Ebola

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

UNCLASSIFIED

Acknowledgments

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Disclaimer

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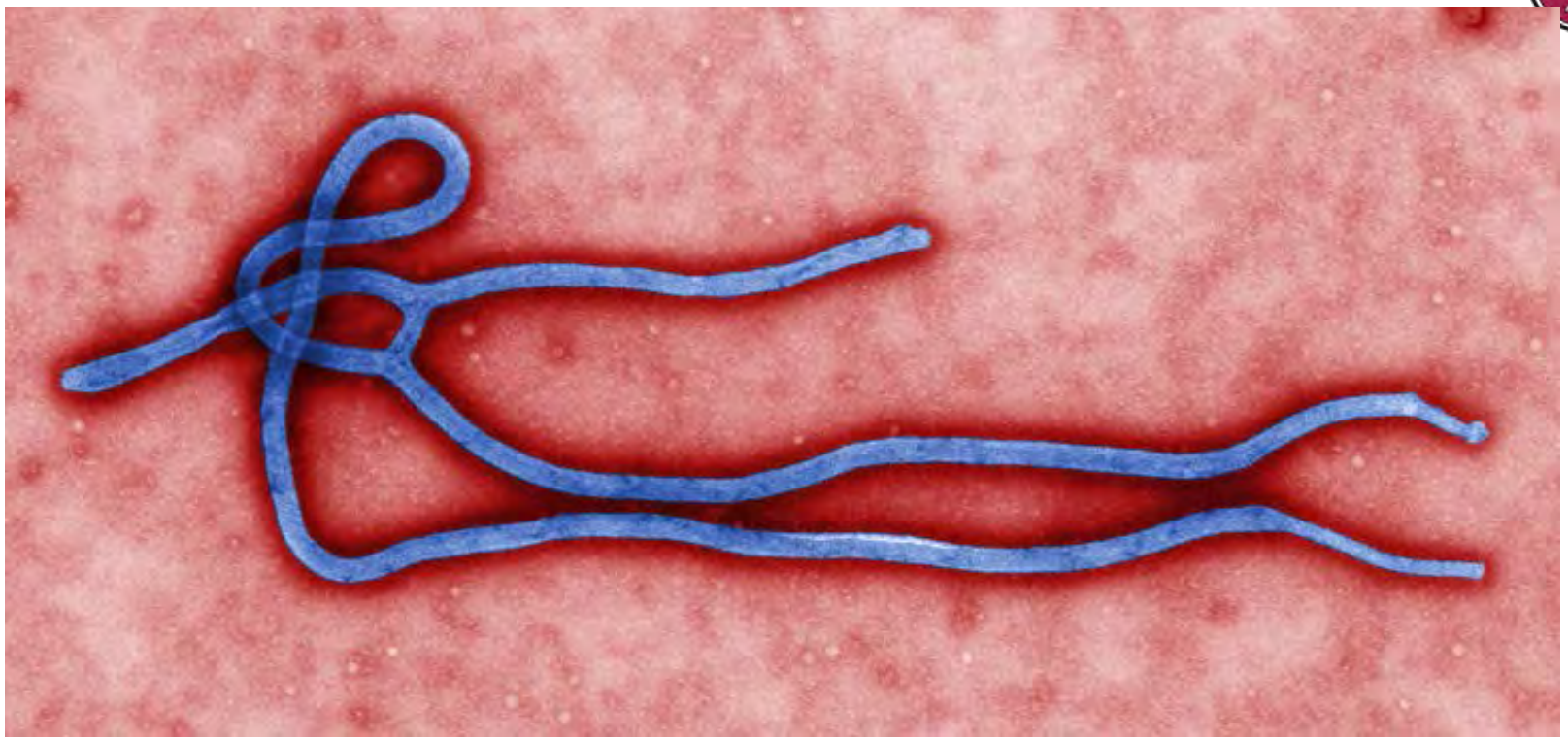


Ebola

Ebola

- Filovirus (Marburg virus is related)
- Several different strains
  - Zaire, Sudan, Ivory Coast, Bundibugyo, (Reston)
- First identified in 1976
- Has become the “prototypical” VHF
  - Classic bleeding diatheses
  - High case fatality rates
  - Significant nosocomial risk
  - Incubation typically 8 – 10 days (range 2-21 days)

Most Recent Ebola Outbreak (as of 16 JAN 2015)

- Affecting Sierra Leone, Liberia, and Guinea, Nigeria, Senegal, United States, Spain, Mali, Scotland
- A record number of cases
  - Cases = 21,373 (8,468 deaths; 40% CFR)
- A comparison of case counts during the week ending 22 DEC 2014 to those from the week ending 11 JAN 2015
  - Guinea from 115 cases to 42 cases (-63%)
  - Liberia from 31 cases to 8 cases (-74%)
  - Sierra Leone from 337 cases to 184 cases (-45%).
  - All three countries have sufficient capacity to isolate patients and bury the dead but the under-reporting of cases and the uneven geographical distribution of beds and cases means that not all EVD cases are isolated in several areas (WHO, 14 JAN).
- The current situation is far from stable

Most Recent Ebola Outbreak

An epidemic with two causes

The persistence of infections throughout 2014 had two causes. The **first** was a lethal, tenacious and unforgiving virus. The **second** was the fear and misunderstanding that fuelled high-risk behaviors. (WHO, 2015)

The latest World Health Organization Report confirmed a total of 30 new confirmed cases of Ebola were reported in the week of April 5 2015. This is the **lowest** weekly total since May 2014.

Most Recent Ebola Outbreak
LESSONS LEARNED

CNN/MSF© 2014

Recommendations for Preparing for Future Epidemics

The world needs to build a **warning and response system** for outbreaks. This system should be **coordinated by a global institution** that is given enough authority and funding to be effective, **enable fast decision making at a global level,**

•Expand **investment in research and development** and clarify regulatory pathways for developing new tools and approaches,

• Improve **early warning and detection systems**, including scalable everyday systems that can be expanded during an epidemic,

• Involve a **reserve corps of trained personnel** and volunteers,

• **Strengthen health systems** in low- and middle-income countries, and

• Incorporate **preparedness exercises** to identify the ways in which the response system needs to improve.

Source Information-NEJM, Bill and Melinda Gates Foundation, Seattle, 2015.

Most Recent Ebola Outbreak
LESSONS LEARNED

Communication:

- Work with Communities, Not against Them
- Share Early, Listen to Beliefs, and Read Rumors

Capacity Building:

- Avoid Blind Spots by Addressing the First Detectors

Source : Dickmann P, Kitua A, Kaczmarek P, Lutwama J, Masumu J, Karimuribo E, et al. Using Lessons learned from previous Ebola outbreaks to inform current risk management [conference summary]. Emerg Infect Dis. 2015 May

Most Recent Ebola Outbreak
LESSONS LEARNED

Get the Incentives & Support Right:

- Honor and respect both foreign and domestic medical staff that have placed their lives and potentially community standing at risk to save the lives of others

Maintain unwavering commitment at national and international levels:

- Both in the form of direct support for response measures or assistance in rebuilding their health services.

Source :WHO Ebola, One Year Response; http://www.who.int/csr/disease/ebola/one-year-report/response-in-2015/en/.

Most Recent Ebola Outbreak
LESSONS LEARNED

Prevent Outbreaks in Unaffected Countries:

- Active surveillance
- Deployment of additional human and material resources
- Introduction of standard performance monitoring and reporting on a weekly basis

Get health systems functioning again – on a more resilient footing:

- Change past thinking about the way health systems are structured
- Restore confidence that health facilities can protect health and heal disease.

Source :WHO Ebola, One Year Response; http://www.who.int/csr/disease/ebola/one-year-report/response-in-2015/en/.

Most Recent Ebola Outbreak
LESSONS LEARNED

Mine every success story:

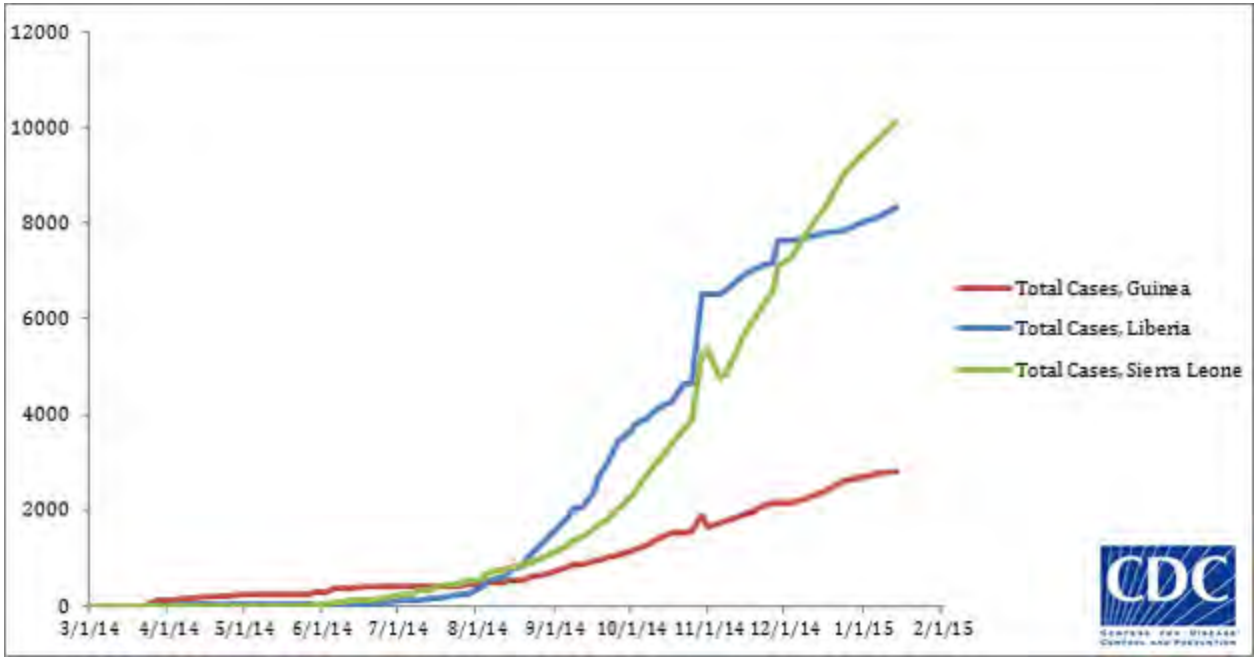
- Each and every survivor is also a success story. Some success stories can serve as models
- Research is needed to determine how areas that have achieved zero transmission can be protected from re-reinfection
- When communities learn first-hand which behaviors carry a high risk, they can and change them

Manage "post-Ebola syndrome":

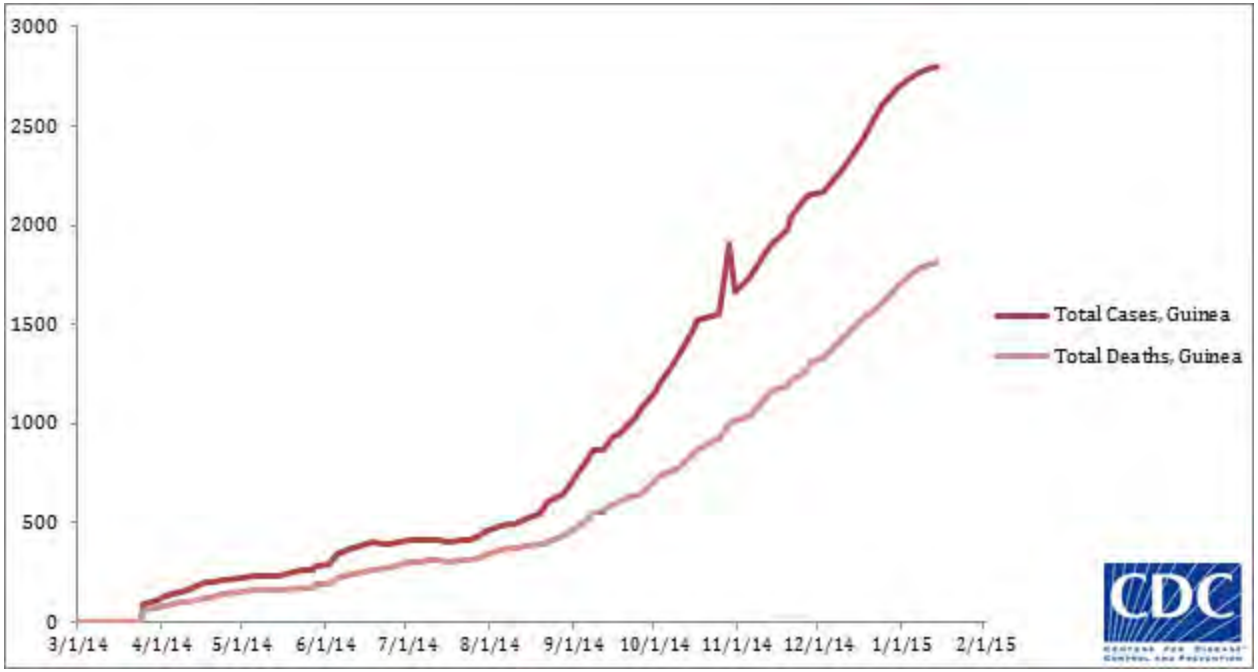
- People who survive the disease, especially women and orphaned children, need psychosocial support and counseling
- Medical symptoms have been documented in what is increasingly recognized as a "post-Ebola syndrome" and need to be managed and assessed.

Source :WHO Ebola, One Year Response; http://www.who.int/csr/disease/ebola/one-year-report/response-in-2015/en/.

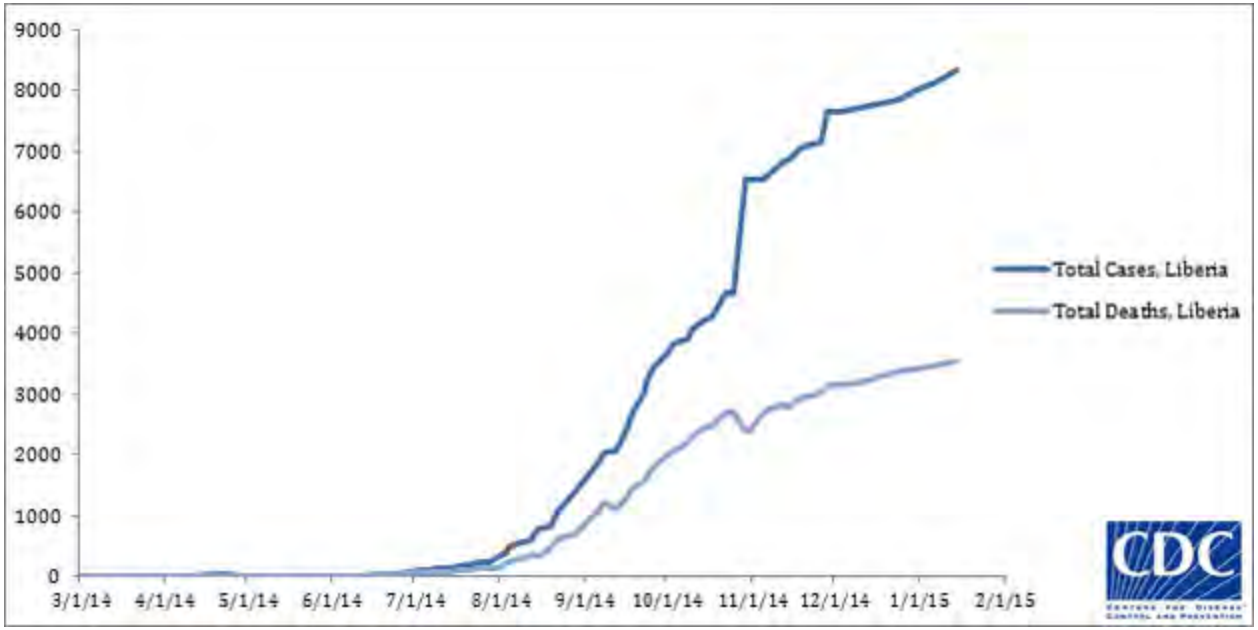
Cumulative Reported Cases



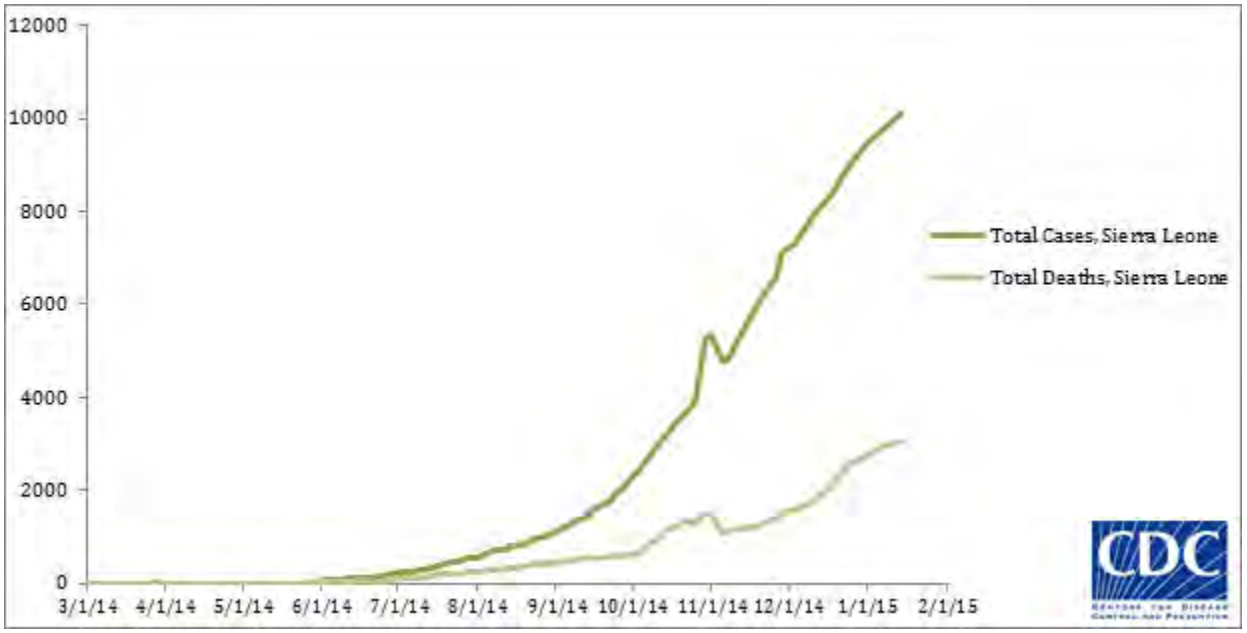
Cumulative Reported Cases: Guinea



Cumulative Reported Cases: Liberia



Cumulative Reported Cases: Sierra Leone



Ebola

- Case Definition
  - **Person Under Investigation (PUI)**
    - A person who has both consistent symptoms and risk factors as follows:
      - Clinical criteria, which includes fever of greater than 38.0 degrees Celsius or 100.4 degrees Fahrenheit, **and**
      - Additional symptoms such as severe headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; **and**
      - Risk factors within the past 21 days before the onset of symptoms
        - » Contact with blood or other body fluids or human remains of a patient known to have or suspected to have EVD;
        - » Residence in—or travel to—an area where EVD transmission is active
        - » Direct handling of bats or non-human primates from disease-endemic areas.

CDC

Ebola

- Case Definition
  - **Probable Case**
    - A PUI whose epidemiologic risk factors include high or low risk exposure(s)
    - **High risk exposures:**
      - Percutaneous (e.g., needle stick) or mucous membrane exposure to blood or body fluids of EVD patient
      - Direct skin contact with, or exposure to blood or body fluids of, an EVD patient without appropriate personal protective equipment (PPE)
      - Processing blood or body fluids of a confirmed EVD patient without appropriate PPE or standard biosafety precautions
      - Direct contact with a dead body without appropriate PPE in a country where an EVD outbreak is occurring*
      - Having lived in the immediate household and provided direct care to an EVD patient while the person was symptomatic

CDC

Ebola

- **Some Risk**
  - In countries with widespread transmission or cases in urban areas with uncertain control measures
    - Direct contact while using appropriate PPE with a person with EVD while that person was symptomatic or with the person's body fluids
    - Any direct patient care in other healthcare settings
  - Close contact in households, healthcare facilities, or community settings with a person with EVD while that person was symptomatic
    - Close contact is defined as being for a prolonged period of time while not wearing appropriate PPE within approximately 3 feet (1 meter) of a person with EVD while the person was symptomatic.

Ebola

- Case Definition
  - **Probable Case**
    - A PUI whose epidemiologic risk factors include high or low risk exposure(s)
    - **Low (but not zero) risk exposures**
      - Having been in a country with widespread transmission or cases in urban areas with uncertain control measures within the past 21 days and having had no known exposures.
      - Other close contact with EVD patients in health care facilities or community settings.
        - » Being within approximately 3 feet (1 meter) of an EVD patient or in the patient's room or care area for a prolonged period of time while not wearing recommended PPE and the person was symptomatic
        - » Having direct brief contact (e.g., shaking hands) with an EVD patient while not wearing recommended PPE and patient was in early stages of disease
        - » Traveled on an aircraft with a person with EVD while the person was symptomatic
        - » In countries without widespread transmission or cases in urban settings with uncertain control measures: direct contact while using appropriate PPE with a person with Ebola while the person was symptomatic or with the person's body fluids

Brief interactions, such as walking by a person or moving through a hospital, do not constitute close contact

CDC

Ebola

- **No identifiable risk (CDC)**
  - Contact with an asymptomatic person who had contact with person with Ebola
  - Contact with a person with Ebola before the person developed symptoms
  - Having been more than 21 days previously in a country with widespread transmission or cases in urban areas with uncertain control measures
  - Having been in a country with Ebola cases, but without widespread transmission or cases in urban settings with uncertain control measures, and not having any other exposures as defined above
  - Having remained on or in the immediate vicinity of an aircraft or ship during the entire time that the conveyance was present in a country with widespread transmission or cases in urban areas with uncertain control measures, and having had no direct contact with anyone from the community.

Ebola

- Case Definition
  - **Confirmed Case**
    - A case with **<u>laboratory-confirmed</u>** diagnostic evidence of Ebola virus infection

Ebola

- Lessons learned from Emory University
  - EMS and transport crews need to comply with hand hygiene
  - Universal compliance with standard infection control precautions needs to be maintained
  - Proper training of how to put on and remove PPE is imperative
  - Prepare transport vehicles

Slides from Dr. Isakov – Emory University

Ebola
PPE and equipment selection

Slides from Dr. Isakov – Emory University

Ebola
Ambulance Disinfection Mission Recovery

- Driver compartment isolation and patient compartment barrier drapes
- Decon, disinfection of ambulance, PPE doffing and waste removal **ALL SUPERVISED**
- Surveillance (monitor for fever amongst medics)

Slides from Dr. Isakov – Emory University

Ebola

- Personal Protective Equipment
  - PPE is in short supply
    - Do not cut corners
    - Ensure your supply chain is monitoring your PPE
    - Do not reuse unless you can ensure optimal cleaning
  - PPE doesn't work unless you use it correctly
    - Training (**Train the RIGHT PPE!!!!**)
    - Supervision when using and removing
    - Do not work if you are ill

Slides from Dr. Ribner– Emory University

Ebola

- Complications of Ebola:
  - Diarrhea
    - Loss of water and electrolytes (may be massive)
    - Dehydration- may be difficult to monitor or replace
    - Replacement with Oral Rehydration Solution or Lactated Ringers may lead to low sodium levels (hyponatremia) and low potassium levels (hypokalemia)
      - Both of the Emory patients had low potassium
    - Exacerbates hypotension

Ebola

- Complications of Ebola:
  - Vomiting
    - Difficult to use oral meds and hydration
    - Electrolyte management is made more difficult
  - Edema
    - Both patients at Emory gained over 20 pounds
    - IV access become difficult if not impossible
      - Early access if you can
    - Masks low intravascular volume

Ebola

- Complications of Ebola:
  - Low Platelets
    - Increases bleeding tendency
    - Need to replace with platelet transfusions
      - This is problematic:
        - » Can't measure platelets in many places
        - » Platelet transfusions not likely available due to storage issues
          - » Whole Blood transfusions
  - Disseminated Intravascular Coagulation
    - Worsens bleeding
    - Need plasma

Slides from Dr. Ribner– Emory University

Ebola

- Emory University patients
  - Presented like what you would expect to see here in the U.S. in a severe infection
    - Severe electrolyte abnormalities
    - Severe edema (with low protein levels)
    - Thrombocytopenia
- Early supportive care and aggressive resuscitation is key
  - Difficult if monitoring equipment is not available and resources are depleted without replacement

Slides from Dr. Ribner– Emory University

Ebola

- A question that has been raised…

J Infect Dis. 1999 Feb;179 Suppl 1:S28-35.

Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidémies à Kikwit.

Rowe AK[1], Bertolli J, Khan AS, Mukunu R, Muyembe-Tamfum JJ, Bressler D, Williams AJ, Peters CJ, Rodriquez L, Feldmann H, Nichol ST, Rollin PE, Ksiazek TG.

⊕ **Author information**

Abstract

A cohort of convalescent Ebola hemorrhagic fever (EHF) patients and their household contacts (HHCs) were studied prospectively to determine if convalescent body fluids contain Ebola virus and if secondary transmission occurs during convalescence. Twenty-nine EHF convalescents and 152 HHCs were monitored for up to 21 months. Blood specimens were obtained and symptom information was collected from convalescents and their HHCs; other body fluid specimens were also obtained from convalescents. Arthralgias and myalgia were reported significantly more often by convalescents than HHCs. Evidence of Ebola virus was detected by reverse transcription-polymerase chain reaction in semen specimens up to 91 days after disease onset; however, these and all other non-blood body fluids tested negative by virus isolation. Among 81 initially antibody negative HHCs, none became antibody positive. Blood specimens of 5 HHCs not identified as EHF patients were initially antibody positive. No direct evidence of convalescent-to-HHC transmission of EHF was found, although the semen of convalescents may be infectious. The existence of initially antibody-positive HHCs suggests that mild cases of Ebola virus infection occurred and that the full extent of the EHF epidemic was probably underestimated.

- Easy Answer = Survivors wear condoms for 3 months

Ebola

- Treatment is primarily supportive
- In the works…
  - Recombinant human monoclonal antibodies
  - Vaccines mostly in pre-clinical stage (few human studies)
    - DNA vaccines
    - Live viral vector vaccines
    - Virus-like particles vaccines
  - Medications:
    - Pyrazinecarboxamide derivative, T-705 (favipiravir)
    - Broad-spectrum nucleoside analogue (BCX4430)
    - Recombinant nematode anticoagulant protein (NAP)
      - inhibits activated factor VII-tissue factor complex

Ebola

- Recombinant Human Monoclonal Antibodies
  - MB-003 (**c13C6**, h13F6 and c6D8)
  - ZMAb (m1H3, **m2G4 and m4G7**)
  - ZMapp = MB-003 + ZMAb
    - Consists of 3 humanized monoclonal antibodies
    - Best components of the MB-003 and ZMAb products
    - Produced in tobacco plants
  - Protected all 18 NHPs when given up to 5 days after infection
  - Human experience
    - To date, 7 ebola patients have received the drug
      - 5 have survived
      - Difficult to decipher if there is a benefit in such small group

Nature. 2014 Aug 29.[Epub ahead of print]

Ebola

- TKM-100802
  - Tekmira Pharmaceuticals Corporation
  - Small interfering RNAs targeting various components of the Ebola virus
  - Macaque study showed 100% protection when given after infection (30 mins, then daily for 6 days)
  - Phase 1 safety study suspended by FDA in July 2014, due to safety concerns (inflammatory, flu-like symptoms)
  - FDA recently allowed for compassionate use
    - Given to an aid worker who returned from Liberia on 5 SEP 2014
      - Also received blood transfusion from Kent Brantly

Lancet. 2010 May 29;375(9729):1896-905.

Ebola

- Pyrazinecarboxamide derivative, T-705 (Favipiravir)
  - Inhibits virus RNA polymerase
  - Broad spectrum antiviral activity against several viruses
    - » Currently in phase 3 development for influenza treatment
  - Activity against Ebolavirus noted in mouse studies
    - » 18 mice challenged with lethal aerosol exposure
      - » Treatment started 1 hour post-challenge, then BID x 14 days
      - » All control mice died 7-8 days later
      - » All mice treated with T-705 survived at 4 weeks
    - » Mice treated 6 days post infection in a separate study
      - » Treatment mice had viremia at treatment start
      - » Virus cleared in 4 days (100% survival at 21 days)
      - » No survival benefit if started at 8 days

Antiviral Res. 2014 Apr;104:153-5 Antiviral Res. 2014 May;105:17-21

Ebola

- Broad-spectrum nucleoside analogue (BCX4430)
  - Inhibits viral RNA polymerase through RNA chain termination
  - Prophylactic studies in mice showed 75-100% protection when given up to 96 hours after infection
  - Treatment studies in macaques up to 48 hours after infection showed 100% protection when challenged with Marburg virus
  - No human trials

Nature. 2014 Apr 17;508(7496):402-5

Ebola

- Recombinant nematode anticoagulant protein (NAP)
  - Directly inhibits the factor VIIa/tissue factor complex
    - » Has antithrombotic potential as shown in phase II surgical trials
  - In Ebola challenge in macaques with NAP either 10 mins or 24 hours after infection
    - » 16 of 17 controls died
    - » 6 or 9 treatment animals died (33% survival vs 6%)
  - A separate Marburg study in 2007 showed less favorable outcomes

Lancet. 2003 Dec 13;362(9400):1953-8.
J Infect Dis. 2007 Nov 15;196 Suppl 2:S372-81.

Ebola

- AVI-6002
  - An experimental combination of 2 phosphorodiamidate morpholino antisense oligomers
  - Specifically target viral mRNA encoding Ebolavirus proteins
  - Found to suppress disease in infected NHPs
  - Phase 1 safety study has been completed
    - 30 healthy adults aged 18-50
    - Dose escalation study
    - Safety was equivalent to placebo groups

Antimicrob Agents Chemother. 2014 Aug 25. [Epub ahead of print]

Ebola

- Clomiphene and Toremifene
  - Screen of Food and Drug Administration (FDA) approved drugs
    - Looked for antiviral activity against Ebolavirus
  - Identified a set of selective estrogen receptor modulators (SERMs),
    - Act as potent inhibitors of EBOV infection.
    - Anti-EBOV activity was confirmed for both in a mouse model.
    - Response appeared to be an off-target effect where the compounds interfere with a step late in viral entry
  - These compounds represent an immediately actionable class of approved drugs that can be repurposed for treatment of filovirus infections. Studies have yet to be started

Sci Transl Med. 2013 Jun 19;5(190):190ra79

Ebola

- Retanizone
  - Novel vitamin A derived (retinoid) thiosemicarbazone derivative
  - Broad spectrum antiviral activity (HIV, HCV, VZV, CMV)
  - Tested against Ebola virus Zaire in lab
    - Showed some evidence of disrupting multiplication of the virus at small concentrations

Antivir Chem Chemother. 2014 Apr 11;23(5):197-215

Ebola

- Vaccines
  - Inactivated ebola virus
  - Virus-like particles
  - DNA vaccines
  - Recombinant viral vector vaccines
    - Adenovirus (both Ad5 and cAd3, “chimp Ad”)
    - Vesicular Stomatitis Virus (VSV)
    - Rabies virus
    - Vaccinia virus
    - CMV
    - Paramyxovirus

Ebola

- Vaccines
  - DNA vaccines
    - Tested in humans in a phase 1 study (2006)
    - Uses 3 different plasmids encoding proteins against Ebola
    - Healthy adults 18-44 years old
    - No significant adverse effects of the vaccine
    - Appeared to be immunogenic
    - Given intramuscularly via a needle free device (Biojector 2000)
    - All subjects produced an immune response to at least one of the 3 antigens encoded by the vaccine
      - » **Specific neutralizing antibody was <u>NOT</u> detected**

Clin Vaccine Immunol. 2006 Nov;13(11):1267-77.

Ebola

- Vaccines
  - Adenovirus vaccines
    - Ad 5 vectors and chimpanzee Ad3 (cAd3) vectors
      - » Phase 1 safety study of Ad5 vector vaccine shown to be safe in a dose escalation study when given intramuscularly
        - » 50% of subjects had neutralizing antidody titers against adenovirus 5 prior to study start
          - » Potentially makes the vaccine less effective
        - » Antibody response to Ebola was 64-82% for the highest dose of vaccine tested
    - cAd3 phase 1 study recently initiated at the NIH and at Oxford
      - » Phase 1 study Shown to be safe
      - » All subjects mounted immune responses (some had T-cell)

Virology. 2006 Mar 15;346(2):394-401
Vaccine. 2010 Dec 16;29(2):304-13.
Nat Med. 2014 Sep 7. [Epub ahead of print]

Ebola

- Vaccines
  - VSV vaccines
    - VSV
      - » In the same family as rabies virus
      - » Infects cattle, horses, pigs (rare human infections)
        - » Causes oral lesions in animals
        - » Can cause mild, flu-like illness in humans (rare cases of encephalitis)
    - Vaccine virus has the glycoprotein removed and replaced with the filovirus glycoprotein
      - » Limits immunity against the vaccine virus
      - » Limits the VSV pathogenicity
      - » Produces antibody response against ebola

Phase I clinical trial scheduled for Oct 2014 at WRAIR

PLoS Negl Trop Dis. 2013 Dec 19;7(12):e2600
PLoS One. 2014 Apr 23;9(4):e94355.
Vaccine. 2014 Sep 29;32(43):5722-5729

Questions?