An Update on Ebola

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Ebola has had infrequent, outbreaks with low numbers infected since it’s discovery in 1976.
Ebola outbreaks prior to current W Africa epidemic, by country

- DRC 6
- Uganda 5
- Gabon 4
- So Sudan 3
- Rep Congo 3
- Ivory Coast 1
- So Africa 1

Largest previous
- 425 cases (Gulu, Uganda)
Background: The virus

- Enveloped, host cell membrane with Ebola glycoprotein
- Non-segmented, negative sense, ssRNA
- 7 genes, 19kb
- Family: *Filoviridae* (*filum*, Latin, thread)
- Genus: *Ebolavirus*
- Species:
  - Zaire (EBOV)
  - Sudan (SUDV)
  - Ivory Coast or Tai Forest (TAFV)
  - Bundibugyo (BDBV)
  - Reston (RESTV)
- BSL-4, Bio-threat category A
Background: Viral Hemorrhagic Fevers

**Filoviridae:**
- Ebola HF – *Ebola Virus*
- Marburg HF – *Marburg Virus*

**Flaviviridae**
- Mosquito-borne
  - Yellow Fever
  - Dengue HF – Den 1, 2, 3, 4
- Tick-borne
  - Kyasanur Forest Disease
  - Omsk HF
Background: Virus Presentation

1967: Marburg, Germany
- Imported Ugandan Green Monkeys
- Laboratory workers fall ill
- 7 of 31 die.
- Virus later identified and named Marburg.

- Predilection for children – 75% < 5 years of age
- High case mortality – 89%
- Egyptian Fruit Bat – *Rousettus aegyptiacus*
Background: Virus Presentation

1976: Yambuku, Congo

- “Green Monkey Fever”
- Villagers fall ill – yellow fever?
- Women >> Men
- Ground Zero - Yambuku Mission Hospital – 200 dead

Mission Nuns and a Priest Self Quarantined – 4 colleagues had died

Please stop, anybody who crosses here may die....
Background: Virus Presentation

- Two vials of blood sent to Belgium – 1 broke
- Peter Piot examined
- WHO ordered vials sent to CDC

- Electron microscopy image of virus
- CDC confirmed it was not Marburg
- New virus – Named it Ebola
Background: Virus Presentation

- International team arrived to help quell the outbreak and study the virus
- Yambuku Mission – 5 syringes
- Pre-natal care and deliveries common
- Also associated with funerals
- Outbreak lasted 3 months and ~300 dead (88% mortality)
- Simultaneous outbreak – Sudan 1976
- Disappeared until 1994

The Ebola River
Background: US Scare

1989: Reston, Virginia

- Imported Philippine Cynomolgus Monkeys – Ferlite Farms (Oct. 2)
- Quarantined in Room F x 30 days
- High numbers of death – euthanized after suspected Simian Hemorrhagic Fever
- USAMRIID diagnosed SHF & Ebola

- Jan 30, 1990: Alice, TX – 100 monkeys arrive
- 46/52 died in one quarantine room Ferlite Farms – Dx’d Ebola
- Room H – High monkey death 29 died before Room F euthanized. All 500 in Room H euthanized (Nov. 30) Transmission or prior infection?
Background: Ebola Reston

2008: Luzon, Philippines

- Ebola Reston identified in 7 of 28 pork samples and 2 humans
- All animals euthanized
Epidemiology: Reservoir

Previously, Filovirus reservoir unknown

Clue 1: A Danish boy contracted Marburg and two other visitors contracted Ebola after having visited Kitum cave in Mt. Elgon, Kenya.

Clue 2: Ebola outbreak in the Congo (April 2005) occurred in 5 men who had been out hunting elephants.

Tests of Kitum cave have revealed no evidence of Filoviruses
Epidemiology: Transmission

- Bushmeat is a primary protein source in West/Central Africa
- Accounts for ½ of meat at market – 20% are primates
- Humans exposed during slaughter
Epidemiology: Transmission

Downstream Effects
- 95% mortality in Great Apes, 77% Chimps
- 1/3 Great Apes Dead
- Desperately require a vaccine as well
Epidemiology: Reservoir

- Primates are not a reservoir
- Bats long suspected
- **Marburg** – *R. aegyptiaca*
- **Ebola** - Little collared and hammerhead fruit bats
- Bats are a delicacy in W. Africa
Pathogenesis: Virulent Factors

**GP = Glycoprotein** – basis of vaccine

**Viral Membrane** – May contain HLA or other human surface receptors

**VP40 and VP24**: Ebola matrix proteins critical for budding

**Ebola RNA**: Packed with **NP protein** for nucleocapsid

**Ebola Polymerase**: Synthesizes positive sense virus RNA

**VP35 and VP30**: IFN antagonist ebola proteins

**Lipid membrane wraps viral particle**
Pathogenesis: Virulent Factors

Viral Pathology:


Circulating infected monocytes express tissue factor leading to DIC

Endothelial and parenchymal cell infection, likely mediated by glycoprotein results in further tissue damage.
Pathogenesis: Virulent Factors

- Infects monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, epithelial cells
- Extensive tissue necrosis
- Systemic inflammatory response
- Capillary leak syndrome
- Induces coagulation defects
- Impaired adaptive immunity
Clinical Manifestations: Ebola Stages

**EBOLA SYMPTOMS:** Occur 2 - 21 days after exposure, but 8 - 10 days is most common

**Dry**

- **Day 4-7**
  - Rash
  - Myalgia

- **1st Stage:** 7 - 9 days
  - Joint pain, sore throat, fever, headache, weakness, muscle soreness

**Wet**

- **Day 4-8**
  - GI sx
  - Myalgia
  - Fatigue

- **2nd Stage:** 10th day
  - Vomiting blood, diarrhea, high fever, extreme fatigue

- **3rd Stage:** 11th day
  - Brain damage, bleeding from nose, mouth, anus

- **4th Stage:** 12th day
  - Coma, organ failure, shock, massive internal bleeding, death

Diarrhea – 4-12 L, Vomiting – 1.5 L

Source: Centers for Disease Control
Marburg and Ebola Vaccine:
Clinical Manifestations: Ebola

Death rates of the 5 Ebola virus species

- Zaire ebolavirus: 79%
- Sudan ebolavirus: 53%
- Bundibugyo ebolavirus: 27%
- Reston ebolavirus: 0%
- Tai Forest ebolavirus: 0%

Source: CDC

W. African outbreak ~70.8%
Outbreak: Ebola Epidemic

December 6, 2013: Guéckédou, Guinea

- Child Zero dies – linked to fruit bat
- Confirmed by WHO - March 2014
- Previous to this – only W. African Ebola outbreak seen was in Cote D’Ivoire
- Lassa Fever suspected
Outbreak: Ebola Epidemic

1. Child – 2y

Meliandou Village, Guéckédou

Dec 6

Adapted from NEJM, Oct. 2014
Outbreak: Ebola Epidemic

1. Child – 2y
2. Sister – 3y
3. Mother
4. Grandmother
5. Nurse
6. Midwife

Méliandou Village, Guéckédou
Dec 13
Outbreak: Ebola Epidemic

1. Child – 2y
2. Sister – 3y
3. Mother
4. Grandmother
5. Nurse
6. Midwife

7. Sister of 4
8. Funeral of 4
9-12 Villagers

Meliandou Village, Guéckédou

Dawa Village, Guéckédou

Jan 26
Outbreak: Ebola Epidemic

- Dandou Village, Guéckédou
  - 6 deaths
  - 13. Cared for 6
  - 3 additional deaths - unknown

- Ghandou Village, Guéckédou

- Meliandou Village, Guéckédou
  - 1. Child – 2y
  - 2. Sister – 3y
  - 3. Mother
  - 4. Grandmother
  - 5. Nurse
  - 6. Midwife

- Dawa Village, Guéckédou
  - 7. Sister of 4
  - 8. Funeral of 4
  - 9-12 Villagers

- Feb 10

- 14. Health Care Worker
Outbreak: Ebola Epidemic

Dandou Village, Guéckédou
- 6 deaths
- 13. Cared for 6
- 3 additional deaths - unknown

1. Child – 2y
2. Sister – 3y
3. Mother
4. Grandmother
5. Nurse
6. Midwife

Meliandou Village, Guéckédou
- 4 deaths
- C6 family of 14
- C7

Dawa Village, Guéckédou
- 4 deaths
- C6 family of 14
- C7

Faux/Gandou Village, Guéckédou
- 14 deaths
- C1
- C2
- C3

Feb 24

15. Doctor

Miacenta
Outbreak: Ebola Epidemic

Dandou Village, Guéckédou
- 6 deaths
- 13. Cared for 6
- 3 additional deaths - unknown

Ghandou Village, Guéckédou
- 14 deaths
  - C1
  - C2
  - C3

Meliandou Village, Guéckédou
- 1. Child – 2y
- 2. Sister – 3y
- 3. Mother
- 4. Grandmother
- 5. Nurse
- 6. Midwife
- 7. Sister of 4
- 8. Funeral of 4
- 9-12 Villagers
- 14. Health Care Worker
- 14 deaths
  - C6 family of 14
  - C7

Dawa Village, Guéckédou
- 4 deaths
  - C6 family of 14
  - C7

Kissidiougou
- 5 deaths
  - 16. Brother of 15
  - 17. Brother of 15
  - C15

C8
C9
C10
C11
C13 + 2 deaths

Miacenta
- 15. Doctor
- C12 Family of Doctor

March 12

Kissidiougou

Dandou Village, Guéckédou

Ghandou Village, Guéckédou

Meliandou Village, Guéckédou

Dawa Village, Guéckédou

Kissidiougou
Outbreak: Ebola Epidemic

Dandou Village, Guéckédou
- 6 deaths
- 13. Cared for 6
- 3 additional deaths - unknown

Ghandou Village, Guéckédou
- 14 deaths
  - C1
  - C2
  - C3

Kissidiougou
- 5 deaths
  - 16. Brother of 15
  - 17. Brother of 15
  - C15

Meliandou Village, Guéckédou
- 1. Child – 2y
- 2. Sister – 3y
- 3. Mother
- 4. Grandmother
- 5. Nurse
- 6. Midwife

Dawa Village, Guéckédou
- 7. Sister of 4
- 8. Funeral of 4
- 9-12 Villagers
- 4 deaths
  - C6 family of 14
  - C7

Miacenta
- 14. Health Care Worker
- 15. Doctor
- C12. Family of Doctor
- C14. Contact of 12

March 16
Outbreak: Ebola Epidemic

111 cases – 79 fatalities (71%)
Outbreak: Ebola Epidemic
Outbreak: Ebola Epidemic

WHO Health Emergency
Outbreak: Ebola Epidemic

Mali’s First Case
Outbreak: Ebola Epidemic

Ebola deaths
Figures up to 18 January 2015

8,641
Deaths - probable, confirmed and suspected
(Includes two in the US and six in Mali)

3,605 Liberia
3,145 Sierra Leone
1,876 Guinea
8 Nigeria

Source: WHO
WHO Ethics Panel on Ebola

11 Aug 2014

- Use of experimental agents acceptable
- Existing supplies very limited or exhausted
- Cannot detract from pillars
  - Clinical care
  - Rigorous infection prevention and control
  - Contact tracing and follow-up
  - Effective risk communication
  - Social mobilization
Treatment: ZMAPP

- 3 humanized mouse monoclonal antibodies
  - c13C6, c2G4, c4G7
- Manufactured in tobacco plants
  - Kentucky plant, Mapp Biopharmaceuticals
  - A few hundred doses projected by end of 2014
  - IV, frozen
- 21 rhesus macaques
  - 3 controls died by day 8
  - 18 that received Zmapp, 3 doses, 3 days apart starting on days 3, 4, or 5 all survived

Treatment: ZMAPP

- **Dr. Kent Brantley (Liberia)**
  - Blood transfusion from 14 yo survivor, then ZMapp at day 9, survived - Emory
- **Ms. Nancy Writebol (Liberia)**
  - Zmapp, survived - Emory
- **Fr. Miguel Pajares (Liberia)**
  - 75 yo Spanish priest, 1 of 3 doses ZMapp, died 2 days later
- **Dr. Abraham Borbor (Liberia)**
  - Deputy chief physician at Monrovia hospital, received ZMapp, died
- **Unnamed Liberian 1**
  - Received ZMapp, survived
- **Unnamed Liberian 2**
  - Received ZMapp, survived
- **William Pooley (Sierra Leone)**
  - British nurse, received ZMapp, survived
Treatment: TKM-Ebola

- Small interfering (si) RNA – Tekmira of Canada
- Targets 3 of 7 proteins produced by Ebola
  - Zaire Ebola L polymerase
  - Zaire Ebola membrane-associated protein (VP24)
  - Zaire Ebola polymerase complex protein (VP35)
- Formulated with lipid nanoparticle technology
  - SNALP- stable nucleic acid lipid particles
- 7 doses protected 4 of 4 rhesus macaques after lethal challenge
- Phase I human trial on hold (Flu-like sx at higher dose) but drug now under Expanded Access Program and partial hold
- Could have 900 courses available early in 2015 - IV, lyophilized
Treatment: Other

Supportive Care – fluid resuscitation!!

- Blood transfusions from survivors
- Hyperimmune globulin from survivors or vaccinated animals
- AVI 7537 (Sarepta) IV RNA inhibitor
- Favipiravir/T-705 (Toyama Chemical/Fuji Film) po polymerase inhibitor
- Brincidofovir – Chimerix (developed for CMV and Adeno) – Phase 2
- BCX4430 (Biocryst) IM synthetic adenosine analogue
- Interferons
Treatment: Ebola Vaccines

All depend upon a viral platform and ebola genes - 3

C. Ad26-EBOV/MVA EBOV – J&J, Janssen, and Bavarian Nordic - Adenovirus 26-EBOV prime boosted by MVA
Treatment: Ebola Vaccines

Chimpanzee Adenovirus Vector Ebola Vaccine — Preliminary Report

Treatment: Phase 2 Ebola Vaccines

- Liberia
  - Design: Head to head
  - GSK vs. Merck vs. None
  - 9000 volunteers
  - Vaccine has arrived in Liberia - Start Date imminent

- Sierra Leone
  - Design: Wedge
  - HCW primarily
  - 6000 volunteers

- Guinea
  - Design: Ring Design
  - Vacc ~50 surrounding contacts of each case
  - 9000 volunteers in two arms (early vs. late)
Epidemiology: Ebola Waning

Ebola is Waning
Must not become complacent!!

NEJM, Oct. 2014
Acknowledgements:

SANARIA
MALARIA ERADICATION THROUGH VACCINATION
Vector: Unknown but chimpanzees, gorillas, duikers implicated. Bats may be reservoir. Distribution: Central Africa.