

CDC PUBLIC HEALTH GRAND ROUNDS

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



Accessible version: <https://youtu.be/v0KaDZ6Zmuo>

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

Virus	<i>Aedes aegypti</i>	<i>Aedes albopictus</i>
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

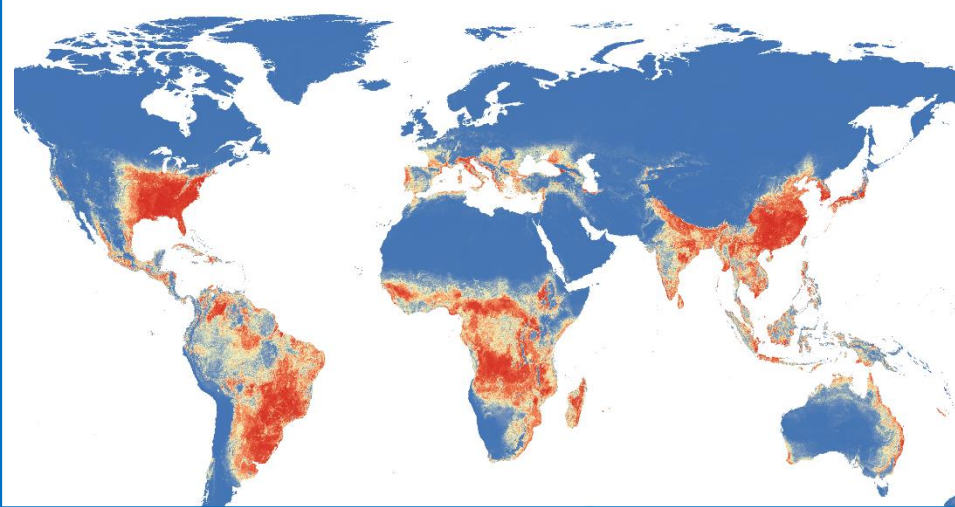
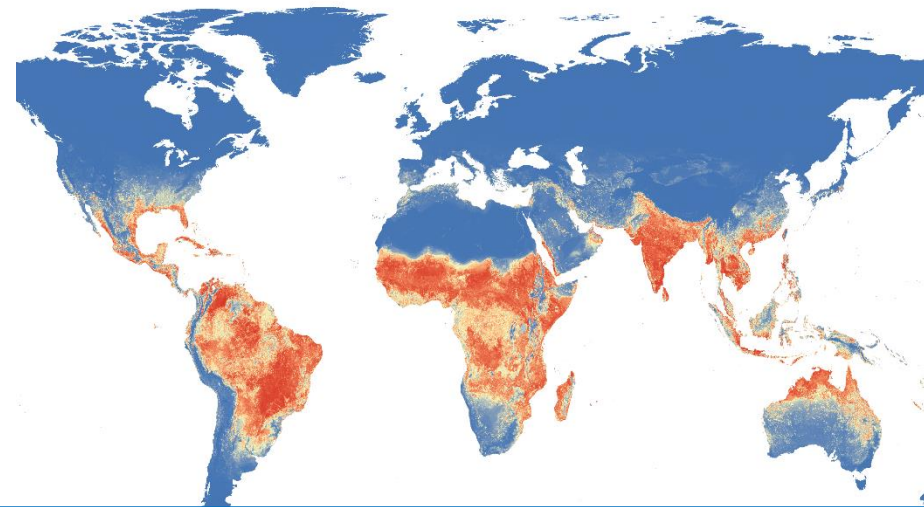


Aedes albopictus

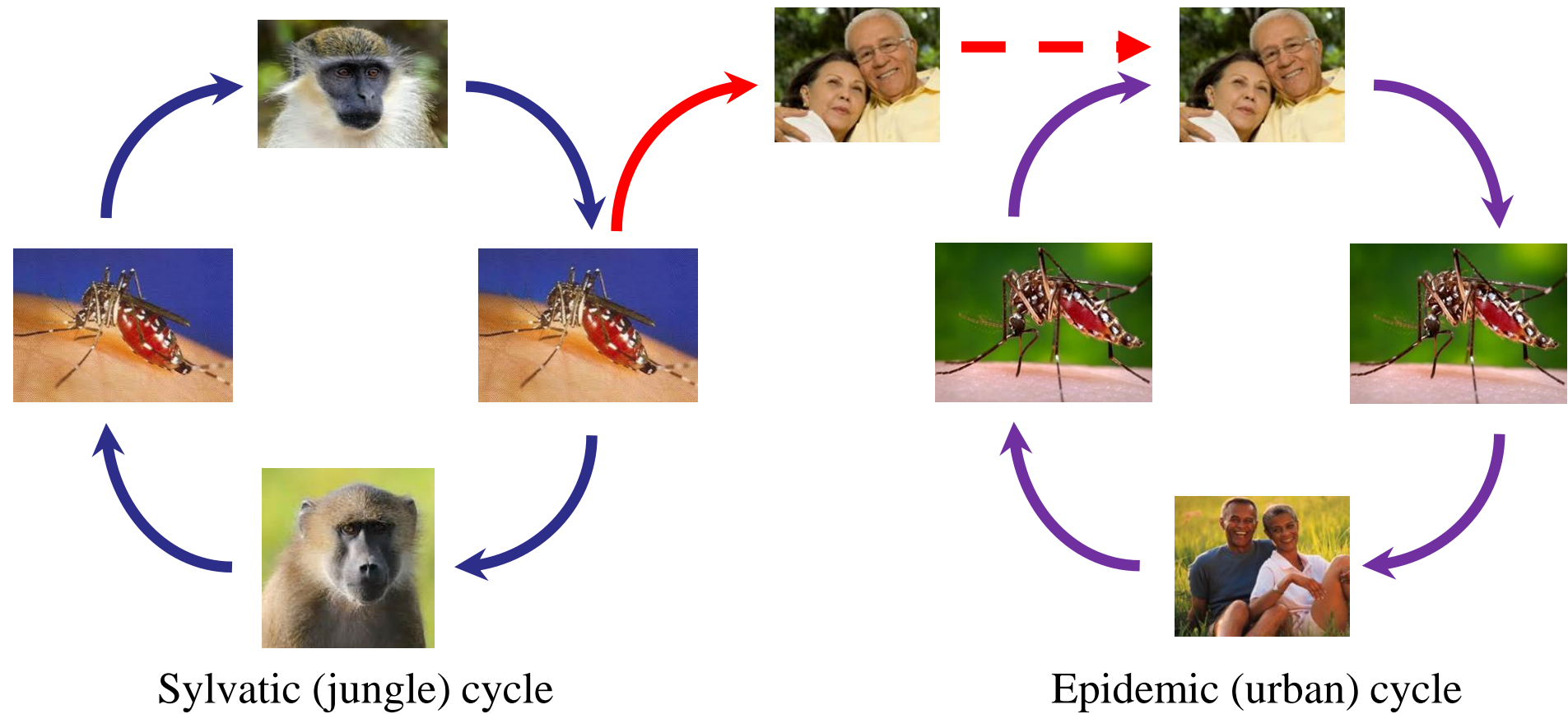
Approximate Distribution of *Aedes aegypti* and *Aedes albopictus* Mosquitoes

Aedes aegypti

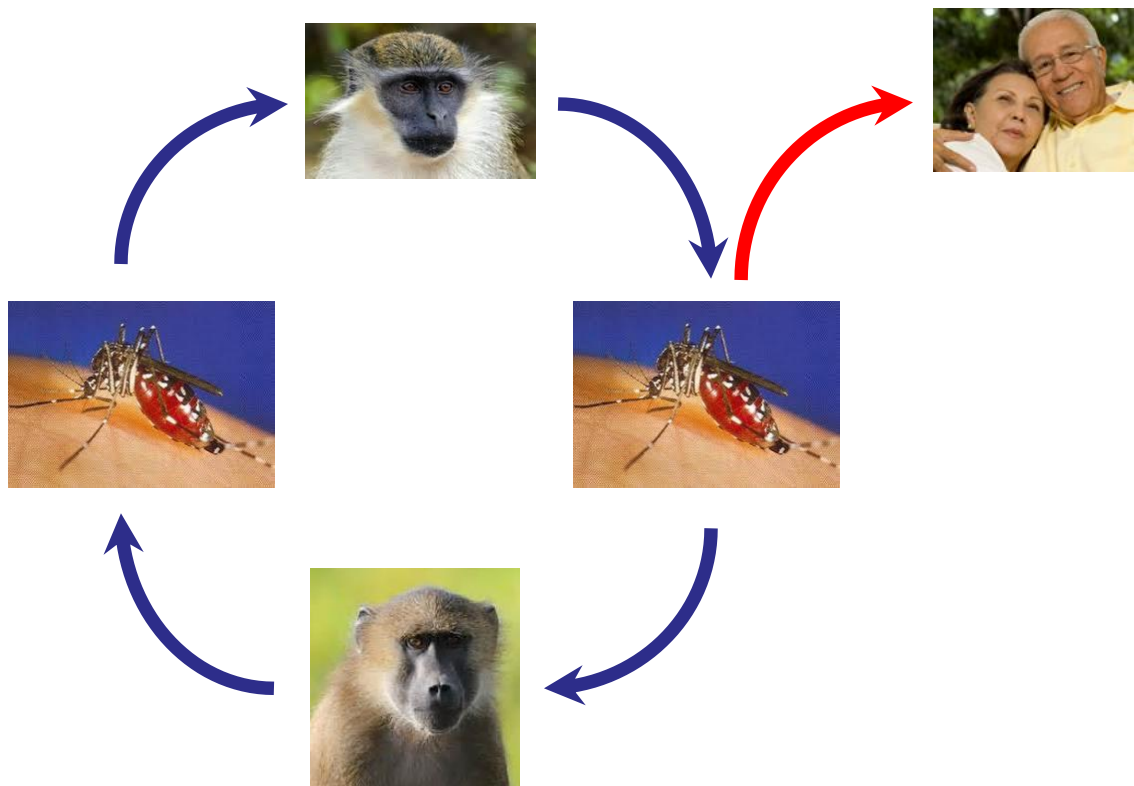
Aedes albopictus



Aedes Mosquito-Borne Virus Transmission Cycles

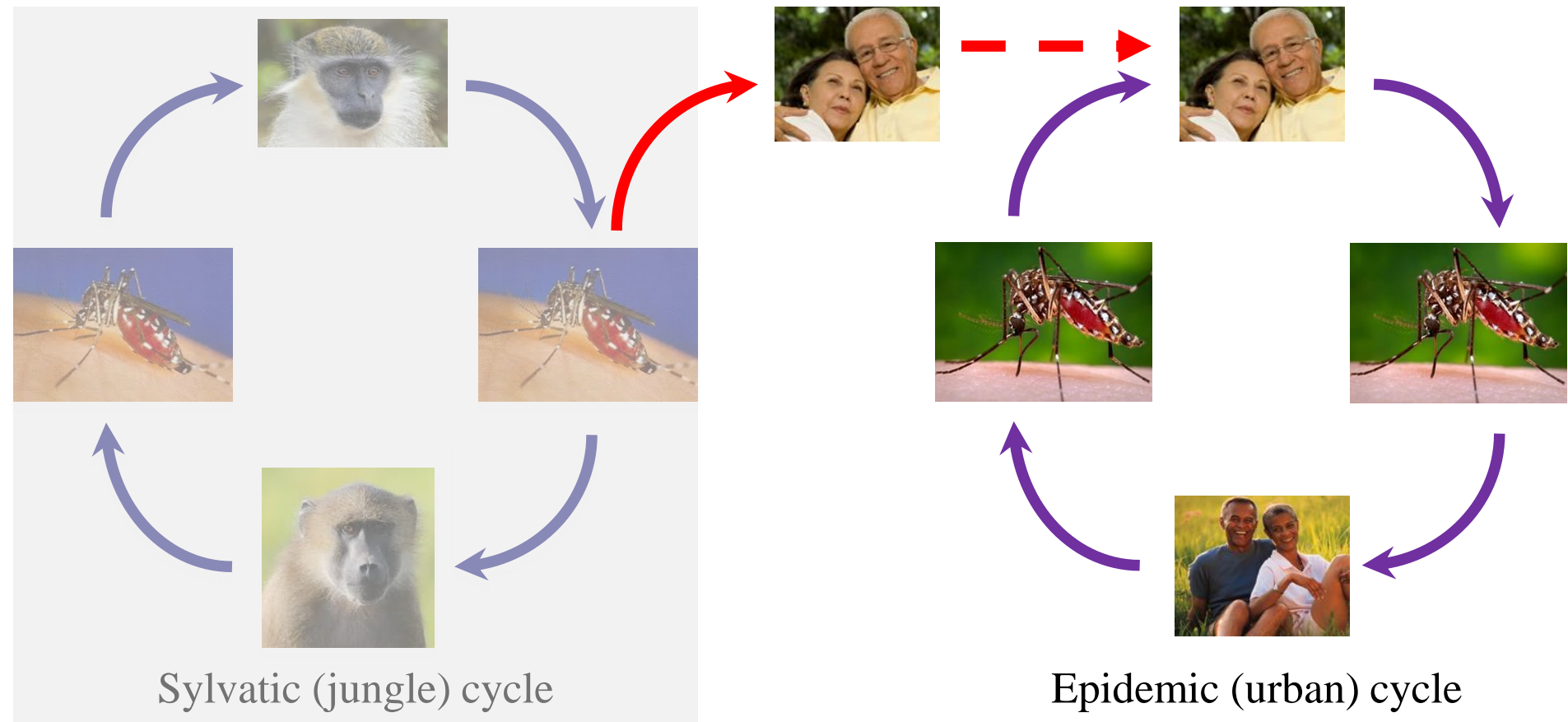


Sylvatic (Jungle) Transmission Cycle



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

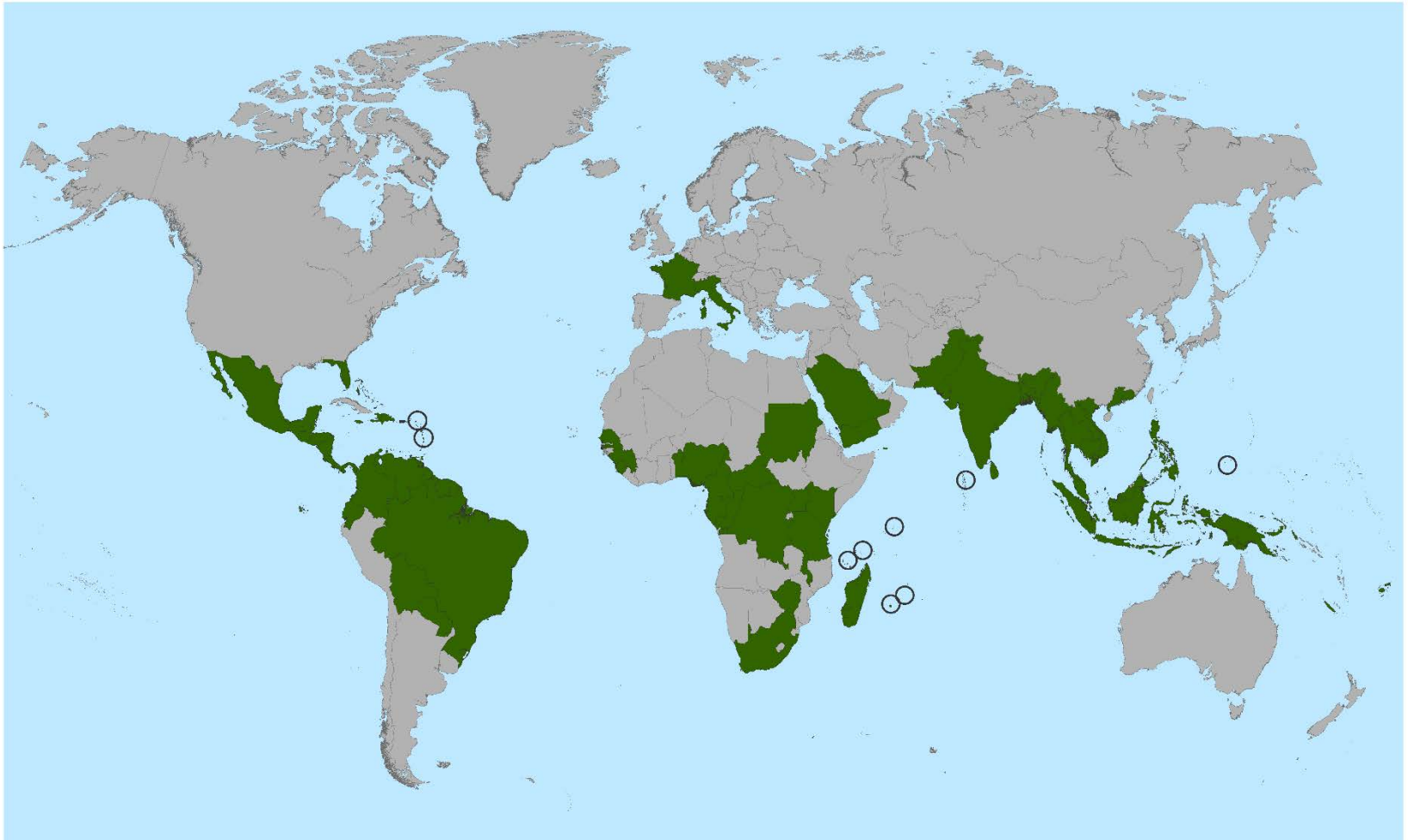
Dengue Virus Disease and Outcomes

- ❑ **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

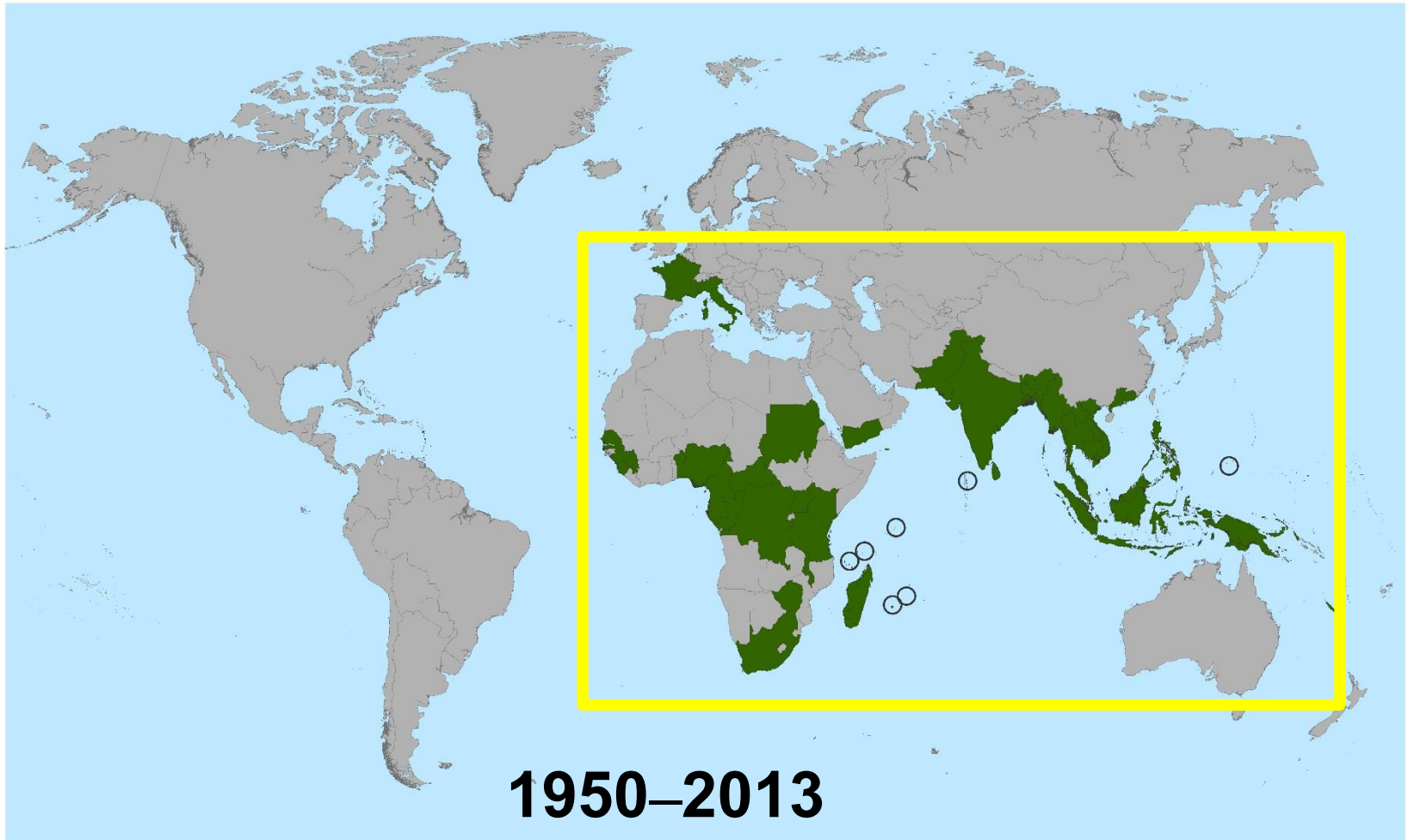
- ❑ **Genus *Alphavirus***
- ❑ ***Aedes aegypti* primary vector**
 - *Aedes albopictus* important in several recent outbreaks
- ❑ **Humans primary amplifying host during outbreaks**
 - Sylvatic transmission in non-human primates in Africa
 - Role of other animals in maintaining the virus not known

Chikungunya Virus: Approximate Geographic Distribution



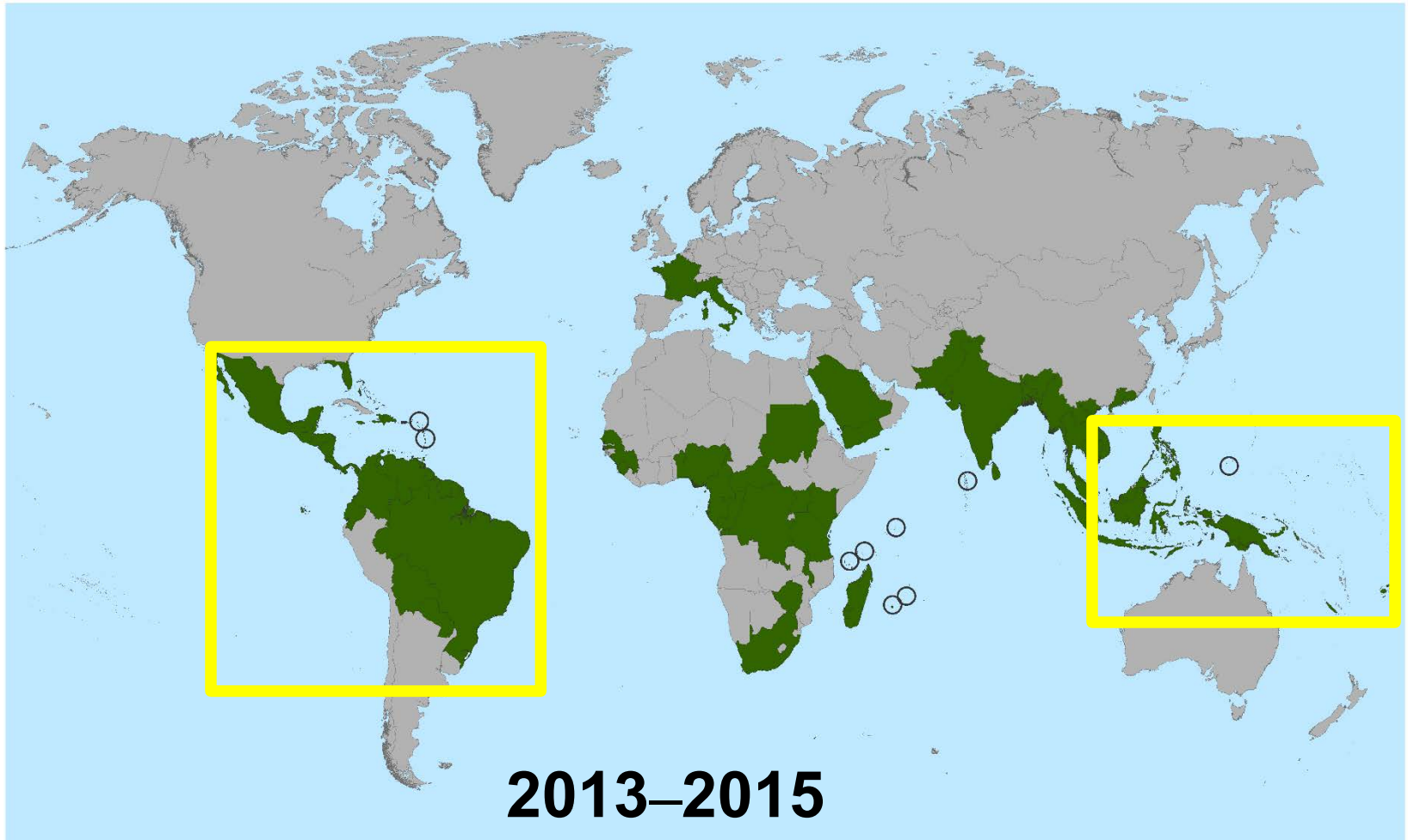
Available at <http://www.cdc.gov/chikungunya>

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

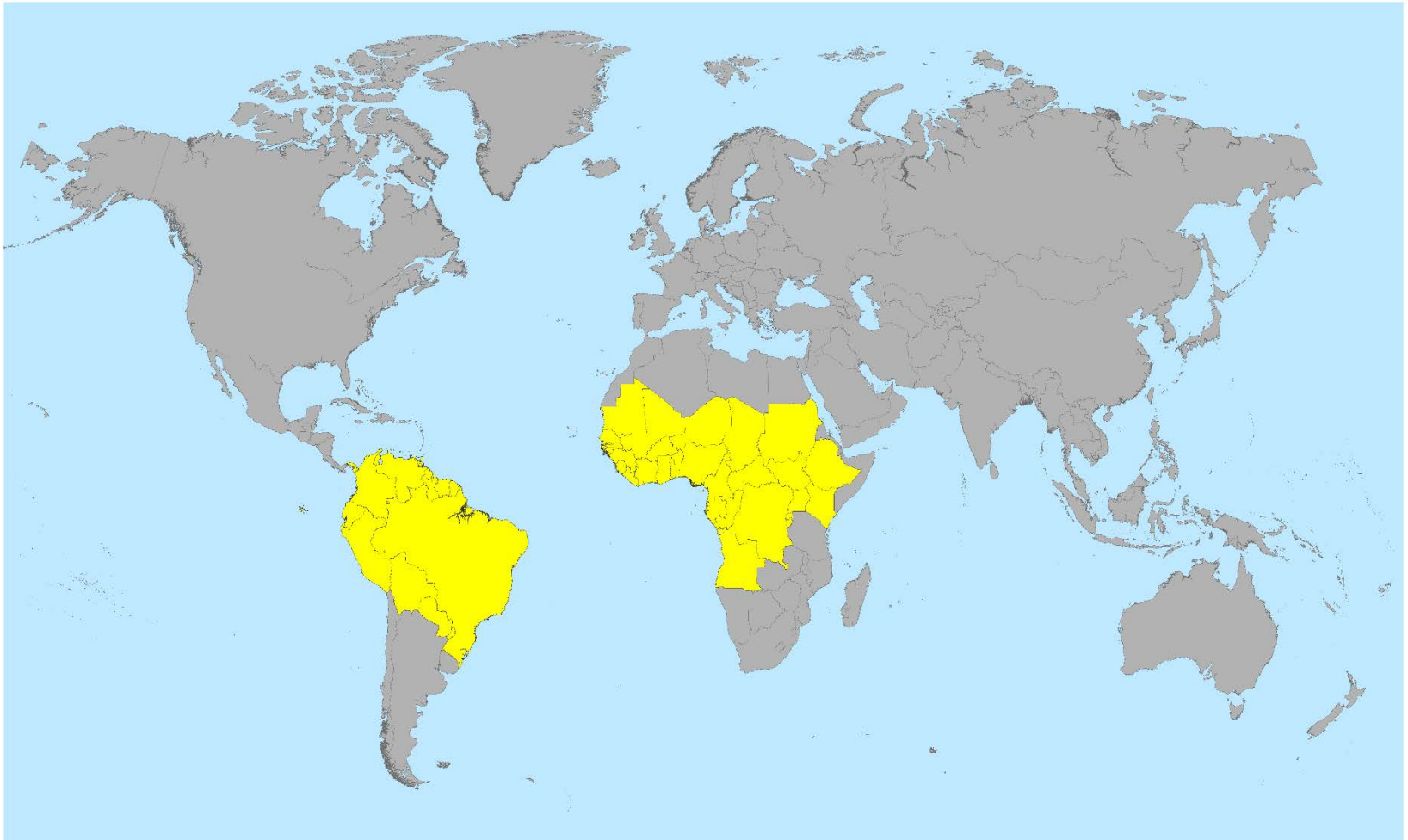
Chikungunya Virus Disease and Outcomes

- ❑ **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**

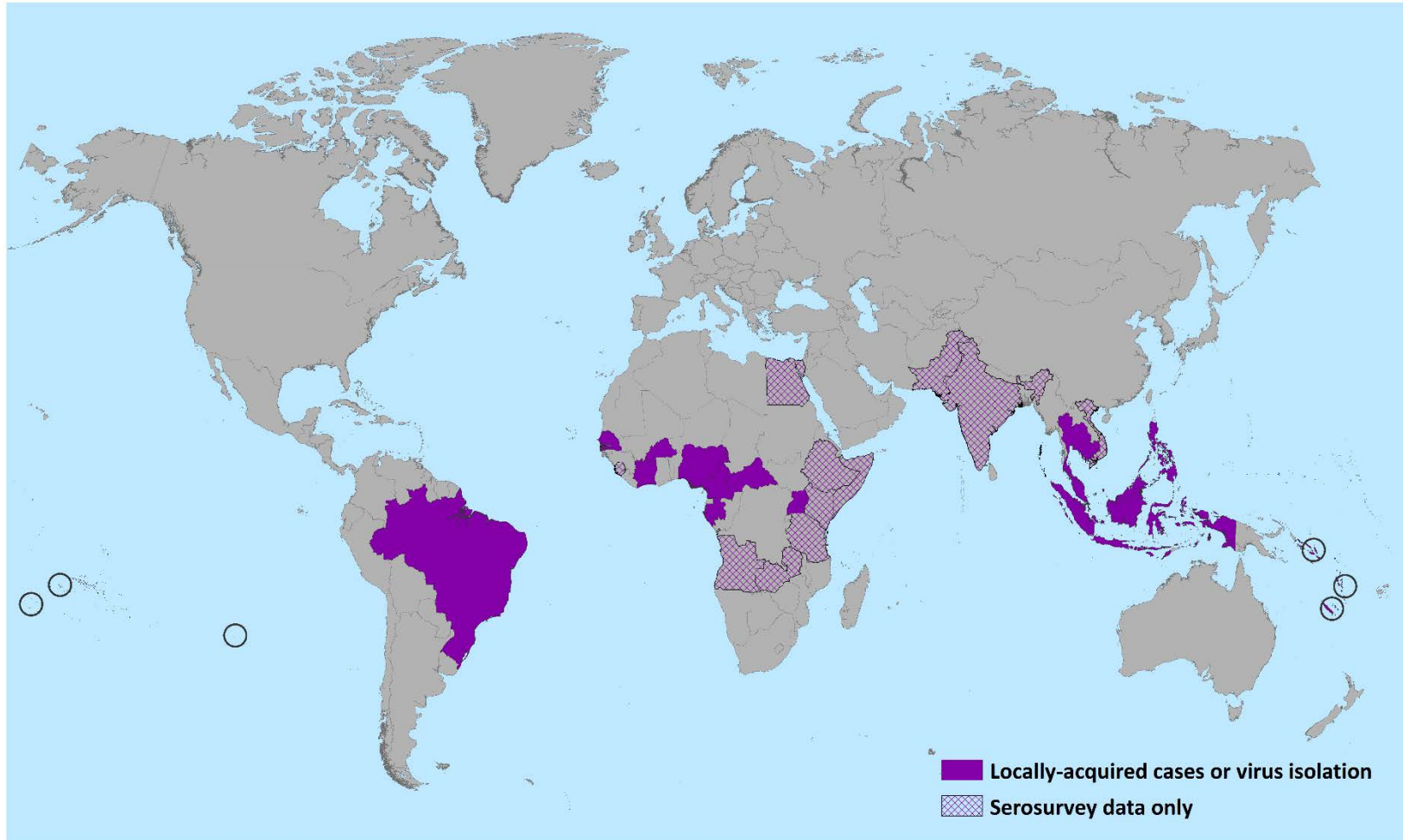
Yellow Fever Virus Disease and Outcomes

- ❑ **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



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**

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

Virus	Vaccine status
Dengue	Phase 3 clinical trials
Chikungunya	Phase 1–2 clinical trials
Yellow fever	Licensed and available
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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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**



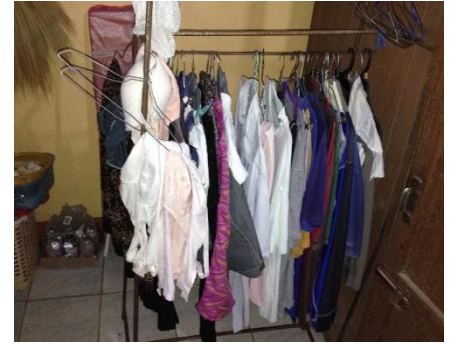
Environments that Favor More Mosquitoes and Transmission of Diseases

- ❑ **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



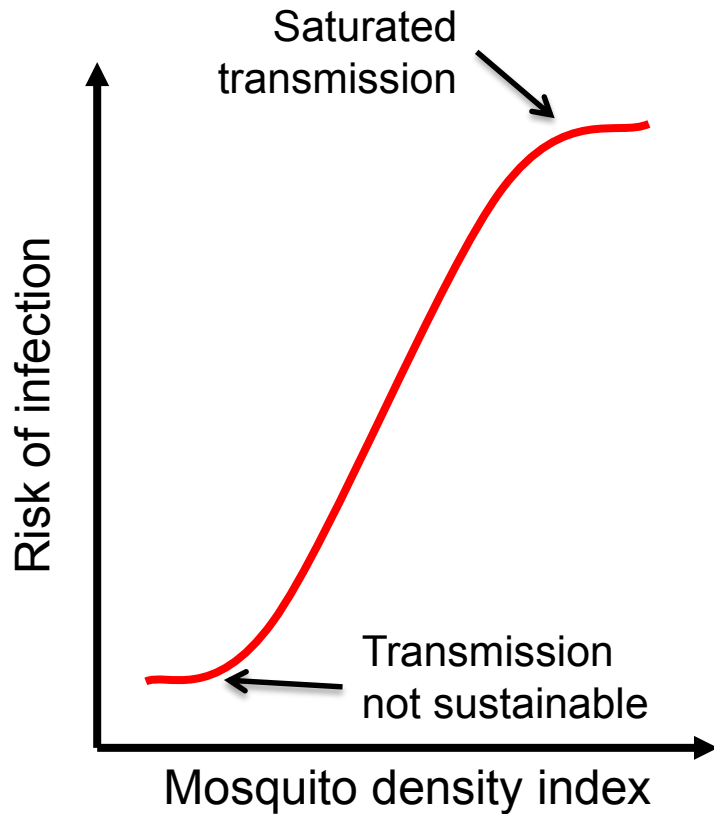
❑ To be effective, vector control measures need to reduce mosquito populations

- 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

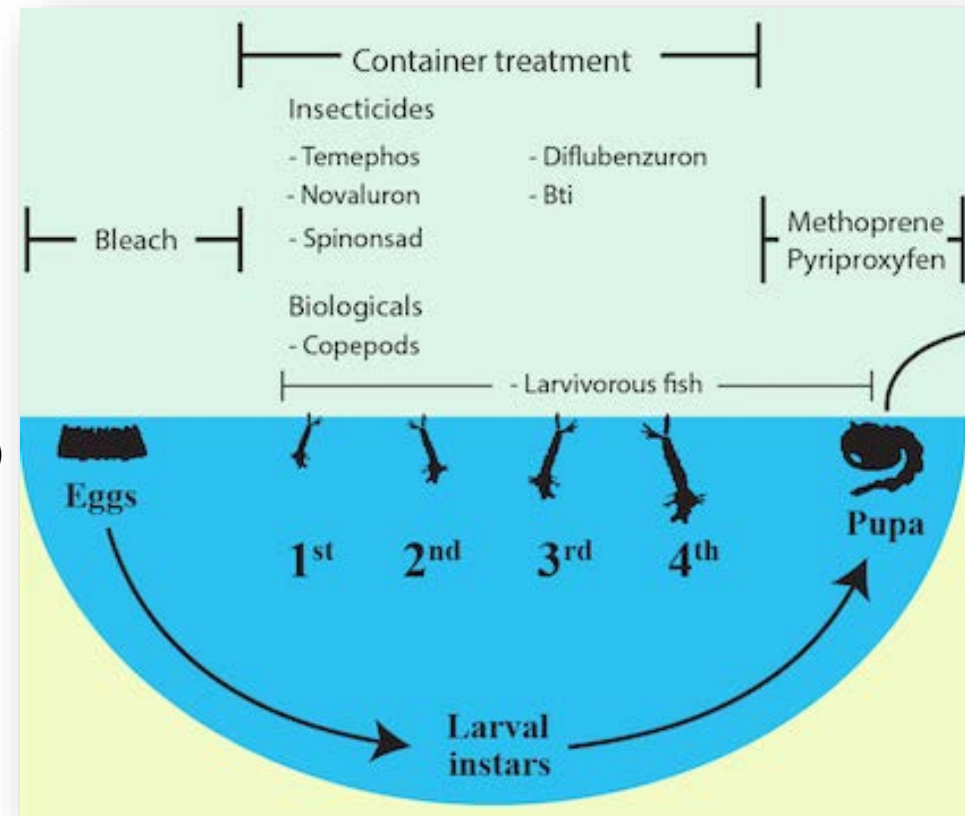
Improving Measures of Entomological Risk



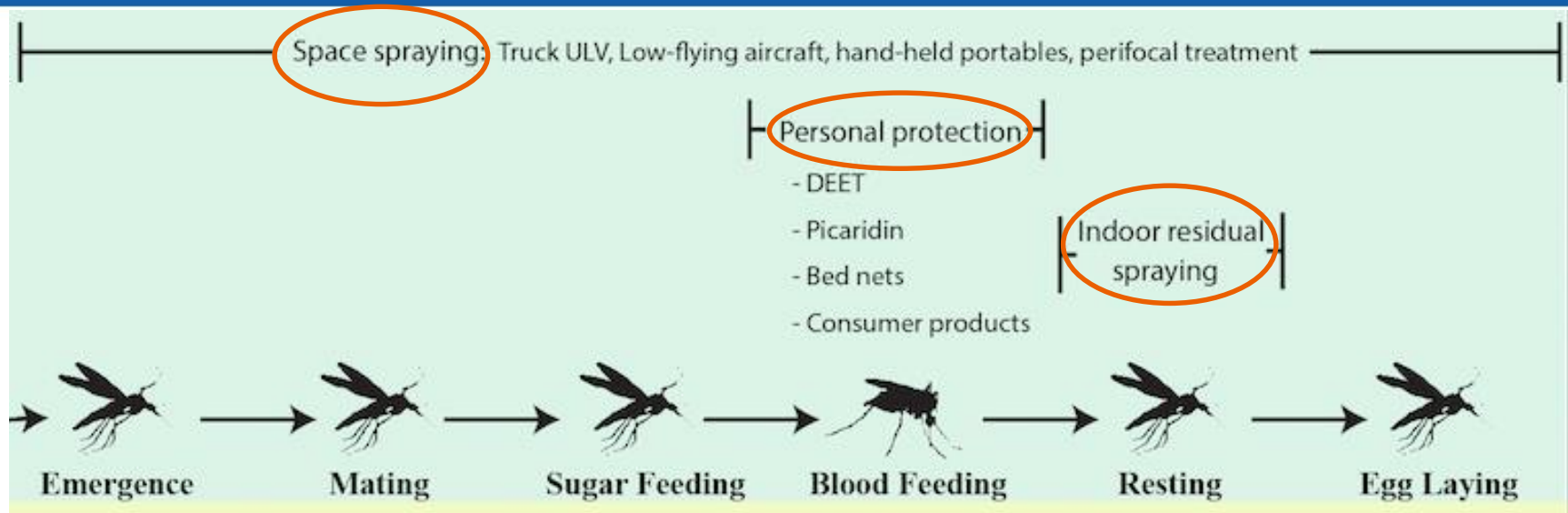
- ❑ **Historical indices for immature mosquitoes do not predict human dengue infection risk**
- ❑ **Shift to pupae and adult mosquitoes indices requires understanding of complex interplay of many factors**
 - Susceptibility of human population; i.e., herd immunity
 - Human biting rate
 - Human host density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



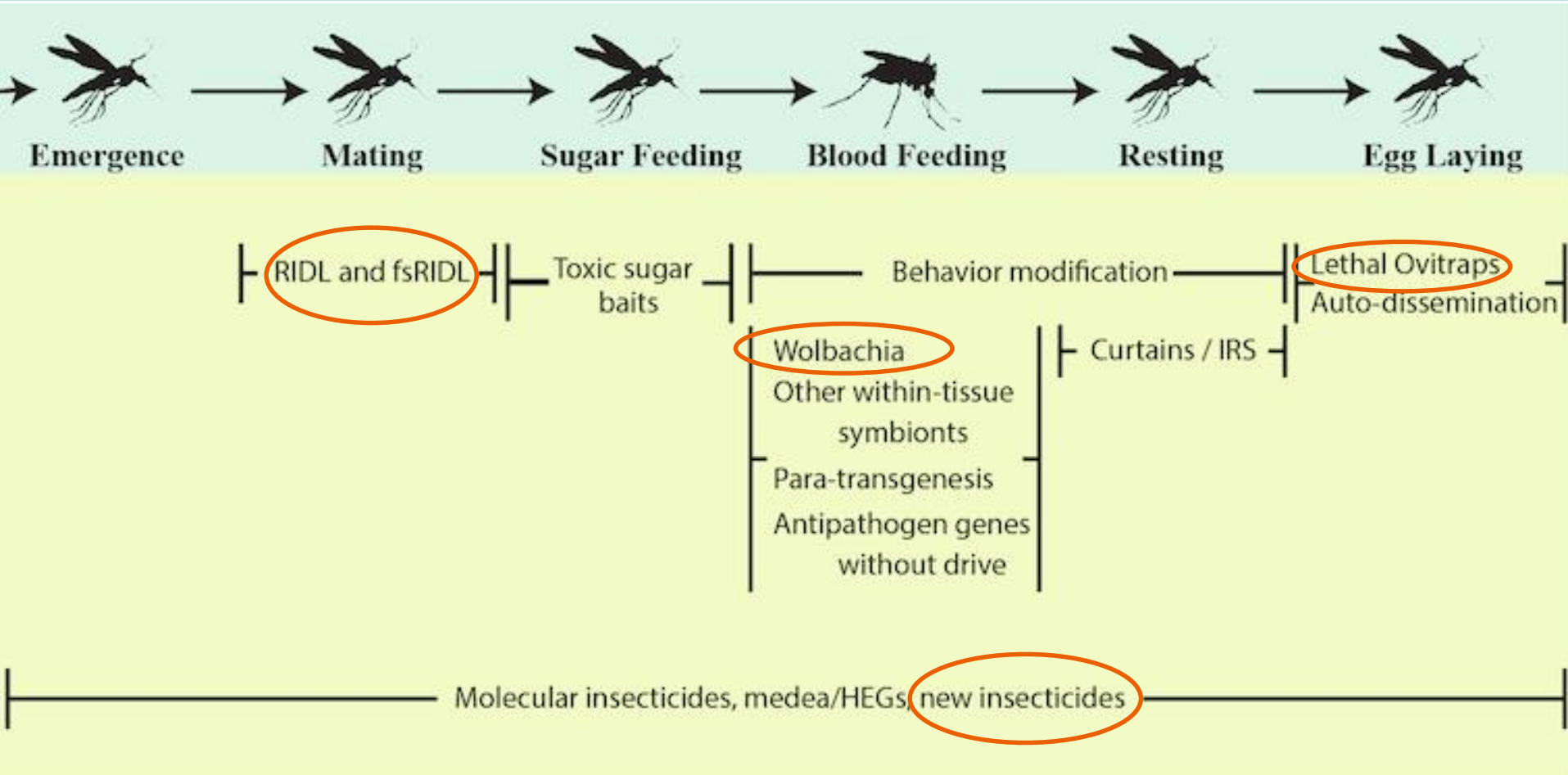
Existing Methods for *Aedes aegypti* Control – Adult Stage



Major categories include

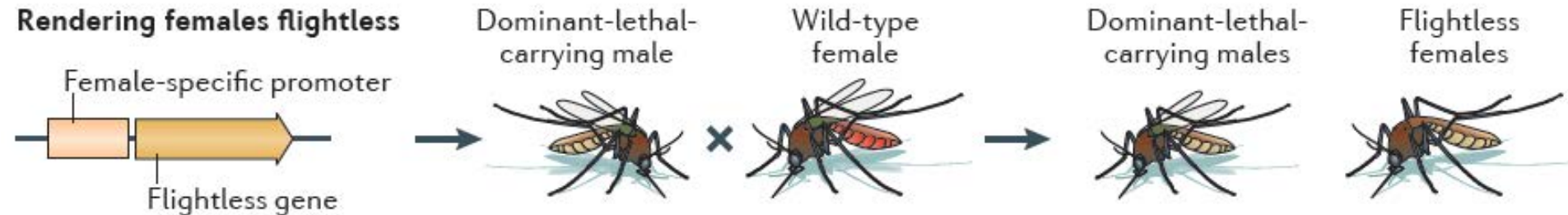
- (1) Space spraying (indoor vs outdoor)
- (2) Indoor residual spraying
- (3) Personal protection

Interventions Currently Under Development



Achee NL, et al. PLoS NTD 2015
RIDL: Release of Insects Carrying a Dominant Lethal

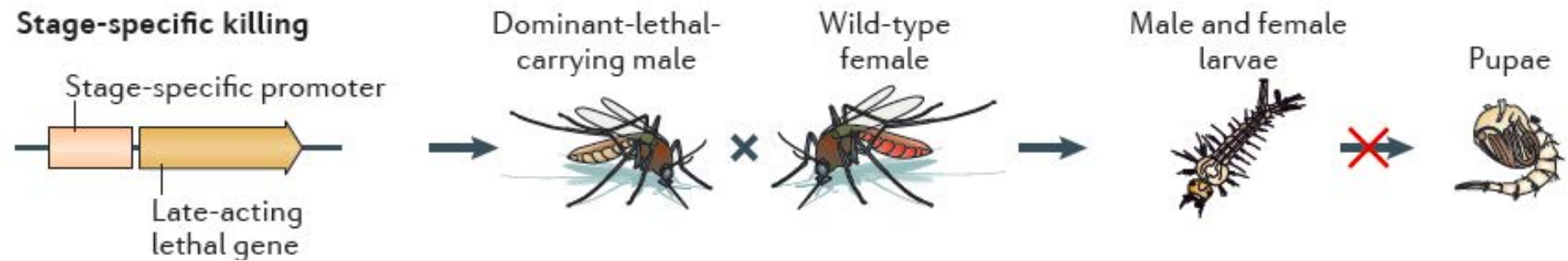
Release of Insects Carrying a Dominant Lethal (RIDL) – Flightless Females



□ 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

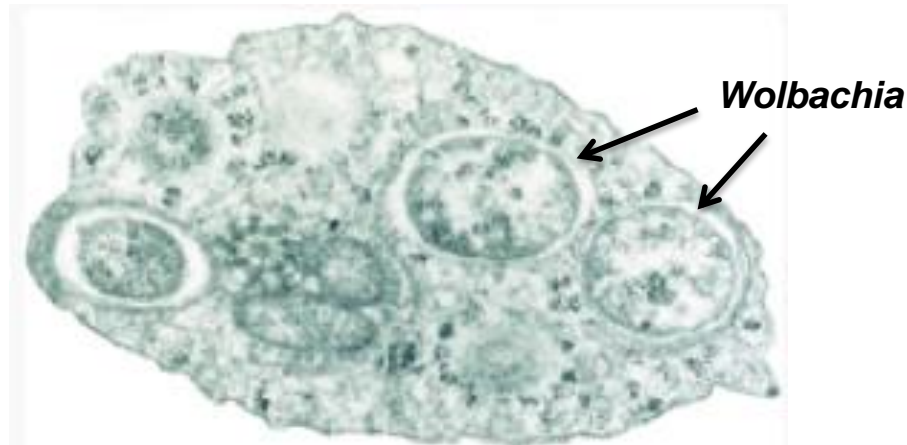
❑ Successful safety testing and mosquito population reduction field trials

❑ Need to evaluate impact on human dengue outcomes

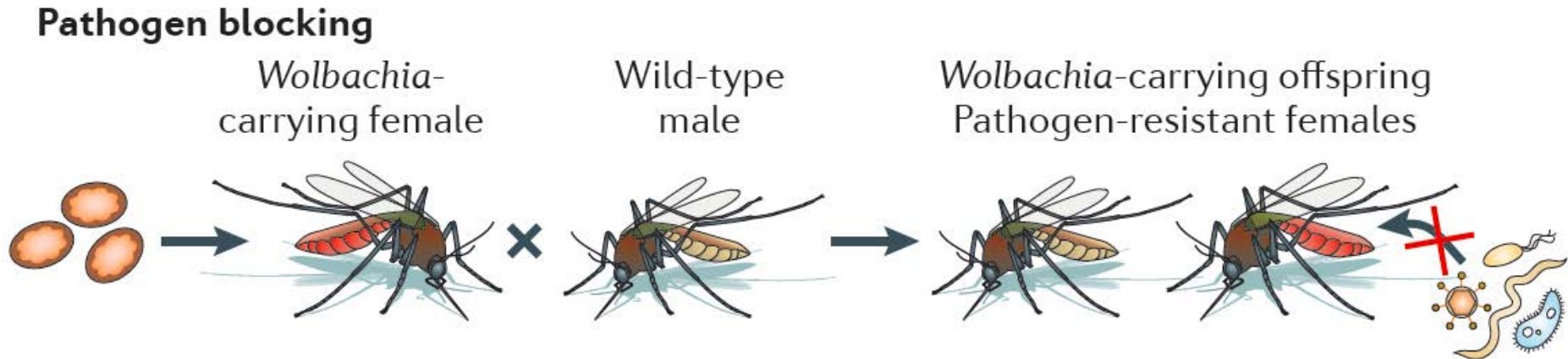
Naturally Occurring Bacteria – *Wolbachia*

- ❑ ***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

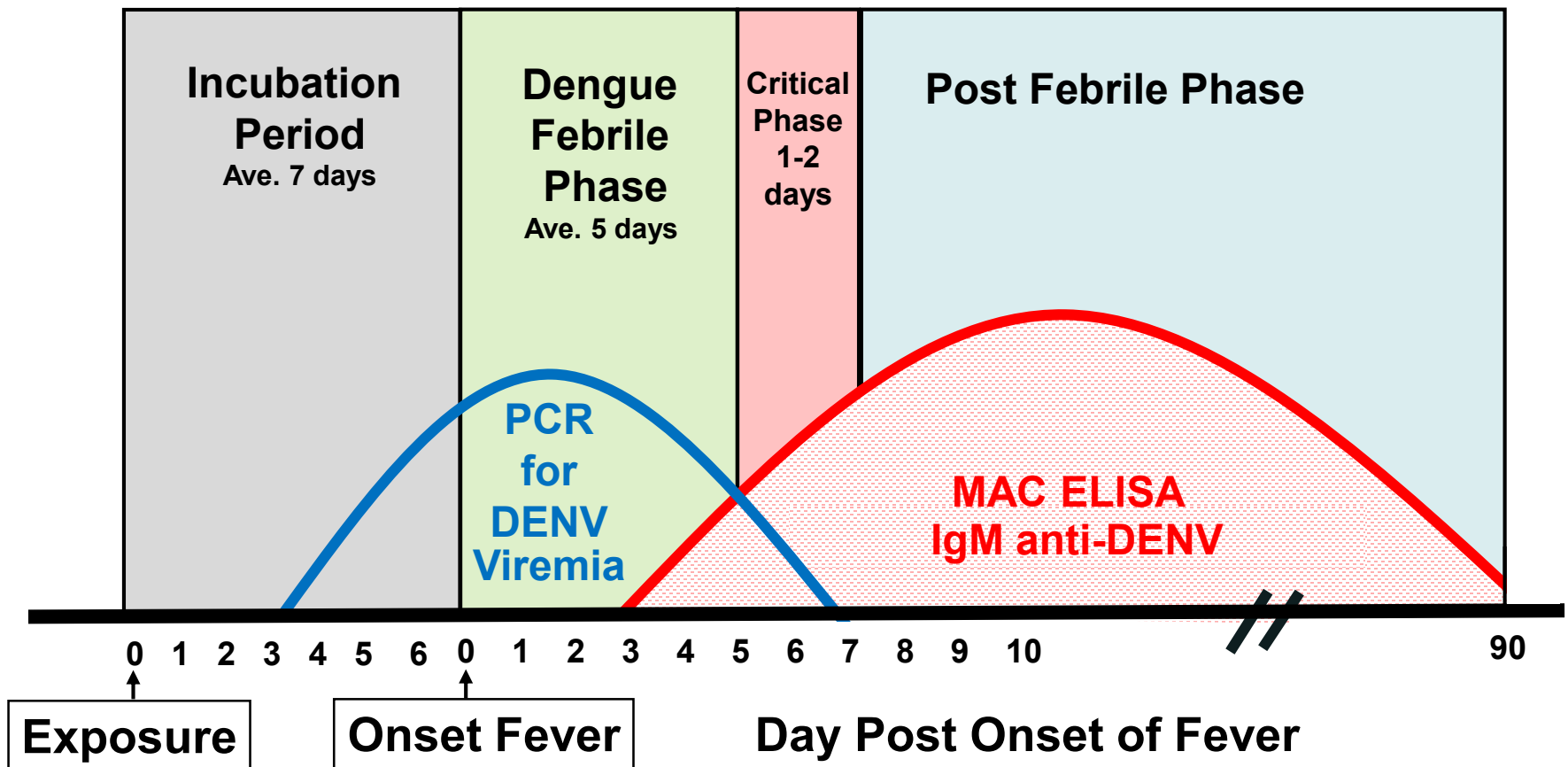


Free CME Training: cdc.gov/dengue/training/cme.html

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



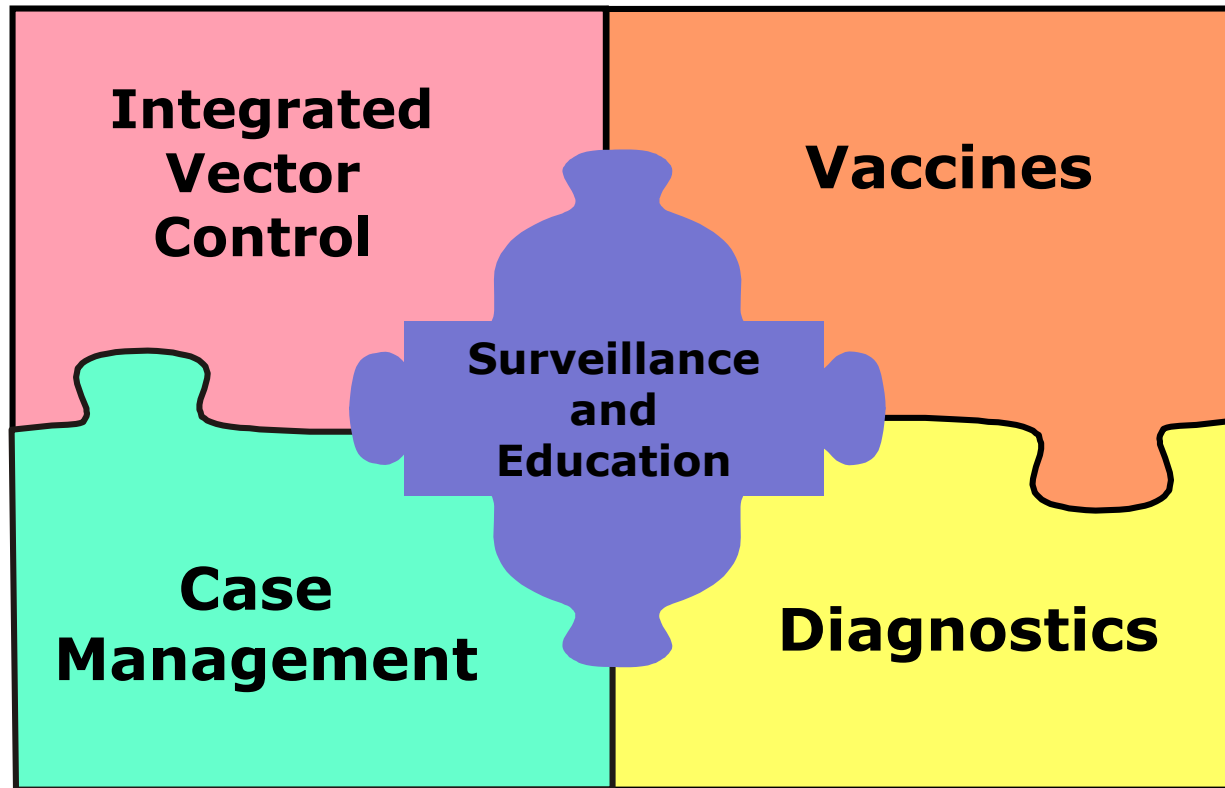
Peeling RW, et al. Nat Rev Microbiol 2010
Santiago GA, et al. PLoS NTD 2013
CDC unpublished data

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
Sanofi Pasteur (Acambis)	Live attenuated chimeric vaccine
Takeda (CDC, InViragen)	Live attenuated chimeric vaccine
Butantan (NIAID)	Live attenuated , engineered mutations in 3 strains and chimeric in 2
GSK (WRAIR)	Cell culture derived inactivated vaccine
Merck (Hawaii Biotech)	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
All DENV's	30.2	-13–57	56.5	44–66	60.8	52–68
DENV 1	55.6	22–84	50.0	25–67	50.3	29–65
DENV 2	9.2	-75–51	35.0	-9–61	42.3	14–61
DENV 3	75.3	-38–100	78.4	53–91	74.0	62–82
DENV 4	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



May 19, 2015



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