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**By law, health care providers must report suspected or confirmed VHF to the local health department immediately (within 1 hr).**

**Even a single case of VHF is considered an outbreak and is a public health emergency.**

**To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).**

**Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.**

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## AGENT

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Hemorrhagic fever viruses are a diverse group of organisms that cause viral hemorrhagic fevers (VHF). VHF viruses are RNA viruses with lipid envelopes. They belong to one of four distinct families:

- **Filoviridae:** Ebola and Marburg viruses
- **Arenaviridae:** Lassa fever virus and a group of viruses referred to as the New World arenaviruses
- **Bunyaviridae:** Crimean Congo hemorrhagic fever virus, Rift Valley fever virus and a group of viruses known as the 'agents of hemorrhagic fever with renal syndrome'
- **Flaviviridae:** dengue, yellow fever, Omsk hemorrhagic fever and Kyasanur Forest disease virus

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## EPIDEMIOLOGY

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### **VHF viruses as Biological Weapons**

Several countries, including the USA and Russia, have conducted research on weaponizing VHF viruses. Aerosolized VHF preparations are considered potentially suitable as biological weapons because they would have a low infectious dose, would cause high morbidity and mortality, would have the potential for person-to-person transmission, and because effective therapy and vaccines are not always available.

The two families of viruses of most concern based on mortality and feasibility of production are the filoviruses and the arenaviruses.

Several species of VHF viruses (dengue, hantavirus, and Crimean-Congo hemorrhagic fever) are not considered to represent a significant bioterror threat.

### **Naturally Occurring Viral Hemorrhagic Fever**

All of the VHF agents cause sporadic disease or epidemics in areas of endemicity. The routes of transmission are variable, but most are zoonotic with spread via arthropod bites or contact with infected animals. Person-to-person spread is a major form of transmission for many of the viruses.

**Ebola** hemorrhagic fever (Central Africa) exhibits case-fatality rates of 50-90%. An outbreak among primates occurred in 1991 at a laboratory in Reston, Virginia. The natural reservoirs and exact patterns of transmission of Ebola virus are not known.

**Marburg** virus (sub-Saharan Africa) has caused outbreaks in Angola resulting in 451 cases (312 fatal) as of July 10, 2005. As with Ebola, the natural reservoirs and exact patterns of transmission of Marburg virus are not known.

Rodents are the primary reservoir for **Lassa** virus (West Africa). Case-fatality rates are lower for Lassa fever than for Ebola and Marburg, and ribavirin has been effective in treating some cases.

A number of uncommon viruses comprise **New World** hemorrhagic fever (South America), which appears to be transmitted via contact with rodents or rodent excreta. Three cases of imported Whitewater Arroyo virus were reported in California in 1999-2000; all were fatal.

**Rift Valley fever** (sub-Saharan and North Africa) is a mosquito-borne disease of mammals that primarily causes mild illnesses in humans, although meningoencephalitis and retinitis can occur.

**Yellow fever** (sub-Saharan Africa and tropical South America) is transmitted by a mosquito vector and causes an estimated 200,000 cases and 30,000 deaths each year in endemic areas. Urban outbreaks with vector-borne transmission have not occurred in the Americas since the 1940's due to public health programs aimed at eliminating the mosquito vector. Illness ranges from mild to severe, with an overall case-fatality rate of 5% to 7%. A vaccine against yellow fever is available.

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## CLINICAL FEATURES

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The clinical features of VHF vary according to the virus. Virus enters the body through mucosal surfaces in contact with infectious fluids, needlesticks or via inhalation. Common presenting complaints are fever, myalgia, and prostration. Clinical examination may initially reveal only as of conjunctival injection, mild hypotension, flushing, and petechial hemorrhages.

In all VHF syndromes the target organ is the vascular bed, and the dominant clinical features result from microvascular damage and changes in vascular permeability. Disease can range from minimally symptomatic to fulminant, and symptomatology varies depending on the specific virus. However, all share the potential for the development of a bleeding diathesis manifested by severe

hemorrhage from mucosal surfaces and petechiae. Full-blown VHF typically evolves to shock and generalized bleeding from the mucous membranes, often accompanied by severe neurological, hematopoietic, or pulmonary involvement.

<b>EBOLA AND MARBURG VIRUS HEMORRHAGIC FEVER: COMMON CLINICAL FEATURES</b>	
<b>Incubation Period</b>	2-21 days
<b>Signs &amp; Symptoms</b>	<p>Prodrome (&lt;1 week): Abrupt onset fever, severe prostration, headache, myalgias</p> <p>Syndrome</p> <ul style="list-style-type: none"> <li>• Maculopapular nonpruritic rash</li> <li>• Jaundice and pancreatitis often occur</li> <li>• Bleeding manifestations (mucous membrane hemorrhages, bloody diarrhea and/or vomiting, petechiae, ecchymoses, oozing of blood at puncture sites) in 30-40%</li> <li>• Shock (with DIC and end-organ failure) often during 2<sup>nd</sup> week of illness</li> </ul> <p>Complications (<math>\geq</math> 2 weeks after onset)</p> <ul style="list-style-type: none"> <li>• Migratory arthralgias</li> <li>• Ocular disease (unilateral vision loss, uveitis)</li> <li>• Orchitis, suppurative parotitis</li> <li>• Pericarditis</li> <li>• Illness-induced abortion among pregnant women</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Leukopenia and thrombocytopenia early in course; leukocytosis late</li> <li>• Elevated amylase and hepatic enzymes, laboratory manifestations of DIC as disease progresses</li> </ul>

<b>LASSA VIRUS HEMORRHAGIC FEVER: CLINICAL FEATURES</b>	
<b>Incubation Period</b>	5-16 days
<b>Signs &amp; Symptoms</b>	<p>Prodrome (&lt; 1 week): Gradual onset fever, weakness, malaise, arthralgias</p> <p>Syndrome</p> <ul style="list-style-type: none"> <li>• Exudative pharyngitis</li> <li>• Severe prostration</li> <li>• Faint maculopapular rash</li> <li>• Neurological involvement common (encephalopathy, coma, seizures)</li> <li>• Bleeding manifestations in 15-20%</li> <li>• Shock (with DIC and end-organ failure) uncommon</li> </ul> <p>Complications (<math>\geq</math> 2 weeks after onset)</p> <ul style="list-style-type: none"> <li>• 8<sup>th</sup> cranial nerve damage with hearing loss</li> <li>• Pericarditis</li> <li>• Illness-induced abortion among pregnant women</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Leukocyte &amp; platelet counts often normal</li> <li>• Elevated hepatic enzymes may occur</li> </ul>

YELLOW FEVER: CLINICAL FEATURES	
<b>Incubation Period</b>	3-6 days
<b>Signs &amp; Symptoms</b>	Prodrome (< 1 week): Fever, headache, myalgias, facial flushing, conjunctival injection  Syndrome <ul style="list-style-type: none"> <li>• Subclinical or mild infections predominate (80%)</li> <li>• 'Moderately severe' form includes high fever, jaundice, vomiting, bleeding manifestations</li> <li>• 'Malignant' form includes fulminant infection with severe hepatic involvement, bleeding manifestations, shock, renal failure, and death</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Leukopenia early, leukocytosis later</li> <li>• Thrombocytopenia</li> <li>• Elevated hepatic enzymes &amp; bilirubin</li> </ul>

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## DIFFERENTIAL DIAGNOSIS

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Most clinicians in the United States have little or no clinical experience with the syndromes that characterize VHF. The variable clinical presentation of VHF adds to the challenge.

**With a VHF virus used as a biological weapon, patients are less likely to have risk factors for natural infection such as travel to Africa, Asia, or South America, handling of animal carcasses, contact with sick animals or people, or arthropod bites within 21 days of symptom onset. The observation of a severe illness with bleeding manifestations as its primary feature, which develops as a point-source epidemic with simultaneous presentation of many cases, should be highly suspicious for VHF.**

The diagnosis of viral hemorrhagic fever should be considered for any patient who presents with:

- Acute onset of fever (<3 weeks duration)
- Severe prostrating or life-threatening illness
- Bleeding manifestations (at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other bleeding)
- No predisposing factors for a bleeding diathesis

The differential diagnosis includes:

### Bacterial and Rickettsial Infections

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|--|--------------------------------|
| • Gram-negative bacterial septicemia                   | • Septicemic plague            |
| • Staphylococcal or streptococcal toxic shock syndrome | • Typhoid fever                |
| • Meningococcemia                                      | • Rocky Mountain spotted fever |
| • Secondary syphilis                                   | • Ehrlichiosis                 |
|  | • Leptospirosis                |

### Viral and Parasitic Infections

- Malaria
- African trypanosomiasis
- Hemorrhagic smallpox
- Measles
- Hemorrhagic varicella
- Rubella
- Viral hepatitis

### Other Conditions

- Thrombotic or Idiopathic thrombocytopenic purpura
- Acute leukemia
- Hemolytic uremic syndrome

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## LABORATORY DIAGNOSIS

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The diagnosis of VHF is based initially on clinical criteria and judgment, with laboratory testing used to confirm or exclude this clinical diagnosis. Laboratory testing requires time and, in the event of an attack, may be delayed or impossible given current laboratory capacities.

A number of test methods can be used to diagnose VHF. These include: antigen-capture testing by ELISA, IgM antibody testing, paired acute-convalescent serum serologies, PCR, immunohistochemistry methods, and electron microscopy. Viral identification in cell culture is the 'gold standard' of viral detection, however this technique is time consuming and extremely dangerous, and should only be attempted by labs with high-level biosafety facilities.

Diagnosis is via blood or serum testing. For serological testing, avoid collection tubes with citrate, oxalate, or EDTA. For PCR tests, use an EDTA tube. Collect acute-phase specimens within 7 days of illness onset. Collect convalescent-phase specimens 7-20 days later, and at least 14 days after illness onset.

Marburg and Ebola viruses may be recovered from soft tissue effusions, semen, and anterior eye fluid, especially during later stages of illness. Lassa virus often can be recovered from throat swabs, pleural effusions, placental tissue, and urine and has been demonstrated in CSF of patients with fever and neurologic signs.

#### **If you consider testing for VHF, you should:**

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830) to facilitate specimen processing & proper specimen transport, and to initiate the public health response.**
- **Notify the laboratory that VHF is suspected, so that they may follow established biosafety procedures.**

## TREATMENT AND PROPHYLAXIS

**These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

### Treatment

Supportive care is essential for patients with all types of VHF and includes maintenance of fluid and electrolyte balance, active hemodynamic monitoring, mechanical ventilation, dialysis, and appropriate therapy for secondary infections. Treatment of other suspected causes of disease, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of VHF. Anticoagulant therapies, aspirin, nonsteroidal anti-inflammatory medications, and intramuscular injections are contraindicated.

Ribavirin has shown in vitro and in vivo activity against Arenaviruses (Lassa fever, New World hemorrhagic fevers) and Bunyaviruses (Rift Valley fever and others). Ribavirin has shown no activity against, and is not recommended for Filoviruses (Ebola and Marburg hemorrhagic fever) or Flaviviruses (Yellow fever, Kyasanur Forest disease, Omsk hemorrhagic fever).

Recommendations for IV ribavirin therapy are shown below. However in a mass casualty situation where the number of persons requiring therapy overwhelms the resources available to deliver IV agents, an oral regimen of ribavirin is recommended.

<b>RIBAVIRIN THERAPY FOR PATIENTS WITH VHF OF UNKNOWN CAUSE OR KNOWN TO BE CAUSED BY AN ARENAVIRUS OR BUNYAVIRUS*</b>		
<b>Patient Group</b>	<b>Contained-Casualty Setting</b>	<b>Mass-Casualty Setting†</b>
<b>Adults</b> (Including Pregnant Women‡)	<ul style="list-style-type: none"> <li>• Loading dose of 30 mg/kg (max 2 gm) IV, then:</li> <li>• 16 mg/kg (max 1 gm) IV q6 hr for 4 days, then:</li> <li>• 8 mg/kg (max 500 mg) IV q8 hr for 6 days</li> </ul>	<ul style="list-style-type: none"> <li>• Loading dose of 2000 mg PO, then:</li> <li>• (Weight &gt;75 kg): 1200 mg/day PO in 2 divided doses for 10 days§</li> <li>• (Weight &lt;75 kg): 1000 mg/day PO in divided doses (400 mg in am and 600 mg in pm) for 10 days§</li> </ul>
<b>Children</b>	Same as for adults	<ul style="list-style-type: none"> <li>• Loading dose of 30 mg/kg PO, then: 15 mg/kg/d PO in 2 divided doses for 10 days</li> </ul>
<p>* Ribavirin is not approved by the US Food and Drug Administration for treatment of VHF and must be used under an Investigational New Drug (IND) protocol, although in a mass-casualty setting, this requirement may need to be modified.</p> <p>† The decision to use oral rather than parenteral medication will depend on available resources.</p> <p>‡ Generally, ribavirin is contraindicated in pregnant women; however, the benefits may outweigh the fetal risk of ribavirin therapy.</p> <p>§ The current available formulation of ribavirin is 200-mg capsules, which cannot be broken open.</p>		
<p><i>Source: Working Group on Civilian Biodefense. Borio et al, JAMA 2002; 287(18):2391-2405.</i></p>		

## **Post Exposure Prophylaxis**

According to the Working Group on Civilian Biodefense, exposure is defined as proximity to an initial release of VHF virus, or close or high-risk contact with a patient suspected of having VHF during the 21 days following onset of symptoms. High risk is defined as having mucous membrane contact or having percutaneous injury involving contact with secretions, excretions, or blood from a patient with VHF. Close contact is defined as those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with VHF.

Previous CDC recommendations (MMWR, 1988) state that prophylaxis with ribavirin should be given to persons exposed to Lassa virus. However, the efficacy of ribavirin prophylaxis for Lassa virus is not well documented and CDC may be reconsidering this recommendation. Instead, the Working Group recommends that persons exposed to VHF be placed under medical surveillance until 21 days after the last exposure, and that if symptoms suggestive of VHF occur or if a temperature of  $\geq 101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ ) is documented, ribavirin therapy should be initiated unless another diagnosis is confirmed (or the etiologic agent is known to be a filovirus or flavivirus). **In the event of an outbreak, SFDPH will provide situational guidance on prophylaxis ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

## **Vaccine**

Yellow fever live attenuated 17D vaccine is effective when administered to travelers to endemic areas. However this vaccine would not be useful in preventing disease if given in the postexposure setting because yellow fever has a short incubation period of 3 to 6 days, and neutralizing antibodies take longer to appear following vaccination.

There is no licensed vaccine for any of the other VHF, though research is underway on several candidates.

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## **INFECTIOUS CONTROL\***

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**These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events ([www.sfdph.org/cdcp](http://www.sfdph.org/cdcp)).**

Filoviruses and arenaviruses are highly infectious after direct contact with infected blood and bodily secretions, and person-to-person transmission has been documented. In Africa, transmission of VHF viruses in healthcare settings has been associated with provision of patient care without appropriate barrier precautions to prevent exposure to virus-containing blood and other body fluids. The risk for person-to-person transmission of VHF virus is greatest during the latter stages of illness when virus loads are highest. No infection has been reported in persons whose contact with an infected person occurred only during the incubation period (i.e., before onset of fever).

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\* For description of Precautions, see chapter on Infection Control

Preventing the transmission of VHF virus infection relies on meticulous compliance with strict infection control measures. The most recent CDC recommendations (May, 2005) for isolation of patients with VHF are as follows:

- Patients who are hospitalized or treated in an outpatient setting should be placed in a private room and **Standard, Contact, and Droplet Precautions** should be initiated. Patients with respiratory symptoms also should wear a **face mask** to contain respiratory droplets prior to placement in their hospital or examination room and during transport.
- Caretakers should use barrier precautions to prevent skin or mucous membrane exposure with patient blood, other body fluids, secretions (including respiratory droplets), or excretions. All persons entering the patient's room should wear gloves and gowns to prevent contact with items or environmental surfaces that may be soiled. In addition, face shields or surgical masks and eye protection (e.g., goggles or eyeglasses with side shields) should be worn by persons coming within approximately 3 feet of the patient.
- Additional barriers may be needed depending on the likelihood and magnitude of contact with body fluids. For example, if copious amounts of any body fluids or feces are present in the environment, plastic apron, leg, and shoe coverings also may be needed.
- Nonessential staff and visitors should be restricted from entering the room of patients with suspected VHF. Maintain a log of persons entering the patient's room.
- 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.
- If the patient requires a surgical or obstetric procedure, consult with SFDPH regarding appropriate precautions for these invasive procedures.
- Although transmission by the airborne route has not been established, hospitals may choose to use **Airborne Precautions** for patients with suspected VHF who have severe pulmonary involvement or who undergo procedures that stimulate coughing and promote the generation of aerosols.

### **Decontamination**

Persons with percutaneous or mucocutaneous exposures to blood, body fluids, secretions, or excretions from a patient with suspected VHF should immediately wash the affected skin surfaces with soap and water. Mucous membranes should be irrigated with copious amounts of water or eyewash solution. Exposed persons should receive medical evaluation and monitoring.

Hemorrhagic fever viruses have lipid envelopes and are not environmentally stable; therefore, these viruses would not be expected to persist in the environment following a bioterrorist attack. Decisions about decontamination of the environment following an intentional release would depend upon the specific events surrounding the attack.

In the healthcare setting, environmental surfaces, inanimate contaminated objects, or contaminated equipment should be disinfected with an approved hospital disinfectant or a 1:100 dilution of household bleach using standard procedures. For grossly soiled surfaces, (e.g., vomitus or stool), a 1:10 dilution of household bleach should be used. Contaminated linens should be incinerated, autoclaved, or placed in labeled, leak-proof bags at the site of use and washed without sorting in a normal hot water cycle with bleach. Hospital housekeeping staff and linen handlers should wear appropriate personal protective equipment (as outlined in the section on isolation practices above) when handling or cleaning potentially contaminated material or surfaces. Contaminated stool, fluids, and secretions can be managed per standard procedures, since VHF viruses are not likely to survive standard US sewage treatment.

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## REFERENCES

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