

Emerging Viral Diseases

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 57 (p. 550); Chapter 73.

I. **Overview.** The environment contains numerous repositories of viruses that are in a constant state of change. As these viruses come in contact with new hosts, a new equilibrium must be established which results in the selection for changes in viral tropism, replicative properties and ability to evade host responses. A consequence of "new" viruses emerging and infecting humans is that some of these agents may have the capability of causing profound pathology and having high fatality rates. In this lecture we will exam examples of "new" viruses entering the human population, and examine the consequences.

II. Concept of Emergence

- A. Definition: Viral diseases whose incidence (in humans) has increased in the past two decades or threatens to increase in the near future.
- B. Mechanisms of emergence of new viral diseases.
 - 1. Evolution of new agents.
 - 2. Spread of known viruses to new geographic areas.
 - 3. Infections in persons living in areas undergoing ecological change resulting in exposure to insects or animals harboring the virus.
- C. Re-emergence of known viral diseases.
 - 1. Development of resistance to vaccines or anti-viral drugs.
 - 2. Breakdown of public health measures for previously controlled infections.
 - 3. Bioterrorism

III. Concept of virus-host equilibrium

- A. Equilibrium human virus:
 - 1. A virus that has a stable relationship with the human host. The virus has adapted to maintain the infection chain in humans.
 - 2. The virus has no contemporary animal host.
- B. Nonequilibrium human virus:
 - 1. A virus that has a stable relationship with *an animal* host.
 - 2. The virus can be strikingly lethal since it hasn't evolved to coexist with humans.
 - 3. The virus will be in a genetic flux until it reaches equilibrium or the human infection chain is broken.
 - 4. HIV, ebola virus and influenza virus are examples.

IV. Hantavirus pulmonary syndrome

- A. An acute and often fatal pulmonary syndrome in adults.
 - 1. Caused by a newly recognized hantavirus.
 - 2. First recognized in the southwestern United States in May, 1993.
 - 3. Laboratory investigation demonstrated:
 - a) Antibody to hantavirus antigens.
 - b) Hantavirus-specific sequences were detected by RT-PCR amplification of viral RNA at autopsy.
- B. At the time of the original outbreak:
 - 1. Four members of the genus hantavirus of the Bunyaviridae family were known human pathogens.
 - 2. There was a worldwide distribution of hantaviruses which were primarily associated with hemorrhagic fever and a renal syndrome.
 - 3. Rodents were known to be the natural hosts.
 - 4. Before 1993 no hantavirus had been shown to cause acute human disease in North America.
 - 5. Before this outbreak, no hantavirus had been associated with pulmonary disease anywhere in the world.
- C. The Deer mouse was shown to be the reservoir for the new hantavirus in the southwest US.
 - 1. *Peromyscus maniculatus* were trapped around homes of several patients and about half were seropositive for the virus.
 - 2. The deer mouse is widely distributed in the US, but not in the southeastern states.
 - 3. Humans were infected by exposure to rodent excreta.
 - a) Aerosol route from urine
 - b) Direct exposure to feces
 - c) No person to person spread
 - 4. Heavy rainfall in 1993 increased the food supply which resulted in an increase in the rodent population. This increased the human exposure to deer mice and the virus.
- D. In retrospective studies, cases of hantavirus respiratory syndrome were found dating back more than 10 years.

V. Re-emergence of Ebola Virus.

- A. Ebola virus and Marburg virus are in the *Filoviridae* family.
- B. Possesses a single-stranded RNA genome, negative polarity, 19 kb.
- C. Biosafety Level 4 agent: extremely pathogenic virus.
- D. No vaccine or antivirals exist.
- E. Natural reservoir of the virus is believed to be the fruit bat.
- F. History:

1. 1967: 31 cases and 7 deaths in Marburg, Germany in a laboratory where workers were preparing cells from monkeys imported from Uganda.
2. 1976: Epidemic in Zaire and Sudan with hundreds of deaths. 90% of the exposed individuals died in the Zaire outbreak; 50% in Sudan.
3. 1979: Another outbreak in Sudan (34 people infected).
4. 1989: Outbreak in Reston, Virginia.
 - a) A colony of cynomolgus Macaques imported from the Philippines was infected with the Ebola virus.
 - b) The isolated virus was shown to be antigenically and genetically distinct from the African Ebola virus.
 - c) It was named the Reston Ebola Virus.
 - i. Highly virulent for nonhuman primates
 - ii. Did not appear to be pathogenic for humans since several animal handlers were infected but did not get sick.
 - iii. Appeared to spread from animal to animal via the aerosol route.
 - iv. Subsequent analyses showed that 11.7% of several thousand monkeys imported from the Philippines and Indonesia were seropositive for the Reston Ebola virus.
5. 1995: Outbreak in Kitwit, Zaire.
 - a) The first case was a charcoal worker who worked in a forest outside of Kitwit.
 - b) Secondary transmission was by close personal contact with infected blood and body fluids. Lack of modern medical facilities and supplies in local hospital promoted the spread of the virus.
 - c) Kitwit is a large and densely populated center close to other large cities. There was more potential in this case for spread of the virus to a larger population.
 - d) There were 233 deaths from 293 cases.
 - e) The rapid response of the CDC helped to control the outbreak:
 - i. Antigen or antibody was identified 9 h after the samples were received in Atlanta.
 - ii. Ebola sequences were identified by RT-PCR 4 hours later.
 - iii. The RT-PCR data showed that the virus was a Zaire subtype that differed from the 1976 subtype by 4 bases in a 528 bp sequence (<1%). The polymerase sequences of the two viruses were identical. Only a 1.6% variation was observed in the sequences of the glycoprotein genes. Therefore, in the 19 year period between the outbreaks in Zaire, the Zaire virus appeared to be very stable.
6. Future outbreaks of Ebola Virus?

- a) Ability to rapidly diagnose viral infection is critical in the control of outbreaks.
- b) Fruit bats are considered the most likely natural host, but transmissions to humans from rat dropping are believed to be rare.
- c) Most outbreaks can be traced to a single event of a human handling the carcass of a chimpanzee or gorilla.

Emerging Viral Diseases

- **The Concept**
- **Factors effecting virus/host evolution**
- **Recent examples**
 - **Hantavirus**
 - **Ebola virus**
 - **HIV**
 - **SARS**

Concept of Emergence

Definition:

Viral diseases whose incidence (in humans) has increased in the past two decades or threatens to increase in the near future.

Emergence of new viral diseases

- 1.** Evolution of new organisms.
- 2.** Spread of known viruses to new geographic areas.
- 3.** Infections in persons living in areas undergoing ecological change resulting in exposure to insects or animals harboring the virus.

Re-emergence of *known* viral diseases

1. Development of resistance to vaccines or antiviral drugs.

2. Breakdown of public health measures for previously controlled infections

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Concept of virus-host equilibrium

The viral **paradox**: the need to replicate vs. the
need to spread

Cellular replication vs. inter-
host replication

Equilibrium human virus

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2. Virus has no contemporary animal host.

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Non-equilibrium human virus

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4. Examples...?

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3. Virus will be in genetic flux until it reaches equilibrium or human infection chain is broken.
4. HIV, Ebola virus, Hantavirus and Influenza virus are examples

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At the time of the original outbreak.

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Hantavirus pulmonary syndrome

Deer mouse was shown to be the reservoir for the new hantavirus in the southwest US

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Re-emergence of Ebola Virus

Re-emergence of Ebola Virus

- Ebola virus and Marburg virus are in the *Filoviridae* family.
- Single-stranded RNA genome, negative polarity, 19 kb.
- **Biosafety Level 4 agent**: extremely pathogenic virus.
- No vaccine or effective antivirals exist.
- Natural reservoirs of the virus are **unproven (but believed to be fruit bats)**

Re-emergence of Ebola Virus

History:

1. 1967 – 31 cases and 7 deaths in Marburg, Germany in a laboratory where workers were preparing cells from monkeys imported from Uganda.

Re-emergence of Ebola Virus

History:

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Re-emergence of Ebola Virus

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3. 1979 – Another outbreak in Sudan (34 people infected).

1989 – Outbreak in Reston, Virginia

- a) A colony of cynomologous Macaques imported from the Philippines was infected with the Ebola virus.

- b) Virus was shown to be **antigenically and genetically distinct from African ebola virus.**

Named Reston Ebola Virus

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- iii. Appeared to spread from animal to animal via aerosol route.
- iv. Subsequent analyses showed that 11.7% of several thousand monkeys imported from the Phillipines and Indonesia were seropositive for Reston ebola virus

1995 – Outbreak in Kitwit, Zaire

- a) First case was a charcoal worker who worked in a forest outside of Kitwit.
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Therefore, in the 19 year period between the outbreaks in Zaire, the Zaire virus appeared to be very stable

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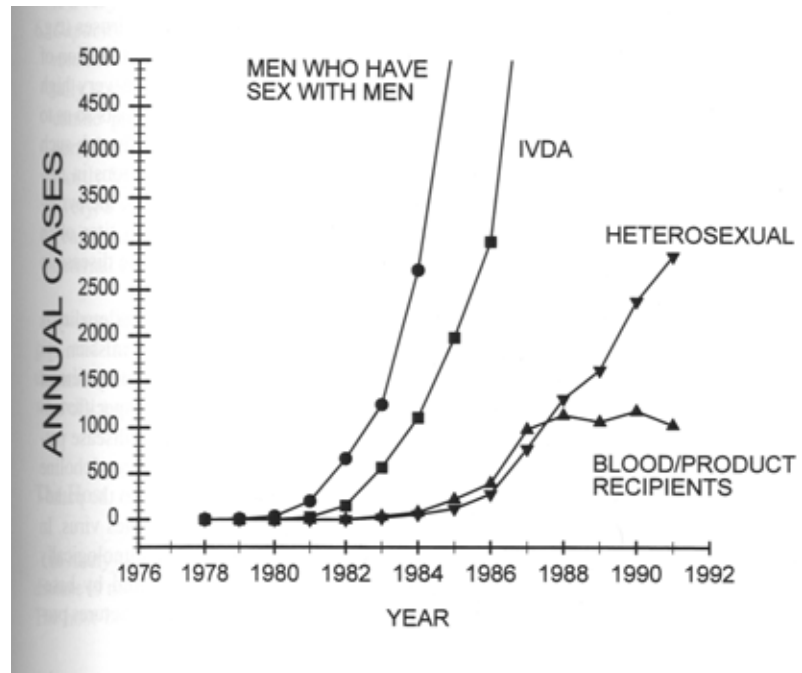
So, what is the picture of Ebola?

- A virus that is not adapted to replication in humans -- not in equilibrium
- Short prodromal period (short time to spread)
- Too lethal for its own good
- **Not an effective pathogen in humans**

HIV - “Ebola in slow motion”

- In humans HIV is a non-equilibrium virus
- Evidence for adaptation?
- Prospects for vaccines

Evidence for adaptation?



The Myxoma story

A case for viral
and host evolution

Myxomatosis

- **Caused by Myxoma virus**
- **Occurs naturally as a mild infection of rabbits in South America (*Sylvilagus* spp.)**
- **In european rabbits (*Oryctolagus* spp.) causes a lethal infection**
- **Idea!** Use as a means of biological control of wild-european rabbits in Australia

Run Rabbit Run

- **Myxoma introduced into Australia in 1950**
- **Initial case-fatality rates of over 99%**
- **Farmers operated “inoculation campaigns” to introduce it into the wild rabbit population**

Virulence of Myxoma Field Isolates

TABLE 15-2. *Virulence of field isolates of myxoma virus, 1951–1981**

	Virulence grade					Number of samples
	I	II	III	IV	V	
Fatality rate (%)	>99	95–99	70–95	50–70	<50	
Mean survival time (d)	<13	14–16	17–28	29–50	NA	
Percentage of isolates by year						
1950–51	100	0.0	0.0	0.0	0.0	1
1952–55	13	20	53	13	0.0	60
1955–58	0.7	5	55	24	15	432
1959–63	1.7	11	61	22	5	449
1964–66	0.7	0.3	64	34	1.3	306
1967–69	0.0	0.0	62	36	1.7	229
1970–74	0.6	5	74	21	0.0	174
1975–81	1.9	3	67	28	0.0	212

*Myxoma virus was successfully introduced into the wild rabbit population in December 1950. The introduced strain was highly virulent and caused epidemics with very high mortality. However, with the passage of time, field isolates exhibited reduced virulence. It is noteworthy that strains of moderate virulence became dominant, probably because strains of lowest virulence were less transmissible and because strains of maximum virulence killed rabbits very quickly.

NA, not applicable.

Data from Fenner F. Biological control as exemplified by smallpox eradication and myxomatosis. Proc R Soc Lond B Biol Sci 1983;218:259–285.

Susceptibility of non-immune rabbits to standard strain

TABLE 15-3. *The susceptibility of nonimmune wild rabbits after successive epidemics of myxomatosis in Lake Urana, Australia.**

No. Epidemics	Fatality rate (%)	Severe disease (including fatalities, %)	Moderate disease (%)	Mild disease (%)
0	90	93	5	2
2	88	95	5	0
3	80	93	5	2
4	50	61	26	12
5	53	75	14	11
7	30	54	16	30

*Rabbits were challenged with a virus of grade III (intermediate) virulence.

Data from Fenner F. Biological control as exemplified by smallpox eradication and myxomatosis. Proc R Soc Lond B Biol Sci 1983;218:259–285.