Rapid Surveillance in Emergency Situations: The Zika Experience

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Zika virus epidemic in latin America 2015-2018

- 75 countries have reported recent transmission,
- WHO estimates 478,000 cases in 2016; 31,000 in 2017 (Jan-Jun)
- Spread beyond Latin America: Florida & Texas, Singapore, SE Asia
- WHO declared PHEIC Feb-Nov 2016
- complications:
  - Guillain-Barre syndrome.
  - Congenital Zika Syndrome (microcephaly). Over 2900 confirmed cases
- Risk estimates of CZS vary from 6% (USA) to 46% (Brazil)
- Risk estimates of microcephaly 3-4% (10-11% in first trimester)

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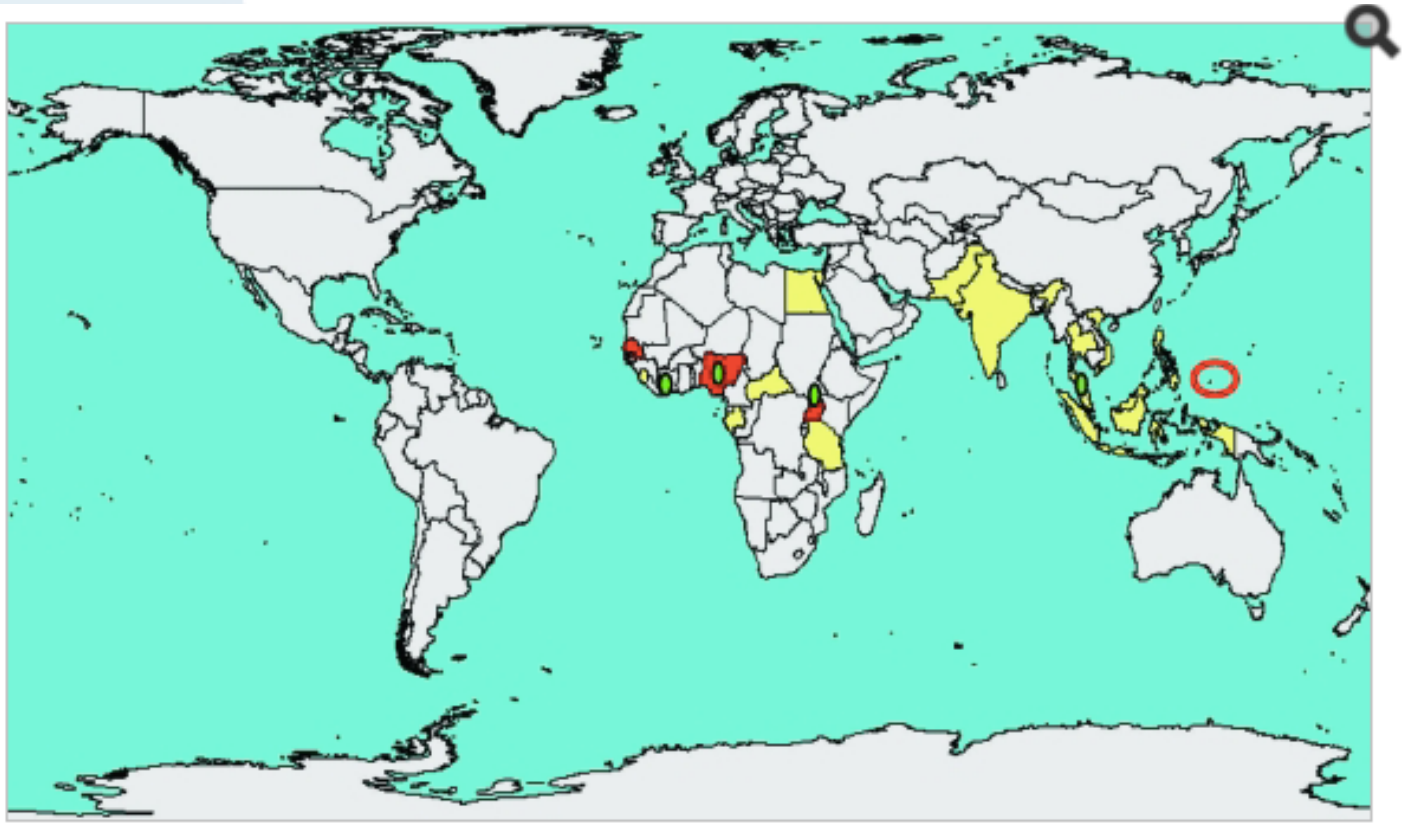
Zika 1947-2007

First isolated 1947 from rhesus monkey, Zika forest, Uganda
14 human cases reported up to 2007



Red: isolated from humans
Yellow: human antibodies
Green: isolated from mosquitos

Hayes E B. Emerg Infect Dis. 2009 Sep;15(9):1347-50

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Zika virus

Flavivirus (like dengue, yellow fever, west nile)

Main life cycle in Africa:
Aedes mosquitos and monkeys,
Humans are occasional hosts.

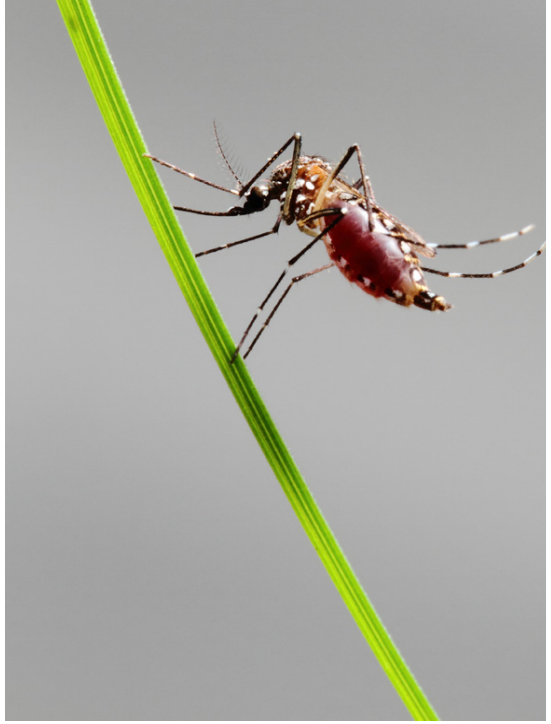
Original African lineage, subsequent Asian lineage
Asian lineage in latin America

Primary vector in urban settings: *Aedes aegypti*

Competent vector: *Aedes albopictus (and other species)*

Other routes of transmission:

- Trans-placental (mother to child)
- Sexual
- Blood transfusion (also needlestick)



Day-biting mosquito

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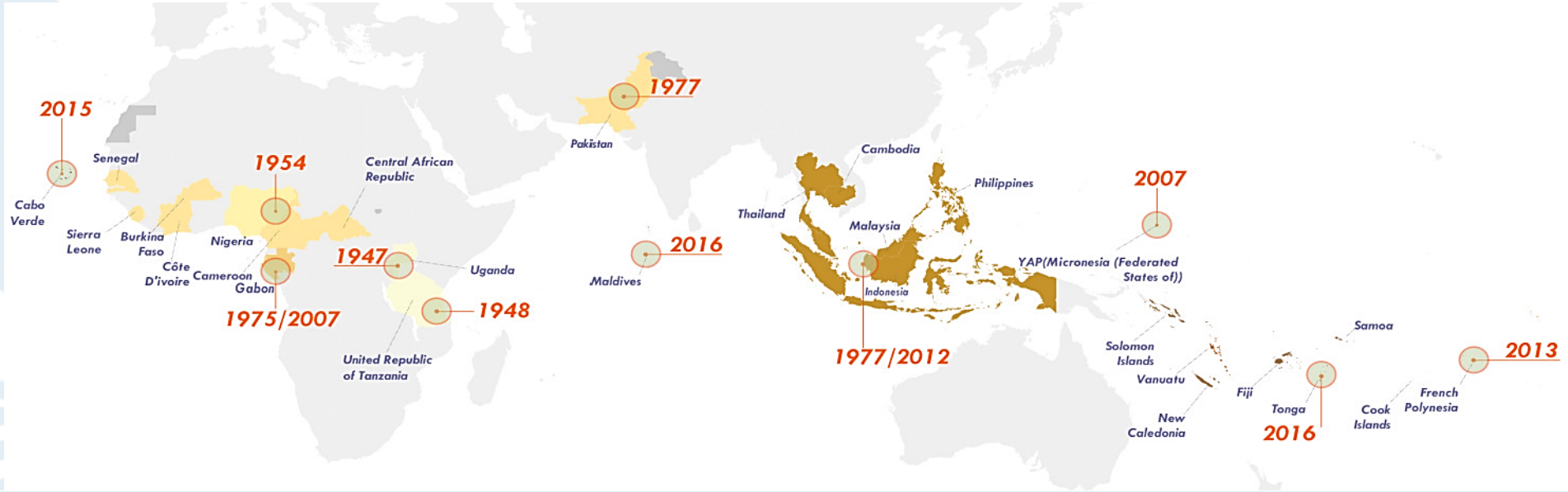
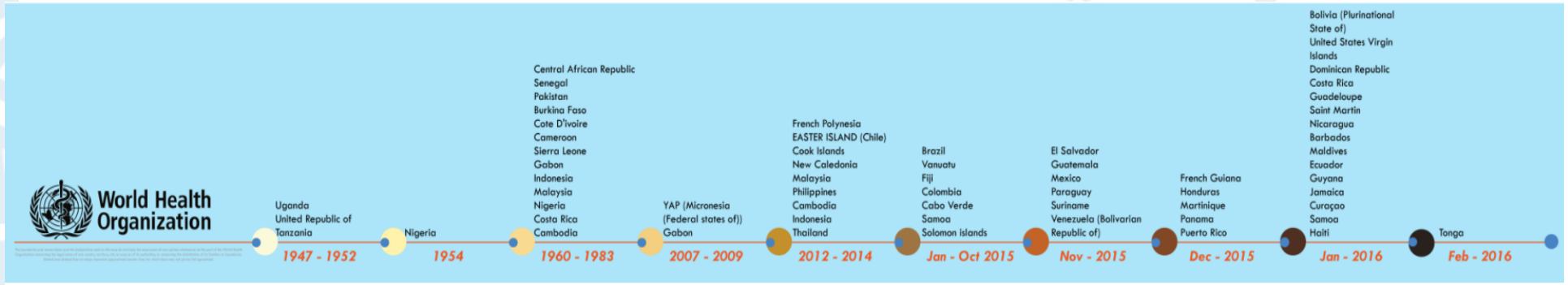
Zika timeline: global





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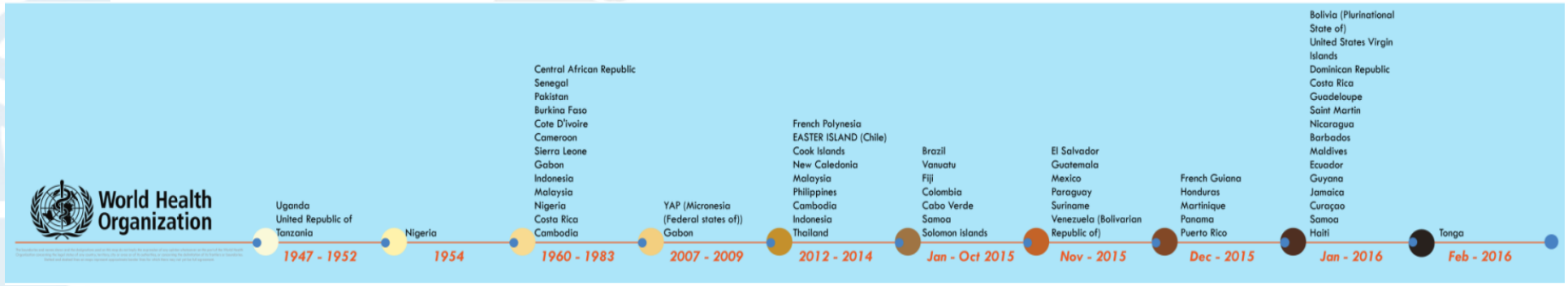
Zika timeline: the Americas



Why is this important?
Zika epidemic like this never seen before
Affects mothers and unborn children

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Zika diagnosis

Most infections have no symptoms (80% in Yap outbreak)

Non-specific viral illness

- Lasts less than 1 week
- Itchy rash, headache, muscle and joint pains, red sore eyes, mild fever
- Similar presentation to dengue (flavivirus) and Chikungunya
- These are also circulating in Brazil

Current diagnostic tests unreliable

- RNA NAT and IgM blood and urine tests of active infection insensitive after first week or two
- Trioplex RT-PCR useful in acute illness to distinguish zika, dengue and chikungunya
- IgG blood tests for exposure cross-react with dengue, yellow fever vaccine, malaria
- Blockade of blocking (BOB) assay to distinguish dengue and zika in development

How reliable are the numbers of cases reported?

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Clinical symptoms: Dengue, Chikungunya and Zika

- 3 viruses often co-circulate, all Ae aegypti vectored

	Dengue	Chikungunya	Zika
Fever	+++++	++++	+
Maculopapular rash	++	++	++++
Conjunctival hyperaemia	+	+	++++
Myalgia/arthralgia	+++	+++++	++
Oedema	Absent	++++	+++
Retro-orbital pain	+++++	+	++
Lymphadenopathy	+	++	+
Cough	Absent	Absent	Absent
Bleeding	++	Absent	Absent
Hepatomegaly	++	+++	Absent
Leukopenia / Thrombocytopenia	+++	+++	Absent

Adapted from Halstead, et al. Health Service Department, Island of Yap, Micronesia

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Microcephaly in Brazil

Apparent increase in microcephaly in neonates first noticed in Pernambuco, NE Brazil 2015

3,530 suspected cases across 20 states in 2015

14,500 suspected cases in 25 states by mid-July 2017

(*Annual microcephaly numbers in Brazil average 163 cases/year 2010-2014*)

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Rates not Numbers

Table 3. Countries and territories reporting microcephaly and/or CNS malformation cases potentially associated with Zika virus infection

Reporting country or territory	Number of microcephaly and/or CNS malformation cases suggestive of congenital Zika infections or potentially associated with a Zika virus infection	Probable location of infection
Brazil	1857[6]	Brazil
Cabo Verde	9	Cabo Verde

Rate of microcephaly per liveborns a year

Cape Verde 0.9 per thousand births
Brazil 0.6 per thousand livebirths
North Eastern Brazil 2.5 per thousand births

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Baby with Typical Head Size

Baby with Microcephaly

Baby with
Severe Microcephaly

TABLE 1—Mode of transmission and clinical findings with selected TORCH infections.

	Mode of Transmission	Hepato Splenomegaly	Cardiac Lesions	Skin Lesions	Hydrocephalus	Microcephaly	Intracranial Calcifications	Ocular Disease	Hearing Deficits
Toxoplasmosis	Food	+	–	Petechiae/purpura maculopapular rash	++	+	+	+	–
Treponema pallidum	Person to person (sexual)	+	–	+		–	–	+	–
Rubella	Person to person	+	+	Petechiae/purpura		+	–	+	++
Cytomegalovirus	Person to person	+	–	Petechiae/purpura		++	+	+	++
Herpes simplex virus	Person to person	+	+	Petechiae/purpura, vesicles		+	–	+	+
Parvovirus B19	Person to person	+	+	Subcutaneous edema, petechiae		–	–	+	–
Zika virus	Arthropods	–	?	–	–[a]	+	+	+	+

Source. Adapted from Neu et al.[10]

[a]There is ventriculomegaly, but it is too early to determine whether this will evolve into intracranial hypertension and hydrocephalus.

doi: 10.2105/AJPH.2016.303115

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Congenital infections

"Congenital Zika syndrome": wider than microcephaly alone.

- Based on 25 case series
- Similarities with rubella and other congenital infections
- Cases range in severity; some babies have neurological abnormalities with normal head circumference.
- Some babies born with normal size heads but do not grow.

What happens when the babies get older?

- Small heads
- Constant irritability and crying
- Spasms and seizures
- Eye and ear defects
- Brain stem dysfunction with swallowing defects
- Marked developmental delay

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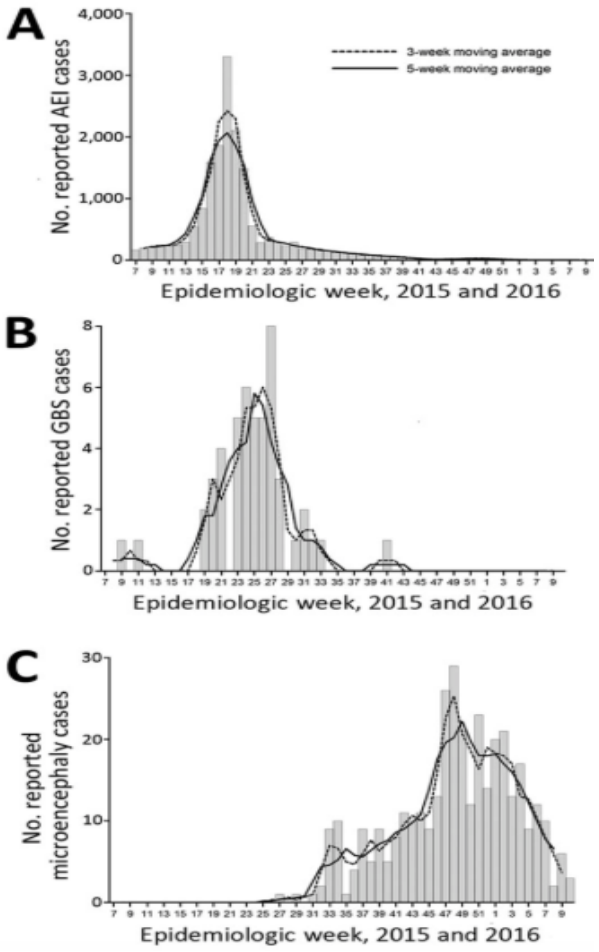
Time sequence of Zika-related cases and complications



Acute rash illness (Salvador, Brazil)

GBS cases (4 weeks later)

Microcephaly cases (6 months later)

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Paploski et al EID Volume 22, Number 8—August 2016

What has happened during this outbreak?

- With no vaccine and limited vector control measures, 93% decline in zika epidemic in 2017 likely due to ex*haustion of the pool of susceptibles*
- This has happened more rapidly than expected

- Confirmed cases in Brazil
  - 2015 – 141,000
  - 2016 – 478,000
  - 2017 – 31,000 (Jan-Jun)

- In Salvador (NE Brazil) 60% have evidence of zika exposure, also 75% dengue and 5% chikungunya (how reliable is this?)

- Epidemic has infected up to 2 million child-bearing women

- 10 s of thousands of babies could have been affected
  - How has birth rate been affected by outbreak?
  - What is the risk at different stages of pregnancy?

- Challenge for society and health services in Americas:
  - Support and linkage to care
  - Babies and their families

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Zika vaccine

- 2015 – nothing!
- But work on related flaviviruses: dengue, West Nile
- Existing animal models, immune assays, vaccine designs
- 2017 – over 40 vaccine candidates
- 13 weeks to first in-human trial
- Now most advanced vaccine in intervention trial (2400 people)
  - US, Peru, Brazil, Costa Rica, Panama, Mexico

- Few cases now, so hard to test.
- Need natural transmission causing real cases to prove vaccine works.

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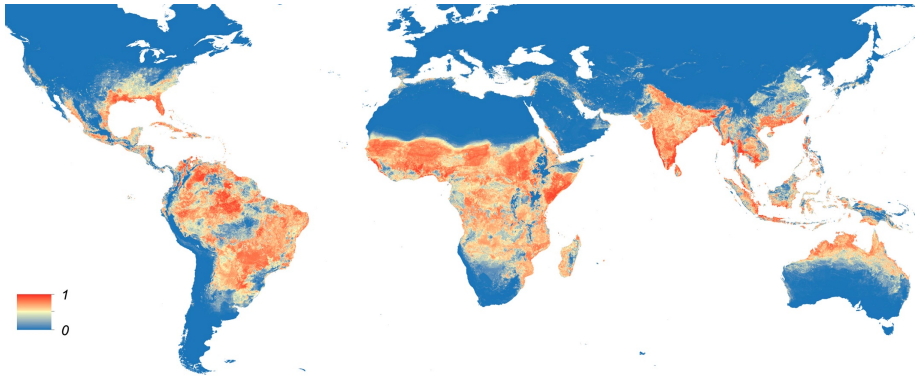
What will happen next?

- Zika still present, but much reduced. Mostly affecting populations at northern (Mexico), western (Ecuador) and southern (Uruguay, Argentina, Chile, southern Brazil) margins,
- If reported numbers are reliable, epidemic is now over until enough children are born to sustain a new outbreak: probably over 10 years until next major epidemic
- Zika found in some non-human primates (marmosets and capuchins) in Brazil. Will this affect human epidemiology?



Potential distribution of Ae aegypti

- It may move on. WHERE?
  - Vector competence and density
  - all of tropics and subtropics potentially at risk

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Biological and genetic vector control

- These techniques face many obstacles: community acceptance, spurious media claims, policy caution
- but scientific reviews consistently show to be safe.

- **Wolbachia bacteria**
  - naturally occur in many different insect species
  - causes cytoplasmic incompatibility in Ae. aegypti when introduced into mosquitos.
  - spreads in a small number of generations, replaces wild population, **reduces reproductive capability**
  - Infected male: no hatched eggs. Infected female: infected eggs.
  - small-scale trials in Vietnam, Indonesia, Colombia, Singapore, Australia and Brazil
  - Expanded trials by Eliminate Dengue Programme (EDP) funded in Colombia and Brazil (£15M grant)

- RIDL (**Release of Insects with Dominant Lethality**)
  - highly species-specific control,
  - uses a lethal gene that causes premature death of progeny, so **larvae die before reaching maturity**
  - males released with RIDL transgene, mate with wild females which produce eggs with RIDL transgene
  - dramatic reductions in native mosquito populations observed in a few weeks
  - trials in Grand Cayman, Malaysia and Brazil..
  - OXITEC establishing Brazilian factory to make 60 million male mosquitoes per week.
  - Will protect ~300,000 people in suppression phase over 4-6 weeks

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Why did zika emerge?

Several non-exclusive hypotheses:

1. Zika has evolved for enhanced mosquito transmission
   (seen in Chikungunya)
2. Asian Zika has adapted for higher viraemia in humans
   (vertical transmission, neuropathology)
3. Introduction into a naïve population susceptible to infection
4. Previous exposure to Dengue may exacerbate Zika disease
   (some evidence, 43% amino acids identical)
5. Human genetic predisposition in latin America

Shan et al., An Infectious cDNA Clone of Zika Virus to Study Viral Virulence, Mosquito Transmission, and Antiviral Inhibitors, Cell Host & Microbe (2016 in press), http://dx.doi.org/10.1016/j.chom.2016.05.004

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Sexual transmission

- 50 reports of sexual transmission globally
  - Mainly symptomatic male to female partner
  - Semen: PCR detection up to 181 d; virus isolation up to 4 week

- Sexual transmission is worrying and challenging for public health but is not sufficient to sustain an epidemic

- Preventing potential sexual transmission to pregnant women and women planning pregnancy (UK guidance):
  - Condom & contraception advice for returning men & partners
  - For 8 weeks after returning if never symptomatic or diagnosed
  - For 6 months if compatible illness or lab-confirmed
  - WHO recommend safe sex for all for 6 months

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