Emerging viruses

- **Emerging virus** - causative agent of a new or previously unrecognized infection

- The term became popular in 1990s, but emerging viruses are not new

- Since the rise of agriculture - 11,000 years ago - new infectious agents have invaded human populations because they can be sustained by numbers that were unknown before agriculture and commerce

- Only recently have we become good at detecting emerging viruses
Emerging viruses

- Expanded host range with an increase in disease not previously obvious
- Transmission of a virus from a wild or domesticated animal to humans - zoonosis
- Cross-species infection may establish a new virus in the population (SIV moving from chimps to humans)
- Often cross-species infection cannot be sustained (e.g. Ebola and Marburg from bats to humans)
Human - animal interface

Viruses belonging to # of genera

- Adapted pathogens (> Homo sapiens)
- Zoonotic pathogens
- Heirloom pathogens (< Homo spp.)
- Heirloom pathogens (> Homo spp.)
Convergent forces of disease emergence

- Globalization
- Rapid air travel
- Deforestation
- Expanding populations ("mega-cities")
- Poverty
- Climate change
- Microbial evolution
- Environmental changes
Over-riding factors driving the emergence of infectious diseases of humans and animals:

*Human population growth and incredible change occurring in all ecosystems brought about by human occupation of almost every corner of the planet*
The Amazon North Region of Brazil

Home to 183 Arthropod-borne and Other Vertebrate Viruses

Sites from which viruses were isolated at the Evandro Chagas Institute
<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Drivers of Emergence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue virus</td>
<td>Flaviviridae</td>
<td>Urban population density, mosquito breeding</td>
</tr>
<tr>
<td>Ebola virus</td>
<td>Filoviridae</td>
<td>Human contact with natural host; bushmeat</td>
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<tr>
<td>Hantaan virus</td>
<td>Bunyaviridae</td>
<td>Agriculture: human/rodent contact</td>
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<tr>
<td>Hendra virus</td>
<td>Paramyxoviridae</td>
<td>Bats to horses to stable workers</td>
</tr>
<tr>
<td>HIV</td>
<td>Retroviridae</td>
<td>Bushmeat trade</td>
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<tr>
<td>Influenza virus</td>
<td>Orthomyxovirida</td>
<td>Pig/bird agriculture</td>
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<tr>
<td>SARS coronavirus</td>
<td>Coronaviridae</td>
<td>Open meat markets</td>
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<tr>
<td>Nipah virus</td>
<td>Paramyxoviridae</td>
<td>Bats to pigs to humans</td>
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<tr>
<td>MERS coronavirus</td>
<td>Coronaviridae</td>
<td>Camel-human contact</td>
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<tr>
<td>Rift Valley virus</td>
<td>Bunyaviridae</td>
<td>Dams, irrigation</td>
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<tr>
<td>Sin Nombre virus</td>
<td>Bunyaviridae</td>
<td>Weather, human/rodent contact</td>
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<tr>
<td>West Nile virus</td>
<td>Flaviviridae</td>
<td>Mosquito</td>
</tr>
<tr>
<td>Zika virus</td>
<td>Flaviviridae</td>
<td>Mosquito</td>
</tr>
</tbody>
</table>
Roles of Evolution

- Leads to the biodiversity of pathogens existing in nature (*quasispecies*)
- Adaptation to new hosts and environments (through variation and selection)
The general interactions of hosts and viruses

- Stable: maintains virus in ecosystem
- Evolving: passage of virus to naive population (same or different host)
- Dead-end: one way passage to different species
- Resistant host: infection blocked

Emerging infections
Stable host-virus interactions

- Both participants survive and multiply
- Some are effectively permanent
  - *Humans are sole natural host for measles virus, herpes simplex virus, HCMV, smallpox*
- May include infection of more than one species
  - *Influenza A virus, flaviviruses, togaviruses*
Evolving host-virus relationship

- Hallmarks are instability and unpredictability
- Outcome of infection may range from benign to death
  - Introduction of smallpox and measles to natives of Americas by Old World colonists and slave traders
  - Introduction of West Nile virus into Western Hemisphere, 1999
  - Introduction of myxoma virus to eliminate rabbits into Australia
Dead-end interaction

- Frequent outcome of cross-species infection
- No sustained transmission from new infected host to others of the same species
- Ebolavirus: humans, chimps, gorillas
- H5N1
- Contribute little to the spread of the natural infection
The complex life cycle of an arbovirus

Stable host-virus interactions
Rodents and insect vectors move European tick-borne encephalitis virus among many hosts
Flaviviruses: Human pathogens
Emerging infections: Two steps

- Introduction
- Establishment and dissemination
Humans are constantly providing new ways to meet viruses

- Dams and water impoundments
- Irrigation
- Massive deforestation
- Rerouting of wildlife migration patterns
- Wildlife parks
- Long distance transport of livestock and birds

- Air travel
- Uncontrolled urbanization
- Day care centers
- Hot tubs
- Air conditioning
- Millions of used tires

- Blood transfusion
- Xenotransplantation
- Societal changes with regard to drug abuse and sex
Encountering new hosts

- Rare chance encounters of viruses with new hosts may never be detected.
- Single-host infections are not transmitted among humans for many reasons.

Or horses, pigs, chickens, bats.
Expanding viral niches

- Successful encounters require access to susceptible and permissive cells
- Population density and health are important factors
- Virus populations will endure in nature only because of serial infections (a chain of transmission)
Diseases of exploration and colonization

- Explosive epidemic spread may occur when a virus enters a naive population
- Smallpox reached Europe from the Far East in 710 AD, attained epidemic proportions
- Smallpox changed the balance of human populations in the New World - killed 3.5 million Aztecs in 2 years (1520 - spread from Hispaniola), allowing conquest by Cortez
Changes in human populations and environments

- Emergence of epidemic poliomyelitis in the beginning of the 20th century
- Known since 4,000 years ago, stable host-virus relationship
Poliomyelitis: A disease of modern sanitation

Not Mutation!
Bats: A source of zoonotic infections

- Many new paramyxoviruses found in flying foxes since 1995, including Nipah and Hendra viruses
- Cause severe disease in domestic animals (horses and pigs) and infect humans

ARTICLE

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Bats host major mammalian paramyxoviruses

66 new paramyxoviruses from 119 bat and rodent species
Nipah virus

- First outbreak Malaysia 1998
  - Outbreak of respiratory and neurological disease on pig farms
  - 105 human deaths, 1 million pigs culled
- Fruit bats are unaffected, excrete virus in urine
- Pig farmers plant mangoes near pigpens
- Pigs spread infection to humans
- Subsequently humans infected by consuming date palm sap contaminated by bats (India, Bangladesh)
- Human to human transmission; infections continue
Hendra virus

- Discovered in Hendra, Australia, September 1994
  - Outbreak killed 14 racehorses and a trainer
- Spread from flying foxes to horses, then to humans
- Horses continue to acquire infection
- Vaccine for horses: One World health
TWiV 296: The real Batman, Linfa Wang

August 3, 2014

Host: Vincent Racaniello

Guest: Linfa Wang

Vincent visits the Australian Animal Health Laboratory in Geelong, Australia and speaks with Linfa about his work on bats and bat viruses.
Changing climate and animal populations

- Hantavirus pulmonary syndrome - first noted in Four Corners area of New Mexico, 1993

- Disease is caused by Sin Nombre virus, endemic in the deer mouse (*Peromyscus maniculatus*, 30% virus positive)

- Originally called Muerto Canyon virus, but residents objected
Changing climate and animal populations

- In 1992-93, abundant rainfall produced a large crop of piñon nuts, food for humans and the deer mouse. Mouse population rose, contact with humans increased.
- Virus is excreted in mouse feces; contaminated blankets or dust from floors provided opportunities for human infection.
- Humans not the natural host for Sin Nombre virus, human disease is rare.
- Not new - earliest known case 1959.
HPS by State, January 2017
n=728

Range of *P. maniculatus*

Deer mouse, white-footed mouse, rice rat, cotton rat

https://www.cdc.gov/hantavirus/surveillance/reporting-state.html

Virology Lectures 2019 • Prof. Vincent Racaniello • Columbia University
Heartland virus disease

- 2012 - new phlebovirus identified in two farmers in Missouri
- >40 subsequent cases identified, Lone Star tick vector
- How long had it been infecting people?

Bunyaviridae

Ebola hemorrhagic fever

- Simultaneous outbreaks in 1976 in DRC (318, 88%) and Sudan (284, 53%)
- Sudan index case: cotton factory workers
- Spread by use of contaminated needles, among family members
- Named after small river in northwestern DRC
Outbreaks of Ebolavirus disease

*Each outbreak represents a new zoonotic spillover*
Biosafety level 4 (BSL-4)

- High mortality
- Person to person transmission
- No approved vaccine or antiviral

Threading the NEIDL https://youtu.be/tqAjkjGq8Ug
Ebolavirus

The image illustrates the replication cycle of Ebolavirus, showing:

- Genomic RNA coated with nucleoproteins (N, VP30)
- Polymerase complex protein (VP35)
- VP24
- Matrix (VP40)
- Glycoprotein (GP)

The replication cycle involves:

1. (-) strand RNA
2. (+) strand mRNA
3. mRNA synthesis
4. Translation

Antagonists to IFN are also depicted.
How are humans infected?

- A classic zoonosis
- Index case: contact with animal carcass* (bushmeat)
- Transmitted to other humans by close contact with infected fluids
- Chains of human infections short
- $R_0 = 2$

*not always identified
Filovirus ecology

- Marburg virus has been isolated from cave-dwelling fruit bat (*Rousettus aegyptiacus*)
- Zaire Ebolavirus RNA, antibodies found in three tree-roosting bats (but not infectious virus)
- Humans, gorillas, chimpanzees are dead-end hosts
What is the origin of Ebolaviruses?

[Diagram showing the origin of Ebolaviruses with Bat reservoirs and transmission to Chimp, Gorilla, and Other.]
Ebolavirus outbreak examples

- Gabon, 1996 (Zaire ebolavirus, 37 cases) A chimpanzee found dead in the forest was eaten by people hunting for food. Eighteen people who were involved in butchering the animal became ill. Ten other cases occurred in their family members.

- Gabon, 1996-97 (Zaire ebolavirus, 60 cases) The index case was a hunter who lived in a forest camp. A dead chimpanzee found in the forest at the time was infected with Ebola virus.
Ebola virus emergence in Guinea


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Human-human transmission

- Contact with infected blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, semen) from someone who is sick or has died
- Contact with contaminated objects (needles, syringes)
- Not by insects, water, food, or aerosol
Host entry

- Mucosal surfaces
- Breaks or abrasions in skin
- Parenteral (e.g. contaminated needles)
- Virus detected in skin, body fluids, nasal secretions, blood, semen
Ebolavirus disease: Clinical features

- Incubation period 2–21 days (not contagious)
- Early symptoms: fever, headache, muscle pain, diarrhea, vomiting, stomach pain
- Peak illness: rash, hemorrhage, convulsions, severe metabolic disturbances, diffuse coagulopathy
- 30–90% case fatality ratio in Africa
Clinical features: Multisystem involvement

- Systemic (prostration)
- Gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhea)
- Respiratory (chest pain, shortness of breath, cough)
- Vascular (conjunctival injection, postural hypotension, edema)
- Neurological (headache, confusion, coma)
Pathogenesis

- Extensive necrosis in parenchymal cells of many organs (liver, spleen, kidney, gonads)
- Broad cell tropism: Monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, epithelial cells
- Elevation of liver enzymes, shock (adrenal)
- Massive lymphocyte death but not infected
Immunopathogenesis

- Many inflammatory mediators produced, especially by infection/activation of monocytes/macrophages
- Imbalanced cytokine production $\Rightarrow$ disease
- Impairment of vascular and coagulation systems
An acute infection?

*Persistence of Ebolavirus in ocular fluid during convalescence 9 weeks after clearance of viremia*
An acute infection?

Evidence of sexual transmission
Presence of viral genome in semen

46/93 men (49%)
What did we learn?

- Every infectious disease is a global problem
  - 4 cases in US: 2 imported (Dallas, NYC), 2 locally acquired
- Ebolavirus vaccines have been ready for clinical trials for some time
- What other viruses should we be preparing for?
SARS - Rise and fall of a zoonotic infection

PNEUMONIA - CHINA (GUANGDONG): RFI

**********************************
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the International Society for Infectious Diseases <http://www.isid.org>
[1]
Date: 10 Feb 2003
From: Stephen O. Cunnion, MD, PhD, MPH <cunnion@erols.com>

This morning I received this e-mail and then searched your archives and found nothing that pertained to it. Does anyone know anything about this problem?

"Have you heard of an epidemic in Guangzhou? An acquaintance of mine from a teacher's chat room lives there and reports that the hospitals there have been closed and people are dying."

--

Stephen O. Cunnion, MD, PhD, MPH
International Consultants in Health, Inc
Member ASTM&H, ISTM
<cunnion@erols.com>
SARS (severe acute respiratory syndrome)

- Outbreak of severe atypical pneumonia, unknown etiology, Guangdong Province, China, Nov 2002
  - 305 cases, 5 deaths
- Incubation period 2-10 days
- Illness begins with prodrome of fever
  - Chills, headache, malaise, myalgia
- Next phase: dry cough, shortness of breath
- 10-20% may require mechanical ventilation
SARS

- A Chinese doctor who treated first patients traveled to Hong Kong on 21 February 2003, stayed on ninth floor of Metropole Hotel
- He died in hospital 22 February
- Infection spread to 10 people in hotel, who flew to Singapore, Vietnam, Canada, US before symptoms evident
- Infection spread to 8000 people in 29 countries, 10% mortality
Probable cases of SARS by date of onset, Hong Kong: n = 1753

Outbreak ends July 2003
Probable SARS Cases Worldwide Reported to WHO as of Sept. 26, 2003

Total: 8,098 cases; 774 deaths (9.6% case fatality)
Origin of SARS-CoV

- Human sera collected before SARS outbreak do not contain antibodies to SARS-CoV
- Early Guangdong SARS cases were in handlers of animals for the exotic food market
- Animal traders had significantly higher prevalence of anti-SARS-CoV antibodies than control groups
MERS-CoV

- Index case September 2012: 60 yo male patient, died of pneumonia, renal failure
- Virus recovered, genome sequenced, binds dipeptidyl peptidase 4 receptor
- Closely related to bat coronaviruses
- Not SARS-CoV
MERS-CoV

- Spread from dromedary camels (endemic in Middle East and Africa)
- Not all infections have camel source
- Role of bats?
- How is the virus transmitted to humans? (mainly very ill)
- Why are so few humans infected? Will it spread?
- Why doesn’t the virus transmit well among humans?
- Camel vaccine in testing (One Health approach)
- Antivirals for infected patients in development
MERS-CoV transmission and geographic range

2399 cases/827 deaths (CFR 34.4%)
How common are host range jumps?

- Dead end: Very common
- Those that produce sustaining transmission: Rare
- Can we predict them? No
- But we can know what is out there, and react (preparedness)
Next time: HIV and AIDS