Introduction to Emerging Vector-Borne Infections

- Several occurrence in the last two decades
- Facilitated through unique changes in human activity and the environment such as:
  - Increase ease of global travel
  - Rapid urbanization and density of human population
  - Profusion of non-degradable containers and tires

Major Vectors of Vector Borne Diseases

- Anopheles gambiae
  - (Malaria)
- Culex pipiens
  - (West Nile, St. Louis Encephalitis, filariasis)
- Aedes aegypti
  - (Dengue, Zika)
- Aedes albopictus
  - (Dengue, Zika, Chikungunya)

Among the various vectors that are efficient in the transmission of diseases, we will focus on three genera in today's presentation. These are: The Anopheles, Culex, and Aedes.

These vectors are increasing in size and distribution due to various man-made factors:
An example that illustrates the role of modern way of life as a facilitator and multiplier can is seen in this slide:

Briefly describe the life cycle depicted in the slide:

Another man-made contribution to the abundance of vectors is climate change. Cooler temperate climates are receding and tropics is expanding.

Discuss the slide:

Average temp of the Tundra: winter -30F, Summer 37-54F; Temperate zone Average 50F; The Tropics has average annual temp of 64F.

Distribution of the various species of the Anopheles around the world.
West Nile Virus (WNV)

- Mosquito-borne virus that may often cause encephalitis or meningitis or myelitis
- First isolated in 1937 from a febrile patient in the West Nile district of Northern Uganda
- Spreads to humans by the bite of an infected mosquito
- A mosquito becomes infected by biting a bird that carries the virus
- Hence, birds are the reservoir and amplifying host (increasing pathogen level) of WNV
- In addition to humans, horses are infected

However, approximately 80% of people who are infected will not show any symptoms

Birds are the natural hosts of West Nile virus

The virus can cause severe disease and death in horses.

What is an Amplifying Host? 

Transmission cycle of EEEV

- Mosquito vector
- Dead-end hosts
- Bridge vector
- Amplifying host

CDC
Epidemiology

- WNV is the prototype of the emerging vector-borne infection in the Western Hemisphere.
- It has also been recognized in eastern Europe, the Middle East, former Soviet Union, South Asia, and Australia.
- Seasonal epidemic in North America.

Further Information: CDC West Nile Activity—US, 2006. MMWR 2007; 56; 556-9

(Epidemiology (…continued))

- There were 9,862 reported cases of WNV in 2003 with 264 fatalities in the US.
- By 2003, only OR, WA, AK, & HI did not report.
- From 1999-2014 there were a cumulative total of 41,762 cases with 1,765 deaths.
- Antigenically related to Japanese encephalitis and St. Louis encephalitis.


West Nile Outbreaks in Non-endemic Areas through 2000

- Israel – 1951-1954, 1957
- France – 1962
- South Africa – 1974
- Romania – 1996
- Italy – 1998
- Russia – 1999
- United States – 1999-2000
- Israel – 2000
- France – 2000

Only 4 states did not report WNV by 2003.

First recognized in 1999 in the US.
Some Possible Pathways of Introduction of WNV in the US

- Infected human host (remote possibility)
- Human-transported vertebrate host
  - Legal/illegal
- Human-transported vector(s)
- Storm-transported vertebrate host (bird)
- Intentional introduction (terrorist event)

This slide shows the distribution of WNV based on sentinel surveillance from crows, that are sensitive to WNV. Counties in NY, CT, RI, NJ and large portion MA showed evidence of the virus, which potentially means the probability of wide scale WNV epidemic in these regions.

Risk Factors

- Overall low risk
  - <1% of people bitten by mosquitoes
- Spending time outdoors
- People >50 at risk for more severe disease
- Risk from medical procedures is low
- Pregnancy and nursing do not increase risk
Symptoms and Signs

- 3-14 days after exposure (Incubation)
- No Symptoms in Most People. (80%)
- Mild Symptoms in Some People. (20%)
  - Fever, headache, myalgia, nausea, vomiting, and sometimes swollen lymph glands or a skin rash on the chest, stomach and back, typically lasting a few days
- Serious Symptoms (encephalitis) (0.67%)
  - High fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness and paralysis. These symptoms may last several weeks, and neurological effects may be permanent.

Transmission

- Bite from infected mosquitoes
  - Basic transmission cycle involves mosquitoes feeding on birds infected with the West Nile virus
  - Infected mosquitoes then transmit West Nile virus to humans and animals when taking a blood meal
- Transfusions and transplants
- Perinatal
  - Vertical transmission
  - Breastfeeding

Transmission Cycle

- Most people older than 60 yrs of age
- About 3-4% of those with febrile disease could develop encephalitis
- Mostly older than 60 yrs of age

1st mosquitoes have to feed on birds that have WNV infection.

When infected mosquitoes bit humans, the virus is introduced.

Other theoretical possibilities include:

- Human Infection is incidental as in recreational activities.
Diagnosis

- Clinical symptoms
  - High fever, confusion, muscle weakness, and severe headaches
- Have been in an area where WNV is present
- Antibody test—blood/Cerebrospinal fluid
  - May not be positive when symptoms first occur; however, the test is positive in most infected people within 8 days of onset of symptoms

Treatment

- No specific treatment
- Seeking clinical support early in the course of the disease may reduce serious complications
- Severe cases, supportive care
  - IV fluids, ventilation, nursing care

Estimated Sensitivity of WNV Surveillance Methods

- Dx is obscure unless augmented with good history and epi data about WNV in the area.
- Ab test from blood or CSF remains +ve remains positive 8 days after infection
- If CNS is involved, residual deficit is irreversible
### WNV Serosurvey Results

<table>
<thead>
<tr>
<th>Location</th>
<th>Participants</th>
<th>Positives</th>
<th>Seroprevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYC 1999 Queens</td>
<td>677</td>
<td>19</td>
<td>2.6</td>
</tr>
<tr>
<td>NYC 2000 Staten Is.</td>
<td>871</td>
<td>4</td>
<td>0.46</td>
</tr>
<tr>
<td>NYC 2000 Suffolk Co.</td>
<td>834</td>
<td>1</td>
<td>0.12</td>
</tr>
<tr>
<td>CT 2000 Fairfield Co.</td>
<td>731</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Prevention

- Use insect repellents containing DEET
- Stay indoors at dawn and dusk
- Wear light colored clothes
- Have good screens on windows
- Eliminate breeding sites
- Dead bird alert
  - Report dead birds to local health department
  - Do not touch the bird with bare hand

### Yellow Fever

- Aedes aegypti
  - (Dengue, Zika, Yellow fever)
**Yellow Fever**
- The yellow fever virus is in the genus *Flavivirus*, in the family *Flaviviridae*.
- It is transmitted to humans through the bite of infected mosquitoes.
- Illness ranges in severity from a self-limited febrile illness to severe hepatitis and hemorrhagic fever.
- The disease is diagnosed based on symptoms, physical findings, laboratory testing, and the possibility of exposure to infected mosquitoes.
- There is no specific treatment for yellow fever; care is based on symptoms.

**Epidemiology Yellow Fever**
- It is a very rare cause of illness in U.S.
- The last epidemic of yellow fever in North America occurred in New Orleans in 1905.
- Many acquire the disease as travelers to endemic areas without being vaccinated.
- As in WNV, risk of infection is through the bite of an infected mosquito.

**Yellow Fever Transmission**
- Transmitted in "jungle cycles" between non-human primates and mosquitoes in S. America and sub-Saharan Africa.
- Humans can acquire yellow fever from jungle mosquitoes.
- Peridomestic transmission from humans to mosquitoes, leading to other humans in "urban cycles" causing yellow fever epidemics in cities and towns of tropical America and Africa.
- Currently, yellow fever transmission occurs almost exclusively in areas of sub-Saharan Africa and South America.
Infectious Disease Epidemiology
BMTRY 713 (Part II Emerging VB Infections)

April 6, 2017
Department of Public Health Sciences

Yellow Fever Early Symptom/Signs

- Patients with yellow fever may be viremic for 3 to 6 days before demonstrating symptoms.
- Initial symptoms include fever and chills, severe headache, back pain, general muscle aches, nausea, fatigue, and weakness.
- This phase may be followed by a short period of symptom remission.
- Hepatic coagulopathy produces hemorrhagic symptoms, including hematemesis, epistaxis, gum bleeding, petechial and purpuric hemorrhages.
- Deepening jaundice and proteinuria frequently occur in severe cases.

Thrombocytopenic Purpura

Normal platelet count 150,000 to 450,000 per ml

Late Stages of Yellow Fever

- hypotension, shock, metabolic acidosis, acute tubular necrosis, myocardial dysfunction, and cardiac arrhythmia. Confusion, seizures, and coma can also occur.
- During epidemics, case-fatality rates 15% to >50% can occur in unvaccinated populations.
- Secondary bacterial infections and kidney failure are complications.
- Symptoms of weakness and fatigue may last several months in people who recover.
- Those who recover from yellow fever generally have lasting immunity against subsequent infection.
Avoid Mosquito Bites
- Use Insect Repellent—use an EPA-registered insect repellent (e.g., DEET, picaridin or oil of lemon eucalyptus)
- Wear Proper Clothing—wear long-sleeves, long pants and socks when outdoors
- Avoid Peak Mosquito Hours—peak biting times for many mosquito species is dusk to dawn, exception is *Aedes aegypti* that bites during day times

Obtain Vaccine if Recommended
- Persons aged ≥ 9 months traveling to or living in endemic areas of S. America and Africa should be vaccinated

Yellow Fever Prevention

Widespread worldwide viral disease carried by female anopheles mosquito, *Aedes aegypti* — mainly a daytime feeder living in human habitat

2.5 billion people at risk world-wide

Causes a spectrum of illnesses.
- Some people do not experience any symptoms.
- Typical dengue: fever, rash, body aches lasting ~ 1 week.
- Dengue hemorrhagic fever (severe): leaking blood vessels, destruction of platelets result in blood clotting abnormalities and cause patient to go into potentially fatal shock because of fluid loss.

What is Dengue?
Dengue Virus

- Causes dengue and dengue hemorrhagic fever
- Is an arbovirus
- Transmitted by mosquitoes
- Composed of single-stranded RNA
- Has 4 serotypes (DEN-1, 2, 3, 4)

Transmission of Dengue Virus by *Aedes aegypti*

<table>
<thead>
<tr>
<th>Days</th>
<th>Extrinsic incubation period</th>
<th>Viremia</th>
<th>Intrinsic incubation period</th>
<th>Viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Human #1</td>
<td></td>
<td>Human #2</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Illness</td>
<td></td>
<td>Illness</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>16</td>
<td></td>
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<td>20</td>
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<td></td>
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</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Replication and Transmission of Dengue Virus (Part 1)

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
Replication and Transmission of Dengue Virus (Part 2)

5. Second mosquito ingests virus with blood
6. Virus replicates in mosquito midgut and other organs, infects salivary glands
7. Virus replicates in salivary glands

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Protection from dengue

- Keep windows closed or use intact screens.
- In areas with high mosquito densities:
  - use mosquito repellents.
  - wear clothing that minimizes skin exposure.
- Do not allow standing water to accumulate around your home.
- Be aware of warnings issued by state and local health departments.

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Zika Virus Infection

Aedes aegypti (Dengue, Zika, Chikungunya, Yellow Fever)
Aedes albopictus (Dengue, Zika, Chikungunya)
Other Modes of Transmission
- Maternal-fetal
  - Intrauterine
  - Perinatal
- Other
  - Sexual
  - Blood transfusion
  - Laboratory exposure
- Theoretical
  - Organ or tissue transplantation
  - Breast milk

Countries and Territories with Active Zika Virus Transmission

Zika Virus Epidemiology
- First isolated from a monkey in Uganda in 1947
- Prior to 2007, only sporadic human disease cases reported from Africa and southeast Asia
- In 2007, first outbreak reported on Yap Island, Federated States of Micronesia
- In 2013-2014, >28,000 suspected cases reported from French Polynesia*
Zika Virus in the Americas
- In May 2015, the first locally-acquired cases in the Americas were reported in Brazil
- Currently, outbreaks are occurring in many countries or territories in the Americas, including the Commonwealth of Puerto Rico and the U.S. Virgin Islands
- Spread to other countries likely

Zika Virus in the Continental United States
- Local transmission of Zika virus has not been reported in the continental United States
- Since 2016, there have been laboratory-confirmed Zika virus cases identified in travelers returning from areas with local transmission
- With current outbreaks in the Americas, cases among U.S. travelers will most likely increase
- Imported cases may result in virus introduction and local spread in some areas of U.S.

Reported Clinical Symptoms Among Confirmed Zika Virus Disease Cases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N (n=31)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28</td>
<td>90%</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>17</td>
<td>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Yap Island, 2007

Zika Virus Clinical Disease Course and Outcomes
- Clinical illness usually mild
- Symptoms last several days to a week.
- Severe disease requiring hospitalization uncommon
- Fatalities are rare
- Guillain-Barré syndrome reported in patients following suspected Zika virus infection
  - Relationship to Zika virus infection is not known
Impact on Gray Matter

Gray matter volume is positively associated with intelligence. Therefore, it is not the size of the brain but the configuration of the Gray matter.
Daryle Keltay, 19, has microcephaly, a condition where babies are born with abnormally small heads and development problems, which his family believe could have been caused by the Zika virus.

Centers for Disease Control and Prevention

### Clinical Features: Zika Virus Compared to Dengue and Chikungunya

<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>

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### Distinguishing Zika from Dengue and Chikungunya

- Dengue and chikungunya viruses transmitted by same mosquitoes with similar ecology
- Dengue and chikungunya can circulate in same area and rarely cause co-infections
- Diseases have similar clinical features
- Important to rule out dengue, as proper clinical management can improve outcome*

Diagnostic Testing for Zika Virus
- Reverse transcriptase-polymerase chain reaction (RT-PCR) for viral RNA in serum collected 5-7 days after illness onset
- Serology for IgM and neutralizing antibodies in serum collected ≥4 days after illness onset
- Plaque reduction neutralization test (PRNT) for ≥4-fold rise in virus-specific neutralizing antibodies in paired sera
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues

Serology Cross-Reactions with Other Flaviviruses
- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses)
- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus

Zika Virus Disease Surveillance
- Consider in travelers with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis within 2 weeks after return
- Inform and evaluate women who traveled to areas with Zika virus transmission while they were pregnant
- Evaluate fetuses/infants of women infected during pregnancy for possible congenital infection and microcephaly
- Be aware of possible local transmission in areas where Aedes species mosquitoes are active

Zika Virus Preventive Measures
- No vaccine or medication to prevent infection or disease
- Primary prevention measure is to reduce mosquito exposure
- Pregnant women should consider postponing travel to areas with ongoing Zika virus outbreaks
- Protect infected people from mosquito exposure during first week of illness to prevent further transmission