Arboviral Diseases

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

WRAIR
Walter Reed Army Institute of Research
Soldier Health • World Health

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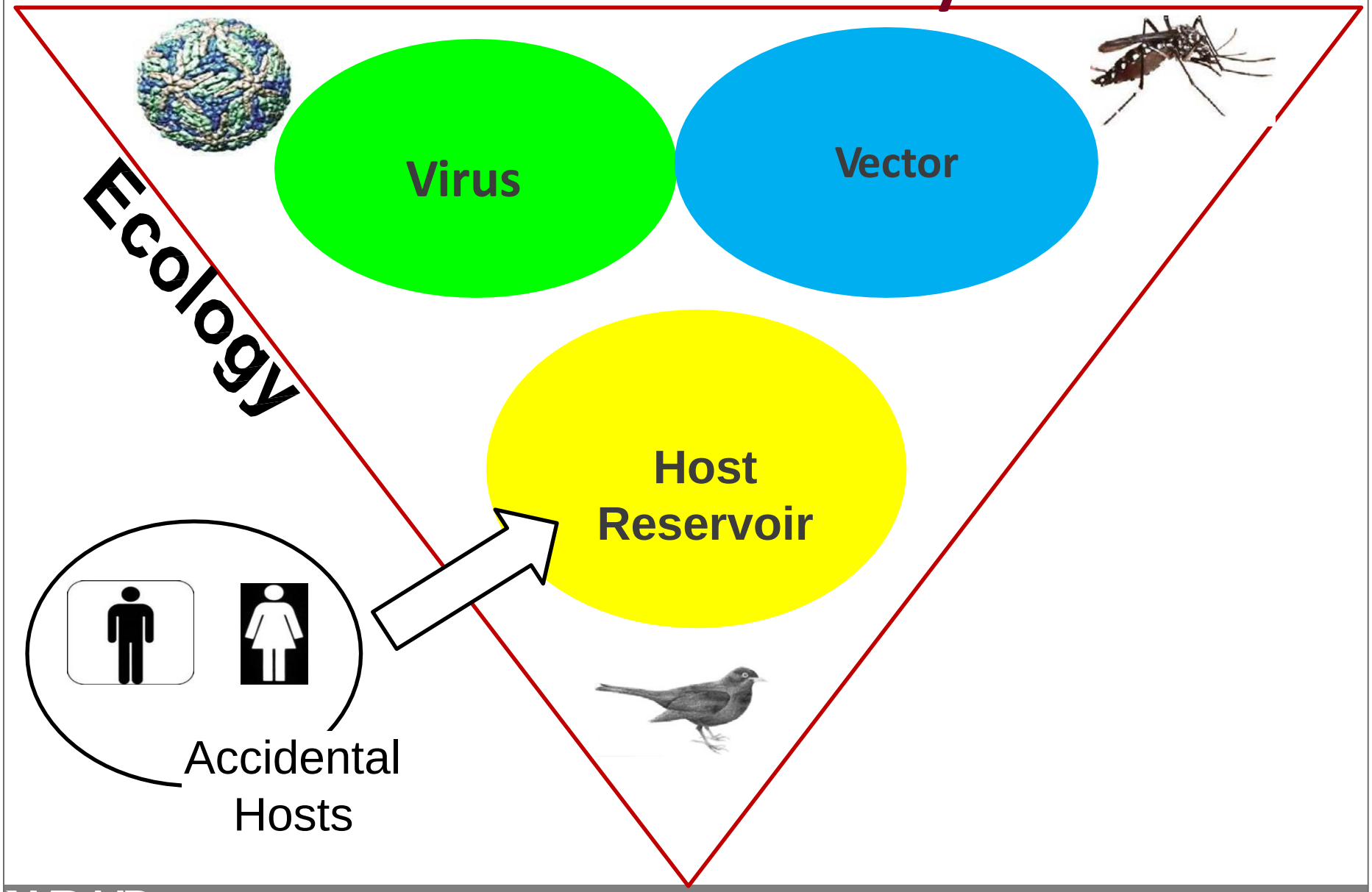
Lecture Objectives

- Increase knowledge of:
  - Arbovirology
  - Epidemiology of tropical viral disease threats
  - Select diseases clinical presentation
    - Separate Lectures for Dengue and Chikungunya
  - Key points related to prevention and treatment

What is an Arbovirus?

- Defined: Arthropod-borne viruses (arboviruses) are **transmitted biologically among vertebrate hosts by hematophagous (blood feeding) arthropod vectors** such as mosquitoes and other biting flies, and ticks.

Arboviral Transmission Dynamics



DOD Infectious Disease Threats

Disease	2010 COCOM panel rank	ID-IDEAL Rank
Malaria	1	2
Dengue	**2**	**3**
Diarrhea, bacterial	3	1
MDR wound pathogens	4	NA
Leishmaniasis	5	19
Q fever (Coxiella burnetti)	6	26
Norovirus / viral diarrhea	7	NA
Influenza	8	NA
Leptospirosis	10	7
Diarrhea, protozoal	11	11
TB	12	NA
CCHF	13	10
HIV	14	8
HFRS	15	17
Chikungunya	16	4
Meningococcal meningitis	17	20
Plague	18	27
Ricketsioses	19	18
Viral encephalitides	20	NA

Transmission Cycle Example - WNV

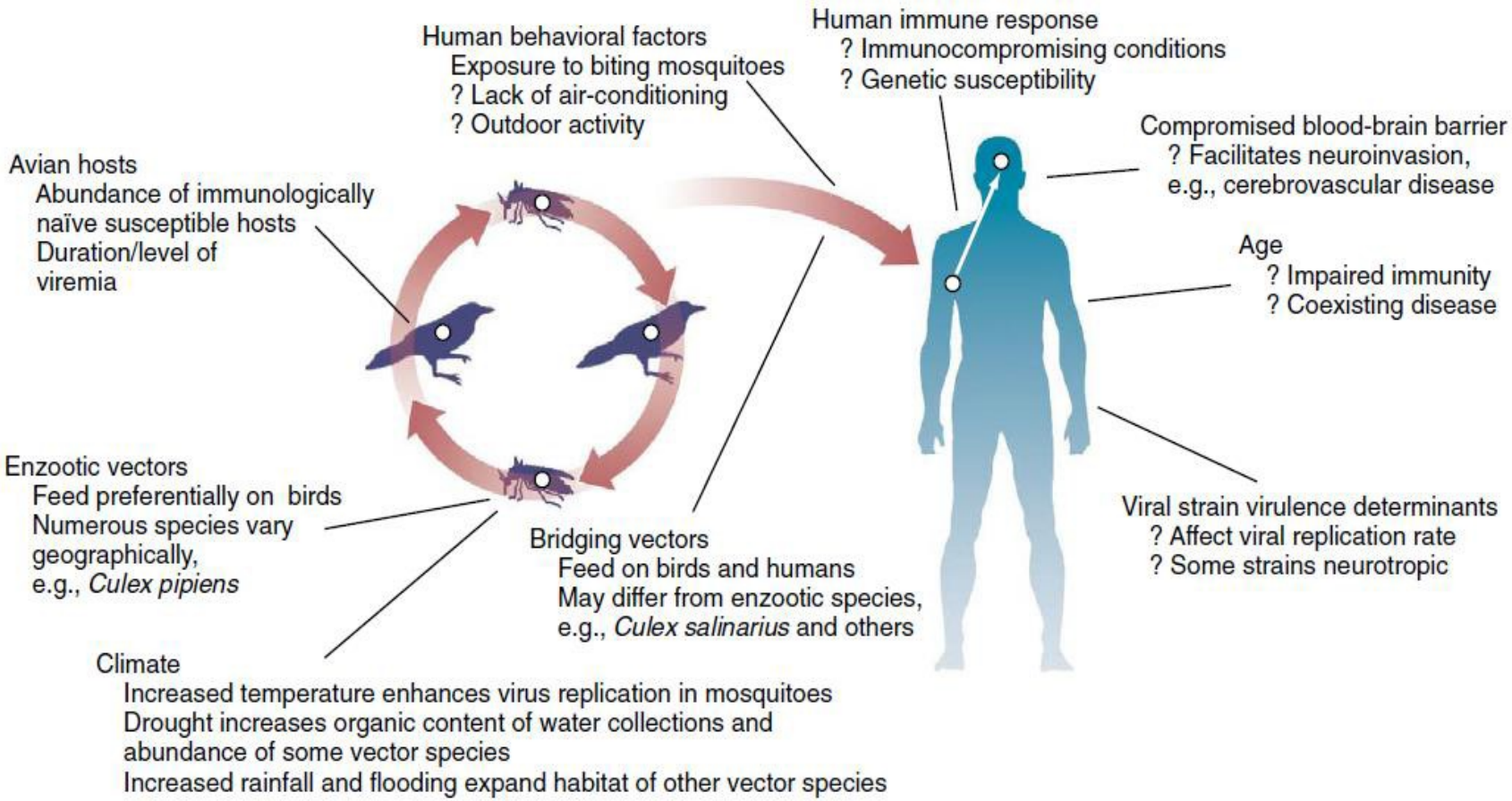


Figure 153-3 West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness.

Arboviruses

- Occur in nearly all parts of the world except the ice caps
- Over 500 distinct viruses, >100 causing human infections
- Nearly all arboviruses included in 4 families:
  - Flaviviridae
  - Togaviridae
  - Bunyaviridae
  - Reoviridae

Arboviral Diseases: Clinical Syndromes

- Systemic Febrile Illness
  - Dengue, Chikungunya, O'nyong-nyong, Ross River, Zika
- Fever with Arthritis
  - Chikungunya, Ross River, O'nyong-nyong
- Encephalitis
  - JE, WNV, TBE, EEE, WEE
- Hemorrhagic Fever
  - Yellow Fever, Dengue, Rift Valley Fever, Chikungunya

Question

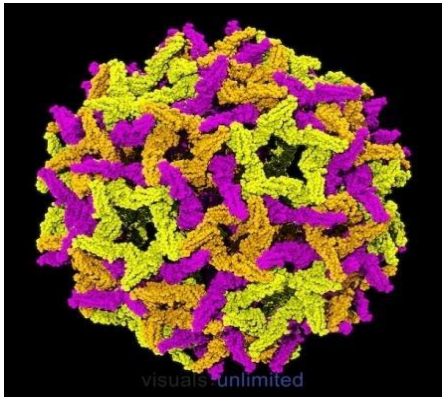
- A 67 YO MALE PRESENTS WITH A FIVE-DAY HISTORY OF A FEBRILE ILLNESS, HEADACHE, SEVERE ABDOMINAL PAIN, ANXIETY, NAUSEA AND VOMITING, DYSPNEA, JAUNDICE, LEUKOPENIA, AND THROMBOCYTOPENIA. HE LIVES IN QUITO ECUADOR. HE DOES NOT DRINK ETOH OR USE TOBACCO. HE IS UP TO DATE ON ALL IMMUNIZATIONS INCLUDING YELLOW FEVER VACCINE RECEIVED 5 DAYS(REQUIRED FOR PLANNED TRAVEL TO PANAMA) PRIOR TO ONSET OF SYMPTOMS. ON ADMISSION, HIS BP WAS 110/70, HR OF 72, A RR OF 20, A TEMP. OF 36°C, AND O2 SATURATION RATE OF 74% ON ROOM AIR. THREE HOURS AFTER ADMISSION, HE WAS TRANSFERRED TO AN INTENSIVE CARE UNIT BECAUSE OF MULTIORGAN SYSTEM FAILURE, OLIGURIC RENAL FAILURE. HE EXPERIENCED A CARDIAC ARRHYTHMIA AND DIED.

- WHAT IS THE MOST LIKELY CAUSE OF THE PATIENT'S DEMISE?

1. YF VACCINE-ASSOCIATED NEUROLOGIC DISEASE (YEL-AND).
2. YF VACCINE-ASSOCIATED VISCEROTROPIC DISEASE (YEL-AVD)
3. SYLVATIC YF
4. SEPTIC SHOCK

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, Japanese encephalitis, Tick Borne Encephalitis, Powassan, Rio Bravo, Saint Louis Encephalitis, West Nile Virus, **Yellow fever**, Zika virus
  - Genus Hepacivirus (1 species)
    - Hepatitis C virus
  - Genus Pegivirus (2 species)



Yellow Fever

Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology

Bali Pulendran

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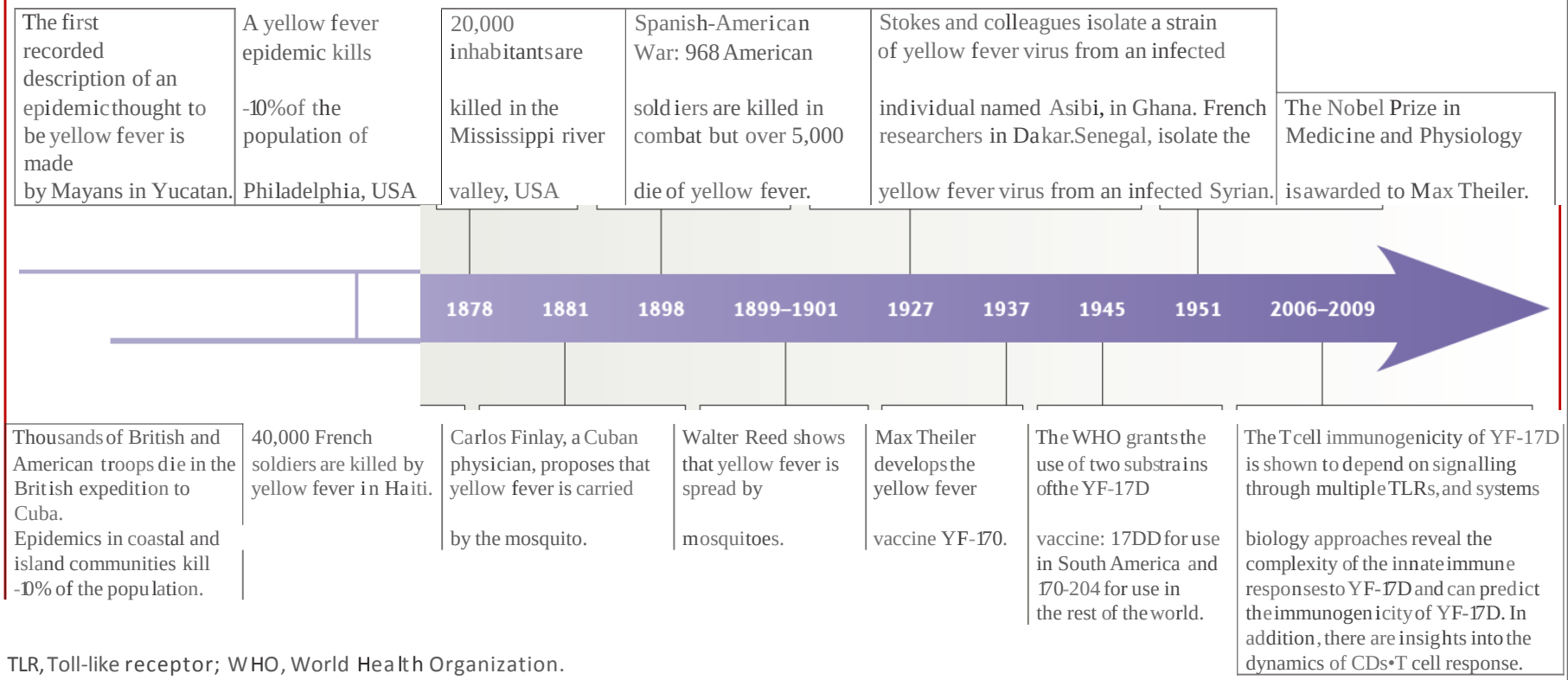
Timeline | **Events in the development and understanding of the YF-170 vaccine**



TLR, Toll-like receptor; WHO, World Health Organization.

Walter Reed Yellow Fever Commission

- Experiment summary
  - 14 non-fatal human challenge cases of YF produced
  - Transmission cycle revealed
  - Reed et al. publish results in JAMA, 1901
  - Army orders Gorgas to complete source reduction
  - In 90 days Havana is free of YF

Havana in 1900

Yellow Fever Virus

- Virus
  - Flavivirus (YF, JE, WNV, DENV)
  - 1 serotype
    - 5 genotypes within serotype

- Vector
  - Mosquito (*Aedes* spp.)

- Phylogenetic analyses
  - Evolved over 3000 yrs
  - YF virus originated in Africa
  - Divided into West and East African lineages
  - W. African lineage
    - Imported into S. America and New World

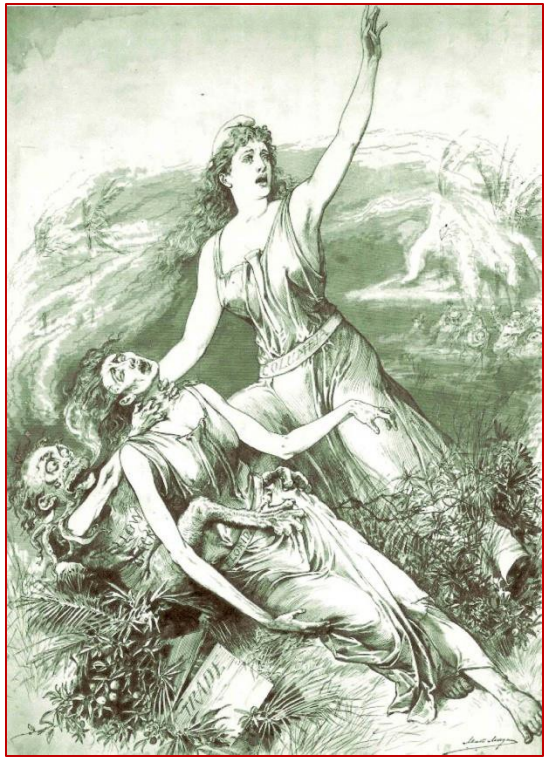
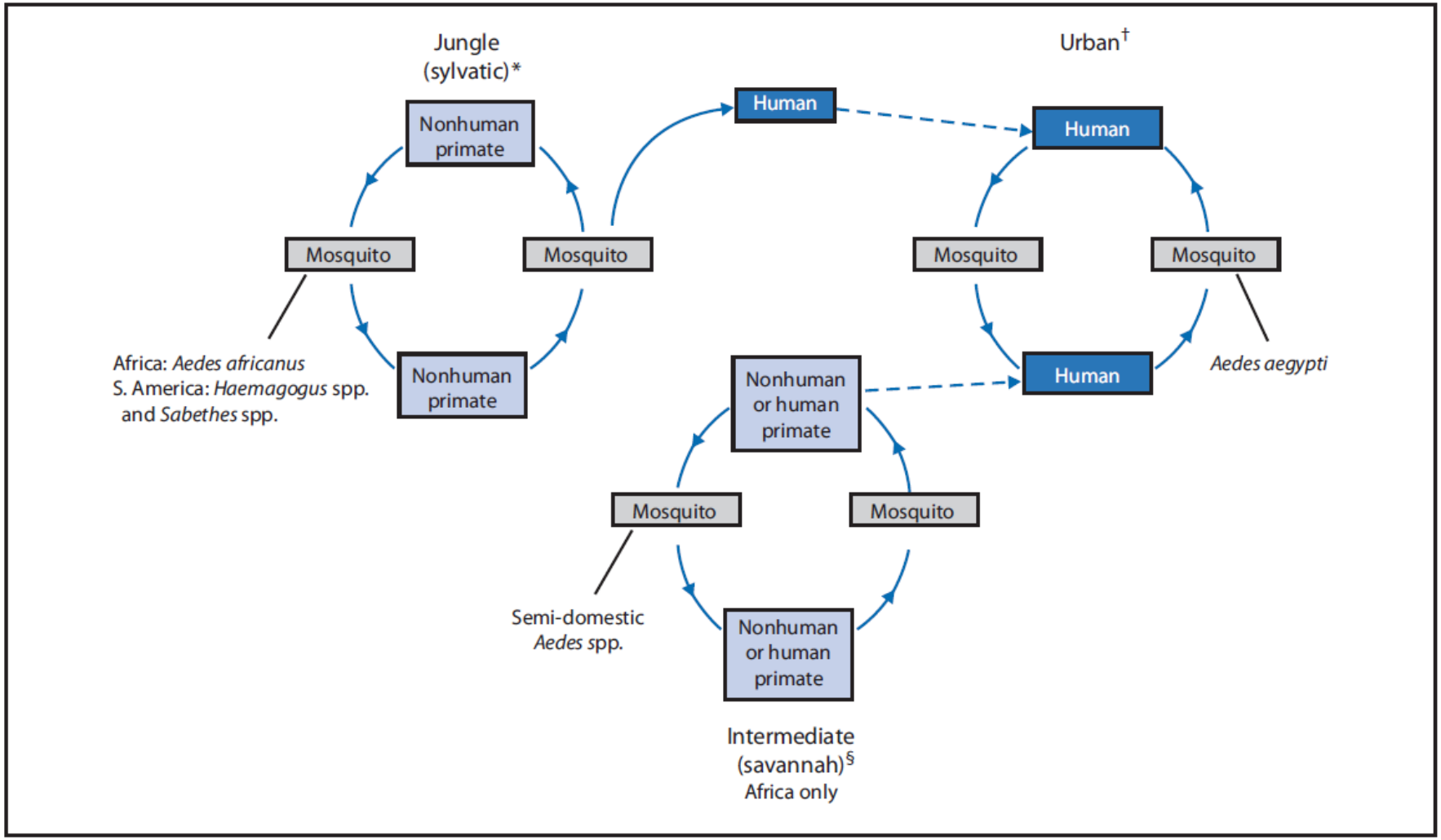


FIGURE 1. Transmission cycles for yellow fever virus



* The jungle (sylatic) transmission cycle involves transmission of the virus between nonhuman primates and mosquito species found in the forest canopy. The virus is transmitted via mosquitoes from nonhuman primates to human when the humans encroach into the jungle during occupational or recreational activities.

† The urban transmission cycle involves transmission of the virus between human and urban mosquitoes, primarily *Ae. aegypti*. Viremic humans traveling from one region to another can feed into and serve as a source of infection for mosquitoes in other transmission cycles (dotted line).

§ In Africa, an intermediate (savannah) cycle involves transmission of YFV from tree hole-breeding *Aedes* spp. to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from nonhuman primate to humans or from human to human via these mosquitoes.

Yellow Fever Risk Map

Figure 3: Areas with risk of yellow fever virus transmission in South America, 2010

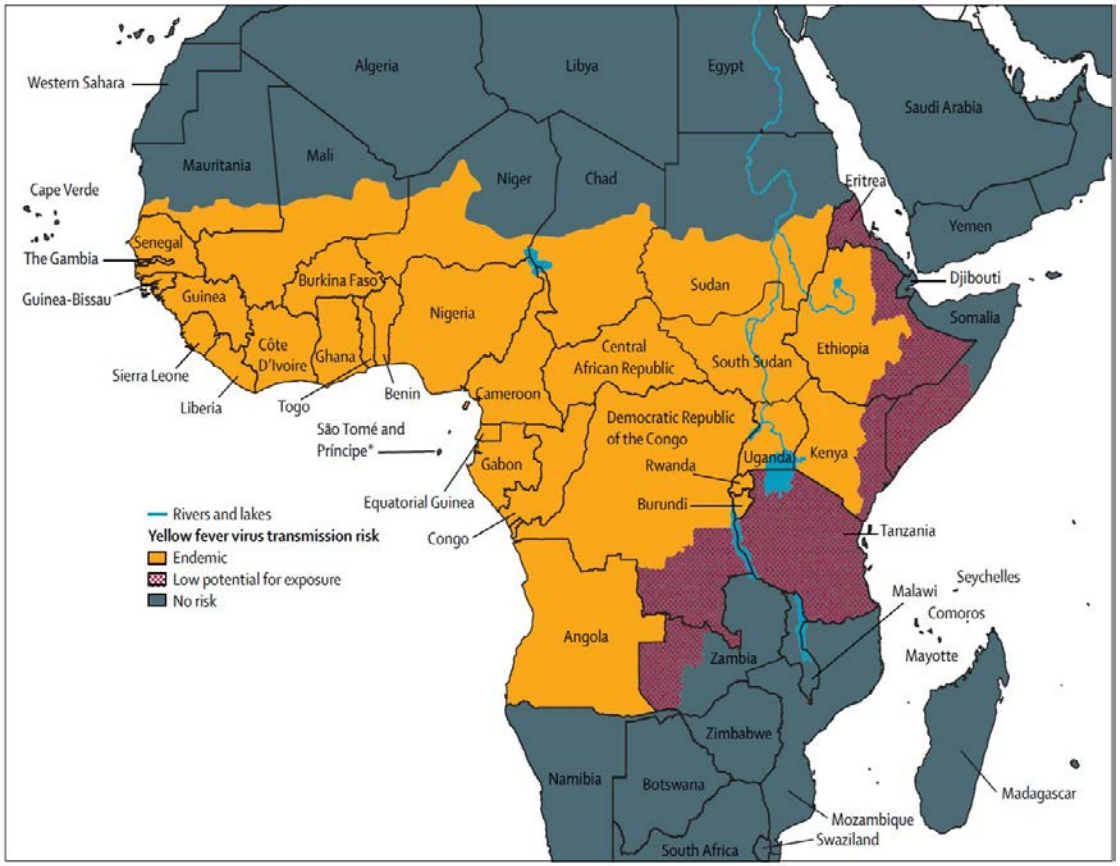


Figure 4: Areas with risk of yellow fever virus transmission in Africa, 2010
*São Tomé and Príncipe was classified as low potential for exposure.

Map is from the following publication: Jentes ES. Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 2011;11:622-32.

Disease Time-Course

- Incubation period: 3-6 days
- Symptoms for ~ 3 days (viremia)
- Defervescence and short term improvement (remission)
- Fever and symptoms return (intoxication)
- Improvement (convalescence)

Figure 5. Yellow fever patient during the period of infection. The patient is febrile and acutely ill, with prominent conjunctival congestion. During this pre-icteric phase, the illness is difficult to differentiate from many other infectious diseases. Virus is present in the blood and the patient is infectious for blood-feeding mosquitoes.

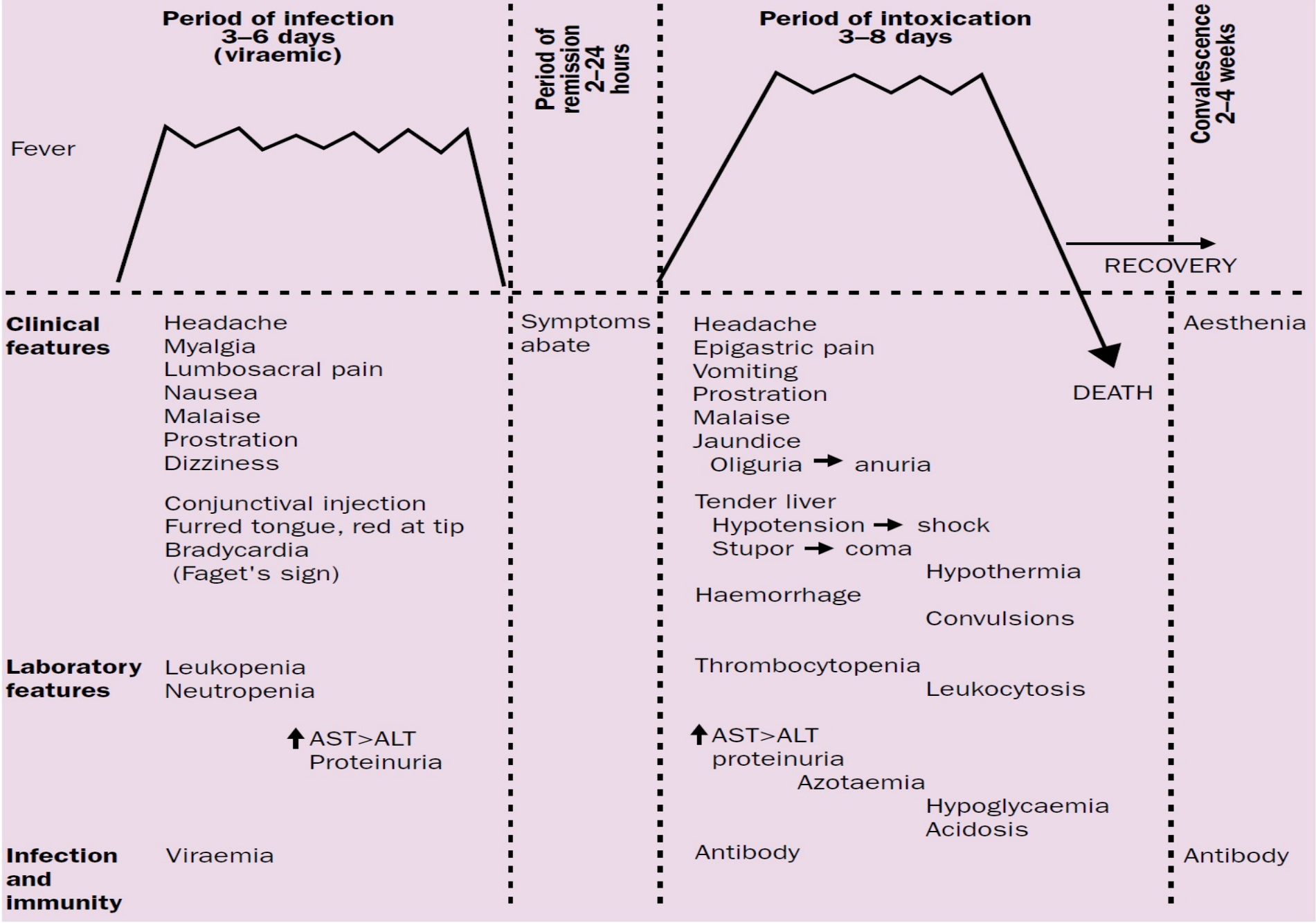


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

Diagnosis

- Clinical Diagnosis
  - h/o travel to endemic area within the incubation period

- Advanced Diagnostics:
  - Virus Isolation (culture)
  - Rapid Diagnostics
    - PCR
      - Remember the window period
    - Antibody or Antigen detection (ELISA)
      - IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
    - Neutralization Ab are more specific for YF

Treatment Overview

- Supportive Care -- no specific therapy
  - Maintain nutrition and prevent hypoglycemia
  - NG tube to prevent gastric distention
  - Treatment of hypotension (IVF, pressors)
  - Supplemental oxygen
  - Correction of bleeding abnormalities
  - Dialysis
  - Treatment of secondary infections
  - Treatment of DIC

Certain medications should be avoided, such as **aspirin or other non-steroidal anti-inflammatory drugs** (such as ibuprofen and naproxen), because these may increase the risk for bleeding

  - PROTECT FROM FURTHER MOSQUITO EXPOSURE

Yellow Fever Vaccine 17D

- Has remained in continuous use since 1936
  - Over 400 million doses given
  - Protects 90%/10 days, 99%/30 days

- Long-lasting immunity
  - Countries may require boosting every 10 years
  - Studies have shown neutralizing Ab decades after dose
    - 81% of US WWII veterans with Ab after > 30yrs

1. WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.
2. Poland JD, Calisher CH, Monath TP. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59:895-900.

Table 1. Yellow fever Vaccine contraindications and precautions

Contraindications	Age, <6 months
	Thymus disease or history of thymus disease
	Immunosuppression
Precautions	Age, 6-12 months
	Age, 60 years for first-time vaccinees
	Pregnancy
	Lactation
	Asymptomatic HIV infection with laboratory verification of adequate immune system function
	Hypersensitivity to eggs
	Hypersensitivity to gelatin
	Family history of adverse events associated with yellow fever vaccine

Yellow Fever Vaccine Reactions

- Common
  - Fever, Headache, body aches 5-10 days
  - Injection site inflammation 1-5 days

- Severe
  - Hypersensitivity reactions (including anaphylaxis)
  - YF vaccine-associated neurologic disease (YEL-AND)
  - YF vaccine-associated viscerotropic disease (YEL-AVD)

Yellow Fever Vaccine Reactions

Viscerotropic (hepatotropic) infection:

- transient viremia
- damage to liver, spleen, kidneys and heart
- hemorrhage
- in nature, occurs only in humans and non-human primates
- molecular mechanisms of infection type are poorly understood

Neurotropic infection:

- infects brain parenchyma and causes encephalitis
- in nature, occurs in susceptible rodents
- in "nature" wild-type viruses do not result in neurotropic disease
- can occur in primates when vaccine strain "reverts" to virulent phenotype→ Vaccine Associated Neurotropic Disease

Current Opinion in Immunology

Yellow Fever Vaccine Reactions

YEL-AND

- primary vaccinees
- 2 to 30 days post-vaccination
- fever (>101.5 °F > 24h) and headache (>24h duration)
- focal neurological dysfunction (aphasia, paresis, etc)
- mental status change
- new-onset seizure or recurrence
- CSF pleocytosis (> 5 WBC/mm^3) or elevated protein (>1.5 times normal)
- three distinct clinical entities
  - neurotropic disease
  - auto-immune CNS disease
  - auto-immune PNS disease
- recovery in 95% (CFR <5%)

YEL-AVD

- primary vaccinees
- 2 to 5 days post yellow fever vaccination
- fever, myalgia and arthralgia
- elevated liver enzymes and bilirubin, sometimes progressing to liver failure
- thrombocytopenia, lymphocytopenia
- rhabdomyolysis
- hypotension, requiring vasopressors
- renal failure, requiring dialysis
- respiratory failure, requiring intubation
- recovery in 40% (CFR > 60%), with higher CRF in women

Current Opinion in Immunology

Question

- A 43 yo male is traveling on business throughout Southeast Asia. He will be traveling for 3 weeks (August) staying in hotels located in major urban centers. Tourist activities are planned in rural areas in Northern Thailand, Viet Nam and Cambodia. Activities will include elephant treks, river rafting, and camping. A previous trip to the same region was abruptly cancelled 4 years ago. He recalls receiving 1 dose of a vaccine to prevent a "brain infection." He has no medical history. He has received all routine childhood vaccinations without adverse events. He has taken doxycycline for malaria prophylaxis in the past without adverse events.

- What is your guidance to the patient regarding Japanese encephalitis?

1. Nothing, he is going to non-endemic areas during a low risk period.
2. JE risk is high where he is travelling and during the period he is travelling, he should ensure use of personal protective measures (PPMs).
3. JE risk is high, he should receive the final 2 doses of the JE vaccine series he started 4 years ago.
4. ★ JE risk is high, he should receive a new, complete series of JE vaccine and use PPMs during his trip.

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, **Japanese encephalitis**, Tick Borne Encephalitis, Powassan, Rio Bravo, Saint Louis Encephalitis, West Nile Virus, Yellow fever, Zika virus
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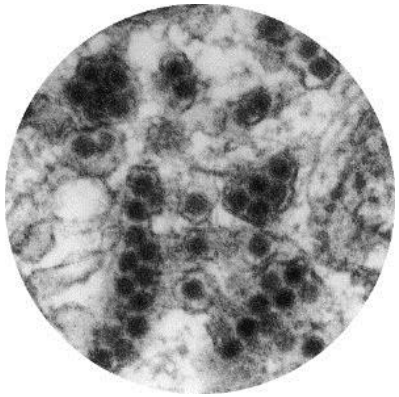


JE Virus

Japanese Encephalitis

- Virus
  - Family Flaviviridae, Genus Flavivirus
- Most common viral encephalitis etiology worldwide
  - 160,000 cases 1966, 16,000 in 1996 (vaccination)
- Risk of Encephalitis following infection
  - ~1/200 in indigenous pop.; ~1/25-50 in foreign born
- Primarily a disease of children
  - Naïve adults at similar risk (i.e., travelers, military)
- Disease has high mortality, morbidity
  - CFR ~25 -30%
  - Long-term neuropsychiatric disability 45 - 50%

Transmission

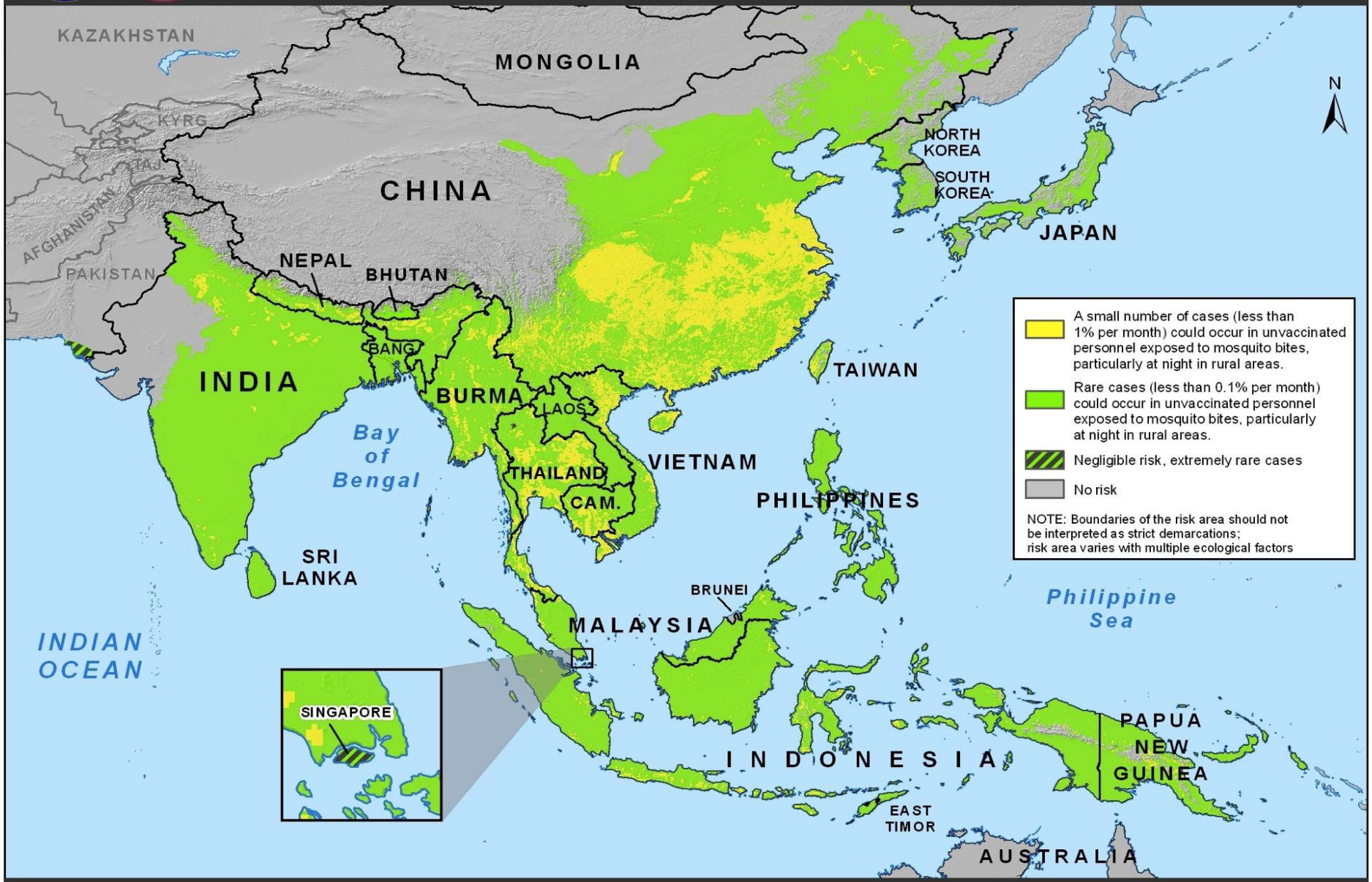
- Vector: *Culex* mosquitoes
  - *Culex tritaeniorhynchus*
    - Breeds in marshes, rice paddies
    - Night-biting

- Zoonotic amplification
  - Domestic pigs
  - Migratory waterfowl

- Seasonal/climate factors
  - Summertime / post-rainy season
    - Increased vector number
    - Increased feeding behaviors
    - Increased viral replication

Japanese Encephalitis

PACOM: Japanese Encephalitis Risk to U.S. Forces



22 May 2013 • DIA-NCMI

Source: NGA Coordinate System: WGS84

Boundary representation is not necessarily authoritative

Clinical Findings

- Incubation period 4 – 14 days
- Earliest symptoms
  - Lethargy, fever, headache, abdominal pain, N & V
- Over several days
  - Lethargy >, agitated delirium, unsteadiness, and abnormal motor movements → somnolence / coma
- Some have sudden convulsion after a brief febrile illness

Clinical Findings

- High fever and altered consciousness
  - Mild disorientation, subtle personality change, severe state of confusion, delirium, and coma
- Nuchal rigidity is a variable finding (1/3 – 2/3 of cases)
- CN palsies, facial paralysis, disconjugate gaze (1/3 of cases)
- Muscular weakness
  - Distributions of flaccid / spastic paralysis
  - Hemiparesis
  - Increased or decreased tone
  - Generalized or asymmetrical

Clinical Findings

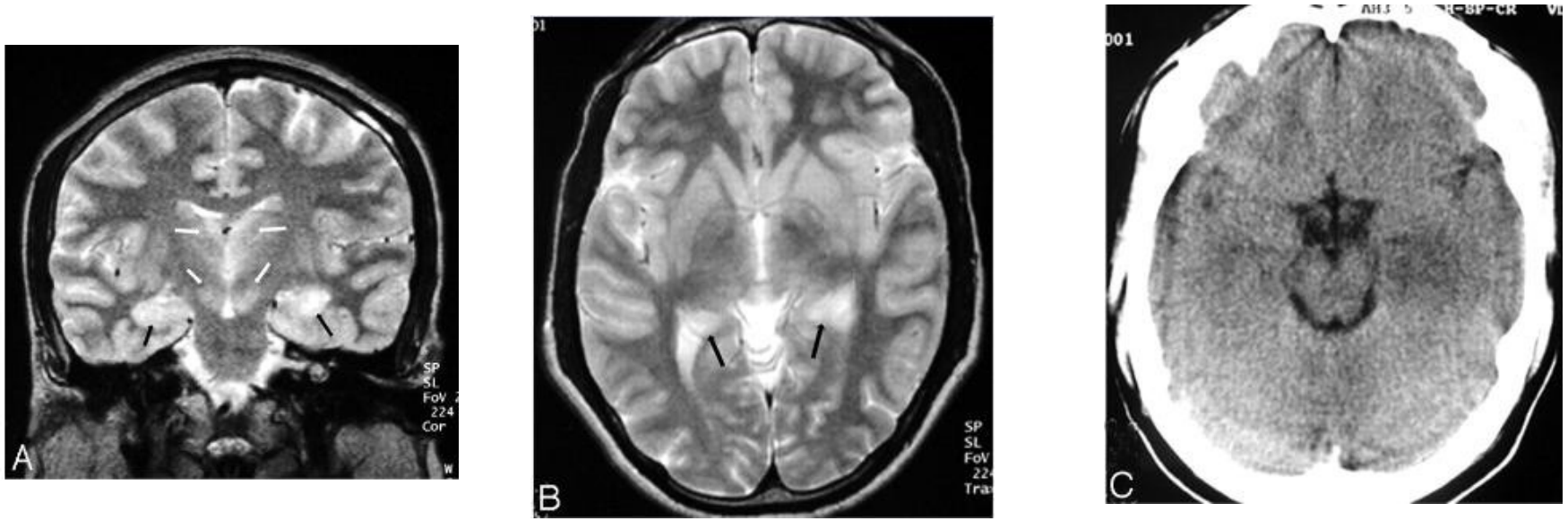
- Hyperreflexia, ankle clonus, and other abnormal reflexes
- Disordered movements
  - Flailing, ataxia, tremor, choreoathetosis, rigidity, masked facies, and other extrapyramidal signs
- Seizures
  - Focal or generalized
  - 85% peds
  - 10% adults

Lab and Imaging

- Peripheral leukocytosis, up to 30k/mm^3 with a left shift
- Hyponatremia
- CSF
  - Opening Pressure > in ~ 50%
  - Pleocytosis <10 to several thousand cells (lymphocytic)
  - Protein may be normal or elevated up to 100 mg/dL
- EEG
  - Diffuse slow waves (theta or delta), seizure activity, periodic lateralized epileptiform discharges (PLEDS)
- EMG
  - Chronic partial denervation, anterior horn cell destruction

Lab and Imaging

- Imaging
  - Diffuse white matter edema and abnormal signals
  - Thalamus, basal ganglia, cerebellum, midbrain, pons, cord



A, Coronal T2-weighted image, bilateral hippocampal body involvement (*black arrows*). Note bilateral thalamic and substantia nigra involvement (*white arrows*).; ***B***, Axial T2-weighted image shows bilateral hippocampal tail involvement (*arrows*).; ***C***, Axial CT scan done at the same time as *A* and *B* shows hypoattenuated left mesial temporal lobe lesion. Note resemblance to Herpes simplex virus encephalitis.

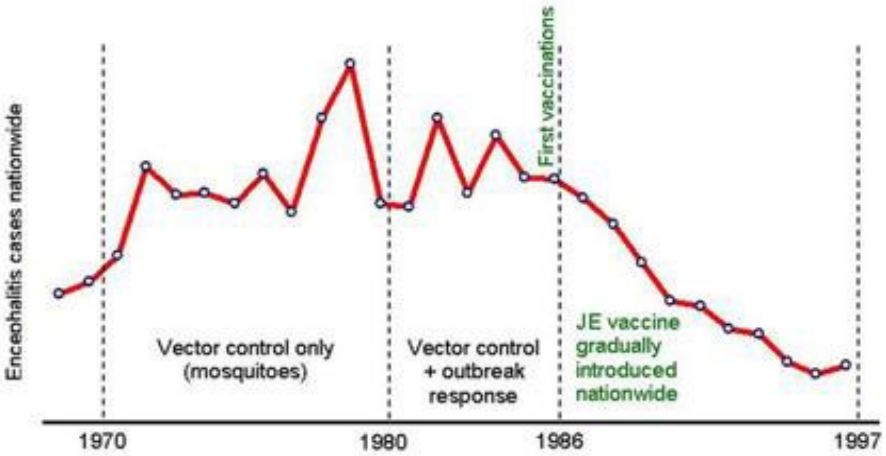
Handique S et al. AJNR Am J Neuroradiol 2006;27:1027-1031

Prevention

- Vector control – difficult in endemic regions
  - Twilight-biting, marsh-breeding mosquitoes
  - Impractical, historically ineffective

- Reservoir control – difficult in endemic regions
  - Swine
    - Segregation impractical
    - Vaccination expensive

- Vaccination
  - Mass pediatric vaccinations



Source: Ministry of Health, Thailand, 1998

JE Vaccines

- Live, attenuated SA 14-14-2 vaccine
  - Produced and used successfully in China for > 20 years
- Inactivated vero-cell derived JEV (Biken, Kaketsuken)
  - Inactivated Beijing JEV grown on Vero cells
- ChimeriVax-JE vaccine (Acambis/sanofi pasteur)
  - Live, recombinant vaccine (based on Yellow Fever 17D)
- Ixiaro (Intercell/Novartis/Biological E)
  - Inactivated vaccine
  - Derived from SA-14-14-2 JEV cultured in Vero cells
  - 2 doses at day 0 and day 28
  - Licensed in US for adult use 2009
  - US licensure for pediatric use, May 2013

IXIARO®
Manufacturer's FDA-approved labeling

- Indication: 2 months of age and older
- Dosing
  - 0.5 mL single dose syringes
  - 2 months to <3 years of age, a single dose is 0.25 mL
  - 3 years of age and older, a single dose is 0.5 mL
- Contraindications
  - Severe allergic reaction (e.g, anaphylaxis) after a previous dose of IXIARO, any other JE vaccine, or any component of IXIARO, including protamine sulfate
- Adverse Events
  - Injection-site pain (15%), redness (15%), fever (>10-20%), irritability (>15%), diarrhea (>10%), headache (>20%) and myalgia (>10%)

IMMUNIZATION SERIES

Complete the primary immunization series at least 1 week prior to potential exposure to JEV.

BOOSTER DOSE

ADMINISTRATION

IXIARO is administered intramuscularly. Do not administer intravenously, intradermally, or subcutaneously. Preferred site for intramuscular injection is as follows:

2 MONTHS TO <3 YEARS	2 MONTHS TO <17 YEARS	2 TO 11 MONTHS
Primary immunization with IXIARO consists of two (2) 0.25 mL doses, administered 28 days apart.	The safety and immunogenicity of a booster dose has not been evaluated.	The anterolateral aspect of the thigh
≥3 YEARS	**≥17 YEARS**	**1 TO <3 YEARS**
Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.	If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.	The anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate)
		≥3 YEARS
		The deltoid muscle

https://www.novartisvaccinesdirect.com/Ixi aro/IxiaroDosingAdministration

THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON WASHINGTON**, DC 20301-1200**

HEALTH AFFAIRS

MAY 07 2013

"**Risk determination, therefore, must take into account human activities and the proximity of high-risk areas rather than broad geographic risk determinations**. The following guidelines should be used for administration of the JE vaccine:

1.Individuals **deploying to areas in Pacific Command (PACOM)** should be administered the JE vaccine in accordance with the latest **PACOM Force Health Protection Guidance.**

2.We advise and highly recommend JE vaccine for Service members, Department of Defense civilians, and beneficiaries who are, or will be, stationed or visiting for more than 30 days in endemic areas. This includes those who would be based in urban areas, but likely to visit endemic rural or agricultural areas during a high-risk period of JE transmission. Administer booster dose after 1 year according to the ACIP recommendations if risk of exposure continues. Timing of additional booster doses has not yet been determined."

THE ASSISTANT SECRETARY OF DEFENSE
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HEALTH AFFAIRS **MAY 07 2013**

"3. We advise recommendation of JE vaccine for the following Service members and beneficiaries:

- Short-term (<1 month) travelers to endemic areas during the JE transmission season if they plan to travel outside of an urban area and have an increased risk for JE exposure.
  1. spending substantial time outdoors in rural or agricultural areas, especially during the evening or night;
  2. participating in extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming); and
  3. staying in accommodations without A/C, screens, bed nets.
- Travelers to an area with an ongoing JE outbreak;
- Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel; and
- Laboratory workers with potential exposure to infectious JE virus."

Question

- A 52-year-old female had malaise and rash after a 9-day business trip to Jakarta, Indonesia;. Symptoms included fatigue and non-specific malaise, followed by headache. On day 4, a maculopapular rash developed (trunk, back, and limbs). The rash was accompanied by generalized myalgia, some loose bowel movements, and an occasional dry cough. She did not develop sweats or rigors. Examination on day 5 showed mild bilateral conjunctivitis, rash, but no lymphadenopathy or tenosynovitis. You treat her symptoms. During a follow up visit on day 7 she reports her husband has become ill with a similar syndrome.

- What is your leading differential diagnosis?
  A. Dengue
  B. Chikungunya
  C. Ross River
  ⭐ D. Zika virus
  E. Leptospirosis

Arboviruses

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    - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus

Zika Virus

- ZIKV (Zika Virus) is a *Flavivirus* (family Flaviviridae) same family as WNV, YFV, JEV and the Dengue viruses.
- Isolated in 1948 from a rhesus monkey
  - Zika forest, near Entebbe, Uganda
- Transmitted to humans by infected mosquitoes

  - Aedes africanus, luteocephalus, aegypti, others (MAY HAVE CROSSED OVER TO CULEX)
- Can be vertically transmitted (mother to fetus during pregnancy)
- On rare occasions, the virus might be transmitted through **contaminated blood products** or **might be transmitted through sexual intercourse** (evidence is insufficient. Currently only 3 *documented* cases of Zika virus being detected in a man's semen and transmitted to his sexual partner). It is still recommended for men that have had the Zika virus to **not have unprotected sex** for at least several months)

References: COL Stephen Thomas, MD, WRAIR Deputy Commander; Dr. Weaver, director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch in Galveston

Zika Virology

Flavivirus from the Latin word *flavus* meaning yellow; reflecting the jaundice seen with Yellow fever

FAMILY: *FLAVIVIRIDAE,*

Genus: *Flavivirus*

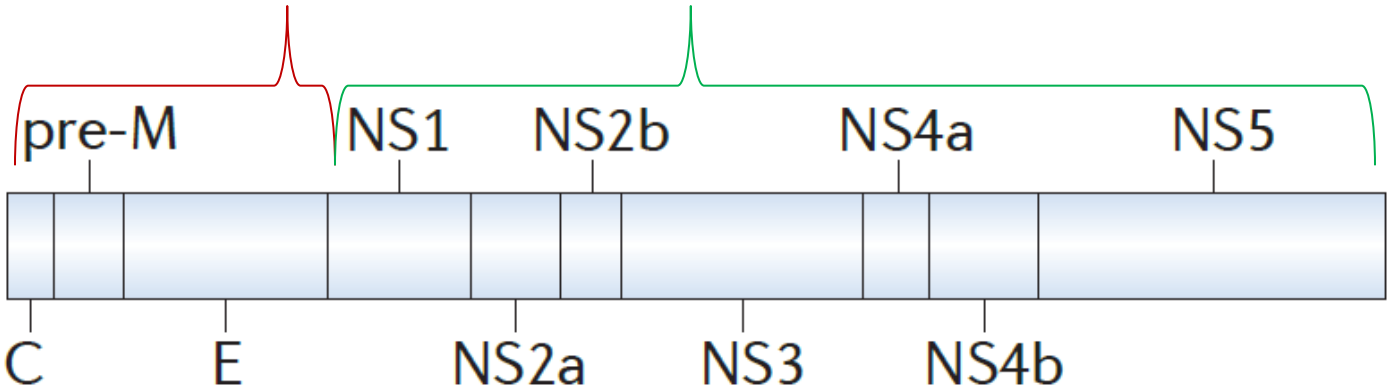
Species: Zika virus (ZIKV)

Antigenic complex: Spondweni

RNA, icosahedral, enveloped, + single-stranded

10794kb genome, 500Å diameter

Genome: 3 structural & 7 non-structural proteins



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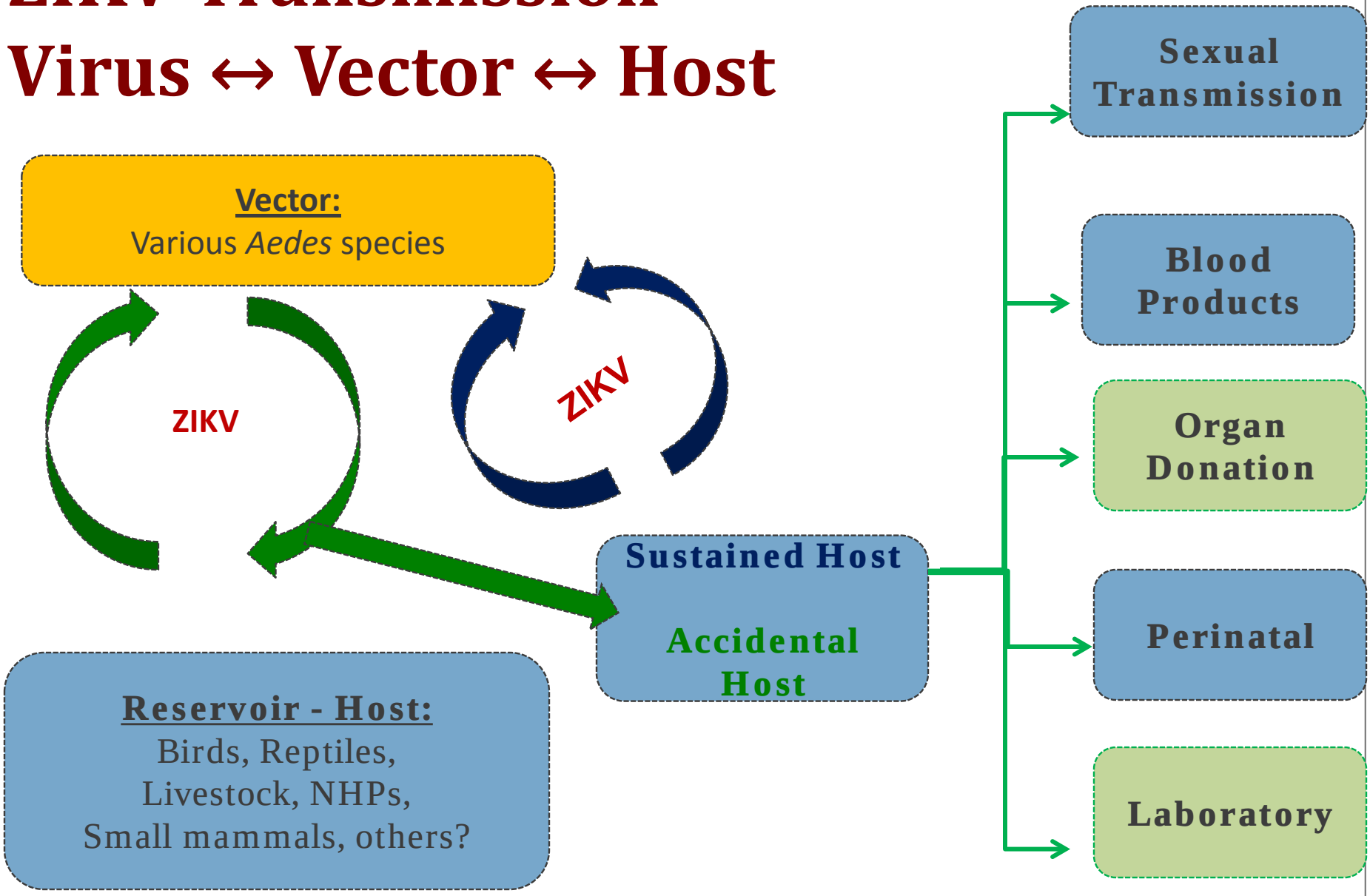
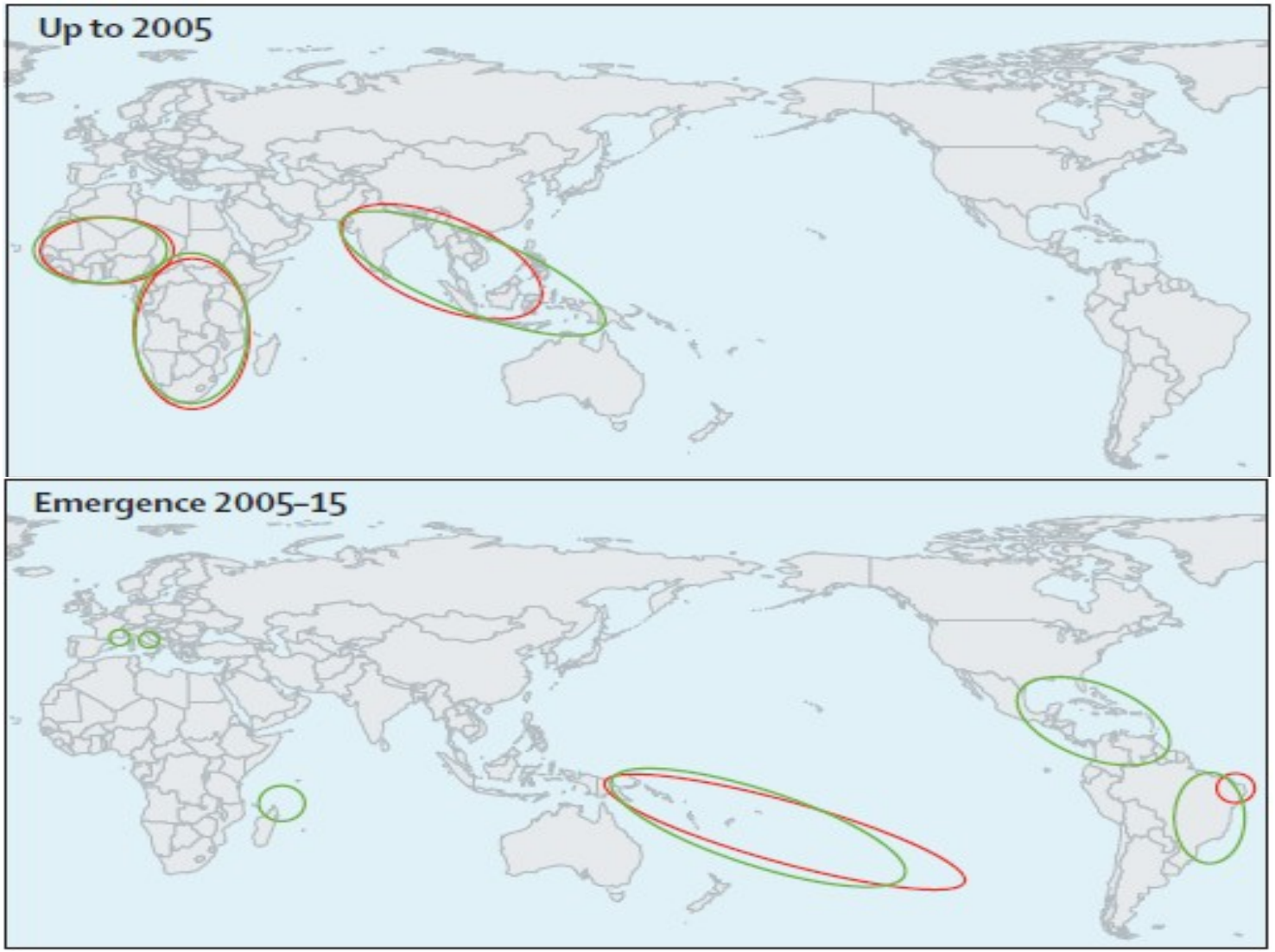
ZIKV Transmission
Virus ↔ Vector ↔ Host



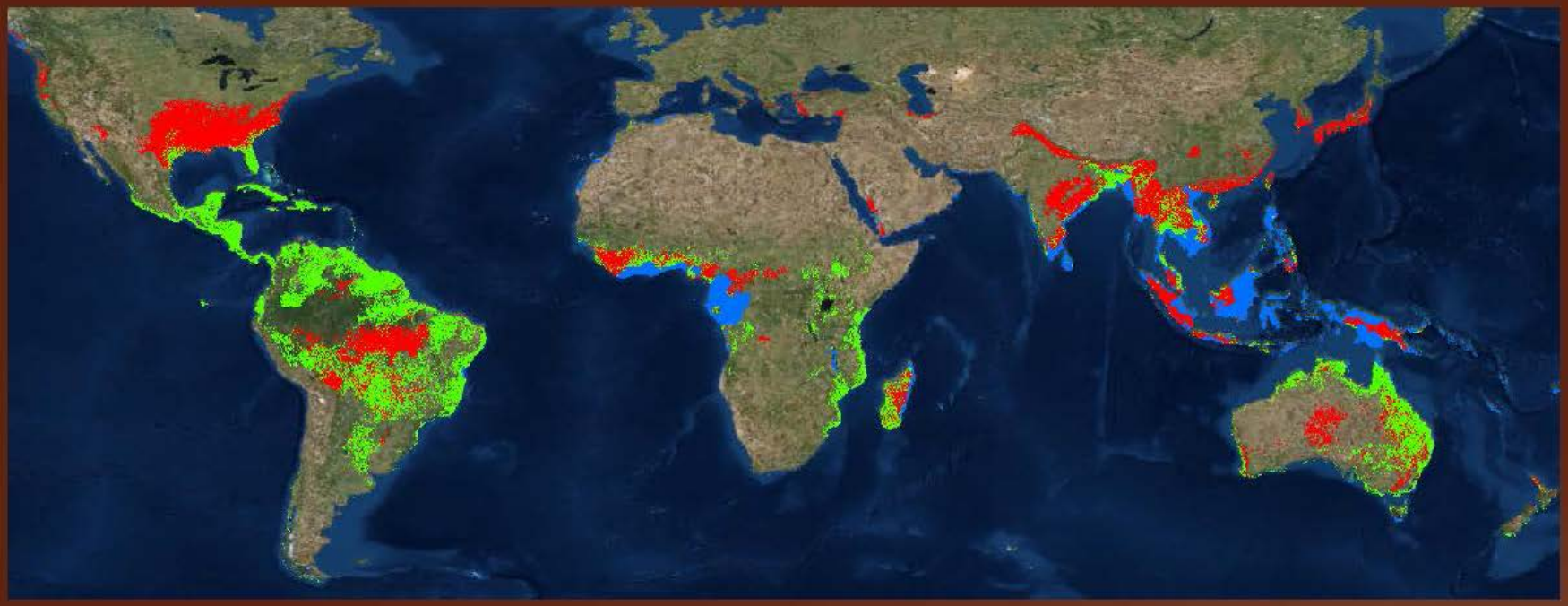
Zika virus: following the path of Dengue and Chikungunya?

Also Hawaii and Guam



Didier Musso et al. The Lancet Volume 386, No. 9990, p243–244, 18 July 2015

Zika Vector Distribution: Global

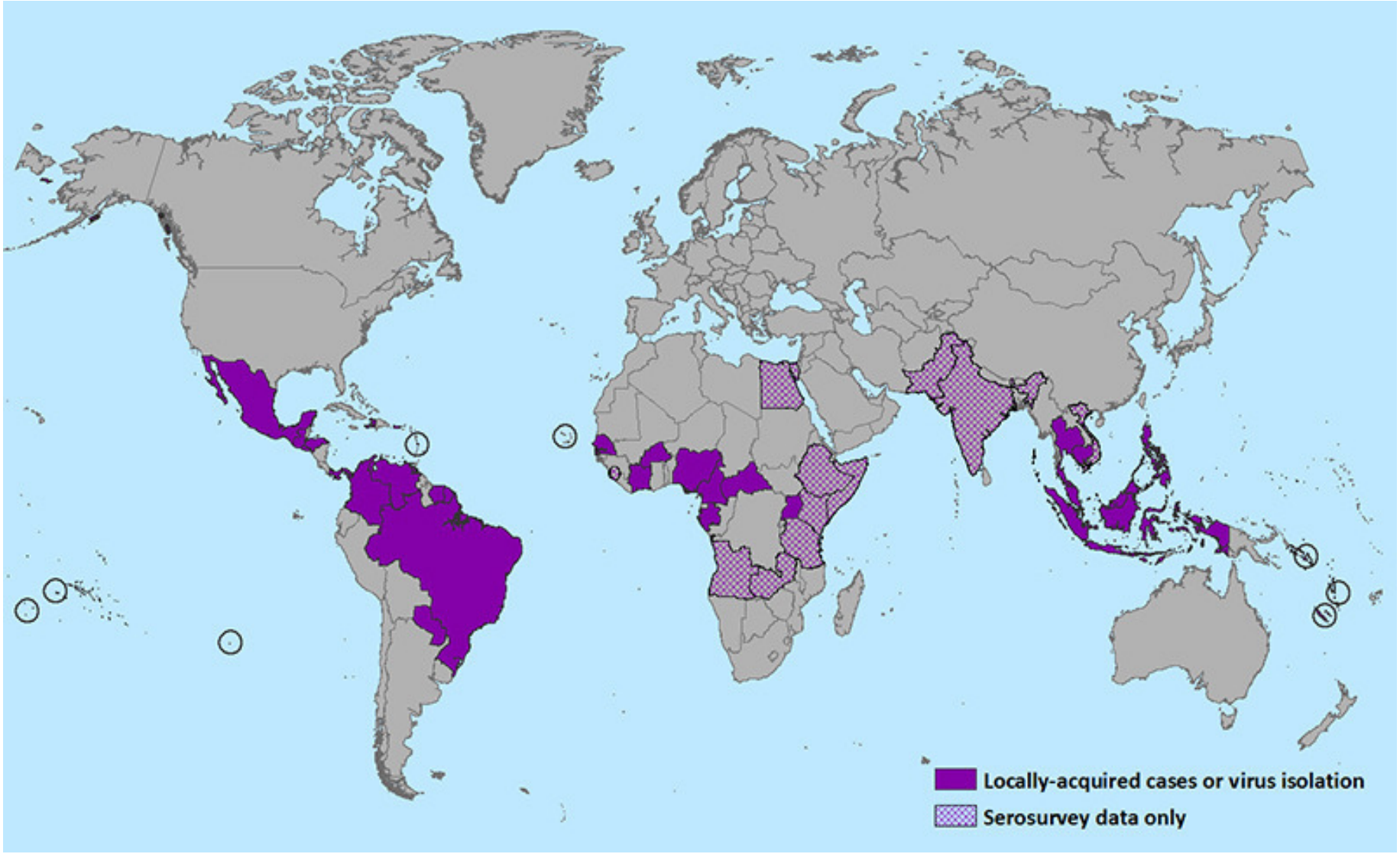


Predicted range of *Ae. albopictus* (maxent model: Dornak, 2011)

Predicted range of *Ae. aegypti* (maxent model: Nyari, 2011)

Predicted range of *Ae. polynesiensis* (maxent model: Dornak, 2011)

Zika Virus



© JAN 2016 CDC

Probable Non-Vector-borne Transmission of Zika Virus, Colorado, USA

Brian D. Foy, Kevin C. Kobylinski, Joy L. Chilson Foy, Bradley J. Blitvich,
Amelia Travassos da Rosa, Andrew D. Haddow, Robert S. Lanciotti, and Robert B. Tesh

Figure. Maculopapular rash on patient 3 infected with Zika virus, Colorado, USA.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 2, February 2015

Potential Sexual Transmission of Zika Virus

- **TAHITI, DECEMBER**

  -44yo male with two clinical episodes c/w ZIKV infection;

  -Hematospermia 8 weeks following 2nd episode.

  -Semen samples

  - 2.9×10^7 and 1.1×10^7 copies/mL
  - Replicative ZIVK particles identified

  -Urine

  - 3.8×10^3 copies/mL

  -Blood

  - Undetectable by rRT-PC

EMERGING INFECTIOUS DISEASES®

Detection of Zika Virus in Semen Volume 22, Number 5—May 2016

PORTON DOWN, UNITED KINGDOM, 2014

- 68 yo male, Zika illness after returning from Cook Is.
- rRT-PCR test result for ZIKV was positive (Ct – 35)
- Convalescent-phase serum, urine, and semen
  - Semen was positive for ZIKV by rRT-PCR
  - 27 and 62 days after onset of febrile illness
  - Ct - 29 and 33 cycles
  - ZIKV-specific PRNT were positive (convalescent)

Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014

Euro Surveill. 2014;19(14):pii=20761.

1,505 BLOOD DONORS WERE TESTED

42 (2.8 %) were confirmed positive by individual testing

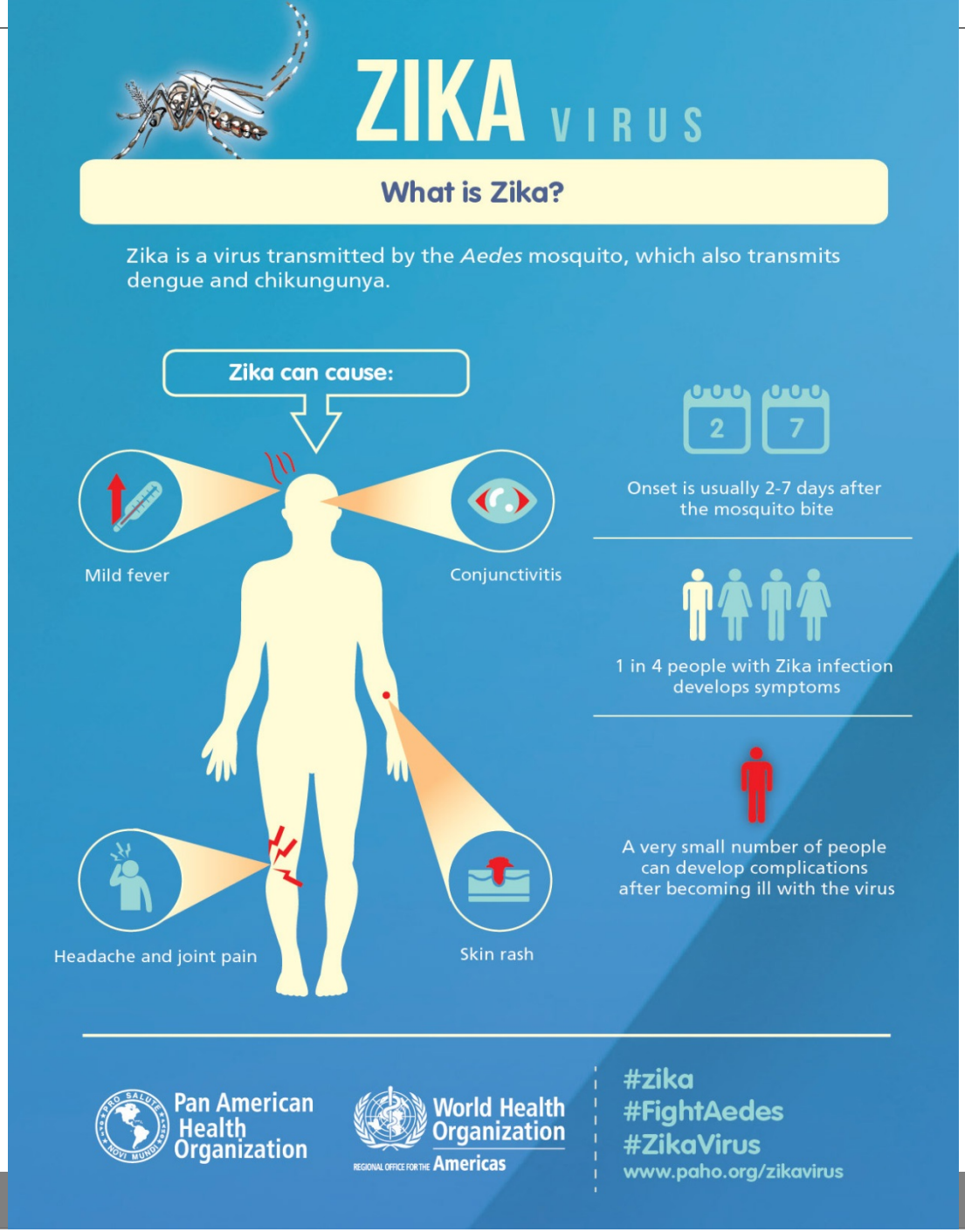
THE TWO SEQUENCED SAMPLES WERE CONFIRMED AS ZIKV

GenBank: KJ680134 and KJ680135

99.6% similarity with the outbreak sequence

42 DONORS TESTED POSITIVE BY RT-PCR

11 declared that they had a Zika fever -like syndrome from 3-10 days after they gave blood


ZIKA VIRUS
What is Zika?
Zika is a virus transmitted by the *Aedes* mosquito, which also transmits dengue and chikungunya.
Zika can cause:
Mild fever
Conjunctivitis
Headache and joint pain
Skin rash
2
7
Onset is usually 2-7 days after the mosquito bite
1 in 4 people with Zika infection develops symptoms
A very small number of people can develop complications after becoming ill with the virus
Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas
#zika
#FightAedes
#ZikaVirus
www.paho.org/zikavirus

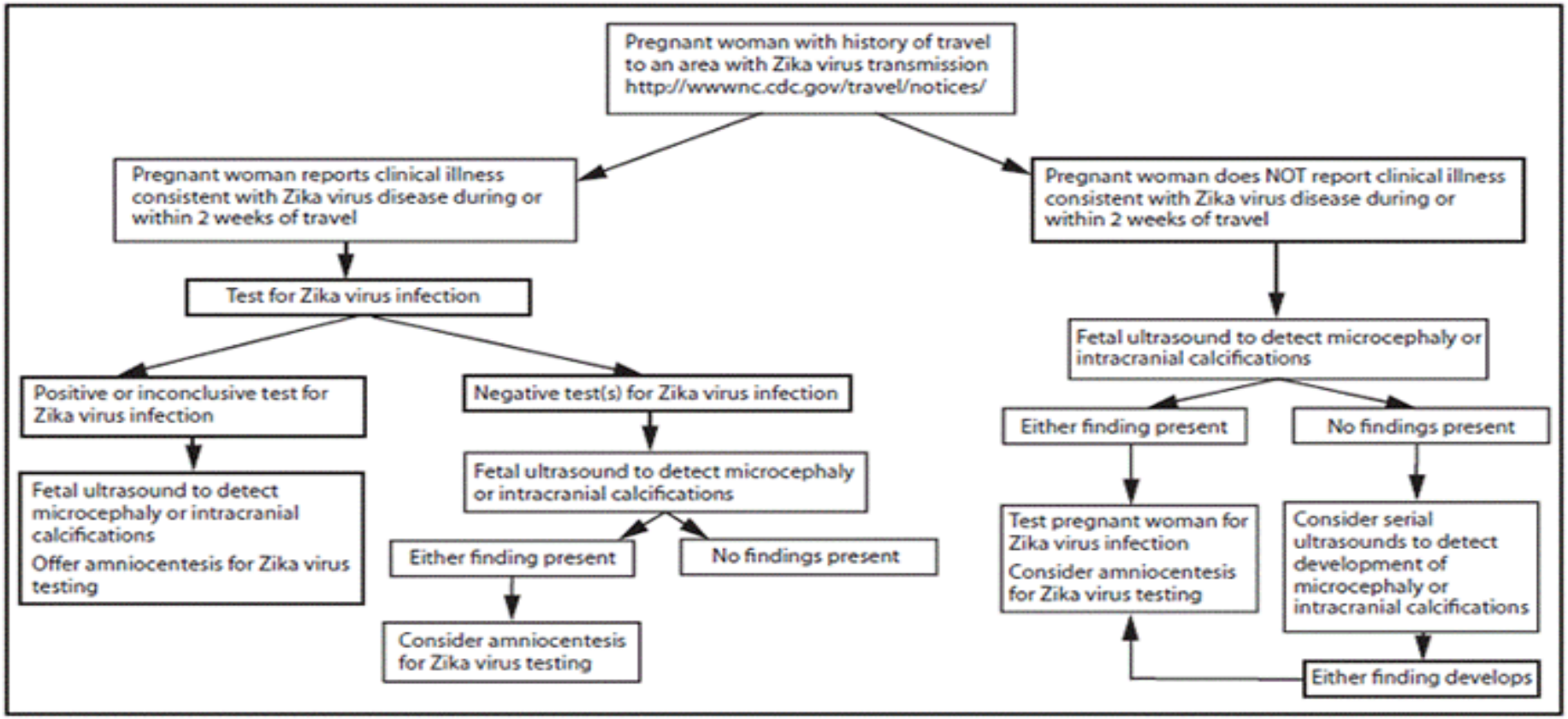
Zika Virus

- Diagnosis
  - Travel to known area of transmission
  - Compatible clinical syndrome
  - Serology (cross reactivity with dengue)
    - IgM ELISA
    - Neutralizing antibodies
  - Molecular
    - RT-PCR
    - Sequencing

Testing IS NOT RECOMMENDED in asymptomatic pregnant women who have traveled to a country with known transmission because there can be false-positive results due to antibodies that are made against other related viruses and the risk to the fetus is not know if the mother tests positive for Zika virus antibodies (© CDC JAN 2016).

The CDC has a comprehensive guidance on their website regarding ZIKV diagnostic testing (http://www.cdc.gov/zika/hc-providers/diagnostic.html).

Interim guidance: testing algorithm*,†, for a pregnant woman with history of travel to an area¶ with Zika virus transmission, with or without clinical illness** consistent with Zika virus disease



*Availability of Zika virus testing is limited;Tests include Zika virus reverse transcription-polymerase chain reaction (RT-PCR) and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. Given the overlap of symptoms and endemic areas with other viral illnesses, evaluate for possible dengue or chikungunya virus infection. a virus RNA by RT-PCR.>

American College of Obstetricians and Gynecologists. Immunization for women. Available at: http://www.immunizationforwomen.org.
American College of Obstetricians and Gynecologists. Zika virus updates. Available at: http://immunizationforwomen.org/providers/Zika-Virus-Updates. Retrieved January 20, 2016.

Zika Virus

- Prevention
  - No vaccine or prophlyactic drug (although a number of groups are working to develop potential candidates).
  - PPMs and vector avoidance

- Treatment
  - Supportive
  - Close resemblance to dengue on presentation likely warrants avoidance of NSAIDS and aspirin until Dx
  - Possible human to human transmission- requires sexual intimacy counseling

Zika Virus

According to the CDC, **outbreaks of Zika** have currently been registered in Brazil, Colombia, El Salvador, French Guiana, Guatemala, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Suriname, Venezuela and Puerto Rico. (21 January 2016)

The CDC has issued a "watch" advisory for Thailand, Cambodia, Indonesia, Malaysia, the Philippines and Maldives, and an "alert" advisory for Central and South America and the Caribbean.

Until more is known, CDC recommends **special precautions** for pregnant women and women trying to become pregnant to reduce the risk of microcephaly, including restricted travel.

Pregnant women and women who are breastfeeding **can and should** use an **EPA-registered insect repellent**.

Zika Virus

CDC has put out a *notice* following reports in Brazil that babies have been born with suspected **microcephaly** or abnormally small heads or other birth defects from mothers who were infected with **Zika virus while pregnant**. Further *studies are needed* to characterize this relationship. (CDC 2016).

NO DEFINITIVE CONNECTION
But TAKE PRECAUTIONS

The relationship seems plausible due to the temporal and spatial association between outbreaks of Zika and microcephaly.
According to a preliminary analysis of research carried out by Brazilian authorities, the greatest risk of microcephaly and malformations appears to be associated with infection during the first trimester of pregnancy (PAHO/WHO 2016).
Transmission of Zika to the fetus has been documented in ALL trimesters (ACOG, 2016).

A case has also been reported in Hawaii and Puerto Rico

The Zika virus

An unprecedented outbreak of the mosquito-borne virus that appears to cause neurological complications, currently circulating in Latin America and the Caribbean

Active cases
Past 9 months
27 countries recording local transmissions
As of January 19

• *Imported cases reported*

El Salvador

Brazil

First case on Latin American mainland was in May 2015

In most infected people Zika only causes short-lived flu-like symptoms

Usually lasts less than week

70 - 80 percent of cases go unnoticed

First identified in a monkey in **Uganda** 1947

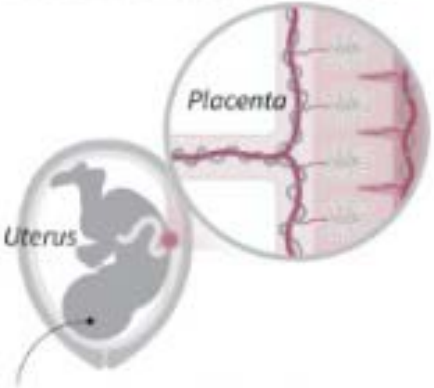
First human case 1952

Before 2015 occurred in Africa, SE Asia, Pacific Islands

- Spread by the mosquito *aedes aegypti*
- Person-to-person transmission not proven
- Cases of possible sexual transmission under investigation

Microcephaly link

Scientists are investigating an alarming rise in microcephaly cases in Zika-affected countries

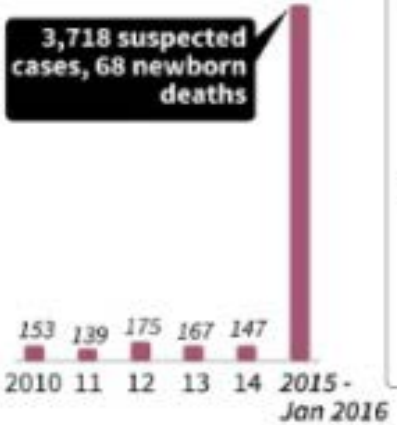


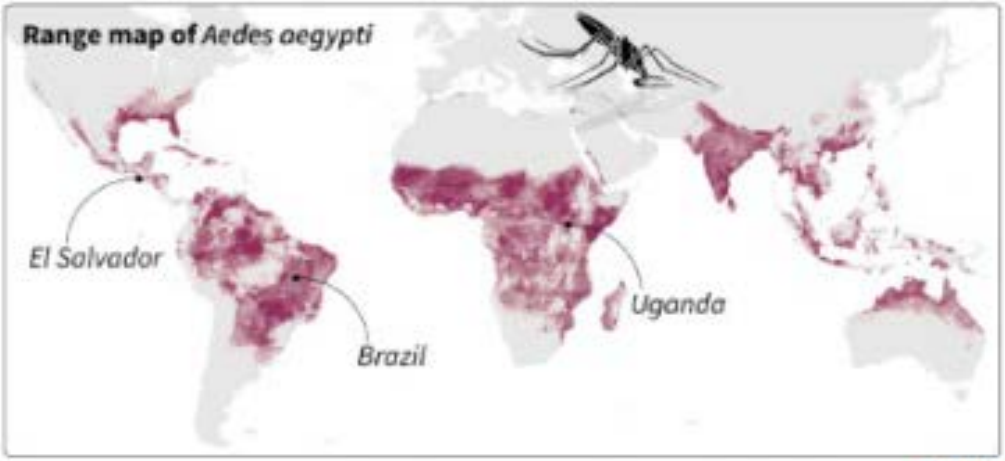
Abnormally small head. Can cause death, or cognitive and psychomotor disabilities

Neurological link

- Possible rare link to **Guillain-Barre syndrome (GBS)**
  - Attacks nervous system, can cause paralysis, death
- **El Salvador caseload of GBS**
  - *Normal monthly average* 14
  - *December 1 - January 6* 46

Rise of microcephaly in Brazil

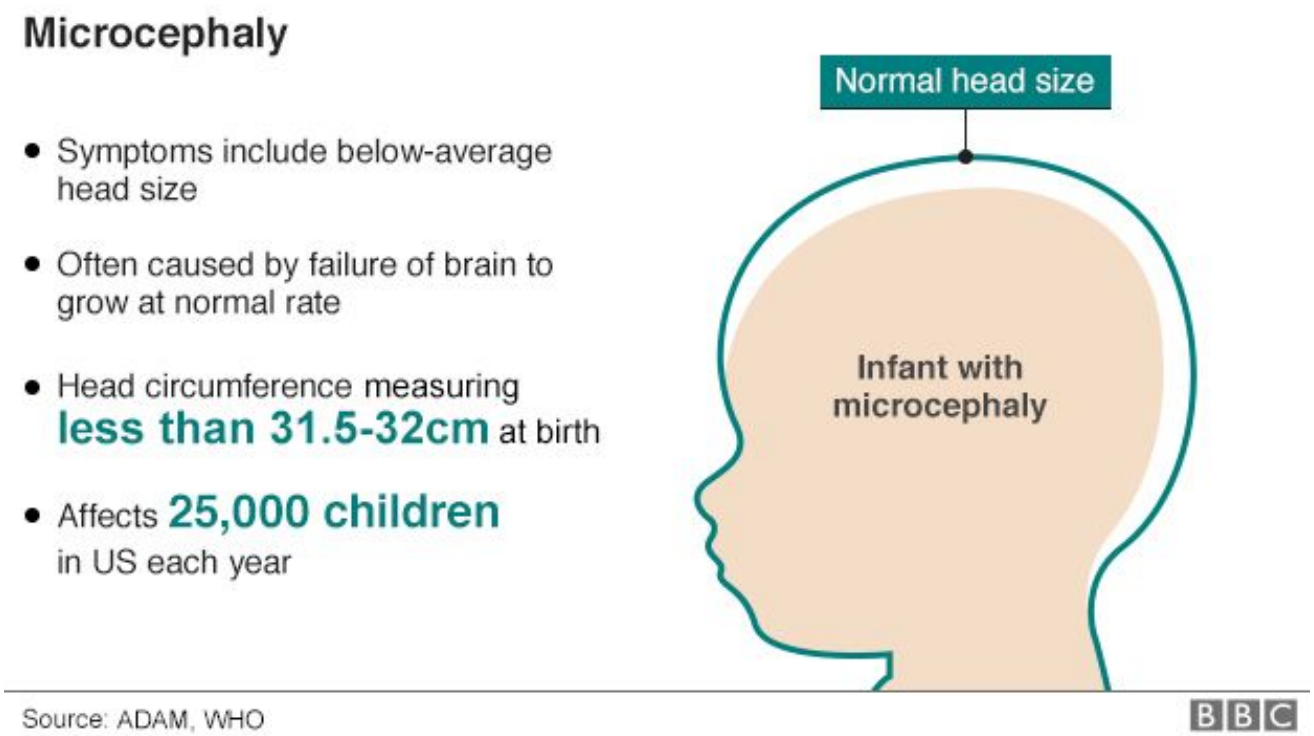




Source: WHO/SEEG/CDC/Ecdc.Europa.eu/BrazilHealth

AFP

Zika Virus



Microcephaly is a birth defect where a baby's head is smaller than expected when compared to babies of the same sex and age. Babies with microcephaly often have smaller brains that might not have developed properly.

National Birth Defects Prevention Network. Major birth defects data from population-based birth defects surveillance programs in the United States, 2006-2010. Birth Defects Research (Part A): Clinical and Molecular Teratology. 2013;97:S1-S172.

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on February 10, 2016, at NEJM.org.

BRIEF REPORT

Zika Virus Associated with Microcephaly

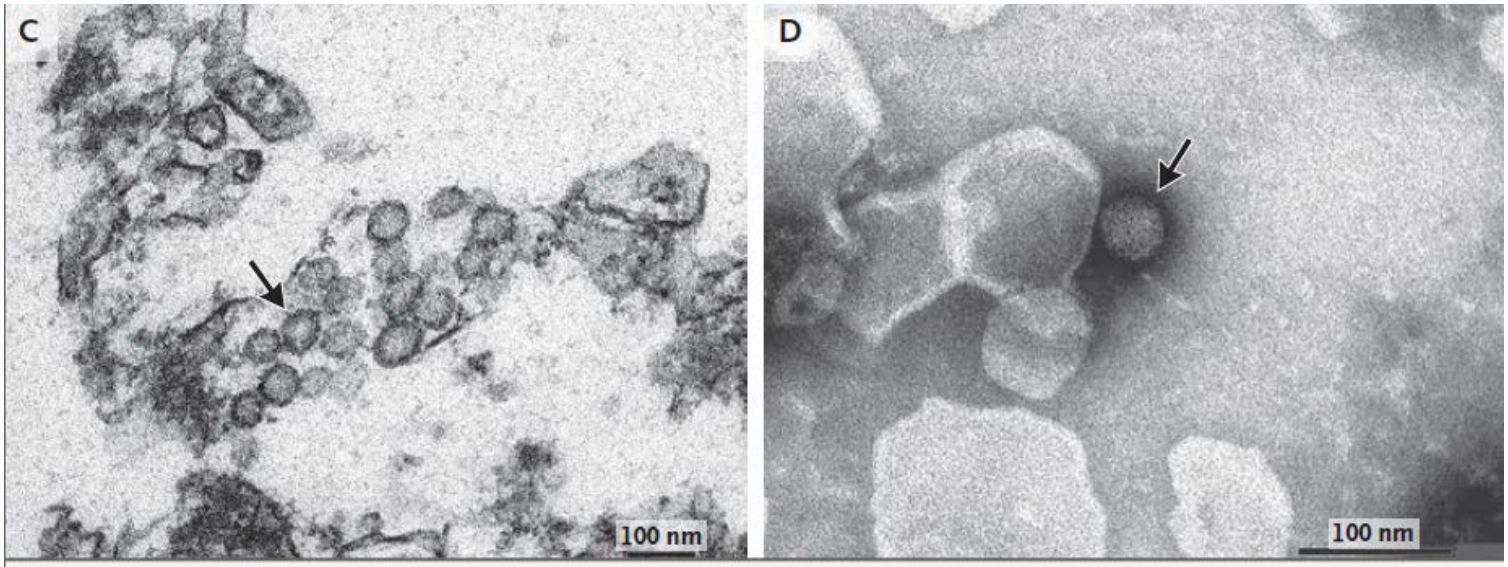


Figure 3. Electron Microscopy of Ultrathin Sections of Fetal Brain and Staining of a Flavivirus-like Particle.

Panel A shows a damaged brain cell with a cluster of dense virions located in the disrupted endoplasmic reticulum. Remains of membranes derived from different cellular compartments and filamentous structures are also seen. A magnified view of the boxed area with virions clearly visible (arrows) is shown in Panel B. Panel C shows a group of enveloped structures with a bright interior, presumably indicating viral replication (arrow). Panel D shows a negatively stained viral particle with morphologic characteristics consistent with those of Flaviviridae viruses (arrow).

Summary

- MUCH OF WHAT IS KNOWN ABOUT ZIKV VIROLOGY COMES FROM EXPERIMENTS CONDUCTED IN THE 1950-1960'S
- EXISTENCE OF RELIABLE ANIMAL MODELS OF INFECTION AND DISEASE UNCLEAR FROM LITERATURE BUT WORK IS ONGOING
- DEVELOPMENT OF NEUTRALIZING ANTIBODIES IN NHPS FOLLOWING INFECTION SUPPORTS THE POTENTIAL TO DEVELOP A PROTECTIVE VACCINE OR IMMUNOTHERAPEUTICS
- SUSTAINED VIREMIA IN NUMEROUS BODY FLUIDS EXPANDS THE POTENTIAL AND ROUTES OF TRANSMISSION

Question

- 32 yo WM presents with complaints of joint pain and severe fatigue 5 days after returning from a vacation in Northeastern Australia. Although he slept indoors, tourist activities were predominantly outdoors. He had no fresh water exposure. Food and beverages were prepared by the hotel and tourism company. He had no animal exposures.

  He is ill appearing and uncomfortable. VS, including temperature, are normal. On exam he has symmetrical tenderness and warmth in his ankle and knee joints, there is a L knee effusion. He has a faint macularpapular, non-pruritic rash on his trunk.

- What infection would be #1 on your differential diagnosis?
  A. Leptospirosis
  B. Malaria
  C. Chikungunya
  D. Dengue ★
  E. Ross River virus

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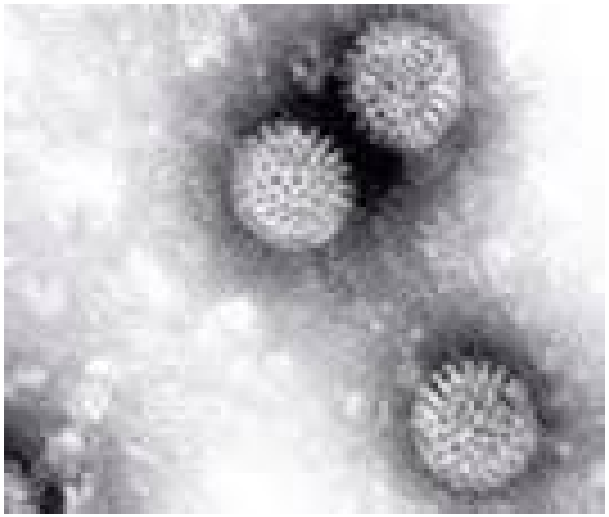
  D. Dengue
  E. Ross River virus

Arboviruses

- Family Togaviridae
  - Genus Alphavirus (30 species, examples below)
    - Barmah Forest, Chikungunya, EEE, O'nyong-nyong, **Ross River**, Sinbis, VEE, WEE
  - Genus Rubivirus (1 species)
    - Rubella



Ross River Virus

- Mosquito-transmitted *Alphavirus (Aedes* spp.*)*
- Endemic /enzootic in Australia and Papua New Guinea
- Most common arboviral disease in Australia
  - Thousands of cases annually (avg. 4,745; 1991-2000)
- Classic syndrome
  - Constitutional symptoms, rash, rheumatic manifestations

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932
0893-8512/01/$04.00+0 DOI: 10.1128/CMR.14.4.909–932.2001
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Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,[1,2] ADRIAN SLEIGH,[1*] AND SCOTT RITCHIE[2]

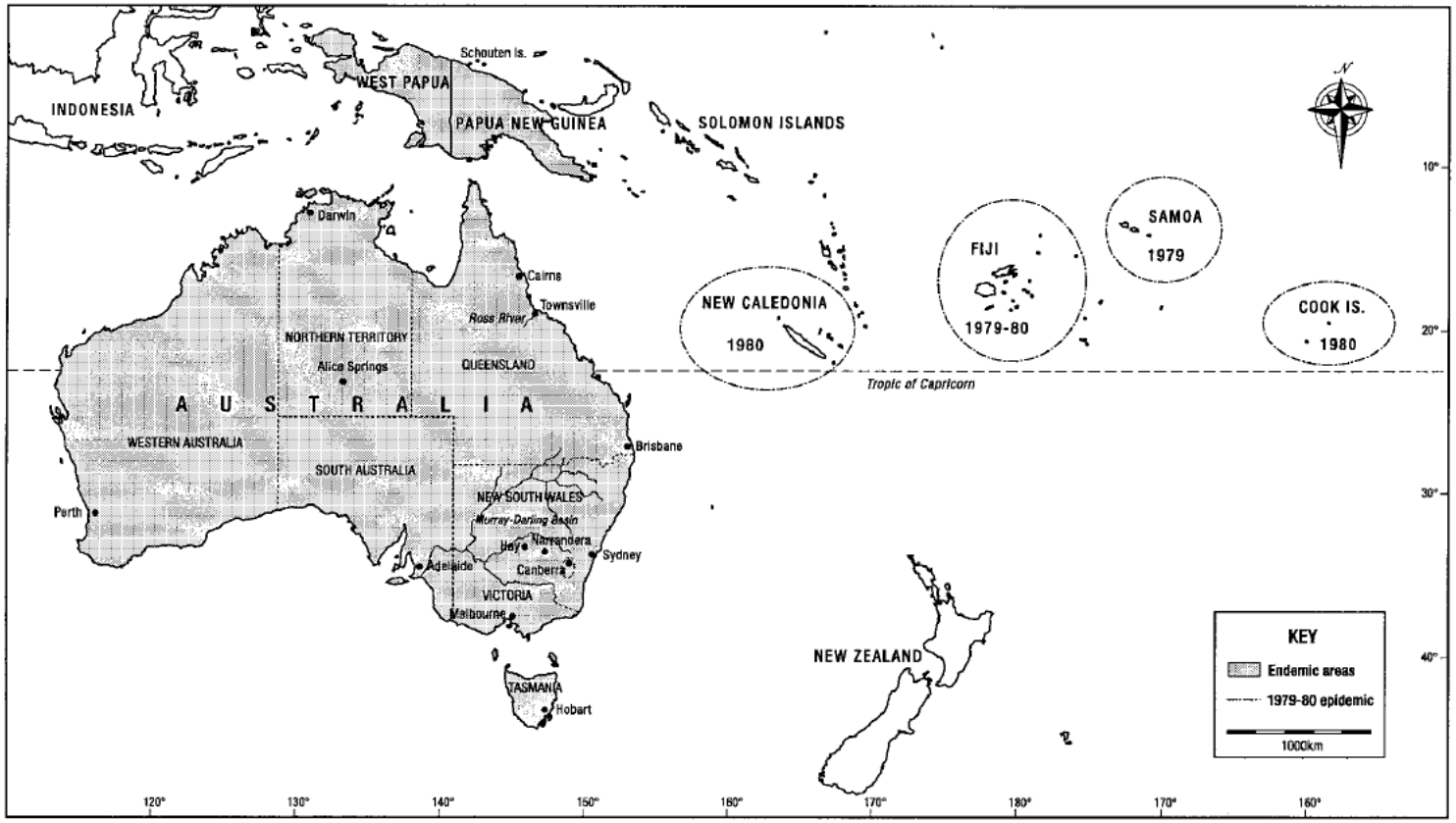
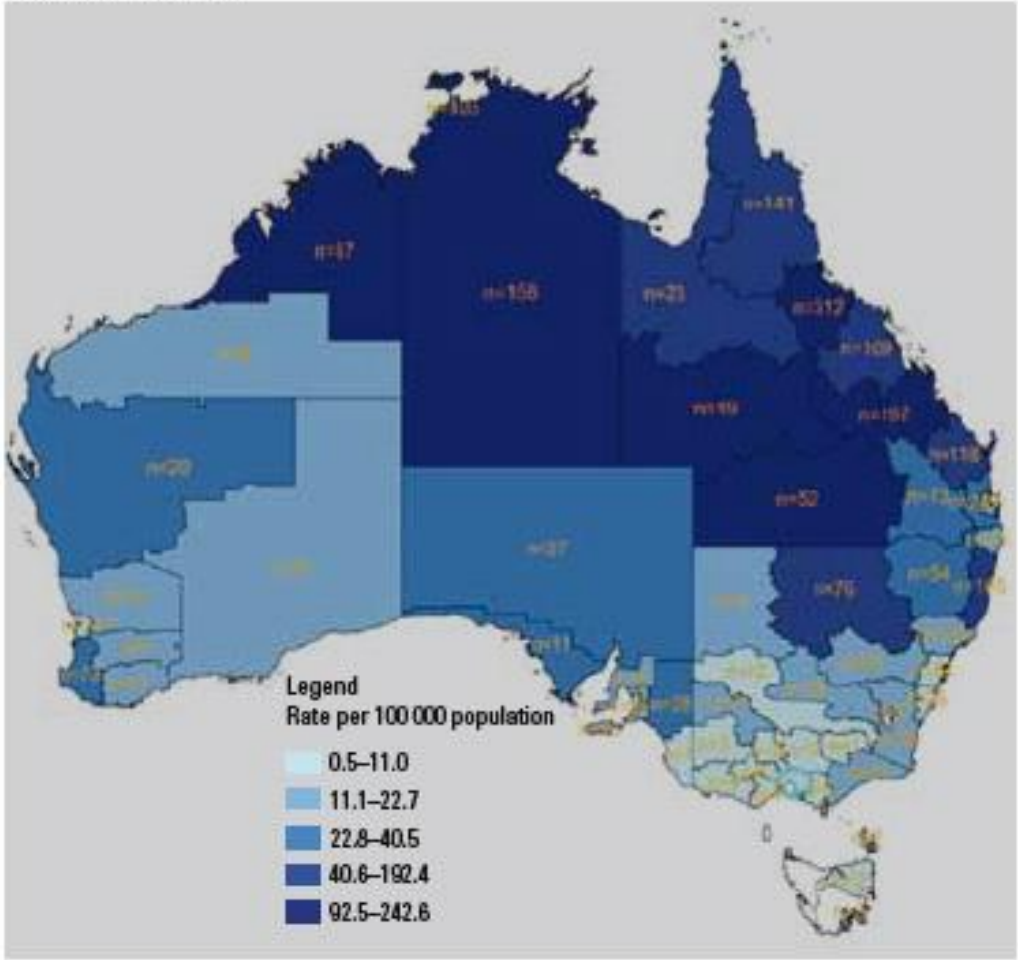


FIG. 1. Map showing cities, towns, and geographical features discussed in the text, areas where RRV is endemic, and the 1979 to 1980 South Pacific epidemic of RRV disease.

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932

Figure 1. Notifications and notification rates of Ross River virus infections, Australia 2006–2007



Reproduced from: Liu C, Begg K, Johansen C, et al. Communicable Diseases Network Australia National Arbovirus and Malaria Committee Annual Report, 2006–2007. Map 2 – Notifications and notification rates of RRV infections, Australia, 2006–07. Comm Dis Intell 2008;32:1. ©Commonwealth of Australia. Reproduced with permission

Ross River Virus Clinical Manifestations

- RRV incubation period ~7 to 9 days
- Asymptomatic infections in ~30%
- Symptoms may last for months or longer (co-morbidities)

- Constitutional symptomatology
  - Fever (1/3 to 1/2 of patients)
  - Rash, fever, and arthralgia may occur in any sequence
  - Fatigue typically affects over 50% of patients
  - Myalgia is common
  - Lymphadenopathy occurs quite often
  - Sore throat and coryza less frequently
  - Diarrhea is rare

- Joint manifestations
  - Symmetrical and acute in onset
  - Tenderness with minor restriction of movement
  - May have extreme redness and swelling
  - Effusions are commonPeripheral joints are predominantly involved
  - Ankles, fingers, wrists, and knees commonly affected

http://www.bing.com/images/search?q=Ross+river+virus&Form=R5FD0#view=detail&id=2AC4DDD2BF5E090FC561D2C0F252A08D93D7BE63&selectedIndex=32

Accessed 9 SEP 2013

- Rash
  - Usually lasts 5 to 10 days
  - May be the sole manifestation of infection
  - Appears mainly on the limbs and trunk
  - Maculopapular, vesicular, or purpuric

Reprinted from AUSTRALIAN FAMILY PHYSICIAN Vol. 38, No. 8, August 2009

Table 2. Frequency of symptoms and signs of Ross River virus[20–23]

Symptoms/sign	Frequency (%)
Joint pains	95
Tiredness	90
Fever	50–60
Myalgia	60
Rash	40–60
Headache	50
Joint swelling	50
Depression	45

Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,[1,2] ADRIAN SLEIGH,[1*] AND SCOTT RITCHIE[2]

TABLE 1. Joints affected by RRV disease

Joint	Frequency of joint involvement (% of cases)				
	Seglenieks and Moore (180) (n = 115)	Aaskov et al.[a] (4) (n = 36)	Mudge and Aaskov (144) (n = 400)	Condon and Rouse (33) (n = 189)	Westley-wise et al. (218) (n = 80)
Fingers		50[c]	80	81	63
Hand	45				
Thumb			53	58	
Wrist	36	70	80	100	61
Elbow	17	40	44	71	
Shoulder		38	47	62	
Hip	4	10	27		
Knee	39	80	80	100	64
Ankle	50	78	88	97	64
Feet	49	36			
Toes			47		
Back	14[b]	36	37	56	
Neck		36	12	70	
Jaw			10	15	

[a] Percentages taken from a bar graph.
[b] Includes back or neck.
[c] Includes fingers and hand.

- Diagnosis
  - Serology
    - Acute and convalescent samples (14 days apart)
    - Demonstrate 4 fold rise in IgG antibody
  - Neutralizing antibodies by PRNT
  - Identify peripheral RNAemia

- Treatment
  - No known treatment which alters disease course
  - Vaccine recently completed Phase 3 Trial in Australia
  - Treat symptoms
    - NSAIDS
    - Physical therapy, hydrotherapy, etc.
    - Reassurance

Arboviruses

- Family Bunyaviridae
  - Genus Nairovirus
    - Crimean–Congo hemorrhagic fever virus (CCHF)
  - Genus Orthobunyavirus
    - California encephalitis virus
    - La Crosse encephalitis virus (LACV)
    - Bunyamwera virus
  - Genus Phlebovirus
    - Rift Valley fever virus (RVFV)
    - Toscana virus (TOSV)

Arboviruses

- Family Reoviridae
  - Subfamily Sedoreovirinae
    - Genus Orbivirus
      - African horse sickness virus (AHSV)
      - Bluetongue disease virus (BTV)
      - Equine encephalosis virus (EEV)
    - Genus Seadornavirus
      - Banna virus (BAV)
  - Subfamily Spinareovirinae
    - Genus Coltivirus
      - Colorado tick fever virus (CTFV)

O'nyong-nyong virus (ONNV)

- Family Togaviridae
  - Genus Alphavirus (30 species, examples below)
    - Barmah Forest, Chikungunya, EEE, **O'nyong-nyong**, Ross River, Sinbis, VEE, WEE
- Primary vector: anopheline mosquito
- Means "severe joint pain" in the Acholi language of E. Africa
- Clinical syndrome similar to CHIKV but restricted to African continent (mostly E. Africa esp. Uganda)
  - Unlike CHIKV, ONNV causes LAD more often and affected joints do not have effusions

Summary

- Arboviral diseases are pervasive and difficult to prevent

- Clinical syndromes overlap across viruses
  - CHIK: constitutional symptoms, joint / tendon, chronic
  - ZIKA: constitutional symptoms, rash, conjunctivitis
  - JE: vaccine preventable disease, high morbid/mortality
  - YF: vaccine preventable, potential for severe adverse rxns
  - DEN: most important arbovirus

- Prevention and treatment
  - Know geographic distribution, PPM, vaccinate (JE/YF)
  - Symptomatic treatment

Questions?