Viral Hemorrhagic Fever Surveillance Protocol

Viral hemorrhagic fever (VHF) is a clinical illness associated with fever and bleeding diathesis caused by viruses belonging to 4 distinct families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (Table 1). The mode of transmission, clinical course, and mortality of these illnesses vary with the specific virus, but each is capable of causing a VHF syndrome.

This protocol is written in the context of the current West African Ebola outbreak of 2014. Prevention and control measures are expected to evolve as more information is gained and will vary depending on the type of VHF. Providers and public health professionals should assure that they are working from the most current guidance.

Provider Responsibilities

1. Remain alert for imported cases of viral hemorrhagic fever (VHF). At this writing, returned travelers from Guinea, Liberia, and Sierra Leone are at highest risk for Ebola virus disease (formerly Ebola hemorrhagic fever); *however the epidemiology of VHF can change rapidly.* Consult www.cdc.gov or http://www.who.int/topics/haemorrhagic_fevers_viral/en/ for information on current outbreaks worldwide. Consider the diagnosis of VHF in returned travelers with illness including:
    a. Fever,
    b. Myalgia,
    c. Severe headache,
    d. Abdominal pain,
    e. Vomiting,
    f. Diarrhea, or
    g. Unexplained bleeding or bruising.
2. Other risk groups include direct contact with a confirmed or highly suspected VHF (Ebola) case. If there are no risk factors (i.e., no travel history AND no direct contact), then alternative diagnoses should be pursued.
3. For any suspected case of VHF:
    a. Immediately place the suspected case in isolation: *At a minimum*, private room, standard, droplet and contact precautions (gown, gloves, mask, goggles and hand hygiene before donning and after doffing personal protective equipment (PPE)) should be used. Please note that Centers for Disease Control and Prevention (CDC) guidelines for infection control have recently changed to require an N-95 mask or powered air purifying respirator (PAPR) and complete coverage of skin and hair for healthcare workers caring for an Ebola patient.

i. CDC guidelines for infection control: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html
ii. WHO guidelines for infection control: http://apps.who.int/iris/bitstream/10665/130596/1/WHO_HIS_SDS_2014.4_eng.pdf?ua=1&ua=1

b. Immediately inform the infection preventionist that a case of suspected VHF is in the health care facility. Immediately inform receiving personnel (infection preventionist and emergency department personnel and emergency medical service workers) if a suspected VHF patient is being transported from one facility to another.
c. Immediately inform the local health department (LHD). Anticipate the need to collaborate with the local health department on:
   i. Obtaining laboratory confirmation of the diagnosis,
   ii. Obtaining clinical information to confirm the diagnosis, and
   iii. Identifying contacts of the case so that their health can be monitored.

Laboratory Responsibilities

1. Immediately report requests for testing for VHF to the Division of Infectious Disease Epidemiology (DIDE) at (304) 558-5358, extension 1. Anticipate the need to obtain clinical and epidemiological information before testing can be cleared with the Centers for Disease Control and Prevention.
2. Use appropriate infection prevention measures when obtaining specimens: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html
3. Follow OLS guidelines for specimen submission. OLS can be reached at (304)-558-3530. Their website is: http://www.wvdhhr.org/labservices/

Local Health Responsibilities

NOTE: A case of viral hemorrhagic fever is potentially a national-level public health emergency. LHDs should anticipate the need to collaborate with state and federal public health epidemiologists on every aspect of epidemiological investigation, contact tracing and implementation of prevention and control measures.

1. Prior to the occurrence of a case of VHF:
   a. Protect employee health.

i. Identify high-risk employees, those who would be expected to:
    1. Interview infectious persons to identify contacts and identify the source of infection.
    2. Enter potentially contaminated environments such as a residence previously occupied by a VHF patient
ii. Assure that high-risk employees are educated about transmission of VHF and personal protective measures. According to CDC, Ebola virus can be transmitted by:
    1. Direct contact (mucous membranes or non-intact skin) with blood or body fluids (including but not limited to urine, saliva, feces, vomit, sweat, breast milk, and semen) of a person who is sick with Ebola (VHF) or
    2. Contact with objects (such as needles and syringes) that have been contaminated with these fluids.
iii. Assure that high-risk employees have access to appropriate personal protective equipment (PPE) (masks such as fit-tested N95 masks or powered air-purifying respirators (PAPR)) and are trained to properly don and doff PPE and observe donning and doffing. Only interview potentially infectious persons in a controlled setting such as an isolation unit of a hospital and then only if absolutely necessary. Strongly consider alternatives such as phone interview or proxy interview.
iv. Assure that employees are familiar with infection control guidelines:
    1. CDC: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html Note that CDC guidelines have recently changed to include use of an N95 fit-tested respirator or a powered air-purifying respirator (PAPR) and complete coverage of all skin and hair.
    2. WHO: http://apps.who.int/iris/bitstream/10665/130596/1/WHO_HIS_SDS_2014.4_eng.pdf?ua=1&ua=1
v. Standard precautions are required for contact tracing. See contact tracing section.

b. Train employees who will be responsible for investigation of a case of VHF. It is not possible to train and drill public health workers for every conceivable public health emergency. The best preparation and training for management of a VHF case is routine case and outbreak investigation. Almost ALL the necessary skills for management of a VHF case – case ascertainment, interviewing suspect and confirmed cases, recommending isolation measures, monitoring and observing infection control practices, tracing contacts – can be practiced during case and outbreak investigation. LHD administrators should assure that LHD staff are able to respond rapidly and completely to reported cases and outbreaks in their jurisdiction.

LHD administrators should review local health department performance on outbreak investigation regularly to assure readiness.

c. Educate providers and health facilities about appropriate recognition, isolation and reporting of a VHF case. In regards to the 2014 West African outbreak of Ebola, excellent source material can be found at: http://www.cdc.gov/vhf/ebola/index.html

2. When a VHF case is reported:
   a. Isolate the case. Immediately assure that the case is under appropriate isolation: *At a minimum*, standard, contact and droplet precautions should be instituted immediately, including *at a minimum*: private room, gowns, gloves, masks, goggles or face shield; with hand hygiene before entry and after/during discarding PPE. Highly suspect or confirmed cases should be isolated in accordance with CDC guidelines: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html
   b. Contact DIDE immediately. A single case of VHF is considered an outbreak. Anticipate the need to collaborate with DIDE and CDC to confirm the case, investigate the case, and institute prevention and control measures. Anticipate the need to work closely with / collaborate with CDC and DIDE throughout the investigation. Anticipate that CDC and DIDE will commit staff to assist with and lead many aspects of the investigation. If multiple West Virginia jurisdictions are involved, it will also be important to collaborate with other West Virginia jurisdictions as well.
   c. Prepare to interview patient.
      i. Observe infection control measures in place for the suspect VHF case-patient. Make recommendations for immediate correction of any infection control issues.
      ii. Phone interview or proxy interview may be the best choice to prevent transmission to the investigation team. If the interview is conducted in the patient room, public health interviewers should use the same personal protection as healthcare workers caring for the suspect case.
   d. Ascertain case status based on data collection.
      i. Collect the information on the WVEDSS Viral Hemorrhagic Fever Report Form. (http://www.dhhr.wv.gov/oeps/disease/WVEDSS/Documents/VHF.pdf) For the 2014 West African Ebola outbreak, there is a specific CDC form that should be used (http://www.dhhr.wv.gov/oeps/disease/zoonosis/other/ebola/documents/cdc-ebola-investigation.pdf) . The form serves as a guide to obtain clinical, epidemiologic, and clinical information as well as close contacts and other potential risk factors. Share the completed form with DIDE.
      ii. Assure that appropriate laboratory specimens are collected and submitted to OLS.
   e. Triage the incident.

i. Consult a medical epidemiologist regarding the diagnosis/case status. Consider an alternative diagnosis if there are no obvious risk factors and/or if the clinical or laboratory findings are not consistent with the diagnosis of VHF. Many travel–related illnesses (malaria, typhoid fever, dengue, chikungunya, meningococcemia, plague, rickettsial disease) present initially with similar symptoms and even leukopenia and thrombocytopenia (e.g., malaria) in the early stages. Malaria, influenza and a variety of other respiratory and gastrointestinal illnesses are likely to be more common in returning travelers than VHF.
ii. If the case is confirmed or highly suspected and an obvious exposure or possible exposure is evident after the initial interview (travel from an endemic area, contact with a known or suspected case, ingestion of bush meat or other illegally imported food, contact with non-human primates or fruit bats), active surveillance will be needed to identify additional cases with the same exposure(s).
iii. If the case is confirmed or highly suspected and there are no obvious risk factors after initial interview, broad active surveillance may be indicated to identify additional cases. The possibility of intentional exposure should be considered if the case does not have known epidemiological risk factors. If intentional exposure is among the possibilities being considered, collaboration with law enforcement on the investigation will also be necessary.

f. Maintain situational awareness through active and enhance passive surveillance.
i. DIDE will help develop a working case definition based on the CDC case definition and incorporating elements of place and time, depending on current epidemiology. For example, the 2014 West African outbreak case definition includes travel to affected West African countries as part of the criteria: http://www.cdc.gov/vhf/ebola/hcp/case-definition.html.
ii. After consultation with DIDE, institute active and enhanced passive surveillance to identify additional cases meeting the case definition. A press release and provider alert should be considered as part of enhanced passive surveillance.
iii. Coordinate risk communication with the West Virginia Bureau for Public Health (WVBPH) to help alleviate public fears and concern.
iv. Confirm newly reported cases by completing information on the WVEDSS form and obtaining appropriate laboratory studies.
v. In collaboration with DIDE, develop a line list of cases in order to manage the outbreak. Keep the line list up to date and share the updated line list with DIDE regularly.
vi. In collaboration with DIDE, develop a list of contacts of VHF cases (see Contact Tracing

section).

g. Environmental control measures.
   i. The residence or other space previously occupied by the VHF patient may be contaminated with blood or body fluids. Discuss options for cleaning and disinfection with Office of Environmental Health Services and potentially incident command. Take appropriate protective measures for staff who will enter the residence. Consider a delay of several days before entering the space to reduce infectivity of any contamination in the environment, if possible.

h. Determine the source of infection and institute control measures. If the source of infection is not obvious and there are numerous cases, advanced epidemiological, environmental and laboratory studies will be needed such as a case-control or cohort study, requiring collaboration with DIDE and CDC. See the outbreak protocol: http://www.dhhr.wv.gov/oeps/disease/ob/Documents/protocols/community-outbreak-protocol.pdf

i. Conduct contact tracing (for confirmed or highly suspected case).
   i. For each confirmed case-patient, identify close contacts. For the 2014 West African outbreak, CDC has developed a case interview form to assist with identifying contacts (http://www.dhhr.wv.gov/oeps/disease/zoonosis/other/ebola/documents/cdc-ebola-investigation.pdf). Close contact is defined as:
      1. Contact with blood or body fluids of the VHF case-patient
      2. Household contact with the VHF case-patient since the onset of illness
      3. Visiting the household of the case-patient since the onset of illness
      4. All persons who were visited by the case-patient after the onset of illness
      5. Direct contact with linens or clothing used by the case-patient after he/she developed symptoms
      6. Direct contact with a deceased VHF case-patient
      7. Being within 3 feet of the VHF case-patient for a prolonged period of time (≥ 1 hour) (not passing by the person in the hallway),
      8. Being in the same room with the VHF case-patient for a prolonged period of time (≥ 1 hour)
      9. Skin-to-skin contact, such as shaking hands with the case-patient
   ii. Line list all close contacts in collaboration with CDC and DIDE. Interview the case using the VHF Report Form. Interview case contacts to obtain information about the type of exposure(s) to assign a risk category. Prioritize contacts in accordance with current CDC guidance. For the 2014 West African Ebola outbreak, use “Interim US Guidance for Monitoring and Movement of Persons with Potential Ebola Virus Exposure” at:

http://www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html .

iii. Arrange direct active monitoring and active monitoring of healthcare contacts in collaboration with the occupational health unit of the healthcare employer. The employer should monitor exposed healthcare workers daily (if they are still at work) and report findings to public health daily for the duration of the surveillance period.

iv. Discuss work, school and travel restrictions with contacts, based on CDC guidance (referenced above). Document any restrictions, using a written health agreement signed by the contact and the health officer. In the health agreement, specifically address:

1. Controlled movement on commercial conveyance
    a. Long distance (air, train, ship, bus)
    b. Short distance (tram, bus, taxi)
2. Work and school attendance
3. Exclusion from public places (shopping centers, groceries, movie theatres)
4. Travel outside the jurisdiction

DO NOT place unnecessary restrictions on contacts. Follow CDC guidelines explicitly: http://www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html . Unnecessary restrictions undermine the credibility of the public health agency and may serve as a disincentive for people to volunteer in West African or US hospitals where Ebola patients are getting treatment. Persons who volunteer for this service are our colleagues and allies: they are helping bring the 2014 West African outbreak under control.

v. Arrange daily monitoring ("direct active monitoring" or "active monitoring") of contacts by contact surveillance field team(s).

vi. For 'direct active monitoring,' each contact surveillance field team should have two people, if possible including at least one local team member. Team members should be fully vaccinated, including current influenza vaccination in order to protect monitored persons from developing febrile illness due to exposure to team members. Teams should be trained to take appropriate precautions during field work and self-monitor for symptoms, including recording their temperature every AM immediately after reporting to work. The purpose of temperature monitoring is two-fold: protection of the monitored persons from exposure to illness in the contact tracer AND early identification of VHF in contact tracers. Fever in contact tracers should be reported to a supervisor immediately. The following safety precautions (based on WHO/CDC guidance) are recommended for contact tracing:

1. Call ahead to contact residence to determine if the contact has developed symptoms. If the contact has developed symptoms, teams should immediately notify a supervisor and await instructions.
2. Upon arrival at the residence, again inquire if anyone in the household has developed symptoms before entering. Do not enter if anyone in the household has developed symptoms. Contact a supervisor if anyone in the household is symptomatic.
3. In the household, avoid direct physical contact like shaking hands or hugging.
4. Maintain a comfortable distance (> 3 feet) when interviewing, observing and recording temperatures.
5. Avoid leaning on objects or sitting down: "Thanks, but I've got to keep moving. I've got a lot of people to check on today."
6. Politely decline any offered food. Eat and snack as needed in order to be able to resist offered food, and honestly say, "thanks, but I've already eaten …"
7. Each contact should have a dedicated quick-read thermometer supplied during the initial interview. During daily monitoring, have the contact take his/her temperature and show the temperature to the contact surveillance team. If the thermometer has been misplaced, give a new thermometer to the contact and leave the thermometer in the household.
8. Do not take the temperature of an obviously symptomatic contact. If you arrive at a contact residence and discover that a contact has developed symptoms, reassure them that an EMS team will transport them to medical care. Then leave the residence and contact your supervisor to inform him/her that the contact has developed symptoms and needs to be transported to a hospital for evaluation.
9. Notify supervisor immediately if contact is not where they said they would be OR is lost to follow up OR expresses the intention to evade surveillance.
10. Contacts should be checked twice daily – once in person and once by phone.
11. All information should be reported back to the data manager daily and entered into a database so that reports can be compiled for incident command.

vii. Educate contacts to:

1. Stay at home as much as possible
2. Restrict close contact with other people
3. Avoid crowded places, social gatherings, and use of public transport

4. Coordinate any necessary travel with the LHD
5. Notify the LHD immediately if fever or symptoms develop. Emphasize that early diagnosis and treatment is critical for the best outcome for the contact. Maintain a positive, supportive and empathic attitude.
6. Respond to questions and report concerns to the contact tracing supervisor.

See CDC guidelines for monitoring exposed persons: http://www.cdc.gov/vhf/ebola/hcp/monitoring-and-movement-of-persons-with-exposure.html#Controlled

viii. Contact monitoring is the single most critical control measure for VHF. Personnel chosen for contact monitoring should be chosen for their *confidence* and *caring* and *competence*. Contact surveillance teams should work to establish a trusting relationship with contacts; they are the face of public health to people who are understandably frightened or concerned. Contact tracers should be assigned as pairs. They should have adequate supportive supervision. Daily monitoring activities should be monitored on a line list or database. Anticipate that DIDE and CDC will identify and coordinate data support, assist with coordination of contact tracing and provide additional staff to help with contact tracing.

j. Identify exposed populations. If a common source exposure is identified, characterize and notify the exposed population.
   i. DIDE/CDC will help establish an exposure definition based on the epidemiological studies or data.
   ii. In accordance with the definition, compile a line list and contact all exposed persons and:
      1. Educate them about signs and symptoms
      2. Advise them how to access medical services if they develop signs or symptoms.
      3. Counsel them regarding travel restrictions, if any.
      4. If resources are available, active surveillance of exposed persons is recommended. If resources are not available, advise exposed persons to self-monitor for 21 days (or appropriate incubation period) after last exposure and contact them at the end of 21 days (or appropriate incubation period) to assure establish final case status.

k. Prevention and control
   i. Environmental exposure: remove persons from a potentially contaminated environment, such as the home of a VHF patient contaminated with blood or body fluids.

ii. Post-exposure prophylaxis (PEP): there is no PEP for VHF.

l. Treatment of cases: Arenavirus and Bunyavirus hemorrhagic fever can be treated with ribavirin. Experimental therapies are available for some other VHFs.

State Health (DIDE) Responsibilities

1. Protect employee health: Implement occupational health protections for employees who would have responsibilities for interviews of infectious patients. Employees should have access to powered air-purifying respirator (PAPR) or fit-tested N-95 respirators. Interviews of infectious persons should only be conducted in controlled settings: isolation units of hospitals, and then only if necessary. Strongly consider phone interview or interview of a proxy to protect from transmission. For additional guidance on occupational health, see LHD section.
2. Maintain outbreak preparedness to include support of investigation of outbreaks, evaluation of outbreak response and preparation of outbreak toolkits and other supporting material. See: http://www.dhhr.wv.gov/oeps/disease/ob/Pages/default.aspx
3. Maintain up to date information at www.dide.wv.gov
4. In the event that a VHF case is reported in West Virginia:
    a. Immediately assure that the case is appropriately isolated using standard, contact and droplet precautions (*at a minimum:* private room, gloves, gowns, masks, goggles, and hand hygiene before donning and after/during doffing PPE). If the case is a strong suspect or confirmed case, he/she should be transferred to a location where current CDC infection control guidelines can be implemented: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html
    b. Immediately report a suspected or confirmed case to CDC as required.
    c. Recommend activation of BPH incident command, if appropriate, i.e., if case is highly suspected or confirmed or if there are extenuating circumstances requiring management of resources beyond the capability of DIDE.
    d. Supplement local response as needed, including:
        i. Drafting alerts, information sheets and press releases
        ii. Elbow-to-elbow support of field investigation, leadership of investigation with CDC support, data support
        iii. Advanced epidemiological studies such as case-control or cohort studies
        iv. Report writing and other assistance with scientific communications
    e. Based on guidance from CDC, prepare a standard line list form (database) for use across

West Virginia jurisdictions for managing the outbreak investigation. The content of the line list will likely include:

i. Case ID number (for linking across contact line list and other databases),
ii. Name,
iii. Age and date of birth,
iv. Sex,
v. Location (hospital, clinic, home),
vi. Employer,
vii. Date of onset of symptoms,
viii. Classification of case (person under investigation, probable, confirmed),
ix. Lab results and date(s),
x. Status of case investigation (assigned, completed) and person(s) responsible for investigation,
xi. Status of contact investigation (assigned, completed) and person(s) responsible for investigation, and
xii. Outcome (alive with no sequelae, alive with complications, deceased)

f. Based on guidance from CDC, prepare contact interview form (see example at: http://www.dhhr.wv.gov/oeps/disease/zoonosis/other/documents/ebola/cdc-ebola-contact-form.pdf) and line list (database) to be used for each identified VHF patient. Each line list should have the name and ID number of the VHF patient and for each contact list:

i. Contact ID number
ii. Name,
iii. Age and date of birth,
iv. Sex,
v. Locating information (address, telephone),
vi. Employer,
vii. Healthcare worker?
viii. Type of contact (household, healthcare worker, etc.)
ix. Priority (rank according to risk category -- high, some, low, none – see: http://www.cdc.gov/vhf/ebola/hcp/monitoring-and-movement-of-persons-with-exposure.html)
x. Reason for rank
xi. Counseling and education of VHF contact: date contacted, by whom
xii. Notes field for interactions with the VHF contact
xiii. Daily status (symptomatic / asymptomatic / lost to follow-up, date and time)
xiv. Final status (well, person under investigation, confirmed case) and date

Use information on the line list (database) to update leadership daily about contact tracing status.

g. With CDC guidance, assist with exposure investigation, and if common source exposure is identified, prepare a line list, scripts and interview forms to support notification of exposed persons. Exposure line list might include:
   i. Name
   ii. Contact information
   iii. Age, date of birth
   iv. Sex
   v. Employee assigned to notification
   vi. Notification status (assigned, completed) and date
   vii. Notes field for interactions with the exposed person
   viii. Twice daily status (temperature, symptoms, date and time)
   ix. Final patient status (well, person under investigation, confirmed case) and date

Disease Prevention Objectives

To prevent disease through education of health care workers and public health workers to: 1) detect index cases and direct contacts rapidly, and 2) use strict adherence to standard precautions, droplet precautions, and contact precautions to minimize exposure to blood and body fluids of living and deceased cases.

Disease Control Objectives

To prevent unnecessary illness and death through rapid identification of populations exposed to VHFs coupled with ***adherence to standard, contact, and droplet precautions***.

To reduce mortality by educating physicians about ribavirin therapy for arenaviruses and bunyaviruses prior to agent confirmation.

Surveillance Objectives

To rapidly detect and confirm a case of VHF if it occurs in WV.

Viral Hemorrhagic Fever Surveillance Protocol

Public Health Significance

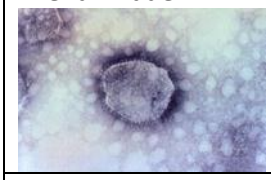
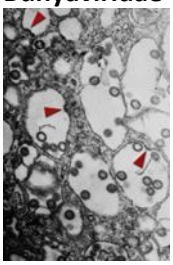
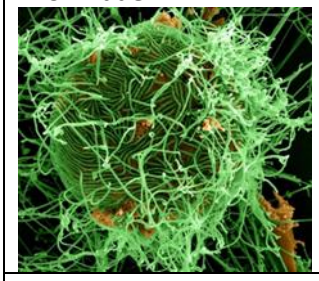
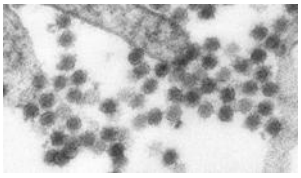
Viral hemorrhagic fevers are caused by enveloped RNA viruses in four families: filoviruses, flaviviruses, arenaviruses and bunyaviruses (Table 1). These viruses are maintained in nature in naturally occurring reservoirs including mosquitoes (yellow fever and dengue); ticks (Crimean-Congo hemorrhagic fever); bats (Marburg and some Ebola strains); rodents (Lassa fever); domestic ruminants (Rift Valley fever); and nonhuman primates (Marburg). The diseases are ordinarily restricted to specific geographic areas and are often named for the geographic location where they were first identified. However, cases can be introduced into non-endemic areas by an incubating human host or reservoir species. Outbreaks can result from introduction of the virus into a new environment or changes in ecology (rainfall, density of vector and reservoir species, land management, etc.). Some diseases have high fatality rates and person-to-person transmission such as Ebola and Marburg. Person-to-person transmission due to poor infection control in healthcare settings in the developing world contributes to large outbreaks of Marburg, Ebola, Lassa fever and Crimean-Congo Hemorrhagic fever. For other viruses (dengue and yellow fever) asymptomatic infection and mosquito transmission are the norm.

Viral hemorrhagic fevers, such as Ebola and Marburg are deeply feared. Managing the fear is as much a part of the public health response as managing the disease. During outbreaks in Africa, healthcare workers are prominent among the victims and healthcare workers may leave their posts rather than face the possibility of death. This fear impacts the quality of care that patients receive. The overwhelmed medical staff may not offer the intense therapy that is required for the patient to get better. They may not want to stand close enough to support the head of a critically ill patient to offer oral rehydration therapy and they may fear a needle stick and therefore not start an intravenous line. Similarly, patients and families may hide an Ebola patient because they fear the stigma and other repercussions. Similar fears exist in association with imported VHF cases in the U.S.

The risk of a bioterrorism attack with VHFs is low, but possible, and would have substantial public health impact because of the high mortality rate of most VHFs. Large quantities of Marburg, Ebola, Lassa, and New World arenaviruses were weaponized by the former Soviet Union and Russia until 1992. Yellow fever and Rift Valley fever were weaponized by the U.S. prior to 1969. The Japanese cult Aum Shinrikyo tried to obtain Ebola as part of an effort to create biological weapons. Yellow fever has reportedly been weaponized by Korea.

Viral Hemorrhagic Fever Surveillance Protocol

Table 1 Selected Viruses Causing Viral Hemorrhagic Fever

Virus Families (Public Health Image Library)	Characteristics of the family (Principles and Practice of Infectious Diseases)	Selected Examples associated with hemorrhagic fever (WHO)
Arenaviridae 	• Round, oval or pleomorphic RNA viruses that form their membranes by budding from the host membrane	• Lassa fever • Junin • Machupo
Bunyaviridae 	• Spherical, lipid membrane-enclosed RNA viruses with glycosylated envelope proteins • Photograph (Rift Valley fever) shows virus budding from cell membranes; however virions from some other viruses in this family mature by budding from intracellular structures • Also includes California encephalitis (La Crosse)	• Rift Valley Fever • Crimean-Congo hemorrhagic fever • Hantaan hemorrhagic fever
Filoviridae 	• Elongated, filamentous RNA virus with membrane formed as the virus buds from the host cell. • Photograph shows viruses budding from a cell in tissue culture	• Marburg virus • Ebola virus
Flaviviridae 	• More than 60 species • 30 are known to cause human disease • Icosahedral RNA viruses with a lipid envelope studded with glycoproteins • Unstable in the environment and sensitive to heat, ultraviolet radiation, disinfectants (including alcohol and iodine), and acid pH • Also includes West Nile virus (photograph), St. Louis encephalitis,	• Dengue fever • Yellow fever • Omsk fever • Kyasanur forest disease

Viral Hemorrhagic Fever Surveillance Protocol

Clinical Description

Because of space and time limitations, clinical description is limited to the most commonly encountered viral hemorrhagic fevers.

Marburg and Ebola

Marburg is named for Marburg, Germany, site of the first recognized Marburg outbreak in 1967, traced back to African green monkeys imported from Uganda. Ebola is named for a small river in what is now Democratic Republic of the Congo.

Onset of illness is acute with fever, headache, myalgia, and extreme fatigue. Early signs also include conjunctivitis, severe sore throat (with trouble swallowing), nausea, vomiting, abdominal pain and diarrhea. Vital signs may demonstrate bradycardia (low heart rate) and tachypnea (rapid breathing rate). Around the fifth day, a perifollicular (around the hair follicles), nonitching, maculopapular rash may appear on the torso, spreading to the face and limbs. The rash becomes confluent and fades in 3 to 10 days, followed by desquamation (skin peeling). In low-resource areas of Africa, this rash is considered pathognomonic (diagnostic), allowing distinction between malaria and viral hemorrhagic fever. About half of patients have bleeding beginning around day 5-7, including epistaxis (nosebleeds), bleeding gums, hematemesis (vomiting blood), melena (blood in the stool), hematuria (blood in the urine), petechiae, ecchymoses (bruises), and hemorrhages from needle sticks. Internal hemorrhage has been documented in fatal cases. Dehydration, prostration, continued high fever, multi-organ failure (respiratory failure, myocarditis, pancreatitis, renal failure, etc.) and shock can occur. Death occurs 6 to 9 days after onset of symptoms. Infection in pregnancy carries a grave prognosis for mother and child.

Recovery is prolonged, and victims may experience ongoing joint pain, eye inflammation or even blindness, hearing loss, orchitis, hepatitis, and neurological (stroke, personality change, psychosis) complications. Mortality varies with the strain of virus and likely with the quality of available medical care. Ebola Zaire carries a case fatality rate (CFR) of 60-90%; Ebola Sudan has a CFR of 40-60%; Bundibugyo Ebola has a CFR of 25%; and the single Taï Forest (formerly Cote d'Ivoire) Ebola case survived. Marburg CFR in Africa is 70-85%; however the CFR in Europe in 1967 was 22%.

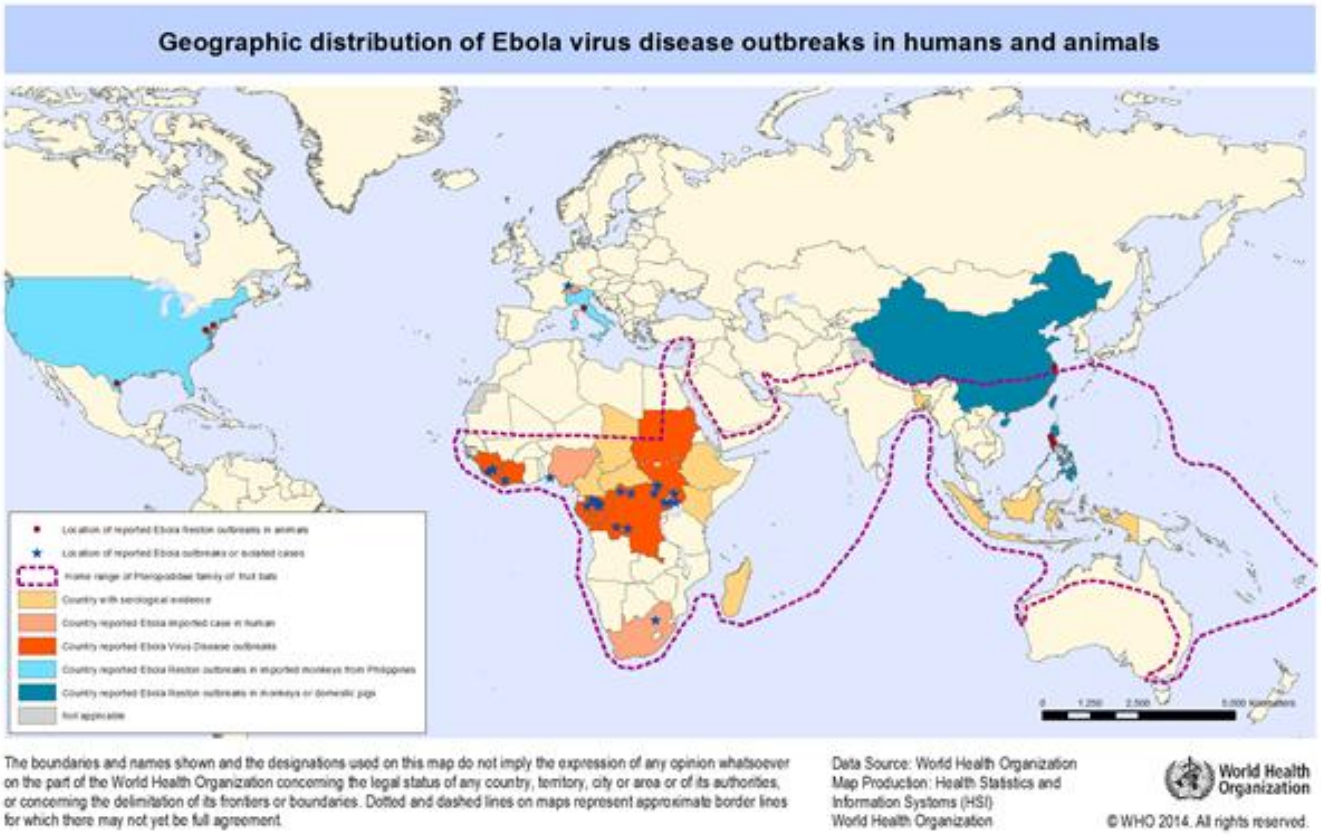
Laboratory findings include leukopenia, lymphopenia and thrombocytopenia early in illness followed by increased neutrophils and atypical lymphocytes. Liver enzymes are elevated (AST/SGOT > ALT/SGPT) but alkaline phosphatase and bilirubin levels are usually normal or only slightly elevated. Hypoproteinemia (low protein in the blood) and proteinuria (protein in the urine) may occur. Metabolic disturbances may occur as well as evidence of disseminated intravascular coagulation (DIC).

Because outbreaks of Ebola and Marburg generally occur in resource-poor countries and even a small number of cases can rapidly overwhelm the austere medical services available, the clinical description of these diseases is incomplete and is expected to evolve as we gain more understanding.

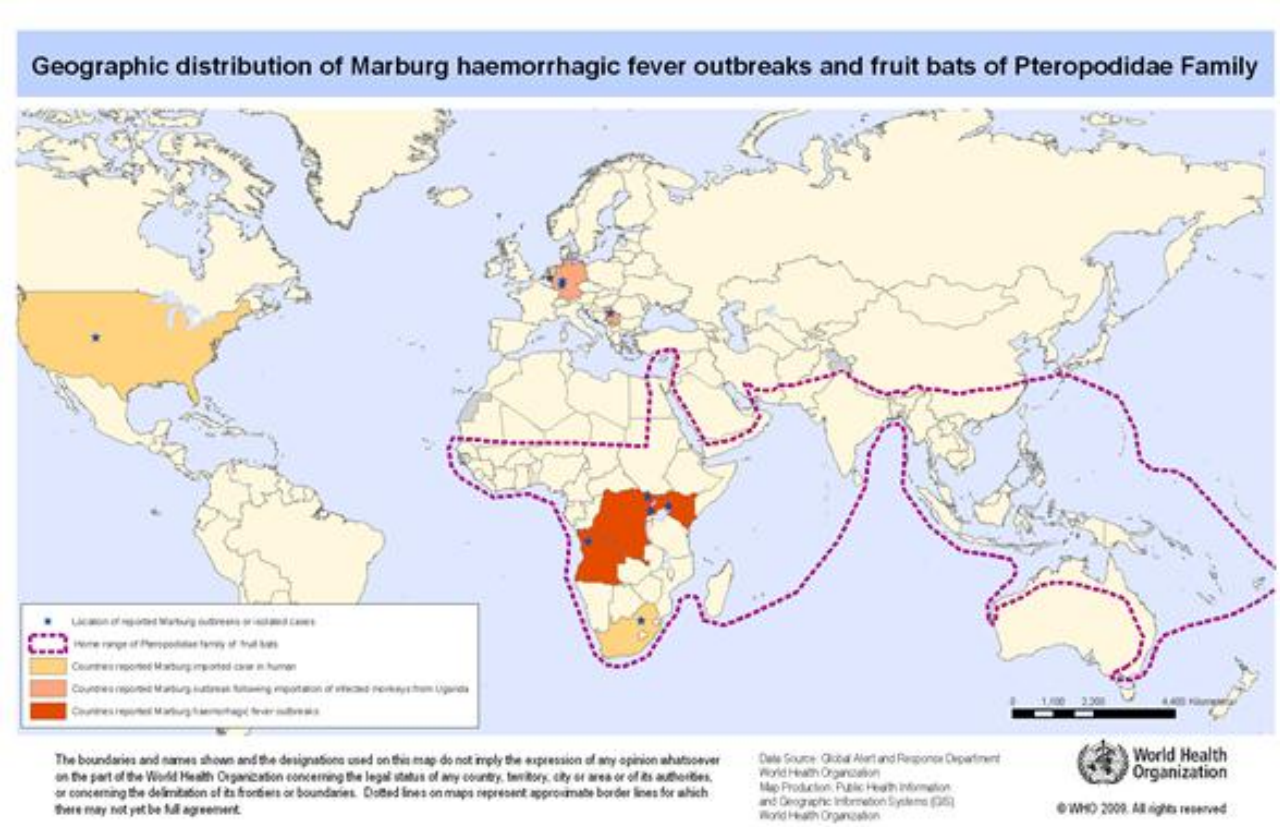
Geographic distribution of Ebola and Marburg are shown in the maps, below from the World Health Organization website. WHO has maps from the 2014 outbreak posted at: http://www.who.int/csr/disease/ebola/maps/en/ Returned travelers would be expected to fall ill within 21 days of last exposure.

Viral Hemorrhagic Fever Surveillance Protocol

WEST VIRGINIA Department of Health & Human Resources
BUREAU FOR PUBLIC HEALTH



Viral Hemorrhagic Fever Surveillance Protocol



Lassa Fever

Named for Lassa, Nigeria, where it was first identified, Lassa fever is the most commonly diagnosed travel-related VHF. After an incubation period of up to 21 days, the individual may experience gradual onset of low-grade fever, headache, malaise and general weakness. Eighty percent of Lassa fever infections are subclinical or mild. After a 4-7 day prodrome, the remaining 20% gradually progress to more severe disease including hemorrhage, persistent vomiting, hypotension, edema, pleural and pericardial effusions, shock and respiratory distress. In fatal cases, death from multi-organ failure typically occurs within 2 weeks of onset; however case-fatality rate is about 2% overall. Disease is more severe in pregnancy.

Lassa fever occurs naturally in West Africa. A returned traveler would be expected to fall ill

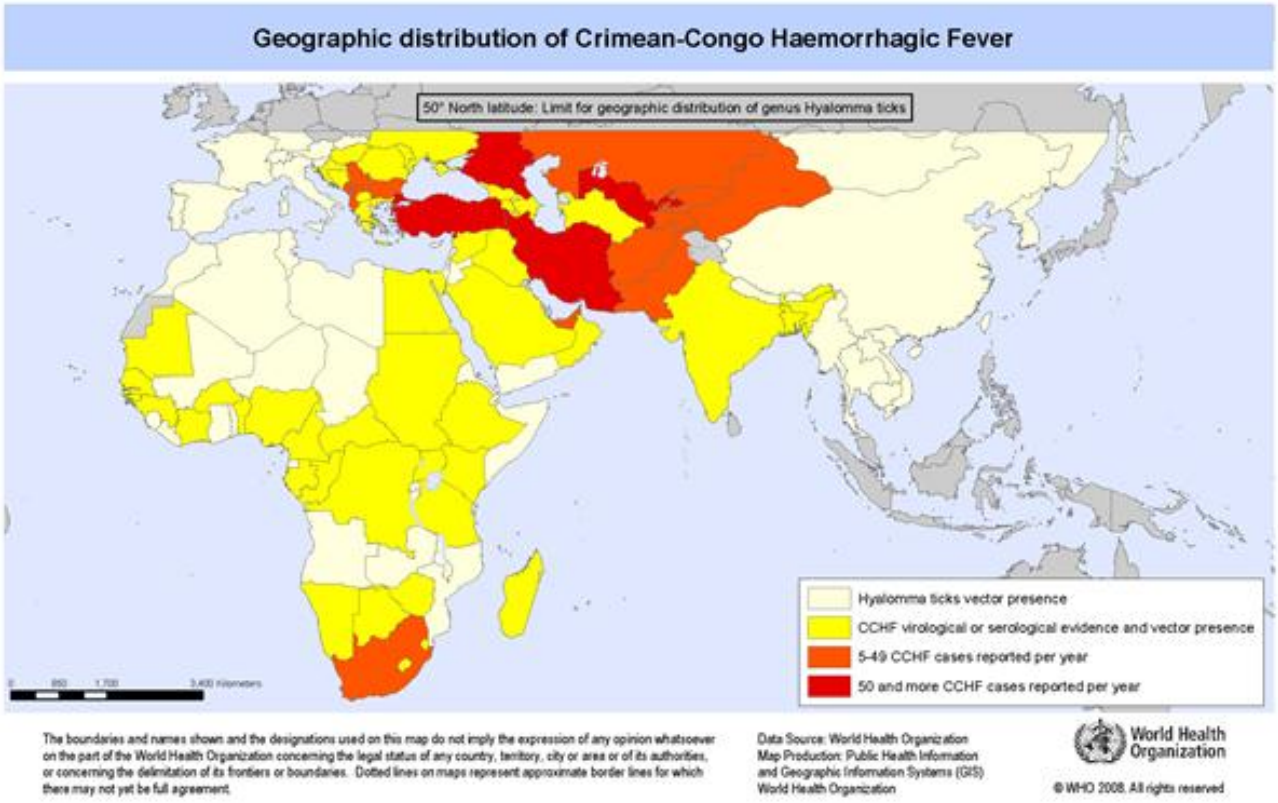
within 21 days of last exposure.

Crimean-Congo Hemorrhagic Fever

Onset is abrupt with fever, headache, myalgia (muscle aches), weakness, rigors (intense chills), nausea, vomiting, diarrhea, abdominal pain, and conjunctival injection. There may be diarrhea, painful eyes and sore throat. After 2-3 days of illness, there may be a brief remission of several hours. During the second phase of illness, hemorrhagic manifestations may occur, including petechiae, epistaxis (nose bleeds), ecchymoses (bruising), bleeding from needle sticks, melena (blood in stool), and hematuria (blood in urine). There may be photophobia, meningismus and mental status changes. The case fatality rate is 25-30%. During the convalescent phase, the patient experiences fatigue and dizziness and may experience sudden onset of deafness.

The returning traveler with Crimean-Congo hemorrhagic fever will present within less than 2 weeks after last exposure. The geographic distribution of Crimean-Congo hemorrhagic fever cases and the vector tick species is indicated in the map below from the World Health Organization.

Viral Hemorrhagic Fever Surveillance Protocol

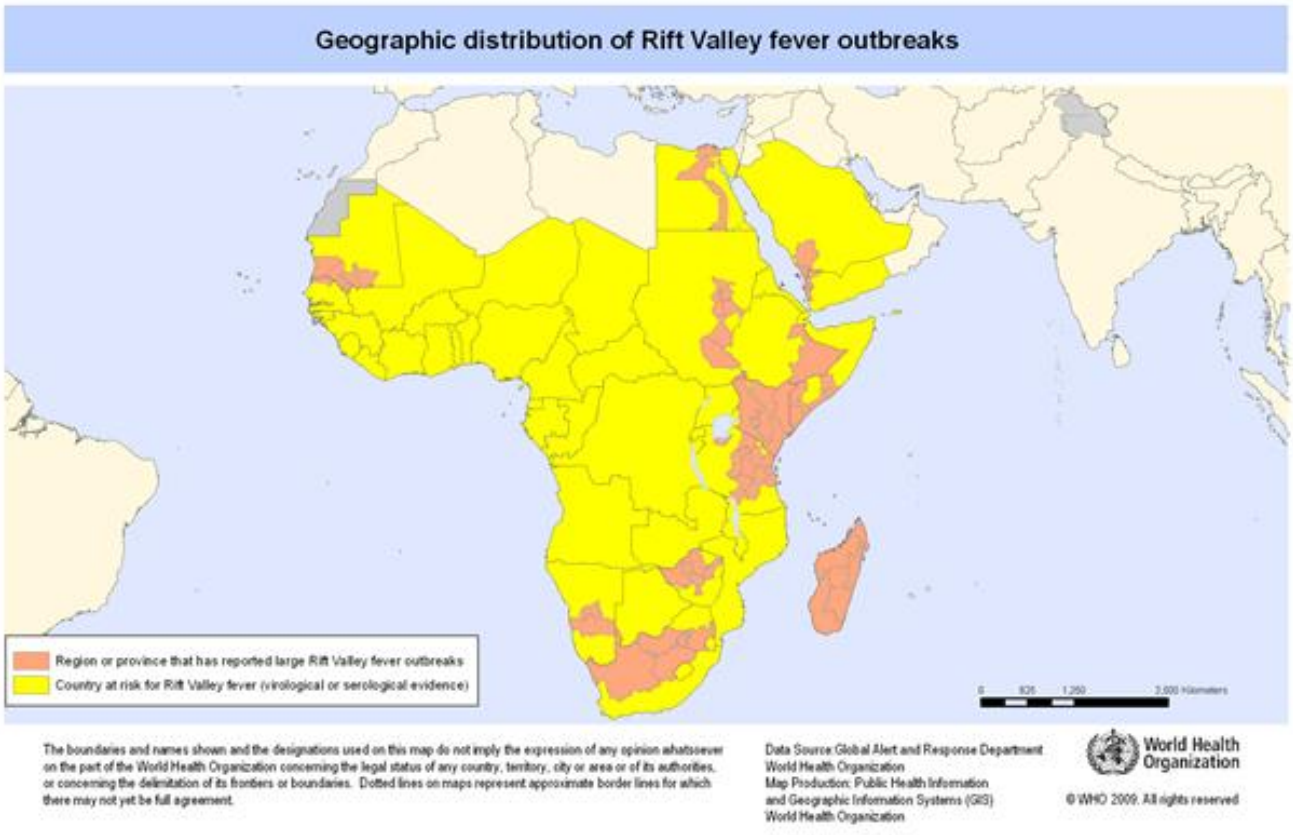


Rift Valley Fever

Rift Valley fever (RVF) was first identified in an infected sheep in the Rift Valley region of Kenya in 1930. Illness is variable ranging from a self-limited febrile illness to hemorrhagic signs and death. For that reason, outbreaks may not be recognized until sufficient severe cases have occurred. Fever, malaise and headaches are non-specific. Progression to large joint pain (elbows, knees, shoulders), nausea, vomiting, abdominal pain, hepatomegaly, jaundice and delirium helps identify the illness as RVF. Acute renal failure occurs in a majority of hospitalized patients, requiring dialysis. Mortality is 40% among hospitalized patients. Fatal cases often have hemorrhagic manifestations similar to other VHF, hepatic necrosis, encephalitis, renal failure and disseminated intravascular coagulation (DIC). Complications can include long-lasting visual disturbance and neurological impairment.

Viral Hemorrhagic Fever Surveillance Protocol

The following map from WHO shows the distribution of RVF.



Etiologic Agent

All VHF viruses are small RNA viruses with lipid envelopes. The lipid envelope probably makes the virus more easily inactivated by hospital disinfectants compared to viruses such as norovirus that do not have a lipid coating.

Arenaviridae comprises 29 named viruses. Arenaviruses are about 110-130 nm and incorporate

host membrane proteins into the lipid viral envelope in the process of budding through the cytoplasmic membrane of the host cell to reproduce. The virus is inactivated by a variety of solvents and acid (pH<5).

Bunyaviridae contains around 300 viruses, and five genera. Bunyaviridae are about 80-120 nm in size.

Filoviridae, like arenaviruses are susceptible to heat and a variety of solvents. These viruses are stable at room temperature for several hours but are inactivated at 60°C for 1 h. They also form their lipid envelope by budding through the host cell. They are about 800 nm long by 80 nm in diameter.

Flaviviridae are 40-60 nm. This family includes West Nile, St Louis encephalitis, dengue virus, yellow fever, Powassan encephalitis, and Japanese encephalitis. Please refer to the arbovirus protocol or dengue protocol for additional information on flaviviridae.

Reservoir

Information about reservoir in the wild is found in Table 2. Once a patient with VHF is admitted to a health facility, the patient and items contaminated with blood or body fluids becomes the reservoir within the health facility.

Table 2 Vector and Reservoir Species and Transmission of VHF viruses***

Family	Genus	Virus*	Disease	Vector/Reservoir in Nature	Nosocomial Spread
Filoviridae	Filovirus	**Ebola**	Ebola HF	Fruit bat reservoir for some strains (Zaire). Primates (Reston, Côte d'Ivorie) and pigs (Reston) have been infected with some strains of Ebola	Nosocomial spread; spread from direct contact with deceased Ebola patients
		Marburg	Marburg HF	Fruit bat reservoir; primates may be a source for index case infection	Nosocomial spread
Arenaviridae**	Arenavirus	**Lassa**	Lassa F.	Rodent reservoir; humans infected by inhalation, ingestion, inoculation with rodent feces	Frequent nosocomial transmission
		New World Arenaviridae	New World HF	Rodent	Yes – Bolivian hemorrhagic fever
Bunyaviridae	Nairovirus	Crimean-Congo HF	CC HV	Tick – mammal—tick cycle; humans infected from tick bite or contact with slaughtered ruminants	Nosocomial outbreaks
	Phlebovirus	**Rift Valley Fever**	Rift Valley HF	Mosquito transmission with amplification through cattle and sheep; humans are infected through mosquito bite or exposure to infected tissues of sheep, goats and cattle	no
	Hantavirus	HF with renal syndrome	HF with renal syn.	Rodent reservoir; human infection through aerosolized rodent urine	no
Flaviviridae	Flavivirus	Dengue	Dengue fever, Dengue HF	*Aedes aegypti* – human cycle	no
		Yellow Fever	Yellow fever	Mosquito – human or mosquito – nonhuman primate cycles	no
		Omsk HF	Omsk HF	Unidentified cycle involving ticks, muskrats, voles	no
		Kyasanur Forest Disease	Kyasanur Forest Disease	Tick—mammal—tick cycle	no

* Bold indicates HFVs that pose a serious bioterrorist threat.

** The new World Arenaviridae include Machupo, the cause of Bolivian HF; Junin, the cause of Argentine HF; Guanarito, the cause of Venezuelan HF; and Sabia, the cause of Brazilian HF.

*** JAMA, May 8, 2002, 287(18):2392; and Annu Rev Pathol Mech Dis. 2013; 8:411-440 and British Med Bull, 2005; 73&74:123-137.

Viral Hemorrhagic Fever Surveillance Protocol

Mode of Transmission

See notes from Table 2. Transmission occurs by a variety of routes, depending on the type of infection. Infections acquired percutaneously are associated with the shortest incubation period and highest mortality.

Aerosolization of HFVs is also a possible mode of transmission during a bioterrorism (BT) event.

Modes of transmission via naturally occurring routes are discussed below.

Filoviridae: Ebola and Marburg

1. Index cases of Ebola have been associated with exposure to carcasses of nonhuman primates or fruit bats.
2. Once the disease is introduced into human populations, most infections occur through chains of human-to-human transmission. Most cases have occurred after direct contact with blood, secretions, or tissues of infected patients. Cases have followed needle-stick injuries or injections with contaminated needles. Nosocomial spread occurs in underfunded African hospitals unable to take appropriate infection control precautions. This is the primary mode of transmission of Ebola and Marburg during outbreaks.
3. High titers of Ebola virus particles are found in blood and levels are much higher in persons who die from Ebola. Ebola virus has been detected in multiple types of body fluids of acutely ill persons, however data is limited because of small numbers of persons studied.
4. Household contacts who have developed Ebola have had direct contact with the ill person. Household contacts who have not had direct contact with the ill person are protected. This suggests that airborne transmission of Ebola does not occur.
5. Transmission of Ebola and Marburg virus occurs after onset of signs and symptoms.
6. Ebola and Marburg have been isolated from seminal fluid of patients 101 and 82 days after disease onset, respectively. In one case, Marburg may have been sexually transmitted.

Arenaviridae: Lassa Fever and New World Arenaviruses

1. In nature, Arenaviruses are transmitted to humans via inhalation of aerosols present in rodent urine and feces, by ingestion of food contaminated with rodent excreta, or direct contact of rodent excreta with abraded skin and mucous membranes.

2. Person-to-person transmission occurs predominantly by direct contact with infectious blood and bodily fluids. Nosocomial outbreaks have been described.
3. Person-to-person airborne transmission has been suspected in a few instances for Lassa fever and Bolivian HF.
4. There are no reports of Arenavirus transmission during the incubation period. However, Lassa fever virus has been detected in semen up to 3 months after acute infection and in urine 32 days after disease onset. Argentine HF has been transmitted to spouses of convalescent patients 7 to 22 days after onset of illness.

Bunyaviridae: Crimean-Congo Hemorrhagic Fever

1. Humans become infected after a tick bite or after the slaughter of sick domestic animal.
2. Nosocomial outbreaks have been described.

Bunyaviridae: Rift Valley Fever

1. Humans acquire Rift Valley Fever from the bite of an infected mosquito, direct contact with infected animal tissues, or aerosolization of virus from infected animal carcasses. In naturally occurring outbreaks, abortion storms (near simultaneous spontaneous abortions in pregnant ruminants regardless of stage of pregnancy) are a 'classic hallmark' of RVF outbreaks. Exposure to infected tissues or body fluids or aborted materials constitutes the main route of exposure.
2. Ingestion of contaminated raw animal milk has been implicated epidemiologically.
3. There is no evidence of person to person transmission of Rift Valley Fever. However laboratory technicians are at risk of acquiring the disease by inhalation of infectious aerosols generated from specimens.
4. If Rift Valley Fever were used as a bioterrorist weapon, susceptible livestock could also be infected which could lead to further mosquito transmission to humans and other animals.

Flaviviridae: Yellow fever, Omsk HF, and Kyasanur Forest Disease

1. Humans acquire yellow fever from the bite of an infected mosquito and acquire Omsk HF and Kyasanur Forest disease viruses from the bite of an infected tick.

2. There are no reported cases of person to person transmission or nosocomial spread of flaviviruses.
3. Infection of laboratory personnel via inhalation of aerosols during cultivation of these viruses has been reported.

Incubation Period

Table 3 Incubation Period in Days for Viral Hemorrhagic Fevers

Virus	Incubation period (days)
Ebola	2-21
Marburg	2-21
Lassa F.	6-21
New World Arenaviruses	7-14 (rarely 5-21)
Rift Valley F.	2-6
Yellow F.	3-6
Omsk HF	2-9
Kyasanur Forest Disease	2-9

Infectious Period

There is no person-to-person transmission prior to onset of symptoms with Filoviruses (Ebola and Marburg) and Arenaviruses. There is no person-to-person transmission with Flavivruses (e.g., Yellow Fever, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease) or for Rift Valley Fever (Bunyaviruses).

Because some of the HF viruses may remain in bodily fluids for a long time following clinical recovery, convalescent patients continue to pose a risk of disease transmission. Therefore

patients convalescing from a Filovirus or an Arenavirus infection should refrain from sexual activity for 3 months after clinical recovery. Viruses have been found in seminal fluid of patients or sexually transmitted after 82 and 101 days after symptom onset for Ebola, 83 days for Marburg, 3 months for Lassa Fever, and 7-22 days for Argentine (Junin) HF. Virus can be shed in urine for 3-9 weeks after infection with Lassa fever.

Outbreak Recognition

There has never been a human case of VHF in WV; therefore, one case of VHF constitutes an outbreak.

Case Definition

Subtype(s)

- Crimean-Congo Hemorrhagic Fever virus
- Ebola virus
- Lassa virus
- Lujo virus
- Marburg virus
- New World Arenavirus – Guanarito virus
- New World Arenavirus – Junin virus
- New World Arenavirus – Machupo virus
- New World Arenavirus – Sabia virus

Background

New World Arenaviruses include: Guanarito, Machupo, Junin, Sabia viruses.

Clinical Criteria

An illness with acute onset with ALL of the following clinical 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
    - 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 viral hemorrhagic fever (VHF) viral antigens in blood by enzyme-linked Immunosorbent Assay (ELISA) antigen detection
- VHF 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

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 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.

Comment(s)

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

Laboratory Notes

DIDE and OLS should be contacted to coordinate submission of isolates to CDC for confirmation. CDC can conduct the following confirmatory tests:

IgM and IgG antibodies
PCR
Virus isolation

Preventive Interventions

Infection control procedures: A private room and standard, contact and droplet precautions are recommended for all suspected, probable, or confirmed cases of VHF and cadavers to prevent direct contact with infected blood and bodily fluids. Specific recommendations:

CDC:
http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html
CDC PPE Recommendations: http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html

WHO:
http://apps.who.int/iris/bitstream/10665/130596/1/WHO_HIS_SDS_2014.4_eng.pdf?ua=1&ua=1

Resources from the University of Nebraska Medical Center on how to put on PPE:
http://app1.unmc.edu/nursing/heroes/pdf/vhfppe/donningBiologicalPPE-EbolaPatients-8.5x11-CC-v1.02.pdf
Resources from the University of Nebraska Medical Center on how to remove PPE:
http://app1.unmc.edu/nursing/heroes/pdf/vhfppe/doffingBiologicalPPE-EbolaPatients-8.5x11-CC-v1.01.pdf

Treatment: Initiate ribavirin therapy for all probable and confirmed cases of arenaviruses and bunyaviruses. Consult an expert clinician on treatment options.

Environmental Exposures: After the source of an exposure has been identified (i.e., common source outbreak), remove people from the environment until decontamination is achieved.

Treatment

The mainstay of treatment for VHF is supportive, with careful maintenance of fluid and

electrolyte balance, circulatory volume, and blood pressure. There are no antiviral drugs or vaccines for post exposure prophylaxis for VHFs.

Drug Therapy

Ribavirin has some in vitro and in vivo activity against Arenaviruses and Bunyaviruses but no utility against Filoviruses or Flaviviruses.

Clinicians should consult an expert about management and treatment of VHFs.

Vaccine

With the exception of Yellow fever live attenuated 17D vaccine, which is highly effective when administered to travelers to endemic areas, there is no licensed vaccine for any of the VHFs. The Yellow fever vaccine is not useful in preventing disease if given in the postexposure setting.

Surveillance Indicators

See outbreak protocol:
http://www.dhhr.wv.gov/oeps/disease/ob/Documents/protocols/community-outbreak-protocol.pdf

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