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## REVIEW ARTICLE

# SELECTED VIRAL HEMORRHAGIC FEVERS

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**Summary**

Group of viral hemorrhagic fevers (VHF) present a range of disorders from relatively moderately serious to human life threatening entities whose mortality reaches high levels. There are classified as acute viral febrile diseases characterized by nausea, myalgia and fatigue, dominating with general alteration of vessel permeability and regulation. Symptoms of bleeding often occur, particularly in severe cases which are usually diffuse and present a symptom of general vessel injury rather than life-threatening condition.

*Key words: viral hemorrhagic fevers; Lassa virus; Junin virus; Machupo virus; Omsk hemorrhagic fever; Kyasanur forest fever; yellow fever, dengue; Ebola; Marburg; Rift Valley fever virus; hantaviruses*

## INTRODUCTION

Viral hemorrhagic fevers constitute a group of infectious diseases not commonly occurring in middle Europe. Detected cases are usually imported infections (Table 1).

What is the risk estimation for a patient (?) – situation in which a person didn´t visit endemic area of VHF occurrence or one was present there but more than 21 days passed since first health problems occurred, is considered as minimal risk. Moderate risk is characterized by individual's endemic area presence but not risk parts namely 21 days before diseases onset. High risk is determined by the presence in risk area 3 weeks before disease onset and by residence lasting more than 4 hours in household with VHF providing health care. For example, laboratory staff member with moderate risk originally but with at least one organ failure or though not being in risk area providing patient or animal care and being in contact with body fluids.

These clinical entities are typical with fever course associated with bleeding and high mortality rate (3, 4). Causative agents of this wide infectious diseases group are RNA viruses encapsulate by lipid membrane. They originated in four different families: *Arenaviridae, Flaviviridae, Filoviridae* and *Bunyaviridae*. It contributes to a big diversity of this diseases group and to difficulties to find out and specify their common signs (5, 6).

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**Table 1.** The list of VHF cases including imported infections world-wide during the time period 2000 - 2010 (1).

| Year/period | Type of viral hemorrhagic fever | Magnitude | Regions involved | Deaths reported |
|---|---|---|---|---|
| 2010 | RVF | 172 humans cases | South Africa | 15 deaths |
| 2010 | CCHF | 100 | Pakistan | 11 |
| 2008-02 | CCHF | 2508 | Turkey | 133 |
| 2008<br>2008 and 2007 | Marburg<br>hemorrhagic fever | 1, 1, 1 | USA, The Netherland, Uganda | Nil, 1, 1 |
| 2008 | Hemorrhagic fever due to novel old World arenavirus | 5 | Zambia and South Africa | 4 |
| 2007 | Ebola hemorrhagic fever | 149 | Uganda | 37 |
| 2007 | Ebola hemorrhagic fever | 249 | Congo | 183 |
| 2006-07 | RVF | 10 | Kenya, Tanzania and Somalia | 10 |
| 2006 | Dengue | 3407 | India | 47 |
| 2006 | Chickungunya outbreaks | 1.39 million suspected cases | India | nil |
| 2005 | Marburg hemorrhagic fever | 12 | Angola | 9 |
| 2004 | Ebola hemorrhagic fever | 20 | Sudan | 5 |
| 2003 | Ebola hemorrhagic fever | 143 | Congo | 128 |
| 2002 | Ebola hemorrhagic fever | 423 | Gabon, Congo | 169 |
| 2000-2001 | Ebola hemorrhagic fever | 425 | Uganda | 224 |
| 2000-2001 | RVF | 516 | Saudi Arabia, Yemen | 87 |

RVF: Rift valley fever; CCHF: Crimean congo Hemorrhagic Fever

***Arenaviridae* tribe includes e.g. African Lassa and Lujo virus and South American viruses Junin, Machupo, Guanarito and Sabia inducing Bolivian, Argentine, Venezuela and Brazil hemorrhagic fever (Figure 1).**

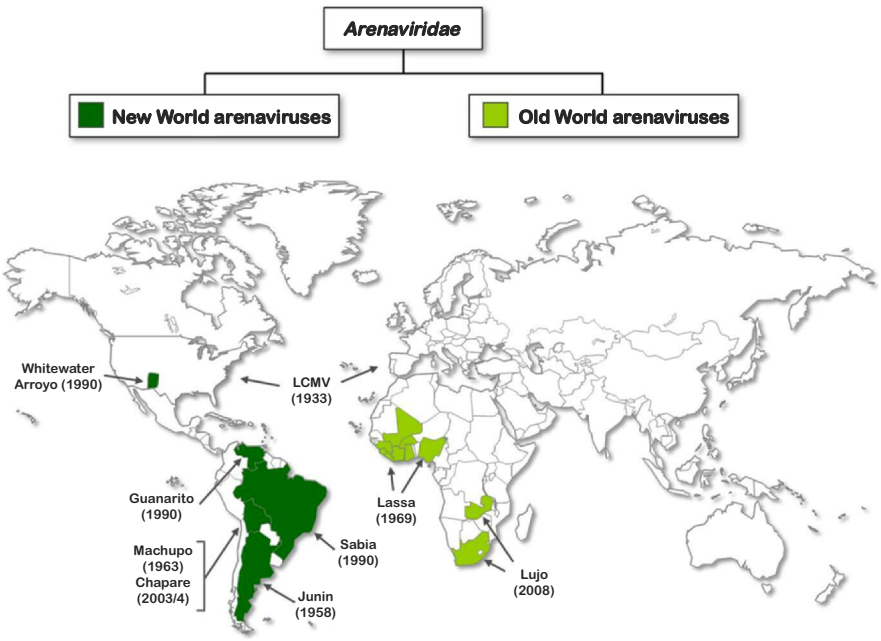


**Figure 1.** Geographic distribution of human pathogenic arenaviruses. This map summarizes the distribution of human pathogenic New and Old World arenavirus species. The year of the first description is indicated in brackets (2).

**The Lassa virus** is a RNA virus formed by 2 linear RNA segments, of 7 200 a 3 400 nt in length, encapsulate by lipid membrane. It was called after Lassa city in Nigeria – site of first occurrence in 1969. Course of diseases could be asymptomatic, mild or could result in patient's death due to multiple organ failure in organism. Typical incubation period ranges between 5 – 21 days. Patients suffer from high fever, headache and myalgia, cough and laryngitis, vomitus and diarrhea. Conjunctivitis could also develop as petechial rash at chest, hand and face areas. In 20% of patients low blood pressure levels, nasal bleeding, gingival and rectal bleeding are present. Encephalitis and meningitis could also develop. In pregnant women infected during 3rd trimester spontaneous abort occurs. Fetus mortality is 100%; mothers die in about 30% of cases. The diseases can be confirmed by the use of RT PCR, serologically by ELISA test, by virus isolation respectively. Patient's status can be relieved by fluid refiling support, anti shock management and mainly by introducing ribavirin therapy. Ribavirin treatment reduces mortality from 55% to 5% only. Vector of the diseases is rodent – rat living in west and middle Africa close to human residence. Unfortunately rat is regarded as delicacy for natives and it is often consummated. Further education is thus very important. Infection could also be transmitted by contact with infected animal excrements, urine, by aerosol with saliva's inhalation, by minor skin defects. The Lassa virus occurrence was also suspected in Congo, Mali and in Senegal. Estimated 5000 individuals die annually of Lassa virus infection worldwide (7, 8).

**The Junin virus** was first isolated in 1958. It induces Argentinian hemorrhagic fever. Frequently it is classified as New World virus due to its geographical occurrence. Clinically typical low fever, chill, headache, myalgia and skin petechial of face, neck and chest areas, conjunctivitis, gingival bleeding, hand tremor and general stupor occur. In 30% of patients we find neurologic involvement, shock, blood expectoration, blood in urine and stool, infinite menstruation period are present. Secondary bacterial infections could develop as complication. The principal diagnostically test is serology with the use of ELISA. Rodents are both vectors and reservoirs of infection. Transmission to humans occurs by inhalation of contaminated dust, by urine, excrements, saliva's, by blood or due to minor trauma of skin surface serving as port of entry for viral aerosol. For the treatment we use immune serum obtained from convalescent. Safe and efficient live attenuated vaccine exists to treat Argentinian hemorrhagic fever. This vaccine was administrated to roughly 150 000 humans and based on animal tests in monkeys we know that it has protective effect in Bolivian hemorrhagic fever too (5, 6).

**The Machupo virus (Bolivian hemorrhagic fever)** is classified as New World virus too. It is an agent belonging to two linear segments RNA viruses group and encapsulated by lipid membrane. Following 7-14 days of incubation period rapid fever increase, headache, myalgia, arthralgia, malaise, skin aesthesia, neurologic and hemorrhagic problems develop in infected individuals. Skin petechiae, face edema, epistaxis, gingival and vaginal bleeding, shock, hand tremor seizures occur and coma develops. Rodents are reservoir of infection. Transmission of infection by inhalation of aerosol containing contaminated urine, blood, saliva, excrements and transmission by close contact with minor skin trauma in humans was proved. In 1994 six fatal cases including human to human transmission within one family in Magdalena city in Bolivia were described (5,6).

***Flaviridae* family is represented by Omsk hemorrhagic fever (middle Asia), Kyasanur forest fever virus (India), virus of yellow fever (Africa, South America) and Dengue (Africa, Asia, North and South America, Pacific region) (9).**

**Omsk hemorrhagic fever (OHF)** is caused by linear RNA virus 10 400 nt size length. Usually two viral strains are described – Kubrin and Bogulovovska strains. To work experimentally with this virus, it is essential to handle it at highest Biosafety level regimen (Biosafety Level 4). This virus is not associated with neurological involvement. Incubation period ranges between 2 and 10 days. Clinical presentation includes two phase fever, headache, cough, dehydration, conjunctivitis, papulovesicular lesions on soft palate and typical splenomegaly. Mortality rate reaches 3%. Serologic ELISA test and virus isolation confirm a diagnosis. Tick of Dermacentor genus is a vector of the disease. Musk-rat and water-rat, amphibians and reptiles in endemic areas (middle Siberia, Omsk and Novosibirsk region) are reservoir. Virus was even successfully isolated from water where affected animals were living. It evokes presumption that it is a very stable virus. Human's infections following ingestion of milk from infected goats and sheep after contact with dead animal bodies have been proved. Musk-rat hunters where infections acquired from dead animals (but frequently tick infection was confirmed too) are at risk. Seven

infections were detected in 1998 in Novosibirsk region, one resulted in death. Regular use of repellents is recommended because of tick presence. Treatment is based on supportive and symptomatic care, mainly by fluid replenishment. According to reference sources, vaccine against tick encephalitis induces immunity development against OHF too (5, 6).

**Kyasanur forest fever.** Causative viral agent was successfully isolated from infected monkey at Kyanasur forest in India (endemic area) in 1957. However, this virus was recently isolated in Saudi Arabia. Small rodents, bats and monkeys are infection reservoir. Tick transmits virus to goat, sheep and cattle. We still have not evidence on transmission by unpasteurized milk to humans. After 3 to 8 days of incubation period fever, headache, myalgia, cough, dehydration, nausea and bleeding typically develop in a patient (5, 6).

**Yellow fever.** This diseases is caused by linear RNA virus of 10 862 nt length. Seven genotypes are known. It occurs in Africa (original area) and in Middle and South America (Figure 2).

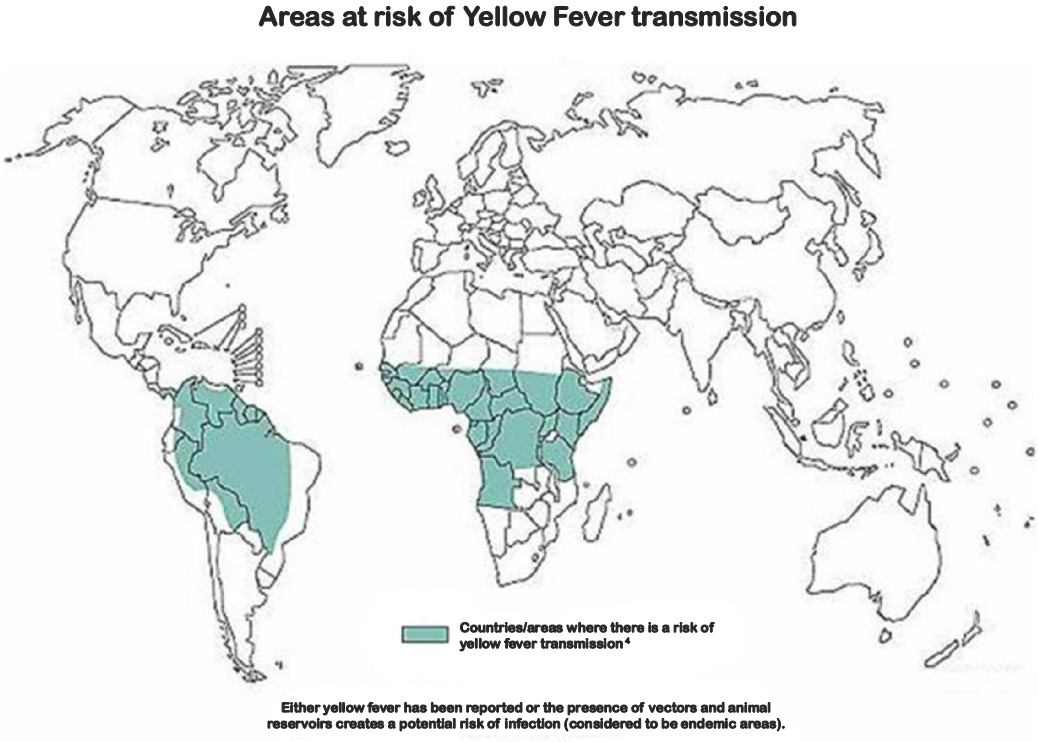


**Figure 2.** Areas at risk of yellow fever transmission (1).

Spanish conquerors imported virus to America. First reports were described by Spanish catholic missionaries, living among Mayo population in the first half of 17$^{th}$ century, in their diaries. Phylogenetically this virus is 3 000 years old. Virus was first isolated from infected man in Ghana in 1972 (Asabi strain prototype). Incubation period ranges between 3 – 6 days. Clinically infection presents with fever, chill, myalgia, headache, vomitus, patients complain of lower abdomen pain. We note jaundice in patients and multi organ failure (liver, kidney, progress in shock consequently) could develop. RT PCR and ELISA tests are carried out to confirm diagnosis. Two cycles of virus transmission are described: sylvatic (rural) and urbanic (Figure 3).

Great yellow fever epidemic passed in 1960 in Ethiopia affecting 30 000 individuals. In 1978 Gambia reported 8 400 patients with 1 600 cases resulting in death. Nigeria was involved with yellow fever epidemic in 1987, 565 cases from reported 1 450 patients were lethal. Other local epidemics in Bolivia, Brasilia, Colombia, Peru, Cameroon, Mali, and Senegal and in Togo were reported in 2007 year. Highly reliable vaccine is available for this disease – attenuated 17D strain effective against

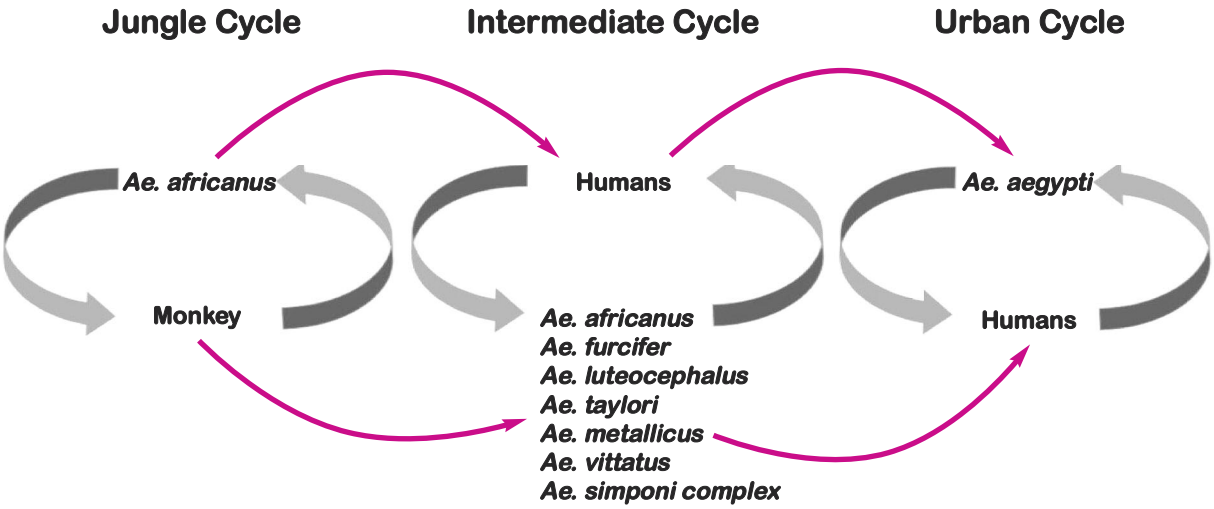


**Figure 3.** Sylvatic and urbanic cycles of yellow fever virus transmission (1).

all known genotypes of this virus. It can´t be administrated in risk groups, i.e. in children, in individuals with immunodeficiency and egg allergy patients (5, 6).

**Dengue.** Dengue epidemic in Philippines and in Thailand in 50´s of the last century raised attention to RNA linear virus of 10 200 length occurring in 4 serologic types. Successful cure of infection caused by 1 serotype does not mean lifelong immunity against all 4 serologic types. Dengue is a recurrent disorder. Infection is caused by different viral serologic types. Moreover, character of infection course predetermined by sequence of inducing viral serologic type. Both older children as adults are

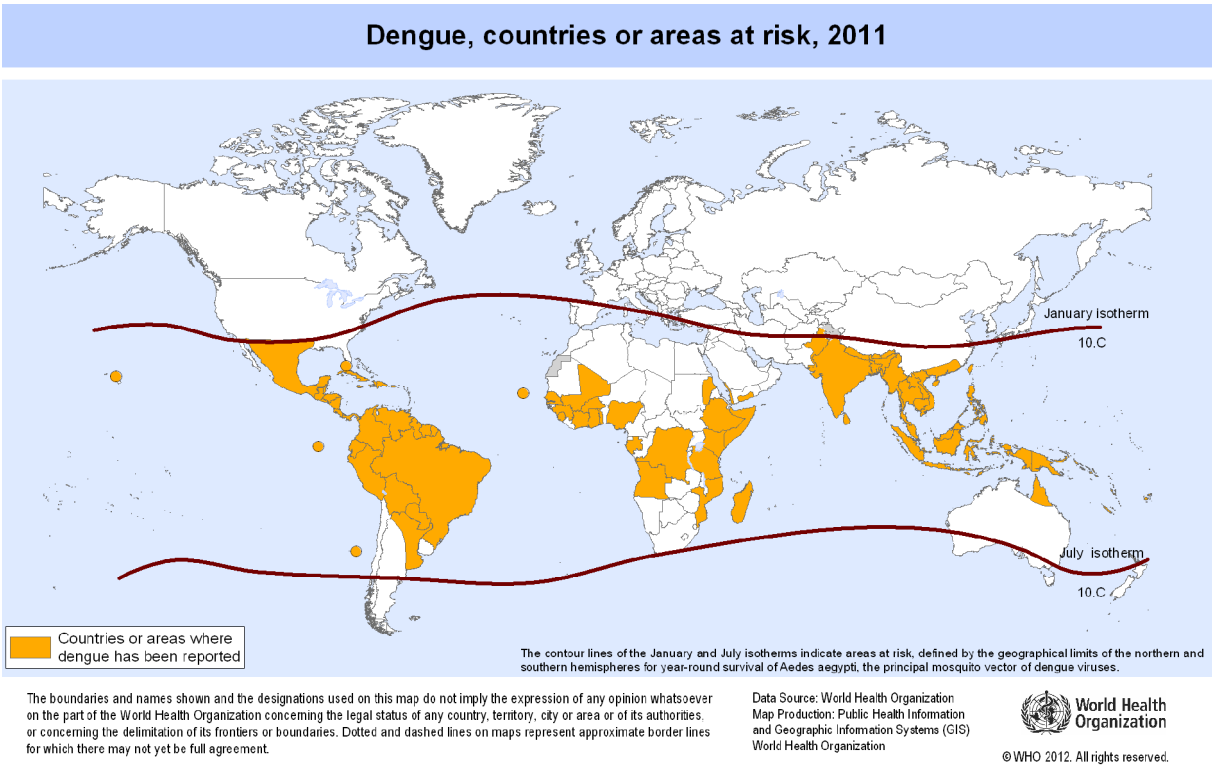


**Figure 4.** The world-wide distribution of dengue virus (2013), (23).

involved. Clinically infection presents by mild or classical fever but even with life-threatening hemorrhagic fever. Human is infected by mosquito, after 4-7 days fever of 38°C to 41°C develops, headache, myalgia, arthralgia, vomitus and photophobia. Than a temperature decrease is present for about 24 hours with consequent skin erythema, maculopapular rash, development of petechial and possible fever recurrence. Diagnosis is confirmed by PCR and serologic ELISA test. Dengue is also typical with two cycles, both as a sylvatic form (associated with monkeys and mosquito species) and urban form (humans and mosquito species). Transovarial type of transmission was described as transmission by sexual intercourse and by blood – transfusion. Humans and primates are the main viral reservoir. Dengue occurs in tropical and subtropical area, in all regions where mosquito species are present.

It seems that shipping in the 18$^{th}$ and in 19$^{th}$ century contributed to worldwide virus spreading in all these regions similar to business activities in Southeast Asia after WWII. Treatment is still largely based on supportive measures as administration of antipyretics, plasma, blood-transfusion and implementation of anti-shock actions. Prevention is important – regular use of insecticides, mosquito net, slop desiccation, still waters and fenland (essential for mosquito survival) elimination. It is indicated that up to 40% of world population (Figure 4) live in areas at risk of dengue infection (5, 6, and 9).

***Filoviridae* family includes Ebola and Marburg viruses, again typical for Africa and west parts of Pacific region (9, 11) (Figure 5).**

Pathogenesis of many VHFs remains unknown. Current model of **Ebola virus (EV)** pathogenesis demon-strates Ebola virus disseminates from infection site (minor trauma) to regional lymph nodes, to liver and spleen (Figure 6).

Though EV does not contaminate lymphocytes, rapid lymphocyte decrease due to apoptosis is a main symptom of the disease. As it is not possible to exclude direct interaction of lymphocytes with viral

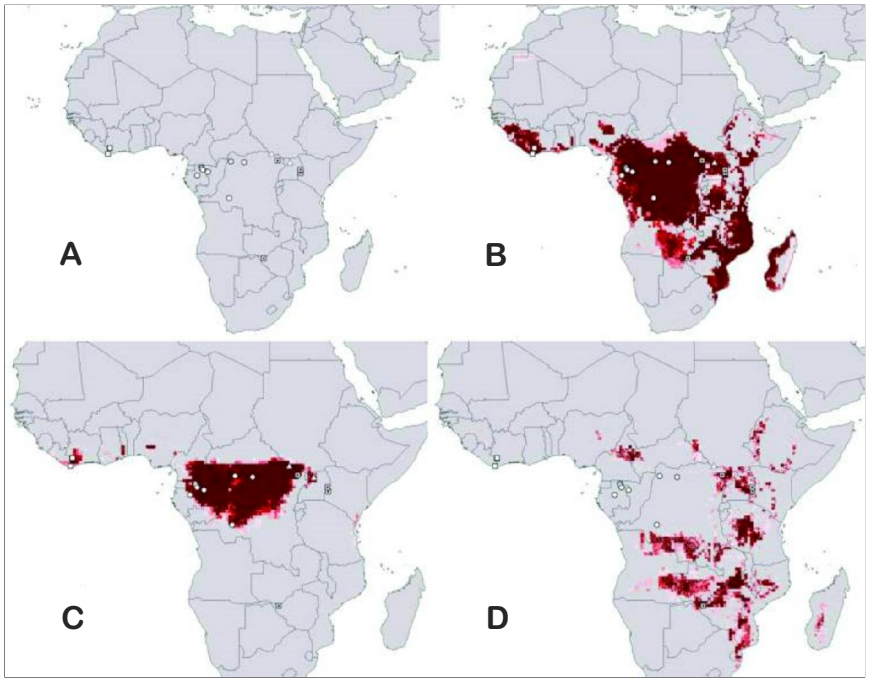


**Figure 5.** Summary of known and predicted geography of filoviruses in Africa. (A) Known occurrence points of filovirus hemorrhagic fevers (HFs) identified by virus species. (B) Geographic projection of ecologic niche model based on all known filovirus disease occurrences in Africa. (C) Geographic projection of ecologic niche model based on all known Ebola HF occurrences (i.e., eliminating Marburg HF occurrences). (D) Geographic projection of ecologic niche model based on all known occurrences of Marburg HF (i.e., eliminating Ebola HF occurrences). Darker shades of red represent increasing confidence in prediction of potential presence. Open squares, Ebola Ivory Coast; circles, Ebola Zaire; triangles, Ebola Sudan; dotted squares, Marburg HF occurrences (24).

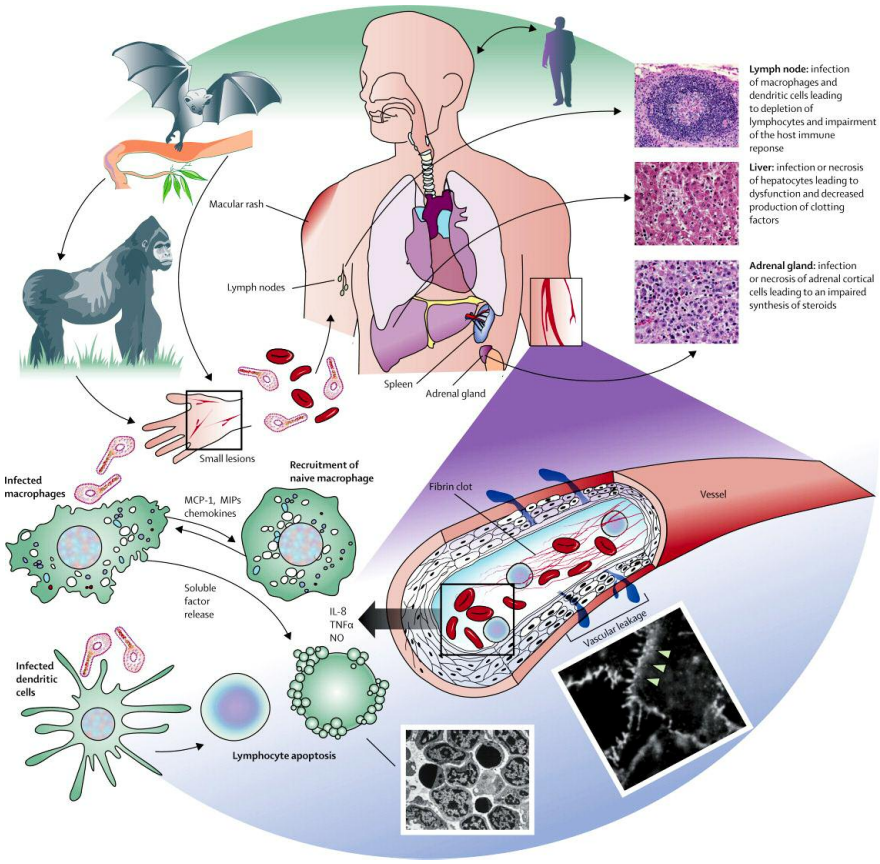


**Figure 6.** Model of pathogenesis for Ebola virus (1).

proteins as one of main reasons of their destruction, its rapid decrease is probably based on combination of dendritic cells dysfunction and release of soluble monocyte and macrophage derived mediators (6).

Incubation period ranges between 3-21 days, consequently fever, headache, myalgia, abdominal pain, vomitus and watery or bloody diarrhea, skin rash, hemorrhage, dehydration, shock and multi organ failure are clinically presented. If patient survives, convalescence takes a long course. Transmission due to close contact with blood, secrets or tissue of infected individuals or gorillas and chimpanzee as well as needle injury were reported. Reservoir of EB was not identified for a long time. First in association with EV epidemic in Congo in 2009, fruit bats (Figure 7) were recognized as reservoir for Ebola (Marburg too).

Bats (*Microchiroptera*) and fruit bats (*Megachiroptera*) belong mammalian genus (*Mammalia*), of the order Chiroptera (*Chiroptera*, from the *Greek* χείρ - *cheir*, "hand" and πτερόν - *pteron*, "wing"). They are the only mammalian capable of flying what resulted in cosmopolitan distribution with center of diversity in tropical regions where there is a higher concentration compared to temperate zone (25).

The majority of food consumed by bats includes insects, fruits and flower nectar, vertebrates and blood. Compared to representative of the same order, subfamily vampire bats (*Desmodontinae*) are characterized by hematophagy – entirely feeding on warm-blooded animals. These mammalians in Latin and in South America are in that geographical altitude regarded as significant reservoir of rabies (26, 27).

This and their other characteristics like feed sort, their population structure in multi-thousand colonies, flying ability, seasonal migration to far distance, daily movement figure, torpor and hibernation, lifetime significantly promote zoonotic host role for broad spectrum of antimicrobial agents able to experience so called spill over, i.e. to cross interspecific borders

**Figure 7.** Fruit bats (41).

and contaminate domestic and wild animals as well as human individuals (27, 28).

There is a limited knowledge on immune system in bats. It is speculated that bats command specific viral inhibitors preventing disease acquire and serving as suitable natural reservoir. Transmission is accomplished by bite, scratching, by saliva, by aerosol containing blood and urine particles but bat dung or *guano* can also be dangerous. Guano could contaminate soil by spores. In equatorial Africa, human consumption of bush meat including bats has been linked to animal-to-human transmission of EV (26 - 29).

Epidemics occur unpredictably time to time, mainly in countries as Congo, Sudan, Gabon, Republic of South Africa, Ivory Coast, Uganda, Philippines and recently in west Africa (Figure 8). There are five identified Ebola virus species, four of which are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). The fifth, Reston virus (*Reston ebolavirus*), has caused disease in nonhuman primates, but not in humans. Any of known antiviral agents including ribavirin is efficient in this infection. Fears of EV are so huge that three Japanese airlines refused to transport monkey deliveries (30, 31).

From molecular genetic analyses we know that the sequence of the Ebola virus strain circulating in massive outbreak in west Africa (2013 – 2015) is similar by its sequences to the Zaire strain (ZEBOV). The ZEBOV strain was responsible for the first epidemic in Zaire (today Democratic Republic of the Congo) in 1976, when (431 of 602 patients died). Mutations in the sequence of the Ebola virus strain circulating in west Africa) sequence obviously resulted in decreased numbers of hemorrhagic cases, thus decreasing mortality rate compared to Zaire strain (mortality rate up to 90%) (31, 32).

Figure 9 shows colorized transmission electron micrograph (TEM) revealed some of the ultrastructural morphology displayed by an EV virion created by CDC microbiologist dr. C. Goldsmith (1).

**Marburg.** Marburg is RNA virus again, of the same length as Ebola (19 000 nt). Virus was denominated according to German city of Marburg where infection due to African green monkeys from Uganda occurred. Lab worker taking care about monkeys and manipulating with monkey tissue samples was infected.

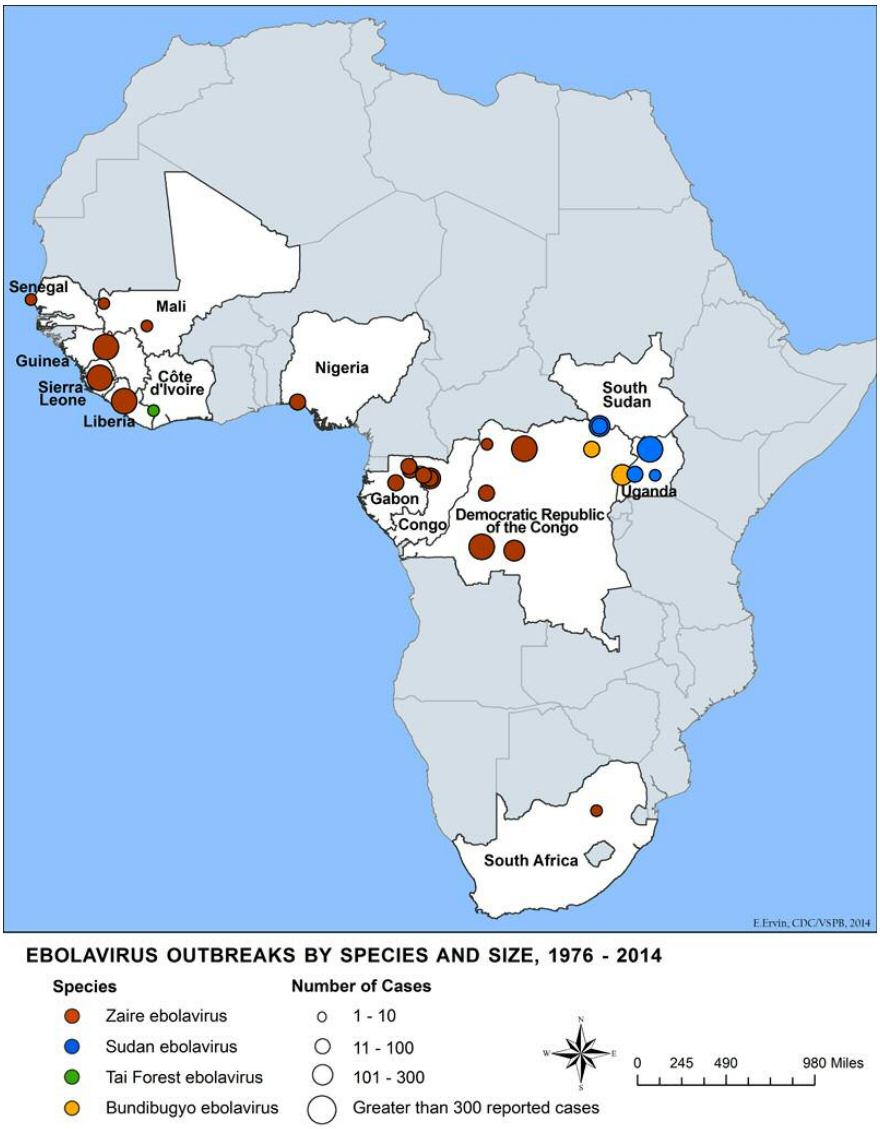


**Figure 8.** EV outbreaks in Africa between 1976 – 2014 (31).

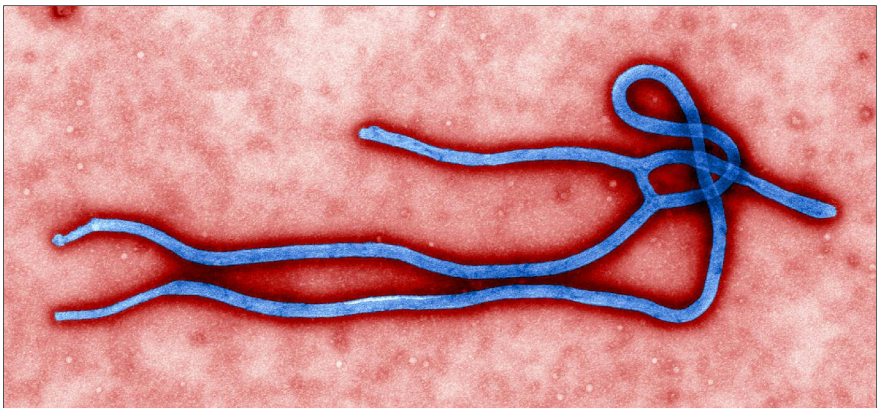

**Figure 9.** Ebola virus virion (1).

Thirty-one affected individuals, from those 25 primary and 6 secondary infections were reported. Seven primarily infections resulted in death. Another epidemic in Frankfurt city and in city of Belgrade was present in 1967.

Incubation period ranges between 3-9 days. Fever, headache, myalgia, abdominal pain, nausea, vomitus, diarrhea, maculopapular rash, lethargy, cough, conjunctivitis and photophobia appear and hemorrhage, gastrointestinal, vaginal, gingival bleeding and shock develop in about 45% of cases. Mortality rate ranges between 25 and 90%. Serologic ELISA tests and PCR or virus isolation are laboratory methods used to confirm diagnosis.

Marburg virus is transmitted by blood, by secrets of infected humans or animals, particularly monkeys. Fruit bats are serving as virus reservoir. Aerosol type of transmission has not been proved in nature yet. Nosocomial infections and laboratory contaminations are known. Epidemics occur (again without a recognized reason) most frequently in Zimbabwe, Republic of South Africa, Kenya, Congo, and Angola and in Uganda. The big epidemic was described in 2004-2005 in Angola where 356 individuals from 422 involved died of Marburg infection.

Limited number of therapeutically approaches is available – rehydration, respiratory supportive measures, blood-transfusions. Preventive measures are focused on local inhabitant's education (Africa) (25, 33).

**Crimean-Congo hemorrhagic fever (Africa, Eastern Europe, middle Asia), Rift Valley fever Africa, the Middle East) and Hantaan virus (Asia, Africa, the Balkan Peninsula) are classified as *Bunyaviridae* family (14).**

**Rift Valley Fever Virus.** The virus was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya. It is a RNA virus organized into 3 linear segments. Incubation period is 2-5 days. Infected either experience no detectable symptoms or develop a mild form of the disease characterized by a feverish syndrome with sudden onset of flu-like fever, muscle pain, joint pain, myalgia, headache, and vomitus. Spontaneous healing develops after one week. About 5 of patients suffer from ophthalmologic problems including temporary blindness, meningoencephalitis, hallucinations, blood emesis in hemorrhagic form and bleeding (e.g. at injection site). In such cases mortality rate reaches 50%. Several mosquito species are vector of a disease. Sheep, cattle, goats, camels and rodents are reservoir. One could contaminate by direct contact with infected animal, by contact with infected animal blood or with tissue fluids. Reverse transcriptase polymerase chain reaction (RT-PCR) assay and virus isolation by cell culture are the most frequently used methods in diagnosis. Inactivated vaccine was tested in vets and in laboratory staff but it is commercially available. Only supporting measures including ventilation and transfusion are accessible. In 2000 year, the first epidemic out of African continent was reported in Saudi Arabia and in Yemen. In association with these epidemic first speculations occurred on when infection arrives in Europe and how is the European shaping of measures (6, 15).

**Hantaviruses.** There are 2 big groups – so called **Old world viruses** including **Hantaan River, Dobrava-Belgrade, Soul, Puumala, Tobetsu, and Topografov, Tula** species which are presented by hemorrhagic fever with renal syndrome or nephropathy. The other group is called **New Word viruses** (Figure 10) including e.g. following species – **Prospect Hill, Isla Vista, Leaky, Blue River, Black Creek Canal** inducing **Hantavirus pulmonary syndrome (HPS).** Viral genome is organized to three linear segments again, encapsulated by lipid membrane.

Typical symptoms in renal involvement are as follows: fever, headache and myalgia, chill, cough, vomiting, renal insufficiency, mild nasal, vaginal and gastrointestinal hemorrhage.

Some species as Tula are almost non-pathogenic, other show different mortality rates – Dobrava 5-35%, Soul 1%.

In pulmonary syndrome, prodromal symptoms include flu-like symptoms such as fever, cough, myalgia, headache, and lethargy. It is characterized by a sudden onset of shortness of breath with rapidly evolving pulmonary edema that is often fatal (shock, heart failure due to pulmonary vessel system hypertension). It has a fatality rate of 40 – 60 %.

Enzyme-linked immunosorbent assay (ELISA), reverse transcriptase polymerase chain reaction (RT-PCR) assay; immunofluorescence tests and virus isolation by cell culture are indicated. Each virus species has its specific vector – rodent specific for geographical area. Transmission to humans occurs coincidentally by contact with rodents, their urine,


**Figure 10.** Distribution of hantaviruses and their reservoir species in the Americas (34).

excrements, saliva, and aerosol inhalation and by bites. Typical is aerosol inhalation containing dried excreta contaminating farmers. Human to human transmission was proved in Argentina. Supportive care is important, dialysis and ribavirin introduced early reducing mortality rate and time of treatment. Recurrent cases were recorded in Brasilia in 1993-2007 years, in Serbia, Montenegro and in Croatia in 2002 (16, 17).

**Environmental cleaning, disinfection, and waste management of VHF**

Due to absence of specific protection, prevention focused to avoid contact with infected sources of infection remains as most important. It is prerequisite to know and trace endemic occurrence areas and keep away from them. Mosquito and tick protection plays an important role (insecticides, repellents, mosquito net, windows net) with rodent population controls at the same time.

Health staff training, safety measures for manipulation with contaminated material, specimen taking, measures to isolate patients – all are matter of course. There are not only requirements dealing with disposable needles and syringes but currently used disposable thermometers. Functioning of hospital departments intended for VHH patients should be under special regulations control. Facilities are also different compared to common infectious department (negative pressure, chemical toilets, disinfection of all body excrements, used material should be sterilized or should be burned, clinical samples transported in duplicated package protection of staff with respirator, eye shields, double gloves, single bed rooms with single entrance through corridor, circulating air over HePa filters, disinfection by germicidal detergents of 0.5% sodium hypochlorite type, 2% glutaraldehyde , 0.5% chlorine solution and soap at random (25, 27, 30, 31, 35).

Regular **cleaning** and **disinfection** of the healthcare facility and proper management of waste generated by taking care of patients are important components of infection control and prevention for any disease. The first principle of environmental cleaning, disinfection, and waste management

is safety. Staff involved in cleaning activities may be exposed to VHF from both human and hospital wastes. Cleaning is a high-risk activity and must be done carefully. Splashes while cleaning and improper waste disposal can further spread infection. Therefore, a limited number of staff should be dedicated to cleaning and disinfecting the facility. Any person – whether ancillary staff or healthcare workers – conducting any cleaning and disinfection of any area potentially contaminated by virus must follow recommended guidelines and wear recommended personal protective equipment (PPE) for cleaners (31, 35, 36, 39).

## CONCLUSION

Let's summarize and generalize some facts on base of each VHF disease characteristics. It is almost impossible to predict viral hemorrhagic fever epidemic. Viral hemorrhagic fevers typically occur sporadically or in local epidemics. Just in the second half of 2012 year three epidemics were reported in Africa: on November 8th, 2012 seventeen cases of Marburg VHF were reported in Uganda, 9 patients died. On October 27th, 2012 Congo reported Ebola infection in 35 people, 24 cases resulted in death. Finally on July 28th, 2012 Uganda reported epidemic of Ebola – 24 individuals with 17 cases of fatal outcome (5, 18).

Supportive care to keep basic life processes is the main therapeutic approach. It is important to ensure sufficient hydration, blood volume, to control mineral levels, to introduce anti-shock measures and to use artificial ventilation if indicated. In some cases ribavirin, classified as ribonucleic analogue, shows efficacy (20, 21).

In our geographical latitude, diagnosis of imported infections could present a problem. It is due to minimal experience and due to atypical course of such viral infections in our patients compared to typical clinical presentation in natives in endemic areas.

Difficulty of experimental work due to high infectivity and pathogenicity of virus inducing hemorrhagic fevers presents other complication. It slows information important for new therapeutic approaches and new drug development research. All manipulation with such viruses must proceed at BSL-4 or BSL-3 (biosafety level). They are the highest levels level of the biocontainment precautions to provide safety for labs and lab staff requiring special training including psychological one and special lab equipment (sealed rooms, sealed containers, positive pressure personnel suits with a segregated air supply, a vacuum room, permanent 24-hours movement monitoring system, etc.). There is a limited list of existing BSL-4 facilities with appropriate equipment and experienced lab staff worldwide. Even at BSL-4 facilities, experimental work and research are significantly limited. For example time granted for experiments with all limits is relatively short what retroactively limits types of experimental work (37, 38).

Research focused on vaccine development is a priority. Original proposal of a „classical" vaccine based on inactivated virus failed. Preferred efforts are based on genetic engineering principles. The NIAID program is an and its virology lab developing Ebola vaccine based on vesicular stomatitis attenuated virus containing sequential part of specific Ebola genome protein. It is a recombinant vector vaccine where viral vector stimulates immune system of vaccinated individuals. Tests with experimental vaccine proved stimulating efficacy in primates. Lassa virus vaccine has been developed on similar principles. Again it is attenuated recombinant virus of vesicular stomatitis expressing Lassa virus glycoprotein. Single dose of a.m. administrated vaccine successfully protected primates in a trial. Nasal spray against Ebola has been tested using human parainfluenza virus type 3 model. This experimental vaccine induced strong immune response in guinea pigs and in monkeys (12, 26, and 27).

Early and correct diagnostics is extremely important and it should be supported by high-quality lab tests primarily based on molecular genetic methods recently (PCR, sequencing).

For the future, we can summarize that Europe has actual experience with imported VHH cases. Unauthorized use of VHH agents as bioterror agents has been essential and must be kept in view. Not least it is a question of natural VHH occurrence. That it is true, is indicated in introduction of this article describing global nature changes at the European continent and recent information about first filovirus with natural occurrence in Europe. It is Ebola-like filovirus called after site of detection – Lloviu virus. Its sequence is in 73.3% identical to Ebola-Zaire sequence and was isolated from dead bats from Cueva del Lloviu cave in southern Spain (22).

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