

# CDC PUBLIC HEALTH GRAND ROUNDS

## Dengue and Chikungunya in Our Backyard: Preventing *Aedes* Mosquito-Borne Diseases



**May 19, 2015**



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# Dengue, Chikungunya, and Other *Aedes* Mosquito-Borne Diseases



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# Viruses Transmitted by *Aedes aegypti* and *Aedes albopictus* Mosquitoes

<b>Virus</b>	<b><i>Aedes aegypti</i></b>	<b><i>Aedes albopictus</i></b>
Dengue 1–4	X	X
Chikungunya	X	X
Yellow fever	X	
Zika	X	

# *Aedes aegypti* and *Aedes albopictus* Mosquitoes

- ❑ *Aedes* (*Stegomyia*) subgenus
- ❑ Lay eggs in peridomestic water containers
- ❑ Live in and around households
- ❑ Peak feeding during daytime
- ❑ *Aedes aegypti* more efficient vector for humans



*Aedes aegypti*

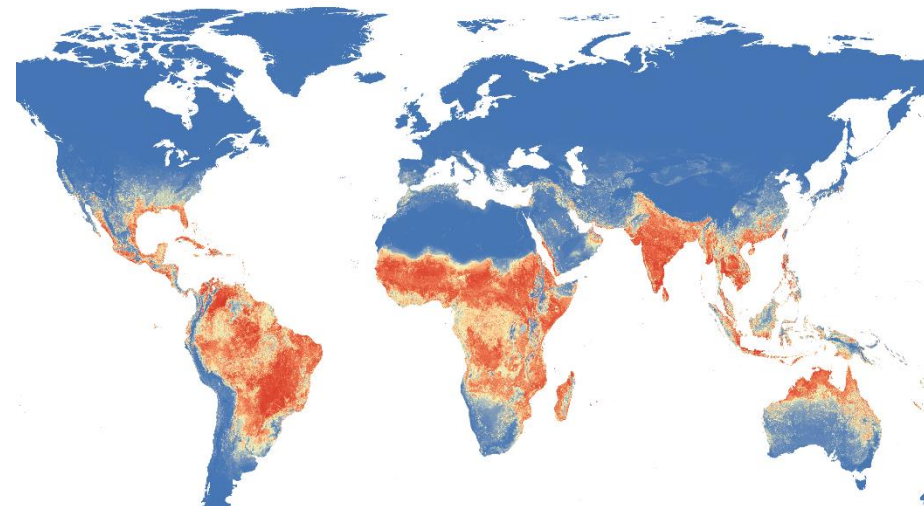


*Aedes albopictus*

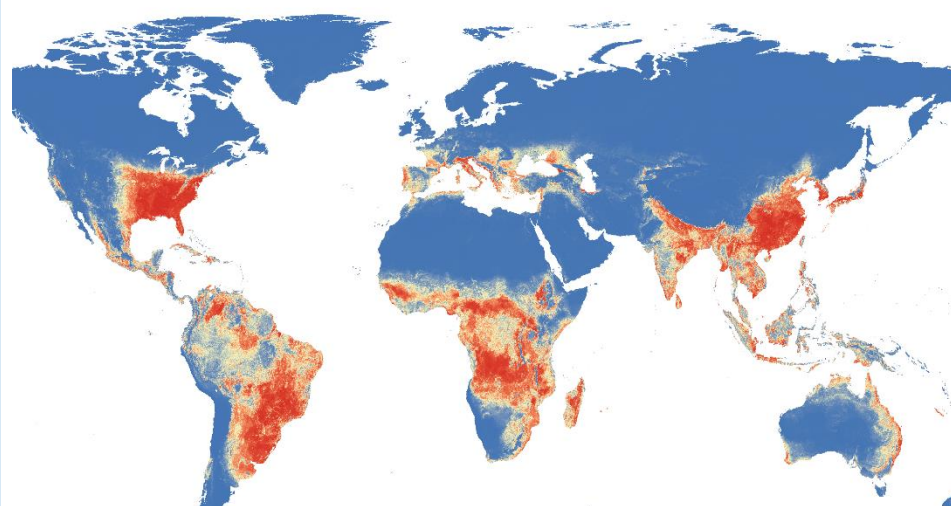


# Approximate Distribution of *Aedes aegypti* and *Aedes albopictus* Mosquitoes

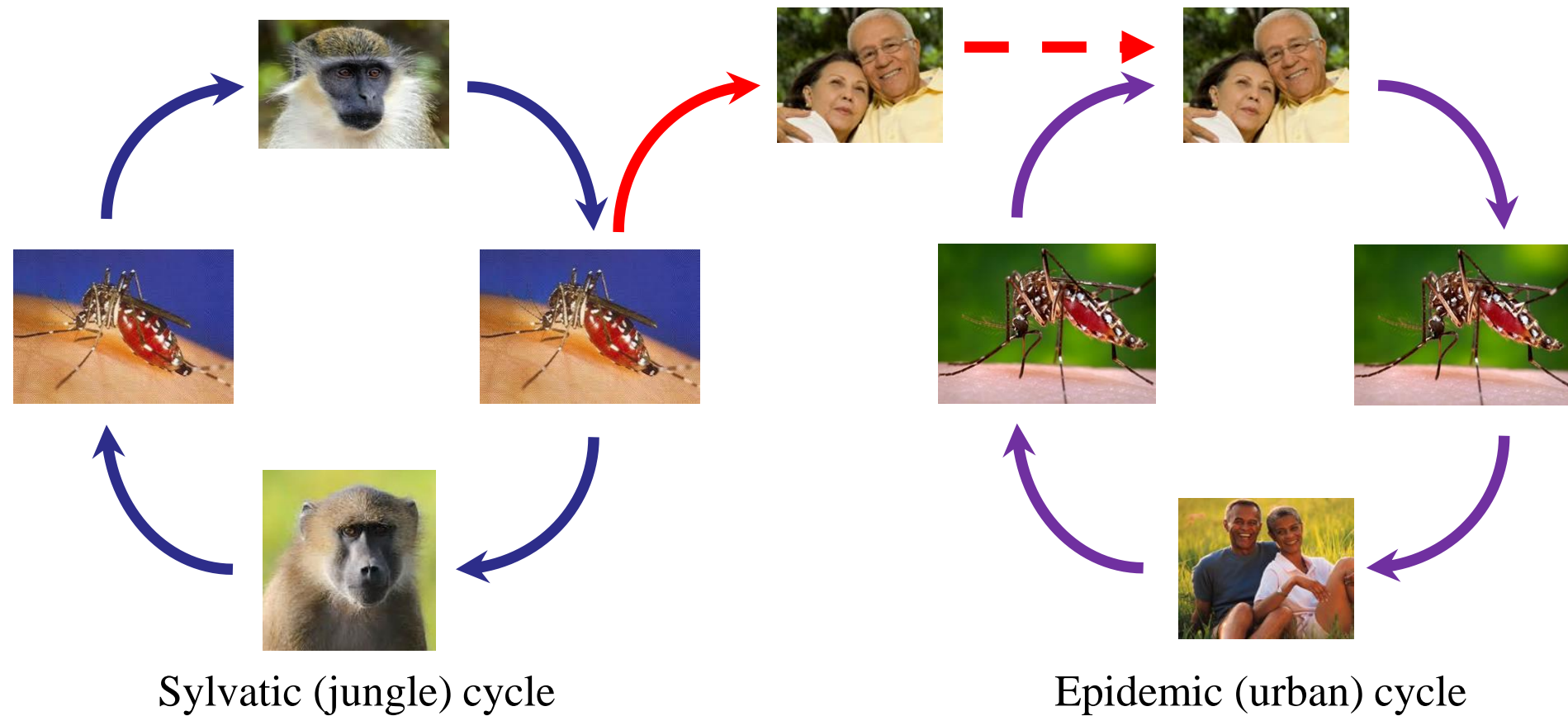
*Aedes aegypti*



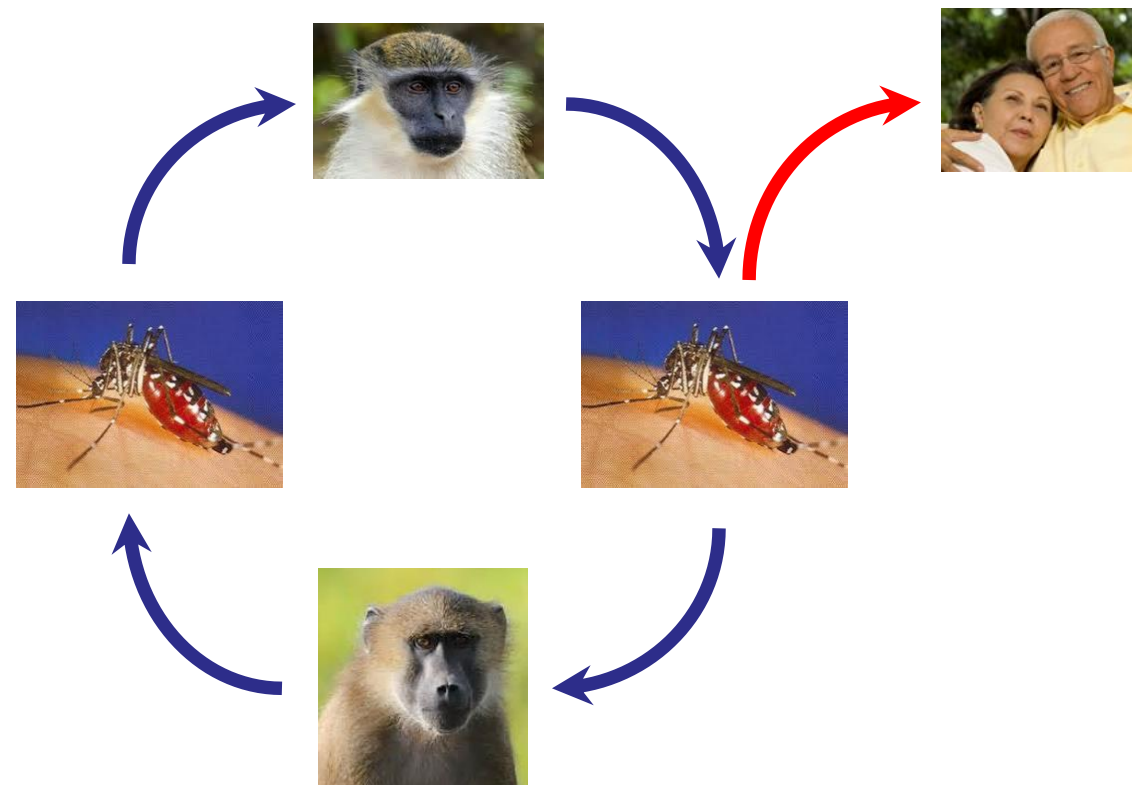
*Aedes albopictus*



# Aedes Mosquito-Borne Virus Transmission Cycles

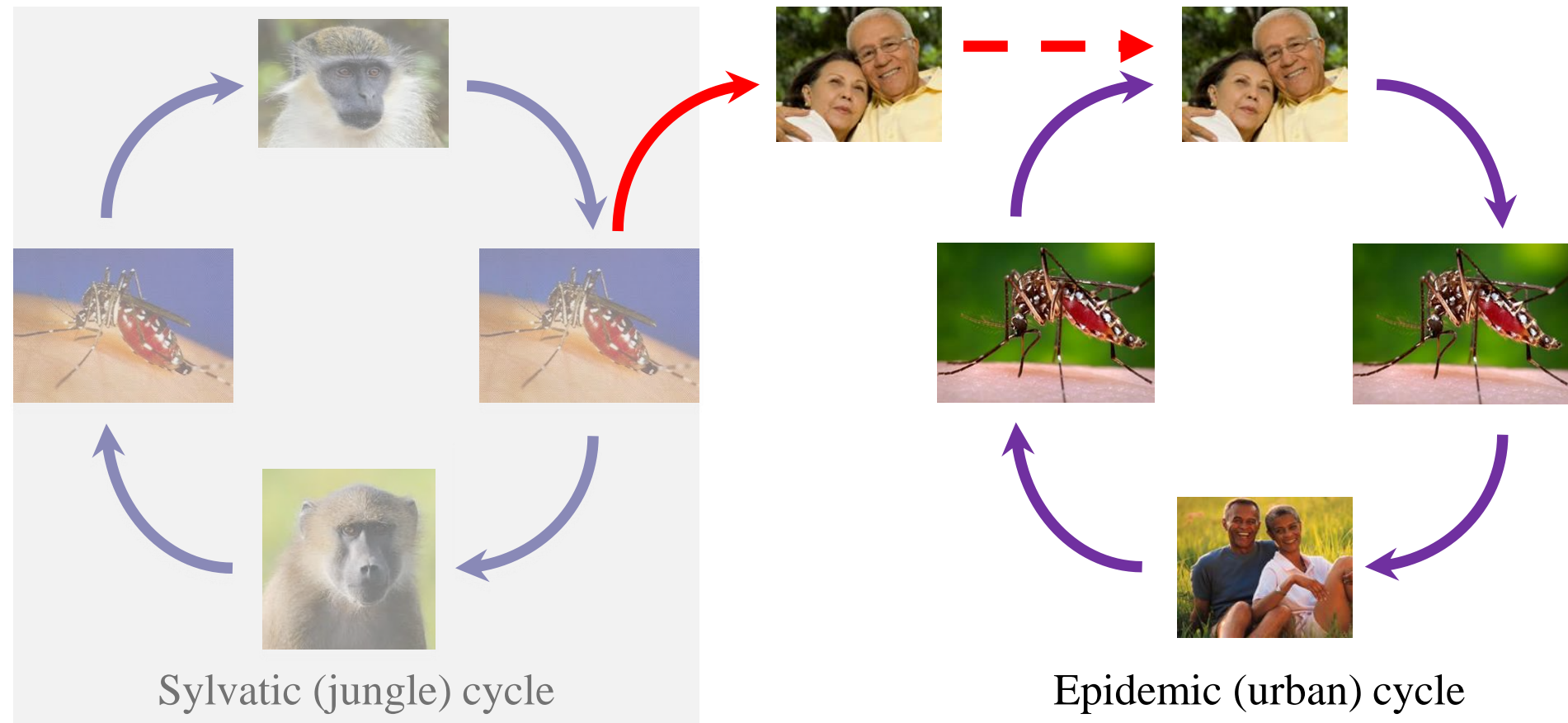


# Sylvatic (Jungle) Transmission Cycle



Sylvatic (jungle) cycle

# Epidemic (Urban) Transmission Cycle





# Dengue Virus Types 1–4

- ❑ **Four related viruses in genus *Flavivirus***
- ❑ ***Aedes aegypti* is primary vector**
  - *Aedes albopictus* also transmits dengue viruses
- ❑ **Humans are primary amplifying host**
  - Transmitted in epidemic (urban) cycle
  - Sylvatic cycle no longer needed to maintain virus

# Dengue Virus Types 1–4: Approximate Geographic Distribution



Bhatt S, et al. Nature 2013

# Dengue Virus Epidemiology

- ❑ **Most important mosquito-borne viral disease**
- ❑ **30-fold increase in incidence over past 50 years**
- ❑ **25% of infected people develop clinical symptoms**
  - Ranges from mild febrile illness to life threatening disease
- ❑ **Estimated 96 million disease cases in 2010**
  - 67 million cases in Asia
  - 16 million cases in Africa
  - 13 million cases in the Americas

# Dengue Virus Disease and Outcomes

- ❑ **Acute febrile illness often with**
  - Headache, retro-orbital pain, myalgia, and arthralgia
  - Maculopapular rash
  - Minor bleeding
- ❑ **5–10% symptomatic patients develop severe disease**
  - Plasma leakage with shock or respiratory distress
  - Severe hemorrhage
  - Organ impairment
- ❑ **Subsequent infection with different type of dengue virus increases risk for severe disease**
- ❑ **Case fatality for severe dengue as high as 10%**
  - Proper case management reduces mortality to <1%

# Chikungunya Virus

- ❑ **Genus *Alphavirus***

- ❑ ***Aedes aegypti* primary vector**

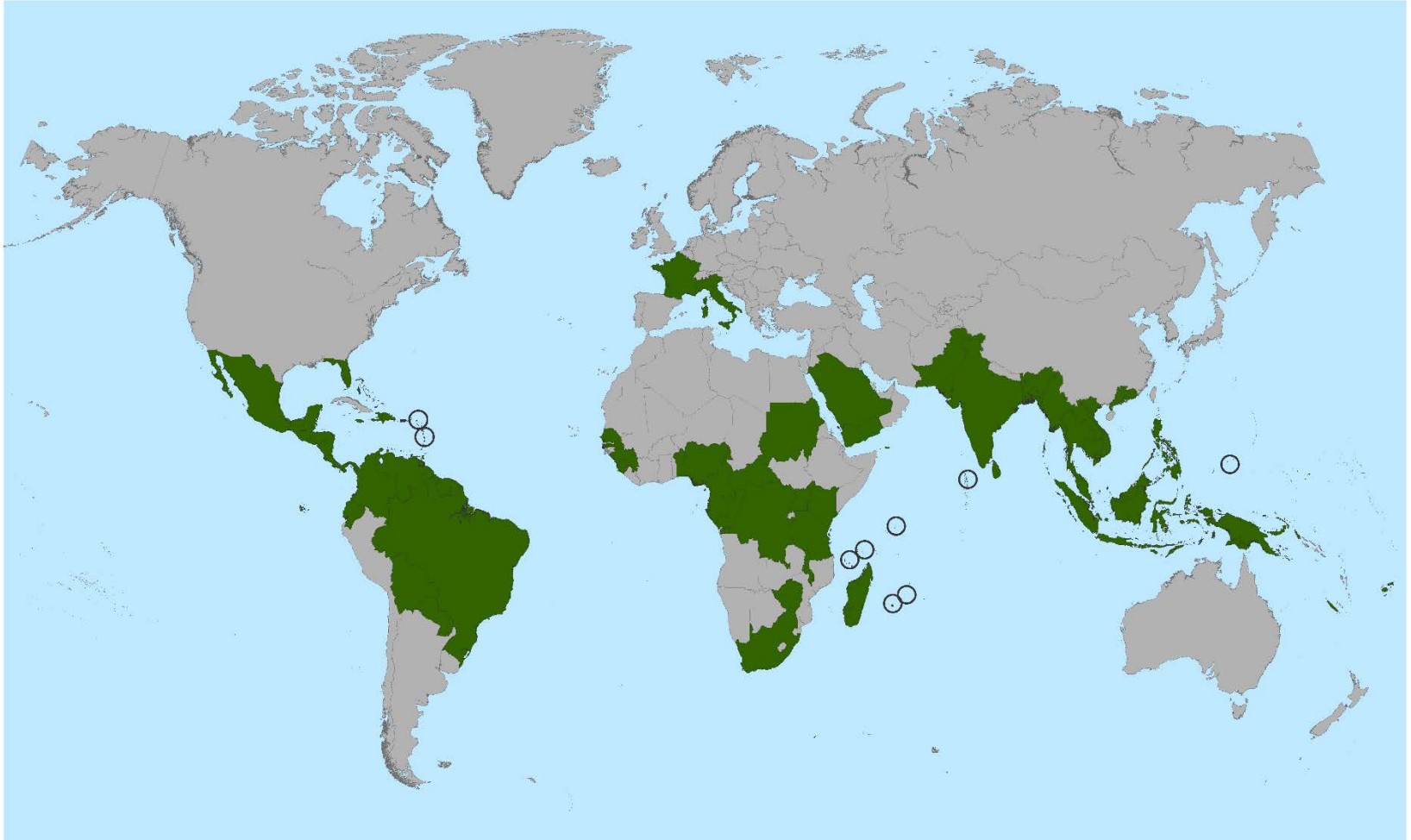
- *Aedes albopictus* important in several recent outbreaks

- ❑ **Humans primary amplifying host during outbreaks**

- Sylvatic transmission in non-human primates in Africa
- Role of other animals in maintaining the virus not known

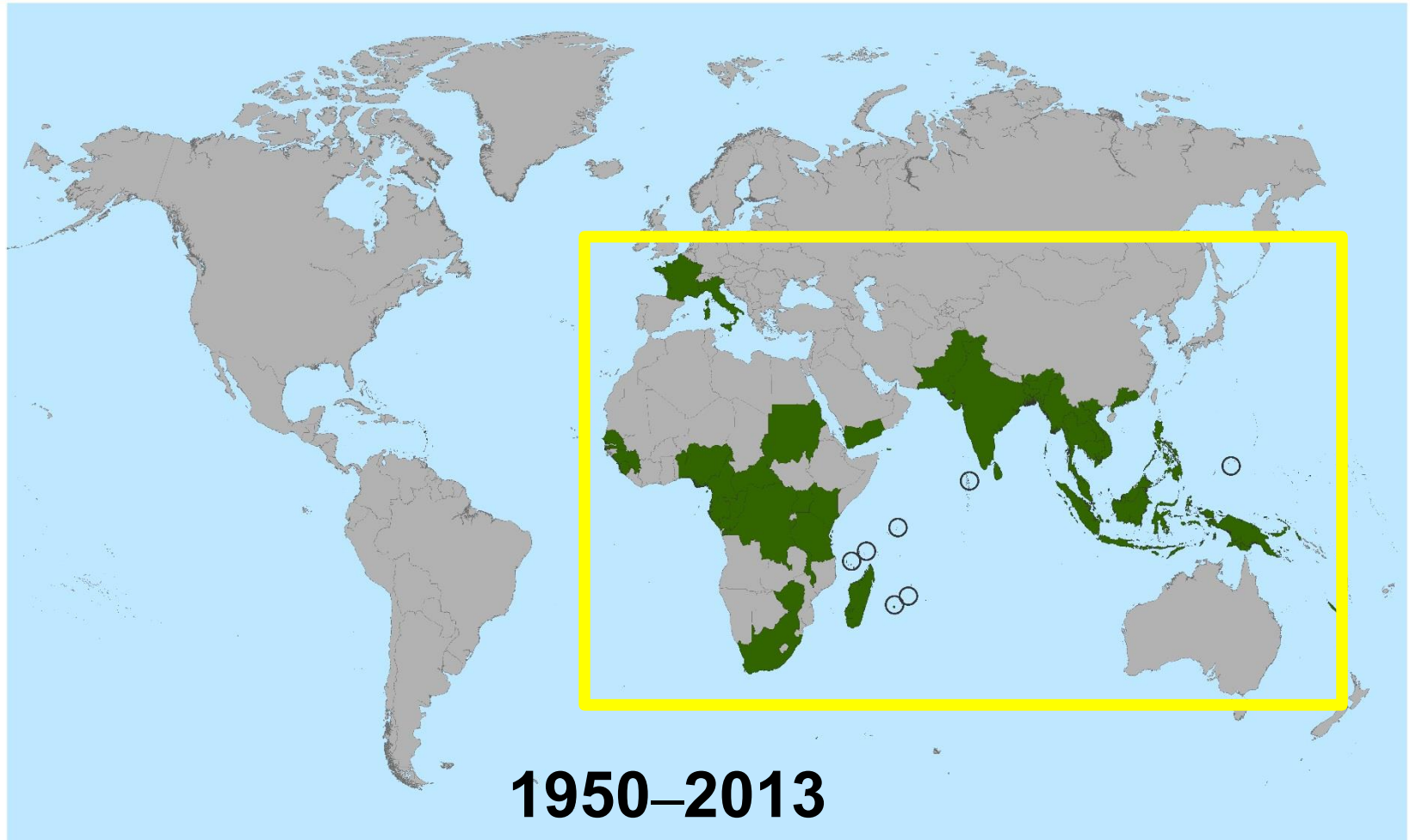


# Chikungunya Virus: Approximate Geographic Distribution



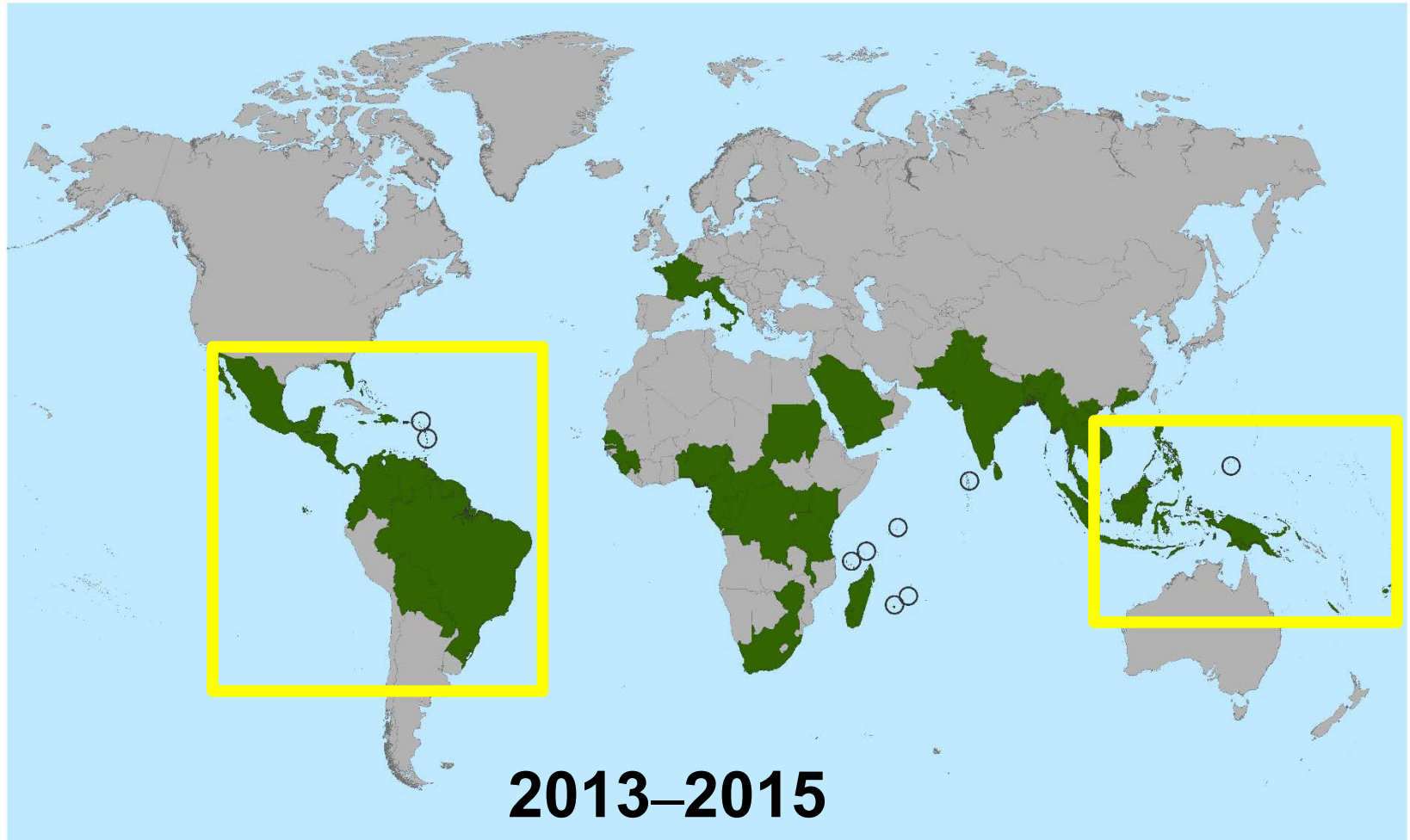
Available at <http://www.cdc.gov/chikungunya>

# Chikungunya Virus: Approximate Geographic Distribution



Available at <http://www.cdc.gov/chikungunya>

# Chikungunya Virus: Approximate Geographic Distribution



Available at <http://www.cdc.gov/chikungunya>

# Chikungunya Virus Epidemiology

- ❑ **Large outbreaks with high infection rates ( $\geq 30\%$ )**
- ❑ **Majority (72%–97%) of infected people symptomatic**
- ❑ **Over 1 million suspected cases reported in 2014**
  - Mostly in the Caribbean, and Central and South America

# Chikungunya Virus Disease and Outcomes

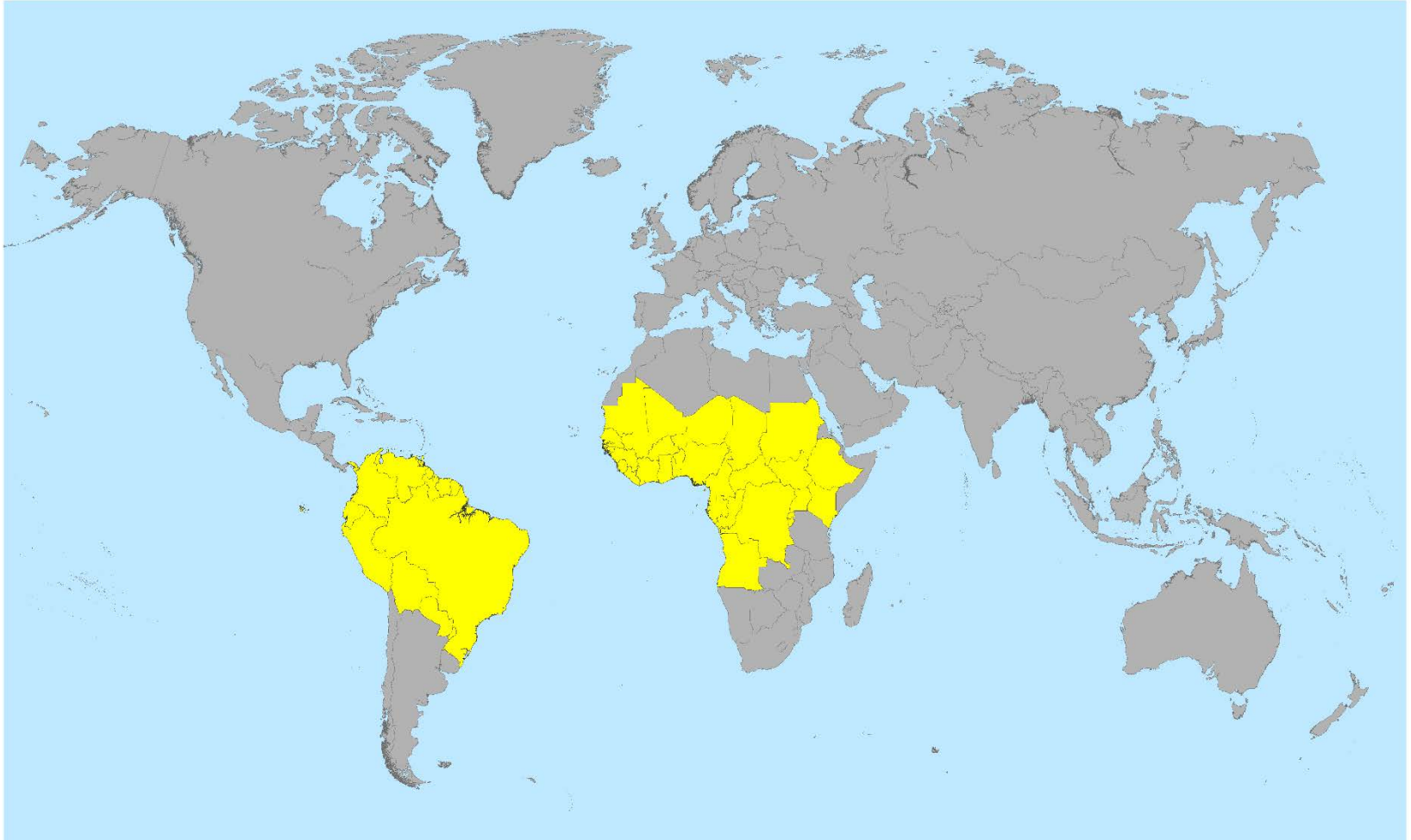
- ☐ **Primary clinical symptoms are fever and polyarthralgia**
- ☐ **Joint pain can be severe and debilitating**
- ☐ **Other common findings include headache, myalgia, arthritis, and maculopapular rash**
- ☐ **Acute symptoms typically resolve in 7–10 days**
- ☐ **Some have persistent rheumatologic symptoms**
- ☐ **Case-fatality is low (<1%) and mostly in older adults**



# Yellow Fever Virus

- ❑ Genus *Flavivirus*
- ❑ Most human infections occur as a result of sylvatic (jungle) transmission
- ❑ Urban outbreaks occur periodically, mostly in West Africa
- ❑ *Aedes aegypti* is primary vector during urban outbreaks

# Yellow Fever Virus: Approximate Geographic Distribution



Jentes ES, et al. Lancet Infect Dis 2011

# Yellow Fever Virus Epidemiology

- ❑ **30% of population infected during urban outbreaks**
- ❑ **10%–20% infected people develop clinical disease**
- ❑ **Estimated 200,000 cases annually worldwide**
- ❑ **85% of reported cases from sub-Saharan Africa**

# Yellow Fever Virus Disease and Outcomes

- ☐ **Acute febrile illness often presenting with headache, myalgia, vomiting, and lumbosacral pain**
- ☐ **15% of symptomatic patients develop severe disease with jaundice, hemorrhage, or multiorgan failure**
- ☐ **Hyperbilirubinemia usually peaks toward the end of the first week of illness**
- ☐ **20%–50% case-fatality in patients with severe disease**

# Zika Virus

- ❑ **Genus *Flavivirus***

- ❑ ***Aedes aegypti* believed to be primary vector**

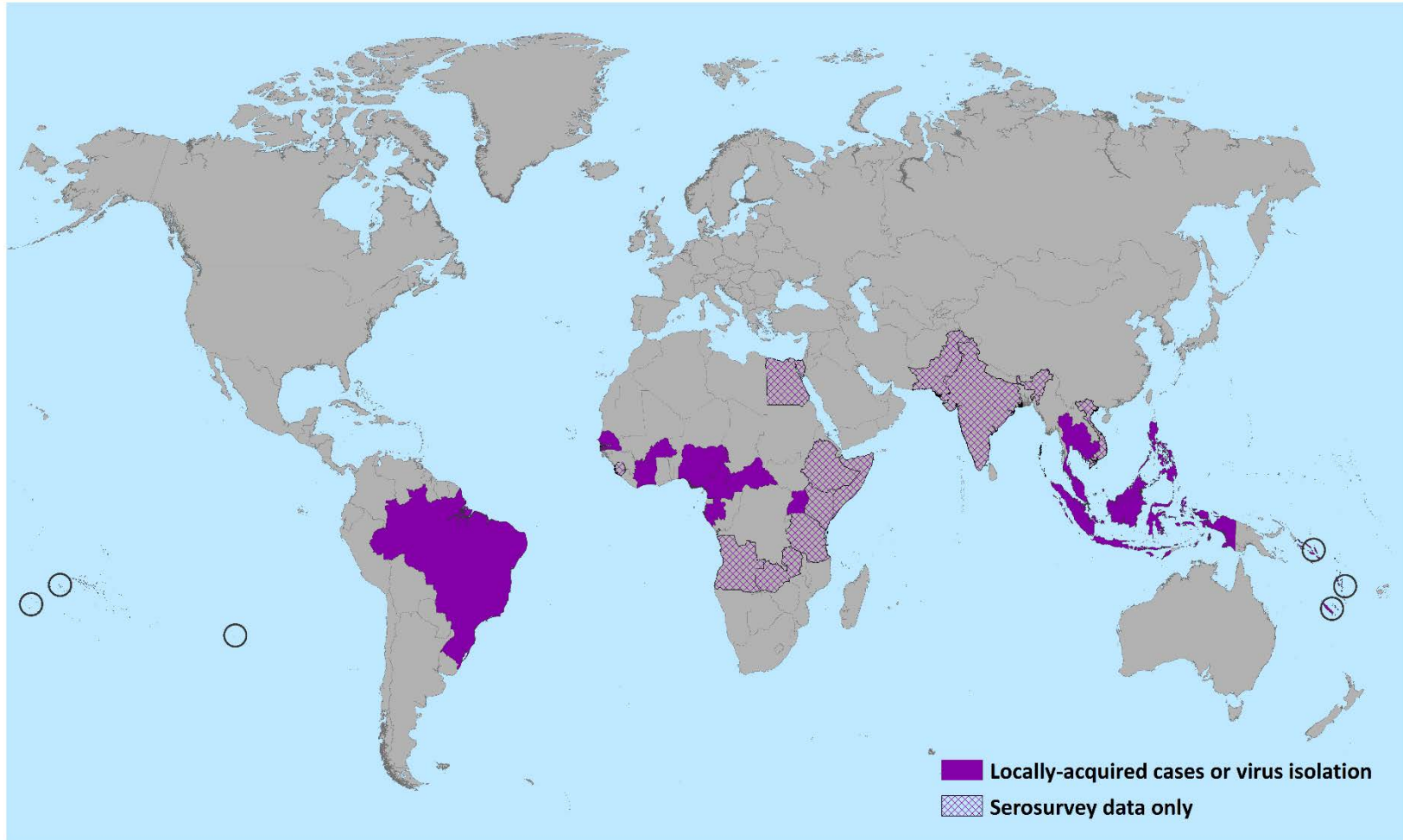
- Other *Aedes* (*Stegomyia*) mosquitoes have played important roles during recent Western Pacific outbreaks

- ❑ **Humans primary amplifying host during outbreaks**

- Sylvatic transmission in non-human primates in Africa
- Role of other animals in maintaining the virus not known



# Zika Virus: Approximate Geographic Distribution



Haddow AD, et al. PLoS NTD 2012

# Zika Virus Disease Epidemiology

- ☐ **2007 outbreak in Yap resulted in an estimated 900 cases (population 7,391)**
- ☐ **Estimated 73% of population infected in Yap**
- ☐ **18% of infected people develop clinical disease**
- ☐ **In 2014–2015, more than 30,000 suspected cases reported from French Polynesia and other Pacific islands**

# Zika Virus Disease and Outcomes

- ☐ **Mild acute illness with a diffuse rash, arthralgia, and conjunctivitis**
- ☐ **Fevers are low grade and 25%–35% of patients may be afebrile**
- ☐ **Symptoms typically resolve over 3–7 days**
- ☐ **Few reports of possible Guillain-Barré syndrome or other severe disease manifestations**
- ☐ **No deaths reported**

# Diagnostic Testing for Dengue, Chikungunya, Yellow Fever and Zika Viruses

- ❑ **Viral RNA in blood within 3–7 days after onset**
- ❑ **IgM antibodies develop toward end of 1st week**
  - Neutralizing antibody testing to confirm results and distinguish infection by closely-related viruses
- ❑ **≥4-fold rise in virus-specific neutralizing antibodies on acute and convalescent specimens**
- ❑ **RT-PCR or immunohistochemical staining on autopsy tissues**

RT-PCR: Reverse transcription-Polymerase chain reaction

# Treatment for Dengue, Chikungunya, Yellow Fever and Zika Viruses

- ❑ **No specific antiviral therapy; treatment is supportive**
- ❑ **Assess hydration and hemodynamic status**
- ❑ **Evaluate for other serious conditions and treat or manage appropriately**
- ❑ **Proper clinical management reduces mortality due to dengue**
  - All suspected cases should be managed as if they have dengue until it has been ruled out



# Vaccines for Dengue, Chikungunya, Yellow Fever and Zika Viruses

<b>Virus</b>	<b>Vaccine status</b>
Dengue	Phase 3 clinical trials
Chikungunya	Phase 1–2 clinical trials
<b>Yellow fever</b>	<b>Licensed and available</b>
Zika	None

# Prevention and Control of Dengue, Chikungunya, Yellow Fever and Zika Viruses

## ❑ **Community-level control efforts**

- Mosquito habitat control
- Apply larvicide and adulticide
- Difficult to sustain at effective levels

## ❑ **Personal protective measures**

- Use air conditioning or window and door screens
- Use mosquito repellents on exposed skin
- Wear long-sleeved shirts and long pants

## ❑ **Protect infected people from further mosquito exposure during first week of illness**

# Summary for Dengue, Chikungunya, Yellow Fever and Zika Viruses

- ❑ ***Aedes aegypti* most important vector during outbreaks**
- ❑ **Recent increased incidence and spread to new areas**
- ❑ **Overlapping geographic areas and clinical features**
- ❑ **No antiviral therapy but proper clinical management can reduce dengue mortality**
- ❑ **Yellow fever vaccine widely used; dengue and chikungunya vaccines in development**
- ❑ **Primary prevention is to reduce mosquito exposure but current vector-control options difficult to sustain**

# The Status and Frontiers of Vector Control



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**U.S. Department of  
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# Environments That Favor More Mosquitoes

- ❑ ***Aedes aegypti* is highly domesticated**
- ❑ **Stored water and discarded non-biodegradable items accumulate rain water, and create abundant mosquito development sites**





# Environments that Favor More Mosquitoes and Transmission of Diseases

## ❑ Rapid urban growth

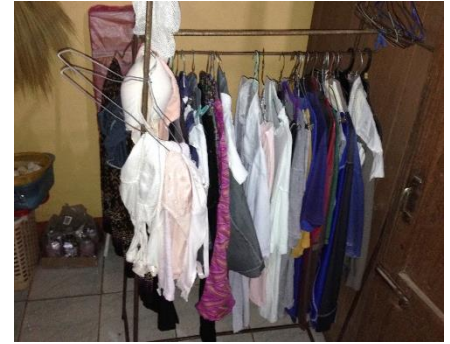
- Lack of adequate water supply
- Lack of solid waste disposal
- Substandard housing

## ❑ High human density support high *Aedes aegypti* densities with close biting contact to humans

- High virus transmission potential



# Ecology of Adult *Aedes aegypti*



- ❑ **Adult females lay eggs on the sides of water holding containers**
  - In about 1 week, eggs hatch & larvae develop into pupae
  - Two days later adults emerge
- ❑ **Adults rest inside houses**
  - Often in quiet, dark places like closets or clothes racks
- ❑ **Adults do not move far**
  - Often living their entire life in a single house or its neighbor
  - Seldom fly 100 meters from their initial resting site

# Population of *Aedes aegypti*

- ❑ **Low population densities (e.g., few numbers of mosquitoes per house)**
- ❑ **Population tends to be focal and dynamic**
  - Number of mosquitoes per house changes over time
  - Geographical distribution of infested houses varies





# Vector Host Relationship of *Aedes aegypti*

- ❑ **Only females feed on blood**
  - For egg development
  - Prefer human source of blood
- ❑ **“Day-biters”**
  - Bite during the day when people are active
- ❑ **Average ~ 1 bite per day**
- ❑ **Biting more often leads to**
  - Increased fitness of mosquitoes
    - Live longer and lay more eggs
  - Increased potential for virus transmission



# **Aedes aegypti Transmits Mosquito-Borne Diseases Efficiently**

## **❑ Biting a human host is required for virus transmission**

- Low vertical virus transmission rate from females to their eggs
- Less than 1:1,500

## **❑ Biting patterns facilitate transmission**

- Some people are bitten more than others, including visitors to homes
- Frequent human biting helps explain explosive epidemics

## **❑ Low entomologic transmission thresholds**

- Epidemics can occur even when mosquitoes populations are low
- They live, bite, and lay eggs close to humans
- They feed frequently and preferentially on human blood

# Vector Control to Stop the Spread of Mosquito-Borne Diseases

## ❑ Vector control measures reduce

- Adult mosquito population density
- Human biting rate
- Infectious mosquitoes; i.e., mosquito survival through the virus incubation period
- Target both larval and adult stages



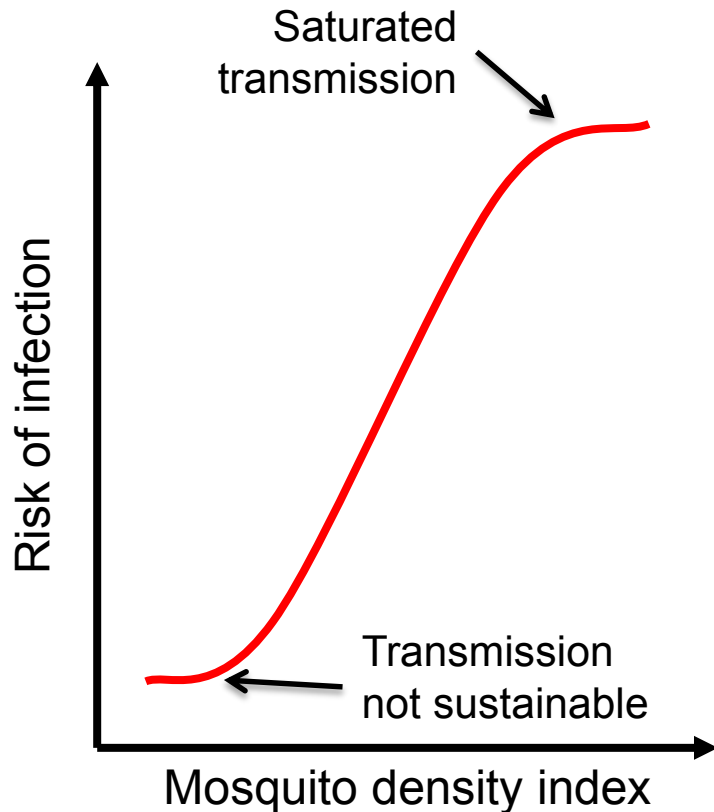
## ❑ To be effective, vector control measures need to reduce mosquito populations

- Target levels at or just below level required for virus transmission
- Threshold density of the vector population

## ❑ They must also sustain those low levels

## ❑ Defining transmission thresholds has been difficult

# Improving Measures of Entomological Risk



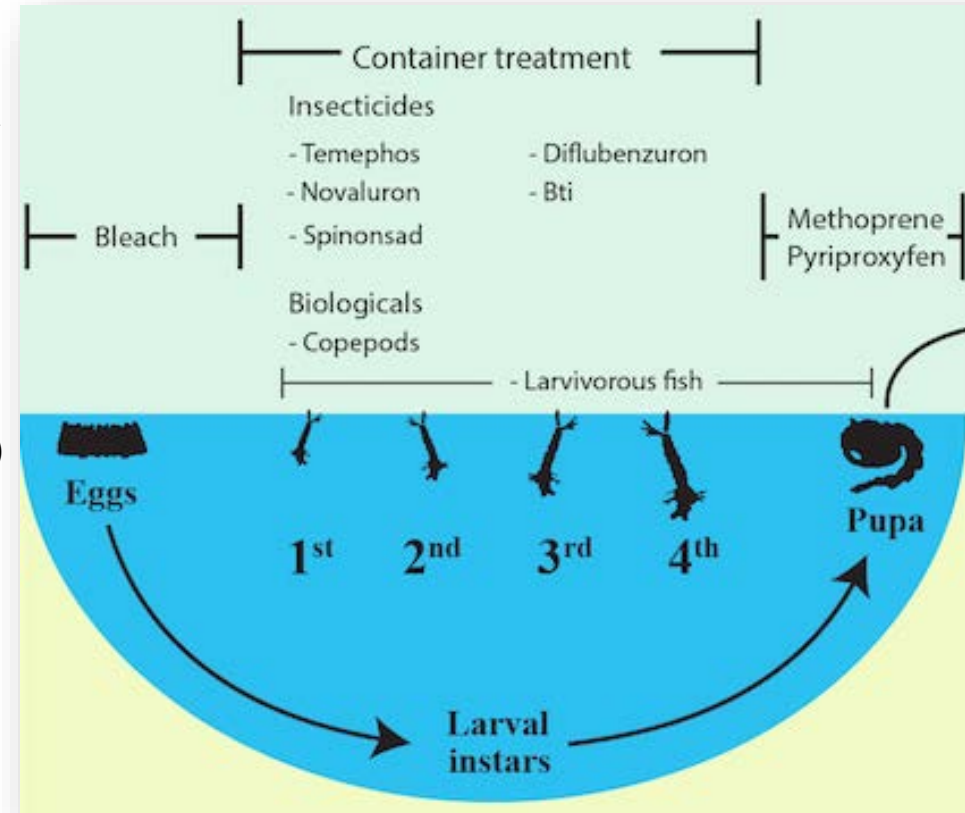
- ❑ **Historical indices for immature mosquitoes do not predict human dengue infection risk**
- ❑ **Shift to pupae and adult mosquitoes indices requires understanding of complex interplay of many factors**
  - Susceptibility of human population; i.e., herd immunity
  - Human biting rate
  - Human host density
  - Virus introduction
  - Weather

# Existing Methods for *Aedes aegypti* Control – Immature Stage

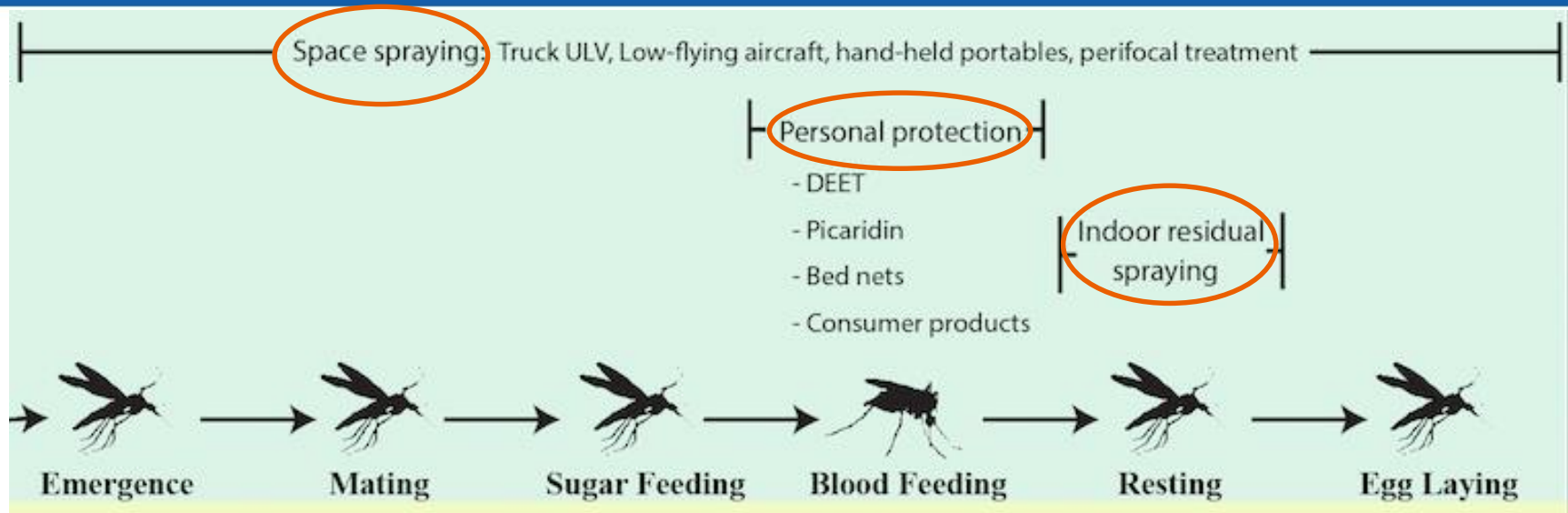
❑ **Difficult to achieve and sustain epidemiologic impact with just larval control**

❑ **Major categories include**

- Containers
  - Cleaning (bleach/wash/dump)
  - Manipulation (covers/treated covers)
  - Treatment (insecticide/bio-control)
- Social campaigns
  - Education and source reduction
- Environmental management
- Legislation
  - Fines and penalties, if larva or pupae found



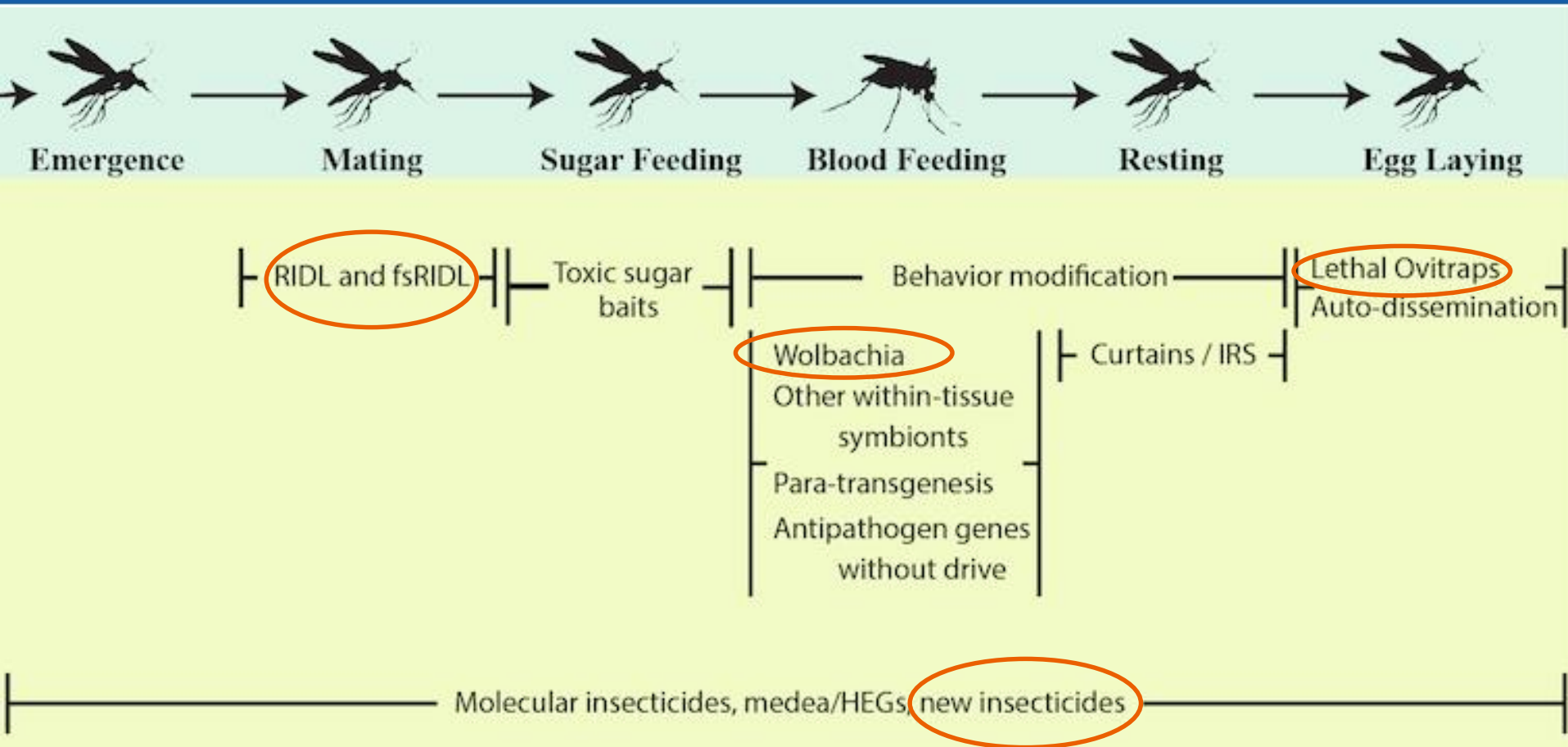
# Existing Methods for *Aedes aegypti* Control – Adult Stage



## Major categories include

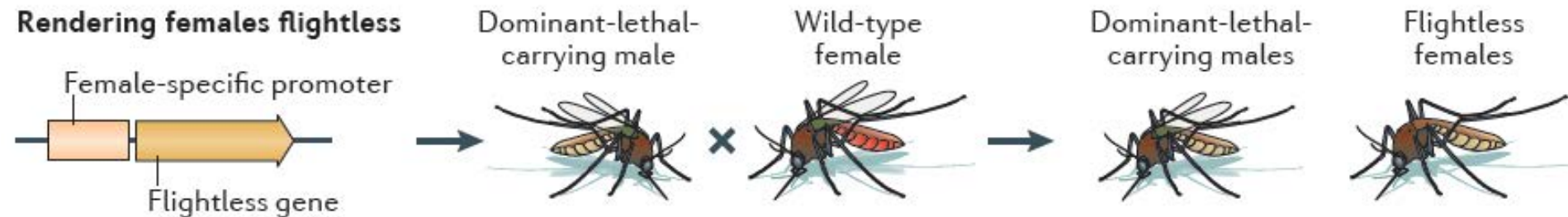
- (1) Space spraying (indoor vs outdoor)
- (2) Indoor residual spraying
- (3) Personal protection

# Interventions Currently Under Development





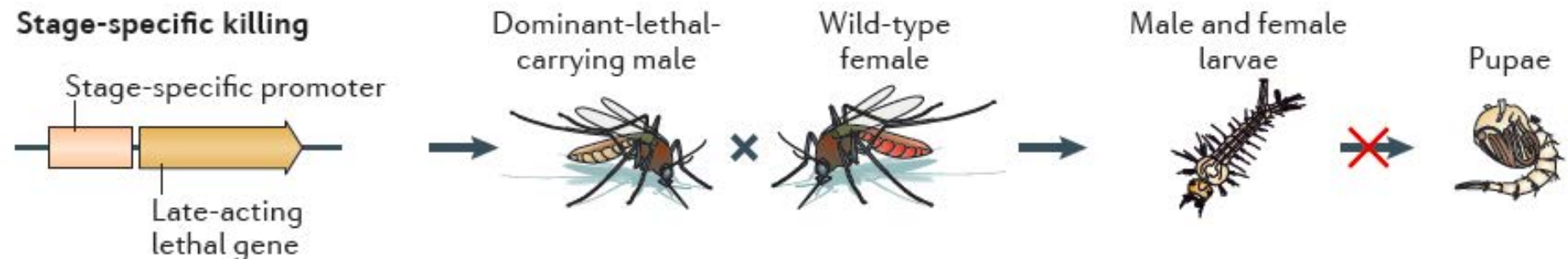
# Release of Insects Carrying a Dominant Lethal (RIDL) – Flightless Females



## □ Flightless females

- Males carrying a female-acting transgene mate with wild-type females
- Female offspring cannot fly
- Female offspring are unable to mate (cannot reproduce) or bite human hosts (cannot transmit virus)
- Heterozygote male offspring can mate and pass along transgene

# Release of Insects Carrying a Dominant Lethal (RIDL) – Kills Larvae



## ❑ Stage-specific killing

- Males carrying a transgene that causes late-acting lethality mate with wild-type females
- Offspring die as pupae
- Reduces population density

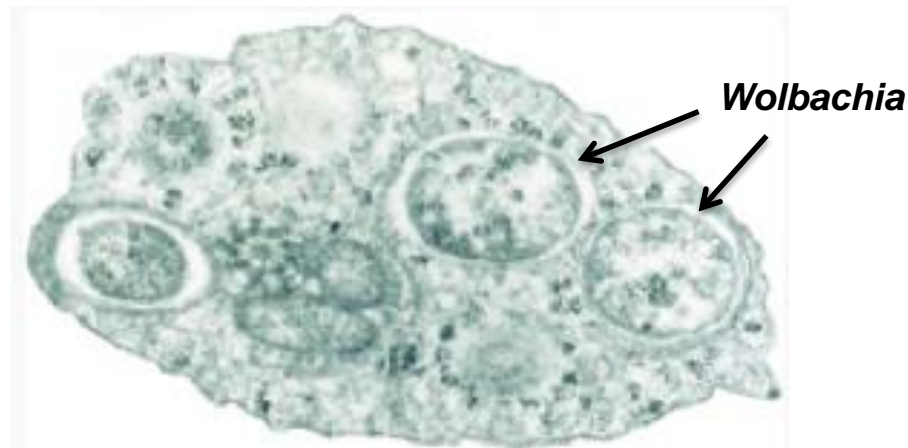
## ❑ Successful safety testing and mosquito population reduction field trials

## ❑ Need to evaluate impact on human dengue outcomes

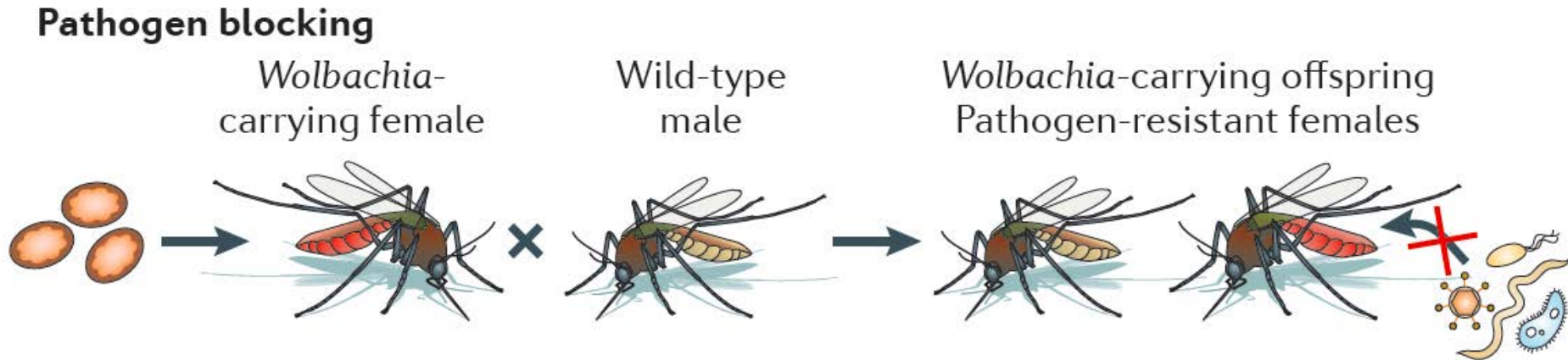
# Naturally Occurring Bacteria – *Wolbachia*

- ❑ ***Wolbachia* is an endosymbiotic bacteria**
  - Commonly infects many insects
- ❑ **Female *Aedes aegypti* experimentally infected with *Wolbachia* can pass the bacteria to their offspring**
- ❑ **Adult female *Aedes aegypti* infected with *Wolbachia* have a 66%–75% reduced capacity to transmit dengue**

*Wolbachia* infected  
insect cell



# Vector Control Using *Wolbachia*



- ❑ Offspring from infected females are favored and spread *Wolbachia* through mosquito populations
- ❑ Field trials have successfully established *Wolbachia* in natural *Aedes aegypti* populations
- ❑ Field trials are testing the impact of releasing *Wolbachia* infected *Aedes aegypti* on human dengue infection and disease

# CDC Autocidal Gravid Ovitrap (AGO) Trap



## ❑ Population reduction

- Removes egg laying and older, potentially dengue infected females

## ❑ Field trials in Puerto Rico detected sustained reduction in *Aedes aegypti*

## ❑ Enhance effectiveness

- By adding attractants
- Removing natural egg laying sites

## ❑ Merits further evaluation

# Working with Industrial Partners to Develop New Insecticides



- ❑ **Three new active ingredients with novel modes of action available for vector control by 2020–2022**
- ❑ **Improvements in indoor residual spray and insecticide-treated materials**
  - Long lasting, repurposed insecticides for areas of high insecticide resistance and dual-treated materials
- ❑ **Outdoor biting protection**
  - Supporting research on the prevention of pathogen transmission by mosquitoes that bite people outdoors



# Combining Vector Control with Vaccines to Reduce Dengue Risk at Community Level

- ❑ **Vector control and vaccines should complement each other – resulting in a greater impact than either alone**
- ❑ **Vector control reduces each susceptible persons' risk of being infected by reducing mosquito:**
  - Population density
  - Human biting rate
  - Survival
- ❑ **Vaccination artificially elevates and sustains herd immunity**
- ❑ **Details for how these various strategies can best be combined need to be determined**



# Summary and Implications

- ❑ ***Aedes aegypti* is an efficient virus vector**
  - Epidemics can occur even at low mosquitoes densities
- ❑ **Lack of appropriate infrastructure in cities allows for increasing *Aedes aegypti* populations with high potential for virus transmission**
- ❑ **Indoor residual insecticides have the greatest potential for reducing human infection and disease**
- ❑ **Emerging insecticide resistance is a growing concern for chemically-based interventions**



# Steps Forward

- ❑ **Need for epidemiologic assessment of interventions**
- ❑ **Insecticides**
  - Insecticide resistance monitoring and management
  - New active ingredients and improving in indoor residual treatments
- ❑ **Promising genetic-based strategies**
  - Release of Insects Carrying a Dominant Lethal (RIDL)
  - *Wolbachia* infected mosquitoes
- ❑ **Scaling-up and maintaining coverage to prevent dengue remains a major challenge**
- ❑ **Integrated interventions will require carefully designed combinations of vector control with vaccines**

# Prevention Strategies *Aedes* Mosquito-Borne Diseases



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# Dengue Infection and Dengue Disease

- ❑ **Dengue infection is largely asymptomatic for ~75%**
- ❑ **For the rest, “dengue fever” or “dengue disease”**
  - Acute febrile illness
  - Can present like many other diseases
- ❑ **Typical course is 4-5 d fever, then resolves**
- ❑ **For ~10% with dengue disease, “severe dengue” develops**

# Proper Case Management Critical to Survival

## ❑ Severe dengue (WHO, 2009)

- Plasma leakage which results in compensated or decompensated shock
- Includes a subset of individuals which develop
  - Dengue hemorrhagic fever
  - Dengue shock syndrome
- Life threatening, requires critical, supportive care

## ❑ Timely diagnosis improves prognosis

## ❑ If properly managed, case fatality rate less than 1%

- Early recognition of plasma-leakage, and compensated or decompensated shock based on presence of “warning signs”
- Proper fluid management and resuscitation of plasma-leakage

# CDC Dengue Case Management E-Learning Course

## ❑ CDC Dengue Case Management Educational tool

- Designed for healthcare providers
- Includes case management steps recommended by WHO and incorporated in many dengue endemic countries

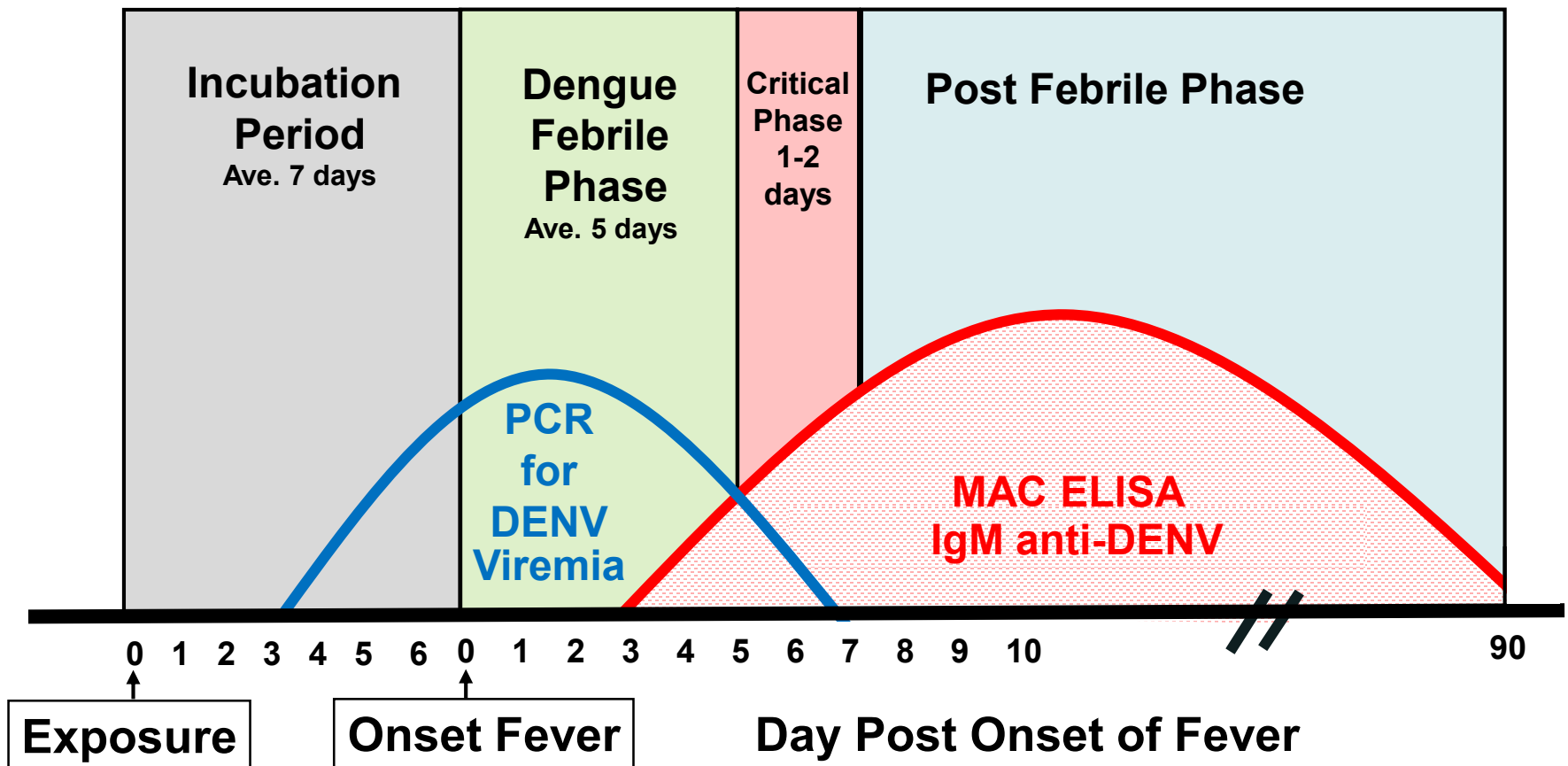


**Free CME Training: [cdc.gov/dengue/training/cme.html](http://cdc.gov/dengue/training/cme.html)**

# Better Diagnostics Leads to Better Outcomes

- ❑ **Dengue is an acute febrile illness syndrome**
  - Similar presentation to chikungunya, leptospirosis, malaria, and other febrile illnesses
- ❑ **Clinical diagnosis often inconclusive**
  - Fever, rash, periorbital pain
- ❑ **Accurate diagnosis needed**
  - Patient case management
  - Public health surveillance
- ❑ **Lab tests depend on timing in course of illness**
  - Cases often present as viremia wanes
  - Both acute and convalescent needed for some serology

# Sensitivity of Dengue Diagnostics Vary Over Course of Illness



Peeling RW, et al. Nat Rev Microbiol 2010  
Santiago GA, et al. PLoS NTD 2013  
CDC unpublished data

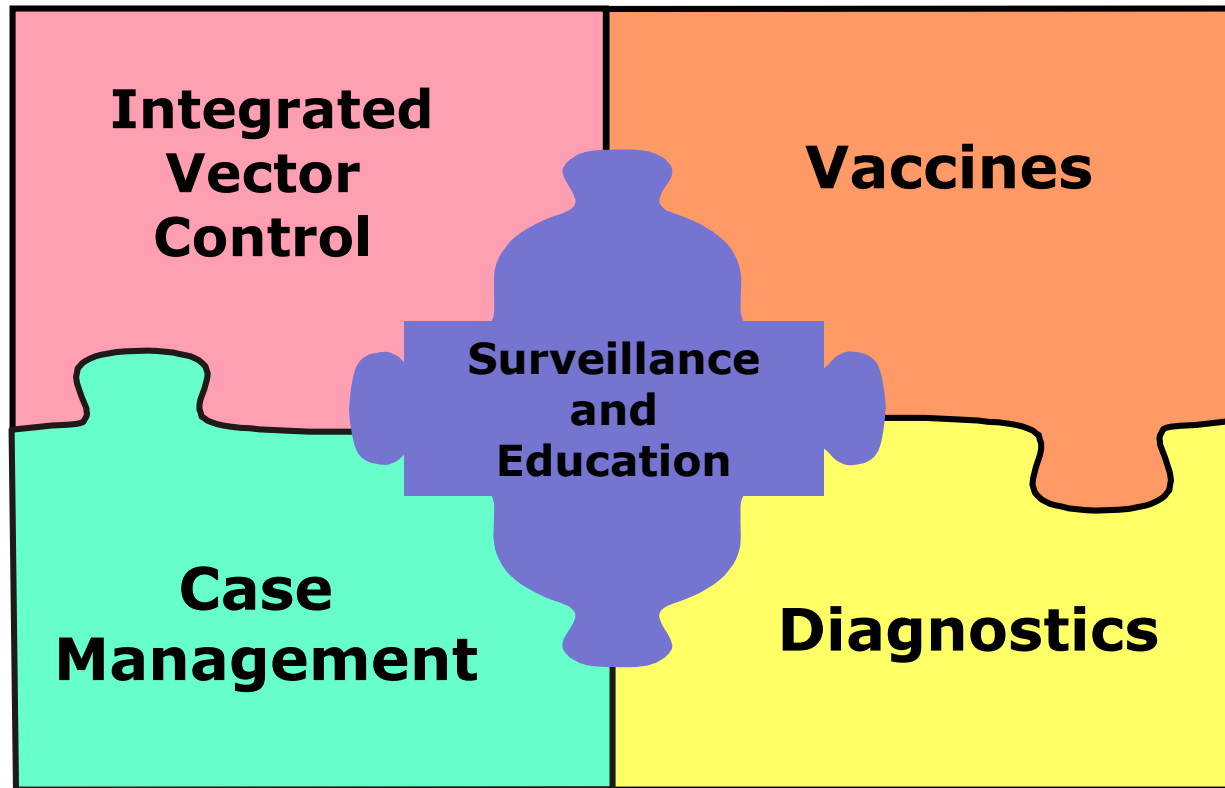
DENV: Dengue virus  
MAC: M antibody capture  
PCR: Polymerase chain reaction

# Dengue Diagnostics Algorithm

Day Post Onset of Fever	Diagnostic Tests		Reliability
	RT-PCR	IgM anti-DENV	
0–3	+	-	~90%
3–7	+	+	~90%
>7	-	+	~90%



# A Framework for Dengue Prevention



Adapted from: Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. New Edition. WHO, 2009  
Global Strategy for Dengue Prevention and Control 2012-2020. WHO, 2012

# Prevention Through Personal Protection

- ❑ **Repellents prevent all mosquito diseases, but...**
  - Must be reapplied
  - Compliance low
- ❑ **Several provide hours-long protection**
  - DEET, Picaridin (Icaridin), IR3535
- ❑ **Insecticide impregnated clothing (permethrin)**
  - Must be periodically reapplied
  - Impractical in endemic area
- ❑ **Do not provide community disease protection**

DEET: N,N-diethyl-m-toluamide

IR3535: 3-[N-Butyl-N-acetyl]-aminopropionic acid, ethyl ester

# Why A Dengue Vaccine?

- ❑ **Mosquito control works, but expensive and difficult to sustain at effective levels**
- ❑ **Vaccines protect the individual and community**
- ❑ **Efficacious *Flavivirus* vaccines exist**
  - Yellow fever, Japanese encephalitis, tick-borne encephalitis
  - Technically feasible
- ❑ **Challenge of dengue vaccine**
  - Must protect against all 4 viruses
  - Implementation: 40% of world's population at risk

# Dengue Vaccine Candidates






Producer (developer)	Approach
<b>Sanofi Pasteur (Acambis)</b>	Live attenuated chimeric vaccine
<b>Takeda (CDC, InViragen)</b>	Live attenuated chimeric vaccine
<b>Butantan (NIAID)</b>	Live attenuated , engineered mutations in 3 strains and chimeric in 2
<b>GSK (WRAIR)</b>	Cell culture derived inactivated vaccine
<b>Merck (Hawaii Biotech)</b>	Subunits of DENV envelop protein

GSK: GlaxoSmithKline

NIAID: National Institute of Allergy and Infectious Diseases

WRAIR: Walter Reed Army Institute of Research

# Dengue Vaccine Clinical Trial Phases

Producer	Clinical Trial		
	Phase I	Phase II	Phase III
Sanofi Pasteur			
Takeda			
Butantan			
GSK			
Merck			

GSK: GlaxoSmithKline

# Sanofi Dengue Vaccine Efficacy Trials

- ❑ **Random, blinded, placebo-controlled (2:1)**
- ❑ **Ages: 2-16 years (highest disease incidence)**
- ❑ **3 doses: given at 0, 6 & 12 months**
  - Vaccine – tetravalent, live, attenuated
  - Placebo – normal saline vaccine diluent
- ❑ **End point: Symptomatic, confirmed dengue fever**
  - Clinical acute febrile illness + PCR-detected viremia
- ❑ **Follow-up: 25 months total (13 months after last dose)**
- ❑ **Longer-term follow-up: 48 months**

# Results of Efficacy Trials Sanofi Vaccine (per protocol results)

DENV Types	Phase IIB–Thailand Ages 4–11, N= 4,002		Phase III–Asia Ages 2–14, N= 10,275		Phase III–Latin America Ages 9–16, N= 20,869	
	Efficacy	95% CI	Efficacy	95% CI	Efficacy	95% CI
<b>All DENV's</b>	<b>30.2</b>	-13–57	<b>56.5</b>	44–66	<b>60.8</b>	52–68
<b>DENV 1</b>	<b>55.6</b>	22–84	<b>50.0</b>	25–67	<b>50.3</b>	29–65
<b>DENV 2</b>	<b>9.2</b>	-75–51	<b>35.0</b>	-9–61	<b>42.3</b>	14–61
<b>DENV 3</b>	75.3	-38–100	78.4	53–91	74.0	62–82
<b>DENV 4</b>	100	25–100	75.3	55–87	77.7	60–88



# Sanofi Vaccine Trials Conclusions

- ❑ **Sanofi vaccine offers only partial protection**
  - DENV 2: 9%–42% efficacy
  - DENV 1: about 50% efficacy
- ❑ **Current data have not shown any vaccine safety issues**
- ❑ **Long-term follow-up needed to evaluate immune cross reactivity from vaccination**
  - Natural immunity to one type of dengue can result in more severe course with subsequent infections with other types of dengue, whether this holds true for vaccine-derived immunity needs to be evaluated

# Dengue Summary

- ❑ **For 40% of the world's population, dengue remains a threat**
- ❑ **Proper case management of severe dengue decreases mortality from ~ 10% to less than 1%**
- ❑ **Lab diagnostics depend on stage of illness**
- ❑ **Vector control and vaccine research holds promise**
- ❑ **Until a safe and effective vaccine is available, enhanced surveillance, rapid diagnosis, and personal protection are still the best methods for preventing dengue**

# Future Directions

- ❑ **Model to evaluate the best way to implement vaccines**
  - Identification of target populations
- ❑ **Develop new vector control options and ways to implement them at community level**
- ❑ **Improve diagnostic tests**
  - Needed for mosquito-borne viruses
  - Point-of-care, rapid diagnostic tests
- ❑ **Increase universal dengue case management training**
- ❑ **Further our understanding of global burden of mosquito-borne diseases**

# **We Can Reduce the Global Burden of Mosquito-Borne Diseases**

- ❑ Timely diagnosis and proper case management can save lives**
- ❑ Safe and effective vaccines are needed**
- ❑ Surveillance needs to be enhanced**
- ❑ Vector control measures should be improved and sustained**
- ❑ Coordination of all of these components will increase the impact of these efforts**

# CDC PUBLIC HEALTH GRAND ROUNDS

## Dengue and Chikungunya in Our Backyard: Preventing *Aedes* Mosquito-Borne Diseases



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Centers for Disease  
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