Lecture Objectives

• Increase knowledge of:
  – Arbovirology
  – Epidemiology of tropical viral disease threats
  – Select diseases clinical presentation
  – Key points related to prevention and treatment
<table>
<thead>
<tr>
<th>Disease</th>
<th>2010 COCOM panel</th>
<th>ID-ID-DEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dengue</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea, bacterial</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MDR wound pathogens</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Q fever (Coxiella burnetti)</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Norovirus / viral diarrhea</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>Influenza</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea, protozoal</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>TB</td>
<td>12</td>
<td>NA</td>
</tr>
<tr>
<td>CCHF</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>HIV</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>HFRS</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Plague</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Ricketsioses</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Viral encephalitides</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>
What is a virus?

• Defined: A sub-cellular agent consisting of a **core of nucleic acid** surrounded by a **protein coat** that must use the **metabolic machinery** of a living host to replicate and produce more viral particles.

• Viruses are known to infect almost all organisms, including bacteria, fungi, plants, insects, and vertebrates.

• 20-300 nm in diameter; a “filterable” agent.
**Virus Structure**

**Capsid**
The capsid contains the virus’ genetic material (DNA or RNA).

**Viral Envelope**
The viral envelope is made from fatty lipid molecules taken from cells in the host.

**Surface Proteins**
These help the virus recognise and bind to cells in the host organism.

**Virus Genetic Material**
(DNA or RNA)
The virus’ genetic material contains the instructions for making new copies of the virus.
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

- Virus
- Vector
- Host Reservoir
- Accidental Hosts
Transmission Cycle Example - WNV

Avian hosts
- Abundance of immunologically naïve susceptible hosts
- Duration/level of viremia

Enzootic vectors
- Feed preferentially on birds
- Numerous species vary geographically, e.g., Culex pipiens

Bridging vectors
- Feed on birds and humans
- May differ from enzootic species, e.g., Culex salinarius and others

Climate
- Increased temperature enhances virus replication in mosquitoes
- Drought increases organic content of water collections and abundance of some vector species
- Increased rainfall and flooding expand habitat of other vector species

Human behavioral factors
- Exposure to biting mosquitoes
  - ? Lack of air-conditioning
  - ? Outdoor activity

Human immune response
- ? Immunocompromising conditions
- ? Genetic susceptibility

Compromised blood-brain barrier
- ? Facilitates neuroinvasion, e.g., cerebrovascular disease

Age
- ? Impaired immunity
- ? Coexisting disease

Viral strain virulence determinants
- ? Affect viral replication rate
- ? Some strains neurotropic

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 5 families:
  - Flaviviridae
  - Togaviridae
  - Bunyaviridae
  - Reoviridae
  - Rhabdoviridae
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, CCHF
50 yo Indian male presents with complaints of chronic pain and mild swelling in his fingers, bilaterally. He has no significant medical history except for a febrile illness he experienced 3 months ago following a trip to visit his family in southern India. He recalls the illness including fever, headache, fatigue, rash, and severe joint pain which lasted for ~9 days and spontaneously resolved without specific treatment. All symptoms resolved except for the joint pains which is why he presents today.

What illness did the man experience following his trip 3 months ago?

A. Chikungunya
B. Dengue
C. Leptospirosis
D. Ross River virus
E. Enteric fever
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
Chikungunya

- Mosquito-transmitted *Alphavirus* (*Aedes* spp.)

- Historically, epidemic transmission patterns
  - Potential of sustained transmission in SE Asia?

- Recent outbreaks have infected hundreds of thousands
  - High clinical attack rates observed
  - Mortality increasingly observed

- Classic syndrome
  - Fever with polyarthritis
Historic Movement of Chikungunya

Fig. 5. Dispersal pattern of CHIKV from Africa to the Indian Ocean and Europe during the past 20–50 years. Viral evolution and spread are represented according to recent phylogenetic studies. Different evolutionary lineages are identified using arrows with specific colours. This figure was reproduced with permission (de Lamballerie et al., 2008).
Countries and territories where chikungunya cases have been reported*
(as of October 14, 2014)

Current or previous local transmission of chikungunya virus
As of October 14:

- 1,382 chikungunya virus disease cases reported in US

- 11 locally transmitted cases reported from Florida

- All other cases occurred in travelers returning from affected areas in the Americas (N=1,355), Pacific Islands (N=8), or Asia (N=8)
Clinical Manifestations

- Majority of infected people become symptomatic
- Incubation period usually 3–7 days (range 1–12 days)
- Acute onset of fever and polyarthralgia
- Joint symptoms usually symmetric
  - Hands and feet
  - Can be severe and debilitating
- Headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, maculopapular rash
- Lymphopenia, thrombocytopenia, elevated creatinine, and elevated hepatic transaminases
# Clinical Manifestations

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency range (% of symptomatic patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76–100</td>
</tr>
<tr>
<td>Polyarthralgias</td>
<td>71–100</td>
</tr>
<tr>
<td>Headache</td>
<td>17–74</td>
</tr>
<tr>
<td>Myalgias</td>
<td>46–72</td>
</tr>
<tr>
<td>Back pain</td>
<td>34–50</td>
</tr>
<tr>
<td>Nausea</td>
<td>50–69</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4–59</td>
</tr>
<tr>
<td>Rash</td>
<td>28–77</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>12–32</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3–56</td>
</tr>
</tbody>
</table>

*Table compiled from a number of different studies.*

Pan American Health Organization  
Preparedness and Response for Chikungunya Virus: Introduction in the Americas  
Clinical Manifestations - Rash
# Chikungunya vs. Dengue

<table>
<thead>
<tr>
<th>Clinical and laboratory features</th>
<th>Chikungunya virus infection</th>
<th>Dengue virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;102°F or 39°C)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Myalgias</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Arthalgias</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++[^b]</td>
</tr>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bleeding dyscrasias</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Elevated hematocrit</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

[^a]: Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; +++ = 70-100% of patients; ++ = 40-69%; + = 10-39%; +/- <10%; - = 0%.[^32,33]

[^b]: Often retroorbital

*Table modified from Staples et al.[^34]*

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**Figure 1.** Affected joints (in black) in a patient with CHIKV polyarthritis presenting 6 weeks after onset of illness.

**Chikungunya viral polyarthritis.**

Raj J Carmona, Saeed Shaikh and Nader A Khalidi

J Rheumatol 2008;35:935-936
# Chikungunya: A Potentially Emerging Epidemic?

Michelle M. Thiboutot, Senthil Kannan, Omkar U. Kawalekar, Devon J. Shedlock, Amir S. Khan, Gopalsamy Sarangan, Padma Srikanth, David B. Weiner, Karuppihah Muthumani

## Table 1. Comparison of clinical features of Chikungunya and Dengue virus.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Chikungunya Virus (CHIKV)</th>
<th>Dengue Virus (DENV)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Fever, asthenia</td>
<td>Common</td>
<td>Common</td>
<td>[6, 8]</td>
</tr>
<tr>
<td>2) Myalgia</td>
<td>Possible</td>
<td>Very common</td>
<td>[6]</td>
</tr>
<tr>
<td>3) Polyarthrits</td>
<td><strong>Very Common, edematous</strong></td>
<td>None</td>
<td>[56]</td>
</tr>
<tr>
<td>4) Tenosynovitis</td>
<td>Yes</td>
<td>None</td>
<td>[57]</td>
</tr>
<tr>
<td>5) Leukopenia</td>
<td>None</td>
<td>Yes</td>
<td>[58]</td>
</tr>
<tr>
<td>6) Thrombocytepaenia</td>
<td>None</td>
<td>Yes</td>
<td>[59]</td>
</tr>
<tr>
<td>7) Rash</td>
<td>Days 1–4, important skin edema</td>
<td>Days 3–7</td>
<td>[6, 35, 58]</td>
</tr>
<tr>
<td>8) Retro-orbital pain</td>
<td>Rare</td>
<td>Common</td>
<td>[60]</td>
</tr>
<tr>
<td>9) Hypotension</td>
<td>Possible</td>
<td>Common, Days 5–7</td>
<td>[60, 61]</td>
</tr>
<tr>
<td>10) Minor bleeding</td>
<td>Chronic polyarthrits up to 1 year</td>
<td>Common</td>
<td>[17, 56]</td>
</tr>
<tr>
<td>11) Second stage</td>
<td>Possible; Tenosynovitis at M2–M3 Raynaud’s syndrome at M2–M3</td>
<td>Fatigue up to 3 mo</td>
<td>[6, 56, 62]</td>
</tr>
</tbody>
</table>

[10.1371/journal.pntd.0000623.t001]
## Atypical Clinical Manifestations

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy</td>
</tr>
<tr>
<td>Ocular</td>
<td>Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephritis, acute renal failure</td>
</tr>
<tr>
<td>Other</td>
<td>Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypoadrenalism</td>
</tr>
</tbody>
</table>

Adapted from Rajapakse et al. 20
Diagnosis

- Confirming a recent CHIKV infection:
  - Isolation of CHIKV, confirmatory identification (IFA, RTPCR, sequencing).
  - Detection of CHIKV RNA by real time RT-PCR.
  - Identification of a positive IgM result + acute symptoms, followed by the demonstration of CHIKV-specific antibody determined by PRNT with viruses in the SFV serogroup.
  - Seroconversion or a four-fold rise in PRNT, HI, or ELISA titers
Treatment

- No specific antiviral therapy; treatment is symptomatic
- Assess hemodynamic status and provide supportive care
- Evaluate for other serious conditions and treat appropriately
- Collect specimens for diagnostic testing
- Acetaminophen or paracetamol for initial fever and pain
- Consider using narcotics or NSAIDs
- If the patient may have dengue, do not use aspirin or other NSAIDs (e.g., ibuprofen, naproxen, toradol) until they have been afebrile ≥48 hours and have no warning signs for severe dengue
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy
Outcomes

• Acute symptoms typically resolve within 7–10 days
• Complications
  – Uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barré syndrome, and cranial nerve palsies
• Severe disease
  – Neonates exposed intrapartum, older adults (e.g., > 65 years), and persons with underlying medical conditions (e.g., hypertension, diabetes, or cardiovascular disease)
• Rheumatologic symptom relapse
  – polyarthralgia, polyarthritis, tenosynovitis
• Persistent joint pains for months to years possible
Persistent Chikungunya

Three clinical components, singly / in combination:

1. Distal polyarthritis / monoarthritis improved with NSAIDs
2. Frequent tenosynovitides in the hands, wrists, or ankles, sometimes responsible for carpal or tarsal tunnel syndromes, highly sensitive to short-term systemic corticotherapy, and
3. Exacerbation of pain in previously injured joints and bones requiring painkillers
Persistent Chikungunya
Persistent Chikungunya

Calcifications in shoulder tendon 18 months after infection

Inflammatory osteoarthritis, foot, 5 years after infection
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

Emerg Infect Dis. 1997;3:77
A 67 yo male from 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 the eastern rain forest of Ecuador. He does not drink ETOH or use tobacco. He is up to date on all immunizations including yellow fever vaccine received 5 days 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. Severe dengue
2. YF vaccine-associated neurologic disease (YEL-AND).
3. YF vaccine-associated viscerotropic disease (YEL-AVD)
4. Sylvatic YF

Arboviruses

• Family Flaviviridae
  – Genus Flavivirus (53 species, examples below)
    • Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever virus, Powassan, Rio Bravo, SLE, TBE, WNV, Yellow fever, Zika virus
  – Genus Hepacivirus (1 species)
    • Hepatitis C virus
  – Genus Pegivirus (2 species)
    • Pegivurs A, Pegivurs B
  – Genus Pestivirus (4 species)
    • Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus
Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology

Bali Pulendran

Timeline | Events in the development and understanding of the YF-17D vaccine

- 1648: The first recorded description of an epidemic thought to be yellow fever is made by Mayans in Yucatan.
- 1762: Thousands of British and American troops die in the British expedition to Cuba. Epidemics in coastal and island communities kill ~10% of the population.
- 1793: A yellow fever epidemic kills ~10% of the population of Philadelphia, USA.
- 1802: 20,000 inhabitants are killed in the Mississippi river valley, USA.
- 1878: Spanish-American War: 968 American soldiers are killed in combat but over 5,000 die of yellow fever.
- 1881: Stokes and colleagues isolate a strain of yellow fever virus from an infected individual named Asibi, in Ghana. French researchers in Dakar, Senegal, isolate the yellow fever virus from an infected Syrian.
- 1898: Walter Reed shows that yellow fever is spread by mosquitoes.
- 1899–1901: Carlos Finlay, a Cuban physician, proposes that yellow fever is carried by the mosquito.
- 1927: Max Theiler develops the yellow fever vaccine YF-17D.
- 1937: The WHO grants the use of two substrains of the YF-17D vaccine: 17/DD for use in South America and 17D-204 for use in the rest of the world.
- 1945: The Nobel Prize in Medicine and Physiology is awarded to Max Theiler.
- 2006–2009: The T cell immunogenicity of YF-17D is shown to depend on signalling through multiple TLRs, and systems biology approaches reveal the complexity of the innate immune responses to YF-17D and can predict the immunogenicity of YF-17D. In addition, there are insights into the dynamics of CD8+ T cell response.

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
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 (sylvatic) 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.

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 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

  – PROTECT FROM FURTHER MOSQUITO EXPOSURE

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.
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.
# Table 1. Yellow fever vaccine contraindications and precautions.

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &lt;6 months</td>
</tr>
<tr>
<td>Thymus disease or history of thymus disease</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Precautions</td>
</tr>
<tr>
<td>Age, 6–12 months</td>
</tr>
<tr>
<td>Age, ≥60 years for first-time vaccinees</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Lactation</td>
</tr>
<tr>
<td>Asymptomatic HIV infection with laboratory verification of adequate immune system</td>
</tr>
<tr>
<td>function</td>
</tr>
<tr>
<td>Hypersensitivity to eggs</td>
</tr>
<tr>
<td>Hypersensitivity to gelatin</td>
</tr>
<tr>
<td>Family history of adverse events associated with yellow fever vaccine</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Viscerotropic (hepatotropic) Infection:</th>
<th>Neurotropic Infection:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• transient viremia</td>
<td>• infects brain parenchyma and causes encephalitis</td>
</tr>
<tr>
<td>• damage to liver, spleen, kidneys and heart</td>
<td>• in nature, occurs in susceptible rodents</td>
</tr>
<tr>
<td>• hemorrhage</td>
<td>• in “nature” wild-type viruses do not result in neurotropic disease</td>
</tr>
<tr>
<td>• in nature, occurs only in humans and non-</td>
<td>• can occur in primates when vaccine strain “reverts” to virulent phenotype→</td>
</tr>
<tr>
<td>human primates</td>
<td>Vaccine Associated Neurotropic Disease</td>
</tr>
<tr>
<td>• molecular mechanisms of infection type are</td>
<td></td>
</tr>
<tr>
<td>poorly understood</td>
<td></td>
</tr>
</tbody>
</table>

*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/mm³) 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*
IIXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2009

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IIXIARO is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV). IIXIARO is approved for use in individuals 2 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration only.

2.1 Dosage and Schedule

Primary Series:

Children 2 months to <3 years of age: Primary immunization with IIXIARO consists of two (2) 0.25 mL doses, administered 28 days apart.

Individuals 3 years of age and older: Primary immunization with IIXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.

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

Booster Dose:

Individuals 17 years of age and older: 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.

Infants, children and adolescents 2 months to <17 years of age: The safety and immunogenicity of a booster dose has not been evaluated.
“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.”
“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; she is an ex-pat living in Australia. 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

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever, Powassan, Rio Bravo, SLE, TBE, WNV, Yellow fever, Zika virus
  - Genus Hepacivirus (1 species)
    - Hepatitis C virus
  - Genus Pegivirus (2 species)
    - Pegivurs A, Pegivurs B
  - Genus Pestivirus (4 species)
    - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus
Zika Virus

• Flavivirus (family Flaviviridae)

• Isolated in 1948 from a rhesus monkey
  – Zika forest, near Entebbe, Uganda

• Serologic evidence of human infection in Africa and Asia

• Transmitted to humans by infected mosquitoes
  – Aedes africanus, luteocephalus, aegypti, others

• Yap Island outbreak (2007) the first outside Asia, Africa

• Human to human transmission suspected
Zika Virus

Figure 1 Approximate known distribution of Zika virus, 1947–2007. Red circle represents Yap Island. Yellow indicates human serologic evidence; red indicates virus isolated from humans; green represents mosquito isolates.
Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Fever*</td>
<td>20 (65)</td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>20 (65)</td>
</tr>
<tr>
<td>Nonpurulent conjunctivitis</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Edema</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (10)</td>
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</table>

* Cases of measured and subjective fever are included.
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</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>7 (100)</td>
<td>20 (65)</td>
<td>1 (100)</td>
<td>1 (100)</td>
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<tr>
<td>Headache</td>
<td>1 (100)</td>
<td></td>
<td>14 (45)</td>
<td>3 (100)</td>
<td>1 (100)</td>
<td></td>
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<tr>
<td>Malaise</td>
<td>1 (100)</td>
<td>5 (71)</td>
<td></td>
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</tr>
<tr>
<td>Maculopapular rash</td>
<td>1 (100)</td>
<td></td>
<td>28 (100)</td>
<td>3 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or myalgia</td>
<td>1 (100)</td>
<td>1 (14)</td>
<td>14 (45)</td>
<td>1 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis and arthralgia</td>
<td>1 (100)</td>
<td>2 (14)</td>
<td>20 (65)</td>
<td>3 (100)</td>
<td></td>
<td></td>
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<tr>
<td>Chills</td>
<td>1 (100)</td>
<td>2 (29)</td>
<td></td>
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<tr>
<td>Dizziness</td>
<td>1 (100)</td>
<td>5 (71)</td>
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<td>Joint swelling or edema</td>
<td>1 (100)</td>
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<td>6 (19)</td>
<td>2 (67)</td>
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<td>Stomachache</td>
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<td>6 (86)</td>
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<tr>
<td>Retro-orbital pain</td>
<td>1 (100)</td>
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<td>12 (39)</td>
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<tr>
<td>Conjunctivitis</td>
<td>1 (14)</td>
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<td>17 (55)</td>
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<td>Anorexia</td>
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<tr>
<td>Vomiting</td>
<td></td>
<td>1 (14)</td>
<td>3 (10)</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Constipation</td>
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<td>1 (100)</td>
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<tr>
<td>Cough</td>
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<td>Hypotension</td>
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<tr>
<td>Hematuria</td>
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<td>Prostatitis</td>
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<tr>
<td>Hematospermia</td>
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<tr>
<td>Sweating</td>
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<td>Lightheadedness</td>
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<td>1 (33)</td>
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*References: Uganda (2), laboratory-acquired (10), Indonesia (5), Micronesia (9), Senegal/United States (4). Blank cells indicate no reported information.
Probable Non-Vector-borne Transmission of Zika Virus, Colorado, USA


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

• Prevention
  – No vaccine or prophlyactic drug
  – PPMs and vector avoidance

• Treatment
  – Supportive
  – Close resemblance to dengue on presentation likely warrants avoidance of NSAIDS and aspirin until Dx
  – Case report of possible human to human transmission requires counseling
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, separate lecture

• Prevention and treatment
  – Know geographic distribution, PMMs, vaccinate (JE/YF)
  – Symptomatic treatment, avoid platelet modifying drugs
Questions?