

Virginia Department of Health
Viral Hemorrhagic Fever: Guidance for Healthcare Providers
Key Medical and Public Health Interventions
after Identification of a Suspected Case

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1. Epidemiology

Viral hemorrhagic fever (VHF) refers to a group of illnesses that are caused by viruses from the following 5 distinct families of viruses:

- *Arenaviridae* (e.g., Lassa virus, Lujo virus; New World viruses: Guanarito, Junin, Machupo and Sabia viruses)
- *Bunyaviridae* (e.g., Crimean-Congo hemorrhagic fever virus, Rift Valley Fever virus, Hantaan virus)
- *Filoviridae* (e.g., Ebola virus and Marburg virus)
- *Flaviviridae* (e.g., yellow fever virus, dengue virus, Omsk hemorrhagic fever virus, Kyasanur forest disease virus)
- *Paramyxoviridae* viruses (specifically Hendra virus and Nipah virus)

These viruses can cause a severe multisystem syndrome whereby the overall vascular system is damaged and the body's ability to respond is impaired. Other key characteristics of viruses that cause VHFs are the following:

- They are all RNA viruses, and all are covered, or enveloped, in a fatty (lipid) coating.
- The viruses are geographically restricted to the areas where their host species live. Most occur in sub-Saharan Africa, Asia or focal areas of South America. Hantavirus is the only VHF that naturally occurs in the eastern United States.
- Their survival is dependent on a natural reservoir (e.g., animal or insect host). The natural reservoir depends on the specific virus involved, but can include ruminants (Crimean-Congo Hemorrhagic fever virus, Rift Valley Fever virus), bats (Ebola and Marburg viruses) or rodents (arenaviruses and hantaviruses).
- Humans are infected when they come into contact with infected hosts. In addition, vectorborne transmission can occur with several viruses via mosquitoes (Rift Valley Fever virus) or ticks

(Crimean-Congo Fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus). After the accidental transmission from the host, person-to-person transmission can occur with some of these viruses through direct contact with symptomatic patients, body fluids, cadavers or contaminated objects (Lassa virus, New World arenaviruses, filoviruses, Crimean-Congo hemorrhagic fever virus).

- Human cases or outbreaks of hemorrhagic fevers caused by these viruses occur sporadically and irregularly in people who live in or travel to endemic areas. The occurrence of outbreaks cannot be easily predicted.
- With a few noteworthy exceptions, there is no cure or established drug treatment for VHF.

Many viruses that cause hemorrhagic fever (e.g., Ebola virus, Marburg virus, Lassa fever virus) are designated as a Category A bioterrorism agents (i.e., easily disseminated or transmitted with a higher rate of mortality than Category B agents) and a select agent, which means that it could be developed as a bioterrorism agent and that possession, use or transfer of these organisms requires registration with CDC or USDA. If VHF is suspected or confirmed, the local health department should be notified immediately so that a public health investigation can be initiated. The epidemiology of several key VHF-causing viruses is described in more detail in [Appendix 1](#).

2. Clinical Manifestations

The incubation period for VHF is variable depending on the etiologic agent involved, but can be as long as 21 days. For this reason, a thorough travel and exposure history is critical. Although some viruses cause relatively mild illnesses, other viruses can cause severe, life-threatening disease. Signs and symptoms vary by disease, but, in general, include fever, headache, muscle pain, erythematous maculopapular rash on the trunk, vomiting, diarrhea, pharyngitis (arenavirus only), abdominal pain, bleeding (not related to injury) and retrosternal chest pain (arenavirus only). Vascular endothelial damage leads to shock and pulmonary edema. Liver injury is common. Signs or symptoms seen with specific viruses include renal failure (hemorrhagic fever with renal syndrome associated with hantaviruses), ecchymoses and bruises (Crimean-Congo hemorrhagic fever), hearing loss and shock in newborns (Lassa fever), and spontaneous abortion and birth defects (Lassa fever). The case-fatality rate varies by the etiologic agent. [Appendix 1](#) includes the clinical manifestations of several key VHF-causing viruses.

3. Specimen Collection and Laboratory Testing

In general, VHF diagnostic testing is available only at CDC. The one exception is that for the 2014 Ebola virus disease outbreak in West Africa, the state public health laboratory (Division of Consolidated Laboratory Services or DCLS) can perform PCR testing for patients suspected to have Ebola virus disease; specific information about specimen collection and testing for Ebola virus disease are available at the DCLS website (<http://www.dgs.virginia.gov/DivisionofConsolidatedLaboratoryServices/HotTopics/tabid/1531/Default.aspx>) and the CDC website (<http://www.cdc.gov/vhf/ebola/index.html>).

Clinicians should notify the local health department (LHD) immediately of any suspected case of VHF to discuss the case and laboratory testing (see <http://www.vdh.virginia.gov/LHD/index.htm>). Clinical specimens should not be sent to DCLS until LHD staff have been consulted and laboratory testing has been approved by LHD/DCLS. Instructions for sample collection and submission for laboratory testing are summarized in Table 1. DCLS will provide information regarding specimen

collection and submission to verify appropriate tests, specimen collection and transport. The DCLS Emergency Duty Officer can be reached 24 hours a day/ 7 days a week at (804) 335-4617.

Table 1. Sample collection instructions for testing suspected viral hemorrhagic fevers at DCLS or CDC*

Test	Acceptable samples	Amount	Instructions
Serology	Serum (red top tube or serum separator) or whole blood (purple, green, or blue top tube)	Minimum sample volume is 4 ml	The following specimen types may be submitted: <ul style="list-style-type: none"> • Serum drawn near admission with clots retained from red top tube • As late a serum as available • Convalescent serum drawn approximately 21 days after first specimen • Post-mortem heart blood Serum samples must be shipped with a cold pack, or on dry ice in a plastic tube. Clots and acute blood for virus isolation must be sent on dry ice in a plastic tube.
Immunohistochemistry (IHC)	Lung, kidney, and spleen tissues are preferred. Other tissues that may be sent include lymph nodes, heart, pancreas, pituitary, brain, or liver.	Consult with DCLS	Specimen packaging requirements: <ul style="list-style-type: none"> • Paraffin blocks are preferred, particularly if death was not recent. • If paraffin blocks are not available, formalin-fixed tissues may be sent. • Ship paraffin blocks or formalin-fixed tissue at room temperature--do not freeze. • An autopsy or surgical report must accompany the specimen.
PCR/ Virus Isolation	Preferred: whole blood (purple, yellow, or blue top tube), fresh frozen tissue. Serum can also be used if only sample available.	Minimum sample volume: 4 ml. Fresh frozen tissues should be at least 1cm ³ , except for biopsies.	Ship sample frozen on dry ice in a plastic tube. Do not freeze glass tubes.

*If VHF is suspected, notify the local health department (LHD) immediately to discuss the case and laboratory testing (see www.vdh.virginia.gov/LHD/index.htm). Specimens should be sent to Division of Consolidated Laboratory Services (DCLS) after LHD has been consulted and testing has been approved by LHD/DCLS. The DCLS Emergency Duty Officer can be reached 24/7 at (804) 335-4617.

4. Diagnosis

The current CDC case definition for VHF is available at <http://www.cdc.gov/nndss/script/casedefDefault.aspx>. Specific viruses described in the case definition include the following: Crimean-Congo Hemorrhagic fever virus, Ebola virus, Lassa virus, Marburg virus, and New World Arenaviruses (Guanarito, Junin, Machupo and Sabia viruses). Note that a case definition is set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions, and should not be used by healthcare providers to determine how to meet an individual patient's health needs.

For the 2014 outbreak of Ebola virus disease in West Africa, the case definition may be found at <http://www.cdc.gov/vhf/ebola/hcp/case-definition.html>.

5. Treatment

Patients with VHF should receive supportive therapy for symptoms and complications, but, in general, there is no other specific treatment or established cure. Supportive therapy includes maintenance of fluid and electrolyte balance, mechanical ventilation, dialysis, steroids (if adrenal involvement), and antibiotics for secondary bacterial infections.

Ribavirin, an anti-viral drug, has been effective in treating some individuals with Lassa fever and Crimean-Congo hemorrhagic fever. Ribavirin treatment has also been shown to be effective against hendra virus and nipah virus in vitro; ribavirin is not effective against filoviruses or flaviviruses. Recommendations for ribavirin treatment in patients with VHF of unknown etiology or known to be caused by an arenavirus or bunyavirus are summarized in Table 2. Other experimental treatments, such as convalescent-phase plasma, have been used in some patients with Ebola virus disease, but there is no scientific evidence of its effectiveness on clinical outcome.

Table 2. Ribavirin therapy for patients with VHF of unknown cause or known to be caused by an arenavirus or bunyavirus*

<u>Contained Casualty Setting</u>	<u>Severe Circumstances Setting: Regimens may be used for treatment in severe circumstances when IV treatment is impractical or unavailable.</u>
Adults (including pregnant women [†])	
Loading dose of 30 mg/kg IV (maximum 2 g) once, followed by 16 mg/kg IV (maximum 1g/dose) every 6 hours for 4 days, followed by 8mg/kg IV (maximum 500 mg/dose) every 8 hours for 6 days.	Loading dose of 2000 mg orally once, followed by <ul style="list-style-type: none"> • Weight >75 kg: 1200 mg/d orally in 2 divided doses for 10 days. • Weight <75 kg: 1000 mg/d orally in 2 doses (400 mg in AM and 600 mg in PM) for 10 days.
Children	
Same as for adults, dosed according to weight.	Loading dose of 30 mg/kg orally once, followed by 15 mg/kg per day orally in 2 divided doses for 10 days.

*Source: Working Group on Civilian Biodefense. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002; 287(18):2391-2405. Ribavirin is not approved by the US Food and Drug Administration for treatment of viral hemorrhagic fever and must be used under an Investigational New Drug protocol, although in a mass-casualty setting, this requirement may need to be modified.

[†]Generally, ribavirin is contraindicated in pregnant women; however, the benefits may outweigh the fetal risk of ribavirin therapy.

6. Postexposure Prophylaxis

Persons exposed to VHF, including close contacts of a patient with VHF, are recommended to be under postexposure surveillance for 21 days. The Working Group on Civilian Biodefense does not recommend prophylactic antiviral therapy for persons exposed to any hemorrhagic fever viruses (including Lassa virus) in the absence of clinical illness (Borio, et al 2002); instead, the group recommends monitoring the exposed person for 21 days and, if symptoms suggestive of VHF develop or fever ($\geq 101^{\circ}\text{F}$) is documented, ribavirin therapy should be initiated unless another diagnosis is confirmed (or the etiologic agent is known to be a filovirus or flavivirus). Other researchers have suggested considering postexposure prophylaxis (PEP) with ribavirin for persons exposed to an arenavirus or bunyavirus, particularly if a high-risk exposure (e.g., needlestick injury) has occurred.

7. Vaccination

FDA-approved vaccines against VHF are not available in the US with the exception of yellow fever vaccine. A human vaccine for Kyasanur Forest Disease and an animal vaccine for Rift Valley Fever do exist and are used in endemic areas; in addition, there are investigational vaccines for Argentine hemorrhagic fever and Rift Valley Fever.

8. Infection Control

The following infection control recommendations should be followed when caring for persons with suspected VHF:

- Patients should be placed in a private room and standard, contact, and droplet precautions (<http://www.cdc.gov/hai/>) should be initiated (Siegel JD, et al 2007).
 - Although transmission by the airborne route has not been established, airborne precautions (<http://www.cdc.gov/hai/>) may be initiated for patients if bioterrorism is suspected or for patients undergoing airborne-generating procedures (e.g., aerosolized or nebulized medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask and high frequency oscillatory ventilation). Airborne precautions entail placement of patient in a negative pressure isolation room with 6-12 air changes per hour, air exhausted directly to the outdoors or passage through a high-efficiency particulate air (HEPA) filter before recirculation, and door kept closed.
 - Clinicians should consult their local health department for additional guidance.
- Healthcare workers should strictly adhere to hand hygiene: Wash hands prior to donning personal protective equipment for patient contact. After patient contact, remove gown, leg/shoe coverings, and gloves, and immediately clean hands. It is important to wash hands before the removal of respirators, face shields, and goggles to minimize exposure of mucous membranes. Wash hands once again after the removal of respirators, face shields and goggles.
- Caretakers should use barrier precautions to prevent skin or mucous membrane exposure of the eyes, nose, and mouth with patient blood, other body fluids, secretions (including respiratory droplets), or prevent contact with items or environmental surfaces that may be soiled.
 - Staff should be trained on the correct use of personal protective equipment (PPE) and demonstrate proficiency in donning and doffing PPE before actual patient care. A trained observer of donning and doffing PPE is strongly recommended.

- PPE should include single gloves and fluid-resistant or impermeable gown, face/eye protection with masks, goggles or face shields. Additional PPE, including double gloves, leg and shoe coverings may be used, especially in resource-limited settings where options for cleaning and laundry are limited. When performing aerosol-generating procedures, use N-95 or higher level respirator.
- Nonessential staff and visitors should be restricted from entering the room of patients with suspected VHF. A log of persons entering the patient's room should be maintained.
- Before exiting the room of a patient with suspected VHF, safely remove and dispose of all protective gear, and clean and disinfect shoes that are soiled with body fluids as described in the section on environmental infection control below.
- To prevent percutaneous injuries, needles and other sharps should be used and disposed of in accordance with recommendations for standard precautions (<http://www.cdc.gov/hai/>).
- If the patient requires a surgical or obstetric procedure, consult your local health department regarding appropriate precautions for these invasive procedures.
- If multiple patients with viral hemorrhagic fever are in a health care facility, they should be cared for in the same part of the hospital to minimize exposures to others.
- The recommendations above are based on Siegel JD, et al 2007 for viral hemorrhagic fevers caused by Lassa, Ebola, Marburg and Crimean-Congo fever viruses. Note that for the 2014 Ebola outbreak, CDC developed extensive infection control guidance (see <http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html> and <http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html>).

9. Decontamination

- Environmental surfaces or inanimate objects contaminated with blood, other body fluids, secretions, or excretions should be cleaned and disinfected using standard procedures (<http://www.cdc.gov/hai/>)
- Disinfection can be accomplished using a U.S. Environmental Protection Agency (EPA)-registered hospital disinfectant or a 1:100 dilution of household bleach (1/4 cup bleach to 1 gallon water). For grossly soiled surfaces, (e.g., vomitus or stool), use a 1:10 dilution of household bleach.
- Soiled linens should be incinerated, autoclaved or placed in double, clearly labeled leak-proof bags at the site of use and discarded. Hospital housekeeping staff and linen handlers should wear appropriate PPE when handling or cleaning potentially contaminated material or surfaces.
- Liquid medical waste such as feces and vomitus can be disposed of in the sanitary sewer following local sewage disposal requirements (<http://www.cdc.gov/hai/>). Care should be taken to avoid splashing when disposing of these materials.
- When discarding solid medical waste (e.g., needles, syringes, and tubing) contaminated with blood or other body fluids from VHF patients, contain the waste with minimal agitation during handling. Properly contained wastes should be managed according to existing local and state regulations for ensuring health and environmental safety during medical waste treatment and disposal. On-site treatment of the waste in an incinerator or a gravity displacement autoclave for decontamination purposes will help to minimize handling of contaminated waste. Alternatively, off-site medical waste treatment resources may be used (<http://www.cdc.gov/hai/>).

10. Postmortem Practices

If VHF is suspected as a cause of death, the district Office of the Chief Medical Examiner should be notified immediately (see <http://www.vdh.virginia.gov/medExam/ContactUs.htm>). Contact with cadavers has been implicated as a source of transmission in previous VHF outbreaks. Prompt burial or cremation of the deceased, with minimal handling, is recommended. No embalming should be done. Remains should be wrapped in sealed leak-proof material and cremated or buried promptly in a sealed casket. If an autopsy is necessary, it should be performed only after consultation and approval with the state health department and CDC and by specially trained persons using VHF-specific barrier precautions, HEPA-filtered respirators and negative-pressure rooms.

11. Public Health Measures

- Suspected or confirmed VHF cases should be reported immediately to the local health department. See <http://www.vdh.virginia.gov/LHD/index.htm>.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of agent and other studies after consultation and approval. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.
- Designated public health authority should begin an epidemiologic investigation.
 - Collect detailed information from the patient to attempt to identify the source of the exposure.
 - Investigate contacts of the patient for compatible illness to investigate a potential common exposure.
 - Implement control measures to prevent disease and additional exposures. Monitor close contacts of VHF patients 21 days. For laboratorians who handled infectious specimens or others who were potentially exposed before identification as a VHF, postexposure monitoring might be recommended based on a risk assessment.
 - VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

12. References and Resources

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13. Appendix 1: Epidemiology and clinical manifestations of specific viruses causing viral hemorrhagic fever by virus family

Note: Other hemorrhagic fever viruses exist in these categories; however, the viruses that pose the most serious risk as biological weapons are the following: arenaviruses (Lassa virus, New World arenaviruses), bunyaviruses (Rift Valley fever virus), filoviruses (Ebola virus, Marburg virus), and flaviviruses (yellow fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus). Dengue virus, Crimean-Congo hemorrhagic fever viruses and hantaviruses are considered less likely to be used as biological weapons (Borio, et al 2002). The role of other hemorrhagic fever viruses as potential weapons is not known.

Arenaviruses

1) Lassa Fever

- Organism: Lassa virus
- Natural reservoir: multimammate rat (*Mastomys* rodent)
- Person-to-person transmission: Yes
- Occurrence: Endemic in parts of West Africa, including Sierra Leone, Liberia, Guinea and Nigeria. Additional countries in which cases have been reported include Mali, Ghana, Côte d'Ivoire, Burkina Faso, Togo, and Benin. An estimated 100,000 – 300,000 infections, including approximately 5,000 deaths, occur annually. In some areas of Sierra Leone and Liberia, it is known that 10%–16% of people admitted to hospitals every year have Lassa fever.
- Incubation period: Typically 1–3 weeks after exposure
- Signs and symptoms: For most (80%) infections, symptoms are mild and include slight fever, general malaise and weakness, and headache. In remaining 20%, disease may progress to more serious symptoms including hemorrhaging (e.g., in gums, eyes, or nose), respiratory distress, vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Neurological symptoms (e.g., hearing loss, tremors, and encephalitis) may be present. Spontaneous abortion is a serious complication of infection with an estimated 95% mortality in fetuses of infected pregnant mothers. Deafness is the most common complication and occurs in ~33% of all cases, regardless of the severity.
- Case-fatality rate: 1% of all infections; ~15%–20% among hospitalized patients

2) New World Arenaviruses

- Organism: multiple (including Machupo, the cause of Bolivian hemorrhagic fever; Junin, the cause of Argentinean hemorrhagic fever; Guanarito, the cause of Venezuelan hemorrhagic fever; Sabia, the cause of Brazilian hemorrhagic fever)
- Natural reservoir: rats and mice
- Person-to-person transmission: Yes
- Occurrence: Depends on the virus and the host, but primarily limited to certain areas in South America
- Incubation period: Depends on the virus, but typically 1–3 weeks after exposure
- Signs and symptoms: Initial symptoms may include fever, headache, anorexia, malaise, muscle pain, with pain especially in the lower back; other symptoms might include nausea, dizziness, abdominal pain, vomiting, diarrhea, sore throat, flushing of the head and torso, or generalized lymphadenopathy. Most patients improve after a week or two, but about 1/3 of untreated cases become severe and life-threatening. Petechiae on the skin or gums, bleeding from the vagina or gastrointestinal tract, and neurologic symptoms may be present.

- For most (80%) infections, symptoms are mild and include slight fever, general malaise and weakness, and headache. In remaining 20%, disease may progress to more serious symptoms including hemorrhaging (e.g., in gums, eyes, or nose), respiratory distress, vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Neurological symptoms (e.g., hearing loss, tremors, and encephalitis) may be present. Spontaneous abortion is a serious complication of infection with an estimated 95% mortality in fetuses of infected pregnant mothers. Deafness is the most common complication and occurs in ~33% of all cases, regardless of the severity.
- Case-fatality rate: 15%–30%

Bunyaviruses

1) Rift Valley Fever (RVF)

- Organism: Rift Valley fever virus
- Natural reservoir: Ruminants (e.g., cattle, sheep and possibly wild ruminants), rats in some areas
- Person-to-person transmission: No
- Occurrence: Rift valley fever was first reported in livestock in Kenya's Rift Valley in the early 1910s. RVF is generally found in eastern and southern Africa, but the virus exists in most of sub-Saharan Africa, including West Africa and Madagascar. In September 2000, a RVF outbreak was reported in Saudi Arabia and subsequently, Yemen. This outbreak represented the first cases of Rift Valley fever identified outside Africa.
- Incubation period: 2–6 days
- Signs and symptoms: Most commonly, people with RVF have either no symptoms or a mild illness associated with fever and liver abnormalities. Typical signs and symptoms include fever, weakness, back pain, and dizziness. Most patients recover within one week after onset of illness. Some patients (8–10%) develop much more severe symptoms, including the following:
 - Ocular disease (blurred and decreased vision), may occur 1–3 weeks after illness onset and may resolve after 10–12 weeks
 - Encephalitis, which can lead to headaches, coma, or seizures, occurs in less than 1% of patients and presents 1–4 weeks after first symptoms appear. Though death from this is rare, neurological deficits may persist.
 - Hemorrhagic fever, which occurs in <1% of patients, may begin with jaundice and other signs of liver impairment, followed by vomiting blood, bloody stool, or bleeding from gums, skin, nose, and injection sites. These symptoms appear 2–4 days and death usually occurs 3–6 days later.
- Case-fatality rate: ~50% among those with hemorrhagic fever

Filoviruses

1) Ebola Virus Disease (EVD)

- Organism: Ebola virus
- Natural reservoir: Unknown, presumed to be fruit bats
- Person-to-person transmission: Yes
- Occurrence: first identified in 1976; since then, sporadic outbreaks have been identified in Africa, primarily in sub-Saharan countries. In December 2013, the largest EVD outbreak began in West Africa and is currently ongoing as of June 2015.
- Incubation period: 2 to 21 days, though 8–10 days is most common
- Signs and symptoms: Fever, headache, joint and muscle aches, weakness, diarrhea, vomiting, stomach pain and lack of appetite are common. Some may experience the following symptoms: rash, red eyes, hiccups, cough, sore throat, chest pain, difficulty breathing, difficulty swallowing and bleeding inside and outside the body.
- Case-fatality rate: 25%–90%

2) **Marburg Hemorrhagic Fever (MHF)**

- Organism: Marburg virus
- Natural reservoir: fruit bat (*Rousettus aegypticus*)
- Person-to-person transmission: Yes
- Occurrence: First identified in 1967 when outbreaks of hemorrhagic fever occurred simultaneously in laboratories in Germany and Yugoslavia. Countries in which MHF has been identified include Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, and Angola. A few cases outside of Africa have been identified and were related to either laboratory exposure or importation after travel to Africa.
- People who have close contact with a human or non-human primate infected with the virus are at risk (includes laboratory or quarantine facility workers) for developing the disease. In addition, hospital staff and family members who care for patients with the disease are at risk if they do not use proper barrier nursing technique.
- Incubation period: 5–10 days
- Signs and symptoms: symptom onset is sudden and marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea may then appear. Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction.
- Case-fatality rate: 23%–90%

Flaviviruses

1) **Yellow Fever**

- Organism: Yellow fever virus (YFV)
- Natural reservoir: nonhuman and human primates
- Person-to-person transmission: Yes (also vectorborne transmission via infected mosquitoes, primarily *Aedes* or *Haemagogus* spp.)
- Occurrence: Endemic in parts of Africa (particularly sub-Saharan West Africa) and Central and South America. Occurrence depends on transmission cycle present in the area. With the sylvatic (jungle) transmission cycle, transmission occurs between nonhuman primates and mosquitoes in the forest canopy in tropical regions of Africa and Latin America. With the intermediate (savannah) transmission cycle, transmission occurs via various *Aedes* spp., humans and nonhuman primates in humid and semihumid areas of Africa. With the urban transmission cycle, transmission occurs between humans and mosquitoes (primarily *Aedes aegypti*) in parts of Africa, particularly West Africa.
- Incubation period: 3–6 days
- Signs and symptoms: Most infected persons are asymptomatic. Symptoms, if present, include fever, chills, headache, backache, general muscle pain, prostration, nausea, and vomiting. Some patients may just experience mild, febrile illness. In approximately 15% of cases, there is a brief remission of symptoms lasting hours to days followed by recurrence of initial symptoms and progression to jaundice and hemorrhagic symptoms. Leukopenia (most pronounced around Day 5 of infection), leukocytosis (usually in second week of infection), elevated liver enzymes, abnormal clotting factors, albuminuria and anuria may be seen as a result of liver and renal failure.
- Case-fatality rate: 20%– 50%

2) **Kyasanur Forest Disease (KFD)**

- Organism: Kyasanur Forest disease virus (KFDV)

- Natural reservoir: Rodents, bats and other small mammals; monkeys appear to be amplifying hosts; arthropod vector: ticks (*Haemaphysalis spinigera*)
- Person-to-person transmission: No
- Occurrence: KFDV was identified in 1957 from a sick monkey from the Kyasanur Forest in India. Since then, approximately 400–500 human cases per year have been reported.
- Incubation period: 3–8 days
- Signs and symptoms: Symptoms begin suddenly with chills, fever, and headache, followed in 3–4 days with severe muscle pain, vomiting, gastrointestinal symptoms and bleeding. Abnormally low blood pressure and low platelet, red blood cell, and white blood cell counts may occur. After 1–2 weeks of symptoms, some patients recover without complication. However, in some patients (10–20%), a second wave of symptoms may occur in the third week, including fever and neurological manifestations, such as severe headache, mental disturbances, tremors, and vision deficits.
- Case-fatality rate: 3%–10%

3) Omsk hemorrhagic fever (OHF)

- Organism: Caused by Omsk hemorrhagic fever virus (OHFV)
- Natural reservoir: rodents (including muskrats and voles); arthropod vector: ticks (*Dermacentor reticulatus*, *Dermacentor marginatus*, *Ixodes persulcatus*)
- Person-to-person transmission: No
- Occurrence: OHF was first described between 1945 and 1947 in Omsk, Russia from patients with hemorrhagic fever, and is endemic in the western Siberia region.
- Incubation period: 3–8 days
- Signs and symptoms: The symptoms begin suddenly with chills, fever, and headache, followed in 3–4 days with severe muscle pain, vomiting, gastrointestinal symptoms and bleeding. Some patients may experience abnormally low blood pressure and low platelet, red blood cell, and white blood cell counts. After 1–2 weeks of symptoms, some patients recover without complication. The illness is biphasic for a subset of patients who experience a second wave of symptoms at the beginning of the third week. These symptoms include fever and encephalitis (inflammation of the brain).
- Case-fatality rate: <1%–3%