Infectious Diseases

Special Lesson

EBOLA VIRUS DISEASE

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Objectives and learning goal

Objectives

- To review all clinically relevant knowledge about Ebola virus disease
- To update the information on the present Ebola virus disease epidemic

Learning goal

To attain an updated knowledge on available relevant information about Ebola virus disease

Contents

The virus

Filoviridae family (filovirus) genera

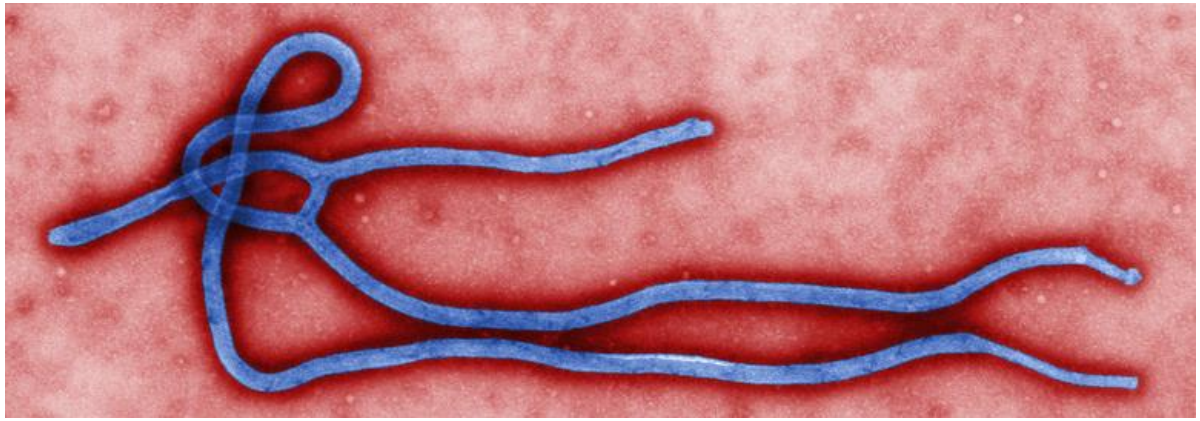
- Cuevavirus
- Marburgvirus, Angola 2004-2005
- **Ebolavirus**, comprises 5 distinct species:
  - Reston ebolavirus — Philippines
  - Taï Forest (Ivory Coast) ebolavirus — Africa
  - Bundibugyo ebolavirus — Africa
  - Sudan ebolavirus — Africa
  - **Zaire ebolavirus** — Africa

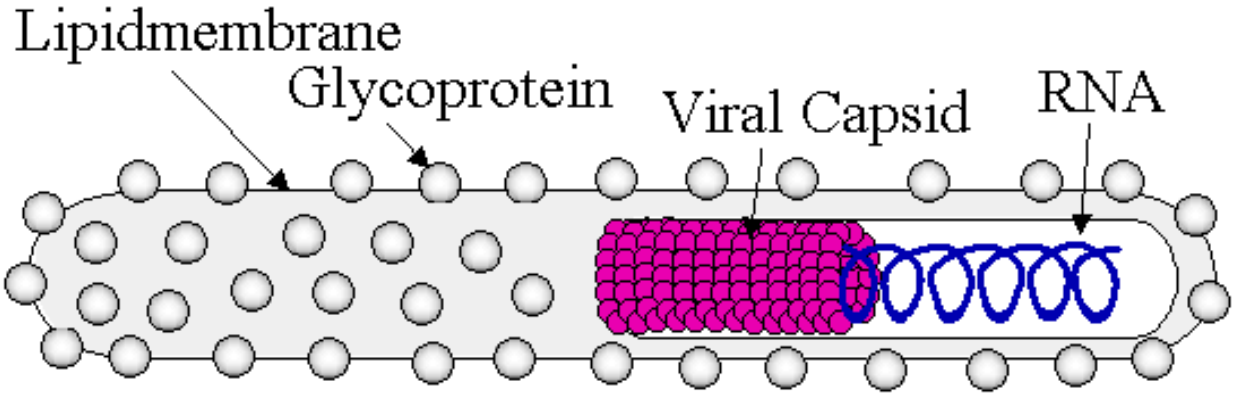
Ebolavirus species

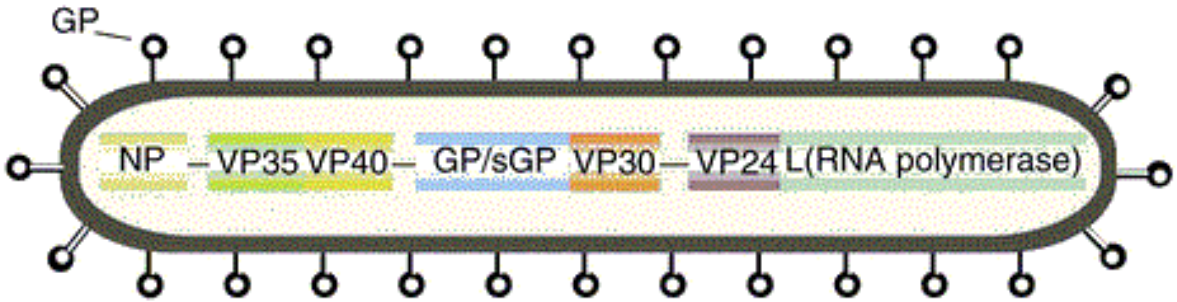
- Pleomorphic
- Filaments of 1,000 (up to 14,000) nm in length, uniform diameter of 80 nm
- Enveloped in a lipid membrane
- Marked genetic stability

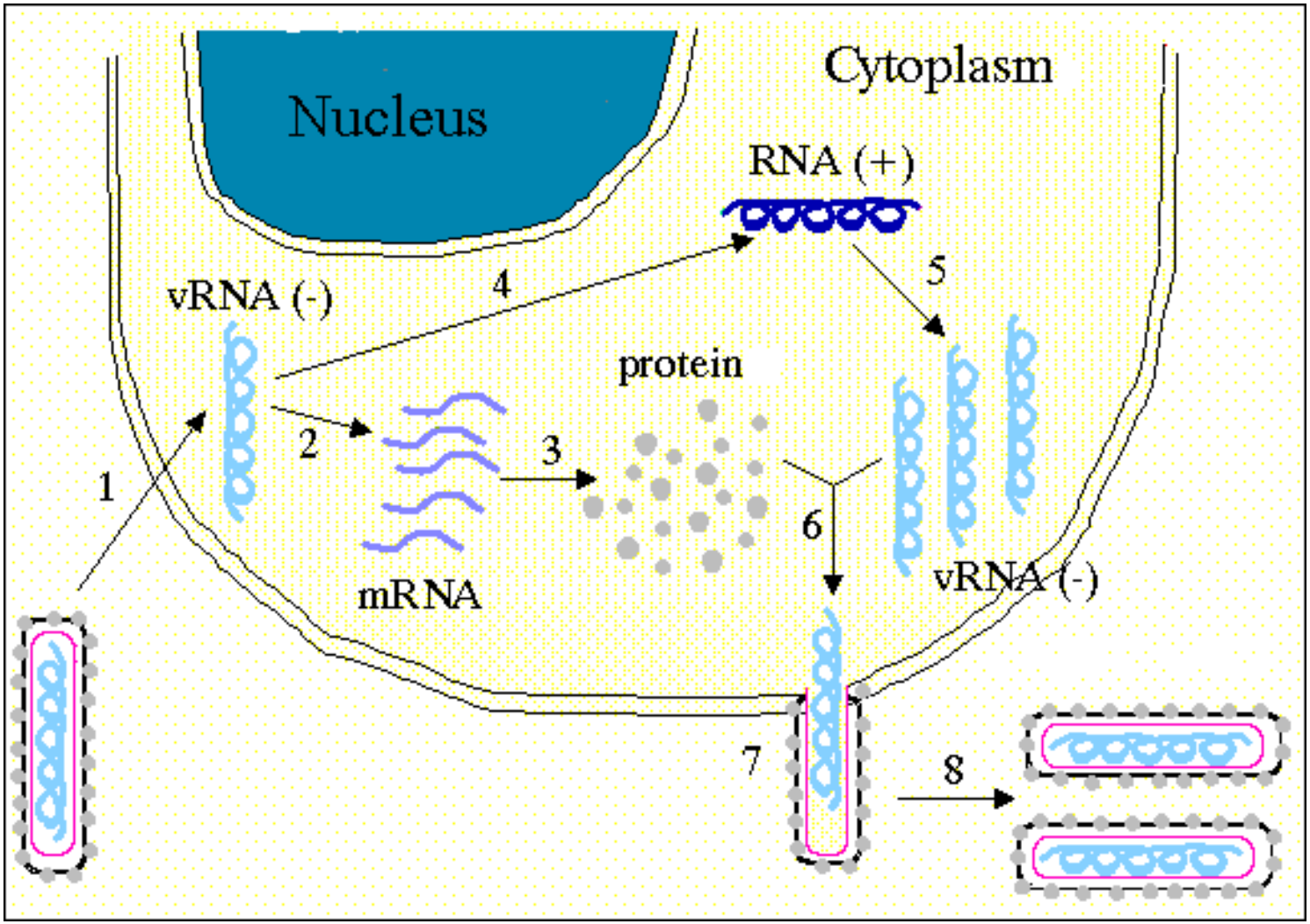
Ebolavirus species

- Each virion has one molecule of single-stranded, negative-sense **RNA**, 19 kb long, with 7 genes:
  - 4 virion structural proteins: VP30, VP35, NP (nucleoprotein), and L (polymerase protein)
  - 3 membrane-associated proteins: VP40, VP24, and GP (glycoprotein)
- Low potential to elicit effective neutralizing antibodies, perhaps due to GP




Lipidmembrane
Glycoprotein
Viral Capsid
RNA


GP
NP
VP35
VP40
GP/sGP
VP30
VP24
L(RNA polymerase)


Nucleus
Cytoplasm
RNA (+)
vRNA (-)
4
5
protein
2
3
1
6
mRNA
vRNA (-)
7
8

Ebola virus is easily killed…

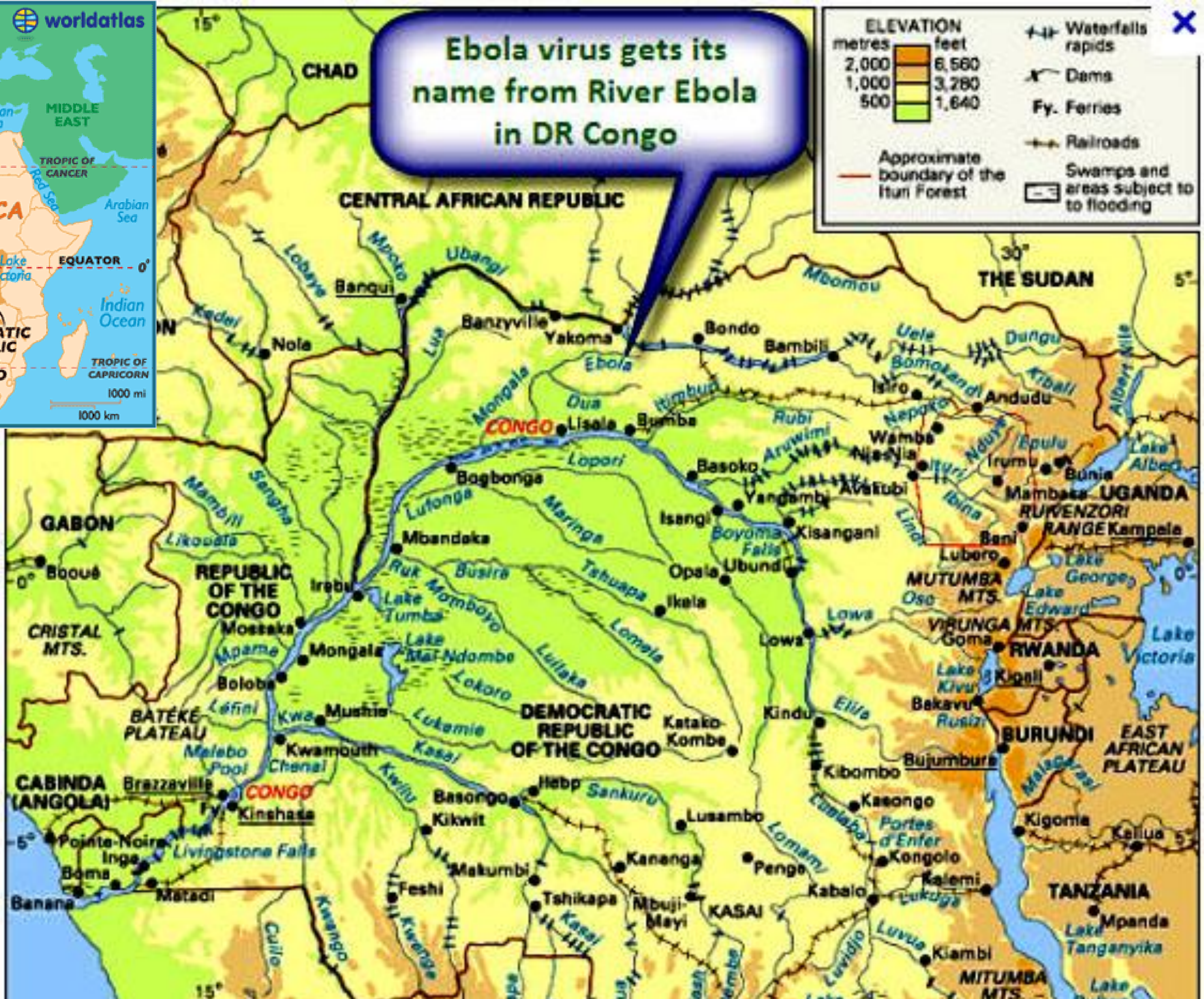
- Using of lipid solvents such as soap
- With commonly used disinfectants such as bleach
- Boiling for 5 minutes
- Heating at 60 °C for 60 minutes
- With acidity

Epidemiology

Brief history of the disease

- Ebola virus infection first appeared in 1976 in 2 simultaneous outbreaks:
  - In Nzara, Sudan
  - In Yambuku, Democratic Republic of Congo (Zaire)
- The latter presented in a village near **Ebola River**, from which the disease takes its name

Ebola virus gets its name from River Ebola in DR Congo

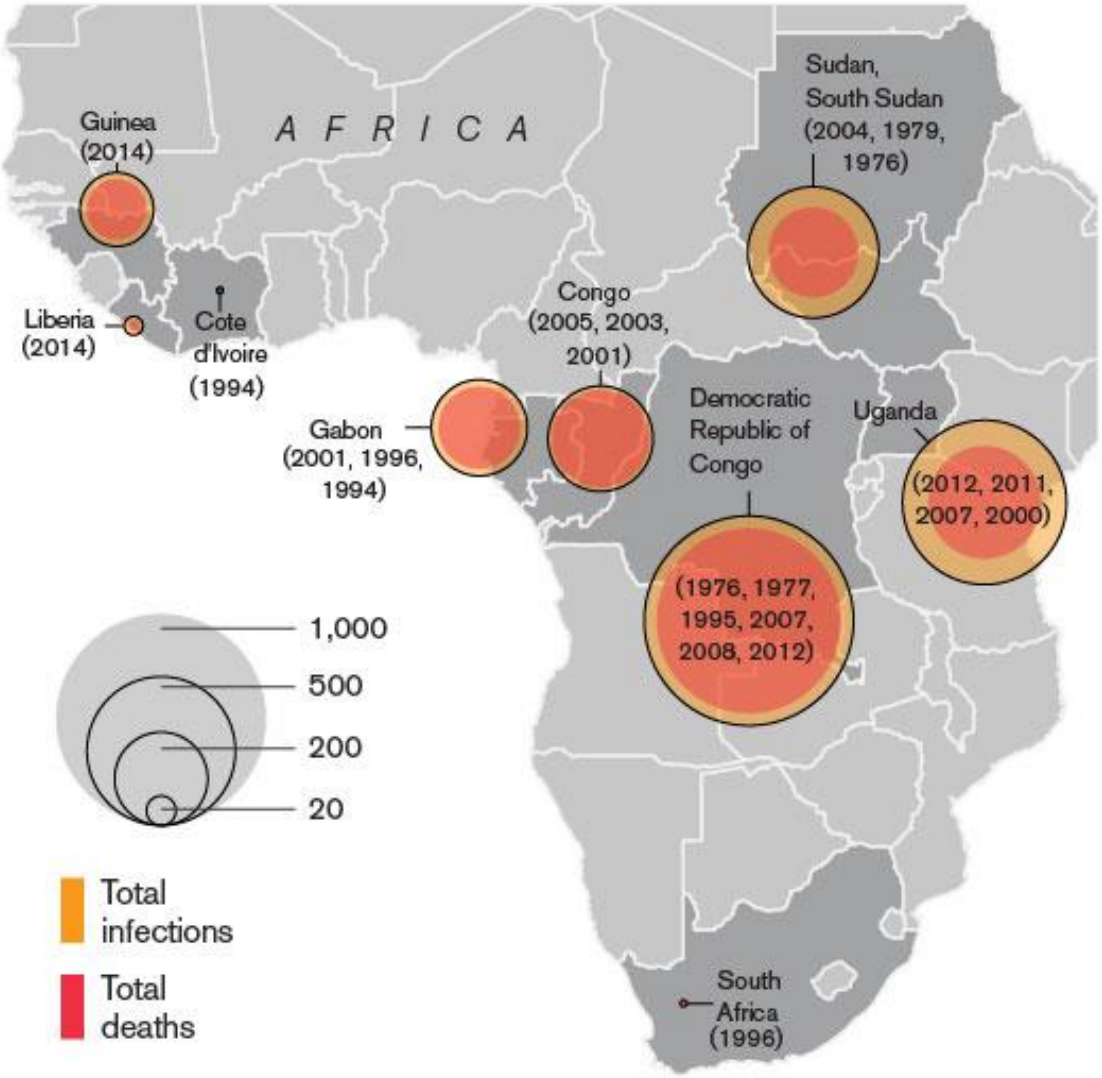


Previous outbreaks

- According to WHO, before 2014:
  - Some 25 outbreaks
  - 1005 cases
  - 739 deaths
  - Fatality rate of up to 90 %
- Most cases in Democratic Republic of Congo
- 6 other countries of central Africa affected

Major Ebola Outbreaks

Confirmed cases and years

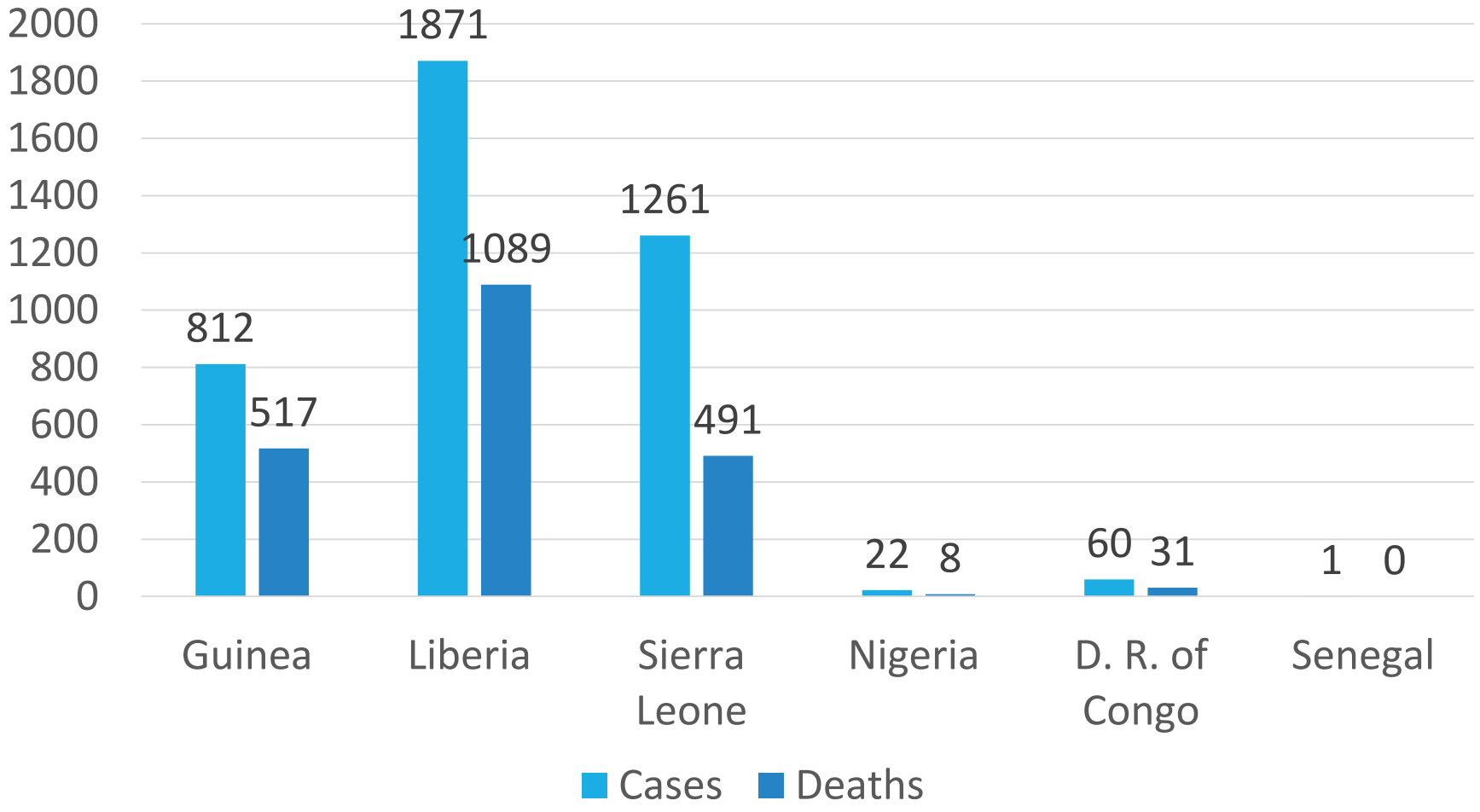


2014 Outbreak

- The largest outbreak so far
- New strain of **Zaire ebolavirus species**
- Both genders, any age, as in previous outbreaks
- Overall fatality rate about 55 %
- Initiates in Guinea, 6 countries affected
- Imported cases, health workers, in US, Spain, UK and Germany
- Almost all cases human to human

Total of confirmed, probable, and suspected cases

WHO, September 5, 2014




Tunisia
Morocco
Algeria
Western Sahara
Libya
Egypt
auritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Senegal
Gambia
Guinea Bissau
Guinea
Burkina Faso
Benin
Togo
Nigeria
Ethiopia
Somalia
Sierra Leone
Liberia
Ivory Coast
Ghana
Central African Republic
Cameroon
Equi Guinea
Gabon
Congo
Democratic Republic of Congo
Uganda
Kenya
Rwanda
Burundi
Tanzania
Angola
Malawi
Zambia
Zimbabwe
Mozambique
Namibia
Botswana
Madagascar
Swaziland
Lesotho
South Africa
0
1000 mi
0
1000 km


Gambia
Senegal
Guinea-Bissau
Guinea
Mali
Sierra Leone
Liberia
Ivory Coast
CDC
SAFER·HEALTHIER·PEOPLE
DJINGARAYE
SIGUIRI
TELIMELE
PITA
DABOLA
KOUROUSSA
BOFFA
FRIA
DUBREKA
Conakry
KOINADUGU
KISSIDOUGOU
KAMBIA
BOMBALI
PORT LOKO
Freetown
TONKOLILI
KONO
GUECKEDOU
MACENTA
MOYAMBA
LOFA
BO
KAILAHUN
NZEREKORE
KENEMA
YOMOU
BONTHE
PUJEHUN
GRAND CAPE MOUNT
MONTSERRADO
BONG
NIMBA
BOMI
MARGIBI
Monrovia
GRAND BASSA
RIVERCESS
Ebola treatment center
Field laboratory
National laboratory
National capital
No active virus transmission
Areas with confirmed and probable cases
Areas reporting suspect cases
0 25 50 100 Miles
0 37.5 75 150 Kilometers
Elizabeth Ervin, CDC/VSPB, Aug 14, 2014

Reservoirs and hosts

- **Reservoirs** or natural hosts (presumed): **fruit bats** of the Pteropodidae family, particularly species of the genera:
  - *Hypsignathus monstrosus*
  - *Epomops franqueti*
  - *Myonycteris torquata*
- Other possible reservoirs: plants, arthropods, and birds
- Accidental **hosts**: non-human primates and human beings, highly lethal for both

Fruit bats

They are not
affected by the virus

Transmission animal-to-human

- Human infection documented from:
  - Fruit bats
  - Chimpanzees, gorillas and monkeys
  - Forest antelope
  - Porcupines
- Virus introduced into humans through close contact with:
  - Body fluids: **blood**, urine, sweat, etc.
  - Organs and other tissues
- **Epidemics can generally be traced to a single initial human case**

Transmission human-to-human

- Direct contact of **broken skin** or **mucous membranes** with **blood, other body fluids or tissues** of infected patients
  - Burial ceremonies if mourners have direct contact with the body of the deceased person
  - Virus may persist in semen for up to 7 weeks after recovery
- Indirect contact with environments contaminated with such fluids, such as needles
- Airborne transmission has not been documented

Transmission – other features

- **Health-care workers** frequently infected, through close contact with patients, if control precautions are not strictly practiced
- **Family** and friends of patients also at high risk
- Only spreads to others **after symptoms** of the disease **appear**

Transmission – other features

- Escape of the virus through small breaks in the skin or sweat glands may occur, which explains the risk of contact transmission
- Types of transmission:
  - Primary: from reservoir
  - **Secondary**: from hosts, animals or **humans**

Pathogenesis

Entering the organism

- Ebola virus enters the patient through:
  - Mucous membranes
  - Breaks in the skin
  - Parenterally
- Initial infection site → regional lymph nodes → blood, liver, spleen, adrenal glands, etc.
- Infects **monocytes**, **macrophages**, **endothelial cells**, **hepatocytes**, **fibroblasts**, dendritic cells, adrenal cortical cells, epithelial cells, etc.

Host response to infection

- After infection, human and nonhuman primates experience an early period of rapid viral multiplication and high level viremia
- Lethal cases are characterized by
  - Mild and ineffective immunologic response
  - Minimal production of proinflammatory cytokines

Pathogenetic mechanisms - I

- Large quantity of virus glycoprotein (GP) produced:
  - Surface glycoprotein (sGP), 50-70 kd, → **inhibits neutrophils**
  - Transmembrane glycoprotein (tmGP), 120-150 kd → binds the virus to the endothelial cells → **vascular leak**
- Release of pro-inflammatory cytokines →
  - **Vascular leak**
  - **Coagulopathy**

Pathogenetic mechanisms - II

- Hepatocellular necrosis → dysregulation of clotting factors and **coagulopathy**
- Adrenocortical necrosis → impaired steroid synthesis → **hypotension**
- Other tissues necrosis
- Although not particularly infected, lymphocytes undergo **apoptosis** resulting in decreased lymphocyte counts

Pathologic findings

- Liver necrosis with Councilman bodies
- Intracellular inclusions that correlate with extensive collections of viral nucleocapsids
- Interstitial pneumonitis
- Cerebral glial nodules
- Small infarcts in tissues
- Inflammatory cells are not prominent

Clinical manifestations

Incubation period

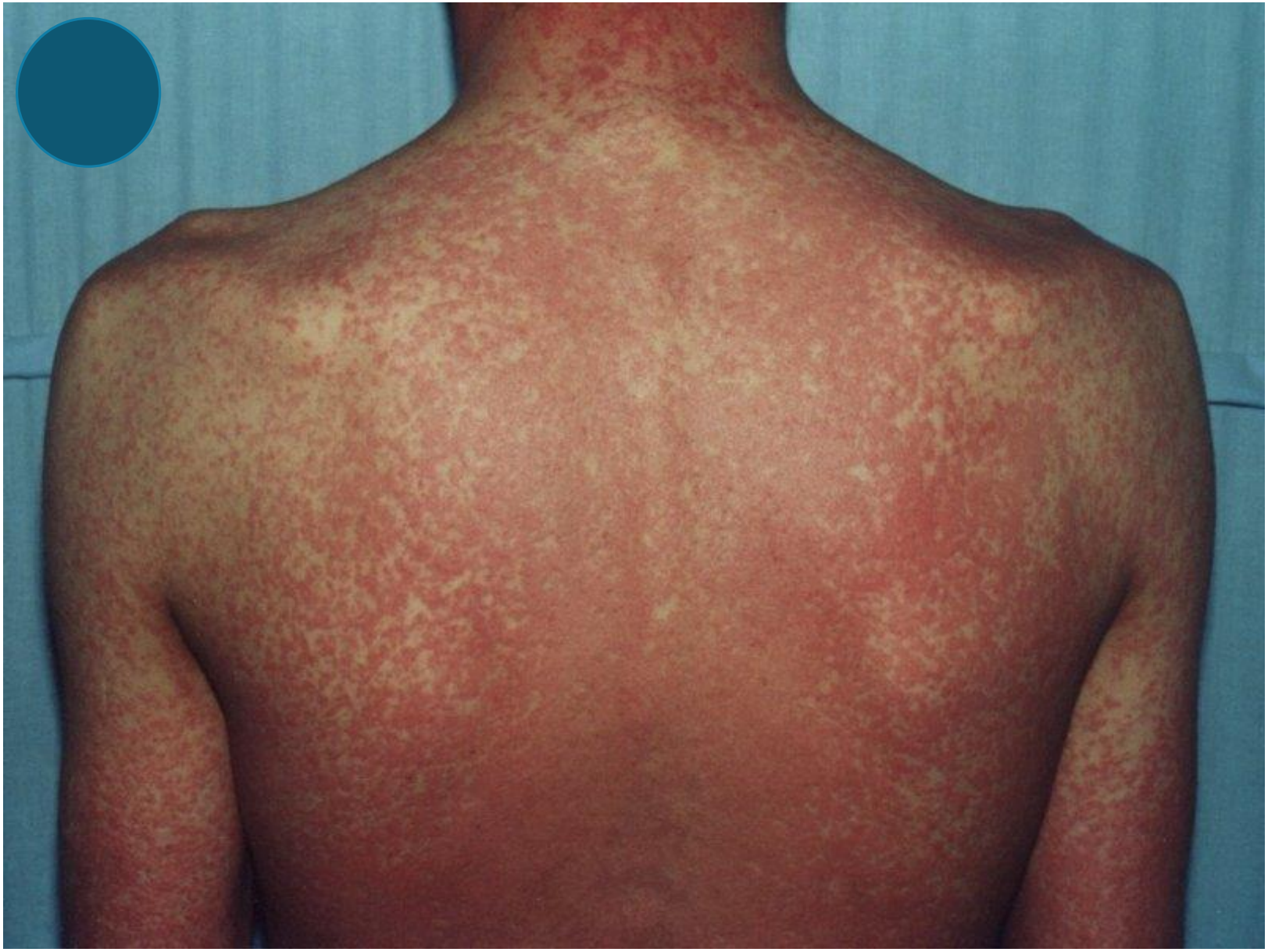
- May be 2 to 21 days
- Generally 8 to 10 days
- May be related to the infection route:
  - About 6 days for injection
  - About 10 days for contact

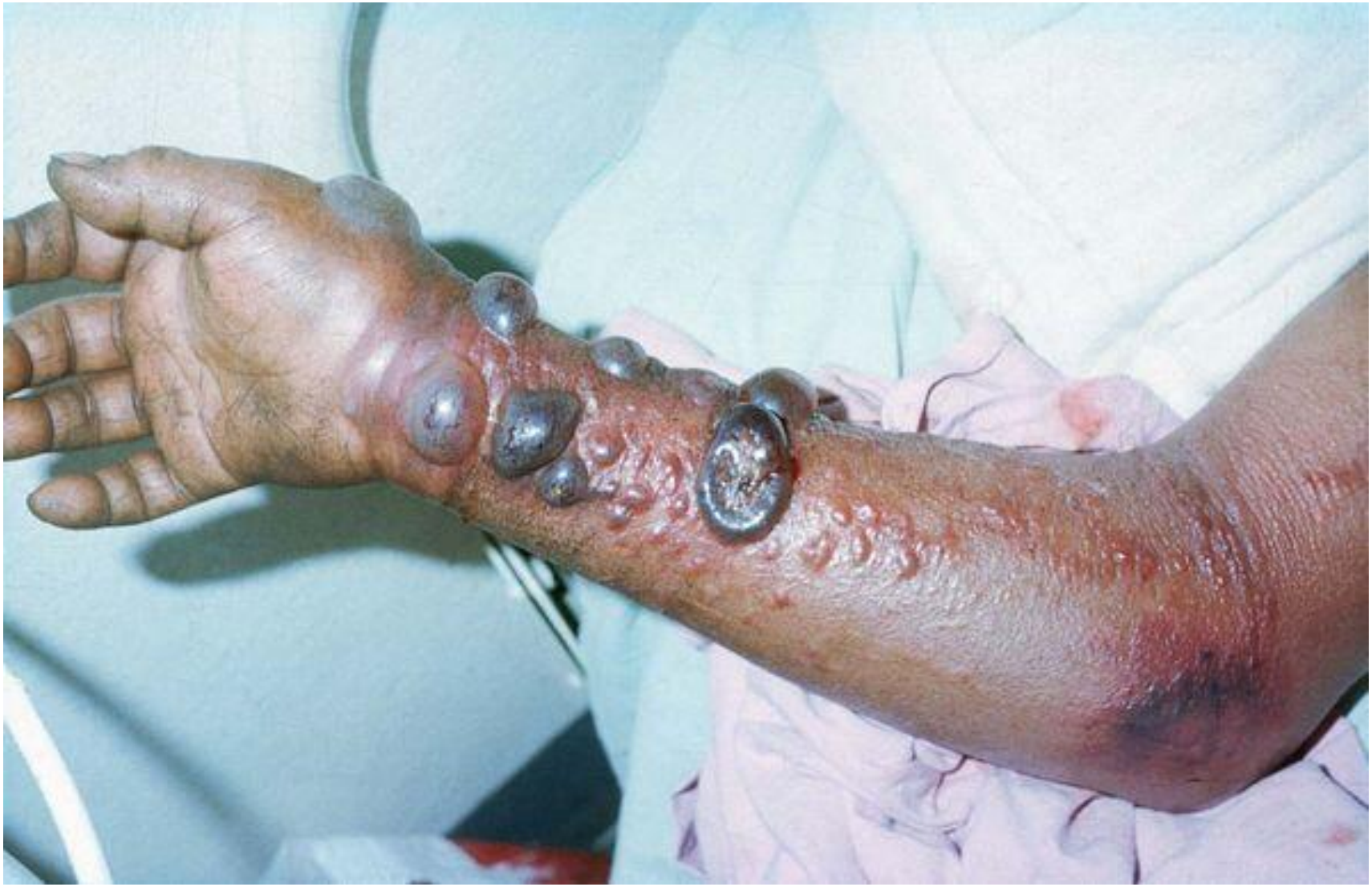
Symptoms

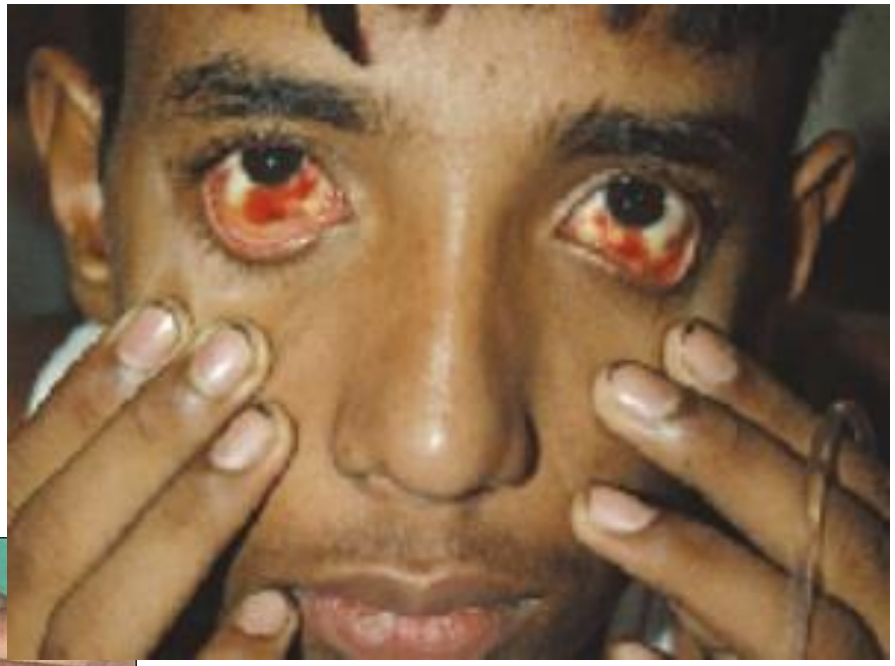
- Often with a **sudden** onset
- Fever (> 38.6 °C or 101.5 °F), chills, lack of appetite, intense weakness, muscle and joint pain, headache, and sore throat
- Followed the next days by abdominal pain, vomiting, diarrhea, chest pain, shortness of breath and confusion

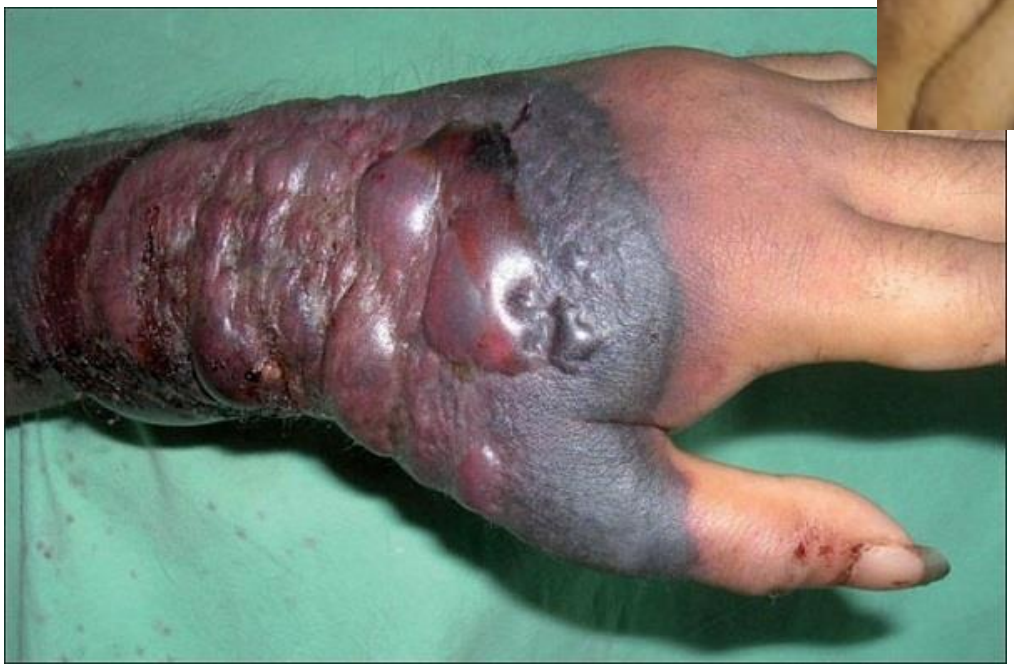
Signs

- Bilateral conjunctival injection, maculopapular rash in the face, neck, trunk, and arms, that can desquamate
- Followed the next days by expressionless facies, and in ½ of cases **bleeding**: petechiae, ecchymosis, oozing from venipuncture sites and mucosal hemorrhage
- Occasionally hiccups, seizures, miscarriages, etc.









Analysis abnormalities

- Neutropenia → neutrophilia with left shift
- Low lymphocyte and platelet counts
- Elevated bilirubin and liver enzymes, AST or GOT > ALT or GPT
- Increased blood urea nitrogen and creatinine
- Increased amylase
- Nonspecific urine analysis abnormalities
- Prolonged PT and aPTT and increased FDP: DIC

Course

- Patients with fatal disease usually develop severe clinical signs early during infection
- Death typically occurs between days 6 and 16 due to complications including septic shock and multi-organ failure
- In non-fatal cases fever and other symptoms persist for several days and then improve around day 6-11
- Survivors frequently have a prolonged convalescence: unilateral orchitis, hepatitis, joint and muscle pains, skin peeling, hair loss, iritis, choroiditis, etc.

Diagnosis

Diagnostic tests

- **Antigen detection with enzyme-linked immunosorbent assay (ELISA)**
- **RNA detection with real time polymerase chain reaction (RT-PCR) assay**
- Antibody detection with ELISA, indirect fluorescence, neutralization, etc.
- Cell culture, electron microscopy

- In **blood**, skin biopsy, other specimens

Differential diagnosis

- Malaria
- Typhoid fever
- Shigellosis, cholera, etc.
- Leptospirosis, relapsing fever, etc.
- Plague
- Rickettsiosis
- Meningitis
- Hepatitis
- Other viral hemorrhagic fevers

CDC case definitions

- **Suspected**: alive or dead person with:
  - Fever and at least three additional symptoms
  - Fever and a history of contact with a person with hemorrhagic fever or a dead or sick animal, or
  - Unexplained bleeding
- **Probable**: suspected + epidemiologic link to a confirmed or probable case
- **Confirmed**: suspected or probable + laboratory confirmation

Treatment

General measures and medications

- Supportive care is the only treatment available
- General measures such as rehydration, control of electrolytes, oxygen, nutrition, painkillers, etc.
- Treatment of concomitant illnesses if needed
- Investigational FDA-allowed drugs:
  - ZMapp, combination of 3 monoclonal antibodies that bind virus proteins
  - TKM-Ebola, RNA inhibitor

Prevention

General measures - I

- Fruit bats, monkeys, etc. should be handled with gloves and other appropriate protective clothing
- Animal products thoroughly cooked before consumption
- Physical contact with patients should be avoided, gloves and appropriate protective equipment should be worn when taking care of them
- Regular hand washing after visiting or taking care of patients

General measures - II

- Died persons should be promptly and safely buried
- Carcasses are infectious only during the first three to four days
- Adequate information should be given to affected communities
- Quarantine may be needed, as initial symptoms are non-specific

Health-care workers precautions - I

- It is important that health-care workers apply **standard precautions** consistently with all patients, in **all work practices**, at **all times**
  - Basic hand hygiene
  - Personal protective equipment, according to the risk of splashes or other contact with infected materials
  - Safe injection practices

Health-care workers precautions - II

- When in close contact (within 1 meter) of patients workers should wear **face protection**, a long-sleeved **gown**, **gloves**, cap, and legs and shoes covers
- Samples taken from suspected human and animal Ebola infection cases for diagnosis are **extreme biohazard risk** and should be:
  - Handled by trained staff under maximum biological containment conditions
  - Processed in suitably equipped laboratories

Vaccine

- No licensed vaccine is available by now
- Several vaccines are being tested, and presumably at least one of them will become available in the near future

Key messages

To remember…

- Ebola virus disease is a deadly acute infection that represents a real and **serious threat** for humanity at this time
- Health professionals should have detailed and updated information on the disease in order to:
  - Convey to their community a balanced information on the disease, to avoid unnecessary fears and misinterpretations
  - Be prepared to attend potentially affected patients
  - Be able to adopt the necessary measures to prevent the transmission of the disease

Further reading

Used references

- World Health Organization. Standard Ebola virus disease. Fact sheet N° 103. Updated April 2014 http://www.who.int/mediacentre/factsheets/fs103/en/
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Preparing the exam

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