

The emerging ZIKA virus: current epidemiology and challenges for its control

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Timeline: the Americas

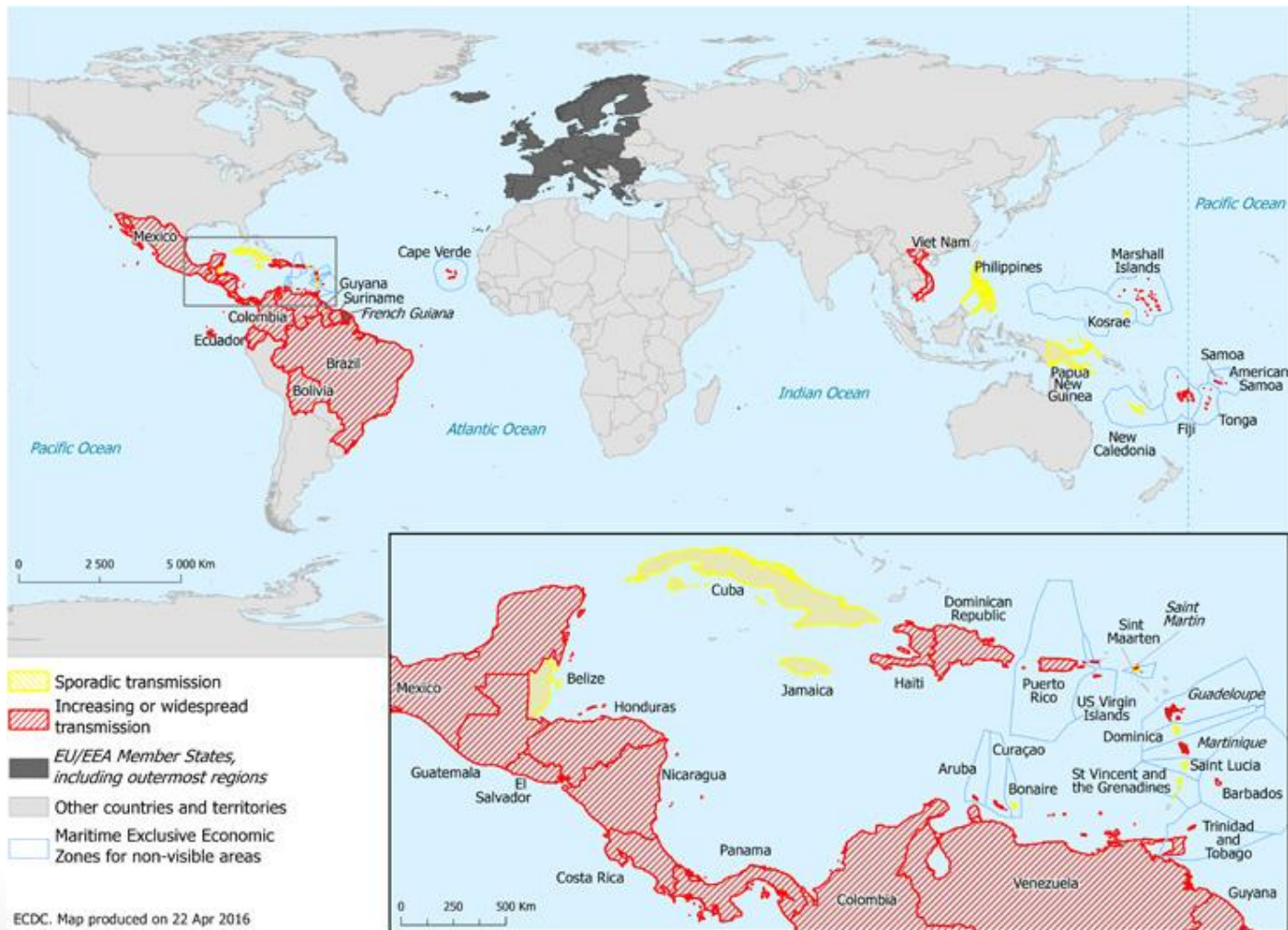


Febr 2015 (North-East Brazil): *an increase in cases of fever, itchy rash, non-purulent conjunctivitis, firstly wrongly diagnosed as dengue/chikungunya*

Current outbreak

- Since early 2015: 42 countries affected (vectorial transmission)
- Steadily widened geographical distribution (within the *Aedes* geographical range)

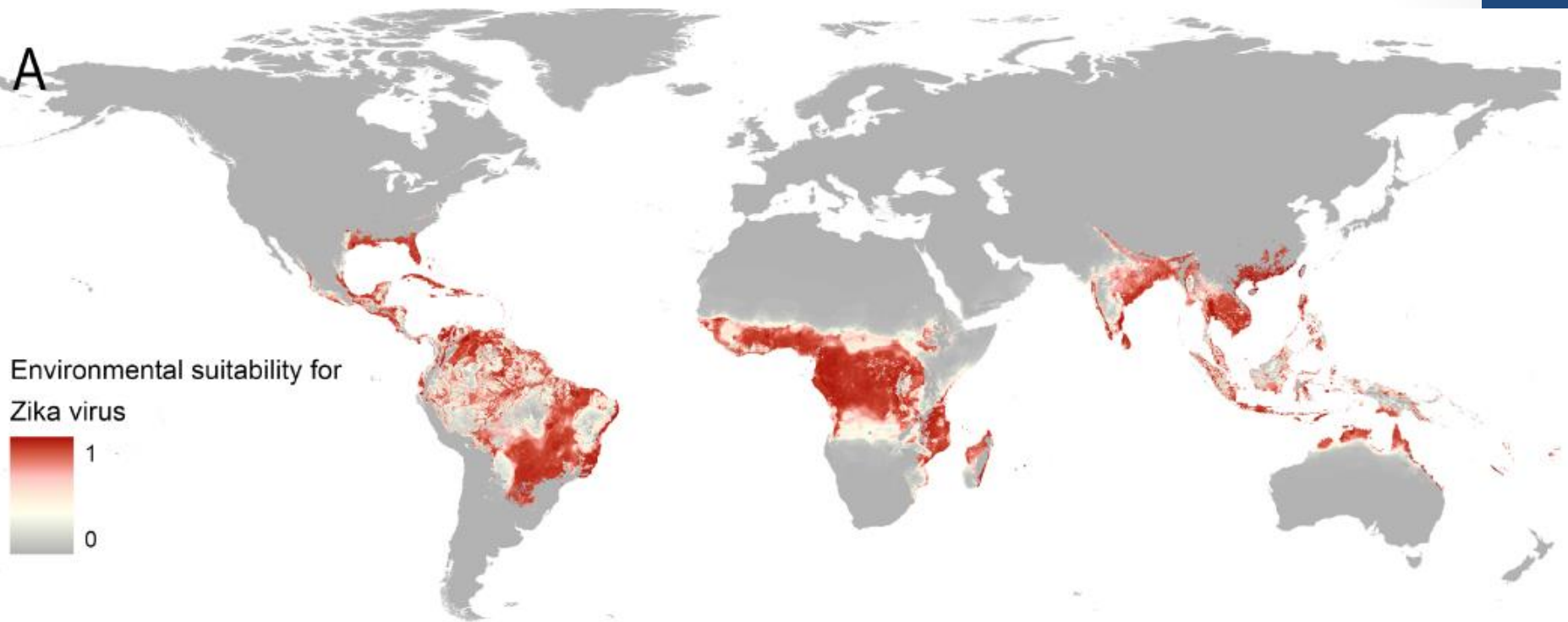
Reported confirmed autochthonous cases of Zika virus infection in the past 9 months (April 22)



Environmental suitability for Zika virus vectorial transmission

2.2 billion people are at risk

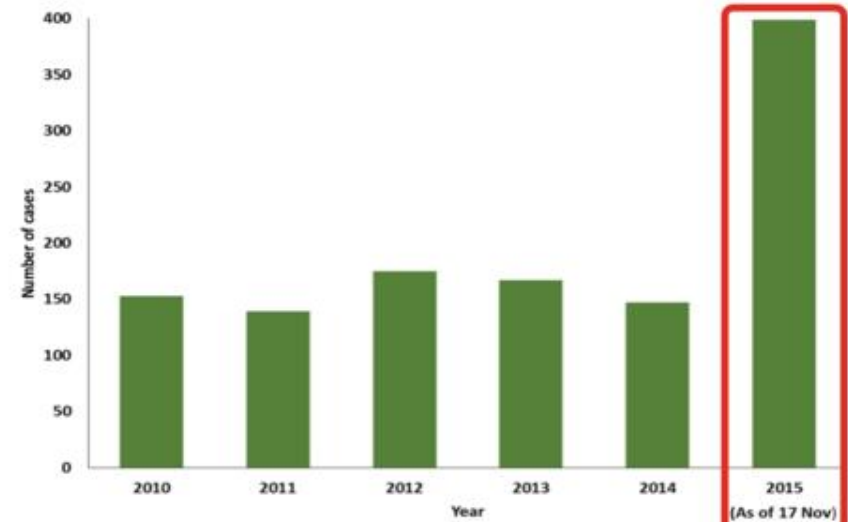
A



'Public Health Emergency of International Concern'

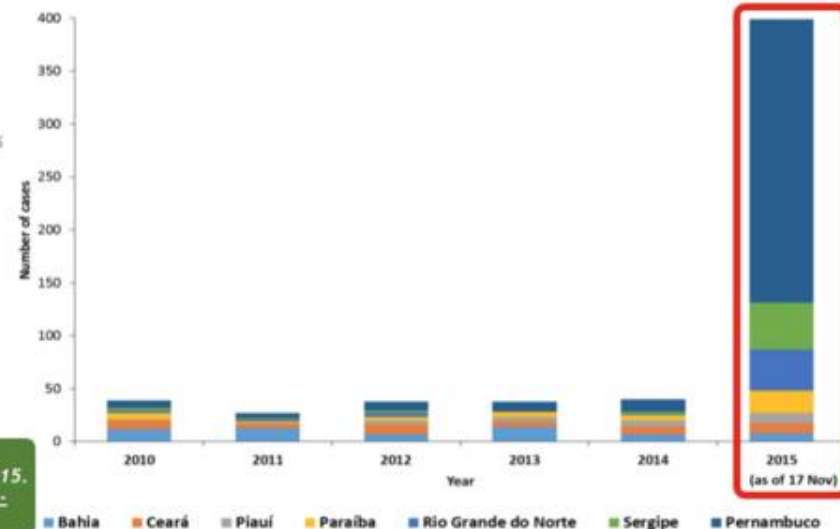
- Brazil 1st officially confirmed Zika: May 2015
- Abrupt jump in congenital microcephaly cases: Nov 2015

Figure 1. Notified cases of microcephaly in Brazil, 2010–2015



Adapted from [1]

Figure 2. Number of cases of microcephaly reported annually in the seven Brazilian states reporting an unusual increase of microcephaly, 2010–2015



Adapted from [1]

Figure 3. States of Brazil with reported confirmed autochthonous cases of ZIKV virus infection 2014–2015, and reported cases of microcephaly in 2015, as of 17 November 2015.



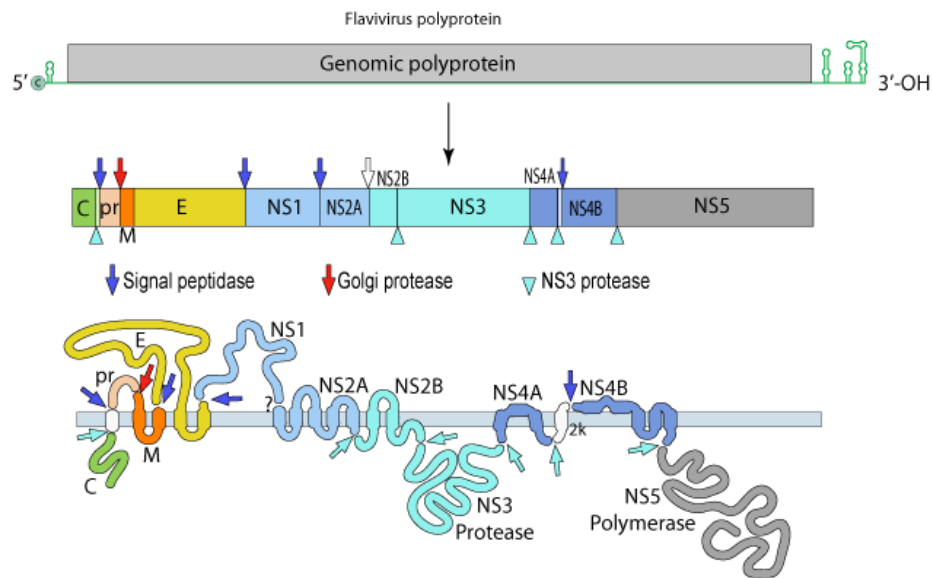
Adapted from [1] and [40]

Modified from Microcephaly in Brazil potentially linked to the Zika virus epidemic. European Centre For Disease Prevention And Control, 24 Nov, 2015. <http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf>

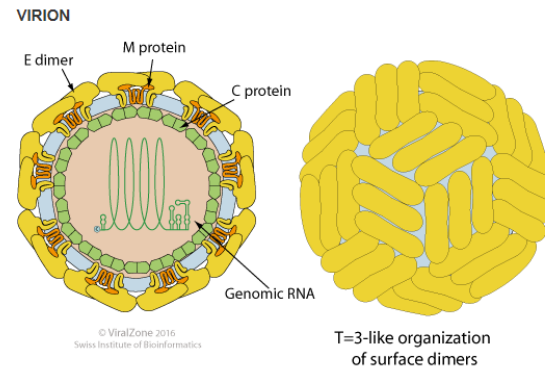
Zika virus

- ARBOvirus, genus *Flavivirus*, family Flaviviridae
- + sense ssRNA viruses
(*other*: dengue, yellow fever)

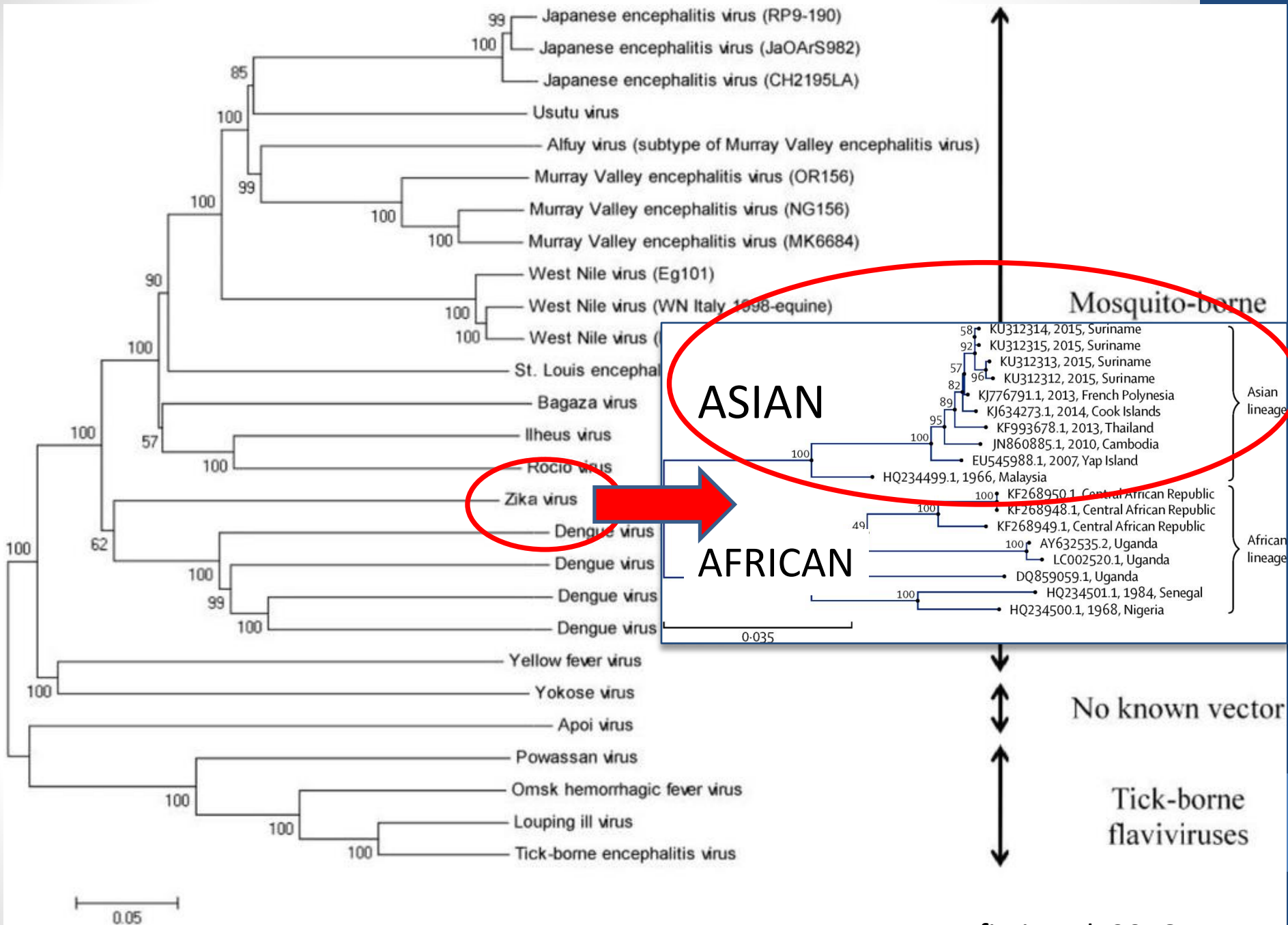
GENOME



Zika virus (strain Mr 766)



Enveloped, spherical, about 50 nm in diameter. The surface proteins are arranged in an icosahedral-like symmetry.



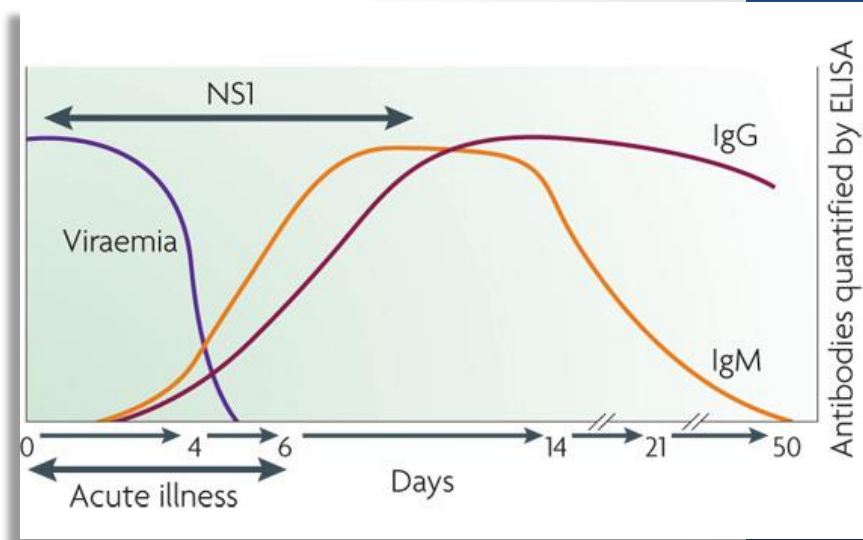
Clinical presentation

- Incubation period
 - Onset of symptoms: 3 to 12 days after infection
- Viraemic period
 - Short viraemic period (3 – 5 days after onset symptoms)
- Symptoms
 - **Rash** with/without fever (28% of cases) and with the following signs and/or symptoms:
 - arthralgia/arthritis
 - conjunctivitis (non-purulent/hyperaemia)
 - general fatigue
 - Most of the infections remain **asymptomatic** (approx. 80%)
- No to very low mortality

Diagnosis

Detection of viral RNA

- RT-PCR serum and saliva during the viraemic period (day 3 and 5)
- Detection in urine up to 10 days after onset



Serology: Zika-specific IgM antibodies

- IgM detectable from day 5 after onset of symptoms
- Detection of Zika-specific IgM requires confirmation by plaque-reduction neutralisation tests (cross-reactivity with antibodies against other flaviviruses)
- Interference with vaccination and infections with other flaviviruses possible

Potential complications: GBS and microcephaly

- **Guillain-Barré syndrome:**

French Polynesia: (*Cao-Lormeau VM et al, 2016*)

- Study of 42 GBS patients, 100% with neutralising AB ZIKA (56% in control group), 88% symptomatic
- Rapid onset, favourable outcome (57% 'walking' 3 months after discharge)
- incidence of 24/100 000 py in ZIKA cases (1-4/100 000 global incidence)
- Pre-exposure to dengue does not seem to increase risk

- **Microcephaly:**

- Fetal abnormalities (fetal death, placental insufficiency, fetal growth restriction, and CNS injury) in 29% of symptomatic ZIKV+ mothers; gestation week 8 to 35 (*Brasil P et al, 2016*)
- estimated risk: 95 cases per 10 000 women infected during the first trimester (*Cauchemez S et al, 2016*)

Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings.

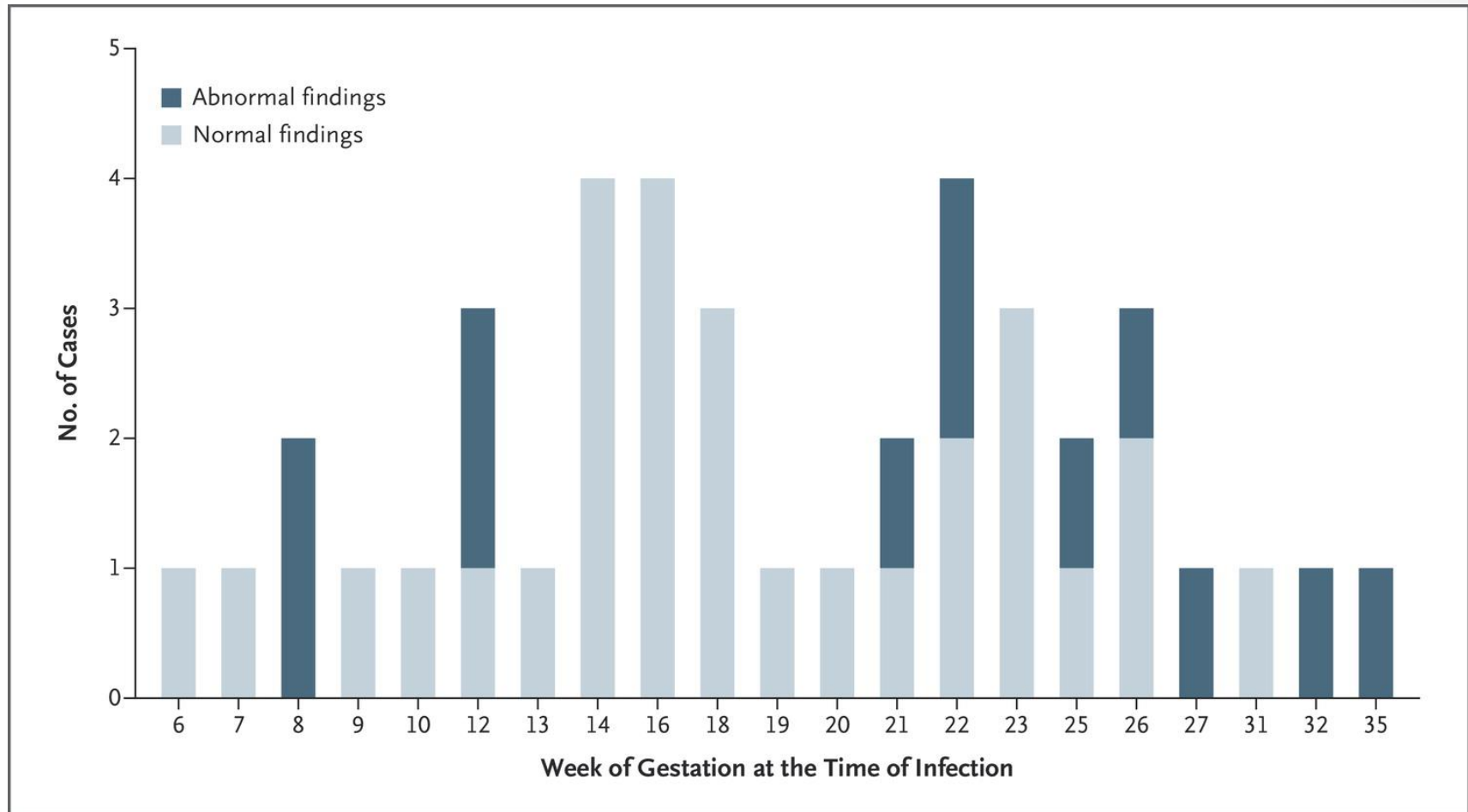


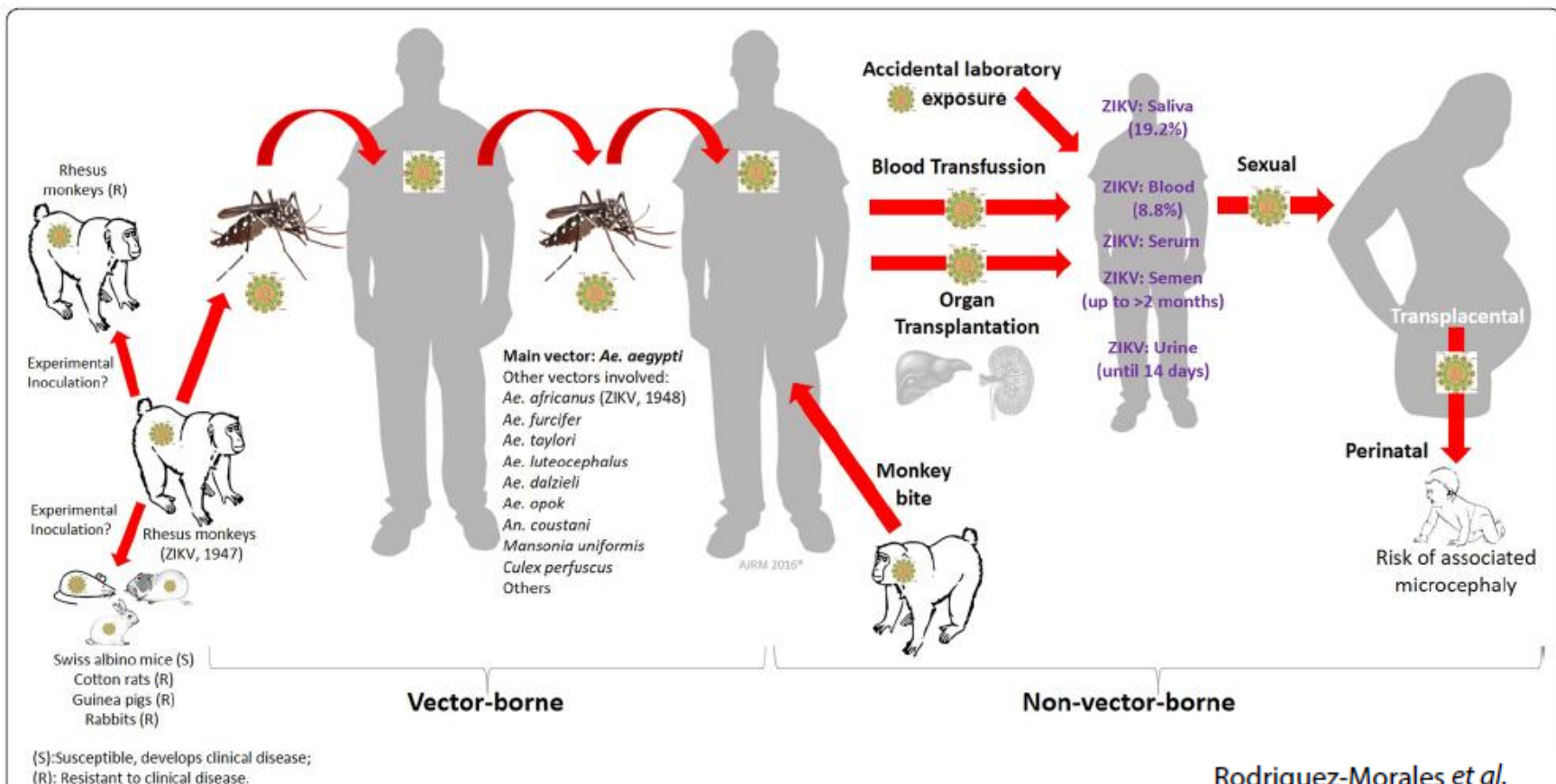
Table 2. Bradford Hill Criteria for Evidence of Causation as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies*

Criterion	Evidence	Criterion Met?
Strength of association	A recent epidemiologic study from French Polynesia suggests a strong association between prenatal Zika virus infection and microcephaly (estimated risk ratio, approximately 50). ² The substantial increase in the number of cases of microcephaly and other brain anomalies that have been associated with the Zika virus outbreak in Brazil suggests a strong association. ^{1,2}	Yes
Consistency	Two epidemiologic studies, one from Brazil and one from French Polynesia, ^{2,14} support the association between prenatal Zika virus infection and microcephaly and other serious brain anomalies. The observed increase in the number of cases of microcephaly after outbreaks of Zika virus infection in Brazil and French Polynesia, as well as preliminary reports of cases in Colombia, support consistency. ^{1,2,42} Case reports of Zika virus infection in fetuses or infants with microcephaly or other brain anomalies who were born to mothers who traveled to areas of active Zika virus transmission support consistency. ^{16,18,19}	Yes
Specificity	Other causes of microcephaly exist; however, on the basis of clinical descriptions that are available for a small number of infants with presumed congenital Zika virus infection, ²⁰ the clinical phenotype linked to the Zika virus appears to be an unusual form of microcephaly that is consistent with the fetal brain disruption sequence.	Yes
Temporality	Zika virus infection in mothers during pregnancy precedes the finding of microcephaly or other brain anomalies in fetuses or infants. ^{14,20} Zika virus outbreaks in Brazil and French Polynesia preceded the increase in the number of cases of microcephaly. ^{1,2}	Yes
Biologic gradient	Infection is a phenomenon that is either present or absent; there is no dose-response relationship. No data are available regarding whether women with an increased viral load have a higher risk of adverse pregnancy or birth outcomes.	NA
Plausibility	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus and rubella virus). ²⁶ Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth, ²⁹ along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of on immunohistochemical staining and identification of Zika virus RNA and live virus, ^{16,17,19} provides strong biologic plausibility.	Yes
Coherence	No results in an animal model of effects of Zika virus on pregnancy have yet been published, but animal models have shown that Zika virus is neurotropic, ^{27,28} a finding that is consistent with prenatal Zika virus infection causing microcephaly and other brain anomalies. Zika virus infects neural progenitor cells and produces cell death and abnormal growth, ²⁹ a finding that is consistent with a causal relationship between Zika virus infection and microcephaly.	Yes
Experiment	No experimental animal model of Zika virus teratogenicity is available.	No
Analogy	No other flavivirus has been shown to definitively cause birth defects in humans, ⁴ but flaviviruses, Wesselsbron and Japanese encephalitis viruses, have been shown to cause stillbirth and brain anomalies in animals. ⁴³ Findings are similar to those seen after prenatal infection with other viral teratogens (e.g., cytomegalovirus, rubella virus). ²⁶	Yes

* The criteria listed here were proposed by Hill.⁴⁰ We have updated a recent analysis by Frank et al.⁴¹

Transmission

- **Vector: *Aedes aegypti* – (*Aedes albopictus*)**
 - Sylvatic cycle involving primary vertebrate hosts (*reservoir*: non-human primates, vertebrate hosts such as zebra, elephants, ...)
 - Urban/peri-urban cycle with humans as reservoir



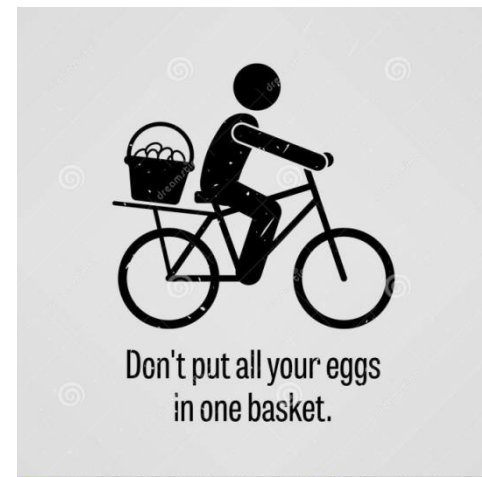
Aedes aegypti:

- diurnal activity, anthropophilic
- urban & peri-urban (mainly), peri-domestic
- breeding in clean water



Good vectors!

- Multiple feeding during a single gonotrophic cycle
- Laying of eggs: dispersed





- **Secondary routes of transmission:**

- **Sexual transmission**

- from cases in Argentina, Chile, France, Italy, New Zealand, Peru, Portugal and US
- PCR + semen

- **Trans-placental transmission**

- Tissue samples newborns with congenital malformations were ZIKA RT-PCR+ (2 cases Rio Grande do Norte)
- Amniotic fluid RT-PCR + (2 cases Paraiba)

- **Blood transfusion**

- 2.8% of asymptomatic blood donors tested PCR + (Fr Polyn)

Case-load in current epidemic

42 countries

13 countries

5 (1) countries

Country	Suspect cases (confirmed)	Guillain-Barré cases (# cases previous period)	Microcephaly/CNS malformation cases (# cases previous period)
Brazil	estimation 500 000 – 1 500 000	1 708 in 2015 (1 439/yr); 19% increase	North-East region ++; Since 10/2015: 7150 cases, 1168 confirmed of unknown cause (163 cases/year)
Colombia	65 338 (3 292)	298 Older age; men 39 cases AFP	50 microcephaly cases, 7 PCR+
Cabo Verde	7 325 (2)	-	2 cases

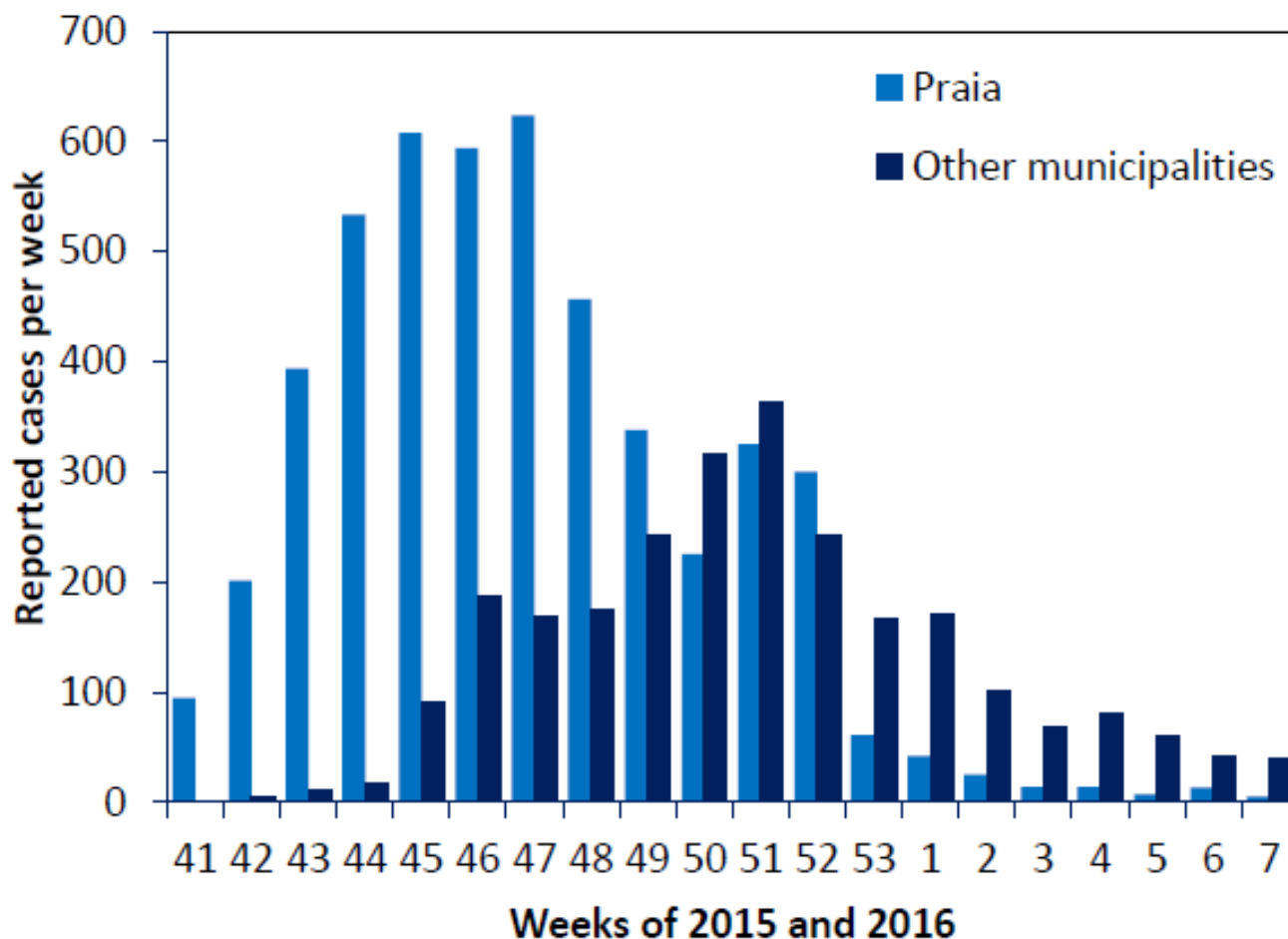
Geographical distribution of CNS malformations

Figure 4. Distribution of microcephaly and /or CNS malformation cases suggestive of congenital infections



Example of epidemic in an island

Figure 4: Suspected cases of Zika virus in Cabo Verde, 2015-2016



Source: Cabo Verde Ministry of Health Epidemiological Bulletin (21 February 2016).

ZIKA control: 3 targets of *Aedes* control

1. Human-Vector contact:

- Mosquito coils, vaporizers, repellents
- Physical barrier (screening on doors/windows)



2. Immature stages control:

- Chemical products (Larvicides)
- Biological products
- Environmental management



3. Adult mosquito control:

- Outdoor space spraying
- Indoor (residual) spraying
- Insecticide treated materials
- Lethal ovitraps
- RIDL/Wolbachia



Challenges of *Aedes* control

Methods with proven efficacy, although variable effectiveness

- Problems inherent to the tools
 - *Aedes* mosquito rest on non-sprayable surfaces (clothes)
- Poor acceptance by end-users
 - Temephos (larvicide) gives a bad smell to water
- Implementation problems
 - Lack of targeting of activities, 'Top-down'
 - Too late implementation
- Problematic sustainability of actions
 - Labour intensive and costly
 - Need for frequent application



ZIKA Challenges

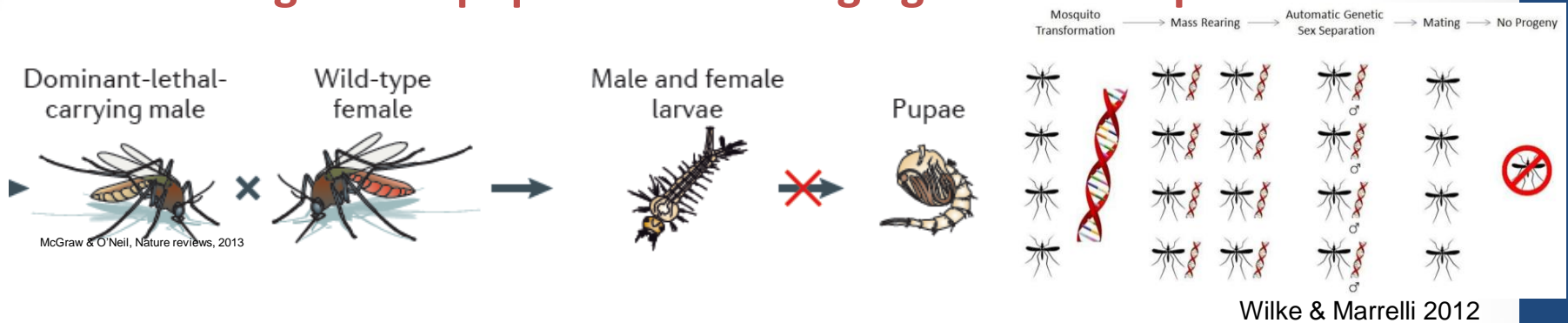
- Still spreading: effectiveness mosquito-control?
- Importance of sexual transmission in endemic areas?
- Enhanced surveillance to understand distribution, spread and nature (standardized case definitions; diagnostic testing)
- Geographical distribution of complicated cases: why?
- Weaknesses in the provision of reproductive health services for women in affected countries: information and care during and after pregnancy, prevention and termination of pregnancy



**UM MOSQUITO NÃO É MAIS
FORTE QUE UM PAÍS INTEIRO.** [27]

new PARADIGMs

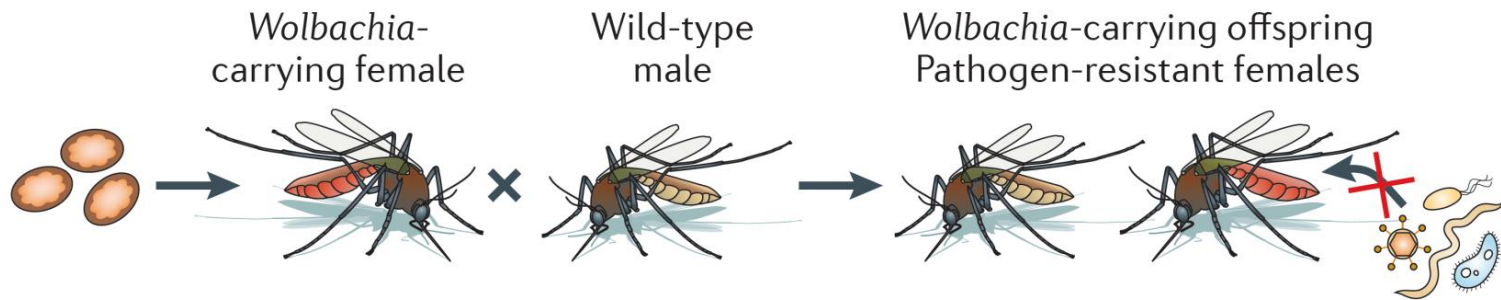
Reducing vector populations through genetic manipulation



Prototype: OX513A (OXITEC) is a transgenic strain of *Aedes aegypti*.

RIDL: Self Limiting Gene Technology

Microbial control of human pathogens in adult vectors: *Wolbachia*



Diagnosis of ZIKV by RT-PCR

