

# Presenter Disclosure Information Alfred DeMaria, Jr., M.D.

Consultant	No relevant conflicts of interest to declare
Grant Research/Support	No relevant conflicts of interest to declare
Speaker's Bureau	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Other Financial or Material Interest	No relevant conflicts of interest to declare

# Why Zika?

# Why Does Zika Virus **Epitomize Lessons Learned About Emerging Infection in** the Past 25 Years?

Transactions of the Royal Society of Tropical Medicine and Hygiene. Vol. 46. No. 5. September, 1952.

#### COMMUNICATIONS

ZIKA VIRUS

(I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

G. W. A. DICK,

The National Institute for Medical Research, London S. F. KITCHEN,

Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.

AND

A. J. HADDOW,

Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.

(From the Virus Research Institute, Entebbe, Uganda.)

The isolation of filterable viruses from mosquitoes taken in Uganda has already been recorded on several occasions. Two of the agents so recovered, although well known, had not previously been identified by isolation from mosquitoes in Uganda, viz. yellow fever virus (Mahaffer et al., 1942; SMITHBURN and HADDOW, 1946; SMITHBURN et al., 1949) and Rift Valley fever virus (SMITHBURN et al., 1948). A third which was called Mengo encephalomyelitis (DICK et al., 1948) (now known to be identical with Columbia SK,MM and encephalomyocarditis viruses (DICK, 1949; WARREN et al., 1949), has been isolated on several occasions from Taenior-hynchus spp. (DICK et al., loc. cit., DICK and HADDOW, (unpublished)). GILLETT and Dick (unpublished) have, however, failed to transmit this agent in the laboratory by three species of *Taeniorhynchus*. The isolation of three hitherto unknown, filterable viruses secured from wild mosquitoes in Uganda has been described,



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Transactions of the Royal Society of Tropical Medicine and Hygiene. Vol. 48. No. 2. March, 1954.

# ZIKA VIRUS: A REPORT ON THREE CASES OF HUMAN INFECTION DURING AN EPIDEMIC OF JAUNDICE IN NIGERIA

BY

#### F. N. MACNAMARA\*

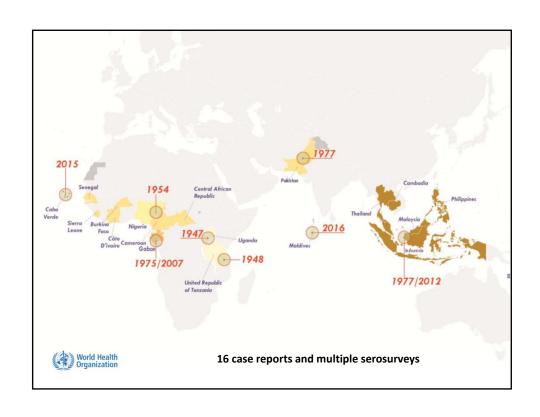
Acting Director, Virus Research Institute, Yaba, Nigeria

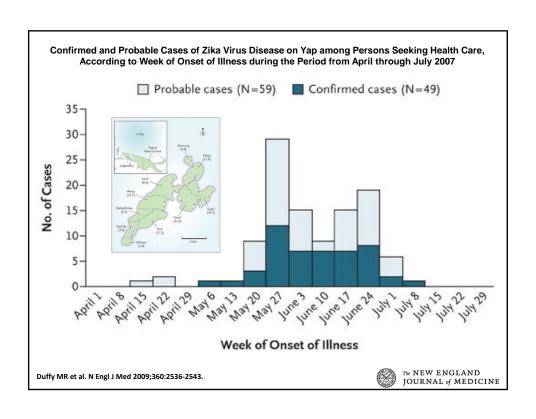
Zika virus was first isolated from a captive rhesus monkey stationed in the forest of Zika near Entebbe, Uganda, during the course of research into the epidemiology of yellow fever (DICK et al., 1952). Later it was isolated from a batch of wild-caught mosquitoes.

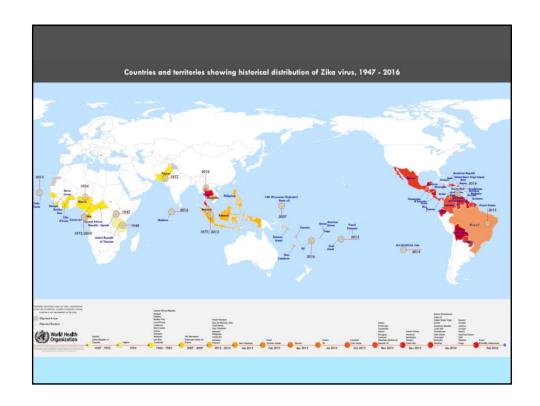
This virus was known by serological surveys to infect man in Uganda and Nigeria (Dick, 1952; Macnamara, 1952) yet nothing was known of the clinical manifestations of the infection.

During the investigation in Afikpo Division, Eastern Nigeria, of an outbreak of jaundice suspected of being yellow fever, Zika virus was isolated from one patient, and two other patients exhibited a rise in titre of serum antibodies against this virus.

Serological examination of specimens taken from other patients was made in an attempt to evaluate the relationship between the occurrence of jaundice and Zika virus.











#### **Epidemiological Alert**

Zika virus infection 7 May 2015

The Pan American Health Organization (PAHO) / World Health Organization (WHO) recommends its Member States establish and maintain the capacity for Zika virus infection detection, clinical management and an effective public communication strategy to reduce the presence of the mosquito that transmits this disease, particularly in areas where the vector is present.

#### Situation summary

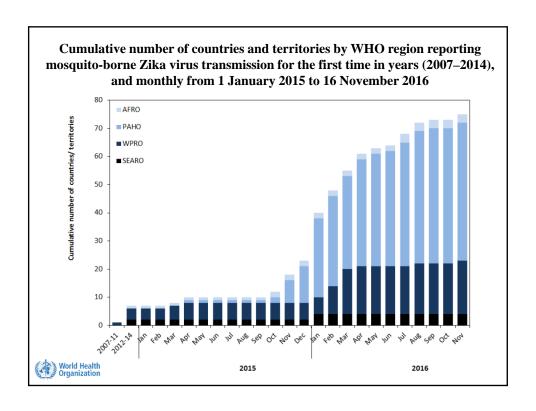
The Zika virus was first isolated in 1947 in Zika Forest (Uganda), in a Rhesus monkey during a study of the transmission of wild yellow fever. It was first isolated in humans in 1952 (Uganda, Tanzania).<sup>1,2</sup> In 1968 the virus was detected in human samples in Nigeria. <sup>3,4</sup>

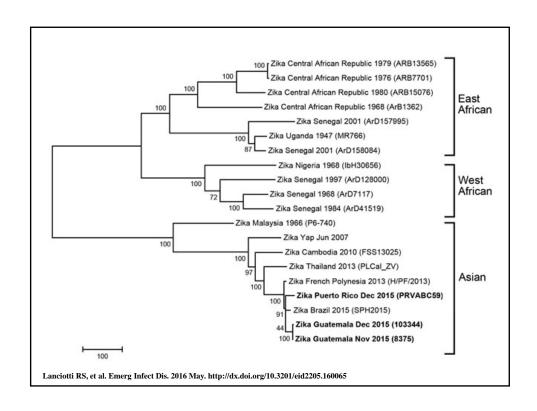
In 2007 the first major outbreak of Zika virus fever occurred on the island of Yap (Micronesia) where 185 suspected cases were reported, of which 49 were confirmed and 59 were considered probable. The

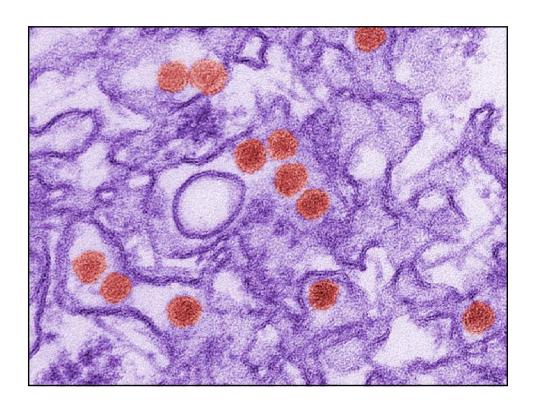
#### Zika virus infection

This is a disease caused by the Zika virus (ZIKAV), an arbovirus the flavivirus genus (family Flaviviridae), very close phylogenetically to viruses such as dengue, yellow fever, Japanese encephalitis, or West Nille virus.

The Zika virus is transmitted by mosquitoes of the genus Aedes, in urban areas (A. aegypti) as well as in the wild.

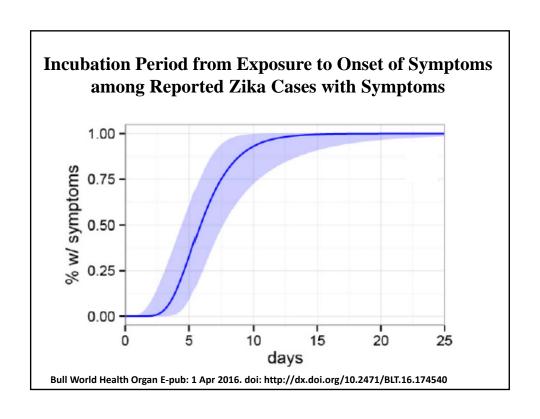


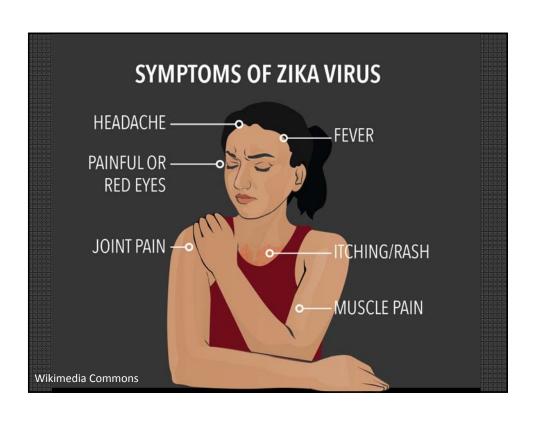




#### Zika Virus

- **❖**Flavivirus, family *Flaviviridae*
- **❖**Positive sense, single-stranded RNA virus
- **❖**3 structural and 7 nonstructural proteins, expressed as a single polyprotein that undergoes cleavage
- **❖**Closest relative Spondweni virus
- **❖**African and Asian lineages
- **❖**Enters skin cells at bite wound and travels to lymphatics and bloodstream
- **❖**Neurotropic







# **Differential Diagnosis**

**❖** Dengue

**❖** Group A streptococci

**❖** Chikungunya

**❖** Rubella

**\*** Leptospirosis

**❖** Measles

Malaria

\* Adenovirus

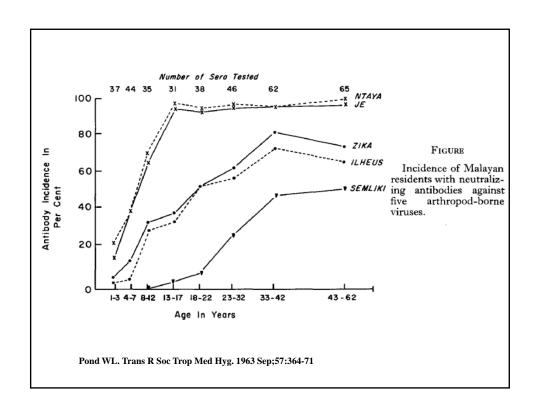
**❖** Rickettsial infection

**\*** Enterovirus

\* Parvovirus

#### Seropositivity Rates (%) for Anti-Zika Antibody

Country	Years	Children	Adults	Total
Uganda	1945-52	11.3	12.7	11.9
Tanzania	1945-52	13.3	19.0	16.7
Nigeria	1955			55.1
Angola	1960	15.9	38.7	27.0
Central African Republic	1961-62			48.8
Nigeria	1966-67	0.0	5.1	1.8
Kenya	1968	2.4	11.2	7.8
Nigeria	1969-71, 1972	52.3	71.7	64.0
Senegal	1972, 1975			58.3
Uganda	1984			6.1
Malaya	1953-54			75.0
Vietnam	1954			4.0
Indonesia	1983			12.7
Borneo	1996-97			44.1
Yap	2007			74.3
French Polynesia	2011-13			0.8
French Polynesia	2014	66.0		50.0
Musso D. Gubler DJ. Clin Micr	nhiol Rev. 2016 Jul-29(3):	487-524		



# Why Zika?





#### **Epidemiological Alert**

Increase of microcephaly in the northeast of Brazil

17 November 2015

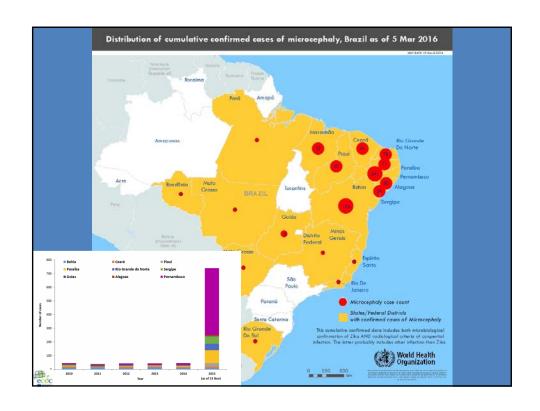
Given the unusual increase in cases of microcephaly in some northeast states of Brazil, the Pan American Health Organization (PAHO) / World Health Organization (WHO) calls upon Member States to remain alert to the occurrence of similar events in their territories and to notify its occurrence through the channels established under the International Health Regulations (IHR).

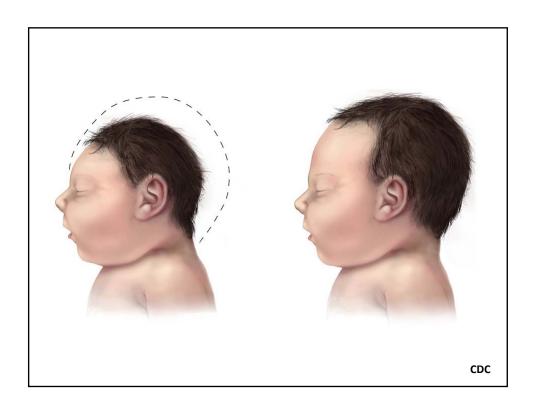
#### **Situation summary**

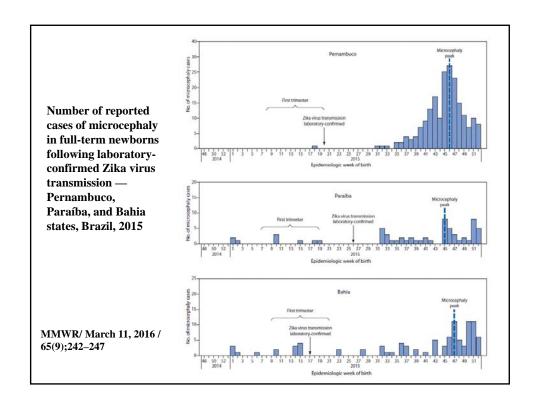
In October 2015 the Brazil Ministry of Health reported an unusual increase in cases of microcephaly in the state of Pernambuco, located in the northeast of Brazil. On average, the state of Pernambuco registered 10 cases of

Microcephaly CIE-10: Q02

Microcephaly is a neurological disorder in which the occipitofrontal circumference is smaller than that







# **Known Causes of Microcephaly**

- **❖**Genetic mutations
- **❖**Exposure to alcohol, drugs or toxic chemicals during pregnancy
- **❖**Malnutrition during pregnancy
- **❖**Infections, such as rubella, during pregnancy
- **❖**Lack of blood supply to the fetal brain

# Factors in Zika Virus Infection in Pregnancy

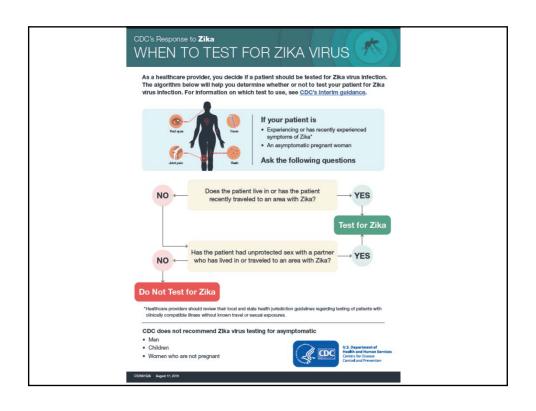
- **\***Viremia
- **❖**Gestational age
- Transplacental transmission
- **\*Placental infection**
- Congenital infection
- \*Antibody specific and cross-reactive

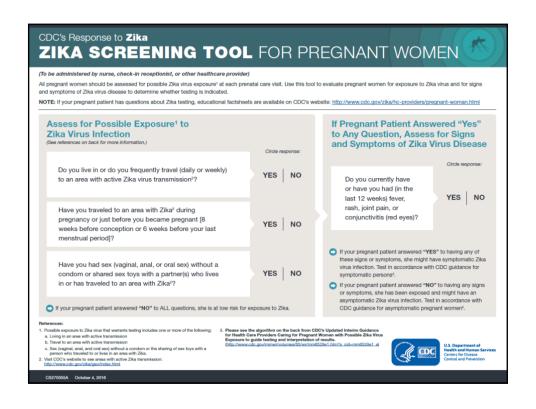
# Why Microcephaly? Why Now?

- **❖**Not noticed before
- **❖Immunity acquired in childhood**
- **❖Interaction with other factor** 
  - **❖Infection due to related viruses**
- **♦** Change in the virus

# **More Than Microcephaly**

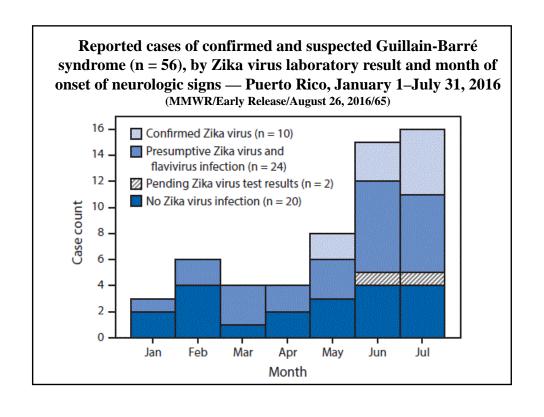
- \*Retinal lesions
- **❖**Sensorineural hearing loss
- **\***Arthrogryposis
- **❖**Neuropsychomotor developmental delay
- **\***Hydrops fetalis
- **❖Fetal demise, miscarriage**





	Suggested timeframe to wait befor		
· · · · · ·	r sex without a condom with a partner infec		
Vomen		Men	
Wait at least 8 weeks after symptoms start or last possible exposure		Wait at least 6 months after symptoms start or last possible exposure	
People living in or frequently traveling	ng to areas with Zika		
	Women	Men	
Positive Zika test	Wait at least 8 weeks after symptoms start	Wait at least 6 months after symptoms start	
No testing performed or negative est	Talk with doctor or healthcare provider	Talk with doctor or healthcare provider	





## Guillain Barré Syndrome

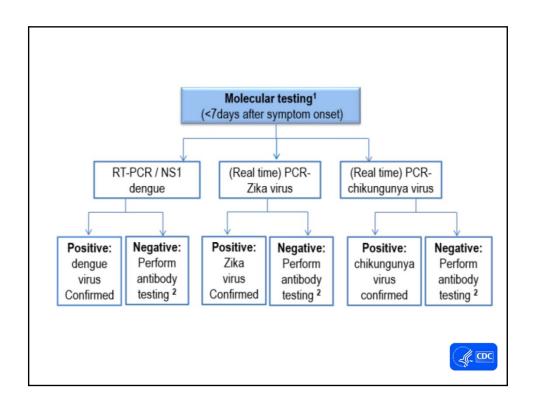
- \*Acute inflammatory demyelinating polyneuropathy (AIDP)
  - \*AIDP with secondary degeneration
- **\***Acute motor axonal neuropathy (AMAN)
  - **❖**Acute motor sensory axonal neuropathy (AMSAN)
- **❖**Miller Fisher syndrome
  - **❖**Cranial nerve involvement, ataxia

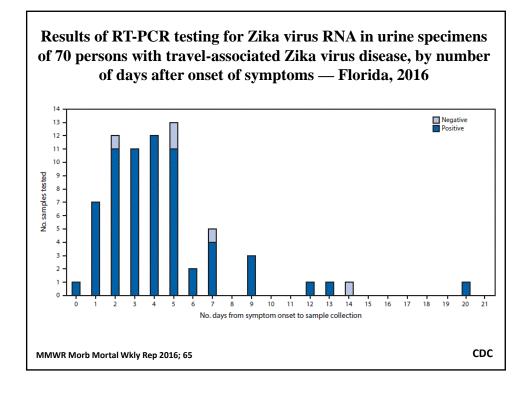
#### Guillain-Barré Disability Scale

- 0 Healthy
- 1 Minor symptoms or signs of neuropathy but capable of manual work/capable of running
- Able to walk without support of a stick (5 m across an open space) but incapable of manual work/running
- Able to walk with a stick, appliance of support (5 m across an open space)
- 4 Confined to bed or chair bound
- 5 Requiring assisted ventilation (for any part of the day or night)
- 6 Death

#### **Zika Virus Infection**

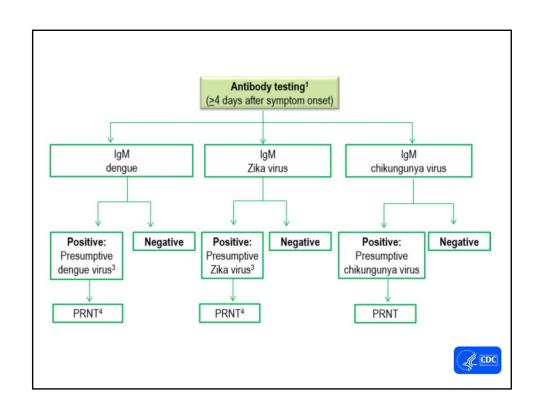
- **♦** Asymptomatic (80%)
- **♦**Symptomatic (20%)
  - **❖**Fever, rash, conjunctivitis
  - Congenital infection
  - **❖**Guillain Barré syndrome
  - **Uveitis**
  - **&**Encephalitis
  - **\***Thrombocytopenia

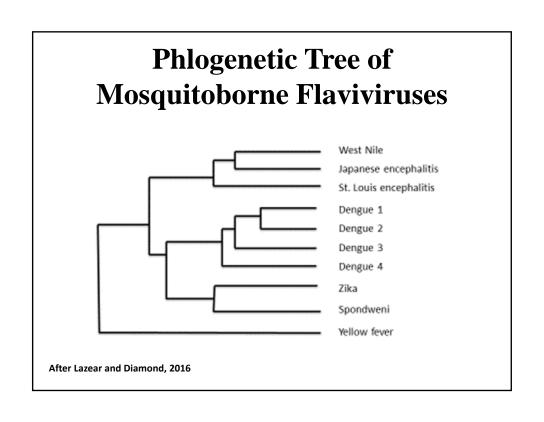


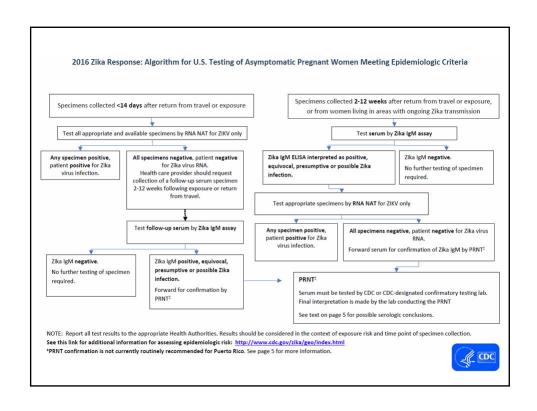


# Prolonged Zika Viral Detection (PCR) (as of 11/22/2016)

- **Serum** (7-14 days)
- ❖ Whole blood RBCs (58-81 days)
- **❖** Viremia in pregnant women (53 days)
- **❖** Newborn (54 days)
- **Semen** (62-188 days)
- **❖** Vaginal fluid (14 days)
- ❖ Saliva (91 days)
- **!** Urine (91 days)
- **❖** Breast milk (4 days)







Zika virus and dengue virus IgM ELISA	Zika virus PRNT	Dengue virus PRNT	Interpretation
Positive or equivocal (either assay)	≥10	<10	Recent Zika virus infection
Positive or equivocal (either assay)	<10	≥10	Recent dengue virus infection
Positive or equivocal (either assay)	≥10	≥10	Recent flavivirus infection; specific virus cannot be identified
Any result (either or both assays)	<10	<10	No evidence of Zika virus or dengue virus infection
Inconclusive in one assay AND inconclusive or negative in the other	≥10	<10	Evidence of Zika virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	<10	≥10	Evidence of dengue virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	≥10	≥10	Evidence of flavivirus infection; specifi virus and timing cannot be determined

#### **Zika Virus Modes of Transmission**

- Established
  - \* Mosquitoborne
  - \* Transplacental
  - \* Intrapartum
  - ❖ Sexual male to female, male to male, female to male
  - ❖ Blood and body fluid laboratory needlestick, caregiver
  - \* Transfusion
- \* Theoretical
  - \* Organ or tissue transplantation
  - ❖ Breast milk

#### **Revised Recommendations for Reducing** the Risk of Zika Virus Transmission by **Blood and Blood Components**

#### **Guidance for Industry**

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to the hip//www.reguiations.gov. Submit written comments to the Division of Dockets Management (HFA-305). Food and Drug Administration. 5530 Fishers Lane. Rm. 1061, Rockville. MD 20852. You should identify all comments with the docket mumber listed in the notice of availability that publishes in the Federal Register. FDA will review any comments we receive and revise the guidance when appropriate.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email cood@fda.his.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email

U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research August 2016

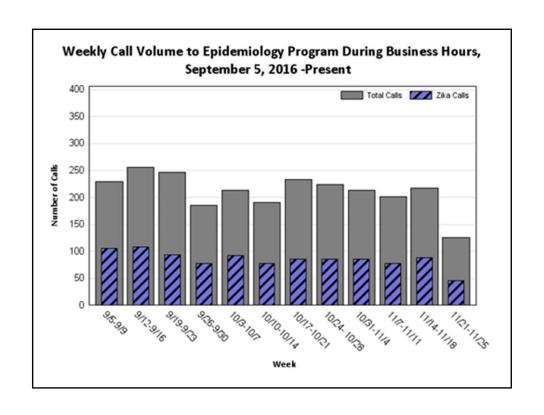
#### **Individual donor NAT**

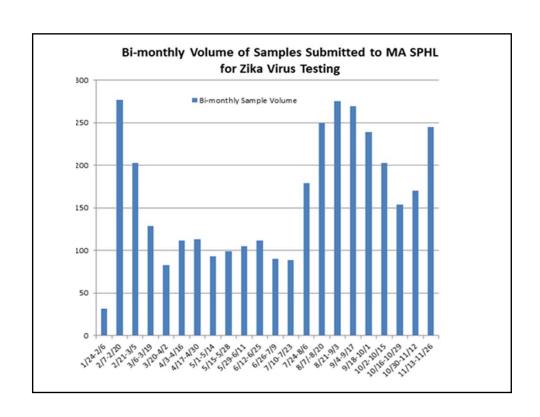
Phase in Florida, Puerto Rico and in 11 other states in 4 weeks and all by 12 weeks

120 day deferral and "look-back"

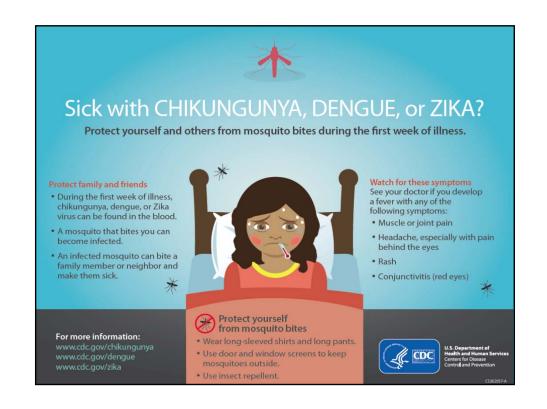
No travel screen with ID NAT

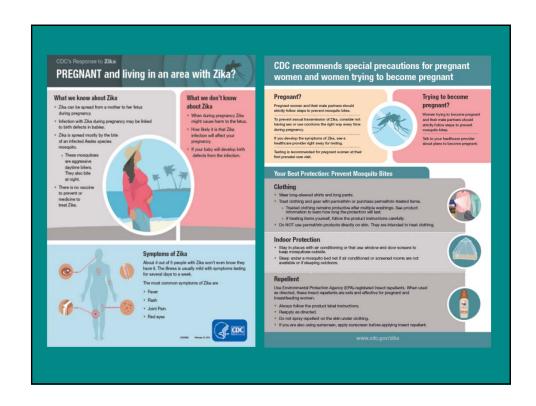


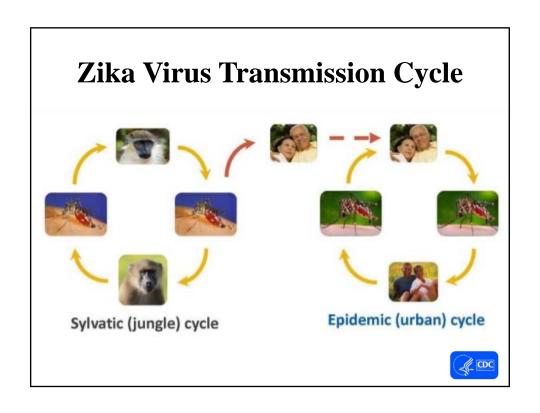




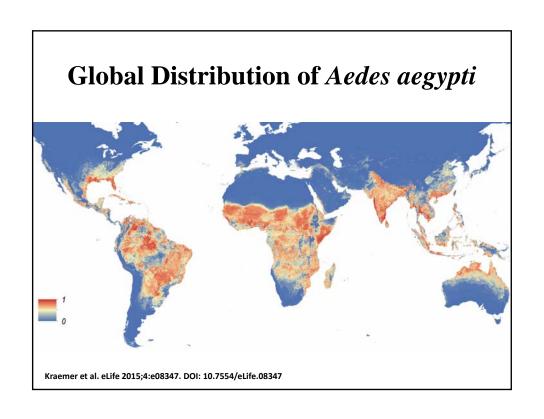


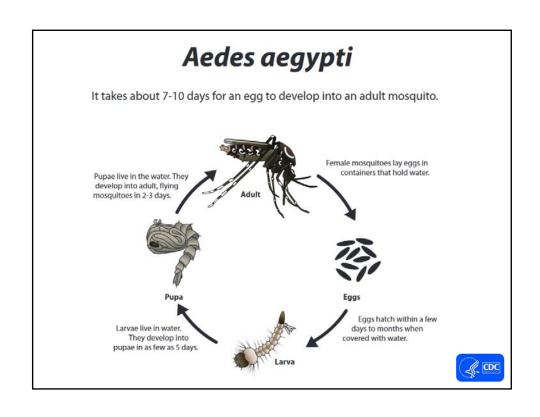


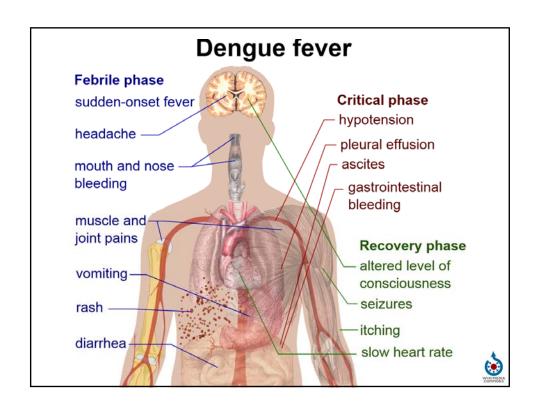


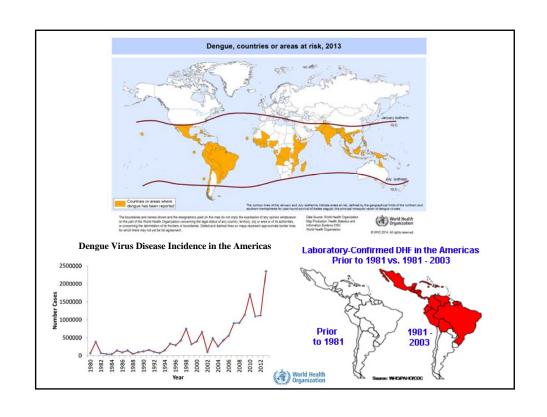




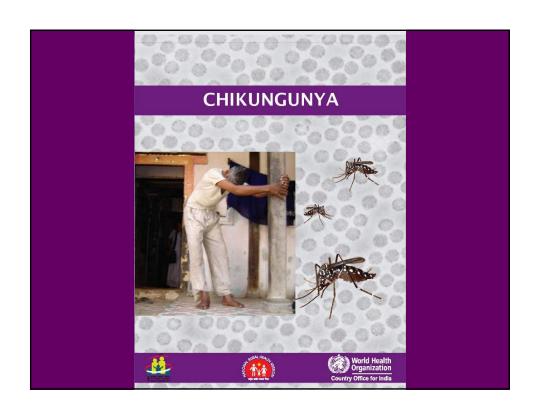


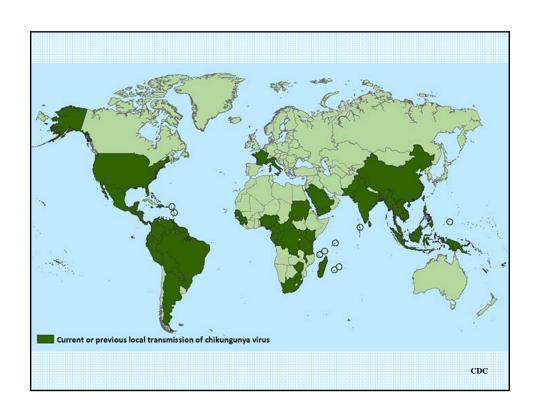


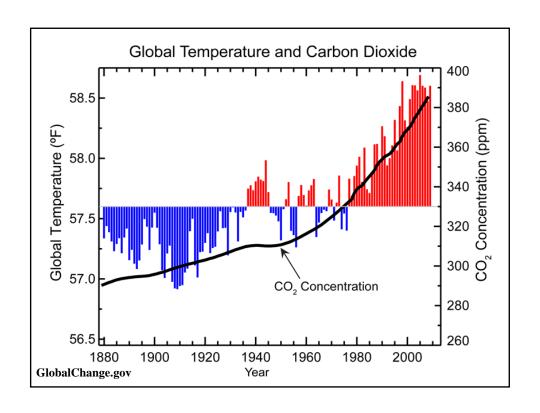




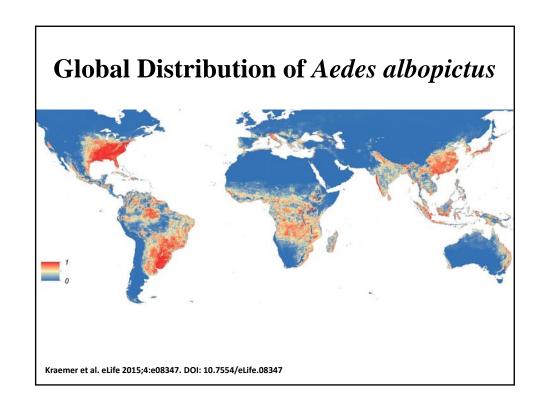


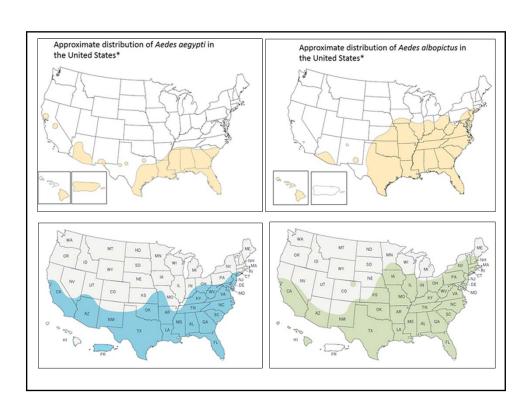


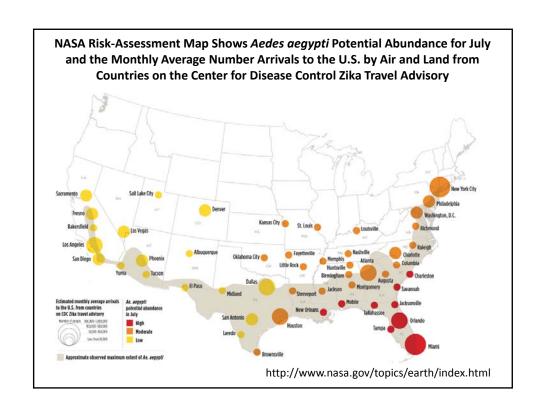


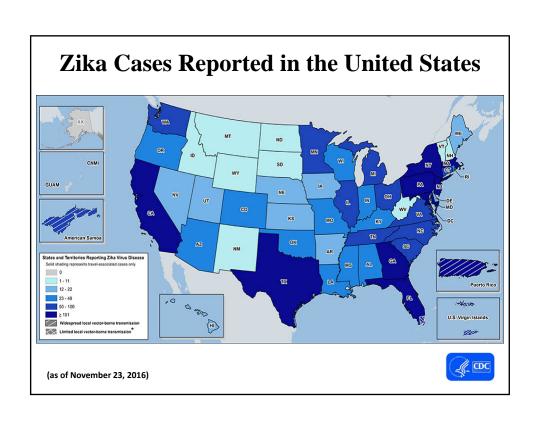


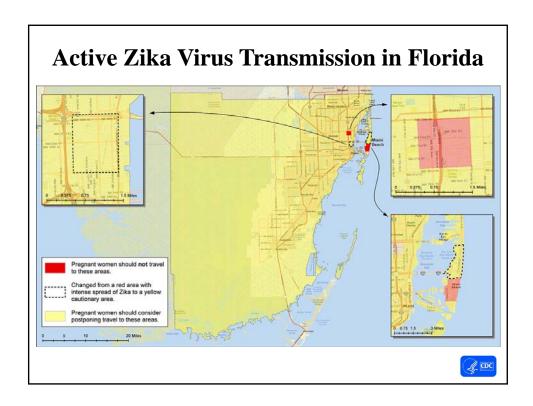






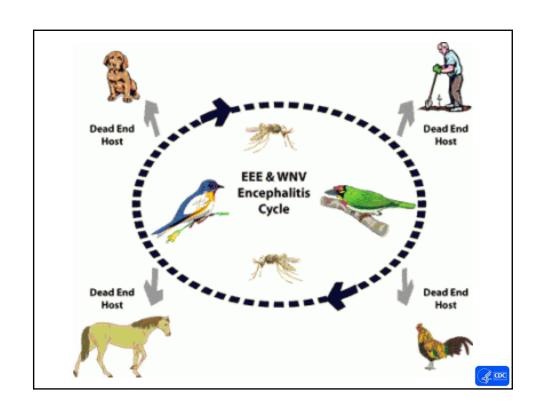






#### **Factors Related to Arbovirus Transmission**

- **❖**Reservoir host present
- **❖** Vector(s) present
  - **❖** Favorable climate
  - \* Habitat and food sources present
- **❖** Vectorial competence
  - **Abundance**
  - ❖ Bites reservoir host
  - **❖** Sustains virus replication
  - $\ \ \, \ \ \, \ \ \, \ \ \,$  Virus incubation period consistent with life cycle and biting behavior
  - ❖ Pathogen reaches saliva
- **❖** Vectorial capacity
  - \* Physiology
  - **❖** Host preference
  - \* Biting behavior
  - **❖** Contact probability



Transmission of E	astern Equine Encephalit Zika Virus – Vectors and	. , ,	, ,
	EEE	WNV	Zika
Virus host reservoir	Birds	Birds	Humans
Amplifying vector(s)			
Primary species	Culiseta melanura	Culex species	<ol> <li>Aedes aegypti</li> <li>A. albopictus</li> </ol>
Breeding habitat	White cedar/red maple swamp	Puddles and containers, dirty water	Containers
Transmitting vector(s)			
Primary species	Coquillettidia perturbans, Aedes vexans, other bridge mosquitoes	Culex species	<ol> <li>Aedes aegypti</li> <li>A. albopictus</li> </ol>
Primary host	Mammals and birds	Birds	1. Humans 2. Mammals
Breeding habitat	Cattail swamps, flood plain	Puddles and containers, dirty water	Containers
Habitat of adults	Rural	Tree canopy, ubiquitous	Peridomestic
Biting habits	Dawn/dusk, outdoors; one host meal	Dawn/dusk, outdoors; one host meal	All day, indoor/outdoor; multiple host meal







## **Prevention**

- \* Reduce mosquito exposure
  - \* Window and door screens
  - \* Mosquito netting
  - \* Staying indoors at peak mosquito times
- \* Reduce mosquito bites
  - \* Clothing
  - **❖** Repellents use according to product label
- \* Reduce mosquitoes
  - \* Reduce standing water
  - \* Mosquito control
    - \* Reduce breeding environment
    - \* Larvicide
    - \* Adulticide

# **Mosquito Repellents**

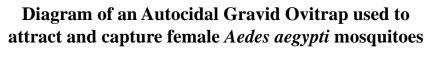
- **❖ DEET (N-N-diethyl-meta-toluamide)** 
  - Should not be used on infants under two months of age and should be used in concentrations of 30% or less on older children
- \* Picaridin (KBR 3023)
- IR3535 (3-[N-butyl-N-acetyl]-aminopropionic acid)
- ❖ Oil of lemon eucalyptus [p-menthane 3, 8-diol (PMD)]
  - \* Should not be used on children under three years of age
- \* Permethrin
  - Intended for use on items such as clothing, shoes, bed nets and camping gear and should not be applied to skin

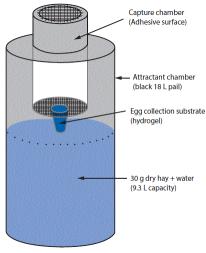
# Mosquito Control Methods Under Development

- \* Pathogenic fungal larvicides
- \* Release of insects with dominant lethality
  - **❖** Female-specific late-acting flightless phenotype
- \* Toxic sugar baits
- \* Symbionts that block transmission
  - \* Wolbachia species
- \* Anti-pathogen genes
- \* Indoor residual spraying, curtains
- Lethal ovitraps
- \* Auto-dissemination of insecticide
- Molecular and other new insecticides

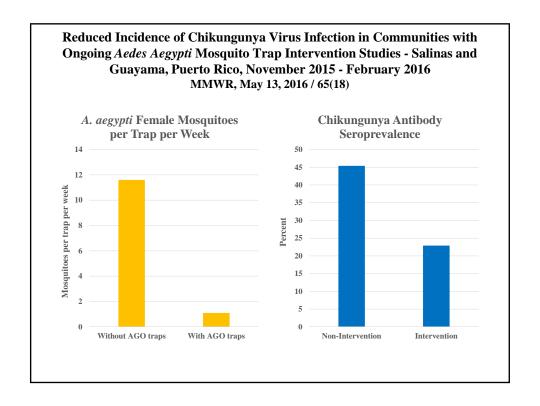






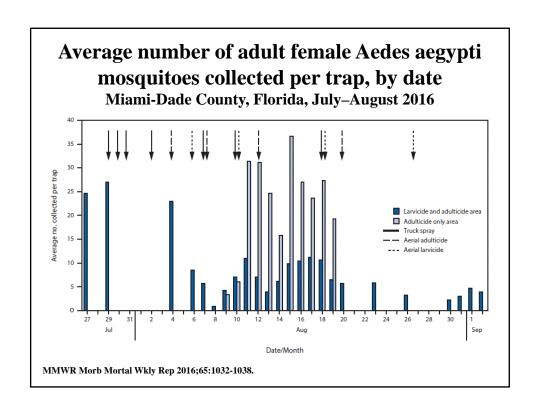


Mackay AJ, Amador M, Barrera R. An improved autocidal gravid ovitrap for the control and surveillance of Aedes aegypti. Parasit Vectors 2013;6:225.

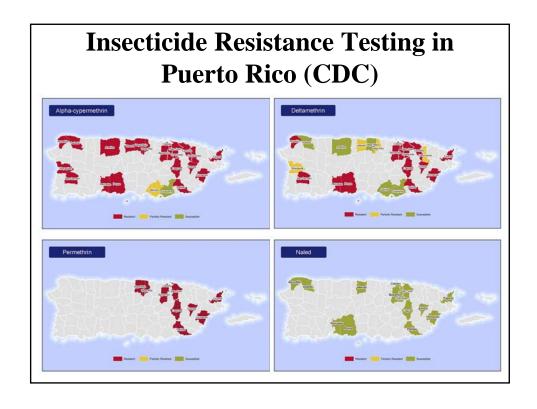












#### What's Next in Mosquitoes? **Togaviruses Flaviviruses** \* Eastern equine **\*** West Nile **\*** Western equine \* St. Louis \* Venezuelan \* Dengue \* Chikungunya \* Yellow fever \* Mayaro \* Zika \* Sindbis **❖ Spondweni** \* Ross River \* Usutu \* Japanese **Bunyaviruses ♦** California group \* Murray Valley (LaCrosse, Jamestown Canyon, etc.) Here before 1999 Cache Valley Here since 1999 **\***Tensaw Could come **\*Rift Valley** Unlikely?

