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## **Zika: The Emerging Infectious Disease**

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1st Qatar workshop for the “Assessing the Threats to Public Health  
2-3 November 2016



# Outline



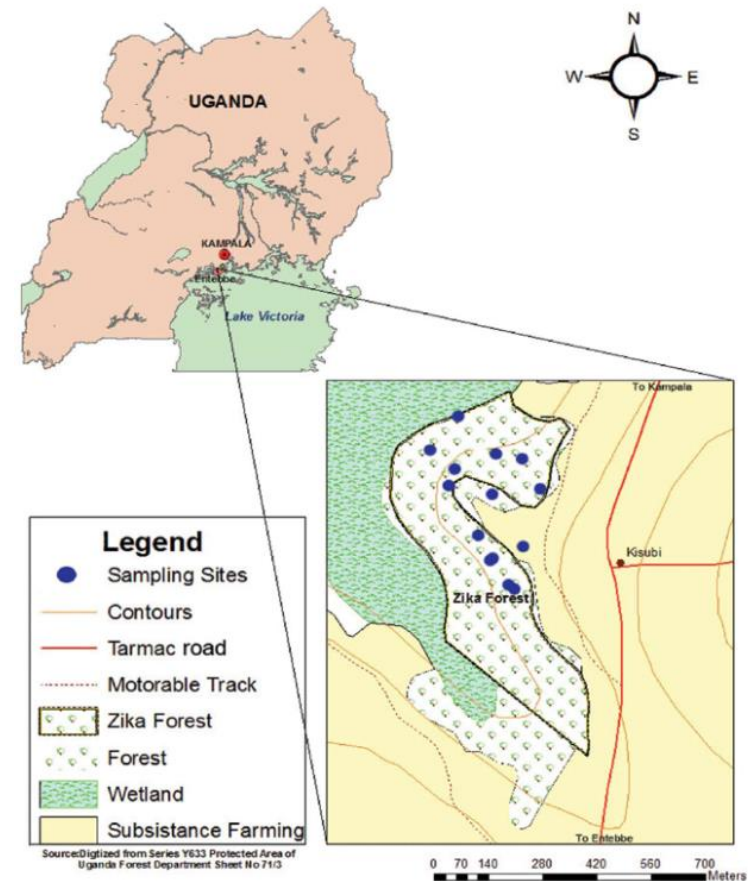
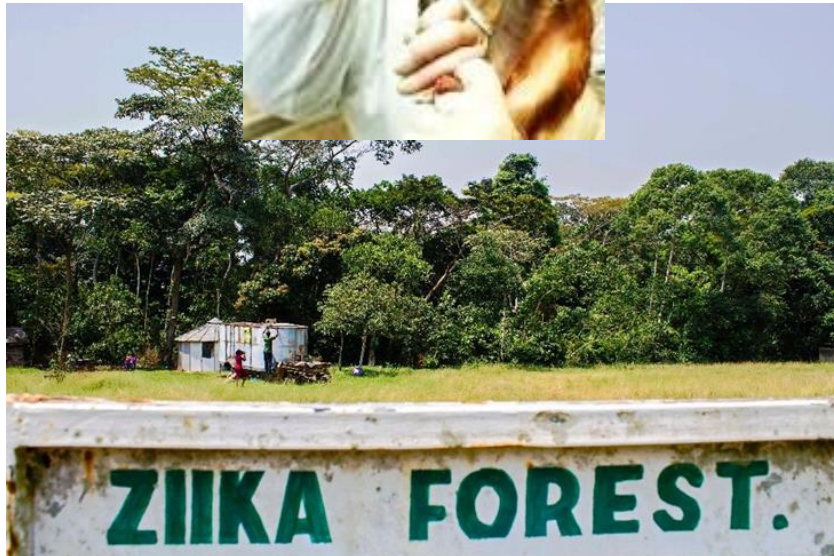
- **History**
- **Virus**
- **Vectors, Transmission & Risk**
- **Current Situation**
- **Zika and pregnancy**
- **Symptoms, Diagnosis and Testing**
- **Unmet Need and Challenges**



# History



Zika was first discovered in 1947, in the “Zika Forest,” Uganda



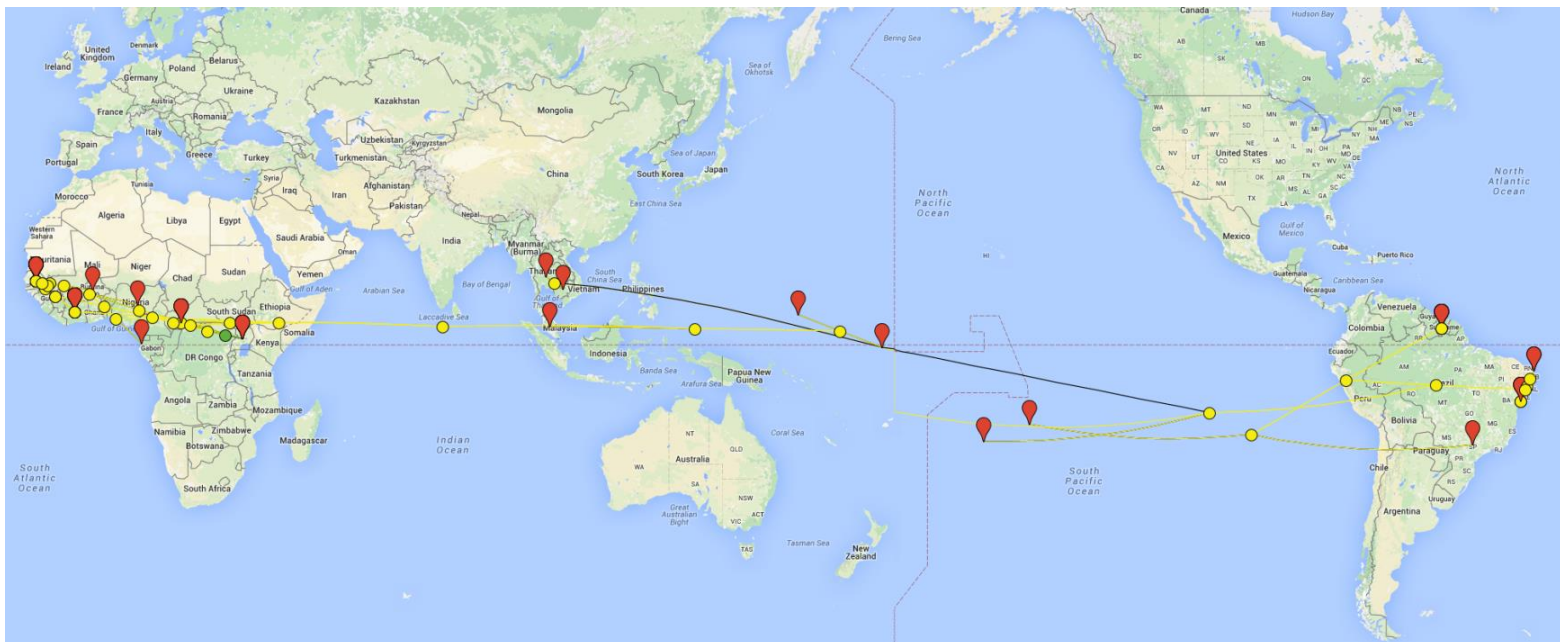
Map of Uganda showing the location of the study area (Zika Forest) and the exact locations of the sampling sites within Zika Forest.

Source: Kaddumukasa et al. Mosquitoes of Zika Forest, Uganda. Jan 2004. pg 105.

# From Ancient to New



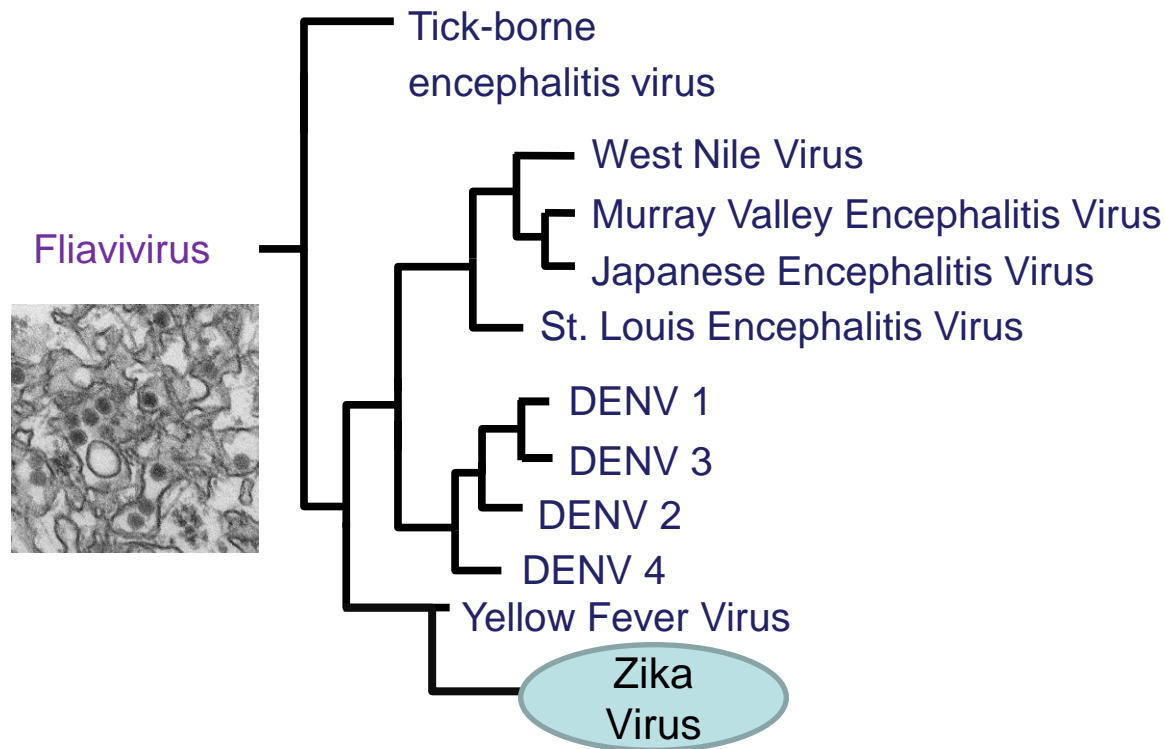
- Since 1947, cases occurred sporadically throughout Africa and southern Asia.
- In 2007, the first case was reported in the Pacific.
  - First major outbreak in Yap (Micronesia)
- In 2013 & 2014, a smattering of small outbreaks and individual cases were officially documented in Africa and the western Pacific.
- In May 2015, Brazil reported its first case of Zika virus.



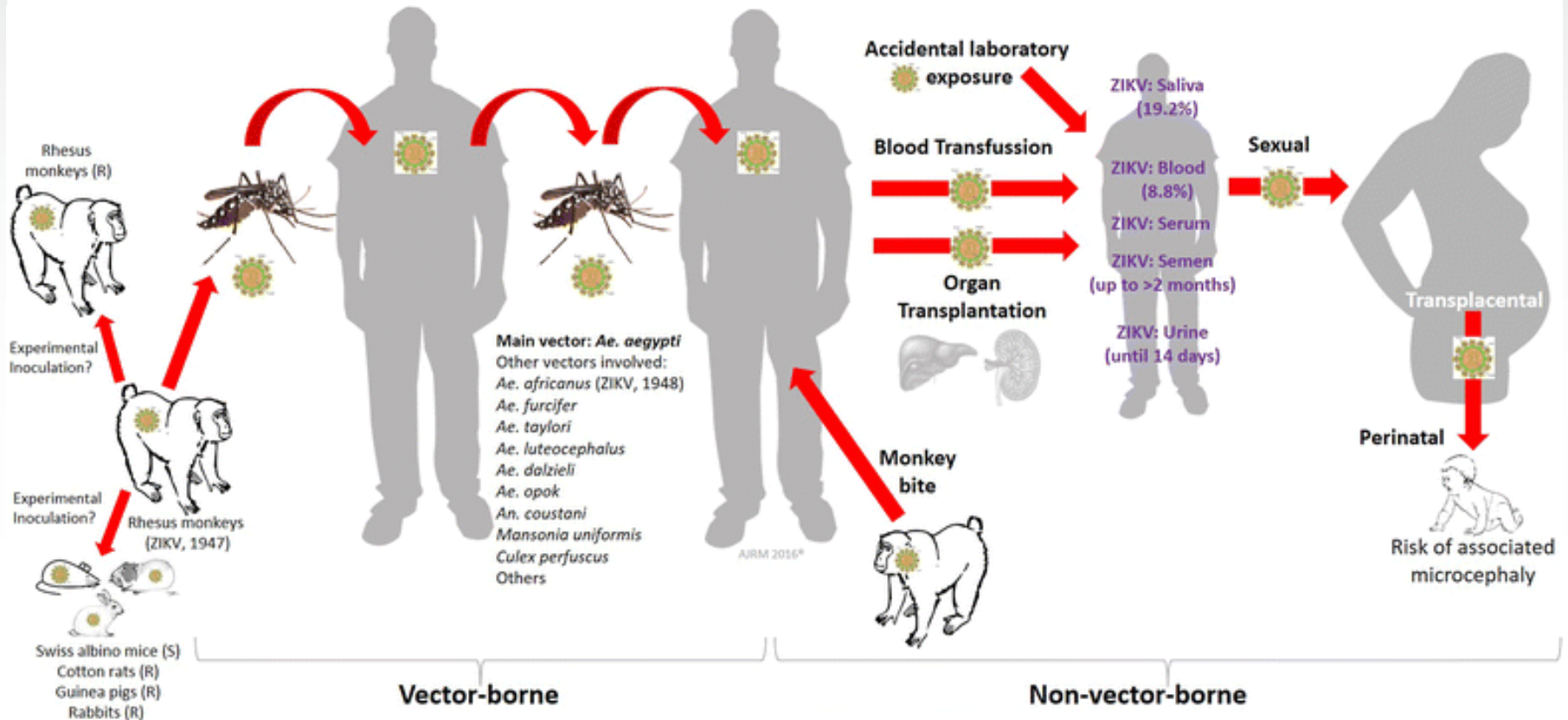
# The Virus



- Belongs to Genus *Flavivirus*, family *Flaviviridae*
- Enveloped icosahedral Single stranded RNA virus
- Two lineages:
  - African and Asian



# Vectors of Zika Infection Transmission & Risks

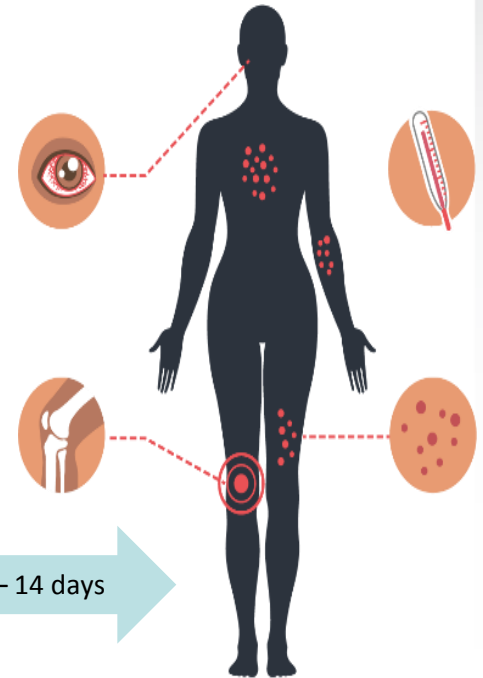
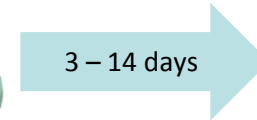
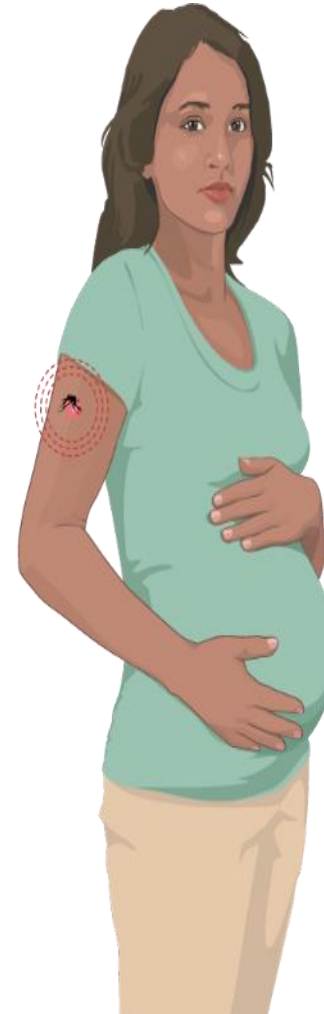


(S): Susceptible, develops clinical disease;  
(R): Resistant to clinical disease.

# Incubation and viremia



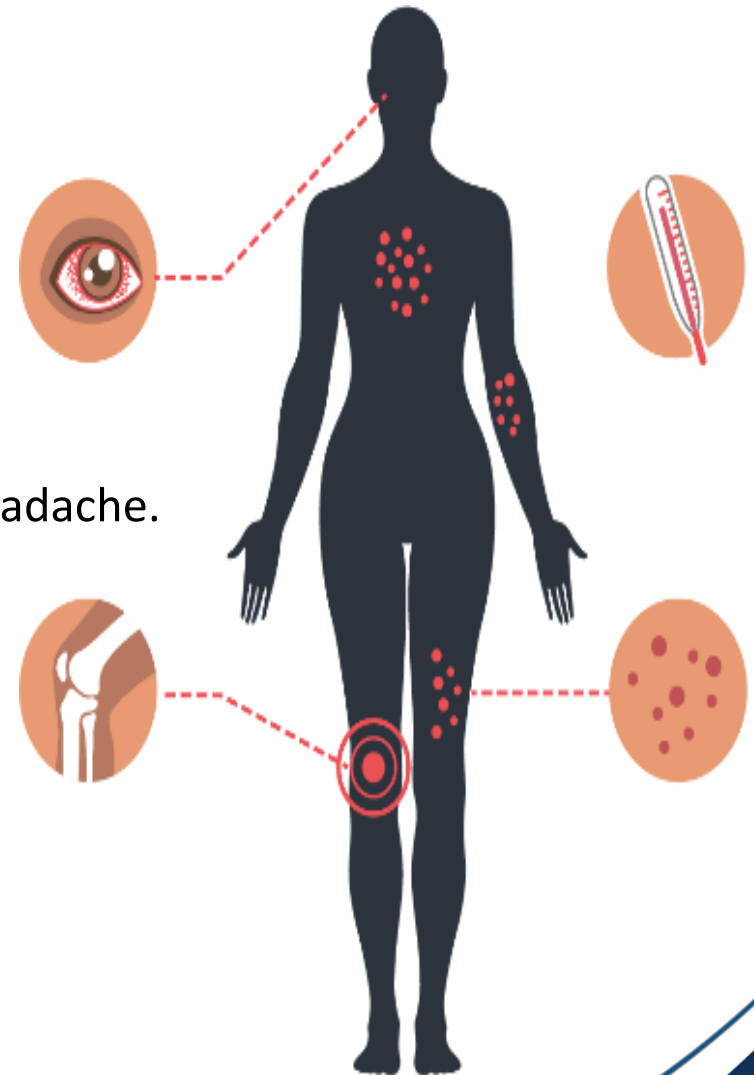
- Incubation period for Zika virus disease is 3–14 days.
- Zika viremia ranges from a few days to 1 week.
- Some infected pregnant women can have evidence of Zika virus in their blood longer than expected.
- Virus remains in semen and urine longer than in blood.



# Symptoms



- Many infections are asymptomatic.
- Most common symptoms
- Acute onset of fever
- Maculopapular rash
- Joint pain
- Conjunctivitis
- Other symptoms include muscle pain and headache.



Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-



# Zika virus and disease: Key facts at a glance



- In susceptible regions, Zika typically infects about 70% of the population within one to two infectious seasons
- The Zika virus is unusually stable relative to other viruses of its type. It can remain infectious for hours on solid surfaces.
- Zika is transmitted both by insect vector bite as well as sexually, and perhaps by other human to human routes (fomites etc.)
- The immediate symptoms of Zika virus infection are subclinical (patients do not seek medical care) in four out of five infections
- Zika virus infection is associated with many long term disease symptoms (pathologies), not just birth defects
- Zika is now known to infect male and female reproductive tract tissues, brain, spinal chord, and many types of glands (salivary, tear ducts, breast, prostate)
- We still have a lot to learn about Zika infection and pathology

# Current Situation in the Americas



- To date, 47 countries and territories in the Americas have confirmed some or wide local, vector-borne transmission of ZKVD since 2015.
- Five countries in the Americas have reported sexually transmitted Zika cases.
- Since the 6 October 2016, no additional countries and/or territories have confirmed vector-borne local transmission of ZKVD in the Americas
- **North America**
  - Mexico: Since the beginning of the outbreak up an upward trend had been observed.
  - USA, the U.S. CDC continues to work with Florida State health authorities to investigate new local-transmission cases of ZKVD. On 14 October 2016, the state of Florida reported Zika virus transmission in a new area within the county of Miami-Dade.
- **Central America**
  - In Central America, Belize, Guatemala, and Panama have reported an increasing trend in cases. In the other countries of Central America, the trend continues to decrease.

# Current Situation in the Americas



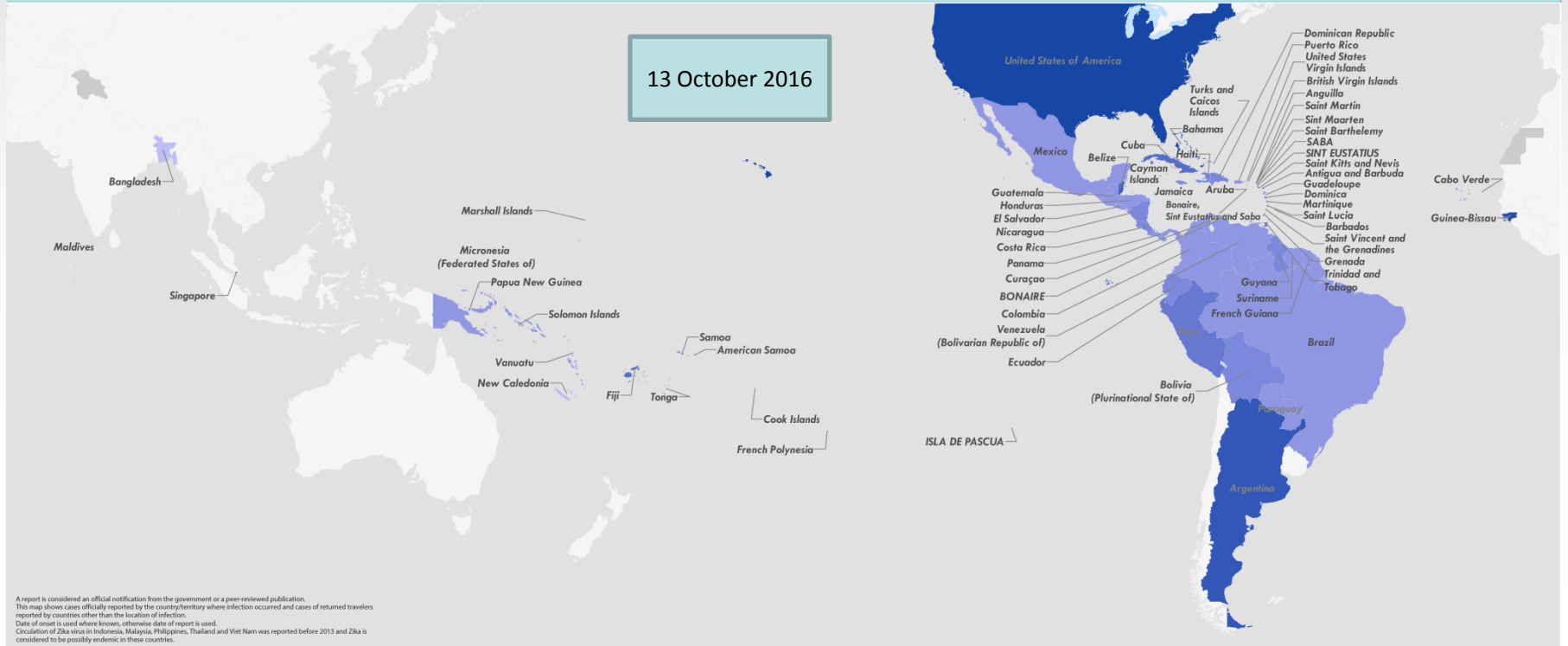
- **Caribbean:**

- Anguilla, new cases continue to be reported with an increasing trend.
- French overseas territories, Saint Martin has had a decrease of suspected cases between In Saint Barthelemy circulation ZKVD remains active with a high number of cases reported in the last two weeks.
- In Sint Maarten, an independent state within the Kingdom of the Netherlands, an increase in confirmed cases has been reported in the last two weeks reported.
- **Puerto Rico, a declining trend in confirmed cases has been observed.**
- Other countries/territories in the Caribbean also show a declining trend of Zika cases.

- **South America:**

- All countries in South America continue to report decreasing numbers of Zika cases.

# Zika virus infections, 2013-2016



Countries where person-to-person transmission occurred are not represented in this map.

Available information does not permit measurement of the risk of infection in any country, the variation in transmission intensity among countries is therefore NOT represented on this map. Zika virus is not necessarily present throughout the countries/territories shaded in this map.



**Total Suspected Cases: 514,757**  
**Total Confirmed Cases: 166,010**  
**Imported Cases: 4,584\***  
**Incidence Rate: 68.2**  
**Deaths: 14**  
**Congenital Syndrome: 2,204**

**[\*Incidence rate (autochthonous suspected + autochthonous confirmed) / 100,000 pop]**



# Current Situation in the US

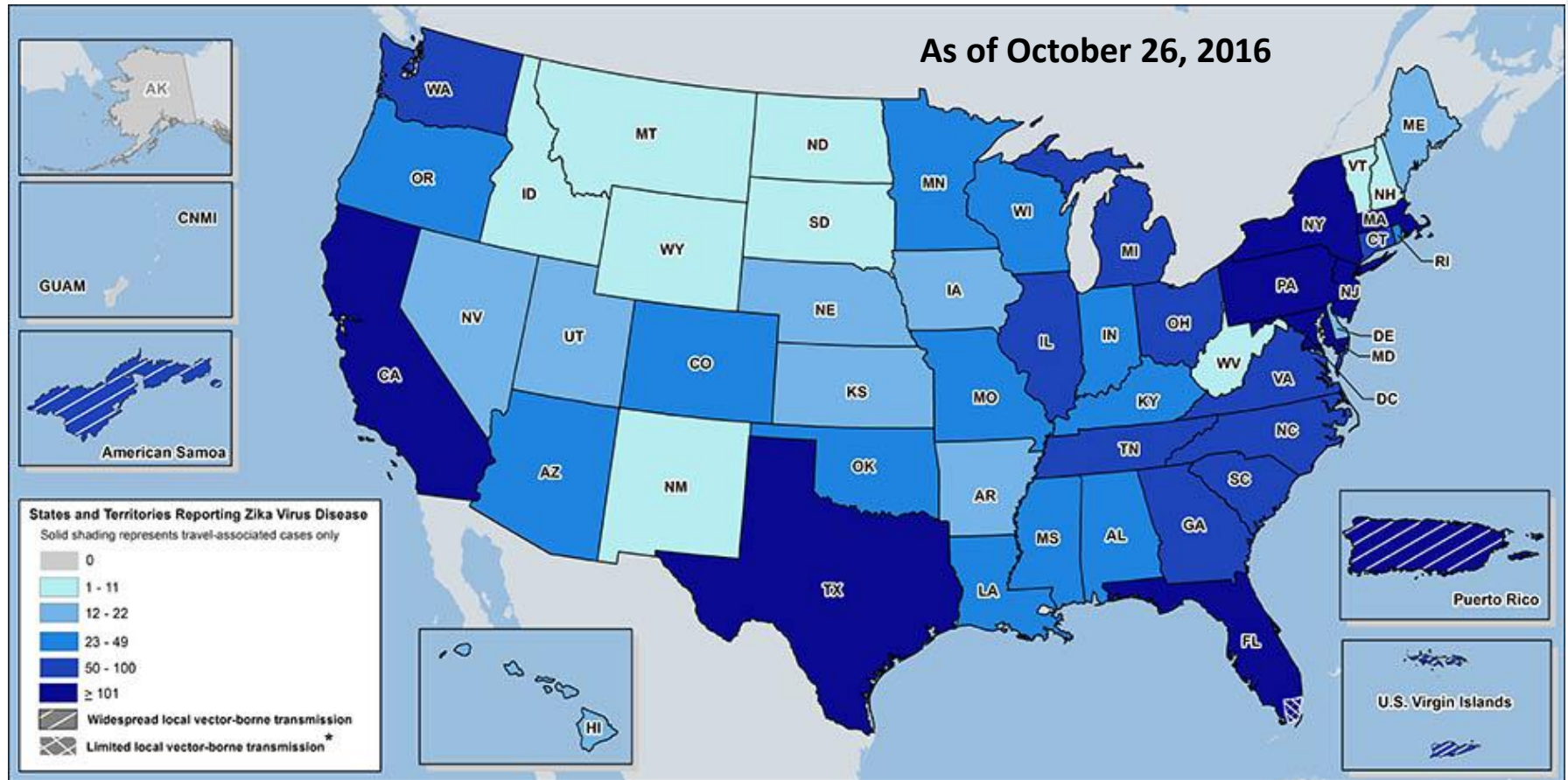


## All 50 States

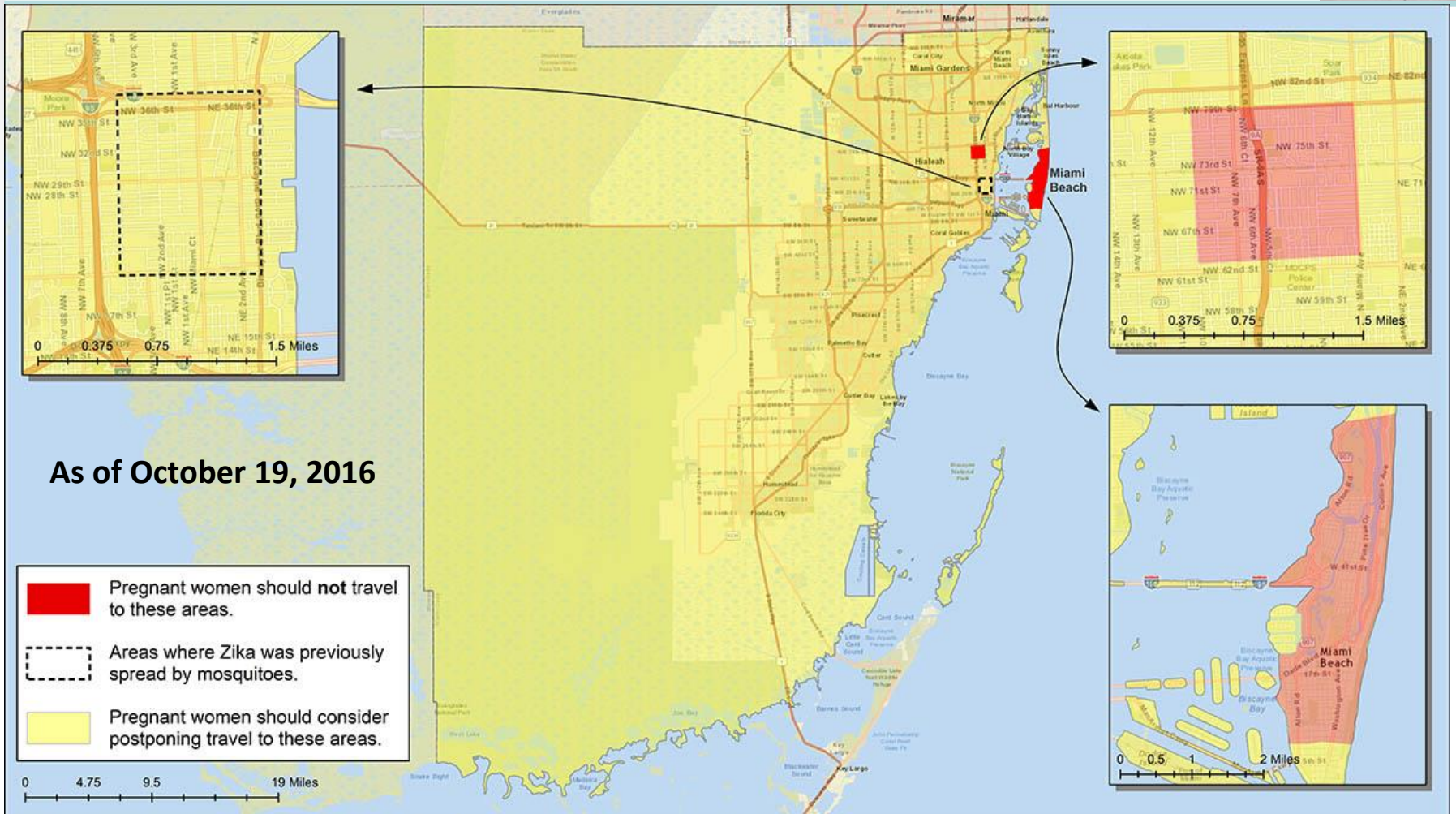


## US Territories

# Laboratory Confirmed Zika Cases Reported in the United States



# Area of active Zika transmission in Miami-Dade County, FL



**Miami-Dade County, FL. Red shows areas where pregnant women should not travel. Yellow shows areas where pregnant women should consider postponing travel.**

# Congenital syndrome associated with Zika virus infection



- 17 countries and territories in the Americas have reported confirmed cases of congenital syndrome associated with Zika virus infection.
- Canada reported two maternal-fetal transmissions of Zika Virus; one with severe neurological anomalies.
- US: Pregnant Women with Any Laboratory Evidence of Possible Zika Virus Infection
  - US States and the District of Columbia: 953
  - Liveborn infants with birth defects: 23
  - Pregnancy losses with birth defects: 5
  - US Territories: 2027



# High Risk Areas in the US



ZIKV is spread in the US by *Aedes aegypti* mosquito, and possibly the *Aedes albopictus* mosquito.



**Aedes aegypti**



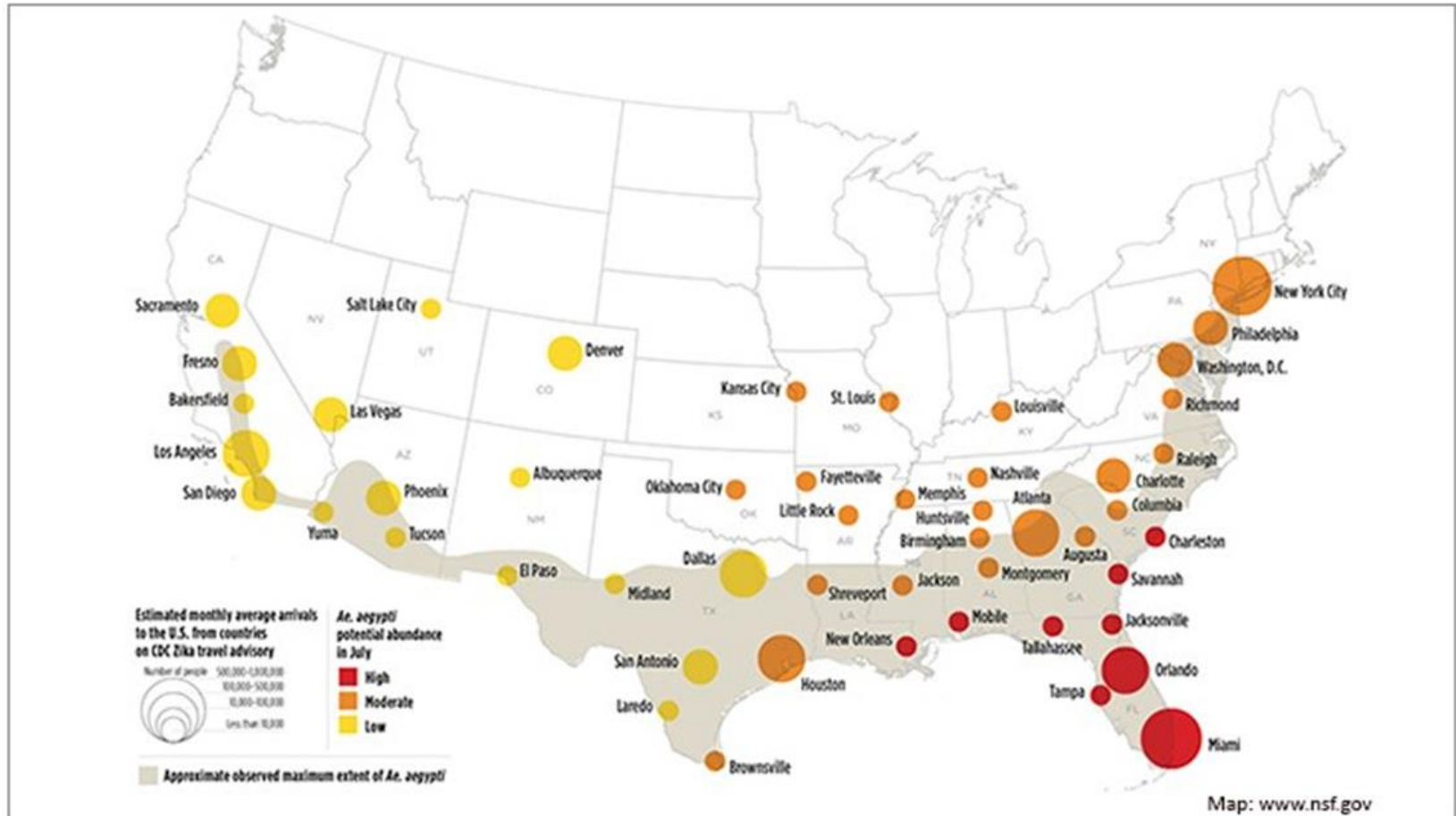
**Aedes albopictus**



# High Risk Areas in the US



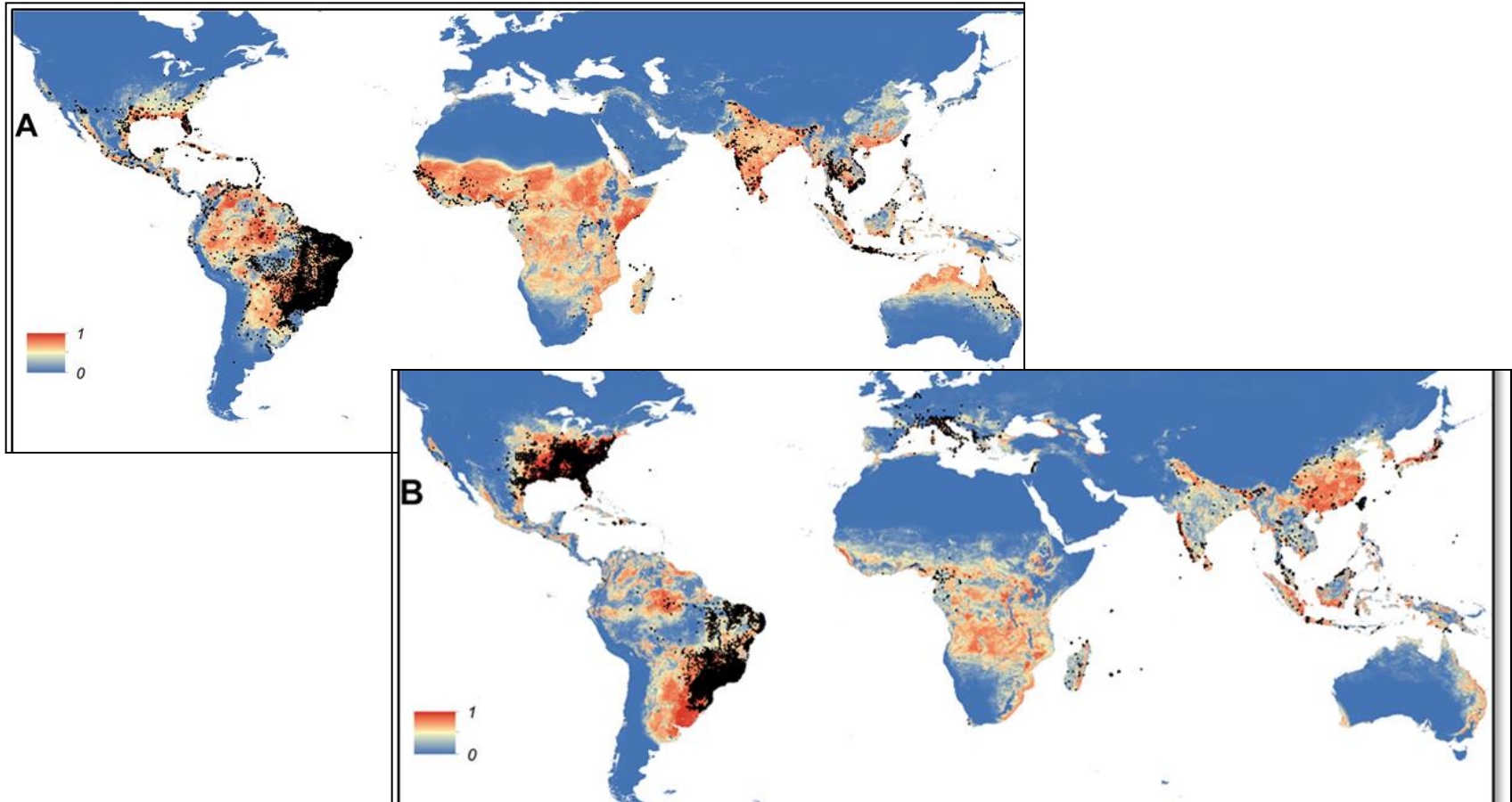
Estimated monthly average arrivals to the US from countries on the US CDC travel advisory and *Aedes aegypti* mosquito potential abundance in July



# Zika Insect Infection Transmission Risks



The distribution of the occurrence database for *Ae. aegypti* (A) and *Ae. albopictus* (B) plotted on the underlying prediction surface.



# Mosquitoes in North-Eastern Qatar



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### First report of some adult mosquitoes captured by CDC gravid traps from North-Eastern Qatar

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*Ochlerotatus dorsalis*

Qatar

#### ABSTRACT

**Objective:** To report six species of female mosquitoes caught in CDC gravid traps for the first time in Qatar.

**Methods:** Five traps were installed in Al-Khor community, north-eastern Qatar during the outbreak season between October-November, 2010 and February-March, 2011.

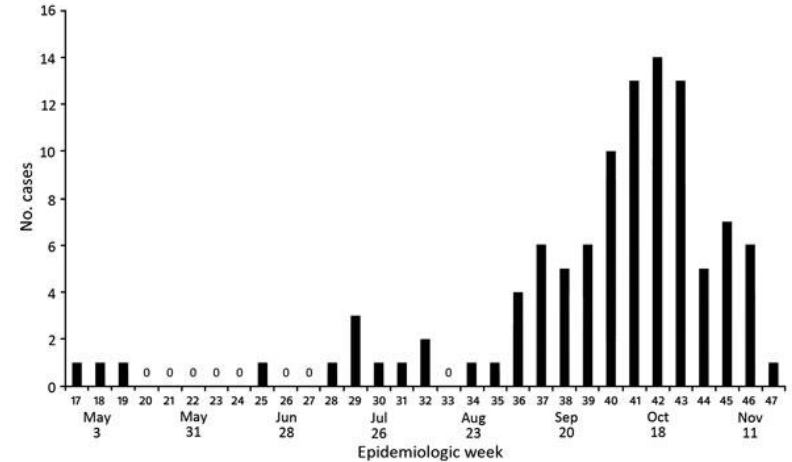
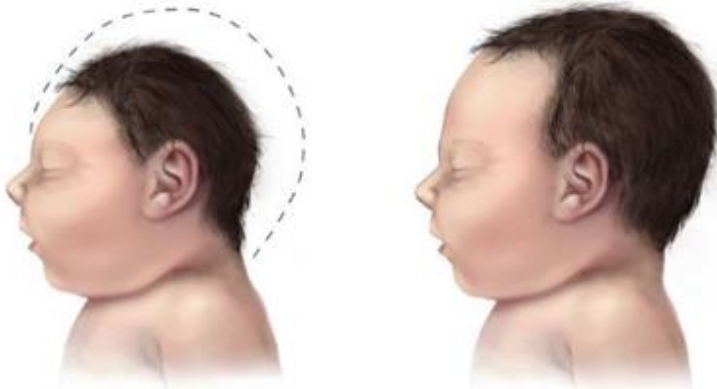
**Results:** The collection revealed that the adult female mosquitoes encountered in the gravid traps were: *Ochlerotatus caspius* (Pallas 1771), *Anopheles stephensi* (Liston 1901), *Culex quinquefasciatus* (Say 1823), *Culex pipiens* biotype *molestus* (Forsk. 1775) (*Cx. pipiens molestus*), *Culex tritaeniorhynchus* (Giles 1901) and *Ochlerotatus dorsalis* (Meigen 1830). Except *Cx. pipiens molestus*, which was previously recorded, the other five species are reported for the first time in Qatar. Among the collected adult females, *Cx. pipiens molestus* was the most abundant (67.2%), followed by *Culex quinquefasciatus* (30.2%). The other species were present in small numbers. All of the recorded species have been collected as larval stages in the previous studies except for *Ochlerotatus dorsalis* which is collected as adult stage for the first time in the current study.

**Conclusions:** The collected species are of potential medical importance that threaten the north-eastern area of Qatar. A surveillance program is urgently required to generate a database of mosquito species in the area.

# Zika Associated Microcephaly in Infants

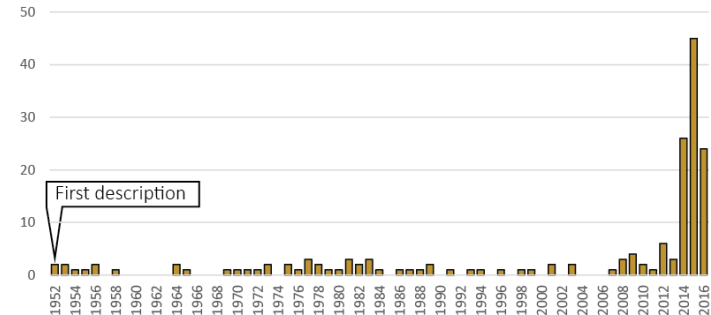


- ZIKV can be passed from mother to fetus (in-utero) during pregnancy, causing birth defects, such as microcephaly, a very serious condition resulting in life-long disabilities



Publications using "Zika" in search, by year, PubMed

Irrelevant publications omitted.  
As at 30JAN2016



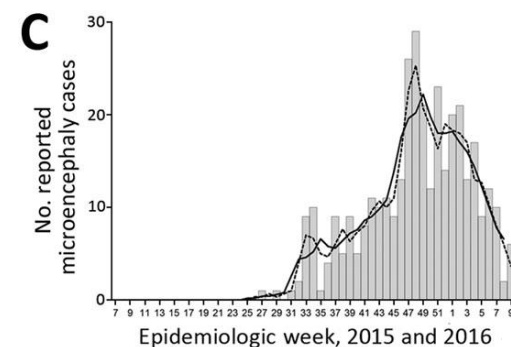
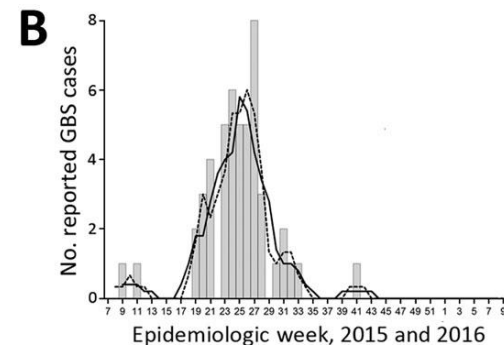
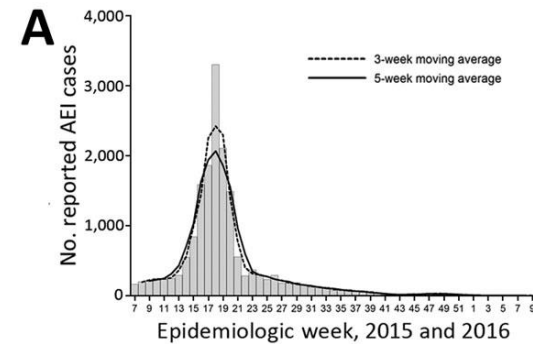
Ian M. Mackay, Ph.D  
virologydownunder.blogspot.com.au  
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# Relationship of Zika Virus Infection with GBS & Microcephaly

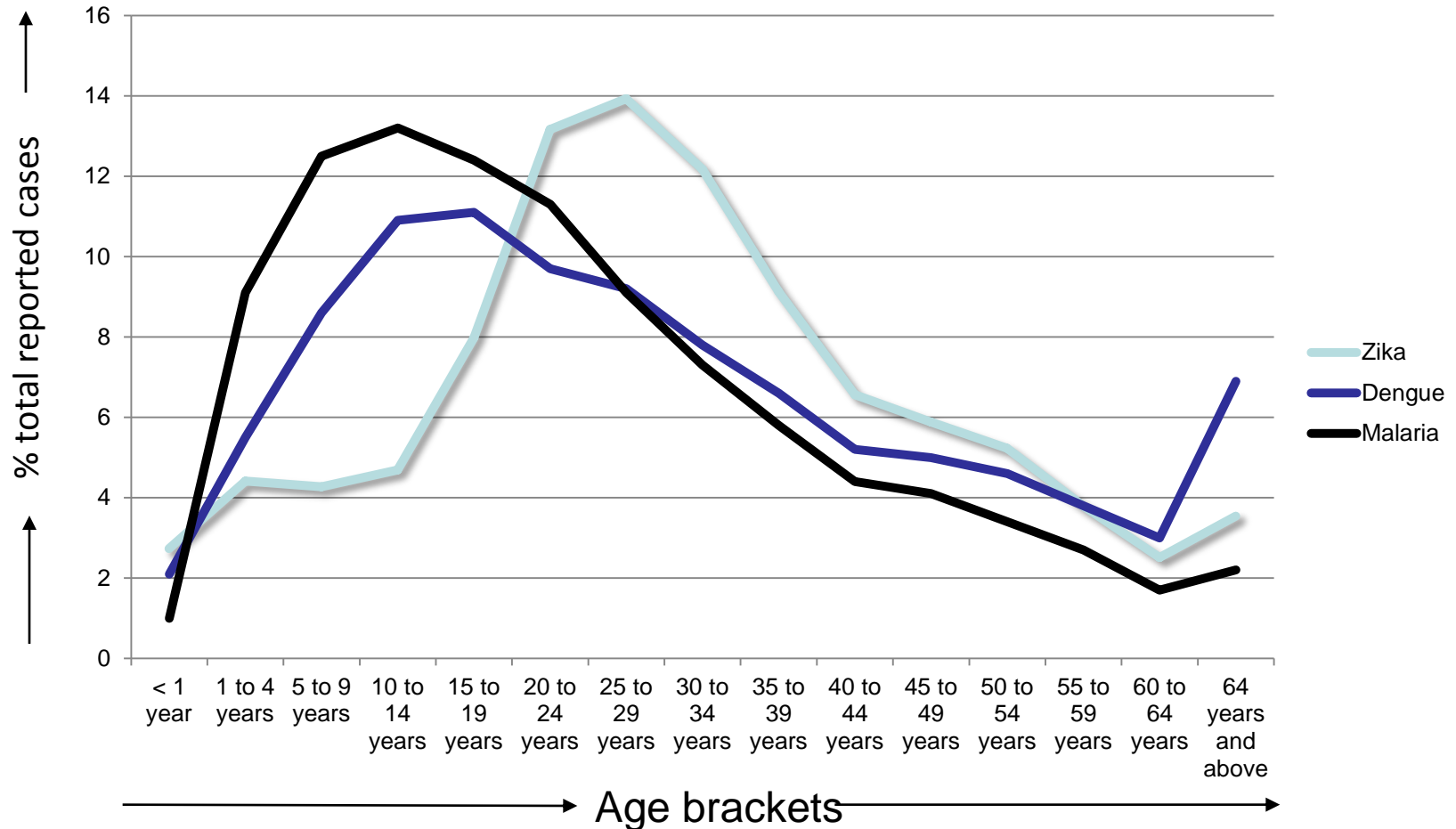


- After acute exanthematous illness (AEI):
  - Number of GBS cases peaked after a lag of 5–9 weeks from the AEI peak
  - Number of suspected cases of microcephaly peaked after a lag of 30–33 weeks from the AEI peak, which corresponded to time of potential infections of pregnant mothers during the first trimester

Source: Time Lags between Exanthematous Illness Attributed to Zika Virus, Guillain-Barré Syndrome, and Microcephaly, Salvador, Brazil; Igor A.D. Paploski<sup>1</sup>, Ana Paula P.B. Prates<sup>1</sup>, Cristiane W. Cardoso, Mariana Kikuti, Monaise M. O. Silva, Lance A. Waller, Mitermayer G. Reis, Uriel Kitron<sup>1</sup>, and Guilherme S. Ribeiro

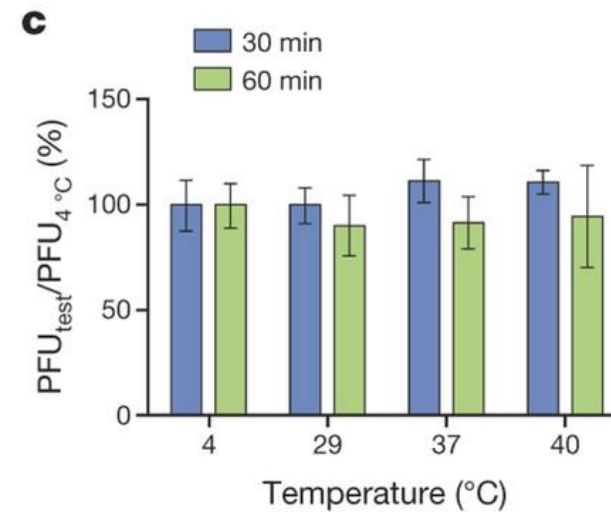
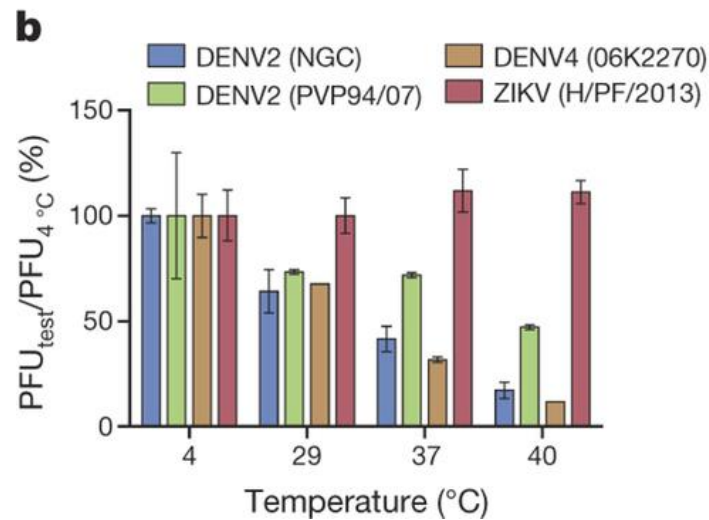
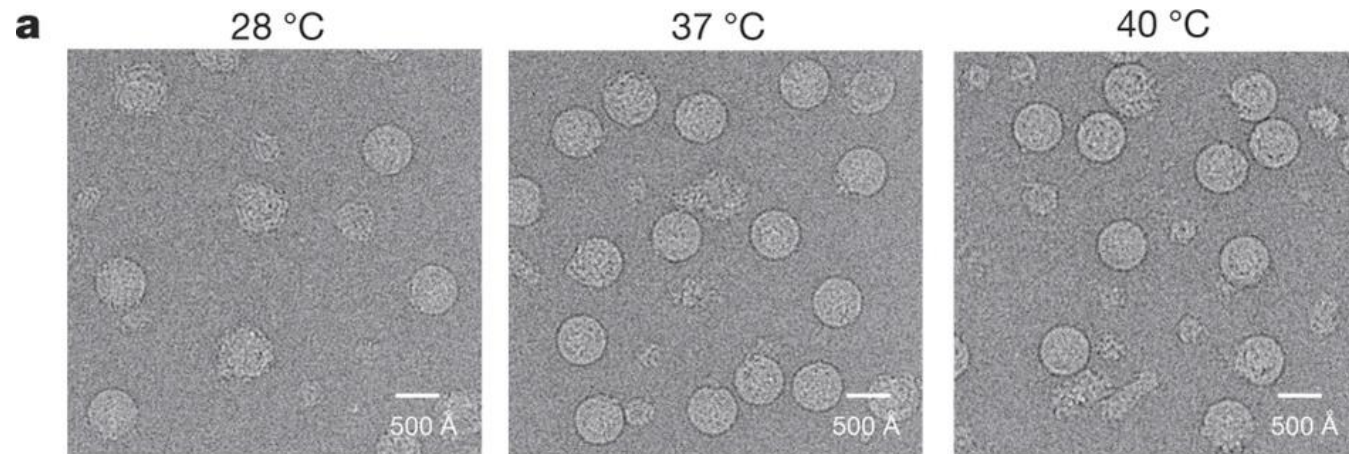


# Zika Virus is both Insect and Sexually Transmitted



Source: Boletín Epidemiológico Semanal, #12, 2016 20 March, Instituto Nacional De Salud (Colombia)

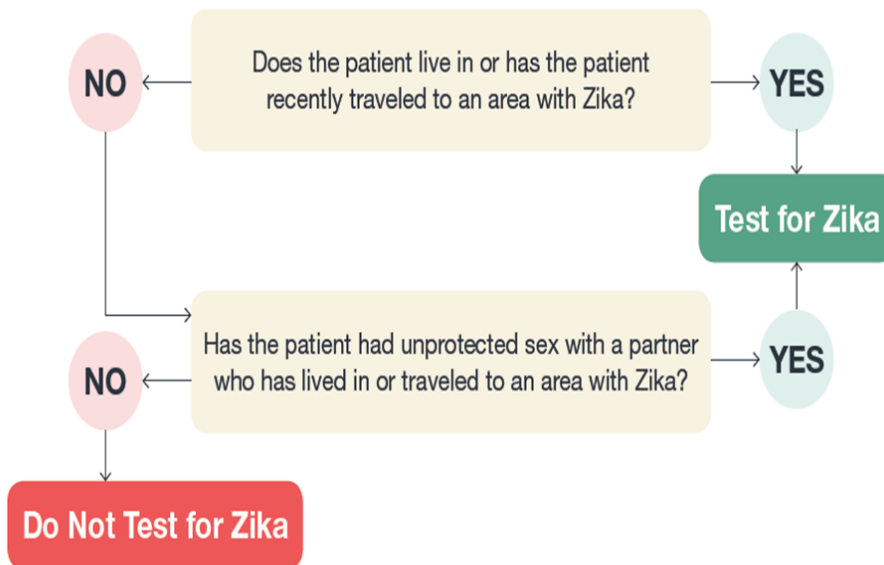
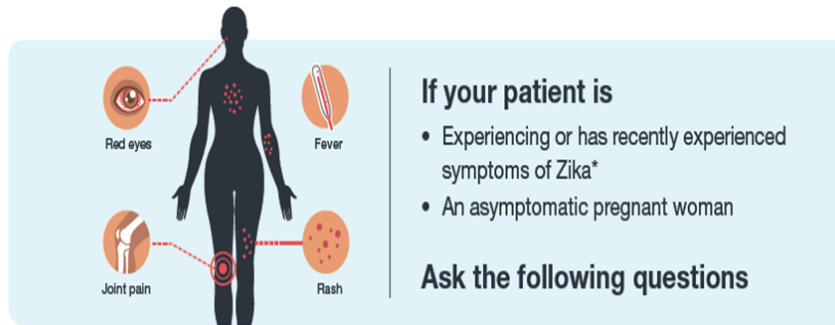
# Zika Virus is Structurally Stable and Persists in Semen, Saliva and Urine



Source: Structure of the thermally stable Zika virus; Victor A. Kostyuchenko et al. Nature (2016)  
doi:10.1038/nature17994 Received 24 March 2016 Accepted 11 April 2016 Published online 19 April 2016



# Diagnosing & Testing



\*Healthcare providers should review their local and state health jurisdiction guidelines regarding testing of patients with clinically compatible illness without known travel or sexual exposures.

CDC does not recommend testing for asymptomatic men, children, and women who are not pregnant.

## Assessing pregnant women:

- All pregnant women should be asked at each prenatal care visit if they:
  - Traveled to or live in an area with Zika during their pregnancy or periconceptional period (the 6 weeks prior to last menstrual period or 8 weeks prior to conception)
  - Had sex without a condom with a partner who has traveled to or lives in an area with Zika
  - Pregnant women who have a possible exposure to Zika virus are eligible for testing for Zika virus infection.

# Diagnosing & Testing



## Differential Diagnosis:

### BACTERIAL

- Scarlet fever (Group A Strep)
- Meningococemia
- Typhoid fever
- Other bacterial septicemia
- Leptospirosis
- Rickettsial diseases

### VIRAL

- Influenza
- Enterovirus
- Measles
- Rubella
- Dengue
- West Nile Virus
- Acute Retroviral Syndrome (HIV)
- Chikungunya
- Other alphaviruses
- Epstein-Barr virus
- Parvovirus
- Roseola virus

### OTHER

- Malaria
- Post-infectious arthritis
- Rheumatologic diseases

# Diagnosing & Testing



Serology cross-reactions with other flaviviruses:

- During first 2 weeks after the start of illness, Zika virus infection can often be diagnosed by performing real-time reverse transcriptase polymerase chain reaction (rRT-PCR) on serum and urine.
- Serology assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies, which typically develop toward the end of the first week of illness.
- Plaque reduction neutralization test (PRNT) for presence of virus-specific neutralizing antibodies in paired serum samples.
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues.

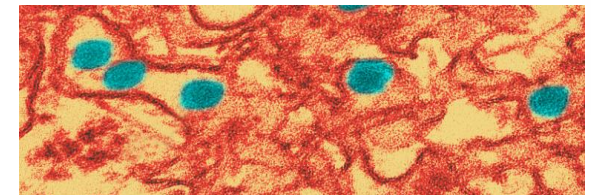


# Diagnosing & Testing



Diagnostic testing for Zika virus:

- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses).
- As viremia decreases over time, a negative rRT-PCR collected after symptom onset does not preclude Zika; in this case, serologic testing should be performed.
- Neutralizing antibody testing may discriminate between cross-reacting antibodies in primary flavivirus infections.



# ZIKV Unmet Medical Needs and Indications



- The epidemiology of ZIKA now shows that women are at greater risk for infection and disease than men.
- Furthermore, there is growing evidence that men, through sexual transmission, are becoming a significant “silent” vector for ZIKV infection; only one in five infected men know that they have been infected and are capable of infecting their partners.
- The impact of ZIKV infection of the reproductive tract of infected men is unknown, but infection and inflammation are known causes of male infertility.

ZIKV Indication	Treatment	Prevention
Infected Men	X	
Pregnancy	X	X
GBS/Autoimmune	X	
Neuropsychiatric	X	
Travelers		X
Community Outbreak Containment	X	X

# Clinical Challenge of the Zika Virus



- Only 20% of infected patients present with acute Zika symptoms
- Viremia can precede clinical symptoms by up to 10 days (blood bank data)
- Definitive diagnosis requires a polymerase chain reaction (PCR)-based test
- Fast moving- basic reproductive ratio (R) for ZIKV varies between 1.2 and 6.6 (70% seroconversion upon herd immunity)
- Acute Zika is fairly benign, most severe outcomes are delayed by 1 to 2 weeks or many months
- MCM must be safe in pregnancy
- Infection and viremia can precede symptoms by up to 10 days
- $R_0$  (ZIKV replication reproductive ratio) varies from 1.2 – 6.6
- Challenging to distinguish from other co-circulating arboviral infections (clinically and serologically)
- ZIKV viremia is low and vanishes 2-3 days after fever/rash onset
- ZIKV rtPCR RNA+ in urine for weeks (virus culture negative, urine Ab+)
- ZIKV culture + in semen (plaque assay) for protracted period (TBD) 60 + days? (top CDC priority to determine)
- As an RNA virus, Zika is likely to rapidly escape single agent medical countermeasures (drugs, vaccines, antibodies) – much like HIV and influenza do.

# Available Medical Countermeasure Development Options



- Insect vector control
- Diagnostics
- Methods to secure blood supply
- Vaccines
  - Prophylactic
    - DNA vaccines
    - Whole Killed Virus
    - Recombinant vectored
    - Subunit (including peptide)
  - Therapeutic
- Drugs (pharmaceuticals)
  - Prophylactic
  - Therapeutic
- Antibodies
  - Monoclonal
  - Oligoclonal
  - Equine Antisera
- Other Biologics
  - Peptide blockers

# Current Medical Countermeasure Interventions



## Vaccines

- No vaccine development efforts initiated prior to Q4 2015

## Other Biologics

- Hyper-immunized animal (horse) serum preparations
- Antibody preparations (polyclonal, oligoclonal, monoclonal)
- Fc Receptor blocking peptides

## Therapeutic Drugs

- Re-purposed anti-Hepatitis C, anti-Dengue, or other anti-infective drugs may be developed; some of these are proven safe in pregnancy, most are not

## Prophylactic Drugs

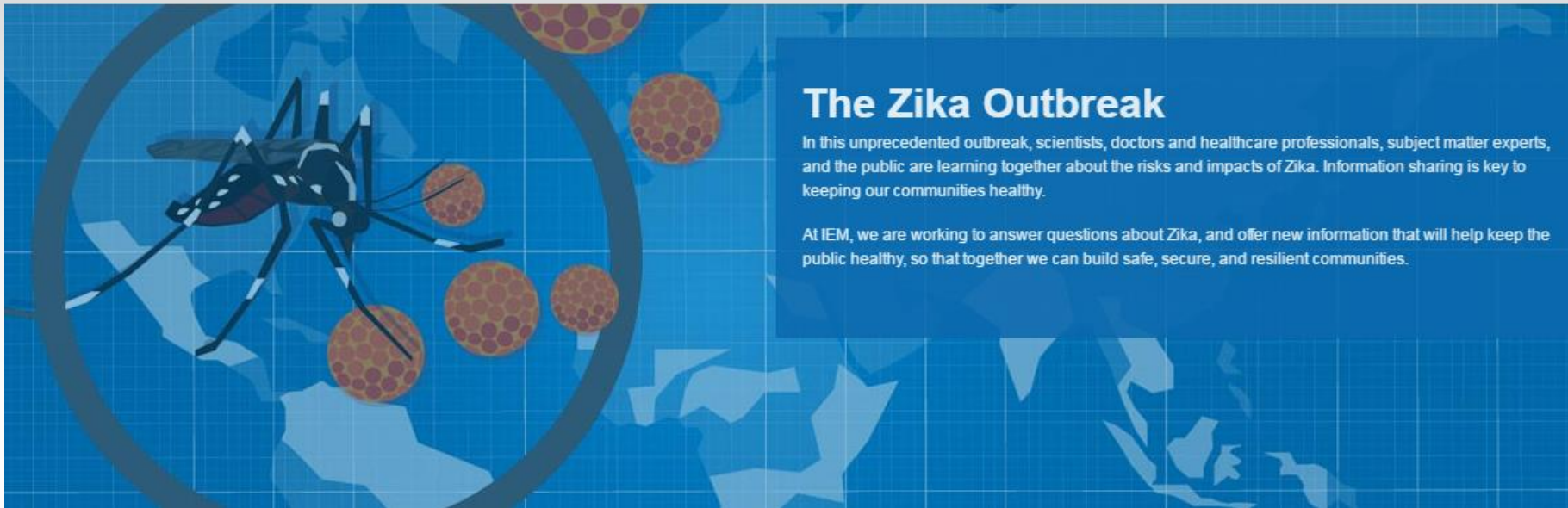
- Other re-purposed drugs

## Drug Combinations

- Multiple mechanisms of action
- This is the strategy that has worked for HIV

**Note, all of these interventions will need to be proven safe in pregnancy**





## The Zika Outbreak

In this unprecedented outbreak, scientists, doctors and healthcare professionals, subject matter experts, and the public are learning together about the risks and impacts of Zika. Information sharing is key to keeping our communities healthy.

At IEM, we are working to answer questions about Zika, and offer new information that will help keep the public healthy, so that together we can build safe, secure, and resilient communities.

***“Perhaps the biggest challenge with Zika will be to recognize it for what it is: A new disease which does not fit the epidemiology or response paradigm of Ebola or dengue, and which will demand effort, resources, unparalleled collaboration, and above all, open mindedness in formulating responses”***