Emerging viruses

Lecture 22
Biology W3310/4310
Virology
Spring 2014

Nothing endures but change
Heraclitus
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
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

- Heirloom pathogens (< Homo spp.): 37
- Heirloom pathogens (> Homo spp.): 6
- Adapted pathogens (> Homo sapiens): 16
- Zoonotic pathogens: 32
Convergent Forces of Disease Emergence

GLOBALIZATION
RAPID AIR TRAVEL

EXPANDING POPULATIONS
"MEGA-CITIES"
POVERTY

DEFORESTATION

MICROBIAL EVOLUTION

ALTERED ECOSYSTEMS
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>Emergence Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue virus</td>
<td><em>Flaviviridae</em></td>
<td>Urban population density; open water storage favors mosquito breeding (e.g., millions of used tires)</td>
</tr>
<tr>
<td>Ebola virus</td>
<td><em>Filoviridae</em></td>
<td>Human contact with unknown natural host in Africa; importation of monkeys in Europe and the United States</td>
</tr>
<tr>
<td>Hantaan virus</td>
<td><em>Bunyaviridae</em></td>
<td>Human contact with rodents as a result of agricultural techniques</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td><em>Retroviridae</em></td>
<td>Transfusions and blood products; sexual transmission; needle transfer during drug abuse</td>
</tr>
<tr>
<td>Human T-lymphotropic virus</td>
<td><em>Retroviridae</em></td>
<td>Transfusions and blood products; contaminated needles; social factors</td>
</tr>
<tr>
<td>Influenza virus</td>
<td><em>Orthomyxoviridae</em></td>
<td>Integrated pig-duck agriculture; mobile population</td>
</tr>
<tr>
<td>Junin virus</td>
<td>* Arenaviridae*</td>
<td>Agriculture techniques favor human contact with rodents</td>
</tr>
<tr>
<td>Noroviruses</td>
<td><em>Caliciviridae</em></td>
<td>New methods for detection; infectious diarrhea</td>
</tr>
<tr>
<td>Machupo virus</td>
<td>* Arenaviridae*</td>
<td>Agriculture techniques favor human contact with rodents</td>
</tr>
<tr>
<td>Marburg virus</td>
<td><em>Filoviridae</em></td>
<td>Unknown; importation of monkeys in Europe</td>
</tr>
<tr>
<td>Rift Valley virus</td>
<td><em>Bunyaviridae</em></td>
<td>Dams, irrigation</td>
</tr>
<tr>
<td>Sin Nombre virus</td>
<td><em>Bunyaviridae</em></td>
<td>Natural increase of deer mice and subsequent human/rodent contact</td>
</tr>
<tr>
<td>West Nile virus</td>
<td><em>Flaviviridae</em></td>
<td>Unknown introduction into United States</td>
</tr>
</tbody>
</table>
Roles of Evolution

• Leads to the biodiversity of pathogens existing in nature

• 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
- **Dead-end**: one way to different species
- **Resistant host**: infection blocked
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
- Virus may acquire new property that increases virulence or spread, or if host changes (e.g. famine or population change during wars)
Dead-end interaction

- Frequent outcome of cross-species infection, but not of intraspecies infections
- Often host is killed so quickly that there is little or no transmission to others (Ebola virus)
- New infected host may not transmit the infection to others of the same species (H5N1)
- Contribute little to the spread of a 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.
Other dead-end infections

- Yellow fever (monkey)
- Marburg, Ebola, Hendra, Nipah, SARS progenitor (bats)
- Lassa, Junin, Sin Nombre (rodents)
- Laboratory animal models
Emerging infections: Two steps

- Introduction
- Establishment and dissemination
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
Expanding viral niches

- Successful encounters require access to susceptible and permissive cells
- Population density and health are important factors
- Virus populations will survive in nature only because of serial infections (a chain of transmission)
Human are constantly providing new ways to meet viruses

- Air travel
- Dams and water impoundments
- Irrigation
- Rerouting of wildlife migration patterns
- Wildlife parks
- Hot tubs
- Air conditioning
- Blood transfusion
- Xenotransplants
- Long-distance transport of livestock and birds
- Moral and societal changes with regard to and drug abuse sex
- Massive deforestation
- Millions of used tires
- Uncontrolled urbanization
- Day care centers
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
Yellow fever virus: Humans change the pattern and pay the price.

Yellow fever deaths, Philadelphia, 1793

Infectious disease arrives from Santo Domingo

October 23: temperature falls to 50F (mosquitoes perish)

July August September October November

Cases ~10,000
Deaths ~5,000

“Yellow Fever will discourage the growth of great cities in our nation”

THOMAS JEFFERSON, 1800

Principles of Virology, ASM Press
Changes in human populations and environments

- Emergence of epidemic poliomyelitis in the beginning of the 20th century: improved sanitation delayed transmission
- Known since 4,000 years ago, stable host-virus relationship
Poliomyelitis: A disease of modern sanitation
Bats: a source of zoonotic infections

• Many new paramyxoviruses found in flying foxes since 1995, including Nipah and Hendra viruses

• Three cause severe disease in domestic animals (horses and pigs) and are known to infect humans
Nipah virus

- First outbreak Malaysia 1998
  - Outbreak of respiratory and neurological disease on pig farms
  - 105 human deaths, 1 million pigs culled

- Fruit bats excrete virus in urine but are unaffected
- 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
Changing climate and animal populations

- Hantavirus pulmonary syndrome - first noted in the 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 to the name
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.
Distribution of *Peromyscus maniculatus* and Location of HPS Cases as of December 21, 2012
Total Cases (N=616 in 34 States)

Deer mouse, white-footed mouse, rice rat, cotton rat
Hantavirus Pulmonary Syndrome Response Continues at Yosemite National Park

Date: August 27, 2012

Park Takes Additional Steps to Protect Public Health

YOSEMITE NATIONAL PARK - The recent diagnosis of hantavirus pulmonary syndrome (HPS) in two Californians, one of whom died, has prompted Yosemite National Park to scale up its public health response and outreach. The National Park Service Office of Public Health learned over the weekend of a confirmed third case, which resulted in a fatality, and probable fourth case, of hantavirus in individuals who visited Yosemite National Park in June of this year. An outreach effort is currently underway by the park concessioner to contact visitors who stayed in “Signature Tent Cabins” at Curry Village from mid-June through the end of August. These individuals are being informed of the recent cases and are being advised to seek immediate medical attention if they exhibit any symptoms of hantavirus.

Hantavirus is a rare but serious disease that occurs throughout the United States. Early medical attention is critical for individuals who contract hantavirus. The disease begins with fever and aches, but can progress rapidly to life-threatening illness. Public health officials believe the four recent visitors might have been exposed while vacationing at Curry Village in Yosemite National Park.
Hantavirus zoonotic infection is a warning that potential human diseases lurk in the wild if we inadvertently intrude upon another host-parasite relationship.
SARS - Rise and fall of a zoonotic infection

PNEUMONIA - CHINA (GUANGDONG): RFI

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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

• 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 (Severe acute respiratory syndrome)

- 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
Spread from Hotel Metropole
(21 February 2003)
249 cases traced to “A” as of March 28, 2003
Probable cases of SARS by date of onset, Hong Kong: n = 1 753, as of 9 June 2003

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

- China (5327)
- Singapore (238 + 1)
- Hong Kong (1755)
- Vietnam (63)
- Canada (251)
- U.S. (29)
- Europe: 10 countries (34)
- Thailand (9)
- Taiwan (346)
- Singapore (238 + 1)
- Australia (6)

Total: 8,098 cases; 774 deaths (9.6% case fatality)
SARS virion
~120 nm
SARS-CoV disease mechanisms

- Transmitted by respiratory droplets
- Virus enters respiratory tract and multiplies in epithelial cells
- Multiplication in alveolar epithelial cells leads to lung injury
- Immune suppression cause of severe disease?
SARS and the economy: impact on global travel
Airport screening and health information, Hong Kong, SARS, 2003
Public Health Responses to SARS

- Epi Surveillance and early warning
- Case investigation, contact tracing
- Interventions
  - Immunization: NOT AVAILABLE
  - Antiviral agents: NOT AVAILABLE
  - Travel restrictions, quarantine: WIDELY USED
  - Public education
- Infection control for healthcare providers and in healthcare settings
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
Antibody to coronavirus in humans, Guangdong Province

<table>
<thead>
<tr>
<th>Occupation</th>
<th>#</th>
<th>Antibody (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild animal trader</td>
<td>20</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Animal slaughterer</td>
<td>15</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Vegetable handler</td>
<td>20</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Control (hosp., nonresp.)</td>
<td>60</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Origin of SARS-CoV

- Virus isolated from Himalayan palm civets in live-animal market in Guangdong (May 2003)
- Evidence that some SARS infections in China were transmitted from civets to humans
- Civet culling and quarantine imposed
- Probably not animal reservoir of the virus:
  - Civet viruses >99.6% identity
  - Virus not often isolated from farm or wild civets
Origin of SARS-CoV

- SARS-like CoVs isolated from different species of horseshoe bats in regions of China >1000 km apart
- Up to 84% of bats examined had anti-SARS-CoV antibodies
- Bat SARS-like-CoVs 88-92% sequence identity with human or civet strains
- Greater genetic diversity in bat viruses than those of humans or civets
- Hypothesis: bats are reservoir of SARS-CoV, transmitted to humans via market animals (e.g. civets)
SARS-CoV - ACE2 interaction

- Large binding interface
- Addition of charge
- Deletion of methyl
- Pro reduces binding surface
- Large glycan
- Lacks hydrophobic pocket

>1000 fold difference in binding affinity
Will SARS Return?

- No further transmission of human SARS-CoV
- December 2003 - January 2004: 4 SARS cases in Guangdong Province, new animal - human transmission
- SARS-CoV precursor continues to circulate in animals; wild game banned in markets
- Re-emergence will be more quickly recognized and contained

CREDIT: MICHAEL REYNOLDS/EPA/NEWSCOM
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
Confirmed Cases of MERS-CoV by Month
(n=178)

Month

2012

2013
CONFIRMED CASES OF MIDDLE EAST RESPIRATORY SYNDROME - CORONAVIRUS 2012 - 2013

MAP DATE: 13 January 2014. Version

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

MERS-CoV

- As of 3/1/14: 184 laboratory confirmed cases, 80 deaths
- Case fatality ratio: $\frac{80}{184} = 43.5\%$
- Mortality ratio unknown
Origin of MERS-CoV

Middle East Respiratory Syndrome Coronavirus in Bats, Saudi Arabia


The source of human infection with Middle East respiratory syndrome coronavirus remains unknown. Molecular investigation indicated that bats in Saudi Arabia are infected with several alphacoronaviruses and betacoronaviruses. Virus from 1 bat showed 100% nucleotide identity to virus from the human index case-patient. Bats might play a role in human infection.

http://dx.doi.org/10.3201/eid1911.131172
Mystery Virus That’s Killed 47 Is Tied to Bats in Saudi Arabia

By DONALD G. McNEIL Jr.

WASHINGTON — Health officials confirmed Wednesday that bats in Saudi Arabia were the source of the mysterious virus that has sickened 96 people in the Middle East, killing 47 of them.

Some Scientists Cast Doubt on Finding of Origins of a Virus

By DONALD G. McNEIL Jr.

Since scientists announced last week that they had tracked a dangerous new coronavirus to bats in Saudi Arabia, a debate has emerged among virologists as to whether there really is enough evidence to back up the claim.

Some professional jealousies also may be fueling the controversy. Dr. W. Ian Lipkin, whose team at the Columbia University Mailman School of Public Health did the lab work, regularly is described as a “microbe hunter” in articles lionizing him for his work in a variety of areas, including West Nile virus, dying honeybees and the 2011 medical thriller movie “Contagion.” And he can be sharp-tongued about his critics.

The first scientist to openly question the discovery was Vincent Racaniello, another virologist at Columbia; he has his own blog and podcast. He posited the theory that the fragment might have come from a mixed virus with pieces of the MERS virus in it, or even from something the bat ate.
MERS-CoV in dromedary camels

Antibodies in serum

PCR positive nasal swab
MERS-CoV

• Are camels the reservoir?
• Why did the virus recently cause human disease?
• What is the role of bats if any?
• How is the virus transmitted to humans?
• Why are so few humans infected? Will it spread?
• Why doesn’t the virus transmit well among humans?
• Should a camel vaccine be prepared?
• Should we produce antivirals for infected patients?
## Coronavirus disease in humans

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCoV-229E</td>
<td>• Respiratory diseases</td>
</tr>
<tr>
<td>HCoV-NL63</td>
<td>• Febrile upper tract infection</td>
</tr>
<tr>
<td>HCoV-OC43</td>
<td>• Lower tract infections</td>
</tr>
<tr>
<td>HCoV-HKU1</td>
<td>• Asthma exacerbation</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>• Atypical pneumonia</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>• Severe pneumonia</td>
</tr>
</tbody>
</table>

- 1686 - 1800, bat CoV
- 1450 - 1191, bat CoV
- 1890, bovine CoV
- 1903, bat CoV
- 2012, camel CoV
Canine parvovirus: Cat-to-dog by two mutations

- Canine parvovirus identified in 1978, cause of new enteric and myocardial infection in dogs
- Evolved from feline panleukopenia virus, another parvovirus
  - *Infects cat, mink, racoon*
Canine parvovirus

- Gains canine Tfr binding
- Gains extra receptor binding
- Spreads worldwide in <1 year

1979 → 1984 → 1990

- Loses extra receptor binding
- Spreads worldwide in <1 year

1976-1978

Infection via thymus

FPV MEV RPV etc.

CPV-2a

CPV-2

two amino acid changes!
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)
Emerging infections can be detected and controlled only by societies willing to pay

- Research and development in academia and industry
- Early detection and identification technology
- Databases of all viral genomes in the ecosystem
- First responder actions combined with rapid communication
- Public health action including vaccines, drug stockpiles, quarantines
- Inter-agency communication and cooperation among local, state, and federal government