Emerging Viruses

- **Arthropod-transmitted viral infections** – Yellow Fever, Dengue, WNV, ZIKA, CHIKV, JEV, EEE, WEE, VEE, Colo Tick Fever, etc
- **Emerging viruses with pandemic potential** – Ebola, SARS, MERS and Nipa
- **Zoonotic virus with no human transmission** – Hantavirus Pulmonary Syndrome

Why aren’t all “viremic” viruses transmitted by mosquitos?

“Arbo” viruses replicate in mosquitos and accumulate in the salivary glands.
We will discuss the viruses most frequently associated with human disease.

Emerging Viruses

- **Vector** - the animal/insect that transmits the virus
- **Reservoir** - the host in which a prolonged viremia allows the natural cycle to continue
There are four major cycles by which arboviruses are transmitted:

1. Bird → Insect → Man (dead end host)

2. Monkey → Insect → Man (reservoir) → Insect → Man (reservoir) → “jungle cycle”

3. Rodent → Insect → Man (dead end host) → Insect

4. Rodent → Insect → Bird

Arbovirus Infections

1. Encephalitis
2. Rash-fevers
3. Hemorrhagic fevers

1. Virus introduced into bloodstream
2. Viremia produced

Early Symptoms
Fever, Chills, Aching
Rapid Onset
Detection of Arbovirus Infection

- **Very difficult!**
  - Many viruses do not grow well in cell culture
- **Specific diagnosis by RT-PCR or by serology (high IgM or rising IgG in sequential samples)**

Characteristics of Selected Arbovirus Encephalitides

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<td><strong>Mortality (%)</strong></td>
<td>50-75</td>
<td>2-20</td>
<td>&lt;1</td>
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<tr>
<td><strong>Sequeleae</strong></td>
<td>80% of survivors</td>
<td>20% of survivors</td>
<td>Low</td>
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<td><strong>Symptoms</strong></td>
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Prevention and Control of Arbovirus Infection

- Breakage of transmission cycle
- Avoidance of endemic areas
- Immunization - Yellow Fever
• Yellow Fever Virus
• Dengue Virus
• West Nile Virus
• ZIKA Virus
• St. Louis Encephalitis Virus
• Equine Encephalitis Viruses (EEV, WEV, VEE)
• Bunyaviruses such as California Encephalitis Virus and LaCrosse Virus
• Colorado Tick Fever
• Tick-borne Flaviviruses (Omsk HF)

EMERGING, Rare but high fatality: Ebola/SARS/MERS/ Nipah
Zoonotic, rare but high fatality: Hantavirus

Yellow Fever Virus

• Flaviviridae: (+) ssRNA, enveloped virus

• Transmitted by certain mosquitoes, monkeys are reservoir

• Humans can serve as reservoir for urban cycle

Would you volunteer for this experiment?
A completely airtight-proof building was divided into two compartments by a wall across which patients were allowed to be moved. The inner compartment was entirely sealed off from the outer; this made it impossible for the nurse or doctor to be contaminated by the virus. A nurse who contracted the disease was sealed off from the outer compartment of the building and treated in the inner compartment. By this means, transmission of the disease was prevented.

Important players: Carlos Juan Finlay, James Carroll, Jesse Lazear
The Panama Canal &
William Crawford Gorgas

(reservoir)
“jungle cycle”

(reservoir)
“urban cycle”

Global Distribution of Yellow Fever

Areas endemic with yellow fever

Outbreaks in Sudan
Yellow Fever Virus

- No effective anti-viral therapy
- Live-attenuated vaccine (YF17D) is effective. All travelers to endemic areas should be vaccinated!

History-vaccine

- 1927, yellow fever virus was isolated
- In 1935, the Asibi strain was adapted to grow in mouse embryonic tissue. After 17 passages the virus, named 17D
- Further cultivated until passage 58 in whole chicken embryonic tissue
- Passage 114, in denervated chicken embryonic tissue only. Remarkable reduction in viral viscero- and neurotropism when the virus was injected intracerebrally into monkeys.
- Passages 227 and 229 viruses immunize 8 human volunteers with satisfactory results, as shown by the absence of adverse reactions and seroconversion for YF within 2 weeks.
- Larger scale immunization was then carried out in Brazil

Dengue Virus

- Flaviviridae: (+) ssRNA, enveloped virus
- Transmitted by certain mosquitoes, monkeys are reservoir
- Man can serve as reservoir for urban cycle
- Infection with one serotype seems to predispose individuals to more severe disease
Suitability for Dengue Transmission

Dengue Virus: Four Serotypes Circulate in Thailand

Hemorrhagic Manifestations of Dengue Infection

Dengue Virus

- Dengue is now found in the US
- CDC says Dengue is under diagnosed
Dengue Virus

- Development of live-attenuated, tetravalent vaccine is on-going
- Problem seems to be “balancing” the dose of the tetravalent vaccine.

Number of seropositive cases of West Nile virus, by week of onset – New York, 1999
West Nile Virus Encephalitis

- **Flaviviridae**: (+) ssRNA, enveloped virus
- Transmitted by certain mosquitoes (including *Culex pipiens*)
- Marsh birds are reservoir
- Humans can serve as reservoir for urban cycle
- Most significant disease in those people over 50 years old

**Transmission Cycle for West Nile Virus**

* Birds such as crows, hawks and flamingos die of acute infection and do not act as reservoirs for the virus

**Spread of West Nile Virus, in Birds, Horses, Mosquitoes, Other Animals, and Humans in the United States, 1999–2002.**
Human West Nile meningoencephalitis cases in USA

![Bar chart showing cases by month and week, 2002.](chart)

Human cases of West Nile virus disease by clinical category and age group United States, 2002

<table>
<thead>
<tr>
<th>WNME</th>
<th>WNF</th>
<th>Unspecified</th>
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</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>0-9</td>
<td>33 (1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>10-19</td>
<td>58 (3)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>20-29</td>
<td>138 (6)</td>
<td>52 (7)</td>
</tr>
<tr>
<td>30-39</td>
<td>265 (11)</td>
<td>121 (17)</td>
</tr>
<tr>
<td>40-49</td>
<td>355 (15)</td>
<td>184 (26)</td>
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<tr>
<td>50-59</td>
<td>334 (14)</td>
<td>118 (17)</td>
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<td>60-69</td>
<td>349 (15)</td>
<td>101 (14)</td>
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<tr>
<td>70-79</td>
<td>499 (21)</td>
<td>67 (10)</td>
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<td>80-89</td>
<td>295 (13)</td>
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<td>90-99</td>
<td>33 (1)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>2,554</td>
<td>764</td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>59</td>
<td>48</td>
</tr>
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Number of West Nile virus neuroinvasive disease cases, by week of illness onset – United States, 2007

![Bar chart showing cases by week, 2007.](chart)
Incidence of West Nile virus neuroinvasive disease by age group
– United States, 2007

* Per 100,000 population.
† Includes meningitis, encephalitis, and acute flaccid paralysis.

THE NEW ENGLAND JOURNAL OF MEDICINE

West Nile Virus among Blood Donors in the United States, 2003 and 2004
Susan A. Shulman, M.D., Cheung Y. Tang, M.D., Gregory A. Foster, M.D.,
Annette G. Wigger, M.D., and Roger R. Dodd, M.D.

CONCLUSIONS
Rapid implementation of a nucleic acid amplification test for the prospective identification of West Nile virus RNA, and the removal of more than 900 potentially infectious related components from the blood supply of the Red Cross, no cases of transfusion-transmitted infection were confirmed among recipients of the pooled blood.
West Nile Virus Vaccines in Development!!

- Chimeric vaccine with YF17D
- Envelope proteins of WNV (subunit vaccine)

ZIKA VIRUS

Congenital Zika Syndrome?

- acute infection by mosquito or infected semen
- All Months of Pregnancy?
- Infection of Fetus
- Severe Spontaneous Abortions Stillbirths?
- Chronic? Microcephaly And ??
Timeline of Symptoms and Radiographic and Laboratory Studies.

Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).

Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings.

Twelve of 42 women (29%) in whom fetal ultrasonography was performed had abnormal findings.

From Zika Virus Review article NEJM, March 30, 2016
Symptoms of infection with Zika virus
(from www.cdc.gov web site):

Most people infected with Zika virus won’t even know they have the disease because they won’t have symptoms. The most common symptoms of Zika are fever, rash, joint pain, or conjunctivitis (red eyes). Other common symptoms include muscle pain and headache. The incubation period (the time from exposure to symptoms) for Zika virus disease is not known, but is likely to be a few days to a week.

People usually don’t get sick enough to go to the hospital, and they very rarely die of Zika. For this reason, many people might not realize they have been infected. Zika virus usually remains in the blood of an infected person for about a week but it can be found longer in some people. Once a person has been infected, he or she is likely to be protected from future infections.

Antivirals and 17D-based vaccines for Zika virus are in development, but this is likely to take years before FDA approval.

Blood supply will be screen for Zika virus (asymptomatic donors)

Question: Once Zika virus is endemic in Brazil and most people develop immunity during childhood, will we still see fetal infections and microcephaly?

What about travelers to areas with Zika virus-infected mosquitoes?

Check out www.cdc.gov and Youtube SciShow Zika virus for updates

St. Louis Encephalitis Virus: second to WNV as a common cause of epidemic encephalitis in the USA
**St. Louis Encephalitis Virus**

- *Flaviviridae: (+) ssRNA, enveloped virus*
- Transmitted by certain mosquitoes, marsh birds are reservoir
- Man can serve as reservoir for urban cycle (2-20% mortality)
- Currently, no specific therapy or vaccine is available

**Eastern, Western, Venzuelan Equine Encephalitis Virus**

- *Togaviridae: (+) ssRNA, enveloped virus*
- Transmitted by certain mosquitoes, marsh birds are reservoir
- Man is dead-end host (short viremia) with 50-70% mortality

**Life Cycle of the EEE Virus**

The complete cycle takes place between wild birds by the bite of Culiseta mosquitoes and between wild birds and wild mammals via Aedes mosquitoes. One-way spread to humans, horses, and pheasants takes place by the bite of Aedes mosquitoes.
Chikungunya Virus Infection

Chikungunya virus infection is a rapid-onset, febrile disease with intense asthenia, arthralgia, myalgia, headache, and rash.

Acute arthritis involving wrist and interphalangeal joints in a patient with Chikungunya infection.

Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors

Timeline of Chikungunya Infection, Symptoms, and Biomarkers
Why is this site a public health hazard?

LaCross and California Encephalitis Virus

- *Bunyaviridae*: (-) segmented RNA, enveloped virus
- Transmitted by certain mosquitoes, small mammals are reservoir
- Secondary viremia allows access to CNS
- There may be >200 bunyaviruses
### Characteristics of Selected Arbovirus Encephalitis

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### Number of Cases of California Encephalitis Virus

![Map of the United States](image)

**Prevention**

---

20
**Colorado Tick Fever**

**Virus family**
- Reoviridae

**Transmission**
- Tick Bite

**Symptoms**
- Like other rash fevers
- Fever, headache, myalgia
  rash, *not severe*

---

**Highest incidence of Colorado Tick Fever**

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**Colorado Tick Fever**

**Lyme Disease**

Areas of predicted Lyme disease transmission.
3. Omsk HF/Spring-Summer HF
Flavivirus, (+) RNA, envelope
Found in eastern Europe, Russia
Live attenuated vaccine is available

CDC website also indicates you can get it from contact with infected muskrat blood and tissues.

Now for the rare and very deadly....

Ebola
SARS/MERS
NIPAH/Hendra
Health workers unload medical supplies in Guinea to deal with Ebola
Characteristics of Filoviruses

- Cause severe hemorrhagic fevers with high mortality
- Bats are likely reservoir
- Human to human transmission by contact with infected fluids
- Vaccine, passive antibody and anti-viral drugs in development

Find more information on emerging viruses at:

nejm.org/topics
Transmission of Ebola Virus

Bat reservoir

Ebola virus can persist in the eye and semen

Ebola: Dr Ian Crozier's left eye turned from blue to green after it became infected with the virus

Ebola Virus: An Emerging Virus with Pandemic Potential

• Emerging virus from bats into humans
• Transmission person to person from infected blood or secretions
• Antiviral drugs, neutralizing Mab, and vaccines in development
Our next emerging virus?

Symptoms of SARS: Fever and atypical pneumonia

Spread from Hotel M

Ref: Lee et al, A major outbreak of Severe Acute Respiratory Syndrome in Hong Kong, NEJN April 7, 2003
Dr. Carlo Urbani, 46, of Italy, the first doctor to realize that the world was dealing with the unfamiliar disease SARS (Severe Acute Respiratory Syndrome). Urbani, a World Health Organization expert on communicable diseases, who died of illness in Bangkok, Thailand, Saturday, March 29, 2003. Urbani became infected while working in Vietnam, where he diagnosed an American businessman hospitalized in Hanoi, who later died. (AP Photo/Guido Picchio)

A portrait of Carlo Urbani is seen at the entrance to a memorial service in Hanoi. (AFP/Hoang Dinh Nam)

Transmission of SARS-CoV

- Respiratory spread, large droplets, close contact
- Fecal-oral spread from shed in waste water?
- Possible spread from virus contaminating surfaces?

Ultrastructural Characteristics of SARS-Associated Coronavirus Growth in Vero Cells
**SARS-CoV: Related to, but distinct from other coronaviruses**

- Human coronavirus 229E
- Porcine epidemic diarrhea virus
- Feline infectious peritonitis virus
- Porcine respiratory coronavirus
- Mouse hepatitis virus
- Rat hepatitis virus
- Bovine coronavirus
- Porcine hemagglutinating encephalomyelitis virus

**Analysis of the N protein**

2005: Chinese horseshoe bats implicated as the reservoir for SARS-CoV!

- Animals can serve as a reservoir for viruses
- International travel contributes to the rapid spread of newly emerged viruses
- Public health measures were effective in stopping the spread of this viral infection

**SARS: An emerging virus**
MERS: Middle East Respiratory Syndrome

The new SARS??

Observant physician follows up on patient with atypical pneumonia.....

BRIEF REPORT

Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia


SUMMARY

A previously unknown coronavirus was isolated from the sputum of a 60-year-old man who presented with acute pneumonia and subsequently died from a fatal outcome in Saudi Arabia. The virus isolated (MERS-CoV) replicated well in cell culture, producing cytopathic effects of rounding, detachment, and syncytium formation. The virus represents a novel betacoronavirus species. The closest known relatives are bat coronaviruses BES144 and HKU3. Here, the clinical data, virus isolation, and molecular identification are presented. The clinical picture was remarkably similar to that of the severe acute respiratory syndrome (SARS) outbreak in 2003 and suggests that animal coronaviruses can cause severe disease in humans.

Regional problem? All known MERS cases so far occurred in the Middle East or were linked to that region.
Beyond borders. A recent study found MERS in camels in Egypt, including animals imported from Sudan and Ethiopia.

MERS: CoV likely from camels to humans and is associated with pneumonia.

- Mortality rate estimated at 45%
- No vaccines, no antivirals.....

Potential for spread of MERS???
Coronaviruses may emerge from animal hosts to cause significant disease in humans

Currently known coronaviruses

- HCoV-229e
- HCoV-OC43
   - "common cold"
- HCoV-NL63
- HCoV-HKU1
   - croup
   - pneumonia in elderly
   - rarely fatal
- SARS-CoV
- MERS-CoV
   - emerge to cause pneumonia
   - with high mortality

Nipah Outbreak

- Between October, 1998 and April 1999 an outbreak of severe encephalitis occurred in Peninsular Malaysia
- 265 cases and 105 deaths (40% mortality)
- 11 cases and 1 death in Singapore
- Most cases occurred in individuals who had contact with swine or worked in the swine industry
- Concurrent respiratory illness in pigs
- Epidemiologic circumstances were not consistent with Japanese encephalitis, JE vaccine was ineffective
EM consistent with paramyxovirus with helical nucleocapsid

Infectious agent was identified
- Nipah virus (family paramyxovirus)
- High mortality rate, no vaccines, no antivirals
- BSL-4 agent
Nipah Virus Disease in Pigs

- Rapid and labored breathing
- Explosive “mile long” nonproductive cough
- Neurologic changes (lethargy and aggressive behavior)

Pathology in Pigs

- Pulmonary infiltrate
- Linear staining of the bronchial epithelium

Control of the outbreak

- Quarantine of pig farms with infected pigs
- Culling of 1.1 million pigs
- Destruction of farms; compensate farmers
Effect of Pig Culling Activities

Isolation of Nipah virus from Malaysian Island flying-foxes

Nipah Virus

- During the Nipah outbreak pigs, humans, cats, and dogs were infected and had illness.
- BSL-4 agents
- Key epidemiologic features
  - No person to person spread in either outbreak (includes family contacts and health care workers)
  - Infection resulted from close contact with sick pigs or horses
The moral of the Nipah virus story:

Don’t plant mango trees near pig pens!

Viruses can emerge into the human population through intermediate hosts.
Why are these patients dying?

Is there a threat to public health?
# Recognized Hantaviruses

<table>
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<th>Distribution</th>
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<td>field mice</td>
<td>Asia</td>
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<td>Prospect Hill</td>
<td>none</td>
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# Newly Recognized Hantaviruses

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<td>U.S.A.</td>
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<tr>
<td>Sin Nombre</td>
<td>Pulmonary Syndrome</td>
<td>deer mice</td>
<td>N. America</td>
</tr>
</tbody>
</table>
Why did Hantavirus Pulmonary Syndrome emerge in 1993?
Carrier. Deer mouse (inset) appears to be the primary reservoir of the newly discovered hantavirus.

Hantavirus Pulmonary Syndrome Cases by Outcome United States, as of February 1, 1995*

<table>
<thead>
<tr>
<th>Year and Month of Onset</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>1993</td>
<td>10</td>
<td>8</td>
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<td>1999</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Eighteen additional cases (eleven deceased) with onset before 1992 not shown.

Health Care Workers Exposure to Hantavirus

- Exposed to Hantavirus: n = 266
  - 100% Sero-negative
- Not Exposed to Hantavirus: n = 131
Zoonoses

Hantavirus Pulmonary Syndrome

Emerging Viruses

• HPS may “emerge” when the environmental conditions are right.
• Developing an antiviral drug is a priority.
• Vaccines would be used only in specific populations.

Emerging Viruses

• Animals provide a reservoir from which viruses can emerge and infect an alternative host species
• Observant physicians are critical for recognizing emerging viruses!!