Florida Department of Health

Beyond the Bite: (Re)Emerging Arboviruses and How to Diagnose Them

ASM-APHL Webinar

December 18, 2024

Presenter

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Division of Disease Control and Health Protection
Florida Department of Health

Learning Objectives

- Recognize the clinical presentation and features of arboviruses.
- Be familiar with recent epidemiological trends and exposures associated with arboviruses.
- Understand the recommended approaches for the diagnosis of select arboviral infections, including optimal utilization of available molecular and serologic methods.

Arboviruses: Arthropod-borne viruses

- Vector-borne diseases: Vectors include mosquitoes, fleas, ticks, sandflies, biting midges.
- Arboviruses:
  - <500 arboviruses worldwide, of which 150 cause human infection. The most prevalent viruses include; dengue (DENV), chikungunya (CHIKV), Zika (ZIKV), yellow fever, Japanese encephalitis (JEV), and West Nile (WNV).
  - Outbreaks are increasing in frequency and magnitude and are impacted by the ecology, economics and social factors.
  - *Aedes* mosquito is a major vector, found in tropical and sub-tropical areas with 3.9 billion people living in these areas.

Arboviruses: Global Burden

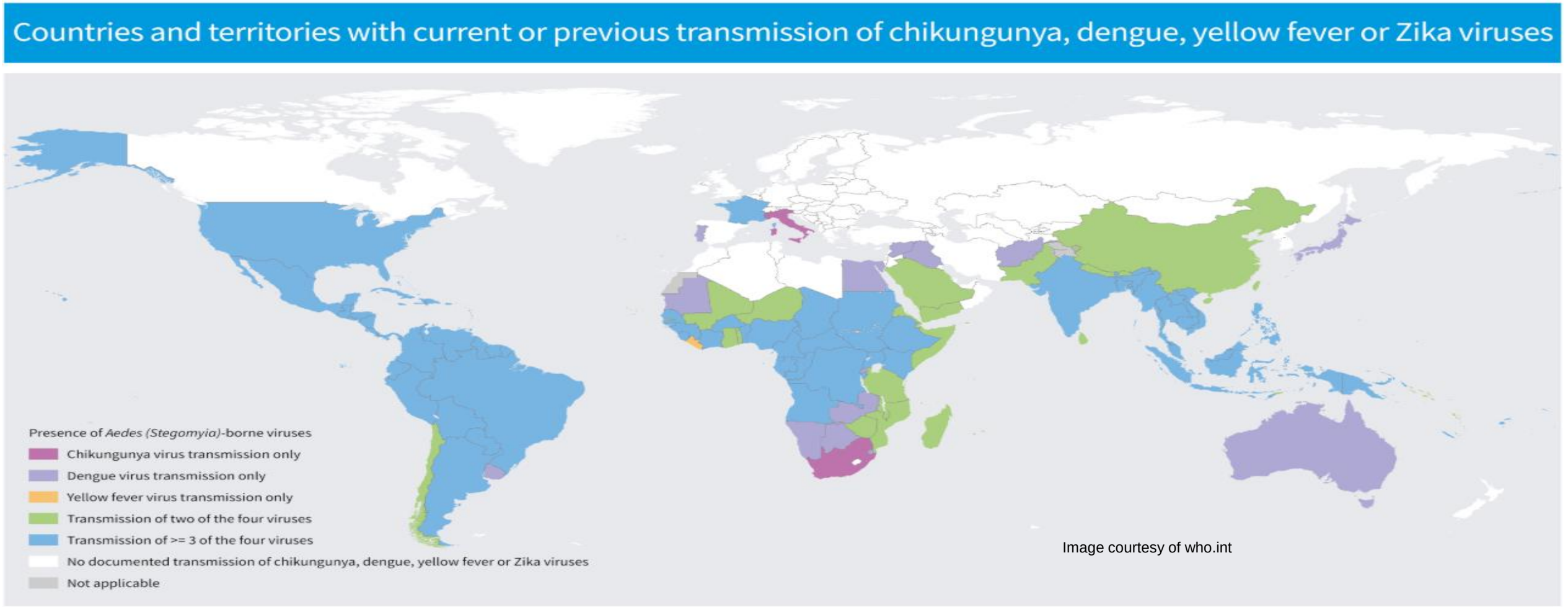


Image courtesy of who.int

Arboviruses in the U.S.

Arboviruses are a considerable public health threat in the U.S.

- Arboviral disease is nationally notifiable and reported by state health departments to Centers for Disease Control and Prevention through the national surveillance system, ArboNET.
- Confirmed and probable cases are documented.
- Cases are reported as neuroinvasive (causing meningitis, encephalitis, acute flaccid paralysis or other neurological illness) or non-neuroinvasive.
- Cases are monitored to determine whether they are domestically (i.e., locally)-acquired or travel-related.

Arboviruses in the U.S., continued

Domestically-acquired arboviruses

- West Nile virus is the leading cause of arboviral disease in the U.S. (CDC report 2024 of 2022 data).
- Other domestic arboviruses cause sporadic outbreaks such as dengue virus, Powassan virus, St. Louis encephalitis virus, La Crosse virus, Jamestown Canyon virus, and eastern equine encephalitis virus.
- Factors such as weather, zoonotic host and vector abundance, and human behavior all contribute to when and where outbreaks occur.
- The U.S. harbors many of the vectors, so while other cases may be travel-associated, the risk of transmission occurring in the local population requires public health surveillance and intervention.

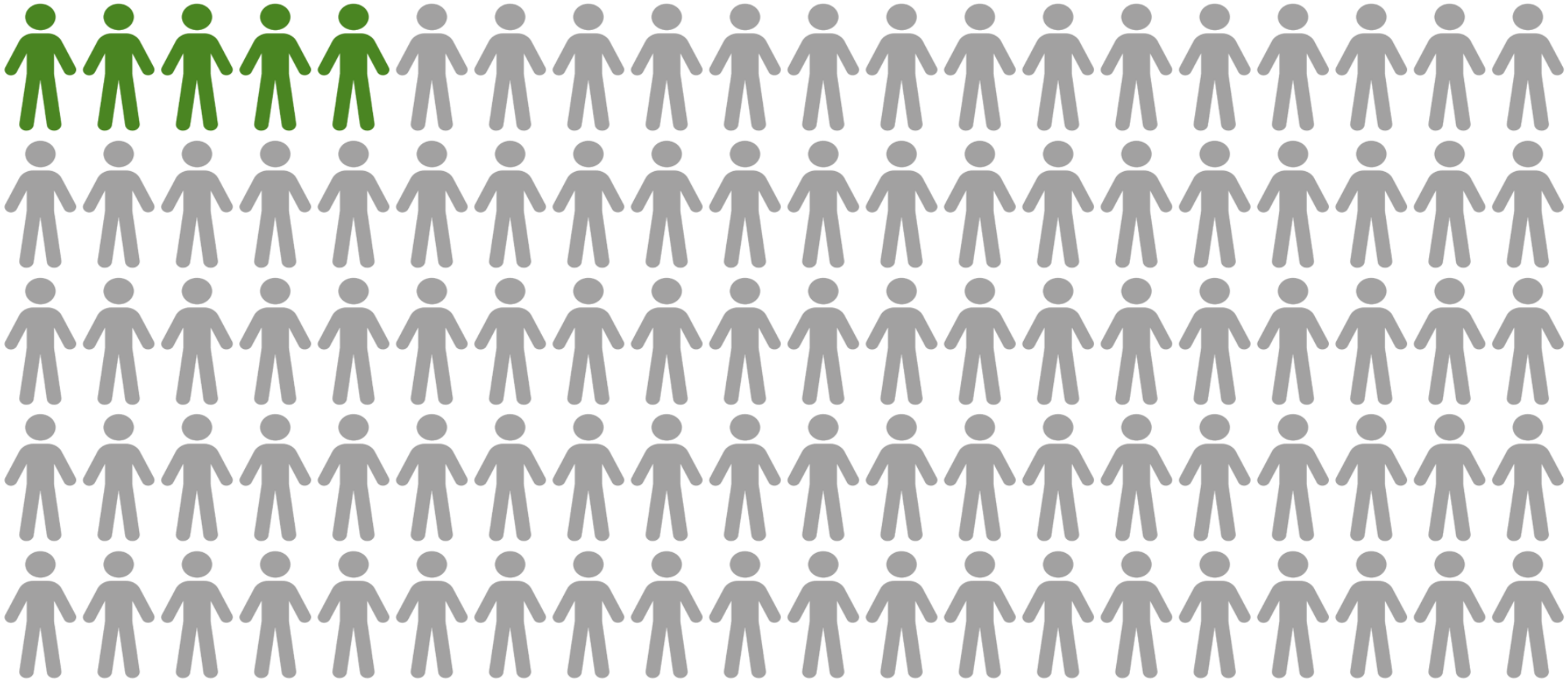
Arboviruses in the U.S., continued

Travel-associated arboviruses

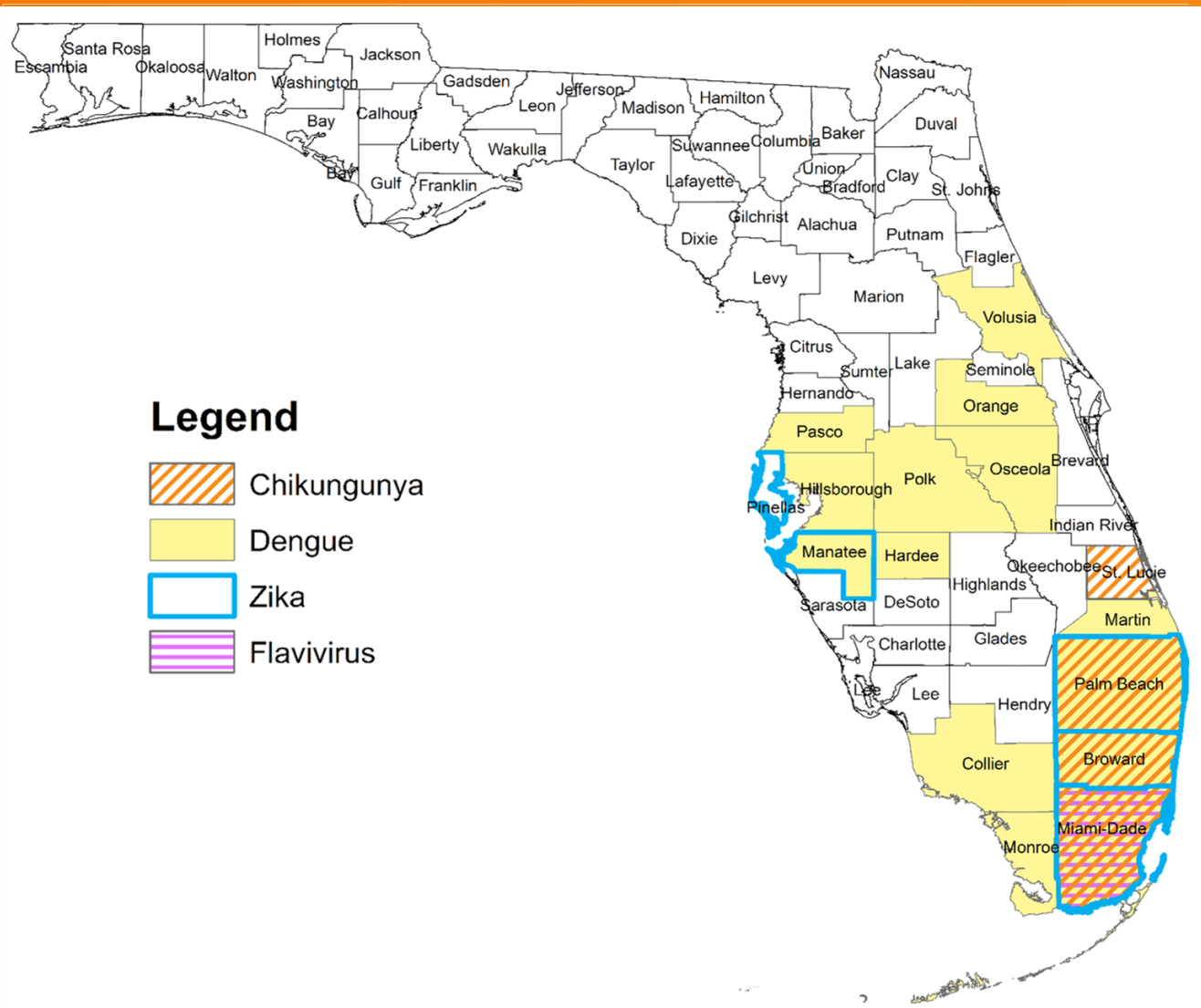
- Dengue virus, Zika virus, chikungunya virus, yellow fever virus and Oropouche virus.
- Florida has many of the vectors in abundance, a large population of travelers to endemic areas, and sees a significant number of travel-related cases.

Image courtesy of knowdengue.com

Only 5% of Arboviral Disease Cases Reported in Florida are Diseases Endemic to the United States



Florida Counties Reporting *Aedes*-Vectored Arbovirus Introductions, 2009–2024*



*Data current through September 9, 2024. One flavivirus and one dengue case had an unknown county of exposure.

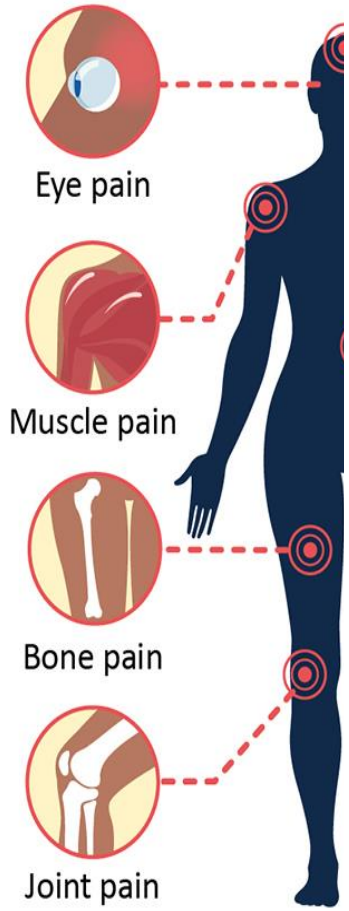
Arboviruses in Florida

2024 Arbovirus activity —— dengue virus and Oropouche virus

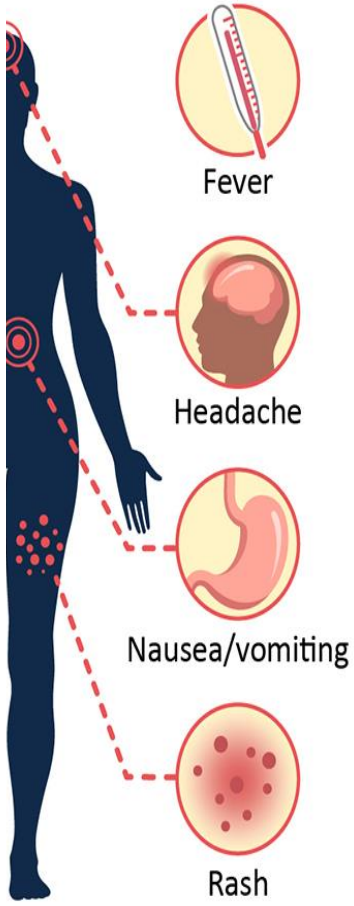
- Locally acquired and travel-associated cases of DENV have been detected, YTD 2024
  - Imported cases = 786
  - Locally-acquired cases = 66
- Travel-associated cases of OROV have been detected, YTD 2024
  - Imported cases = 90

DENV Clinical Presentation

Dengue infection – DENV 1, 2, 3, and 4



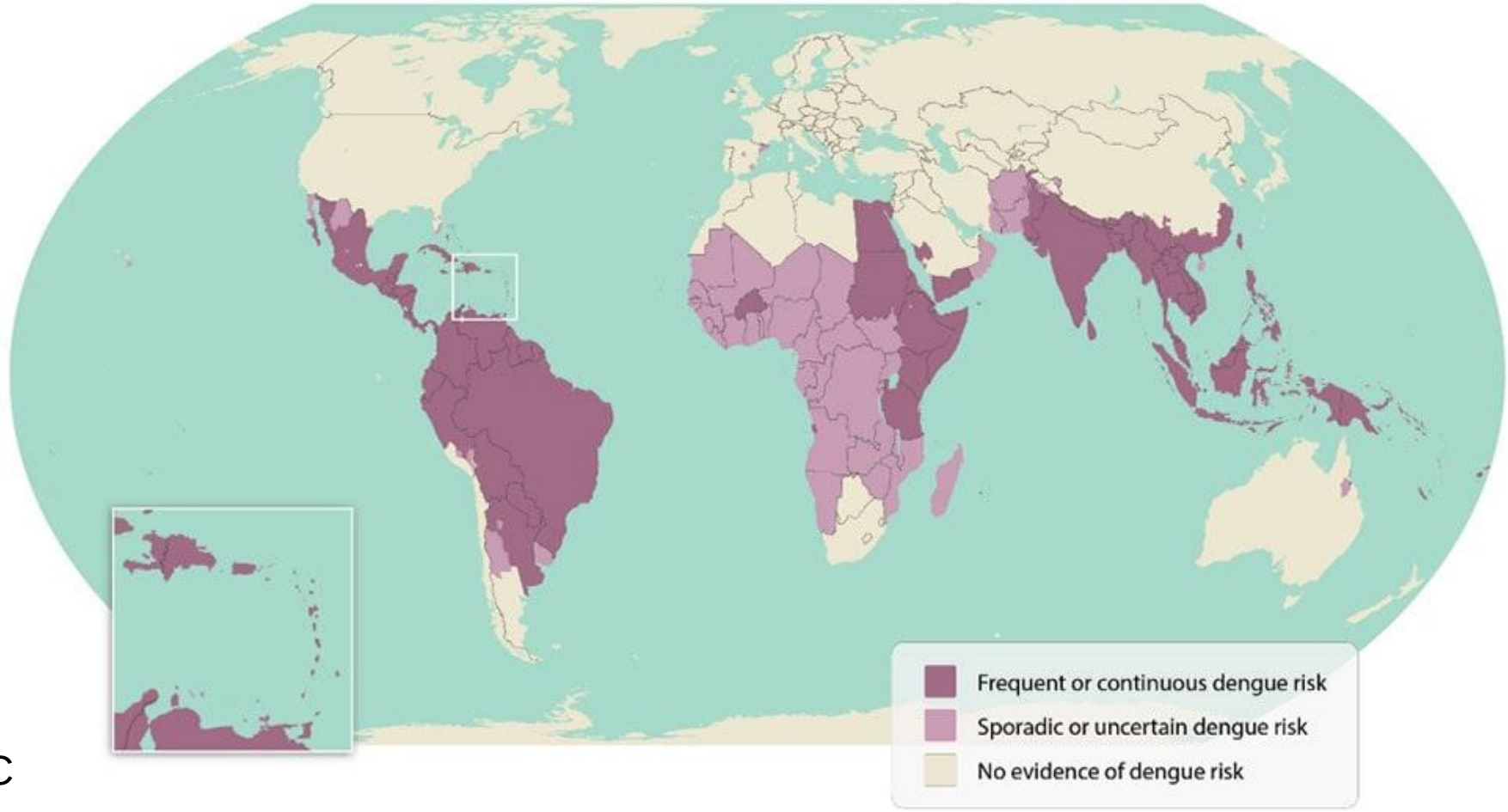
- Often asymptomatic with ~1 in 4 symptomatic with symptoms typically lasting ~1 week
- Warning signs of severe infection include:
  - Abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, restlessness, and liver enlargement
  - Severe infection (hemorrhagic fever) is due to plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, organ failure and sometimes death
  - Secondary infection with dengue is a risk factor for developing severe dengue



Risk of Dengue

Risk factors:

- More mosquitos/ mosquito bites
- Travel to endemic areas



Graphic courtesy of CDC

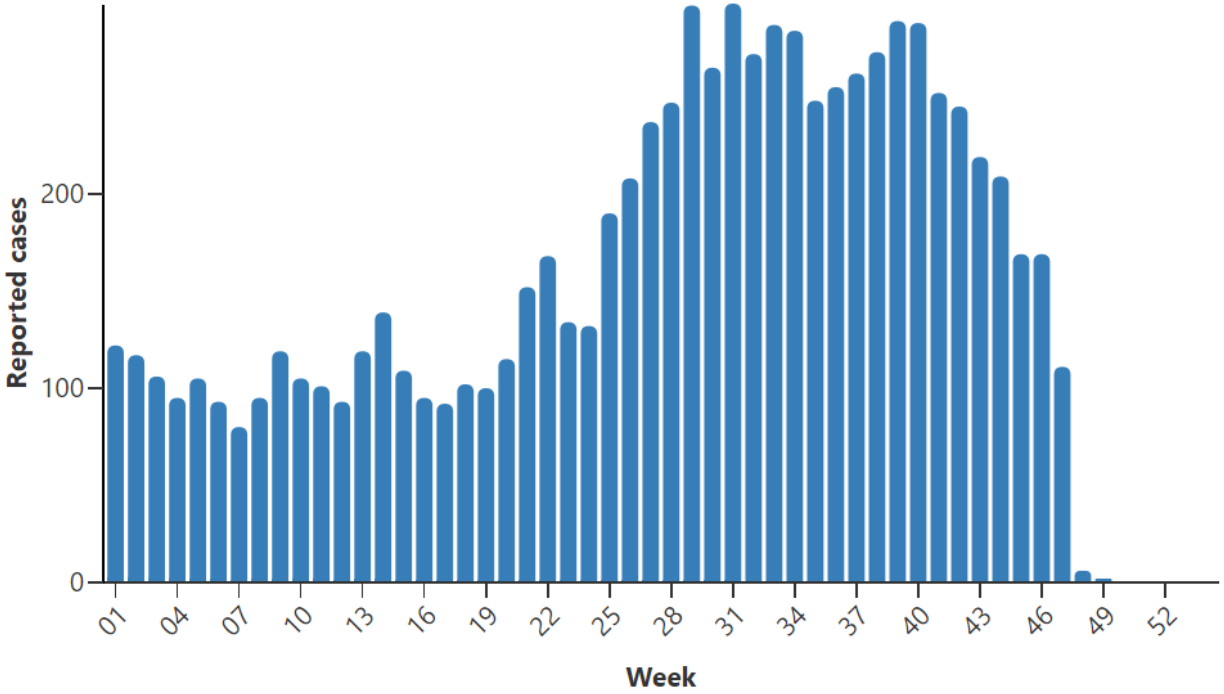
Global Dengue Cases

Reported dengue cases have doubled in 2024

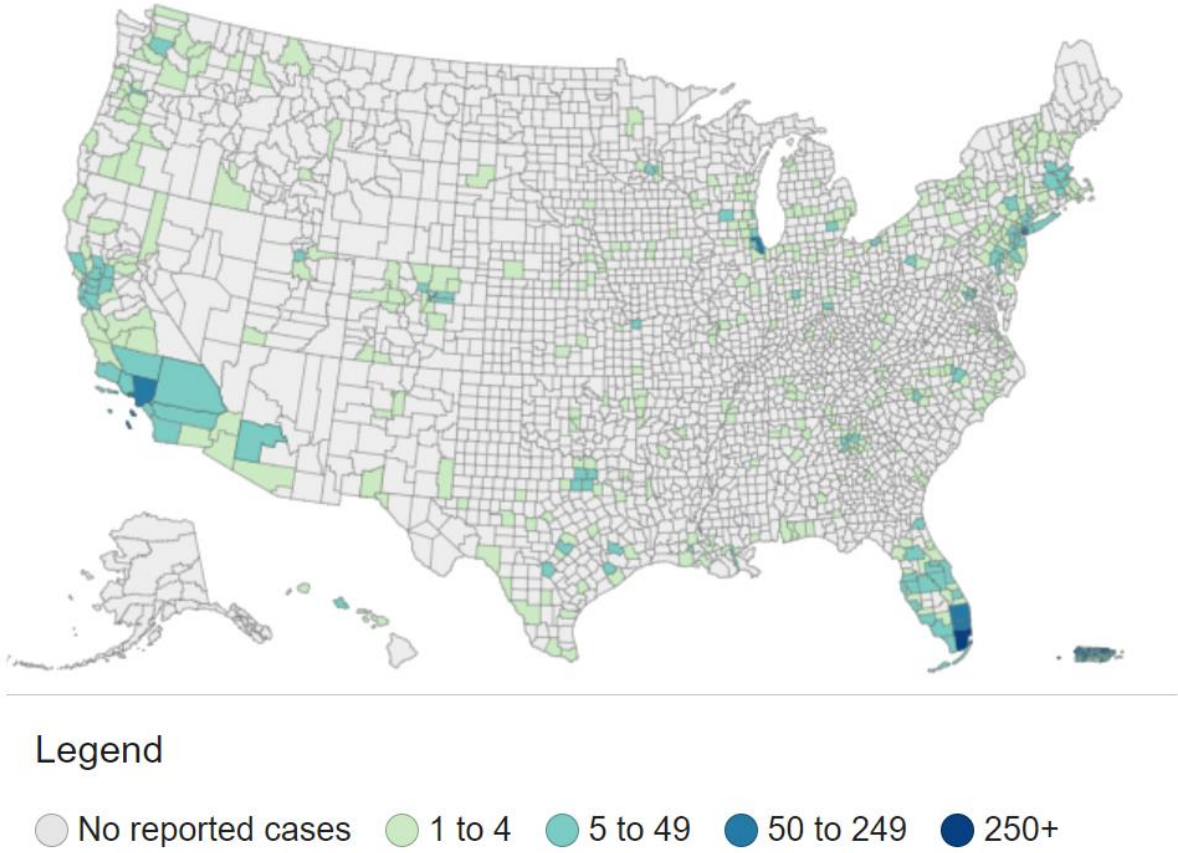
- The World Health Organization (WHO) has reported an 8-fold increase in global incidence between 2000 and 2019.
- In 2023, >5 million cases were reported from 80 countries with outbreaks reported in 23 countries.
- In 2024 so far, the number has more than doubled with more >10.6 million cases reported in North and South America alone.

Graphic: Time Magazine

Dengue in the U.S. 2024



All data are provisional and subject to change, and case numbers for recent weeks may be incomplete due to delays in reporting and data processing.



Graphics courtesy of CDC

DENV Diagnostic Testing

Molecular testing

- RT-PCR DENV multiplex for detection of dengue virus and serotype
- Available in public health laboratories (some commercial laboratories)
- Perform testing within 7 days of symptom onset
- Specimen: serum, plasma, whole blood, cerebrospinal fluid (CSF)

DENV Diagnostic Testing, continued

Antibody testing

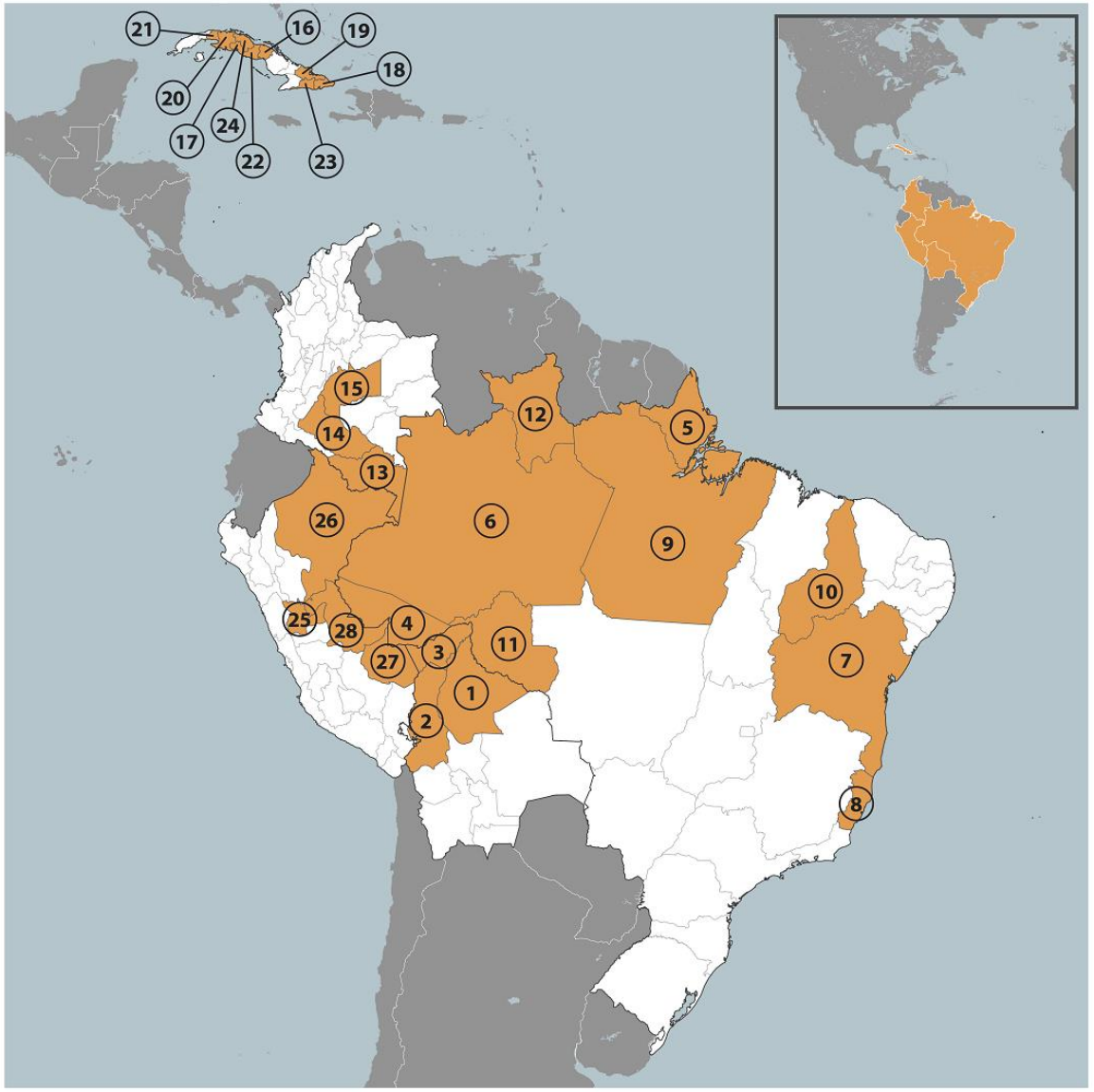
- IgM antibody testing by MAC-ELISA
- Perform testing in the acute phase of illness to aid in diagnosis – IgM antibody is detectable 4-5 days after symptom onset
- Available in public health laboratories, clinical and commercial labs
- Specimen: serum, CSF

Antigen testing

- Detection of the non-structural protein 1 (NS1)
- Perform testing within 7 days of symptom onset
- Available in public health laboratories, clinical and commercial labs
- Specimen: serum (whole blood, plasma)

Emerging Arbovirus

- Oropouche virus (OROV) is an orthobunyavirus.
- First identified in Trinidad in 1955
- Most outbreaks have occurred in the Amazon region.
- Second most common arbovirus in Brazil until ZIKV and CHIKV.
- As of July 16, 2024:
  - >7,500 cases in Caribbean basin
  - Identified in Cuba in May



Graphic from CDC Travel Health Notices

OROV Diagnostic Testing

Molecular testing

- RT-PCR for detection of Oropouche virus
- Available at CDC and a few state public health laboratories
- Perform testing within 7 days of symptom onset
- Specimen: serum, cerebrospinal fluid (CSF)

Serology testing

Plaque Reduction Neutralization Testing (PRNT)

- Detection of neutralizing antibodies specific to OROV
- Available at CDC and in development at PHLs

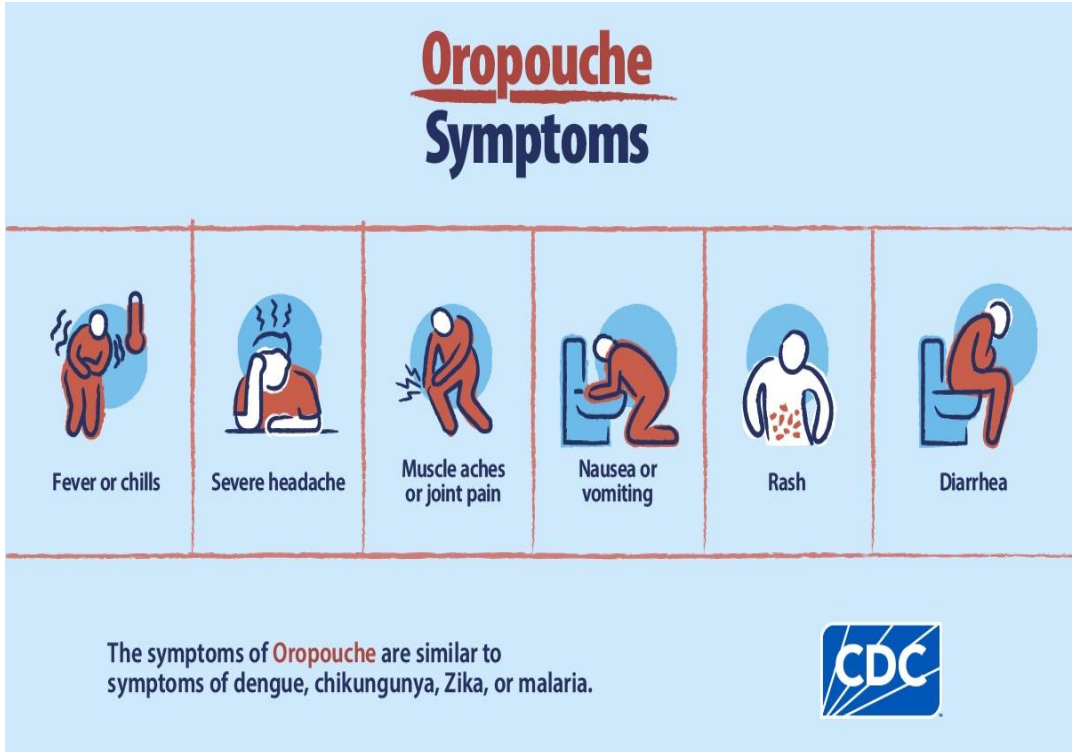
EIA testing

- In development

OROV Clinical Presentation

Clinical Presentation

- Incubation period is 3-10 days after being bitten by an infected *biting midge* or mosquito.
- Most people infected with OROV are symptomatic.
- Symptoms last 2-7 days.
- Neuroinvasive disease occurs in ~4% of patients.
- In Brazil, cases of vertical transmission associated with adverse pregnancy outcomes, e.g., fetal death and congenital abnormality have been documented.



Graphic courtesy of CDC

OROV Challenges with Diagnostics

Laboratory Developed Tests

- Florida BPHL is performing this LDT under the enforcement discretion provided for assays needed for “immediate response”

Availability of Validation Materials

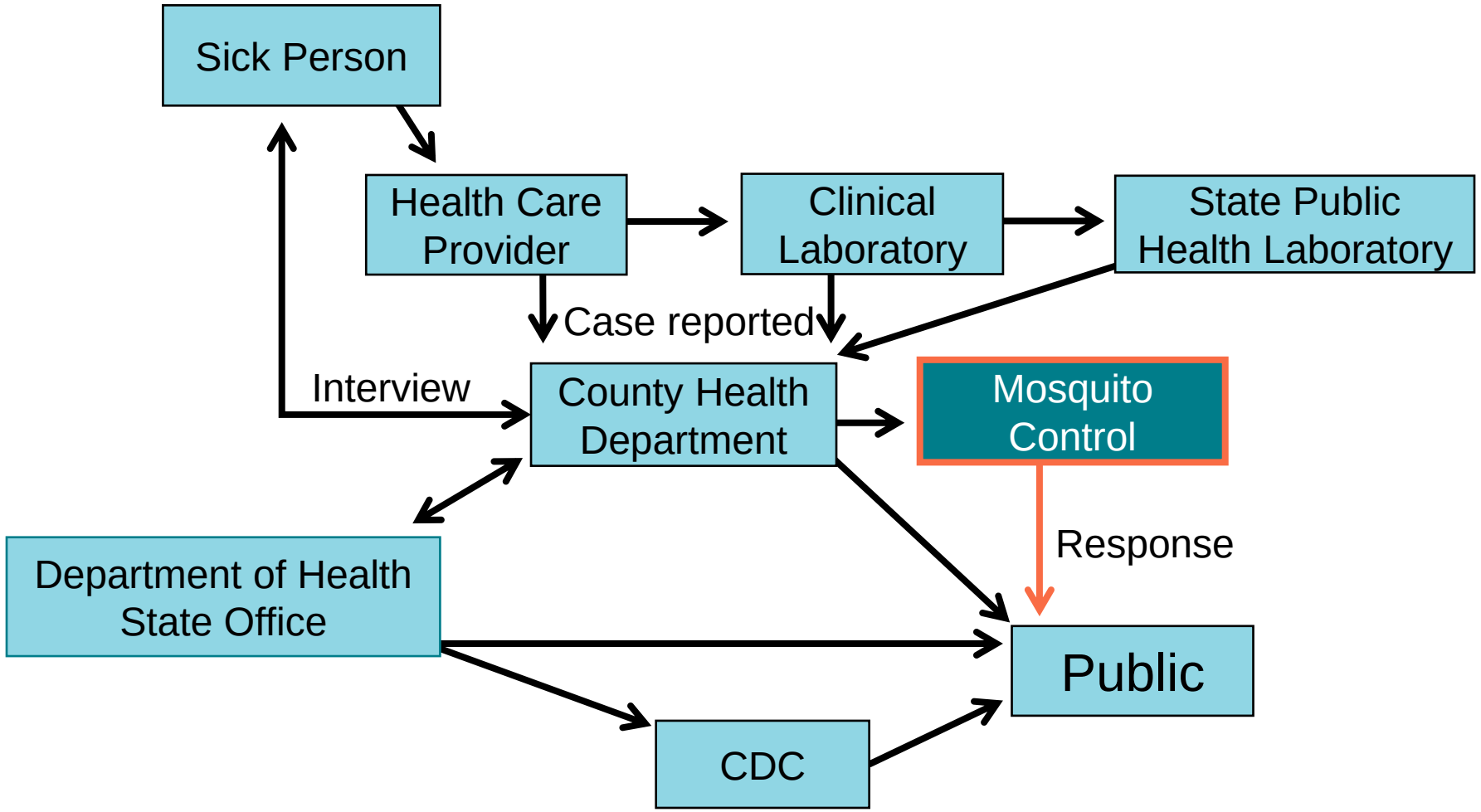
- Limited availability of positive specimens (using cultured virus)
- Determining specificity (since PCR targets ***Orthobunyavirus oropoucheense***)

510 *Mem Inst Oswaldo Cruz*, Rio de Janeiro, Vol. *112*(7): 510-513, July 2017

Multiplexed reverse transcription real-time polymerase chain reaction for simultaneous detection of Mayaro, Oropouche, and Oropouche-like viruses

Felipe Gomes Naveca[1]/+, Valdinete Alves do Nascimento[1], Victor Costa de Souza[1], Bruno Tardelli Diniz Nunes[2], Daniela Sueli Guerreiro Rodrigues[2], Pedro Fernando da Costa Vasconcelos[2,3]

Public Health: Case Investigation



Public Health: Surveillance Testing

Surveillance – ArboNET, sentinel chickens, syndromic surveillance

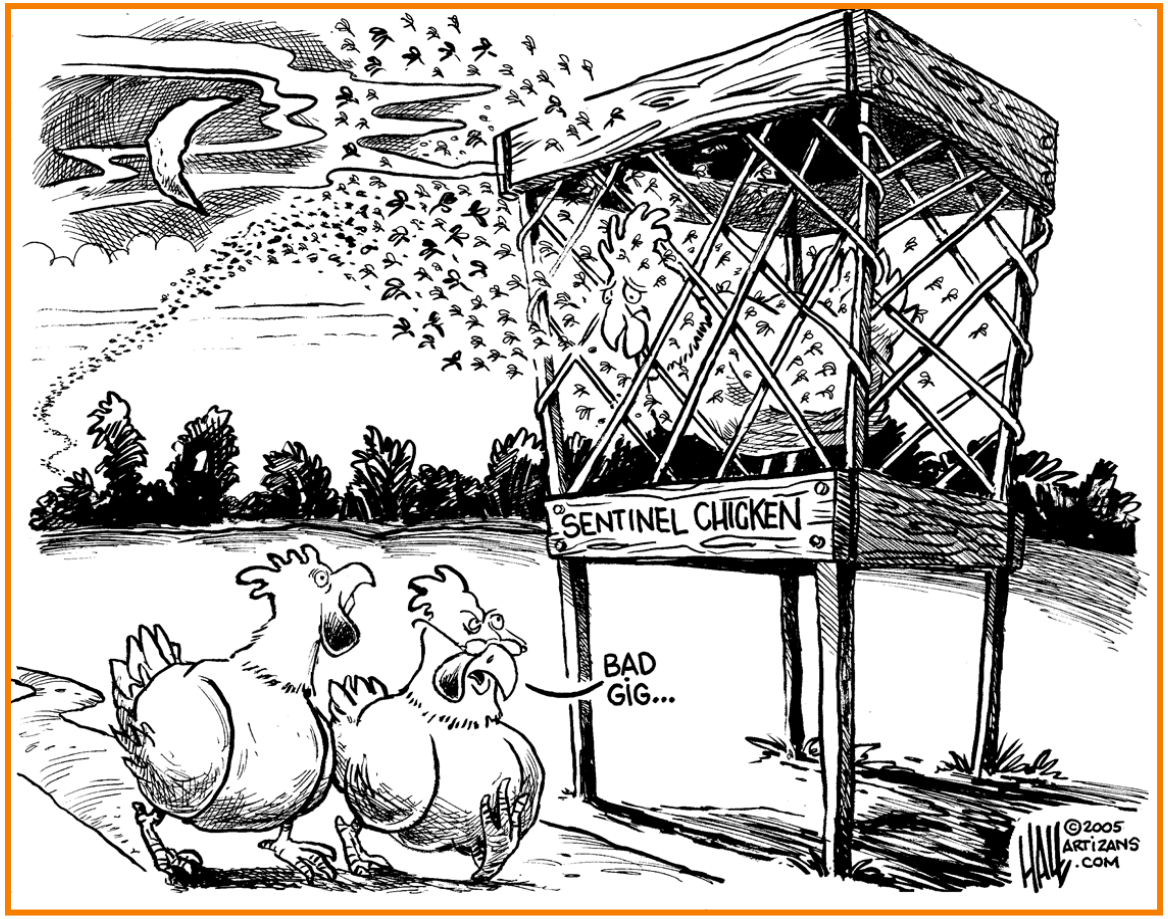
- Florida has the vectors.
- Vectors are biting year-round (although we do see an uptick in the summer months).
- Surveillance of the vectors and human cases to provide vector control, provide education to the public regarding protection.

Culex quinquefasciatus

Arbovirus Surveillance in Florida

Sentinel Chickens

- Performed throughout the state year-round.
- Sera from sentinel chickens is tested for antibodies to flaviviruses (SLEV/WNV) and to alphaviruses (EEEV/HJV).
- Seroconversion = recent virus transmission in the area of the flock. PH action is triggered if the number of positives is above baseline levels.

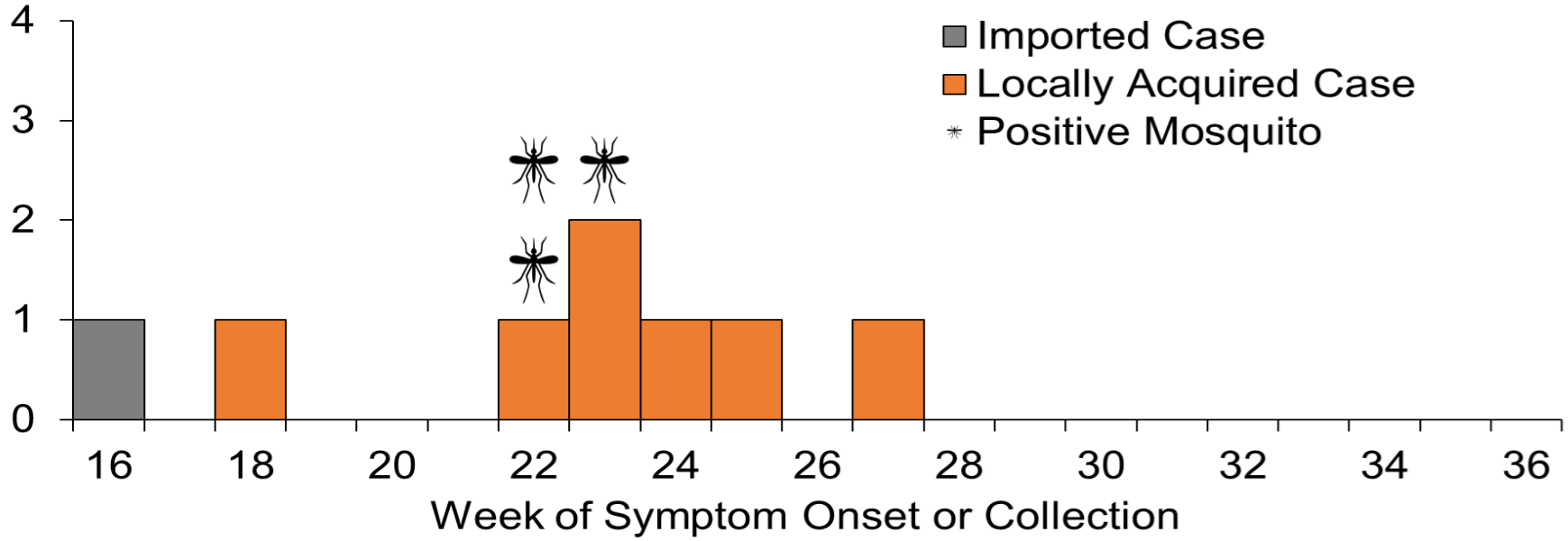


MS Stock Photo

Arborvirus Surveillance in Florida

Mosquito Pool Testing

- Performed when there is a known geographic area and targeting specific virus.
- Example below shows 7 human cases and 3 positive mosquitoes for malaria in 2023.



Florida HEALTH

Syndromic Surveillance

Data Sources:

Emergency Departments, Urgent Care Centers

Hospital Admissions

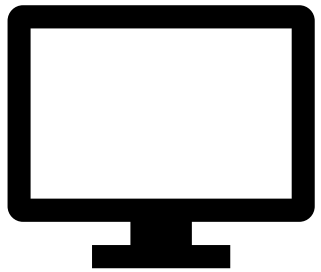
Poison Control Center

Mortality Data

Emergency Medical Services

2 hours

Deidentified Patient Data



ESSENCE-FL*

Hospital or Health Care Facility

Review medical record

State reportable disease database

*Electronic Surveillance System for the Early Notification of Community Based Epidemics (ESSENCE-FL)

Summary

- Arboviruses pose a significant public health threat and cases are increasing, particularly for dengue.
- Arboviruses are cyclical in nature and emergence and re-emergence of these viruses is occurring.
- Climate and travel contribute to this dynamic.
- Surveillance and diagnostic testing are crucial to public health efforts to prevent outbreaks.

Acknowledgements

Bureau of Public Health Labs

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CDC Fort Collins

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Diagnosis of Arboviral Infections

What test(s) to order when and why

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Director, STI Testing
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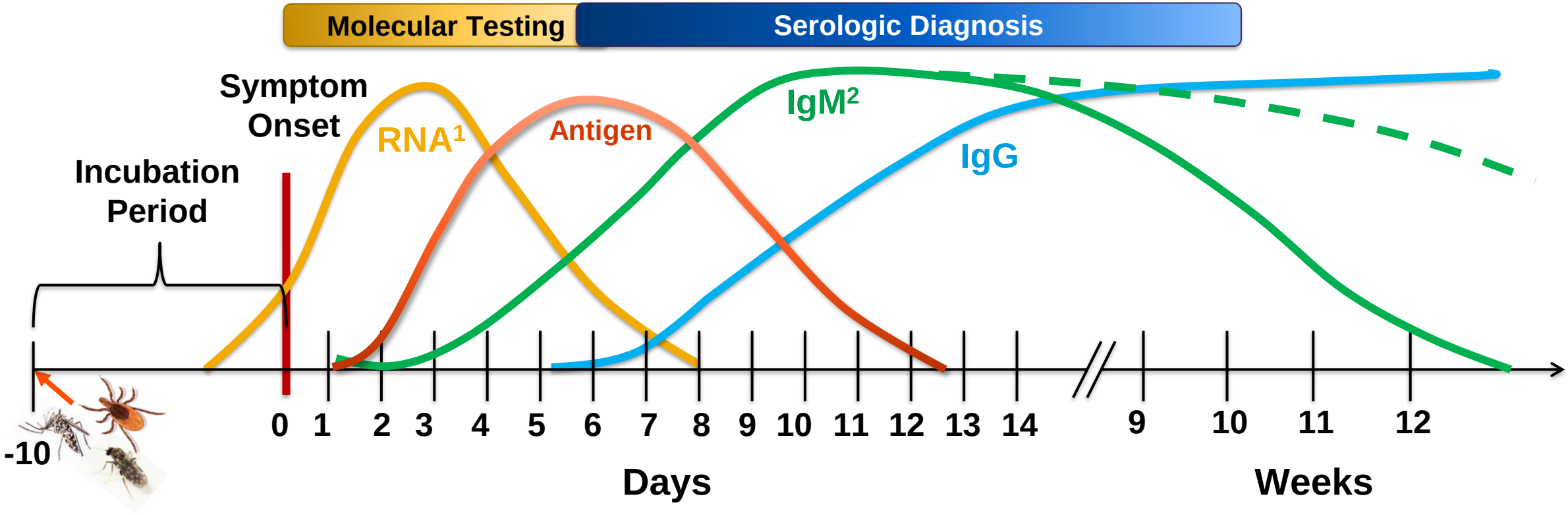
Learning Objective

- Understand the recommended approaches for diagnosis of select arboviral infections, including optimal utilization of available molecular and serologic methods
  - Focus on:
    - Dengue Virus
    - Eastern Equine Encephalitis Virus
    - Oropouche Virus

Molecular vs. Antigenic vs. Serology Testing

Test selection should be guided by symptom duration at time of presentation



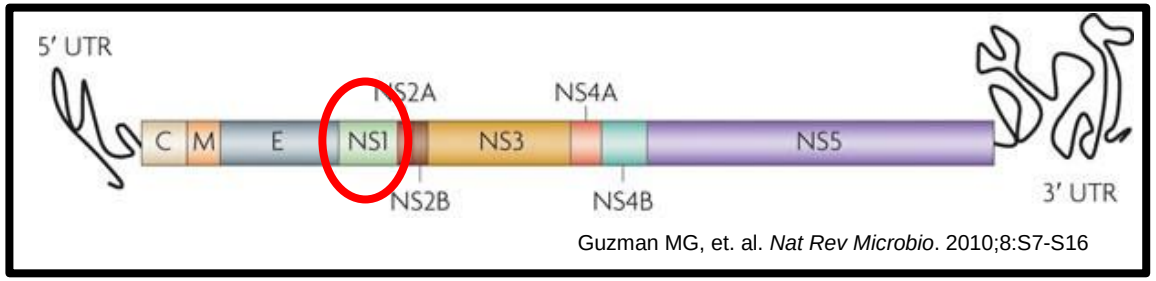
[1] Duration can vary based on specimen source

[2] IgM can remain detectable for longer (up to 500 days for WNV!)

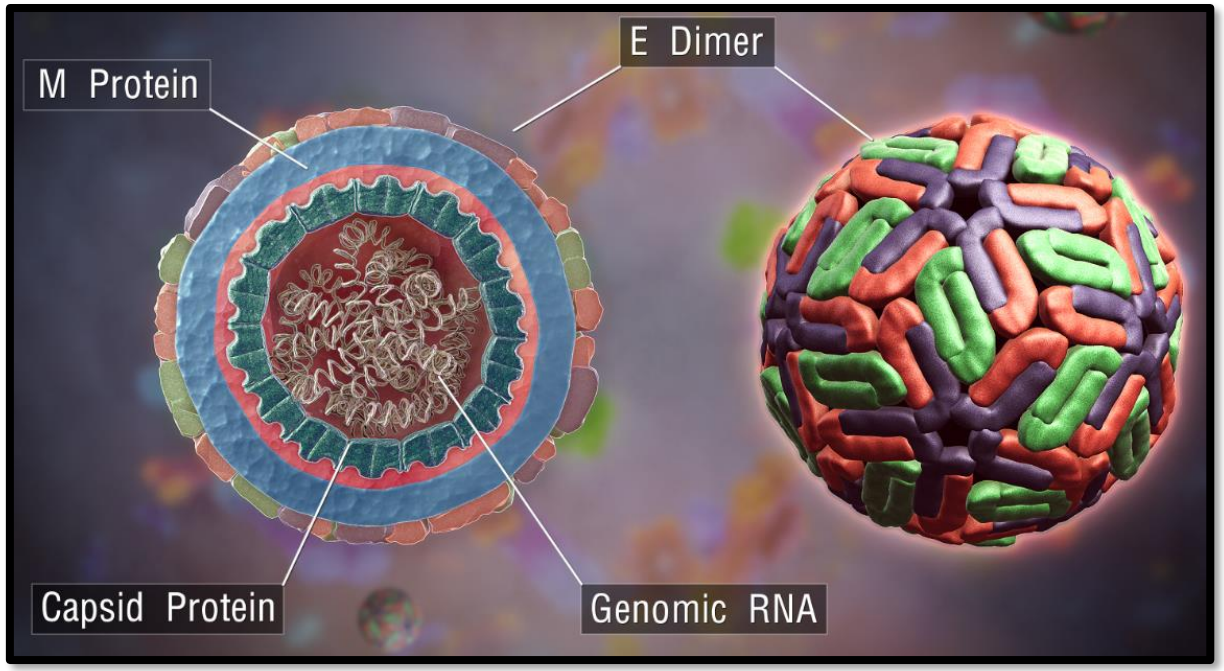
1 Dengue Virus
(CDC HAN-00511)

Dengue Virus Structural Components Impacting Diagnostics

- Flavivirus → +ssRNA genome
  - 3 structural & 7 nonstructural (NS) proteins
  - 4 serotypes (DENV 1-4)
    - Abs do **not** cross-neutralize → ADE
    - ~70%-80% homology of envelope (E) and NS1 proteins
      - Main antigens used for Ab detection!



Guzman MG, et. al. *Nat Rev Microbio*. 2010;8:S7-S16



Common Dengue Virus Diagnostic Assays

	Sample Type	Target Analyte	Testing Method
Direct Detection	Acute serum/plasma (1-5 days post-onset)	RNA	RT-PCR >> mNGS
		NS1 Antigen	ELISA / LFA
	Urine	Viral Isolation	Cell culture
Indirect Detection	Paired sera: - Acute (1-5 d) - Convalescent (>2 wks)	IgM and IgG	MAC-ELISA IgG ELISA IgM / IgG LFAs
	Post-Acute sera		PRNTs

MAC-ELISA, IgM Antibody Capture ELISA; PRNT, Plaque Reduction Neutralization Test

DENV Molecular Assays

- FDA Approved/Cleared:
  - CDC DENV 1-4 rRT-PCR & Trioplex rRT-PCR assay (DENV, ZIKV, CHIKV)
  - BioFire® Global Fever Special Pathogens Panel (DENV, CHIKV, *Plasmodium, Leptospira*)
- Manabe YC, *et al. Lancet Infect Dis* (2022;22:1356-64)
  - Prospective, cross-sectional study to evaluate panel across 10 clinics in 4 regions
  - Enrolled 1875 acutely febrile patients ≥ 6 months old
  - Accuracy of each panel target compared to results of 2 NAATS w/ different gene targets

	Number	Chikungunya virus	Dengue virus
Africa	599	0	1 (0·2%)
North America	188	0	0
Central or South America	433	0	121 (27·9%)
Southeast Asia	655	27 (4·1%)	144 (22·0%)
Overall total	1875	27 (1·4%)	266 (14·2%)

Data are n or n (%). *The *Leptospira* genus is divided into three groups, with pathogeni
detection of all *Leptospira* group 1 species.

Table 2: **Analytes detected by the Global Fever Panel by region and overall**

	PPA		NPA	
	TP/(TP + FN)	% (95% CI)	TN/(TN + FP)	% (95% CI)
Dengue virus (serotypes 1, 2, 3, and 4)†				
Fresh	249/263	94·7% (91·2–97·1)	1206/1206	100% (99·7–100)
Frozen	17/20	85·0% (62·1–96·8)	386/386	100% (99–100)
Overall	266/283	94·0% (90·6–96·5)	1592/1592	100% (99·8–100)

- High PPA/NPA for other targets (92.7%-98.3% / 99.2%-100%)

DENV Molecular Assays

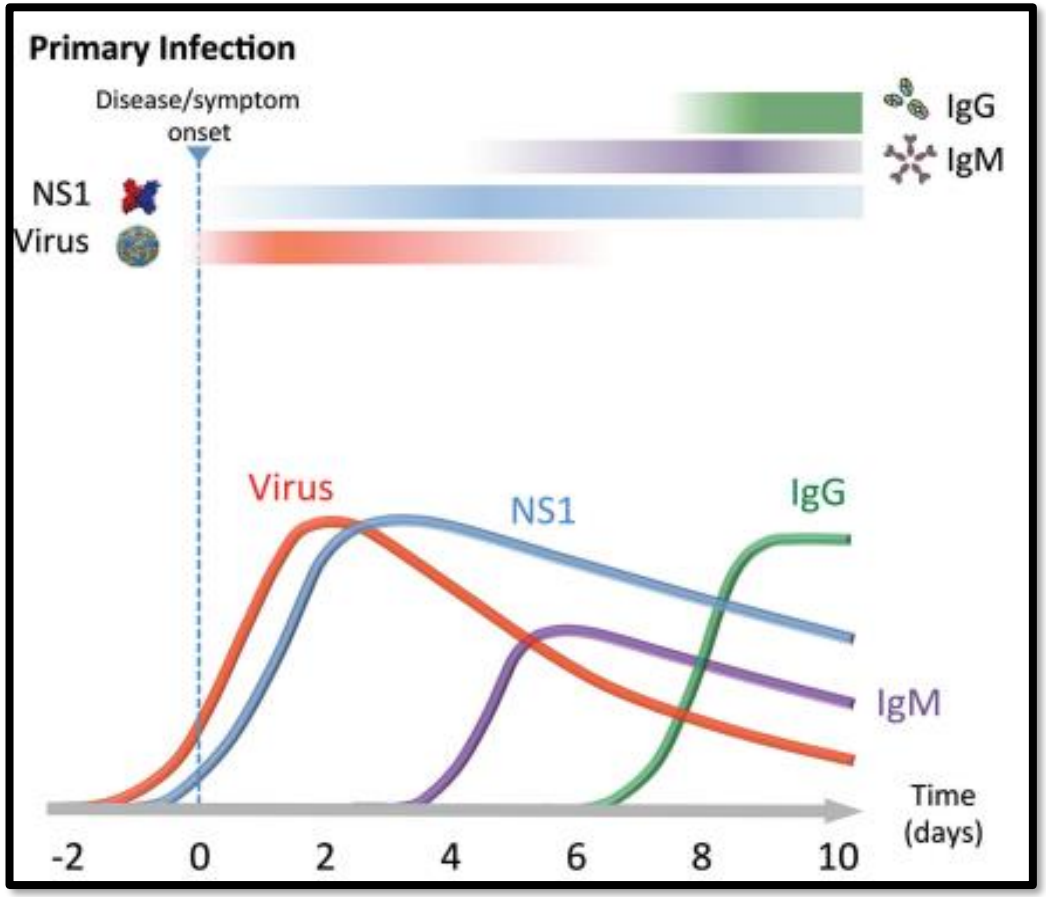
- Performance varies on multiple factors:
  - Assay method
  - DENV gene target
  - **DENV serotypes***
  - **Specimen type***
  - Timing of specimen collection
  - **Primary vs. repeat infection***

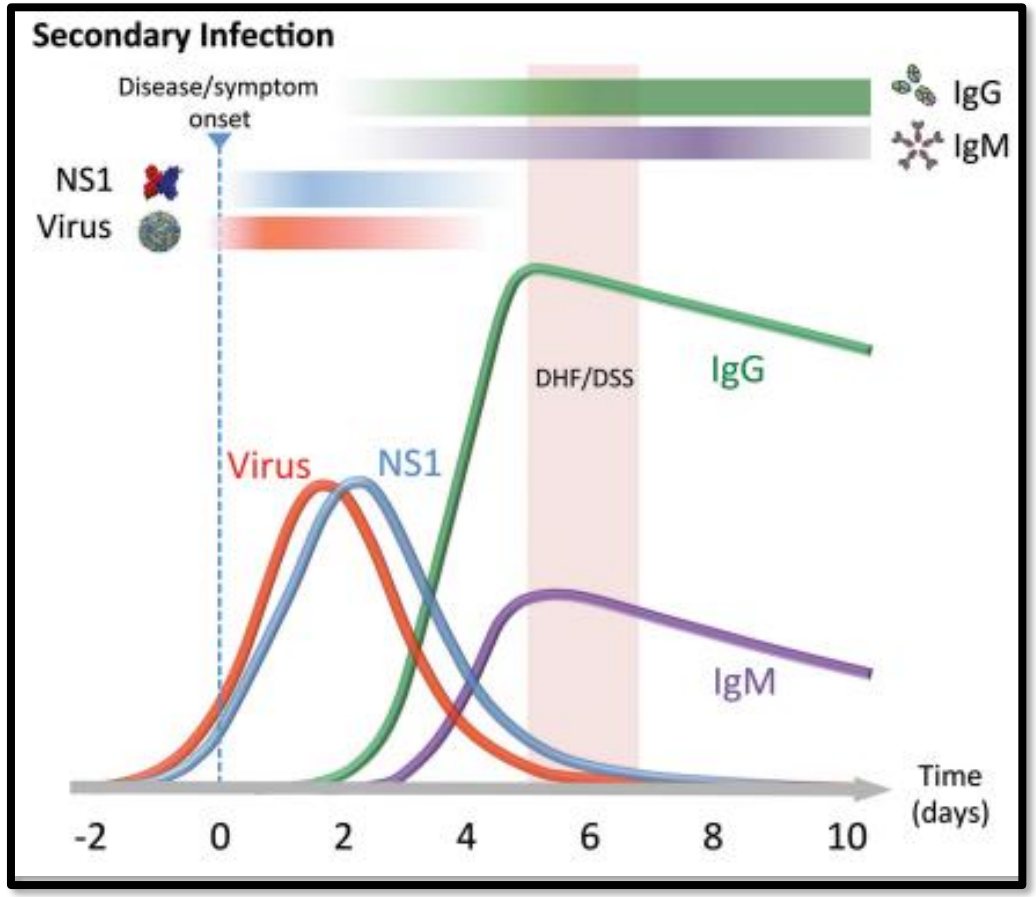
Parameter	rRT-PCR Assay		
	Geno-sen's (Genome Dx)	**RealStar (Altona Dx)**	**Simplexa (Focus Dx)**
Gene Target	Not Specified	Not Specified	DENV1/3 - NS5 DENV2 - NS3 DENV4 - capsid
Sensitivity			
DENV-1 (n=46)	91.3%	78.3%	95.7%
DENV-2 (n=37)	89.2%	86.5%	91.9%
DENV-3 (n=33)	90.9%	90.9%	90.9%
DENV-4 (n=46)	71.7%	80.4%	93.5%
Specificity (n=70)	100%	95.7%	100%

Najioullah F, Viron F, Cesaire R. *Virology J*. 2014;11:164-167

Impact of Specimen Source and Prior Infection on NAAT Performance Characteristics

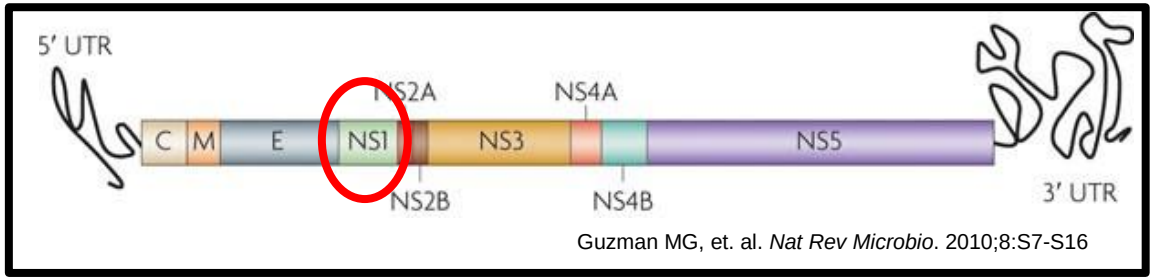
- Shorter viremia during secondary infection
  - Patients with DHF/DSS often NAAT negative





Muller DA, Depelsenaire ACI, Young PR. *J Infect Dis*. 2017;215:S89-S95

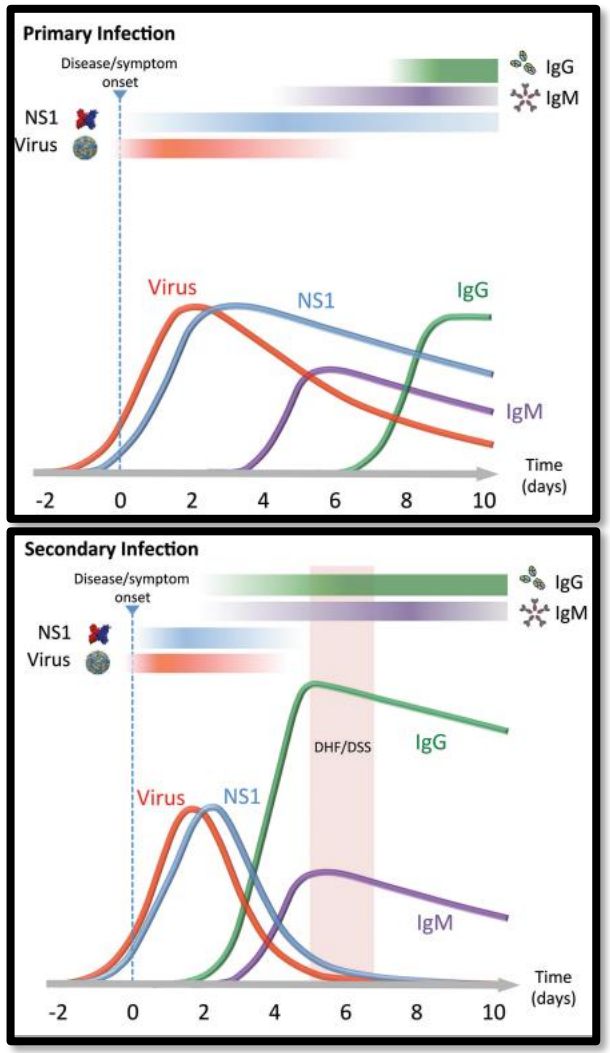
DENV NS1 Antigen Detection



Guzman MG, et. al. *Nat Rev Microbio*. 2010;8:S7-S16

- Conserved, membrane associated glycoprotein secreted from infected cells at high concentrations
- Duration of antigenemia depends on prior infection
  - 1° - 1 to 11 days (up to 18 days)
  - 2° - 1 to 7 days (anamnestic response)
- Alternative to NAAT for detection during acute phase
- <u>Many</u> NS1 ELISAs and LFAs commercially available (all qualitative)
  - FDA-cleared: InBios DENV Detect NS1 ELISA
  - >10 LFAs for NS1 +/- IgM/IgG detection
  - Macedo JVL, *et al. Diag Microbiol Infect Dis* (2024;109:116227)
    - 34 study meta-analysis assessing accuracy of NS1 LFAs

	Pooled Sens (95% CI)	Pooled Spec (95% CI)
vs. NS1 ELISA	77% (76% - 78%)	98% (97% - 100%)
vs. DENV NAAT	61% (59% - 62%)	93% (92% - 94%)



Muller DA, Depelsenaire ACI, Young PR. *J Infect Dis*. 2017;215:S89-S95

DENV IgM and IgG Detection Assays

- Variety of methods:
  - HI, Comp Fix, Blots, IFAs, PRNTs, LFAs, ELISAs
  - IgM Capture ELISAs (MAC-ELISAs)
    - ↑ sensitivity/specificity vs. indirect ELISAs
  - FDA-cleared: InBios DENV Detect MAC-ELISA
- Antibody kinetic keys:
  - 1° - IgM 3-5 d; IgG >7d
  - 2° - IgG <7d >> IgM
- Differentiation b/w 1° vs 2° infection
  - IgM:IgG ratio using ELISA index values
  - IgG avidity testing
- Serologic testing challenges:
  - Delayed seroconversion in acute disease / prolonged positivity
  - Variable sensitivity across DENV serotypes
  - Cross-reactivity due to conserved E protein across flaviviruses
    - 34%-54% of pts with Zika virus DENV IgM/IgG pos

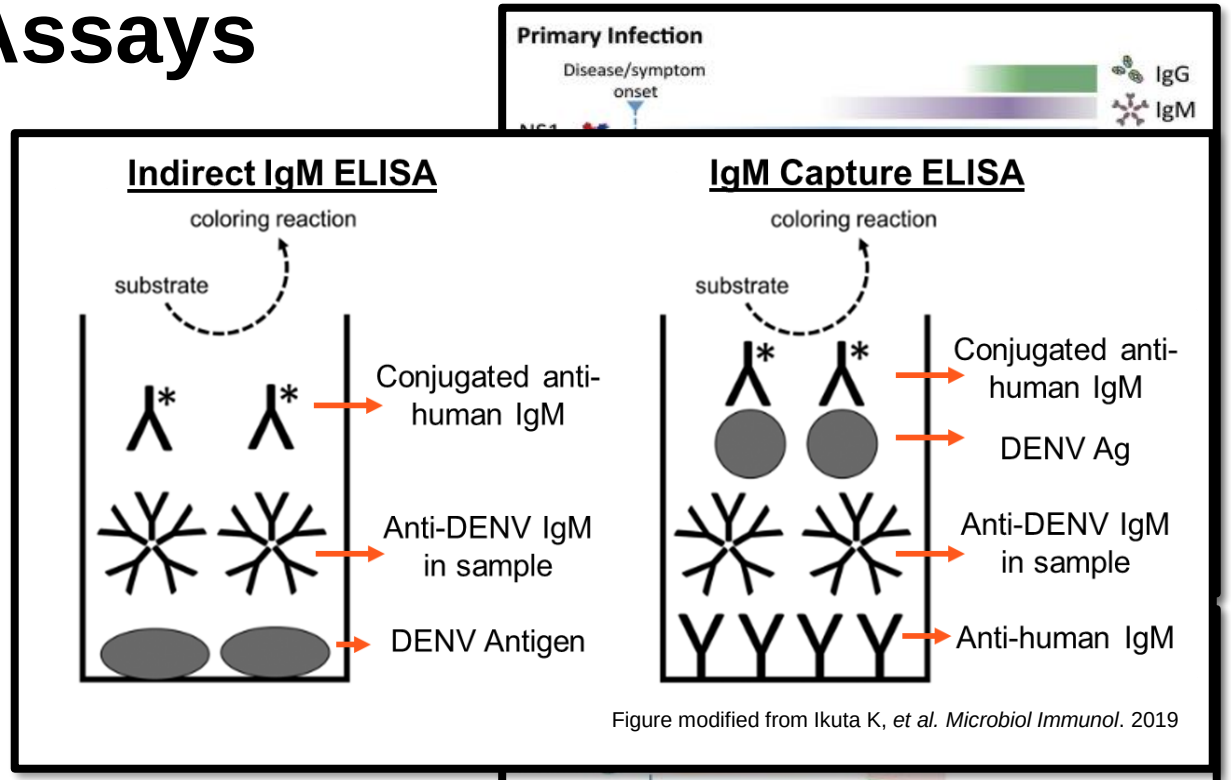
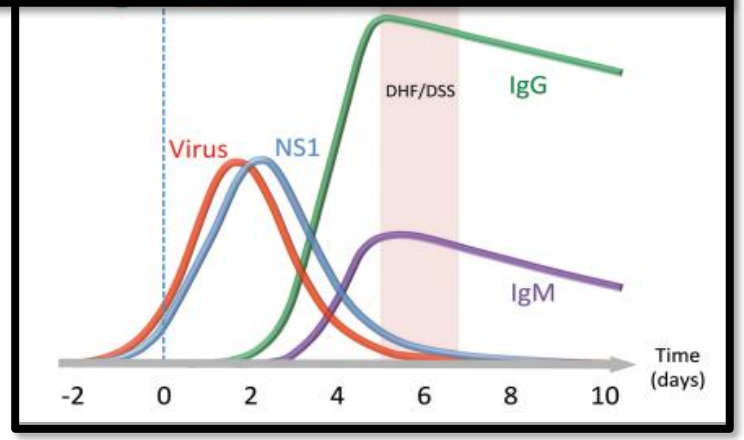


Figure modified from Ikuta K, *et al. Microbiol Immunol*. 2019



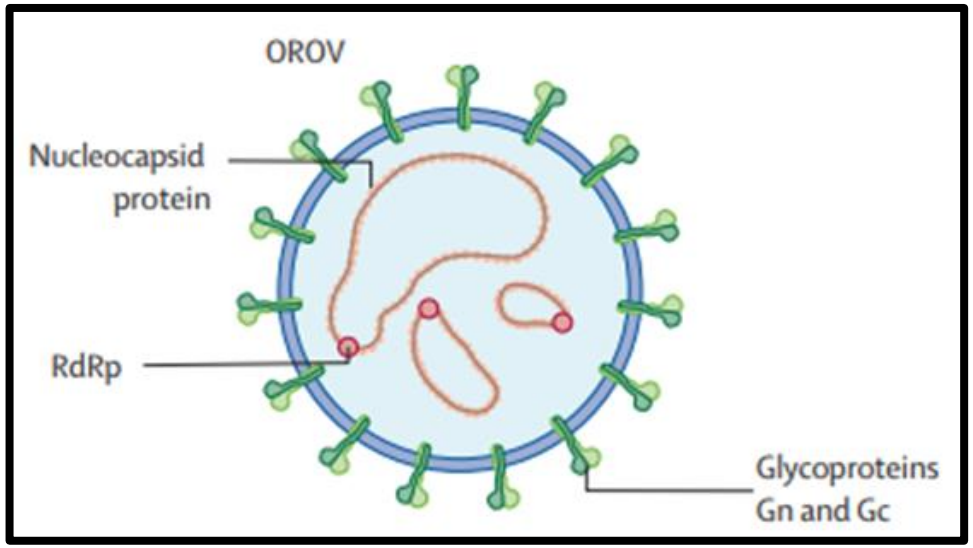
Muller DA, Depelsenaire ACI, Young PR. *J Infect Dis*. 2017;215:S89-S95

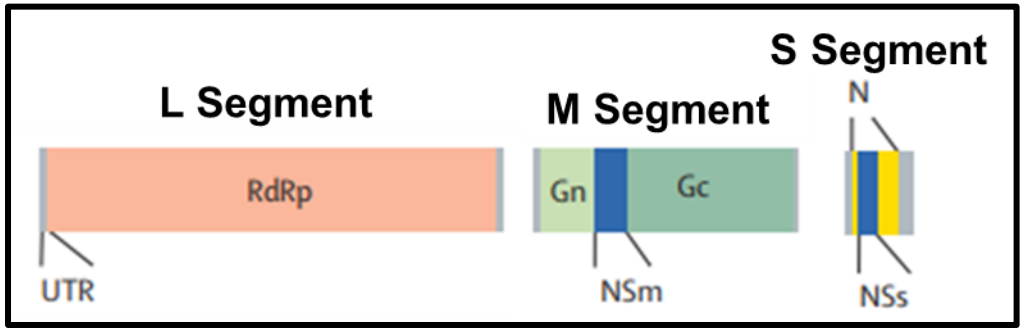
Lopex AL, *et al. Lancet Glob Health,* 2021
van Meer, MPA, *et al. J Clin Virol,* 2017
Maeki T, *et al. J Infect Chemother*, 2019

2 Oropouche Virus (CDC HAN-00515)

Oropouche Virus: The Basics

- -ssRNA, segmented genome
  - Reassortment!
    - Iquitos virus
    - Madre de Dios virus
    - Perdões virus
  - Antibodies not cross-protective → antibody dependent enhancement (ADE)



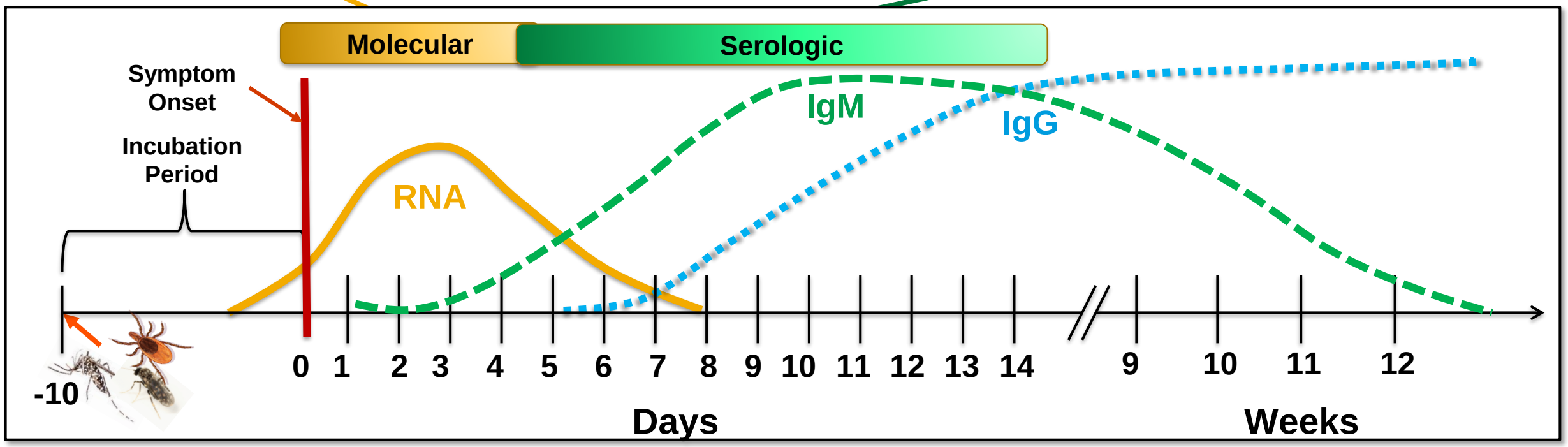


Wesselmann KM, *et al. Lancet*. 2024;24:e439-e452

OROV – Diagnostic Testing

- rRT-PCRs target S or M segments
  - 93% sensitive w/in 5 days in serum
  - Urine/CSF/saliva detection w/in 5 days also
  - Viral load range: 10^4 to 10^8 copies/mL
  - M segment used for typing

- Immune responses not well defined…many methods developed
- Serologic tests target NC or Glycoprotein antigens
  - NC → robust immune response, but cross-reactive
- CDC Recommendations:
  - PRNT ≥ 6 days post-symptom onset
- IFAs/ELISAs under development…but tricky to validate…

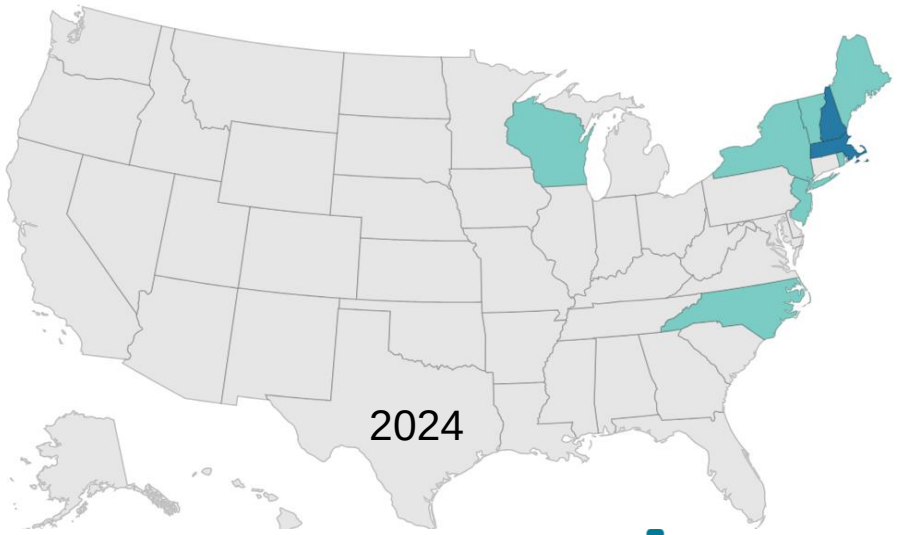


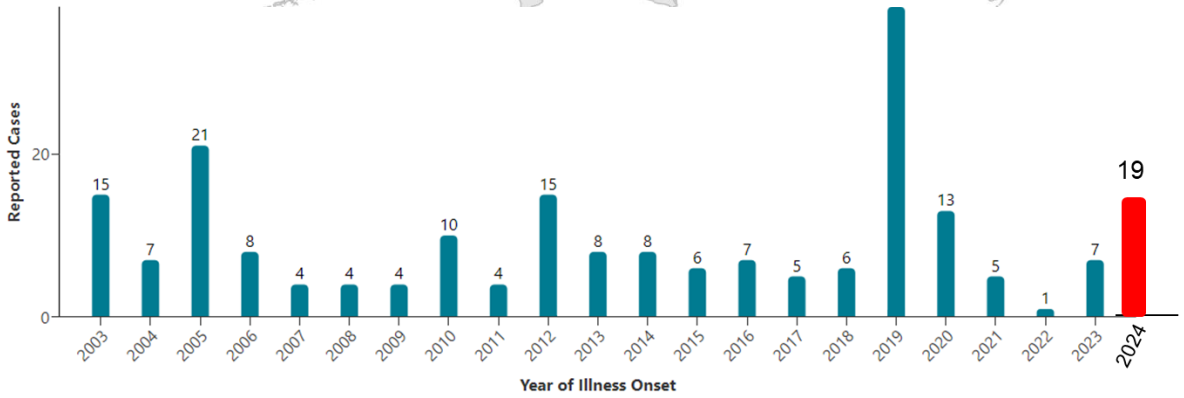
Wesselmann KM, *et al. Lancet*. 2024;24:e439-e452 I Pastula DM, *et al. Am Neuro Assoc*. 2024;DOI: 10.1002/ana27139

3 Eastern Equine Encephalitis Virus

Refresher on Eastern Equine Encephalitis Virus (EEEV)

- Alphavirus transmitted by *Culex, Coquillettidia, Aedes* mosquitos with passerine birds as the environmental reservoirs
- Clinical presentation
  - 4-10 day incubation period
  - Majority are asymptomatic
    - Acute fever, influenza-like illness (1-2 wks)
    - Lifelong immunity to reinfection
  - <5% develop neurologic manifestations
    - HA, N/V, confusion, seizure, meningismus, etc
    - ~30% of patients expire w/in 2-10 days of onset
    - ~50% of survivors remain with neurologic sequelae

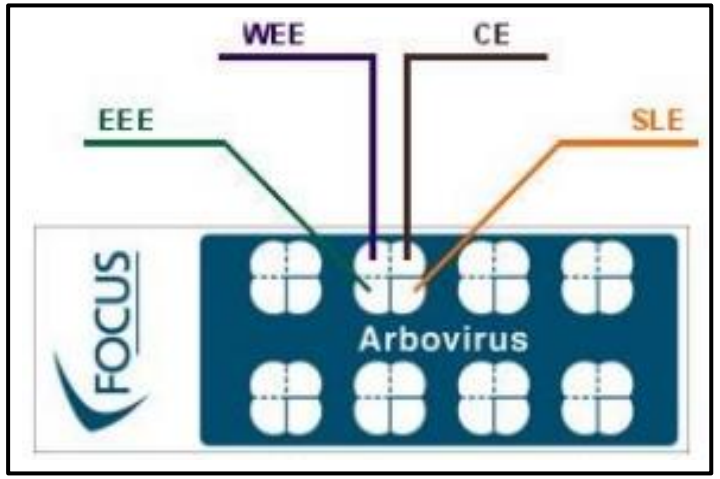


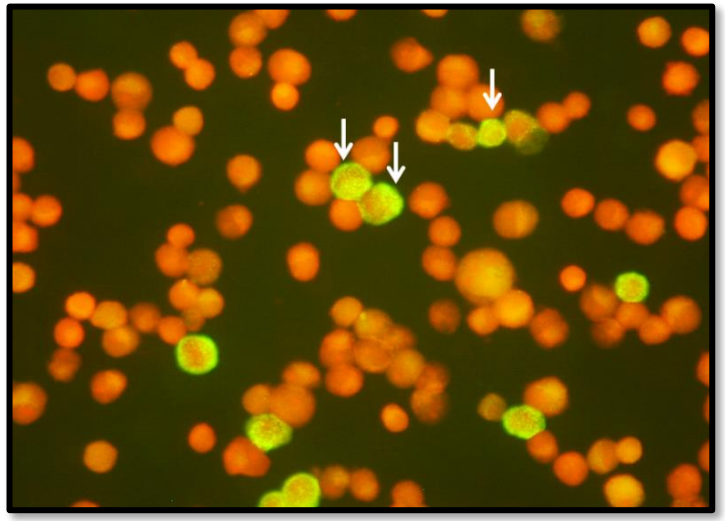


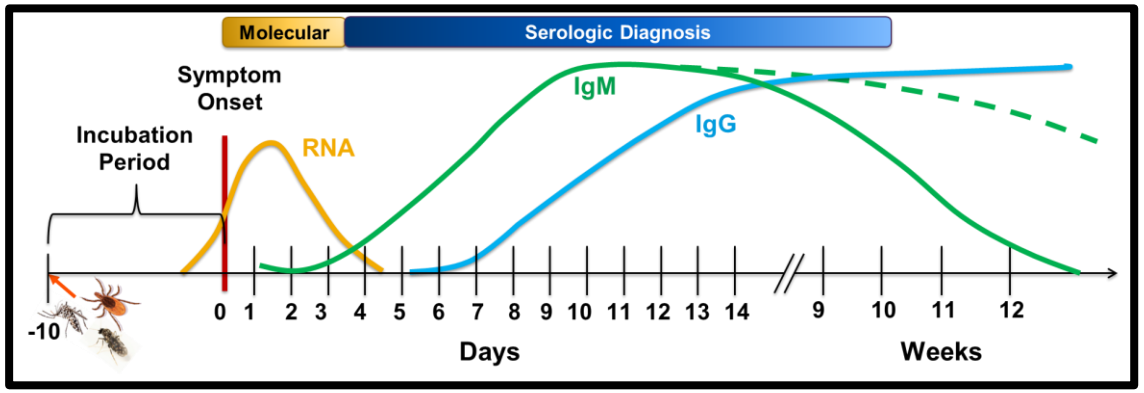
Data and Maps for Eastern Equine Encephalitis | Eastern Equine Encephalitis Virus | CDC

Diagnosing EEEV Infections Can Be Challenging

- Molecular testing not routinely available – PHL/CDC
  - Low/transient viremia → ↓ Sensitivity in blood/CSF
- Reference standard method: IgM detection in CSF / Serum
- Few commercially available assays:
  - Focus (DiaSorin) multiplex IFA for IgM/IgG is FDA-cleared (serum)
    - EEEV, WEEV, St. Louis Encephalitis, California Encephalitis viruses
    - IgM = acute/recent infection; IgG less valuable…
  - Dim, but definite fluorescence in >5% of cells = Positive
  - Serial dilution of CSF / serum:
    - Serum positive if ≥ 1:16
    - Lab-dependent endpoint titer cut-offs (1:1 to 1:10) for CSF positivity

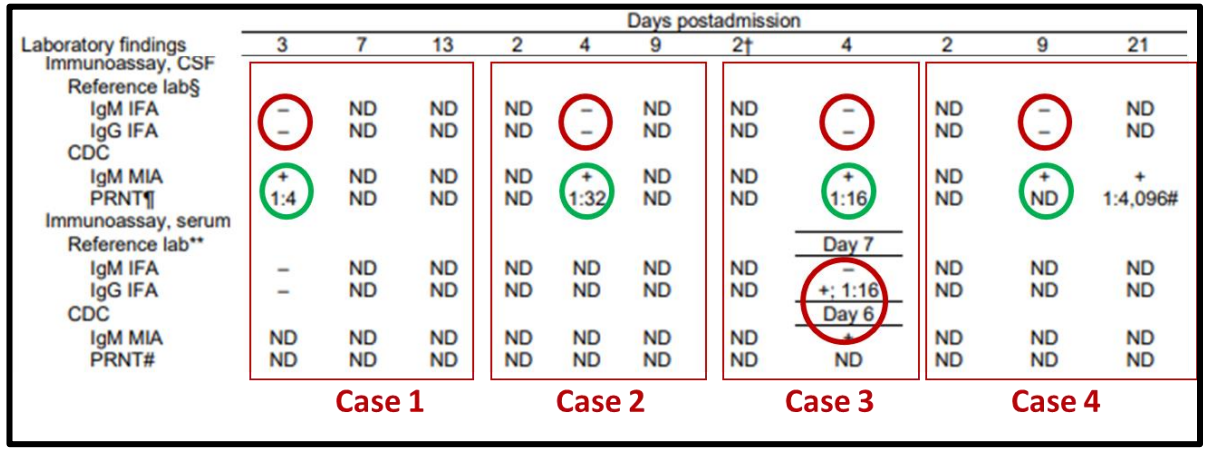






EEEV Diagnostics

- Brown SC, *et al. Emerg Infec Dis*. (2021;27[8]:2042-2051)
  - Described diagnostic testing of 4 EEE cases in CT
  - Ref Lab testing using Multiplex IFA w/ CSF cut-off threshold ≥ 1:4 → all pts negative
    - CDC MIA & PRNT → all positive
    - Retest at 1:1 dilution → all remained negative



- Sherwood JA, *et al. J Clin Microbiol* (2015;53[8]:2768-2772)
  - Retrospective evaluation of EEEV diagnosis in 8 pts in NY (1966-2014)
  - All testing performed at NYS DoH and CDC
    - 2/8 pts CSF tested for EEEV IgM → both positive on day 2 (1:32) and 6 (1:1)
    - 1/8 pts sera tested for EEEV IgM → pos on day 6 (≥1:256)
  - **6/8 pts CSF tested for EEEV RNA… → 5/6 positive on days 1-6!**

What About mNGS for Detection of Arboviral Pathogens?

nature medicine

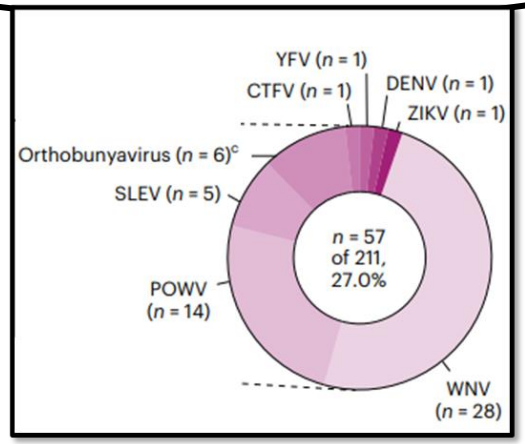
Article

https://doi.org/10.1038/s41591-024-03275-1

Seven-year performance of a clinical metagenomic next-generation sequencing test for diagnosis of central nervous system infections

Patrick Benoit[1], Noah Brazer[1], Mikael de Lorenzi-Tognon[1], Emily Kelly[1], Venice Servellita[1], Miriam Oseguera[1], Jenny Nguyen[1], Jack Tang[1], Charles Omura[1], Jessica Streithorst[1], Melissa Hillberg[1], Danielle Ingebrigtsen[1], Kelsey Zorn[2], Michael R. Wilson[3,4], Tim Blicharz[5], Amy P. Wong[5], Brian O'Donovan[5], Brad Murray[5], Steve Miller[1,5] & Charles Y. Chiu[1,6,7]

Received: 21 April 2024



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

M.R. Wilson, H.A. Sample, K.C. Zorn, S. Arevalo, G. Yu, J. Neu
D. Stryke, B. Briggs, C. Langelier, A. Berger, V. Douglas, S
F.C. Chow, B.D. Fulton, J.L. DeRisi, J.M. Gelfand, S.N. Nacc
J. Dien Bard, J. Murkey, M. Carlson, P.M. Vespa, T. Vijaya
S. Campeau, R.M. Humphries, J.D. Klausner, C.D. Ganzc
N.A. Ocampo, L.L. Zimmermann, S.H. Cohen, C.R. Polag

Cerebrospinal fluid metagenomics has greatest added value as a test for Powassan virus among patients in New England with suspected central nervous system infection

Erik H. Klontz[a], Isaac H. Solomon[b], Sarah E. Turbett[a], Jacob E. Lemieux[c], John A. Branda[a,*]

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ORIGINAL RESEARCH

Use of Metagenomic Next-Generation Sequencing to Identify Pathogens Involved in Central Nervous System Infections

Liying Zhan[1,*], Zhihua Lv[2,*], Yunjing Zhang[3,*], Jingdi Chen[4], Lu Wang[1], Raojuan Huang[5], Yaqi Sun[5], Wei Wu[1]

Untargeted metagenomic sequencing identifies Toscana virus in patients with idiopathic meningitis, southern Spain, 2015 to 2019

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Eurosurveillance

Fabiana Gámbaro[1], Ana Belén Pérez[2,3,4], Matthieu Prot[1], Eduardo Agüera[2,3,5], Artem Baidaliuk[1], María Paz Sánchez-Seco[4,6], ez-Garcia[3,6,7,8], Etienne Simon-Loriere[1,8]

Performance of clinical metagenomics in France: a prospective observational study

Jacques Fourgeaud*, Béatrice Regnault*, Vichita Ok, Nicolas Da Rocha, Émilie Sitterlé, Meryem Mekouar, Hél
Catherine Milliancourt-Seels, Florence Jagorel, Delphine Chrétien, Thomas Bigot, Éric Troadec, Isabelle Marqu
Danielle Seilhean, Bénédicte Neven, Pierre Frange, Agnès Ferroni, Marc Lecuit, Xavier Nassif, Olivier Lortholar
Philippe Pérot†, Marc Eloit‡, Anne Jamet‡

Clinical application and evaluation of metagenomic next-generation sequencing in pathogen detection for suspected central nervous system infections

scientific reports

Lei Yuan, Xin Yu Zhu, Lan Min Lai, Qiang Chen, Yang Liu & Rui Zhao

mNGS Arboviral Pearls:

- High initial suspicion important predictive factor
- Detects arboviruses w/o alternative dx testing
- Sensitivity impacted due to transient/low viremia → serology remains of value

Thank you!

Questions & answers