Dengue & Zika Viruses

"Dengue" is Spanish for fastidious/careful
Swahili word "dinga"
Ka-dinga pepo – “cramp-like seizure caused by evil spirit”

A large portion of the human population is at risk

"Flaviviruses are the most important arboviruses in the world"
Flavivirus genome

Flavivirus Life Cycle
Minus-strand synthesis requires genome cyclization

Homologous regions of the 5' and 3' UTRs allow the viral RNA to form a circular structure

3' UTR of flaviviruses encode a subflaviviral RNA (sfRNA)

Host endonuclease Xrn1 digests viral RNA
Secondary structures in the 3' UTR are resistant to degradation

sfRNA affects viral dissemination into salivary glands

Why would earlier dissemination into salivary glands be beneficial?
4 serotypes of DENV are currently circulating

DENV-4 < 900 yrs

DENV-2 < 1500 yrs

DENV-1 < 300 yrs

DENV-3 = ??? yrs

DENV infections are mainly asymptomatic

Severe Disease

DSS

DHF

“Dengue Fever”

Unreported DF

Asymptomatic Infections

WHO

390 million infections/yr

96 million symptomatic
Dengue Fever (DF)
- High fever
- Headache
- Retro-orbital pain
- Myalgias/arthralgias
- Fatigue
- Nausea, vomiting
- Cutaneous rash
- Thrombocytopenia
- Leukopenia

Severe Dengue
- Plasma leakage resulting in shock
- Accumulation of serosal fluid sufficient to cause respiratory distress
- Severe bleeding
- Severe organ impairment

DENV circulates in tropical and subtropical regions
All four DENV serotypes are present in endemic areas

1970

9 countries

2004

DENV is now endemic to >100 countries

Why is severe dengue increasing?

Sequential infection with different DENV serotypes leads to “inappropriate” immune response

Primary Infection
Dengue Fever (DF)

Secondary Infection
Dengue Fever (DF) + Severe Dengue (DHF/DSS)

DENV Serotypes Share Partially-Conserved, but Non-Neutralizing Epitopes

“Original Antigenic Sin”
Cross-Reactive Antibodies Mediate Infection of FcγR-bearing Cell Types

**Antibody-Dependent Enhancement (ADE)**

Antibodies to Both E and prM Found in Human Sera Are Able to Enhance Infection

Antibodies that bind to prM allow entry of immature virions

Model: cleavage of prM occurs in target cell (furin)

Antibodies that recognize immature DENV (anti-prM) may dominate during *in vivo* infection and mediate high levels of enhancement

Rodenshuis-Zybert/Smit *Plos Pathogens* 2010
Dejnirattisai/Screaton *Science* 2010
Antibody titers may be important for risk of severe disease

Children with antibody titers between 1:21 – 1:80 have a higher risk for developing severe dengue

Only licensed dengue vaccine based on YFV

Recommended for use in areas where DENV is endemic due to risk of enhanced disease in individuals who have not been previously infected
Zika Outbreak 2015 - 2016

**The New York Times**

*Zika Virus a Global Health Emergency, W.H.O. Says*

By MICHAEL R.潟BER and SELLY O. MARQUEZ Aa. [May 1, 2016]

**BBC NEWS**

*Zika virus: Sexual transmission 'more common than thought'*

Los Angeles Times

Scientists offer first direct proof that Zika virus in Brazil causes birth defects

**CNN**

What real threat does Zika pose to the Rio Olympics? History has an answer

By Dr. Ford Vox, Special to CNN

Updated 8:44 AM ET on February 12, 2016

**The Washington Post**

$1.8 billion to fight Zika: CDC moves to highest alert level

By Steven Mufson and Lena H. Sun

February 8, 2016

---

**History of Zika Virus**

- **1940**
  - 1947 – isolated from a sentinel Rhesus macaque in Zika forest (Uganda)
  - 1948 – isolated from *Aedes africanus* mosquito
- **1954**
  - 1st human isolate
- **2007**
  - Yap State
  - Estimated 5,005 residents infected
- **2013**
  - French Polynesia Outbreak
- **2014**
  - New Caledonia, Cook Islands, Easter Island
  - Brazil
- **2015**
  - Cape Verde
- **2017**
  - 2014 – 2016 Brazil
Global spread during the outbreak

What other virus followed this pattern?

Zika Pathogenesis & Disease

Incubation period 3 – 14 days

Typical disease has similar symptoms to other flaviviruses:
Fever
Rash
Headache
Joint pain
Conjunctivitis
Muscle pain
Usually resolve in a week

<table>
<thead>
<tr>
<th>Features</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Transmission:

- Mosquito to human
- Mother to child in utero
- Sexual transmission

How is this different from other arboviruses?

Associations with microcephaly and Guillame-Barre

French Polynesian Outbreak 2014:

2016 Outbreak:

- Also an increase in miscarriages

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of states</th>
<th>Average annual no. cases</th>
<th>SD</th>
<th>Total no. cases</th>
<th>No. SDs above mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>2</td>
<td>14.1</td>
<td>4.7</td>
<td>11</td>
<td>-0.7</td>
</tr>
<tr>
<td>Northeast</td>
<td>9</td>
<td>43.5</td>
<td>5.6</td>
<td>471</td>
<td>76.3</td>
</tr>
<tr>
<td>Southeast</td>
<td>3</td>
<td>65.2</td>
<td>6.8</td>
<td>58</td>
<td>-1.1</td>
</tr>
<tr>
<td>South</td>
<td>1</td>
<td>21.5</td>
<td>6.2</td>
<td>3</td>
<td>-3.0</td>
</tr>
<tr>
<td>Center-West</td>
<td>4</td>
<td>13.0</td>
<td>5.1</td>
<td>31</td>
<td>3.5</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>157.3</td>
<td>17.7</td>
<td>574</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Why haven't we seen this with Zika before?

**Hypothesis 1:** Previous outbreaks too small to see effects

**Hypothesis 2:** New outbreak targeted a naïve population

Hypothesis 3: Virus evolved to be more pathogenic

2016 outbreak: **Much** larger than previous outbreaks

In African & Asian countries people are exposed young & are immune for life

In Pacific Islands & Brazil, everyone was susceptible

A single mutation in Zika facilitated its entry into neuronal cells

*Yuan et al 2017 Science*
Does Dengue exposure increase Zika pathogenesis?

In light of the new DENV cohort data, studies accounting for antibody titers are necessary in vivo.

What might account for these conflicting findings?

Things you should know about DENV/ZIKV:

• Importance of the 3' UTR during infection in mammals vs mosquitoes
• How flaviviruses make negative sense RNA strands during replication
• 4 serotypes of DENV have sylvatic origins
• Implications of secondary infection with another serotype of DENV – How this informs vaccine development and their use
• How ZIKV transmission differs from other arboviruses
• ZIKV outbreaks have followed a similar pattern as other mosquito-borne viruses
• Hypotheses for why ZIKV had never previously been associated with neurological symptoms