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Ebola Virus Disease and Its Potential to Spread Beyond Africa

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PROGRAM GOAL

To provide an Accredited CME program for health care providers on the current status of Ebola.

OBJECTIVES

Upon completion of this educational activity, the participant will be able to:

1. Review the fundamentals of Ebola including epidemiology, pathophysiology, and risk factors.
2. Recognize current outbreak trends and public perception of Ebola.
3. Understand the importance of military involvement in Ebola containment.
4. Examine Ebola reporting and notification measures for providers in rural practice and beyond.
5. Evaluate options for treatment and vaccines in rural practice and beyond.

EBOLA IS LISTED AS A CDC CATEGORY A DISEASE

Based on severity of the clinical presentation and potential for high mortality

The ability to cause panic and disrupt economic activity

Ability to drain critical resources and potentially disrupt the U.S. healthcare system

Reference:

Centers for Disease Control and Prevention. Biological and chemical terrorism: strategic plan for preparedness and response, recommendations of the CDC Strategic Planning Workgroup 2000. MMWR Morb Mortal Wkly Rep. 2000;49(RR-4):1–14.

EBOLA RESEARCH IN THE U.S. MUST BE CONDUCTED UNDER BSL-4

Biosafety Level - 4 containment is required against Category A biological agents and natural agents of public health importance that require special containment procedures.

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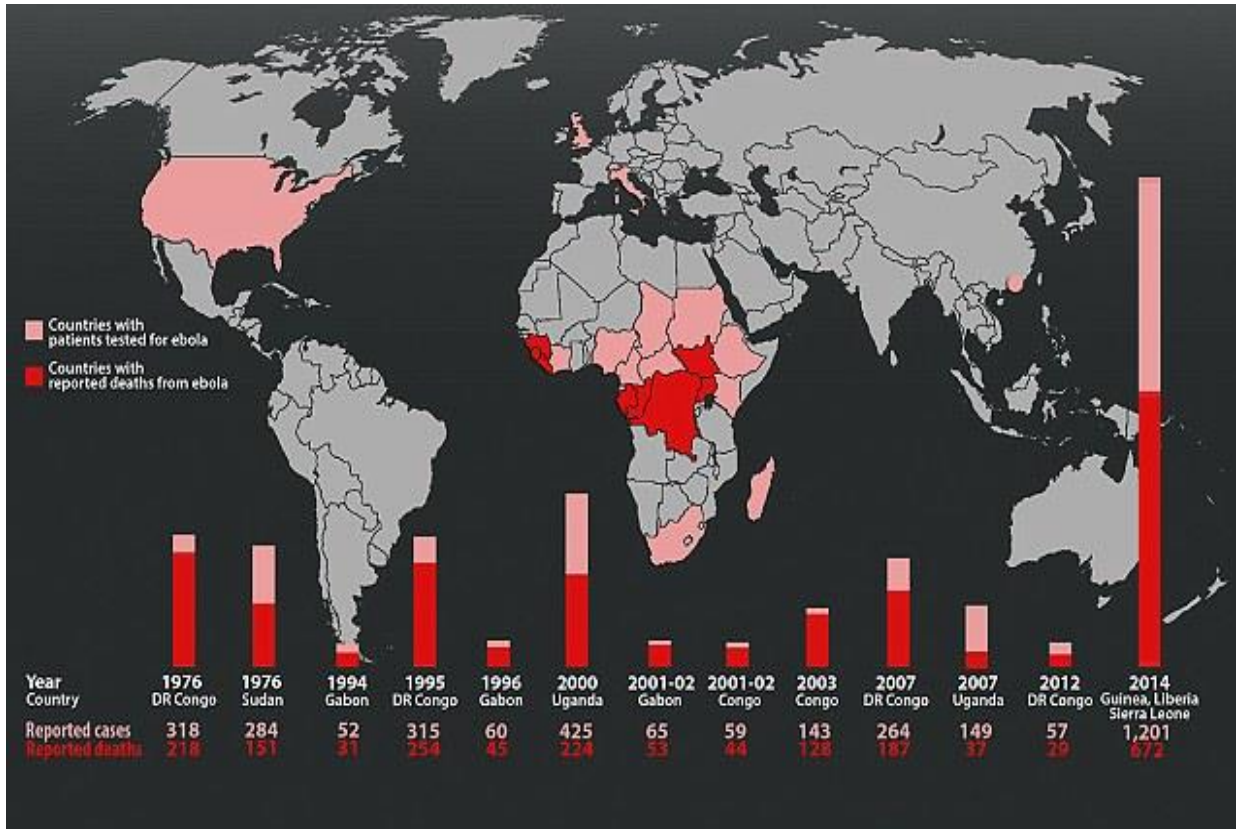
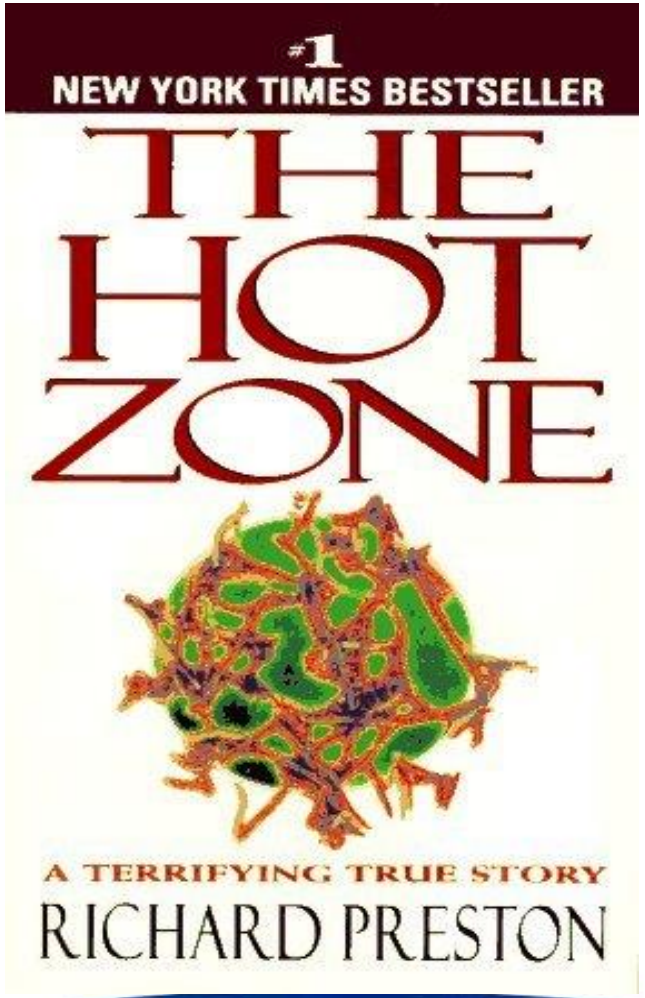
PORTABLE BIOSAFETY LEVEL 4 PREPAREDNESS EXERCISES

PREVENTING THE SPREAD OF EBOLA VIRUS DISEASE

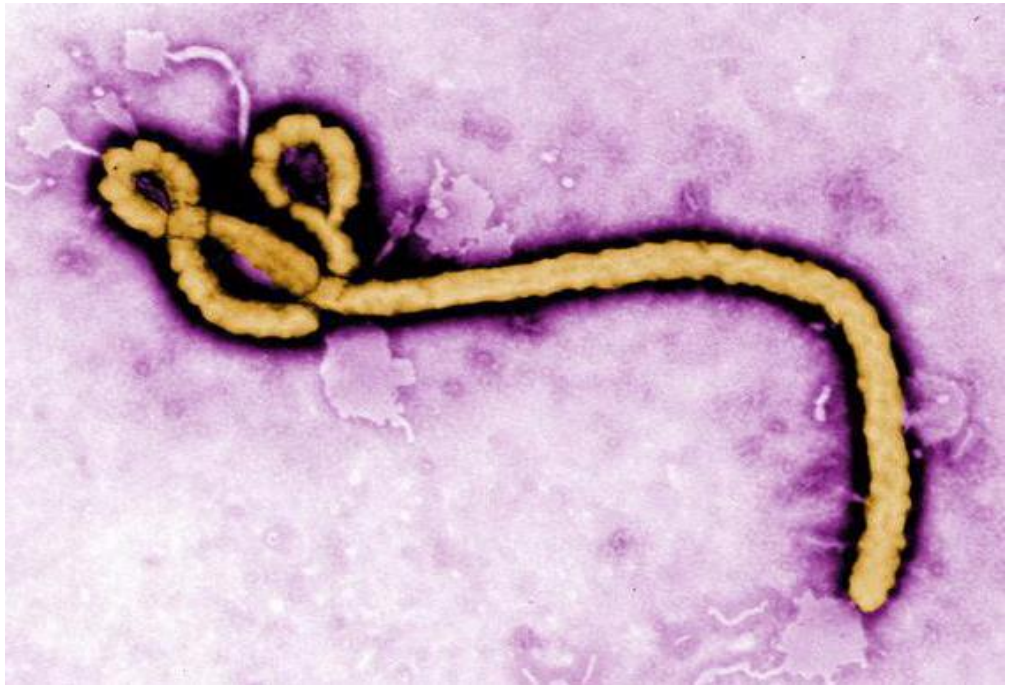


How Ebola Virus Disease has slowly spread across central Africa over three decades

HOW THE PUBLIC PERCEIVES EBOLA

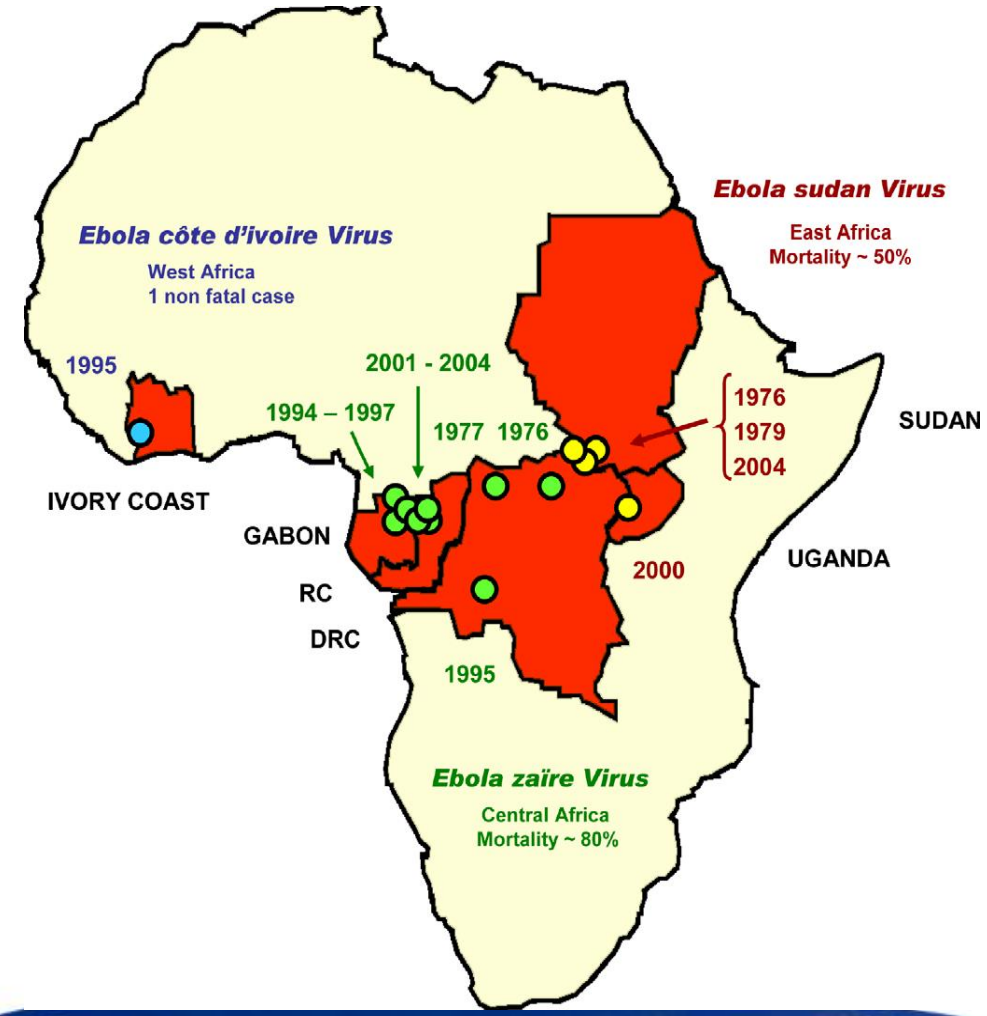


EBOLA VIRUS DISEASE/PREVENTION



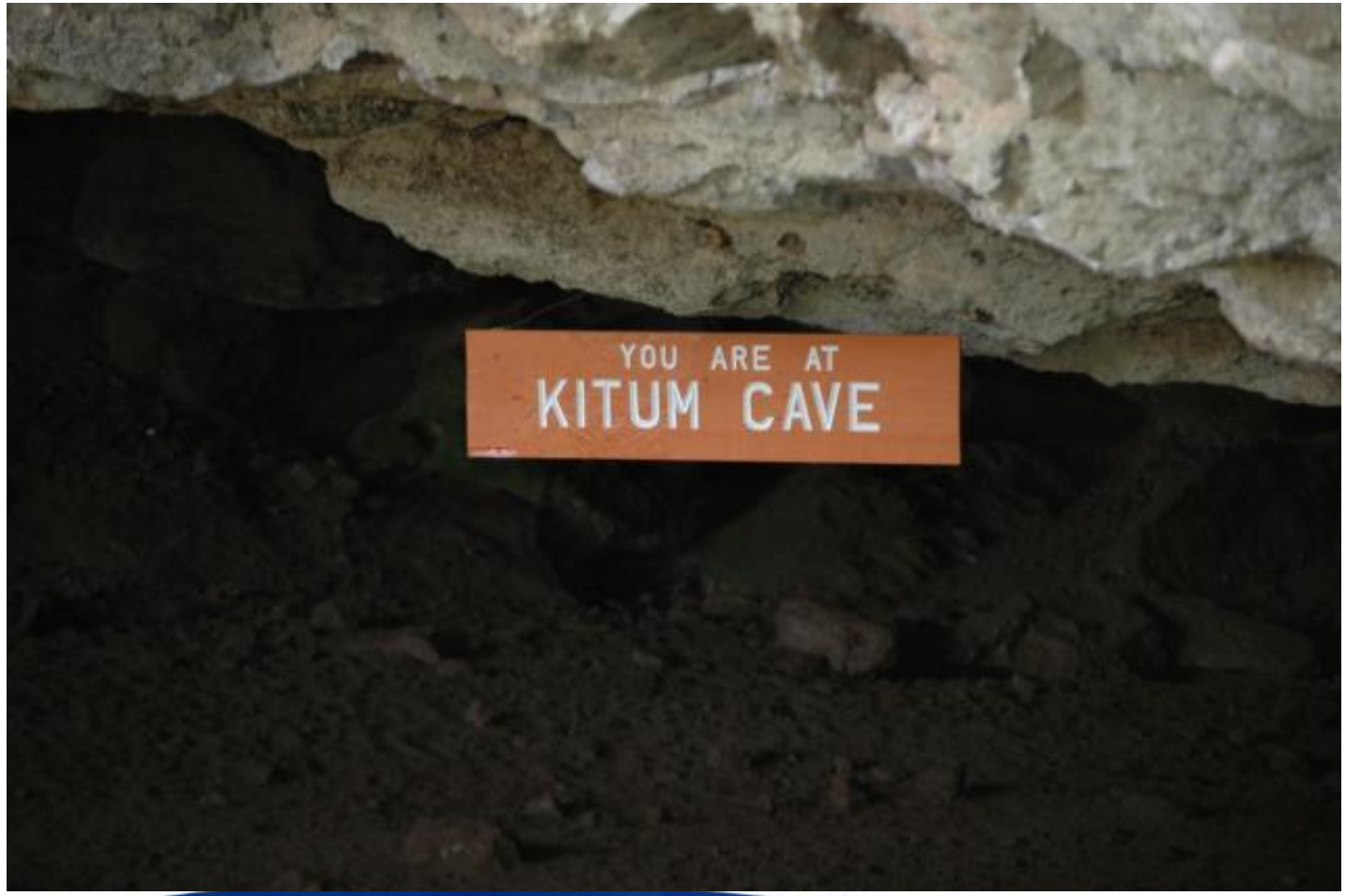
- Ebola Virus Disease (EVD) is caused by a filo-virus resulting in the disease of Viral hemorrhagic fever.
- The virus is spread through direct contact (through broken skin or mucous membranes) with infected body fluids (blood, urine, feces, saliva, and other secretions) of a person who is sick with Ebola.

EPIDEMIOLOGY OF PREVIOUS OUTBREAKS



- Ebola viruses, an emerging zoonotic disease in Sub-Saharan Africa
- First recognized in mid 1970's

MYSTERY OF KITUM CAVE



WHO IS AT RISK FOR EBOLA?

- Those involved in harvesting or consumption of the bush meat trade
- Family members of patients sick with Ebola especially those involved in direct care of the patients
- Healthcare Workers
- Those involved with burial or disposal of deceased Ebola patients
- Laboratory workers

WHERE DOES THE VIRUS GO BETWEEN OUTBREAKS?

Ebola Virus

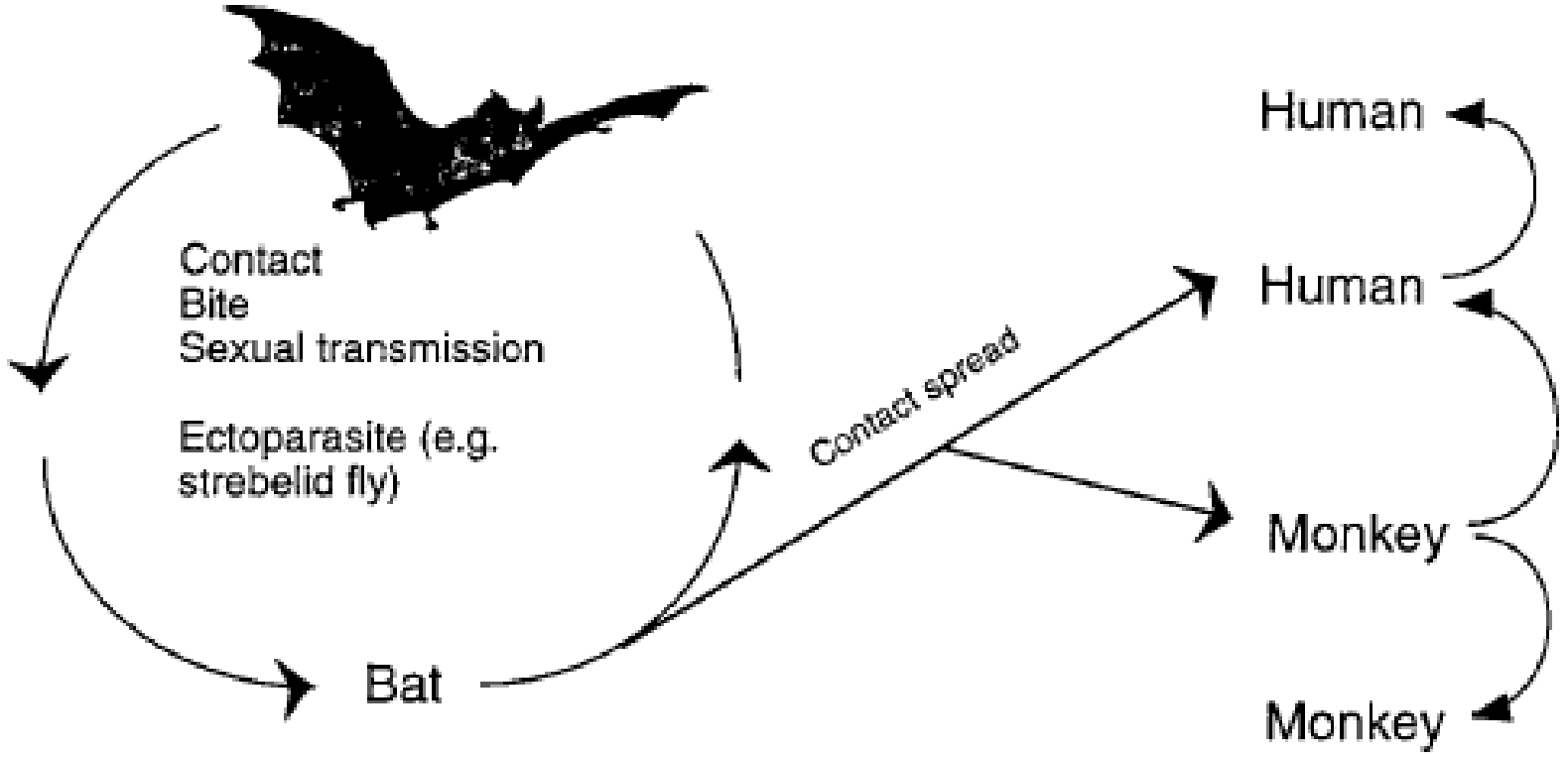
- Unknown reservoir (isolated from bats in Uganda cave)
- Researchers hypothesize that it is Zoonotic
- Human to Human transmission through direct contact

Ebola-Reston

- Occurred in the U.S (Reston, Virginia)
- Why only to non-human primates?
  - Four scientists found to have antibodies to virus
- Circumstantial evidence of airborne transmission
  - Spread within and between rooms

Marburg Virus

- Transmission from animal host unknown
- Human to Human (direct contact with infected animals and thru exchange of fluids from animals to caretakers)

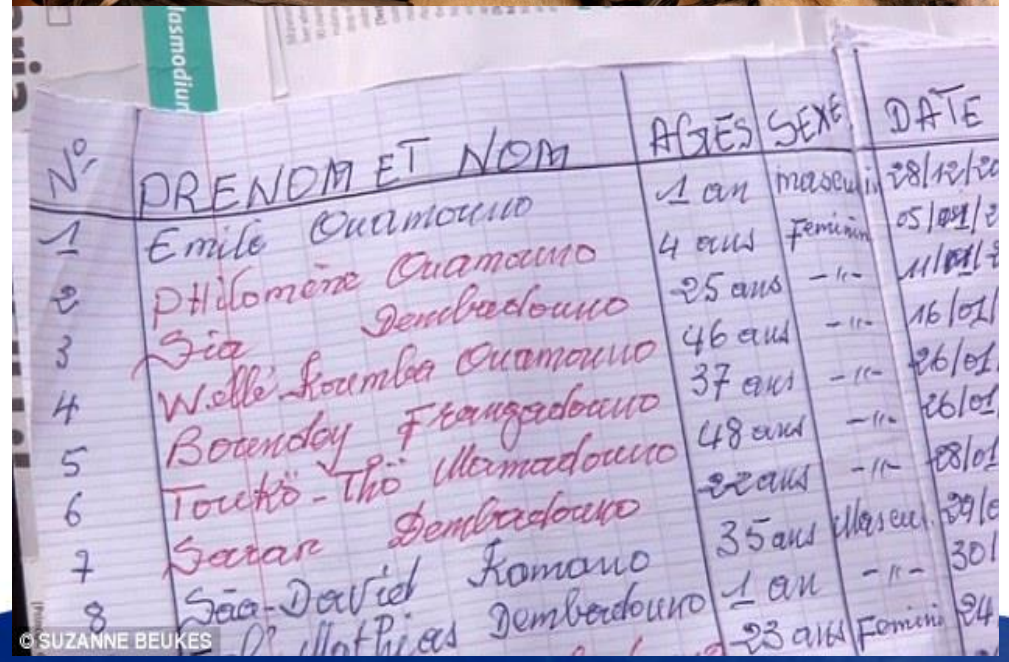


Characteristics of reservoir/vector species, by virus

Ecology of Marburg and Ebola Viruses: Speculations and Directions for Future Research

Thomas P. Monath *Research and Medical Affairs, OraVax, Inc., Cambridge Massachusetts*

ORIGIN OF WEST AFRICAN EBOLA OUTBREAK



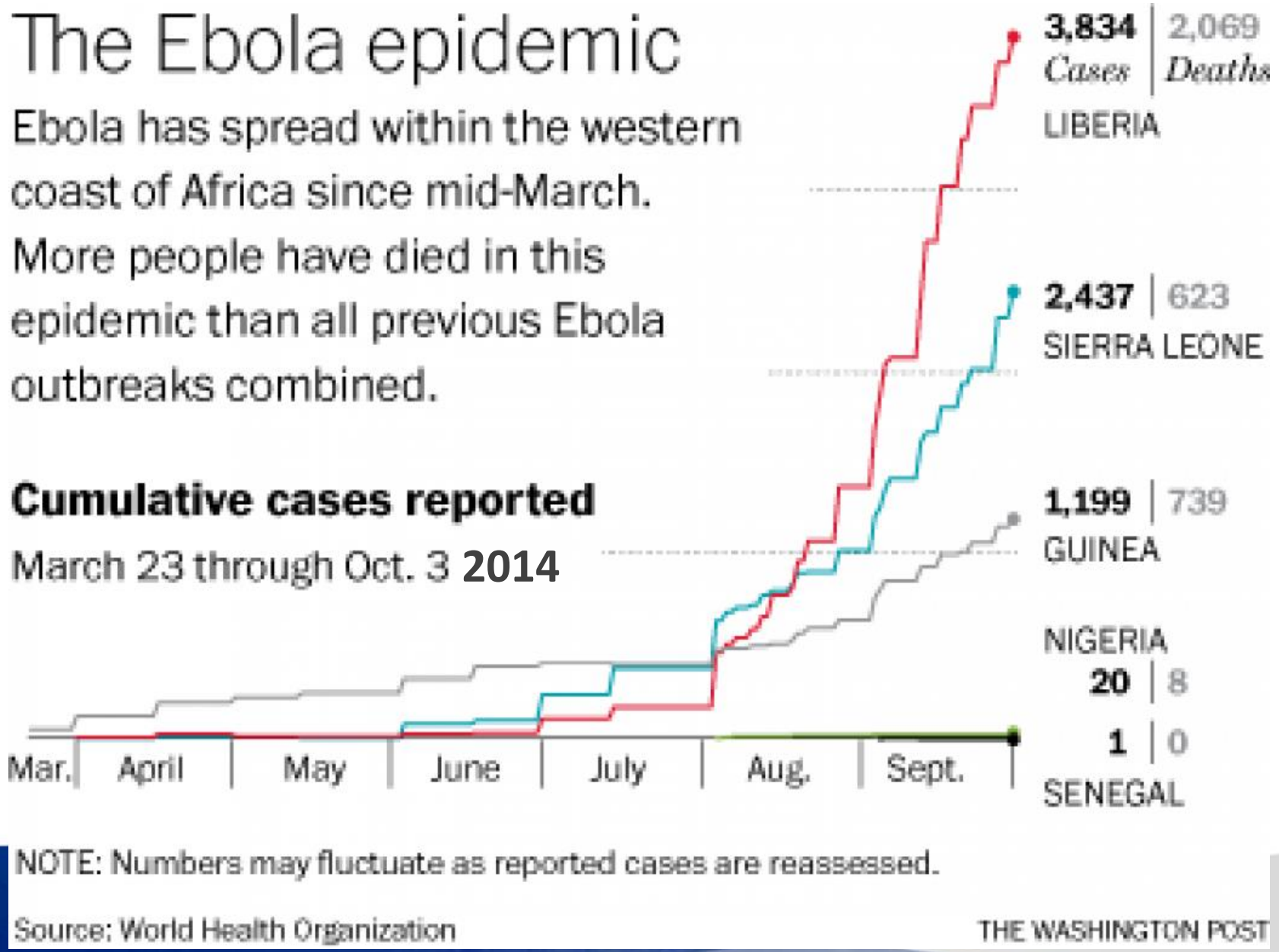
- Patient zero was a child who became sick in early Dec 2013
- While the source of the infection remains unknown fruit bats are known to harbor the virus

WHAT MADE THIS WEST AFRICAN OUTBREAK DIFFERENT?

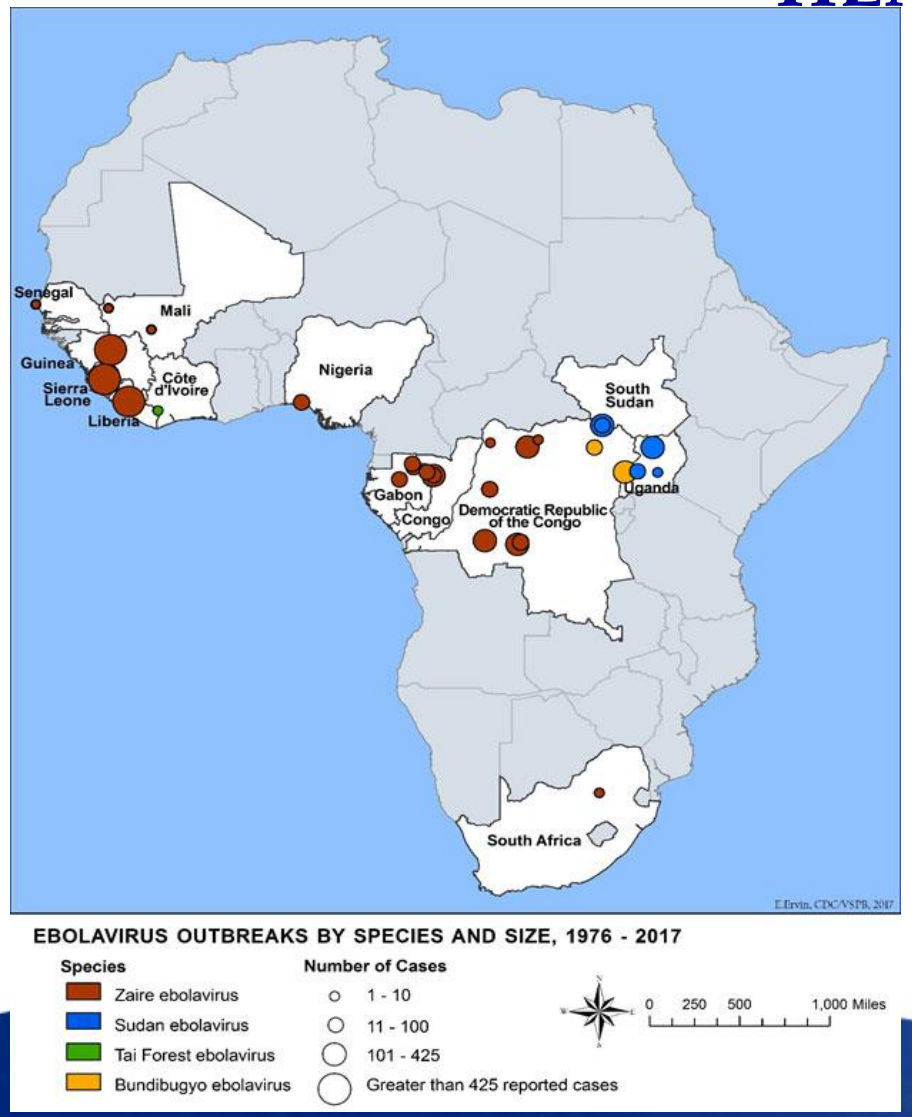
INTENSE URBAN TRANSMISSION

- Lack of health infrastructure and PPE necessary to protect health workers
- Rumors regarding source of Ebola have made controlling epidemic more challenging

- Necessity for quick removal and disposal of infected bodies


The Ebola epidemic
Ebola has spread within the western coast of Africa since mid-March. More people have died in this epidemic than all previous Ebola outbreaks combined.
Cumulative cases reported
March 23 through Oct. 3 2014
3,834 | 2,069
Cases | Deaths
LIBERIA
2,437 | 623
SIERRA LEONE
1,199 | 739
GUINEA
NIGERIA
20 | 8
1 | 0
SENEGAL
Mar.
April
May
June
July
Aug.
Sept.
NOTE: Numbers may fluctuate as reported cases are reassessed.
Source: World Health Organization
THE WASHINGTON POST

LATEST EVD REPORTING ACCORDING TO THE WORLD HEALTH ORGANIZATION



- On May, 2017, the Ministry of Public Health of the DRC notified international public health agencies of a cluster of suspected cases of Ebola Virus Disease (EVD) in the Likati health zone

PREDOMINANT AIR ROUTES OF TRAVEL OUT OF WEST AFRICA

Fig. 1: Air traffic connections from West African countries to the rest of the world

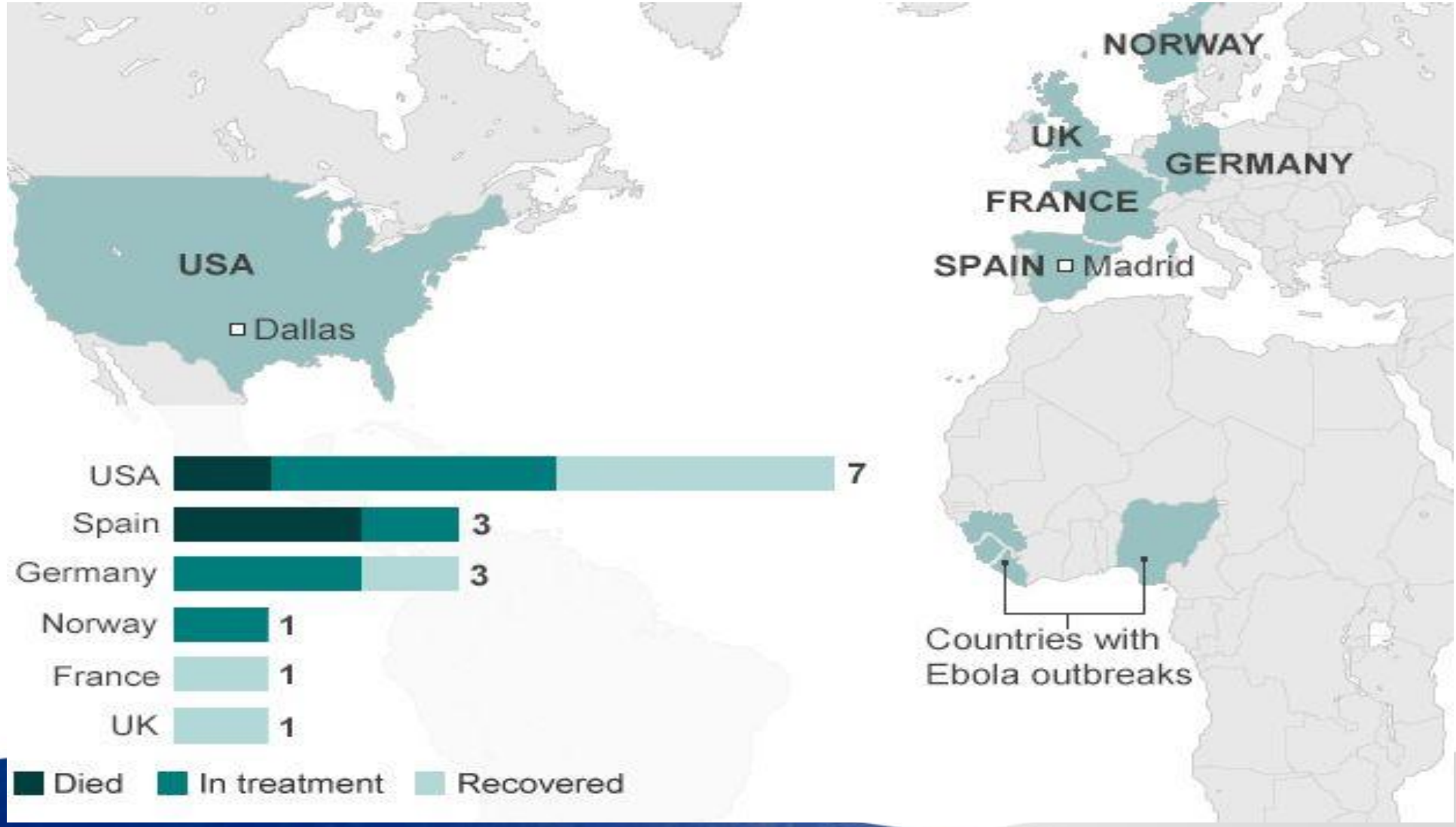
Air traffic connections from West African countries to the rest of the world. Guinea, Liberia, and Sierra Leone are not well connected outside the region. Nigeria, in contrast, being the most populous country in West Africa with more than 166 million people, is well connected to the rest of world. For historical reasons, all these countries have the strongest ties with European countries.

EBOLA CASES DIAGNOSED IN THE U.S.

On 21 Sept, 2014 Thomas Duncan travelled to Dallas Texas, after being in contact with friend who died of EVD in Monrovia

He subsequently became symptomatic with EVD and spread the virus to 2 hospital nurses in Dallas

SPREAD OF EBOLA OUT OF WEST AFRICA SUMMER 2014

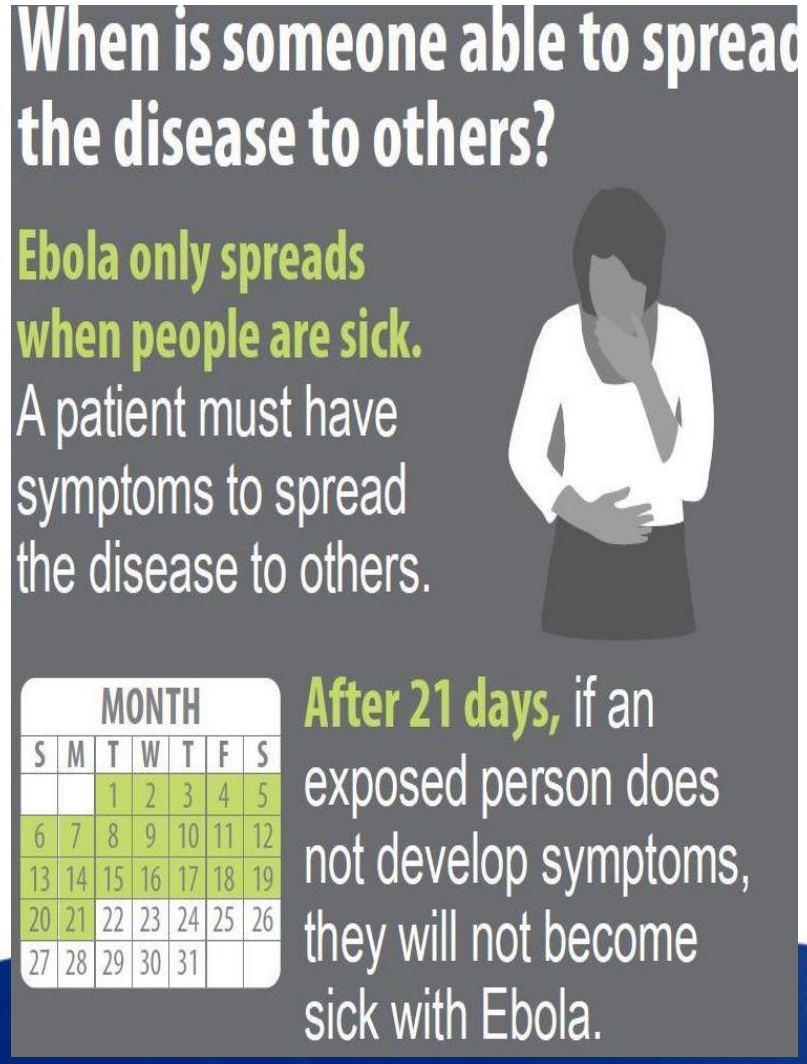


U.S. MILITARY WAS DEPLOYED IN 2014 AS PART OF OPERATION UNITED ASSISTANCE TO COMBAT THE EBOLA EPIDEMIC IN WEST AFRICA

First time U.S. Military was deployed to a location outside the U.S. to stem the tide of an Ebola Virus Epidemic.

Soldiers were required to pass through quarantine period prior to return to U.S. territory.

SYMPTOMS OF EBOLA TYPICALLY INCLUDE:



- Fever (greater than 38.6°C or 101.5°F)
- Severe headache
- Muscle pain
- Weakness
- Diarrhea
- Vomiting
- Abdominal (stomach) pain
- Hemorrhagic manifestations

Symptoms may appear anywhere from 2 to 21 days after exposure to Ebola virus, although 8-10 days is most common.

Ebola can only be spread to others after symptoms begin

EBOLA IS A FILOVIRUS: (MEANING THREAD-LIKE IN APPEARANCE)

FILO-VIRUSES GENERAL FACTS

- **Replication**
  - RNA virus with a rapid ability to hijack host cells and turn them into virus factories
- **Structure**
  - Pleomorphic: Long sometimes branched filament shaped like a Shepherd's crook.
  - Each Virus contains one molecule of single stranded, negative sense RNA
- **Infectivity or the measure of its ability to infect a new host is moderate**
- **Much higher in healthcare setting**

INCUBATION PERIOD

- Ebola Incubation at 2 – 21 Days
- Marburg Incubation: : 3-9 days
- EVD (in general) - Death can occur in one week following symptom development
- Ebola can kill in as little as 3 days (depends on host and level of inoculation)

HOW DOES EBOLA KILL?

When you look at the nitty-gritty details of an Ebola infection, a surprising fact surfaces: the virus isn't what ends up killing you.

"As in many of these emerging zoonotic diseases, it's the overproduction of *cytokine molecules* that ultimately leads to rapid cellular death and the coagulopathy often seen as the hallmarks of the disease".

Reference: Ebola Virus Pathogenesis: J of Virology, Sept 2003 9733-9737.

SEVERITY OF EBOLA INFECTION NOT ALWAYS DUE TO THE VIRUS

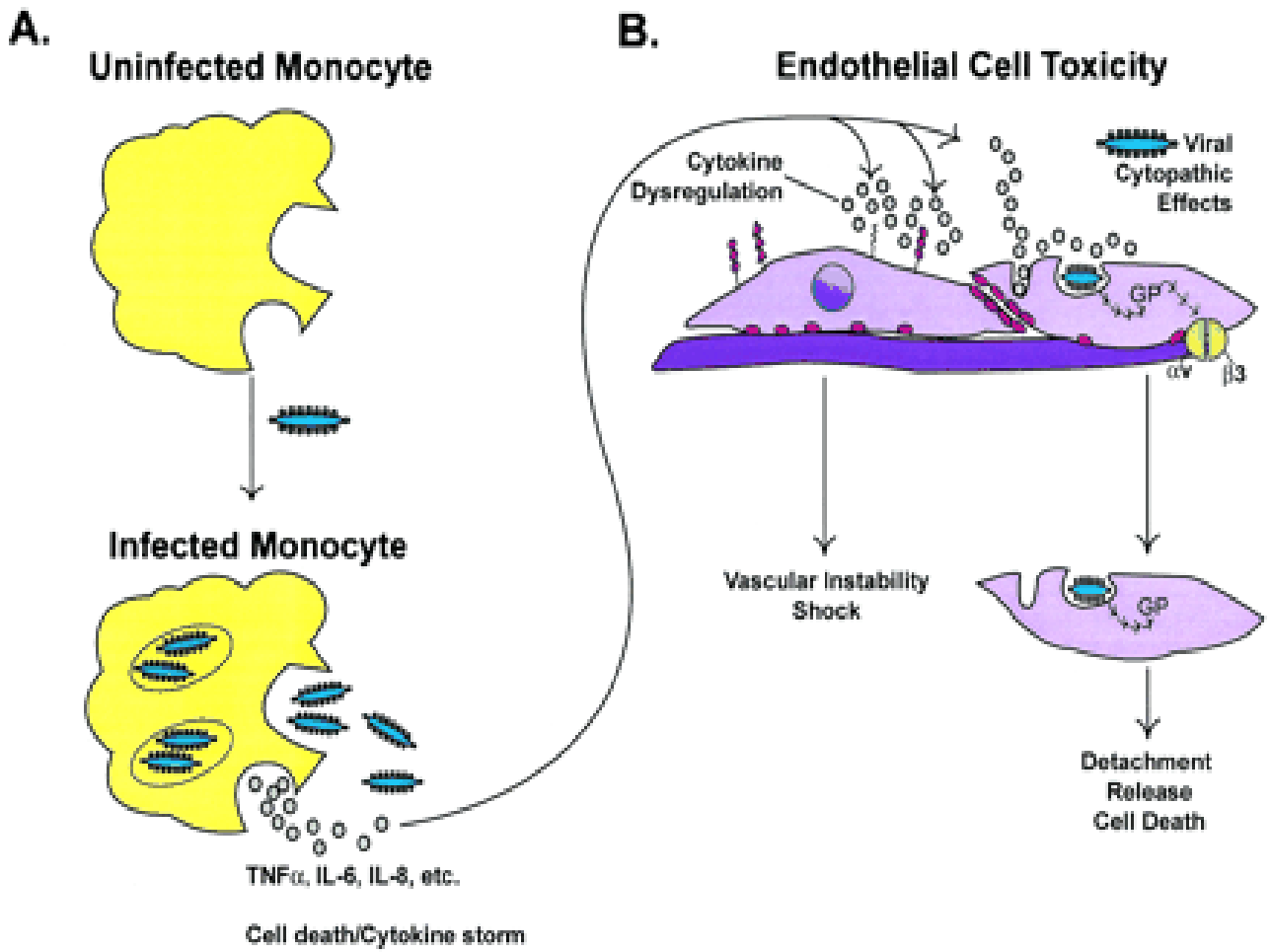
Studies of people infected with Ebola have found a diversity of reactions is not necessarily due to the virus: Some people resist the infection, while others have a more moderate reaction, while those who are most susceptible to bleeding, organ failure and hemorrhage most likely succumb.

After studying mice with different genetics, researchers found the severity of the Ebola infection seemed to line up with specific gene patterns.

DESTRUCTION OF THE IMMUNE SYSTEM

1. Dendritic cells are early targets of infection and are believed to be key in EVD pathogenesis
2. Infects mononuclear phagocytes and macrophages
   - Interferes with Antigen presentation process
   - Stimulates antigen trafficking and cytokine production
   - Extensive cell death of blood leukocytes (specifically monocytes)
   - Lymphopenia (reduction in lymphocyte)
2. Macrophages and circulating monocytes help transmit virus to other tissues

MODEL FOR CYTOKINE RELEASE



Reference: Ebola Virus Pathogenesis: J of Virology, Sept 2003 9733-9737.

FILOVIRUS GENETICS

- Ebola and Marburg viruses both encode 7 structural proteins
- Two Main Categories:
  - Associated with the nucleocapsid transcription and replication
  - Associated with the envelope assembly and receptor binding and virus entry

PATHOGENESIS OF EBV INFECTION

S-Glycoprotein

1. Inhibits early activation of neutrophils
   - Binds to neutrophils via CD16b cell surface receptor
   - CD16b activates neutrophils via lateral membrane interaction with CR3
2. Adsorbs neutralizing antibodies

Glycoprotein

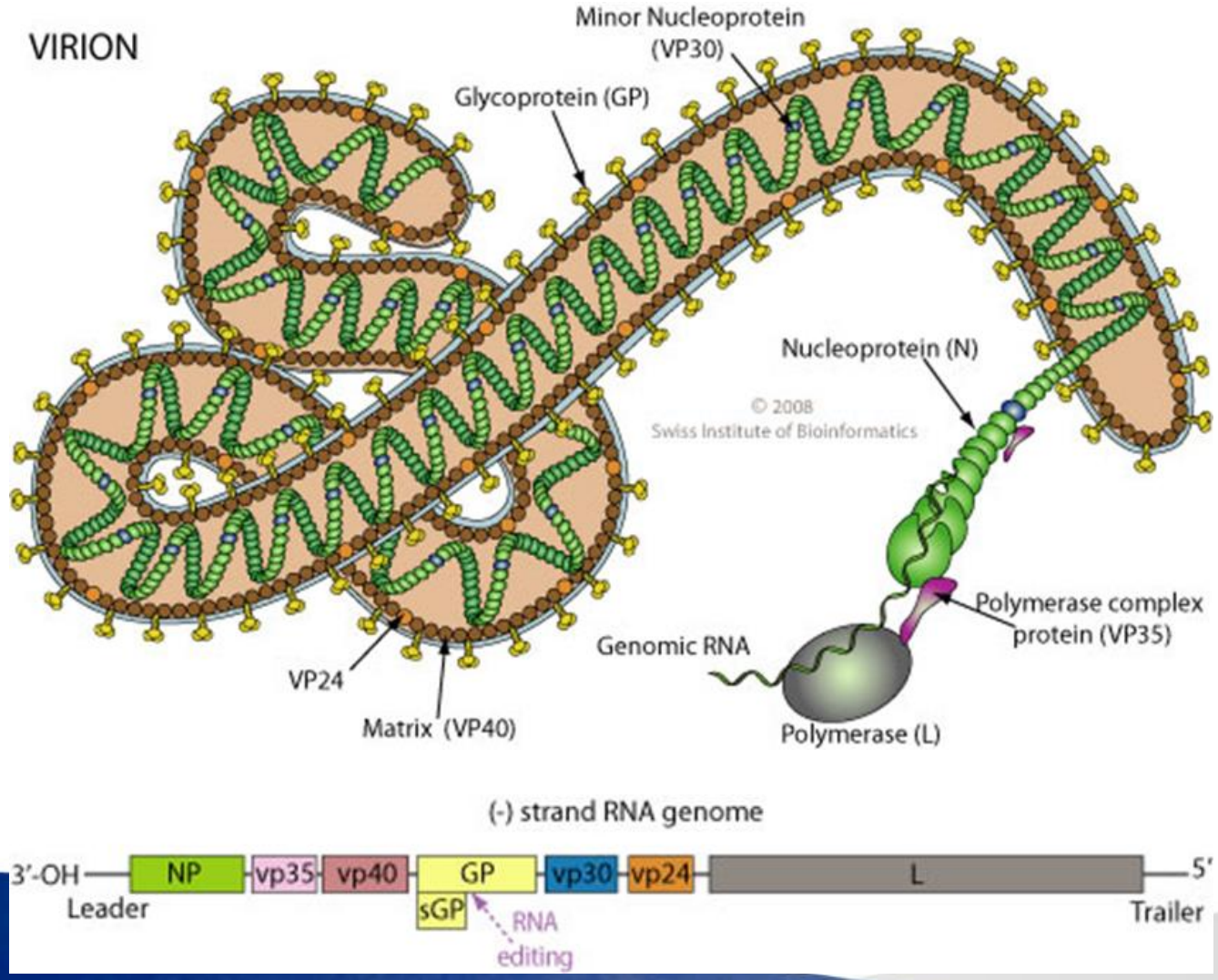
1. Specific region of GP induces cytotoxic effects in endothelial cells
   - Rapid release of vasoactive agents from infected cells
   - Induces cell rounding and detachment from extracellular matrix
   - Increases cell membrane permeability

EVD PATHOGENESIS, CONTINUED

2. Proteolytic activation of GP precursor via cleavage
   - EBO-Z GP is enzymatically cleaved
   - Prerequisite for fusion between viral envelope and host cell membrane
   - Enables virus to replicate in host →systematic infection

3. Two sequences contribute to evasion of host immunity
   - Possible immunosuppressive sequence in GP_2 molecule
   - Amino acid sequence at amino terminus suppresses lymphocyte mitogen-stimulated proliferation in vitro

EBOLA VIRUS GENOME



Other Structural Proteins include:

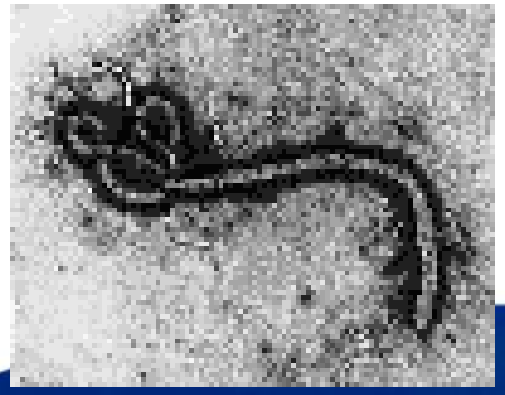
- VP30- Minor structural protein associated with the nucleocapsid
- Polymerase L- Transcription and Replication (largest and least abundant protein)
- VP35- Cofactor in transcription and Replication (Cofactor in polymerase complex)
- VP40- Matrix protein
  - Virus assembly and budding
  - Forms hexamers
- VP24- Minor Matrix Protein
  - Possibly uncoating virus during infection

Potential Vaccine Candidates

- Biotechnology company to collaborate with the US National Institute of Allergy and Infectious Diseases (NIAID) to develop a vaccine against the Ebola virus.
  - New vaccine uses DNA encoding three Ebola proteins and one nucleoprotein, followed by a boost with a replication-defective adenovirus expressing Ebola antigens
  - Scientists at the US Army Medical Research Institute of Infectious Diseases report a simple method for generating Ebola virus–like particles.

Vaccine, Continued

- Reverse genetics vs Forward genetics
  - Genetics concerned with genetic material whose nucleotide sequence is known -analyzes its contribution to the phenotype of the organism by varying the nucleotide sequence
  - Observe the results of such variation in the living organism, in living cells, or in vitro on macromolecules




Ebola Zaire (EVD)
cAd 4 Vaccine
Oct 2014
EboAdc4-8746-9876
5 doses