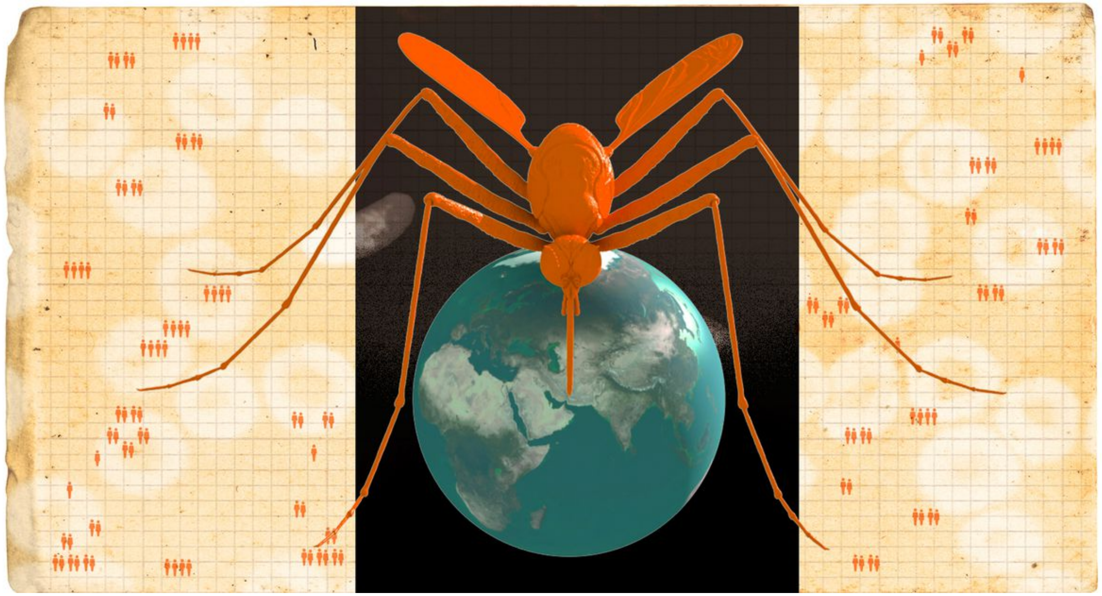
18 décembre 2019 – Collège de France

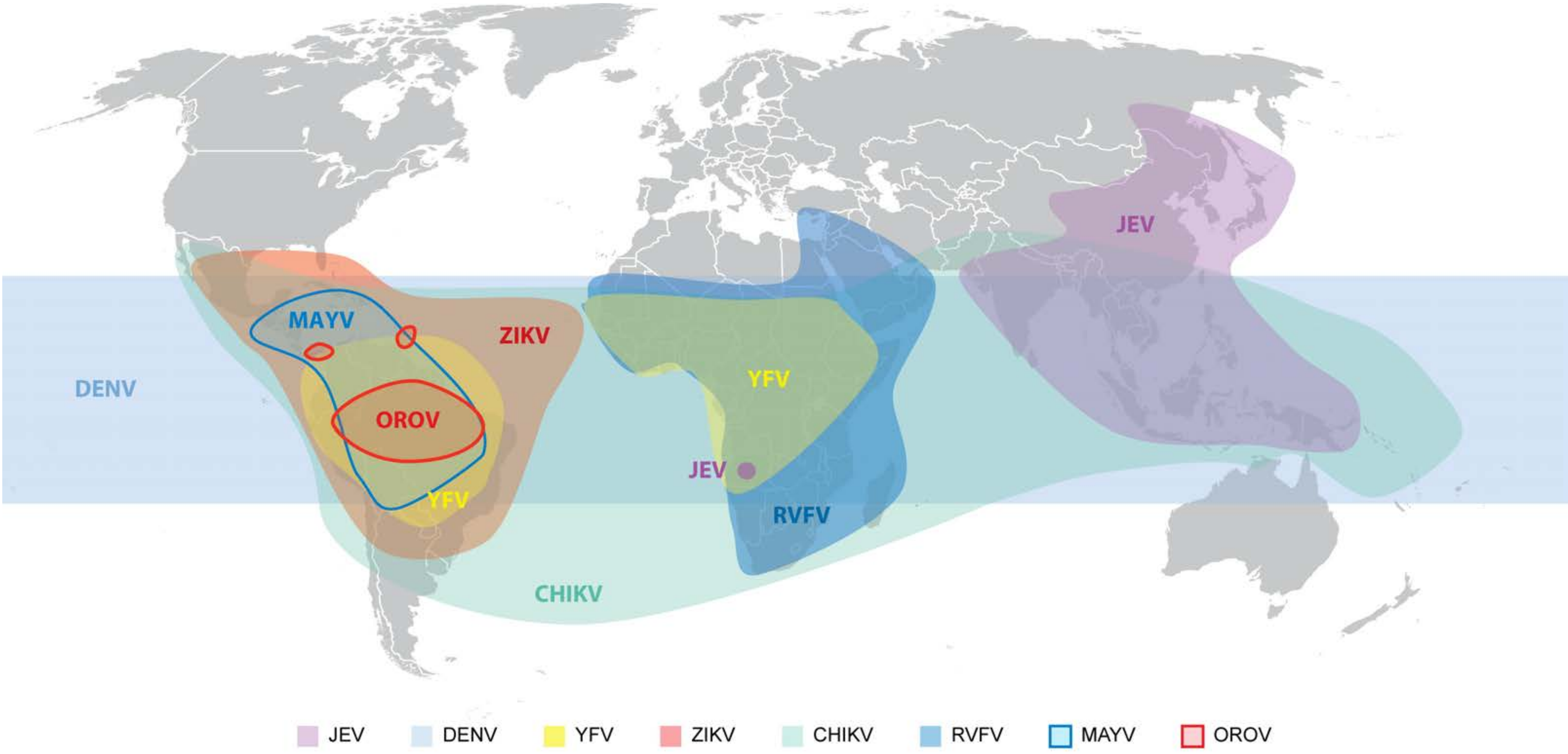
Des moustiques, des virus et des hommes



Louis Lambrechts

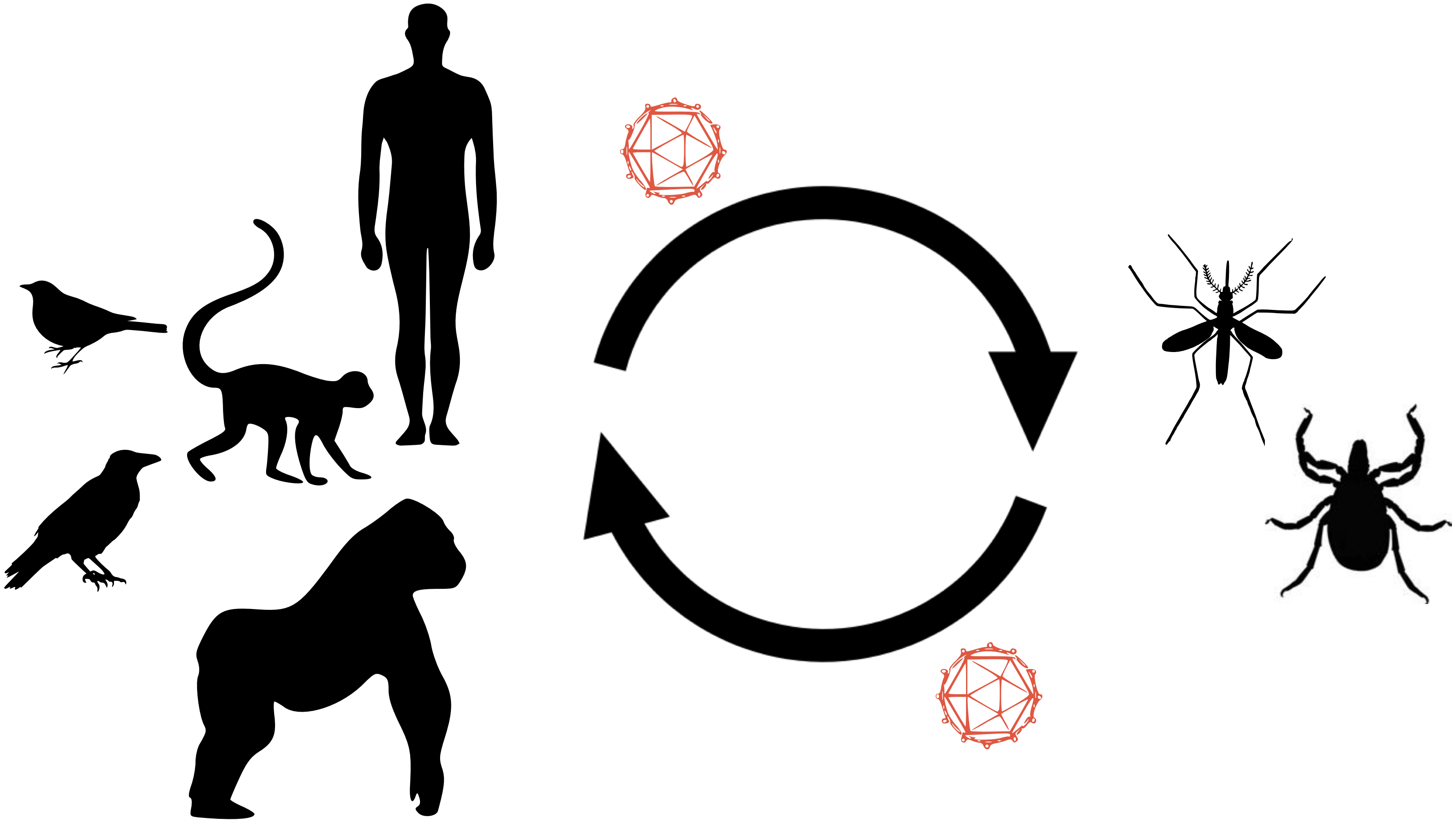
Unité Interactions Virus-Insectes, Institut Pasteur-CNRS UMR 2000, Paris, France
Laboratoire d'Excellence Biologie Intégrative des Maladies Infectieuses Emergentes

Emerging mosquito-borne viruses



Weaver *et al. Annu Rev Med* 2018

Arthropod-borne viruses (Arboviruses)



Outline

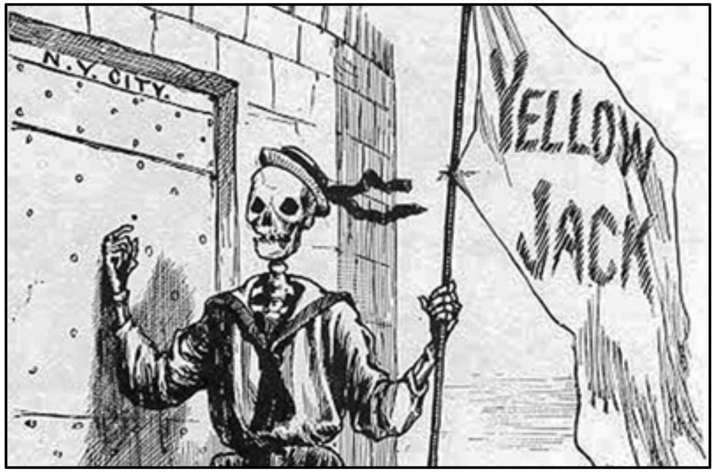
1. **Examples of emerging arboviruses**
   - Yellow fever
   - Dengue
   - Zika
2. **Factors underlying arbovirus emergence**
   - Globalization
   - Urbanization
   - Ineffective control
3. **Control of emerging arboviruses**
   - Conventional vector control
   - Innovative strategies

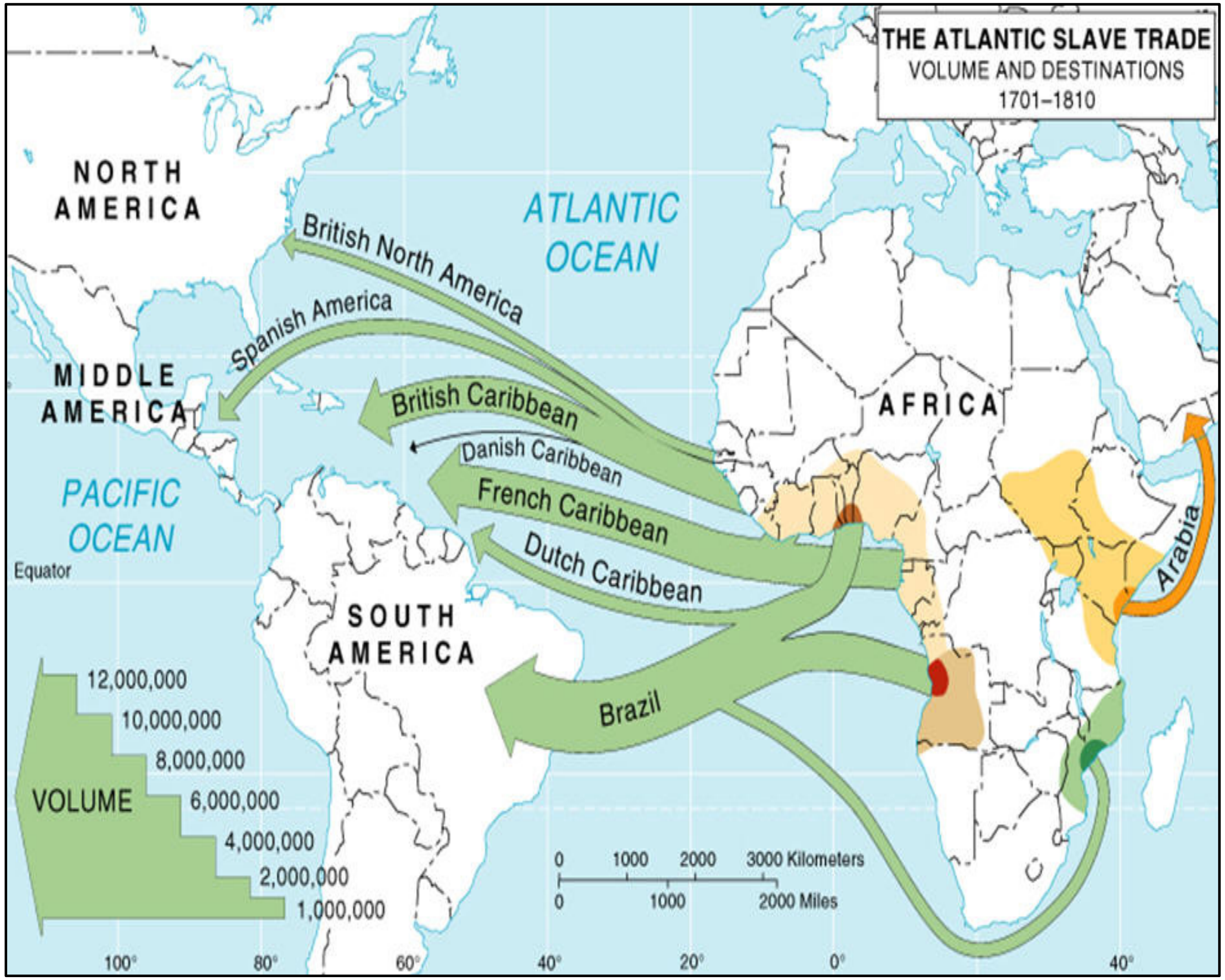
Outline

1. **Examples of emerging arboviruses**
    - Yellow fever
    - Dengue
    - Zika
2. **Factors underlying arbovirus emergence**
    - Globalization
    - Urbanization
    - Ineffective control
3. **Control of emerging arboviruses**
    - Conventional vector control
    - Innovative strategies

Yellow fever virus (YFV)

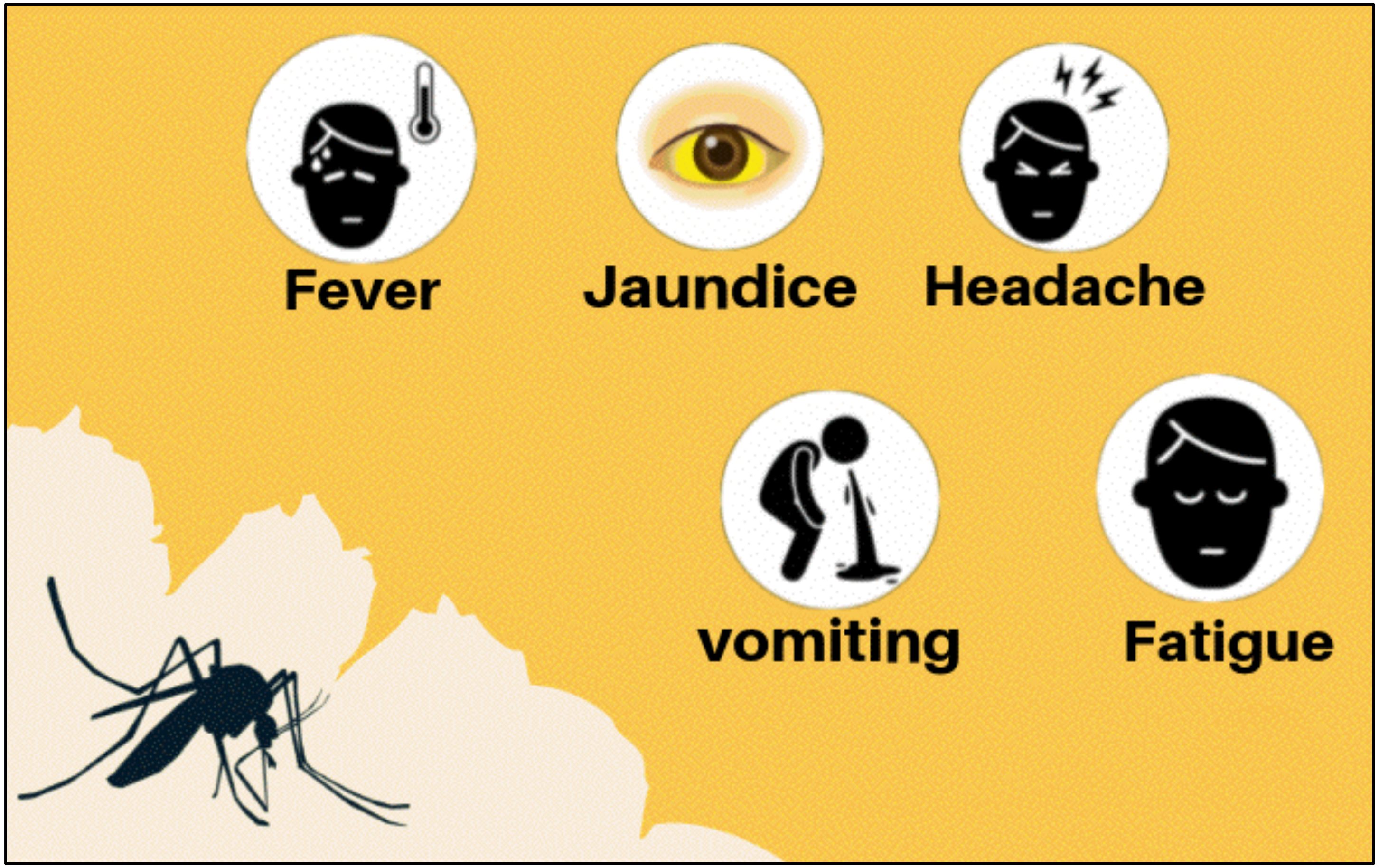
- Originally from tropical Africa
- Subsequently established in South America





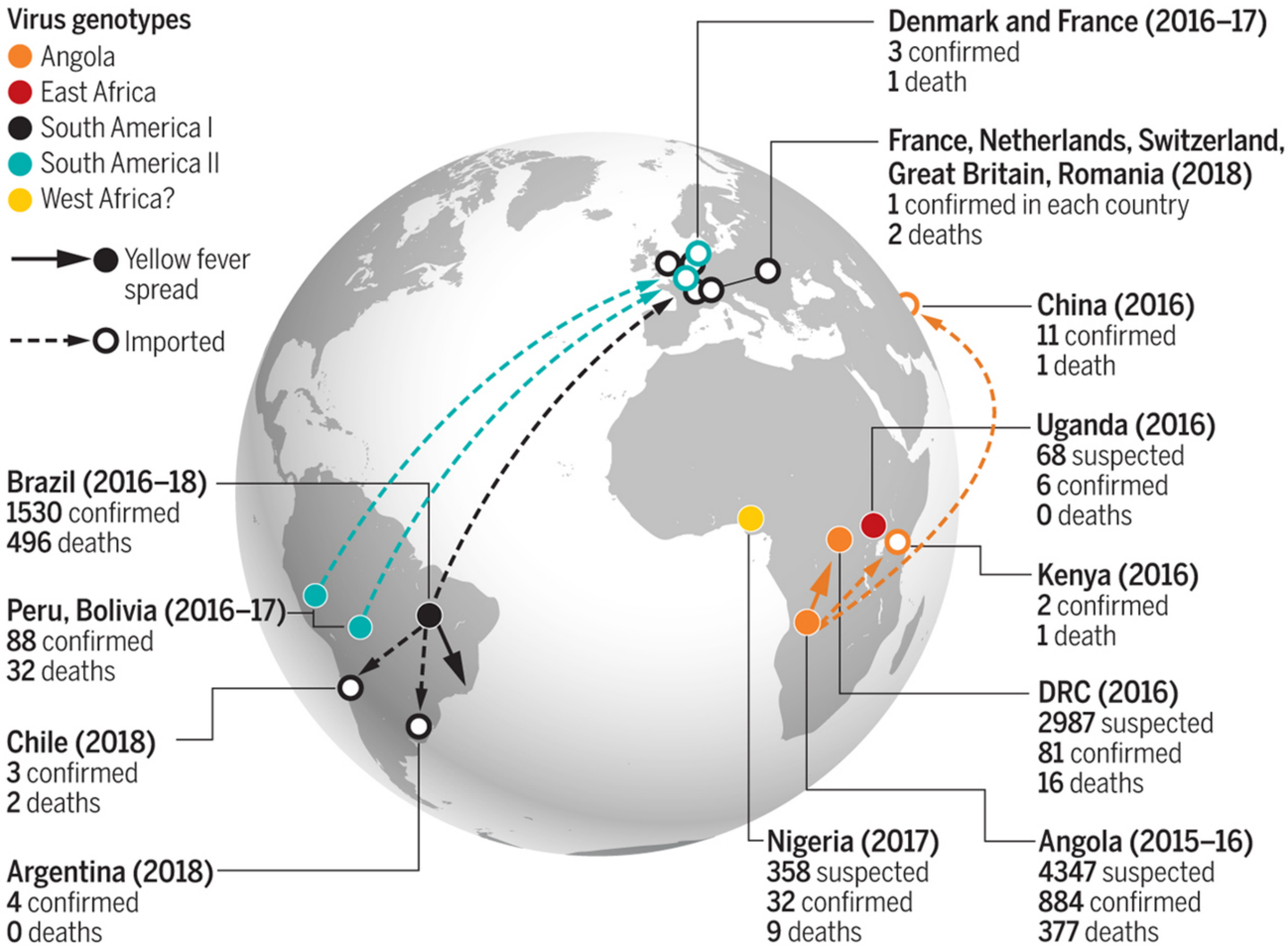
Yellow fever

- Hemorrhagic fever
- Case-fatality rate up to 50%
- 200,000 cases /year
- 30,000 deaths /year



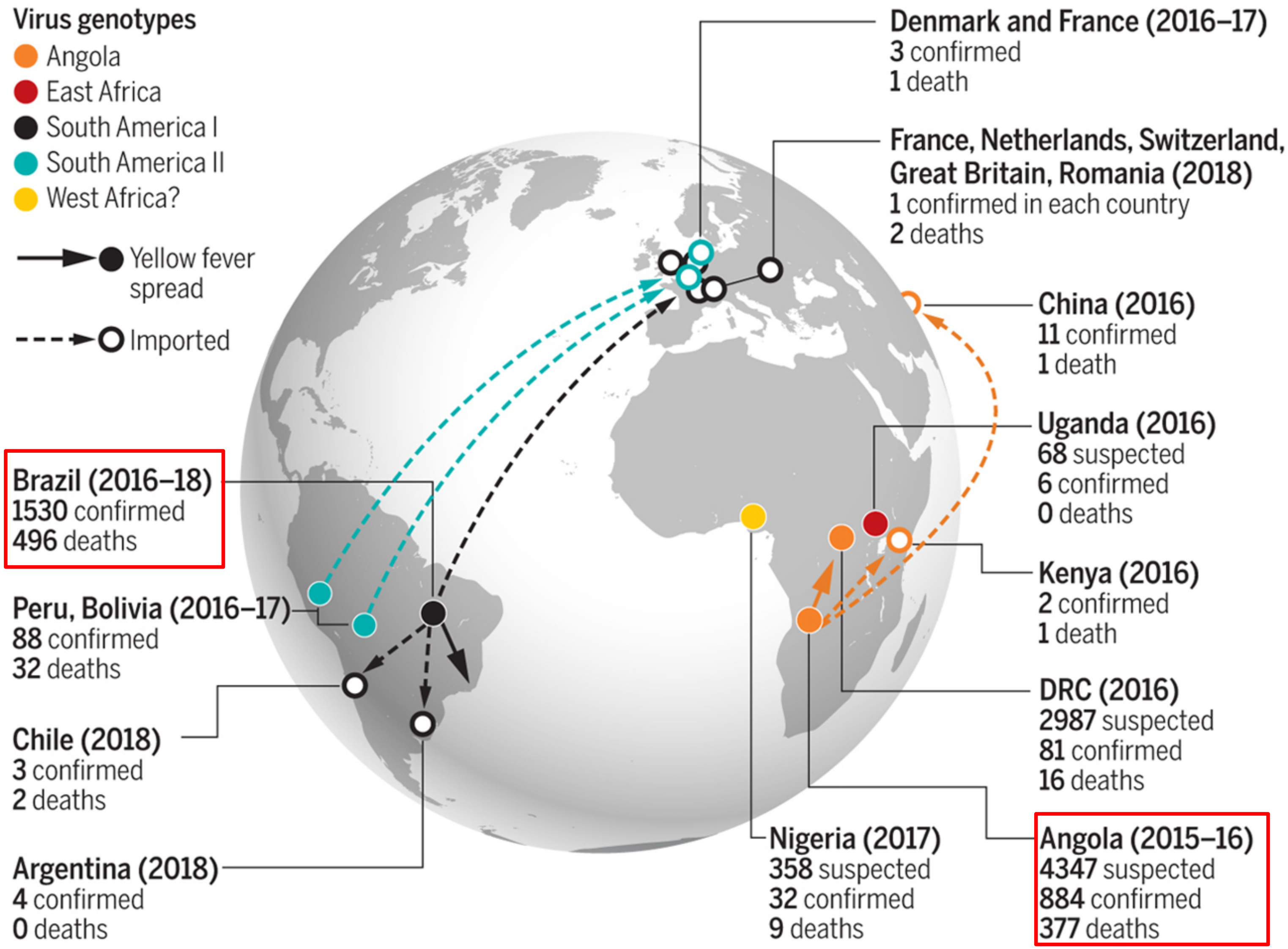
WHO

Yellow fever outbreaks 2016-2018



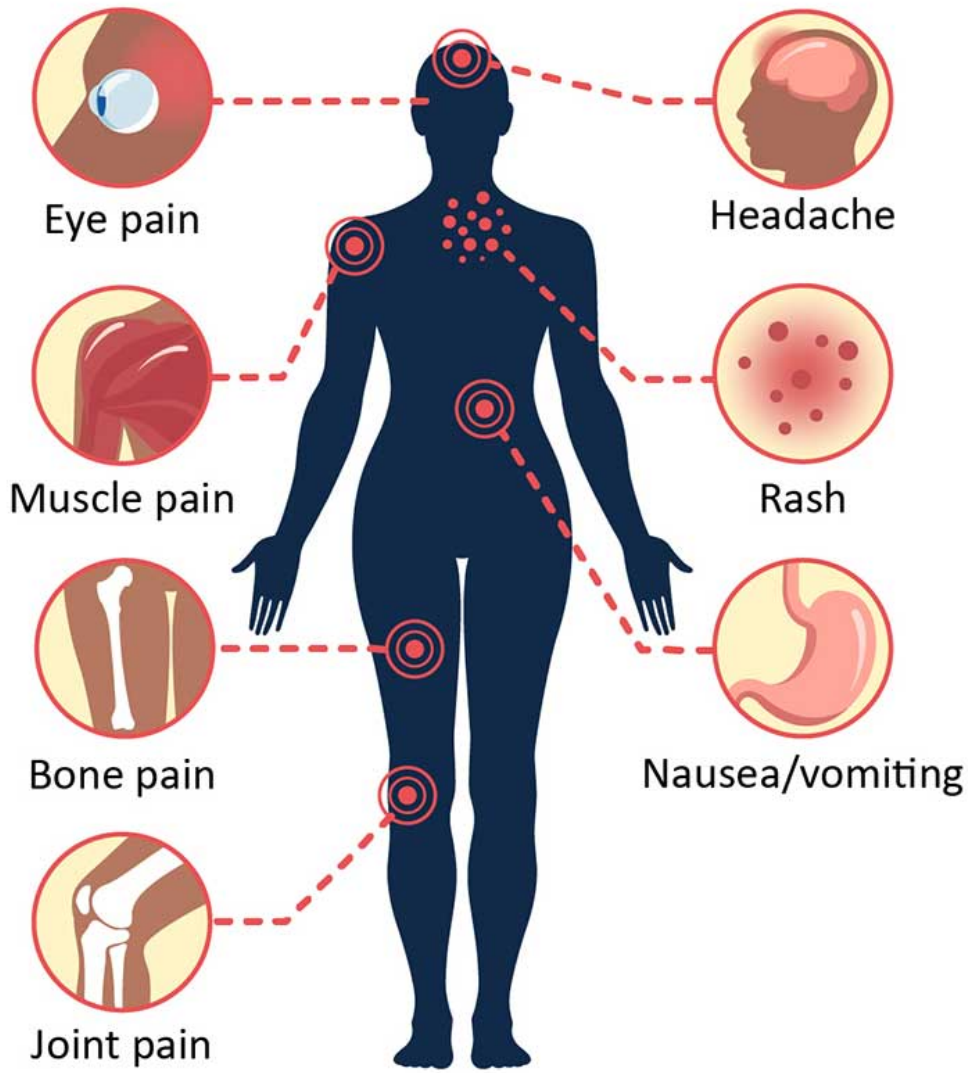
Barrett *Science* 2018

Yellow fever outbreaks 2016-2018



Barrett *Science* 2018

Dengue fever



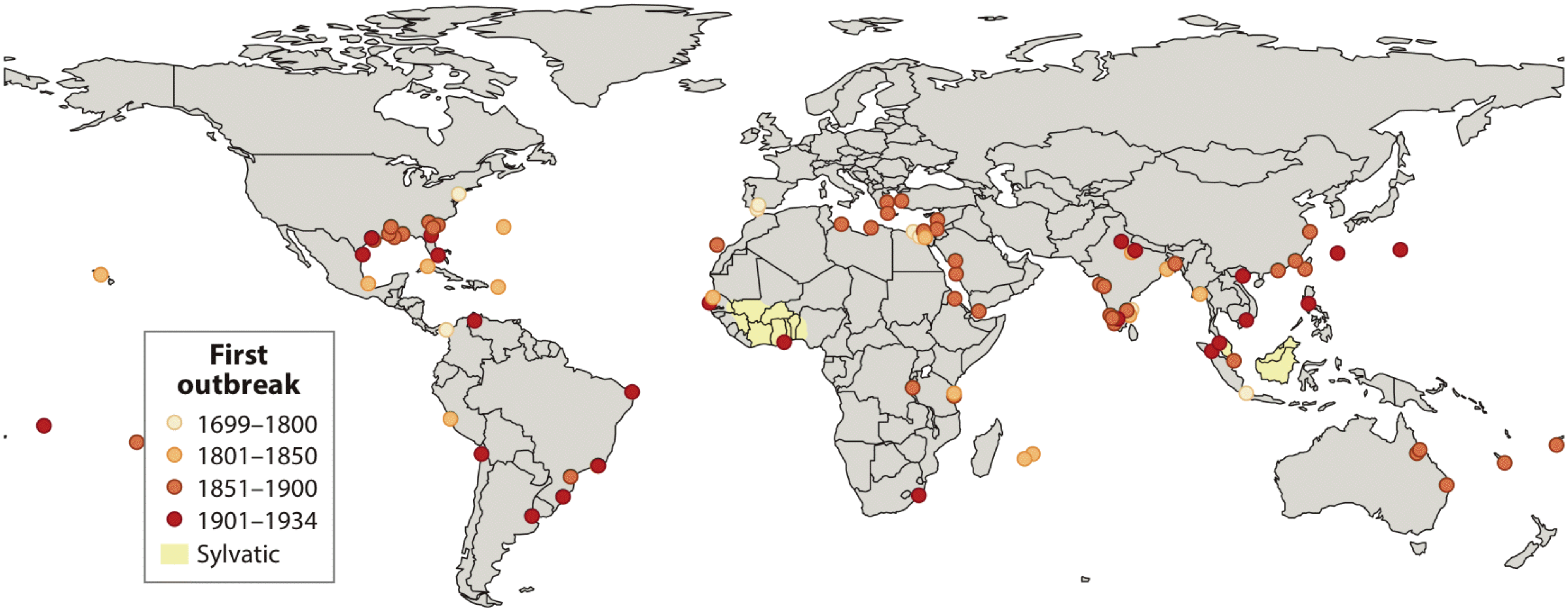
- 4 billion people at risk
- 100 million cases /year
- 20,000 deaths /year

DENV-1, -2, -3, and -4

- Genetically close but distinct
- Immunologically cross-reactive

DENV global emergence

1. First urban outbreaks in port cities increasing after 18th century

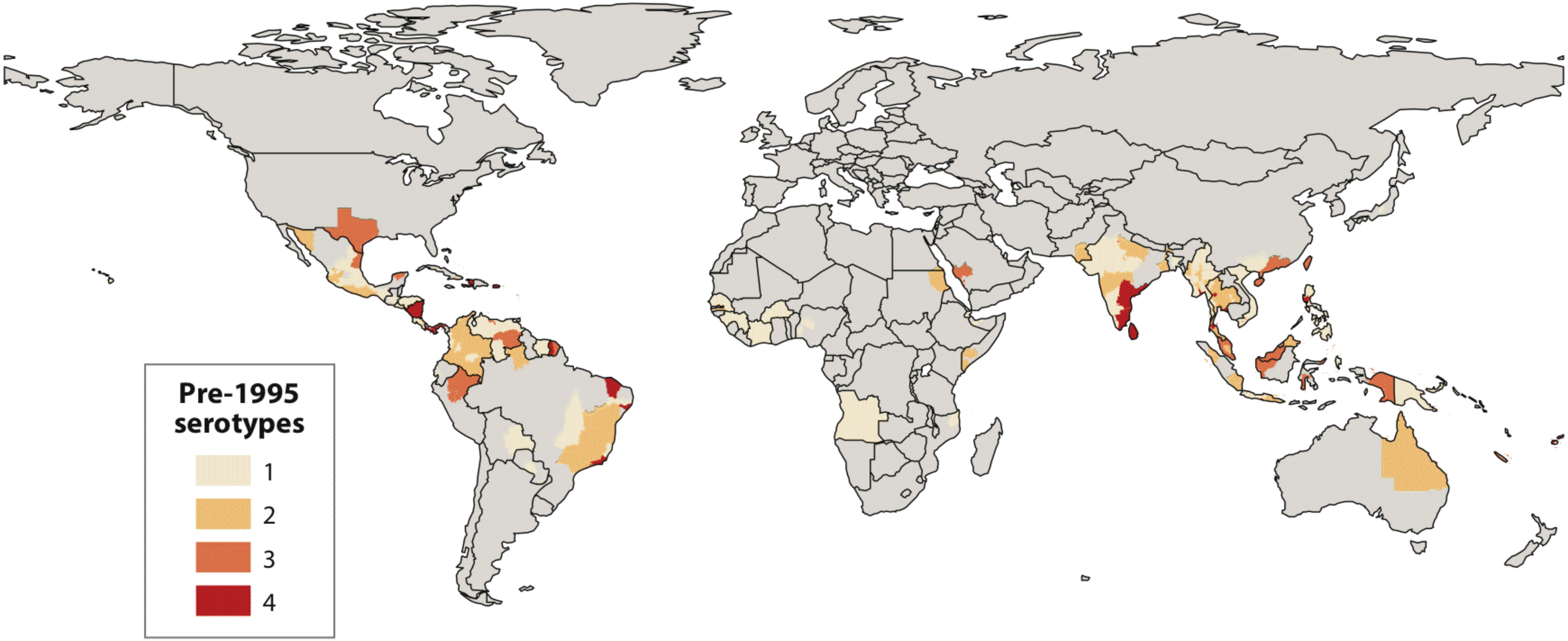


Cities with evidence of dengue-like illness prior to 1945

Brady & Hay *Annu Rev Entomol* 2020

DENV global emergence

2. Co-circulation of serotypes and emergence of hemorrhagic dengue

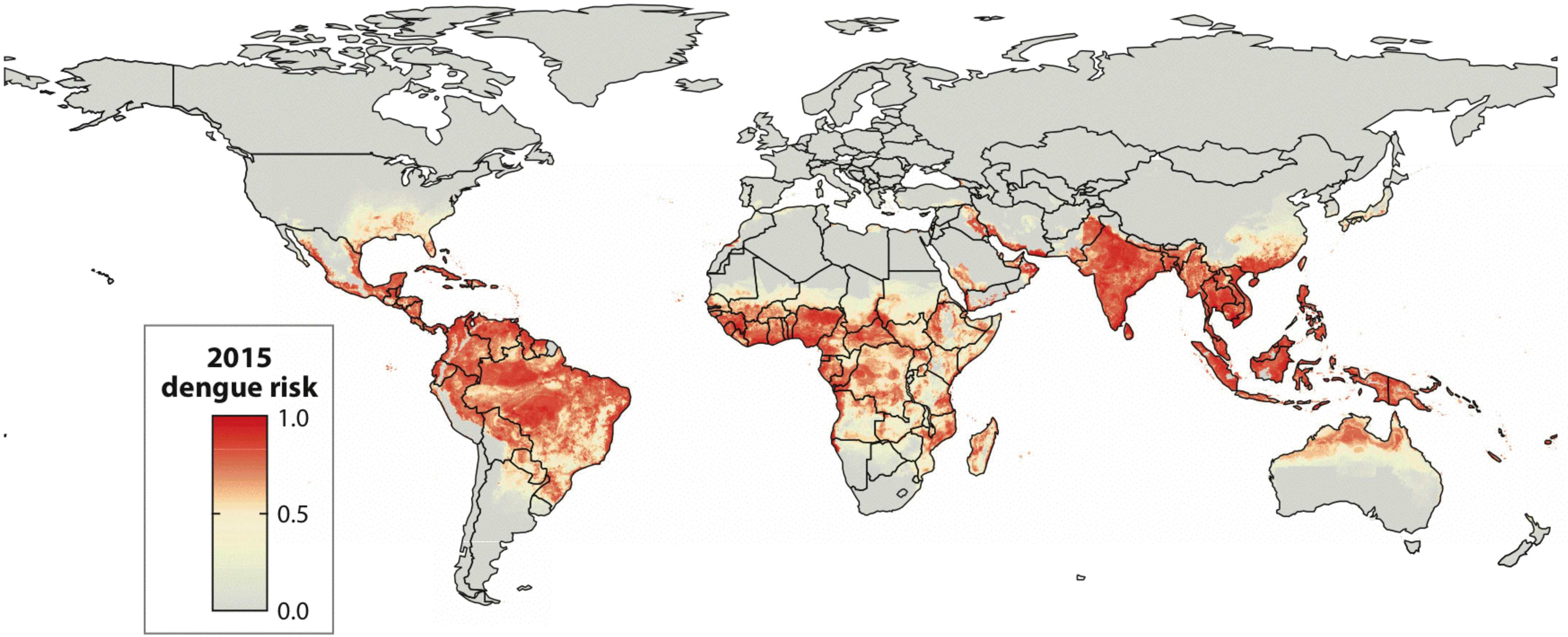


Cumulative number of DENV serotypes during 1945-1994

Brady & Hay *Annu Rev Entomol* 2020

DENV global emergence

3. Consolidation throughout tropical belt and into rural areas

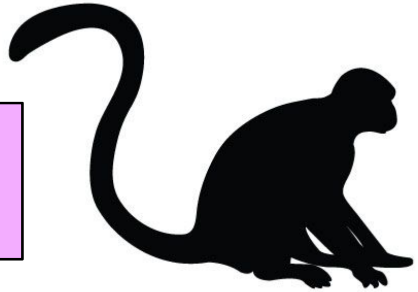


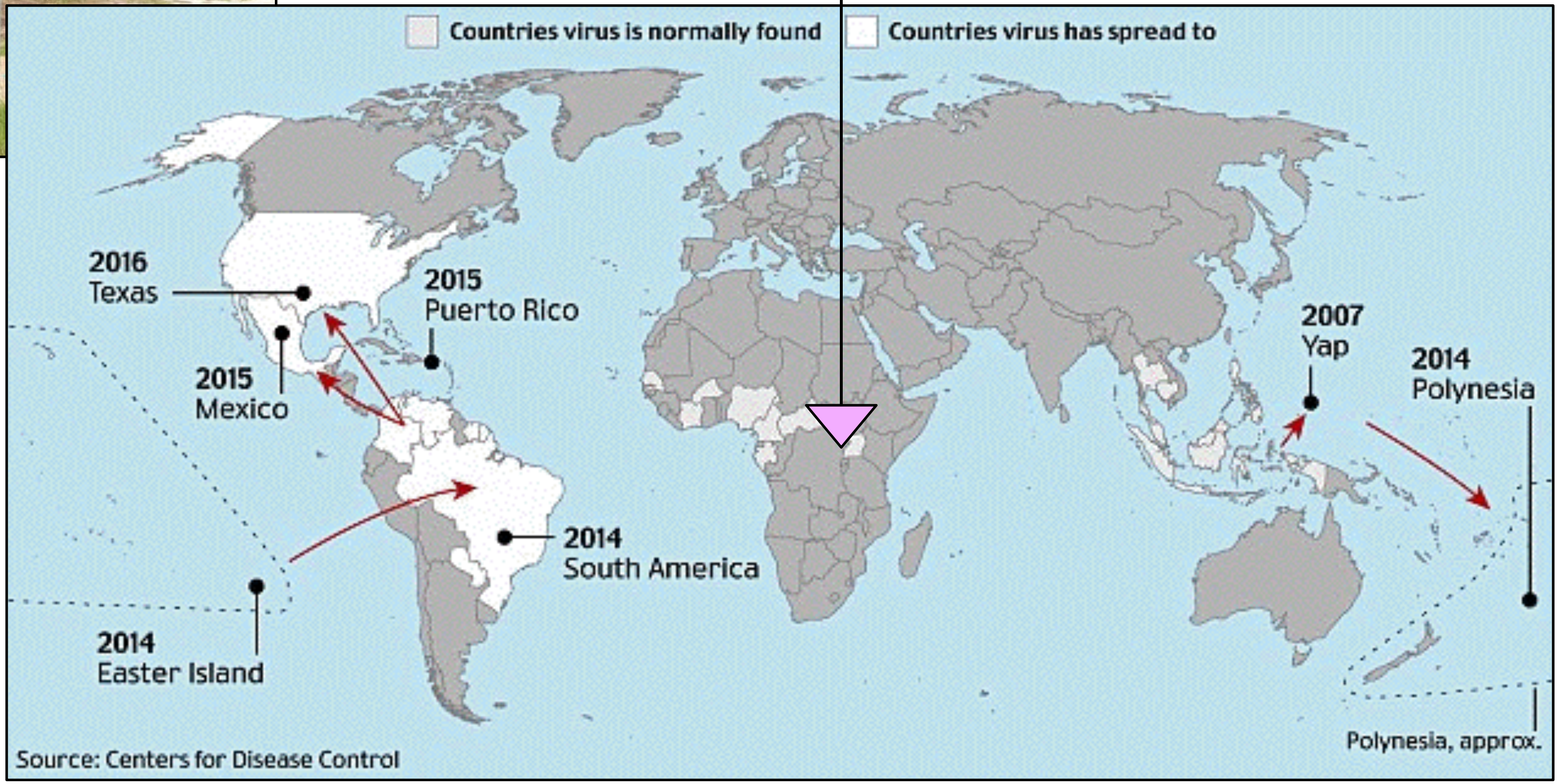
Contemporary predicted global distribution of dengue risk

Brady & Hay *Annu Rev Entomol* 2020

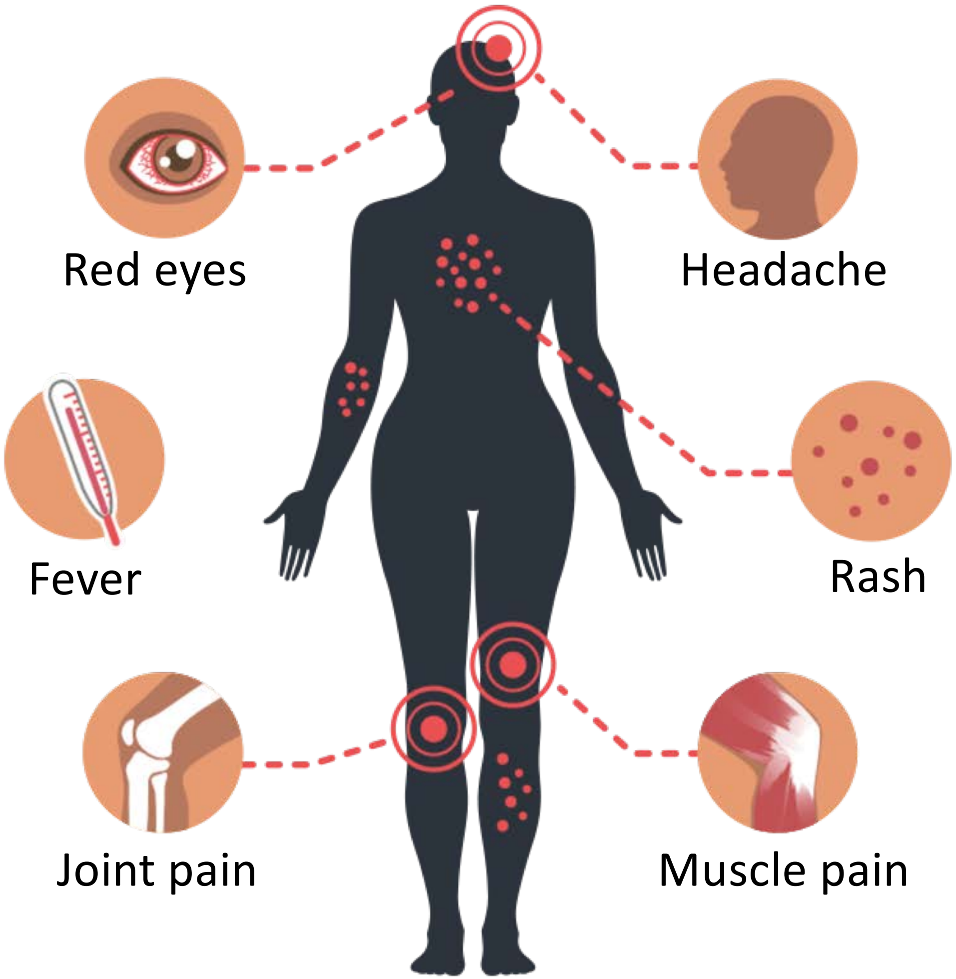
Global Zika virus (ZIKV) emergence

1st isolation
Uganda 1947





ZIKV clinical features



Infection

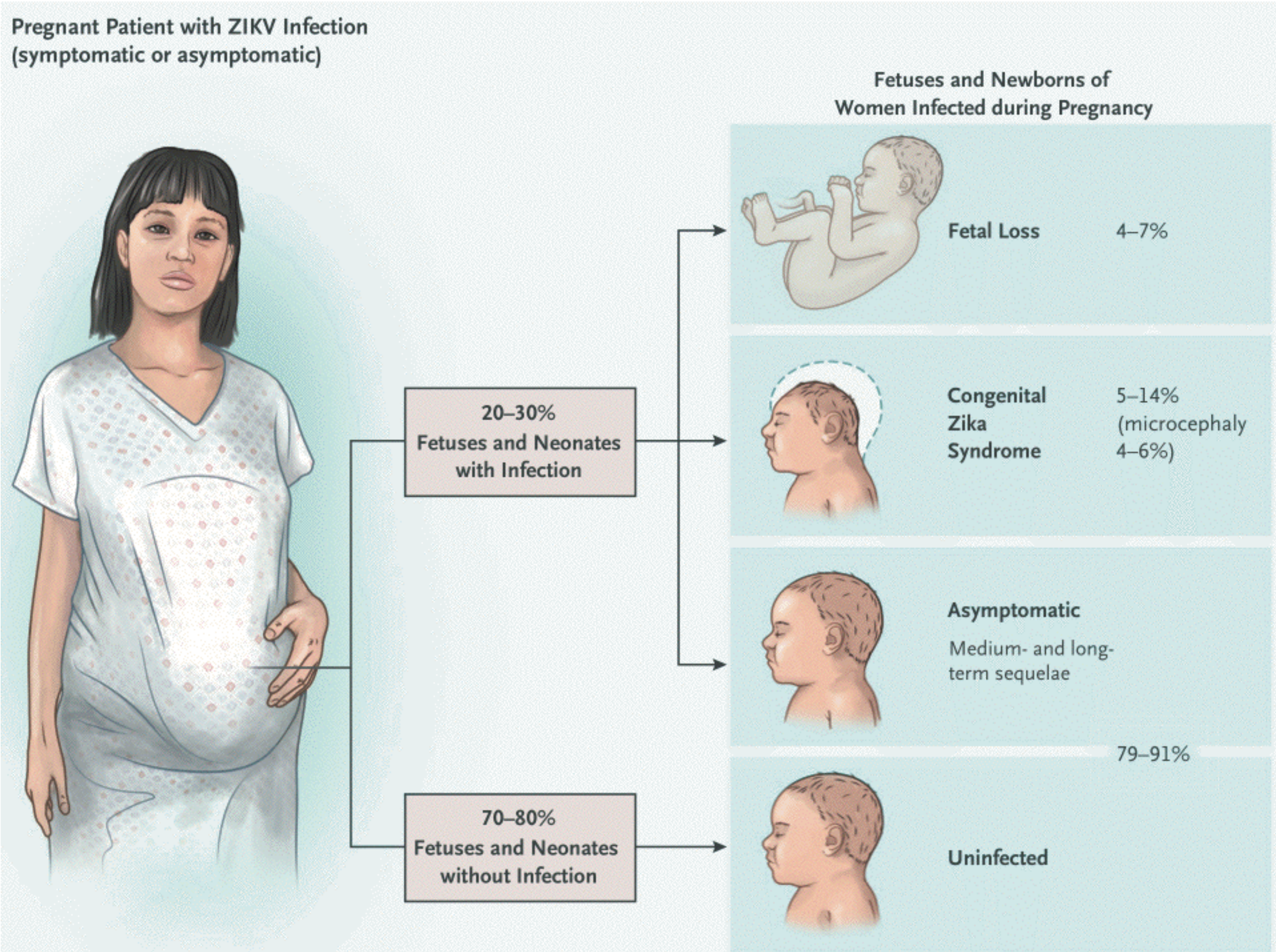
- Mosquito-borne
- Sexual
- Pregnancy

Disease

- Asymptomatic 50-80%
- Mild disease 20-50%
- Severe complications <1%
- Case-fatality rate <0.01%

Musso et al. *NEJM* 2019

ZIKV-associated fetal and birth defects

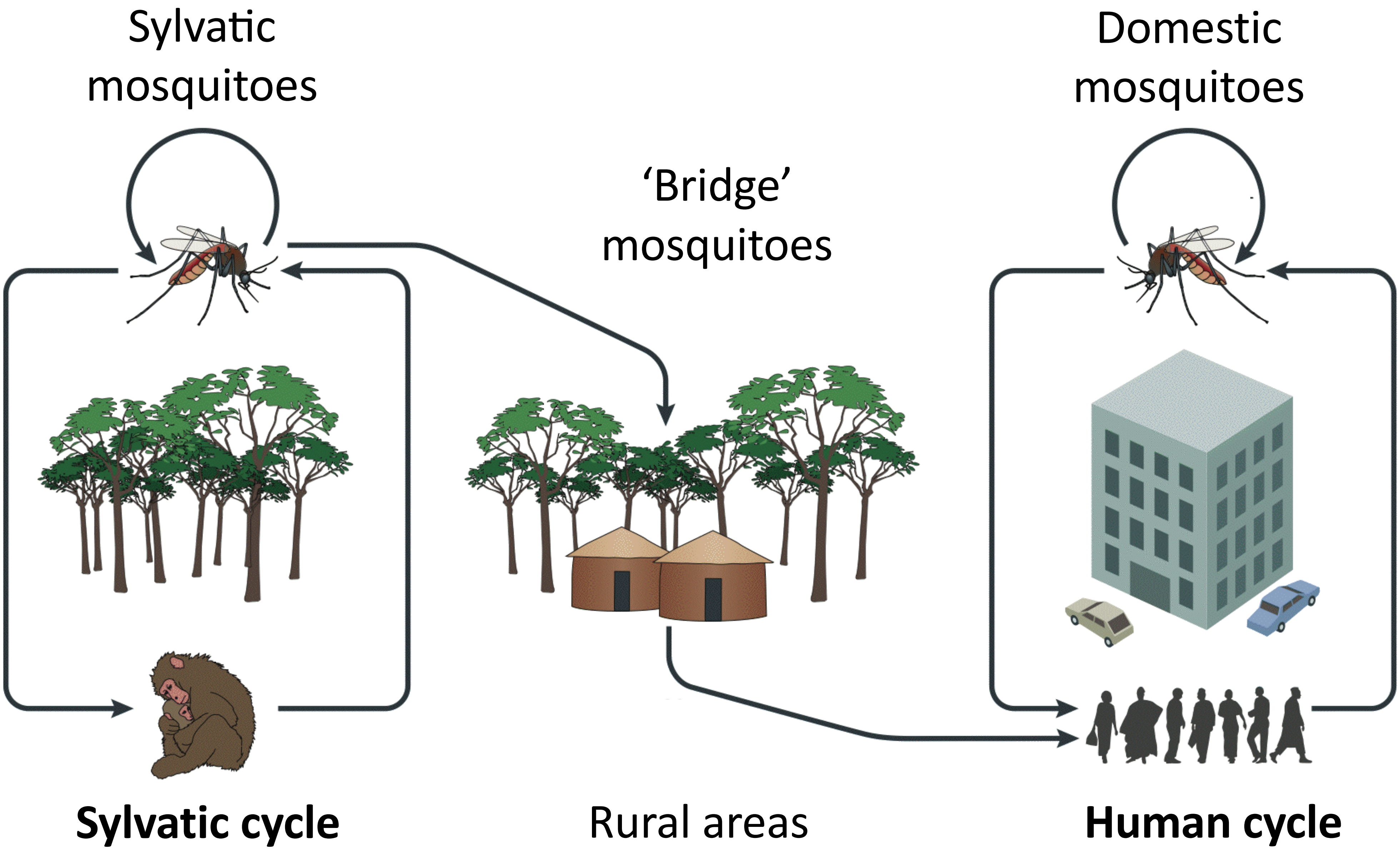


Musso et al. *NEJM* 2019

Outline

1. **Examples of emerging arboviruses**
   - Yellow fever
   - Dengue
   - Zika
2. **Factors underlying arbovirus emergence**
   - Globalization
   - Urbanization
   - Ineffective control
3. **Control of emerging arboviruses**
   - Conventional vector control
   - Innovative strategies

Arbovirus transmission cycles



Vasilakis *et al. Nat Rev Microbiol* 2011

Factors driving arbovirus emergence

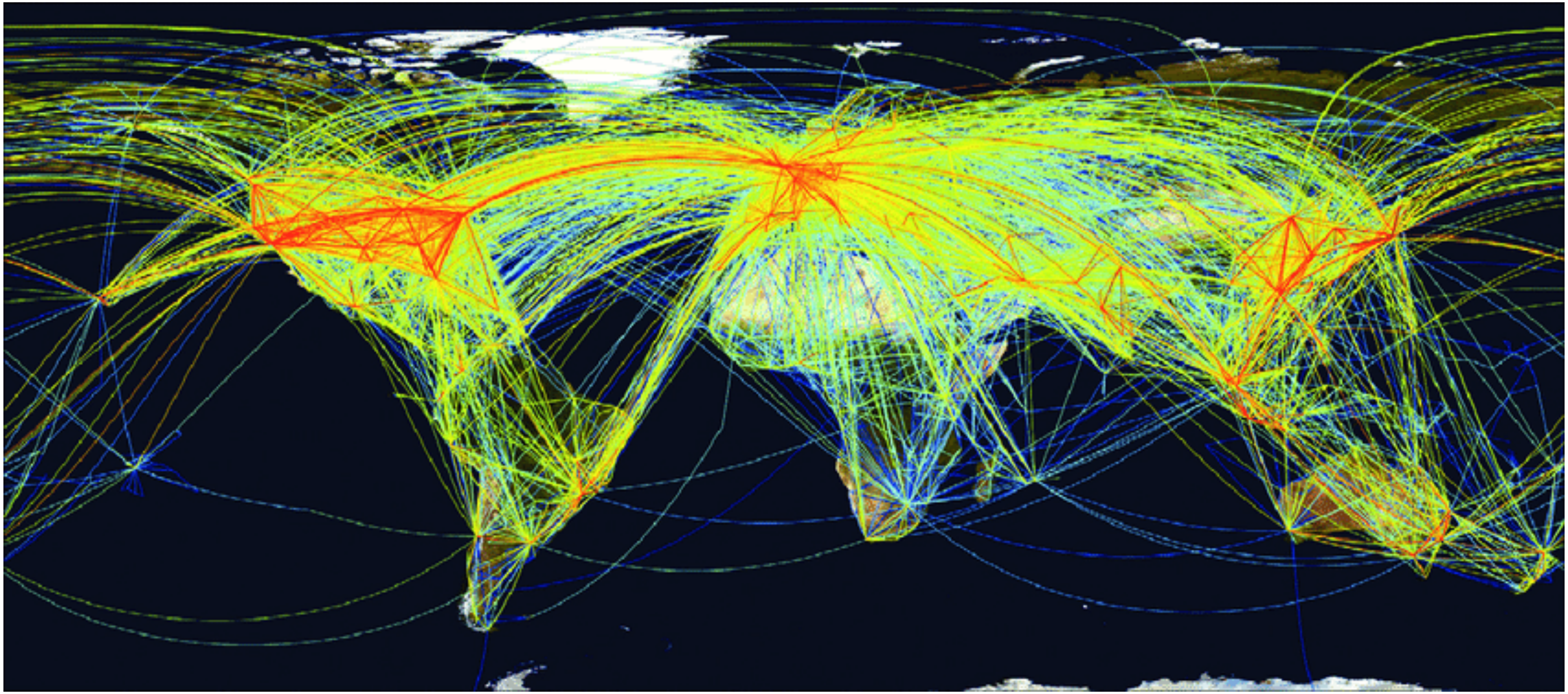
Globalization

Urbanization

Limited prevention methods:

- Few licensed vaccines
- Pesticide-based control of vector populations difficult to sustain

Global aviation network

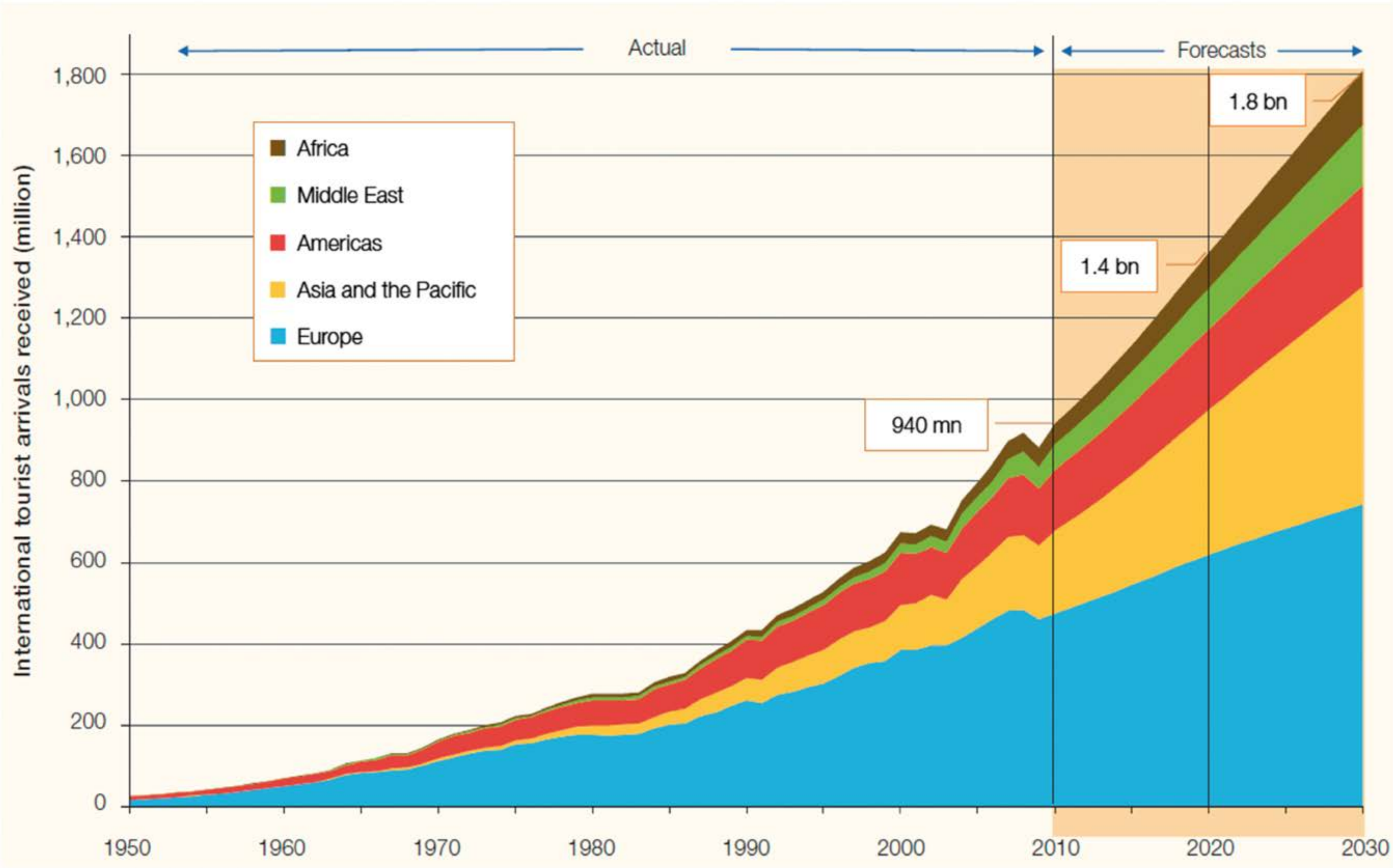


Lines show direct links between airports and passenger capacity

- Red: >1000 passengers/day
- Yellow: >100 passengers/day
- Blue: >10 passengers/day

Kilpatrick & Randolph *Lancet* 2012

International tourist arrivals



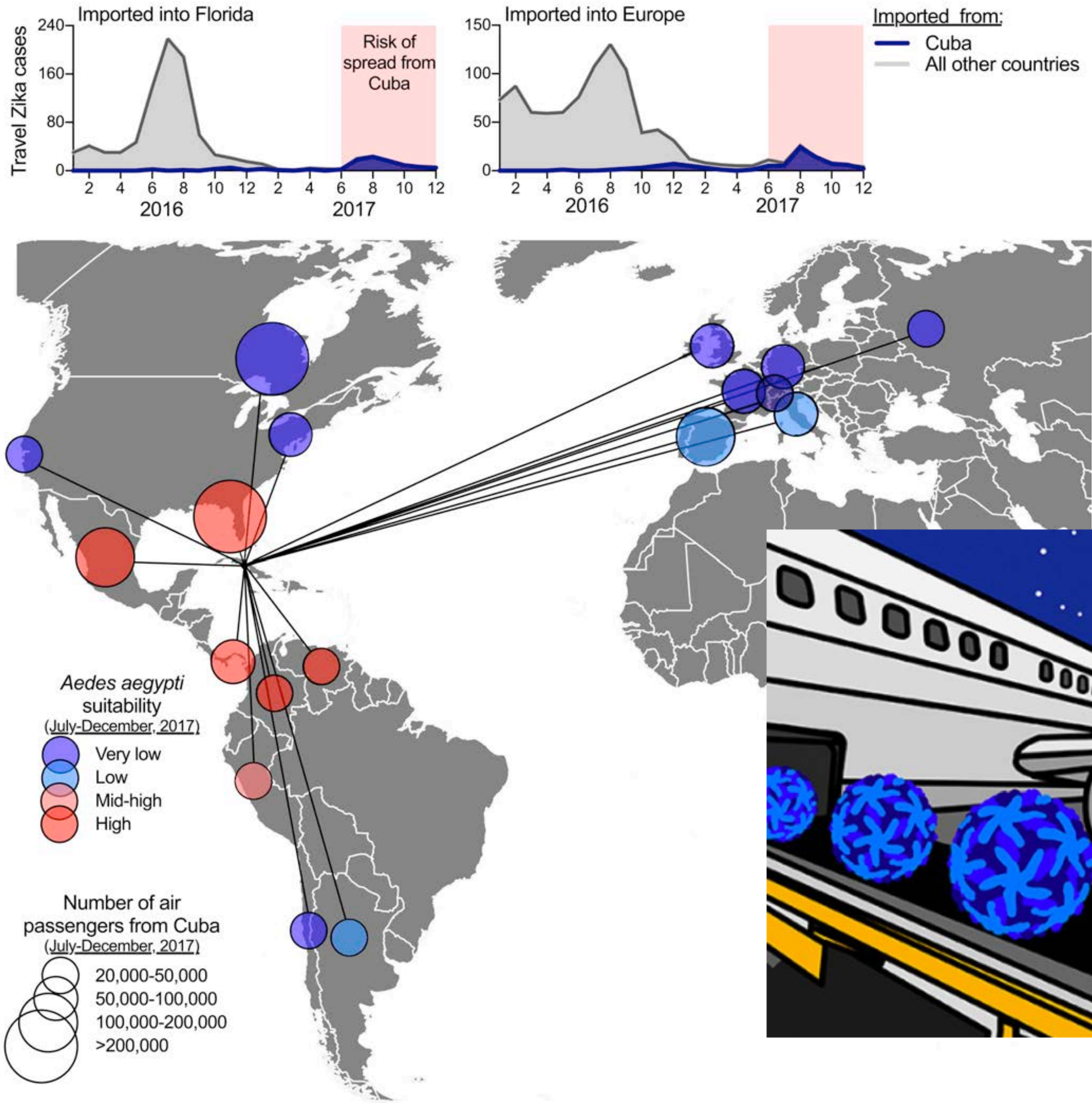
Source: UNWTO (2016a)

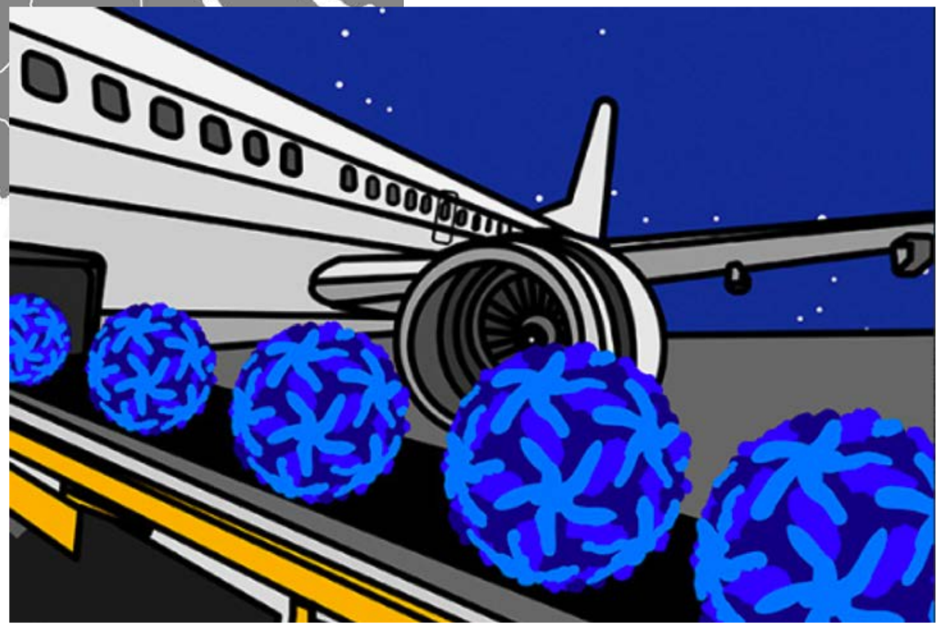
Glaesser *et al. J Travel Med* 2017

International travel mediates arbovirus dispersal

www.grubaughlab.com

Travel surveillance uncovers ZIKV outbreak in Cuba

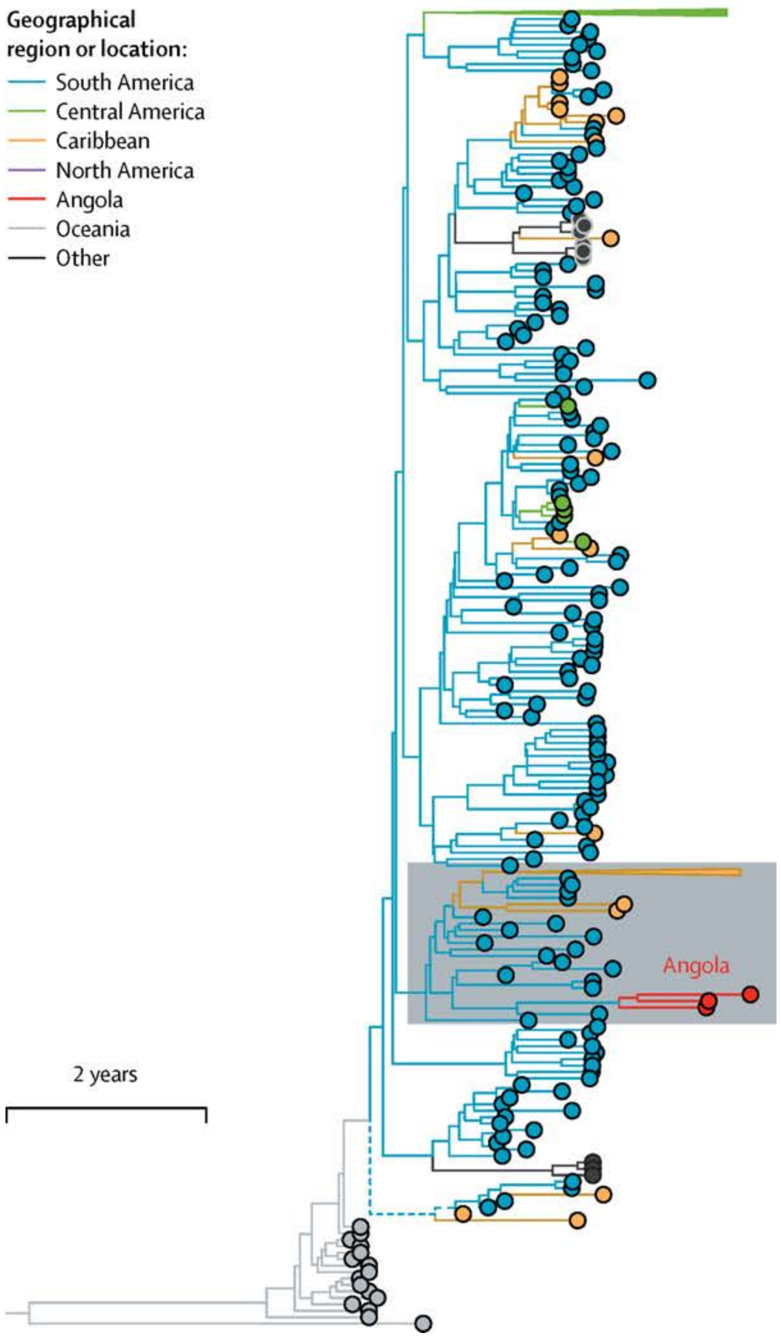




>98% of all travel-associated Zika cases during June–December 2017 came from Cuba

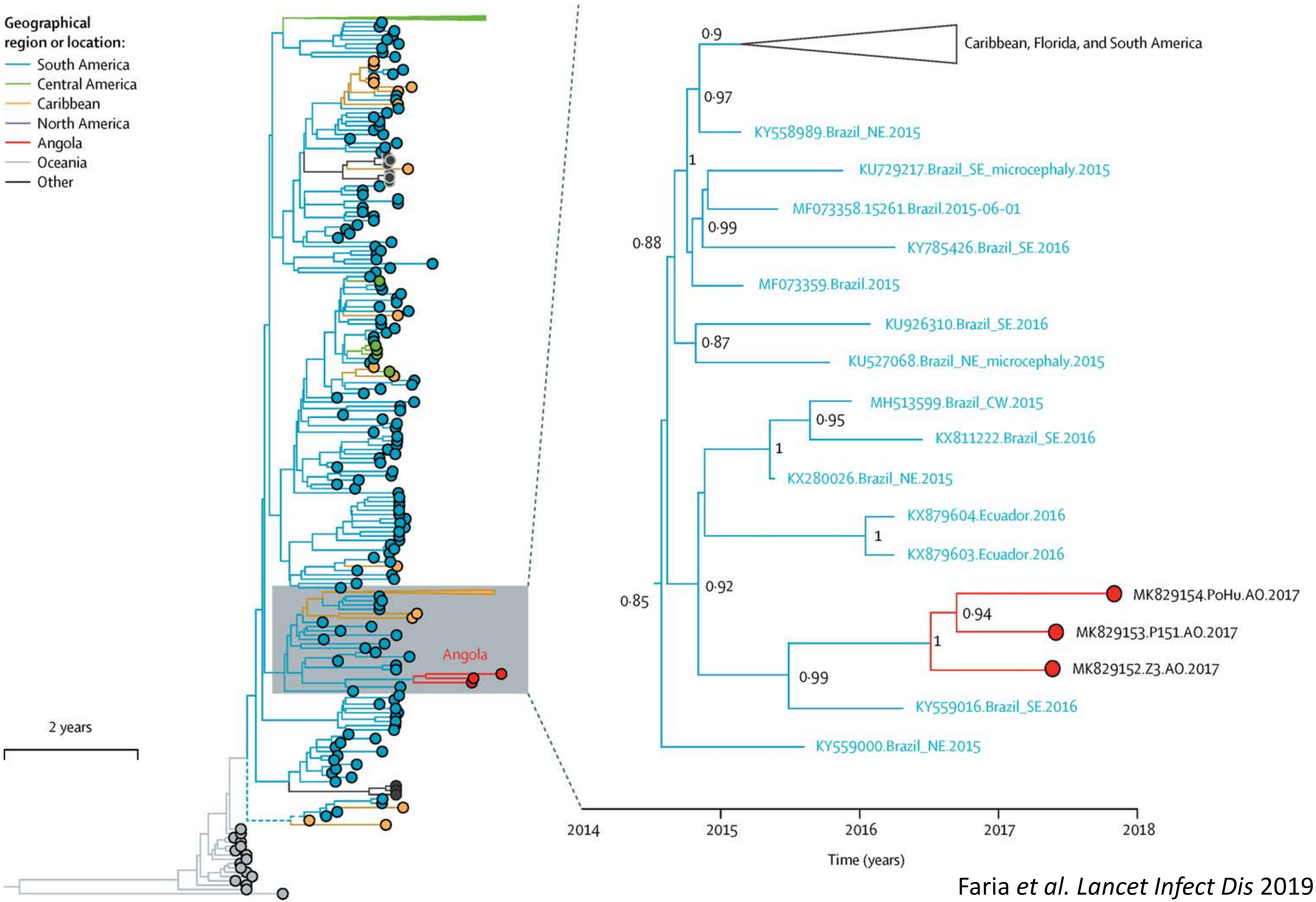
Grubaugh *et al. Cell* 2019

ZIKV introduction into Angola from Brazil



Faria *et al. Lancet Infect Dis* 2019

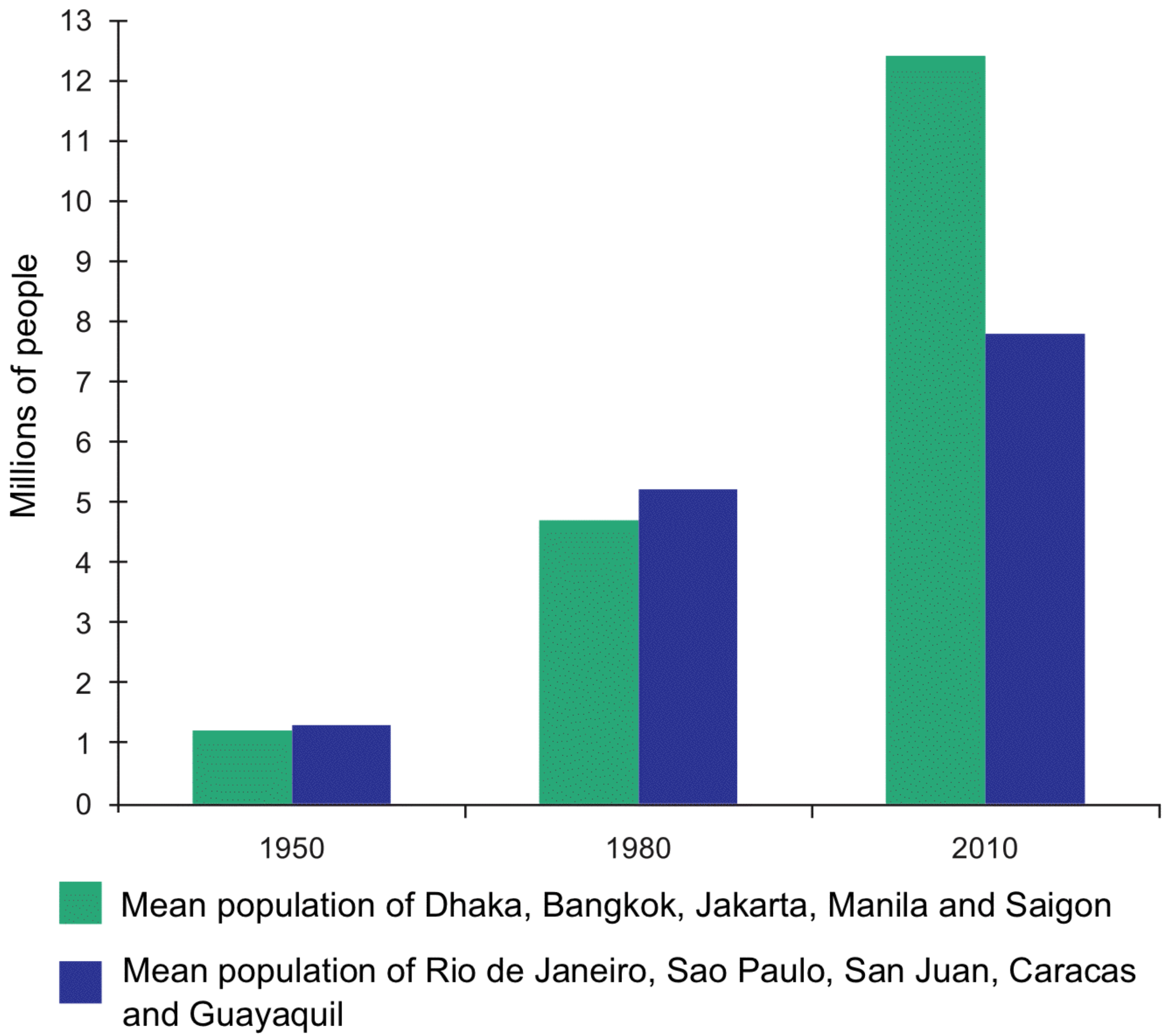
ZIKV introduction into Angola from Brazil



Faria *et al. Lancet Infect Dis* 2019

Urbanization

Urban growth in tropical megacities



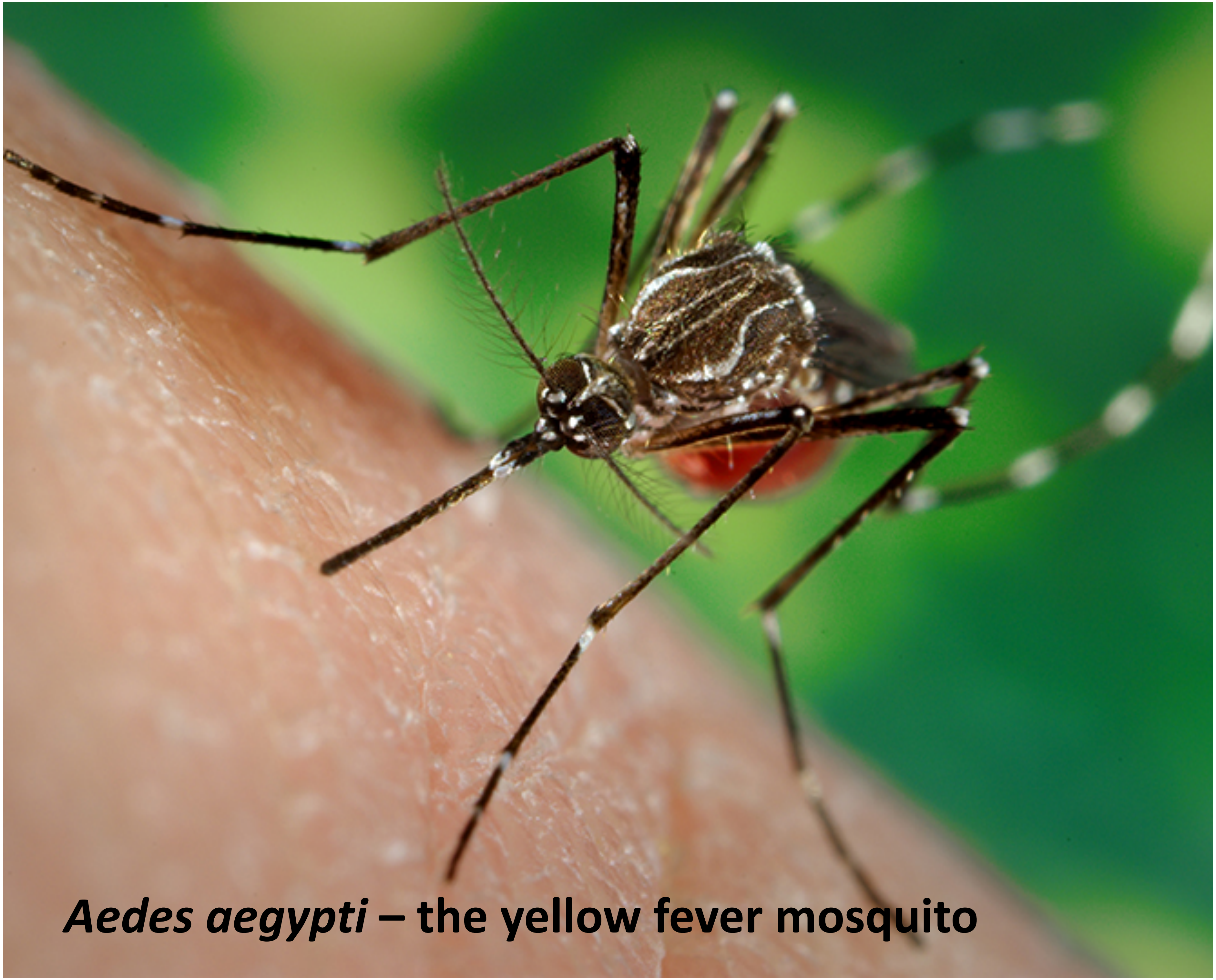
Gubler *Trop Med Health* 2011

Domestic *Aedes* vectors of arboviruses

Aedes aegypti

Aedes albopictus

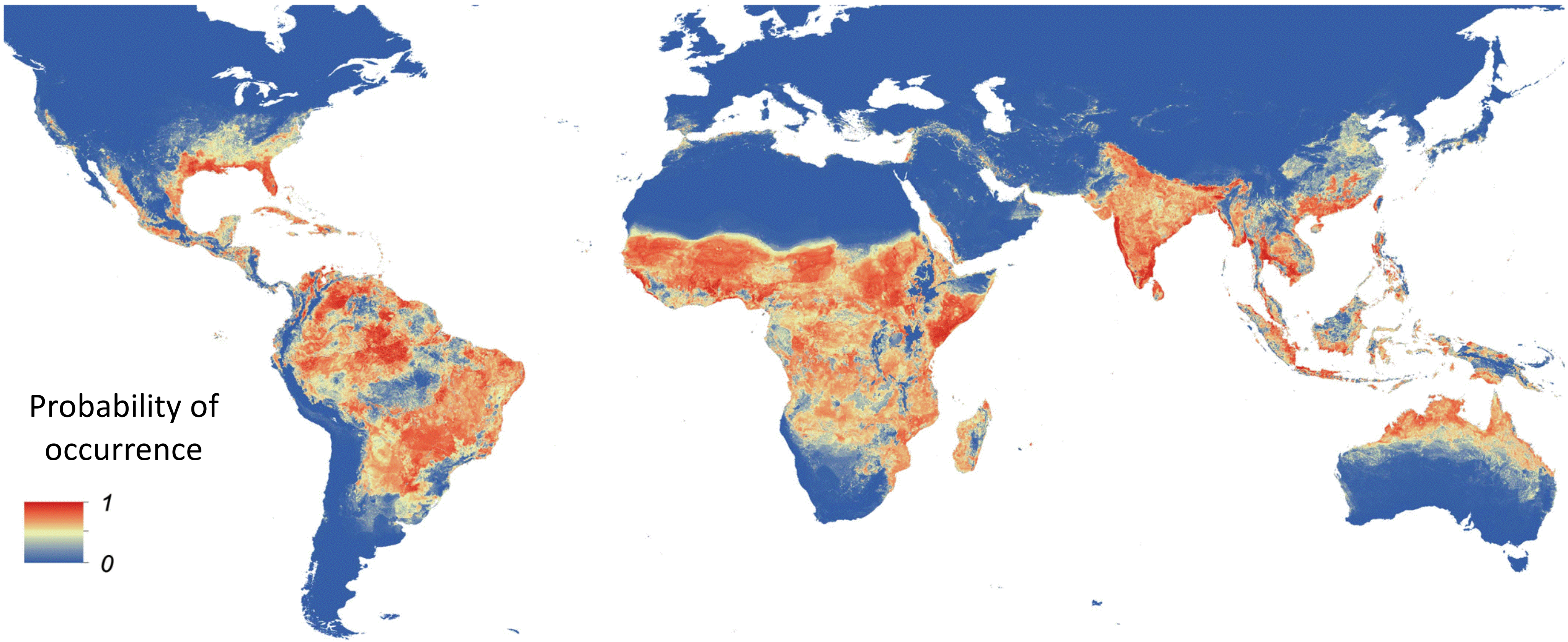
- Thrive in the human environment
- Breed in artificial containers
- Feed on humans preferentially
- Bite during daytime
- Lay dessication-resistant eggs



Aedes aegypti **– the yellow fever mosquito**

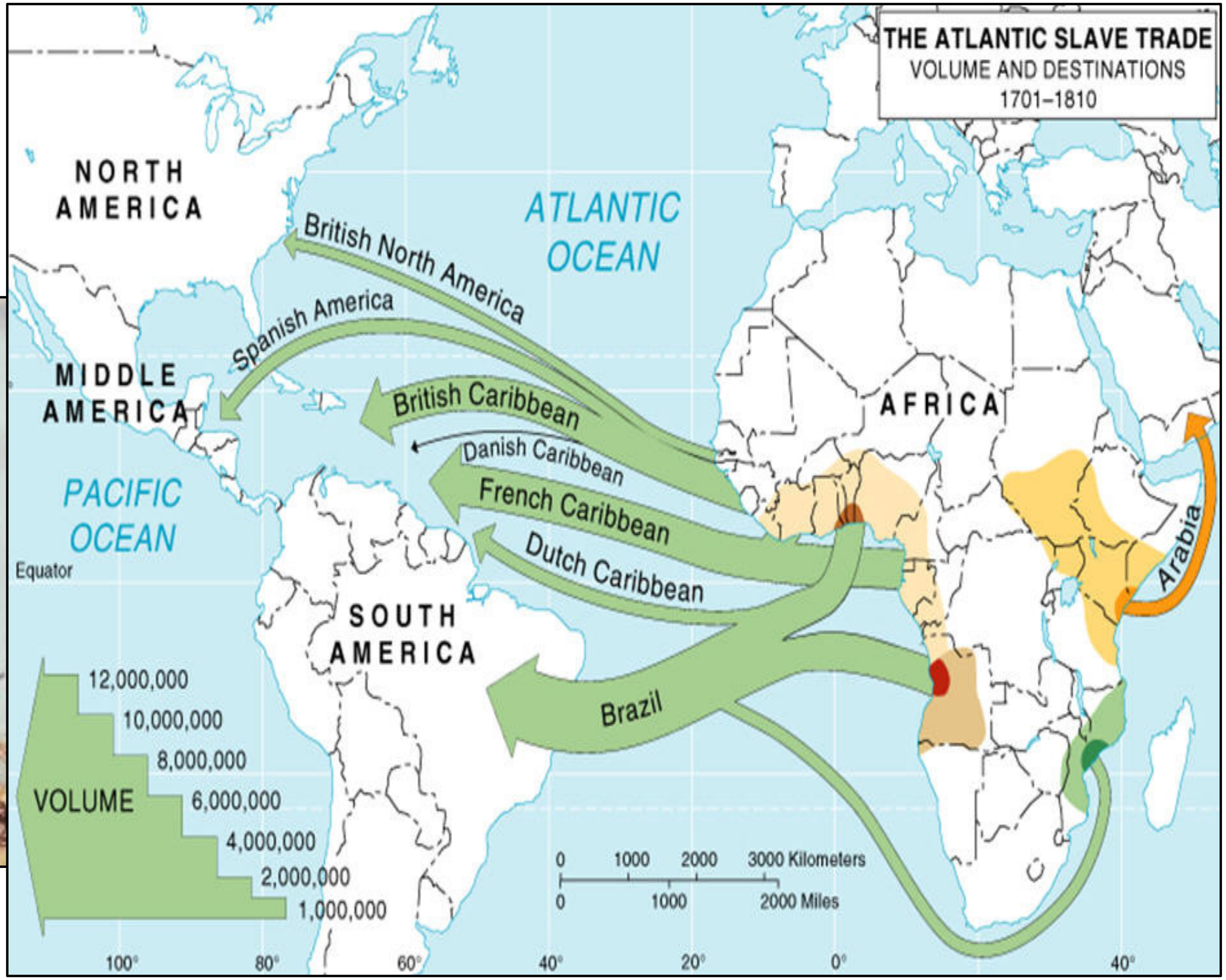
Aedes aegypti

- Originally from Africa
- Spread out in the last few centuries
- Found in tropical and sub-tropical regions

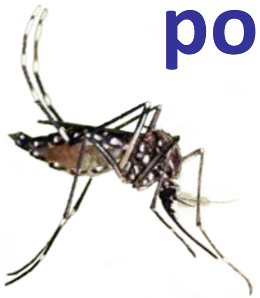


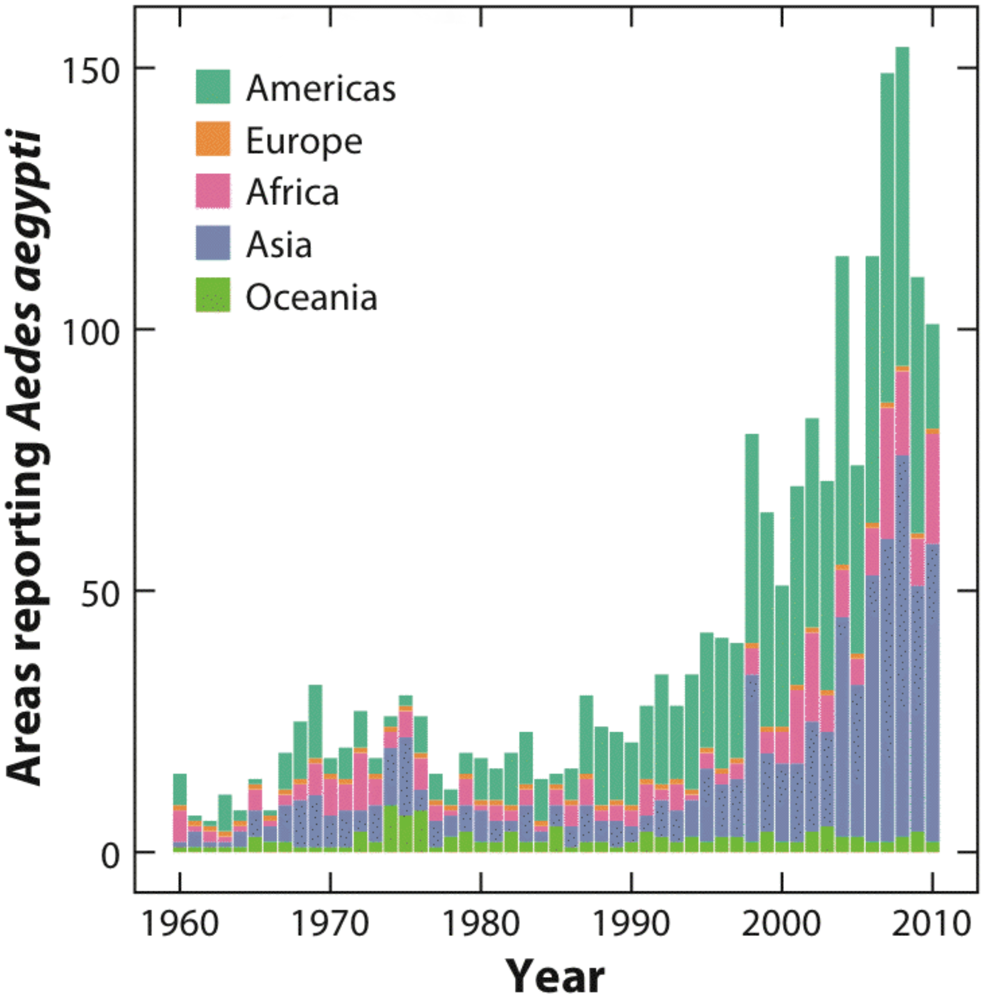
Kraemer *et al. Elife* 2015

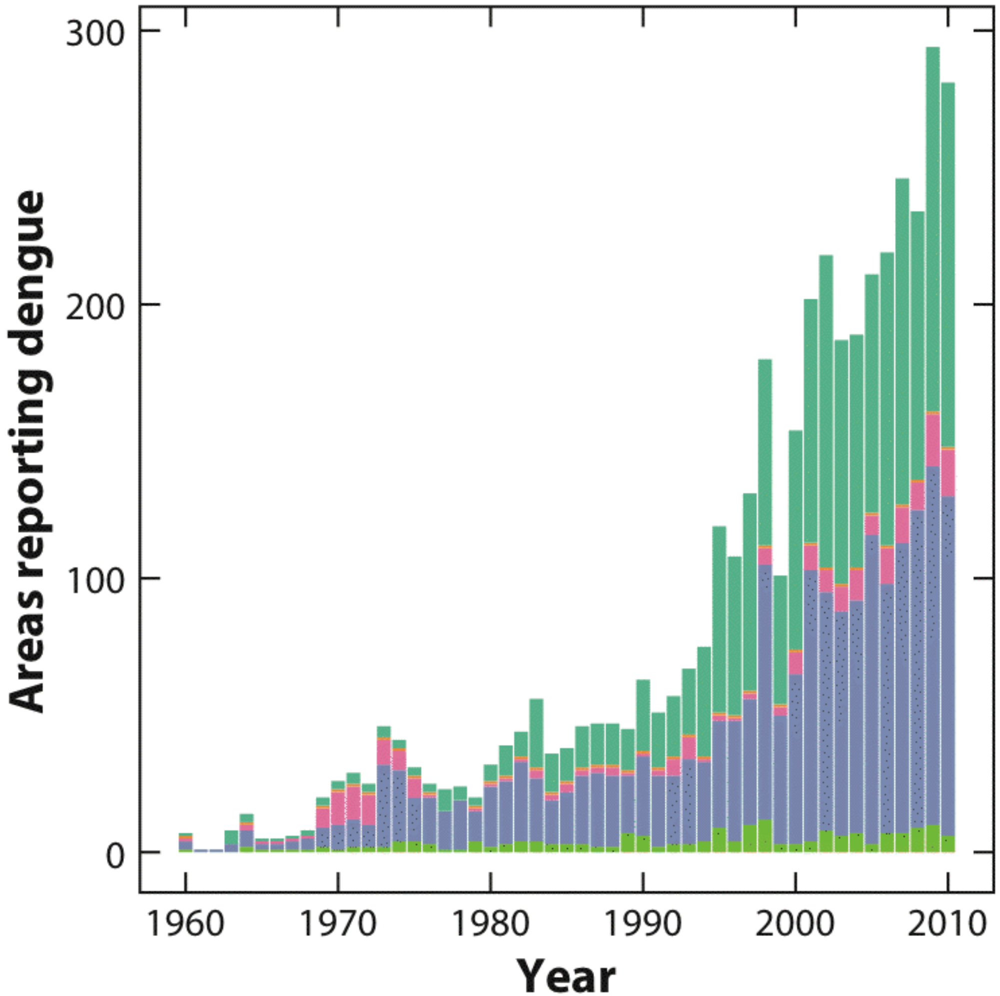
Spread of *Aedes aegypti* out of Africa



Aedes aegypti expansion enabled and possibly drove dengue emergence

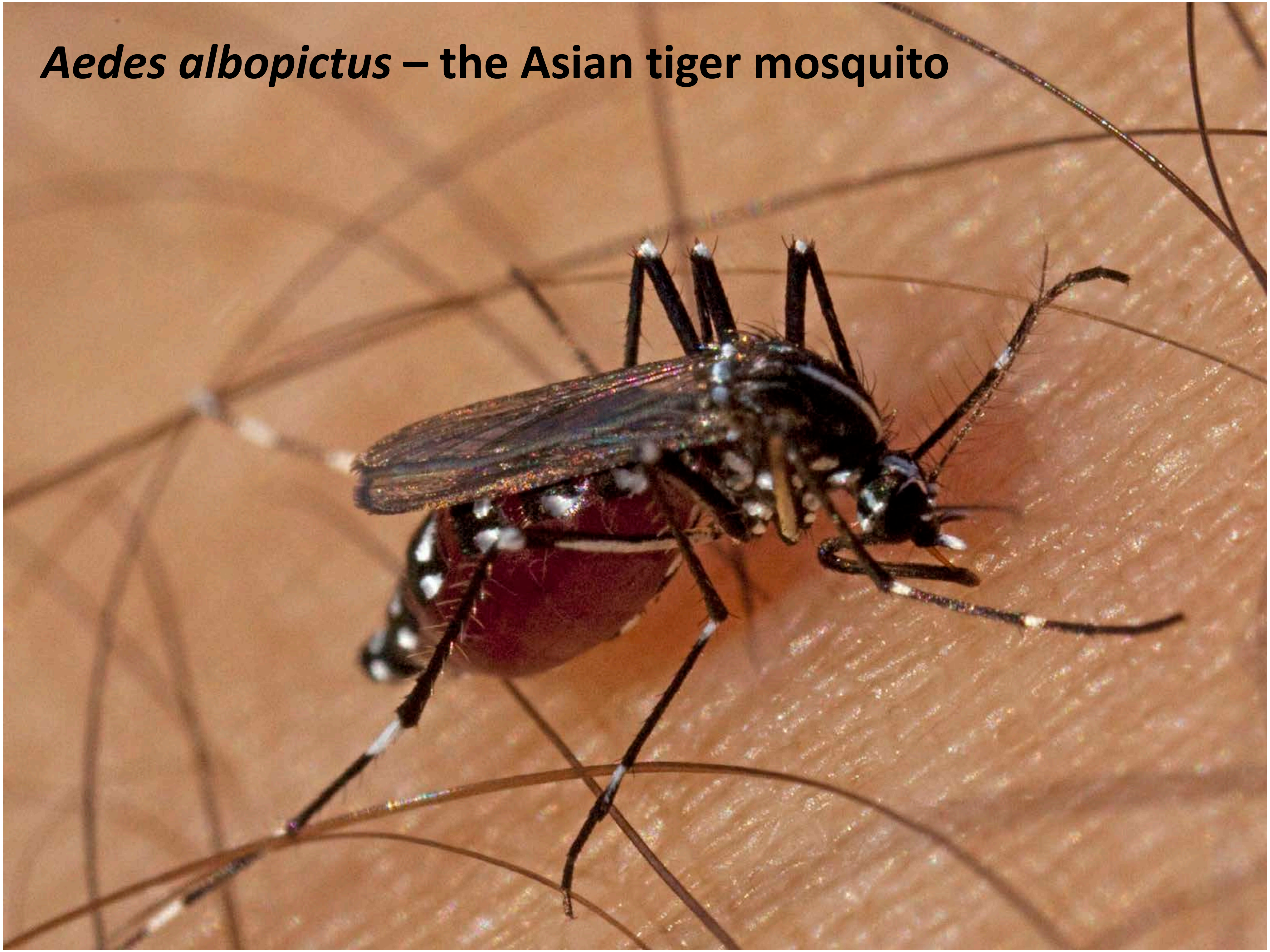






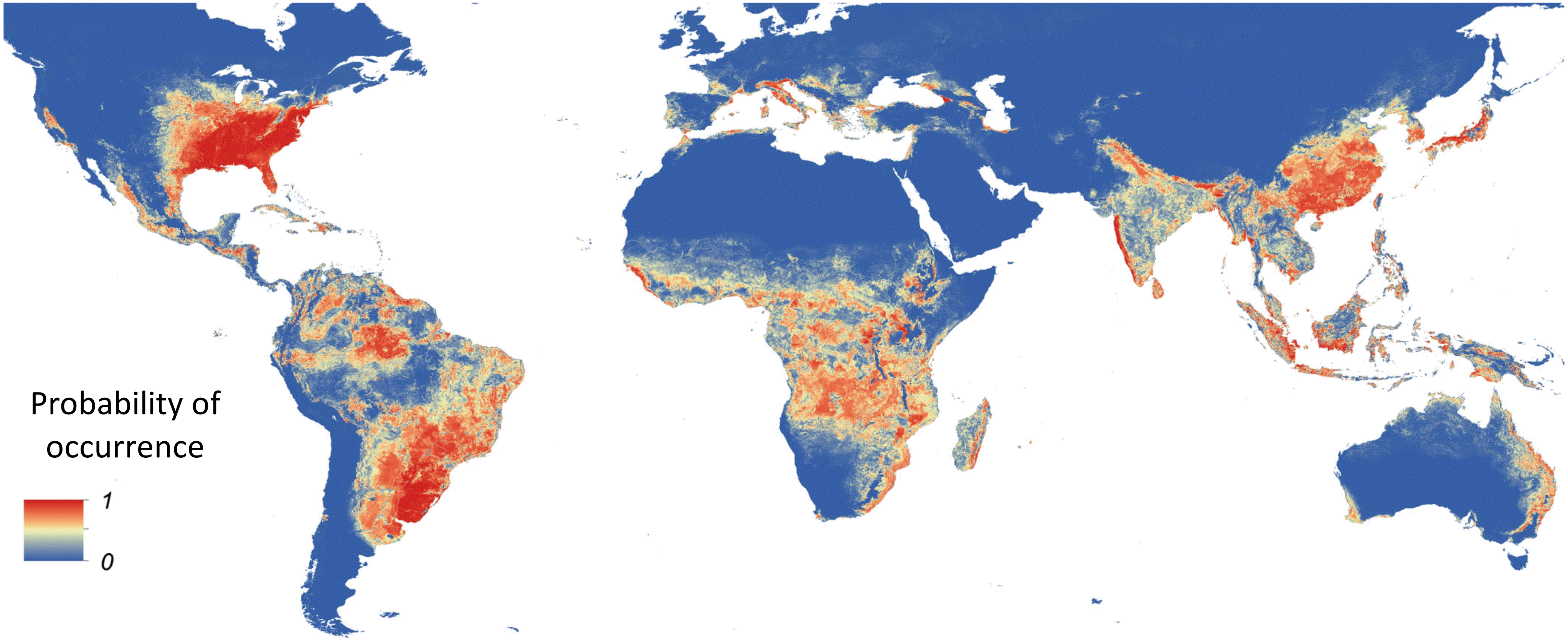
Brady & Hay *Annu Rev Entomol* 2020

Aedes albopictus – the Asian tiger mosquito



Aedes albopictus

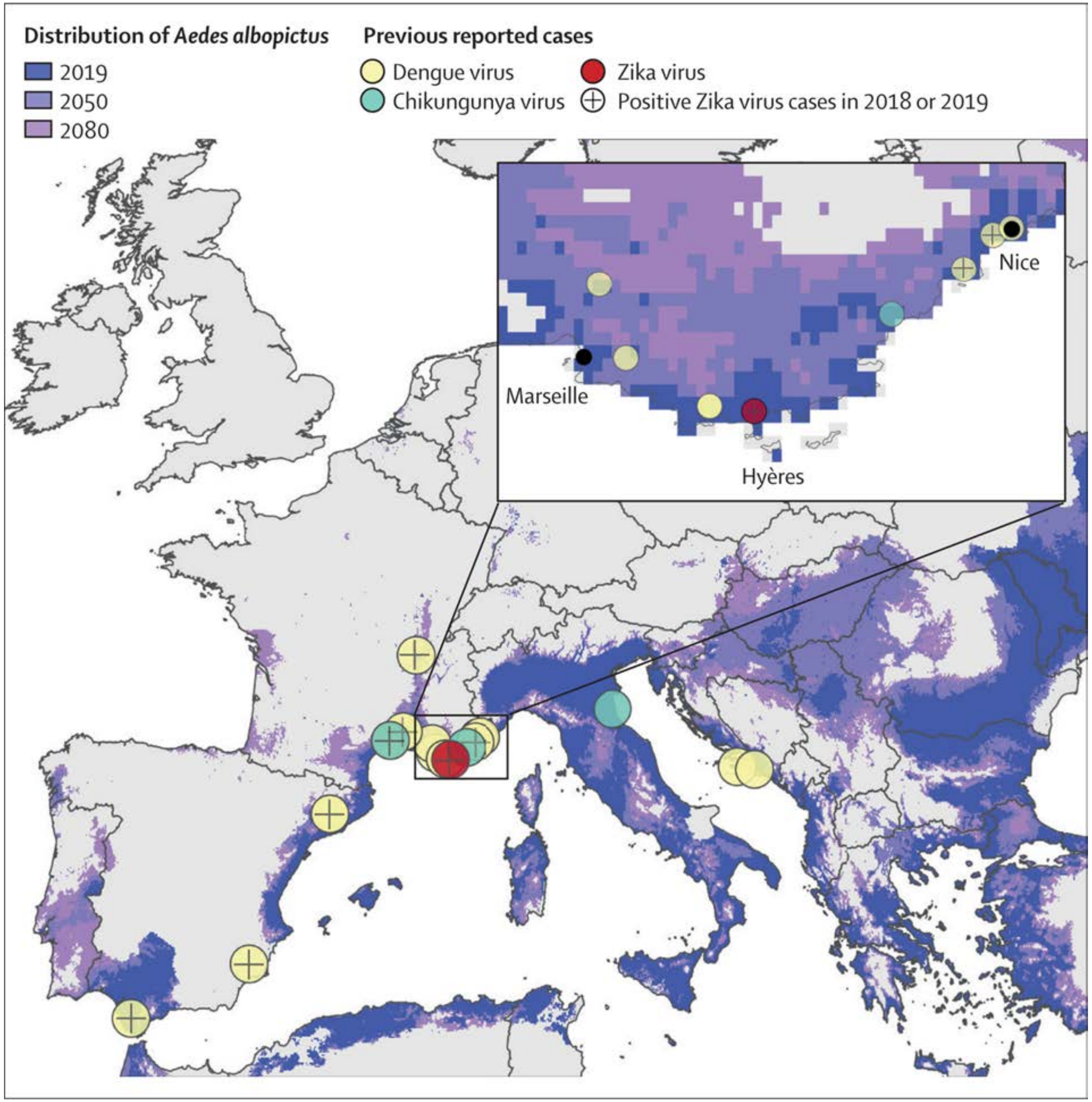
- Originally from Asia
- Spread out in the last few decades
- Found in tropical and temperate regions



Kraemer *et al.* *Elife* 2015

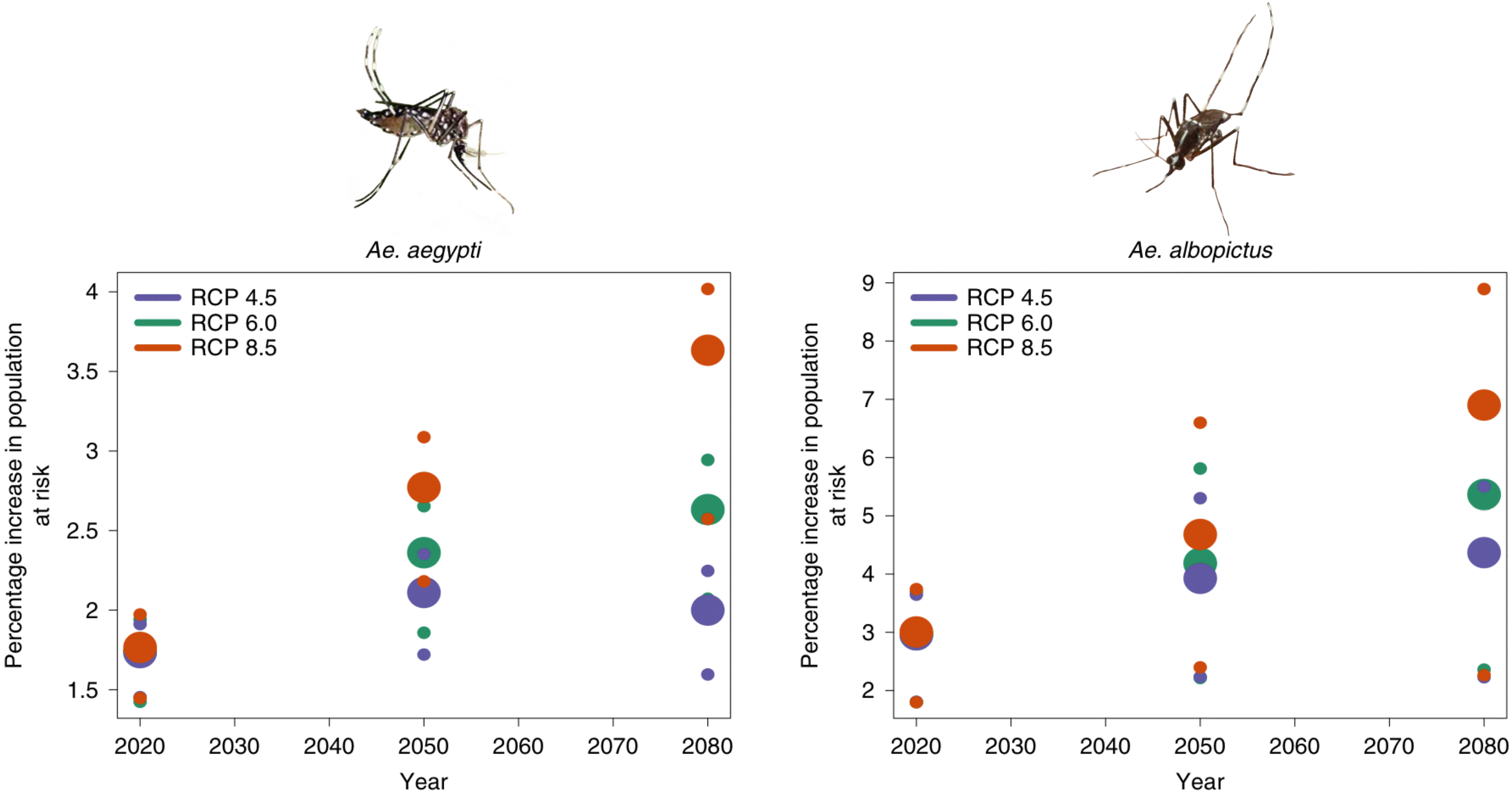
Global spread of *Aedes albopictus*

Aedes albopictus is responsible for local transmission of arboviruses in Europe



Brady & Hay *Lancet Infect Dis* 2019

Geographical expansion of *Aedes*-infested areas



Global population predicted to live in *Aedes*-suitable areas for 3 climatic scenarios:

- RCP 4.5 = conservative
- RCP 6.0 = medium
- RCP 8.5 = worst-case

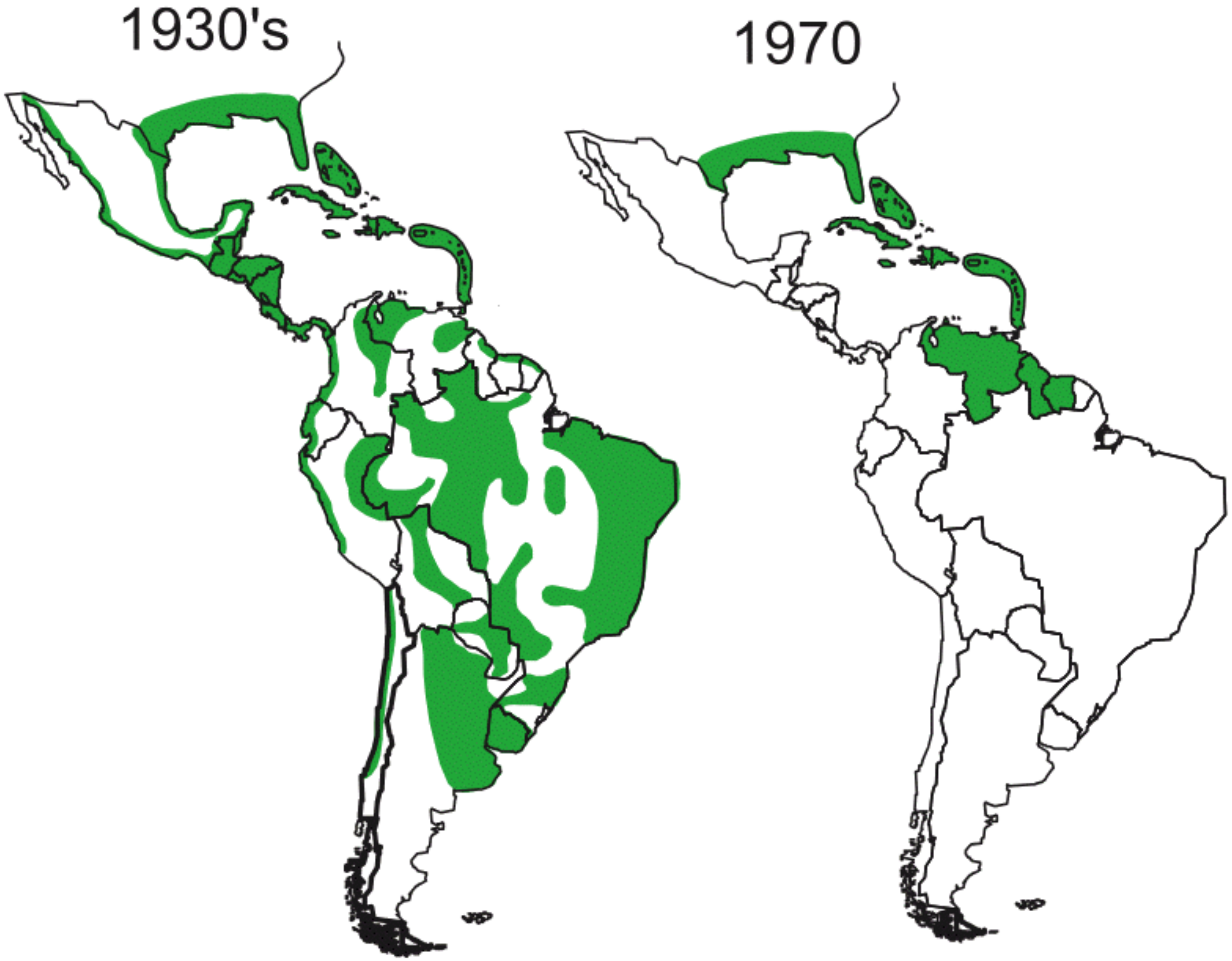
Kraemer *et al. Nat Microbiol* 2019

Outline

1. **Examples of emerging arboviruses**
   - Yellow fever
   - Dengue
   - Zika
2. **Factors underlying arbovirus emergence**
   - Globalization
   - Urbanization
   - Ineffective control
3. **Control of emerging arboviruses**
   - Conventional vector control
   - Innovative strategies

Conventional vector control

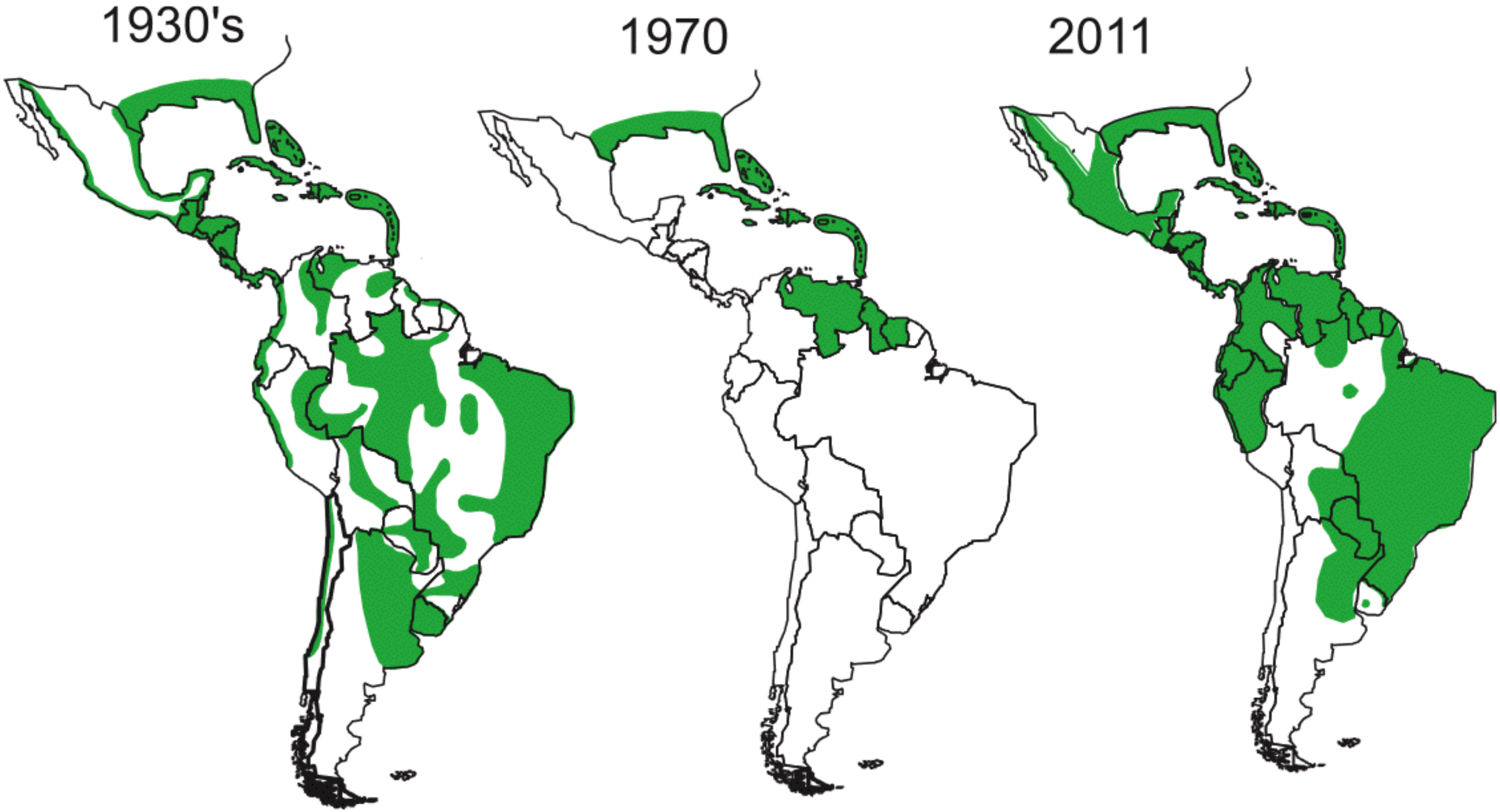
PAHO *Aedes aegypti* eradication campaign



- *Ae. aegypti* eliminated from 20 countries between 1947 and 1962

Gubler *Trop Med Health* 2011

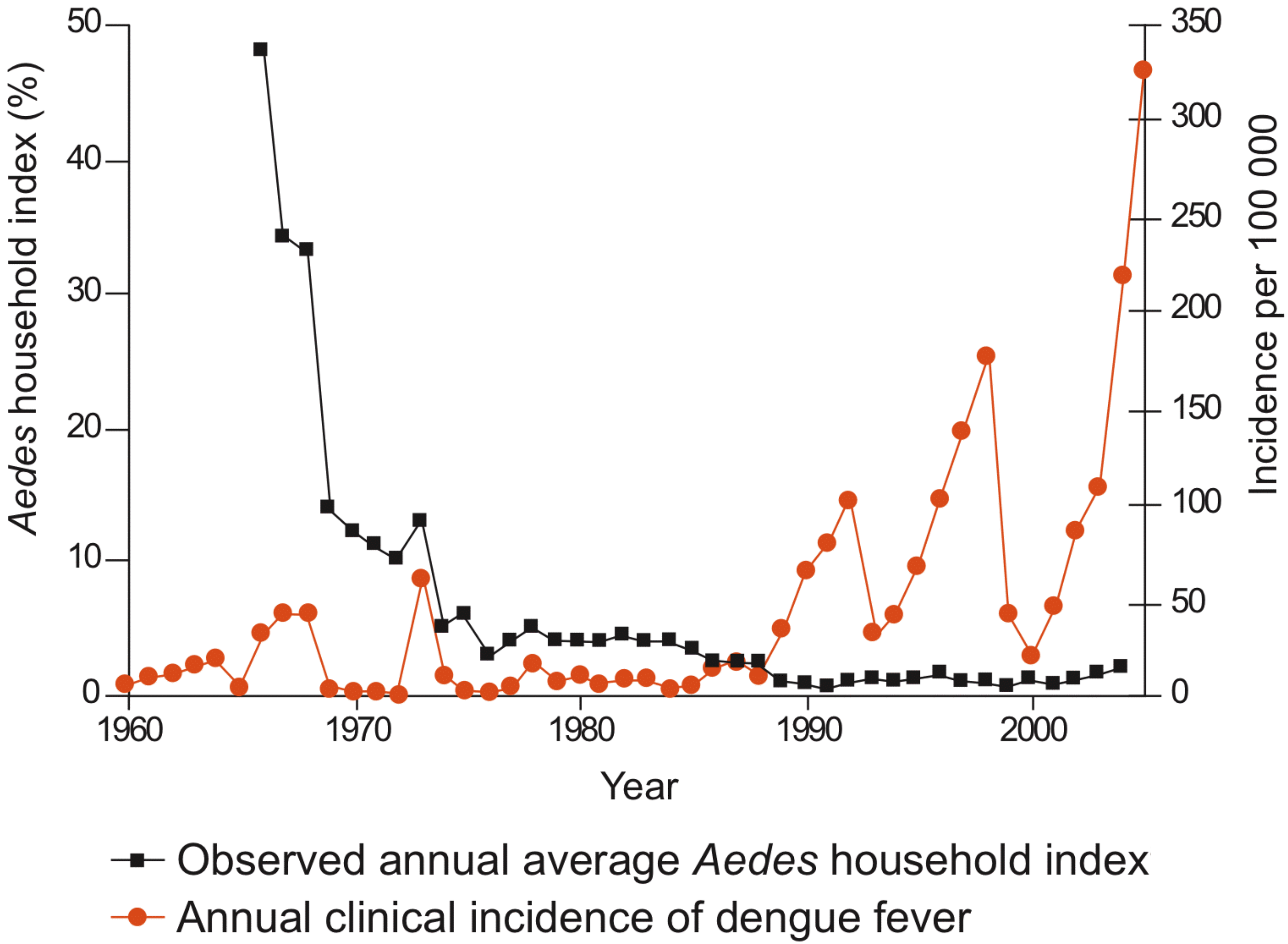
PAHO *Aedes aegypti* eradication campaign



- *Ae. aegypti* eliminated from 20 countries between 1947 and 1962
- *Ae. aegypti* reinfestation after end of program in 1985

Gubler *Trop Med Health* 2011

Dengue re-emergence in Singapore despite intensive vector control program



Egger *et al. Bull WHO* 2008

Basic reproduction number of arboviruses

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Basic reproduction number of arboviruses

$$R_0 = \frac{ma^2p^nb}{-\ln(p)}\frac{c}{r}$$

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Basic reproduction number of arboviruses

$$R_0 = \frac{ma^2p^nb}{-\ln(p)} \underbrace{\frac{c}{r}}_{HUMAN}$$

c = human host competence

r = daily recovery rate of infected humans

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Basic reproduction number of arboviruses

$$R_0 = \underbrace{\frac{m a^2 p^n b}{-\ln(p)}}_{VECTOR} \; \underbrace{\frac{c}{r}}_{HUMAN}$$

- m = vector density per person
- a = daily probability of human biting
- p = daily probability of vector survival
- n = duration in days of extrinsic incubation period (EIP)
- b = vector competence
- c = human host competence
- r = daily recovery rate of infected humans

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Medical interventions indirectly target human-related parameters

p = daily probability of vector survival

a = daily probability of human biting

n = duration in days of extrinsic incubation period (EIP)

m = vector density per person

b = vector competence

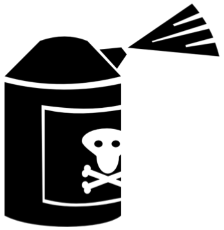
$$R_0 = \frac{ma^2p^nb}{-\ln(p)}\,\frac{c}{r}$$

c = human host competence

r = daily recovery rate of infected humans

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Conventional vector control strategies target primarily vector-related factors



a = daily probability of human biting

p = daily probability of vector survival

n = duration in days of extrinsic incubation period (EIP)

m = vector density per person

b = vector competence

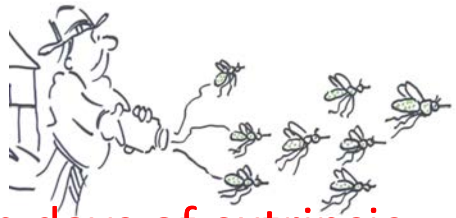
$$R_0 = \frac{ma^2p^nb}{-\ln(p)}\,\frac{c}{r}$$

c = human host competence

r = daily recovery rate of infected humans

R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Vector population modification strategies target vector-arbovirus interactions



p = daily probability of vector survival

a = daily probability of human biting

n = duration in days of extrinsic incubation period (EIP)

m = vector density per person

b = vector competence

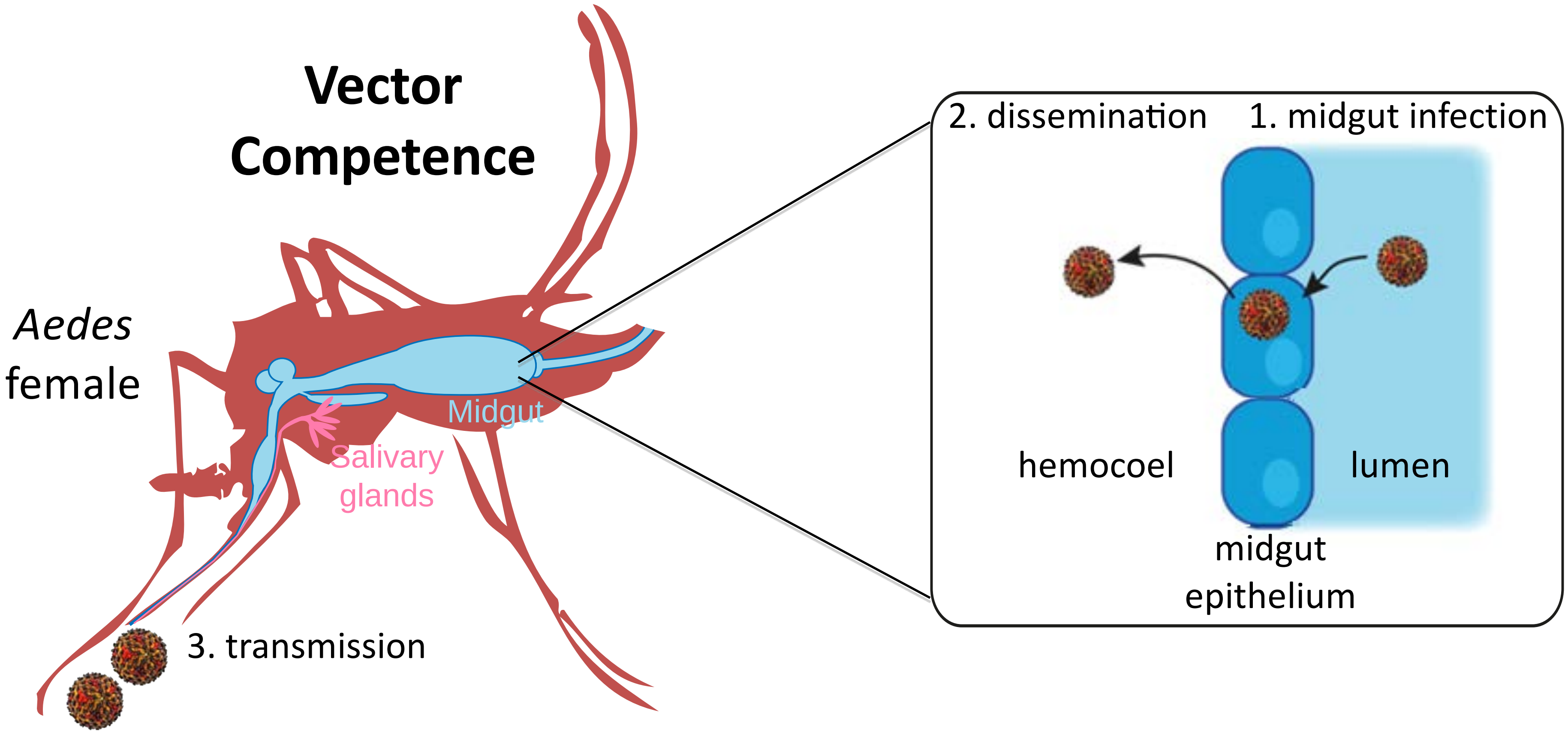
$$R_0 = \frac{ma^2p^nb}{-\ln(p)}\frac{c}{r}$$

c = human host competence

r = daily recovery rate of infected humans

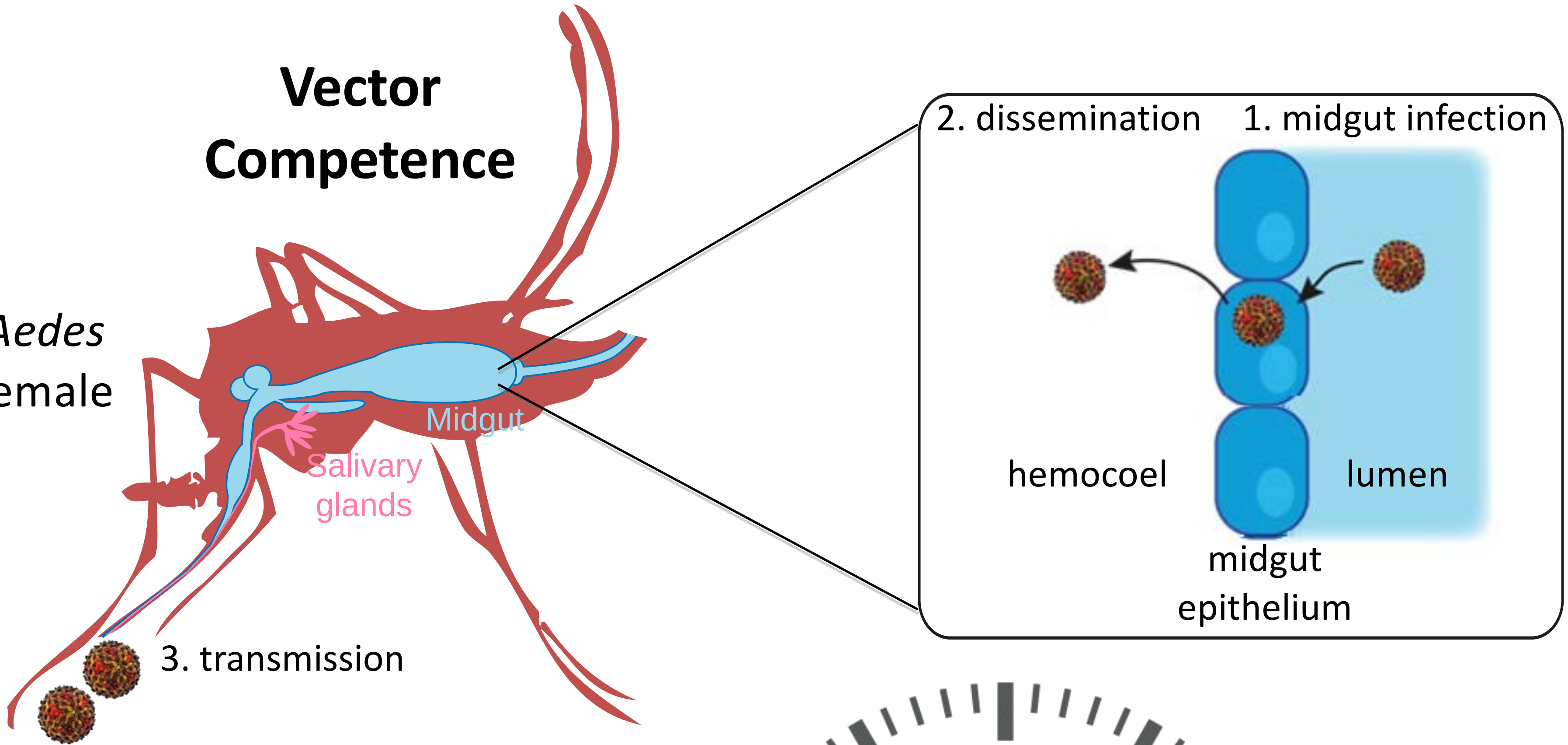
R_0 is the total number of infectious vector bites that arise from one infected person introduced into a susceptible human population

Arbovirus–mosquito interactions

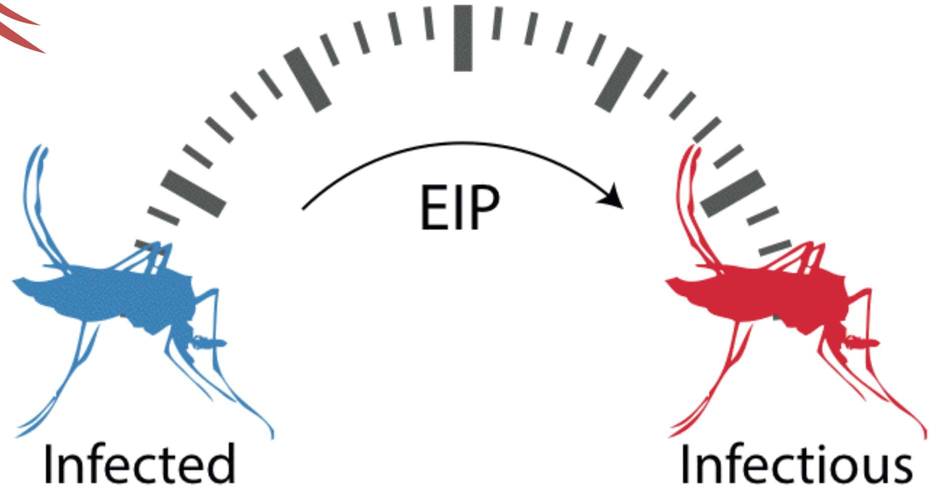


Arbovirus–mosquito interactions

Vector Competence

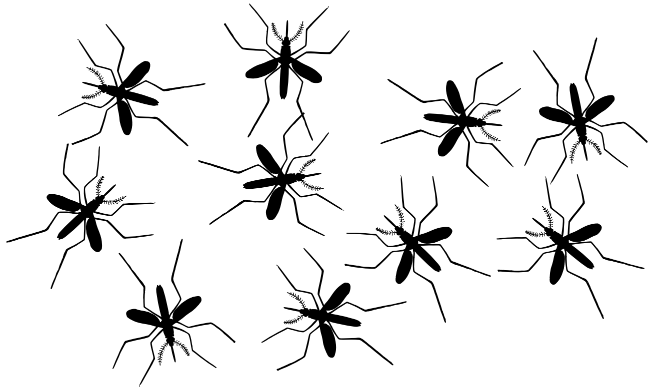


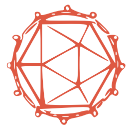
Extrinsic Incubation Period



Arbovirus prevention
by modification of vector populations

Wild target population

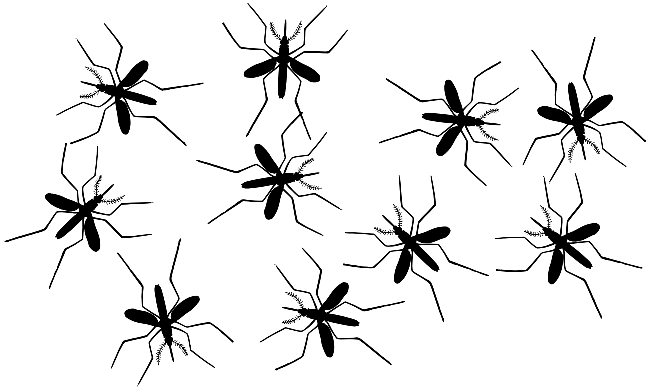


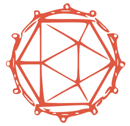


Virus transmission

Arbovirus prevention
by modification of vector populations

Wild target population



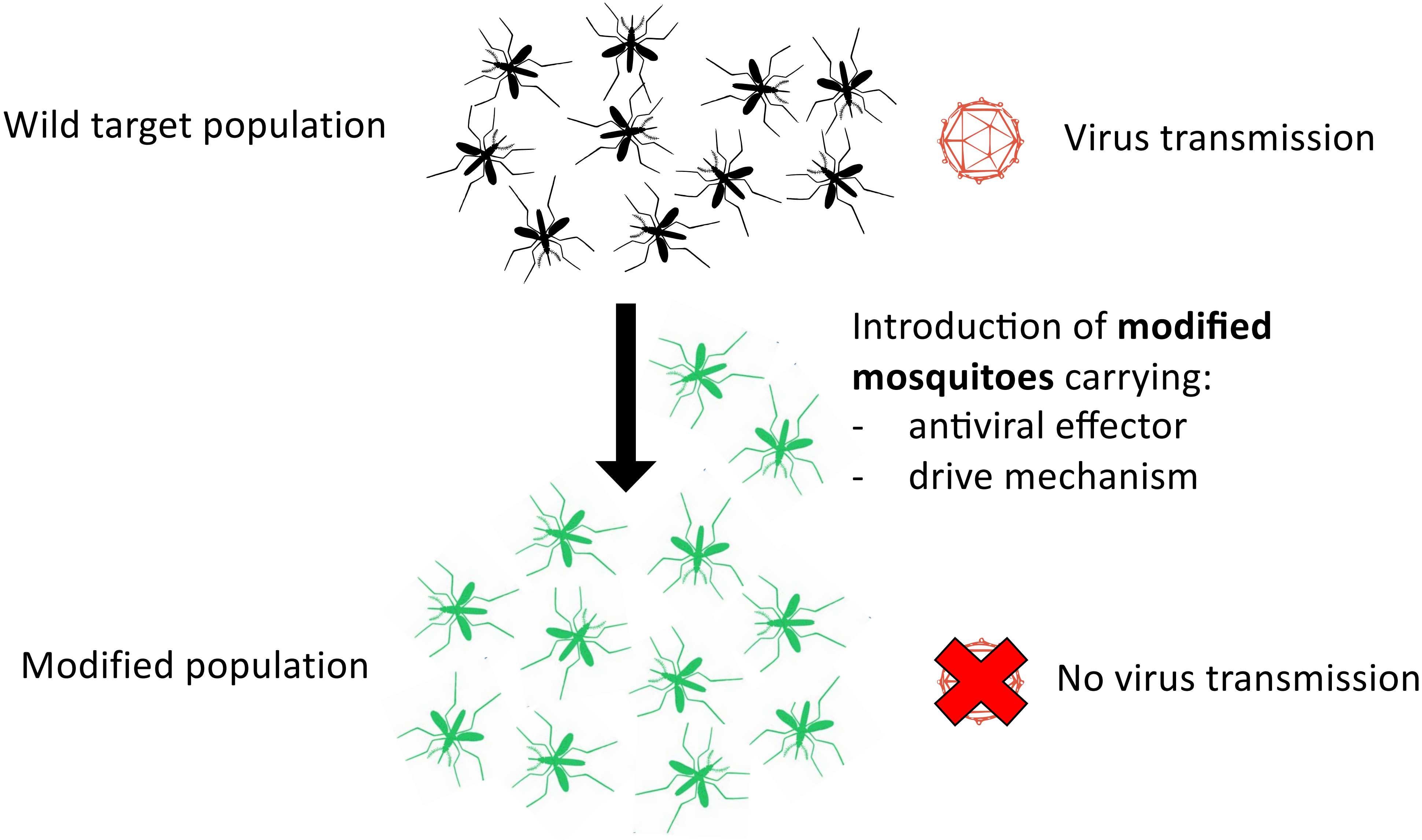


Virus transmission

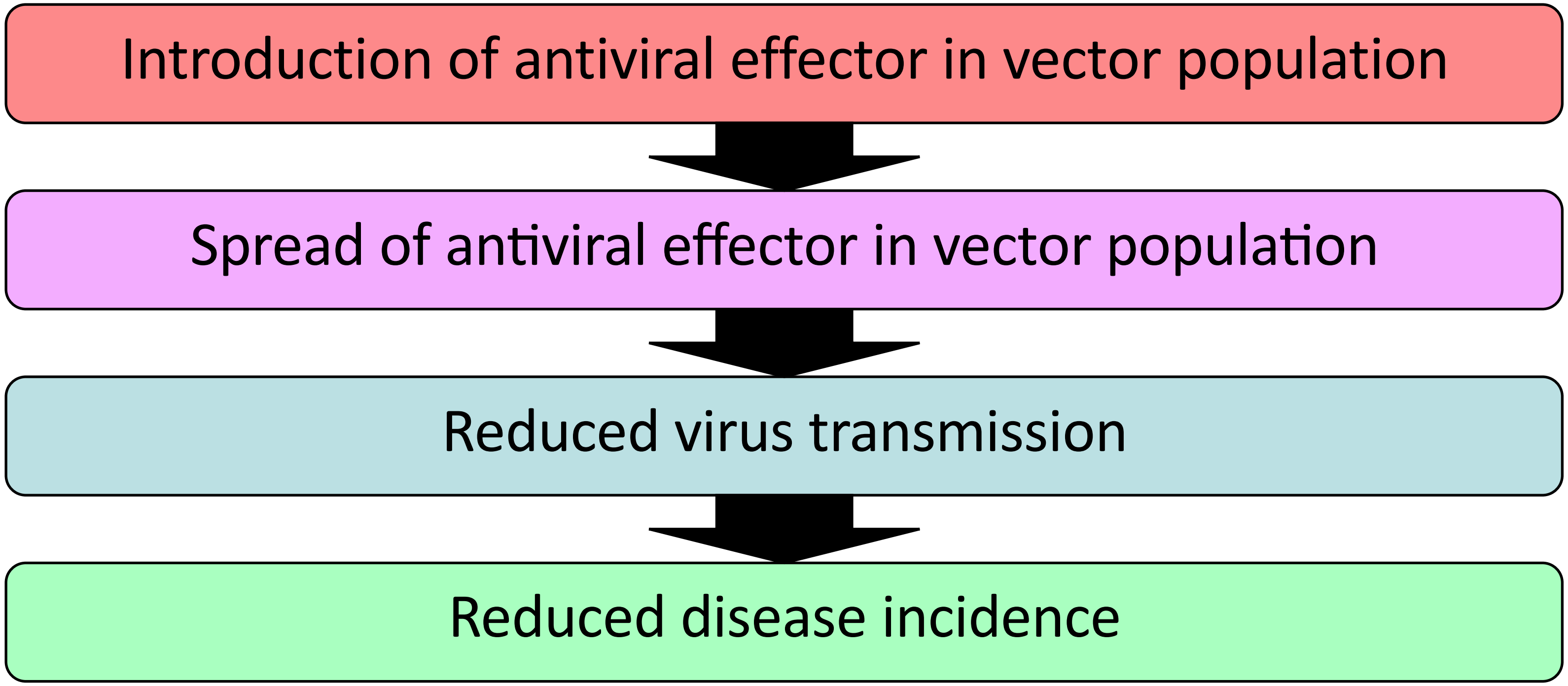
Introduction of **modified mosquitoes** carrying:

- antiviral effector
- drive mechanism

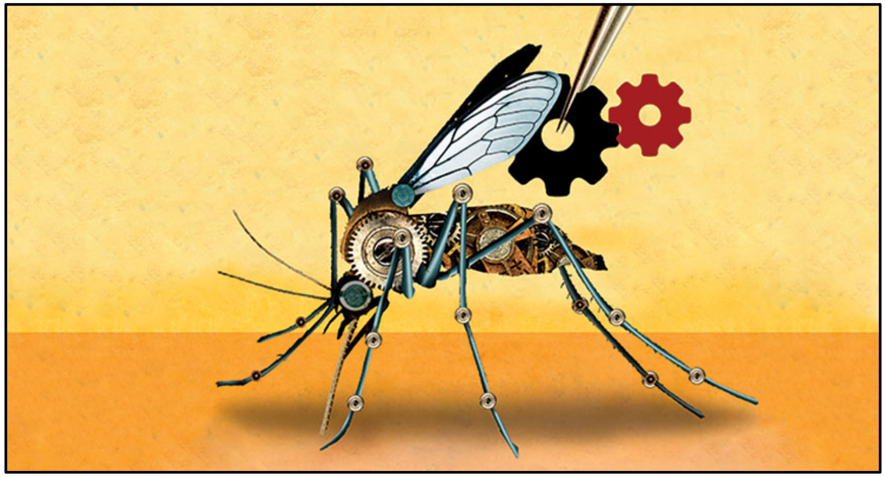
Arbovirus prevention by modification of vector populations



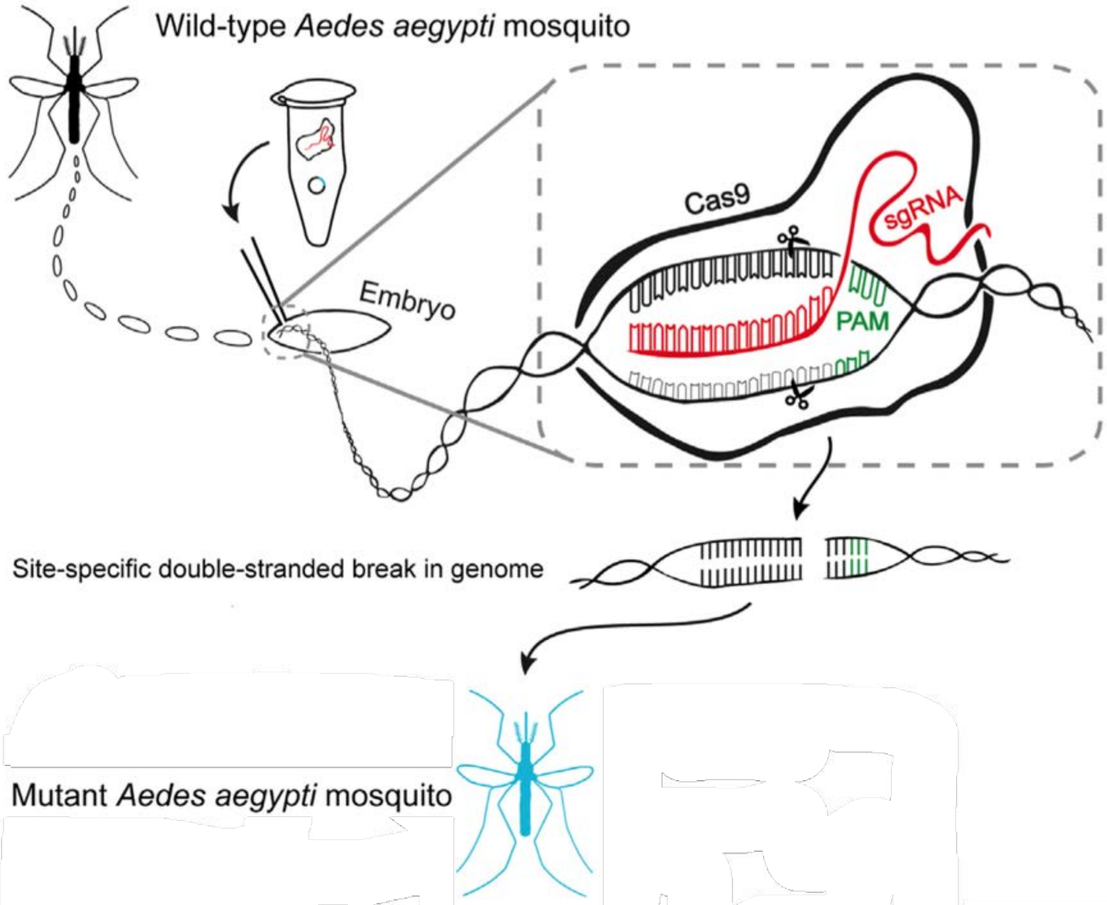
Arbovirus prevention
by modification of vector populations



Mosquito genetic engineering

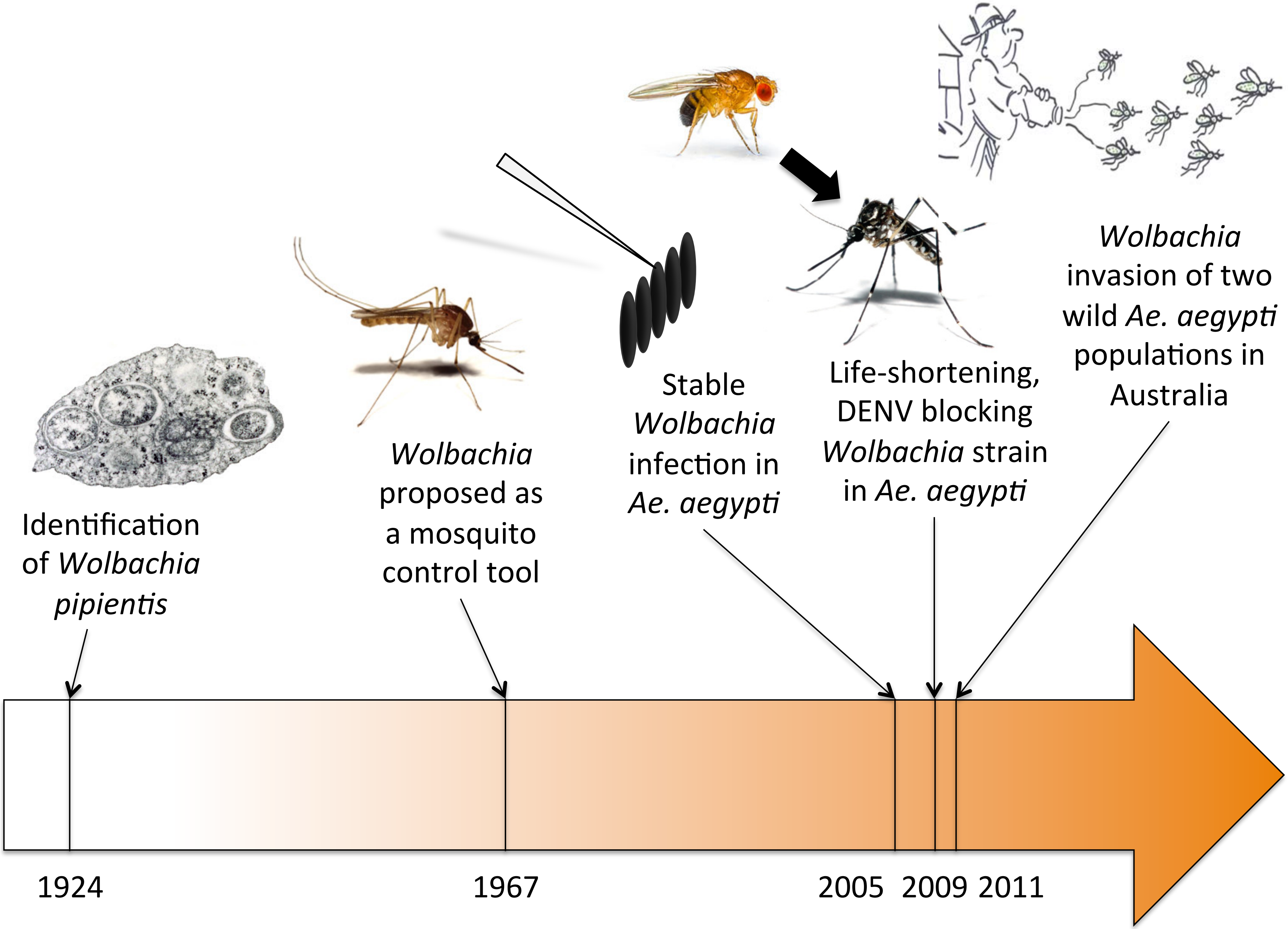


CRISPR/Cas9 gene editing
in the mosquito *Aedes aegypti*



Kistler *et al. Cell Rep* 2015

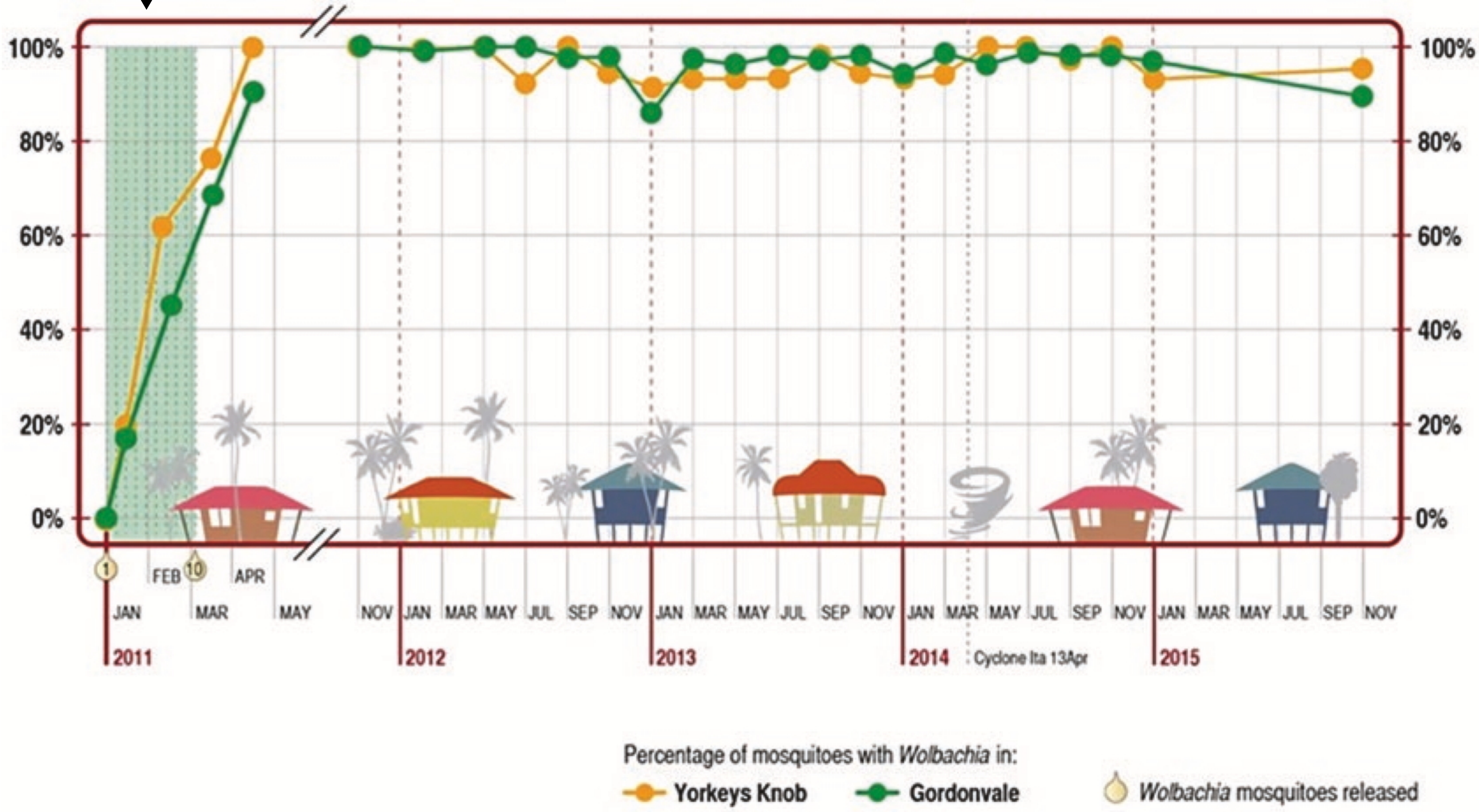
Wolbachia



Lambrechts *et al. Lancet Infect Dis* 2015

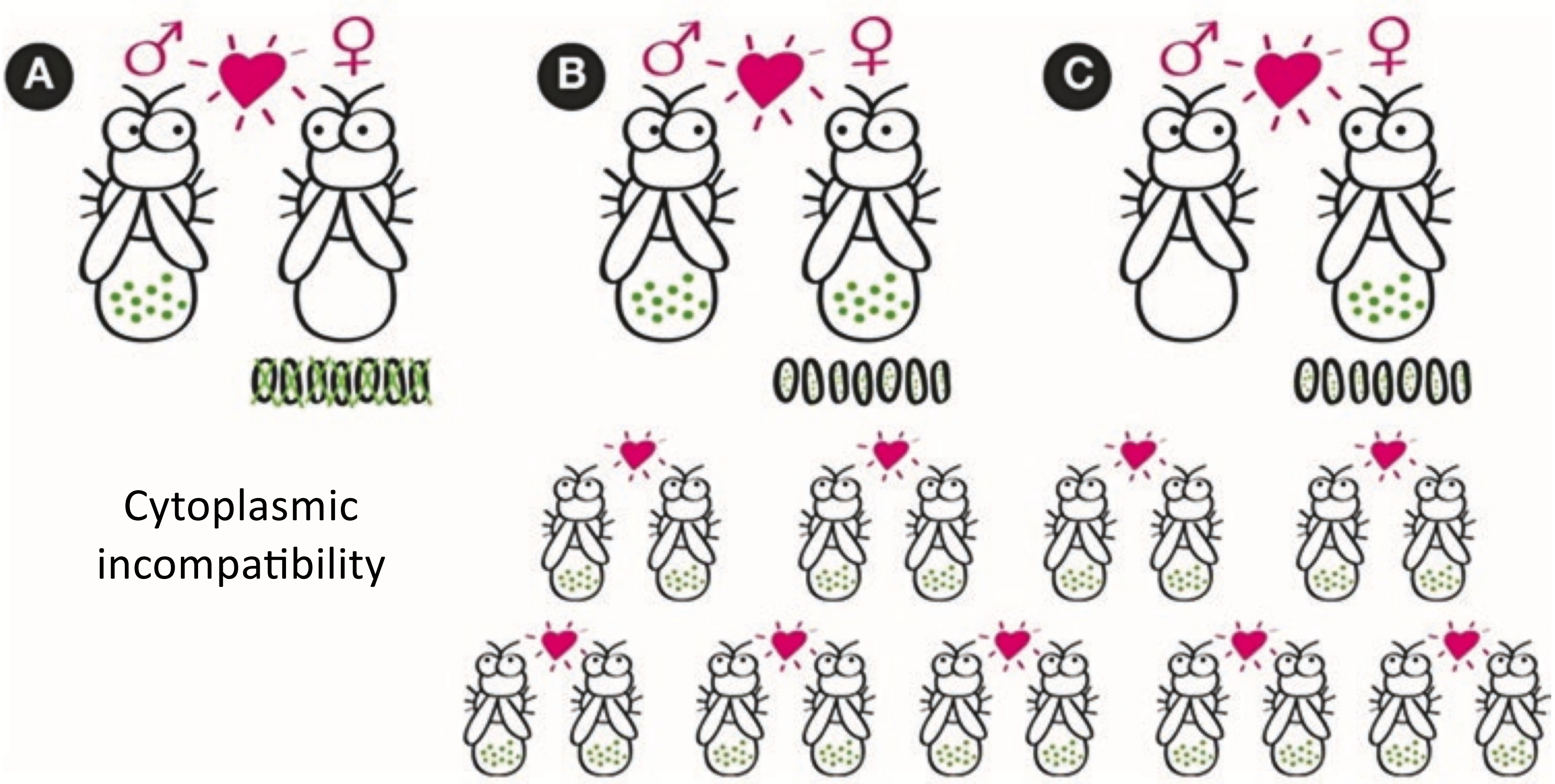
Wolbachia invades and persists in natural populations of *Aedes aegypti*

10 weeks of releases



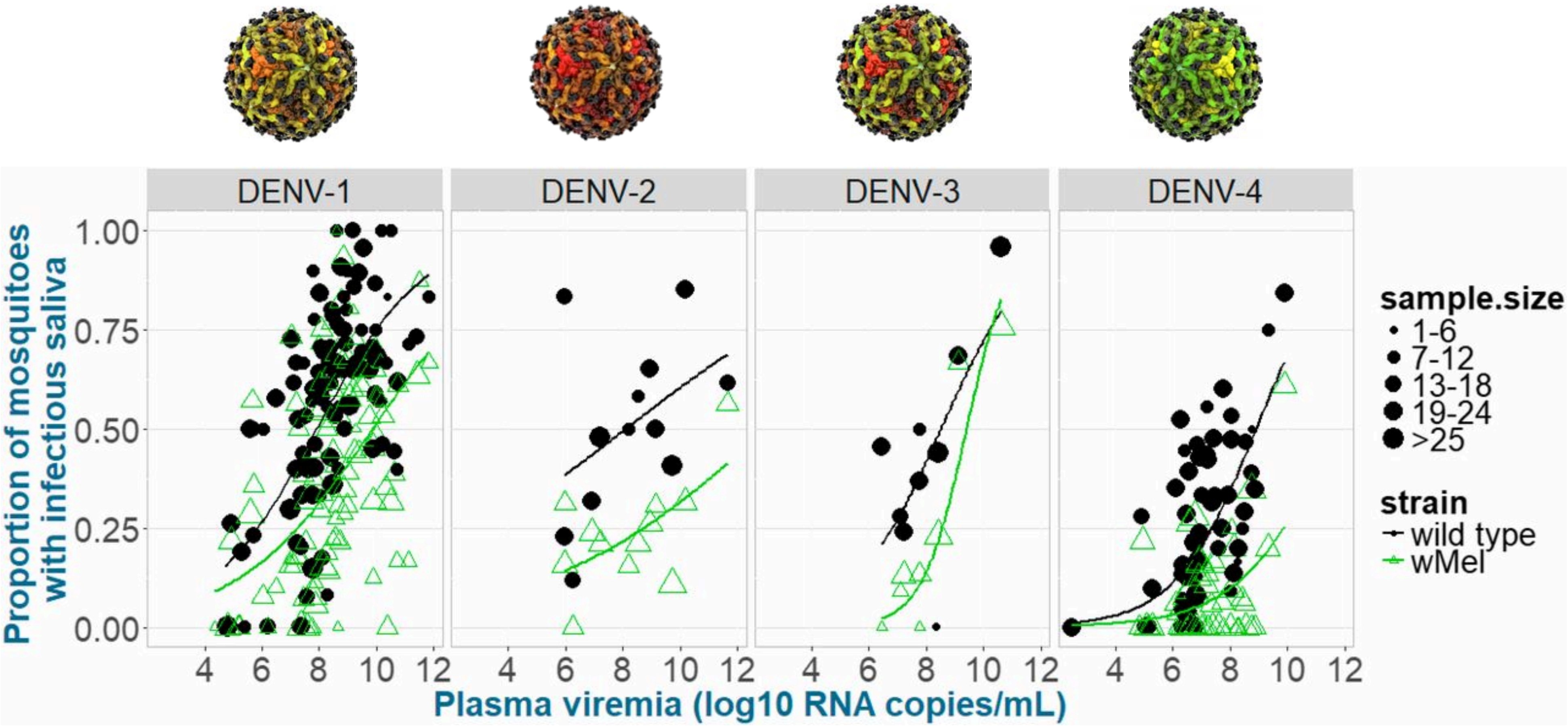
O'Neill *Adv Exp Med Biol* 2018

Cytoplasmic incompatibility drives the rapid spread of *Wolbachia* in mosquito populations



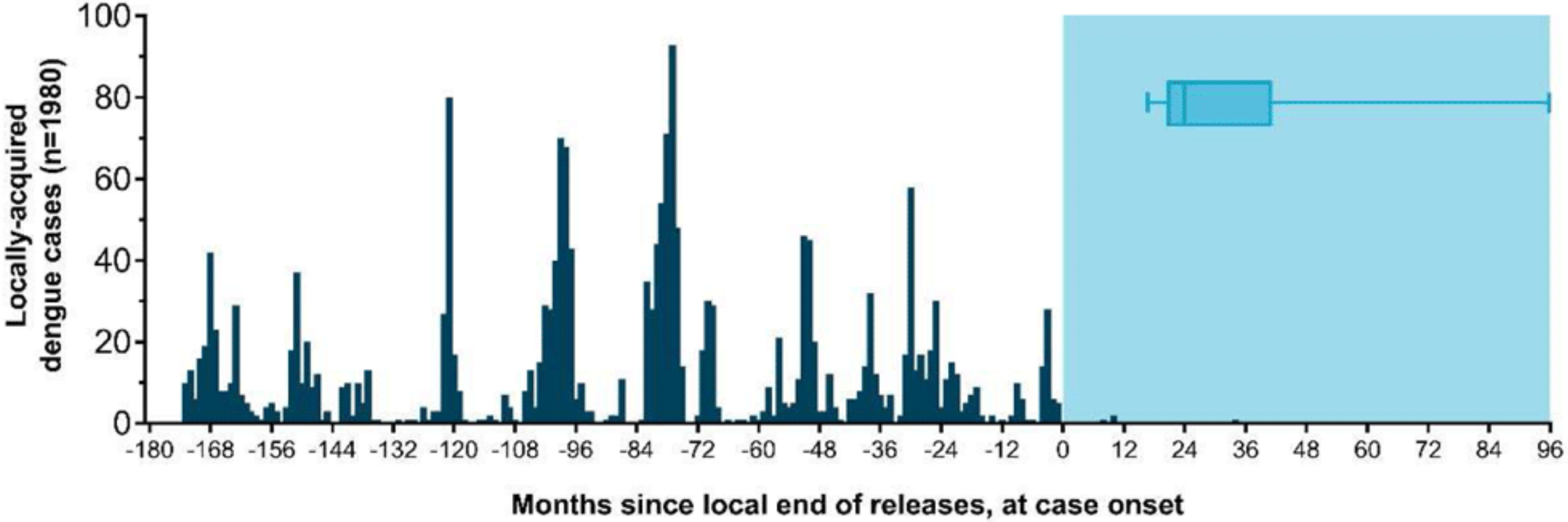
O'Neill *Adv Exp Med Biol* 2018

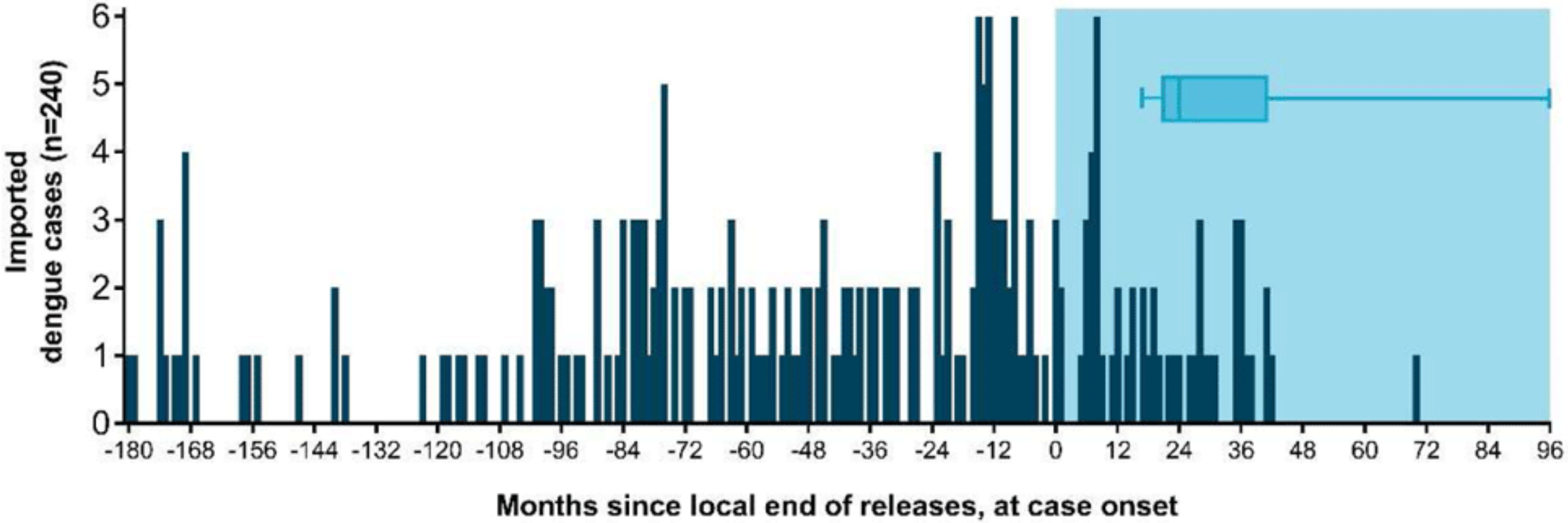
Wolbachia reduces DENV transmission by *Aedes aegypti* from naturally-infected people



Carrington *et al. PNAS* 2018

Dengue case notifications before and after *Wolbachia* releases January 2000 – March 2019





Ryan *et al. Gates Open Res* 2019

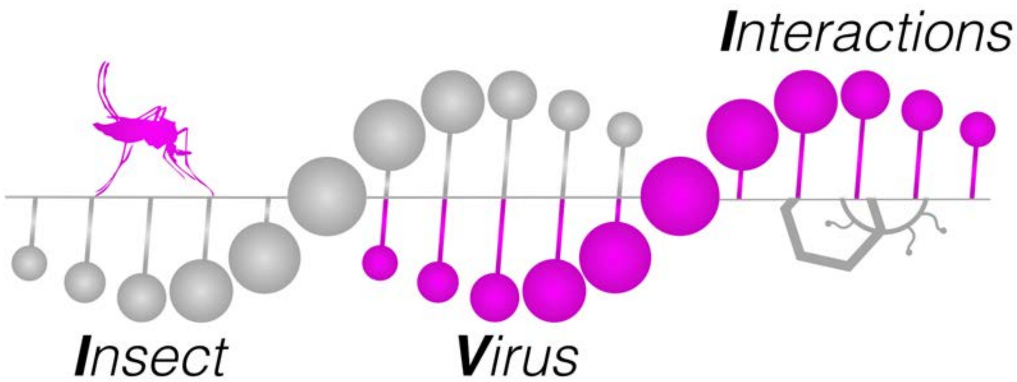
Conclusions

- **Main drivers of arbovirus emergence:**
  - Globalization
  - Urbanization
  - Lack of effective control

- **Other factors:**
  - Lack of political will and resources
  - Decay in public health infrastructure
  - Changing life style
  - Virus evolution

- **Innovative vector control strategies:**
  - Promising results with *Wolbachia*
  - Field trials to measure epidemiological impact

Thank you for your attention



Website: research.pasteur.fr/en/team/insect-virus-interactions

Contact: louis.lambrechts@pasteur.fr

Twitter: @LambrechtsLab