Arboviral Diseases

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Paul B. Keiser, Feb 2014

UNCLASSIFIED
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)

Surface proteins
These help the virus recognise and bind to cells in the host organism

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

Virus genetic material
(DNA or RNA)
The virus’ genetic material contains the instructions for making new copies of the virus
What is an arbovirus?

• Arboviruses are **Arthropod-borne**.
• They are transmitted to vertebrates by hematophagous (blood feeding) arthropod vectors
  – mosquitoes
  – other biting flies
  – ticks
Arboviruses

• Occur in nearly all parts of the world.
• Over 500 distinct viruses, ~100 causing human infections
• Nearly all arboviruses fall into one of 4 families:
  – Flaviviridae
  – Togaviridae
  – Bunyaviridae
  – Reoviridae
Classification Scheme

<table>
<thead>
<tr>
<th>Nucleic acid</th>
<th>Symmetry of capsid</th>
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<table>
<thead>
<tr>
<th>Family name</th>
<th>Properties</th>
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## Classification Scheme

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<td><strong>Virion diam. (nm)</strong></td>
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<tr>
<td><strong>Genome size (total in kb)</strong></td>
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</tbody>
</table>

### Source:
Flint et al. 2000. *Principles of virology*
Factors in Arboviral Disease

- Virus
- Vector
- Host Reservoir

Ecology
Arbovirus Features

• Able to replicate in both the arthropod vector and the vertebrate (bird or animal) host.
• Transmission to vertebrate occurs as the vector regurgitates while taking its blood meal.
• Viremia must reach high enough levels in the host to continue the cycle before reduced by the host immune system.
• Able to infect multiple species of animals and birds, but often limited to a specific arthropod vector.
Arbovirus Features

• In the tropics, transmission is year-round.
• In temperate climates, transmission to vertebrates is seasonal and the virus requires an overwintering strategy.
  – Transovarial transmission in the vector.
  – Migration with avian host.
• Disease is usually more severe in newly exposed hosts and species.
  – Deforestation
  – Irrigation
  – Urbanization
  – Travel
What makes a good arbovirus reservoir?

• The host/reservoir is present in large numbers and is readily accessible to vectors in time and space.
• The host is attractive to arthropod vectors and allows vectors to feed upon it.
• The host is susceptible to virus infection, experiences low mortality from infection, and becomes viremic with a titer of sufficient magnitude and duration to infect susceptible blood-feeding vectors.
• The life history of the host proceeds in such a way that immunologically susceptible individuals enter the population at times of active transmission.
• Host herd immunity remains low.
How do you determine if a vector is involved?

- Four criteria establish vector competence:
  - Isolation of the disease-producing agent from wild-caught specimens
  - Demonstration of its ability to become infected by feeding upon a viremic host
  - Demonstration of its ability to transmit by bite
  - Field evidence confirming association of the infected arthropod with the vertebrate population in which the infection is occurring.
Arboviral diseases: clinical syndromes

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

• Family *Flaviviridae*
  – Genus *Flavivirus*
    • Tick-borne viruses
      – Mammalian tick-borne virus group
        » *Kyasanur forest disease virus* (KFDV)
        » *Tick-borne encephalitis virus* (TBEV)
    • Mosquito-borne viruses
      – Dengue virus group
        » *Dengue virus* (DENV)
      – Japanese encephalitis virus group
        » *Japanese encephalitis virus* (JEV)
        » *Murray Valley encephalitis virus* (MVEV)
        » *St. Louis encephalitis virus* (SLEV)
        » *West Nile virus* (WNV)
      – Yellow fever virus group
        » *Yellow fever virus* (YFV)
      – Zika Virus
## Threat Assessment – ID Risk

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<tr>
<th>Disease</th>
<th>2010 COCOM panel</th>
<th>ID-IDEAL</th>
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Japanese Encephalitis (JEV)

• Most common cause of viral encephalitis worldwide
  – 160,000 reported cases 1966
  – 16,000 reported in 1996, decline is due to
    • Large-scale vaccination programs in Thailand
    • Urbanization in Japan, Taiwan, ROK
  – Annual est ≥ 50K
    • 2.5 cases/10,000 population at risk

• Primarily a disease of children
  – Naïve adults at risk -- i.e., travelers

• Most infections are subclinical/self-limited
  – Clinical cases have high mortality, morbidity
    • CFR ~25 -30%
    • Long-term disability 45 - 50%
JEV - Clinical Findings

• Incubation period 4 – 14 days
  – Sudden onset fever, chills and aches
    • Lethargy, HA, meningismus, N/V
  – Acute Flaccid Paralysis
    • Rapid onset paralysis despite normal consciousness
      – Weakness legs > arms, asymmetric
    • Flaccid paralysis also occurs in 5%-20% of comatose patients with "classic" JE

• Course
  – Occasionally fulminant
    • Short prodrome, deep coma, respiratory depression, posturing, death
  – Usually, improvement over ~ 1 week
  – Neuropsychiatric sequelae resolves over years or is permanent
JEV - Transmission

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

• Zoonotic amplification
  – Domestic pigs
  – Migratory waterfowl
  – Domestic waterfowl?
  • Ducks

• Seasonal/climate factors
  – Summertime / post-rainy season
  • Increased vector number, feeding behaviors
  • Increased viral replication
JEV - Prevention

• Vector control – difficult in endemic regions
  – Impractical, historically ineffective
  – Twilight-biting, marsh-breeding mosquitoes
• Reservoir control – difficult in endemic regions
  – Swine
    • Segregation impractical
    • Vaccination expensive
  – Other potential reservoirs
• Vaccination
  – Mass pediatric vaccinations
  – Apparently highly effective
West Nile Virus

• Widely distributed;
  – Infects >300 bird species
  – Infects >60 mosquito species

• Transmission by blood product transfusion documented before routine screening.

• Most infections are sub-clinical/self-limited.
  – 1:5 develop fever
  – 1:150 develop CNS disease
  – Incidence increases with age.
Yellow Fever
Yellow Fever Virus

- Molecular sequencing
  - 1 serotype, 5 genotypes

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

• Urban, sylvatic and savannah cycles
• Non-human primates can be a reservoir.

Aedes spp.
(Africa)

Haemagogus spp.
(Americas)

• Vertical transmission, infected ova survival
Jungle yellow fever

Rainforest zone

Monkey

Mosquito

Urban yellow fever

Aedes aegypti

Dry savanna Urban areas

Human

Monkey

Sylvatic yellow fever (Africa only)

Moist savanna vegetational zone

Haemogogos spp (South America)

Ae aegypti

(Africa)

Ae africanus

Ae luteocephalus

Ae furcifer

Ae vittatus

Ae simpsoni complex and other spp
Yellow Fever – South America

Yellow Fever - Africa

Yellow Fever: Acute Period

• Incubation of 3 to 6 days
• Clinical spectrum of disease
  – Mild, febrile illness → Fatal VHF
• Severe YF
  – Fever, Chills, Headache
  – Lumbosacral pain, Myalgia
  – Anorexia, Nausea, Vomiting
  – Gingival hemorrhages, Epistaxes
  – Bradycardia despite ↑ temperature (Faget's sign)
Yellow Fever: Acute Period

• Symptoms for ~ 3 days (period of viremia)
• Defervescence and improvement (~ 24 hours)
• Fever and symptoms return
  – Vomiting, Epigastric pain, Prostration, Jaundice

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.
Yellow Fever: Hemorrhagic Phase

- Hemorrhage
  - “Coffee-ground” hematemesis (*vomito negro*)
  - Melena, Petechiae, Ecchymoses

- Intravascular volume depletion

- Liver damage/jaundice

- Renal failure
  - ↑ Albuminuria
  - ↓ Urine output (UO)
Yellow Fever: Hemorrhagic Phase

• Death (in 20% to 50% of severe cases)
  – 7th to 10th day of illness
  – ↑ jaundice, hemorrhages, ↑ HR, ↓ BP, ↓ UO, ↓ Temp.
  – Agitated delirium, Intractable hiccups, Stupor, Coma

• Laboratory findings
  – ↓ WBC, ↓ Plts
  – ↑ Bilirubin, ↑ Serum transaminase levels
  – ↑ PT and PTT
  • ↓ synthesis of clotting factors + ↑ consumption

• ST-T wave changes in the electrocardiogram.
Yellow Fever: Convalescent Phase

• Prolonged convalescence
  – Profound asthenia lasting 1 to 2 weeks

• Late death
  – End of convalescence
  – Weeks after recovery from the acute illness
  – Rare phenomenon
  – Attributed to cardiac complications or renal failure

• Elevations of serum transaminase levels
  – Persist for at least 2 months after onset of acute illness
Period of infection 3–6 days (viraemic)

**Clinical features**
- Headache
- Myalgia
- Lumbosacral pain
- Nausea
- Malaise
- Prostration
- Dizziness
- Conjunctival injection
- Furred tongue, red at tip
- Bradycardia (Faget’s sign)

**Laboratory features**
- Leukopenia
- Neutropenia
- AST > ALT
- Proteinuria

Infection and immunity
- Viraemia

Period of remission 2–24 hours

**Symptoms abate**
- Headache
- Epigastric pain
- Vomiting
- Prostration
- Malaise
- Jaundice
- Oliguria ➔ anuria
- Tender liver
- Hypotension ➔ shock
- Stupor ➔ coma
- Haemorrhage
- Convulsions
- Thrombocytopenia
- Leukocytosis
- AST > ALT
- Proteinuria
- Azotaemia
- Hypoglycaemia
- Acidosis

Period of intoxication 3–8 days

**Convalescence 2–4 weeks**

**RECOVERY**
- Aesthenia
- DEATH

20–50%
Yellow Fever: Diagnosis

• Clinical Diagnosis
  – Exposure history

• Advanced Diagnostics:
  – Virus Isolation (culture)
  – Rapid Diagnostics
    • PCR
      – may not be positive late in disease
    • Antibody or Antigen detection (ELISA)
      – IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
  • Neutralization Ab are more specific for YF
Yellow Fever: 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.
Zika virus

• Zika virus is an emerging arboviral infection.
• Like other flaviviruses it has the capacity to mutate, adapt and infect urban mosquitoes in particular *Aedes aegypti*.
• Like dengue, we are observing an emerging human infection influenced by human migration and urban transmission.
• It is the first *Flaviviridae* of the genera *flavivirus* that has demonstrated sexual transmission.
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.
Arboviruses

- Family *Togaviridae*
  - Genus *Alphavirus*
    - *Eastern equine encephalitis virus* (EEE)
    - *Ross River Virus* (RRV)
    - *Venezuelan equine encephalitis virus* (VEE)
    - *Western equine encephalitis virus* (WEE)
    - *Chikungunya*
Alphaviruses - Venezuelan Equine Encephalitis Virus

• First recognized in Venezuela in 1938.
• A 1995 outbreak in Colombia and Venezuela affected >75,000 people with 300 fatalities.
• Transmitted by >10 different mosquito species.
• Bats and birds are reservoirs; horses and rodents serve as amplifiers.
• Human-to-human transmission is also suspected.

• Diagnosis: serology.
• Treatment: supportive.
Alphaviruses: Ross River Virus

• Ross River virus (RRV) is a mosquito-transmitted *Alphavirus* that is endemic and enzootic in Australia and Papua New Guinea
• RRV causes the most common arboviral disease in Australia
• Asymptomatic infections occur in ~30%
• Symptomatic infections typically include constitutional effects, rash, and rheumatic manifestations
• Symptoms may last for months, longer in those with co-morbidities
Alphaviruses: Ross River Virus Disease

• Diagnosis
  – Serology: 4x rise in IgG over 14 days

• Treatment
  – No known treatment will alter the disease course
  – Treat symptoms
    • NSAIDS
    • Physical therapy, hydrotherapy, etc.
    • Reassurance
Togaviruses (Alphaviruses)  
Chikungunya
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Chikungunya - Threat Assessment

• Travelers
  – Historically South and Southeast Asia, Africa.
  – Transmission in the Caribbean confirmed in Dec 2013.

• Military
  – Prolonged convalescence due to arthritis.
  – Viet Nam: 15% of FUO caused by dengue or CHIK
  – Reunion Island outbreak (French)
    • Attack rate (~33%)
    • Lingering clinical manifestations
Chikungunya distribution

Reported human chikungunya virus infections
No reported human infections

Chikungunya: Clinical Manifestations

- Clinical attack rates vary by population: 25-90%
- Children and older adults with co-morbidities experience largest burden of disease
- Hospitalization rates up to 66%.
- High Case:Fatality ratios
# Chikungunya: Clinical Manifestations

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<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency range (% of symptomatic patients)</th>
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<tbody>
<tr>
<td>Fever</td>
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<tr>
<td>Polyarthralgias</td>
<td>71–100</td>
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<td>Headache</td>
<td>17–74</td>
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<td>Myalgias</td>
<td>46–72</td>
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<td>Back pain</td>
<td>34–50</td>
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<td>Nausea</td>
<td>50–69</td>
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<td>Vomiting</td>
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<td>Rash</td>
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<td>Conjunctivitis</td>
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*Table compiled from a number of different studies.*[^1]
Chikungunya: Clinical Manifestations

hypermelanosis
## Chikungunya vs. Dengue

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<tr>
<th>Clinical and laboratory features</th>
<th>Chikungunya virus infection</th>
<th>Dengue virus infection</th>
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<tbody>
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<td>Fever (&gt;102°F or 39°C)</td>
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<tr>
<td>Myalgias</td>
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<td>+/-</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Rash</td>
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<td>Thrombocytopenia</td>
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</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 polyarthitis presenting 6 weeks after onset of illness.*

**Chikungunya viral polyarthitis.**

Raj J Carmona, Saeed Shaikh and Nader A Khalidi

J Rheumatol 2008;35:935-936
## Chikungunya -- Atypical 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.\textsuperscript{20}
Chronic Chikungunya

1. Distal mono- or polyarthritis; improves with NSAIDs.
2. Frequent tenosynovitis of the hands, wrists, or ankles, sometimes leading to carpal or tarsal tunnel syndromes; highly sensitive to systemic steroids.
3. Exacerbation of pain in previously injured joints and bones requiring painkillers.
Chronic Chikungunya
Chronic Chikungunya

Calcifications in shoulder tendon 18 months after infection

Inflammatory osteoarthritis, foot, 5 years after infection
Chikungunya - Treatment

• No vaccine or antiviral licensed
• Illness is usually self-limiting
• Symptomatic treatment only
  – Rest to the patient and mild movements of joints
  – Cold compresses to inflamed joints
  – Liberal fluid intake or IV fluids
  – Analgesics and NSAIDS
• Convalescence can last weeks to years
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)
### Threat Assessment – ID Risk

<table>
<thead>
<tr>
<th>Disease</th>
<th>2010 COCOM panel</th>
<th>ID-I 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><strong>CCHF</strong></td>
<td><strong>13</strong></td>
<td><strong>10</strong></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>Rickettsioses</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Viral encephalitides</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>
Crimean Congo Hemorrhagic Fever

- Transmitted by ticks (*Hyalomma* species) and in unpasteurized milk
  - Milkers, shepherds, abbatoir workers.
- Blood from patients is highly infectious.
- Nosocomial outbreaks with fatalities reported.
- Infects reticuloendothelial system and hepatocytes.
- Mortality rates range from 20% to 35%

- Covered later.
Arboviruses: Summary

- Arboviruses represent significant threats to military readiness.
- By definition they are transported by arthropods, but other modes of transmission have been documented.
- Clinical presentations vary:
  - fever, febrile arthritis, encephalitis, hemorrhagic fever.
- Treatment is supportive.
- Diagnosis may require acute and convalescent sera or specific PCR assays.
- A significant proportion of patients have prolonged convalescence or long-term sequelae.