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Yellow fever
Ebola

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Yellow fever

- mosquito-borne viral hemorrhagic fever with a high case-fatality rate
- acute, systemic infection with organ dysfunction and hemorrhage
- vector: *Aedes* sp. in Africa, *Haemagogus* sp. in South America
- etiological agent:
  - member of the family *Flaviviridae*, enveloped, positive-sense, single-stranded RNA virus that replicates in the cytoplasm of infected cells
  - single serotype, antigenically conserved = vaccine protects against all strains of the virus
  - 1927 - first isolation from human. First proven mosquito-borne viral infection
  - cause infection of human and primates (both serve as reservoir)
- life-long immunity develops after the infection

Epidemiology

- **WHO**
  - from 1980 –↑ numbers of cases worldwide
  - 200 000 reported cases/year (10 – 250x more in reality)
  - > 60 000 deaths/year
  - 90 % of all cases in Africa (↑ inhabitants in city agglomeration + ↑ % infected mosquitoes + ↓ vaccinaton prevalence rate)
- tropical regions of South America and sub-Saharan Africa where the disease is endemic
- endemic YF has never been reported in Asia (only imported infections)

 https://www.cdc.gov/yellowfever/maps/south_america.html

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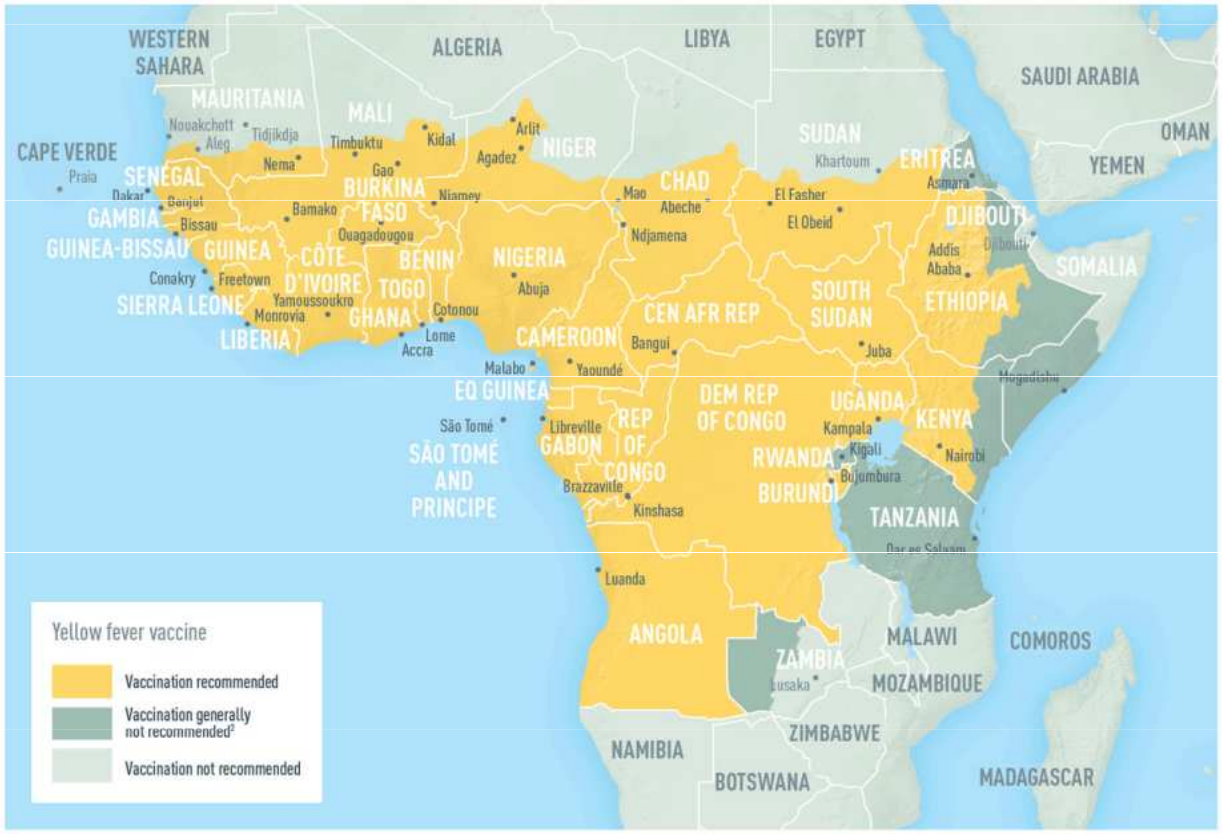


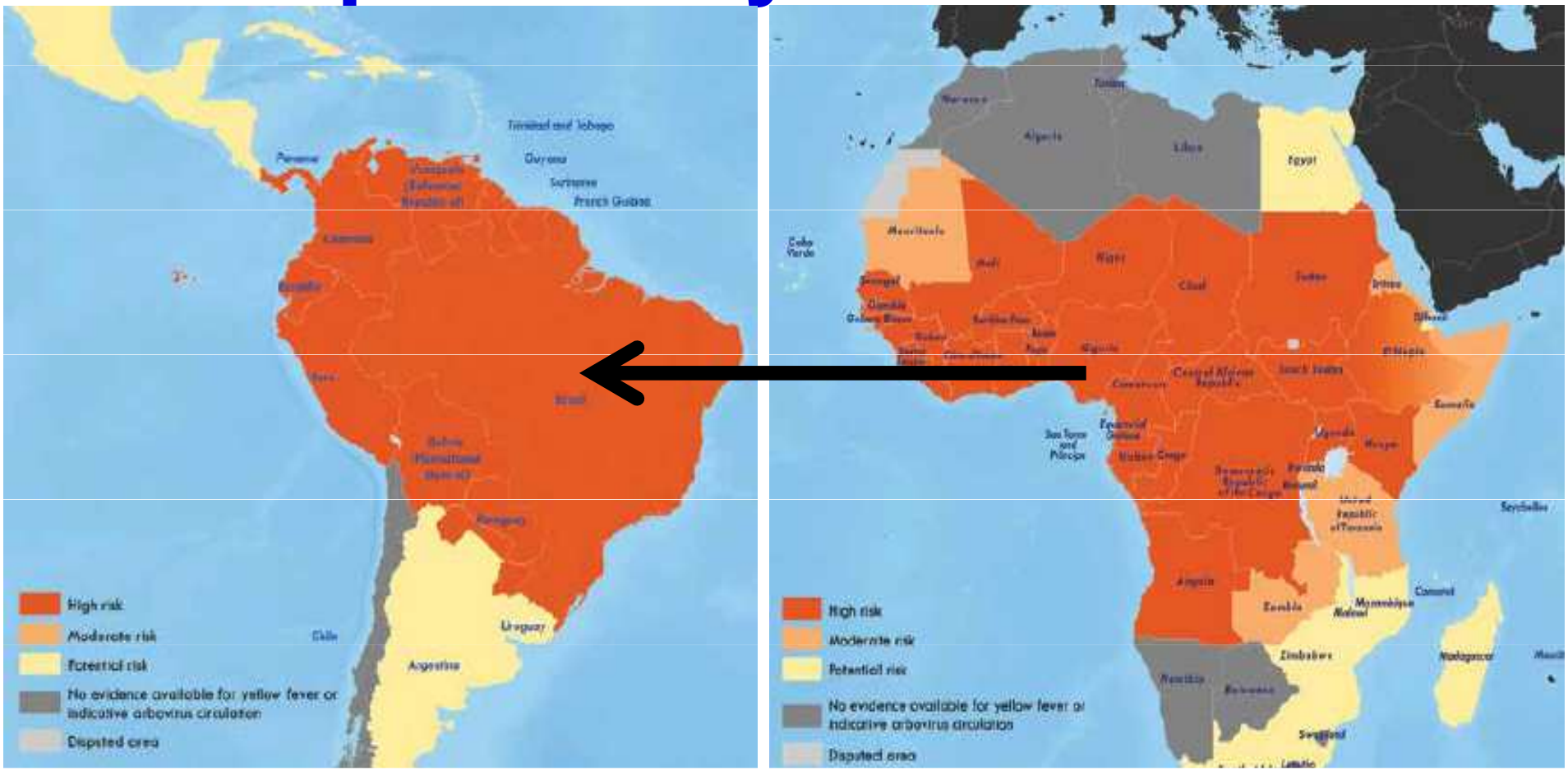
MAP 3-14. **Yellow fever vaccine recommendations in Africa**[1]

[1] Current as of September 2016. This map, which aligns with recommendations also published by the World Health Organization (WHO), is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

[2] Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).

https://www.cdc.gov/yellowfever/maps/africa.html

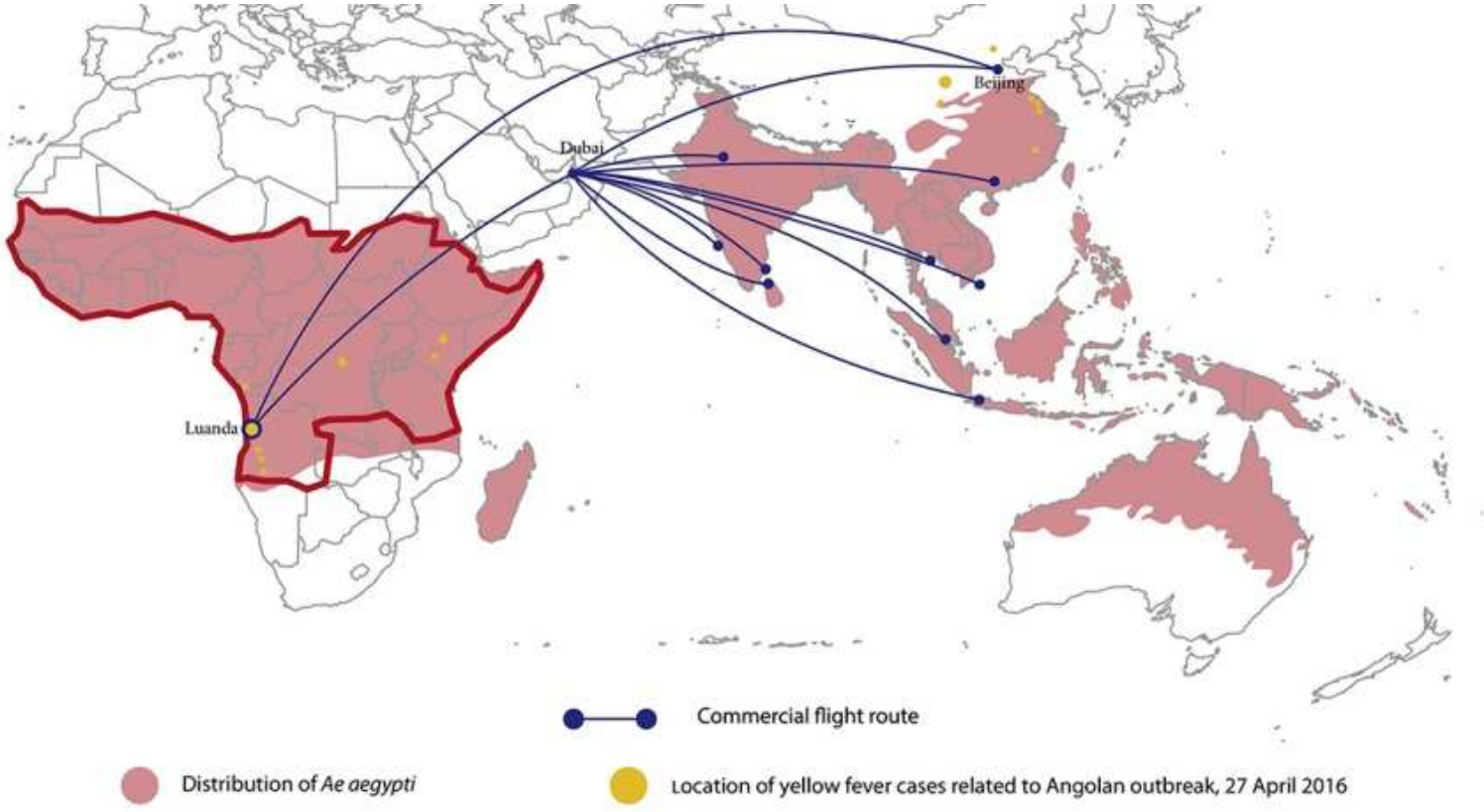
Spread of yellow fever



- **17c. - transatlantic slave trade** = most important way of spreading from Africa to western hemisphere
  - 1648 Yukatan – 1. epidemics at western hemisphere
- **17c. – 19c. – multiple epidemics at North America and Europe** (ports)
  - 1793 – Philadelphia – approx. 10 % of inhabitants died; 1880 – epid. related with Panama canal construction

A global strategy to Eliminate Yellow fever Epidemics (EYE) 2017-2026. WHO 2018. ISBN 978-92-4-151366-1. Bryant JE. Out of Africa. www.ncbi.nlm.nih.gov/pmc/articles/PMC1868956

Pandemic potential of YF



2016

- outbreak in Luanda, Angola → spreading to Kinshasa (DRC) and China (first cases in Asia) - 11 chinese workers returned from Angola
- real danger of rapid spreading in Asia (air transport, non-immunised travelers, presence of vector – *Aedes aegyptii*)
- there was no further spread in China - air temperatures were lower than necessary for vector activity

A global strategy to Eliminate Yellow fever Epidemics (EYE) 2017-2026. WHO 2018. ISBN 978-92-4-151366-1.

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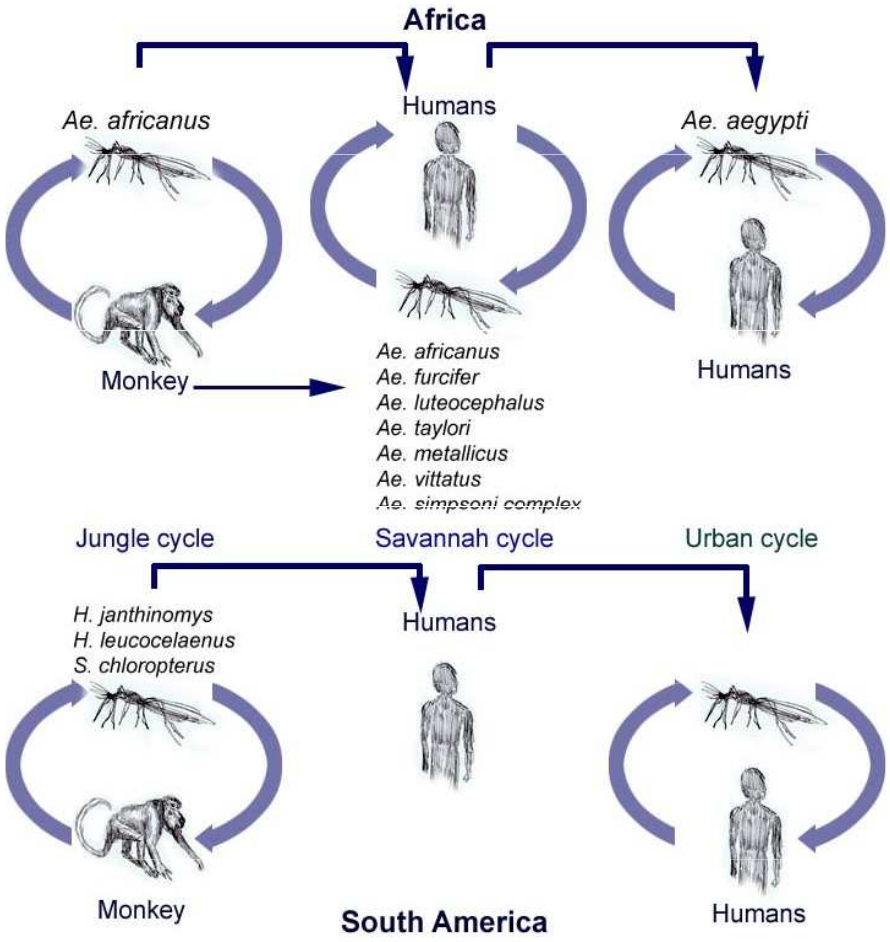
YF transmission cycles



1. **Sylvatic cycle** (ape-mosquito-human, "jungle yellow fever") – Africa, SA
2. **Intermediate cycle** („savanah cycle“)– Africa
3. **Urban cycle** (human-mosquito-human, "urban yellow fever„) – Africa, SA

http://www.goodtrips.org/?page_id=808

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Transmission

1. infected female mosquito bite - virus replication at the site of inoculation (dendritic cells in epidermis) →
2. regional lymph nodes →
3. other organs via the lymph and then the bloodstream (viremia) →
4. other tissues (large amount replication of virus in the liver, lymph nodes, and spleen)

- Incubation period: 3-6 days

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Clinical manifastation

1. Subclinical infection
2. Abortive, nonspecific febrile illness without jaundice
3. Life-threatening disease with fever, jaundice, renal failure, and hemorrhage

Stages of classical illness

1. Period of infection („red period“)

- 3-4 days lasting viremia
- malaise, headache, photophobia, pain in the lower extremities, myalgia, anorexia, nausea, vomiting, restlessness, irritability, and dizziness - nonspecific, impossible to distinguish yellow fever from other acute infections
- PE: patient appears acutely ill, flushed skin, conjunctivitis, epigastric tenderness, +- hepatomegaly, tongue - red at the tip and sides with a white coating in the center, Faget's sign (↓puls rate relative to ↑temperature (39-41ºC)
- Lab.: leukopenia (1500 to 2500 per ul) relative neutropenia; elevated serum transaminase

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2. Period of remission

- lasting up to 72 hours
- abatement of fever and symptoms
- patients with abortive infections recover at this stage

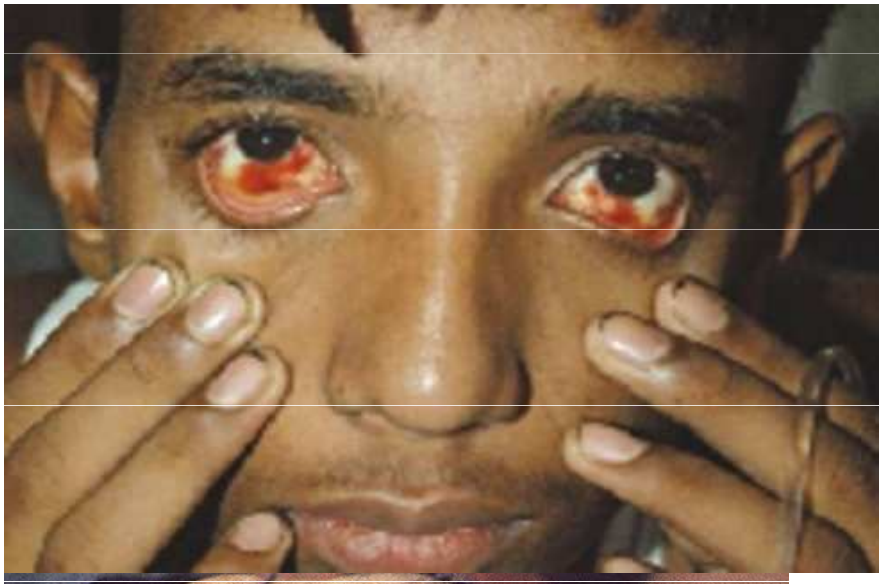
3. Period of intoxication (sever yellow fever, „yellow period“)

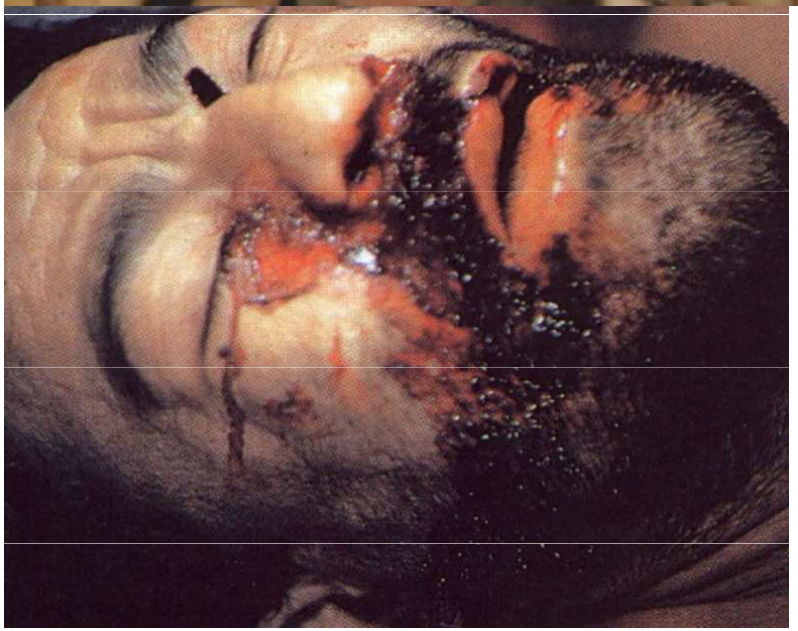
- approxx. 15 % of infected enter this stage (>50% travelers from nonendemic countries)
  - 20 – 50% mortality (non-treated), 5% (treated)
  - survivors – without consequences + life-long immunity
- return of fever, nausea, vomiting, epigastric pain, jaundice, oliguria and hemorrhagic diathesis (coffee-grounds hematemesis, melena, hematuria, metrorrhagia, petechiae, ecchymoses, epistaxis, oozing of blood from the gums, and bleeding from needle puncture sites)
- ↓viremia, ↑antibodies

3) Period of intoxication

- **Organ dysfuncion**:
  - **Liver -** apoptosis of hepatocytes in the midzone of the liver lobule, no disruption of the architecture of the liver, healing is complete without postnecrotic fibrosis (in nonfatal cases)
  - **Kidney -** direct viral injury and nonspecific changes due to hypotension and the hepatorenal syndrome
  - **The hemorrhagic diathesis** - decreased synthesis of vitamin K-dependent coagulation factors by the liver, disseminated intravascular coagulation, and platelet dysfunction
  - **Encefalopathy** - result of microvascular dysfunction
  - **Myocardial injury** - rare, arrythmias, myocardial insufficiency

  → MOF - high levels of proinflammatory cytokines (IL-1, IL-6, TNF-α - as in bacterial sepsis, SIRS)





Lab:

- ↓ Leuko, relat. lymfocytosis, ↓ PLT
- AST (↑↑) > ALT (due to concomitant viral injury to the myocardium and skeletal muscle)

  ALP normal

  ↑ bilirubin typically between 85-170 umol/L
- decreased synthesis of coagulation factors (f. II, V, VII, IX, X)
- ↑myoglobin +↑CK (myositis)

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Yellow fever - diagnostic

1. **sérology**: ELISA - IgM antibodies, ↑ lvl in acute faze, ↓ in covalescens
   - can be cross-reactions with other flaviviruses, particularly in Africa where multiple flaviviruses circulate
   - the neutralization test is more specific but requires a specialized laboratory
2. **PCR**: viral genom detection from blood or tissue samples
3. **Liver sample histology** – only post mortem. During illness high risk of fatal bleeding (see Liver in organ dysfuncion, slide 14)

- positive results must be confirmed by WHO or CDC certified laboratory

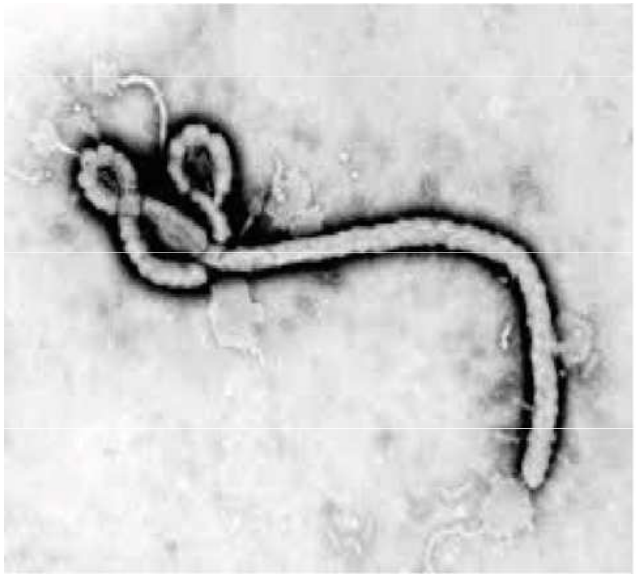
Yellow fever - treatment

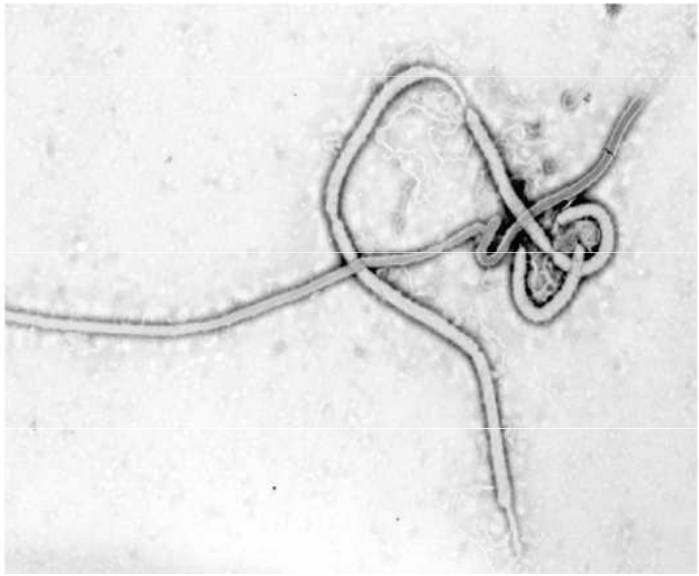
- no specific antiviral therapy available
- **supportive care** = modern intensive care (generally not available in remote areas)
  - maintenance of nutrition
  - prevention of hypoglycemia
  - nasogastric suction to prevent gastric distention and aspiration
  - hypotension - fluid replacement and vasoactive drugs (norepinephrine, terlipressine)
  - oxygen
  - management of metabolic acidosis
  - treatment of bleeding - fresh-frozen plasma
  - renal failure - dialysis if indicated
  - treatment of secondary infections

Yellow fever - prevention

1. Mosquito bite prevention (repelents (DEET), clothing, mosquito net etc.)
2. Vaccination:
   - the primary tool for prevention of YF
   - vaccine protects against all strains of the virus
   - live-attenuated vaccine (f.e. Stamaril®)
   - single dose provides lifelong protection for most people, booster is not recommended
   - Vaccine is recommended for people aged 9 months or older and who are traveling to or living in areas at risk for yellow fever virus in Africa and SA
     - CAVE !!! age < 9 months, > 60 years, pregnancy, immunocompromised patients – high risk of sever adver effects (as at all live vaccines)
   - Yellow fever vaccine may be required for entry into certain countries

Ebola





Center for Disease Control
Viral Pathology Branch
Atlanta, Georgia 30333
Negative No. 15917
Specimen Marburg '76
Preparation
Magnification 49200
Date 10/13, 19 76
Source: Fred Murphy

RNA, non-segmented, family *Filoviridae* (from latin „filum“ = thread like)
6 types:

- **Zaire ebola virus** – most common, the deadliest, mortality 55-88%, central and west Africa
- **Sudan ebola virus** – mortality as in Zaire, Sudan (1970, 2004), Uganda (2000)
- **Tai Forest ebola virus** (former Cote d´Ivoire ebola virus) – west Afrika
- **Bundibugyo ebola virus** – mortality 22-30%, Uganda (2007), DRC (2012)
- **Reston ebola virus** – in Phillipines (not in Africa), infects only nonhuman primates
- **Bombali ebola virus** – newly izolated from bats, infectiosity for humans not known

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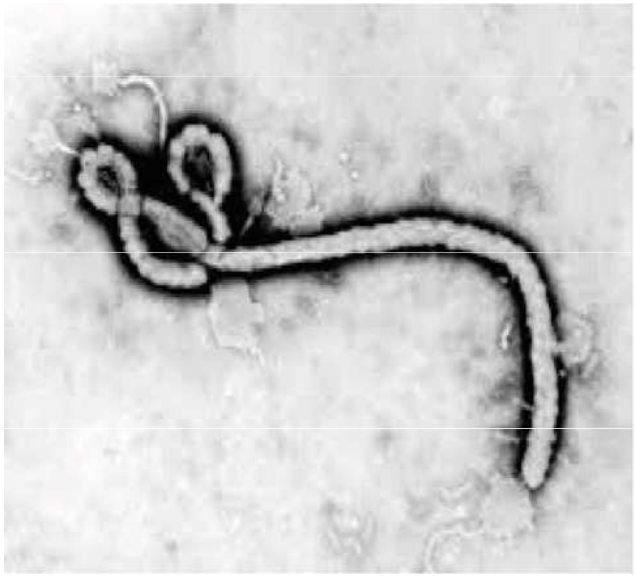
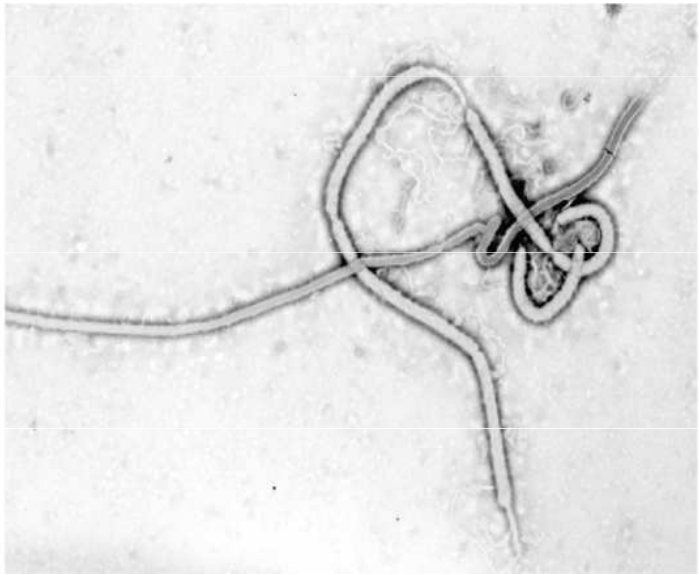
Ebola





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Ebolavirus – the most virulent patogen known

- natural reservoirs are not yet identified (probably some species of bats)
- stable for a long time at room temperature, in blood or water for
- sensitive to high temperatures, UV light, γ radiation

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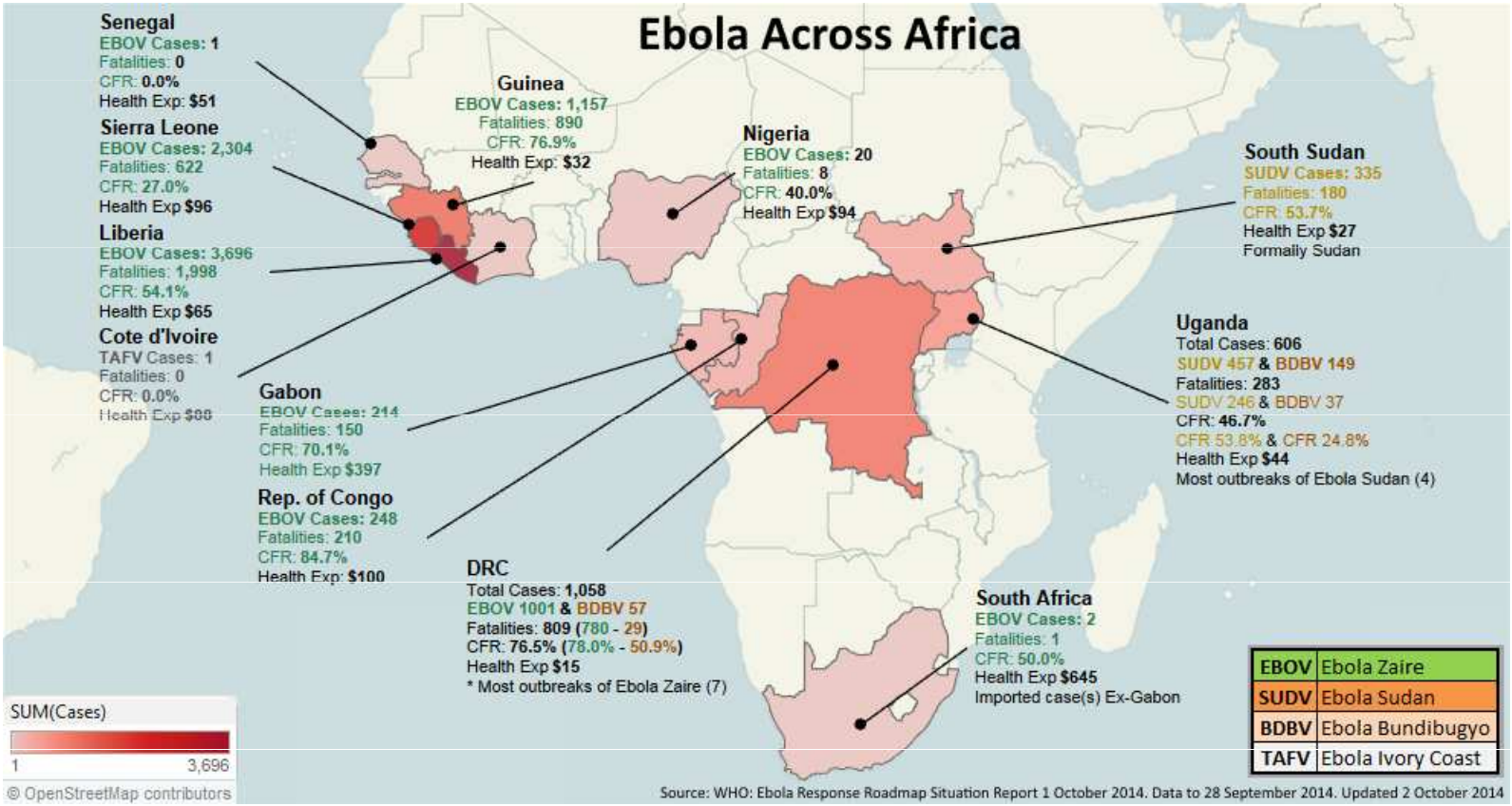

since 1976

- several outbreaks, in remote, isolated areas of small villages, low population density, near rain forrests
- Fewer than 100 cases, contained within a period of weeks to a few months

2013-2016

- the biggest epidemy in history - Guineia, Liberia, Siera Leone, Nigeria, Senegal, and Mali (Zaire ebola virus)
- Almost 29k confirmed cases, 11,000 deaths (40% mortality). 881 infected healthcare workers - 60 %percent died

Boštíková V. očkování proti virové hemoragické horečce Ebola experimentální vakcínou rVSVDG-ZEBOV-GP v Dekokratické republice Kongo. Vakcinologie 2019;3:106-109.
WHO-ebola virus disease-external situation report.

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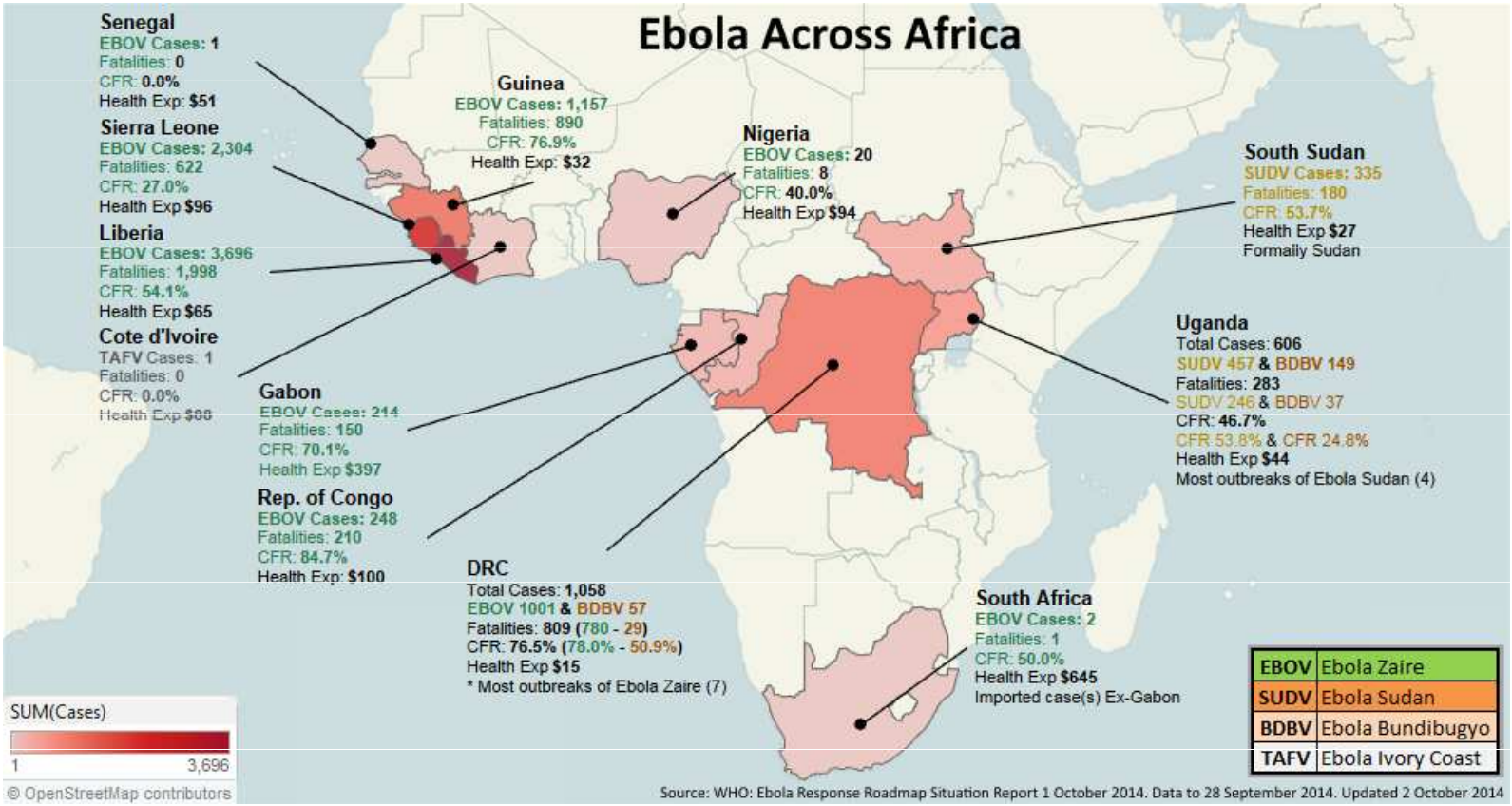

August 2018 – June 2020

10. epidemy of ebola in DRC, 2. biggest in history

- EBOV-Zaire
- 3470 confirmed cases with 2287 deaths, a fatality rate of 66 %
- 162 zdravotnických pracovníků

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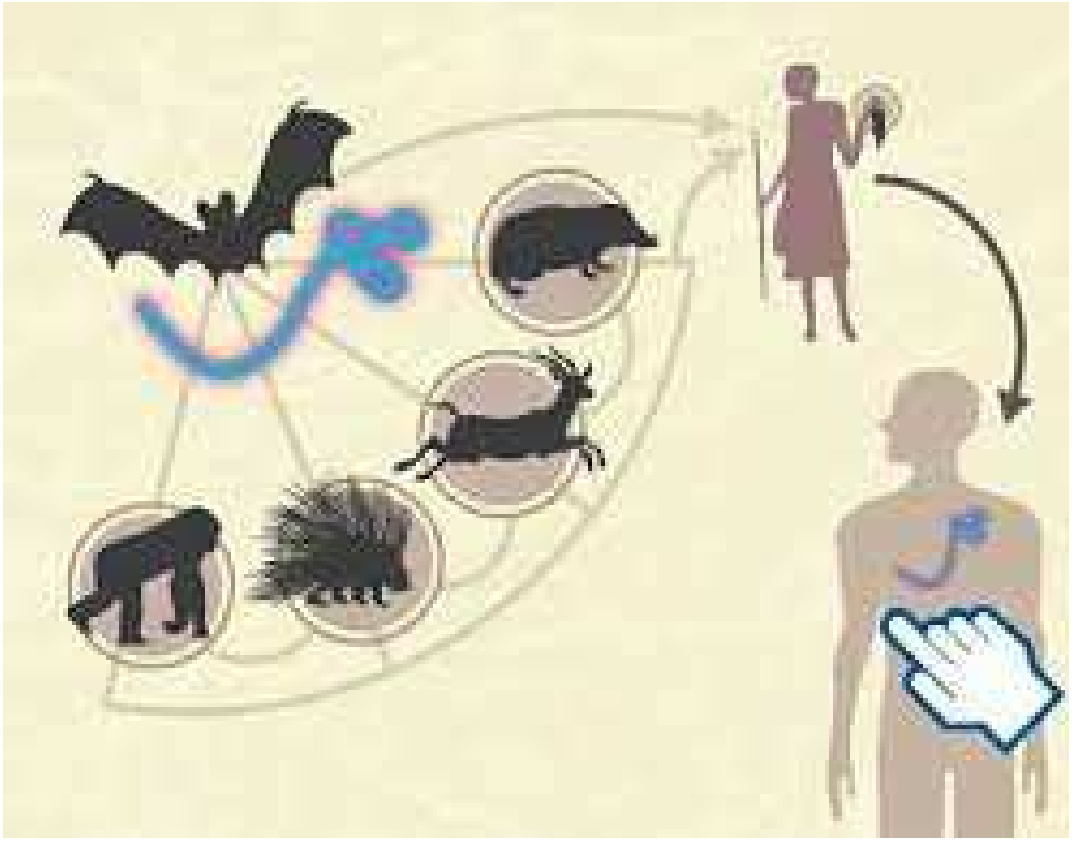
Patogenesis

- most data obtained from laboratory experiments (mice, guinea pigs, nonhuman primates)
- virus → musous membranes (mouth, eyes), broken skin → necrosis of macrophages and dendritic cells → release of large amount of new virions → virus-induced suppression of type I interferon responses → rapid spred to lymph nodes and bloodstream → infected almost all body cells
- lymfocytes and neurons are only cell types not infected
- failure of adaptive immunity (impaired dendritic cell function and lymphocyte apoptosis) → ability of filoviruses to cause a severe, frequently fatal illness

Transmission



Rezervoir and the mode of transmission

- greatest mystery
- data suggest bats and other wild animals

Transmission

Direct contact

- body fluids of infected human and animal
- high risk – blood, feces and vomitus
- also detected in urine, semen, saliva, aqueous humor, vaginal fluid, and breast milk

Indirect contact

surfaces and objects – beding, clothes, needles …

Others

- accidental infection of workers in any Biosafety-Level-4 (BSL-4) facility where filoviruses are being studied
- bioterrorism

- airbourne transmisson wasn´t proven

. Chlíbek R. et al. Horečka ebola a marburská horečka – epidemie virových hemoragických horeček. KMIL 2006;12(6):217-223.

Transmission – „Bushmeat“

- available source of livelihood
- source of infection - insufficiently heat-treated meat of an infected animal (raw, dried), organs, body fluids (bat soup, grilled bat, primate meat…)

- DRC – yearly hunted >6 mil tons of wildlife meat
  - approx 90 tons of meat is illegaly imoprted to USA every yeatr
  - ↑spreading infection risk

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Clinical manifestation

- **Incubation:** 6-12 days (range 2-21 days) – prolonged incubation = difficulty to find contacts, ↑ risk of spreading the infection

Symptoms:

- abrupt onset of fever and chills, fatigue, headache, loss of appetite
- **Rash** – diffuse erythematous, nonpruritic maculopapular rash by day 5 to 7 of illness, usually involves the face, neck, trunk, and arms, and can desquamate
- **Gastrointestinal** –common, first few days of illness, watery diarrhea (up to 10 liters per day) nausea, vomiting, and abdominal pain → severe fluid loss → dehydration → hypotension → hypovolemic shock → death
- **Hemorrhage** –blood in the stool, petechiae, ecchymoses, oozing from venipuncture sites, and/or mucosal bleeding
  - clinically significant hemorrhage in the terminal phase of illness and in pregnancy

Clinical manifestation

- **Neurologic** – meningoencephalitis, days 8 to 10 of illness.
- **Cardiac** – relative bradycardia, pericarditis, myocarditis
- **Respiratory** – tachypnea, shortness of breath, hypoxia, hypoventilation due to respiratory muscle fatigue
  - respiratory failure also as consequence of fluid resuscitation
- **Ocular** – conjuncitivitis, uveitis (also in convalescnece)
- death usually during 2. week of illness

- Lab.: leukopenia with lymphopenia, trombocytopenia, elevated ALT, AST, coagulation abnormalities (prolonged PT, aPTT, ↑fibrin degradation products), proteinuria, azotemia, electrolyte abnormalities (↓Na, ↓K, ↑K, ↓Mg, ↓Ca)

Clinical manifestation

Remember....

- major hemorrhage is less common than previously described (usualy at the end of the fatal course)
- volume losses from vomiting and diarrhea made a greater contribution to severe illness

Convalescence - can persist for more than two years

- weakness, fatigue, muscle and joint pain, insomnia, headache, urinary frequency, memory loss, and failure to regain weight that was lost during illness

Diagnosis

Determine the risk of exposure

Level of Risk	Type of Contact
Low	Casual contact with a feverish but ambulant and self-caring patient (e.g., sharing a seating area or public transportation; receptionist tasks).
High	Direct contact with any material soiled by bodily fluids from a probable or confirmed case.
	Percutaneous injury (e.g., with needle) or mucosal exposure to bodily fluids, tissues, or laboratory specimens of a probable or confirmed case.
	Participation in funeral rites with direct exposure to human remains in or from an affected area without appropriate personal protective equipment.
	Direct contact with bushmeat or bats, rodents, primates, living or dead in or from affected areas.

https://www.researchgate.net/profile/Suresh_Rewar/publication/275965188/figure/tbl2/AS:669689235644425@1536677764331/Diagnostic-Tests.png

Diagnosis

Symptomatic patients with identifiable risk

- infection control precautions should be used, health care workers - personal protective equipment recommended for the care of patients with Ebola virus disease (or highest available)
- patients should be isolated in a single room with a private bathroom, closed door
- inform the hospital infection control program, hospital leadership, local and state health departments
- phlebotomy and laboratory testing limited to tests that are essential for diagnosing or ruling out Ebola virus

- Ebola virus belongs to category bio-safety level 4 (BLS-4) („VNN - vysoce nebezpečné nákazy“ in czech)
- only 2 hospitals in Czech republic are capable to take care of BLS-4 – Bulovka univerzity hospital Prague, Těchonin military hospital

Protective Ebola suit

Image: AFP BBC

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Diagnosis

Asymptomatic individuals with identifiable risk

- monitoring for symptoms and signs of Ebola virus disease
- should be monitored for 21 days after the last known exposure
- immediately report the development of fever or other clinical manifestations suggestive of Ebola virus disease
- self-monitoring and reporting versus direct observation by a designated health official
- need for travel restrictions, restricted movement within the community, and/or quarantine

Diagnosis - testing

- **„OraQuick Ebola rapid Antigen Test“**
  - rapid diagnostic test–10/2019 FDA approval
  - rapid patient isolation and treatment – epidemiologically significant
- **serology -** ELISA – antigen and antibodies
- **PCR -** blood, tissues
- **virus isolation -** VERO cells
- **electron microscopy**
- **skin biopsy** → PCR

Diagnosis - testing

Time Line of Infection	Diagnostic Tests Available
Within a few days after symptoms begin	• Antigen-capture ELISA testing • IgM ELISA • PCR • Virus isolation
Later in disease course or after recovery	• IgM and IgG antibodies
Retrospectively in deceased patients	• Immunohistochemistry testing • PCR • Virus solation

ELISA, enzyme-linked immunosorbent assay; IG, immunoglobulin, PCR, polymerase chain reaction.

Treatment

Specific antivarals are not available

- 4 experimental drugs in trials
  - 3x monoclonal antibody
  - 1x nucleotide analgue - remdesivir

Supportive care

- fluid and electrolytes replacement, transfusions
- complex intensive care – oxygen, artificial ventilation, hemodialysis

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Prevention

- protective personal equipement (see above)
- strict isolation
- desinfeciton of surfaces, body fluids

- reproduction rate (RR) = 2-4

Vaccinaton

Ring vaccination strategy - contacts and their contacts = approx. 120-150 people in 1 ring

Prevention

2018 rVSV-ZEBOV-GP
2019 approved by FDA, EMA as ERVEBO®

- live attenuated vesicular stomatitis virus (VSV) carries ebola Zaire surface glykoprotein
- 2 doses
- antibodies at least for 1 year
- even in pregnancy (100% mortality of ebola in pregnant women)
- efficiency 95,8-98,5 %

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Thank you for your attention !

COVID-19 pandemic, 1.wave

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