Ebola virus: the biology, epidemiology, and sociology

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Outline

• Brief overview of viruses

• Biology of Ebola
  – Emergence/History
  – Symptoms and treatment
  – Outbreaks
  – Structure
  – Replication
  – Pathogenesis
  – Transmission

• Emerging pathogens
Overview of Viruses

Electron micrograph of a *Bacillus subtilis* bacterial cell next to a bacteriophage virus particle.

Size comparison
Eukaryotic cell: tennis court
Bacteria cell: tennis ball
Virus: sunflower seed

Photo courtesy of Dr. David Morgan in Indiana University Electron Microscopy facility
The wide world of viruses

Influenza  Ebola  HIV

Mimivirus  Sindbis  Bacteriophage

Rabies
Building blocks of a virus

All viruses contain:
1. nucleic acid
   - RNA or DNA

2. protein (capsid)
   - 1 or more types
   - From virus or host

Other components that may be in viruses:
- lipids (from cell membrane)
- enzymes (RNA polymerase, etc)
- carbohydrate moieties (glycoproteins)

Informs the shape of the virus
The wide world of viruses

- West Nile
- SARS
- MERS
- Rabies
- Measles
- Herpes
- Chicken pox
- Epstein Barr
- Smallpox
- Common cold
- HIV
- Ebola
- Influenza
Dead or alive… or neither?

- Viruses cannot perform cellular functions on their own, therefore are not considered “alive”
  - Metabolism and energy production
  - Reproduction
- Likewise, something that is not alive, cannot be killed
  - Viruses are typically considered neutralized, inactivated, or damaged
- Viruses are obligate, intracellular pathogens
  - Obligate: NEEDS a host cell
  - Intracellular: must ENTER the host cell to utilize resources
  - Pathogen: Causes disease
Viral motives

• Viruses don’t “intend” to cause disease

• Programmed to replicate more of themselves

• To do this, they use the cell’s resources
  • Steal resources
  • Manipulate or inhibit cell’s processes

• Disease is a consequence of this
The biology of Ebola
First appearance: Zaire 1976

- August 1976 - 30 y.o. male comes to Belgian mission hospital in Yambuku (Bumba Zone N.W. Zaire).

- Presents with high fever, severe diarrhea, and continuous nose-bleed.

- Treated for dysentery and malaria, then disappears.

★ - Approx location of village of Yambuku
Zaire, continued…

- Region biologically diverse with many animal species including primates that are hunted as a food source.

- First documented death
  - Mabalo Lokela - local teacher. Treated for malaria with chloroquine on September 1st.
  - Returns seriously ill September 5th. Diarrhea, nosebleed, high fever, dehydrated, bleeding from gums, blood in diarrhea and vomit.
  - Died September 8th

- Burial ritual: Body is voided of all contents of alimentary canal by family members.

- Within days of Lokela’s death 21 of his family and friends came down with the disease. 18 died.

- Spreads quickly causing general panic in region.

- Bumba zone medical director arrives and provides first medical description of disease.
Symptoms associated with Ebola

Description of patient
- High temperature around 39°C (102-103 F)
- Frequent vomiting of black, digested blood, but of red blood in a few cases
- Diarrheal emissions with blood
- Bloody nose
- Retrosternal and abdominal pain
- state of stupor, prostration with heaviness in the joints

“…rapid evolution toward death after a period of about 3 days, from a state of general health.”
- Dr. Ngoi Mushola, Bumba Zone medical director.
Treatment for Ebola

• Currently, no vaccine available
  • Research and development

• Intravenous fluids, electrolytes, maintaining oxygen and blood pressure levels significantly improve chances of survival if done EARLY

• Immunity: antibodies post-survival last ~10 years at least

• Unknown if re-infection can occur with same or different strain
Distribution of outbreaks of Ebola virus hemorrhagic fever in Africa

Major Ebola Outbreaks  April 2014

Confirmed cases and years

2014 outbreak
CDC, updated June 6, 2015
Countries with Widespread Transmission

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases (Suspected, Probable, and Confirmed)</th>
<th>Laboratory-Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>3669</td>
<td>3237</td>
<td>2435</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>12884</td>
<td>8630</td>
<td>3913</td>
</tr>
<tr>
<td>Total</td>
<td>16553</td>
<td>11867</td>
<td>6348</td>
</tr>
</tbody>
</table>

Countries with Former Widespread Transmission and Current, Established Control Measures

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases (Suspected, Probable, and Confirmed)</th>
<th>Laboratory-Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>10666</td>
<td>3151</td>
<td>4806</td>
</tr>
<tr>
<td>Total</td>
<td>10666</td>
<td>3151</td>
<td>4806</td>
</tr>
</tbody>
</table>

Mortality rate: 25-90%
Distribution of outbreaks of Ebola virus hemorrhagic fever in Africa

<table>
<thead>
<tr>
<th>Filovirus (species)</th>
<th>Year</th>
<th>Outbreak location</th>
<th>Place of origin</th>
<th>Human cases (% mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marburg virus</td>
<td>1967</td>
<td>Marburg and Hamburg, Germany Belgrade, Yugoslavia</td>
<td>Uganda</td>
<td>32 (23)</td>
</tr>
<tr>
<td></td>
<td>1975</td>
<td>Johannesburg, South Africa</td>
<td>Zimbabwe</td>
<td>3 (33)</td>
</tr>
<tr>
<td></td>
<td>1980</td>
<td>Nairobi, Kenya</td>
<td>Western Kenya</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>Kisumu, Kenya</td>
<td>Western Kenya</td>
<td>1 (100)</td>
</tr>
<tr>
<td></td>
<td>1999–2000</td>
<td>Watse, DRC</td>
<td>DRC</td>
<td>?</td>
</tr>
<tr>
<td>Ebola virus (Zaire)</td>
<td>1976</td>
<td>Yambuku, DRC</td>
<td>DRC</td>
<td>318 (88)</td>
</tr>
<tr>
<td></td>
<td>1977</td>
<td>Tandala, DRC</td>
<td>DRC</td>
<td>1 (100)</td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>Minkouka, Gabon</td>
<td>Gabon</td>
<td>49 (59)</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>Kikwit, DRC</td>
<td>DRC</td>
<td>315 (77)</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Mayibout, Gabon</td>
<td>Gabon</td>
<td>31 (68)</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Boué, Gabon and Johannesberg, South Africa</td>
<td>Gabon</td>
<td>60 (75)</td>
</tr>
<tr>
<td>(Sudan)</td>
<td>1976</td>
<td>Maridi, Sudan</td>
<td>Southern Sudan</td>
<td>284 (53)</td>
</tr>
<tr>
<td></td>
<td>1979</td>
<td>Nzara and Yambio, Sudan</td>
<td>Southern Sudan</td>
<td>34 (65)</td>
</tr>
<tr>
<td>(Reston)</td>
<td>1989</td>
<td>Gulu District, Uganda</td>
<td>Uganda</td>
<td>&gt;400 (~50)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>Reston, Virginia (also Pennsylvania and Texas)</td>
<td>Philippines</td>
<td>1 (0)(^a)</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Siena, Italy</td>
<td>Philippines</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>Alice, Texas</td>
<td>Philippines</td>
<td>0</td>
</tr>
<tr>
<td>(Côte d'Ivoire)</td>
<td>1994</td>
<td>Tai Forest, Ivory Coast and Basel, Switzerland</td>
<td>Tai Forest, Ivory Coast</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

\(^a\)Reston virus has been traced only to a single monkey-breeding facility in the city of Calamba, Philippines.

\(^b\)In one study, mortality in monkeys was estimated at 82% (89).

DRC, Democratic Republic of the Congo.

- Burn-out and disappearance of virus in population then re-emergence.
- Signs that this is not a well adapted human virus. Zoonotic.
Where does Ebola come from?: 
Host versus reservoir

Various primates, including great apes: “accidental host”

Antibodies to Ebola and viral RNA found in symptomless fruit bats
Possible reservoir?
Ebola: Structure

- Helical structure
  - Formed by the RNA
  - \( \sim 80\text{nm} \) diameter, 800-1000nm length
- Lipid envelope
- Single-stranded RNA genome
  - 7 genes, coding for 8 proteins
  - 18-19 kilobases (Human genome = \( \sim 3 \) gigabases)
Ebola: Structure

- **Structural proteins**
  - Glycoprotein
    - 2 forms
  - Nucleoprotein
  - Matrix proteins
    - VP24 and VP40

- **Replication proteins**
  - RNA polymerase
  - VP30 and VP35
    - RNA Replication complex
Ebola: Structure
Ebola: Replication Cycle

1. Entry into cell: glycoproteins
2. Uncoating and release into cytoplasm
3. Transcription: Make more RNA (mRNAs and genome)
4. Translation: Make viral proteins
   • Uses ER and Golgi for glycoproteins
5. Assemble new virus particles
6. Budding and release of new virus particles from host cell
   • Takes portion of the cell’s membrane with it
Pathogenesis of Ebola

- Infection of mucosal epithelial cells: mouth, nose, eyes

- Infection of immune cells: monocytes, macrophages, etc.

- Dissemination of virus via blood and lymphatic system

- Infect endothelial cells lining the blood vessels leads to blood loss

- Infect a variety of tissue including liver and adrenal glands
  - Affect production of clotting factors
  - Affect production of steroids therefore affecting blood pressure
Pathogenesis of Ebola

Endothelial cells that line the blood vessels.
Virus interactions with host & immune system

- VP35 inhibits part of immune system signaling response
- Glycoprotein binds to neutrophils and affects function
- Infection of macrophage and dendritic cells causes destruction of key antigen presenting cells
- Loss of antigen presenting cells and cytokines secreted by infected cells lead to lymphocyte loss
- Overall, virus causes dysregulation and dysfunction of immune response
Human transmission of Ebola

The nature of disease leads to large amounts of infected fluid leaving the body. The primary means of transmission are:

1) Via mucosal surfaces
2) Through skin abrasions
3) Parenteral introduction (re-using contaminated needles)
4) Aerosol? This has been seen for Reston strain with monkey infection

Transmission is not particularly efficient. Only 23% of family members sleeping in the same room as patient became infected. Close contact is required so care givers are most at risk.

Transmission is also limited by the debilitating nature of the disease.
Timeline of infection (or so we thought)

- Incubation period (time before symptoms): 4-10 days (now known to be up to 21 days)
- Potential generation time (shedding virus): Approx 4-16 days (can be longer)

Laboratory diagnosis:
Detection of viral RNA or antibodies.
- Challenge: require sophisticated technology not available in remote regions of Africa.

Skin biopsies
- Can safely ship samples

Clinical diagnosis:
Very difficult due other infections causing similar early symptoms (malaria, typhoid etc.).
Disease emergence

- Societal Influences
- Evolution of the pathogen
- Naïve Host Populations
- Break down of Public Health System
- Environmental Change
- Cross-species transmission
Disease emergence

Evolution of the pathogen
- No way to vaccinate

Naïve Host Populations
- Access to bushmeat and bats

Societal Influences
- Burial Rituals
- Distrust of Healthcare workers

Break down of Public Health System
- Protocols
- Transportation
- Healthcare workers becoming ill
- Inability to quarantine
- Resources: hospital, IV, sterile facilities, etc

Environmental Change

Cross-species transmission
- Access to bushmeat and bats
Careers that involve Virology

Scientists
• Research and Development
  • Vaccine/antiviral development
  • Basic science research
• Pharmaceuticals
• Biosafety
  • Safety protocols
  • Bioterrorism
• Storage/Transportation of medications

Policy
• Advisors/Staff to congressmen/women
• Attorneys and politicians
• Ethics

Media
• Science journalism
  • Educating the public

Business
• Biotechnology companies
• Pharmaceutical industry

Center for Disease Control
• Epidemiology – tracking outbreaks
• Establishing biosafety policies

Science Organizations
• National Institutes of Health and National Science Foundation

Medical Professionals
• Doctors, nurses

Research interesting careers, find out how to get there
Acknowledgments

Dr. Pranav Danthi, Indiana University

Dr. Richard W. Hardy, Indiana University

Other sources of interest for Virology material:
www.virologyblog.ws/ : Dr. Vincent Rancaniello, Columbia University
Figures

- Monster virus [http://pre01.deviantart.net/5bae/th/pre/i/2013/142/2/6/zombie_virus_color_by_sparksflystudios-d667ig2.jpg](http://pre01.deviantart.net/5bae/th/pre/i/2013/142/2/6/zombie_virus_color_by_sparksflystudios-d667ig2.jpg)
- Replication cycle [http://www.bu.edu/muhlbergerlab/replication.jpg](http://www.bu.edu/muhlbergerlab/replication.jpg)
- Immune system [http://www.nature.com/nri/journal/v7/n7/fig_tab/nri2098_F1.html](http://www.nature.com/nri/journal/v7/n7/fig_tab/nri2098_F1.html)