

**Outline**

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**Immediately report** any suspected or confirmed cases of viral hemorrhagic fevers to:

**SFDPH Communicable Disease Control  
(24/7 Tel: 415-554-2830)**

- By law, health care providers must report suspected or confirmed cases of viral hemorrhagic fever to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

**Also notify your:**

- Infection Control Professional  
Clinical Laboratory

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## INTRODUCTION

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Viral hemorrhagic fevers (VHFs) refer to a group of illnesses caused by several families of viruses, including:

- **Filoviridae** (Ebola and Marburg viruses)
- **Arenaviridae** (Lassa fever and New World hemorrhagic fever)
- **Bunyaviridae** (Rift Valley fever, Crimean-Congo fever, and "agents of hemorrhagic fever with renal syndrome")
- **Flaviviridae** (yellow fever, Omsk hemorrhagic fever, Kyasanur Forest disease, and dengue)

Many VHF viruses are virulent, and some are highly infectious (e.g., filoviruses and arenaviruses) with person-to-person transmission from direct contact with infected blood and bodily secretions. Effective therapies and prophylaxis are extremely limited for VHF; therefore, early detection and strict adherence to infection control measures are essential.

The Working Group for Civilian Biodefense considers some hemorrhagic fever viruses to pose a more serious threat as potential biological weapons based on risk of morbidity and mortality, feasibility of production, and ability to cause infection through aerosol dissemination. These include Ebola, Marburg, Lassa fever, New World arenaviruses, Rift Valley fever, yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease.<sup>1</sup> Therefore, this chapter will focus only on these VHF viruses and will not include a discussion of dengue fevers, hemorrhagic fever with renal syndrome (e.g., hantavirus), and Crimean-Congo hemorrhagic fevers.

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

Of the potential ways in which VHF could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes.

**An intentional release of a VHF virus would have the following characteristics:**<sup>2</sup>

- Multiple similarly presenting cases clustering in time:
  - acute nonspecific febrile illness with onset 2 to 21 days after the initial release (may include fever, myalgias, rash, and encephalitis)
  - severe illness with a fever and hemorrhagic manifestations
- Atypical host characteristics: unexpected, unexplained cases of acute illness in previously healthy persons, or people with hemorrhagic symptoms who have no conditions predisposing for hemorrhagic illness
- Unusual geographic clustering: cases occurring in an area where naturally occurring VHF is not endemic
- Absence of risk factors: patients lack VHF exposure risk factors (e.g., travel to a VHF endemic country such as South America, Africa, or Asia; handling animal carcasses; contact with people sick with VHF).

In the event of an intentional release, some VHF could infect susceptible animals and potentially lead to establishment of the disease in the environment.

### **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. Epidemiologic characteristics for each virus are described in the tables below.

**EPIDEMIOLOGIC CHARACTERISTICS OF VHF VIRUSES**

Virus		Worldwide Occurrence	Reservoir/ Vector	Transmission
Filoviruses	<b>Ebola</b>	<ul style="list-style-type: none"> <li>Identified in 1976 during outbreaks in the Democratic Republic of Congo (formerly known as Zaire) and Sudan. Four species of Ebola virus are recognized and named after the region where they were discovered: Ivory Coast, Sudan, Zaire, and Reston</li> <li>Reported cases of naturally occurring infections have occurred in Africa: Democratic Republic of Congo (1976, 1995), Sudan (1976, 1979, 2004), Gabon (1994, 1996, 2001-02), Ivory Coast (1994), Uganda (2000-01), Republic of Congo (2001-02, 2003-04, 2005)</li> <li>Laboratory-acquired infections have occurred in England (1976)</li> <li>Ebola has been introduced to quarantine facilities in United States (1989, 1990, 1996), Italy (1992), Philippines (1996)</li> </ul>	unknown <sup>A</sup> / unknown	<p>Person-to-person transmission<sup>B</sup> occurs via:</p> <ul style="list-style-type: none"> <li>Contact with blood, secretions, or tissue of infected patient<sup>C</sup> (sexual transmission may occur up to 3 months after clinical illness ends)</li> <li>Contact with cadaver</li> <li>Airborne transmission (suspected)</li> <li>Parenteral inoculation (unsterilized needles, accidental needle sticks)</li> <li>Contact with blood, secretions, or tissue of infected nonhuman primate</li> <li>Exposure in laboratory</li> </ul>
	<b>Marburg</b>	<ul style="list-style-type: none"> <li>Identified in 1967 in Germany when laboratory staff handling tissues from African green monkeys became infected</li> <li>Reported cases of naturally occurring infections have occurred in: South Africa<sup>D</sup> (1975), Western Kenya (1987, 1980), Democratic Republic of Congo (1998-2000), Angola (2004-2005)</li> <li>Laboratory-acquired infections have occurred in Germany (1967)</li> </ul>	unknown <sup>E</sup> / unknown	<ul style="list-style-type: none"> <li>Exposure in laboratory</li> </ul>
Arenaviruses	<b>Lassa</b>	<ul style="list-style-type: none"> <li>Identified in 1969 in Nigeria</li> <li>Lassa fever is endemic in West African countries between Nigeria and Senegal. There are an estimated 100,000-300,000 annual infections in West Africa. Nosocomial outbreaks and endemic transmission are more common during the dry season (January – April). Outbreaks have occurred in Sierra Leone, Guinea, Liberia, and Nigeria.</li> <li>Lassa fever is occasionally imported to other countries through travel</li> </ul>	multimammate mouse/ none	<ul style="list-style-type: none"> <li>Inhalation of aerosols of rodent excreta,</li> <li>Ingestion of food contaminated with rodent excreta</li> <li>Contact of rodents OR rodent excreta with open skin or mucous membranes</li> </ul> <p>Person-to-person transmission via:</p> <ul style="list-style-type: none"> <li>Contact with infectious blood and bodily fluids</li> <li>Parenteral inoculation (unsterilized needles accidental needlesticks)</li> <li>Airborne transmission (suspected)</li> <li>Exposure in laboratory</li> </ul>
	<b>New World HF</b>	<ul style="list-style-type: none"> <li>New World HFs (or South American HF) include Junin, Machupo, Guanarito, and Sabia</li> <li>Reported cases of naturally occurring infections have occurred in South America: Argentina, Bolivia, Venezuela, Brazil</li> <li>An additional New World HF, Whitewater Arroyo, was isolated from 3 cases in California</li> </ul>	rodents (mouse, wood rat)/ none	<ul style="list-style-type: none"> <li>Exposure in laboratory</li> </ul>

Bunyavirus	<b>Rift Valley Fever</b>	<ul style="list-style-type: none"> <li>Reported cases of naturally occurring infections have occurred in Sub-Saharan Africa, Egypt (1977-8, 1993), Kenya &amp; Somalia (1997-8), Saudi Arabia (2000-01), Yemen (2000-01), Tanzania (2006)<sup>3</sup></li> </ul>	ruminants (sheep, cattle, goats, buffalo)/ mosquito	<ul style="list-style-type: none"> <li>Bite of an infected mosquito</li> <li>Direct contact with infected animal tissue (ruminants)</li> <li>Inhalation of aerosol from infected animal carcasses (ruminants)</li> <li>Transmission by ingestion of contaminated raw animal milk (suspected)</li> <li>Exposure in laboratory</li> </ul>
	<b>Yellow Fever</b>	<ul style="list-style-type: none"> <li>Yellow fever is endemic in Sub-Saharan Africa and tropical regions of South America (mostly in forested regions). From 2000-2004 there were 2570 cases reported in Africa and 629 in South America.<sup>4</sup></li> <li>Most outbreaks occur in: <ul style="list-style-type: none"> <li>West Africa and Central Africa – in Savanna zones during the rainy season</li> <li>Urban and Jungle regions of sub-Saharan Africa</li> <li>South America – forested areas of Bolivia, Brazil, Columbia, Ecuador, Peru, Venezuela, French Guiana, Guyana</li> </ul> </li> </ul>	primate/ <i>Aedes</i> and <i>Haemagogus</i> mosquitoes	<ul style="list-style-type: none"> <li>Bite of an infected mosquito</li> <li>Exposure in laboratory</li> </ul>
Flavivirus	<b>Kyasanur Forest disease virus</b>	<ul style="list-style-type: none"> <li>First identified in 1957 from a sick monkey from the Kyasanur forest in the Karnataka State, India. Recently, a similar virus was discovered in Saudi Arabia.</li> <li>Kyasanur Forest disease is only found in the Karnataka State in India, where 400-500 cases are reported annually.<sup>5</sup></li> </ul>	Vertebrates <sup>F</sup> / Tick <sup>G</sup>	<ul style="list-style-type: none"> <li>Bite of an infected tick;</li> <li>Inhalation of aerosols by laboratory workers during cultivation of these viruses</li> </ul>
	<b>Omsk HF</b>	<ul style="list-style-type: none"> <li>Omsk HF (OHF) was first identified in 1947 in Omsk, Russia. Epizootics began occurring in western Siberia among newly introduced muskrats (for fur trade) and caused large outbreaks in humans from 1945-1958.<sup>6</sup></li> <li>Cases of Omsk HF have been reported in central Asia (western Siberian regions of Omsk, Novosibirsk, Kurgan, Tyumen). From 1988-1997, there were 165 cases of Omsk reported from these regions.<sup>7, 8</sup> Naturally occurring infections peak in spring/early summer and autumn.<sup>6</sup> Few cases have occurred in recent years.<sup>9</sup></li> </ul>	rodents (vole, muskrat) – possibly water-borne/tick	<ul style="list-style-type: none"> <li>Bite of an infected tick</li> <li>Contact with blood, secretions, or tissue of an infected animal</li> <li>Inhalation of aerosols by laboratory workers during cultivation of these viruses</li> <li>Ingestion of contaminated raw goat milk</li> <li>Waterborne (suspected)</li> <li>Airborne (suspected)</li> </ul>

<sup>A</sup> Fruit bats are currently a candidate reservoir. Asymptomatic infections occur in bats within the geographical range of human Ebola outbreaks.<sup>10</sup>

<sup>B</sup> The initial transmission of Marburg and Ebola viruses from animals to humans is not understood.

<sup>C</sup> Risk of transmission is greatest during the latter stages of illness when viral loads are highest, while transmission rarely (if ever) occurs before the onset of symptoms.

<sup>D</sup> Case most likely exposed in Zimbabwe, traveling nurse also became infected.

<sup>E</sup> Fruit bats are currently a candidate reservoir. Serological evidence of infections has been noted in fruit bats in the areas of human Marburg cases.<sup>11</sup>

<sup>F</sup> Not well understood – vertebrate hosts include: rodents, bats, small mammals, monkeys

<sup>G</sup> Not well understood

## OCCURRENCE OF VHF VIRUSES IN THE UNITED STATES

Virus	United States Occurrence
<b>Ebola</b>	Ebola-Reston virus has been introduced into quarantine by monkeys imported from the Philippines on three occasions. In two of the three incidents (1989, 1990), four humans were infected with Ebola-Reston but did not become ill (developed antibodies).
<b>Marburg</b>	NA
<b>Lassa Fever</b>	Lassa fever is rarely encountered in the United States. In 2004, a case of imported Lassa fever occurred in a New Jersey resident who became infected while traveling in West Africa. None of the contacts of the patient developed any symptoms compatible with Lassa fever within the incubation period. This was the first reported case of Lassa fever imported into the United States since 1989. <sup>12</sup>
<b>New World HF</b>	Three cases of Whitewater Arroyo virus were reported in California in 1999-2000; all were fatal. Whitewater Arroyo has been isolated from woodrats in North America, but these were the first reported cases of human disease.
<b>Rift Valley virus</b>	NA
<b>Yellow Fever</b>	Virus spread from West Africa to United States through slave trade vessels, caused significant outbreaks, including: <ul style="list-style-type: none"> <li>• Philadelphia (1793) – 10% of population died</li> <li>• Mississippi (1878) – 100,000 cases</li> </ul> <p>Yellow fever has been imported into the United States by non-immunized travelers to yellow-fever endemic countries 3 times since 1924:</p> <ul style="list-style-type: none"> <li>• 1996 (Brazil to Tennessee)<sup>13</sup></li> <li>• 1999 (Venezuela to Marin County, CA)<sup>4</sup></li> <li>• 2002 (Brazil to Texas)<sup>14</sup></li> </ul> <p>All cases were fatal</p>
<b>Kyasanur Forest disease virus</b>	NA
<b>Omsk HF</b>	NA

## CLINICAL FEATURES

The clinical features of VHF vary according to the virus and are detailed by disease below. However, in the case of bioterrorism, the virus may not initially be known; therefore, clinical features of VHFs, in general, are also provided.

### CLINICAL FEATURES OF VIRAL HEMORRHAGIC FEVER<sup>A</sup>

<b>Early Signs</b>	<ul style="list-style-type: none"> <li>• High fever, headache, malaise, fatigue, arthralgias/ myalgias, prostration, nausea, abdominal pain, nonbloody diarrhea</li> <li>• Mild hypotension, relative bradycardia, tachypnea, conjunctival involvement , pharyngitis, rash or flushing</li> </ul>
<b>Progression (1-2 weeks)</b>	<ul style="list-style-type: none"> <li>• Hemorrhagic manifestations (e.g., petechiae, hemorrhagic or purpuric rash, epistaxis, hematemesis, melena, hemoptysis, hematochezia, hematuria)</li> <li>• CNS dysfunction (e.g., delirium, convulsions, cerebellar signs, coma)</li> <li>• Hepatic involvement (e.g., jaundice, hepatitis)</li> </ul>
<b>Complications and Sequelae</b>	<ul style="list-style-type: none"> <li>• Shock, DIC, multi-system organ failure</li> <li>• Illness-induced abortion in pregnant women</li> <li>• Transverse myelitis</li> <li>• Uveitis</li> <li>• Pericarditis</li> <li>• Orchitis</li> </ul>

	<ul style="list-style-type: none"> <li>• Parotitis</li> <li>• Pancreatitis</li> <li>• Hearing or vision loss</li> <li>• Impaired motor coordination</li> <li>• Convalescence may be prolonged or complicated by weakness, fatigue, anorexia, cachexia, alopecia, arthralgias</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Leukopenia (except in Lassa)</li> <li>• Leukocytosis</li> <li>• Thrombocytopenia</li> <li>• Elevated liver enzymes</li> <li>• Anemia or hemoconcentration</li> <li>• Coagulation abnormalities (e.g., prolonged bleeding time, prothrombin time, and activated partial thromboplastin time, elevated fibrin degradation products, and increased fibrinogen)</li> <li>• Proteinuria, hematuria, oliguria, and azotemia</li> </ul>
<sup>A</sup> Adapted from <sup>1</sup> CNS, central nervous system; DIC, disseminated intravascular coagulation.	

**Ebola/Marburg:**

Case-fatality of Ebola ranges from 50% to 90% and that for Marburg, from 23% to 70%.

**Considerations for pregnant women:** High mortality from Ebola infection in pregnant women (95.5%), as well as high rates of fetal and neonatal loss (100%) have been reported. <sup>15</sup>

<b>CLINICAL FEATURES OF EBOLA/MARBURG</b>		
<b>Incubation Period</b>	<b>Prominent Clinical Features</b>	<b>Laboratory Findings</b>
<b>2-21 days</b>	<ul style="list-style-type: none"> <li>• Acute onset of fever, myalgias/arthralgias, headache, prostration, fatigue (&lt; 1 week)</li> <li>• Nausea, vomiting, abdominal pain, diarrhea, chest pain, cough, pharyngitis, hiccups</li> <li>• Maculopapular rash (day 5 after symptom onset)</li> <li>• Hemorrhagic manifestations</li> <li>• Photophobia, conjunctival inflammation, lymphadenopathy, hepatitis, pancreatitis (common)</li> <li>• CNS dysfunction</li> <li>• Shock with DIC and organ failure (week 2 after symptom onset)</li> <li>• Complications and sequelae: arthralgias, ocular disease, parotitis, orchitis, hearing loss, pericarditis, transverse myelitis</li> </ul>	<ul style="list-style-type: none"> <li>• Leukopenia (early)</li> <li>• Leukocytosis (late)</li> <li>• Thrombocytopenia (early)</li> <li>• Elevated liver enzymes</li> <li>• Elevated amylase</li> <li>• Lab features of DIC</li> </ul>

**Lassa Fever**

Most people infected with Lassa fever have a mild or subclinical presentation (80%). Severe disease occurs in 12-20%, with overall case-fatality around 1% (10-25% mortality in hospitalized patients). During an outbreak, a clinical combination of fever, pharyngitis, retrosternal pain, and proteinuria was predictive of laboratory-confirmed disease in 70% of cases. Findings associated

with death include hypotension, peripheral vasoconstriction, oliguria, edema, pleural effusions, and ascites. Lassa fever requires a high index of suspicion because clinical features are nonspecific and vary from patient to patient. Recovery generally begins around day 10 but may be accompanied by prolonged weakness and fatigue.<sup>16</sup>

**Considerations for children:** Clinical features of Lassa fever infection in children may be even more difficult to diagnose due because of heterogeneous presentation. One syndrome in children less than 2 years old is marked by severe generalized edema, abdominal distension, and bleeding manifestations (this is associated with high case fatality of 75%.<sup>16</sup>)

**Considerations for pregnant women:** Case-fatality in pregnant women is higher than in nonpregnant women, and risk of death increases in the third trimester (30%). Evacuation of uterus (i.e., delivery, spontaneous abortion, or evacuation of retained products of conception) can significantly reduce risk of death in the pregnant woman. Lassa virus infection leads to a high rate of fetal and neonatal death (>80%).<sup>17</sup>

CLINICAL FEATURES OF LASSA FEVER <sup>A</sup>		
Incubation Period	Prominent Clinical Features	Laboratory Findings
3-16	<ul style="list-style-type: none"> <li>• Gradual onset of fever, weakness, pain, arthralgias</li> <li>• Chest and back pain, exudative pharyngitis, cough, abdominal pain, vomiting (very common)</li> <li>• Diarrhea and proteinuria (common)</li> <li>• Facial and pulmonary edema, mucosal bleeding, pleural effusions, neurological involvement (encephalopathy, coma, seizures), ascites, shock (less common)</li> <li>• Illness-induced abortion among pregnant women</li> </ul> <p>Complications &amp; Sequelae: 8<sup>th</sup> cranial nerve damage with hearing loss, pericarditis</p>	<ul style="list-style-type: none"> <li>• Leukocyte &amp; platelet counts often normal</li> <li>• Elevated liver enzymes may occur</li> </ul>

<sup>A</sup> Adapted from <sup>1, 2, 6</sup>

### **New World Hemorrhagic Fevers**

The New World hemorrhagic fevers (Junin, Machupo, Guanarito, Sabia) have similar clinical features and progression. Mortality ranges from 15% to 30% and recovery generally takes 2-3 weeks. Sequelae are not common.<sup>6</sup>

**Considerations for pregnant women:** Case-fatality from New World Hemorrhagic Fever infection in pregnant women is higher than non-pregnant women. Infection also leads to a high rate of fetal death.<sup>6</sup>

<b>CLINICAL FEATURES OF NEW WORLD HEMORRHAGIC FEVERS<sup>A</sup></b>		
<b>Incubation Period</b>	<b>Prominent Clinical Features</b>	<b>Laboratory Findings</b>
<b>7-12 days (range 5-19)</b>	<ul style="list-style-type: none"> <li>• Gradual onset of fever, malaise, myalgias (especially lower back), pharyngitis</li> <li>• Drowsiness, dizziness, tremor, epigastric pain and/or constipation, photophobia, retro-orbital pain, conjunctivitis, lymphadenopathy, postural hypotension</li> <li>• Hemorrhagic manifestations (e.g., petechial rash [oral and dermal], facial flushing, facial edema, capillary leak syndrome, membrane hemorrhage, narrowing pulse pressure, vasoconstriction)</li> <li>• CNS dysfunction (e.g., hyporeflexia, gait abnormalities, palmomental reflex, tremors, other cerebellar signs)</li> <li>• Shock, coma, seizures</li> </ul>	<ul style="list-style-type: none"> <li>• Leukopenia</li> <li>• Thrombocytopenia</li> <li>• Proteinuria</li> <li>• Rising hematocrit</li> </ul>
<sup>A</sup> Adapted from <sup>1, 2, 6</sup>		

### **Rift Valley Fever**

Rift valley fever (RVF) has not been documented to spread from person to person; however, low titers of virus have been isolated from throat washings. There has been one case where vertical transmission was suspected.<sup>18</sup> Historically the case-fatality estimate of RVF is less than 1%; however, a recent outbreak in Saudi Arabia (2000-01) had an overall case-fatality of 14-17% (33% case fatality in patients admitted to RVF unit because of severe disease). Factors associated with high mortality include hepatorenal failure, severe anemia, hemorrhagic or neurological manifestations, jaundice and shock.<sup>3, 19</sup>

<b>CLINICAL FEATURES OF RIFT VALLEY FEVER<sup>A</sup></b>		
<b>Incubation Period</b>	<b>Prominent Clinical Features</b>	<b>Laboratory Findings</b>
<b>2-6 days</b>	<ul style="list-style-type: none"> <li>• Fever, nausea, vomiting</li> <li>• Abdominal pain, diarrhea, jaundice</li> <li>• CNS dysfunction</li> <li>• Hemorrhagic disease (1-17%)</li> <li>• Ocular involvement (photophobia, retro-orbital pain, retinitis, vision loss, scotoma)</li> <li>• Renal involvement or failure</li> <li>• Shock</li> </ul>	<ul style="list-style-type: none"> <li>• Thrombocytopenia</li> <li>• Leukopenia</li> <li>• Severe anemia</li> <li>• Elevated liver enzymes</li> <li>• Elevated LDH and CK</li> </ul>
<sup>A</sup> Adapted from <sup>1-3, 6, 19</sup>		
CNS, central nervous system; CK, creatine kinase; LDH, lactate dehydrogenase.		

## Yellow Fever

Yellow fever may resolve after a very mild course or may progress to moderate or severe illness (15%) after a short remission. Death occurs in 7-10 days after onset of illness.<sup>2, 6</sup>

CLINICAL FEATURES OF YELLOW FEVER <sup>A</sup>		
Incubation Period	Prominent Clinical Features	Laboratory Findings
3-6 days	Prodrome: <ul style="list-style-type: none"> <li>• Acute onset of fever, headache, myalgias,</li> <li>• Facial flushing, conjunctival injection</li> </ul> Illness may resolve, enter remission (lasts hours or days), or progress to: <ul style="list-style-type: none"> <li>• High fever, headache, severe myalgias (especially back), nausea, vomiting, abdominal pain, weakness, prostration, bradycardia</li> <li>• Hemorrhagic manifestations</li> <li>• Fulminant infection with severe hepatic involvement</li> <li>• Shock, myocardial failure, renal failure, seizures, coma</li> <li>• Pneumonia, sepsis</li> </ul>	<ul style="list-style-type: none"> <li>• Leukopenia (early),</li> <li>• Leukocytosis (late)</li> <li>• Thrombocytopenia</li> <li>• Elevated liver enzymes and bilirubin</li> <li>• Albuminuria</li> <li>• Azotemia</li> <li>• Alkaline phosphatase levels only slightly elevated</li> </ul>

<sup>A</sup>Adapted from:<sup>1, 2, 6</sup>

## Kyasanur Forest disease

Kyasanur Forest disease is characterized by biphasic illness: 50% of patients who go on to develop the second phase with meningoencephalitis. Case-fatality ranges from 3% to 10%.

CLINICAL FEATURES OF KYASANUR FOREST DISEASE		
Incubation Period	Prominent Clinical Features	Laboratory Findings
2-9 days	Phase I (6-11 days): <ul style="list-style-type: none"> <li>• Acute onset of fever, myalgias, headache (6-11 days)</li> <li>• Conjunctival involvement, soft palate lesions, GI symptoms</li> <li>• Hyperemia of face and trunk (but no rash)</li> <li>• Lymphadenopathy</li> <li>• Hemorrhagic manifestations (not severe)</li> </ul> Phase II: <ul style="list-style-type: none"> <li>• Afebrile period of 9-21 days followed by meningoencephalitis (50% of patients)</li> </ul>	<ul style="list-style-type: none"> <li>• Leukopenia</li> <li>• Lymphopenia or lymphocytosis</li> <li>• Thrombocytopenia</li> <li>• Abnormal liver function</li> </ul>

GI, gastrointestinal.

## Omsk Hemorrhagic fever

Omsk hemorrhagic fever (OHF) is similar to Kyasanur Forest disease. Some also characterize OHF as a biphasic illness with the first phase lasting 5-12 days with an estimated 30-50% of patients

going on to experience remission of fever, febrile illness, and more severe disease. Case fatality ranges from 0.5% to 3%. Recovery may take weeks, but sequelae are not common.<sup>1, 7</sup>

CLINICAL FEATURES OF OMSK HEMORRHAGIC FEVER <sup>A</sup>		
Incubation Period	Prominent Clinical Features	Laboratory Findings
3-8 days (range 1-10 days)	<ul style="list-style-type: none"> <li>• Acute onset of fever, headache, myalgias</li> <li>• Cough, conjunctivitis, soft pallet lesions, GI symptoms</li> <li>• Hyperemia of face and trunk (but no rash)</li> <li>• Lymphadenopathy, splenomegaly</li> <li>• Hemorrhagic manifestations (not severe)</li> <li>• Pneumonia, CNS dysfunction, meningeal signs, diffuse encephalitis</li> </ul>	<ul style="list-style-type: none"> <li>• Leukopenia</li> <li>• Thrombocytopenia</li> </ul>
<sup>A</sup> Adapted from <sup>2, 6, 7</sup> CNS, central nervous system; GI, gastrointestinal.		

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## DIFFERENTIAL DIAGNOSIS

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A high index of suspicion is required to diagnose VHF because there are no readily available rapid and specific confirmatory tests. In addition, the VHF viruses can have a nonspecific appearance or resemble a wide range of much more common illnesses.

With a VHF virus used as a biological weapon, patients are less likely to have risk factors for natural infection such as travel to VHF-endemic countries (Africa, Asia, or South America), 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 in several related cases should be highly suspicious for VHF.

The Working Group for Civilian Biodefense suggests considering VHF in any patient with the following clinical presentation:

- Acute onset of fever (<3 weeks duration) in severely ill patient
- Hemorrhagic manifestations (at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other bleeding)
- No conditions predisposing for hemorrhagic illness
- No alternative diagnosis

### Differential Diagnosis—Infectious Conditions (viral, rickettsial, bacterial and parasitic)<sup>1, 2</sup>

- |  |                            |
|--|----------------------------|
| • Gram-negative bacterial septicemia                                       | • influenza                |
| • toxic shock syndrome ( <i>Staphylococcus</i> ,<br><i>Streptococcus</i> ) | • measles                  |
| • meningococemia   | • rubella                  |
| • secondary syphilis   | • dengue hemorrhagic fever |
| • septicemic plague  | • hemorrhagic varicella    |
| • salmonellosis ( <i>Salmonella typhi</i> )                                | • hemorrhagic smallpox     |
|  | • Viral hepatitis          |

- shigellosis
- *Chlamydia* infection
- borreliosis
- leptospirosis
- rickettsiosis
- hantavirus pulmonary syndrome
- malaria
- African trypanosomiasis

Noninfectious Conditions<sup>1, 2</sup>

- thrombotic or idiopathic thrombocytopenic purpura
- acute leukemia
- hemolytic-uremic syndrome
- collagen-vascular diseases

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## LABORATORY DIAGNOSIS AND RADIOGRAPHIC FINDINGS

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Viral hemorrhagic fevers are a risk to laboratory personnel. Clinicians should immediately notify their laboratory, local health department, and infection control professional when VHF is suspected. In the event of an outbreak, public health authorities will provide recommendations for specimen collection based on this situation (e.g., identification of etiologic agent, laboratory capacity).

Diagnosis of VHF requires a high index of suspicion because the disease initially presents with nonspecific symptoms and non-specific results of routine lab tests. Routine laboratory findings for specific HF viruses are listed in the clinical features tables.

A number of test methods can be used to diagnose VHF at specialized laboratories. These include antigen-capture testing by enzyme-linked immunosorbent assay (ELISA), IgM antibody testing, paired acute-convalescent serum serologies, reverse transcriptase polymerase chain reaction (RT-PCR), immunohistochemistry methods, and electron microscopy. Viral identification in cell culture is the gold standard of viral detection; however, this may only be attempted at a Biosafety Level 4 (BSL-4) facility. Combined ELISA Ag/ IgM has high specificity and sensitivity for early diagnosis of Lassa fever and provides prognostic information (presence of indirect fluorescent antibody early in disease associated with death).<sup>20</sup>

**If you are testing or considering testing for viral hemorrhagic fever, you should:**

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that viral hemorrhagic fever is under suspicion.**

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## TREATMENT AND PROPHYLAXIS

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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.sfdcp.org](http://www.sfdcp.org)).

### Treatment

Medical management should follow the guidelines below:

MEDICAL MANAGEMENT RECOMMENDATIONS	
Category	Medical Management
Exposed Persons	Medical Surveillance No post-exposure prophylaxis is recommended <sup>A</sup>
Suspected VHF Case of <u>Unknown Viral Type</u>	Supportive Care + Ribavirin Therapy <sup>B</sup>
Suspected or Confirmed VHF Case known to be <u>caused by an Flavivirus or Filovirus</u>	Supportive Care Only
Suspected Confirmed VHF Case known to be <u>caused by an Arenavirus or Bunyavirus</u>	Supportive Care + Ribavirin Therapy

<sup>A</sup> Previous CDC recommendations state that Ribavirin should be given to high-risk contacts of persons with Lassa fever. The Working Group on Civilian Biodefense recommends medical surveillance only, and notes that the CDC guidelines may be under review.

<sup>B</sup> Ribavirin therapy should be initiated promptly unless another diagnosis is confirmed or the etiologic agent is known to be a Flavivirus or Filovirus.

**Medical Surveillance:** Persons should be instructed to record their temperature twice daily and report any temperature of 38.0°C or 100.4 °F or higher (or any other signs or symptoms) to their clinician and/or the proper public health authorities. Patients should be advised not to share thermometers between family members and to properly disinfect thermometers after each use.

**Supportive Care:** Supportive care, including careful maintenance of fluid and electrolyte balance and circulatory volume is essential for patients with all types of VHF. Mechanical ventilation, dialysis, and appropriate therapy for secondary infections may be indicated. 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 Therapy:** Ribavirin is recommended for: (1) suspect or probable cases of *VHF of unknown viral type* or (2) suspect, probable, or confirmed cases *caused by an Arenavirus or Bunyavirus*. 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 intravenous (IV) ribavirin therapy are shown below. Use of oral ribavirin may be necessary if the number of patients exceeds the medical care capacity for individual medical management.

**RIBAVIRIN THERAPY FOR PATIENTS WITH VHF OF UNKNOWN CAUSE OR CAUSED BY AN ARENAVIRUS OR BUNYAVIRUS<sup>A</sup>**

	<b>IV Therapy in Contained Casualty Situation<sup>B</sup></b>	<b>Therapy in a Mass-Casualty Setting<sup>B</sup></b>
<b>Adult</b>	<p><b>Ribavirin,</b></p> <ul style="list-style-type: none"> <li>• Loading dose 30 mg/kg (max 2 gm) IV,</li> </ul> <p>Followed by:</p> <ul style="list-style-type: none"> <li>• 16 mg/kg (max 1 gm) IV q6 hr for 4 days,</li> </ul> <p>Followed by:</p> <ul style="list-style-type: none"> <li>• 8 mg/kg (max 500 mg) IV q8 hr for 6 days</li> </ul>	<p><b>Ribavirin,</b></p> <ul style="list-style-type: none"> <li>• Loading dose of 2000 mg PO,</li> </ul> <p>Followed by:</p> <ul style="list-style-type: none"> <li>• (Weight &gt;75 kg): 1200 mg/day PO in 2 divided doses (600 mg in am and 600 mg in pm) for 10 days<sup>C</sup></li> <li>• (Weight &lt;75 kg): 1000 mg/day PO in divided doses (400 mg in am and 600 mg in pm) for 10 day<sup>C</sup></li> </ul>
<b>Children<sup>D</sup></b>	Same as for adults	<ul style="list-style-type: none"> <li>• Loading dose of 30 mg/kg PO,</li> </ul> <p>Followed by:</p> <ul style="list-style-type: none"> <li>• 15 mg/kg/d PO in 2 divided doses for 10 days</li> </ul>
<b>Pregnant women<sup>E</sup></b>	Same as for non-pregnant adults	Same as for non-pregnant adults

<sup>A</sup> Ribavirin is not labeled for use in treatment of VHF by the US Food and Drug Administration (FDA) for treatment and must be used under an Investigational New Drug (IND) protocol.

<sup>B</sup> Use of oral vs. parenteral treatment will depend on resource availability

<sup>C</sup> The current available formulation of ribavirin is 200-mg capsules, which cannot be broken open.

<sup>D</sup> IV and oral ribavirin are not approved for children by the FDA; however, the benefits may outweigh the risk of ribavirin therapy.

<sup>E</sup> Ribavirin is contraindicated in pregnant women; however, the benefits may outweigh the fetal risk of ribavirin therapy.

Passive immunotherapy with convalescent human plasma has been used in the treatment and prophylaxis of several VHFs with inconclusive results. Some suggest passive immunotherapy for treatment of New World HF based on effectiveness in Argentine HF (Junin).<sup>1, 16, 21, 22</sup>

**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. *High risk* contacts are defined as persons who “have had mucous membrane contact with a patient (such as during kissing or sexual intercourse) or have had percutaneous injury involving contact with a patient’s secretions, excretions, or blood.” *Close contact* is defined as, “those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with VHF prior to initiation of appropriate precautions.”<sup>1</sup> Medical surveillance (see above) is recommended for 21 days following the potential exposure or contact with the ill person.

Previous recommendations from the Centers for Disease Control and Prevention (CDC)<sup>23</sup> state that prophylaxis with ribavirin should be given to persons exposed to Lassa virus. However, because the efficacy of ribavirin prophylaxis for Lassa virus is unknown, the Working Group also recommends that persons exposed be placed under medical surveillance until 21 days after the last exposure.<sup>1</sup> The CDC recommendation is under review.

## Vaccine

A licensed vaccine against yellow fever is effective if given prior to exposure. It is used for travelers going to endemic areas. This vaccine does not prompt development of antibodies rapidly enough to be used in the post-exposure setting. A rare, but serious adverse reaction to yellow fever vaccine, viscerotropic and neurotropic disease, has recently been recognized and reported.<sup>24</sup>

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

### **Developmental VHF Therapeutics**

Additional therapeutic candidates for vaccine, treatment, and prophylaxis of VHFs are currently under development.

<b>DEVELOPMENTAL VHF THERAPEUTICS</b>	
<b>Virus</b>	Candidates for vaccine, treatment, and prophylaxis
<b>Ebola/Marburg</b>	<ul style="list-style-type: none"><li>• A live attenuated recombinant vaccine for Ebola and Marburg HF has produced protective immune responses in non-human primates</li><li>• A vaccine used as a PEP produced some protective effect for Ebola in non-human primates when administered soon after infection (20-30 min)<sup>25</sup></li><li>• A Phase I clinical trial for an Ebola DNA vaccine was safe and produced an immune response in humans</li><li>• Treatment with small interfering RNAs (siRNAs) produced protective immune response in an animal model (guinea pigs)<sup>26</sup></li></ul>
<b>Lassa Fever</b>	<ul style="list-style-type: none"><li>• An attenuated recombinant vaccine produced protective immune responses in non-human primates<sup>27</sup></li></ul>
<b>New World HF</b>	<ul style="list-style-type: none"><li>• Live-attenuated vaccine available as investigational new drug in Argentine HF<sup>28</sup></li><li>• Passive immunotherapy with convalescent human serum has been effective in Argentine HF<sup>16</sup></li></ul>
<b>Rift Valley virus</b>	<ul style="list-style-type: none"><li>• Vaccine available as investigational new drug<sup>29</sup></li></ul>
<b>Yellow Fever</b>	<ul style="list-style-type: none"><li>• Licensed vaccine available (see above)</li></ul>
<b>Kyasanur Forest disease virus</b>	<ul style="list-style-type: none"><li>• Formalin inactivated vaccine licensed and used in endemic areas<sup>30</sup></li></ul>
<b>Omsk HF</b>	<ul style="list-style-type: none"><li>• NA</li></ul>

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## **COMPLICATIONS AND ADMISSION CRITERIA**

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Patients with filovirus infection (Ebola and Marburg viruses) often experience hemorrhagic and severe central nervous system (CNS) manifestations along with fever and jaundice during the first week of illness. In the second week patients defervesce and either improve markedly or die as a result of multiorgan dysfunction, shock, and disseminated intravascular coagulation. Survivors may develop one or more complications including arthralgia, orchitis, hepatitis, transverse myelitis, or uveitis.

Death from Lassa virus infection, when it occurs, is typically during the second week of illness and is associated with hypotension, edema, and capillary leak syndrome. Up to one-third of Lassa

fever survivors develop sensorineural deafness. The arenaviruses (Lassa and New World viruses) share a propensity to cause fetal demise and high mortality rates in pregnant women.

Among the bunyavirus infections (Rift Valley fever and Crimean-Congo hemorrhagic fever), a fulminant, fatal form of the disease with hemorrhage, hepatitis, and organ failure occurs in a minority of patients. Rift Valley fever encephalitis is known to occur in a small percentage of those affected.

Although many infections with yellow fever are clinically inapparent, patients may develop multisystem illness dominated by an icteric hepatitis and a severe bleeding diathesis. In the latter stages of illness encephalopathy, shock, and death may ensue. Patients who recover frequently suffer from secondary bacterial infections.

The need for hospitalization and life support will be apparent in patients with bleeding diatheses, CNS dysfunction, shock, or severe hepatorenal dysfunction. Patients exhibiting milder manifestations of VHF or who appear to be in the early stages of disease could benefit from hospitalization for supportive care and close observation. Treatment with intravenous ribavirin should be initiated in patients known to have arenavirus or bunyavirus infection and in those with VHF of unknown etiology pending viral identification.

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## INFECTION 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.sfcddcp.org](http://www.sfcddcp.org)).

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected VHF cases. Public health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public.

Many VHF viruses are virulent, and some are highly infectious (e.g., filoviruses and arenaviruses) with *person to person transmission* from direct contact with infected blood and bodily secretions. Effective therapies and prophylaxis are extremely limited for VHF; therefore, early detection and strict adherence with infection control measures are essential. Transmission rarely (if ever) occurs before the onset of symptoms. Risk of transmission is greatest during the latter stages of illness when viral loads are highest.

Among household contacts, secondary transmission for Ebola and Marburg ranges from 10 to 20%. In the 1995 Ebola outbreak in the Democratic Republic of Congo, transmission did not occur among household contacts with no direct physical contact with patients. Persons with physical contact

with patients were at increased risk of transmission, and those with body fluid contact had the greatest risk.<sup>31, 32</sup>

Guidance on infection control precautions have been published by both the CDC and the Working Group for Civilian Biodefense in 2005 and 2002 respectively; these contained some inconsistencies.<sup>1, 33</sup> More recent guidance was provided by the CDC's Healthcare Infection Control Practices Advisory Committee.<sup>34</sup>

For patients infected or suspected to be infected with VHF healthcare workers and visitors should use Standard, Contact and Droplet Precautions with eye protection. Single gloves are adequate for routine patient care; double-gloving is advised during invasive procedures (e.g., surgery) that pose an increased risk for blood exposure. Routine eye protection (i.e. goggles or face shield) is particularly important. Fluid-resistant gowns should be worn for all patient contact. Airborne Precautions are not required for routine patient care; however, use of airborne infection isolation room (AIIR) is prudent when procedures that could generate infectious aerosols are performed (e.g., endotracheal intubation, bronchoscopy, suctioning, autopsy procedures involving oscillating saws). N95 or higher level respirators may provide added protection for individuals in a room during aerosol-generating procedures. When a patient with a syndrome consistent with hemorrhagic fever also has a history of travel to an endemic area, precautions are initiated upon presentation and then modified as more information is obtained. Patients with hemorrhagic fever syndrome in the setting of a suspected bioweapon attack should be managed using Airborne Precautions, including AIIRs, since the epidemiology of a potentially weaponized hemorrhagic fever virus is unpredictable.<sup>34</sup>

All persons exposed to 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.

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## PEARLS AND PITFALLS

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1. Since effective postexposure prophylaxis is unavailable for VHF, strict adherence to infection control measures is essential for limiting the spread of disease.
2. The risk for person-to-person transmission of VHF is highest during the latter phases of illness, when viral loads are high and disease manifestations are most severe.
3. VHF viruses are not endemic in the United States, with the rare exception of Whitewater Arroyo virus which caused three cases of human disease in California in 1999-2000 and may have been related to wild rodents. Nearly all U.S. cases of VHF have been acquired by overseas travelers or by scientific research personnel.

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