

Fact Sheet

Hemorrhagic Fever Viruses (VHF)

Unless otherwise noted, all information presented in this article is derived from Borio L, Inglesby T, Peters CJ, et al., for the Working Group on Civilian Biodefense. Hemorrhagic fever viruses as biological weapons: medical and public health management *JAMA*. 2002;287(18):2391-2405.

Background

The hemorrhagic fever viruses (HFVs) are a diverse group of organisms that are all capable of causing clinical disease associated with fever and bleeding disorder, classically referred to as viral hemorrhagic fever (VHF). These organisms can be divided into four distinct families of viruses.

1. *Filoviridae*: Ebola and Marburg viruses
2. *Arenaviridae*: Lassa fever virus and a group of viruses referred to as the New World arenaviruses (eg, Junin, Machupo, Guanarito, and Sabia viruses)
3. *Bunyviridae*: Crimean Congo hemorrhagic fever virus, Rift Valley fever virus, and a group of viruses known as the “agents of hemorrhagic fever with renal syndrome” (eg, Hantaan, Dobrava-Belgrade, Seoul, and Puumala viruses)
4. *Flaviviridae*: dengue, yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease viruses

In nature, HFVs are generally transmitted to humans from animal hosts and arthropod vectors (carriers), although in the case of Marburg, the virus’s natural reservoir is still unknown. Since the first case of Marburg was reported in 1967, there have been at least 20-25 human outbreaks of VHF related to Ebola or Marburg viruses, mostly occurring in Africa. None of the HF viruses occurs naturally in the United States. However, risk factors for infection include: travel to geographic areas where these viruses are endemic (eg, areas of Africa, Asia, the Middle East, and South America); handling of carcasses of infected animals; close contact with infected animals or people; and/or a bite from an arthropod carrying an HFV.

HFVs as Biological Weapons

HFVs are considered to be a significant threat for use as biological weapons due to their potential for causing widespread illness and death. Because of their infectious properties, associated high rates of morbidity and mortality, and ease of person-to-person spread, Ebola, Marburg, Junin, Rift Valley fever, and yellow fever viruses have been deemed to pose a particularly serious threat, and in 1999 the HFVs were classified as category A bioweapons agents by the U.S. Centers for Disease Control and Prevention (CDC).

Several HFVs have reportedly been weaponized in the past by the U.S., the former Soviet Union, and possibly North Korea. The U.S. is believed to have developed Rift Valley fever and yellow fever viruses as biological weapons as part of its offensive BW program until the program’s shutdown in 1969. The former Soviet Union is also suspected of having weaponized Ebola, Marburg, Lassa, Junin, and Machupo viruses. North Korea may have weaponized yellow fever.

An attack using an HFV as a biological weapon could affect both human and animal populations. Rift Valley fever virus, for example, which is usually transmitted by mosquitoes, can infect livestock, which, in turn, can infect more mosquitoes, widening the scope of an outbreak.

In the U.S. Department of Health and Human Services (HHS) Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Implementation Plan, published in April 2007, Ebola, Marburg, and Junin viruses are specified as top priority threats for medical countermeasure development.¹ (See “The History of Bioterrorism: Viral Hemorrhagic Fevers,” a short video from the CDC available at: <http://www.bt.cdc.gov/training/historyofbt/06vhf.asp>)

Signs and Symptoms

Following an aerosol dissemination of any of the HFVs of concern, cases would likely appear within 2 to 21 days after exposure, depending on the specific virus involved. Patients would present with fever, rash, body aches, headaches, and fatigue; internal and external bleeding could occur later.

Diagnosis of VHF is based on clinical presentation of symptoms and confirmed by laboratory testing. This can be challenging because numerous symptoms might be present. There are no rapid clinical diagnostic tests available.

The mechanisms and symptoms for each disease are slightly different, but infection with any of these viruses may lead to thrombocytopenia (a low number of platelets in the blood) and coagulation abnormalities that may lead to prolonged bleeding. Because these illnesses are not endemic to the U.S., the diagnosis of any case of VHF in a person without the classic

travel and exposure risk factors (mentioned above) would be cause for suspicion of bioterrorism. Suspected cases of viral hemorrhagic fever should be reported immediately to a local or state health department.

Transmission

Most of what is known about the transmission of the HFVs is derived from naturally occurring outbreaks.

Some HFVs such as Rift Valley fever and the *Flaviviridae* viruses are not transmissible from person-to-person, while Ebola, Marburg, Lassa fever, New World *Arenaviruses*, and Crimean-Congo hemorrhagic fever viruses are transmissible among humans. While little is known about the routes of transmission for HFVs, it appears that direct contact with an infected person is associated with the highest risk of morbidity and mortality. Airborne transmission of the viruses is rare but has not been ruled out.

All of these viruses, including Rift Valley fever and *Flaviviridae*, may be transmitted to laboratory personnel by way of aerosolization generated during specimen processing. For that reason, any research done on these viruses must be conducted in high containment (BSL-4) laboratories.

An outbreak of Ebola occurred in November 2007 in Uganda's Bundibugyo district. (See www.allAfrica.com, keyword "Ebola," for articles and updates on Uganda's Ebola outbreak.) This particular outbreak was contained after approximately six weeks of efforts that included education of the public, implementation of barrier precautions in isolation clinics, and restrictions of inter-district travel and commerce. Containment was dependent on infected individuals seeking attention and family members maintaining distance from isolation centers. Social gatherings, traditional burial practices, and other activities involving close human contact were also limited to help limit the spread of the virus. (For further details on this outbreak and the response, see "Uganda Seeks Coordinated Response to Ebola Outbreak" and "DRC Shuts Border with Uganda as Ebola Outbreak Persists," reported in *Biosecurity Briefing*.^{2,3})

High-Priority VHFs as per HHS PHEMCE Implementation Plan

HFV	Source of Human Infection	Incubation Period	Symptoms	Lethality	Treatment
Ebola HF and Marburg HF	Primates/unknown	2 to 21 days	High fever, rash, weight loss, exhaustion, muscle pain, headaches, lesions, internal and external bleeding	50% to 90%	Supportive care
Argentine HF (Junin Virus)	Rodents	10 to 16 days	Fever, headaches, malaise, anorexia, nausea, dehydration, hypotension, infrequent urination, bleeding	15% to 30%	Ribavirin effectively reduces lethality, supportive care

Infection Control Measures

An understanding of the epidemiology, the clinical presentation, and the recommended medical and public health responses to a biological attack with any of the HFVs of greatest concern is key to decreasing morbidity and mortality. For example, contact with blood and bodily fluids of infected individuals and animals should be avoided. This is essential to preventing infection.

Healthcare workers caring for patients with suspected or confirmed VHF should use special protective measures: strict hand hygiene and double gloves; impermeable gowns; leg and shoe coverings; face shields or goggles for eye protection; and either N-95 masks or powered air-purifying respirators (to diminish the chance of airborne transmission).

If resources are available, patients should be cared for in a negative pressure isolation room to comply with airborne precautions (also used for the care of patients with tuberculosis). (See CDC Isolation Precaution Guidelines.⁴)

Prophylaxis and Treatment

Currently, there are no approved antiviral medications for the treatment of any of the HFVs. Ribavirin, an antiviral drug, when used in combination with interferon (a drug approved for the treatment of chronic hepatitis C), is active against two families of hemorrhagic fever viruses (*Arenaviridae* and *Bunyaviridae*). Unfortunately, no antiviral medications have been shown to be useful in the treatment of the other families of viruses (*Filoviridae* and *Flaviviridae*).

Because there are no approved antiviral drugs to prevent or treat VHFs, treatment is primarily supportive. Prevention of HFVs is essential and is primarily dependent on standard barrier precautions and identification of high-risk individuals who have had close contact with infected persons.

Countermeasures

A licensed, publicly available vaccine exists only for yellow fever virus. The vaccine is very effective in protecting travelers to endemic areas; however, vaccination would not be useful following a bioterrorist attack because yellow fever has a very short incubation period. Even if victims were vaccinated following a known exposure, they would likely develop the disease before they developed protective antibodies. There are no licensed human vaccines for any other VHF.

Vaccines, antivirals, and diagnostic tests for Ebola, Marburg, and other HFVs are in various stages of development at the

Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID) and at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), in collaboration with private institutions and academia.

There is an urgent need for rapid diagnostic tests, effective vaccines, and drug therapies for the HFVs of greatest concern. The HHS PHEMCE Implementation Plan has placed a high priority on development of rapid diagnostics and broad spectrum antiviral treatment for Ebola, Marburg, and Junin viruses.¹

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See Also

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