Emerging Arboviruses in Texas

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Infectious disease is one of the few genuine adventures left in the world. The dragons are all dead and the lance grows rusty in the chimney corner......About the only sporting proposition that remains unimpaired by the relentless domestication of a once free living human species is the war against those ferocious little fellow creatures, which lurk in the dark corners and stalk us in the bodies of rats, mice, and all kinds of domestic animals; which fly and crawl with the insects, and waylay us in our food and drink, and even in our love.

Hans Zinsser, 1935

“Rats, Lice and History”
# Arthropod-borne Virus Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Envelope Type</th>
<th>Important Species</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togaviridae (Alphavirus)</td>
<td>Enveloped ss (+)RNA</td>
<td>EEE(^1), WEE(^1), VEE Chikungunya(^2)</td>
<td></td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Enveloped ss (+)RNA</td>
<td>SLE(^1,2), WNV(^1), JE(^2), Dengue(^1,2), Yellow fever(^2), Powassan fever(^1)</td>
<td></td>
</tr>
<tr>
<td>Bunyaviridae (some genus)</td>
<td>Enveloped ss (-)RNA</td>
<td>California Encephalitis Complex, La Crosse(^1), Rift Valley Fever(^2)</td>
<td></td>
</tr>
<tr>
<td>Reoviridae (Coltivirus)</td>
<td>Naked ds (+/-)RNA</td>
<td>Colorado tick fever(^1)</td>
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</tbody>
</table>

1 = important in the US  
2 = important worldwide
Emerging Arboviruses in Texas: Historical References

• Dengue
  - First recognized outbreak of dengue-like illness in 1895-1896: more than 16,000 cases in Austin area*
  - 1922: more than 500,000 cases (“Galveston outbreak”)*

• St. Louis encephalitis virus
  - First identified in 1933, first recognized outbreak in Texas in 1964

• West Nile virus
  - Introduced to US in 1999 and Texas in 2002

• Chikungunya?
  - 71 imported cases to 23 states; None reported to CDC from Texas

*Beaumier et al. Current Tropical Medicine Reports, 2014
Dengue Virus

• **Flavivirus**
• Four serotypes
  - DEN-1, DEN-2, DEN-3, DEN-4
• Lifelong immunity
• Complicated illness with secondary infection of different serotype
• Three classifications of disease
  - Dengue Fever (DF)
  - Dengue Hemorrhagic Fever (DHF)
  - Dengue Shock Syndrome (DSS)

Transmission

• Indirect transmission
  - Urban: human-mosquito-human-cycle
  - Sylvatic cycle: non-human primate cycle (Wang et al. 2000)

• Vectors
  - *Aedes aegypti*, primary vector
  - *Aedes albopictus*
  - Can transmit virus for life of insect once infectious
  - Transovarial transmission

www.who.int/topics/dengue/en
www.medicineinfood.com
Transmission of Dengue Virus

1. Virus transmitted to human in mosquito saliva
2. Virus replicates in target organs
3. Virus infects white blood cells and lymphatic tissues
4. Virus released and circulates in blood
Case Definitions

- **2007 WHO Case Definition:**
  - **Dengue Fever (DF):** fever and two or more of the following signs/symptoms: retro-orbital or ocular pain, severe headache, rash, myalgia, arthralgia, leukopenia (<3,500), or hemorrhagic manifestations.
  - **Dengue Fever with warning signs:** DF with 2 or more of the following: abdominal pain, persistent vomiting, clinical fluid accumulation, mucosal bleeding, liver enlargement (>2 cm), or an increased hematocrit with rapid decreased platelet count

www.who.int/topics/dengue/en
Case Definitions

• **Dengue hemorrhagic fever (DHF):** fever for 2-7 days, hemorrhagic tendencies, thrombocytopenia and evidence of plasma leakage.

• **Dengue shock syndrome (DSS):** same clinical characteristics as DHF along with rapid, weak pulse and narrow pulse pressure (<20 mmHg) or hypotension.

• **DSS:** highest risk of fatality without proper treatment
Hemorrhagic Dengue

- Antibody-dependent enhancement theory
- Abs against a specific serotype play a pathogenic role
- Abs unable to neutralize
- Small dermal vessel injuries, petechiae, hepatic necrosis and DIC
  - DEN-1 --> DEN-2; or DEN-3 --> DEN-2
  - Infants 5-8 mos of age
Treatment/Management

• Acetaminophen
• Avoid aspirin, NSAIDS
• Presence of warning signs or hemorrhagic manifestations:
  - Maintain hydration, fluid and electrolyte therapy
  - Serial hematocrits, platelet count, monitor consciousness
• Severe bleeding, DSS:
  - Whole blood transfusion 20 ml/kg as bolus
  - Platelet rich plasma transfusion if platelets < 10,000/mm³
  - Fluid therapy at 10 ml/kg/h and reduce stepwise to 3 ml/kg/h for maintenance
• Vaccines being developed
• Prevention: vector control, education, and surveillance

www.who.int/topics/dengue/en
Diagnostics: Immune Response

• In primary infections, IgM detectable 3-5 days post onset; last 1-2 months

• In 20-30% of patients, IgM may not be detected in secondary infection

• IgG rises rapidly after onset of symptoms. Persists for long periods of time

• PCR (+) up to 5 days post-onset

• PRNT detection (convalescent)
Epidemiology

- 50 million cases worldwide per year
- 25,000 deaths annually
  - DF: 2.5% case fatality rate
  - DHF: up to 20% case fatality
- 500,000 cases per year require hospitalization
- Explosive outbreaks
  - Attack rates: 40-50%, up to 80-90%
- Endemic in 100 countries
  - Africa, Americas, Eastern Mediterranean, Southeast Asia, Western Pacific
- 2.5 billion people reside in dengue-transmission areas

www.who.int/topics/dengue/en
Epidemiology

Countries / areas at risk of dengue transmission, 2006

Epidemiology of Dengue in Texas (Last 34 years)

• Last outbreak in Texas was 1941 along the gulf coast
  - Extensive control of *Aedes aegypti*

• 1980, South Texas: Active surveillance identified 63 cases along border (43% acquired infection in Texas)

• 1999, Laredo, TX: 2 acquired cases on Texas side of border. No cases diagnosed with dengue at time of illness.

• 2005, Brownsville, TX: 3/24 cases locally acquired

• 2013, South Texas: 24 locally acquired cases (peaked in October)
Dengue in Houston: the Perfect Storm

• Proximity to dengue-endemic areas
• Vast shipping; both air and ship travel entry points; NAFTA
• High proportion of its ~4 million residents who routinely travel to and from dengue-endemic areas
• Dense urban population
• Abundance of Aedes sp.
• Mild winters and year-round survival of mosquitoes
• Passive surveillance, lack of diagnostic testing available
Our Study

• Between 2002-2005, many people presented to local hospitals and clinics with arboviral-like illness, but tested negative for antibodies against WNV and SLEV

• **Goal:** Investigate retrospectively if dengue was circulating in the area

• **Specimens:** 3,768 acute-phase CSF and serum samples obtained from the City of Houston Public Health Laboratory

• **Testing:** anti-DENV IgM ELISA, PRNT, and PCR

• **Data Collection:** Chart abstractions and interviews on IgM positive cases

Murray et al. AJTMH 2013
Results

• We identified 47 (1.2%) with detectable anti-DENV IgM antibodies; 38 (81%) specimens were serum and 9 (19%) were CSF.

• PCR positive for DENV-2 in two subjects

• PRNT positive mostly for DENV-2 in five subjects

• 19 met case definition for dengue fever; 2 fatal cases

• 2 had history of travel to Mexico, 1 to RGV

  - No geographic clustering
Fatal Cases

• Case #1: 92 y.o. African-American female:
  - Admitted June 2003; Dx with viral meningitis and encephalitis.
  - Died 10 days after onset.
  - Bedridden for 2 yrs; no recent travel outside of Houston
  - CSF was positive for anti-DENV IgM; PRNT neg.
  - Likely recent primary DENV infection that manifested as encephalitis

• Case #2: 49 y.o. Hispanic female:
  - Admitted July 2004 for AMS, septic shock, severe sepsis, pleural effusion, and DIC with complaints of fever, headache, and abdominal pain.
  - Final diagnosis: recurrent severe sepsis with anoxic brain injury
  - Hx of frequent travel to Mexico, including a visit just prior to illness onset.
  - Patient’s clinical picture strongly suggest DSS
Epidemic Curve of Dengue IgM Positive Cases

Month and Year of Symptom Onset

* = History of travel to Mexico;  X = Fatal Case
St. Louis Encephalitis (SLE) virus and West Nile Virus (WNV)

- Arbovirus (arthropod-borne), mosquito vector; Flaviviridae family

- Members of the Japanese encephalitis (JE) serogroup complex

- RNA virus with lipid/glycoprotein envelope
Transmission: SLE and WNV

• Natural transmission → mosquito vector
  - Houston: Culex quinquefasciatus
  - Birds are reservoir host

• Experimental studies suggest infection with one could provide protection against the other

• Newly discovered means of transmission with WNV in humans (2002)
  - Transplant
  - Transfusion
  - Transplacental
  - Breastfeeding
  - Laboratory acquired
St. Louis Encephalitis Virus in the US

Source: CDC
WNV Clinical Cases by Year, 1999-2012

- Total no. of clinical cases = 37,088
- Total no. of WNND = 16,114
- Total no. of deaths = 1,549
Decade of WNV Transmission in Texas

Nolan et al. *Emerging Infectious Diseases*, 2013
Total no. of clinical cases = 1,868
Total no. of WNND = 844
Total no. of deaths = 89

Total estimated acute care and loss of productivity costs: $47 million

Murray et al., *Emerging Infect Diseases*, Nov. 2013
WNV Incidence per 100,000 population in 2012

48% of cases from Tarrant, Dallas, Collin, and Denton counties

Murray et al., EID 2013
<table>
<thead>
<tr>
<th>Case Characteristics, WNV 2012 Outbreak</th>
<th>All cases, n=1,868 (%)</th>
<th>Attack Rate/100K pop</th>
<th>WNV Fever, n= 1,024 (%)</th>
<th>WNND, n= 844 (%)</th>
<th>Deaths, n= 89 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1,028 (55.0)</td>
<td>8.1</td>
<td>519 (50.7)</td>
<td>509 (60.3)</td>
<td>56 (62.9)</td>
</tr>
<tr>
<td>Female</td>
<td>840 (45.0)</td>
<td>6.5</td>
<td>505 (49.3)</td>
<td>335 (39.7)</td>
<td>33 (37.1)</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 18 years</td>
<td>70 (3.8)</td>
<td>1.0</td>
<td>42 (4.1)</td>
<td>28 (2.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>18-24</td>
<td>71 (3.8)</td>
<td>2.7</td>
<td>42 (4.1)</td>
<td>29 (3.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>25-44</td>
<td>439 (23.5)</td>
<td>6.2</td>
<td>283 (27.6)</td>
<td>156 (18.3)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>45-64</td>
<td>728 (39.0)</td>
<td>11.7</td>
<td>424 (41.4)</td>
<td>304 (36.0)</td>
<td>13 (14.6)</td>
</tr>
<tr>
<td>65 +</td>
<td>560 (30.0)</td>
<td>20.0</td>
<td>233 (22.8)</td>
<td>327 (38.7)</td>
<td>71 (79.8)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Non-Hispanic</td>
<td>1,273 (68.1)</td>
<td>11.1</td>
<td>738 (72.1)</td>
<td>535 (63.4)</td>
<td>54 (60.7)</td>
</tr>
<tr>
<td>Black</td>
<td>117 (6.3)</td>
<td>4.0</td>
<td>43 (4.2)</td>
<td>74 (8.8)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>318 (17.0)</td>
<td>3.2</td>
<td>134 (13.1)</td>
<td>184 (21.8)</td>
<td>22 (24.7)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>160 (8.6)</td>
<td>11.2</td>
<td>109 (10.6)</td>
<td>51 (6.0)</td>
<td>12 (13.5)</td>
</tr>
</tbody>
</table>
West Nile Virus
Clinical Features in Humans

• Incubation 2 to 15 days
• ~ 80% infected persons asymptomatic
• ~ 20% infected persons flu-like symptoms
  • Fever, HA, rash, nausea, vomiting
• < 1% (1 out of 150) “neuroinvasive disease”
  • WNM: Meningitis (fever, HA, stiff neck, CSF pleocytosis)
  • WNE: Encephalitis (altered mental status) or meningoencephalitis
  • Acute flaccid paralysis
• 10 % case fatality ratio for those with severe disease
• Dx: IgM positive CSF or sera
Houston WNV Cohort: Study Methods

• Study initiated in 2002 following introduction to Houston
• Cases of WNV identified through local surveillance
• Medical chart abstractions completed on all cases (n=302)
• Cases invited to enroll in 10 year prospective, longitudinal cohort study, 247 cases currently enrolled
  - Interviews and blood draws q. 6 mos
  - Subjective symptoms
  - Objective measurements: CES-D, Barthel Index, MMSE
  - Other studies using the cohort: risk factors for encephalitis and death, clinical predictors for death, genetic susceptibility, immune functioning
## Sequelae following Infection

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>60.1%</td>
</tr>
<tr>
<td>2 years</td>
<td>46.4%</td>
</tr>
<tr>
<td>3 years</td>
<td>40.6%</td>
</tr>
<tr>
<td>4 years</td>
<td>38.9%</td>
</tr>
<tr>
<td>5 years</td>
<td>41.9%</td>
</tr>
</tbody>
</table>

- **Most commonly reported sequelae:** depression/personality change, weakness, fatigue, difficulty walking, blurred vision, paralysis, memory loss, confusion, headaches, tremors

- **Depression:** 31% new onset depression; 75% have CES-D scores indicative of clinical depression. Can continue up to 8 yrs (Murray et al, EID 2007 and Nolan et al, J Clin Psych 2012)

- **CKD in 40% of participants; statistically associated with neuroinvasive disease** (Nolan et al. PLoS One 2012)
Kaplan-Meier Survival Curve: Percentage of Study Participants Continuing to Report West-Nile Virus-related Symptoms by Days Post-Infection based on Initial Diagnosis

What’s next?
Chikungunya

• Vector: *Aedes* species mosquitoes

• “that which bends up”
  - Fever, headache, fatigue, rash, nausea, vomiting, muscle pain, severe joint pain
  - Fatality rare

Chikungunya

Source: PNAS
More than 188,000 suspected or confirmed cases in 19 countries reported since first identified Dec. 6th, 2013

Rift Valley Fever

• Family *Bunyaviridae*

• Mostly eastern and southern Africa, but has spread over the past 15 yrs to west Africa and Middle East.

• Severe disease in livestock (especially abortion)

• Transmission to humans: bite of infected mosquito (Aedes sp.) or contact with infected tissues, blood, fluids from infected livestock.
  
  - No human-to-human

• Disease in people usually self-limiting, <1% CFR
Prevention of Emerging Arboviral Diseases

• Surveillance, surveillance, surveillance
  - Humans (active + “enhanced” passive), sentinel species, mosquitoes
  - Multidisciplinary “One Health” approach is critical

• Public education

• Prevention of bites

• Did I mention surveillance?
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