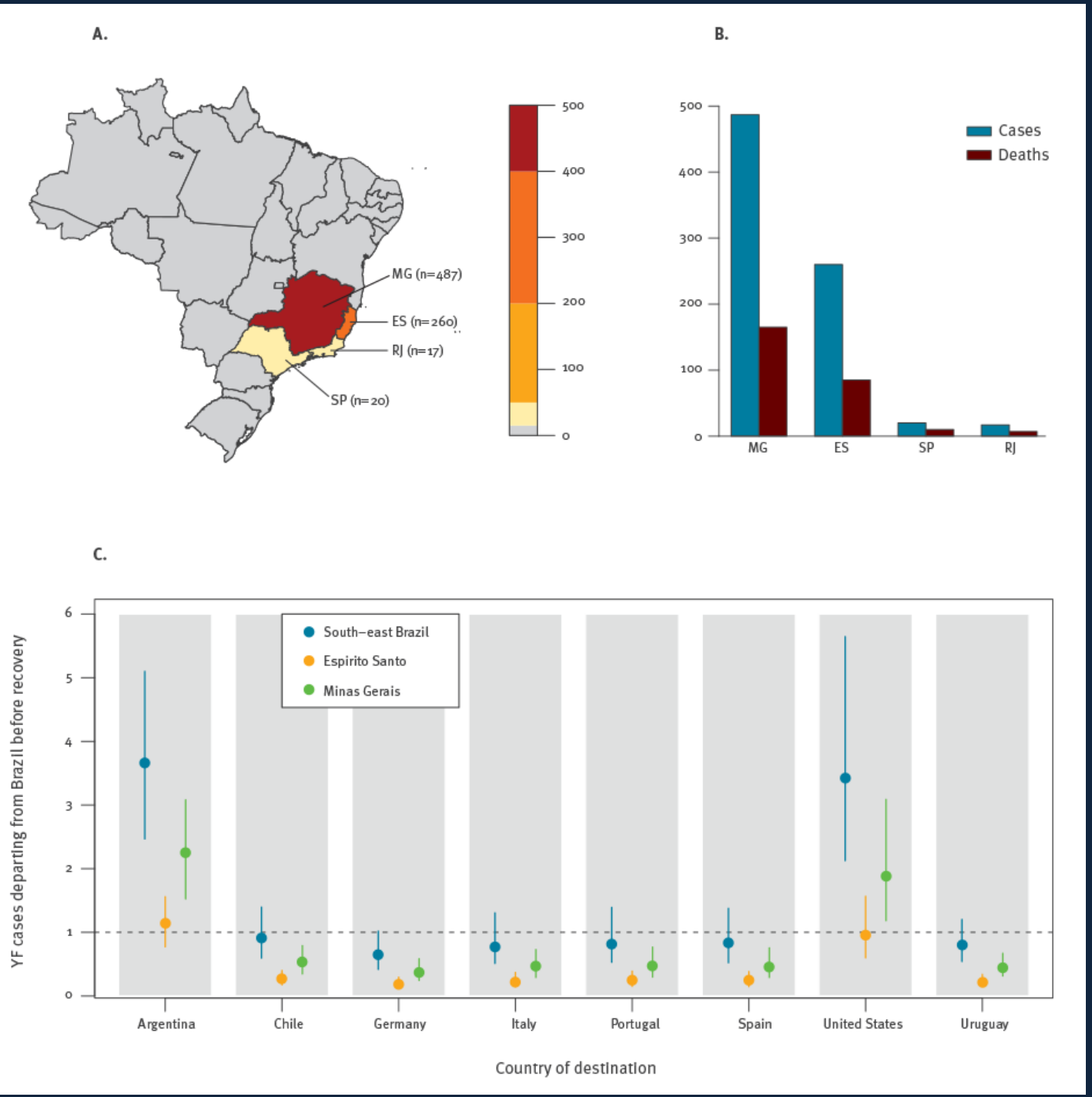


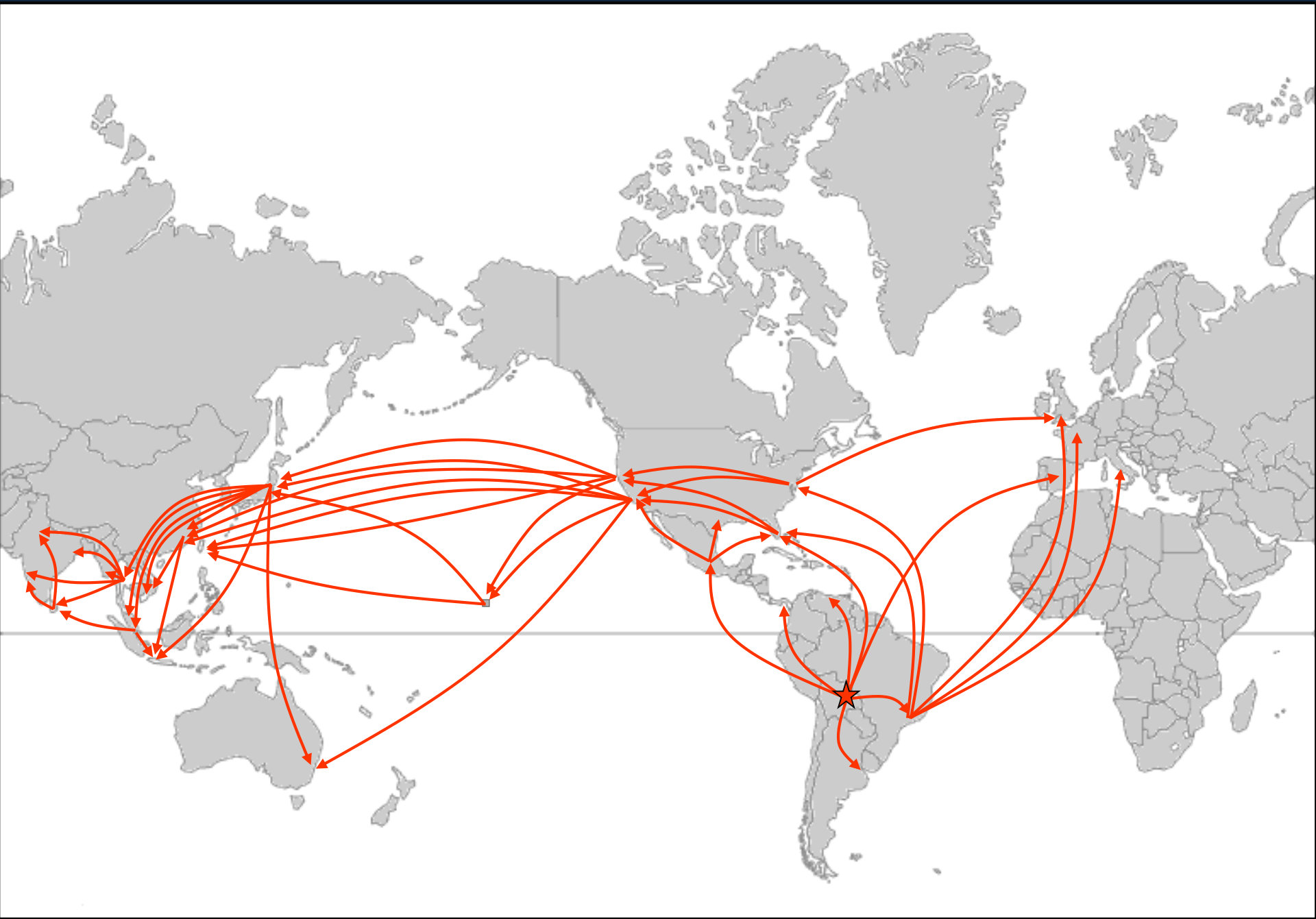
Figure 2. Geographic distribution of human cases (confirmed/suspected) and confirmed epizootics of yellow fever, 31 January, 2 March, and 18 May 2017.



Source: Data published by the Brazil Ministry of Health (Monitoring of yellow fever cases and deaths), compiled and reproduced by PAHO/WHO


A.
MG (n=487)
ES (n=260)
RJ (n=17)
SP (n=20)
500
400
300
200
100
0
B.
Cases
Deaths
MG
ES
SP
RJ
C.
South–east Brazil
Espirito Santo
Minas Gerais
YF cases departing from Brazil before recovery
Argentina
Chile
Germany
Italy
Portugal
Spain
United States
Uruguay
Country of destination

POTENTIAL GLOBAL SPREAD OF URBAN YELLOW FEVER



Why Have we Seen Such a Dramatic Geographic Expansion in Epidemic *Aedes*-Transmitted Diseases?

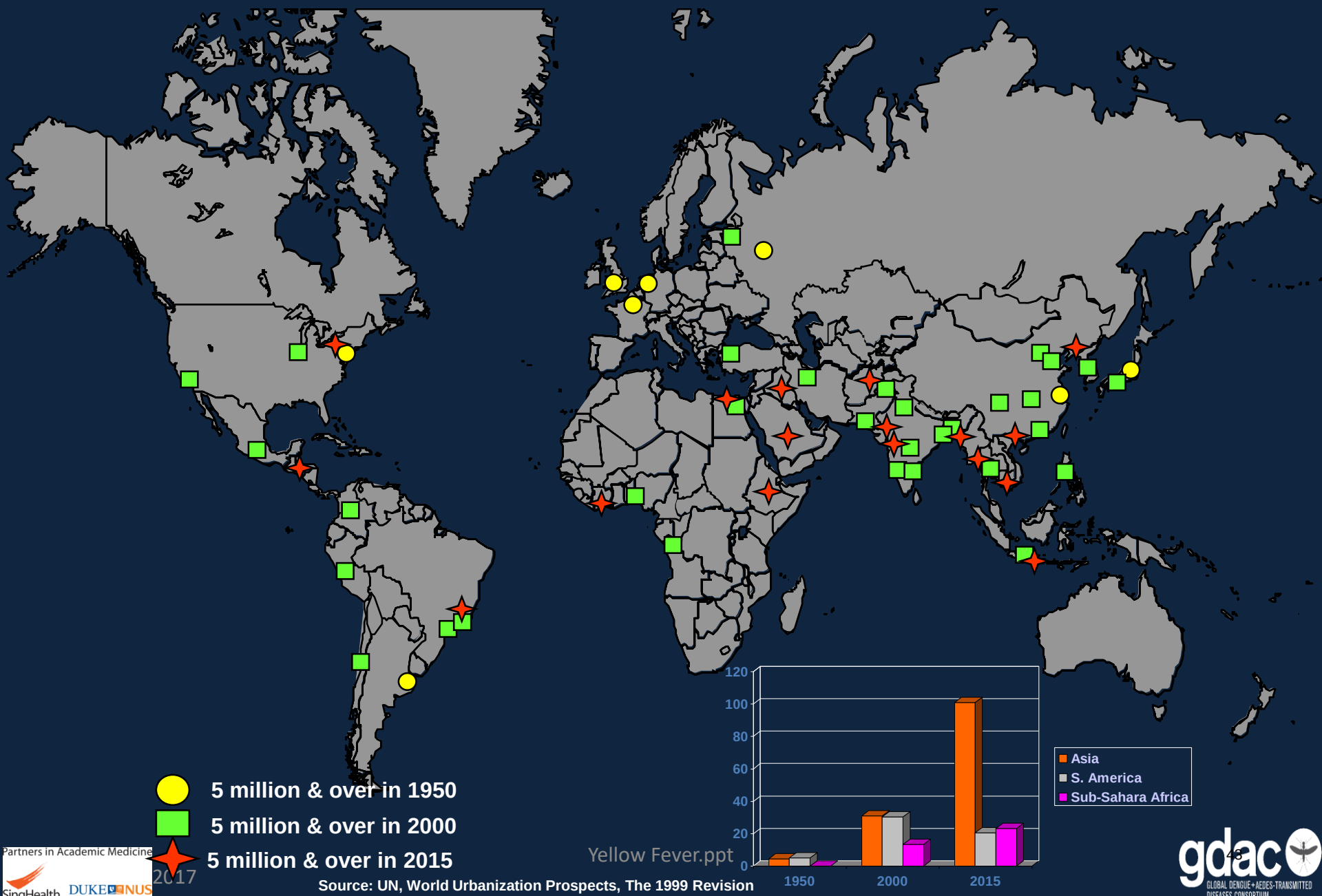
Major Drivers

- Demographic changes (Pop Growth)
  - Environmental change
    - Unprecedented urban growth
    - Changing lifestyles
- Increased transmission and emergence of viruses with greater epidemic potential
- Modern transportation (Globalization)
  - Increased movement of people, animals, commodities & pathogens
- Lack of effective vector control

The Global Threat of Urban Epidemics of Arboviral Diseases

- Unplanned urban growth unprecedented
- Crowded tropical urban centers provide ideal ecological conditions to maintain viruses and mosquito vectors
- At risk population exceeds 3.6 billion people

Urban Agglomerations, 1950, 2000, 2015

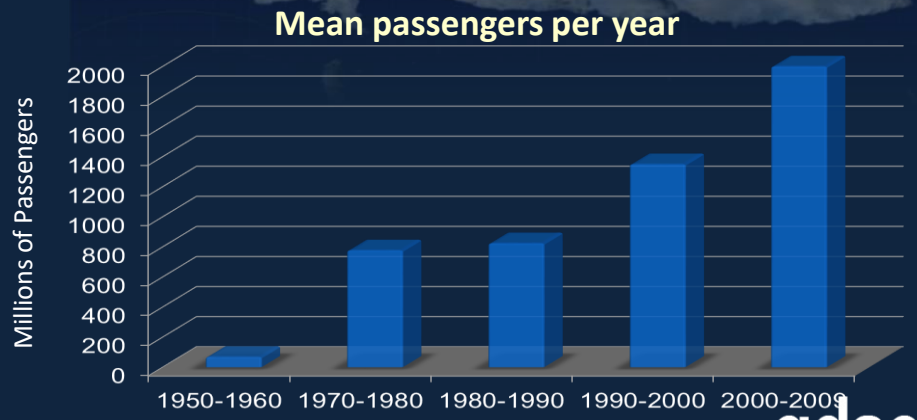


Source: UN, World Urbanization Prospects, The 1999 Revision

The Global Threat of Urban Epidemics of Arboviral Diseases

- Globalization and modern transportation provides ideal mechanism to move viruses and vectors among population centers

- In 2017, estimated 3 billion passengers will travel by air



Why have we seen such a dramatic increase in epidemic arboviral diseases?

- Complacency, Lack of Political Will
- Policy Changes
- Changes in Public Health
- Changing Life Styles/Behavior
- Microbial Adaptation
- Technology
- Intent to Harm
- Climate Change?

Global Threat of Epidemic Arboviral Diseases

- Disease and Trade-interwoven History
  - 14th century, Europe discovers exotic goods from Asia
- Global Trade Flourishes
  - 18th, 19, 20th centuries
- New Millennium
  - Integrated global economic system with a transnational flow of capital, products, people, animals, knowledge, and pathogens
  - Rapid spread of epidemic infectious disease from point of origin

What can we do to prevent and control Aedes-transmitted Diseases?

Mosquito Control –

Has failed to prevent epidemic dengue for 40 years

Traditional *Aedes aegypti* Control Methods have Failed

- Space spraying
- Perifocal control around cases
- Targeted source reduction
- Integrated vector management
- Community participation
- Bio-control?
- Genetic control?

Commonwealth Games 2010: toxic cloud being used to tackle dengue fever

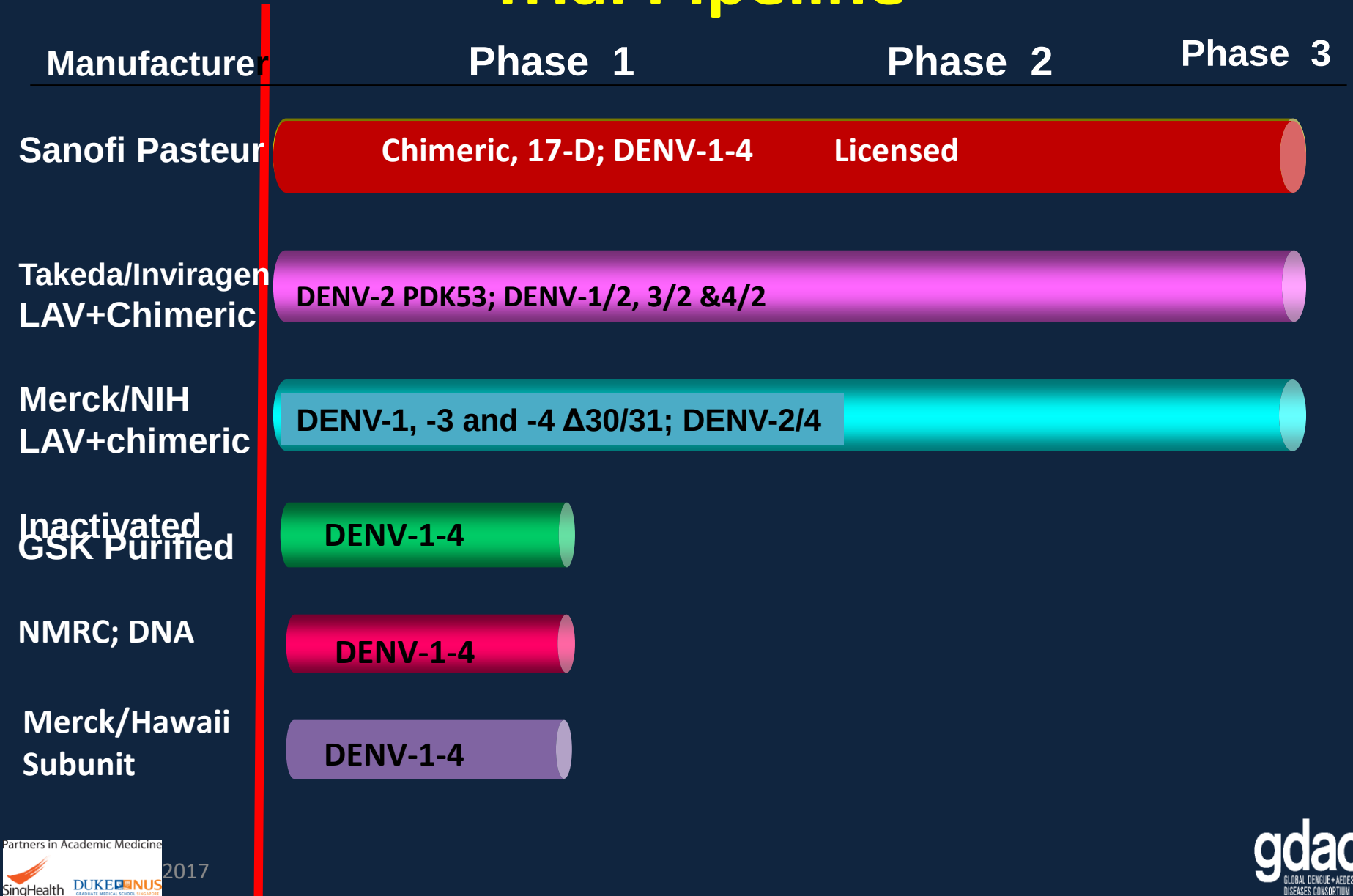
Promising New Tools in the *Aedes*-Transmitted Diseases Control Pipeline

- Vaccines
- Antiviral drugs
- Therapeutic antibodies
- Mosquito control

What can we do to prevent and control Aedes-transmitted Diseases?

- Vaccines
  - Yellow Fever
  - Dengue
  - Zika?
  - Chikungunya?
  - Other viruses?

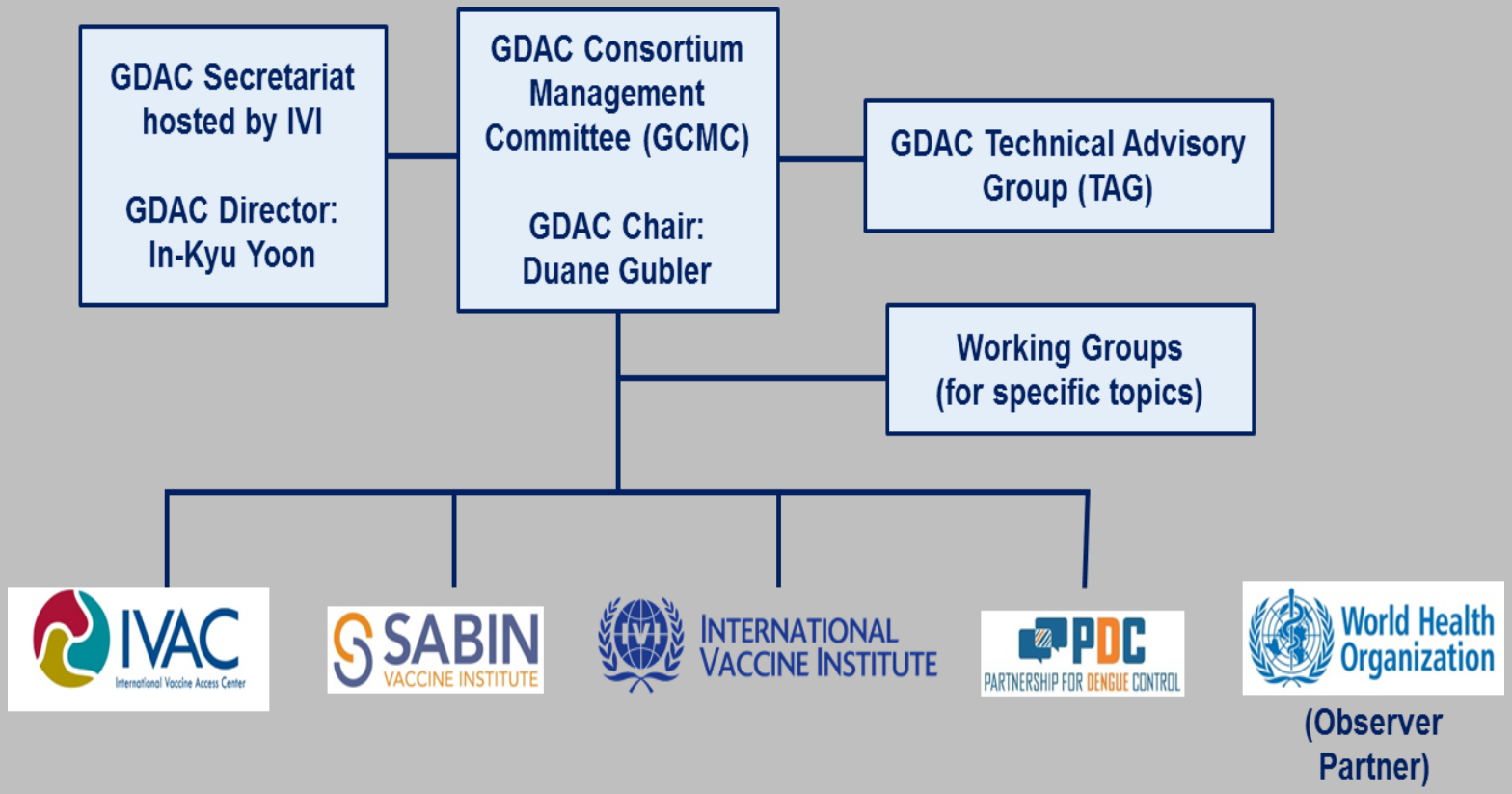
Tetravalent Dengue Vaccines in Clinical Trial Pipeline



The Global Threat of Urban Aedes-Transmitted Epidemic Arboviral Diseases

- Vaccines unavailable or inadequate supply
- Antiviral drugs for arboviruses ineffective or unavailable
- Biological markers for severe disease unavailable

Global Dengue and *Aedes*-transmitted Diseases Consortium (GDAC)



Existing Methods

Immature control

Major categories

- Container cleaning (bleach/wash/dump)
- Container manipulation (treated covers/polystyrene beads)
- Container treatment
- Social campaigns (education, source reduction)
- Environmental Management
- Legislation

Container treatment

Insecticides

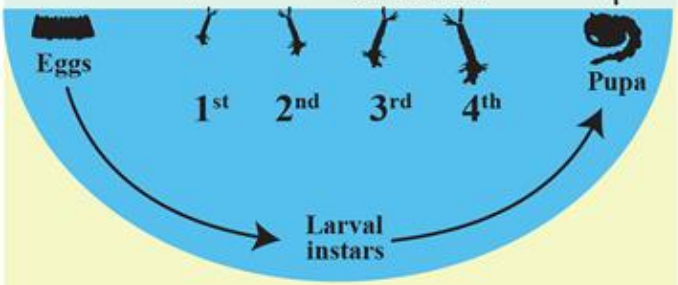
- Temephos
- Novaluron
- Spinonsad
- Diflubenzuron
- Bti

Bleach

Methoprene
Pyriproxyfen

Biologicals

- Copepods
- Larvivorous fish



New entomopathogenic fungi

Adult control

Major categories

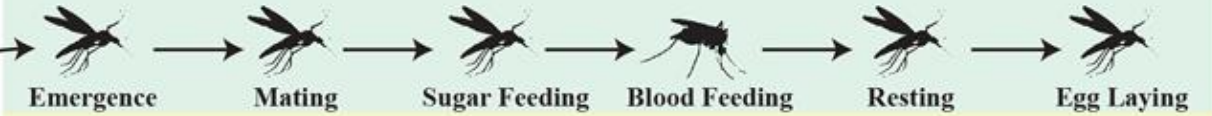
- Space spraying
- Indoor residual spraying
- Personal protection

Space spraying: Truck ULV, Low-flying aircraft, hand-held portables, perifocal treatment

Personal protection

- DEET
- Picaridin
- Bed nets
- Consumer products

Indoor residual spraying



RIDL and fsRIDL

Toxic sugar baits

Behavior modification

Lethal Ovitraps
Auto-dissemination

Wolbachia
Other within-tissue symbionts
Para-transgenesis
Antipathogen genes without drive

Curtains / IRS

Molecular insecticides, medea/HEGs, new insecticides

Methods under Development

Promising New Tools in Mosquito Control Pipeline

Lethal Ovitraps

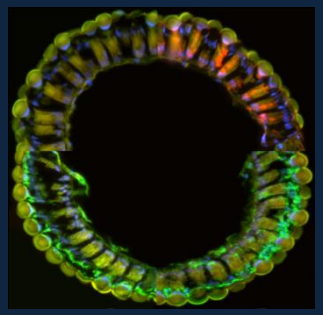
New Residual Insecticides

Spatial Repellants

Sterile Male Release

IT curtains/screens

Wolbachia Viral Interference



- Uncertainties
- Must be used properly by trained personnel
- Surveillance for resistance
- Important to realize that none of these will likely control dengue if used alone

What can we do to prevent and control Aedes-transmitted Diseases?

Mosquito Control –

What methods do we use?

- Indoor residual spray
- Larvalcontrol

Harbourage spraying with residual pyrethroid insecticide

Control of Aedes albopictus

Courtesy Scott Richie

GDAC Paradigm to Rollback Dengue and Other *Aedes*-Transmitted Diseases Using New Tools in the Control Pipeline

Integration and Synergy

International mobilization of resources

- Build public health capacity
- Fund program implementation
- Fund research

What is the Risk of Urban Epidemics of Aedes-Transmitted Diseases Today?

Risk Factors

- Unplanned urban growth unprecedented
- Crowded tropical urban centers provide ideal ecological conditions to maintain viruses and mosquito vectors
- Globalization provides ideal mechanism to move viruses and vectors among population centers
- Aedes aegypti and Ae. albopictus have global distribution
- At risk susceptible human population exceeds 3.6 billion people
- Vector control has been unable to prevent epidemic dengue, chikungunya and Zika
- Vaccines unavailable or inadequate supply

Factors that Decrease the Risk of Epidemic Aedes-Transmitted Diseases in the United States

- Living Conditions
  - Housing construction
  - Window and door screens
  - Air conditioning
  - Reliable piped water systems
  - Waste management
- Human Behavior
  - Social practices
  - Television
- Human Population Density
- Mosquito species
- Mosquito biology and behavior
- Privatized mosquito control

Global Threat of Urban *Aedes*-transmitted Epidemic Diseases

Conclusions

- Risk of epidemic arboviral diseases is highest in history
- Vaccines and drugs are unavailable or in short supply
- Vector control has been ineffective in preventing epidemic spread
- We can expect more emergent epidemic viruses transmitted by *Aedes Stegomyia* mosquitoes
- Control is possible if we combine vaccines with best vector control tools

Global Threat of Urban *Aedes*-transmitted Epidemic Diseases

CONCLUSIONS

- We need to quantify impact of vaccines vs mosquito control
- We need to get serious about developing and implementing more effective prevention and control programs in urban centers of endemic countries
- We need more focused research on:
  - Vaccines
  - Mosquito control
  - Effective combined use of both

Thank you for your participation!

- Please complete the webinar evaluation
- The webinar recording & slides will be available CSTE's website in the webinar library: http://www.cste.org/?page=WebinarLibrary

CSTE National Office
2872 Woodcock Boulevard, Suite 250
Atlanta, Georgia 30341

T 770.458.3811
F 770.458.8516
mphillips@cste.org