Arboviral Diseases

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
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

- Virus
- Vector
- Host Reservoir

Ecology

Accidental Hosts
## DOD Infectious Disease Threats

<table>
<thead>
<tr>
<th>Disease</th>
<th>2010 COCOM panel rank</th>
<th>ID-Ideal Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Dengue</strong></td>
<td><strong>2</strong></td>
<td><strong>3</strong></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>
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<tr>
<td>Chikungunya</td>
<td>16</td>
<td>4</td>
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<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>Rickettsioses</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Viral encephalitides</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>
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 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)
Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology

Bali Pulendran

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

The first recorded description of an epidemic thought to be yellow fever is made by Mayans in Yucatan, Philadelphia, USA.

A yellow fever epidemic kills -10% of the population.

20,000 inhabitants are killed in the Mississippi river valley, USA.

Spanish-American War: 968 American soldiers are killed in combat but over 5,000 die of yellow fever.

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.

The Nobel Prize in Medicine and Physiology is awarded to Max Theiler.


Thousands of British and American troops die in the British expedition to Cuba. Epidemics in coastal and island communities kill -10% of the population.

40,000 French soldiers are killed by yellow fever in Haiti.

Carlos Finlay, a Cuban physician, proposes that yellow fever is carried by the mosquito.

Walter Reed shows that yellow fever is spread by mosquitoes.

Max Theiler develops the yellow fever vaccine YF-170.

The WHO grants the use of two substrains of the YF-17D vaccine: 17DD for use in South America and 170-204 for use in the rest of the world.

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 response 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

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 (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 primates 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 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

- 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.
**Table 1. Yellow fever Vaccine contraindications and precautions.**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Age, &lt;6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus disease or history of thymus disease</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Precautions</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Age, 6-12 months</td>
<td></td>
</tr>
<tr>
<td>Age, 60 years for first-time vaccinees</td>
<td></td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Lactation</td>
<td></td>
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<tr>
<td>Asymptomatic HIV infection with laboratory verification of adequate immune system function</td>
<td></td>
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<tr>
<td>Hypersensitivity to eggs</td>
<td></td>
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<tr>
<td>Hypersensitivity to gelatin</td>
<td></td>
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<tr>
<td>Family history of adverse events associated with yellow fever vaccine</td>
<td></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 viscerotrophic disease (YEL-AVD)
## Yellow Fever Vaccine Reactions

<table>
<thead>
<tr>
<th>Viscerotopic (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-human primates</td>
<td>• can occur in primates when vaccine strain “reverts” to virulent phenotype → Vaccine Associated Neurotropic Disease</td>
</tr>
<tr>
<td>• molecular mechanisms of infection type are poorly understood</td>
<td><strong>Current Opinion in Immunology</strong></td>
</tr>
</tbody>
</table>
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
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
  – 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
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
PACOM: Japanese Encephalitis Risk to U.S. Forces

A small number of cases (less than 1% per month) could occur in unvaccinated personnel exposed to mosquito bites, particularly at night in rural areas.

Rare cases (less than 0.1% per month) could occur in unvaccinated personnel exposed to mosquito bites, particularly at night in rural areas.

Negligible risk, extremely rare cases

No risk

NOTE: Boundaries of the risk area should not be interpreted as strict demarcations; risk area varies with multiple ecological factors.

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/mm³ 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.

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
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

<table>
<thead>
<tr>
<th>2 MONTHS TO &lt;3 YEARS</th>
<th>2 MONTHS TO &lt;17 YEARS</th>
<th>2 TO 11 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary immunization with I XiARO consists of two (2) 0.25 mL doses, administered 28 days apart.</strong></td>
<td><strong>The safety and immunogenicity of a booster dose has not been evaluated.</strong></td>
<td><strong>The anterolateral aspect of the thigh</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>≥3 YEARS</th>
<th>≥17 YEARS</th>
<th>1 TO &lt;3 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary immunization with I XiARO consists of two (2) 0.5 mL doses, administered 28 days apart.</strong></td>
<td><strong>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.</strong></td>
<td><strong>The anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>≥3 YEARS</th>
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</thead>
<tbody>
<tr>
<td><strong>The deltoid muscle</strong></td>
</tr>
</tbody>
</table>

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https://www.novartisvaccinesdirect.com/ixiaro/IxiaroDosingAdministration
“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.”
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

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
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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
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

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

Virus ↔ Vector ↔ Host

Vector: Various *Aedes* species

Reservoir - Host:
- Birds, Reptiles,
- Livestock, NHPs,
- Small mammals, others?

Sustained Host

Accidental Host

- Sexual Transmission
- Blood Products
- Organ Donation
- Perinatal
- Laboratory
Zika virus: following the path of Dengue and Chikungunya?

Also Hawaii and Guam

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.
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
    - $2.9 \times 10^7$ and $1.1 \times 10^7$ copies/mL
    - Replicative ZIKV particles identified
  - Urine
    - $3.8 \times 10^3$ copies/mL
  - Blood
    - Undetectable by rRT-PC
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

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 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

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.

#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.>

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

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

First case on Latin American mainland was in May 2015

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

First identified in a monkey in Uganda 1947
First human case 1952
Before 2015 occurred in Africa, SE Asia, Pacific Islands

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
    - December 1 - January 6

Rise of microcephaly in Brazil
3,718 suspected cases, 68 newborn deaths

Range map of Aedes aegypti

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

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
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.

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

Legend
Rate per 100,000 population
- 0.5–11.0
- 11.1–22.7
- 22.8–40.5
- 40.6–192.4
- 92.5–242.6

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 common Peripheral 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\textsuperscript{20–23}

<table>
<thead>
<tr>
<th>Symptoms/sign</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pains</td>
<td>95</td>
</tr>
<tr>
<td>Tiredness</td>
<td>90</td>
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<tr>
<td>Fever</td>
<td>50–60</td>
</tr>
<tr>
<td>Myalgia</td>
<td>60</td>
</tr>
<tr>
<td>Rash</td>
<td>40–60</td>
</tr>
<tr>
<td>Headache</td>
<td>50</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>50</td>
</tr>
<tr>
<td>Depression</td>
<td>45</td>
</tr>
</tbody>
</table>
# Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,¹,² ADRIAN SLEIGH,¹* AND SCOTT RITCHIE²

## TABLE 1. Joints affected by RRV disease

<table>
<thead>
<tr>
<th>Joint</th>
<th>Seglenieks and Moore (180) (n = 115)</th>
<th>Aaskov et al.⁹ (4) (n = 36)</th>
<th>Mudge and Aaskov (144) (n = 400)</th>
<th>Condon and Rouse (33) (n = 189)</th>
<th>Westley-wise et al. (218) (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingers</td>
<td>50⁹</td>
<td>80</td>
<td>81</td>
<td>63</td>
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<tr>
<td>Hand</td>
<td>45</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thumb</td>
<td>53</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>36</td>
<td>70</td>
<td>80</td>
<td>100</td>
<td>61</td>
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<tr>
<td>Elbow</td>
<td>17</td>
<td>40</td>
<td>44</td>
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<tr>
<td>Shoulder</td>
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<td>47</td>
<td>62</td>
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<td></td>
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<tr>
<td>Hip</td>
<td>4</td>
<td>10</td>
<td>27</td>
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<tr>
<td>Knee</td>
<td>39</td>
<td>80</td>
<td>80</td>
<td>100</td>
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<td>Ankle</td>
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<td>Feet</td>
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<td>Toes</td>
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<td>Back</td>
<td>14⁹</td>
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<td>Neck</td>
<td>36</td>
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</tr>
<tr>
<td>Jaw</td>
<td>10</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Percentages taken from a bar graph.
² Includes back or neck.
³ 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 encephalosisis 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 morbidity/mortality
  – YF: vaccine preventable, potential for severe adverse reactions
  – DEN: most important arbovirus

• Prevention and treatment
  – Know geographic distribution, PPM, vaccinate (JE/YF)
  – Symptomatic treatment
Questions?