VIRAL HEMORRHAGIC FEVER
(VHF)

REPORTING INFORMATION

- **Class A:** *Report immediately via telephone* the case or suspected case and/or a positive laboratory result to the local public health department where the patient resides. If patient residence is unknown, report immediately via telephone to the local public health department in which the reporting health care provider or laboratory is located. Local health departments should report immediately via telephone the case or suspected case and/or a positive laboratory result to the Ohio Department of Health (ODH).
- Reporting Form(s) and/or Mechanism:
    - *Immediately via telephone*.
    - For local health departments, cases should also be entered into the Ohio Disease Reporting System (ODRS) within 24 hours of the initial telephone report to the ODH.
- Key fields for ODRS reporting include: import status (whether the infection was travel-associated or Ohio-acquired), date of illness onset, and all the fields in the Epidemiology module.

AGENTS AND DISEASES

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "viral hemorrhagic fever" is used to describe a severe multi-organ system syndrome. The three most common VHFs are Ebola virus disease, Lassa fever and Marburg hemorrhagic fever. Please see the IDCM chapter on Ebola virus disease for specific guidance.

Lassa fever is an acute viral illness that occurs in West Africa. The illness was discovered in 1969 when two missionary nurses died in Nigeria. The cause of the illness was found to be Lassa virus, named after the town in Nigeria where the first cases originated. The virus, a member of the virus family Arenaviridae, is a single-stranded RNA virus and is zoonotic. In areas of Africa where the disease is endemic, Lassa fever is a significant cause of morbidity and mortality. It is mild or has no observable symptoms in about 80% of people infected with the virus; the remaining 20% have a severe multi-system disease. Lassa fever is also associated with occasional epidemics, during which the case-fatality rate can reach 50%.

Marburg hemorrhagic fever is a rare, severe type of hemorrhagic fever which affects both humans and non-human primates. Caused by a genetically unique zoonotic RNA virus of the family Filoviridae, its recognition led to the creation of this virus family. The five species of Ebola virus are the only other known members of the family Filoviridae. Marburg virus was first recognized in 1967, when outbreaks of hemorrhagic fever occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia (now Serbia). A total of 31 people became ill, including laboratory workers as well as several medical personnel and family members who had cared for them. The first people infected had been exposed to African green monkeys or their tissues. In Marburg, the monkeys had been imported for research and to prepare polio vaccine.

CASE DEFINITION

Clinical Description

An illness with acute onset with ALL of the following clinical findings:

- A fever > 40°C
- One of more of the following clinical findings:
    - Severe headache
    - Muscle pain

- Erythematous maculopapular rash on the trunk with fine desquamation 3-4 days after rash onset
- Vomiting
- Diarrhea
- Pharyngitis (arenavirus only)
- Abdominal pain
- Bleeding not related to injury
- Retrosternal chest pain (arenavirus only)
- Proteinuria (arenavirus only)
- Thrombocytopenia

Laboratory Criteria for Diagnosis

One or more of the following laboratory findings:

- Detection of VHF viral antigens in blood by enzyme-linked Immunosorbent Assay (ELISA) antigen detection
- VHR viral isolation in cell culture for blood or tissues
- Detection of VHF-specific genetic sequence by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) from blood or tissues
- Detection of VHF viral antigens in tissues by immunohistochemistry

Criteria for Epidemiologic Linkage

One or more of the following exposures within the 3 weeks before onset of symptoms:

- Contact with blood or other body fluids of a patient with VHF
- Residence in or travel to a VHF endemic area
- Work in a laboratory that handles VHF specimens
- Work in a laboratory that handles bats, rodents, or primates from endemic areas
- Exposure to semen from a confirmed acute or convalescent case of VHF within 10 weeks of that person's onset of symptoms

Case Classification

Suspect: Case meets the clinical and epidemiologic linkage criteria.

Confirmed: Case meets the clinical and laboratory criteria.

Comment: VHF refers to viral hemorrhagic fever caused by either Ebola, Lassa, Lujo, or Marburg virus, a new world arenavirus, or Crimean-Congo hemorrhagic fever.

SIGNS AND SYMPTOMS

Because the symptoms of Lassa fever are so varied and nonspecific, clinical diagnosis is often difficult. Symptoms include fever, retrosternal pain, sore throat, back pain, cough, abdominal pain, vomiting, diarrhea, conjunctivitis, facial swelling, proteinuria and mucosal bleeding. Neurologic problems have also been described, including hearing loss, tremors and encephalitis.

Marburg hemorrhagic fever onset is sudden and is marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk, may appear. Nausea, vomiting, chest pain, sore throat, abdominal pain and diarrhea then may appear. Symptoms become increasingly severe and may include jaundice, pancreatitis, severe weight loss, delirium, shock, liver failure, massive hemorrhage and multi-organ dysfunction. Because many of the signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases, such as malaria or typhoid fever, diagnosis of the disease can be difficult, especially if only a single case is involved.

DIAGNOSIS

Lassa fever is most often diagnosed by using ELISA, which detects IgM and IgG antibodies as well as Lassa antigen. The virus itself may be cultured within 7 to 10 days. Immunohistochemistry performed on tissue specimens can be used to make a post-mortem diagnosis. The virus can also be detected by reverse transcription-polymerase chain reaction (RT-PCR); however, this method is primarily a research tool.

ELISA testing, IgM-capture ELISA, PCR, and virus isolation can be used to confirm a case of Marburg hemorrhagic fever within a few days of the onset of symptoms. The IgG-capture ELISA is appropriate for testing persons later in the course of disease or after recovery. The disease is readily diagnosed by immunohistochemistry, virus isolation, or PCR of blood or tissue specimens from deceased patients.

Do not attempt to culture any specimens. The Special Pathogens Branch at CDC works with Biosafety Level 4 (BSL-4) viruses. These viruses are highly pathogenic and require handling in special laboratory facilities designed to contain them. The hospital should be instructed to hold on to any blood, serum, CSF, respiratory secretions and other tissue collected. The local health department and ODH will coordinate the shipment of all laboratory specimens for testing. ODH Outbreak Response and Bioterrorism Investigation Team (614-995-5599) will follow up on the laboratory specimens**.**

EPIDEMIOLOGY

Occurrence

VHF viruses are distributed throughout the world. Each virus is associated with one or more nonhuman hosts, restricting natural occurrence of VHF to the areas inhabited by these species. Viruses causing hemorrhagic fevers are initially transmitted to humans when the habitats of the infected reservoir hosts and humans overlap. Risk of VHF is associated with human incursion into such areas. In general, humans are incidental ("dead-end") hosts for these enzootic diseases.

Mode of Transmission and Source

The reservoir, or host, of Lassa virus is a rodent known as the multimammate rat. These rodents breed very frequently, produce large numbers of offspring, and are numerous in the savannas and forests of West, Central, and East Africa. The virus is in urine and droppings, therefore, the virus can be transmitted through direct contact with these materials, through touching objects or eating food contaminated with these materials, or through cuts or sores. Contact with the virus also may occur when a person inhales tiny particles in the air contaminated with rodent excretions (aerosol or airborne transmission). Finally, because multimammate rats are sometimes consumed as a food source, infection may occur via direct contact when they are caught and prepared for food. Lassa fever may also spread through person-to-person contact. This type of transmission occurs when a person comes into contact with virus in the blood, tissue, secretions, or excretions of an individual infected with the Lassa virus. Person-to-person transmission is common in healthcare settings where proper personal protective equipment is not available or used.

Marburg virus is indigenous to Africa. While the geographic area to which it is native is unknown, this area appears to include at least parts of Uganda, Kenya, Zimbabwe, Democratic Republic of the Congo, and Angola. The reservoir host of Marburg virus is the African fruit bat, *Rousettus aegyptiacus*. Fruit bats infected with Marburg virus do not show obvious signs of illness. Persons who have handled infected monkeys and have come in direct contact with their fluids or cell cultures, have become infected. Spread of the virus between humans has occurred in a setting of close contact, often in a

hospital. Droplets of body fluids, or direct contact with persons, equipment, or other objects contaminated with infectious blood or tissues are all highly suspect as sources of disease.

Incubation Period
Lassa fever: 7-21 days
Marburg hemorrhagic fever: 5-10 days

PUBLIC HEALTH MANAGEMENT

Case

Investigation

Obtain information about the patient's occupation, history of travel outside the United States, contact with wild animals or lab animals, contact with a suspected or confirmed case of viral hemorrhagic fever, or close contact with an ill individual who traveled to a viral hemorrhagic fever-endemic area.

Treatment

Ribavirin, an antiviral drug, has been used with success in Lassa fever patients. It has been shown to be most effective when given early in the course of the illness. Patients should also receive supportive care consisting of maintenance of appropriate fluid and electrolyte balance, oxygenation and blood pressure, as well as treatment of any other complicating infections.

A specific treatment for Marburg hemorrhagic fever is unknown; however, supportive therapy should be provided. This includes balancing the patient's fluids and electrolytes, maintaining their oxygen status and blood pressure, replacing lost blood and clotting factors and treating for any complicating infections.

Isolation

Ohio Administrative Code (OAC) 3701-3-13 (DD) states:
"Viral hemorrhagic fever (VHF): a person with confirmed or suspected viral hemorrhagic fever shall be placed in airborne isolation until no longer considered infectious."

Clinicians evaluating suspect cases should use standard (e.g. hand hygiene), airborne (e.g. N-95 respirator) and contact (e.g. gowns and gloves) precautions.

Contacts

Investigation

Currently there is no post exposure prophylaxis available for individuals exposed to these agents. Investigation of contacts and source of infection: Identify all close contacts in the three weeks after the onset of illness. Initiate quarantine and active surveillance of contacts by having contacts take and maintain record of body temperature twice a day for 3 weeks after last exposure. If temperature is greater than 101°F (38.3°C), hospitalize patient immediately and initiate appropriate isolation precautions. Specific treatment such as Ribavirin is most effective if given within 6 days of illness onset.

When a suspect case is reported, the local health department needs to start identifying close contacts. Often this starts with the family. The emergency room chart or the medical record may provide names of emergency contacts or family members. The local health department needs to identify all persons who had "close contact"

with the patient for the 21 days prior to the onset of the patient's illness, and thereafter until the patient is released from isolation.

"Close contact" as described above means direct contact with the patient's oral secretions. This generally means face-to-face contact, but can also include sharing food, drink, cigarette, eating utensil or toothbrush and intimate contact such as kissing. "Close contact" may also include traveling together in a car.

On identifying close contacts of a suspected case, quarantine should be initiated. The local health department can refer them to their own physician or possibly the emergency room to receive appropriate medical evaluation.

Contacts should also be advised to be alert for the early symptoms of VHFs (fever, headache, nausea, vomiting, stiff neck, joint and muscle aches, sore throat, and weakness, followed by diarrhea, vomiting and stomach pain, rash, red eyes, hiccups and internal and external bleeding), and to seek prompt medical attention if they start to get sick.

What are viral hemorrhagic fevers?

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "viral hemorrhagic fever" is used to describe a severe multisystem syndrome (multisystem in that multiple organ systems in the body are affected). Characteristically, the overall vascular system is damaged, and the body's ability to regulate itself is impaired. These symptoms are often accompanied by hemorrhage (bleeding); however, the bleeding is itself rarely life-threatening. While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease.

The Centers for Disease Control and Prevention (CDC) Special Pathogens Branch (SPB) primarily works with hemorrhagic fever viruses that are classified as biosafety level four (BSL-4) pathogens. A list of these viruses appears in the SPB disease information index. The Division of Vector-Borne Infectious Diseases, also in the CDC National Center for Infectious Diseases, works with the non-BSL-4 viruses that cause two other hemorrhagic fevers, dengue hemorrhagic fever and yellow fever.

How are hemorrhagic fever viruses grouped?

VHFs are caused by viruses of five distinct families: arenaviruses, filoviruses, bunyaviruses, flaviviruses and paramyxoviruses. Each of these families share a number of features:

- They are all RNA viruses, and all are covered, or enveloped, in a fatty (lipid) coating.
- Their survival is dependent on an animal or insect host, called the natural reservoir.
- The viruses are geographically restricted to the areas where their host species live.
- Humans are not the natural reservoir for any of these viruses. Humans are infected when they come into contact with infected hosts. However, with some viruses, after the accidental transmission from the host, humans can transmit the virus to one another.
- Human cases or outbreaks of hemorrhagic fevers caused by these viruses occur sporadically and irregularly. The occurrence of outbreaks cannot be easily predicted.
- With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs.

In rare cases, other viral and bacterial infections can cause a hemorrhagic fever; scrub typhus is a good example.

What carries viruses that cause viral hemorrhagic fevers?

Viruses associated with most VHFs are zoonotic. This means that these viruses naturally reside in an animal reservoir host or arthropod vector. They are totally dependent on their hosts for replication and overall survival. For the most part, rodents and arthropods are the main reservoirs for viruses causing VHFs. The multimammate rat, cotton rat, deer mouse, house mouse, other field rodents and the African fruit bat are examples of reservoir hosts. Arthropod ticks and mosquitoes serve as vectors for some of the illnesses. However, the hosts of some viruses remain unknown – Ebola virus is a well-known example.

Where are cases of viral hemorrhagic fever found?

Taken together, the viruses that cause VHFs are distributed over much of the globe. However, because each virus is associated with one or more particular host species, the virus and the disease it causes are usually seen only where the host species live(s). Some hosts, such as the rodent species carrying several of the New World arenaviruses, live in geographically restricted areas. Therefore, the risk of getting VHFs caused by these viruses is restricted to those areas. Other hosts range over continents, such as the rodents that

carry viruses which cause various forms of hantavirus pulmonary syndrome (HPS) in North and South America, or the different set of rodents that carry viruses which cause hemorrhagic fever with renal syndrome (HFRS) in Europe and Asia. A few hosts are distributed nearly worldwide, such as the common rat. It can carry Seoul virus, a cause of HFRS; therefore, humans can get HFRS anywhere where the common rat is found. While people usually become infected only in areas where the host lives, occasionally people become infected by a host that has been exported from its native habitat. For example, the first outbreaks of Marburg hemorrhagic fever, in Marburg and Frankfurt, Germany, and in Yugoslavia, occurred when laboratory workers handled imported monkeys infected with Marburg virus. Occasionally, a person becomes infected in an area where the virus occurs naturally and then travels elsewhere. If the virus is a type that can be transmitted further by person-to-person contact, the traveler could infect other people. For instance, in 1996, a medical professional treating patients with Ebola virus disease (EVD) in Gabon unknowingly became infected. When he later traveled to South Africa and was treated for EVD in a hospital, the virus was transmitted to a nurse. She became ill and died. Because more and more people travel each year, outbreaks of these diseases are becoming an increasing threat in places where they rarely, if ever, have been seen before.

How are hemorrhagic fever viruses transmitted?
Viruses causing hemorrhagic fever are initially transmitted to humans when the activities of infected reservoir hosts or vectors and humans overlap. The viruses carried in rodent reservoirs are transmitted when humans have contact with urine, fecal matter, saliva, or other body excretions from infected rodents. The viruses associated with arthropod vectors are spread most often when the vector mosquito or tick bites a human, or when a human crushes a tick. However, some of these vectors may spread virus to animals, livestock, for example. Humans then become infected when they care for or slaughter the animals. Some viruses that cause hemorrhagic fever can spread from one person to another, once an initial person has become infected. Ebola, Marburg, Lassa and Crimean-Congo hemorrhagic fever viruses are examples. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids. For example, contaminated syringes and needles have played an important role in spreading infection in outbreaks of Ebola virus disease and Lassa fever.

What are the symptoms of viral hemorrhagic fever illnesses?
Specific signs and symptoms vary by the type of VHF, but initial signs and symptoms often include marked fever, fatigue, dizziness, muscle aches, loss of strength, and exhaustion. Patients with severe cases of VHF often show signs of bleeding under the skin, in internal organs, or from body orifices like the mouth, eyes, or ears. However, although they may bleed from many sites around the body, patients rarely die because of blood loss. Severely ill patient cases may also show shock, nervous system malfunction, coma, delirium, and seizures. Some types of VHF are associated with renal (kidney) failure.

How are patients with viral hemorrhagic fever treated?
Patients receive supportive therapy, but generally speaking, there is no other treatment or established cure for VHFs. Ribavirin, an antiviral drug, has been effective in treating some individuals with Lassa fever or HFRS. Treatment with convalescent-phase plasma has been used with success in some patients with Argentine hemorrhagic fever.

How can cases of viral hemorrhagic fever be prevented and controlled?
With the exception of yellow fever and Argentine hemorrhagic fever, for which vaccines have been developed, no vaccines exist that can protect against these diseases. Therefore, prevention efforts must concentrate on avoiding contact with host species. If prevention methods fail and a case of VHF does occur, efforts should focus on preventing further

transmission from person to person, if the virus can be transmitted in this way. Because many of the hosts that carry hemorrhagic fever viruses are rodents, disease prevention efforts include

- Controlling rodent populations;
- Discouraging rodents from entering or living in homes or workplaces;
- Encouraging safe cleanup of rodent nests and droppings.

For hemorrhagic fever viruses spread by arthropod vectors, prevention efforts often focus on community-wide insect and arthropod control. In addition, people are encouraged to use insect repellant, proper clothing, bednets, window screens, and other insect barriers to avoid being bitten.

For those hemorrhagic fever viruses that can be transmitted from one person to another, avoiding close physical contact with infected people and their body fluids is the most important way of controlling the spread of disease. Barrier nursing or infection control techniques include isolating infected individuals and wearing protective clothing. Other infection control recommendations include proper use, disinfection, and disposal of instruments and equipment used in treating or caring for patients with VHF, such as needles and thermometers.

In conjunction with the World Health Organization, the CDC has developed practical, hospital-based guidelines, titled "Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting". The manual can help healthcare facilities recognize cases and prevent further hospital-based disease transmission using locally available materials and few financial resources.

What needs to be done to address the threat of viral hemorrhagic fevers?
Scientists and researchers are challenged with developing containment, treatment, and vaccine strategies for these diseases. Another goal is to develop immunologic and molecular tools for more rapid disease diagnosis, and to study how the viruses are transmitted and exactly how the disease affects the body (pathogenesis). A third goal is to understand the ecology of these viruses and their hosts in order to offer preventive public health advice for avoiding infection.

From the CDC website: http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/vhf.htm.