Harvard Brazil Collaborative Course
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LECTURE

Dengue Fever

Mary Elizabeth Wilson, MD
Harvard School of Public Health
mewilson@hsph.harvard.edu

Objectives

- Describe the epidemiology of dengue fever in Brazil and globally
- Describe the consequences of infection
- Review transmission cycles
- Define factors that influence vector populations
  - (e.g., location, abundance, extrinsic incubation)
- Describe approaches to dengue control
- Review receptivity of region to other vector-borne viruses

References

- Key references
  - **Simmons CP, Farrar JJ, Chau NvV, Wills B. Dengue. N Engl J Med 2012; 366:15:1423-32.
  - Teixeira MG, Costa Mda C, Barreto F, Barreto ML. Dengue: twenty-five years since reemergence in Brazil. Cad Saude Publica 2009;25 Sup 1:S7-S18.
  - Bhatt S, et al. The global distribution and burden of dengue. Nature 2013;496:504-7.

References: General

- WHO. Dengue. Guidelines for diagnosis, treatment, prevention and control. 2009. 160 pp. Online.
- Martin et al. The epidemiology of dengue in the Americas over the last three decades: a worrisome reality. Am J Trop Med Hyg 2010;82:128-135.
- Regis LN, et al. Sustained reduction of the dengue vector population resulting from an integrated control strategy applied in two Brazilian cities. PLoS One. July 2013
- Shepard DS, et al. Economic impact of dengue illness in the Americas. AJTMH 2011;84:200-207.

Questions for Discussion

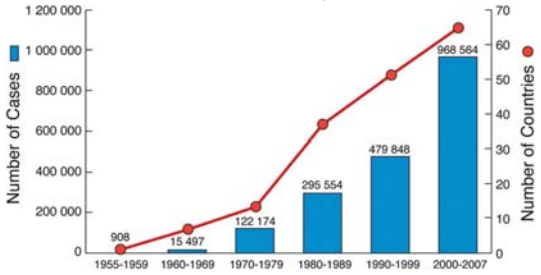
- Why is dengue causing larger and more severe epidemics?
- Where is the virus between epidemics?
- Where do new serotypes come from?
- Explain the seasonality and the year-to-year changes in the epidemiology.
- Why does mortality vary by region?

Dengue

- Mosquito-transmitted flavivirus
- Single-stranded RNA virus
- Four major serotypes (DENV 1, DENV 2, DENV 3, DENV 4)
- >3.6 bil persons live in at-risk areas
- Present in tropical and subtropical areas worldwide

The increasing dengue problem, 1955–2007

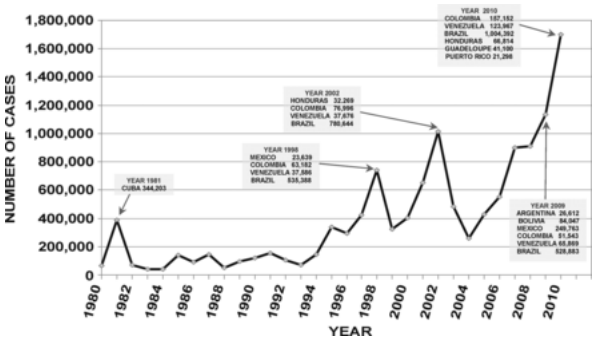
More cases, more places



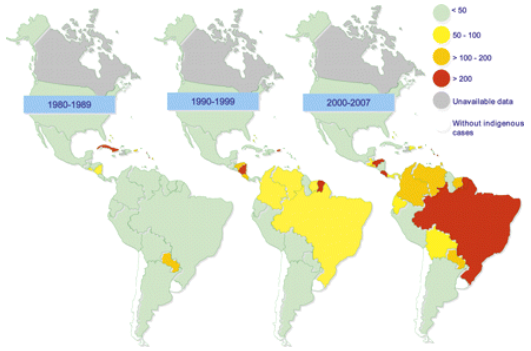
Laughlin C A et al. J Infect Dis. 2012;206:1121-1127

The Journal of Infectious Diseases

Dengue in the Americas



Average Incidence of Dengue per 100,000, 1980-2007



AJTMH 2010;82:128.

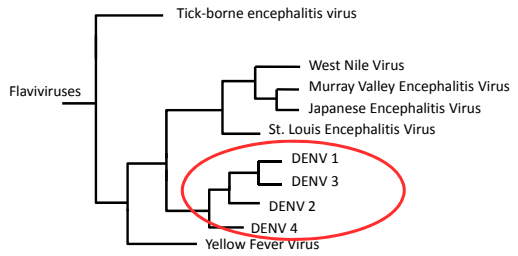
Disease Burden Estimates

2010 data

- 390 million infections/year
- 96 million with symptoms
- Global burden:
  - Asia 70% (half in India)
  - Africa 16%
  - Americas 14% (>half in Brazil and Mexico) [13.3m sx; 40.5m inapparent]
  - Oceania 0.2%

Bhatt et al. Nature; 2013:496:504-07.

Dengue Virus (DENV)



- Long-term protection to infecting virus-type
- No long-term cross protective immunity
- Can be infected up to 4 times during ones lifetime

Dengue Infections

- Incubation 4-7 days (3-14)
- Infection
  - Asymptomatic or mild
    - Ratio of asymptomatic to symptomatic: 2:1 to 10:1
  - Acute febrile illness (dengue fever)
  - Dengue hemorrhagic fever (DHF)
  - Dengue shock syndrome (DSS)
  - No chronic carrier state

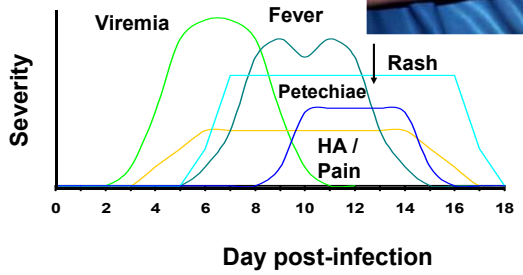
Clinical Findings

- Headache, fever, myalgia
- Nausea, vomiting
- Rash (50%)
- Laboratory
  - Low WBC
  - Low platelets
  - Abnormal liver function

Clinical Course

- Initial febrile phase
  - Lasts 3-7 days
  - Most recover without complications
- Critical phase (at defervescence)
  - Small percent develop vascular leak syndrome
  - Can develop shock, hemorrhage
- Spontaneous recovery phase

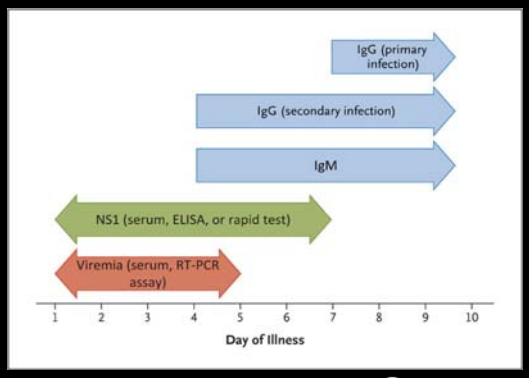
Dengue Hemorrhagic Fever/Shock Syndrome



WHO Classification
Dengue or Severe Dengue

- Dengue: recover, no major complications
- Severe dengue:
  - Plasma leakage resulting in shock and/or
  - Accumulation of serosal fluid -> respiratory distress
  - Severe bleeding
  - Severe organ impairment

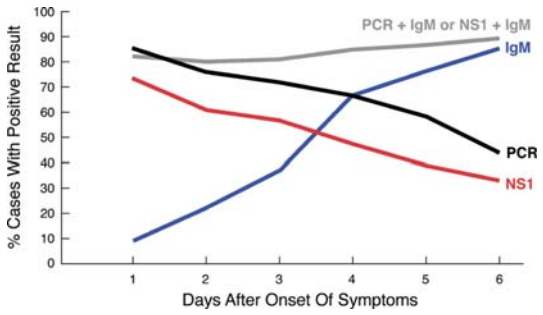
Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection



Simmons CP et al. N Engl J Med 2012;366:1423-1432.

The NEW ENGLAND JOURNAL of MEDICINE

Sensitivity of dengue diagnostic tests.



Laughlin C A et al. J Infect Dis. 2012;206:1121-1127

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.

The Journal of Infectious Diseases

Risk Factors for Severe Disease

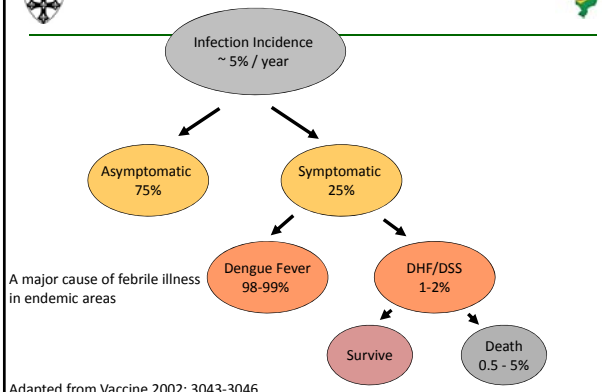
- Young age
- Female sex
- High body mass index
- Virus strain
- Host genetic make-up
- Second infection with different serotype
  - Antibody-dependent enhancement of virus

Severe & Complicated Dengue

- Mortality > 20% (<1% with good care)
- Risk for DHF increased ~100x with 2nd infection (different serotype)
- Thailand, 2 cohort studies
  - DHF rate 0 in primary infection
  - 1.8% and 12.5% with 2nd
- Virulence may also vary by genotype

Am J Epidemiol 1984;120:653
AJTMH 1988;38:172

Dengue Virus Infection



A major cause of febrile illness in endemic areas

Adapted from Vaccine 2002; 3043-3046

Treatment

- Current: close observation; judicious use of parenteral fluids
- Clinical trials
  - Chloroquine
  - Prednisolone
  - Balapiravir
  - Statins, other antiviral

Vaccines

- Multiple vaccines are in development
- Vaccine trials are ongoing
  - Will provide better understanding of the immunology of dengue
  - Several are in phase 2 and 3 clinical trials
- Vaccines will not solve dengue problem

Aedes aegypti

Aedes Aegypti

- Wide distribution in urban areas
  - Well adapted to contemporary urban life
- Breeding sites
  - Discarded plastic containers, cans
  - Used tires, flowerpots, tree holes
  - Construction sites
- Enters homes; prefers human blood
- Nervous feeder; multiple hosts

Aedes Aegypti

- Usually do not disperse beyond 100 m
- Most movement of dengue viruses occurs via movement of viremic hosts
- Females typically distribute eggs among multiple sites

Vertical Transmission of Dengue Virus

- Transovarial (vertical) transmission of virus can occur (female MQ to eggs)
- *Ae aegypti eggs* subjected to adverse hatching conditions can remain viable in the environment >100 days
- Resistant to desiccation

Vector Dispersal Horizontal and Vertical

- Study site: Singapore
- *Ae aegypti* & *Ae albopictus* fed rubidium-laced blood; female offspring released
- Female movement traced (oviposition sites)
- Findings:
  - Horizontal: radius of 320 m
  - Vertical: release on level 12 of 21-story apt; dispersed to top and bottom

Liew C, Curtis CF. Med Vet Entomol 2004;18:351-60.

Environmental Influences on Vector

- Presence or absence
- Abundance; longevity of adult
- Time for development
- Frequency of biting
  - Blood feeding frequency increases with higher temperatures
- Extrinsic incubation period (time for virus to disseminate in mosquito)
- Seasonality of pathogen transmission

Extrinsic Incubation Period

- Time between entry of organism into vector and time when vector can transmit pathogen
- Sensitive to environmental conditions
- If extrinsic incubation period exceeds lifespan of vector, it cannot transmit infection

Extrinsic Incubation and Dengue

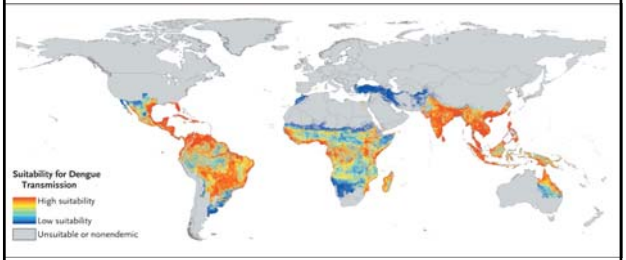
- Temperature: inverse relationship with EI period (<20 C *Ae aegypti* eggs do not hatch)
  - 12 days for mosquitoes at 30 C
  - 7 days at 32 and 35 C
- Temperature required for effective transmission depends on virus & vector

Watts et al. Am J Trop Med Hyg 1987;36:143-52.

Dengue/Mosquito Interaction

- *Aedes aegypti* needs viral titer 10^5-10^7 particles/ml of blood to become infected
- Vector serves to select viruses that produce high viremia in humans

Global Dengue Risk



Simmons NEJM 2012;366:1424

Figure 4. Map of all airports included in risk model.

Gardner L, Sarkar S (2013) A Global Airport-Based Risk Model for the Spread of Dengue Infection via the Air Transport Network. PLoS ONE 8(8): e72129. doi:10.1371/journal.pone.0072129
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0072129

PLOS | ONE

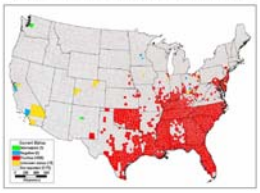
Distribution of Dengue Virus Vectors, United States, 2005

Aedes aegypti

Reported distribution of *Aedes aegypti* in the U.S., 2005

Aedes albopictus

Reported distribution of *Aedes albopictus* in the U.S., 2005



Source: Chester G. Moore, Ph.D., Colorado State University

WHO: Dengue Risk Areas and Year-round Survival of *Ae. Aegypti*

Cities with one million or more population, 2000

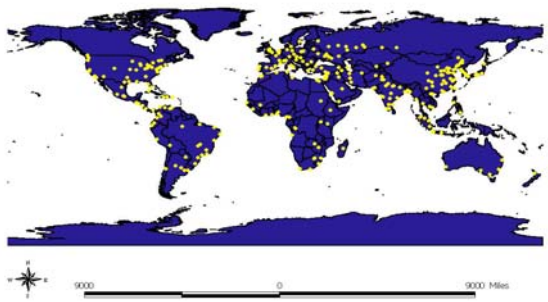
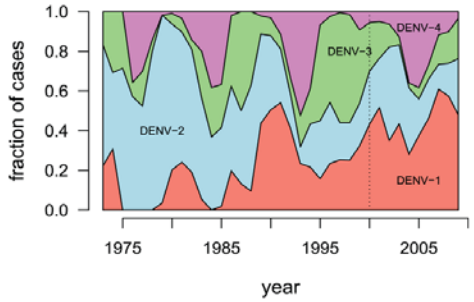


Figure 2. Estimated relative prevalence of the 4 serotypes in Thailand.

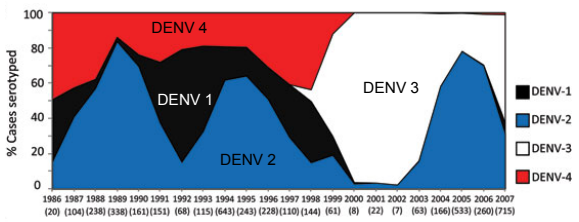


Chao DL, Halstead SB, Halloran ME, Longini IM (2012) Controlling Dengue with Vaccines in Thailand. PLoS Negl Trop Dis 6(10): e1876. doi:10.1371/journal.pntd.0001876
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001876

PLoS NEGLECTED TROPICAL DISEASES

Distribution of Dengue Virus Types: 1986-2007*

(number of DENV-2 each year)

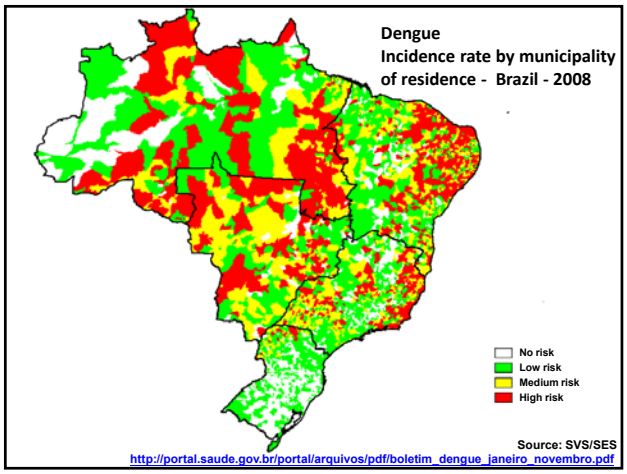


*As percent of positive patient isolates

McElroy et al. Emerg Infect Dis 2011;17:66.

Increase in Dengue Fever

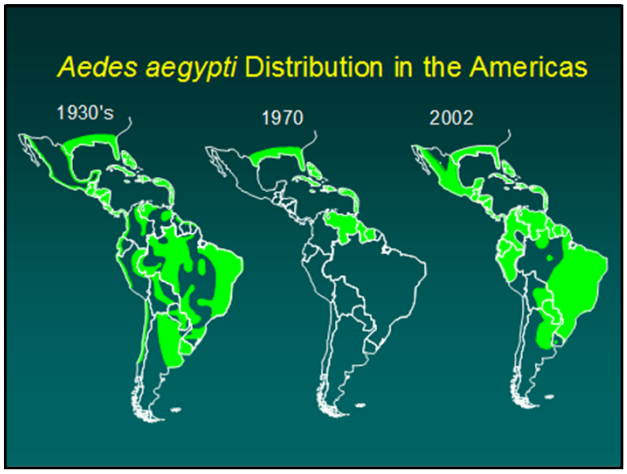
- Travel and migration
  - Dispersal of competent vectors
- Urbanization, especially in tropics
- Growing population
  - More urban areas large enough to sustain ongoing viral circulation
- Poor housing, inadequate water supply
- Poor vector control and resistance



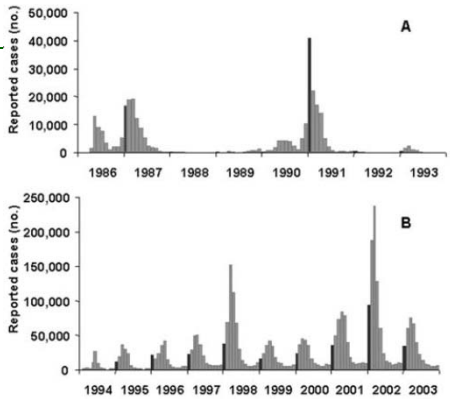
Chronology of Dengue in Brazil

- 1981-1993: localized epidemics
  - 1981 outbreak DENV 1 & DENV 4 in NW
  - 1986 DENV 1 in Rio de Janeiro State
  - 1990 intro DENV 2 Rio State; first confirmed DHF
- 1994-2002: epidemic/endemic countrywide
  - 1994-1999 *Ae aegypti* dispersed countrywide
  - 1999 widespread outbreaks
  - 2000 intro DENV 3 in Rio State
  - 2002 large outbreaks (dengue deaths>malaria deaths)

Siqueira et al. EID 2005;11:48

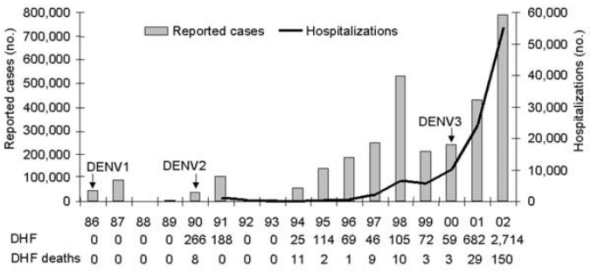


Brazil: Reported Dengue Cases per Month, 1986-2003



Siqueira et al. EID 2005;11:49

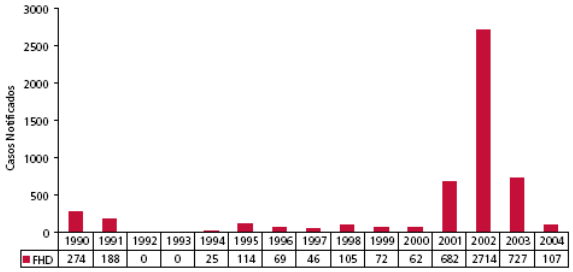
Reported Cases & Hospitalizations: DF/DHF, Brazil 1986-2002



Siqueira et al. EID 2005;11:50

Cases of Dengue Hemorrhagic Fever

Figura 12.3: Número de casos notificados de febre hemorrágica da dengue. Brasil, 1990 – 2004.



Secretaria de Vigilancia em Saude 2005

Regional Incidence of Dengue

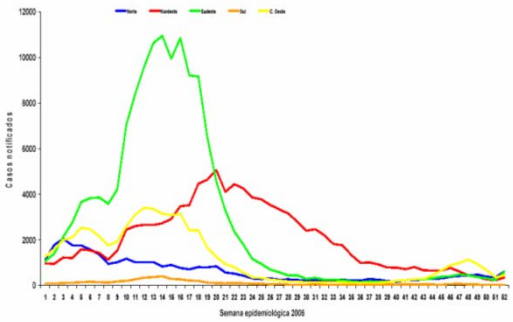
per 100,000 population (wk 1-23)

	2008	2009	Serotype 09
North	429	296	DENV 1,2
Northeast	434	226	DENV 1,2
Southeast	438	150	DENV 1,2,3
South	55	27	DENV 3
Midwest	424	475	DENV 1,2,3
Bahia	215	631	DENV 2
Overall	380	189	

Ministerio da Saude, 2009

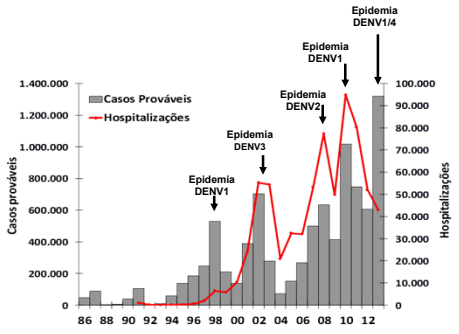
Dengue Cases Notified by Week by Region, 2006

Gráfico 1. Casos Notificados de Dengue por Semana Epidemiológica segundo Região, Brasil, 2006



Secretarias de Estado da Saude

Reported Cases and Hospitalizations DF/DHF by Month, Brasil, 1986 – 2013*



Source: FHD Brasil, 1986-2013*

* - until September

Dengue: Brazil 2012

- Clinical dengue: 565,510 (>1 million, 2010)
- Severe dengue: 4055
- Deaths: 284 (7%)
- Serotypes: DENV 1,2,3,4
- Dengue cases in the Americas: >1.1 million

Aedes Albopictus: Asian Tiger Mosquito

Studies

- Mosquitoes survived better in slum areas (mark, release, recapture study)
  - *Ae. aegypti* home preference (Rio: 98% found near homes
- *Ae. albopictus* potential role as bridge vector
  - Will feed on wide range of hosts
  - Can survive in rural and forest environments

Maciel-de-Freitas R et al. AJTMH 2007;l76:659.
Lorenco-de-Olivera R et al. J Vector Ecol 2004;29:94

Photo by Felix Lam

Chikungunya Virus

Chikungunya Virus

- Alphavirus, family *Togaviridae* (first identified in Tanzania, 1953)
- Emerged in Indian Ocean islands 2005
- Has moved to India, other countries in region; explosive outbreaks; high attack rates
- Spread by *Aedes aegypti* and *Ae albopictus*
- Will it spread to the Americas?

Chikungunya Virus

- Point mutation of virus associated with enhanced replication of virus in mosquito midgut (*Ae. albopictus*)
- More rapid dissemination into mosquito salivary glands
- 100-fold higher virus concentration in mosquito saliva
- Mutation absent initially (Reunion outbreak); later found in >90% isolates

Tsetsarkin KA, et al. A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS Path Dec 2007.

Shipping: Containerization

- ~90% of non-bulk cargo worldwide moves by containers stacked on container ships
- >20 million containers make >200 m voyages/yr
- Ships can hold >14,500 units
- Often goes directly from ship to destination, where it is opened

Fig 3.5, p. 157. IOM workshop report, 2010.

Preparedness and Response for Chikungunya Virus Introduction in the Americas

CDC and PAHO

http://www.paho.org/hq/index.php?option=com_content&view=article&id=3545&Itemid=2545&lang=en

Vector Control

- Current vector control strategies have not controlled dengue
- Resistance of mosquitoes to pesticides is increasing
- New approaches
  - Sterile mosquitoes
  - Symbiotically infected mosquitoes
  - Novel traps to attract adults

Wolbachia: Biological Control Agent

- *Wolbachia pipientis*: intracellular insect bacterium; maternally-inherited agent
- Embryonic introduction of *Wolbachia* into *Aedes aegypti*
- Can spread rapidly in uninfected host populations by inducing cytoplasmic incompatibility
  - Embryos from uninfected females die when mated with infected males
- Also influence mosquito ability to transmit
  - Reduce life span or reduce viral proliferation

Sterile Insect Technology

- Rear, sterilize, and release large number of disabled insects
- Sterile insects mate with wild insects; decrease reproductive potential of target
- Open field trial of engineered *A. aegypti*
  - Released across 10 hectares for 4-wk period
- Grand Cayman Island (Caribbean)
- Successful mating with wild females and fertilized their eggs

CDC Yellow Fever Vaccine Recommendations in the Americas
CDC Yellow Book
Current as of 2012

Questions for Discussion

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- Where is the virus between epidemics?
- Where do new serotypes come from?
- Explain the seasonality and the year-to-year changes in the epidemiology.
- Why does mortality vary by region?