

## 10-ID-19

**Title:** Update to Viral Hemorrhagic Fever (VHF) Case Definition

### I. Statement of the Problem

Viral Hemorrhagic Fever (VHF), caused by Ebola or Marburg viruses, Lassa virus, new world Arenaviruses (Guanarito, Machupo, Junin, Sabia), or Crimean Congo hemorrhagic fever, was added to the Nationally Notifiable Condition list in June of 2009. That position statement contained inconsistencies in case classification criteria between narrative and table in Section VII. In addition, a previously unknown old world Arenavirus (Lujo virus) was identified as the cause of a nosocomial outbreak in South Africa and Zambia during 2008 (17). This Position Statement corrects errors in the 2009 position statement and recommends addition of Lujo virus to those reportable under this case definition.

### II. Background and Justification

#### *Background*<sup>1</sup>

Viral hemorrhagic fevers are a group of febrile illnesses caused by several distinct families of viruses, all of which are enveloped and have RNA genomes. The group includes the filoviruses, Ebola virus and Marburg virus), old-world arenaviruses (Lassa virus and Lujo virus), the new-world arenaviruses (Guanarito, Machupo, Junin, and Sabia viruses), and Rift Valley fever and Crimean Congo hemorrhagic fever viruses. Humans are not the natural reservoir for any of these viruses, and human cases or outbreaks of hemorrhagic fevers caused by these viruses occur sporadically and irregularly (with the exception of Lassa virus and Junin virus, with infections occur with more regularity in endemic areas). Humans are initially infected via transmission from a zoonotic host. However, most VHF are capable of human-to-human transmission and can cause outbreaks of human disease. Although some types cause relatively mild illnesses, many of these viruses can cause severe, life-threatening disease. Severe illness is characterized by vascular damage and increased permeability, multi-organ failure, and shock. This position statement addresses hemorrhagic fevers caused by two filoviruses (Ebola and Marburg viruses), old-world arenaviruses (Lassa virus and Lujo virus), new-world arenaviruses (Guanarito, Machupo, Junin, and Sabia viruses) and Crimean Congo hemorrhagic virus. Two other related syndromes—hantavirus pulmonary syndrome and yellow fever—are addressed in their own position statements.

Ebola and Marburg are filoviruses that belong to the family *Filoviridae* and can cause severe hemorrhagic fever in humans and nonhuman primates. Confirmed cases of Ebola hemorrhagic fever have been reported in the Republic of Congo, Côte d'Ivoire, Liberia, Democratic Republic of Congo, Gabon, Sudan, and Uganda. Occupational infection of laboratory workers resulting from needle-stick injury has occurred in England and Russia. Marburg virus is also indigenous to Africa. Although the precise geographic range for Marburg virus is unknown, it includes at least

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<sup>1</sup> Much of the material in the background is directly quoted from Rollin and Ksiazek's sub-chapter on viral hemorrhagic fevers in *Health Information for International Travel 2008*. See the References for further information on this source.

parts of Uganda, western Kenya, Zimbabwe, the Democratic Republic of Congo, and Angola. Nosocomial transmission of Marburg virus also occurred in South Africa. The reservoir hosts for Ebola and Marburg viruses have not yet been fully characterized; however, strong virologic, molecular, and serologic data suggest that fruit bats are an important host for these viruses. Outbreaks can occur when a patient infected through zoonotic exposure transmits the virus to other close human contacts. Person-to-person transmission is often amplified in the health-care setting.

The Arenaviridae are a family of viruses whose members are generally associated with rodent-transmitted disease in humans. Each virus usually is associated with a particular rodent host species in which it is maintained. Arenavirus infections are relatively common in humans in some areas of the world and can cause severe illnesses. Pathogenic arenaviruses include the some old-world arenaviruses (Lassa virus and Lujo virus) and new-world arenaviruses (Guanarito, Machupo, Junin, and Sabia). Human infection occurs through exposure to excretions of infected rodents. Some arenavirus infections are associated with secondary person-to-person transmission, especially in health care settings.

Although most Lassa virus infections are mild, some are severe, causing a hemorrhagic fever that is often fatal. Lassa fever is limited to rural areas of West Africa, with hyper-endemic areas in eastern Sierra Leone, Guinea, Liberia, and Nigeria. Peridomestic exposure to infected rodents is the most likely source of human infection. Transmission to humans can occur via inhalation of primary aerosols from rodent urine, by ingestion of rodent-contaminated food, or by direct contact of broken skin with rodent excreta. Rodent infestation facilitated by inappropriate food storage increases the risk of human infection. Person-to-person spread of Lassa virus has also been described, most notably by large droplet and contact transmission in the hospital setting. Airborne transmission is not believed to be an important route of infection from person to person. Laboratory handling of infectious specimens and contact with contaminated medical equipment are also associated with transmission. Numerous instances of imported Lassa fever among travelers from West Africa to the US or Europe have been documented. Most recently, in January 2010, a case of Lassa fever was identified in a patient in Pennsylvania, who had recent travel to Liberia

In 2008, a new arenavirus was identified as cause of a South African outbreak involving five human cases, four of which were fatal. The index case infection apparently occurred in Zambia from an unknown source with nosocomial transmission to the other 4 human cases (3 health care workers, 1 other contact). This new virus, Lujo virus, is classified as an old-world arenavirus and is distantly related to Lassa virus.

Crimean-Congo hemorrhagic fever (CCHF) is caused by infection with a tick-borne virus (*Nairovirus*) in the family *Bunyaviridae*. Crimean-Congo hemorrhagic fever is found in Eastern Europe, particularly in the former Soviet Union and throughout the Mediterranean, in northwestern China, central Asia, southern Europe, Africa, the Middle East, and the Indian subcontinent. Ixodid (hard) ticks, especially those of the genus, *Hyalomma*, are both a reservoir and a vector for the CCHF virus. Numerous wild and domestic animals, such as cattle, goats, sheep and hares, serve as amplifying hosts for the virus. Transmission to humans occurs through contact with infected animal blood or ticks. CCHF can be transmitted from one infected human

to another by contact with infectious blood or body fluids. Documented spread of CCHF has also occurred in hospitals due to improper sterilization of medical equipment, reuse of injection needles, and contamination of medical supplies.

Because of their potential for high mortality rates in infected persons and their potential for transmission from person to person, Lassa virus and some other arenaviruses and filoviruses causing viral hemorrhagic fever have been designated as category A bioterrorism agents.

### *Justification*

Viral hemorrhagic fever meets the definition of a nationally and **immediately** notifiable condition—as specified in CSTE position statement 08-EC-02—for the following reason(s):

- The condition has special importance for international health regulations (IHR).
- The condition is included on the list of Category A bioterrorism agents and toxins.
- A majority of state and territorial jurisdictions—or jurisdictions comprising a majority of the US population—have laws or regulations requiring **immediate** reporting of viral hemorrhagic fever to public health authorities.
- The Centers for Disease Control and Prevention (CDC) requests **immediate-extremely urgent** notification of any cases of viral hemorrhagic fever suspected of being intentional. For all other cases of viral hemorrhagic fever, notification will be **immediate-urgent**. The CDC has condition-specific policies and practices concerning its response to and use of notifications.

### **III. Statement of the desired action(s) to be taken**

- 1) Viral hemorrhagic fever caused by Ebola or Marburg viruses, Lassa virus, Lujo virus, new world Arenaviruses (Guanarito, Machupo, Junin, Sabia), or Crimean-Congo hemorrhagic fever should be added to the Nationally Notifiable Condition list.
- 2) CSTE requests that CDC adopt this standardized reporting definition for viral hemorrhagic fever to facilitate more timely, complete, and standardized local and national reporting of this condition.

### **IV. Goals of Surveillance**

To provide information on the temporal, geographic, and demographic occurrence of viral hemorrhagic fever to facilitate its prevention and control.

### **V. Methods for Surveillance:**

Surveillance for viral hemorrhagic fever should use the following recommended sources of data and the extent of coverage listed in Table V.

**Table V.** Recommended sources of data for case identification and extent of coverage for ascertaining cases of viral hemorrhagic fever.

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
clinician reporting	x	
laboratory reporting	x	
reporting by other entities (e.g., hospitals, veterinarians, pharmacies)	x	
death certificates	x	
hospital discharge or outpatient records	x	
extracts from electronic medical records	x	
telephone survey		
school-based survey		
other _____		

## VI. Criteria for case identification

### A: Narrative: A description of suggested criteria that may be for case ascertainment of a specific condition.

Report any illness to public health authorities that meets any of the following criteria:

1. A person for whom a diagnostic test specific for VHF has been ordered.
2. A person with ALL of the following findings:
  - a fever > 40°C;
  - one or 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
    - pharyngitis (arenavirus only)
    - diarrhea
    - bleeding not related to injury
    - thrombocytopenia
    - proteinuria (arenavirus only)
    - retrosternal chest pain (arenavirus only)
  - one or more of the following epidemiological risk factors:
    - contact within the past 3 weeks with blood or other body fluids of a patient with VHF
    - residence in—or travel within the past 3 weeks to—a VHF endemic area

- work within the past 3 weeks in a laboratory that handles VHF specimens
- work within the past 3 weeks in a laboratory that handles bats, rodents, or primates from endemic areas
- exposure within the past 3 weeks to semen from a confirmed acute or convalescent case of VHF within 10 weeks of the person’s onset of illness

4. A person whose death certificate lists VHF (i.e., Ebola, Lassa, Lujo, Marburg, new world Arenavirus, or Crimean-Congo hemorrhagic fever) as a cause of death or a significant condition contributing to death.

*Other recommended reporting procedures*

- All cases (suspected or confirmed) of viral hemorrhagic fever should be reported.
- Reporting should be ongoing and routine.
- Reporting should be immediate.

**B. Table of criteria to determine whether a case should be reported to public health authorities:**

**Table VI-B.** Table of criteria to determine whether a case should be reported to public health authorities. Requirements for reporting are established under State and Territorial laws and/or regulations and may differ from jurisdiction to jurisdiction. These criteria are suggested as a standard approach to identifying cases of this condition for purposes of reporting, but reporting should follow State and Territorial law/regulation if any conflicts occur between these criteria and those laws/regulations.

Criterion	Reporting
<i>Clinical Evidence</i>	
fever (> 40°C)	N
severe headache	O
muscle pain	O
erythematous maculopapular rash on the trunk with fine desquamation 3–4 days after rash onset	O
retrosternal chest pain	O1
pharyngitis (sore throat)	O1
Vomiting	O
Diarrhea	O
bleeding not related to injury	O
Proteinuria	O1
Thrombocytopenia	O
healthcare record contains a diagnosis of viral hemorrhagic fever	S

death certificate lists viral hemorrhagic fever as a cause of death or a significant condition contributing to death	S
<i>Laboratory Evidence</i>	
detection of VHF viral antigens in blood or tissues by ELISA	S*
VHF viral isolation in cell culture from blood or tissues	S*
detection of VHF-specific genetic sequence by RT-PCR from blood or tissues	S*
Detection of VHF viral antigens in tissues by immunohistochemistry	S*
Detection of IgM or IgG in blood by ELISA	S*
<i>Epidemiological Evidence</i>	
contact with blood or other body fluids of a patient with VHF within the past 3 weeks	O
residence in—or travel within the past 3 weeks to—a VHF endemic area	O
work within the past 3 weeks in a laboratory that handles VHF specimens	O
work within the past 3 weeks in a laboratory that handles bats, rodents, or primates from endemic areas	O
exposure within the past 3 weeks to semen from a confirmed acute or convalescent VHF case within 10 weeks of the person's onset of illness	O

Notes:

VHF = viral hemorrhagic fever caused by Ebola, Lassa, Lujo or Marburg virus, a new world arenavirus or Congo-Crimean hemorrhagic fever.

S = This criterion alone is sufficient to report a case

O = At least one of any “O” criteria in each category (e.g., clinical presentation and epidemiologic evidence) —in conjunction with all other “N” criteria—is required to report a case. A number following an “O” indicates that this criterion only applies to a specific virus causing VHF (see below).

1 = Additional criteria that apply only to the Arenaviruses (Lassa, Lujo or new world arenaviruses including Junin, Machupo, Sabia, or Guanarito)

\* A requisition or order for any of the “S” or “N” laboratory tests is sufficient to meet the reporting criteria.

### C. Disease Specific Data Elements:

Disease-specific data elements to be included in the initial report are listed below.

Epidemiologic:

contact within the past 3 weeks with blood or other body fluids of a patient with VHF

residence in—or travel within the past 3 weeks to—a VHF endemic area

work within the past 3 weeks in a laboratory that handles VHF specimens

work within the past 3 weeks in a laboratory that handles bats, rodents, or primates from endemic areas  
exposure within the past 3 weeks to semen from a confirmed acute or convalescent case of VHF within 10 weeks of the person's onset of illness

## **VII. Case Definition for Case Classification**

### **A. Narrative: Description of criteria to determine how a case should be classified.**

#### *Clinical presentation criteria*

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

- fever > 40°C
- one or 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 (Arenaviruses only)
  - abdominal pain
  - bleeding not related to injury
  - retrosternal chest pain (Arenaviruses only)
  - proteinuria (Arenaviruses only)
  - thrombocytopenia

#### *Laboratory criteria for diagnosis*

One or more of the following laboratory findings:

- detection of VHF viral antigens in blood by ELISA antigen detection
- VHF viral isolation in cell culture for blood or tissues
- detection of VHF-specific genetic sequence by RT-PCR from blood or tissues
- detection of VHF viral antigens in tissues by immunohistochemistry

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

#### *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 area
- exposure to semen from a confirmed acute or convalescent case of VHF within the 10 weeks of that person's onset of symptoms

*Case classification*

Suspected: Case meets the clinical and epidemiologic linkage criteria

Confirmed: Case meets the clinical and laboratory criteria

**B. Classification Tables**

**Table VII-B.** Criteria for defining a case of viral hemorrhagic fever.

Criterion	Confirmed	Suspected
<i>Clinical Evidence</i>		
fever (> 40°C)	N	N
severe headache	O	O
muscle pain	O	O
erythematous maculopapular rash on the trunk with fine desquamation 3–4 days after rash onset	O	O
retrosternal chest pain	O1	O1
pharyngitis (sore throat)	O1	O1
vomiting	O	O
diarrhea	O	O
abdominal pain	O	O
bleeding not related to injury	O	O
proteinuria	O	O1
thrombocytopenia	O	O
<i>Laboratory Evidence</i>		
detection of VHF viral antigens in blood or tissues by ELISA antigen detection	S	
VHF viral isolation in cell culture from blood or tissues	S	
detection of VHF-specific genetic sequence by RT-PCR from blood or tissues	S	
Detection of VHF viral antigens in tissues by immunohistochemistry	S	

<i>Epidemiological Evidence</i>		
contact with blood or other body fluids of a patient with VHF within the past 3 weeks		O
residence in—or travel within the past 3 weeks to—a VHF endemic area		O
work within the past 3 weeks in a laboratory that handles VHF specimens		O
work within the past 3 weeks in a laboratory that handles bats, rodents, or primates from endemic areas		O
exposure within past 3 weeks to semen from a confirmed acute or convalescent VHF case within 10 weeks of onset of illness		O

Notes:

VHF = viral hemorrhagic fever caused by Ebola, Lassa, Lujo or Marburg virus, a new world Arenavirus, or Congo-Crimean hemorrhagic fever.

S = This criterion alone is sufficient to classify a case

N = All “N” criteria in the same column—in conjunction with at least one of any “O” criteria in each category (e.g., clinical presentation and laboratory findings) in the same column—are required to classify a case. A number following an “N” indicates that this criterion is only required for a specific clinical presentation (see below).

O = At least one of any “O” criteria in each category (e.g., clinical presentation and laboratory findings) in the same column—in conjunction with all other “N” criteria in the same column—is required to classify a case. A number following an “O” indicates that this criterion is only required for a specific clinical presentation (see below).

1 = Additional criteria that apply only to Arenavirus (Lassa, Lujo or new world arenaviruses, including Junin, Machupo, Sabia, Guanarito)

### VIII. Period of Surveillance

Surveillance should be ongoing. This revision to the surveillance case definition will be effective January 1, 2011.

### IX. Data sharing/release and print criteria

- Notification to CDC should be **immediate-extremely urgent** for suspected or confirmed cases when an intentional release is suspected as the cause of infection.
- Notification should be **immediate-urgent** for all other suspected and confirmed cases.

- Immediate notifications of VHF cases of international concern by the CDC's Special Pathogens Branch to WHO will occur for confirmed cases in accordance with the International Health Regulations.

## X. References

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